SURFACE MODIFICATION OF PLASTICIZED POLY(VINYL CHLORIDE) TO RETARD PLASTICIZER MIGRATION AND ENHANCE BIOCOMPATIBILITY

A Thesis Presented

by

LAKSHMI S.

to

The Division of Polymer Chemistry
in partial fulfilment of the requirements
for the Degree of
Doctor of Philosophy

of

SREE CHITRA TIRUNAL INSTITUTE
FOR
MEDICAL SCIENCES AND TECHNOLOGY
TRIVANDRUM

January 1999

DECLARATION

I, Lakshmi S hereby declare that I had personally carried out the work depicted in the thesis entitled "SURFACE MODIFICATION OF PLASTICIZED POLY(VINYL CHLORIDE) TO RETARD PLASTICIZER MIGRATION AND ENHANCE BIOCOMPATIBILITY " except where external help sought are acknowledged.

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CERTIFICATE

This is to certify that Ms. LAKSHMI S in the division of Polymer Chemistry of this Institute, has fulfilled the requirements of the regulations relating to the nature and prescribed period of research for the Ph. D degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum. The work relating to her thesis entitled "SURFACE MODIFICATION OF PLASTICIZED POLY(VINYL CHLORIDE) TO RETARD PLASTICIZER MIGRATION AND ENHANCE BIOCOMPATIBILITY" was carried out under my direct supervision.

Dr. A. Jayakrishnan
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The thesis

entitled

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To my parents.....

Acknowledgments

It has been an honour and privilege for me to have worked with Dr. A. Jayakrishnan, Head, Polymer Chemistry Division, SCTIMST, one of the most revered and illustrious personality in the scientific community. I express my irredeemable depth of gratitude, indebtedness and obligation for his critical and enthusiastic guidance, inspiration and inexhaustible encouragement throughout the course of the investigation.

I would like to record my depth of gratitude to Dr. K. Srinivasan, Dr. Prabha. D. Nair and Dr. Jaisey Mathai, the members of my Doctoral Advisory Committee for their valuable suggestions, constant encouragement and sincere advice.

I wish to thank the Director, SCTIMST and the Head, BMT Wing, SCTIMST for providing the necessary facilities throughout the course of the work.

I am indebted to Dr. K. Rathinam, Group Leader, Toxicology, Dr. P. V. Mohanan and Mr. Asokan Kuttiyil for their expertise and assistance in blood compatibility evaluation and bacterial adhesion studies. Thanks are also due to Dr. T. V. Kumary and Mrs. S. Usha Vasudev for their help in carrying out the cytotoxicity evaluation of samples.

I also express my sincere thanks to Dr. S. N. Pal, Executive Director, Hindustan Latex, Ltd., Thiruvananthapuram for the generous supply of plasticized PVC sheet, Mr. B. Ajit Kumar, Kolf laboratory, University of Utah, USA for the XPS analysis and Mr. K. Sreekumar for the SEM analysis.

I owe my sincere thanks to all my colleagues in the Institute especially Mrs. M. S. Latha, Mrs. S. R. Jameela, Ms. Latha Ranganathan, Mrs. Sumi Mary George and Mr. M. C. Sunny for their friendly co-operation, help and warm companionship.

I greatly acknowledge University Grants Commission, New Delhi for the financial support during the course of the work.

Thanks are also due to Mr. C. V. Radhakrishnan and Mr. A. M. Shanmugham of River Valley Technologies, STPT, Thiruvananthapuram for their efforts to make the thesis in the present form.

Above all I bow my head before the God for all His blessings.

LAKSHMI S

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SYNOPSIS

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Surface modification of polymers has developed into an attractive way of fabricating biomaterials having appropriate bulk and surface properties. The surface properties of biomaterials assume great importance because the biological responses towards a biomaterial is largely controlled by their surface chemistry and structure (Ratner *et al.*, 1996). Thus, the basic physical properties as well as the surface properties are equally important as far as a biomaterial is concerned. The rationale for surface modification of a biomaterial is to retain the key physical properties of the biomaterial while modifying only the outermost surface to influence the biointeraction. Biomaterials can be surface modified by physico-chemical or biological methods. The commonly used surface modification techniques include non-covalent coating on the surface, surface confined chemical reactions, coupling or grafting reactions, plasma modification as well as incorporation of biologically active molecules on the surface.

Plasticized poly(vinyl chloride) (PVC) finds wide applications in medicine and related fields. PVC, even though not a highly blood compatible polymer is the material of choice for making various extracorporeal devices like storage bags for blood and blood components, blood transfusion tubings, storage bags for enteral and parenteral nutrition etc. It also finds wide applications as a food

packaging material and as pharmaceutical wrappings (Brody & Marsh, 1997). PVC being a rigid polymer, makes use of different additives to improve processing and performance capabilities. Of all the additives, the plasticizers which impart flexibility and low temperature properties to PVC forms the major portion. The most commonly used plasticizer for medical grade PVC is the low molecular weight compound di-(2-ethylhexyl) phthalate (DEHP) (Vergnaud, 1983). The additives are not held onto the base polymer by covalent linkages and hence the permanence of these chemicals is rather low. The lipid soluble DEHP can easily migrate into lipophilic admixtures like blood, fatty foods etc., contaminating the medium and at the same time adversely affecting the physical properties of PVC (Sjoberg *et al.*, 1985). The phenomenon of plasticizer migration from plasticized PVC has been extensively studied (Papaspyrides & Duvis, 1989). DEHP is known to produce adverse effects in liver, kidney, pituitary glands and even acts as a hepatocarcinogen in laboratory animals (Morgenroth, 1993; Tsutsui *et al.*, 1993). Concern still exists in the use of DEHP in PVC used in medical and related applications. Various attempts have been made to prevent or reduce plasticizer migration from plasticized PVC. These include coating PVC with different polymers (Ljunggren, 1984), grafting other polymers on the surface (Krishnan *et al.*, 1990), glow discharge treatment (Ishikawa *et al.*, 1983) etc. In this thesis, the possibilities of reducing or preventing plasticizer migration from plasticized PVC using various surface modification techniques are presented. The surface modification techniques employed are chemical surface modification using phase transfer catalysis (PTC) and chemical grafting of a hydrophilic polymer poly(ethylene glycol) (PEG) onto the surface.

The introductory chapter gives an overview of the various surface modification techniques employed for polymeric biomaterials, various surface characterization techniques, application of plasticized PVC in medicine and related fields and the various problems associated with it, toxicological problems associated with DEHP, the literature on the modification of PVC with emphasis on those to reduce plasticizer migration, the principles of PTC and the aim and scope of the study.

Chapter 2 discusses the materials and experimental methods involved in the investigation. This consists of characterization and estimation of the plasticizer content in plasticized PVC, various surface modifications employed like surface confined chemical reactions via PTC and surface grafting, characterization of the surface modified PVC by gravimetric, spectrophotometric, scanning electron microscopic and contact angle methods, methods used for the quantitative estimation of the plasticizer migrated into solvents of varying polarity, mechanical properties like ultimate stress and strain and some biocompatibility evaluation of the most promising surface modified PVC.

Chapter 3.1 discusses the surface confined nucleophilic substitution of diethyldithiocarbamate (DTC) onto plasticized PVC in aqueous medium via PTC. Here DTC was reacted with plasticized PVC in water in the presence of a catalyst such as tetrabutylammonium hydrogen sulphate (TBAH) to prepare PVC having DTC groups on its surface. The DTC substituted PVC was cross-linked by UV irradiation. The surface modification was confirmed by IR, sulphur analysis and by gel content estimation. The plasticizer migration resistance of the surface cross-linked PVC in petroleum ether was measured as a function of reaction time, temperature of reaction, concentration of reactants, nature of the catalyst and

time of irradiation. The direct substitution of DTC on plasticized PVC followed by photocross-linking significantly reduced the plasticizer migration from PVC. However, the method resulted in major changes in the physical properties of PVC.

Chapter 3.2 deals with the results obtained by the direct cross-linking of plasticized PVC via PTC using a dianion such as sulphide ion. The process is similar to the vulcanization of rubber but confined to the surface of plasticized PVC. Substitution of the labile chlorine atom in PVC using the sulphide anion was expected to form intermolecular cross-links on the surface of PVC to retard plasticizer migration. The formation of sulphur cross-links on the surface was confirmed by X-ray photoelectron spectroscopy (XPS), sulphur analysis and by gel content estimation. The surface morphology, optical clarity and the mechanical properties of the modified PVC were evaluated. The substitution reaction was standardized by following the plasticizer migration in petroleum ether from plasticized PVC tubes reacted under various conditions. The surface modified plasticized PVC was found to be migration resistant even after 6 months of incubation in petroleum ether. The migration resistance was further confirmed by HPLC analysis. The surface modified PVC was also found to be migration resistant in solvents of varying polarity like cotton seed oil and PEG-400 even under accelerated extraction conditions. Sterilization by autoclaving and gamma irradiation of the modified PVC were not found to produce any adverse effect on the migration resistance in petroleum ether. The results of the study clearly showed that surface cross-linking by sulphide anion via PTC provides a simple viable method to solve the problem of plasticizer migration from plasticized PVC.

Chapter 3.3 discusses the surface cross-linking of plasticized PVC via PTC using thiosulphate anion. The nucleophilic substitution was confirmed by IR, XPS, sulphur analysis and by gel content estimation. The surface morphology, optical clarity and mechanical properties of the surface modified PVC were studied. The substitution reaction was standardized by following the plasticizer migration in petroleum ether from plasticized PVC tubes reacted under various conditions. The modified PVC was found to be highly migration resistant in petroleum ether. The surface modified PVC also showed significant reduction in plasticizer migration in cotton seed oil under accelerated condition but no reduction in migration was observed in a hydrophilic polar media such as PEG-400. This is possibly due to lower extent of cross-links on the surface as well as due to the hydrophilc sulphonate groups on the surface which reduce the migration in non polar solvents only. The study showed that substitution of thiosulphate anions for the chlorine atoms of PVC significantly reduces plasticizer migration only in non-polar organic solvents and not in polar hydrophilic media.

Chapter 3.4 deals with results obtained by grafting a hydrophilic polymer PEG on plasticized PVC via Williamson ether synthesis and the plasticizer migration resistance of the modified PVC. Different molecular weight PEGs (200, 400, 600 & 4000) were used as their sodium salts for grafting on PVC again taking advantage of the labile chlorine atoms of PVC. The grafting was confirmed by IR and contact angle measurements. Significant reduction in plasticizer migration was observed from grafted PVC for short periods of time examined.

Chapter 3.5 deals with the results obtained from some of the *in vitro* biocompatibility evaluation of promising surface modified samples. The *in vitro*

blood compatibility was assessed by static platelet adhesion, whole blood clotting assay and by haemolysis assay. The toxicological evaluation was carried out by *in vitro* cell culture method using direct contact assay. The bacterial adhesion studies were carried out using a gram positive bacteria *Staphylococcus aureus*. The biocompatibility studies showed that grafting of PEG-4000 on plasticized PVC significantly improved the blood compatibility of plasticized PVC, the grafted sheets were non-toxic and grafting significantly reduced *S. aureus* adhesion on plasticized PVC. The plasticized PVC reacted with sodium sulphide showed reduced platelet adhesion, was found to be non toxic and showed reduced *S. aureus* adhesion compared to unmodified PVC. But the modified PVC did not exhibit any significant antithrombogenic behavior as evidenced by whole blood clotting time assay. The thiosulphate substituted PVC even though showed reduced platelet adhesion was found to be haemolytic compared to unmodified PVC and toxic by cell culture assay. The surface showed extensive adhesion of *S. aureus* and did not exhibit any antithrombogenicity as evidenced by the whole blood clotting assay.

Finally chapter 4 contains the summary, conclusions and future prospects of the investigations reported in this thesis.

CHAPTER 1
INTRODUCTION

INTRODUCTION

1.1 Biomaterials - Present Scenario

A biomaterial can be defined as a material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body (Williams *et al.*, 1992). The term 'biomaterial' includes all materials used for medical applications that are interfaced with living systems or other systems developed for extracorporeal uses. The natural tissues in our body can get damaged due to diseases, trauma or ageing. Allografts or xenografts appears to be the ideal and logical materials for replacements. Shortage of organs for implantation and the need for chronic immunosuppression however, make them less reliable. Therefore, a variety of other materials have been tried as biomaterials. These include metals, glasses, polymers (both natural and synthetic), ceramics, carbon and composites made from various combinations of these (Hoffman, 1984). Since polymers can be tailor made to match the mechanical and physical characteristics of many parts of the body, they find maximum applications as biomaterials. The global scenario of plastic demand in medical devices by 2000 AD will be around 10.2 million tons. Among polymers, synthetic polymers make up by far the broadest and most diverse

class of biomaterials, making the medical market the fourth largest area of plastic application (Lantos, 1988). The medical device market in India in 1996 was about $ 790 million (Sundaresan, 1997). They are used as implants and components of reconstructive surgery, as components in medical instruments and equipments, as packaging materials and finally as a wide variety of disposable devices. The main reasons for this wide applicability of polymers are the availability of synthetic polymers in a wide variety of chemical compositions and physical properties, their ease of fabrication into complex shapes and structures, their easily tailored surface properties and favourable cost performance ratio (Szycher & Robinson, 1980). Although hundreds of synthetic polymers are available, only ten or twenty polymers are mainly used in medical device fabrications from disposables to long term implants. This is because, the success of a biomaterial in the body depends on factors such as the material properties, design and biocompatibility and hence these aspects should be rigorously satisfied.

1.2 Surface Modification of Polymers for Biomedical Applications

1.2.1 Need for Surface Modification of Biomaterials

The most important challenge in biomaterials research, is the development of materials that maintain mechanical integrity and biocompatibility together. It is well known that surface composition is inevitably different from the bulk and it is the surface of the biomaterial which first comes in contact with living body. Since the primary interaction between a biomaterial and living tissue occurs in a very narrow interface zone, biocompatibility depends greatly upon the material

surface properties such as structure, energy (wettability, free energy), chemical composition, stability of the surface configuration etc., (Kasemo & Lausama, 1988). The biological responses towards a biomaterial are thus largely controlled by their surface chemistry and structure. If the biological response is very strong, then the biomaterial will be unable to perform its intended function. One of the most important aspects of biocompatibility is the non-self-recognition of polymers by the biological system. If the polymer has appropriate bulk properties to remain in the biological system and surface properties to make it unrecognizable by the body, then it will be highly biocompatible. These two requirements may not be present contemporaneously in materials.

Surface modification of polymers has developed into an attractive way of fabricating materials having appropriate bulk and surface properties. Such synthetic approaches potentially can maintain a polymer's desirable bulk properties and at the same time provide new, different interfacial properties. The most important advantage of surface modification strategy is the possibility of designing separately the substrate and the surface, i.e., the substrate with suitable physical and mechanical properties for its targeted applications and the surface with improved biocompatibility as well as physiological activity. Surface modification also allows the separate fabrication of the substrate and the surface. According to Ikada (1994) almost all of the next generation biomaterials clinically used should have excellent properties both in bulk and surface and thus surface modification is in many cases essential for a material to be applied in medicine. The rationale for the surface modification of biomaterials is to retain the key physical properties of a biomaterial like durability, functionality and mechanical properties while modifying only

the outermost surface to influence the biointeraction. Surface modification of biomaterials is commonly employed to improve blood and tissue compatibility, to control protein adsorption, to influence cell adhesion and migration, to improve lubricity, to improve wear resistance and corrosion resistance, to alter transport properties etc. Polymers can be surface modified by physico-chemical methods as well as by incorporation of biologically active molecules.

1.2.2 Physico-Chemical Surface Modification

Physico-chemical surface modification can be carried out by changing physically or chemically the atoms or molecules on the existing polymer surface or by over coating the existing surface with a material having different composition. Physico-chemical surface modification of polymers can be broadly divided into:

1. Surface confined chemical reaction.
2. Non-covalent coating of the surface.
3. Covalent grafting of polymers.

The current hypothesis shows that hydrogels or hydrophilic surfaces exhibit good blood compatibility. However, very hydrophobic inert surfaces such as fluoro polymers or silicones are also known to be biocompatible. Thus, physico-chemical methods are used to increase the hydrophilicity or hydorphobicity of the surfaces to improve biocompatibility.

1.2.2.1 Surface Chemical Modification

Surface chemical reaction can be carried out either non-specifically (by leaving a distribution of different functional groups on the surface) or specifically (by

changing only one functional group into another with a high yield). Non-specific surface modification can be carried out using chemical etchants, corona discharge, radio frequency glow discharge etc. Chromic acid is the most commonly used etchant for polymers (Blais *et al.*, 1974) and is used to convert hydrophobic polymer surfaces to hydrophilic surfaces by dissolution of amorphous regions and surface oxidation. The surface oxidation of polyethylene by chromic acid results in the formation of hydroxyl, carbonyl and sulphate groups (Ramon & Sefton, 1986), etching of polystyrene surfaces with sulphuric acid increases surface energy and improves cell adhesion and spreading (Martin & Rubin, 1974). Another non-specific surface modification commonly used for polymeric materials is plasma modification. Plasma processes represent a new, powerful and versatile tool for tailoring surfaces and developing improved biomaterials. Plasmas are atomically and molecularly dissociated gaseous environments and the electrons, ions, metastables, radicals and various radiative components present in it are able to interact and modify the surface of polymers independent of chemistry and geometry (Hoffman, 1987). The polymer surfaces can be modified by adding, subtracting or rearranging surface species, resulting in the functionalization, etching or cross-linking of the material surface layer. Plasmas can be used to modify existing surfaces by ablation or etching reactions using non-depositing gases like oxygen, argon etc., (Piglowski *et al.*, 1994) or in a deposition mode using non-polymerizing gases like ammonia (Cohn, 1988), water vapour etc., in order to introduce organic functional groups like amine, hydroxyl etc., on inert polymer surfaces. The new reactive surface functionality can act as anchoring sites for further derivatization of the surfaces. Good review articles on plasma deposition

and its application to biomaterials are available (Yasuda & Gazicki, 1982; Hoffman, 1988; Ratner *et al.*, 1990).

Almost all the classical chemical reactions like oxidation, hydrolysis, sulfonation, quaternization, alkylation, hydrogen abstraction etc., can be used to introduce new functional groups specifically on the surface of polymers. These functional groups can be introduced onto the surface with controlled selectivity and the methodologies available have been reviewed (Whitesides, 1990; Bergbreiter, 1992).

1.2.2.2 Non-Covalent Coating on the Surface

This includes mainly simple solvent coating, physical adsorption, incorporation of surface active bulk additives in the material, vapour deposition of carbon, metal, parylene etc., and deposition of Langmuir-Blodgett (LB) films on the surface. Being simple, solvent coating method offers an attractive mode of surface modification, so far as the modification effect last for the intended period of function of the biomaterial. Coating hydrophilic polymers having very low interfacial energies has been widely attempted to improve the biocompatibility of polymers (Francois *et al.*, 1996). Hydrogel-coated catheters, surgical drains and gloves greatly reduces frictional resistance (Wheeler *et al.*, 1996). Coating surfaces with a large inert, polysaccharide, ethyl hydroxyethyl cellulose greatly improves the biocompatibility (Elam & Elam, 1993). Physical adsorption of high molecular weight poly(ethylene glycol) (PEG), a well accepted blood compatible polymer has been carried out onto various hydrophobic surfaces. (Kato *et al.*, 1981). Highly durable coatings can be made by using PEG-containing amphipathic copolymers

(Amiji & Park, 1992; Matsuda & Ito, 1994). LB deposition method covers a surface with a highly ordered layer. A wide range of chemical structures like phospholipids, fatty acids etc., can form LB films and there are many options for incorporating new chemistries at the surface. The stability of these coatings can be increased by cross-linking or polymerizing the groups after deposition (Iwasaki *et al.*, 1997). A number of groups have investigated LB films for various biomedical applications (Hayward & Chapman, 1984; Bird *et al.*, 1989; Meller *et al.*, 1989; Cho *et al.*, 1990; Knobler, 1990; Ulman, 1991; Li *et al.*, 1997). Surface modifying additives (SMA's) can be added in low concentrations to a material during fabrication and will spontaneously rise to the surface to reduce the interfacial energy (Ward, 1989). Usually diblock polymers are used as SMA's, where one block will be compatible with the base polymer and the other block is made of polymer having very low interfacial energy. Plasma polymerization processes are widely investigated whereby smooth, ultra thin, pinhole free coatings of various polymers like ethylene, perfluoro gases, siloxane etc., can be deposited on various polymers, which strongly adhere to the substrate. Plasma fluorinated dacron vascular graft showed very high patency (Hoffman *et al.*, 1986). Vapour deposition of elements on the surface is another widely studied surface modification technique. Various elements such as titanium and carbon, were deposited on surface of materials for application as medical devices. Titanium deposition improves the histocompatibility of various polymers (Yan *et al.*, 1989). Deposition of low temperature isotopic carbon on various polymer surfaces greatly improves the blood compatibility (Baquey *et al.*, 1989; Cenni *et al.*, 1995) as well as provides an excellent substrate for attachment of seeded endothelial cells (Boyd *et al.*, 1987).

1.2.2.3 Covalent Grafting of Polymers on the Surface

Surface grafting of polymers leads to an overlayer of a second polymer covalently linked to the substrate polymer. Covalent grafting approaches can be divided into graft coupling and graft polymerization. In graft polymerization, the polymer chains are synthesised *in situ* on the reactive polymer surface, whereas graft coupling binds preformed polymer molecules using functional groups on the surface by chemical reactions.

1.2.2.3.1 Graft Coupling of Polymers on the Surface: Chemical graft coupling has been widely attempted for surface modification of polymers. The majority of surface modification involves covalent immobilization of bioinert hydrophilic polymer chains on the surface (Desai & Hubbell, 1991; Dunkrik *et al.*, 1991; Tseng & Park, 1992; Llanos & Sefton, 1993; Matsuda & Sugawara, 1995). A prerequisite of this binding method is that it solely relies on the presence of complementary reactive groups on polymer and surface or either one of them. An example of the graft coupling method is illustrated in Figure 1.1

1.2.2.3.2 Graft Polymerization of Monomers on the Surface: A more general process applicable to almost all polymers, is radiation grafting and related methods and have been widely used for the surface modification of biomaterials. Comprehensive review articles are available on this topic (Hoffman *et al.*, 1983; Stannett, 1990). Radiation, particularly ionizing and UV radiation are most commonly used. Among many other synthetic methods, free-radical polymerization has almost exclusively been used for surface grafting. To initiate

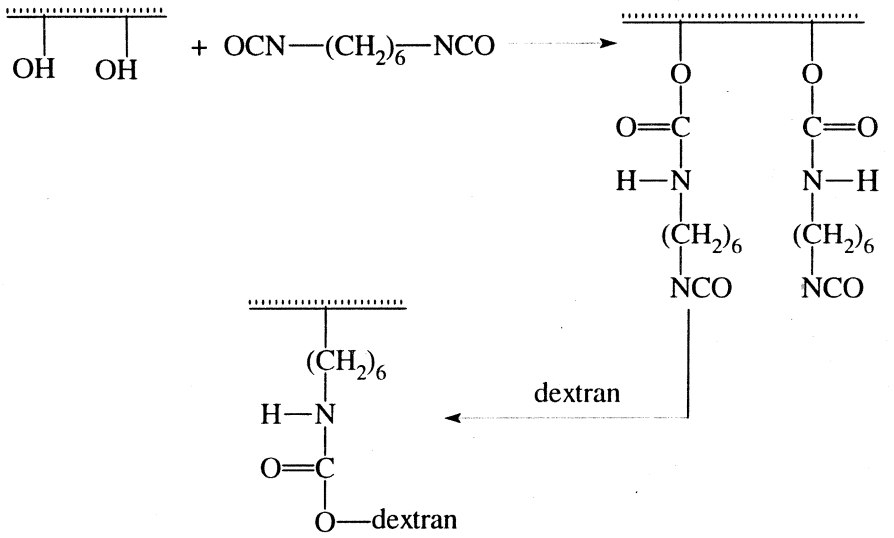


Fig. 1.1 Graft coupling of dextran onto poly(vinyl alcohol) (Adapted from Taniguchi *et al.*, 1982)

the radical polymerization from a substrate surface, free radical or peroxides should be generated on the surface. The active species can be produced by high energy radiation or by chemical procedures such as using redox systems (Feng *et al.*, 1985). Figure 1.2 illustrates schematically some of these processes. The energy sources commonly used to produce active species on polymer surfaces are: 1. ionizing radiation such as gamma rays (Krishnan *et al.*, 1990; Singh *et al.*, 1990; Hari & Sharma, 1991), 2. UV radiation (Mori *et al.*, 1982), 3. photoinitiated chain transfer reaction (Allmer *et al.*, 1990), 4. high energy ion beams (Svorcik *et al.*, 1997), 5. low temperature plasmas (Fujimoto *et al.*, 1993) and 6. ozone gas (Fujimoto *et al.*, 1993a). The usual source of ionizing radiation is cobalt^{60}, produced by neutron irradiation of naturally occurring cobalt^{59} in a nuclear reactor. Sources of UV radiation are commonly deuterium or high pressure mercury lamps.

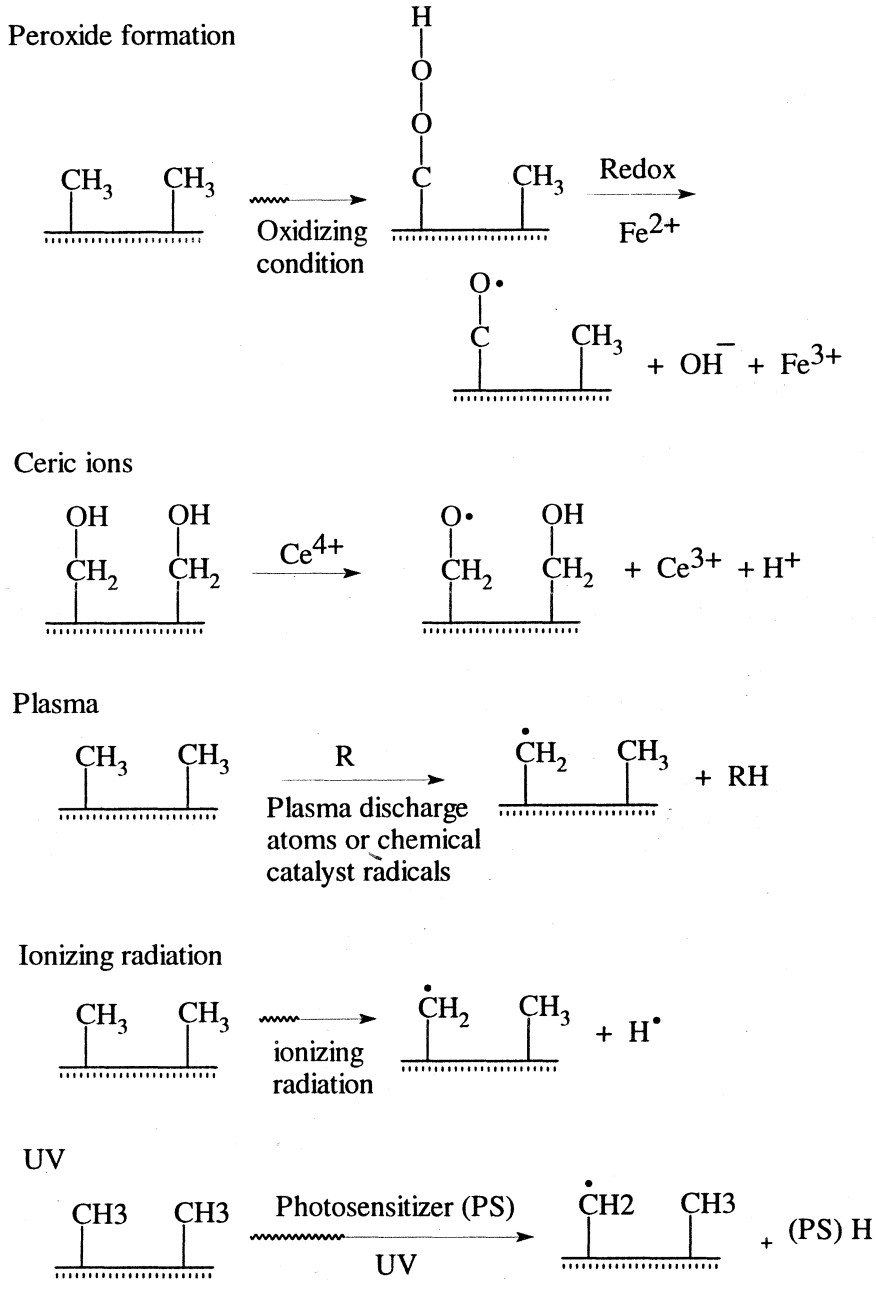


Fig. 1.2 Methods of surface activation for graft polymerization (Adapted from Hoffman, 1984a)

1.2.3 Biological Surface Modification

One of the most practical methods of improving the biocompatibility of polymers is the immobilization of biologically active molecules like bioactive substances, proteins, as well as living cells and micro-organisms on polymeric supports (Piskin & Hoffman, 1986; Szycher, 1991; Hoffman, 1992). Three major methods of immobilization commonly used are physical adsorption, physical entrapment and covalent attachment.

The most extensively studied biomolecule for immobilization on polymer surface is the anionic polyelectrolyte heparin, to improve the blood compatibility of polymers. Heparin has been incorporated onto polymer surfaces via ionic interaction with quaternized surfaces (Gott *et al.*, 1963; Miyama *et al.*, 1986; Nagaoka & Noishiki, 1989), stabilizing further by glutaraldehyde cross-linking (Lagergren & Eriksson, 1971), coating the surface with heparin complexing polymer like poly(amido amine) (Barbucci *et al.*, 1991), covalent coupling of poly(amido amine) on polymer surface followed by heparin complexation (Barbucci *et al.*, 1985), coating surfaces with heparin-poly(vinyl alcohol) hydrogel (Ramon & Sefton, 1986), direct covalent immobilization of heparin on poly etherurethaneurea (Ito *et al.*, 1986) and heparin immobilization on surfaces using different spacer arms (Park *et al.*, 1988; Han *et al.*, 1989). Some of these techniques are illustrated in Figure 1.3.

Some of the other biologically active molecules used for immobilization onto polymers to improve biocompatibility are listed in Table I.

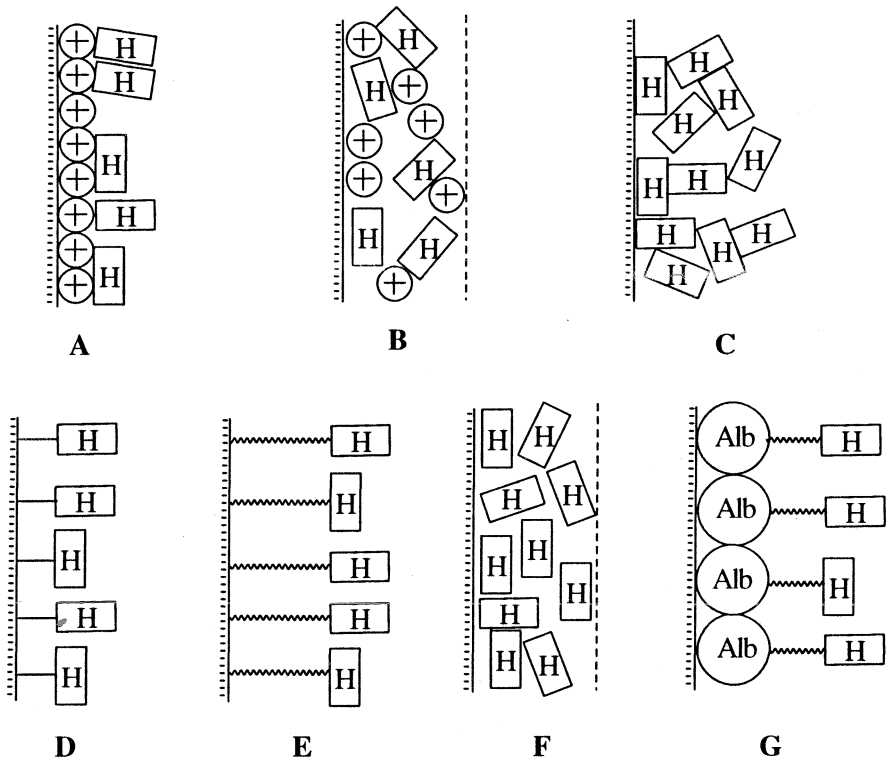


Fig. 1.3 Schematic representation of various methods for heparinization of surfaces (Adapted from Kim & Feijen, 1985). (A) heparin bound ionically on a positively charged surface; (B) heparin ionically complexed to a cationic polymer, physically coated on a surface; (C) heparin self-cross-linked physically coated on a surface; (D) heparin covalently linked to a surface; (E) heparin covalently immobilized via spacer arms; (F) heparin dispersed into a hydrophobic polymer; (G) heparin-albumin conjugate immobilized on a surface.

1.2.4 Surface Characterization Techniques

The surface modified region is usually thin and consists of only minute amounts of material. Hence it is essential that the modified surfaces should be characterized at the molecular level. Techniques commonly used for the

Table I
Some of the biologically active molecules immobilized on polymer surfaces to improve biocompatibility

Bioactive molecule	Purpose	References
Albumin	Blood compatibility	Sipehia *et al.*, 1986; Eberhart *et al.*, 1987; Pitt & Cooper,1988; Matsuda & Inoue, 1990; Mulvihill *et al.*, 1990; Tsai *et al.*, 1990; Tseng *et al.*, 1993.
Urokinase	Blood compatibility	Sugitachi *et al.*, 1981; Senatore *et al.*, 1986; Oshiro *et al.*, 1988.
Prostaglandin derivatives	Blood compatibility	Akashi *et al.*, 1989.
Thrombomodulin	Blood compatibility	Kishida *et al.*, 1994.
Recombinant hirudin	Blood compatibility	Phaneuf *et al.*, 1997.
Adhesive peptides like RGDS	Cell adhesion and growth	Kevin *et al.*, 1996.
Collagen	Soft tissue adhesion	Ikada, 1994.
DNA	Immunoadsorbent	Ikada, 1994.
Protein A	Immunoadsorbent	Messerschmidt *et al.*, 1988.
Oligosaccharides	for selective phagocytosis	Fallon & Schwortz, 1985.
Urease	Artificial Kidney	Pozniak *et al.*, 1995.

characterization of bulk properties are not suitable for surface characterization as they are not sensitive enough to detect the thin surface region. Over the last decade, a number of surface-sensitive techniques have emerged as potent tools which permit an assessment of the surface properties and are now used extensively in biomaterials research (Andrade, 1985; Feldman & Mayer, 1986; Ratner, 1988). In particular, X-ray photoelectron spectroscopy (XPS), also known as electron spectroscopy for chemical analysis (ESCA) and fourier transform infrared spectroscopy coupled with attenuated total internal reflectance (FTIR-ATR) capability provide information on surface chemical composition,

while contact angle measurements provide information on physical properties such as surface energy. Novel techniques such as atomic force microscopy (AFM) and scanning tunnelling microscopy (STM) which allow three-dimensional measurements on a nanometer scale are also used. Each of these techniques supplies different and often complementary information. The choice of a suitable technique(s) is affected by what kind of information one is looking for. Table II shows some of the surface analysis techniques and the depth of probe.

1.3 Poly(Vinyl Chloride) (PVC) as a Biomaterial

1.3.1 Applications of PVC in Medicine and Related Fields

PVC is, in terms of sales volume, the largest member of a group of polymers commonly referred to as vinyls. The use of PVC has become very important to the health care industry. Plasticized PVC, the plastic used in the first blood bag introduced by Carl Walter in 1947, remain the material of choice even today. During the last 40 years, PVC has become the most widely used material in the medical disposable market. Thus, about 2,86,000 tones of PVC were consumed in the US medical market, representing about 6% of total US market of polymers (Sundaresan, 1997). The success of PVC is due to its ability to fulfill the complex needs of the medical device industry. The factors that currently position PVC as the most widely used thermoplastic for medical devices are transparency, low toxicity, inertness, range of flexibilities, chemical stability, low friction, radio-frequency weldability, ease of fabrication, biocompatibility performance, sterilization performance and cost effectiveness. Plasticized PVC is durable and

Table II
Some of the most commonly used surface analysis techniques and depth of probe

Method	Principle	Depth Analyzed	References
Contact angle	Liquid wetting of surfaces	3-20 Å	Neumann & Good., 1979; Andrade, 1985.
FTIR-ATR	IR radiation is absorbed in exciting molecular vibrations	1 - 5 μm	Allara, 1982; Nguyen, 1985; Leyden & Murthy, 1987.
SEM	Secondary electron emission caused by a focused electron beam is measured and spatially imaged	5Å	Sawyer & Grubb, 1987.
XPS	X-rays cause the emission of core electrons of characteristic energy	10-250 Å	Dilks, 1981; Swift *et al.*, 1983; Ratner & McElory, 1986; Ratner, 1988; Briggs, 1994; Chan, 1994.
AES	A focused electron beam causes the emission of auger electrons	50-100 Å	Swift *et al.*, 1983.
SIMS	Ion bombardment leads to the emission of surface secondary ions and the m/e of emitted ions measured	10Å- 1μm	Briggs, 1986; Briggs *et al.*, 1989; Vickerman *et al.*, 1989; Davis & Lynn, 1990.
STM	Measurement of the quantum tunneling current between the metal probe tip and a conductive surface	5Å	Binnig & Rohrer, 1986; Albrecht *et al.*, 1988; Hansma *et al.*, 1988; Avouris, 1990; Miles *et al.*, 1990.
AFM	Measurement of the attraction and repulsive force between atom at the tip of the probe and atoms on the surface	5Å	Albrecht *et al.*, 1988; Hansma *et al.*, 1988; Rugar & Hansma, 1990.

Adapted from (Ratner *et al.*, 1996)

disposable, and these features are desirable for medical disposables today in the fight against AIDS and Hepatitis. PVC has proven to be a safe and reliable polymer for replacing glass for storage of blood and its components in blood banks. The

importance of PVC as a biomaterial is readily appreciated if an examination is made of its usage in the medical field. The market share of PVC among polymeric materials used in medical devices was about 25% in 1988 in the developed countries in which 65% accounted for flexible tubings, and 23% and 12% accounted for films and moldings (Blass *et al.*, 1992). PVC packaging applications fall into three general categories: films and sheets, bottles and others (including coatings and cap liners). About 28% of PVC in packaging involves food applications, 31% medical uses and 41% non-food end uses (Brody & Marsh, 1997). PVC is used extensively in food-contact applications such as meat wrap. Rigid PVC sheets are mainly used as drug blister packaging, including unit-dose packets. Flexible bags or containers are used in the health care industry for collection and storage of fluid components like blood, blood plasma, intravenous solutions, peritoneal dialysis solutions, enteral and parenteral nutritions and many more. The use of PVC is now restricted to procedures out side the body or at the most, devices with short term contact with the body. However, the use of PVC has become very important to the health care industry, where the versatility and performance benefits can be tailored to end-use applications.

1.3.2 General Properties of PVC

When first developed in the 1930s, PVC found little applicability or market place acceptance because of its tendency to thermally degrade or dehydrochlorinate when heated. PVC is an amorphous, rigid polymer due to the large side group chlorine with a glass transition temperature (T_g) of 75–105°C. PVC is normally polymerized from vinyl chloride monomer by free radical polymerization

(suspension, mass, emulsion and solution) into the following polymer structure (Figure 1.4).

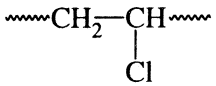


Fig. 1.4 Structure of PVC

The melting point of PVC is markedly affected by polymerization temperatures, crystallinity and stereoregularity and it ranges from 165–210°C. The major areas of thermal activity in the differential thermal analysis curve of PVC are 60–80°C showing the T_g, 165-210°C showing the melting point, 285°C the beginning of dehydrochlorination and 450°C the start up of depolymerization. PVC has a high melt viscosity, hence it is difficult to process. But the unique property of PVC is its ability to be formulated with a variety of additives into compounds that can be as hard as glass or as soft as gum rubber.

1.3.3 The Importance of Additives in PVC Compounding

PVC makes extensive use of different additives to meet different plastic performance requirements and processing capabilities. The additives are physically dispersed in the PVC matrix without significantly affecting the molecular structure of the matrix. They are normally classified according to their specific functions rather than on a chemical basis (Gachter & Muller, 1990). They are

1. Mechanical property modifiers which includes plasticizers, toughening agents, interfacing agents (makes additives and plastics compatible), blowing agents, reinforcements etc.
2. Processing aids such as lubricants (internal or external), processing stabilizers, melt flow promoters etc.
3. Physical property modifiers such as blowing agents, flame retardents etc.
4. Surface property modifiers such as adhesion promoters, slip agents, antiblock agents, antiwear agents, antistatic agents etc.
5. Optical property modifiers such as nucleating agents, dyes, pigments etc.
6. Antiaging modifiers such as fungicides, antioxidants, UV stabilizers etc.
7. Electrical property modifiers such as mineral and /metallic agents, glass microballons etc.
8. Formulation and manufacturing cost-reducing agents like particulate fillers, blowing agents, reinforcements etc.

For medical grade PVC, all these ingredients should satisfy some requirements regarding their suitability with respect to toxicological and other appropriate properties.

1.3.3.1 The Role of Plasticizers

Of all the additives present in formulations of flexible PVC, the plasticizer contributes the major portion ranging up to 40% by weight (Ljunggren, 1984). The primary role of these agents is to reduce the rigidity of plastics and render them more flexible. Briefly, the plasticization on the molecular level is the weakening or

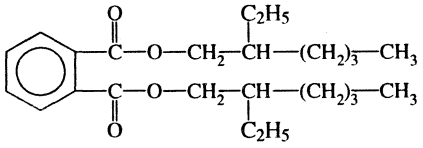
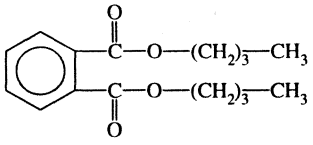
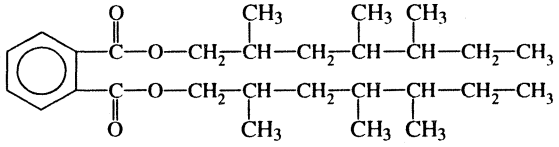
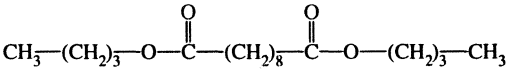
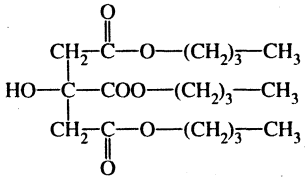
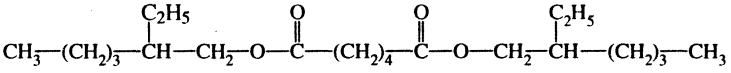
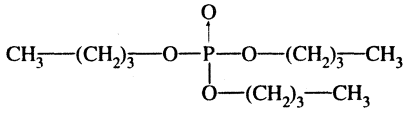
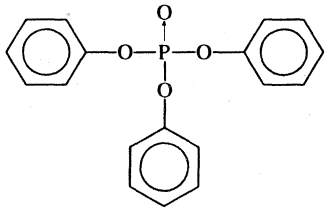
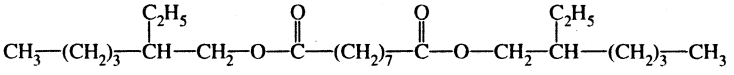
masking of selective bonds between polymer chains while leaving others strong, to make possible the shaping, flexing or molding of the material. Plasticizers provide workability and distensibility and reduce melt viscosity, lower the Tg, increase elongation and impact strength, reduce tensile strength and hardness and lower the elastic modules of the plastic. PVC can thus be obtained in a wide range of stiffness, from rigid and somewhat brittle types to very flexible rubber like types depending upon the amount of plasticizer incorporated. Esters such as phthalates, trimellitates, phosphates, citrates etc., are the most commonly used plasticizers (Krauskopf, 1993; Hirose & Shioya, 1994) for PVC. Table III shows the names and structures of some of the important plasticizers for PVC. The most preferred plasticizer for medical grade PVC is di-(2-ethylhexyl) phthalate (DEHP) (Vergnaud, 1983) because it is the most inert plasticizer currently available, provides optimum properties to PVC, is available in high purity and is highly economical compared to others.

1.3.4 Problems Associated with Plasticized PVC in Medicine and Related fields

The plasticizer molecules are not held onto the base polymer by covalent linkages and hence the permanence of these chemicals are low. DEHP is a lipid soluble suspected carcinogen, hepatotoxin and teratogen which has been shown to leach from PVC products containing lipophilic admixtures (Sjoberg *et al.*, 1985). Where contact times are short there is no difficulty, but for a number of applications in which PVC may be in contact with a patient for longer periods, extraction of plasticizer is much less acceptable. Stiffining of PVC tubes due to plasticizer

Table III

The name and structure of some of the most commonly used plasticizers for PVC

Name	Structure
Di-(2-ethylhexyl) phthalate	
Di-n-butyl phthalate	
Diisodecyl phthalate	
Di-n-butyl sebacate	
Tri-n-butyl citrate	
Di-(2-ethylhexyl) adipate	
Tributyl phosphate	
Triphenyl phosphate	
Di-(2-ethylhexyl) azelate	

migration may cause patients considerable discomfort when a feeding or wound drainage tube is removed after prolonged use (Biggs & Robson, 1984). Blood stored in PVC bags or flowing through PVC tubes for long periods will also extract plasticizer. While DEHP has been considered to be of low toxicity to man, it is naturally desirable to avoid any extra burden on a patient's system particularly for patients undergoing regular haemodialysis or blood transfusion. Thus, the plasticizer migration from plasticized PVC can produce two adverse reactions.

1. Changes in physical and mechanical properties of PVC due to loss of plasticizer.
2. Possible toxic and biological effects arising from the transfer of plasticizer to humans.

1.3.4.1 Route of Exposure of DEHP to Humans

Due to its extensive use, DEHP is now a ubiquitous component in the environment and can be isolated from human tissue at a concentration in the range of 1-5 μg/g (Griffiths *et al.*, 1985; Sjoberg & Gustafsson, 1986; Wams, 1987). The relatively low vapour pressure of DEHP (<0.1 mm Hg @200°C) and high dermal lethal dosage (LD) values seen in animals precludes exposure by inhalation and absorption less likely routes of entry. Medical treatments and dietary sources provide the principal route of exposure to DEHP. DEHP can be efficiently absorbed from the alimentary canal and thus about 40-50% of administered doses can be absorbed. The migration of DEHP from flexible PVC-based medical devices and storage bags into physiological fluids has been a subject of major concern for many

years (Jaeger & Rubin, 1970; Thomas & Thomas, 1984). It has been found that DEHP can seep out from the PVC bags used for storing blood and its components and accumulates in the stored fluids (Marcel & Noel, 1970; Jaeger & Rubin, 1972; Sasakawa & Mitomi, 1978; Nassberger *et al.*, 1987; Racz *et al.*, 1993). Jaeger and Rubin (1970) have shown that DEHP can be detected at significant levels of 5 mg/dL of plasma in human blood stored in PVC bags.

The plasticizer has been detected in the storage media particularly in blood and blood products (Labow *et al.*, 1986; Chawla & Hinberg, 1991; Plonait *et al.*, 1993), infusion fluids (Mazur *et al.*, 1989; Smistad *et al.*, 1989) as well as fatty foods (Castle *et al.*, 1988, 1990, 1990a). DEHP is found in a variety of food stuffs including fish, meat, milk, cheese and vegetables wrapped using PVC 'cling films' (Burg, 1988). The toxicity of phthalate esters has raised serious questions about their use as plasticizers for polymers used in medical, pharmaceutical and food packaging applications (Bruck, 1982; Castle *et al.*, 1987; Castle *et al.*, 1988; Lanina *et al.*, 1992). Several governments have imposed restrictions on the use of PVC films for food packaging (Castle *et al.*, 1988a).

1.3.4.2 Toxicity of DEHP

The LD value of DEHP was summarized in the toxicology update by Burg (Burg, 1988). Some of the values are shown in Table IV.

Table IV
The lethal dosage values of DEHP

Animal and mode of administration	Lethal dosage
Rat/oral/L.D.50	26g/kg;
Rabbit/ oral/L.D50.	34g/kg;
Mouse/i.p/L.D.50	14.2g/kg;
Rat/i.p/L.D. 10	0.3g/kg;
Guinea pig/dermal	10g/kg;
Rabbit/dermal	20g/kg;
Human T.D 10*	0.143g/kg

* Tolerable Dose

These high values show that the acute toxicity of this chemical is rather low. The adverse effects of DEHP exposure in humans are not well understood since it has not been studied extensively. But long term feeding studies in rodents have clearly shown that this chemical can produce adverse effects in various organs like liver, testis, pituitary glands and even can act as a hepatocarcinogen (Kluwe *et al.*, 1985; Melnick *et al.*, 1987). This, along with the alarming high consumption figures of this plasticizer have raised concern in the medical and related fields (Myhre, 1988).

1.3.4.2.1 Hepatotoxicity: DEHP belongs to a unique class of compounds called peroxisome proliferators (Rao & Reddy, 1987), is itself carcinogenic and possesses tumour promoting activity in mouse liver (Ward *et al.*, 1986). DEHP is known to cause peroxisome proliferation in rodents and after prolonged administration, hepatocarcinogenesis (Tsutsui *et al.*, 1993). The hepatocarcinogenicity of DEHP was demonstrated in rodents such as rats and mice (Popp *et al.*, 1985; Rao *et al.*, 1990). Rats fed with DEHP greatly induced enzyme activity

levels in liver such as peroxisomal palmitoyl-CoA dehydrogenase, mitochondrial carnitine acetyltransferase (Dirven *et al.*, 1990; Ganning *et al.*, 1990) and glutathione-S-transferase (Rathinam *et al.*, 1990). Other adverse effects include increased liver weight and peroxisome number, as well as oxidative DNA damage (Takagi *et al.*, 1990; Tamura *et al.*, 1991). All these effects were found to vary in a dose-dependent manner (Ahmed *et al.*, 1990; Khaliq & Srivastava, 1993).

1.3.4.2.2 Reproductive toxicity: DEHP displays reproductive and developmental toxicity in a variety of mammalian and non-mammalian species (Morgenroth, 1993). Administration of high doses of DEHP to rats induced severe testicular atrophy coincident with the reduction of lactate dehydrogenase activity, Zn, K and Mg concentrations (Oishi, 1994). DEHP and its active metabolite mono-(2-ethylhexyl) phthalate (MEHP) suppressed preovulatory granulosa cell estradiol in adult cycling rats (Davis *et al.*, 1994) as well as a decrease in progesterone production (Treinen & Heindel, 1992) and sperm count (Tandon *et al.*, 1991). The testicular damage has been observed to vary with the age of the animal, immature rats being more sensitive than mature ones (Sjoberg *et al.*, 1986). The reproductive toxicity of DEHP and MEHP is mainly due to a direct effect on Sertoli cells and Leydig cell (Oishi, 1990; Thysen *et al.*, 1990; Heindel & Powell, 1992; Grasso *et al.*, 1993; Jones *et al.*, 1993). DEHP as well as MEHP were found to be fetotoxic (Tomita *et al.*, 1986) and mutagenic (Douglas *et al.*, 1986).

1.3.4.2.3 Toxic Effects on Humans: Blood transfusions will result in inadvertent exposure of the patient to both DEHP and its metabolite MEHP. DEHP was shown

to be present in postmortem heart and gastrointestinal tissue from critically ill infants who had received varying amount of blood products (Hillman *et al.*, 1975). In storage applications of plasticized PVC, the migrated DEHP in small quantities is known to bind platelet membrane as well as red cell membrane and protect it from haemolysis during storage (Labow *et al.*, 1986). Although, opinion is divided over the effect on humans, it has been demonstrated by a series of studies in Rhesus monkeys that abnormalities in hepatic scan and bromosulfophthalein persisted for up to 26 months after transfusion as did histologic abnormalities (Kevy & Jacobson, 1982). Patients undergoing maintenance haemodialysis receive a yearly dose of DEHP which is 10-20 times that which produced hepatotoxicity in the transfused Rhesus. The metabolism of DEHP by the human body is rapid and does not appear to generate unacceptable byproducts. Thus, it is still argued that the benefits of using flexible PVC for storage of blood products and transfusion fluids outweigh the risks. However, it is obviously not desirable that patients with less than perfect health should be dosed with plasticizer and there may be unforeseen long-term problems with dialysis patients or with ailing new born infants.

1.4 Chemical Modifications of PVC

The chlorine atoms of PVC are highly reactive and several attempts have been made to substitute the labile chlorine atoms with various functionalities such as dithiocarbamate, thiolate, xanthate, dithiophosphate etc. (Okawara & Ochiai, 1980). The substitution reactions were carried out in aprotic solvents such as dimethylformamide (DMF). Some of the nucleophilic substitution reactions that PVC can be readily subjected to are shown in Figure 1.5.

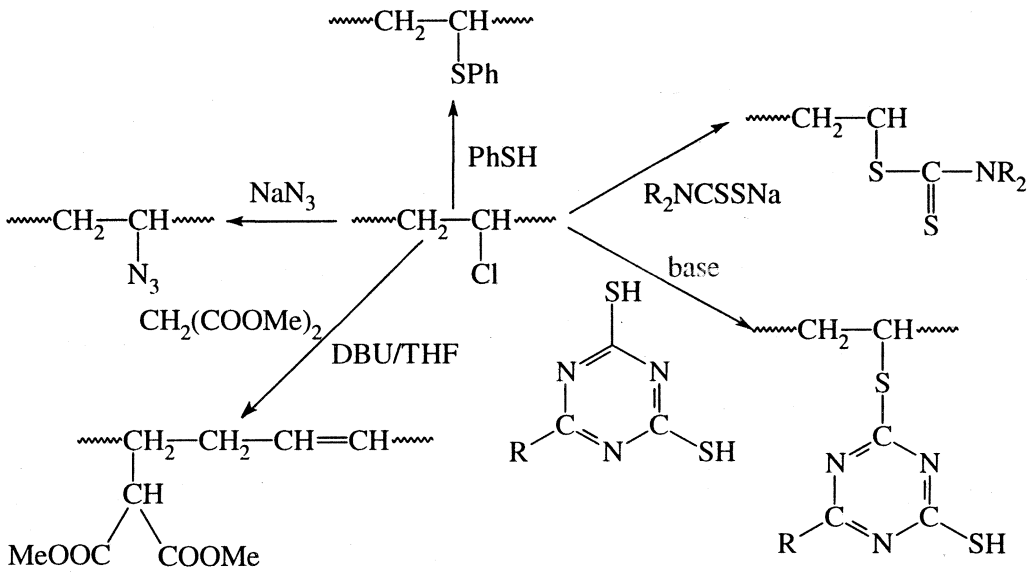


Fig. 1.5 Some nucleophilic substitution reactions of PVC (Adapted from Okawara & Ochiai, 1980)

Okawara and Ochiai (1980) have reported that the substitution of PVC resin suspended in water by azide can take place feasibily, if some cationic surfactant is added to the suspension. The kinetics, structure and the properties of various thiols substituted PVC from PVC resin suspended in water was studied in the presence of phase transfer catalyst (PTC) (Marian & Levin, 1981; Nkansah & Levin, 1983). Chemical modification of PVC with various phenolic groups has been carried out recently (Robila *et al.*, 1995). The labile chlorine atoms of PVC can be readily replaced with hydrogen using organo boron reagents (Pourahmady & Bak, 1994) to improve the thermal stability of PVC. The nucleophilic substitution of the chlorine atoms of PVC by a peptide such as glutathione thiol was carried out by Bromberg

and Levin (1994). Low temperature plasma (O_2, Ar and air) was also used to modify the surface of plasticized PVC to produce textured layer on the polymer surface (Brovikova & Menagarishviley, 1994). Grafting hydrophilic polymers onto PVC surface has been widely attempted. Lee and Lai dehydrochlorinated PVC to produce active double bonds which are used to graft monomers like glycidyl methacrylate or 2-hydroxyethyl methacrylate (HEMA) using benzoyl peroxide as the free-radical initiator (Lee & Lai, 1994, 1995). Several modifications of PVC have been attempted for biomedical applications. Thus, Krishnan *et al* (1990) grafted hydrophilic polymers onto PVC using gamma irradiation to reduce plasticizer migration and to improve the blood compatibility of plasticized PVC. Paul *et al* (1982) have described the grafting of N-vinyl-N-methylacetamide hydrogels onto PVC for improving the blood compatibility. Sugitachi *et al* (1981) immobilized a plasminogen activator, urokinase on plasticized PVC to improve the blood compatibility. Mori *et al* (1982) immobilized PEG on plasticized PVC tube to reduce protein adsorption and platelet adhesion. Clinical application of the modified tubes showed that they were highly antithrombogenic (Nagaoka and Nakao, 1990). Albumin functionalized using glycidyl methacrylate was grafted onto PVC by gamma irradiation (Kamath & Park, 1994) to reduce platelet adhesion and hence to improve the blood compatibility. Attempts were also made to incorporate heparin onto PVC surface. Here PVC was reacted with ethylene diamine to produce aminated PVC and the modified PVC was treated with poly(amido amine) which can complex heparin effectively (Ferruti *et al.*, 1982).

1.5 Attempts to Prevent Plasticizer Migration

Plasticizer migration from PVC has attracted the interest of numerous investigators due to the high consumption figures of this polymer used in the plasticized form. Plasticizer migration into various liquid media has been extensively studied (Messadi & Vergnaud, 1982; Papaspyrides & Duvis, 1989). Diffusion of low molecular weight substances in to and out of a polymer occurs mainly in the amorphous phase. In the rubbery state ie., in the case of plasticized PVC, in contact with an extracting solvent such as petroleum ether, the diffusion phenomenon generally confirms to Fick's law describing the flux of the diffusion species per unit area as a function of its concentration gradient. As the plasticizer goes out, the system gradually turns to nonrubbery and deviation from Fickian kinetics was observed. Thus conformity to Fick's law is usually limited for the very initial stages of the migration process.

Various attempts have been made to reduce plasticizer migration from plasticized PVC. These include simple techniques such as placing paper or metal foil on the surface of PVC film (Lyon & Clark, 1973), coating PVC with various polymers like polyurethanes (Ljunggren, 1984), polyacrylates (Hirooka *et al.*, 1975) and polyesters (Vesperman, 1979). Use of polymeric plasticizers such as polymeric adipates and sebacates, high molecular weight plasticizers such as tri(ethylhexyl)trimellitate (Archer *et al.*, 1982) and blending PVC with other polymers have also been attempted (Schwarz & Bley, 1988). Further, attempts were made to modify the PVC itself by cross-linking using peroxides during processing (Oth & Mathieu, 1968). Duvis *et al* (1991) attempted to reduce

plasticizer migration from plasticized PVC by irradiation with UV light but was not highly effective. Even after long irradiation periods of 5-10 days, reduced migration pattern was observed only with high viscosity oil at low temperatures. Grafting of hydrophilic monomers onto the surface of plasticized PVC sheets by gamma irradiation has been attempted to reduce plasticizer migration (Krishnan *et al.*, 1990, 1991, 1991a). Surface grafting reduced the plasticizer migration significantly, but the process itself was cumbersome and not easily adaptable in real life situations. Plasma modification techniques have been widely attempted to reduce plasticizer migration. Thus the surface of PVC was cross-linked by plasma at low temperature to form an antimigration thin layer (Yang & Yang, 1989). The antimigration ability of plasma-treated PVC increased by 6-7 times. The effect of plasma treatment by non-polymer forming gas plasma (Ar, H_2, N_2 and NH_3) and of plasma polymerization of hydrocarbons (methane, ethylene and acetylene) on the surface of plasticized PVC sheets on plasticizer loss was examined by Iriyama & Yasuda (1988). Both plasma treatment by non-polymer forming gas and plasma polymerization of hydrocarbons on the PVC surface prevented volatilization of plasticizer well. Ishikawa *et al* (1983) used glow discharge treatment to surface modify plasticized PVC. The modified surfaces showed reduced plasticizer migration level in platelet concentrate. The amount of DEHP migrated from untreated bag was 150–200 μg/mL/day whereas from the treated bag was only 20–40μg/mL even after 48 h. Glow discharge treatment increases surface wettability, but enhances the adhesion of platelets on the surface. Plasma modification techniques have several limitations. They are expensive, are

not highly reproducible and cannot be employed for modifying large surface area of samples.

The use of dithiocarbamated PVC for reducing plasticizer migration has been disclosed in two US patents (Levin, 1989; 1993). In one attempt, diethyldithiocarbamated PVC was prepared and coated onto the surface of plasticized PVC which was further subjected to cross-linking by heat. In another attempt, flexible PVC was substituted using diethyldithiocarbamate in aqueous media with the aid of a phase transfer catalyst and subsequently cross-linked by heat or the substitution reaction itself was conducted at high temperatures thereby accomplishing the substitution and cross-linking in one step. Significant reduction in plasticizer migration has been claimed in both processes although detailed data were not available. The physical and mechanical properties of such modified PVC have not been dealt with in both patents either.

In recent years, two different approaches to prevent plasticizer migration from flexible PVC were reported by Jayakrishnan and coworkers (Jayakrishnan *et al.*, 1995; Jayakrishnan & Sunny, 1996). One approach was based on synthesizing a photocross-linkable derivative of PVC, coating the surface of plasticized PVC with the derivative and photocross-linking the surface with UV light. Thus, azidated PVC was prepared by nucleophilic substitution of chlorine atom on PVC using the azide ion. The azidated PVC was coated onto plasticized PVC and cross-linked photochemically thereby creating a barrier for diffusion of the plasticizer (Jayakrishnan *et al.*, 1995). It was shown that plasticizer migration could be significantly reduced by this technique. The second approach reported involved direct azidation of plasticized PVC itself predominantly on the surface.

This was achieved with the aid of a phase transfer catalyst (PTC) in aqueous media. Photoirradiation of the surface by UV light led to surface cross-linking which created a barrier for the diffusion of the plasticizer (Jayakrishnan & Sunny, 1996). This was an improvement over the earlier mentioned coating technique. There was no need for synthesizing azidated PVC, coating and drying etc. Coating also involved the use of organic solvents. The method was effective in containing plasticizer migration without significantly affecting the bulk properties of PVC. The technique afforded the creation of a thin cross-linked network on the surface of plasticized PVC since the reaction was conducted in aqueous media and the reagents could not penetrate to the bulk of the polymer. But azidation of PVC was accompanied by dehydrochlorination and hence the clarity of the sheets were adversely affected as a result of the modification limiting their application in real life situations.

Thus, it appears that phase transfer catalyst assisted nucleophilic substitution of PVC in water can possibly lead to a surface which can be cross-linked thermally or photochemically to create a barrier for the diffusion of the plasticizer from the matrix of PVC. This approach is further investigated using differnt nucleophiles in most of the work reported in this thesis. Since the technique involve the use of a phase transfer catalyst to effect the nucleophilic substitution, the principls of phase transfer catalysis is discussed below.

1.6 Phase Transfer Catalysis (PTC)

PTC provides an elegant and efficient way of affecting reaction between components present in two immisible phases. Thus, PTC is concerned with

reactions between chemical species situated in different phases. Common cases are reactions between salts dissolved in water (Liquid-Liquid PTC) or present in the solid state (Solid- Liquid PTC) with the other substance being dissolved in organic media. Without PTC such heterogeneous reactions are usually slow and inefficient or do not occur at all.

PTC is a field of chemistry originated in synthetic organic chemistry in the late 1960's. The term 'PTC' was first coined by Starks (Starks, 1971). The fundamentals and applications of PTC techniques have been thoroughly reviewed (Goldberg, 1992; Dehmlow & Dehmlow, 1993; Starks & Liotta, 1994). Special reviews concerning the role of PTC in preparation and chemical modification of polymers have also been published (Frechet, 1984; Sherrington, 1984).

The main function of a PTC is to carry one of the reactant in a heterogeneous system from its normal phase to the normal phase of the other reactant in such a form that a high reaction rate can be observed. This can be illustrated by a classical example of cyanide displacement on alkyl chlorides. Simply heating and stirring

$$R—Cl\ (org) + NaCN\ (aq) \longrightarrow R—CN\ (org) + NaCl\ (aq)$$

this heterogeneous mixture leads to almost zero yield of cyanoalkane, but if we add a catalytic amount of quaternary salt to the system, a rapid reaction takes place with almost 100% yield within 1-2 h. The reaction scheme is shown in Figure 1.6.

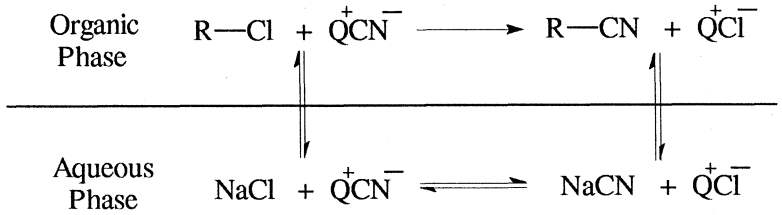


Fig. 1.6 Scheme for the general outline of the catalysis sequence

The uncatalyzed reaction does not take place because the cyanide ions present as sodium cyanide in the aqueous medium cannot cross the interface between the aqueous-organic phase. This is because the aqueous solvation energy of sodium ion is greater than that in the organic phase. The cyanide ion cannot cross without the sodium ion because that would destroy the electrical neutrality of each phase. In contrast to sodium ion, the quaternary ions with sufficiently large organic groups (butyl or higher), when associated with cyanide anion are poorly solvated in water and prefer organic solvents. The organic phase solvation of the quaternary cation is much stronger than the aqueous phase solvation of the cyanide anion. Thus the quaternary salts having high compatibility with the organic phase, transfers cyanide ion into the organic phase as Q^+CN^-. Once the anion reaches the organic phase they rapidly react with the alkyl halide. The co-produced Q^+Cl^- is rapidly reconverted into Q^+CN^- and the reaction proceeds to completion. In the presence of the catalyst three equilibria exist. The Q^+ cation crosses the interface and carry the anion with it. At the beginning of the reaction, the chief anion present is cyanide ion. This gets carried to the organic phase (equilibrium 1) where it reacts with chloro alkane to produce cyano alkane and chloride anion. The chloride anion then

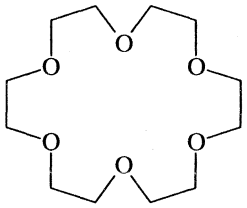
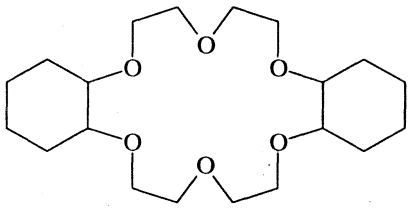
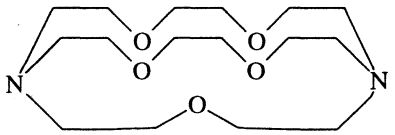
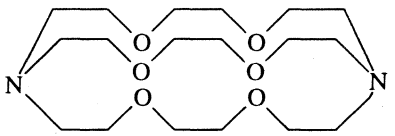
gets carried into the aqueous phase (equilibrium 2). Equilibrium 3 is taking place entirely in the aqueous phase allowing Q^+CN^- to be regenerated. All the equilibria are normally reached much faster than the actual reaction, so the latter is the rate determining step.

The anions associated with many quaternary cations and crown ether complexes of sodium and potassium ions were found to be highly reactive even in relatively non-polar media. This high reactivity is what which makes these agents effective PTCs. According to Ugelstad *et al* (1966), this high reactivity of quaternary salt resulted from its having a greater distance separating the anion and the cation, and therefore a reduced cation-anion interaction energy as compared to the sodium or potassium salt.

Extensive use has been made of two types of catalysts, quaternary salts and macrocyclic ethers. Quaternary salts such as ammonium, phosphonium and sulphonium salts which can form ion pairs with various anions are the most extensively used catalysts because of relatively low cost and commercial availability. Alternate types are crown ethers, cryptates and dialkyl poly(ethylene oxide)s which form reversible complexes with many cations. Table V shows some of the most commonly used PTCs and their structures.

The use of PTC bound to polymeric supports has been reported. They are called triphase catalysts. The catalytic functional group commonly anchored to the polymer support are quaternaryammonium salts, phosphonium salts, crown ethers and cryptates. Chloromethylated 2-4% cross-linked polystyrene and silica gel are used as the matrix. The catalytic activity of these anchored catalysts was lower

Table V
The name and structure of some of the most commonly used PTC

Name	Structure
Tetrabutylammonium hydrogen sulphate	$(C_4H_9)_4N^+HSO_4^-$
Tetrabutylammonium bromide	$(C_4H_9)_4N^+Br^-$
Tetrabutylammonium iodide	$(C_4H_9)_4N^+I^-$
Benzytriethylammonium chloride	$(C_2H_5)_3C_6H_5CH_2N^+Cl^-$
18-Crown-6	
1.5 Dicyclohexo-18-crown-6	
[2.2.1.] Cryptate	
[2.2.2.] Cryptate	

than that of the corresponding non immobilized catalysts. But they have additional advantages of simplified product work-up, easy and quantitative catalyst recovery.

Thus liquid-liquid PTC and liquid-solid PTC are excellent techniques for conducting many kinds of simple displacement reactions. Frequently, they are better than the use of homogeneous conditions even with super dipolar aprotic solvents such as DMF, dimethylsulfoxide (DMSO) or hexamethylphosphoramide (HMPA). Some of the important advantages of PTC mediated reactions are:

1. Use of expensive anhydrous or aprotic solvents can be avoided.
2. Significant acceleration of reaction rate.
3. Lower reaction temperature is needed.
4. Easier work up of the product in many cases and economy.

1.7 Aim and Scope of the Work

Although several attempts have been made to prevent plasticizer migration from flexible PVC, none has achieved the goal of stopping the migration of plasticizer from PVC-based devices. Also, many of the techniques employed led to significant changes in the physical and mechanical properties of PVC. The surface properties were also affected. In the case of plasticized PVC meant for medical and related applications, the surface properties are very important and surface modification should not make the surface properties worse. In this work, attempts have been made to prepare migration resistant plasticized PVC with enhanced blood compatibility.

Since it has been demonstrated that the direct substitution of azide anions for the surface chlorine atoms of plasticized PVC via PTC in water followed by photocross-linking reduced plasticizer migration significantly but changed the colour of the material (Jayakrishna & Sunny, 1996), a similar attempt was first made using diethyldithiocarbamate (DTC) as a nucleophile for chlorine displacement on PVC as DTC is known to be a thermally and photochemically labile group. Therefore, one aim of this study was to carry out direct nucleophilic substitution of chlorine atoms on the surface of plasticized PVC with DTC in aqueous media using the technique of PTC and induce photocross-linking on the surface to create a barrier for the diffusion of the plasticizer.

Sulphide ions being powerful nucleophiles, chlorine substitution in PVC using a metal sulphide can lead to surface cross-linking in a single step, sulphide being a dianion. Hence, another objective of the work was to produce direct surface cross-linking on plasticized PVC using an alkali metal sulphide such as sodium sulphide.

Thiosulphate anion is another potential anion which can act as a powerful nucleophile. The organic thiosulphates once formed can be cross-linked using acid, base, reducing or oxidizing agents (Okawara and Ochiai, 1980). Therefore, yet another aim was to substitute the chlorine atoms on the surface of flexible PVC by thiosulphate anion in water with the aid of PTC and cross-link the surface using NaOH, HCl etc.

PEG, a neutral hydrophilic polymer is well known for its biocompatibility properties. Therefore another aim of the study was to device a simple method to covalently graft a hydrophilic polymer onto the surface of plasticized PVC. Covalent grafting of PEG onto PVC surface will greatly improve the blood

compatibility of PVC. A hydrophilic surface on PVC can also act as a barrier for the diffusion of the plasticizer. Most of the work reported on PEG grafting involves introduction of a functional group foreign to PEG (Harris, 1992). For instance, PEG has been grafted onto aminated poly(ethylene terephthalate) (PET) after activating the hydroxyl groups using cyanuric chloride as shown in Figure 1.7 (Desai & Hubbell, 1991). Making use of the labile nature of chlorine on PVC, attempts will be made to graft PEG onto the surface of plasticized PVC using the classical Williamson ether synthesis reaction. Mono-and disodium salt of PEG will be synthesized from PEG of different molecular weights and will be grafted onto plasticized PVC. The method will not introduce a functional group foreign to PEG on the polymer surface.

Plasticized PVC surface modified using the techniques mentioned above will be examined for their migration resistant properties using standard protocols for testing migration resistance. Migration of the plasticizer will be examined in solvents such as hexane, cotton seed oil, paraffin oil and a hydrophilic medium such as poly(ethylene glycol)-400.

The surface properties of the material after modification will be examined using SEM, IR spectroscopy, XPS and contact angle measurements.

The mechanical properties such as ultimate stress and ultimate strain of surface modified PVC sheets will be determined to assess their suitability for various applications.

Since the major use of plasticized PVC in the medical field is for storing blood and its components, another aim of the study will be to carry out evaluation of the blood compatibility of the surface modified PVC in comparison with the

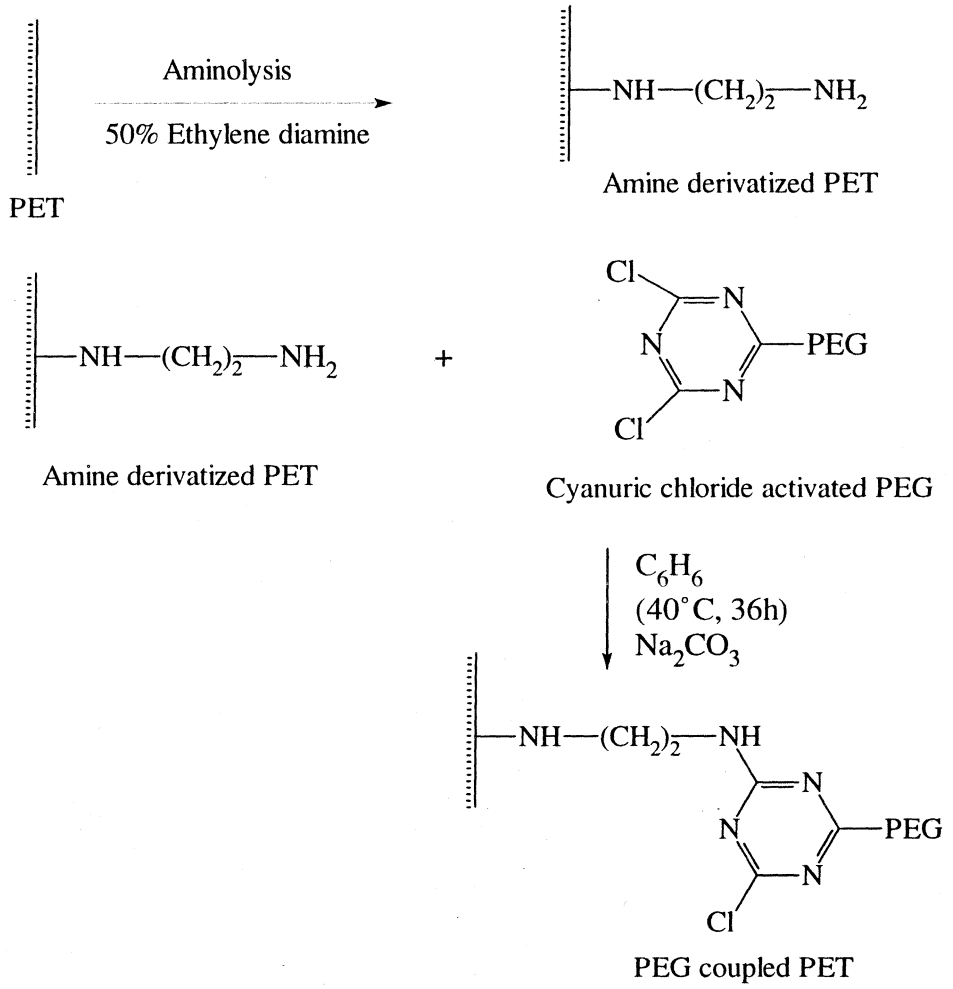


Fig. 1.7 Scheme showing the surface grafting of cyanuric chloride activated PEG on aminated PET surface (Adapted from Desai & Hubbell, 1991)

unmodified PVC. Platelet and bacterial adhesion studies, cytotoxicity assay and whole blood clotting time assays will be carried out on the most promising surface modified specimens.

CHAPTER 2
MATERIALS AND METHODS

MATERIALS AND METHODS

2.1 Materials

Medical grade plasticized PVC tubes with outer diameter 0.9 cm were procured from Solmed, Solvay, Denmark. Medical grade plasticized PVC sheet having a thickness of 0.4 mm, was a generous gift from Hindustan Latex Ltd., Trivandrum. Analar grade sodium sulphide and cetylpyridinium chloride (CPC), a PTC were purchased from Central Drug House (CDH), Ltd., New Delhi. Other PTCs like tetrabutylammonium hydrogen sulphate (TBAH), tetrabutylammonium bromide (TBAB), tetrabutylammonium iodide (TBAI), benzyltriethylammonium chloride (BEAC) and hexyltrimethylammonium bromide (HTMAB) were from Spectrochem. Ltd., Bombay. Metallic sodium, sodium diethyldithiocarbamate (DTC), poly(ethylene glycol) (PEG) having molecular weights 200, 400 and 600 Da and high performance liquid chromatographic (HPLC) grade hexane were also obtained from Spectrochem. Ltd., Bombay. Another PTC 18-Crown-6 and thin layer chromatographic (TLC) plates (type T-6895) were purchased from Sigma Chemicals Co., St. Louis, USA. PEG of molecular weight 4000 Da was from Romali Chemicals, Bombay. Di-(2-ethylhexyl)phthalate (DEHP) was procured

from Indo-Nippon Chemical Co., Ltd., Bombay. Tetrahydrofuran (THF), petroleum ether (b.p. 60–80°C), liquid paraffin oil and sodium thiosulphate were purchased from S. D. Fine Chemicals, Bombay. Tryptone soya broth (TSB) was obtained from Himedia Laboratories, Bombay. Culture of *Staphylococcus aureus* (a clinical pus isolate, 01/TX/97) was obtained from the microbiology laboratory of the Institute. All other reagents and chemicals were of analytical or equivalent grade and were obtained from locally available sources. The blood samples used for platelet adhesion studies were taken from healthy calf by juglar venic puncture. Fresh rabbit blood anticoagulated with acid citrate dextrose (ACD) was used for haemolysis and without anticoagulant was used for whole blood clotting time assay. Fresh human blood anticoagulated with ACD was taken from the author herself.

2.2 Methods

2.2.1 Characterization of the Plasticizer Present in PVC Tubes and Sheets

The plasticizer present in plasticized PVC sheet and tube was identified as DEHP using spectroscopic and TLC methods. The plasticizer was extracted from plasticized PVC tube and sheet using hexane. The infrared (IR) spectrum of pure DEHP in HPLC grade hexane recorded using a Nicolet IR spectrophotometer (Nicolet, Model 410, USA) is shown in Figure 2.1. The corresponding spectrum of the plasticizer extracted from plasticized PVC tube is shown in Figure 2.2. The spectrum of the plasticizer extracted from plasticized PVC sheet using HPLC grade hexane was similar to Figure 2.2 (spectrum not shown). The IR spectrum of plasticizer extracted from plasticized PVC tube/sheet (Figure 2.2) is exactly

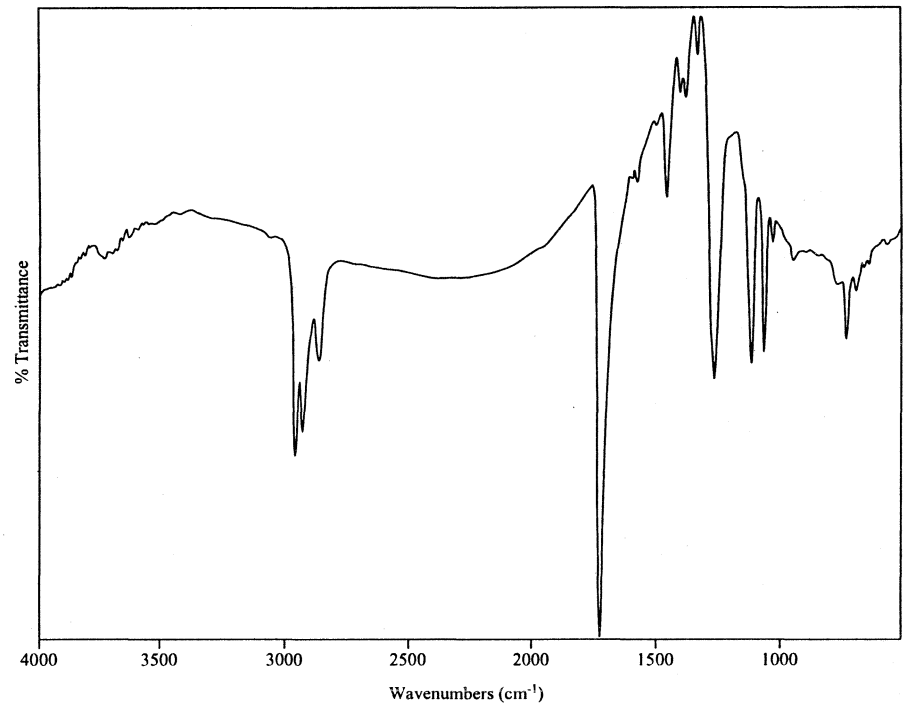


Fig. 2.1 IR spectrum of the pure DEHP in hexane

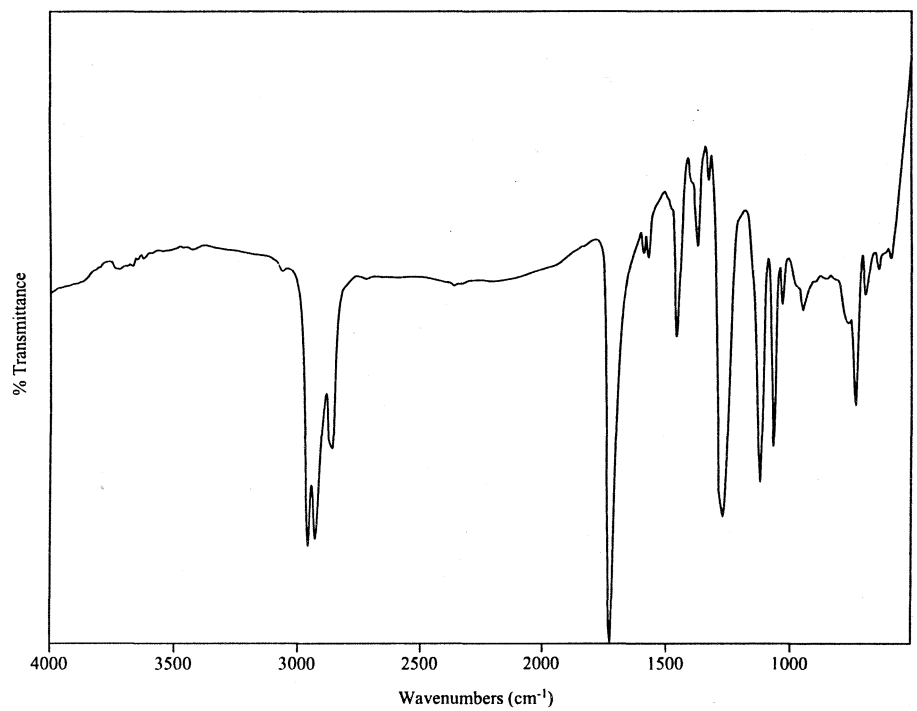


Fig. 2.2 IR spectrum of the plasticizer extracted from PVC tube in hexane

identical to the spectrum of pure DEHP (Figure 2.1) showing all characteristic peaks. The UV spectra of the plasticizer extracted from plasticized PVC tube/sheet using HPLC grade hexane as well as pure DEHP in hexane was recorded using UV spectrophotometer (Milton Roy, Genesys 2, USA) using advanced scanning mode. The UV spectra of the hexane extract from plasticized PVC tube/sheet (Figure 2.3) was compared with that of pure DEHP in hexane (Figure 2.4). The two spectra are identical. The IR and UV spectra of the plasticizer extracted from plasticized PVC tube/sheet using hexane are similar to that of pure DEHP in hexane, thus confirming the identity of the plasticizer present in plasticized PVC tube/sheet as DEHP. Further characterization was carried out by TLC using the hexane extract of plasticized PVC tube/sheet and pure DEHP. For TLC, the chromatogram of the hexane extract from plasticized PVC tube/sheet was run side-by-side with pure DEHP in hexane on TLC plates using 1:1 methanol/hexane as the eluent. The R_f value of the hexane extract from plasticized PVC tube/sheet as well as pure DEHP in hexane were identical (0.65). TLC analysis also thus confirmed the identity of the plasticizer present in plasticized PVC tube/sheet as DEHP.

2.2.2 Determination of Total DEHP Content of Plasticized PVC Tubes and Sheets

The plasticizer DEHP present in PVC sheet and tube was completely extracted using a soxhlet apparatus with hexane as the solvent at 60°C for 48 h. The absorbance of the extract was then measured at 275 nm using UV spectrophotometer. The amount of DEHP present in the extract was then calculated from a calibration curve for DEHP in hexane. The total DEHP content of plasticized

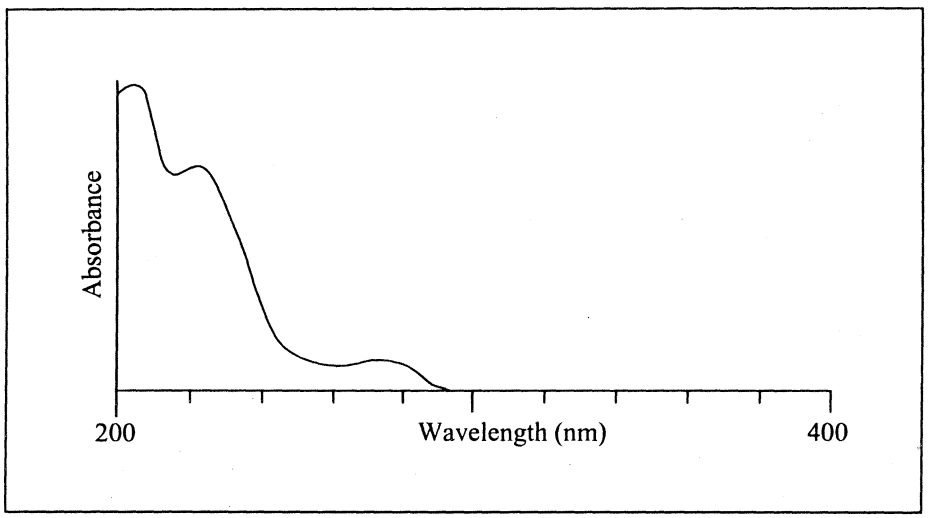


Fig. 2.3 UV spectrum of the plasticizer extracted from PVC

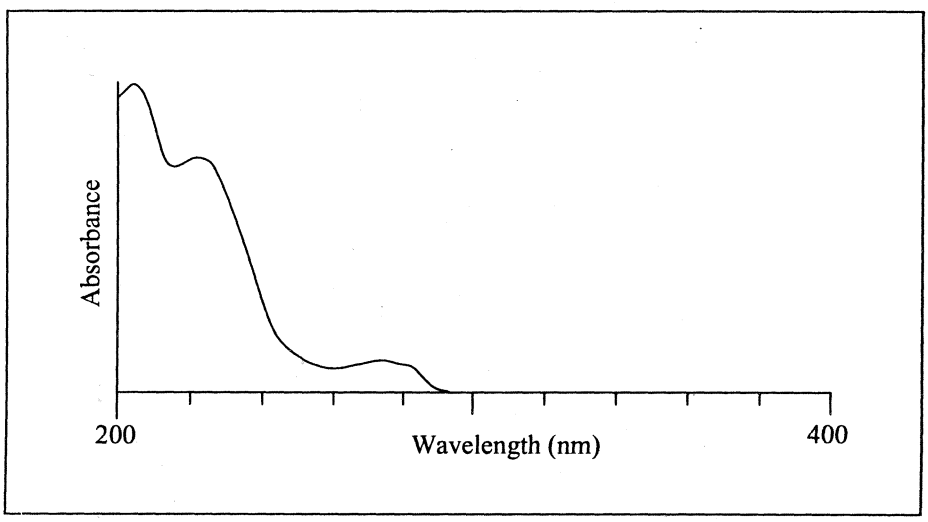


Fig. 2.4 UV spectrum of the pure DEHP in hexane

PVC sheet was found to be 20% by weight and that of plasticized PVC tube was 36% by weight.

2.2.3 Cleaning of Plasticized PVC tube and sheet

Plasticized PVC tubes (~ 1.5 cm) and sheets (2.5×1.5 cm or 10 cm×1 cm or 3 cm×3 cm or 1 cm×1 cm) were cleaned thoroughly by rinsing with 0.1% non-ionic soap solution (Laxbro, Bombay) for 2 min, washed profusely with running tap water for another 5 min and finally rinsed with distilled water. The sheets and tubes were then dried in an air oven at 50°C.

2.2.4 Photocross-linking of Plasticized Diethyldithiocarbamate Substituted PVC Tubes and Sheets Prepared via Phase Transfer Catalysis (PTC)

2.2.4.1 Preparation of Plasticized DTC-PVC via PTC

The optimized reaction conditions for the preparation of DTC-PVC via PTC are as follows. PVC tubes (~ 1.5 cm long) were treated with DTC (0.2 mol dm^{-3}) in the presence of TBAH (0.03 mol dm^{-3}) in 10 mL distilled water at 55°C for 24 h with occasional shaking in a temperature controlled water bath. Sheets (10 cm×1 cm or 2.5 ×1.5 cm) were immersed in 30 mL of water containing 0.2 mol dm^{-3} of DTC and 0.03 mol dm^{-3} of TBAH at 55°C for 24 h with occasional shaking. After the reaction, the specimens were thoroughly washed with running tap water followed by distilled water, and subjected to mild sonication in a bath type sonicator for 1 min to remove any surface adhering reactants and dried in an air oven at 50°C to constant weight. The optimum reaction

conditions as described above were arrived at by following the extent of plasticizer migration from the modified PVC tubes (after photocross-linking the surface). For that, plasticized PVC tubes were reacted with different concentrations of DTC (0.05–0.8 mol dm^{-3}), in the presence of TBAH (0.01–0.1 mol dm^{-3}) as well as with some other PTCs (0.03 mol dm^{-3}) at various temperatures (50-60°C) for various reaction times (2–24 h) with occasional shaking.

2.2.4.2 Photocross-linking of Plasticized DTC-PVC

Irradiation of the samples was carried out using a 125 W mercury vapour lamp (Philips - HPL-N, India) enclosed in a wooden box. The samples were hung in air using copper wire at a distance of 15 cm from the centre of the lamp and irradiated for various periods of time (1–5 h).

2.2.5 Surface Cross-linking of Plasticized PVC Tubes and Sheets Using Sodium sulphide via PTC

The optimized reaction conditions for the substitution of sulphide dianion for the chlorine atoms of plasticized PVC are as follows. Plasticized PVC tubes (~ 1.5 cm long) were treated with sodium sulphide (7 mol dm^{-3}) in the presence of TBAH (0.15 mol dm^{-3}) in 10 mL water at 80°C for 5h in a water bath with occasional shaking. In the case of plasticized sheets, specimens (10 cm×1 cm, 2.5 cm×1.5 cm, 4 cm×4 cm, 3 cm×3 cm, 1 cm×1 cm) were immersed in 30 mL distilled water containing sodium sulphide (7 mol dm^{-3}) and TBAH (0.15 mol dm^{-3}) heated at 80°C for 5 h. After the reaction, the specimens were washed profusely with running tap water followed by mild sonication in distilled

water in a bath type sonicator to remove any surface adhering reactants. The samples were dried in an air oven at 50°C to constant weight and kept in a desiccator for further studies. As discussed in the previous section, the optimum reaction conditions for the nucleophilic substitution was arrived by following the plasticizer migration from plasticized PVC tubes reacted with sodium sulphide under various reaction conditions. For that, plasticized PVC tubes were reacted with sodium sulphide (2–7 mol dm^{-3}) in the presence of TBAH (0.01–0.2 mol dm^{-3}) as well as in the presence of various other PTCs (0.15 mol dm^{-3}). The temperature of the reaction was varied from 60–80°C and time of reaction from 1–5 h.

2.2.6 Substitution of Chlorine Atoms of Plasticized PVC Tubes and Sheets by Thiosulphate Anion via PTC

2.2.6.1 Preparation of Thiosulphate Substituted Plasticized PVC

The optimum conditions for the substitution of thiosulphate anion for the chlorine atoms of PVC as determined by the plasticizer migration studies are as follows. Plasticized PVC tubes (~ 1.5 cm long) were treated with sodium thiosulphate (3 mol dm^{-3}) in the presence of TBAH (0.15 mol dm^{-3}) in 10 mL distilled water at 80°C for 5 h with occasional shaking in a temperature controlled water bath. In the case of sheets, specimens (10 cm×1 cm, 2.5 cm×1.5 cm, 4 cm×4 cm, 3 cm×3 cm, 1 cm× 1 cm) were immersed in 30 mL distilled water containing sodium thiosulphate (3 mol dm^{-3}) and TBAH (0.15 mol dm^{-3}) heated at 80°C for 5 h with occasional shaking in a water bath. After the reaction, the specimens were thoroughly washed with running tap water followed by distilled

water and subjected to mild sonication, in a bath type sonicator for 1 min to remove any surface adhering reactants. The samples were then dried in an air oven at 50°C to constant weight. Thorough washing is very important, as the reactants strongly adhered onto the surface of modified tubes or sheets. In order to optimize the reaction condition , the extent of plasticizer migration was followed from plasticized PVC tubes reacted with sodium thiosulphate under various reaction conditions. Plasticized PVC tubes were reacted with sodium thiosulphate (1.5–5 mol dm^{-3}) in the presence of TBAH (0.05–0.3 mol dm^{-3}) as well as with various other PTCs (0.15 mol dm^{-3}), for various periods of time (1–5 h) and at different temperatures (60–80°C) with occasional shaking.

2.2.6.2 Attempts to Produce Surface Cross-linking on Plasticized PVC

Attempts were made to induce surface cross-linking the thiosulphate substituted PVC. The organic thiosulphates are known to form cross-linking upon reacting with an oxidising or reducing agent as well as by an acid or base (Orzeszko, 1994). The thiosulphate substituted PVC tubes were treated with 1M NaOH at 60°C for 1 h , with an oxidising agent such as hydrogen peroxide (30%) at room temperature for 1 h or with 4 M HCl solution at room temperature for 1 h. The tubes were then washed thoroughly with water and dried in an air oven at 50°C to constant weight and kept in a desiccator for further migration studies.

2.2.7 Surface Grafting of PEG onto Plasticized PVC Tubes and Sheets

PEG of different molecular weights (200, 400, 600 and 4000 Da) were grafted onto plasticized PVC via Williamson ether synthesis. Here, sodium salt of PEG

was reacted with labile chlorine atoms on plasticized PVC tube or sheet.

2.2.7.1 Preparation of Sodium Salt of PEG

The synthesis of sodium salt of PEG (M.Wt used were 200, 400, 600 and 4000 Da) was carried out by reacting PEG with metallic sodium equivalent to or half equivalent to the hydroxyl group of PEG. PEGs of molecular weight 200, 400 and 600 are liquids at room temperature. These liquids were thoroughly dried over anhydrous calcium sulphate before reaction with metallic sodium. With 25 mL of PEG-200, the amount of sodium used was 6.44g (hydroxyl equivalent). With 25 mL of PEG-400, the amount of sodium used was 3.22 g (hydroxyl equivalent) and 1.61g (half equivalent of hydroxyl group). With 25 mL of PEG-600, the amount of sodium employed was 2.15 g (hydroxyl equivalent). In the case of PEG-4000 which is a solid (m.p. 55°C), 5 g of the sample was treated with 0.0575 g (hydroxyl equivalent) of metallic sodium in the melt. The reaction of PEG with metallic sodium was carried out at 70–90°C until the whole of sodium dissolved. In the case of PEG-200, 400 and 600 upon reaction with sodium, the medium became highly viscous and dark brown in colour. The viscosity as well as the reactivity of the solution was lost upon storage even in a desiccator for more than a week . The grafting of PEG using this solution imparts a dark colour to PVC tubes or sheet. The sodium salt of PEG-4000 was a light yellow to light brown liquid above 60°C. The grafting of PEG-4000 imparts only a slight brown coloration to plasticized PVC tube or sheet. The sodium salt of PEG once prepared was used immediately for grafting reactions without storage.

2.2.7.2 Grafting of PEG of Different Molecular Weights onto PVC Sheets & Tubes

Freshly prepared sodium salt of PEG was used for all the grafting studies. Plasticized PVC tubes (~ 1.5 cm) were dipped in sodium salt of PEG at various temperature (30–90°C) for various periods of time (5–120 min). The tubes were then taken out, washed thoroughly with running tap water, and then with distilled water to remove the surface adhering PEG if any. In the case of PVC sheets, the sheets (2×2 cm or 10×1 cm, 3 cm×3 cm, 1 cm×1 cm) were immersed in sodium salt of PEG-4000 at 70°C for various periods of time, and the reaction was quenched by immersing the sheets in water, washed thoroughly with running tap water followed by distilled water and dried in an air oven at 50°C to constant weight.

2.2.8 Physico-Chemical Characterization of Surface Modified and Unmodified Plasticized PVC*

2.2.8.1 Percentage Weight Change

The percentage weight change of the plasticized PVC tubes or sheets due to the substitution of the chlorine atoms of plasticized PVC by various nucleophiles was determined by measuring the weight of the plasticized PVC sheet before and after surface modification using an analytical balance (Sartorius, Germany). The percentage change in weight was calculated with respect to the initial weight of plasticized tubes or sheets. In the case of weight increase due to surface modification the percentage weight increase was calculated as follows.

$$\% \text{ Weight increase } = \frac{\text{Wt of modified PVC - Wt of unmodified PVC}}{\text{Wt of unmodified PVC}} \times 100$$

In the case of weight decrease, the percentage weight decrease was calculated as follows.

$$\% \text{ Weight decrease } = \frac{\text{Wt of unmodified PVC - Wt of modified PVC}}{\text{Wt of unmodified PVC}} \times 100$$

2.2.8.2 Determination of Percentage Water Absorption

Percentage water absorption of the surface modified and unmodified PVC tubes or sheets was determined gravimetrically at room temperature (27°C). Preweighed plasticized PVC tubes or sheets were incubated in distilled water for different periods of time. The weight of the plasticized PVC was then determined after blotting them using a filter paper to remove the surface adhering water and the percentage water absorbed was calculated using the following relation

$$\text{Water absorption (\%)} = \frac{\text{Wt of PVC after swelling - Wt of PVC before swelling}}{\text{Wt of PVC before swelling}} \times 100$$

2.2.8.3 Scanning Electron Microscopy (SEM)

The surface morphology of surface modified as well as unmodified plasticized PVC sheets were examined using SEM. Sheets (0.5× 0.5 cm) both unmodified and surface modified were used for the study. The samples were placed on double-sided adhesive tape fixed on aluminium stubs with the non embossed surface on the top.

The samples were sputter-coated with gold using an ion sputter in vacuum (Hitachi, Model E_{101}, Japan) and examined in the microscope (Hitachi, Model S_{2400}, Japan).

2.2.8.4 Contact angle measurements

Contact angle measurements were carried out using a contact angle goniometer (Rame - Hart, Inc., Model 100, USA).

Captive air-in-water and octane-in-water contact angles were determined after incubating the samples in double distilled water for 24 h. The plasticized PVC sheet was then placed on glass slides and fastened on both ends using teflon tapes. The slide was then immersed in a Perspex tank containing double distilled water. The air and octane droplets were introduced on to the smooth surface of PVC sheet in water using a micrometer syringe having a bent needle. The air/water and octane/water contact angles were then measured. A minimum of ten readings were taken and averaged .

2.2.8.5 Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (FTIR-ATR)

The infrared spectra of pure DEHP in hexane as well as the plasticizer extracted from plasticized PVC tube/sheet were recorded using a FTIR spectrophotometer (Nicolet, Model 410, USA) using sodium chloride window. The surface spectrum (FTIR-ATR) of modified and unmodified plasticized PVC sheets were recorded using FTIR spectrophotometer having a baseline horizontal ATR accessory (Nicolet). Sheets were pressed against Zn-Se crystal provided with the ATR cell

of the FTIR (Nicolet) spectrophotometer. Spectra were collected at a resolution of 2 cm^{-1}.

2.2.8.6 X-ray Photoelectron Spectroscopy (XPS)

XPS was employed to obtain information on the surface chemistry of unmodified and modified plasticized PVC sheets. XPS was done using a Hewlet Packard Model 5950 B, electron spectrometer equipped with a monochromatized X-ray source of Al-Kα radiation at 1486.6 eV at the University of Utah, Salt Lake City, USA.

2.2.8.7 Ultra-Violet Spectroscopy

The UV spectra of pure DEHP in hexane and the plasticizer extracted from plasticized PVC tube/sheet were recorded using a UV-Visible spectrophotometer (Milton Roy, Genesys 2, USA) using advanced scanning mode. The UV spectrum of DEHP in hexane as well as plasticizer extracted from plasticized PVC tube/sheet was recorded after scanning in the UV range between 200 to 400 nm.

2.2.8.8 Gel Content Estimation

Surface cross-linking led to the formation of a three dimensional gel network on the surface of plasticized PVC. In order to have an idea about the extent of three-dimensional cross-links formed on the surface, attempt was made to separate this cross-linked network from the uncross-linked fraction in plasticized PVC. The modified and unmodified PVC tubes were treated with 50 mL THF at room

temperature for 24 h. The uncross-linked PVC and all the additives in it undergo complete dissolution in THF. The undissolved fraction was essentially the surface cross-linked network which was separated, washed thoroughly with THF and dried in vacuum and weighed in an analytical balance. The percentage gel content was calculated based on the initial weight of the plasticized PVC tubes.

$$\text{Gel content (Wt \%)} = \frac{\text{Weight of gel}}{\text{Weight of tube}} \times 100$$

2.2.8.9 Sulphur Content of Surface Cross-linked Surfaces

The total sulphur content of modified plasticized PVC sheets and more precisely in the surface cross-linked gel isolated from surface modified plasticized PVC was determined by the conventional method. The sheet or gel (0.5 g) was heated in a Parr Bomb filled with oxygen at about 600°C. The sulphur dioxide produced in the reaction, react with dilute hydrogen peroxide solution contained in the reaction flask to produce an equivalent amount of sulphuric acid. It was then precipitated as barium sulphate using barium chloride. The total sulphur content was then gravimetrically determined from the amount of precipitated barium sulphate.

2.2.8.10 Optical Clarity

The optical clarity of the surface modified and unmodified plasticized PVC tubes was determined spectrophotometrically. The samples were cut longitudinally and placed in the light path of a UV-Vis spectrophotometer (Milton Roy, Genesys 2, USA) and the percentage transmittance in the visible region (400–700 nm) was measured.

2.2.8.11 Mechanical Properties

The tensile strength and percentage elongation of the unmodified and modified PVC sheets were measured using an Instron series automated materials testing system as per the ASTM method D 882 for thin plastic sheeting (ASTM, 1982). Exactly (10×1 cm) PVC strips were used for the study. The thickness of the sheets was measured using a screw gauge. The samples were tested at room temperature at a cross-head speed of 100 mm/min. At least six samples were tested in each case and standard deviation of the values was also taken. Mechanical properties were measured as above using unmodified and modified plasticized PVC sheets kept at 4°C for 30 d as well as with sheets sterilized by autoclaving.

2.2.8.12 Sterilization

2.2.8.12.1 Autoclaving: Plasticized PVC tubes sheets and tubes were autoclaved in a stainless steel autoclave at 121°C at 15 psi (1.03×10^5 Nm^{-2}) pressure for 15 min.

2.2.8.12.2 Gamma irradiation: Plasticized PVC tubes and sheets were gamma sterilized using a Panoramic Batch Irradiator (PANBIT), using a Co^{60} source for 2.5 Mrads at a dose rate of 0.4–0.49 Mrads/h.

2.2.9 Plasticizer Migration Studies

2.2.9.1 Migration in Petroleum Ether

Migration of DEHP from surface modified and unmodified specimens (both tubes and sheets) was examined in petroleum ether (b.p. 60–80°C) at 30°C.

Previously weighed modified and control PVC tubes and sheets (tubes of ~ 1.5 cm long and sheets 2.5×1.5 cm) were kept in 25 mL of petroleum ether in stoppered Erlenmayer flasks and were occasionally shaken. The volume of the liquid was supposed to be infinite (Messadi & Vergnaud, 1982). The amount of DEHP migrated was assayed using a UV-Vis spectrophotometer (Milton Roy, Genesys 2, USA) at 275 nm. Aliquots of 0.1 mL were withdrawn at various time intervals and diluted to 5 mL with petroleum ether and the absorbance was read at 275 nm. An equal volume of the solvent was immediately added to the extraction medium. In the case of thiosulphate and sodium sulphide reacted plasticized PVC, the extraction medium was used as such even after 3 or 6 months of incubation in petroleum ether for UV measurement without further dilution. The amount of DEHP migrated was calculated from a calibration curve of DEHP in petroleum ether and is expressed as weight percentage of DEHP migrated in the case of plasticized PVC tube/sheet. Each point on the release curves represents an average of three determinations. Migration studies were also carried out with both unmodified and surface modified PVC tubes sterilized by autoclaving as well as by gamma radiation.

2.2.9.2 High Performance Liquid Chromatography (HPLC)

The DEHP released from unmodified and modified PVC tubes into hexane was followed using HPLC (Waters Associates, USA, model 244, μ-porasil column equipped with 486 tunable wavelength detector). Unmodified and modified plasticized PVC tubes (~ 1.5 cm length) were extracted using 25 mL each of HPLC grade hexane. 10 μL from each extraction medium was injected into the column. Chloroform was used as the mobile phase and a flow rate of 1 mL min^{-1}

was maintained. The amount of plasticizer migrated was quantitatively determined from a standard curve of DEHP in HPLC grade hexane.

2.2.9.3 Accelerated Migration Studies

Accelerated migration studies in vegetable oil such as cotton seed oil, and a highly hydrophilic medium such as PEG of molecular weight 400 Da were carried out at 70°C for about 4 days for testing migration of plasticizer according to standard protocols (USP, 1985). In the case of PEG grafted PVC a hydrocarbon such as paraffin oil was also used as extraction medium in addition to cotton seed oil. Preweighed modified and unmodified PVC tubes were kept in 20 mL of these media at 70°C in separate glass vials in an incubator. The samples were then removed at various time periods, rinsed with 0.5% soap water, methanol, and finally in ether and dried in an air oven at 50°C and weighed. Drying was repeated until constant weight was obtained. The amount of plasticizer migrated was then calculated from the percentage loss of weight of the specimen.

$$\text{DEHP migrated (wt \%)} = \frac{\text{Loss of weight of specimen}}{\text{Initial weight of the specimen}} \times 100$$

2.2.9.4 Migration in Ethanol-Water Mixture

Migration of plasticizer into ethanol-water mixture was carried out according to British Pharmacopoeia (British Pharmacopoeia, 1993). The extraction solvent used was ethanol diluted to have a relative density of 0.9378. Standard solution containing 0.02, 0.01, 0.005, 0.002 and 0.001% w/v of DEHP in extraction solvent

was prepared and absorbance was measured at 272 nm and a calibration curve was plotted. The modified and unmodified PVC sheets (3 cm×3 cm) were immersed in the extraction solvent (10.3 mL) previously heated to 37°C. The sheets were incubated in the extraction medium in stoppered Erlenmayer flasks without shaking, at 37°C for 60 min. The container was then removed from the incubator, the contents swrilled well and the absorbance was measured at 272 nm. The percentage w/v of DEHP migrated was calculated from the calibration curve.

2.2.10 Biocompatibility Studies

2.2.10.1 Static Platelet Adhesion Studies

Static platelet adhesion studies were carried out with platelet rich plasma from fresh calf blood. The blood was drawn into polypropylene tube containing 3.8% sodium citrate solution (1 mL for 9 mL blood), mixed gently by inversion and then centrifuged for 10 min at 750 r.p.m. to obtain platelet rich plasma (PRP). Unmodified and modified plasticized PVC sheets (1×1 cm) immersed overnight in phosphate buffered saline (PBS, Appendix I), were used for the adhesion studies. The samples were incubated in PRP for 1 h at 37°C. After incubation, the sheets were taken out, rinsed with PBS with gentle agitation to remove the weakly adhered platelets. The surface adhered platelets were then fixed with 2.5% glutaraldehyde solution (GA) in PBS for 30 min at room temperature. The sheets were then dehydrated with several dilution of ethanol-water mixtures and dried in a critical point drying apparatus (Model HCP-2, Hitachi Koki Co. Ltd., Japan) using liquid carbon dioxide as the transition fluid. The specimens were then mounted on stubs

and sputter coated with 4–6 nm of gold prior to viewing in SEM (Hitachi, Model $S\text{-}_{2400}$, Japan).

The tubes modified with PEG-4000 were used for storing human blood for 48 h. After storage, the tubes were washed with PBS and fixed with 2.5% GA. The fixed tubes were cut into small piece and viewed in SEM after sputter coating the surface with gold.

2.2.10.2 Haemolysis Assay

Haemolytic potential of the unmodified and modified PVC sheets was determined according to a modified form of O'leary method (O'Leary & Guess, 1969) ie., rabbit blood was used instead of human blood. Rabbit blood (0.2 mL) anticoagulated with ACD (Appendix B) was added to 12.5 ml of PBS containing modified as well as unmodified PVC sheets (0.5×0.5 cm) in different test tubes. A separate positive (100% haemolysis induced by replacing the PBS with 12.5 mL of 0.1% sodium carbonate solution) and a negative (0% haemolysis, PBS with no material added) control were also set up. Each set of experiments were done in duplicate. All the test tubes containing samples and the control sheets were incubated for 60 min at 37°C. After incubation, the tubes were centrifuged at 3000 r.p.m for five minutes. The percentage haemolysis was calculated by measuring the optical density (OD) of the supernatant solution at 545 nm in a UV-Vis spectrophotometer as per the following formula

$$\% \text{ Haemolysis} = \frac{\text{OD of the test sample - OD of negative control}}{\text{OD of positive control}} \times 100$$

2.2.10.3 Whole Blood Clotting Time

The kinetic method to measure the thromboresistant property was used (Xianghuai *et al.*, 1996). Modified and control PVC sheets (4×4 cm) were placed on different watch glasses. 0.1 mL of fresh rabbit blood was placed directly on the surface of the sheets. After predetermined time, the specimens were transferred into a beaker containing 50 mL of distilled water. The red blood cells which had not been trapped in thrombus were haemolyzed, and the free heamoglobin was distributed dispersively in the water. The concentration of the free haemoglobin in the water was measured as absorbance at 540 nm using a spectrophotometer (Beckman Spectrophotometer, Model 35). It has been found that the optical density of the heamolyzed solution changes with time. The optical density of the solution versus time was plotted.

2.2.10.4 Cytotoxicity Assay

Cytotoxicity assay was done with the surface modified and unmodified plasticized PVC sheets (0.5×0.5 cm) using direct contact of the material with a monolayer of mouse fibroblast cells (L_{929}). The test was carried out according to ASTM standards (ASTM, 1991).

L_{929} cells were subcultured from stock culture (National Centre for Cell Sciences, Pune) by trypsinization and seeded onto multi well tissue culture dishes. Cells were fed with Dubeleco Minimum Essential Media (MEM) supplemented with bovine serum and incubated at 37°C in 5% carbon dioxide atmosphere. When the cells attained a monolayer, the material was kept in contact with the cells.

After 24 h contact, the morphology of the cells was assessed using a phase contrast inverted microscope (Leica, WILD MPS32, Germany) in comparison with negative (cells on tissue culture plate without the material) and positive control (a toxic material like copper wire placed in contact with the cells).

2.2.10.5 Bacterial Adhesion Studies

Adhesion of a gram positive bacteria *Staphylococcus aureus* (*S. aureus*) onto unmodified and modified PVC sheets was carried out in tryptone soya broth (TSB). The extent of adhesion was followed by counting the number of bacteria/field in a light microscope after fixing and staining the adhered bacteria using Hucker crystal violet (Desai *et al.*, 1992).

Both unmodified and modified PVC sheets (1×1 cm) were sterilized by autoclaving. The sterile sheets were incubated in TSB inoculated with $1–5 \times 10^6$ bacteria mL^{-1} for 24 h in a bacteriological incubator at 37°C with occasional shaking. After the incubation period, the films were rinsed in sterile saline three times to remove the non adherent bacteria and the surface adhered bacteria were fixed using 10% neutral buffered formalin for 4 h at room temperature. The sheets were again rinsed with sterile saline and the fixed bacteria were stained with Hucker crystal violet (Sonnenwirth, 1980). The stained bacteria adhered onto the polymer sheets were observed by brightfield optical microscope (Olympus, Japan CH-2) at a magnification of $\times 1000$ in the oil immersion mode and the number of bacteria per field of view was visually counted. Five fields were randomly counted per sheet, and six sheets were observed for unmodified and modified PVC.

CHAPTER 3
RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

3.1 Phase Transfer Catalysed Substitution of Diethyldithiocarbamate onto Plasticized PVC followed by Photocross-linking to Reduce Plasticizer Migration

3.1.1 Background

Diethyldithiocarbamate (DTC) is produced by the reaction of secondary amine (diethyl amine) with a base and carbon disulphide (Katritzky *et al.*, 1987).

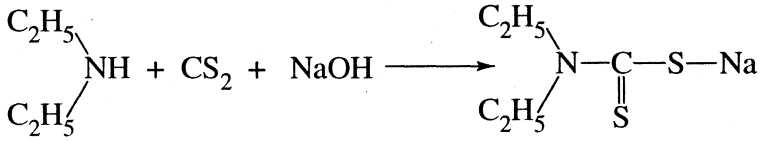


Fig. 3.1.1 Scheme for the preparation of diethyldithiocarbamate

The dithiocarbamate anion is a very powerful nucleophile and hence it is a very good candidate for nucleophilic substitution. Extensive studies have been carried out on the carbamation of various polymers. Thus carbamation of chloromethylated polystyrene (Okawara *et al.*, 1963), poly(vinyl chloride) (Okawara *et al.*, 1966; Nakagawa *et al.*, 1967; Levin, 1989, 1993), chlorinated polyethylene (Nakagawa &

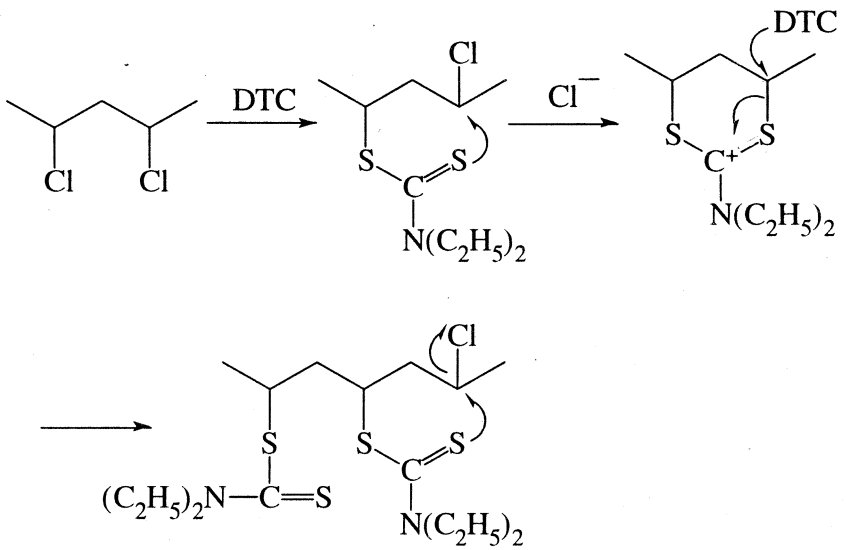


Fig. 3.1.2 Scheme showing the neighbouring group participation in DTC substitution.

Yamada, 1972), poly(epichlorohydrin) (Kohjiya *et al.*, 1981), 1-chlorobutadiene (Hongu *et al.*, 1977; Yamashita *et al.*, 1977) have been investigated. The nucleophilic substitution of chlorine atoms of PVC with DTC can be feasibly achieved in the temperature range of 50-60°C in DMF without accompanied dehydrochlorination, which is one of the inherent problems associated with PVC modification (Okawara *et al.*, 1966a). This is due to the neighbouring group participation via the intermediary cyclic carbocation as shown in Figure 3.1.2 as well as due to the high nucleophilicity of DTC.

Okawara and Ochiai (1980) have reported that dithiocarbamate substituted PVC (DTC-PVC) is highly reactive and can be used to produce cross-linkable polymer. DTC-PVC is a thermal as well as photosensitive polymer. The DTC-PVC is known to produce free radicals upon UV-Visible light irradiation (Okawara *et al.*, 1963;

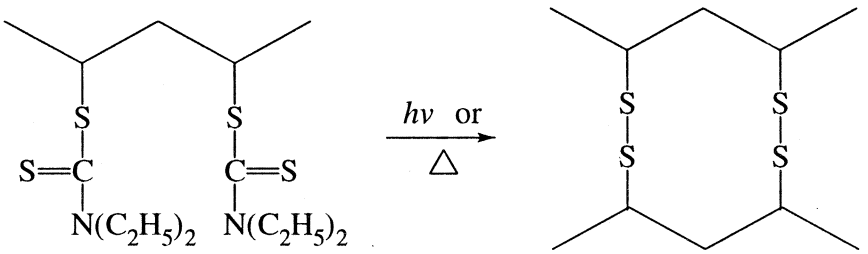


Fig. 3.1.3 Scheme showing the cross-linking of DTC-PVC.

1970). Photolysis of DTC groups leads to the homolytic fission of the C-S bonds resulting in the formation of thyl radicals which in the absence of other active group would lead to cross-linking of PVC as shown in figure 3.1.3. as well as could photograft the monomer coexisted (Nakai & Okawara, 1969; Nagaoka *et al.*, 1981). The mechanism of these photolytic cleavages was deduced from the detailed researches (product examination and kinetic study), on the photolysis of model compounds such as DTC (Okawara *et al.*, 1966) and xanthates (Okawara *et al.*, 1965). These reactions were utilized to design photo sensitive polymers and has been applied to prepare the materials for artificial organs (Mori *et al.*, 1982).

Jayakrishnan *et al* (1995) had shown that coating plasticized PVC sheet with a photoactive polymer (azidated PVC) followed by photocross-linking the coated surface greatly reduced plasticizer migration. A US patent claimed reduced plasticizer migration from DTC-PVC coated onto plasticized PVC film followed by themal cross-linking (Levin, 1989). However, both these methods involved the preparation of substituted PVC and the use of organic solvents for coating. Yet another US patent by the same author claimed reduced plasticizer migration from plasticized PVC substituted with DTC via PTC followed by thermal cross-linking

(Levin, 1993). Thermal cross-linking is accomplished by heating the substituted specimen either in air or in vacuum. Alternatively, the reaction itself is conducted at a very high temperature (~ 90°C) to induce cross-linking during the substitution step itself. Jayakrishnan & Sunny (1996) had shown that direct substitution of azide groups onto plasticized PVC sheet via PTC followed by photocross-linking greatly reduced plasticizer migration. In view of the fact that such direct substitution of nucleophiles onto PVC was possible in aqueous media in the presence of a PTC, this work was undertaken to substitute DTC onto PVC in water followed by photocross-linking the surface. The plasticizer migration of such modified PVC was examined and physico-chemical characterization of the modified PVC was carried out.

3.1.2 Surface Carbamation of Plasticized PVC

In order to confine the substitution reaction onto the surface chlorine atoms of plasticized PVC, the reaction was carried out in water at a lower temperature (55°C). The proces is schematically depicted in Figure 3.1.4.

DTC is a known photo labile group. Upon photolysis, it undergoes homolytic bond fission resulting in the formation of a thyl radical which in the absence of other photo reactive groups undergoes cross-linking resulting in the formation of a sulphur bridge as discussed above (Figure 3.1.3). The diffusivity of plasticizer molecules such as DEHP through such a cross-linked network may then be considerably retarded as the sulphur bridges formed on the surface of flexible PVC are expected to act as a barrier to plasticizer migration.

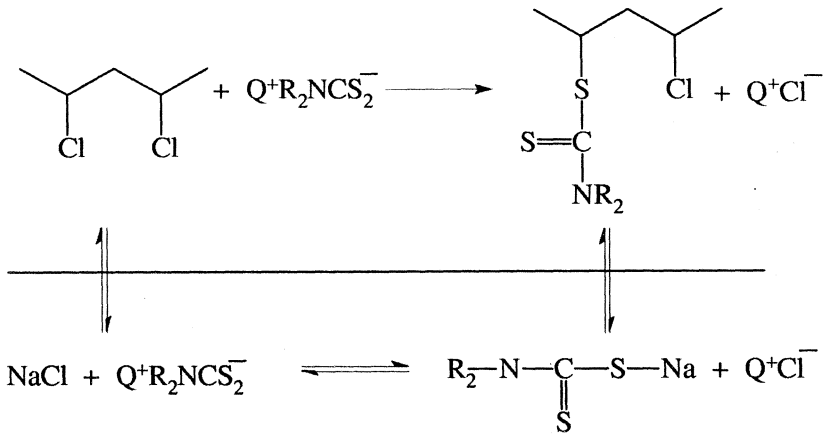


Fig. 3.1.4 Scheme showing the dithiocarbamate substitution of PVC via PTC

3.1.3 Physico-Chemical Characterization of Modified PVC

Plasticized PVC was thus reacted with DTC in the presence of various PTCs at 55°C for 24 h as discussed in section 2.2.4.1. The optimum conditions for the substitution reaction were arrived by following the extent of plasticizer migration from plasticized PVC tubes reacted under various conditions as discussed in this chapter (Section 3.1.4). The optimum reaction condition was to react plasticized PVC with DTC in the presence of TBAH at 55°C for 24 h. The concentration of reagents used was as follows. [DTC] = 0.2 mol dm^{-3} and [TBAH] = 0.03 mol dm^{-3}. The substituted PVC was then photocross-linked by UV irradiation for various periods of time (Section 2.2.4.2). The physico-chemical characterizations were carried out with PVC surface modified under optimized reaction conditions.

3.1.3.1 FTIR-ATR Spectra

The nucleophilic substitution of the surface chlorine atoms of PVC by DTC group as well as the photolysis of the surface incorporated DTC group by UV irradiation was confirmed by comparing the surface IR spectra of unmodified, DTC-PVC and photocross-linked plasticized DTC-PVC sheet (Section 2.2.8.5). Figure 3.1.5 shows the FTIR-ATR spectrum of unmodified plasticized PVC sheet. Figure 3.1.6 shows the corresponding spectrum of plasticized DTC-PVC sheet (a), DTC-PVC sheet subjected to UV irradiation for a period of 1 h (b) and that of DTC-PVC sheet subjected to UV irradiation for a period of 4 h (c).

The spectrum of plasticized DTC-PVC (Figure 3.1.6a) shows a number of additional peaks in the 900–1500 cm^{-1}, in comparison to the spectrum of unmodified plasticized PVC (Figure 3.1.5). These peaks can be attributed to the vibrations involving interaction between C=S stretching and C–N stretching of DTC group present in DTC-PVC. The surface spectrum of DTC-PVC film also shows the characteristic peak of C=S stretching vibration at 1202 cm^{-1} which is absent in the spectrum of unsubstituted PVC sheet. The presence of these peaks in the spectrum of DTC-PVC clearly confirmed the substitution of DTC group for the surface chlorine atoms of plasticized PVC. At the same time, the spectrum of DTC-PVC subjected to photoirradiation for 1 h (Figure 3.1.6b) shows a significant reduction in the intensity of the peak at 1202 cm^{-1} showing the photolytic cleavage of the DTC groups on the surface. The spectrum of DTC-PVC sheet irradiated for a period of 4 h (Figure 3.1.6c) shows almost complete disappearance of the peak at 1202 cm^{-1} showing the photolysis of the DTC group resulting in the formation of surface cross-linking via sulphur bridges.

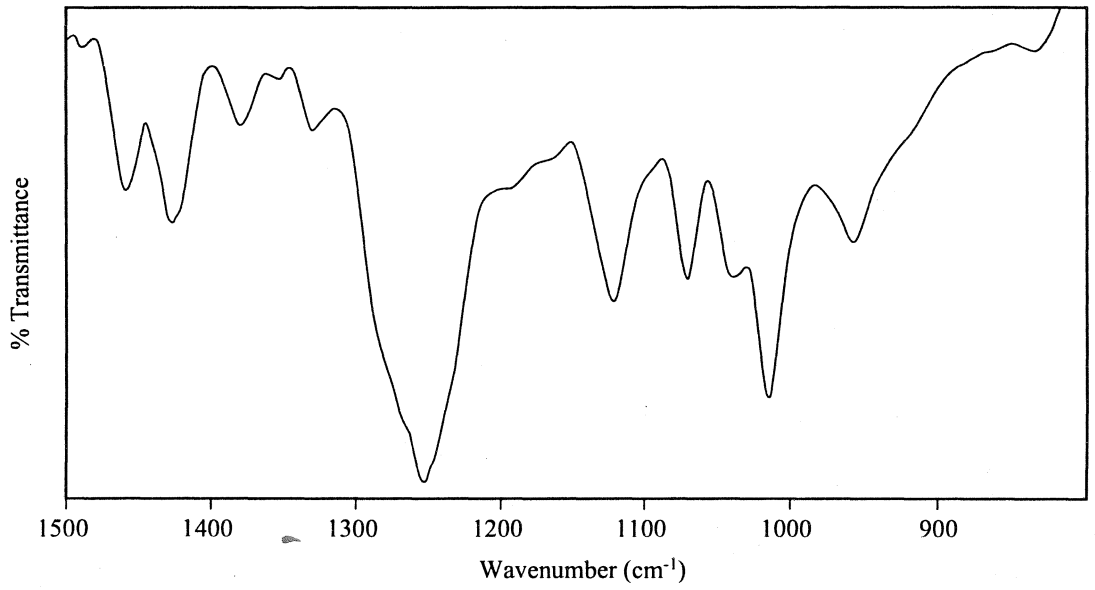


Fig. 3.1.5 FTIR-ATR spectrum of unmodified plasticized PVC

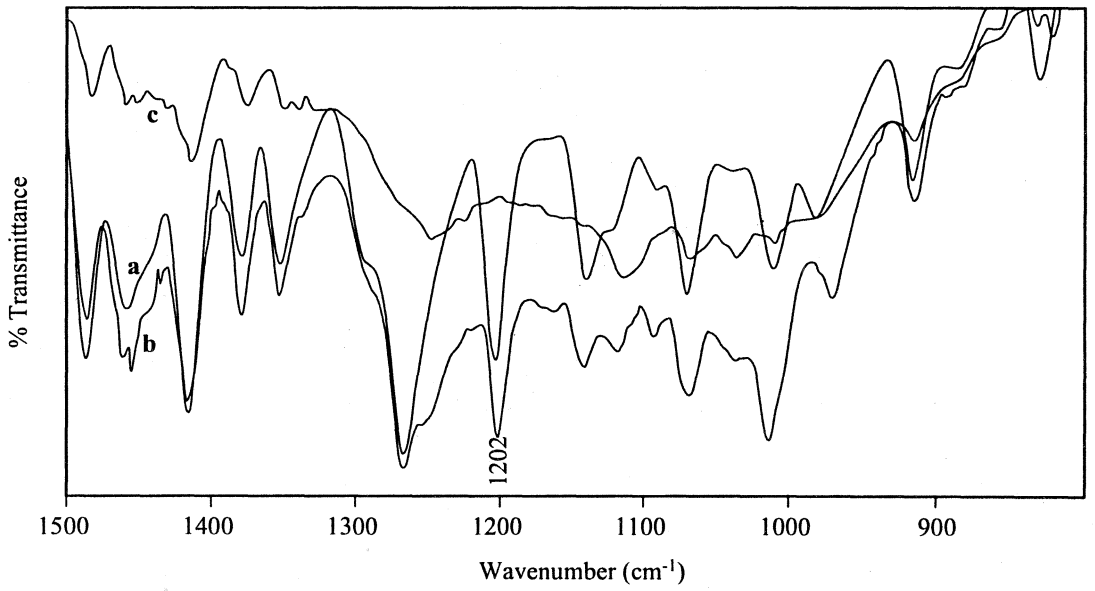


Fig. 3.1.6 FTIR-ATR spectrum of DTC substituted plasticized PVC (a), DTC substituted plasticized PVC photoirradiated for 1 h (b) and DTC substituted plasticized PVC photoirradiated for 4 h (c)

The C-S stretching vibrations occur in the 600–700 cm^{-1} and the S–S stretching in the 400–500 cm^{-1}. These peaks are naturally very weak and hence very difficult to detect (Silverstein *et al.*, 1981). The presence of these bonds particularly S–S type on the surface of photocross-linked PVC was unable to detect since ATR crystal used for IR determination was made of Zn–Se. The Zn–Se crystal shows transmittance only in the 700–4000 cm^{-1} and hence any peaks beyond 700 cm^{-1} cannot be clearly detected using this ATR accessory. Thus FTIR-ATR spectra was unable to give direct evidence for the presence of sulphur cross-links on the surface of photocross-linked plasticized PVC.

3.1.3.2 Gel Content Estimation

The DTC substituted PVC immediately after the reaction was completely soluble in THF. Photoirradiation of plasticized DTC-PVC resulted in the formation of surface cross-linked gel due to the formation of mainly sulphur linkages as discussed in section 3.1.2. The cross-linked gel formed on the surface of DTC-PVC following photoirradiation is completely insoluble in common solvents of PVC. The cross-linked surface network was separated by dissolving the photoirradiated DTC-PVC in THF at room temperature (Section 2.2.8.8). Whereas the unmodified PVC and all the other additives in it undergo complete dissolution in THF, the cross-linked network does not dissolve and could be physically separated and subjected to gravimetric estimation. Figure 3.1.7 shows the amount of cross-linked gel isolated from the surface of photocross-linked DTC-PVC tube as a function of irradiation time. The amount of gel formed on the surface increases with time of irradiation initially and remains almost constant for 4 and 5 h irradiated sample.

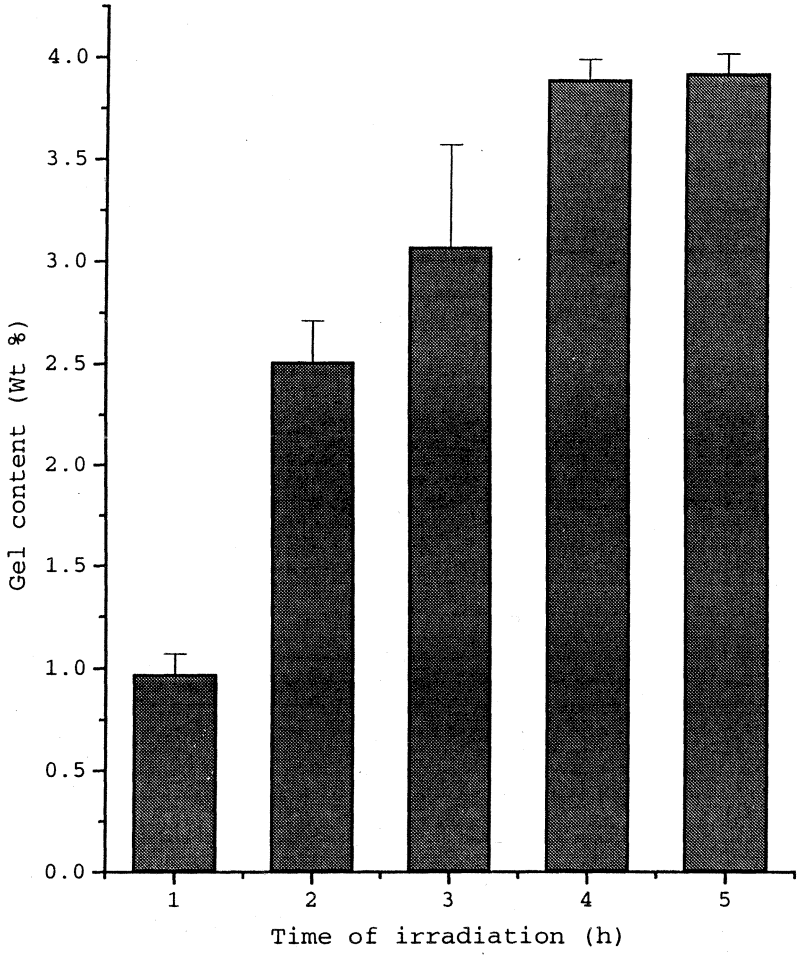


Fig. 3.1.7 The amount of cross-linked gel formed on the surface of plasticized PVC tubes reacted with DTC in the presence of TBAH at 55°C for 24 h followed by photocross-linking as a function of irradiation time. [DTC] = 0.2 mol dm^{-3}; [TBAH] = 0.03 mol dm^{-3}.

The increase in gel content with time of irradiation is due to photolysis of surface substituted DTC group leading to greater extent of surface cross-linking at longer irradiation time. There was virtually no change in the weight of gel formed with 4 and 5 h irradiated samples, thus showing almost complete surface cross-linking. The maximum gel content formed was estimated to be less than 4% of the weight of plasticized PVC tubes. This low value of gel content is presumably due to the cross-linking being confined only to the surface region of plasticized PVC.

3.1.3.3 Sulphur Estimation

The formation of cross-linking on the surface of DTC-PVC following photoirradiation via sulphur bridges was further confirmed by sulphur estimation of photocross-linked DTC-PVC and unmodified plasticized PVC sheet as well as from the isolated surface cross-linked gel (Section 2.2.8.9). The photocross-linked DTC-PVC sheet was found to contain 1.5% by weight of sulphur, whereas in unmodified PVC there was no detectable sulphur present. This low value of sulphur content in photocross-linked DTC-PVC is presumably due to DTC substitution being confined mainly to the surface region of sheet. In the case of surface cross-linked gel, the amount of sulphur as expected was very high ie., 9.6% by weight of the gel. The presence of large amount of sulphur in the surface cross-linked gel clearly indicates that the cross-linking of the surface is mainly taking place via sulphur linkages as the uncross-linked DTC-PVC is completely soluble in THF.

3.1.3.4 Surface Morphology

Figure 3.1.8 shows the SEM of unmodified (a), DTC substituted (b) and photocross-linked (c) plasticized PVC sheets. As can be seen, there appeared to be no significant change in the surface morphology of the sheets before and after surface modification. The dust like particles on the surfaces is due to the presence of low molecular weight plasticizer and other additives migrated onto the surface. Thus, no change in surface morphology was observed due to nucleophilic substitution as well as by photocross-linking plasticized PVC under the magnification the sheets were observed.

Fig. 3.1.8a SEM of unmodified plasticized PVC sheet

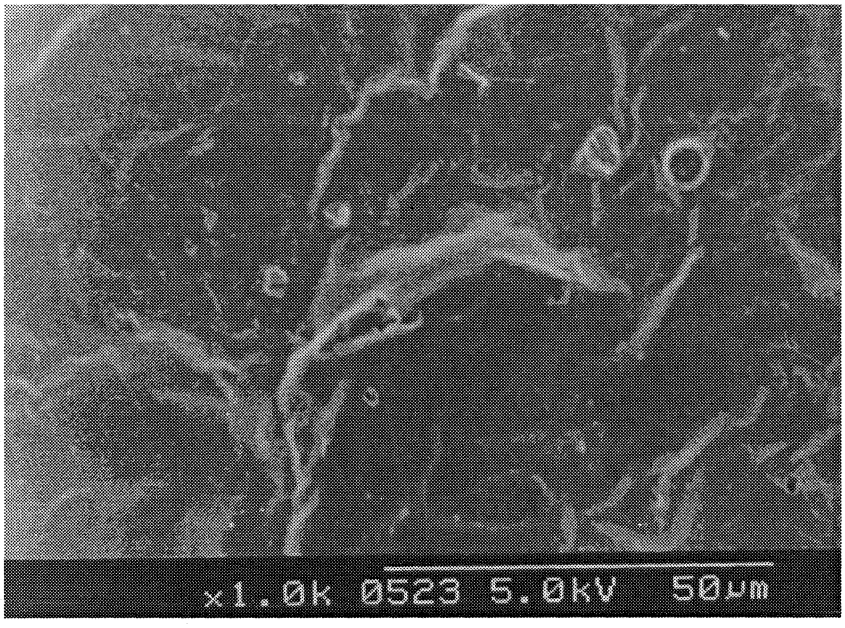


Fig. 3.1.8b SEM of DTC substituted plasticized PVC sheet

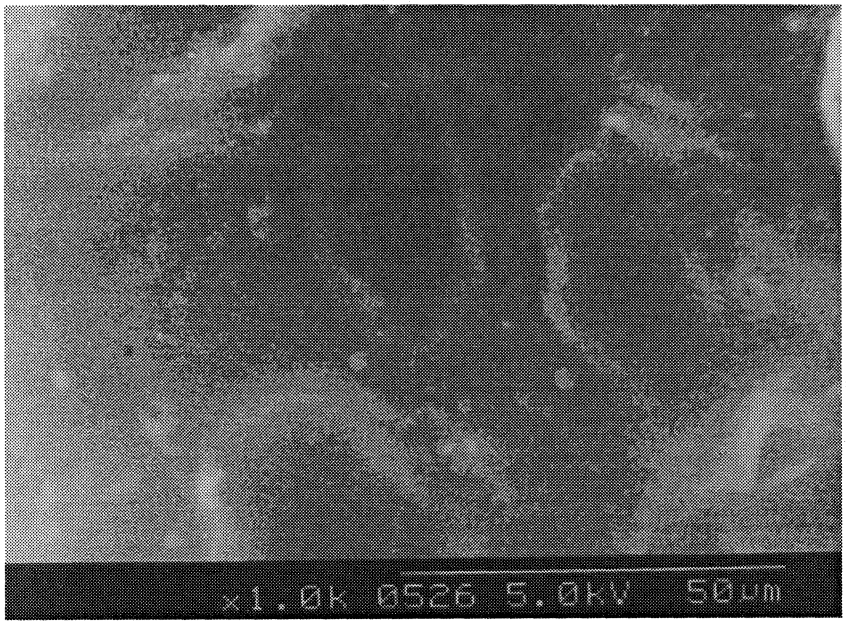


Fig. 3.1.8c SEM of DTC substituted plasticized PVC sheet photoirradiated for 4 h

3.1.3.5 Optical Clarity

Since the PVC-based devices are mainly used for storage applications, the clarity of the material is a very important property. The embossed plasticized PVC sheets commonly used for storage applications have very low transparency compared to tubes. At 700 nm plasticized PVC tube shows a percentage transmittance of about 83% whereas embossed sheet shows a percentage transmittance of only 38%. So plasticized PVC tubes were chosen for determining the change in optical clarity of plasticized PVC as a result of surface modification. Figure 3.1.9 shows the percent transmittance of unmodified PVC tube and DTC substituted PVC tube before and after photocross-linking. It has been found that the percentage transmittance of plasticized PVC tube was only slightly affected by DTC substitution. The DTC substituted PVC showed a percentage transmittance of 69% at 700 nm. Photocross-linking further reduced the transmittance of tubes. Thus 4 h photo-irradiated tubes showed a percentage transmittance of 62% at 700 nm. Photocross-linking the surface enhanced the coloration of the tube as evidenced from the increase in absorbance in the 500 nm region. The decrease in the percentage transmittance of the photocross-linked PVC tube below 500 nm is mainly due to the formation of some amount of conjugated double bonds during photoirradiation.

But the extent of coloration of PVC tubes as a result of DTC substitution is much lower compared to azide substituted PVC tubes. Azidation of plasticized PVC tubes produce a brown coloration. The coloration is attributed to the formation of some unsaturation by dehydrochlorination. Sodium azide has basic character,

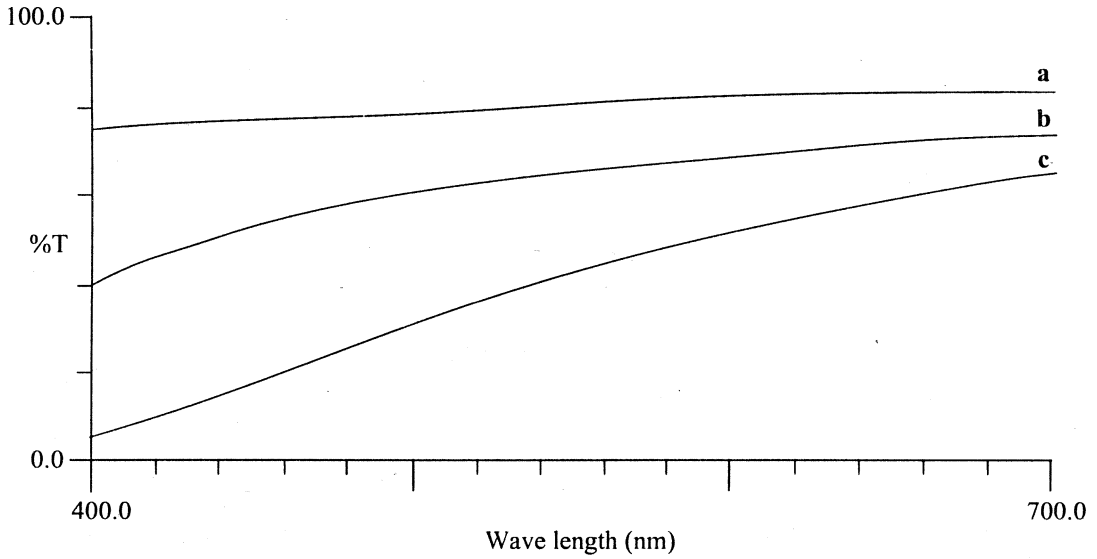


Fig. 3.1.9 Percentage transmittance of unmodified PVC tube (a), DTC-PVC tube (b) and DTC substituted PVC tube irradiated for 4 h (c).

and is expected to induce dehydrochlorination of PVC (Gilbert, 1984). When the plasticized DTC substituted PVC tube showed a percentage transmittance of 69% at 700 nm, the azide substituted PVC tubes showed a percentage transmittance of only about 49.8%. However, it was observed that when the DTC substituted PVC specimens were exposed to atmosphere, they became gradually opaque resulting in the complete disappearance of clarity over a period of time. This appeared to be due to absorption of moisture from the atmosphere by the modified specimens as evidenced by the water absorption experiment discussed below.

3.1.3.6 Percentage Water Absorption

Even after thorough drying in the air oven, the DTC substituted PVC tubes became gradually opaque due to moisture absorption upon exposure to the atmosphere. Figure 3.1.10 shows the percentage water absorption by weight of

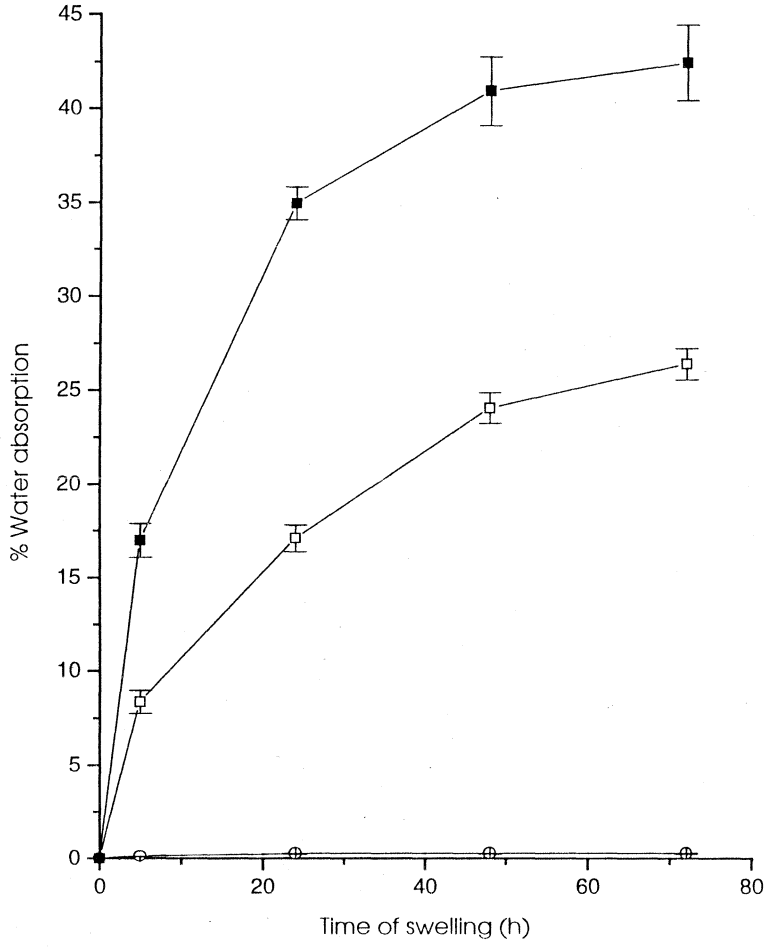


Fig. 3.1.10 Percentage water absorption as a function of time of incubaton in distilled water of unmodified plasticized PVC sheet, sheet reacted with DTC in the presence of TBAH and DTC-PVC sheet photoirradiated for 5 h. [DTC] = 0.2 mol dm^{-3}; [TBAH] = 0.03 mol dm^{-3}; Unmodified PVC (○), DTC-PVC (■) and DTC-PVC photoirradiated for 5 h (□).

unmodified plasticized PVC sheet, plasticized PVC sheet reacted with DTC in the presence of TBAH for 24 h at 55°C and 5 h photocross-linked DTC-PVC sheets after incubation in distilled water for various period of time (Section 2.2.8.2). The amount of water absorbed by unmodified plasticized PVC sheet was found to be very low *i.e.,* only about 0.26% in 48 h. The DTC-PVC on the other hand showed a very high tendency to absorb water *i.e.,* it absorbs about 40% by weight in 48 h. Although photoirradiation decreased the tendency of water absorption by DTC-PVC sheets, it was about 24% after 48 h of incubation.

3.1.4 Plasticizer Migration

The optimization of the reaction conditions was carried out by following the plasticizer migration from modified PVC tubes. The migration of the plasticizer, DEHP from unmodified and modified PVC tubes was examined in petroleum ether at 30°C (Section 2.2.9.1). Figure 3.1.11 shows the amount of plasticizer migrated from PVC tubes reacted at 55°C for various time periods in the presence of TBAH as the PTC and photoirradiated for 4 h. It can be seen that as the time of reaction is increased from 2 h to 24 h (2, 4, 6, & 24 h) there is a gradual decrease in the extent of DEHP migration. Among the samples, the plasticizer migration was found to be minimal from specimens reacted for 24 h. While the unmodified PVC tubes lost more than 25% of the plasticizer in 40 h, migration from PVC tubes reacted with DTC for 24 h was less than 5%. The reduced migration from specimens reacted for prolonged period is believed to be due to the higher degree of DTC substitution on them and hence higher extent of surface cross-linking upon photoirradiation. As the time of reaction increases, the extent of DTC substitution increases. The

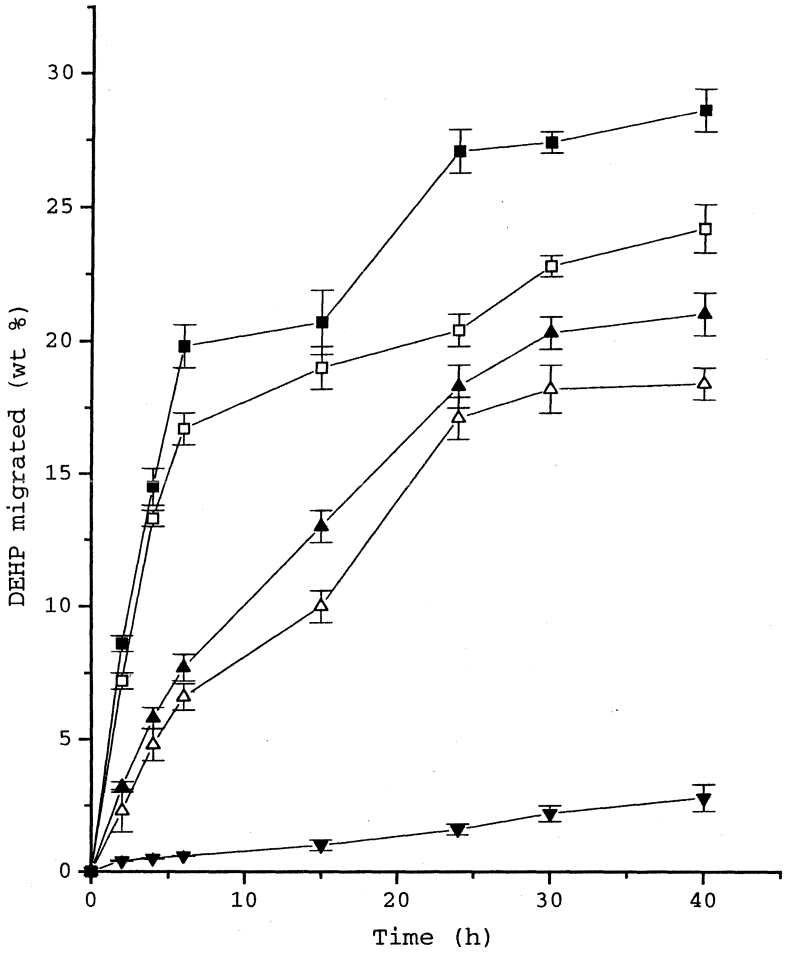


Fig. 3.1.11 Amount of DEHP migrated into petroleum ether at 30°C as a function of time from plasticized PVC tubes reacted with DTC in the presence of TBAH at 55°C for various periods of time and irradiated for 4 h. [DTC] = 0.2 mol dm^{-3}; [TBAH] = 0.03 mol dm^{-3}; Unmodified PVC (■), PVC tubes reacted for 2 h (□), 4 h (▲), 6 h (△) and 24 h (▼).

increase in substitution with time of reaction was further confirmed by examining the increase in weight of flexible PVC tubes as a function of reaction time. It has been found that as the extent of DTC substitution increases, the weight of PVC tube increases. Table VI shows the percentage increase in the weight of plasticized PVC tubes upon reaction with DTC. The maximum weight increase was found for 24 h reacted tubes. Therefore all further surface modifications were carried out by reacting PVC with DTC for 24 h.

Table VI
Percentage increase in weight of PVC tubes on nucleophilic substitution of chlorine atoms with DTC at 55°C for various reaction periods using TBAH as the catalyst. [TBAH] = 0.03 mol dm^{-3}; [DTC] = 0.2 mol dm^{-3}

Time of reaction (h)	Increase in weight (%) ± SD*
2	0.91 ± 0.05
6	1.25 ± 0.03
15	1.84 ± 0.15
24	2.24 ± 0.03

* Average of three determinations.

All PTCs do not behave equally well for all kinds of reactions (Starks & Liotta, 1978). The effect of different PTCs on the extent of nucleophilic substitution of chlorine atoms of PVC with DTC as reflected by the migration of the plasticizer after photocross-linking was examined. PVC tubes were reacted with DTC in the presence of various PTCs for 24 h at 55°C and subsequently photocross-linked for 4 h. Both quaternary salts as well as macrocyclic ether type PTC were employed. The various catalysts used were TBAH, TBAB, TBAI, CPC and 18-crown-6. The migration of DEHP from the surface cross-linked PVC was carried out in petroleum ether for 24 h at 30°C. Figure 3.1.12 shows the amount of DEHP migrated from

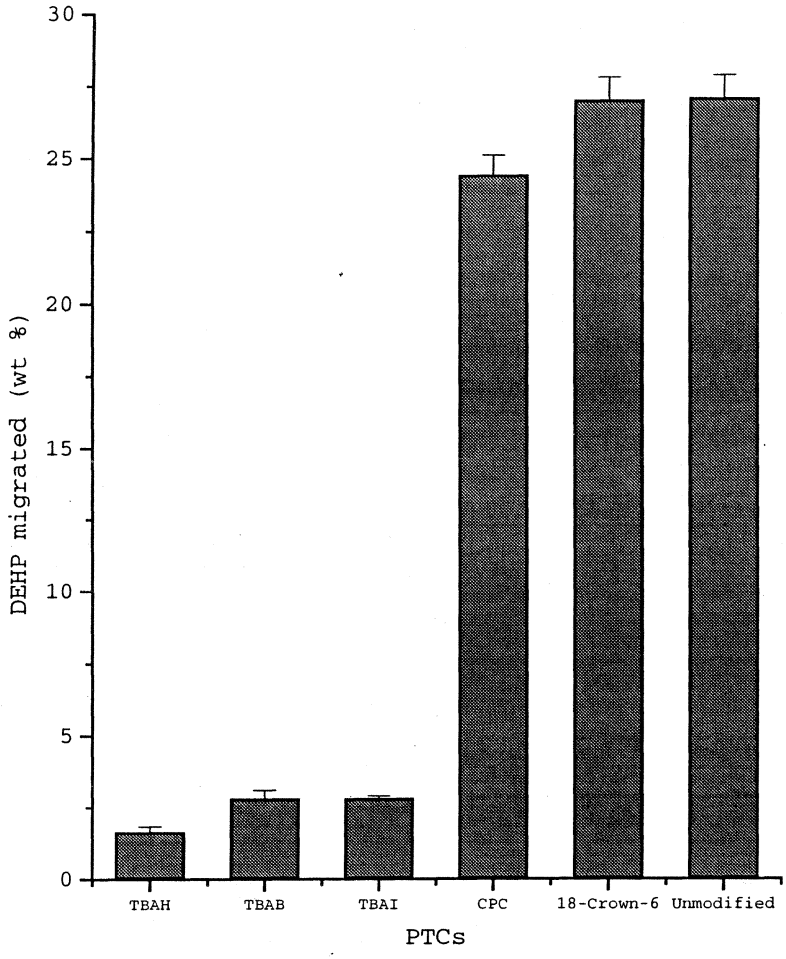


Fig. 3.1.12 Amount of DEHP migrated into petroleum ether at 30°C in 24 h from unmodified plasticized PVC tubes and tubes reacted with DTC at 55°C for 24 h in the presence of various PTCs and irradiated for 4 h. [DTC] = 0.2 mol dm^{-3}; [PTCs] = 0.03 mol dm^{-3}.

tubes reacted with DTC in the presence of various PTCs. It can be seen that apparently no reaction was taking place in the presence of CPC and 18-crown-6 as evidenced by the extent of migration from reacted tubes being almost similar to that of unsubstituted PVC at 24 h incubation in petroleum ether. CPC is a good surfactant rather than a PTC (with only one long alkyl group and a pyridyl group at the quaternary center ($C_{16}H_{33}N^+C_5H_5Cl^-$) and hence it has a tendency to form micelles in the aqueous phase rather than to be get partitioned into the organic solid phase. So it cannot efficiently transfer the DTC anion onto solid PVC surface and hence no reduction in plasticizer migration was observed with PVC tubes reacted with DTC in the presence of CPC. The mechanism of transfer by macrocyclic ether like 18-crown-6 is different from that of the quaternary salts. The macrocyclic ethers form reversible complexes with many cations. So they transfer the entire molecule and not the anion alone as in the case of quaternary salt. Using the simple lock and key approach, they form reversible complexes with cations depending upon their cavity size. 18-crown-6 has cavity dimensions of the same magnitude as the diameter of the potassium ion (2.6–3.2 Å) and hence it is more specific towards potassium ions than sodium ions. Literature has shown that 18-crown-6 is used for both sodium and potassium salts in organic reaction and hence exact correspondence between cavity size and ionic diameter is not always very critical. Eventhough 18-crown-6 is considered to be one of the most efficient catalyst for carrying out solid-liquid PTC reaction ie., transfer from solid to liquid organic phase, it was found to be completely inefficient in the present case ie., reverse process of anion transfer onto solid PVC surface. On the other hand the tetrabutylammonium salts ($(C_4H_9)_4N^+X^-$) are very stable and have sufficient

organic structure to get sufficiently well partitioned into the organic phase and are considered to be good catalysts for many displacement reactions. They can be easily removed after reaction by simply washing with water. The tetrabutylammonium salts were found to be highly efficient in effecting the nucleophilic substitution in the case of solid PVC also. Of all the catalysts, TBAH was found to be the most efficient catalyst for this substitution reaction. The other catalysts TBAB and TBAI were found to be less efficient compared to TBAH. The activity of quaternary salt as PTC usually depend markedly on the anion originally present in it. Thus anion selectivity plays a very important role in PTC mediated reactions. Quaternary salts are known to associate strongly with large soft anions like iodide ions rather than with small highly hydrated ions such as chloride (Starks & Liotta, 1978). The slightly lower efficiency found with TBAB and TBAI compared to TBAH can thus be attributed to the greater association of quaternary salts with iodide or bromide anion. Bisulphate anion has been reported to have lower association with quaternary salt compared to bromide or iodide anion (Dehmlow & Tissel, 1976). The increased association naturally reduces the amount of quaternary salt in the active form ie., $Q^{+}R_2NCS_2^{-}$ and hence the reaction rate. In the present substitution reaction the transfer of DTC anion to solid PVC surface is taking place to an appreciable extent even with TBAI which is known to associate strongly with quaternary cation. This is presumably due to the low extent of hydration as well as the presence of appreciable organic structure of the DTC anion which favourably effects it partitioning into the organic solid phase.

The effect of the concentrations of TBAH and DTC on nucleophilic substitution and thereby preventing the migration of DEHP was examined. Figure 3.1.13 shows

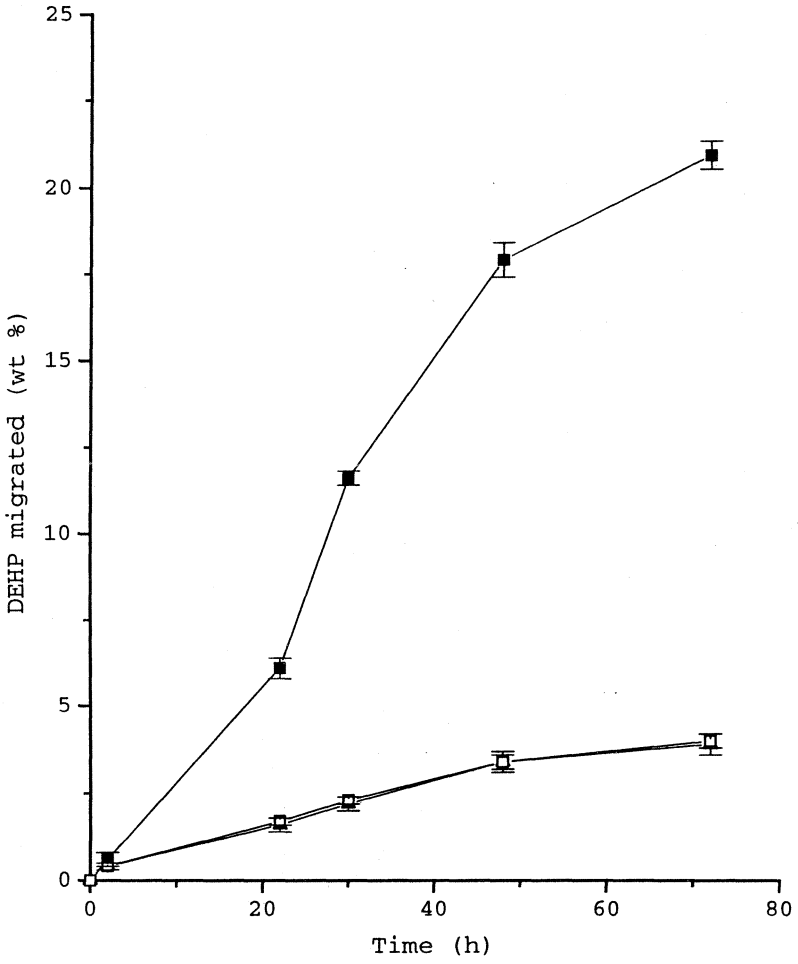


Fig. 3.1.13 Amount of DEHP migrated into petroleum ether as a function of time at 30°C from plasticized PVC tubes reacted with DTC in the presence of various concentrations of TBAH at 55°C for 24 h and irradiated for 4 h. [DTC] = 0.2 mol dm^{-3}; [TBAH] = 0.01 (■), 0.03 (▲) and 0.1 (□) mol dm^{-3}.

the amount of DEHP migrated as a function of time from PVC tubes reacted in the presence of different concentrations of TBAH at a constant concentration (0.2 mol dm^{-3}) of the nucleophile (DTC). Time and temperature of the reaction were fixed as 24 h and 55°C respectively and the time of photoirradiation as 4 h. As can be seen, the catalyst concentration required for achieving effective substitution was very small. As the concentration of the catalyst (TBAH) was increased the extent of substitution was found to increase. Beyond 0.01 mol dm^{-3}, the catalyst did not exert any effect on the extent of DEHP migration. This meant that the extent of nucleophilic substitution did not change beyond a certain catalyst concentration. Usually in the case of low molecular weight compounds, the rate of PTC mediated reactions are linearly dependent on the catalyst concentration. But in the case of PVC the dependence was found to be non-linear (Starks & Liotta, 1978). The rate of the reaction remains almost constant above a certain level of catalyst concentration. The reason for this behaviour was assumed to be due to the aggregation of quaternary salt DTC around or through the polymer chains, and that the adsorbed DTC quaternary salts reacts with PVC in a bimolecular process.

Figure 3.1.14 shows the migration of DEHP as a function of time from tubes modified at different nucleophile concentrations. Here the catalyst concentration was fixed as 0.03 mol dm^{-3}, the time and temperature of the reaction as 24 h and 55°C and time of irradiation as 4 h. The plasticizer migration was found to be minimum at a DTC concentration of 0.2 mol dm^{-3}. Further increase in the concentration of DTC resulted in slightly increased plasticizer migration. The exact reason for this observation is not known at present. Concentrated aqueous solutions are usually preferred for PTC mediated reaction. This is because increasing the

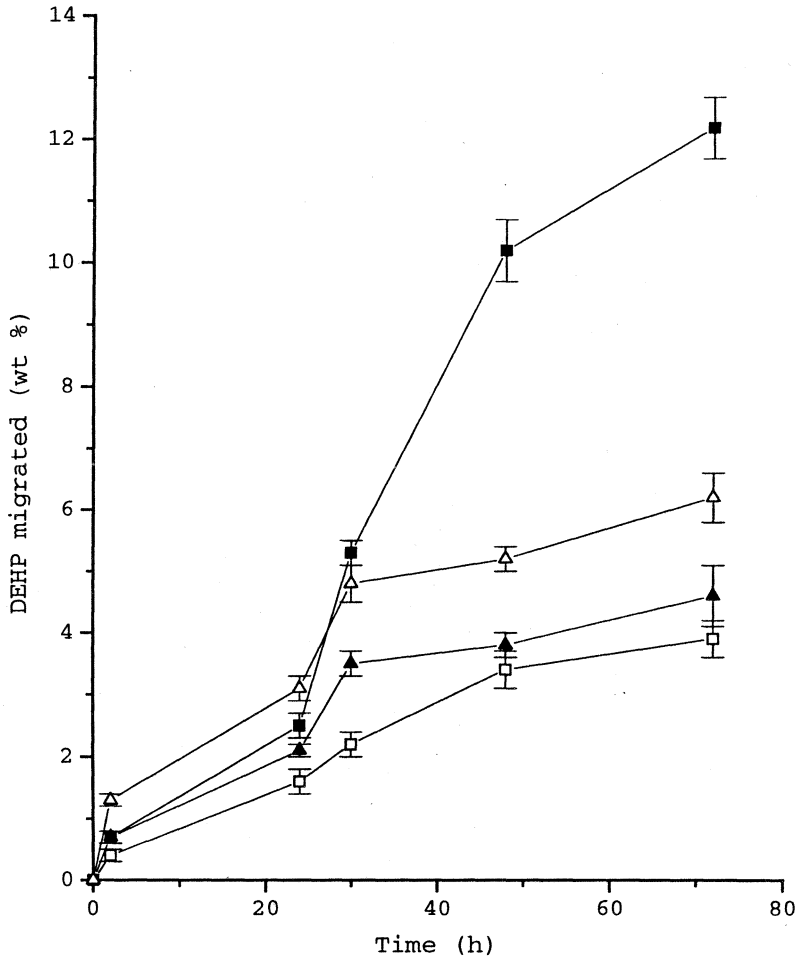


Fig. 3.1.14 Amount of DEHP migrated into petroleum ether as a function of time at 30°C from plasticized PVC tubes reacted with various concentrations of DTC in the presence of TBAH at 55°C for 24 h and irradiated for 4 h. [TBAH] = 0.03 mol dm^{-3}; [DTC] = 0.05 (■), 0.2 (□), 0.4 (▲) and 0.8 (△) mol dm^{-3}.

inorganic salt concentration in the aqueous phase greatly reduced the extent of anion hydration facilitating the transfer reaction.

Figure 3.1.15 shows the extent of DEHP migrated from plasticized PVC tubes reacted with DTC in the presence of TBAH for 24 h at different temperatures ie., 50, 55 and 60°C. It can be seen that reduced migration was observed from samples reacted at 55°C onwards. Not much significant differerence in plasticizer migration was observed from tubes reacted at 55 and 60°C. At higher temperatures of reactions, the DTC-PVC tubes were found to be very sticky even after drying. So the reaction temperature of 55°C have been fixed as optimum temperature of reaction.

The effect of the time of UV irradiation on plasticizer migration was also investigated. Figure 3.1.16 shows the extent of DEHP migration with time of irradiation of DTC-PVC tubes. As the time of irradiation increases, the migration of the plasticizer decreases correspondingly. Even tubes irradiated for 1h show significant reduction in plasticizer migration. It has already been reported that UV irradiation of PVC alone without modification does not have any effect on the migration of the plasticizer (Duvis *et al.*, 1991) from plasticized PVC. So the decrease in plasticizer migration observed in the present case, as a result of UV irradiation is mainly due to the formation of surface cross-linking on PVC by the photolysis of substituted DTC group. This further corroborated the gel content results discussed in section 3.1.3.2, which also showed an increase in gel content due to surface cross-linking with increase in time of UV irradiation.

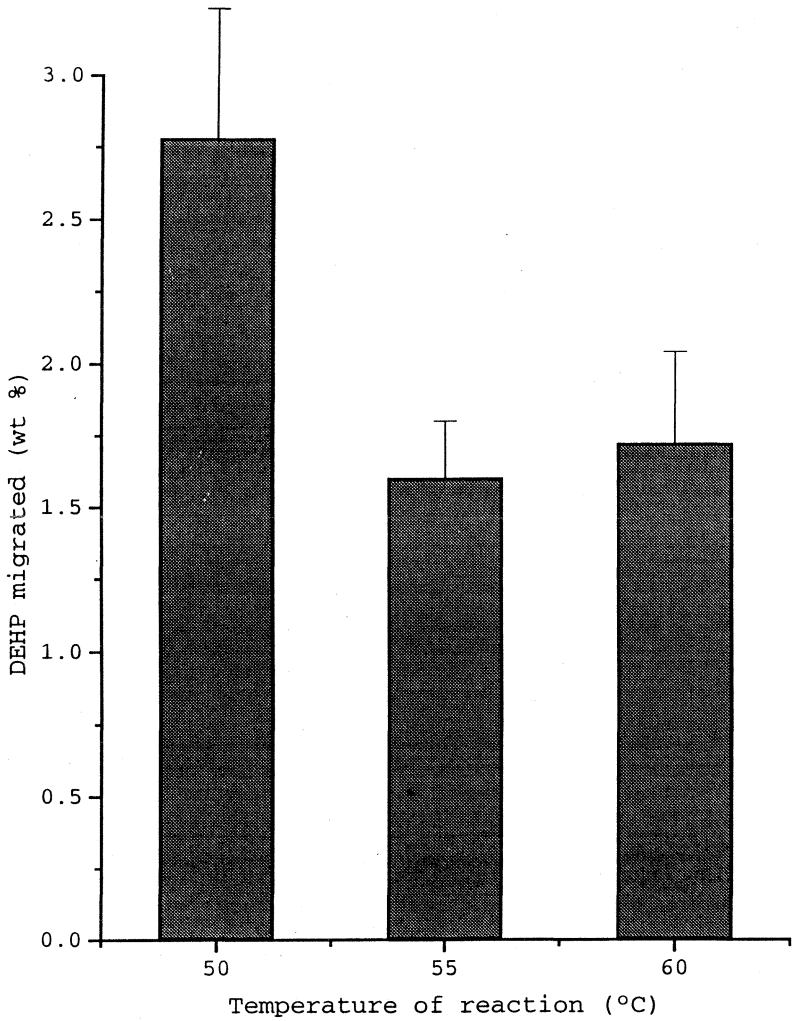


Fig. 3.1.15 Amount of plasticizer migrated into petroleum ether at 30°C for 20 h from plasticized PVC tubes reacted with DTC in the presence of TBAH for 24 h at various temperatures of reaction and photoirradiated for 4 h. [DTC] = 0.2 mol dm^{-3}; [TBAH] = 0.03 mol dm^{-3}.

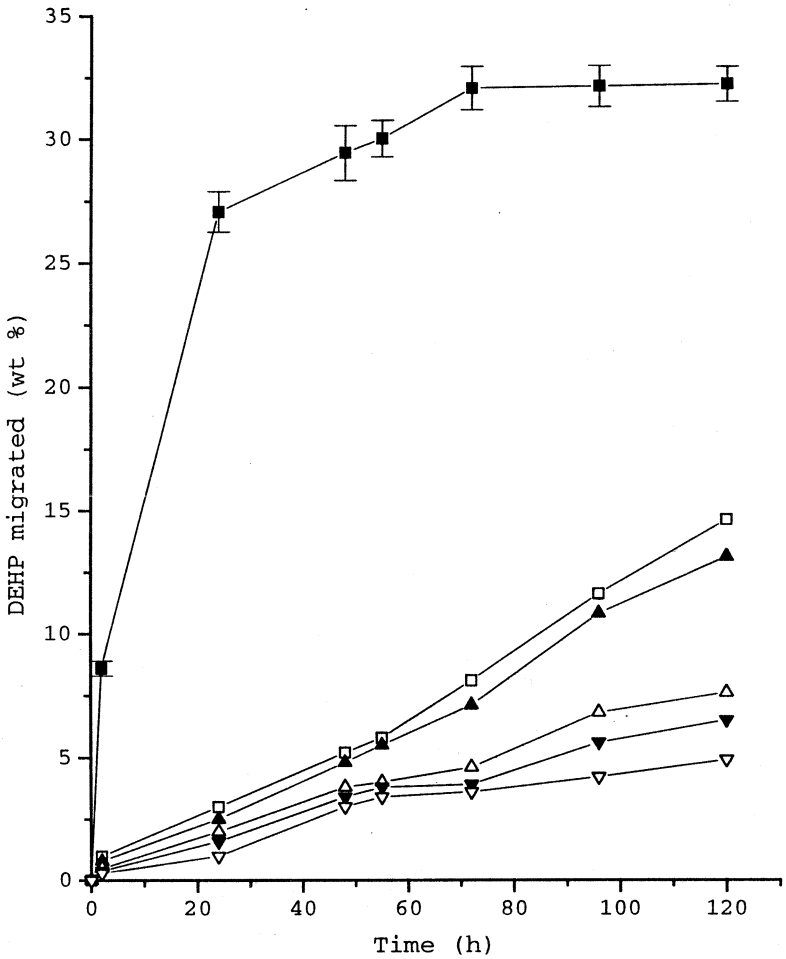


Fig. 3.1.16 Amount of DEHP migrated into petroleum ether as a function of time at 30°C from plasticized PVC tubes reacted with DTC in the presence of TBAH at 55°C for 24 h and irradiated for various periods of time. [DTC] = 0.2 mol dm^{-3}; [TBAH] = 0.03 mol dm^{-3}; Unmodified PVC (■); DTC-PVC irradiated for 1 h (□), 2 h (▲), 3 h (△), 4 h (▼) and 5 h (▽).

From the above discussion, it can be concluded that the surface cross-linking of plasticized DTC-PVC is mainly taking place during photo irradiation. This can be further confirmed by examining the migration of DEHP from DTC-PVC tubes without irradiation. Figure 3.1.17 shows the amount of plasticizer migrated as a function of time from unmodified PVC, from DTC-PVC without photoirradiation as well as from DTC-PVC photoirradiated for 5 h. The unirradiated specimen showed slightly different profile of migration from the control initially, but on prolonged incubation in the extraction media, both the unmodified PVC and the unirradiated DTC-PVC lost almost similar amounts of DEHP. The slight retardation in migration from unirradiated DTC-PVC specimen seen in the early stage is possibly because of some cross-linking that occurred on the surface by day light since dithiocarbamates are known to be highly light sensitive. In comparison, the photocross-linked material lost only less than 5% of its plasticizer even after 5 days of incubation in petroleum ether.

As discussed in section 1.5 migration of the plasticizer from plasticized PVC is highly diffusion controlled. The diffusion of small molecules through rubbery polymers can be predicted on the basis of Ficks law. This can be verified by plotting the extent of plasticizer migrated as a function of the square root of time since the plasticizer molecules in plasticized PVC is equally dispersed throughout the matrix. Figure 3.1.18 shows the extent of plasticizer migration from unmodified PVC tubes and tubes reacted with DTC under optimized reaction conditions and photoirradiated for 5 h as a function of the square root of time of plasticizer migration. In the case of unmodified PVC tube, high rates of plasticizer migration were initially observed and Fickian behaviour held good during the initial stages.

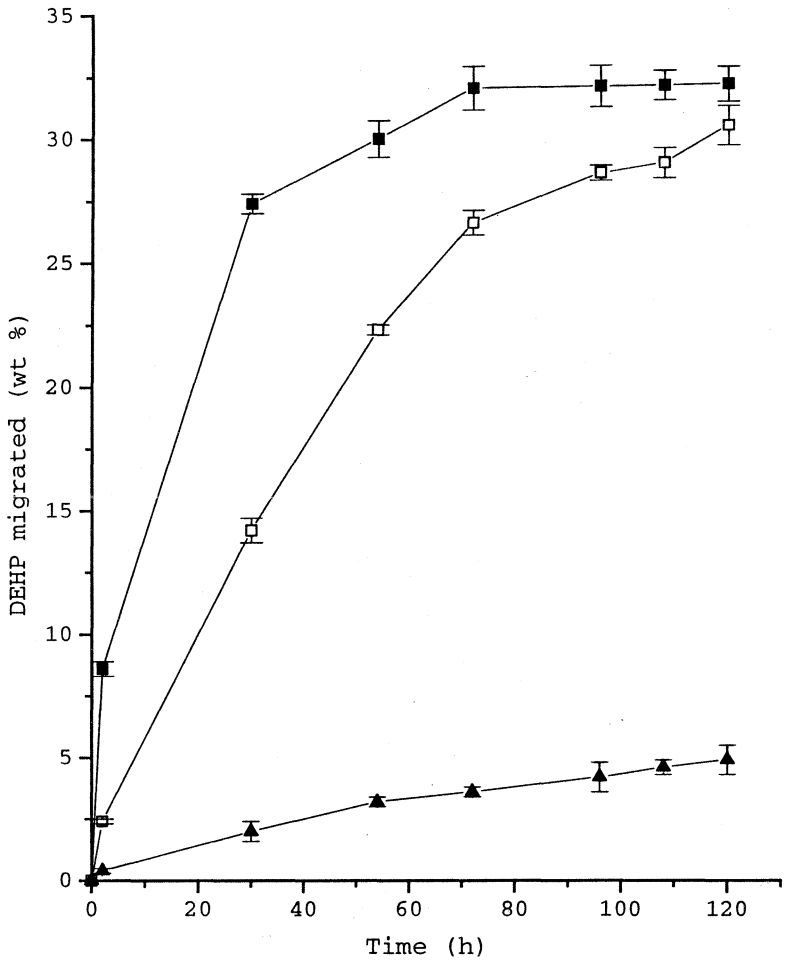


Fig. 3.1.17 Amount of DEHP migrated into petroleum ether as a function of time at 30°C from unmodified PVC tube, tube reacted with DTC in the presence of TBAH at 55°C for 24 h before and after photoirradiation for 5 h. [DTC] = 0.2 mol dm^{-3}; [TBAH] = 0.03 mol dm^{-3}; Unmodified PVC tube (■), DTC-PVC tube before irradiation (□) and DTC-PVC tube after irradiation for 5 h (▲).

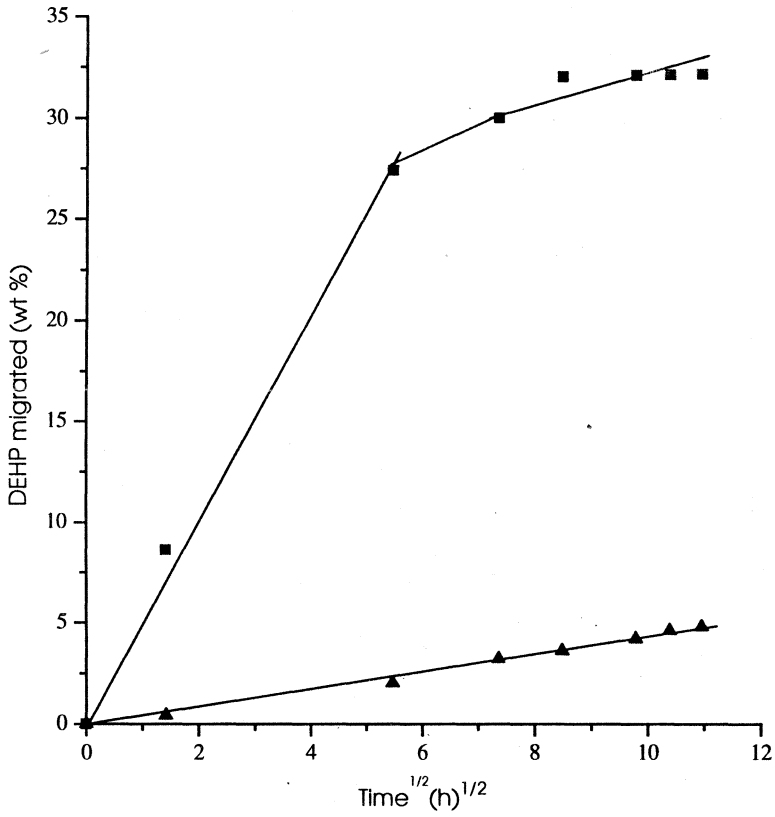


Fig. 3.1.18 Amount of DEHP migrated into petroleum ether at 30°C as a function of the square root of the time showing Fickian behaviour in the case of PVC tube reacted with DTC at 55°C for 24 h in the presence of TBAH and irradiated for 5 h and non-Fickian behaviour in the case of unmodified PVC at longer migration time. [DTC] = 0.2 mol dm^{-3}; [TBAH] = 0.03 mol dm^{-3}; Unmodified PVC (■) and Photocross-linked PVC (▲).

But after some time a transition occurs above that non-Fickian bebaviour was observed. The photocross-linked DTC-PVC tubes on the other hand, shows typical Fickian behaviour, confirming that the plasticizer removal is not highly favoured from the surface cross-linked PVC (Papaspyrides, 1986). Diffusion through a polymer occurs by the small molecules passing through voids and other gaps between the polymer molecules. In the case of plasticized PVC sheet which is rubbery at room temperature, the molecular segments have considerable mobility and there is appreciable free volume in the polymer and hence the diffusion rates are high. Once a significant amount of plasticizer was lost, the polymer become non- rubbery. The polymer segments have little mobility and also a reduction in free volume occurs. These changes greatly affect the diffusion rate and hence the diffusion kinetics become non-Fickian. The presence of rigid covalent cross-links on the surface of plasticized DTC-PVC greatly reduced the gaps or voids on the surface. The cross-linked layer on the surface has little mobility and hence has very low free volume. So the rate of plasticizer diffusion through the photocross-linked DTC-PVC tube is significantly reduced even in the rubbery state and the migration pattern shows typical Fickian behaviour.

Apart from plasticized PVC tubes, plasticized PVC sheets can be surface modified by this PTC mediated reaction. Figure 3.1.19 shows the amount of DEHP migrated from unmodified plasticized PVC sheet, plasticized PVC sheet reacted with DTC as well as from plasticized sheet reacted with DTC followed by photocross-linking for 4 h as a function of time. As in the case of plasticized PVC tubes, the photoirradiated DTC-PVC sheets show significant migration resistance compared to unmodified PVC sheet. The extent of plasticizer migration from

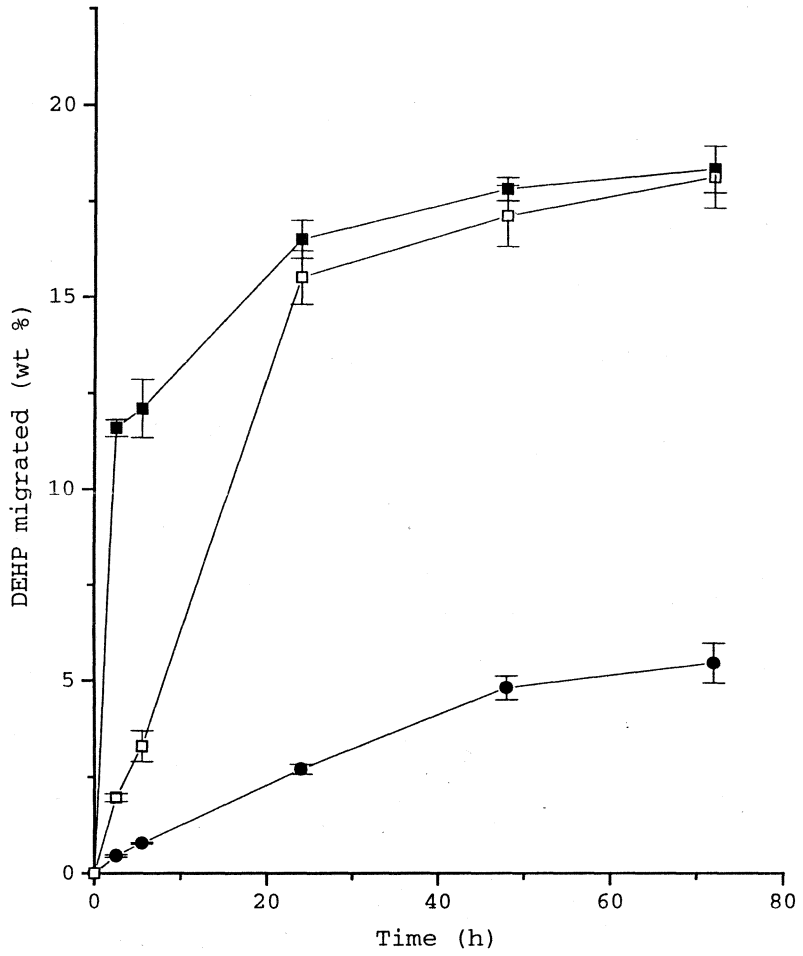


Fig. 3.1.19 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from unmodified plasticized PVC sheet, PVC sheet reacted with DTC in the presence of TBAH at 55°C for 24 h as well as from DTC-PVC sheets photoirradiated for 4 h expressed in terms of weight percentage of sheets. [DTC] = 0.2 mol dm^{-3}; [TBAH] = 0.03 mol dm^{-3}; Unmodified PVC (■), DTC substituted PVC (□) and DTC substituted PVC photoirradiated for 4 h (●).

unirradiated DTC-PVC sheet is slightly less than that of unmodified PVC sheet. This can be attributed to some cross-linking induced by natural light as in the case of PVC tubes.

The extent of plasticizer migration from sheets were slightly higher than that of tubes even though the concentration of plasticizer in tube is greater than that of sheets. After 24 h of incubation in petroleum ether photocross-linked DTC-PVC sheets lost about 2.7 percentage by weight of plasticizer whereas photocross-linked DTC-PVC tubes lost only 1.6 percentage by weight of the plasticizer. This can be attributed to larger surface area available with sheets compared to tubes facilitating greater diffusion of the plasticizer.

3.1.5 Mechanical Properties

The ultimate tensile strength and percentage elongation (Section 2.2.8.11) values for unmodified PVC sheets were compared with unirradiated DTC-PVC as well as photocross-linked DTC-PVC. Table VII shows the ultimate stress-strain properties of the unmodified and surface modified PVC sheets. Since medical applications of plasticized PVC mainly involves storage applications mostly at low temperatures, the mechanical properties of the modified PVC were also compared with unmodified PVC after storing at 4°C for 30 days. Sterilization is a very important step as far as medical applications of PVC are concerned. Medical grade PVC is mainly sterilized by autoclaving. So the mechanical properties of the modified and unmodified PVC sheet were also compared after autoclaving the samples. Substitution of chlorine on the surface of PVC by DTC resulted in a decrease in the ultimate tensile stress as well as the percentage elongation of the

material. This decrease in mechanical properties may be due to some extent of cross-linking already formed on the surface due to day light. On photocross-linking the surface, there was further decrease in these mechanical properties. The ultimate tensile strength as well as the elongation at break of the photocross-linked PVC decreases by approximately 30% compared to unmodified PVC sheet. The decrease in values was very similar to that observed in the case of PVC modified by azidation followed by photocross-linking (Jayakrishnan & Sunny, 1997). The reduced stress-strain values are presumed to be due to the surface cross-linking of the sheets. The storage of photocross-linked PVC sheet at 4°C for 30 d did not adversely affect the mechanical properties. But autoclaving the photo-crosslinked PVC sheet further reduced the tensile strength (by 11%) and its percentage elongation (by 36%). This is possibly due to some additional cross-linking as well as degradation reaction taking place due to thermal effects during sterilization.

Table VII
Stress-Strain properties of unmodified plasticized PVC sheet and sheet reacted with DTC for 24 h at 55°C in the presence of TBAH and UV irradiation time of 4 h. [DTC] = 0.2 mol dm^{-3}; [TBAH] = 0.03 mol dm^{-3}

Sample	Ultimate stress (MPa ± SD)*	Ultimate strain (% ± SD)*
Unmodified PVC	19.38±0.57	437±26.3
DTC-PVC	15.35±0.66	366±22.7
DTC-PVC photocross-linked	13.04±0.35	288.7±12
Unmodified PVC refrigerated for 30 d	18.48±0.65	466.1±30.7
DTC-PVC photocross-linked refrigerated for 30 d	13.27±0.29	307.7±9.2
Unmodified PVC autoclaved	19.84±0.95	522.5±13
DTC-PVC photocross-linked autoclaved	11.6±0.82	184.7±19

* Average of six determinations.

The investigation reported in this chapter has shown that photocross-linking of DTC substituted PVC can result in decreased migration of the plasticizer from both PVC tubes and sheets. The DTC substitution on the surface as well as the photolysis of the DTC group was confirmed by FTIR-ATR. Photocross-linking of DTC-PVC resulted in the formation of surface confined gel which increases with time of irradiation. The formation of sulphur bridges on the surface was confirmed by the quantitative estimation of sulphur from the surface cross-linked gel. The modification did not produce pronounced changes in the surface morphology of PVC as evidenced from SEM. Although the reaction was conducted at a lower temperature in order to confine the substitution reaction to the surface chlorine atoms of PVC and prevent the nucleophile from diffusing extensively into the bulk of the substrate, it was found that the method results in alteration of the physical properties of PVC, mainly its transparency. As shown by the water absorption data, the modified specimens became opaque gradually on exposure to atmosphere or absorbed huge amount of water. This will be a great disadvantage in any medical applications of PVC. Levin (1993) has reported reduced migration from PVC specimens reacted with DTC at a very high temperature ($\sim$ 90°C). Increasing the temperature allows the nucleophile to diffuse into the matrix of PVC thereby cross-linking not only the surface but also the inside of the matrix leading to further deterioration of the physical and mechanical properties. Although photocross-linking the surface after DTC substitution at a lower temperature appears to reduce the plasticizer migration into extraction media such as petroleum ether, the specimens still absorbed large amounts of water. This property of the modified PVC apparently makes it very unappealing and limiting in scope in real life applications.

3.2 Surface Cross-linking of Plasticized PVC via Phase Transfer Catalysis using Sodium Sulphide to Prevent Plasticizer Migration

3.2.1 Background

Instead of resorting to the substitution of chlorine atoms of plasticized PVC by monoanions such as azide, dithiocarbamate etc., and subsequently cross-linking the surface photochemically or thermally, nucleophilic substitution using a dianion such as sulphide can possibly achieve surface cross-linking in a one step process to prevent plasticizer migration. Sulphide ions are similar to thiolate anions and are known as strong nucleophiles. The reaction of an alkyl halide with sodium sulphide is a well known reaction and results in the formation of corresponding disulphides (March, 1978). The use of PTC is beneficial for this type of substitution reaction (Julia *et al.*, 1982). In the absence of a catalyst, the yield of bis(3-penten-2-yl) sulphide from 4-chloro-2-pentene and sodium sulphide is reported to be only 14%, but in the presence of a PTC such as TBAB the yield is reported to be 94% (Tolstikov *et al.*, 1986). It has been reported that sulphide anions can be partitioned easily from the aqueous phase to an organic phase when associated with a quaternaryonium counterion and hence are ideal substrates for PTC reactions (Dehmlov & Dehmlov, 1993). Landini and Rolla (1974) have demonstrated that almost quantitative yield of symmetrical disulphides can be obtained by reacting various alkyl halides with sodium sulphide in the presence of PTCs like tetrabutylammonium chloride or tributylhexadecylphosphonium bromide with vigorous stirring as shown below.

$$RX \underset{\text{(Organic)}}{} + \underset{\text{(Aqueous)}}{Na_2S} \xrightarrow{C_{16}H_{33}P^{+}Bu_3Br^{-}} R—S—R$$

Even sterically hindered halides can be converted into disulphides by reaction with sodium sulphide. A number of patents originated in 70's show the formation of sulphides from alkyl and aryl halides in the presence of PTCs (Mitchell *et al.*, 1975; Tozzi & Cassandrini, 1976). The nucleophilic substitution of chlorine atoms of PVC resin with sodium sulphide and other sulphur nucleophiles were studied by Nakamura *et al* (1979). According to them, sodium sulphide showed higher reactivity towards PVC compared to many other sulphur nucleophiles like alkyl and aryl thiols, dithiocarbamates, thiocyanates etc. This chapter describes the nucleophilic substitution of chlorine atoms on the surface of plasticized PVC using sodium sulphide in aqueous media via PTC, physico-chemical characterization of the modified surface and the evaluation of the plasticizer migration resistance of the surface modified plasticized PVC in petroleum ether as well as in various other physiological media.

3.2.2 Surface Cross-linking of Plasticized PVC Using Sulphide Dianion

As discussed in section 3.1.2, inorder to confine the nucleophilic substitution on the surface region of plasticized PVC, the substitution reaction should be carried out in aqueous media. It is also evident from the previous chapter that transfer of anions onto solid PVC surface is possible in aqueous media in the presence of a PTC. In this solid-liquid PTC mediated reaction, the catalyst will transfer the

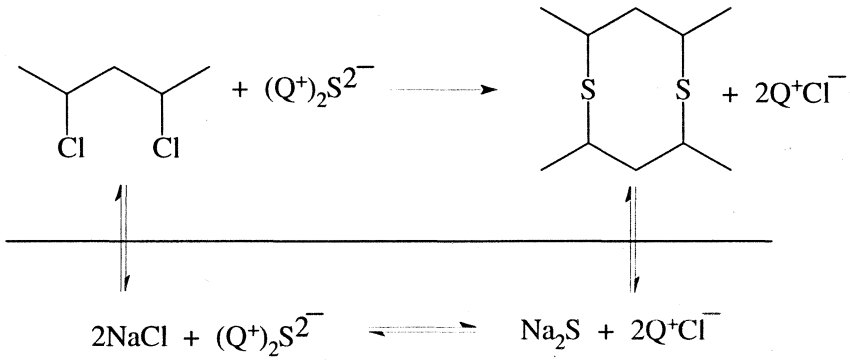


Fig. 3.2.1 Scheme for the PTC mediated surface modification of PVC using sodium sulphide

sulphide dianion from the aqueous phase to solid PVC surface. Usually divalent anions are known to be transferred with difficulty compared to monoanions in PTC mediated reactions (Starks & Liotta, 1978). But sulphide dianion, which is a strong nucleophile can be easily transferred from the aqueous phase to the organic phase as evidenced from various reported reactions (Dehmlov & Dehmlov, 1993). If the anion transfer is possible then theoretically, it should result in the formation of a sulphur bridge between two labile chlorine atoms on the surface of PVC as shown in Figure 3.2.1.

The surface cross-linking process is some thing similar to the vulcanization of rubber, but conducted on plasticized PVC in aqueous media, only the labile chlorine atoms on the surface of the PVC will be involved in the substitution reaction. Thus, logically the bulk properties of the polymer would not be much affected by such surface modifications. If a significant number of sulphur bridges are formed between carbon atoms on the adjacent polymer chains, the diffusivity of DEHP

would be restrained. These predictions have been vindicated by the experimental data.

3.2.3 Physico-Chemical Characterization of Sulphur Cross-linked Plasticized PVC

Plasticized PVC was reacted with sodium sulphide in the presence of a PTC to obtain surface modified PVC as discussed in section 2.2.5. The optimum condition for the substitution reaction was arrived by following the extent of plasticizer migration from plasticized PVC tubes reacted with sodium sulphide in the presence of PTC by varying the reaction conditions (Section 3.2.4.1). Briefly, plasticized PVC was reacted with sodium sulphide in the presence of a PTC (TBAH) at 80°C for about 5 h with occasional shaking ([sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}; Section 2.2.5). Plasticized PVC reacted with sodium sulphide under the above condition will be represented as surface modified PVC throughout this chapter. The physico-chemical characterizations were carried out with plasticized PVC surface modified according to the above mentioned optimized reaction conditions.

3.2.3.1 FTIR- ATR Spectra

The surface characterization of the surface modified PVC sheet was carried out by FTIR-ATR spectra and XPS. The characteristic IR absorptions of various sulphur bonds occur in the following regions. The S–S stretching in the 400–500 cm^{-1}, C–S stretching vibrations in the 600–700 cm^{-1}, C=S stretching in the region 1020–1250 cm^{-1}, the sulphate groups in the 1185–1414 cm^{-1} and S–H in the 2500–2600 cm^{-1} (Silverstein, 1981). Figure 3.2.2a shows the FTIR-ATR spectrum

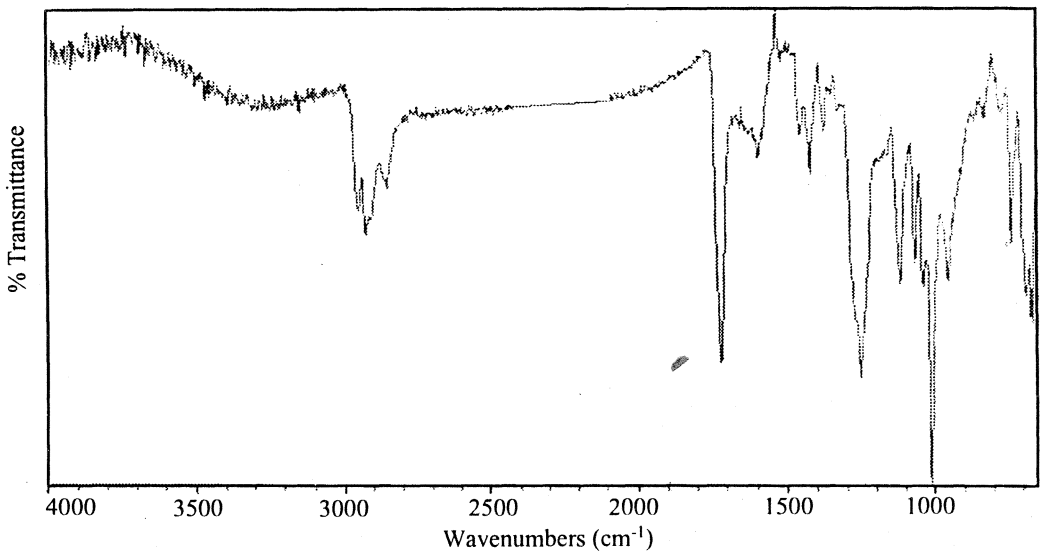


Fig. 3.2.2a FTIR-ATR spectrum of unmodified plasticized PVC sheet.

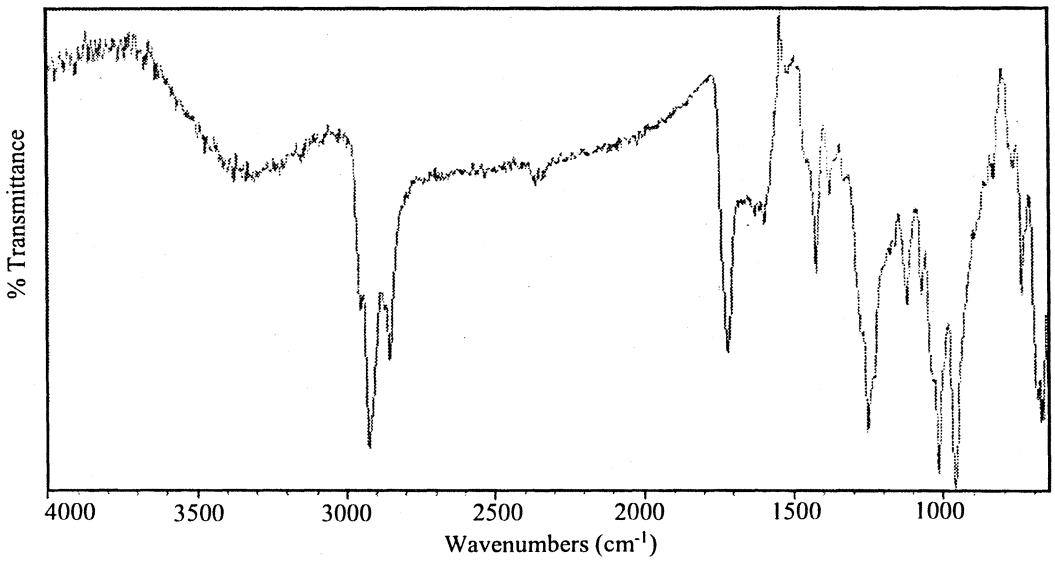


Fig. 3.2.2b FTIR-ATR spectrum of plasticized PVC sheet reacted with sodium sulphide at 80°C for 5 h in the presence of TBAH. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}.

of unmodified plasticized PVC sheet in the range 900–4000 cm^{-1}. The spectrum shows a strong C=O vibration at 1720 cm^{-1} which is unexpected in PVC. This peak arise due to the contamination of the surface by the migration of additives mainly plasticizer (DEHP) present in plasticized PVC (Figure 2.2). Figure 3.2.2b shows the corresponding spectrum of surface modified plasticized PVC sheet. The spectrum of surface modified PVC was found to be rather identical to that of unmodified PVC sheet. No peaks corresponding to S-O (1000–1250 cm^{-1}) stretching vibrations or S–H (2500-2600 cm^{-1}) vibrations were seen in the spectrum of PVC treated with sodium sulphide in the presence of TBAH. This rules out the presence of sulphonate or thiol groups on surface modified plasticized PVC.

The C–S stretching vibrations occur in the 600–700 cm^{-1} and the S–S stretching in the 400–500 cm^{-1}. As discussed in the previous chapter (Section 3.1.3.1), these groups were unable to be detected by the IR spectrum. So the IR spectrum of the modified surface was rather unable to provide direct evidence for the presence of sulphur bridges on the surface of plasticized PVC.

Since the reaction medium was highly basic (pH - 14), some dehyrochlorination reaction accompanying the substitution reaction was expected on PVC. The dehydrochlorination of PVC will result in the formation of conjugate double bonds. The conjugated double bonds in PVC show absorption at 1670 cm^{-1} (Gilbert, 1984). The spectrum of surface modified plasticized PVC in this region is rather identical to unmodified PVC. No significant peak can be detected at 1670 cm^{-1} in both the spectra. This points to the fact that the extent of dehydrochlorination on sodium sulphide reacted PVC surface is not significant compared to substitution reaction.

3.2.3.2 X-ray Photoelectron Spectroscopy (XPS)

Since IR spectrum cannot provide direct evidence for the presence of sulphur atoms on the surface of modified PVC, further characterization was carried out by XPS. XPS is the ideal surface characterization technique, particularly for detecting sulphur atoms on surfaces. More XPS data have so far been reported for sulphur than for any other element (Swartz, 1973). An extensive study of sulphur compounds was done by Linberg (Linberg *et al.*, 1970). The binding energies of the core electrons are affected by the valence electrons and therefore by the chemical environment of the atom. So any factor that affect the electron density about an atom is expected to result in a chemical shift in its electron binding energy. Thus chemical shift can provide valuable information about the electronic environment of elements on the surface. This makes XPS a powerful tool for determining the exact nature of surface atoms. Hercules reported the first correlation chart of binding energies of sulphur 2p electrons and functional groups (Hercules, 1970). The range of S_{2p} binding energies is approximately 10 eV making possible the use of the chemical shift for structural studies in sulphur chemistry by XPS (Swartz, 1973). It has been reported that sulphides have the lowest S_{2p} binding energies, whereas the sulphates have the highest. Figure 3.2.3 shows the elemental survey spectra (0–1000 eV) from XPS analysis of the unmodified plasticized PVC (a), plasticized PVC reacted with sodium sulphide in the absence of PTC (b) and surface modified PVC (c). Since the flood gun of 10 eV was on during the scanning process, the binding energies have been corrected (Corr. BE.) by adding 10 eV to the observed value.

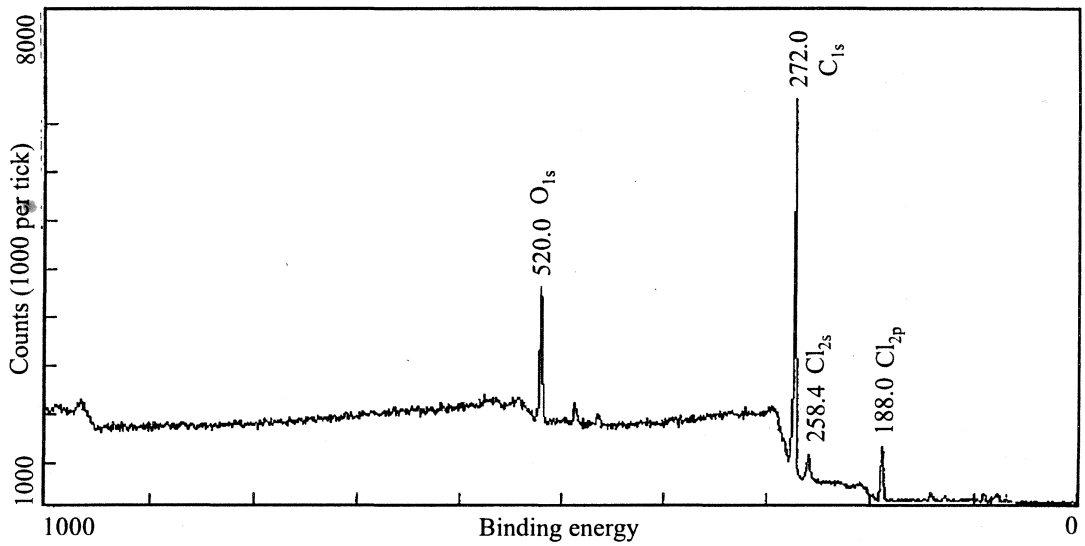


Fig. 3.2.3a XPS elemental survey spectrum of unmodified plasticized PVC sheet.

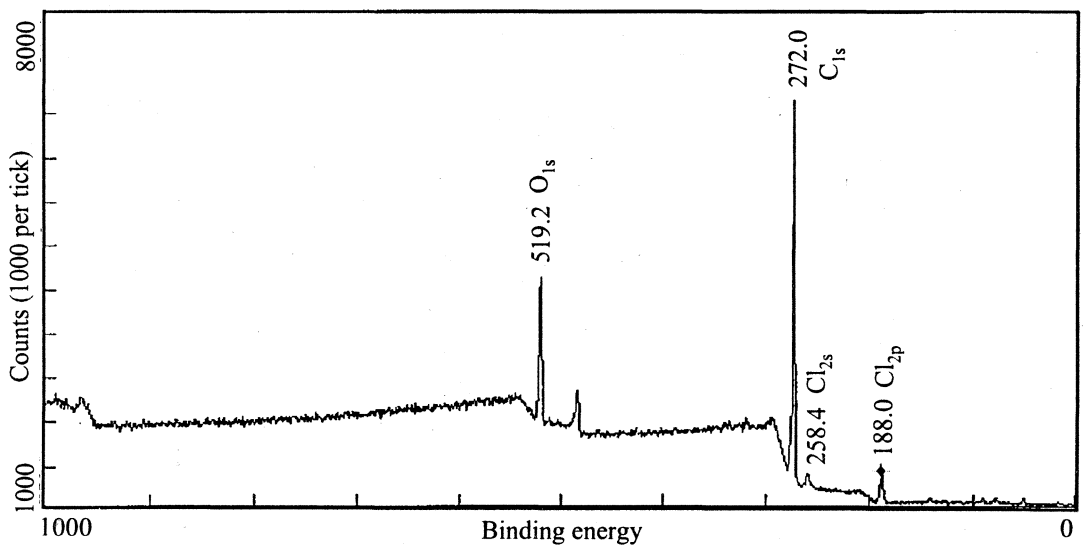


Fig. 3.2.3b XPS elemental survey spectrum of plasticized PVC sheet reacted with sodium sulphide in the absence of PTC at 80°C for 5 h.

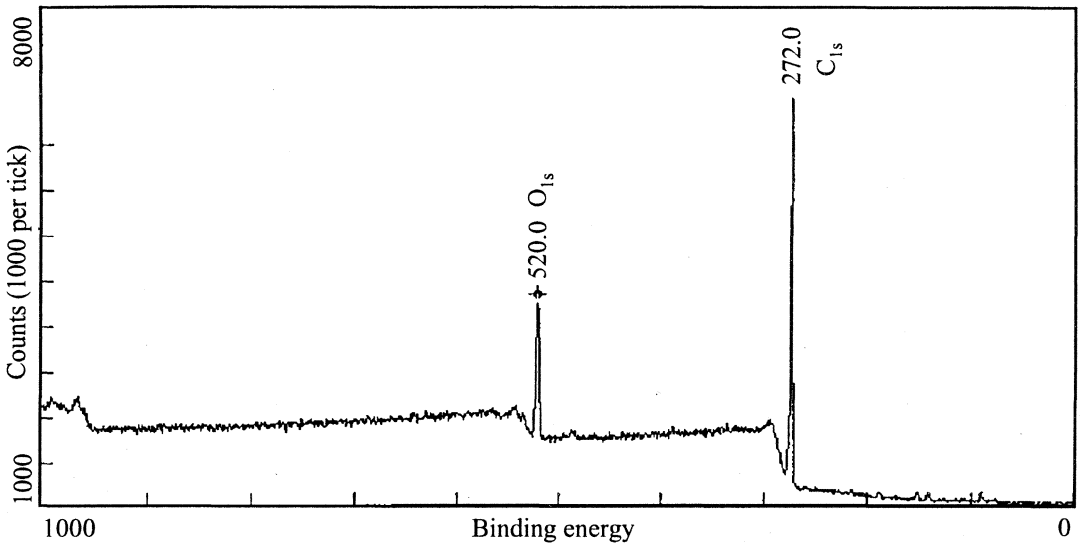


Fig. 3.2.3c XPS elemental spectrum of surface modified plasticized PVC sheet.

The spectra of unmodified plasticized PVC sheet (Figure 3.2.3a) and PVC sheet treated with sodium sulphide in the absence of PTC (Figure 3.2.3b) were exactly identical showing peaks for oxygen (O_{1s} at 519.2, Corr. BE. $\sim$ 530 eV), carbon (C_{1s} at 272, Corr. BE. $\sim$ 282 eV) and chlorine (Cl_{2s} and Cl_{2p} at 258.4 and 188 eV, Corr. BE. $\sim$ 269 and $\sim$ 200 eV respectively). On the other hand, some of the above peaks were absent in the corresponding spectrum of surface modified plasticized PVC (Figure 3.2.3c). The spectrum showed two prominent peaks. One at 520 eV (Corr. BE. $\sim$ 530 eV) for the oxygen O_{1s} electron and the other at 272 eV (Corr. BE. $\sim$ 282 eV) for the carbon C_{1s} electron. Contrary to what was expected, no peaks for sulphur or even chlorine atoms were present in the spectrum. This point to the fact that the surface concentration of the sulphur and chlorine atoms on surface modified plasticized PVC sheet may be very small to be detected from this survey scan.

The high resolution spectra in the 0-250 eV binding energy region, where the sulphur peaks can be effectively detected were taken for all the three samples (Figure 3.2.4). In this region, the spectra of the unmodified plasticized PVC sheet (Figure 3.2.4a) and sheet reacted with sodium sulphide in the absence of PTC (Figure 3.2.4b) were almost identical, whereas the PVC sheet reacted with sodium sulphide in the presence of PTC (TBAH) (Figure 3.2.4c) showed pronounced differences. The important peaks present in the spectrum of unmodified PVC can be assigned to chlorine, Cl_{2p} at 188 eV (Corr. BE. $\sim$ 200 eV); Silicon, Si_{2s} at 140.8 (Corr. BE. $\sim$ 151 eV) and Si_{2p} at 89.6 (Corr. BE. $\sim$ 100 eV); Zinc, Zn_{3s} at 127.2 (Corr. BE. $\sim$ 140 eV) and Zn_{3p} at 76.8 (Corr. BE. $\sim$ 87 eV) respectively. The spectrum of PVC sheet treated with sodium sulphide in the absence of PTC (Figure 3.2.4b) shows all the above peaks similar to unmodified PVC. In addition to these peaks the spectrum shows a peak at 50.4 (Corr. BE. $\sim$ 61 eV) corresponding to sodium, Na_{2s} electron. This may arise due to contamination from the sodium sulphide reagent used. As expected, the spectrum shows no peak for sulphur atom and so any chance of surface nucleophilic substitution and hence cross-linking in the absence of PTC can be eliminated. The spectrum of PVC sheet reacted with sodium sulphide in the presence of PTC shows a prominent peak at 150.4 (Corr. BE. $\sim$ 160.9 eV) due to the S_{2p} peak of sulphur atoms and another peak at 214.4 (Corr. BE. $\sim$ 225 eV) due to S_{2s} peak of sulphur atoms on the surface. The spectrum did not show any peak for sodium atom at 50.4 (Corr. BE. $\sim$ 61 eV). The presence of sulphur peaks clearly shows the substitution of chlorine atoms on the surface by sulphide anion resulting in sulphur cross-linking of the surface. The chlorine Cl_{2p} peaks shows significant decrease in intensity in this spectrum

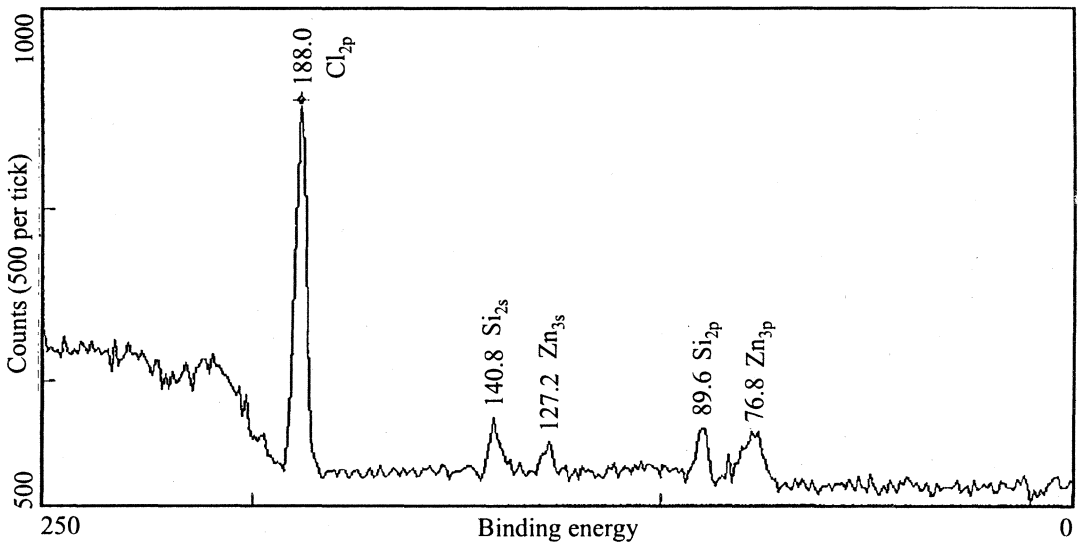


Fig. 3.2.4a XPS high resolution spectrum in the 0-250 eV region of unmodified plasticized PVC sheet.

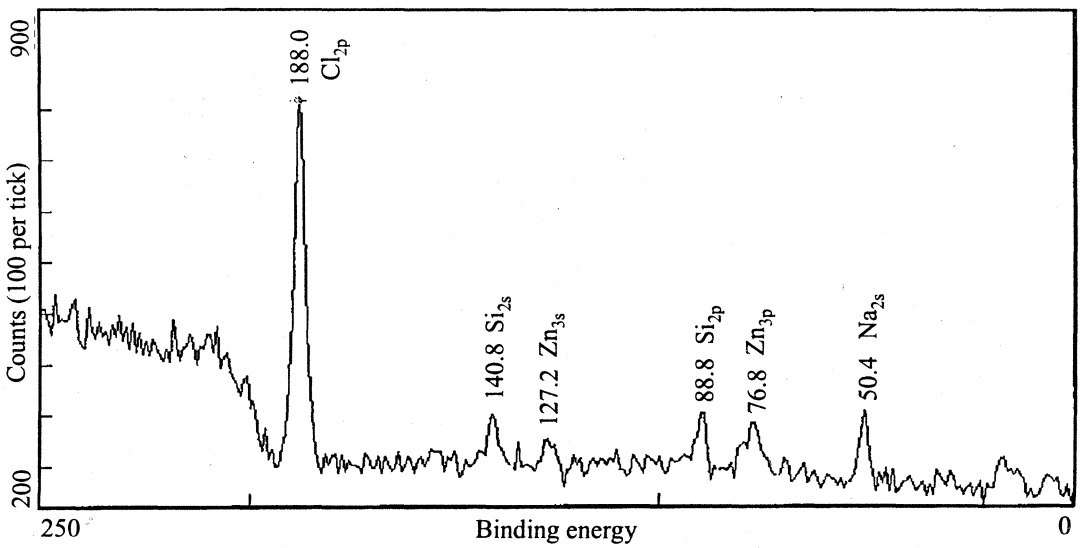


Fig. 3.2.4b XPS high resolution spectrum in the 0-250 eV region of plasticized PVC sheet reacted with sodium sulphide in the absence of PTC at 80°C for 5 h.

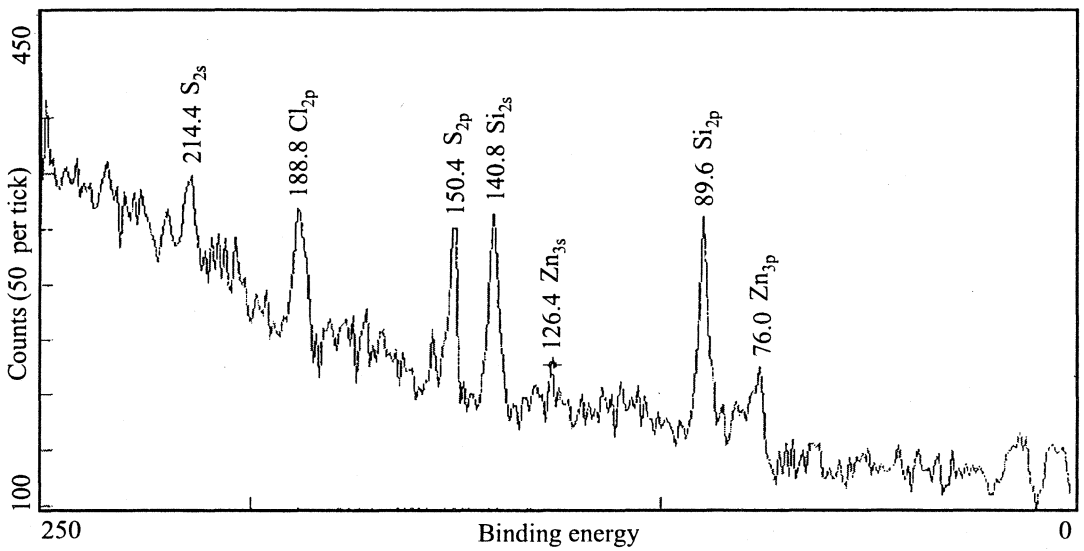


Fig. 3.2.4c XPS high resolution spectrum in the 0-250 eV region of surface modified plasticized PVC.

compared to the spectrum of unmodified PVC sheet. Table VIII shows the surface elemental composition as estimated from the wide scan data of XPS analysis and expressed as atom percent for the element detected.

Table VIII

Surface elemental composition as estimated from the wide scan XPS spectra of unmodified PVC sheet, sheet reacted with sodium sulphide at 80°C for 5 h in the absence of TBAH and sheet reacted with sodium sulphide in the presence of TBAH expressed as atom percent. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}

Sample	O_{1s}	C_{1s}	Cl_{2p}	S_{2p}	Zn_{3p}	Si_{2p}	Na_{2s}
Unmodified PVC	10	81	5.8	0	1.2	1.7	
PVC reacted with sodium sulphide	12	79	3.7	0	0.5	1.3	3.6
PVC reacted with sodium sulphide in presence of PTC	12	83	0.8	1.1	0.5	2.8	

Flexible PVC sheets used in medical and related applications contain various additives to improve its performance and processing capabilities as discussed in

section 1.3.3. These additives being not held onto base polymer by valence bonding can migrate to the surface of plasticized PVC. Therefore the presence of unexpected peaks for zinc, silicon and oxygen in the XPS spectra of plasticized PVC sheets are possibly due to these additives on the surface. Zinc possibly arise from zinc stearate stabilizers commonly used in medical grade PVC, silicon possibly from the lubricants used in extrusion or from atmospheric contamination and oxygen from the organic plasticizers as well as stabilizers used as additives in the compounded PVC. The IR spectra (Section 3.2.3.1; Figure 3.2.2) corroborates the presence of additives such as plasticizers on the surface of plasticized PVC. The table (Table VIII) clearly shows the presence of sulphur exclusively on surface modified PVC. The relative percentage composition of the sulphur atoms on the surface modified PVC is very small accounting to only 1.1%. Thus XPS analysis confirmed the presence of sulphur bridges on the surface of modified PVC. The major element present on the surface of unmodified and modified PVC sheet is carbon. Even though the theoretical composition of carbon and chlorine atoms in PVC is 67 and 33% respectively (Ratner *et al.*, 1993), the surface composition of chlorine atoms on plasticized PVC is usually found to be much less due to the presence of various other additives. The total concentration of chlorine on plasticized PVC has been reported by Ratner *et al* (1993) to be about 7-10% only. In the present case the percentage composition of chlorine atoms on the surface of plasticized unmodified PVC was found to be only 5.8%. The surface composition of chlorine atoms on the plasticized PVC sheet is highly variable and hence cannot be used as an indication of the extent of nucleophilic substitution. But the presence of sulphur atoms on the surface modified PVC can be taken as a clear indication of nucleophilic substitution

since sulphur atom is totally absent on unmodified plasticized PVC sheet as well as sheet treated with sodium sulphide in the absence of TBAH.

Figure 3.2.5 shows the high resolution spectra in the 148-168 eV region (where the S_{2p} electrons shows characteristic peak) of unmodified plasticized PVC (Figure 3.2.5a) as well as surface modified plasticized PVC sheet (Figure 3.2.5b). The unmodified PVC sheet shows no characteristic peak in this region (Figure 3.2.5a) whereas the surface modified plasticized PVC sheet shows the characteristic peak of sulphur (S_{2p} electrons) with a mean value of 151.73 eV (Corr. BE. $\sim$ 162.4 eV). The presence of sulphur S_{2p} peaks in the spectrum of surface modified plasticized PVC clearly established the presence of sulphur bridges on modified PVC sheet. Only a single peak for sulphur was present in the spectrum (Figure 3.2.5b) showing the presence of only one type of sulphur atoms on the surface. The low value of binding energy shows that all the sulphur present on the surface of modified PVC is in the reduced form ie., in the sulphide form which once again confirmed the formation of R-S-R type of cross-linking on the surface of modified PVC sheet.

Figure 3.2.6 shows the high resolution spectra of carbon C_{1s} of unmodified PVC sheet (Figure 3.2.6a), PVC sheet treated with sodium sulphide in the absence of PTC (Figure 3.2.6b) and surface modified plasticized PVC sheet (Figure 3.2.6c). Table IX shows the summary of the peak fit results for the C_{1s} narrow scan spectra of the sample set.

The chemical shift of C_{1s} electron of carbon atom depends on the electronegativity of the atom attached to it. Usually the C_{1s} spectrum can provide valuable information about the surface composition of polymers. The XPS

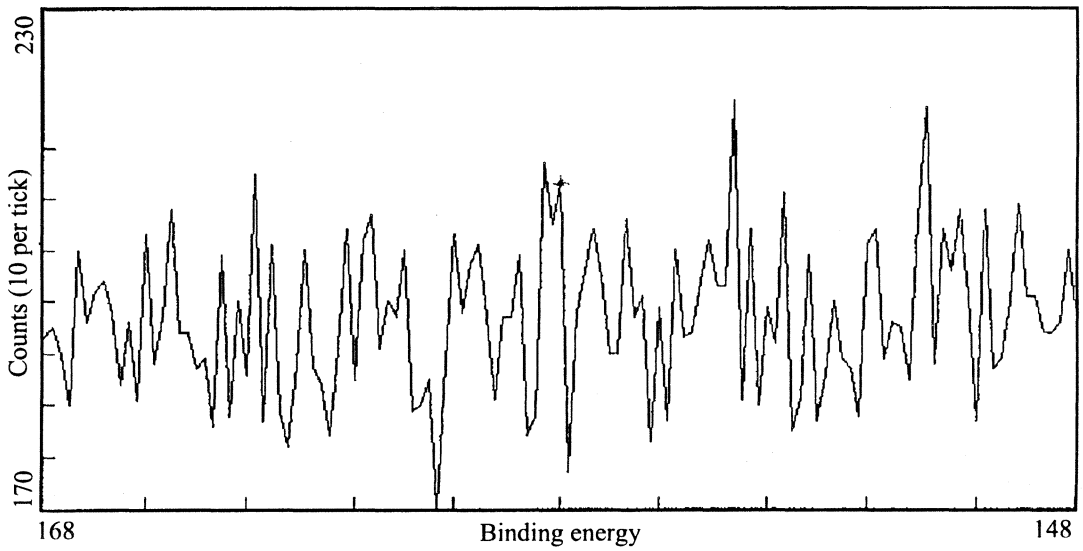


Fig. 3.2.5a XPS high resolution S_{2p} spectrum of unmodified plasticized PVC sheet.

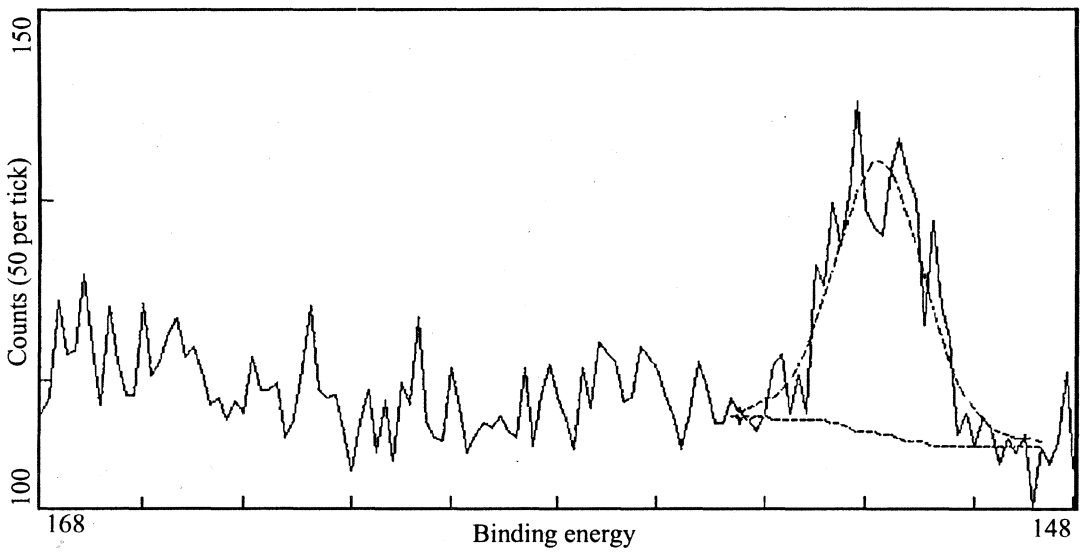


Fig. 3.2.5b XPS high resolution S_{2p} spectrum of surface modified plasticized PVC sheet.

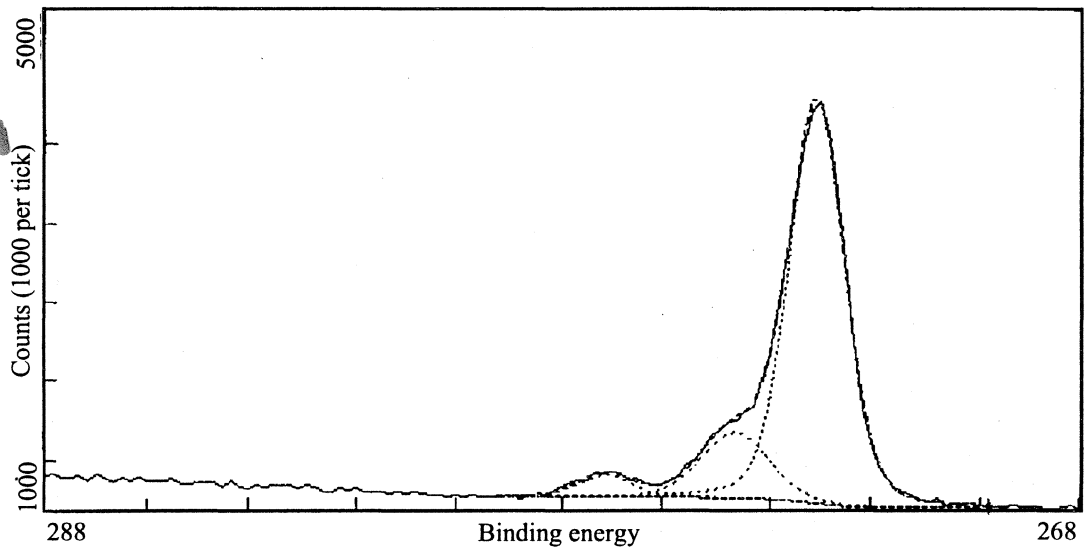


Fig. 3.2.6a XPS high resolution C_{1s} spectrum of unmodified plasticized PVC sheet.

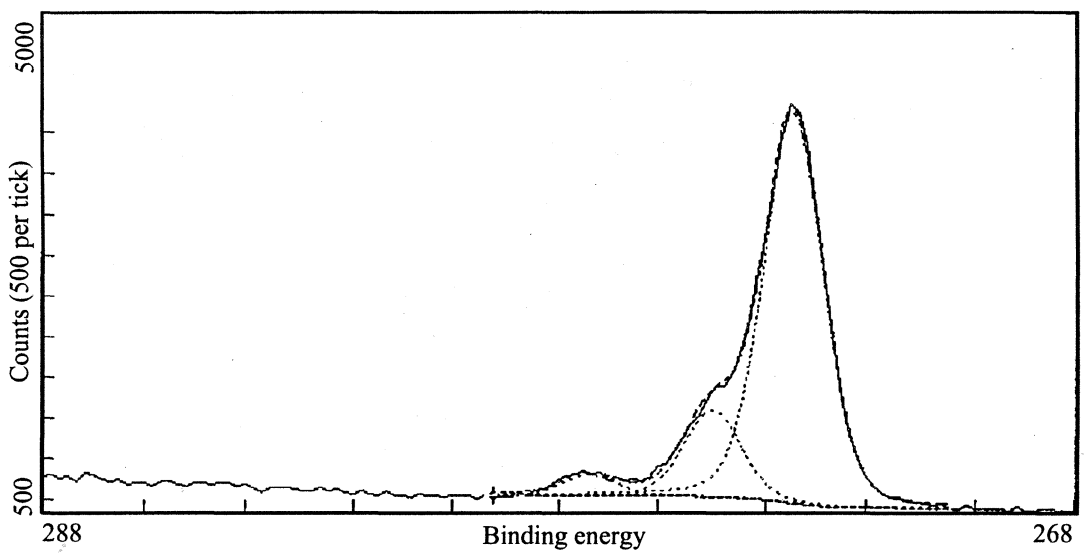


Fig. 3.2.6b XPS high resolution C_{1s} spectrum of plasticized PVC sheet reacted with sodium sulphide in the absence of PTC at 80°C for 5 h.

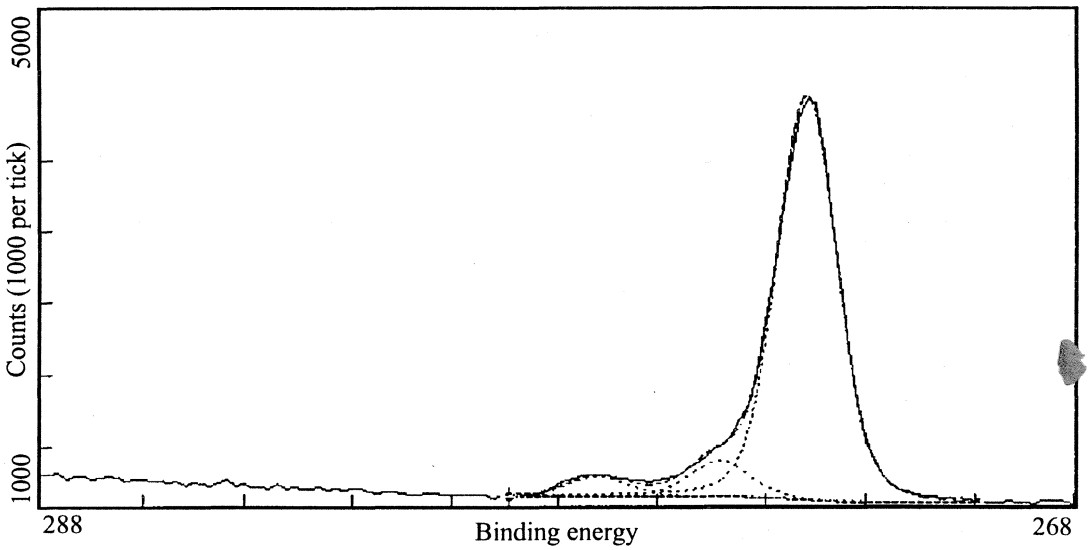


Fig. 3.2.6c XPS high resolution C_{1s} spectrum of surface modified plasticized PVC sheet.

spectrum of cast PVC sheet should show two peaks of equal intensity at 284 eV and 286 eV due to the presence of CH_2 carbon and due to CH–Cl carbon atom respectively. But the XPS spectrum of plasticized PVC sheet on the other hand shows prominent difference with two peaks having different intensity due to the small amount of chlorine atoms on the surface of plasticized PVC as discussed above. The XPS spectrum of plasticized PVC sheet shows three peaks, the characteristic peak near 284 eV is due to the CH_2 carbon atoms of PVC, whereas the peak at 286 eV is due to the CH–Cl carbon atoms of PVC. The peak near 288 eV is due to carbonyl oxygen, which arise from the presence of additives such as plasticizers on the surface of PVC sheet (Ratner *et al.*, 1993). The C_{1s} peaks in the spectra of unmodified plasticized PVC (Figure 3.2.6a) and PVC sheet reacted with sodium sulphide in the absence of PTC (Figure 3.2.6b) were found to be identical to that reported by Ratner *et al* (1993). In the spectrum of surface modified

PVC sheet (Figure 3.2.6c) there was a characteristic shift of 286 eV peak towards the lower binding energy region and the percentage composition corresponding to peak near 286 eV decreased showing the substitution of chlorine atoms (Table IX). Since sulphur atom is having a slightly lower electronegativity value compared to chlorine atom, the substitution of chlorine by sulphur atoms naturally decreases the binding energy of the C_{1s} electrons due to greater shielding by the core electrons and hence peak shifts towards the lower energy level. So the high resolution C_{1s} spectra of unmodified and surface modified PVC sheet indirectly gives evidence for the presence of sulphur bridges on the surface of modified PVC.

Table IX
Summary of the peak fit results for the C_{1s} narrow scan spectra of unmodified plasticized PVC sheet, PVC sheet reacted with sodium sulphide at 80°C for 5 h in the absence of PTC, PVC sheet reacted with sodium sulphide in the presence of TBAH. [Sodium sulphide] = 7 mol dm^{-3} and [TBAH] = 0.15 mol dm^{-3}

Sample	Corr. BE.	% surface composition
Unmodified	284.6	65.0
	286.2	12.7
	288.7	3.4
Sodium sulphide alone	284.6	63.1
	286.1	13.2
	288.5	3.0
Sodium sulphide + PTC	284.6	72.4
	286.2	6.5
	288.6	3.6

3.2.3.3 Gel Content Estimation

The nucleophilic substitution of sulphide anion for two chlorine atoms on the surface of PVC naturally produces a surface cross-linked gel, insoluble in normal

solvents of PVC. The extent of gel formed on the surface of modified PVC can be estimated after isolating the gel from the surface. The surface cross-linked gel was isolated by dissolving modified PVC in THF as discussed in section 2.2.8.8. Except the surface cross-linked gel, the PVC and all the other additives present in it are completely soluble in THF. The surface cross-linked gel isolated from surface modified plasticized PVC tubes by dissolving it in THF was in the form of a light yellow thin fibrous sheet. Figure 3.2.7 shows the gel content in weight percent determined gravimetrically from surface modified plasticized PVC tubes as a function of time of reaction. Surface cross-linked gel was found to be formed on tubes even within 5 min of reaction with sodium sulphide in the presence of PTC at 80°C. The gel content isolated from plasticized PVC tube was found to increase with time of reaction initially and reached almost a constant value after about 4 h of reaction at 80°C. The maximum gel content obtained after 4 h of reaction corresponds to about 1.35% of the weight of the plasticized PVC tube. This low value of gel content shows that the formation of gel is highly surface confined. As in the case of photocross-linked DTC-PVC tubes (Section 3.1.3.2), the gel obtained was found to be completely insoluble in almost all solvents including water, but swells in solvents of PVC such as THF and cyclohexanone.

3.2.3.4 Sulphur Estimation

The presence of sulphur linkages on the surface of modified PVC was further confirmed by quantitatively estimating the amount of elemental sulphur present in the surface cross-linked gel (Section 2.2.8.9). The surface cross-linked gel from modified PVC was found to contain 1.9% by weight of sulphur whereas no sulphur

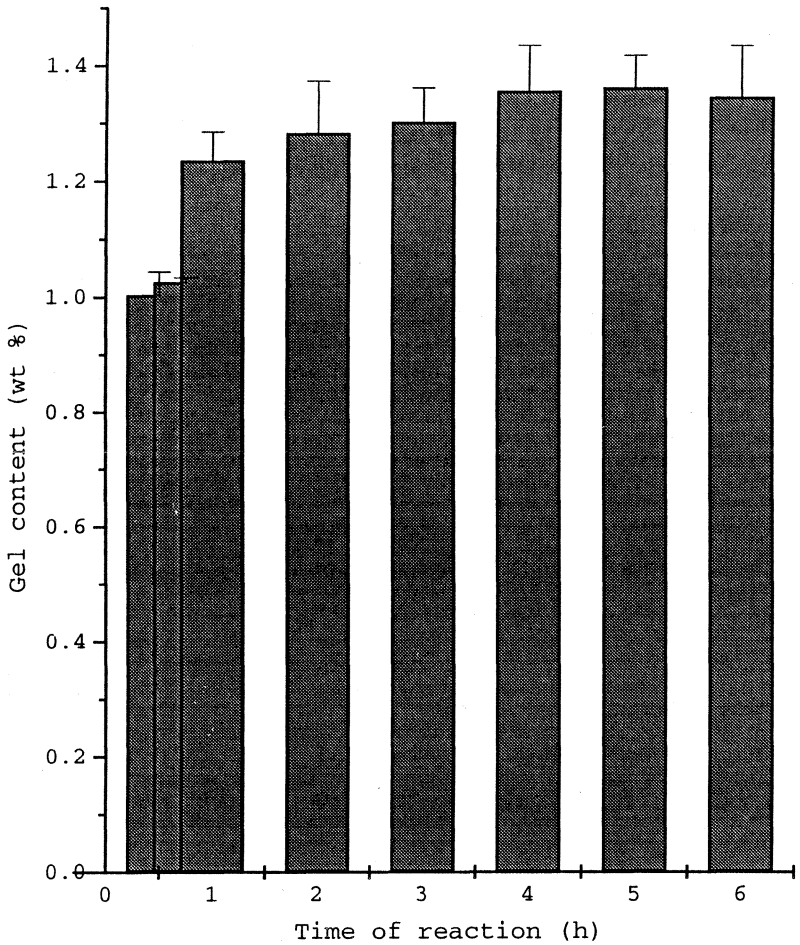


Fig. 3.2.7 Amount of gel formed as a function of time of reaction from plasticized PVC tubes reacted with sodium sulphide in the presence of TBAH at 80°C for various periods of time. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}.

was detected in unmodified plasticized PVC sheet. These results corroborate the XPS observations discussed earlier (Section 3.2.3.2). The amount of sulphur present in the gel isolated from surface modified plasticized PVC was found to be much less compared to plasticized PVC reacted with DTC (Section 3.1.3.3).

3.2.3.5 Surface Morphology

Figure 3.2.8 shows the SEM of the unembossed surface of unmodified plasticized PVC sheet (a) and surface modified plasticized PVC sheet (b) (Section 2.2.8.3). There appeared to be no significant changes in the surface morphology of the sheets before and after surface modification. Surface cross-linking therefore does not produce any significant changes in the surface morphology of sheets.

3.2.3.6 Optical Clarity

As discussed in section 3.1.3.5 the optical clarity of PVC based devices are very important in most of its medical applications. Due to reasons discussed there, plasticized PVC tubes were used for comparing the optical clarity of unmodified and surface modified plasticized PVC. The percentage transmittance of the plasticized unmodified PVC tube, tube reacted with sodium sulphide in the absence of PTC and surface modified PVC tubes in the visible range (400–700 nm) is shown in Figure 3.2.9 (Section 2.2.8.10). The percentage transmittance of unmodified PVC tube and tube reacted with sodium sulphide in the absence of PTC are identical. The percentage transmittance of the surface modified tube was also found to be almost similar to that of unmodified PVC tube. The transmittance

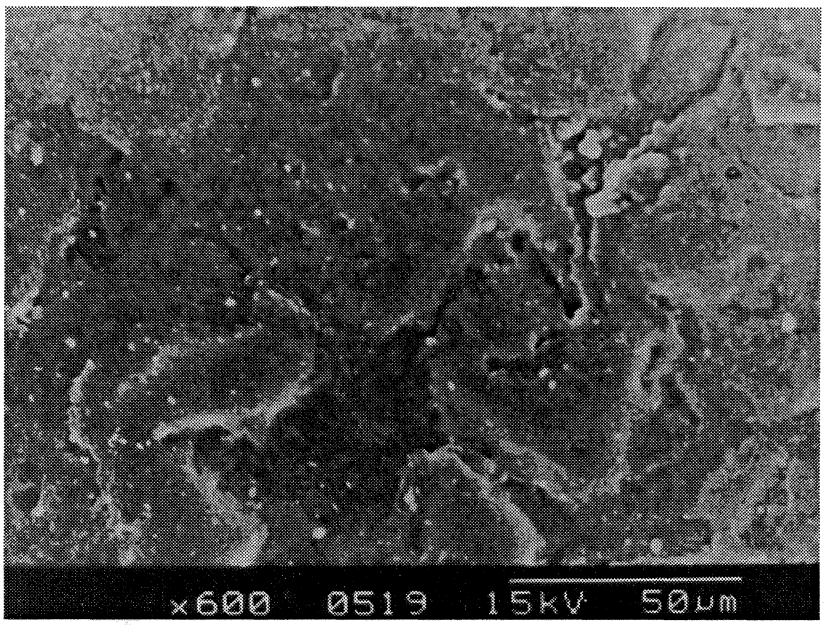


Fig. 3.2.8a SEM of unmodified plasticized PVC sheet.

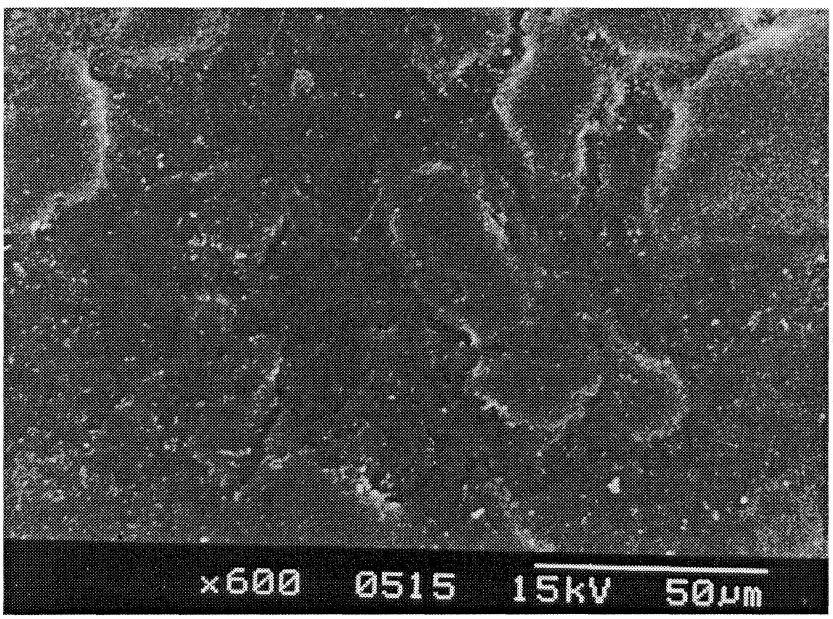


Fig. 3.2.8b SEM of plasticized PVC sheet reacted with sodium sulphide in the presence of TBAH at 80°C for 5 h. [TBAH] = 0.15 mol dm^{-3}; [Sodium sulphide] 7.0 mol dm^{-3}.

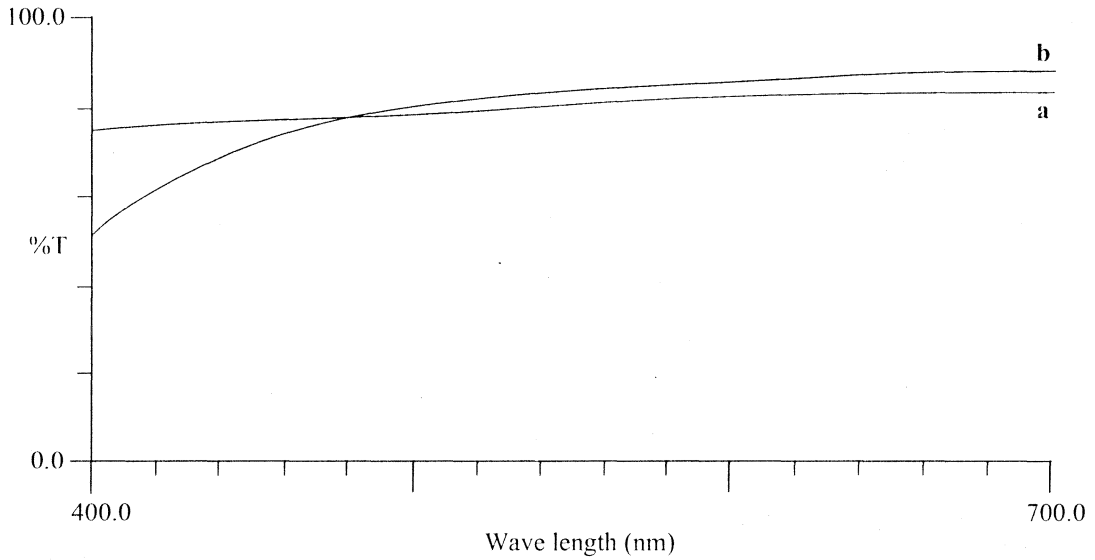


Fig. 3.2.9 The percentage transmittance of unmodified plasticized PVC tube and PVC tube reacted with sodium sulphide in the presence of TBAH at 80°C for 5 h in the 400–700 nm range. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}; Unmodified (a) and Surface modified (b).

showed a slight decrease in the region below about 500 nm possibly due to presence of sulphur atom on the surface. Formation of conjugated double bonds accompanying dehydrochlorination can also lead to absorption below 500 nm. However, since no such conjugation was detected by the IR spectra, it is believed that the slight decrease in transmittance below the 500 nm region is possibly due to the presence of sulphur on the specimen.

3.2.3.7 Percentage Water Absorption

The surface modified plasticized PVC showed a slight tendency to absorb water upon incubation in distilled water compared to unmodified plasticized PVC sheet. Figure 3.2.10 shows the percentage water absorption by weight of unmodified

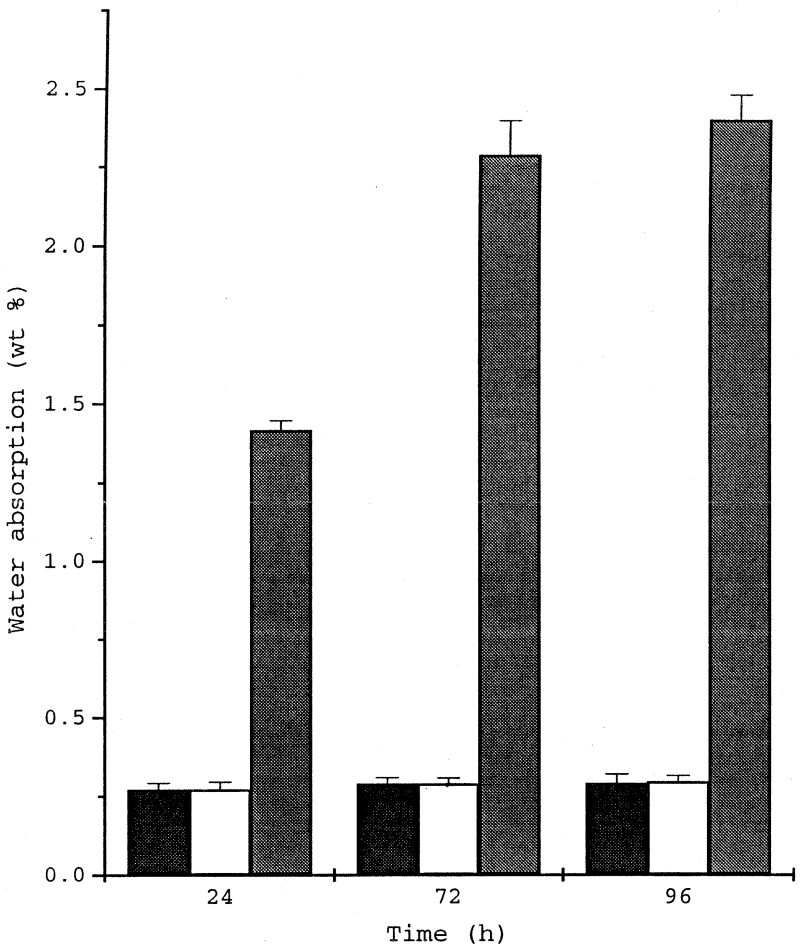


Fig. 3.2.10 Percentage water absorption as a function of time of incubation of unmodified plasticized PVC sheet and sheet reacted sodium sulphide in the presence and absence of TBAH at 80°C for 5 h. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}; Unmodified (■), PVC reacted with sodium sulphide in the absence of TBAH (□) and PVC reacted with sodium sulphide in the presence of TBAH (■).

plasticized PVC sheet, plasticized PVC sheet reacted with sodium sulphide in the absence of PTC and surface modified plasticized PVC sheet after 24, 72 and 96 h of incubation in distilled water (Section 2.2.8.2). The amount of water absorbed by unmodified plasticized PVC sheet and sheet reacted with sodium sulphide in the absence of PTC were found to be identical. The surface modified PVC sheet absorbs about 1.4% by weight of water whereas the unmodified plasticized PVC sheet absorbs only 0.2% water in 24 h. Sulphur atoms are known to have only a very weak tendency of hydrogen bonding compared to oxygen atoms (Lee, 1983). However, the water absorption shown by surface modified plasticized PVC can only be explained due to such weak hydrogen bonding by sulphur atoms and possibly by the plasticization of water molecules in the interstitial space of the cross-linked surface.

3.2.3.8 Contact Angle

The absorption of water by the surface cross-linked PVC sheet was further confirmed by measuring the under water air and octane contact angles of surface modified plasticized PVC sheet compared to unmodified plasticized PVC sheet (Section 2.2.8.4). Table X shows the air and octane contact angles of unmodified plasticized PVC sheet and surface modified plasticized PVC sheet after incubation in water for 24 h. The surface modified plasticized PVC sheet after incubation in water shows a significant reduction in the contact angles compared to the unmodified PVC sheet. This low value of contact angle of modified PVC is presumably due to the presence of water molecules on the surface of the incubated

samples. This provides an additional evidence for the incorporation of water molecules within the cross-linked matrix of surface modified PVC sheet.

Table X
Air and octane contact angles for the unmodified plasticized PVC sheet and sheet reacted with sodium sulphide in the presence of TBAH at 80°C for 5 h. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}

Sample	Contact angle (°)	
	Air	Octane
Unmodified PVC	60.3±3	85.7±4
Surface modified PVC	36.5±1	47.3±3

3.2.4 Migration Resistance of Surface Modified PVC

3.2.4.1 Optimization of Reaction Conditions

The optimum reaction conditions for the preparation of migration resistant plasticized PVC by surface cross-linking was determined by following the plasticizer migration from tubes reacted by varying the reaction parameters such as time, temperature, concentration of reagents etc. Figure 3.2.11 shows the extent the plasticizer migration from plasticized PVC tubes reacted with sodium sulphide in the presence of various PTCs. The various PTCs employed in this reaction were quaternary salts like TBAH, TBAB, TBAI, HTMAB, BEAC and macrocyclic ether such as 18-crown-6. The extraction of DEHP from the surface modified PVC tubes were carried out in petroleum ether for 48 h at 30°C. Apparently no reaction was taking place in the presence of HTMAB, BEAC and 18-crown-6 as evidenced by the extent of migration from modified PVC tubes being almost similar to that of unmodified PVC tubes after 48 h of incubation in petroleum ether. HTMAB

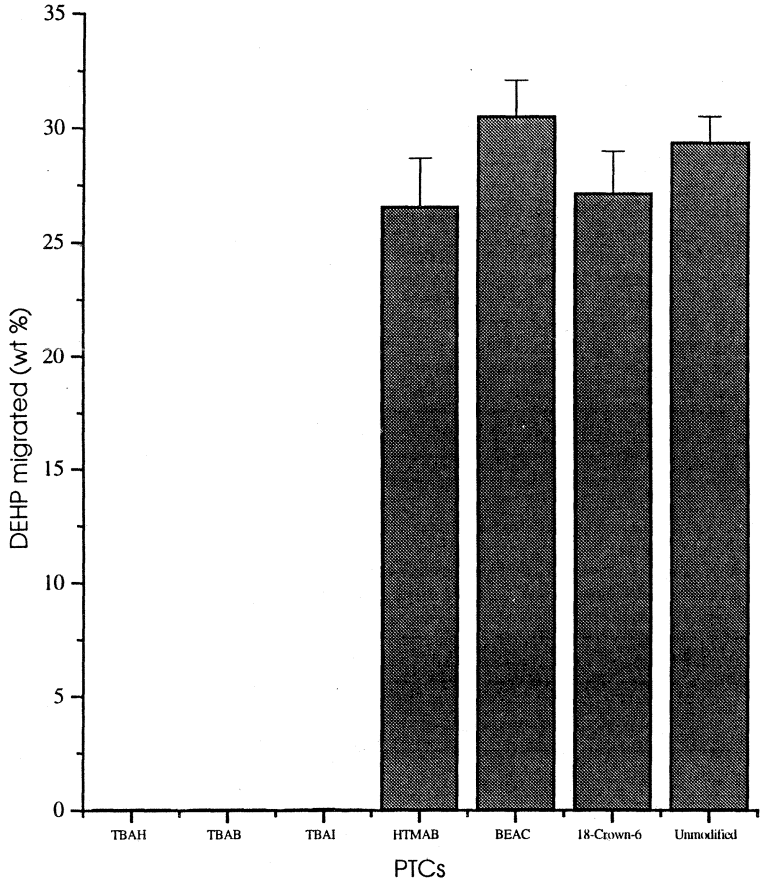


Fig. 3.2.11 Amount of DEHP migrated in 48 h into petroleum ether at 30°C from unmodified plasticized PVC tubes and tubes reacted with sodium sulphide in the presence of various PTCs at 80°C for 5 h. [Sodium sulphide] = 7 mol dm^{-3}; [PTC] = 0.15 mol dm^{-3}.

similar to that of CPC, discussed in the previous chapter (Section 3.1.4) is a good emulsifying agent rather than a good PTC since it is having only one long alkyl group and three small methyl groups ($C_6H_{13}N^+(CH_3)_3Br^-$). These surfactants have a tendency to form micelles and remain in the aqueous phase rather than to transfer the anion to organic phase. This clearly shows that surfactants cannot carry anion transfer onto solid PVC surface. BEAC ($C_6H_5CH_2(C_2H_5)_2N^+Cl^-$) has been widely used for a variety of reactions, particularly alkylation and dichlorocarbene reaction, but it is usually a poor catalyst for simple displacement reaction. BEAC does not have much lipophilicity to get partitioned well into the organic phase. Usually the highly reactive benzyl group undergoes intermolecular displacements and hence decomposes during its use as catalyst. In this solid-liquid PTC reaction, BEAC was found to be least effective among the catalysts studied. The most versatile catalyst for the liquid-solid PTC reaction, 18-crown-6 was found to be quite ineffective in this substitution reaction similar to that of DTC substitution discussed in the previous chapter. The ion pairs formed as a result of crown ether complexes as well as with BEAC are not sufficiently lipophilic to effect efficient transfer of anions onto solid PVC surface. It was found that the tetrabutylammonium salts were the most versatile catalysts for this two phase solid-liquid nucleophilic substitution reaction similar to DTC substitution discussed in the previous chapter (Section 3.1.4). Catalysts where all the alkyl chains are butyl or larger appear to activate anions strongly because they provide for near-maximum cation-anion interionic distances and hence very efficient for various displacement reactions (Starks & Liotta, 1978). Both TBAH and TBAB were found to be equally efficient for the substitution reaction. TBAI was also found to transfer the sulphide

anions efficiently onto solid PVC surface as evidenced by the very low plasticizer migration value. But the extent of migration can be considered to be slightly higher than that from tubes modified in the presence of TBAH and TBAB. Among the two efficient catalysts TBAH and TBAB, TBAH was chosen as the PTC for further studies.

The effect of concentration of the reactants upon the extent of plasticizer migration was determined by varying the concentrations of sodium sulphide and TBAH. Figure 3.2.12 shows the amount of DEHP migrated as a function of time from plasticized PVC tubes reacted in the presence of different concentrations of TBAH at a constant concentration of sodium sulphide (7 mol dm^{-3}). Since it is difficult to differentiate the values below a catalyst concentration of 0.05 mol dm^{-3} the corresponding values are given in the form of Table also. Table XI shows the amount of DEHP migrated into petroleum ether at 30°C from PVC tubes reacted with sodium sulphide (7 mol dm^{-3}) at 80°C for 5 h in the presence of various concentrations of TBAH (0.01–0.2 mol dm^{-3}). The table clearly shows that the amount of catalyst required to achieve effective substitution was very small similar to that discussed in the previous chapter. As the concentration of TBAH was increased, initially an improvement in plasticizer migration resistance was observed. As discussed in the previous chapter, at a catalyst concentration of 0.01 mol dm^{-3} the extent of substitution was not very high as evidenced from the migration data. At catalyst concentrations of 0.05 and above, a significant reduction in plasticizer migration was achieved. Here also unlike ordinary PTC mediated reactions the extent of substitution is not linearly dependent on catalyst concentration. The rate of reaction with solid PVC was found to be constant

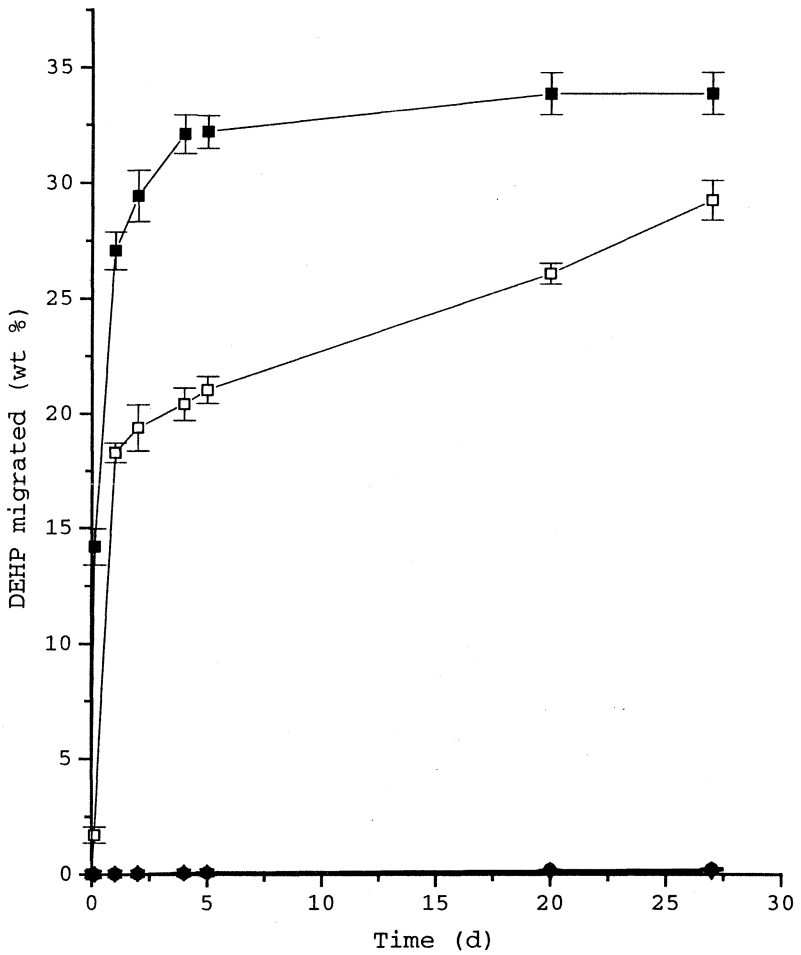


Fig. 3.2.12 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from unmodified plasticized PVC tubes and PVC tubes reacted with sodium sulphide in the presence of various concentrations of TBAH at 80°C for 5 h. Unmodified PVC (■), [TBAH] = 0.01 (□), 0.05 (○), 0.1 (▲), 0.15 (▼) and 0.2 (♦) mol dm^{-3}.

above a certain level of catalyst concentration as discussed in the previous chapter. The reason as cited earlier was possibly due to the aggregation of quaternary salt sulphide around or through the polymer chains, and that the adsorbed quaternary salts reacts with PVC in a bimolecular process.

Table XI
Amount of DEHP migrated into petroleum ether at 30°C expressed as weight percentage from unmodified PVC tubes as well as tubes reacted with sodium sulphide in the presence of various concentrations of TBAH at 80°C for 5 h. [Sodium sulphide] = 7 mol dm^{-3}

Time of release (d)	TBAH concentration in mol dm^{-3}					
	0.01	0.05	0.1	0.15	0.2	Unmodified
0.125	1.71	0.004	0.005	0.005	0.007	14.19
1	18.3	0.01	0.019	0.011	0.034	27.07
2	19.38	0.03	0.03	0.02	0.035	29.42
4	20.42	0.05	0.06	0.06	0.08	32.1
5	21.04	0.07	0.075	0.07	0.09	32.2
20	26.05	0.18	0.15	0.09	0.18	33.8
27	29.21	0.21	0.18	0.11	0.22	33.8

Figure 3.2.13 shows the extent of plasticizer migration from PVC tubes reacted with various concentrations of sodium sulphide (2–7 mol dm^{-3}) at 80°C for 5 h at a constant concentration of TBAH (0.15 mol dm^{-3}). At a nucleophile concentration of 2 mol dm^{-3}, the pattern of plasticizer migration was almost similar to that of unmodified PVC tubes. From a concentration of 4 mol dm^{-3} onwards, a significant reduction in migration profile was observed. The PTC mediated reactions are highly sensitive to the concentration of the inorganic salt present. Almost concentrated solutions are always beneficial for this type of reaction (Starks & Liotta, 1978). This is because when the aqueous medium became concentrated the medium efficiently partition the catalyst towards the organic phase and hence greatly facilitating the

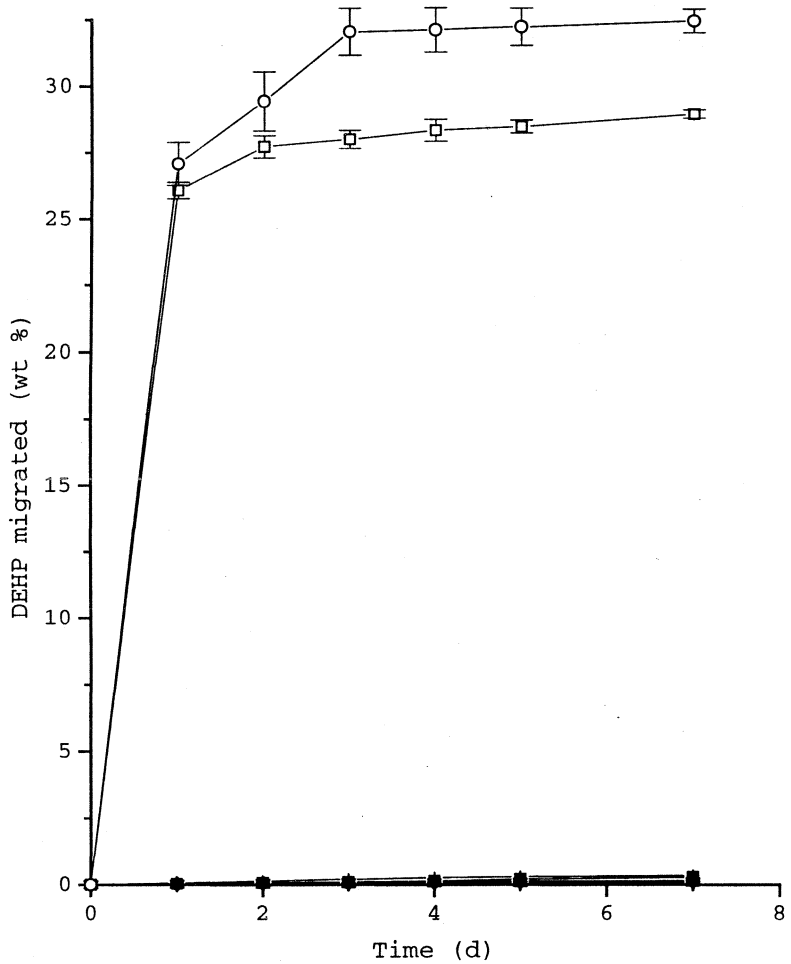


Fig. 3.2.13 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from unmodified plasticized PVC tubes and tubes reacted with various concentrations of sodium sulphide in the presence of TBAH at 80°C for 5 h. [TBAH] = 0.15 mol dm^{-3}; Unmodified PVC (o), [Sodium sulphide] = 2 (□), 4 (+); 5 (♦), 6 (▼) and 7 (▲) mol dm^{-3}.

substitution reaction. Plasticized PVC tubes reacted with sodium sulphide having concentrations of 5, 6 and 7 mol dm^{-3} showed very low plasticizer migration. The least migration level was found at a concentration of 7 mol dm^{-3}. Since this figure also cannot differentiate between the values, the corresponding values are given in Table XII. So an optimum nucleophile concentration of 7 mol dm^{-3} was used thought out the experiment.

Table XII
Amount of DEHP migrated into petroleum ether at 30°C expressed in weight percentage from unmodified plasticized PVC tubes as well as tubes reacted with various concentrations of sodium sulphide in the presence of TBAH at 80°C for 5 h. [TBAH] = 0.15 mol dm^{-3}

Time of release (d)	Concentration of sodium sulphide (mol dm^{-3})					
	2	4	5	6	7	Unmodified
1	26.07	0.06	0.02	0.02	0.011	27.07
2	27.71	0.13	0.05	0.05	0.02	29.42
3	27.98	0.2	0.07	0.07	0.03	32.03
4	28.32	0.27	0.08	0.08	0.06	32.10
5	28.45	0.3	0.1	0.09	0.07	32.20
7	28.9	0.34	0.11	0.10	0.08	32.40

The optimum time required for adequate surface cross-linking to prevent plasticizer migration was determined by following the plasticizer migration from tubes reacted for different periods of time. Figure 3.2.14 shows the extent of plasticizer migration from PVC tubes reacted with sodium sulphide (7 mol dm^{-3}) in the presence of TBAH (0.15 mol dm^{-3}) at 80°C for various periods of time. It was found that there is a dramatic decrease in plasticizer migration even from tubes reacted for 2h. Tubes reacted with sodium sulphide for 1 h showed only a slight decrease in plasticizer migration compared to that of unmodified PVC tube. The minimum plasticizer migration was observed from PVC tubes reacted for 4 h and

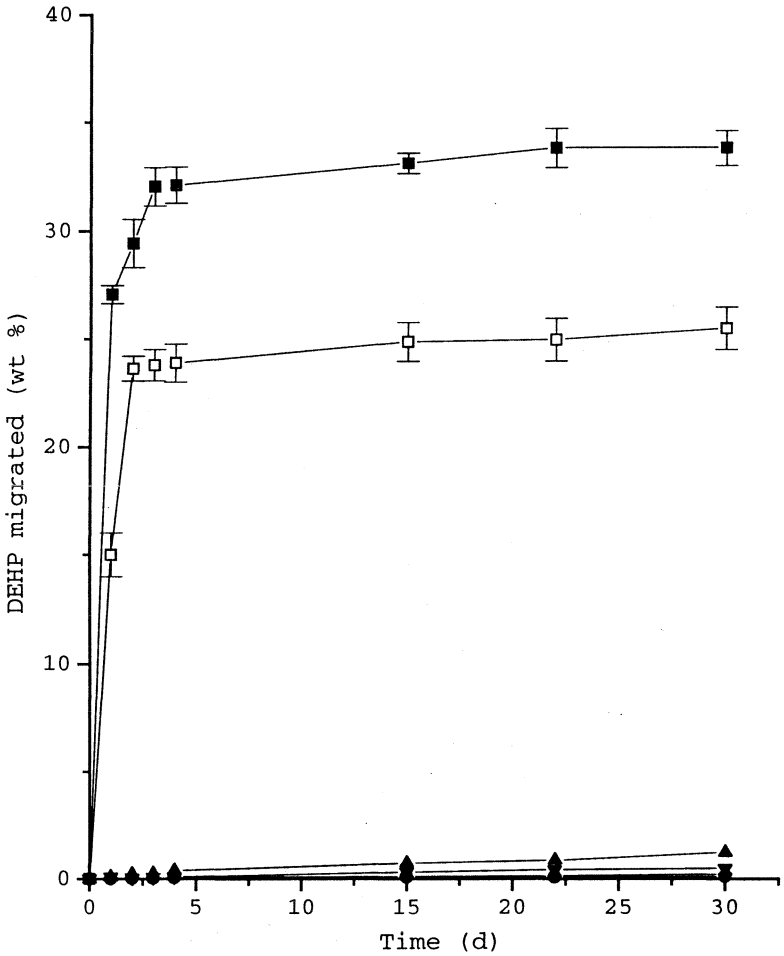


Fig. 3.2.14 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from unmodified plasticized PVC tubes and tubes reacted with sodium sulphide in the presence of TBAH at 80°C for various periods of time. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}; Unmodified PVC (■), Time of reaction 1 h (□), 2 h (▲), 3 h (▼), 4 h (♦), 5 h (○) and 6 h (●).

above. So a standard reaction time of 5 h was fixed for the modification. These observations were in turn corroborated by the gel content estimation of modified tubes (Section 3.2.3.3)

Figure 3.2.15 shows the extent of plasticizer migration form PVC tubes reacted with sodium sulphide (7 mol dm^{-3}) in presence of TBAH (0.15 mol dm^{-3}) for 5 h at different temperatures ie., 60, 70 and 80°C. The extent of migration was found to decrease as the temperature increases. As the temperature of reaction increases the migration resistance of the modified tubes increases. This can be attributed to greater extent of surface cross-linking at higher reaction temperature. The least migration was observed with tubes modified at 80°C. So the optimum temperature for the preparation of migration resistant PVC was fixed as 80°C.

3.2.4.2 Plasticizer Migration Over Prolonged Periods

Since migration experiments described so far have shown that surface modified PVC was highly migration resistant, the migration resistance of such modified material was examined over a 6 months period. Figure 3.2.16 shows the amount of plasticizer migrated into petroleum ether from surface modified PVC tubes reacted under standard reaction conditions. For comparison, migration from unmodified PVC tube as well as tube reacted with sodium sulphide in the absence of PTC is also shown in the figure. As can be seen, the surface modified PVC tube remains completely migration resistant even after 6 months of incubation in petroleum ether which is a potential extractant of DEHP, whereas the unmodified PVC tubes lost almost all its plasticizer within 24 h. It was found that the PVC tube reacted with sodium sulphide in the absence of PTC showed the same migration pattern as that

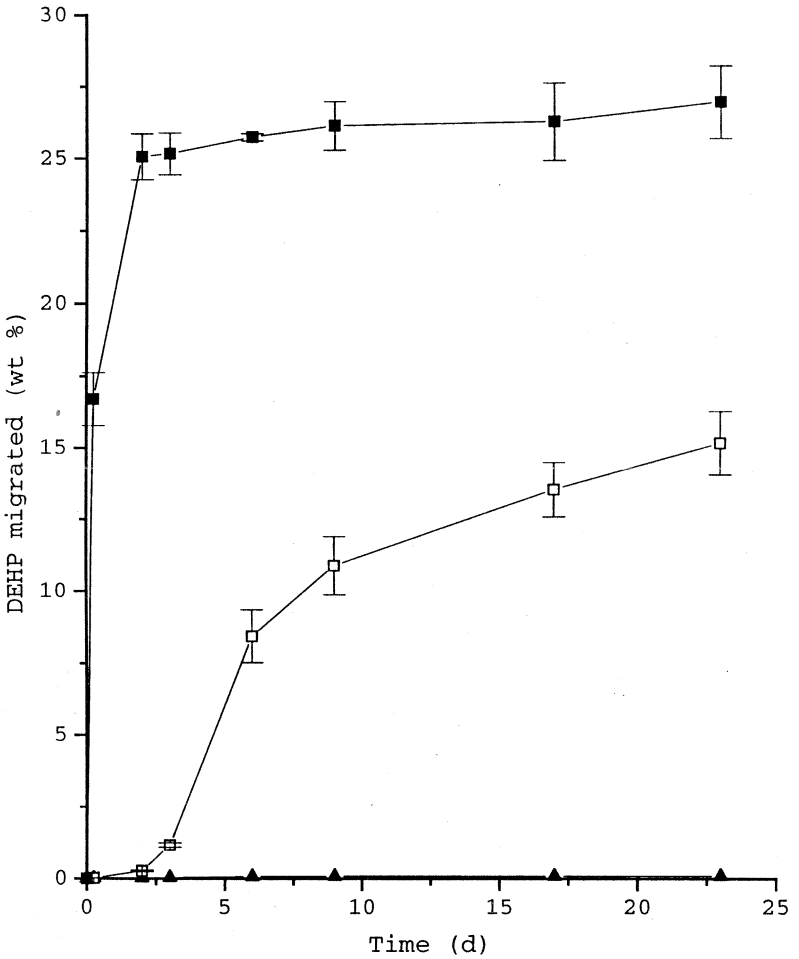


Fig. 3.2.15 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from plasticized PVC tubes reacted with sodium sulphide in the presence of TBAH for 5 h at various temperatures. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH = 0.15 mol dm^{-3}; Temperature = 60°C (■), 70°C (□) and 80°C (▲).

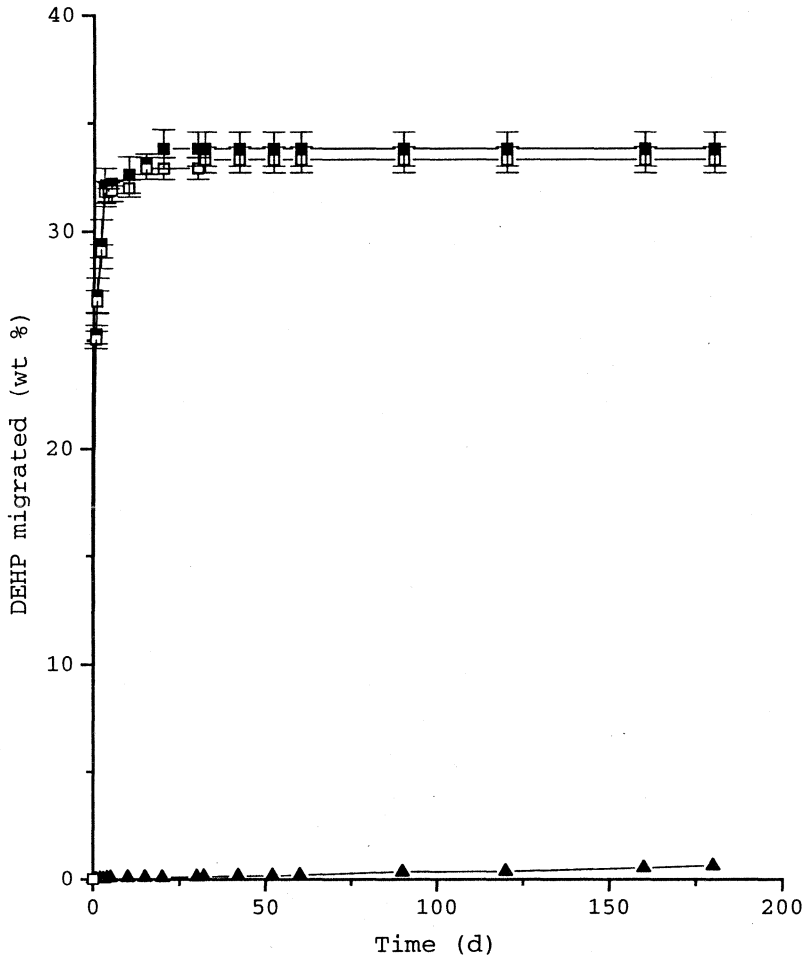


Fig. 3.2.16 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from unmodified plasticized PVC tubes and tubes reacted with sodium sulphide in the presence and absence of TBAH at 80°C for 5 h. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}; Unmodified PVC (■), PVC reacted with sodium sulphide in the absence of TBAH (□) and PVC reacted with sodium sulphide in the presence of TBAH (▲).

of unmodified PVC. In order to examine whether there is any significant loss of the plasticizer DEHP into the reaction medium the weight of the tubes before and after reaction was determined. No significant weight loss of PVC tubes was observed during modification. PVC tubes were reacted with sodium sulphide (7.0 mol dm^{-3}) at 80°C for 5 h in the absence of TBAH and in the presence of TBAH. As controls, tubes were heated in water at 80°C for 5 h. Table XIII shows the weight of the PVC tubes before and after reaction as well as the percentage decrease in weight. Plasticizer loss was very negligible in the case of specimens heated in water whereas the weight loss seen in the case of tubes treated with sodium sulphide in the absence and in the presence of TBAH was slightly higher. The slightly higher weight loss seen in the case of tubes reacted with sodium sulphide in the absence of TBAH compared to PVC in water alone can be attributed to the highly alkaline nature of the reaction medium facilitating the extraction of additives to a slightly higher extent than pure water. In the case of tubes reacted with sodium sulphide in the presence of TBAH, the weight loss is more than that observed in the case of specimen reacted with sodium sulphide alone. It is speculated that this higher value results from the substitution of two chlorine atoms of PVC by one sulphur atoms and also due to the alkaline medium facilitating the extraction of slightly larger amount of DEHP and other additives in PVC.

The extent of plasticizer (DEHP) migration into the reaction medium from plasticized PVC tube reacted with sodium sulphide in the presence of TBAH was quantified by extracting the reaction medium with hexane and estimating the DEHP content spectrophotometrically at 275 nm. The extractant medium shows only a very small amount of DEHP corresponding to only about 0.05 weight percent

of tube. This clearly shows that insignificant extent of DEHP migration was taking place into the reaction medium while modification and hence the migration resistance observed is mainly due to surface cross-linking.

Table XIII
Percentage decrease in weight of plasticized PVC tubes treated at 80°C for 5 h in water, reacted with sodium sulphide in the absence and presence of TBAH. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}

Sample	Initial weight	Weight after reaction	weight loss(%)*
PVC tube heated with water alone	0.9366	0.9361	0.05±0.008
PVC tube reacted with sodium sulphide alone	0.9033	0.9011	0.24±0.06
PVC tube reacted with sodium sulphide and PTC	0.8804	0.8735	0.78±0.01

* Average of three determinations

The absence of any reaction between sodium sulphide and DEHP during surface modification was confirmed by T.L.C analysis of DEHP reacted with sodium sulphide in the presence of TBAH (Section 2.2.1). DEHP after reaction with sodium sulphide was extracted with hexane and the T.L.C of the hexane extractant was run side by side with pure DEHP in hexane using 1:1 methanol /hexane as the eluent. T.L.C of reacted DEHP showed only one spot similar to that of standard DEHP with a R_f value of 0.65.

All the migration experiments described so far were carried out on plasticized PVC tubes modified by the nucleophilic substitution of sodium sulphide under phase transfer condition. In order to examine the effect of surface modification on the migration resistance of the plasticizer from plasticized PVC sheet, medical grade plasticized PVC sheets were surface modified under conditions which were

optimized for the plasticized tubes. Figure 3.2.17 shows the plasticizer migration profile from surface modified PVC sheets reacted with sodium sulphide in the presence of TBAH at 80°C for 5 h as in the case of PVC tubes as a function of time in petroleum ether at 30°C. As in the case of tubes, the surface modified plasticized PVC sheets although much lower in thickness also became highly migration resistant as a result of the surface modification. Thus this surface modification can be considered to be equally efficient for preparing migration resistant plasticized PVC sheet as well as tubes.

3.2.4.3 Plasticizer Migration after Various Modes of Sterilization

Since sterilization is a very important step for plasticized PVC, used in medical applications, the surface modified plasticized PVC tubes were subjected to two common modes of sterilization (Section 2.2.8.12) and the migration resistance after sterilization was examined. The surface modified and unmodified PVC tubes were sterilized by autoclaving (Section 2.2.8.12.1) as well as by gamma irradiation (Section 2.2.8.12.2). Table XIV shows the amount of DEHP migrated from unmodified and surface modified PVC tubes subjected to two different modes of sterilization into petroleum ether at 30°C.

No increase in plasticizer migration was observed from surface modified plasticized PVC tubes even after these two modes of sterilization compared to the unsterilized sample. The sterilization modes infact slightly increased the migration resistance of the surface modified PVC tubes. The amount of DEHP migrated from unmodified PVC tube without sterilization as well as after autoclaving are almost identical showing that autoclaving the tubes have no effect on the plasticizer

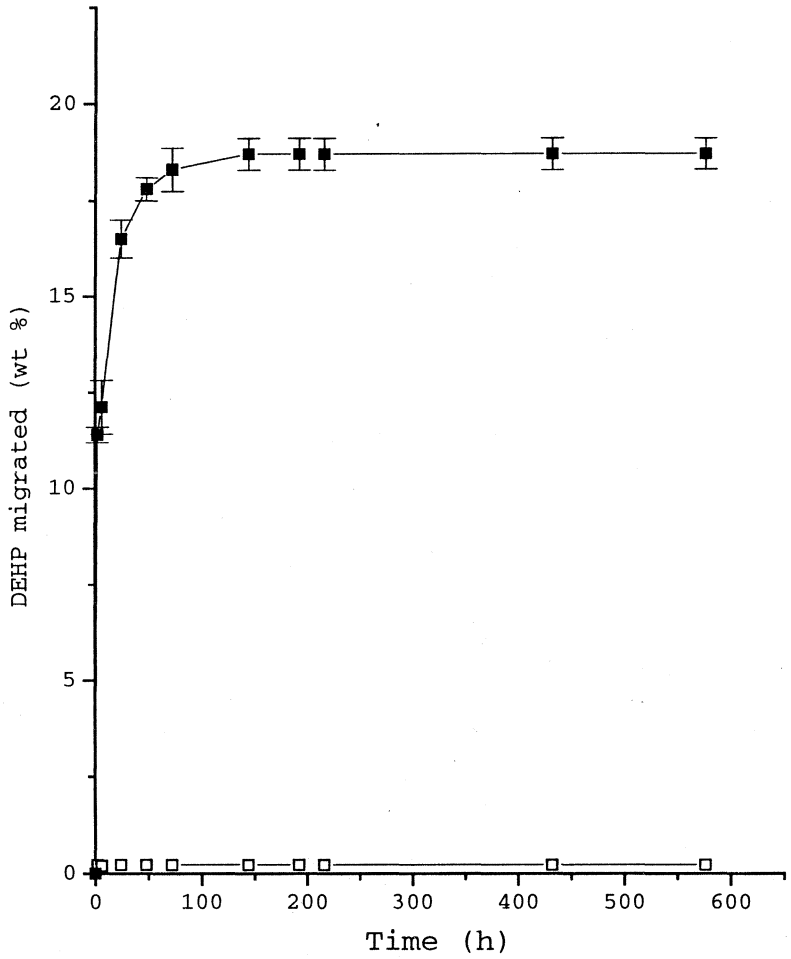


Fig. 3.2.17 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from unmodified plasticized PVC sheet and sheet reacted with sodium sulphide in the presence of TBAH at 80°C for 5 h. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}; Unmodified PVC (■) and Surface modified PVC (□).

Table XIV
Amount of DEHP migrated from unmodified plasticized PVC tubes and PVC tubes reacted with sodium sulphide in the presence and absence of TBAH at 80°C for 5 h into petroleum ether at 30°C after different modes of sterilization.
[Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}

Sample	Mode of sterilization	Time of incubation in petroleum ether	DEHP migrated (wt%)
Unmodified PVC	Unsterilized	24 h	27.07±0.8
Unmodified PVC	Autoclaving	24 h	27.32±0.9
Unmodified PVC	Gamma irradiation	24 h	25.88±0.4
PVC reacted with sodium sulphide in the absence of TBAH	Unsterilized	24 h	26.8±0.5
Surface modified plasticized PVC	Unsterilized	30 d	0.11
Surface modified plasticized PVC	Autoclaving	30 d	0.06
Surface modified plasticized PVC	Gamma irradiation	30 d	0.02

migration of plasticized PVC. The tube reacted with sodium sulphide in the absence of TBAH shows almost the same extent of plasticizer migration compared to unmodified PVC tube. In the case of unmodified PVC tubes sterilized using gamma irradiation, there is a slight reduction in the migration of plasticizer after 24 h of incubation in petroleum ether. This decrease in DEHP migration for the gamma sterilized specimens can be attributed to some amount of cross-linking taking place during gamma irradiation. Gamma irradiation of PVC always resulted in chain scission leading to cross-linking reaction. In the case of surface modified PVC tubes the amount of DEHP migrated from autoclaved PVC tubes are found to be slightly less than that of unsterilized modified PVC tubes. This may be due to some amount of degradation of the tubes during autoclaving due to thermal effects.

Gamma irradiation of the surface modified PVC tubes further decreased the amount of plasticizer migration. This can be attributed to greater extent of chain scission of polymer during gamma irradiation and hence greater cross-linking of the surface. This greater extent of chain scission may be presumably due to the presence of sulphur atoms on the surface which decreases the stability of adjacent bonds.

3.2.4.4 Accelerated Plasticizer Migration in Cotton Seed Oil and PEG-400

Since the modified PVC was found to be highly migration resistant in hydrocarbon solvents such as petroleum ether, further migration studies were carried out with extraction solvents having different polarity. A non polar lipophilic extractant such as cotton seed oil and a highly hydrophilic and polar extractant ie., PEG-400 were used as discussed in section 2.2.9.3. Accelerated migration studies were carried out at 70°C in these two media. Figure 3.2.18 shows the migration profile from surface modified and unmodified PVC tubes in these two media. The surface cross-linked PVC tubes were thus found to be completely migration resistant in these two media even after 4 days of extraction under accelerated conditions.

3.2.4.5 Plasticizer Migration in Ethanol-Water Mixture According to British Pharmacopoeia

The extent of plasticizer migration in ethanol/water mixture according to British Pharmacopoeia (BP) (Section 2.2.9.4) is shown in Table XV.

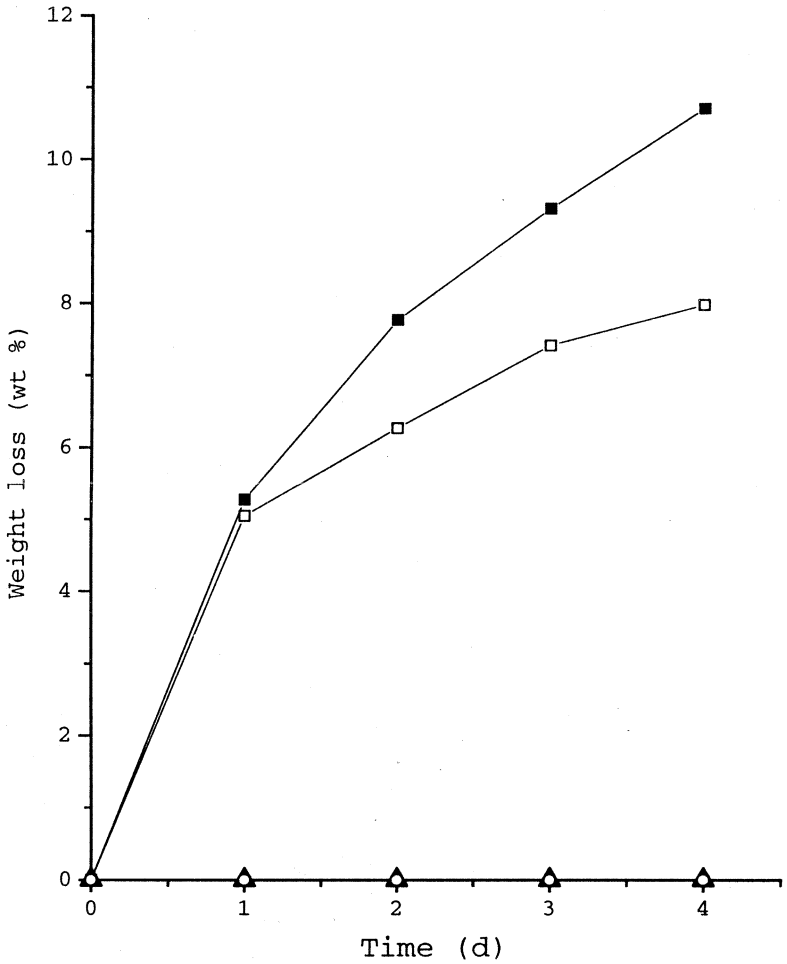


Fig. 3.2.18 Percentage weight loss as a function of time in cotton seed oil and PEG-400 at 70°C from unmodified PVC tubes and tubes reacted with sodium sulphide in the presence of TBAH at 80°C for 5 h. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3} Unmodified PVC in cotton seed oil (■), Unmodified PVC in PEG-400 (□), Surface modified PVC in cotton seed oil (▲) and Surface modified PVC in PEG-400 (o).

Table XV
Extent of DEHP migrated from unmodified and surface modified plasticized PVC sheets into ethanol/water mixture

Sample	DEHP migrated % w/v
Unmodified plasticized PVC sheet	0.007
Surface modified plasticized PVC sheet	0.002

According to BP the amount of DEHP migrated from plasticized PVC sheet should be less than 0.01% w/v. Since medical grade plasticized PVC sheets were used in the present study, the extent of migration from even the unmodified sheet was found to be less than the permissible level. The significant fact is that the extent of plasticizer migration from surface modified PVC sheet was found to be much lower compared to unmodified PVC sheet in this polar extraction medium also.

3.2.5 Mechanical Properties

Since the nucleophilic substitution reaction of chlorine by sulphide anion is confined to the surface of plasticized PVC sheet, the bulk properties will not be much affected. Table XVI shows the ultimate stress-strain properties of the sulphide cross-linked as well as unmodified PVC sheets. Since PVC is mainly used for storing various biological fluids at low temperatures, the mechanical properties of the surface modified sheets were determined after storing at 4°C for 30 days. Plasticized PVC is commonly sterilized by autoclaving. So, the mechanical properties of both unmodified and modified PVC sheet after autoclaving were also determined.

The unmodified PVC sheets under various conditions like heating in water at 80°C for 5 h or autoclaving as well as storing at 4°C did not show any significant

Table XVI
Mechanical properties of unmodified plasticized PVC sheet and sheet reacted with sodium sulphide in the presence of TBAH at 80°C for 5 h. [Sodium sulphide] = 7 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}

Sample	Ultimate stress (M Pa)±SD*	Ultimate strain (%) ± SD*
Umodified PVC	19.38±0.57	437.7±26.3
Unmodified at 80°C for 5 h	18.95±1.16	436.2±41.9
Unmodified at 4°C for 30 d	18.48±0.65	466.1±30.7
Unmodified autoclaved	19.84±0.95	522.5±13.0
Surface modified PVC	17.82±0.72	313.3±28.3
Modified at 4°C for 30 d	17.10±0.61	328.2±15.0
Modified autoclaved	18.66±0.48	273.0±4.1

* Average of six determinations

changes in the mechanical properties. But at the same time, the mechanical properties of the surface modified PVC sheets are somewhat affected as evidenced from the ultimate stress and elongation values. The ultimate tensile strength of the surface modified PVC sheet was slightly affected ($p>0.01$) ie., decreases by 8 percentage compared to the unmodified PVC sheet. This decrease is presumably due to some degradation during modification. The percentage elongation of modified PVC sheet as expected due to surface cross-linking shows a significant reduction ($p>0.001$) compared to unmodified PVC sheet ie., a decrease of about 28 percent. The storage of sheets at 4°C did not cause any further decrease in the mechanical properties of the modified PVC sheets. But autoclaving further decreased the percentage elongation of the sheets, ie., a decrease of about 13 percent compared to surface modified PVC sheet. This can be attributed to some additional cross-linking during autoclaving. The extent of plasticizer migration from the autoclaved surface modified PVC sheets was also found to be lower than that of

the surface modified PVC tube as discussed in section 3.2.4.3.

The data obtained from this investigation demonstrate that sulphide anion even though being a dianion can be easily transferred from aqueous to organic solid PVC surface using tetrabutylammonium salts as the PTC. The nucleophilic substitution of the chlorine atoms on the surface of plasticized PVC tubes and sheets takes place feasibly with this transferred dianion, resulting in the formation of surface cross-linked network. The formation of sulphur linkages on the surface was confirmed by XPS. XPS shows the complete absence of sulphur on unmodified PVC as well as PVC reacted with sodium sulphide in the absence of PTC thus confirming the formation of sulphur bridges via PTC. The sulphur cross-links were further confirmed by isolating the cross-linked gel and estimating the sulphur content in the gel. The optical clarity of the tubes were found to be only slightly affected as a result of modification. Not much significant differences were found between the surface morphology of unmodified and surface modified PVC sheets. The surface modified PVC sheets absorb some amount of water presumably due to the entrapment of water in the cross-linked network. This was further confirmed by the decrease in the air and octane contact angles of water incubated modified samples. Only a slight reduction in the mechanical properties of the surface cross-linked PVC was observed compared to the unmodified sheets. The surface modified plasticized PVC was found to be highly migration resistant in petroleum ether even after 6 months of incubation. The surface cross-linked plasticized PVC sheets and tubes were found to be plasticizer migration resistant in other physiological media like cotton seed oil and PEG-400 even under accelerated conditions. The method provides a simple

and elegant way of solving the problem of plasticizer migration from plasticized PVC used in biomedical and food-packaging applications.

3.3 Surface Cross-linking of Plasticized PVC via Phase Transfer Catalysis Using Sodium Thiosulphate to Prevent Plasticizer Migration

3.3.1 Background

The thiosulphate ion ($S_2O_3^{2-}$) is a structural analogue of the sulphate ion where one oxygen atom is replaced by one sulphur atom. The structure of the thiosulphate ion has been established as $S–SO_3^{2-}$. The two sulphur atoms are not equivalent and the unique chemistry of the thiosulphate ion is dominated by the sulphide like sulphur atom which is responsible for the reducing properties and complexing abilities of the thiosulphates. The thiosulphate chemistry has been reviewed (Milligan & Swan, 1962; Distler, 1967).

The nucleophilic attack by thiosulphate on alkyl halides results in the formation of S-alkyl thiosulphates and can be represented as follows.

$$RX + Na_2S_2O_3 \longrightarrow R—S—SO_3^-—Na + NaX$$

These organic thiosulphates are otherwise known as Bunte salts. Extensive reviews on the preparation and classical reactions of Bunte salts have appeared (Milligan & Swan, 1962; Distler, 1967; Hogg, 1979). They can be hydrolyzed with acids to give the corresponding mercaptans (Kice, 1963; Otzeszko, 1994) or converted to disulphides, tetrasulphides or pentasulphides upon treating with an acid, base, oxidizing agent or reducing agent (Milligan *et al.*, 1963). The reaction of ammonium thiosulphate and polyepichlorohydrin has been reported to proceed

homogeneously in a 7:1 mixture of hexamethyl phosphortriamide and water to yield the corresponding organic thiosulphate (Okawara & Ochiai, 1980). An aqueous solution of this organic thiosulphate can be converted into a cross-linked gel upon treatment with an acid, alkali, oxidizing or a reducing agent. The cross-linking of S-S type was suggested in this case since the formation of –SH or $-S^-$ was confirmed for the model compound under similar condition. A German patent claimed the two phase preparation of alkyl and aralkyl thiosulphates in a two phase system of water and an organic solvent by nucleophilic substitution of the halogen of the alkyl or aralkyl halide by thiosulphate in the presence of a PTC (Chapelet *et al.*, 1979). This chapter deals with the possibility of surface cross-linking plasticized PVC with thiosulphate anion in aqueous media under phase transfer conditions, surface characterization of the thiosulphate substituted PVC and evaluation of the migration resistance of the plasticizer DEHP from thiosulphate substituted PVC.

3.3.2 Surface Nucleophilic Substitution of PVC with Thiosulphate Anion

The attempt was to substitute the surface chlorine atoms of PVC tubes or sheets with thiosulphate anion to induce surface cross-linking. The surface confined nucleophilic substitution reaction of plasticized PVC with sodium thiosulphate was carried out in water in the presence of a PTC (Section 2.2.6) similar to the dithiocarbamate (Section 3.1) and sulphide ion (Section 3.2) substitution reaction discussed earlier. Briefly, the standard reaction condition is to treat plasticized PVC with aqueous sodium thiosulphate in the presence of TBAH at 80°C for 5 h. ([Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}). Here, the

soluble organic cation of the quaternary salt Q+ carry the thiosulphate anion from the aqueous phase to the organic solid phase for the nucleophilic substitution and the reaction product chlorine back to the aqueous phase similar to dithiocarbamate substitution (Section 3.1.2) and sulphide anion transfer described in the previous chapter (Section 3.2.2). Since the reaction was carried out in aqueous medium, the substitution would take place preferentially on the surface of plasticized PVC. Surprisingly, it has been found that under appropriate catalyst concentration the direct substitution of thiosulphate anion onto PVC itself produced a cross-linked surface. When PVC resin was reacted with ammonium thiosulphate in DMF the product obtained was insoluble in THF, which is a good solvent for unsubstituted PVC. Similarly PVC resin reacted with an aqueous solution of sodium thiosulphate via PTC in the solid-liquid two phase system also resulted in the formation of a product insoluble in THF. The formation of surface cross-linked gel on PVC reacted with sodium thiosulphate can be explained as follows. The thiosulphate anion being a dianion ($^{-}S\text{-}SO_3^{-}$) can directly react with two chlorine atoms of the polymer chain resulting in the formation of cross-linked gel. In addition to this type of surface cross-linking, the possibility of the presence of other functional groups on the surface cannot be eliminated. Since the reaction medium is highly acidic (pH 3.4) some of the organic thiosulphates formed on the surface can get cleaved to form a S–S type of cross-linking similar to that suggested by Okawara & Ochiai (1980) in the case of polyepichlorohydrin. Some of the hydrolyzed group may also be present as mercaptans. The rest may be present as unhydrolyzed organic thiosulphate. The various possible reactions taking place on the surface can be summarized as follows.

$$2RX + Na_2S_2O_3 \longrightarrow R{-}S{-}SO_3{-}R + 2NaX$$

$$RX + Na_2S_2O_3 \longrightarrow R{-}S{-}SO_3{-}Na + NaX$$

$$R{-}S{-}SO_3Na \longrightarrow R{-}SH \longrightarrow R{-}S{-}S{-}R$$

So the surface chemistry of thiosulphate substituted PVC is believed to be highly complex with different types of functional groups. Since the surface of plasticized PVC, gels on reaction with thiosulphate the diffusivity of the plasticizer DEHP will be low as the cross-linked surface can act as a barrier to prevent migration as observed in the previous chapters.

3.3.3 Physico-Chemical Characterization of Thiosulphate Substituted Plasticized PVC

3.3.3.1 FTIR-ATR

As discussed in section 3.3.2 the thiosulphate substituted PVC produces a highly complex surface and hence attempts were made to characterize the substituted surface. The surface characterization of the thiosulphate substituted PVC sheet was carried out by FTIR-ATR spectroscopy and XPS as in the case of PVC reacted with sodium sulphide (Section 3.2). Due to reasons discussed earlier (Section 3.1.3.1 and 3.2.3.1) the C–S stretching vibrations occur in the 600–700 cm^{-1} are very difficult to detect from the FTIR-ATR spectra in the case of thiosulphate substituted PVC also. Figure 3.3.1a shows the FTIR-ATR spectrum in the 900–2000 cm^{-1} region of unmodified plasticized PVC sheet. Figure 3.3.1b shows the corresponding spectrum of plasticized PVC sheet reacted with sodium thiosulphate in the absence of PTC

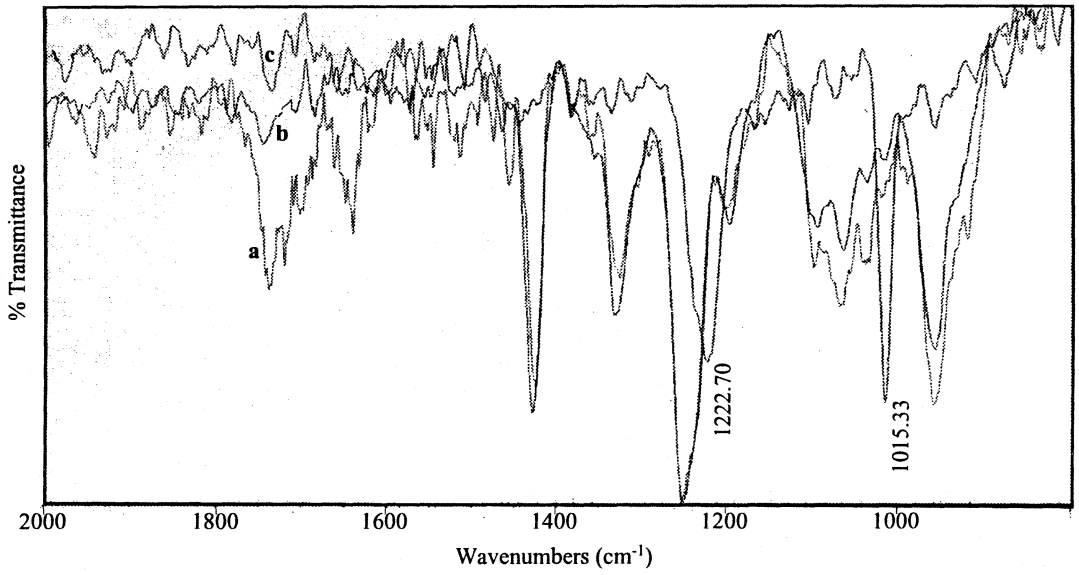


Fig. 3.3.1 FTIR-ATR spectra of unmodified plasticized PVC sheet (a), PVC sheet reacted with thiosulphate in the absence of TBAH (b) and PVC sheet reacted with thiosulphate in the presence of TBAH (c).

and figure 3.3.1c shows the spectrum of plasticized PVC sheet reacted with sodium thiosulphate in the presence of PTC ie., TBAH. The two spectra (Figure 3.3.1a and 3.3.1b) are exactly identical with no additional peaks in the spectrum of plasticized PVC sheet treated with thiosulphate in the absence of PTC (Figure 3.3.1b). The spectrum of plasticized PVC sheet reacted with sodium thiosulphate in the presence of PTC (TBAH) (Figure 3.3.1c), shows marked differences in the 1000–1500 cm^{-1} region. The thiosulphate substituted PVC shows two prominent peaks at 1015 and 1222 cm^{-1} which are absent in the case of unmodified PVC sheet. These peaks in the spectrum of thiosulphate substituted PVC can be attributed to the S-O stretching vibrations on the surface similar to that reported in the case of thiosulphate substituted polyepichlorohydrin (Okawara & Ochiai, 1980). The presence of these peaks in the spectrum of thiosulphate substituted PVC can be

taken as a clear evidence for the incorporation of thiosulphate groups on the surface of thiosulphate substituted PVC. Since PVC sheet treated with thiosulphate in the absence of PTC showed no S–O stretching peaks, any possibility of thiosulphate adhering on the surface of PVC can be eliminated. The presence of S–O stretching vibrations on the surface of thiosulphate substituted PVC shows the presence of R–SSO_3–R or R–SSO_3Na groups on the surface.

The thiosulphate substituted PVC (Figure 3.3.1c) shows no significant peak at 1670 cm^{-1} compared to unmodified PVC, so the possibility of dehyrochlorination reaction accompanying the nucleophilic substitution reaction leading to double bond formation can be eliminated. Since S–O stretching vibrations can be clearly seen in the spectrum of thiosulphate substituted PVC, the nucleophilic substitution on the surface was confirmed.

3.3.3.2 X-ray Photoelectron Spectroscopy (XPS)

Further surface characterization of the thiosulphate substituted PVC was carried out by XPS. XPS provides a very sensitive method for determining sulphur atoms on surfaces. Even the various oxidation states of the sulphur atoms can be detected by XPS, since it shows a chemical shift of about 10 eV for the various oxidation states of sulphur atoms as discussed in section 3.2.3.2. Figures 3.3.2a and 3.3.2b shows the elemental survey scan in the 0–1000 eV region of the unmodified and thiosulphate substituted plasticized PVC sheet. Since the flood gun of 10 eV was on during the time of scanning, the corrected binding energy (Corr. BE.) of electrons were calculated by adding 10 eV to the observed binding energy as discussed in section 3.2.3.2. The unmodified PVC sheet (Figure 3.3.2a) shows four prominent

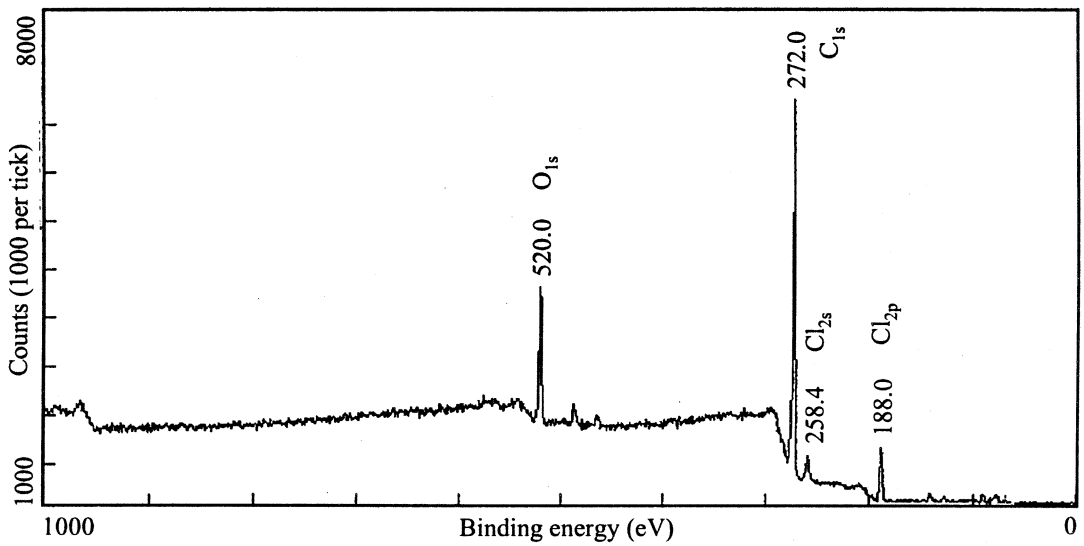


Fig. 3.3.2a XPS elemental survey scan in the 0–1000 eV region of unmodified plasticized PVC sheet.

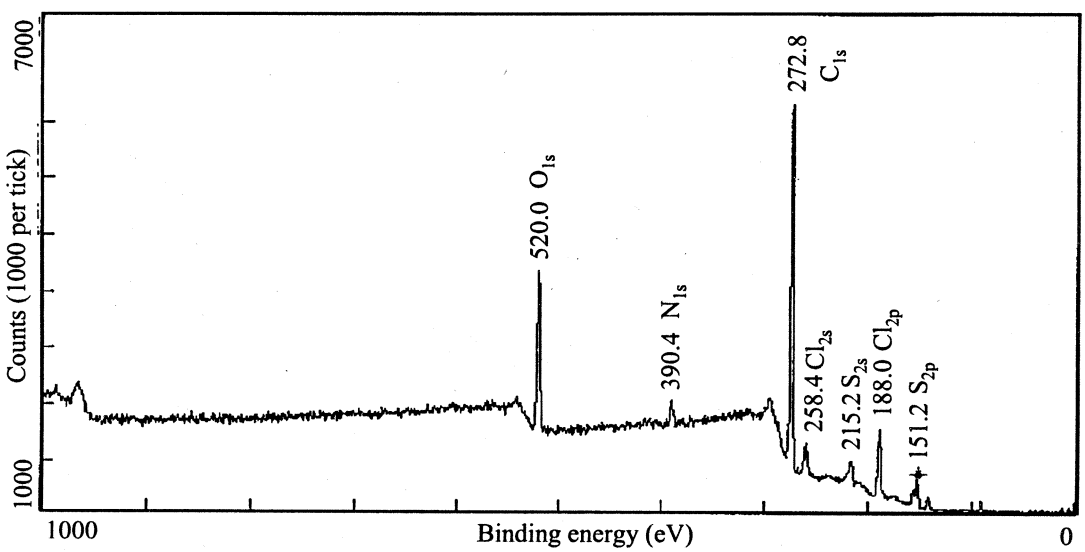


Fig. 3.3.2b XPS elemental survey scan in the 0–1000 eV region of plasticized PVC sheet reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}.

peaks in the XPS spectrum. The peak at 520 eV (Corr. BE. ~ 530 eV) corresponds to the oxygen (O_{1s}) electron, the peak at 272 eV (Corr. BE. ~ 282 eV) corresponds to the carbon (C_{1s}) electron, the peak at 258.4 eV (Corr. BE. ~ 270 eV) corresponds to chlorine (Cl_{2s}) electron and the peak at 188 eV (Corr. BE. ~ 200 eV) corresponds to the chlorine (Cl_{2p}) electrons. The spectrum of the thiosulphate substituted PVC sheet (Figure 3.3.2b) on the other hand shows a number of additional peaks. Thus, the peak at 215.2 eV (Corr. BE. ~ 226 eV) corresponds to the sulphur (S_{2s}) electron, the peak at 151.2 eV (Corr. BE. ~ 162 eV) also corresponds to the sulphur atom ie., the (S_{2p}) electron and another peak at 390.4 eV (Corr. BE. ~ 400 eV) corresponds to the nitrogen (N_{1s}) electron. The peaks at 215.2 and 151.2 eV region present in the spectrum of thiosulphate substituted plasticized PVC sheet clearly showed the presence of sulphur atoms on the surface and hence confirmed the substitution of chlorine atoms by the thiosulphate anions. The only unexpected peak in the spectrum of the thiosulphate substituted PVC sheet, is due to the nitrogen N_{1s} electrons on the surface. The presence of nitrogen on the surface may be due to contamination from the quaternary salt (TBAH) used as the PTC during the nucleophilic substitution reaction. In the case of thiosulphate substituted PVC sheet, the sulphur atoms were detected even in the survey scan unlike in the case of sodium sulphide reacted PVC discussed in the previous chapter (Section 3.2.3.2). This means that the amount of sulphur present on the surface of thiosulphate substituted PVC is much higher compared to the surface modified PVC discussed in the previous chapter (Section 3.2.3.2).

Figure 3.3.3a & 3.3.3b shows the XPS spectra of unmodified and thiosulphate substituted plasticized PVC sheet in the 0–250 eV region where peaks of many

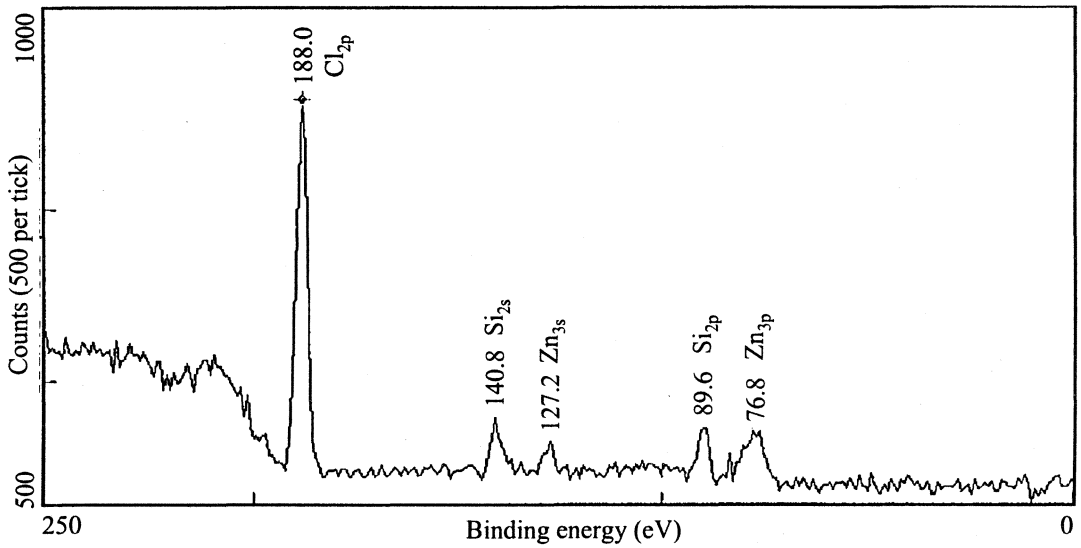


Fig. 3.3.3a XPS elemental survey scan of unmodified plasticized PVC sheet in the 0–250 eV region.

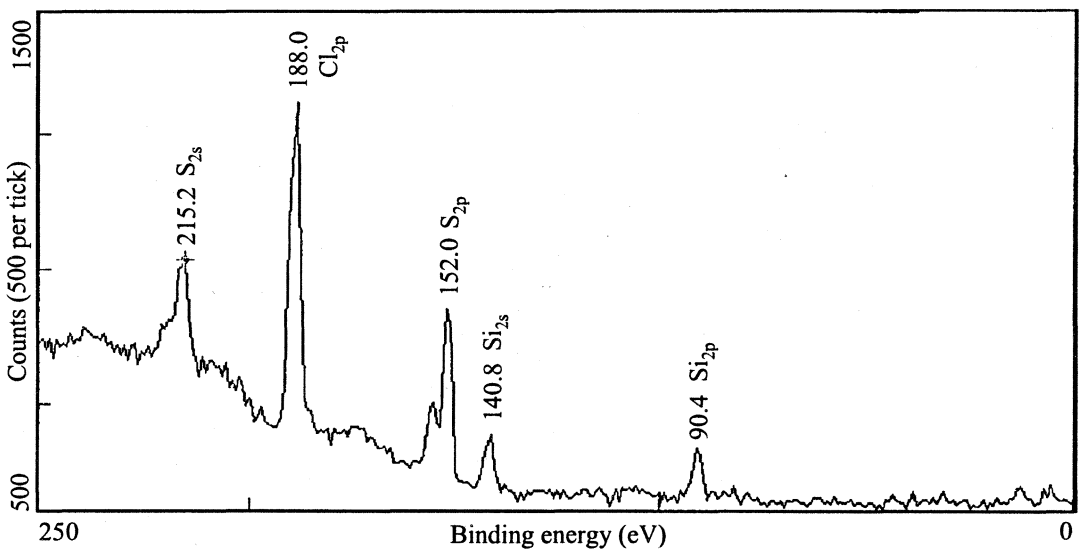


Fig. 3.3.3b XPS elemental survey scan in the 0–250 eV region of plasticized PVC sheet reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}.

elements of interest appear. The unmodified PVC sheet shows a prominent peak at 188 eV (Corr. BE. ~ 198 eV) for the chlorine (Cl_{2p}) electrons. The other peaks present in the spectra can be attributed to the silicon (Si_{2s}) electron at 140.8 eV (Corr. BE. ~ 151 eV), Zinc (Zn_{3s}) electron at 127. 2 eV (Corr. BE. ~ 137 eV), Silicon (Si_{2p}) at 89.6 eV (Corr. BE. ~ 100 eV) and Zinc (Zn_{3p}) at 76.8 eV (Corr. BE. ~ 87 eV). The thiosulphate substituted PVC shows (Figure 3.3.3b) prominent peaks for sulphur atom in this region which are absent in the corresponding spectrum of unmodified plasticized PVC sheet (Figure 3.3.3a). Five peaks were found in the spectrum of thiosulphate substituted PVC of which the peaks at 90.4 eV (Corr. BE. ~ 100eV) and at 140.8 eV (Corr. BE. ~ 151 eV) can be attributed to silicon atoms (Si_{2p} & Si_{2s}) and the peak at 188 eV (Corr. BE. ~ 198 eV) due to chlorine Cl_{2p} electrons. The peak at 215.2 eV (Corr. BE. ~ 225 eV) is due to the sulphur atoms present on the surface of the thiosulphate substituted PVC sheet and arise from S_{2s} electrons. The doublet peak at 152 eV (Corr. BE. ~ 162 eV) arise from sulphur S_{2p} electrons. The presence of a doublet peak for S_{2p} electrons in the spectra shows the presence of two types of sulphur atoms having different oxidation states. Another point is the absence of any peak at 50.4 eV (Corr. BE. ~ 60) corresponding to sodium Na_{2s} electrons in the spectrum of thiosulphate substituted PVC. So most of the SO_3 groups present on the surface may be in the form of R–SSO_3–R or R–SSO_3H. Thus, the spectra in the 0–250 eV region gives a clear picture of the surface composition of the unmodified and thiosulphate substituted plasticized PVC sheet. Table XVII shows the surface elemental composition of unmodified and thiosulphate substituted plasticized PVC sheet determined by XPS analysis and expressed as atom %.

Table XVII
Surface elemental composition (atom %) by XPS analysis of unmodified plasticized PVC sheet and PVC sheet reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}

Sample	O_{1s}	S_{2p}	C_{1s}	Cl_{2p}	Zn_{3p}	Si_{2p}	N_{1s}
Unmodified PVC	10	0	81	5.8	1.2	1.7	0
Thiosulphate substituted PVC	11	5.2	73	6.0	0	1.7	3.0

Table XVII shows that carbon, chlorine, silicon, oxygen and zinc were detected on the surface of unmodified PVC sample. Here O, Si and Zn were not expected in the spectrum of PVC. The presence of these elements in the spectrum can be attributed to additives present in plasticized PVC, Zn possibly arise from zinc stearate stabilizer and the Si possibly from the lubricants used in extrusion or from atmosphere contamination as discussed in section 3.2.3.2. No sulphur was detected on the surface of unmodified PVC whereas about 5.2% of sulphur was detected on the surface of thiosulphate substituted PVC. The amount of sulphur detected on the surface of thiosulphate substituted PVC is higher than that of PVC reacted with sodium sulphide (Section 3.2.3.2). In order to find the exact nature of the sulphur atoms on the surface of thiosulphate substituted PVC a high resolution spectra of S_{2p} electron was taken in the 148 to168 eV region. Figure 3.3.4a and 3.3.4b show the high resolution spectra of S_{2p} electrons, for the unmodified and thiosulphate substituted plasticized PVC. The spectrum of unmodified PVC sheet shows no prominent peak in this region which is a clear indication of the complete absence of sulphur atoms on the surface as discussed in section 3.2.3.2. The narrow scan spectra of thiosulphate modified PVC sheet on the other hand shows prominent S_{2p} peaks in this region. The spectra showed two chemical shifts,

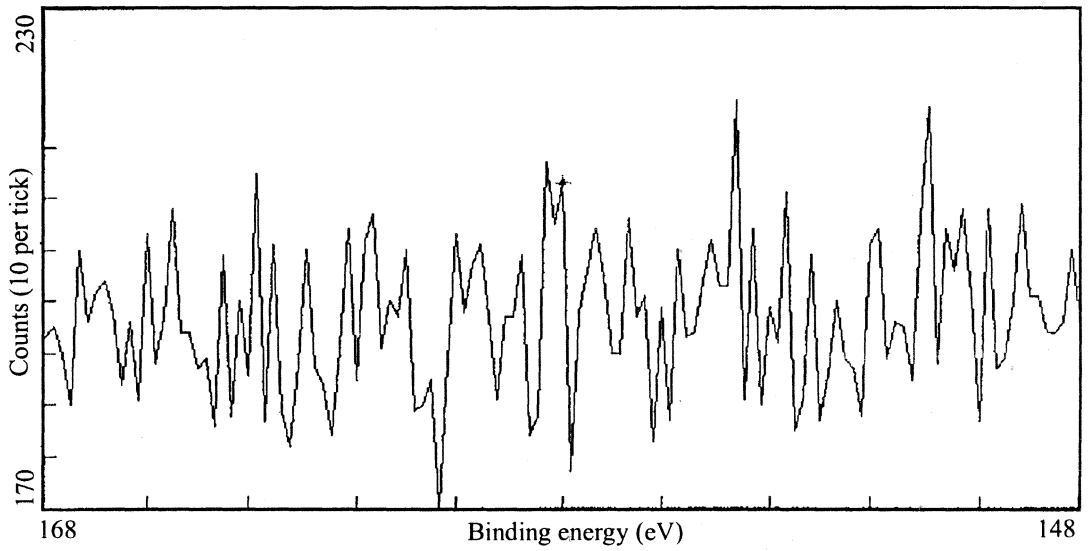


Fig. 3.3.4a XPS high resolution spectra of S_{2p} electrons of unmodified plasticized PVC sheet.

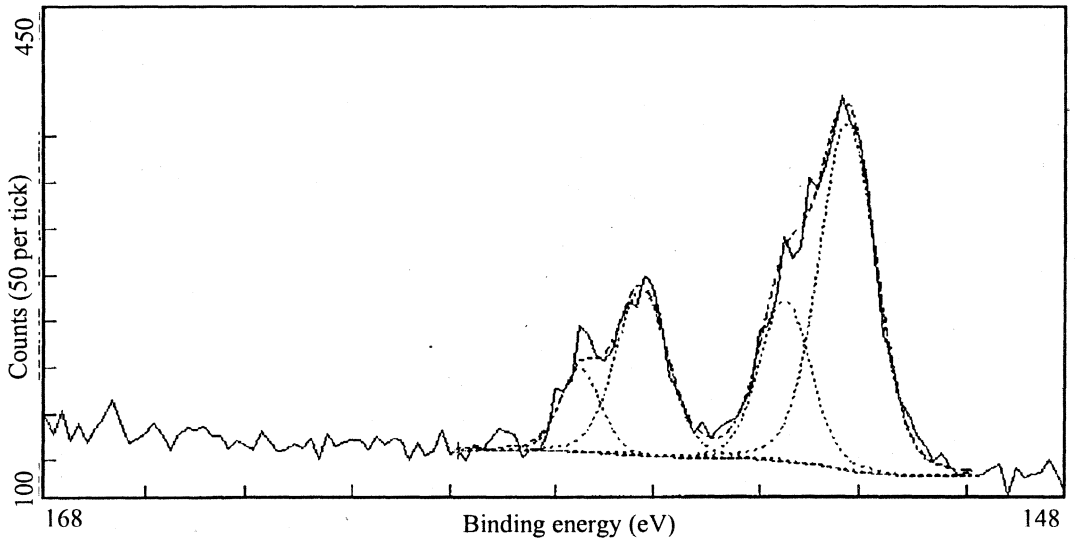


Fig. 3.3.4b XPS high resolution spectra of S_{2p} electrons of plasticized PVC sheet reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}.

each of which has a doublet of $2p_{3/2}$ and $2p_{1/2}$ electrons. The lower binding energy component is in some relatively reduced state, while the other component is probably in the sulphonate form. The presence of two different types of sulphur atoms once again confirmed the presence of thiosulphate groups on the surface which has two different types of sulphur atoms. Table XVIII shows the peak fit results of the narrow scan spectra of the thiosulphate substituted plasticized PVC sheet. The atom (%) composition of the two different types of sulphur atoms on the surface were found to be different. If all the substituted thiosulphate groups exist as $^{-}SSO_3^{-}$, then the composition of the two forms of sulphur atoms on the surface should be identical. The low value for the sulphate form of sulphur atoms once again confirmed the existance of different functional groups on the surface of thiosulphate substituted plasticized PVC.

Table XVIII
Peak fit results of the narrow scan XPS spectra of S_{2p} electrons on plasticized PVC sheet reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}

Binding energy	Corr. BE. (eV)	Element	Rel. Area	Atom %
152.22	163	S2p3	156	4.3
153.43	164.2	S2p1	127	
156.23	167	S2p3	70	1.9
157.43	168.2	S2p1	53	

Another major element present on the surface of PVC is the carbon. The C_{1s} XPS spectra of organic surfaces usually can give a wealth of information as discussed in the section 3.2.3.2. Figure 3.3.5a & 3.3.5b shows the high resolution C_{1s} spectra of unmodified and thiosulphate substituted plasticized PVC sheet. In the case of thiosulphate substituted PVC also, as in the case of sodium sulphide

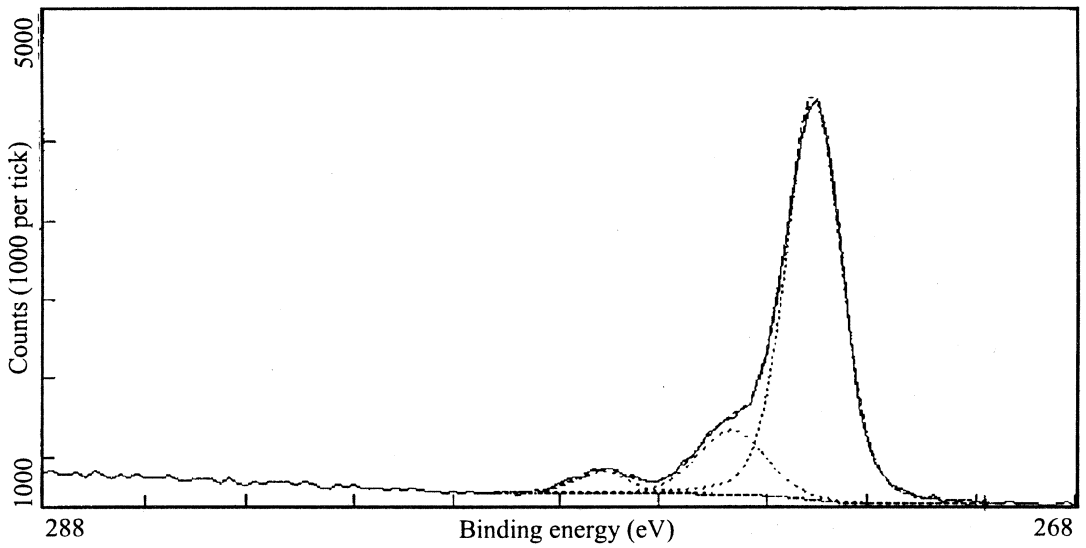


Fig. 3.3.5a XPS high resolution spectrum of C_{1s} electrons of unmodified plasticized PVC sheet.

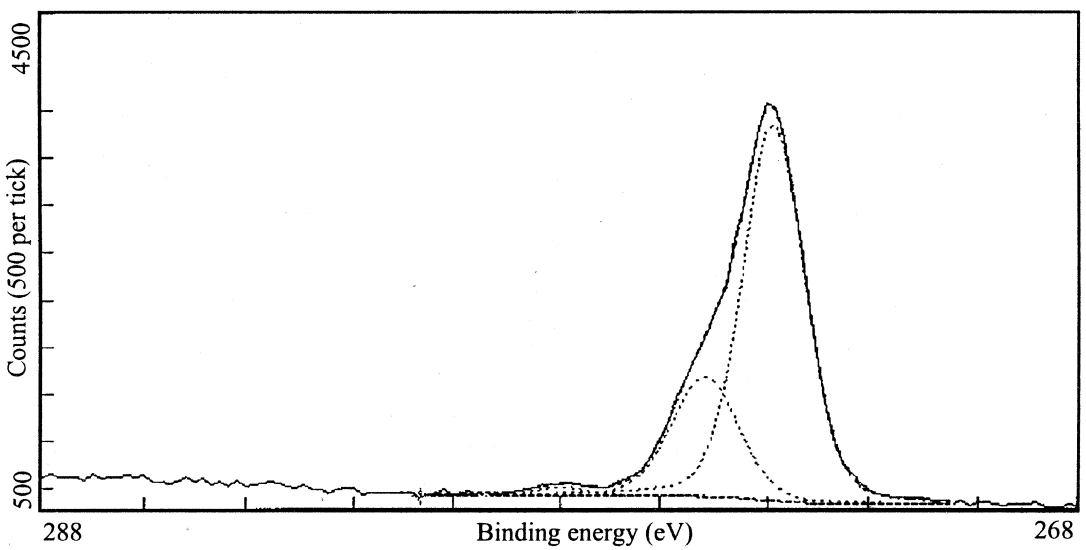


Fig. 3.3.5b. XPS high resolution spectra of C_{1s} electrons of plasticized PVC sheet reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}.

reacted PVC (Section 3.2.3.2) the chlorine atoms of PVC are being replaced by sulphur atoms. The sulphur atom is not having much difference in electronegativity compared to chlorine atoms and hence the chemical shifts are not so prominent and hence C_{1s} spectrum is not much informative. The C_{1s} spectrum of unmodified PVC sheet once again confirmed that contaminants are present on the surface. Instead of two peaks of almost equal intensity at 285 and 286.5 eV expected from the CH_2 and CHCl groups present in PVC (Ratner *et al.*, 1993), the spectrum of the unmodified plasticized PVC (Figure 3.3.5a) shows a large hydrocarbon peak at 284.6 eV, a C–Cl/C–O peak at 286.2 eV and a small ester peak near 288.7 eV. The spectra of thiosulphate substituted PVC (Figure 3.3.5b) showed a slight difference compared to the unmodified PVC. Here, the peak at 284.6 and 286.2 shows marked differences compared to unmodified plasticized PVC. This once again confirmed the complex nature of the surface of thiosulphate substituted plasticized PVC. Table XIX shows the summary of the peak fit results for the C_{1s} narrow scan spectra of unmodified and thiosulphate substituted plasticized PVC sheet.

Table XIX
Summary of the peak fit results for the C_{1s} narrow scan spectra of unmodified plasticized PVC sheet, PVC sheet reacted with sodium thiosulphate at 80°C for 5 h in the presence of TBAH. [Sodium thiosulphate] = 3 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}

Sample	Corr. BE. (eV)	% surface composition
Unmodified PVC	284.6	65.0
	286.2	12.7
	288.7	3.4
Thiosulphate	284.6	59.8
substituted PVC	285.9	20.4
	288.7	0.9

Thus the XPS data confirmed the nucleophilic substitution of thiosulphate on PVC surface.

3.3.3.3 Gel Content Estimation

The cross-linked network on the surface of thiosulphate substituted plasticized PVC tube was separated after dissolving the thiosulphate substituted PVC in THF as discussed in section 2.2.8.8. The gel obtained was in the form a very thin layer. Figure 3.3.6 shows the variation of gel content determined gravimetrically with time of reaction from thiosulphate substituted plasticized PVC tubes. The gel was found to be formed on tubes even within 5–10 min of reaction with sodium thiosulphate in the presence of TBAH at 80°C. An appreciable increase in gel content was found after 2 hours of reaction. The gel obtained was very low compared to photocross-linked DTC-PVC (Section 3.1.3.2) as well as sulphide cross-linked PVC (Section 3.2.3.3). The maximum gel content obtained even after 6 h of reaction was very low corresponding to less than 1% of the total weight of the plasticized PVC tubes used. This low value shows that the gel formation is highly surface confined. Again unlike in the case of DTC-PVC (Section 3.1.3.2) as well as sulphide cross-linked PVC (Section 3.2.3.3) the amount of gel was not constant after certain time of reaction. The amount of gel formed on the surface of plasticized PVC tube reacted with sodium thiosulphate in the presence of TBAH slightly increases with time of reaction even after 6 h reaction. The gel formed was insoluble in all solvents including water, but swells in solvents for PVC such as THF and cyclohexanone. Organic thiosulphates as in the case of polyepichlorohydrin reported earlier were found to be highly soluble in water.

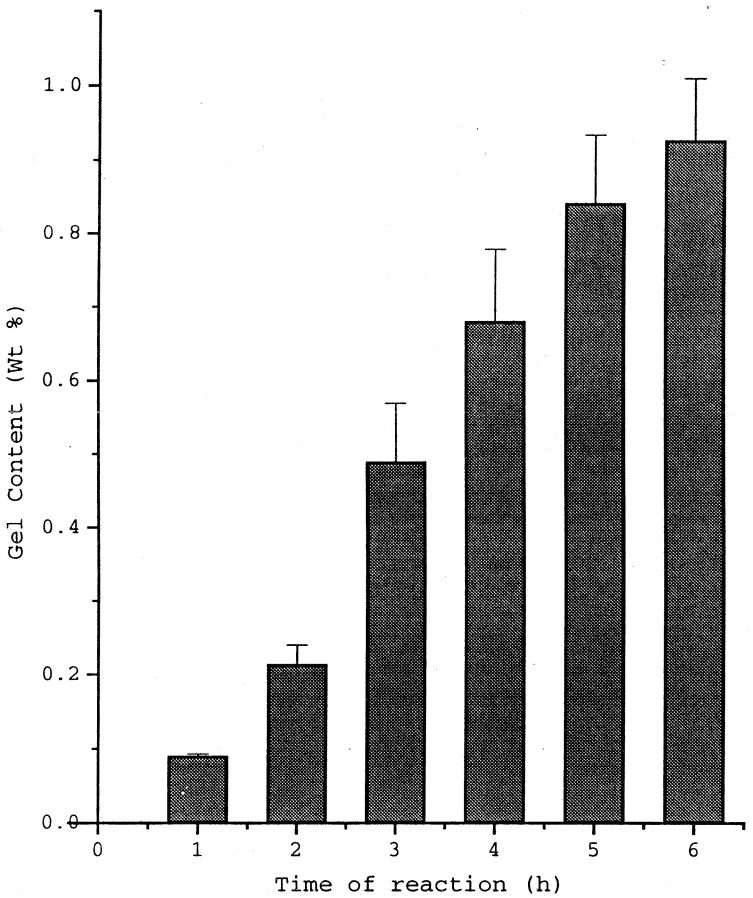


Fig. 3.3.6 Amount of gel formed as a function of time of reaction from plasticized PVC tubes reacted with sodium thiosulphate in the presence of TBAH at 80°C. [Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}.

This once again confirmed the formation of surface cross-linking on plasticized PVC reacted with sodium thiosulphate, since the gel obtained from thiosulphate substituted PVC was insoluble in water.

3.3.3.4 Sulphur Estimation

The substitution of chlorine atoms of PVC by thiosulphate anion was further confirmed by quantitatively estimating the amount of elemental sulphur present in the surface cross-linked gel (Section 2.2.8.9). The surface cross-linked gel from the thiosulphate substituted plasticized PVC tube was found to contain 11.4% by weight of sulphur, whereas no sulphur was detected from the unmodified plasticized PVC. This result corroborated the results obtained from the XPS analysis. The amount of sulphur present in the gel isolated from the surface of thiosulphate modified PVC was found to be higher than that of dithiocarbamate substituted PVC (Section 3.1.3.3) and sulphide cross-linked PVC (Section 3.2.3.4) eventhough the weight percent of gel isolated from thiosulphate substituted PVC was much lower.

3.3.3.5 Surface Morphology

Figure 3.3.7a and b show the SEM of the surfaces of thiosulphate substituted and unmodified plasticized PVC sheet (Section 2.2.8.3). No significant differences in the surface morphology were observed between the two samples. The nucleophilic substitution of the chlorine atoms of PVC by thiosulphate anion *per se* does not change the surface morphology of plasticized PVC sheet.

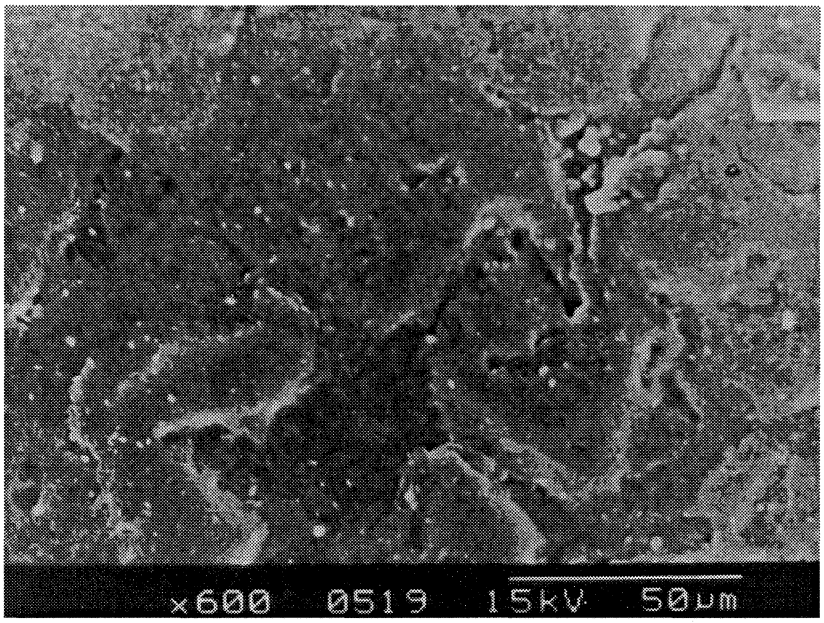


Fig. 3.3.7a SEM of the smooth surface of unmodified plasticized PVC sheet.

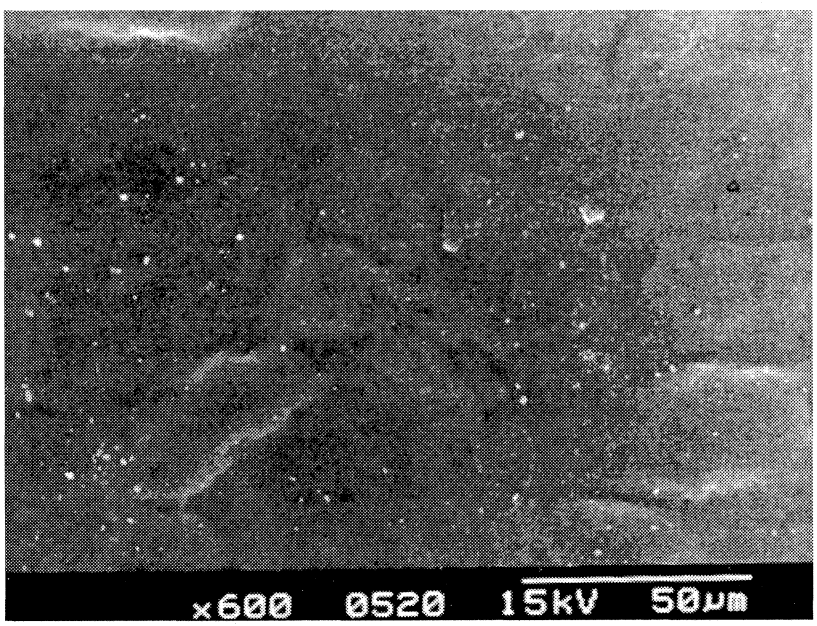


Fig. 3.3.7b SEM of the smooth surface of plasticized PVC sheet reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}.

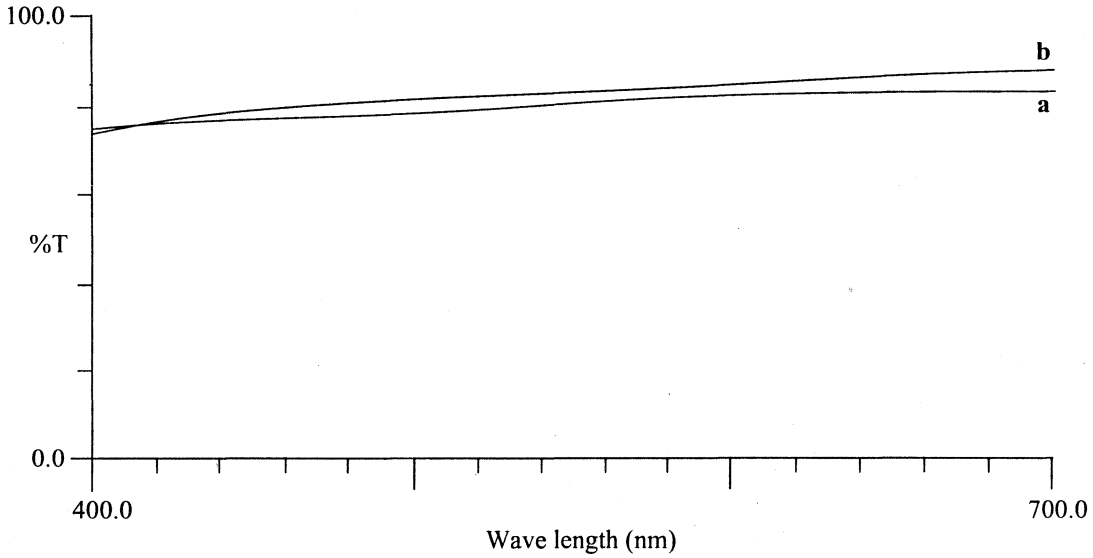


Fig. 3.3.8 Percentage transmittance of unmodified plasticized PVC tube and PVC tube reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h in the 400–700 nm range. [Sodium thiosulphate] = 3 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}; Unmodified PVC (a) and Thiosulphate substituted PVC (b).

3.3.3.6 Optical Clarity

The substitution of thiosulphate onto PVC took place without any dehydrochlorination reaction as discussed in section 3.3.3.1. The substituted PVC tubes looked clear and transparent as unmodified plasticized PVC tubes. The percentage transmittance of the unmodified (a) and thiosulphate substituted plasticized PVC tube (b) in the 400–700 nm region is shown in Figure 3.3.8 (Section 2.2.8.10). It can be seen that the clarity of the tubes was not affected at all by the nucleophilic substitution. The percentage transmittance for the unmodified and thiosulphate substituted plasticized PVC tubes are almost identical at all wavelengths. The absence of any absorbance in the region below 500 nm in the case of thiosulphate substituted plasticized PVC rules out dehydrochlorination

reaction accompanying the substitution reaction.

3.3.3.7 Percentage Water Absorption

Fig. 3.3.9 shows the extent of water absorption of unmodified and thiosulphate substituted plasticized PVC sheet after 24 and 72 h of incubation in distilled water (Section 2.2.8.2). Only a slight increase in weight was observed in the case of thiosulphate substituted PVC sheets compared to unmodified PVC. The extent of water absorption is much lower compared to sodium sulphide reacted PVC even though hydrophilic groups like $-SO_3-$ were present on the surface of thiosulphate substituted PVC. This may be possibly due to lower cross-link density on the surface and hence lower entrapment of water in the cross-linked network compared to plasticized PVC sheet reacted with sodium sulphide discussed in section 3.2.3.7.

3.3.3.8 Contact Angle Measurements

Table XX shows the air and octane contact angles of unmodified plasticized PVC sheet and thiosulphate substituted plasticized PVC sheet after incubation in water for 24 h (Section 2.2.8.4). The thiosulphate substituted plasticized PVC sheet shows a significant reduction in the contact angles compared to the unmodified plasticized PVC sheet eventhough the extent of water absorption by the thiosulphate substituted PVC is not very high compared to that of unmodified plasticized PVC sheet. This low value of contact angle is possibly due to the presence of hydrophilic functional groups on the surface of thiosulphate substituted plasticized PVC surface.

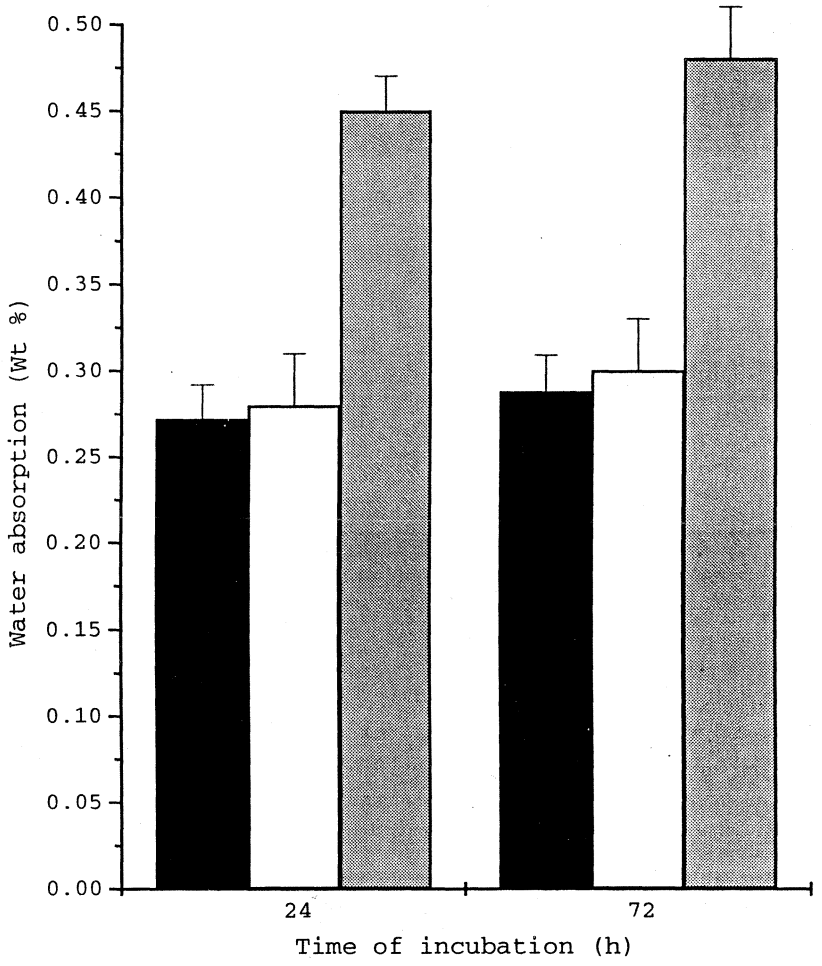


Fig. 3.3.9 Percentage water absorption as a function of time of incubation in distilled water of unmodified plasticized PVC sheet, sheet reacted with sodium thiosulphate in the absence of TBAH and sheet reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}. Unmodified PVC (■), Thiosulphate treated PVC (□) and Thiosulphate substituted PVC (▩).

Table XX
Air and octane contact angles for the unmodified plasticized PVC sheet and plasticized PVC sheet reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3 mol dm^{-3}; [TBAH]= 0.15 mol dm^{-3}

Sample	Contact angle (°)*	
	Air	Octane
Unmodified PVC sheet	60.3±3	85.7±4
Thiosulphate substituted PVC sheet	20.7±4	18.6±2

*Average of eight determinations

3.3.4 Plasticizer Migration from Thiosulphate Substituted and Unmodified PVC

3.3.4.1 Optimization of Reaction Condition

The optimization of the nucleophilic substitution reaction was achieved by following the plasticizer migration from thiosulphate substituted PVC and unmodified PVC into an organic extractant for DEHP such as petroleum ether. Figure 3.3.10 shows the amount of plasticizer migrated in 48 h from unmodified plasticized PVC tubes and PVC tubes reacted with sodium thiosulphate in the presence of 0.15 mol dm^{-3} of various PTCs at 80°C for 5 h. The various catalysts used were 18-crown-6, TBAH, TBAB, TBAI, HTMAB and BEAC as in the case of PVC reacted with sodium sulphide (Section 3.2.4.1). Similar to that observed in the previous chapter, the catalysts HTMAB, BEAC and 18-crown-6 were found to be inefficient in carrying out the transfer of anions from the aqueous phase to solid PVC surface due to reasons discussed in section 3.2.4.1. The amount of plasticizer migrated into petroleum ether from PVC tubes reacted with sodium

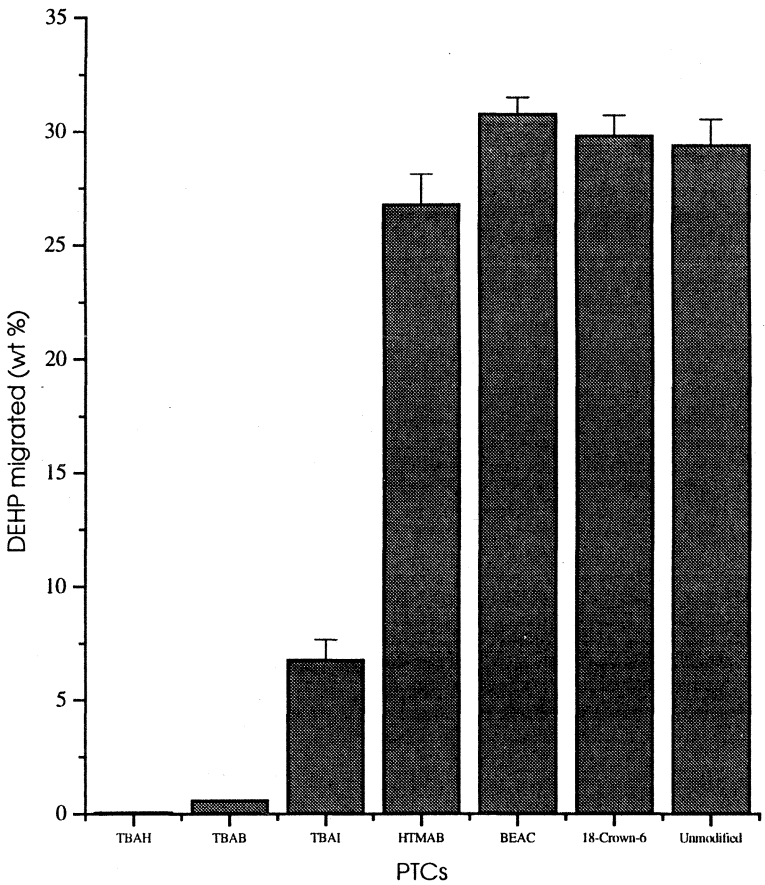


Fig. 3.3.10 Amount of DEHP migrated in 48 h into petroleum ether at 30°C from unmodified plasticized PVC tubes and tubes reacted with sodium thiosulphate in the presence of various PTCs at 80°C for 5 h. [Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}.

thiosulphate in the presence of these catalysts were almost similar to that of unmodified PVC tubes ie., apparently no reduction in plasticizer migration occurs. The least efficient catalyst was found to be BEAC. It has been found that TBAH is the most versatile catalyst for the thiosulphate substitution reaction on PVC. TBAB also showed high efficiency in carrying out the substitution reaction as evidenced by the high migration resistance of the PVC tubes reacted with thiosulphate in the presence of TBAB but not as efficient as TBAH. This observation was slightly different from that found in the previous chapter, where both TBAH and TBAB were found to be equally efficient in carrying out the anion transfer. TBAI was found to be having the least efficiency in carrying out the nucleophilic substitution compared to the other two tetrabutylammonium salts. This once again confirmed the fact that tetrabutylammonium salts were the most versatile catalysts for the two phase solid-liquid thiosulphate substitution reaction among the catalysts studied, similar to the DTC substitution (Section 3.1.4) as well as sulphide substitution (Section 3.2.4).

The effect of concentration of the reactants upon the extent of plasticizer migration was determined by varying the concentrations of sodium thiosulphate and TBAH. Figure 3.3.11 shows the amount of DEHP migrated as a function of time from plasticized PVC tubes reacted in the presence of different concentrations of TBAH at a constant concentration of sodium thiosulphate (3.0 mol dm^{-3}) at 80°C for 5 h. As the values were so small to differentiate from the graph, the corresponding values are given in the form of table also (Table XXI). The table clearly shows that the amount of catalyst required for efficient anion transfer is very small as in the case of plasticized PVC reacted with sodium sulphide. As

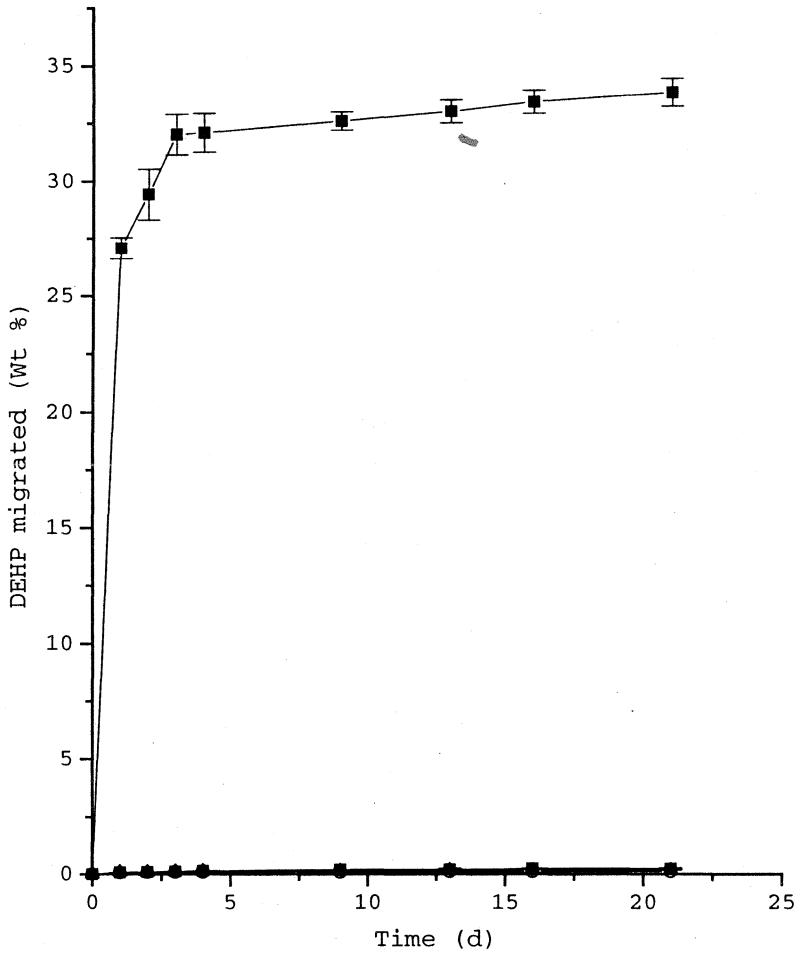


Fig. 3.3.11 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from unmodified plasticized PVC tubes and PVC tubes reacted with sodium thiosulphate in the presence of various concentrations of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3.0 mol dm^{-3}. Unmodified PVC (■), [TBAH] = 0.05 (◪), 0.01 (●), 0.15 (○) and 0.2 mol dm^{-3} (▲).

discussed in the previous chapter as the concentration of TBAH was increased, the extent of plasticizer migration decreases and remains almost constant after a concentration of about 0.15 mol dm^{-3}. The substitution of thiosulphate on PVC via PTC once again confirmed the fact that PTC mediated substitution reaction on PVC is not linearly dependent on the concentration of the catalyst unlike oridinary PTC mediated reactions. The extent of substitution reaction is constant above a certain catalyst concentration and the possible reason for this unusual behavior is due to the aggregation of the quaternary salt thiosulphate around or through the polymer chain and reacting with PVC in a bimolecular process.

Table XXI
Amount of DEHP migrated into petroleum ether at 30°C expressed as weight percent from unmodified and thiosulphate substituted plasticized PVC tubes in the presence of various concentrations of TBAH at 80°C for 5 h.
[Sodium thiosulphate] = 3.0 mol dm^{-3}

Time of release (d)	Unmodified	TBAH concentration in mol dm^{-3}			
		0.05	0.1	0.15	0.3
1	27.07	0.066	0.068	0.061	0.073
2	29.42	0.093	0.093	0.068	0.076
3	32.03	0.123	0.120	0.072	0.84
7	32.40	0.145	0.127	0.071	0.89
9	32.60	0.197	0.150	0.083	0.88
13	33.00	0.206	0.189	0.095	0.105
16	33.56	0.234	0.214	0.105	0.107
21	33.80	0.239	0.214	0.108	0.118

The effect of the concentration of the nucleophile, ie., sodium thiosulphate on the extent of plasticizer migration was examined as a function of time in petroleum ether at 30°C. Figure 3.3.12 shows the extent of plasticizer migration from plasticized PVC tubes reacted with various concentrations of sodium thiosulphate at 80°C for 5 h in the presence of 0.15 mol dm^{-3} of TBAH. The concentration

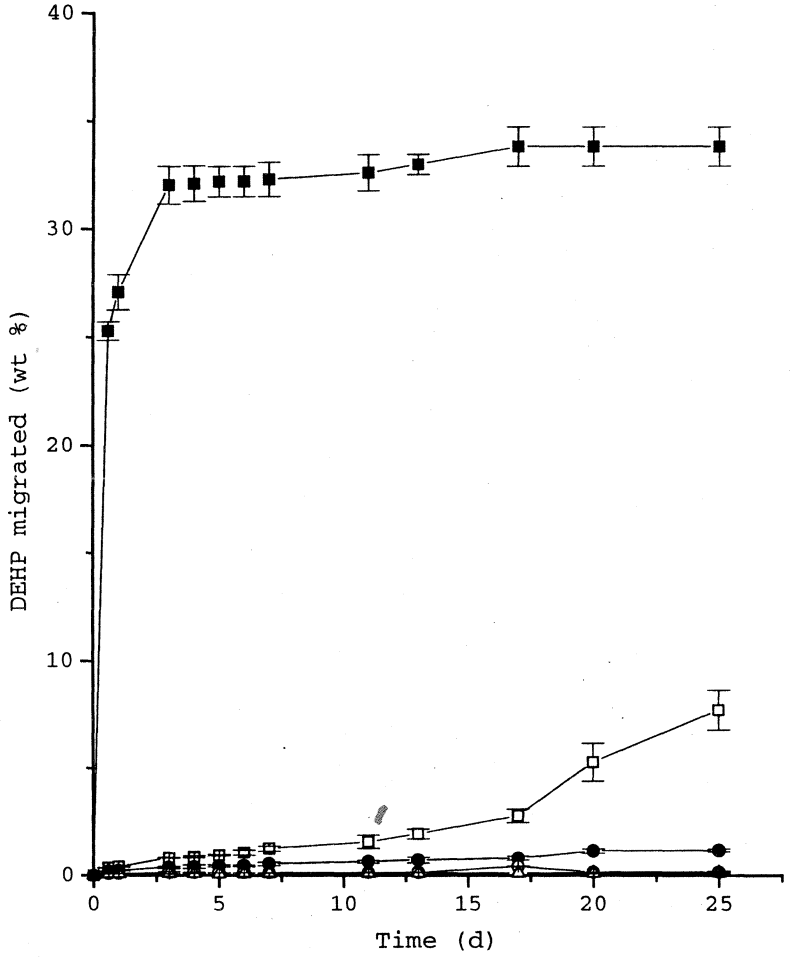


Fig. 3.3.12 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from unmodified plasticized PVC tubes and tubes reacted with various concentrations of sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [TBAH] = 0.15 mol dm^{-3}; Unmodified PVC tube (■), [Sodium thiosulphate] = 1.5 (□), 2 (•), 2.5 (○), 3 (▲) and 4 (△) mol dm^{-3}.

of sodium thiosulphate required to produce significant reduction in plasticizer migration was found to be much less compared to sodium sulphide discussed in the previous chapter. Even at a low thiosulphate concentration of 1.5 mol dm^{-3} the extent of plasticizer migration was much lower compared to that from unmodified plasticized PVC tubes. It has been found that the extent of migration showed significant decrease at a nucleophile concentration of 2.5 mol dm^{-3}. The lowest migration profile was observed from plasticized PVC tubes reacted with sodium thiosulphate concentration of 3.0 mol dm^{-3} onwards. So an optimum thiosulphate concentration of 3.0 mol dm^{-3} was used for further modifications. Table XXII shows the extent of plasticizer migration from plasticized PVC tubes reacted with various concentrations of sodium thiosulphate in the presence of TBAH.

Table XXII
Amount of DEHP migrated into petroleum ether at 30°C expressed as weight percentage from unmodified PVC tube and tube reacted with various concentrations of sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [TBAH] = 0.15 mol dm^{-3}

Time of DEHP release (d)	Unmodified	Concentration of sodium thiosulphate (mol dm^{-3})					
		1.5	2	2.5	3	4	5
0.6	25.29	0.349	0.191	0.079	0.047	0.075	0.08
1	27.07	0.407	0.229	0.092	0.061	0.081	0.092
3	32.03	0.826	0.375	0.125	0.072	0.081	0.1
4	32.10	0.866	0.409	0.126	0.071	0.082	0.102
5	32.20	0.956	0.447	0.127	0.068	0.082	0.102
6	32.24	1.070	0.452	0.127	0.065	0.084	0.106
7	32.40	1.262	0.539	0.128	0.075	0.094	0.107
11	32.80	1.572	0.644	0.128	0.08	0.097	0.108
13	33.00	1.947	0.717	0.141	0.095	0.105	0.108
17	33.62	2.788	0.816	0.142	0.105	0.108	0.108
20	33.80	5.279	1.152	0.153	0.108	0.114	0.113
25	33.80	7.689	1.184	0.153	0.111	0.118	0.119

The optimum time required to produce migration resistant plasticized PVC was determined by following the plasticizer migration from plasticized PVC tubes reacted with sodium thiosulphate in the presence of TBAH at 80°C for different periods of time. Figure 3.3.13 shows the extent of plasticizer migration as a function of time from plasticized PVC tubes reacted with sodium thiosulphate for various periods of time. It was found that significant decrease in plasticizer migration was found from tubes reacted for 3 h onwards. Tubes reacted for 1 h shows only a slight reduction in migration profile compared to the unmodified plasticized PVC. The plasticizer migration was assayed from tubes reacted with sodium thiosulphate at 80°C upto a period of 6 h and the migration pattern showed the tendency to decrease with increase of reaction time. This decrease in plasticizer migration pattern can be attributed to the increased surface cross-linking of PVC tubes with time of reaction. The data corroborated the gel content estimation, where the percentage gel content also increases with time of reaction. Since 5 h reacted tubes shows very low plasticizer migration, an optimum time of 5 h has been chosen for further studies.

The effect of temperature of reaction on plasticizer migration resistance was also evaluated. Figure 3.3.14 shows the extent of plasticizer migrated in 24 h from plasticized PVC tubes reacted with sodium thiosulphate in the presence of TBAH for 5 h at various temperatures of reaction. The extent of plasticizer migration decreases significantly with increase in temperature of reaction. Significant plasticizer migration resistance was observed from tubes reacted at 80°C and hence that temperature was used for further modification.

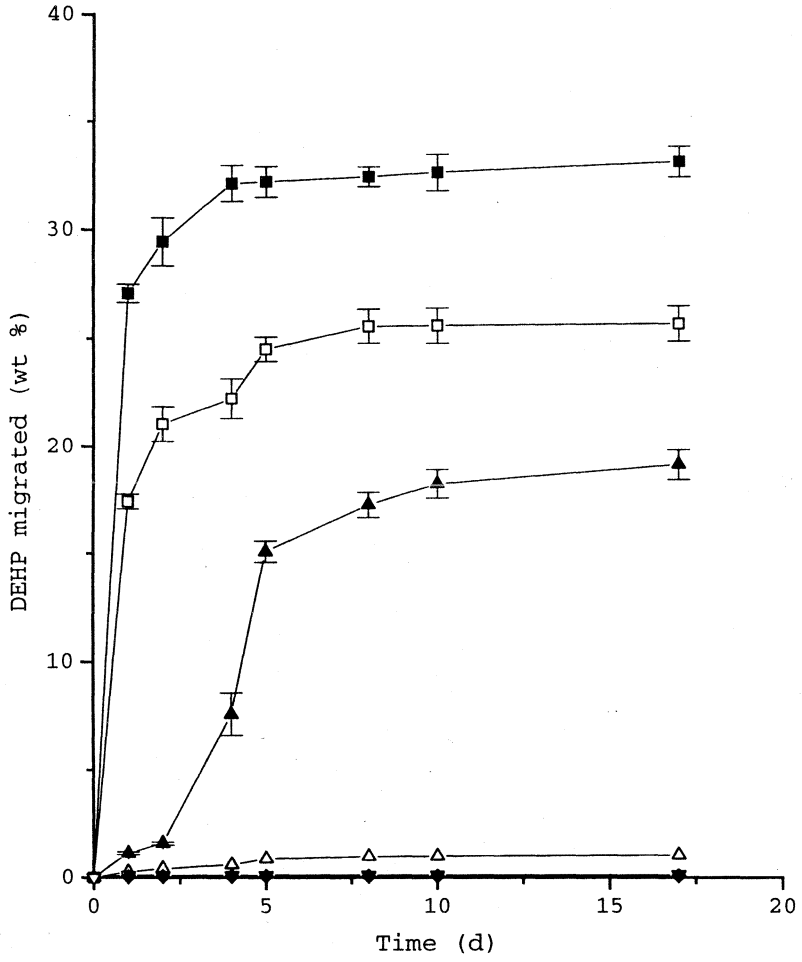


Fig. 3.3.13 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from unmodified plasticized PVC tubes and tubes reacted with sodium thiosulphate in the presence of TBAH at 80°C for various periods of time. [Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}; Unmodified PVC (■), 1 h (□), 2 h (▲), 3 h (△), 4 h (▼), 5 h (▽) and 6 h (♦).

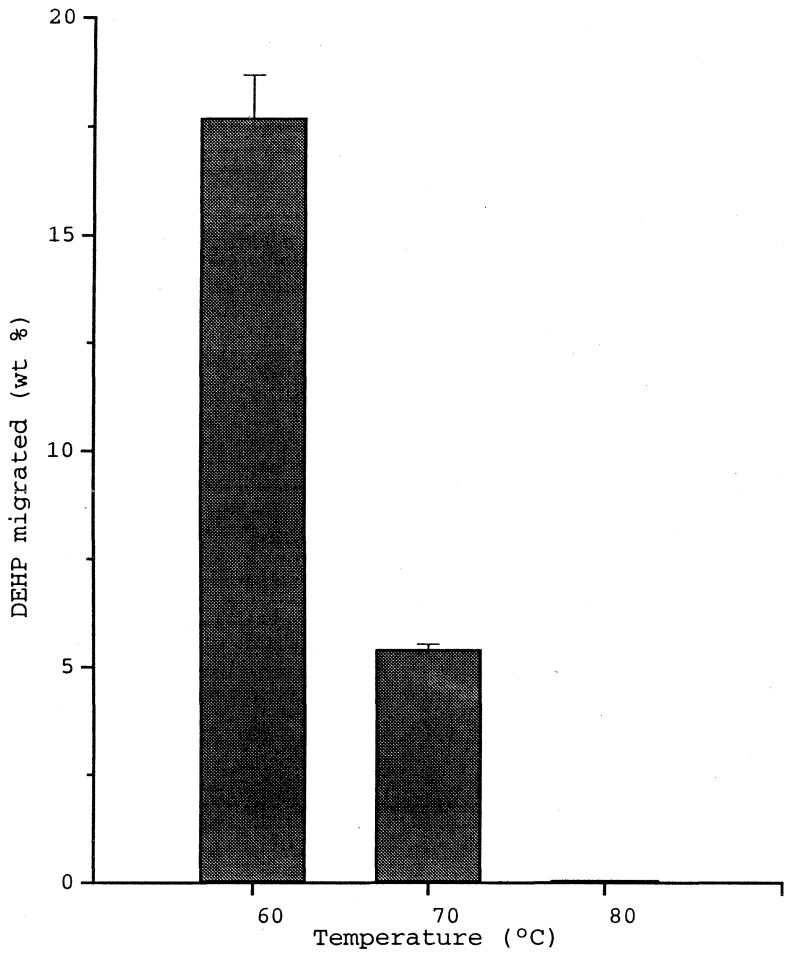


Fig. 3.3.14 Amount of DEHP migrated in 48 h into petroleum ether at 30°C from plasticized PVC tubes reacted with sodium thiosulphate in the presence of TBAH for 5 h at different temperatures. [Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}.

Eventhough not expected, the substitution of thiosulphate anion on to PVC produced a surface gel which reduced the plasticizer migration very efficiently in petroleum ether, attempts were made to improve the migration resistance by further surface cross-linking. Surface cross-linking of thiosulphate substituted plasticized PVC tubes were carried out by treating with an acid, base, or oxidizing agent (Section 2.2.6.2). The various cross-linking agents and conditions used were as follows. Thiosulphate substituted PVC tubes were treated with 1 M sodium hydroxide (NaOH) at 60°C for 1 h, 4 M hydrochloric acid (HCl) at 30°C for 1 h and 30% hydrogen peroxide (H_2O_2) at 30°C for 1 h according to Okawara and Ochiai in the modification of polyepichlorohydrin (Okawara & Ochiai, 1980). These treatments are expected to possibly result in additional cross-linking on the surface of thiosulphate substituted plasticized PVC via the following reactions.

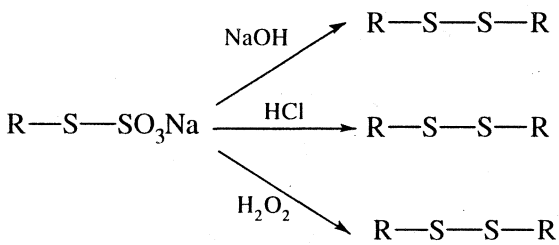


Table XXIII shows the percentage of DEHP migrated from thiosulphate substituted plasticized PVC tube and from thiosulphate substituted PVC tubes treated with the above reagents. However, such additional cross-linking reactions did not produce any improvement in the plasticizer migration resistance of the thiosulphate substituted PVC tubes, possibly because such reactions on the surface were not very significant.

Table XXIII
Wt % of DEHP migrated into petroleum ether at 30°C after 48 h of incubation in petroleum ether from thiosulphate substituted PVC tubes subjected to different cross-linking methods

Sample	Wt % of DEHP migrated after 48 h incubation in petroleum ether*
Thiosulphate substituted PVC	0.068±0.002
Substituted PVC treated with NaOH	0.092±0.008
Substituted PVC treated with HCl	0.072±0.01
Substituted PVC treated with H_2O_2	0.08±0.008

*Average of three determinations

3.3.4.2 Plasticizer Migration Over Prolonged Periods

Since this method of surface modification was found to prevent plasticizer migration very significantly in organic extractant, an extended migration study was undertaken to examine the migration resistance of the thiosulphate substituted PVC for a prolonged period in petroleum ether. Figure 3.3.15 shows the amount of plasticizer migrated into petroleum ether from thiosulphate substituted plasticized PVC tubes as well as from unmodified PVC tubes as a function of time for about 2 months. The thiosulphate substituted PVC tubes showed significant migration resistance compared to unmodified PVC tubes. The modified tubes lost only less than 1% of the plasticizer even after 2 months of incubation in petroleum ether whereas the unmodified PVC tubes loses almost all its plasticizer within 24 h.

This result was further corroborated by the HPLC analysis. The unmodified and thiosulphate substituted plasticized PVC tubes were incubated in HPLC grade hexane and the extract were then subjected to chromatographic analysis.

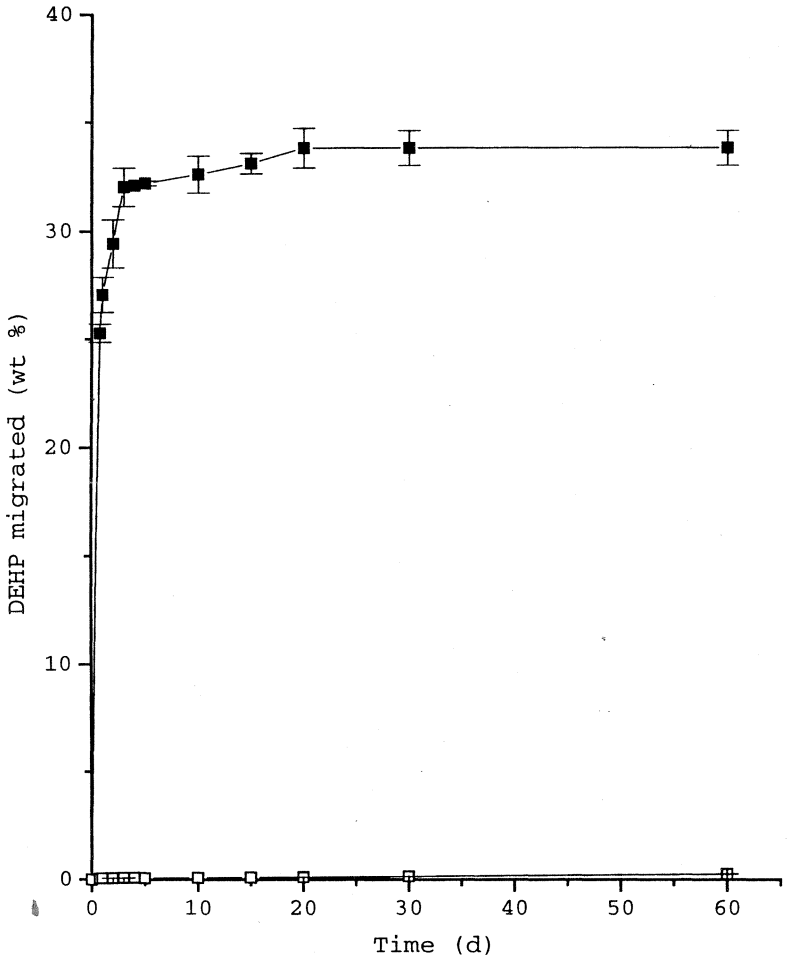


Fig. 3.3.15 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from unmodified plasticized PVC tubes and PVC tubes reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}; Unmodified PVC (■) and Thiosulphate substituted PVC (□).

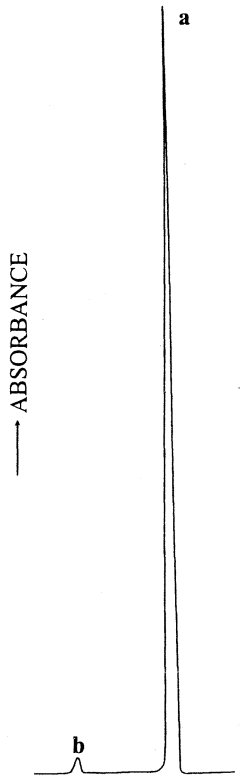


Fig. 3.3.16 Chromatogram of hexane extract of unmodified PVC tube (a) after 24 h of incubation and thiosulphate substituted PVC tube (b) after 2 months of incubation.

Figure 3.3.16 shows the chromatogram from unmodified PVC after 24 h and from modified PVC tubes after 2 months of incubation. The data dramatically demonstrate that the thiosulphate substituted plasticized PVC tubes are highly plasticizer migration resistant in potential organic extractant like hexane. The hexane extract contain 280 mg mL^{-1} of the plasticizer after 24 h whereas the extract from the modified PVC tubes after 2 months contains only 5 mg mL^{-1} of the plasticizer.

Most of the migration experiments described so far were carried out on plasticized PVC tubes modified by the nucleophilic substitution of sodium

thiosulphate under PTC condition. Inorder to examine the effect of surface modification on the plasticizer migration resistance of the plasticized PVC sheets, medical grade plasticized PVC sheets were subjected to surface modification under conditions which were optimized for the tubes. Thus, PVC sheets were reacted with aqueous sodium thiosulphate at 80°C for 5 h in the presence of TBAH as the catalyst. Similar to thiosulphate substituted PVC tubes, the substituted PVC sheets were also found to be highly migration resistant in petroleum ether. Figure 3.3.17 shows the extent of plasticizer migration from unmodified and thiosulphate substituted PVC sheet as a function of time. It can be seen that the method works well in the case of plasticized PVC sheets, similar to tubes.

3.3.4.3 Plasticizer Migration after Various Modes of Sterilization

The thiosulphate substituted plasticized PVC tubes were subjected to two common modes of sterilization and the plasticizer migration resistance was evaluated. The tubes were sterilized by autoclaving (Section 2.2.8.12.1) and by gamma irradiation (2.2.8.12.2). Table XXIV shows the weight percentage of DEHP migrated from sterilized PVC tubes in petroleum ether at 30°C.

It can be seen that gamma irradiation increased the migration resistance of thiosulphate substituted PVC tubes. The unmodified PVC tubes also showed a slight decrease in plasticizer migration upon gamma irradiation. This is due to chain scission leading to cross-linking of the base polymer. The improvement in migration resistance of the thiosulphate substituted PVC tubes on gamma irradiation can be attributed to higher extent of cross-linking on the surface due to chain scission of the base polymer as well as from the substituted thiosulphate

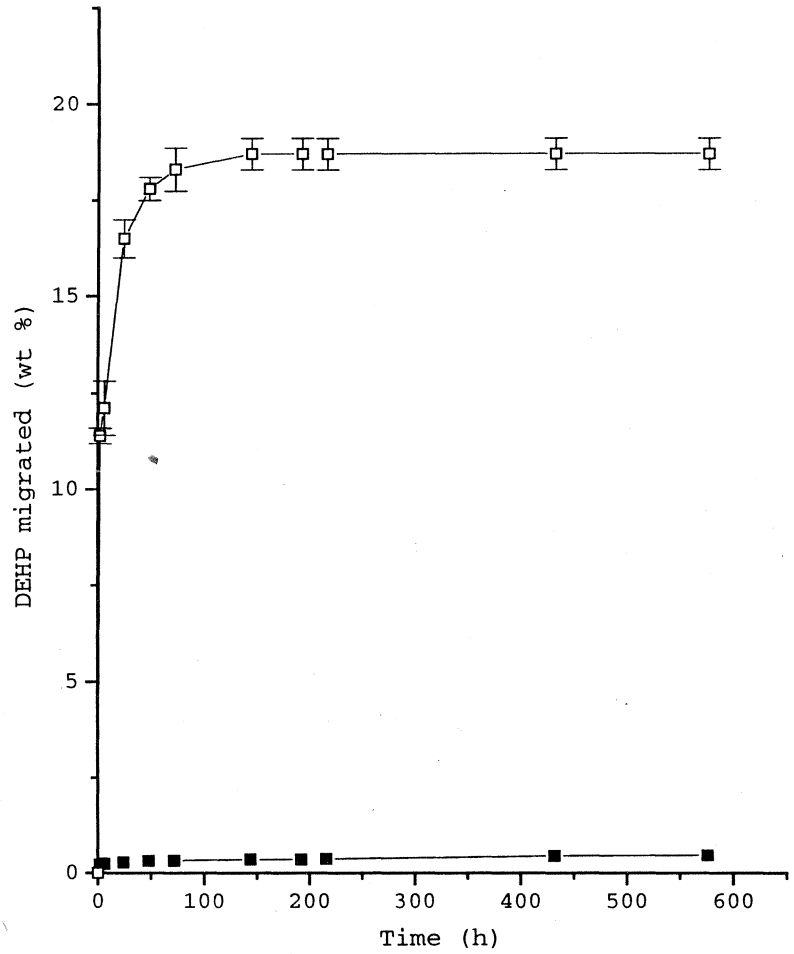


Fig. 3.3.17 Amount of DEHP migrated as a function of time in petroleum ether at 30°C from unmodified plasticized PVC sheet and PVC sheet reacted with sodium thiosulphate in the presence TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}; Unmodified PVC sheet (□) and Thiosulphate substituted PVC (■).

groups on the surface. The presence of sulphur atoms on the surface may possibly facilitate greater chain scission in thiosulphate substituted plasticized PVC.

Table XXIV
Amount of DEHP migrated into petroleum ether at 30°C from unmodified PVC tubes as well as from PVC tubes reacted with sodium thiosulphate at 80°C for 5 h in presence of TBAH after different modes of sterilization.
[Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}

Sample	Mode of sterilization	Time of incubation in petroleum ether	DEHP migrated (wt %)
Unmodified PVC	Unsterilized	24 h	27.07 ±0.8
Unmodified PVC	Autoclaving	24 h	27.32 ±0.9
Unmodified PVC	Gamma irradiation	24 h	25.88 ±0.4
Thiosulphate substituted PVC	Unsterilized	30 d	0.14 ±0.002
Thiosulphate substituted PVC	Autoclaving	30 d	0.18 ±0.005
Thiosulphate substituted PVC	Gamma irradiation	30 d	0.022±0.008

There is apparently no reaction between the plasticizer DEHP and sodium thiosulphate during the surface modification. The UV spectrum of the extracted solution was exactly identical to that of unreacted DEHP. T.L.C analysis showed that no reaction product is formed when DEHP was treated with sodium thiosulphate in the presence of PTC. Only a single spot could be detected in the fraction extracted using hexane, the R_f value of which was same as that of DEHP (0.65) (Section 2.2.1). This confirmed the fact that the only reaction between the plasticized PVC and sodium thiosulphate in the presence of PTC is the nucleophilic substitution of chlorine on the surface of PVC by thiosulphate anion.

3.3.4.4 Accelerated Plasticizer Migration in Cotton Seed Oil and PEG-400

Since the thiosulphate substituted PVC was found to be highly migration resistant in potential organic extractant such as petroleum ether, further migration

studies were carried out with two different media having different polarities ie., cotton seed oil and PEG-400 under accelerated conditions (Section 2.2.9.3). Figure 3.3.18 shows the accelerated migration profile in these two media from unmodified and thiosulphate substituted PVC tubes. The thiosulphate substituted PVC tubes showed migration resistance in cotton seed oil a solvent having low polarity, compared to the unmodified tubes. The extent of weight loss in thiosulphate substituted PVC was very low compared to unmodified PVC in 4 d. In a highly hydrophilic and polar media such as PEG-400, the thiosulphate substituted PVC tubes lost all its migration resistance, infact it showed a higher level of plasticizer migration compared to the unmodified tube. The migration pattern from thiosulphate substituted PVC in PEG-400 was found to be entirely different compared to that of PVC reacted with sodium sulphide discussed in the previous chapter (Section 3.2.4.4). Whereas sulphide cross-linked plasticized PVC tubes discussed in section 3.2.4.4 showed complete migration resistance in PEG-400, the thiosulphate substituted plasticized PVC showed a slightly higher migration pattern compared to unmodified PVC. This is possibly due to lower cross-link density on the surface of thiosulphate substituted PVC and mainly due to the presence of hydrophilic sulphonate groups on the surface which greatly augments extraction with hydrophilic media.

3.3.4.5 Plasticizer Migration in Ethanol-Water Mixture According to BP

The migration assay was also carried out in a standard extracting media ie., ethanol/water mixture according to BP (Section 2.2.9.4). Table XXV shows the extent of plasticizer migration from thiosulphate substituted and unmodified

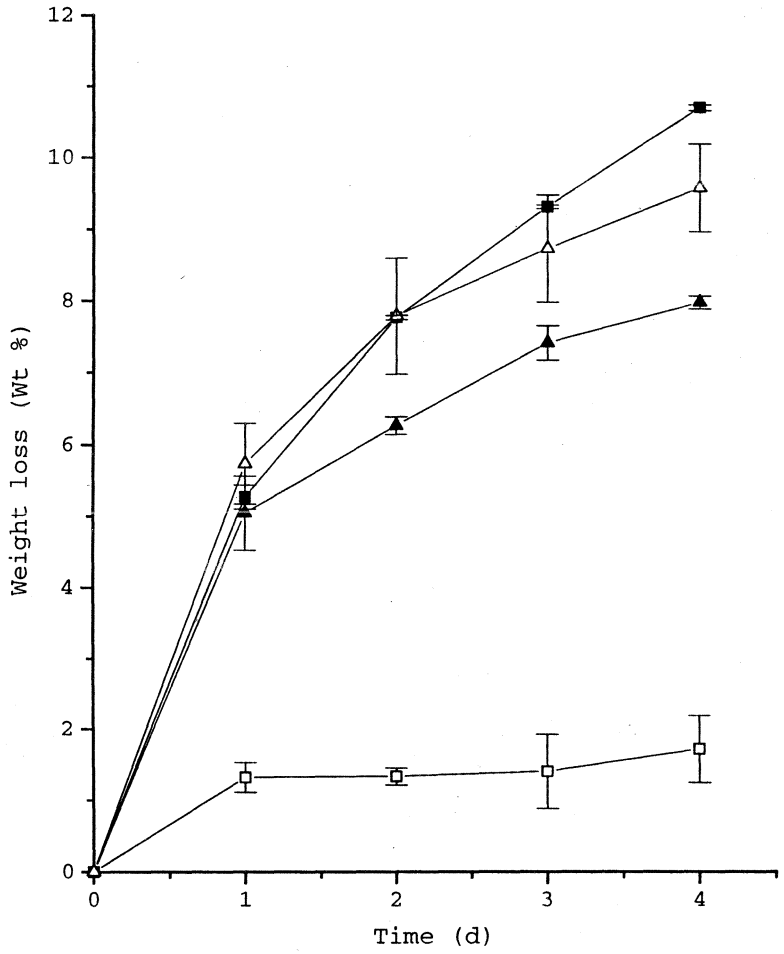


Fig. 3.3.18 Percentage weight loss as a function of time in cotton seed oil and PEG-400 at 70°C from unmodified plasticized PVC tubes and tubes reacted with sodium thiosulphate in the presence of TBAH at 80°C for 5 h. [Sodium thiosulphate] = 3 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}; Unmodified PVC in cotton seed oil (■), Unmodified PVC in PEG-400 (▲), Thiosulphate substituted PVC in cotton seed oil (□) and in PEG-400 (△).

PVC sheet in this extraction media. The extent of migration from unmodified plasticized PVC sheet was found to be less than the permissible level of 0.01%. The thiosulphate substituted PVC on the other hand shows a higher extent of migration in this extraction solvent. This observation corroborated the higher extent of plasticizer migration found in another polar, hydrophilic medium ie., PEG-400.

Table XXV
Plasticizer migrated (w/v) from plasticized PVC sheet into ethanol/water mixture from unmodified PVC sheet and sheet reacted with sodium thiosulphate for 5 h at 80°C in the presence of TBAH as the catalyst.
[Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}

Sample	DEHP migrated (% W/V)
Unmodified PVC	0.007
Thiosulphate substituted PVC	0.140

Thus polar extraction media were found to accelerate the plasticizer migration level from the thiosulphate substituted PVC whereas the nonpolar solvents completely failed to extract plasticizer from the modified PVC compared to unmodified. The high migration resistance of thiosulphate substituted PVC in non polar organic extractants can be attributed to the presence of hydrophlic sulphonate groups acting as a barrier to the diffusion of the highly non-polar plasticizer as well as to some extent of surface cross-linking on the surface. It has been shown earlier that surface grafting of PVC with hydrophilic polymer such as methacrylic acid and hydroxyethylmethacrylate prevent the diffusion of DEHP into non-polar media such as hexane whereas the migration into polar media such as PEG-400 were not significantly altered by such surface grafting (Krishnan *et al.*, 1990; 1991). The presence of sulphonate groups on thiosulphate substituted PVC on the other hand

accelerate the extraction with hydrophilic solvents like PEG-400 as well as with ethanol-water mixture.

3.3.5 Mechanical Properties

The appropriate mechanical properties of PVC are very important in most of its biomedical applications. The desirable values of mechanical properties of plasticized PVC for medical applications have been given in the American Society for Testing Materials (ASTM, 1982). The mechanical properties of plasticized PVC sheets after thiosulphate substitution were measured with respect to ultimate stress and ultimate percentage elongation inorder to examine whether surface modification induced any changes in these properties. Table (XXVI) shows the stress-strain properties of unmodified and thiosulphate substituted plasticized PVC sheets.

Table XXVI
Mechanical properties of unmodified plasticized PVC sheet and sheet reacted with sodium thiosulphate at 80°C for 5 h in the presence of TBAH. [Sodium thiosulphate] = 3.0 mol dm^{-3}; [TBAH] = 0.15 mol dm^{-3}

Sample	Ultimate stress (M Pa)± SD*	Ultimate strain (%) ± SD*
Unmodified PVC	19.38±0.57	437.7±26.3
Unmodified at 80°C for 5 h	18.95±1.16	436.2±41.9
Unmodified at 4°C for 30 d	18.48±0.65	466.1±30.7
Unmodified autoclaved	19.84±0.95	522.5±13
Thiosulphate substituted PVC	18.26±1.16	366.6±34.3
Thiosulphate substitued PVC at 4°C for 30 d	17.2 ±0.75	400.1±16.1
Thiosulphate substituted PVC autoclaved	15.97±1.68	371.6±35.8

* Average of six determinations

The mechanical properties of unmodified PVC sheets were not significantly affected as a result of heating at 80°C for 5 h as well as due to autoclaving. The mechanical properties of the thiosulphate substituted PVC sheets were somewhat affected. The ultimate stress of thiosulphate substituted PVC decreases by 5% and the ultimate strain by 16% compared to the unmodified PVC sheet. This lowering of mechanical properties is due to the surface cross-linking produced on the surface of thiosulphate substituted plasticized PVC. Autoclaving further reduced the mechanical properties of thiosulphate substituted PVC as evidenced by the decrease in the stress value. The ultimate stress of autoclaved thiosulphate substituted PVC decreases by 17.5%. This decrease in stress value during autoclaving can be attributed to some degradation reaction accompanying the sterilization process.

The data obtained thus establish that surface nucleophilic substitution of chlorine atoms of PVC with sodium thiosulphate can feasibly take place in a two phase system using TBAH as the PTC. The nucleophilic substitution reaction proceeds without any dehydrochlorination as evidenced by the IR and UV-Vis spectra of the thiosulphate substituted PVC sheet. The substitution significantly changed the surface chemistry of the plasticized PVC. The nucleophilic substitution results in the formation of surface which is highly complex with a variety of functional groups. The substitution directly produced a surface cross-linked gel which is insoluble in all solvents of PVC. The surface cross-linked gel increases with time of reaction. The presence of sulphonate groups on the surface of thiosulphate substituted PVC was confirmed by IR as well as by XPS. The optical clarity of the thiosulphate substituted PVC was found to be similar to that of

unmodified PVC. The surface morphology of the thiosulphate substituted PVC was found to be similar to that of unmodified PVC sheet. The extent of water absorption by the thiosulphate substituted PVC was found to be only slightly higher than that of unmodified PVC. Even then, the presence of hydrophilic sulphonate groups on the surface greatly reduced the under water air and octane contact angles of thiosulphate substituted PVC. The surface modification only slightly reduced the mechanical properties of plasticized PVC. Thiosulphate substitution on the surface tremendously improved the plasticizer migration resistance of plasticized PVC in non-polar solvents. This is attributed to the presence of some surface cross-linking as well as due to the presence of hydrophilic sulphonate groups acting as a barrier to the diffusion of the highly non-polar plasticizer. The substituted PVC was found to be migration resistant in petroleum ether even after 2 months of incubation. On the other hand, in polar solvents plasticizer migration was observed. This is possibly due to the presence of hydrophilic sulphonate groups on the surface as observed by previous workers when hydrophilic monomers were grafted onto the surface of plasticized PVC (Krishnan *et al.*, 1990, 1991).

3.4 Surface Grafting of Poly(Ethylene Glycol) onto Plasticized Poly(Vinyl Chloride) to Reduce Plasticizer Migration

3.4.1 Background

One of the most commonly employed surface modification techniques to improve the blood compatibility of polymers is by grafting water soluble polymers onto the surface. According to Ikada (Ikada, 1984) a biomaterial surface with diffuse hydrophilic surface would be highly blood compatible. These diffused surface layers having high water content can prevent protein adsorption which is the first and crucial step in surface induced coagulation cascade and adhesion of platelets, bacteria etc. Of all the neutral, hydrophilic and water soluble polymers commercially available, poly(ethylene glycol) (PEG) is reported to be the most mobile, most dynamic and the least interactive one (Andrade *et al.*, 1996). Low molecular weight polymers (less than 10,000 Daltons) are referred to as PEG, while those with higher molecular weights are known as poly(ethylene oxide) (PEO). The keen interest shown in PEG derives from its unique set of properties. The molecule is soluble in water and in a number of organic solvents (Bailey & Koleske, 1991). PEG is known to be non-toxic and has been approved by the United States Food and Drug Administration (FDA) for internal consumption (Harris, 1992). It is rapidly cleared from the body and is not immunogenic (Abuchowski, 1977; Richter & Akerblom, 1984; Harris, 1992). PEG and its derivatives are readily available in a range of purities and molecular weights and are relatively inexpensive and easy to obtain. PEG is usually effective at excluding other polymers from its surroundings when in an aqueous environment (Harris, 1992). This property can be translated

into protein rejection, reduced platelet adhesion, bacterial repulsion etc.,(Merril & Salzman, 1983; Jeon *et al.*, 1991; Osterberg *et al.*, 1995) as well as prevents recognition by the immune system (Lasic & Martin, 1996) once incorporated onto the surface of various polymers. PEG coating on the surface of various polymers provides an effective lubricious surface. The surface consisting of PEG must present to blood a layer containing mostly water and bound, but locally mobile PEG segments. NMR studies have shown that water solvated PEG has very high segmental mobility (Nagaoka *et al.*, 1984). Different hypotheses have been proposed to explain the passivity of PEG modified surfaces towards protein adsorption. These include the low interfacial free energy of the hydrated surface (Coleman *et al.*, 1982; Lee *et al.*, 1988), the unique structural interaction of the soluble chains within the water matrix (Nagaoka *et al.*, 1983), rapid movement of hydrated chains and formation of large excluded volume (Andrade *et al.*, 1987; Harris, 1992) and steric repulsion forces (Amiji & Park, 1994).

Several techniques have been used to prepare PEG rich polymer surfaces. The simplest modification is by physical adsorption of high molecular weight (Mol. Wt.>100,000 Daltons) PEG (Kato *et al.*, 1981). But such simple adsorption is highly unstable and will peel off after some time in the biological environment. PEG containing amphipathic block copolymers were commonly employed for physical adsorption. This can lead to a more stable surface due to hydrophobic interaction between the substrate and the hydrophobic segment of the chain (Lee & Andrade, 1988; Lee *et al.*, 1989, 1990; Amiji & Park, 1992; Freij-Larsson *et al.*, 1996). Pluronics® having longer hydrophobic segments with 56 or more propylene oxide residues, greatly reduced the adsorption of plasma proteins and

platelet adhesion on polymer surfaces (Amiji & Park, 1992). These triblock copolymers have also been surface cross-linked by radiation (Amiji & Park, 1993). Another technique to obtain dense, stable PEG-rich surfaces is by synthesis of interpenetrating polymer networks containing immobilized PEG (Drumheller & Hubbell, 1995). An interpenetrating polymer network of PEO and polyether substituted siloxane also showed considerable blood compatibility (Chaikof *et al.*, 1990). Desai and Hubbel (1991) had developed a technique to incorporate large amount of PEO onto various surfaces by a process called surface physical interpenetrating network (SPIN), using high molecular weight PEO.

The most effective way of creating a permanent PEG rich surface is by covalent grafting of PEG or PEG derivatives onto the surface. Commonly used techniques include direct coupling of PEG molecules which leads to surfaces containing pendant PEG chains. They usually require chemical derivatization of the terminal hydroxyl groups of PEG prior to reaction with a functionalized surface. The topic of PEG derivatives has been reviewed recently. (Herman *et al.*, 1995; Zalipsky, 1995). Han *et al* (1989; 1991) reacted unmodified PEG with surfaces containing isocyanate groups. Desai and Hubbell (1991) grafted cyanuric chloride activated PEG to amine derivatized PET surfaces and the modified surface greatly reduced protein and platelet adhesion. Amino functionalized PEG grafted onto cyanuric chloride derivatized PET surface greatly reduced protein adsorption (Gombotz *et al.*, 1991). Grafting of PEG onto cellulose membranes was carried out via esterification reaction between carboxyl terminated PEG with hydroxyl group of cellulose (Kishida *et al.*, 1992). Coupling of diamino-PEG of different molecular

weights onto carboxylated polystyrene greatly reduced protein adsorption (van Delden *et al.*, 1996).

Another widely attempted method of incorporation of PEO onto base polymer is by block copolymerization (Grainger *et al.*, 1989; Chen & Ruckenstein, 1991). Polyurethane with PEO soft segment is highly blood compatible. The blood compatibility of various polyurethanes having PEO segments have been reviewed (Ito & Imanishi, 1989). Polyurethane with PEO grafted side chains have also been found to be highly blood compatible (Brinkman *et al.*, 1990).

For inert surfaces without any functional groups, PEG coupling can be carried out after the introduction of functional groups. Reactive functional groups utilize initiating species such as free radicals or peroxides, which are generated on polymer substrates by UV irradiation, gamma irradiation or plasma discharge. Methoxy PEG monomethacrylate monomers are commonly employed for this type of modification. Mori and Nagaoka photografted methoxy poly(ethylene glycol) methacrylates on PVC surface containing photoactive dithiocarbamate groups to reduce thrombogenicity (Mori *et al.*, 1982). Clinical application of the PEG-grafted PVC tubes showed reduced potential for thrombogenicity compared to control PVC tubes (Nagaoka & Nakao, 1990). A photoactive PEG , PEG phenyl-azide was synthesized and was photografted onto variety of polymer surfaces to reduce platelet adhesion (Tseng & Park, 1992). PEG-methacrylate was grafted onto silastic films by gamma irradiation in the presence of cuprous ions (Sun *et al.*, 1986, 1987). Tseng *et al* (1995) immobilized ethylene glycol-butadiene block copolymers onto dimethyl dichlorosilane-coated glass by gamma irradiation. Electron beam irradiation was used to immobilize PEG onto surfaces grafted with hydrophilic

polymer such as methacrylic acid (Sofia & Merrill, 1998). Glow discharge plasma deposition of PEG precursors have been tried on a variety of materials (Lopez *et al.*, 1992). Plasma technique have been extensively used to immobilize PEG onto various polymers (Fujimoto *et al.*, 1993; Lee *et al.*, 1997)

PEG grafted surfaces also plays an important role in biological surface modification. The grafted chain can be used as a spacer molecule to couple bioactive molecules like enzymes (Harris,1992).

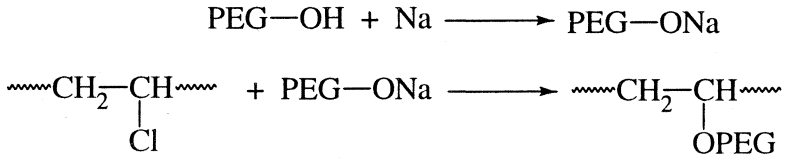
Abribat *et al* (1994) had shown that hydroxyl groups in bulk PEO and poly(propylene oxide) can be alkylated with alkyl halides using a strong base, such as KOH, in the absence of a solvent. Lora *et al* (1993) reported the surface modification of polyphosphazenes by a metathetical exchange reaction between the trifluoroethoxy group with sodium salt of PEG. Sodium salt of PEG-20,000 was used to immobilize PEG on various halogenated surfaces via Williamson ether synthesis (Litauszki *et al.*, 1997)

This chapter describes the surface grafting of PEG of different molecular weights onto plasticized PVC, physico-chemical characterization of the grafted surface and the evaluation of the plasticizer migration resistance of the grafted PVC compared to unmodified plasticized PVC in various extraction solvents.

3.4.2 Surface Grafting of PEG onto Plasticized PVC

Our attempt was to graft PEG of different molecular weights onto the surface of plasticized PVC by a simple technique without derivatizing PEG. The strategy here was to make use of the labile nature of the chlorine atoms present on PVC to

covalently couple sodium salt of PEG (Na-PEG). The grafting takes place via the classical Williamson ether synthesis as shown below.



The optimum reaction condition for grafting was arrived by following the extent of plasticizer migration from plasticized PVC tubes grafted with PEG of different molecular weights by varying the time and temperature of grafting. Briefly, the sodium salt of PEG (Na-PEG) was prepared by reacting PEG of different molecular weights with metallic sodium equivalent to both the hydroxyl groups of PEG ie., the disodium salt. The disodium salt of PEGs of different molecular weights will be represented as Na-PEG-Mol.Wt throught out the chapter. The monosodium salt of PEG was also prepared by reacting PEG with half equivalent of metallic sodium to the hydroxyl group of PEG (Section 2.2.7.1). The grafting of Na-PEGs onto plasticized PVC was carried out by dipping plasticized PVC in neat Na-PEG (Section 2.2.7.2). An excess amount of Na-PEG was heated to 70°C and held at this temperature for the duration of the reaction. The plasticized PVC was then immersed in the sodium salt of PEG in the melt for various periods of time. Plasticized PVC reacted with Na-PEGs of different molecular weights will be represented generally as PEG-grafted PVC in general or specifically as PEG-Mol. Wt-grafted PVC. The PEG grafted PVC was then washed thoroughly with running tap water, followed by distilled water and dried in an air oven at 50°C to constant

weight. The method allows PEG to be grafted on the surface of plasticized PVC without introducing any functional groups foreign to PEG. Since the reaction was carried out in the melt, only the surface chlorine atoms will get substituted and hence the reaction will be highly surface confined. The bulk properties of the plasticized PVC therefore, are not expected to be adversily affected. PEG being a highly blood compatible polymer, can also improve the interfacial properties of the polymer. All the low molecular weight PEG (PEG-200, 400 & 600) used in this study became a dark brown, highly viscous solution on reaction with metallic sodium. Grafting plasticized PVC using these Na-PEG solutions imparts a dark coloration to PVC greatly affecting its clarity. In the case of PEG-4000, the sodium salt (Na-PEG) formed was a light yellow to light brown clear, viscous liquid above 50-60°C and grafting Na-PEG-4000 onto plasticized PVC produced only slight colour changes. The Na-PEG once prepared was used immediately for the surface modification.

3.4.3 Physico-Chemical Characterization of PEG Grafted Plasticized PVC

3.4.3.1 FTIR-ATR Spectra

Surface infrared spectroscopy couples the analytical method of infrared spectroscopy with the physical phenomenon of total internal reflection to enable the molecular vibrations within the surface regions of materials to be studied. Figure 3.4.1 shows the FTIR-ATR spectra in the 800-2000 cm^{-1} region of unmodified plasticized PVC sheet (a), plasticized PVC sheet treated with pure PEG-4000 at 70°C for 15 min (b) and plasticized PVC sheet reacted with Na-PEG-4000 at 70°C

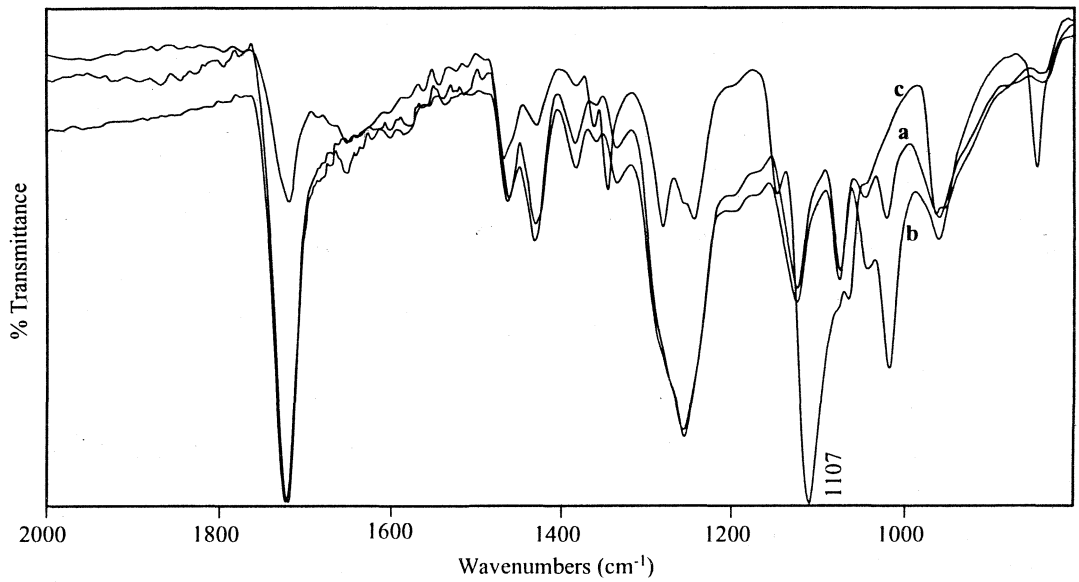


Fig. 3.4.1 FTIR-ATR spectrum of unmodified PVC sheet (a), PVC sheet treated with pure PEG-4000 (b) and PVC sheet reacted with Na-PEG-4000 at 70° C for 15 min (c).

for 15 min (c). The IR spectra of unmodified PVC sheet (Figure 3.4.1a) and PVC sheet treated with PEG-4000 (Figure 3.4.1b) are identical. This clearly shows that no grafting reaction on PVC is taking place on treatment with PEG alone. The surface spectrum of plasticized PVC reacted with Na-PEG-4000 (Figure 3.4.1c) on the other hand shows pronounced differences compared to unmodified plasticized PVC. Most of the peaks characteristic of unmodified PVC were not found in the spectrum of PEG grafted PVC showing coverage of plasticized PVC surface by PEG molecules. The characteristic ether peak was found at 1107 cm^{-1} (due to C-O-C ether stretching) in the case of PEG grafted PVC. The corresponding peak is absent in the spectra of unmodified PVC and PVC treated with pure PEG-4000. Thus the IR spectrum clearly confirmed the presence of PEG molecules on the surface of plasticized PVC surface reacted with Na-PEG-4000.

3.4.3.2 Contact Angle Measurements

Grafting of PEG onto PVC produced an aqueous gel network on the surface of plasticized PVC. Such materials can be of considerable interest as blood and tissue interfaces. The aqueous gel-aqueous solution interface is very difficult to study mainly due to hydrodynamic effect. The contact angle technique can be used to characterize the gel surface and the gel-water interface. The captive bubble method is the most suitable technique for probing gel water interface. The advantage of this method is that the gel surface is fully hydrated and hence the environment is fixed. Thus, air-in-water and octane-in-water contact angles permit one to probe the gel-water interface in the fully hydrated *in situ* state and obtain estimates of γ_{sv}^{d}, γ_{sv}^{p} and γ_{sw}. The polar and dispersion component of PEG-4000 grafted and unmodified plasticized PVC was calculated according to Andrade *et al* (1979). For this, under water air and octane contact angles were measured for PEG grafted and unmodified PVC sheets (Section 2.2.8.4). Table XXVII shows the under water air and octane contact angle as well as the calculated surface energy parameters of unmodified and plasticized PVC sheet reacted with Na-PEG-4000 at 70°C for various periods of time. There is considerable decrease in the dispersion component and considerable increase in the polar component of the surface free energy of PVC on PEG grafting. Varying the grafting time from 5 min to 30 min, did not produce any significant changes in the surface parameters. The total interfacial energies of plasticized PVC reacted with Na-PEG-4000 for even 5 min was found to be almost near zero. The lowest values were found with sheet reacted with Na-PEG-4000 for 10 & 15 min. A slight increase in the values was found in the case of sheet reacted for 30 min. This

may be possibly due to the presence of greater extent of plasticizer molecules on the surface since extraction of plasticizer molecules takes place simultaniously with grafting as discussed in section 3.4.4.1. For PEG-4000 grafted PVC sheet (15 min, 70°C) the dispersion component decreases by (~35%) and the polar component increases by (~222%) compared to unmodified plasticized PVC. The decrease in dispersion component and the increase in the polar component clearly shows the incorporation of polar PEG molecules on the surface. The unmodified plasticized PVC sheet, which is hydrophobic shows a very high total interfacial free energy of about 12 ergs/cm^2.

Table XXVII
Under water air and octane contact angles as well as the calculated surface energy parameters of unmodified plasticized PVC sheet as well as plasticized PVC reacted with Na-PEG-4000 at 70°C for various periods of time

Sample	θair* (°)	ϕoctane* (°)	γ_{sv}^{d} (ergs cm^{-2})	γ_{sv}^{p} (ergs cm^{-2})	γ_{sw} (ergs cm^{-2})
Unmodified PVC	60.26	94.27	33.21	14.57	12.03
5 min grafted	20.94	159.5	20.04	47.35	~ 0
10 min grafted	18.73	160.1	20.78	47.53	~ 0
15 min grafted	18.37	158.5	21.4	47.05	~ 0
30 min grafted	22.43	152.6	21.79	44.99	0.13

*Average of six determinations

The solid/water interfacial free energy of all the PEG grafted PVC surfaces were found to be virtually zero indicating the highly hydrophilic nature of the surface as opposed to the unmodified PVC surface which is hydrophobic in nature. Therefore, according to the minimum interfacial energy hypothesis, the grafted surface should exhibit low protein and cellular adhesion and would be promising as a blood compatible surface. The hypothesis states that if the gel-water interface has

a very low interfacial free energy, then protein adsorption should be very low and highly reversible.

3.4.3.3 Weight Change

Attempts to quantify the extent of grafting by monitoring the increase in weight of PVC due to grafted PEG was not successful since the reaction conducted at 70°C always resulted in a slight decrease in weight of PVC, due to loss of plasticizer from PVC into the reaction medium. The loss of plasticizer into the reaction medium was estimated by treating plasticized PVC sheets with PEG-4000 at 70°C for various periods of time. Table XXVIII shows the decrease in weight of PVC sheets. Because pure PEG, and not its sodium salt, was used in these experiments, no grafting was expected and the decrease in the weight of the specimen was due to loss of the plasticizer into the medium. Since small amounts of PEG may get adsorbed onto the surface but this was not taken into account since treating PVC with PEG under the reaction conditions always resulted in some measurable weight loss for the specimens

Table XXVIII
Weight loss of plasticized PVC sheets treated with PEG-4000 (not the sodium salt) at 70°C for various periods of time

Time of reaction (min)	Weight loss (%) $\pm$ SD*
5	1.42 $\pm$ 0.22
10	1.65 $\pm$ 0.13
15	1.99 $\pm$ 0.30
30	3.03 $\pm$ 0.49

*Average of eight determinations

3.4.3.4 Surface Morphology

Figure 3.4.2 shows the SEM of the surface of unmodified plasticized PVC sheet (a) and PEG-4000 grafted plasticized PVC sheet (b). The SEM photograph of air dried PEG-4000 grafted PVC surface sputter coated with gold showed dark patches, believed to be due to the presence of the grafted layer of PEG on the surface. This was further corroborated by subjecting the grafted sheets to critical point drying followed by examination in the SEM as discussed in the next chapter (section 3.5.1).

3.4.3.5 Optical Clarity

As discussed in the previous chapters the optical clarity of PVC based devices is very important in medical and related applications. Plasticized PVC tubes were used for comparing the optical clarity of unmodified and PEG-4000 grafted plasticized PVC. Figure 3.4.3 shows the percentage transmittance of the unmodified plasticized PVC tube and PVC tube reacted with Na-PEG-4000 at 70°C for 15 min in the visible region (400-700 nm). From the spectra it can be seen that the clarity of the PVC tube is not affected to any great extent due to the surface grafting. The slight decrease in transmittance below the wavelength of 500 nm region is possibly due to some dehydrochlorination of the sample accompanying the grafting process since the alkoxide anions are known to be strong bases.

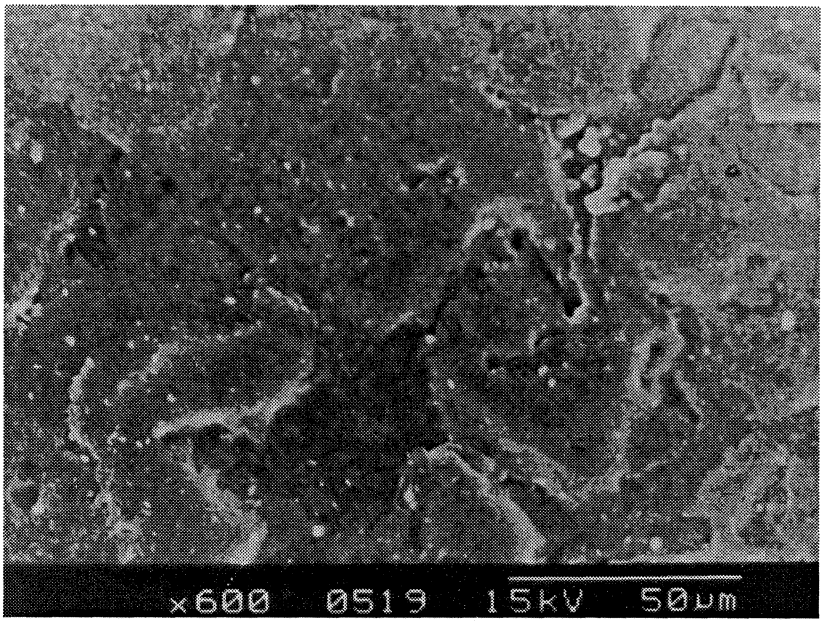


Fig. 3.4.2a SEM showing the surface morphology of unmodified plasticized PVC sheet.

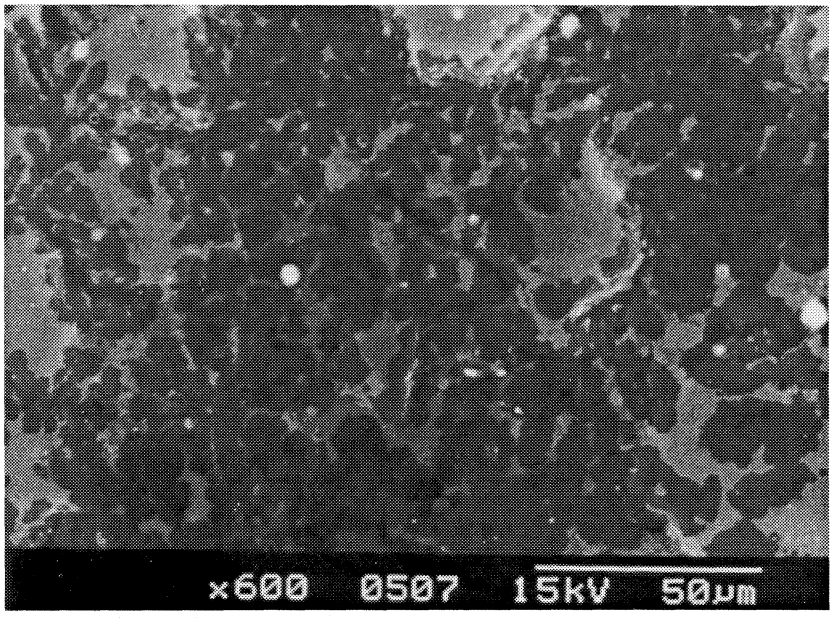


Fig. 3.4.2b SEM showing the surface morphology of PEG-4000 grafted PVC sheet.

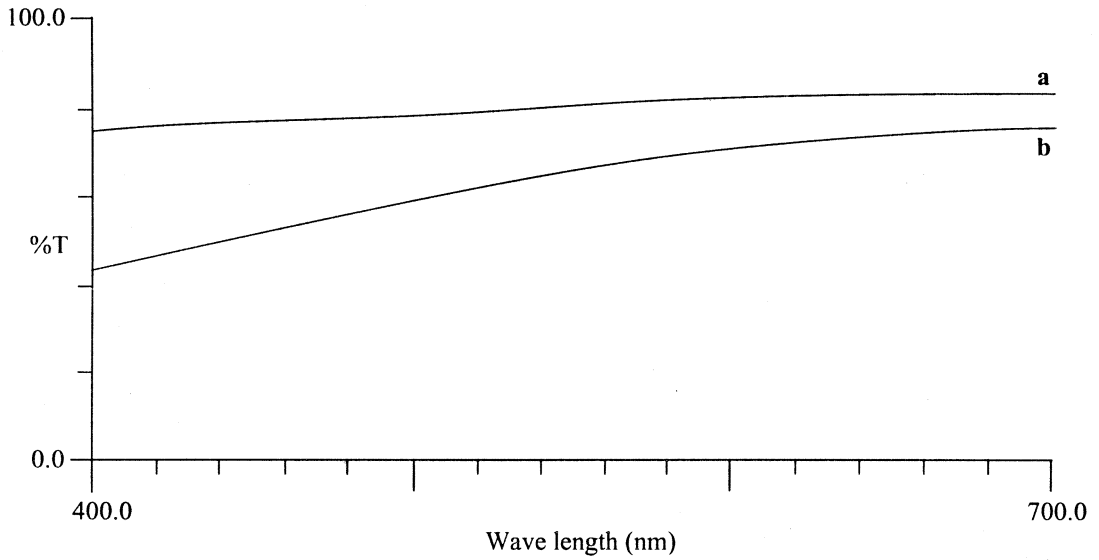


Fig. 3.4.3 The percentage transmittance of unmodified plasticized PVC tube and PVC tube reacted with Na-PEG-4000 at 70°C for 15 min in the 400-700 nm range. Unmodified PVC tube (a) and PEG-4000 grafted PVC tube (b).

3.4.4 Plasticizer Migration from PEG Grafted Plasticized PVC

3.4.4.1 Optimization of Reaction Condition

The optimization of reaction conditions of PEG grafting to reduce plasticizer migration was carried out by comparing the plasticizer migration profile under various reaction conditions. Low molecular weight PEG ie., PEG-400 is mainly used for optimizing the reaction conditions. Figure 3.4.4 shows the amount of the plasticizer migrated from plasticized PVC tubes reacted with Na-PEG-400 at different temperatures for 30 min. The migration was least from tubes grafted at 70°C. Apparently no grafting is taking place at 30°C. The decrease in plasticizer migration from PEG-400 grafted plasticized PVC is presumably due to the hydrophilic PEG surface acting as a barrier for the diffusion of the lipophilic

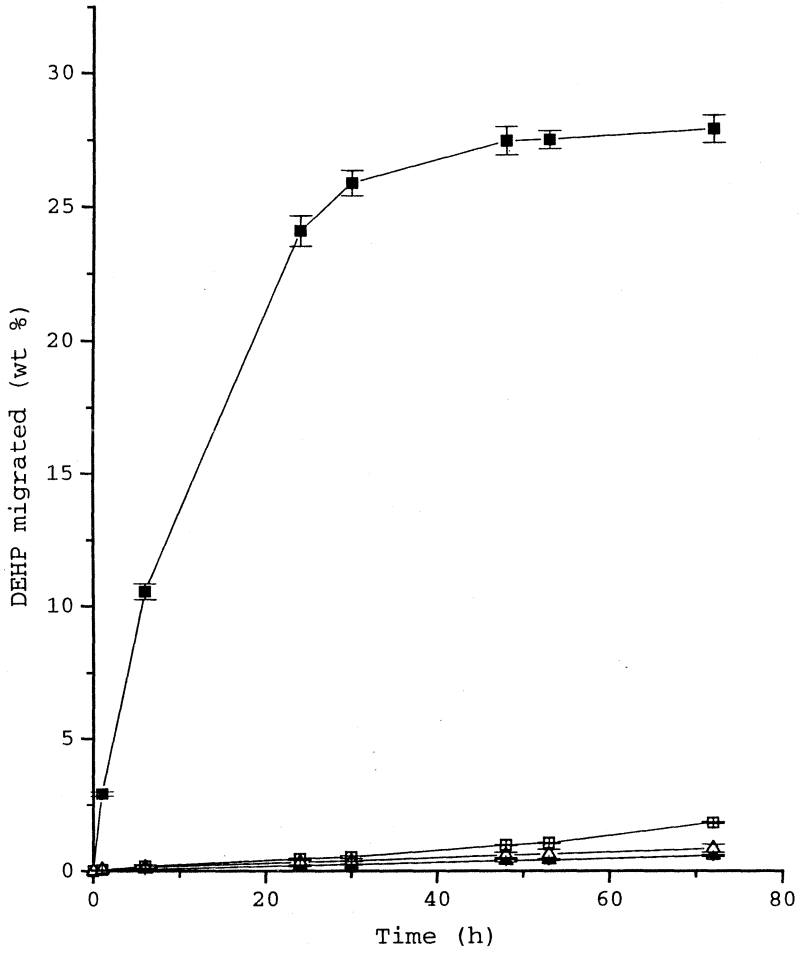


Fig. 3.4.4 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from plasticized PVC tubes reacted with Na-PEG-400 for 30 min at various temperatures. 30°C (■), 50°C (□), 70°C (▲) and 90°C (△).

DEHP from the PVC matrix. This was demonstrated by Krishnan *et al* (1990) where gamma radiation was used to graft hydrophilic polymers onto PVC surface to reduce plasticizer migration.

Figure 3.4.5 shows the amount of plasticizer migrated from plasticized PVC tubes reacted with Na-PEG-400 at 70°C for various periods of time into petroleum ether at 30°C. The extent of migration from tube reacted with Na-PEG-400 for 15 min and 30 min are almost identical. Higher reaction time slightly increased the extent of plasticizer migration. Grafting of PEG onto plasticized PVC always resulted in the migration of plasticizer into the reaction medium. As discussed in section 3.4.3.2 on the under water contact angles of PEG-4000 grafted PVC sheets, the slightly increased migration profile of the plasticizer seen with increase in reaction time is possibly due to the result of the pores and channels generated inside the polymer matrix during the migration of the plasticizer, facilitating the diffusion of DEHP to a higher degree.

Figure 3.4.6 shows chromatogram of the hexane extract after 24 h of incubation in hexane from unmodified plasticized PVC tube and tube reacted with Na-PEG-400 at 70°C for 15 min. 10μL each of the extract was injected into the column from the hexane extract of PEG-400 grafted PVC tube and from unmodified PVC tube. The figure dramatically shows the reduction in plasticizer migration from Na-PEG-400 reacted plasticized PVC tube.

Figure 3.4.7 shows the extent of migration of plasticizer from PVC tubes treated with disodium (Na-PEG-400) and monosodium salts of PEG-400 at 70°C for 30 min. It can be seen that the extent of migration from PVC tubes reacted with disodium salt was slightly lower compared to the monosodium salt. This could

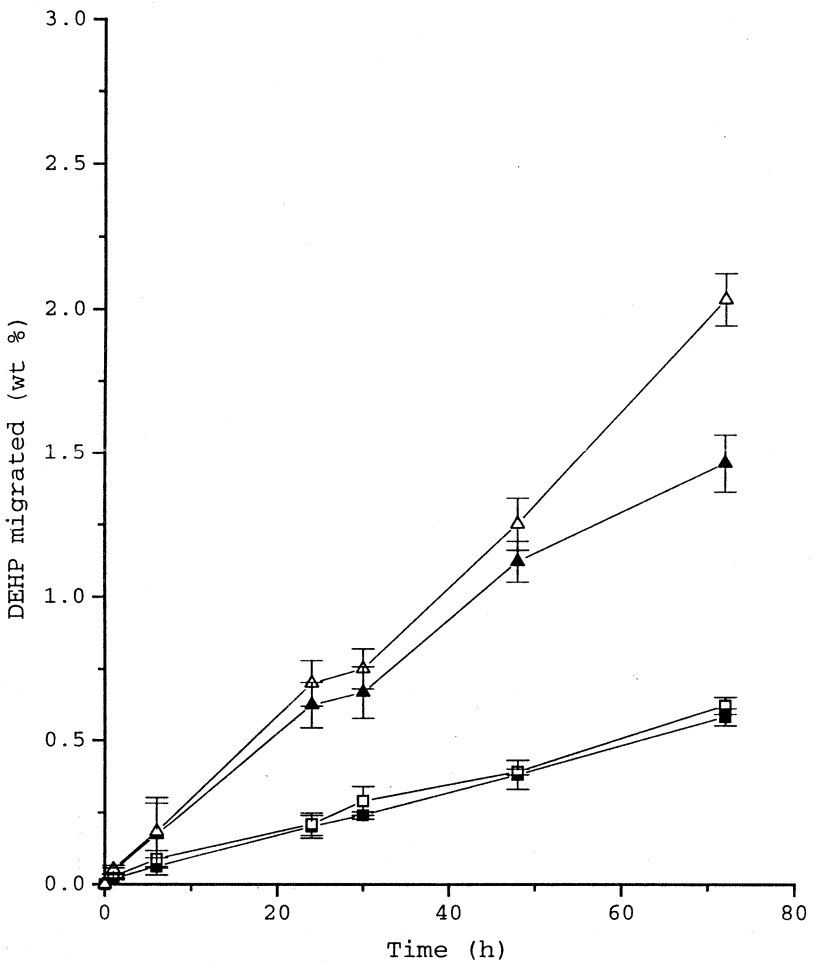


Fig. 3.4.5 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from plasticized PVC tubes rected with Na-PEG-400 at 70°C for various periods of time. 15 min (■), 30 min (□), 45 min (▲) and 60 min (△).

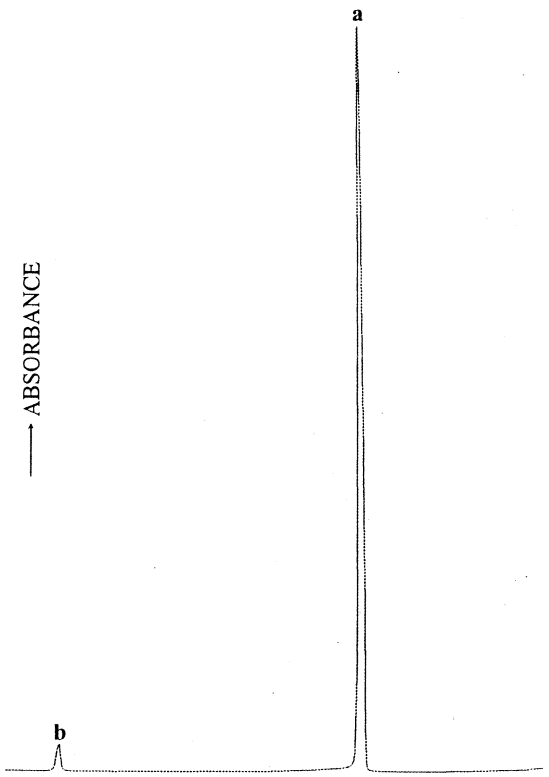


Fig. 3.4.6 Chromatogram of hexane extract of unmodified PVC tube (a) and PEG-400 grafted PVC tube (b) after 24 h incubation.

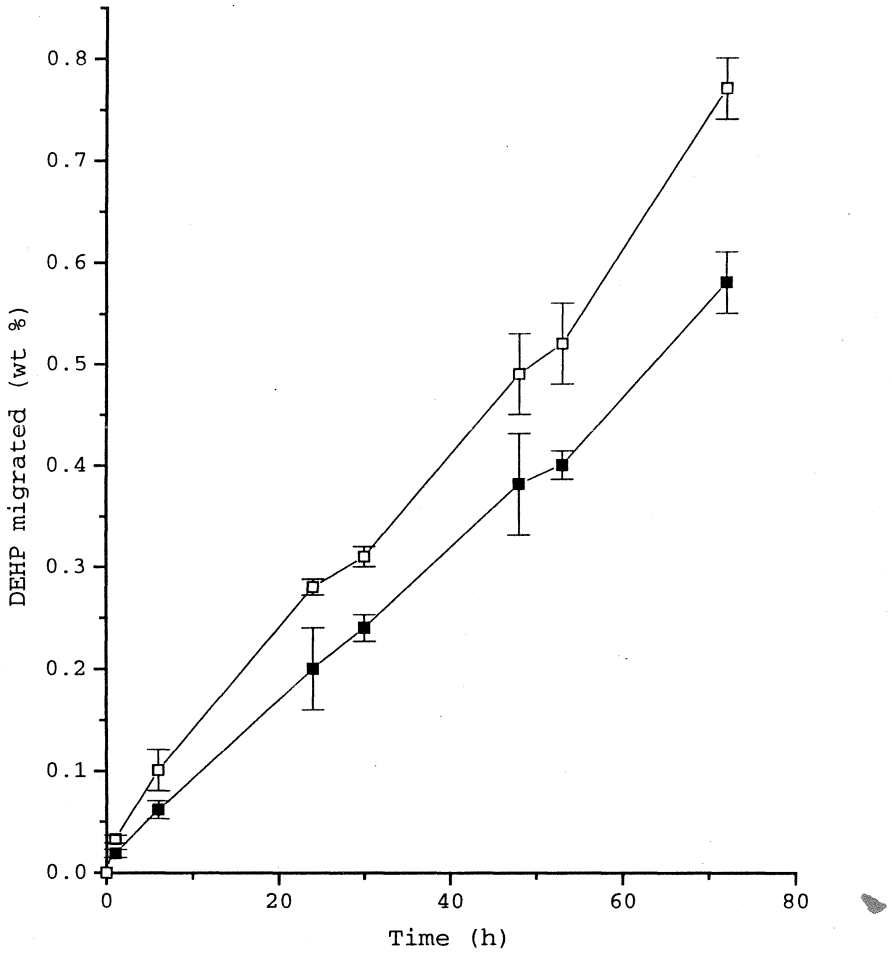


Fig. 3.4.7 Amount of DEHP migrated as a function of time into petroleum ether at 30°C from plasticized PVC tubes reacted with disodium and monosodium salt of PEG-400 at 70°C for 30 min. Monosodium salt (□) and disodium salt (■).

possibly be attributed to the additional cross-linking, feasible along with grafting in the case of disodium salts.

Figure 3.4.8 shows the extent of plasticizer migration from PVC tubes reacted with Na-PEGs of different molecular weights at 70°C. The different molecular weights of PEG examined were 200, 400, 600 and 4000 Daltons. As the molecular weight of PEG increases from 200 to 4000, the extent of migration slightly increases. The difference however, does not appear to be significant, except for the PVC reacted with Na-PEG-4000. The lower migration seen with plasticized PVC reacted with lower molecular weight Na-PEG is possibly due to its increased reactivity of these small molecules which results in a higher graft yield. However, the extent of grafting could not be determined quantitatively due to reasons discussed in section 3.4.3.3. Since the grafting of low molecular weight PEG on plasticized PVC imparts a dark coloration to plasticized PVC, mainly due to dehydrochlorination accompanying the grafting process, PEG of molecular weight 4000 is preferred for the grafting process.

In order to find whether simple adsorption of PEG on the surface of plasticized PVC has any effect on reducing plasticizer migration, plasticizer migration studies were carried out using plasticized PVC treated with pure PEG-4000 at 70°C for 15 min as control in addition to unmodified plasticized PVC tube. Figure 3.4.9 shows the amount of plasticizer migrated as a function of time from unmodified plasticized PVC tubes and plasticized PVC tubes treated with pure PEG-4000 as well as plasticized PVC tube reacted with Na-PEG-4000 at 70°C for 15 min. It can be seen that PVC tubes treated with pure PEG-4000 exhibit the plasticizer migration profile almost similar to that of unmodified plasticized PVC tubes. This

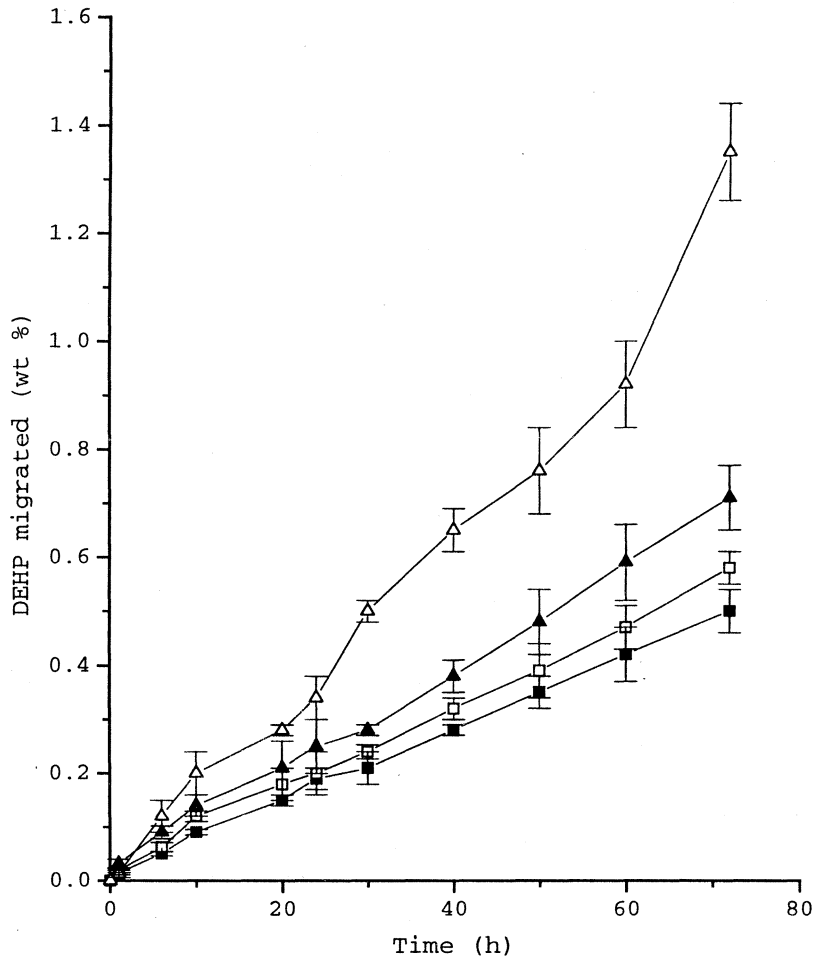


Fig. 3.4.8 Amount of DEHP migrated as a function of time at 30°C from plasticized PVC tubes reacted with different molecular weights of Na-PEG at 70°C. Na-PEG-200 (■), Na-PEG-400 (□), Na-PEG-600 (▲) and Na-PEG-4000 (△).

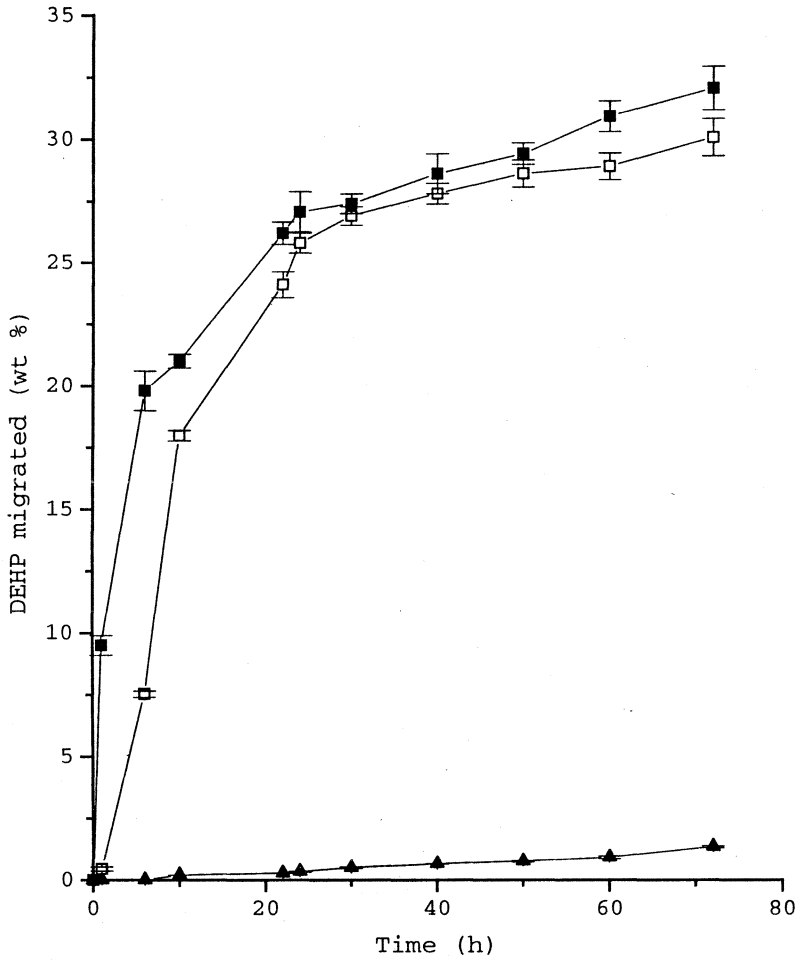


Fig. 3.4.9 Amount of DEHP migrated into petroleum ether as a function of time at 30°C from unmodified plasticized PVC tubes, PVC tubes treated with pure PEG-4000 at 70°C for 15 min and PVC tubes reacted with Na-PEG-4000 at 70°C for 15 min. Unmodified PVC tubes (■), Tubes treated with pure PEG-4000 (□) and Tubes reacted with Na-PEG-4000 (▲).

clearly demonstrates that the increased migration resistance of plasticized PVC reacted with Na-PEG-4000, is due to grafting of PEG onto the surface rather than physical adsorption. In 72 h, the extent of migration from the unmodified PVC tube having a total plasticizer content of 36 wt% was 32.03% where as from PEG-4000 grafted PVC tube the extent of migration was only 1.35%. Thus , while almost the entire plasticizer diffuses out from unmodified PVC tubes, very little migration takes places from PEG-4000 grafted plasticized PVC.

All the migration experiments so far discussed in this chapter were carried out on plasticized PVC tubes. In order to examine the effect of surface modification on the migration resistance of the plasticizer from plasticized PVC sheet, medical grade plasticized PVC sheets were surface modified under conditions which were optimized for the plasticized tubes. Figure 3.4.10 shows the amount of plasticizer migrated as a function of time from plasticized PVC sheets reacted with Na-PEG-4000 for various periods of time at 70°C. Above 5 min of reaction time, the extent of plasticizer migration showed a decreasing trend for 10 and 15 min reaction and there after the extent of migration slightly increased ie., for 30 min reaction. In 72 h the extent of migration from PEG-4000 grafted PVC sheet, (15 min at 70°C) was only 0.875%. Thus as in the case of tubes, the PEG-4000 grafted PVC sheets were found to show lower plasticizer migration compared to unmodified plasticized PVC.

3.4.4.2 Accelerated Plasticizer Migration in Cotton Seed Oil and Paraffin Oil

Figure 3.4.11 shows the plasticizer migrated under accelerated condition (70°C) into cottonseed oil and paraffin oil from unmodified plasticized PVC tubes and

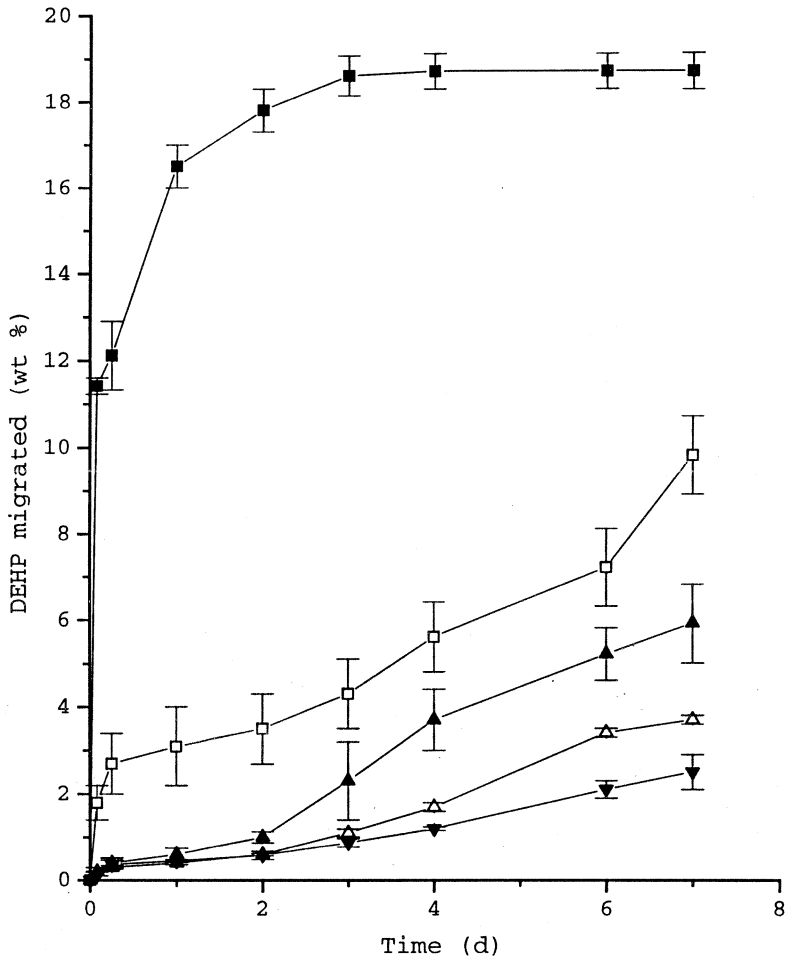


Fig. 3.4.10 Amount of DEHP migrated as a function of time into petroleum ether at 30° C from unmodified PVC sheet as well as sheet reacted with Na-PEG-4000 at 70°C for various periods of time. Unmodified PVC sheet (■), Sheet reacted with Na-PEG-4000 for 5 min (□), 10 min (▲), 15 min (▼) and 30 min (△).

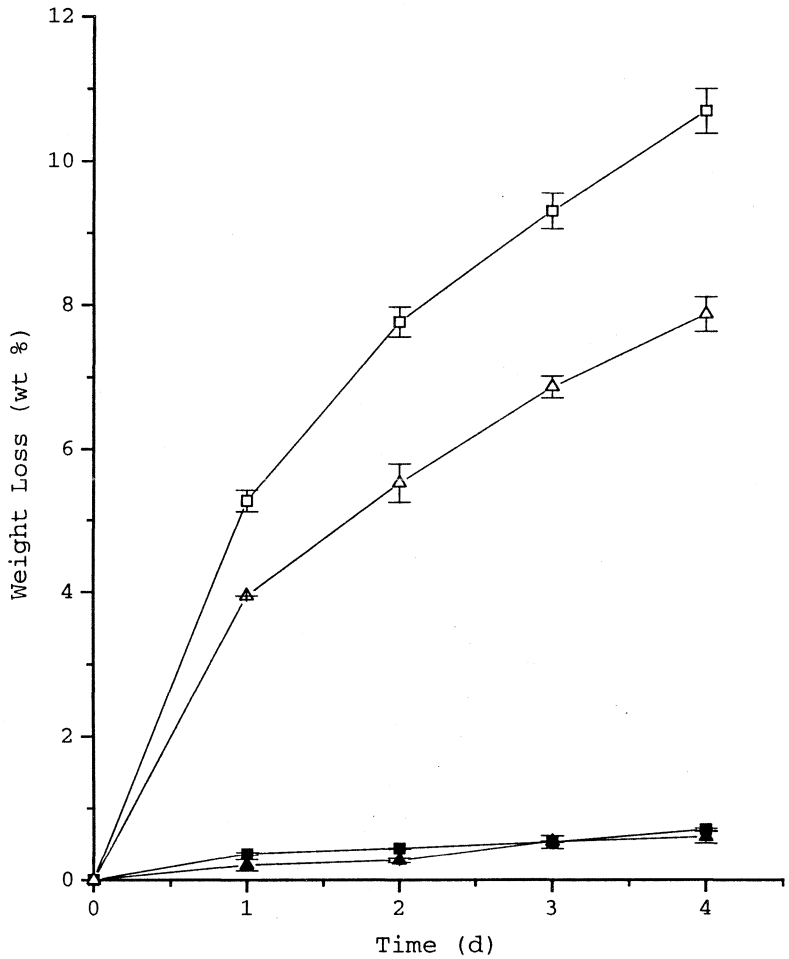


Fig. 3.4.11 Accelerated migration profile of DEHP into cotton seed oil and paraffin oil at 70°C from unmodified plasticized PVC tubes and tubes reacted with Na-PEG-400 at 70° for 30 min. Unmodified PVC tubes in cotton seed oil (□) and in paraffin oil (△); PEG-400 grafted tube in cotton seed oil (■) and in paraffin oil (▲).

tubes reacted with Na-PEG-400 at 70°C for 30 min. The extent of plasticizer migration from PEG-400 grafted plasticized PVC tube was found to be significantly less than that of the unmodified PVC tubes. These results imply that plasticizer migration from PEG-grafted plasticized PVC into fatty foods will be considerably less when such PVC is used as packaging for foodstuffs.

3.4.4.3 Plasticizer Migration in Ethanol-Water Mixture According to BP

The extent of plasticizer migration in ethanol/water mixture according to BP is shown in Table XXIX.

Table XXIX
Migration of plasticizer from unmodified plasticized PVC sheet and PEG-4000 grafted plasticized PVC sheet into ethanol/water mixture according to BP

Sample	DEHP migrated (% w/v)
Unmodified PVC sheet	0.007
PEG-4000 grafted PVC sheet	0.0064

The table shows no significant difference in the amount of plasticizer migrated from unmodified and PEG-4000 grafted plasticized PVC sheet. The incorporation of hydrophilic PEG molecules on the surface however has not increased the extent of plasticizer migration from surface grafted plasticized PVC sheets.

3.4.5 Mechanical Properties

The mechanical properties of the PEG-4000 grafted PVC was determined according to ASTM standards and compared with unmodified PVC sheet. Table XXX shows the ultimate stress-strain properties of the PEG-4000 grafted and unmodified plasticized PVC sheet. It can be seen that the mechanical properties

of the PEG-grafted PVC sheet is not significantly different from that of unmodified plasticized PVC sheets. The ultimate stress of the PEG-4000 grafted plasticized PVC sheet decreases by 11.6% and ultimate strain by 8%. This small decrease in the mechanical properties may be presumably due to the loss of small amount of plasticizer into the reaction medium while grafting as well as some amount of dehydrochlorination accompanying the grafting process. The mechanical properties of the grafted PVC sheet after storing at 4°C for 30 days or steam autoclaving did not show any further reduction in the mechanical properties of PEG-grafted PVC.

Table XXX
Stress-Strain properties of plasticized unmodified PVC sheet and plasticized PVC sheet reacted with Na-PEG-4000 for 15 min at 70°C

Material	Ultimate stress (M Pa$^{\pm}$SD*)	Ultimate strain (%$^{\pm}$SD*)
Unmodified PVC	19.38$^{\pm}$0.57	437.7$^{\pm}$26.3
Unmodified PVC at 4°C for 30 d	18.48$^{\pm}$0.65	466.1$^{\pm}$30.7
Unmodified PVC, steam autoclaved	19.84$^{\pm}$0.95	522.5$^{\pm}$13.0
PEG-4000 grafted PVC	17.12$^{\pm}$0.53	402.0$^{\pm}$19.9
PEG-4000 grafted PVC at 4°C for 30 d	17.62$^{\pm}$1.31	435.2$^{\pm}$30.0
PEG-4000 grafted PVC, steam autoclaved	18.58$^{\pm}$1.02	444.2$^{\pm}$2.40

*Average of six determination

The results obtained from this investigation demonstrate that Williamson reaction provides a simple, novel method to graft PEG of different molecular weights onto plasticized PVC. Low molecular weight PEGs showed a very dark brown coloration on treatment with metallic sodium. With PEG- 4000, the solution remained light brown or yellow in colour and grafting imparted only a slight coloration to plasticized PVC. The method is simple and straightforward. The grafting on the surface was confirmed by FTIR-ATR as well as by contact angle

measurements. The IR spectrum clearly shows the presence of PEG molecules on the surface of grafted surface. The air and octane contact angles of PEG grafted PVC surface are significantly lower compared to unmodified plasticized PVC. The solid/water total interfacial free energy of PEG-4000 grafted PVC is almost zero. So according to minimum interfacial energy hypothesis, the grafted surface should show very low interaction and hence should be highly biocompatible. The optical clarity of the plasticized PVC tube is slightly affected below the wavelength of 500 nm due to some amount of dehydrochlorination. The grafting of PEG does not significantly affect the mechanical properties of plasticized PVC sheets. The PEG grafted plasticized PVC showed a pronounced decrease in plasticizer migration even into a potential organic extractant such as petroleum ether. Migration under accelerated condition in oil media such as cotton seed oil and paraffin oil was also considerably lower from PEG-400 grafted PVC tubes. The PEG grafted PVC should therefore be suitable for packaging oily foods.

3.5 *In Vitro* Biocompatibility Evaluation of Surface Modified Plasticized PVC

As discussed in section 1.3.1, the major applications of plasticized PVC in medical field are for storing blood and its components. Materials used for blood contacting applications require characterization for blood compatibility to confirm their safety. Most of the materials in contact with blood are incompatible to a greater or lesser extent due to their physical and chemical structure which either disrupts the blood's formed cellular elements or activates several of the plasmatic protein system. The blood material interaction is a highly complex process. The first event is the adhesion of proteins on the surface, followed by adhesion and activation of platelets, activation of leukocytes, complement systems etc., activation of plasmatic proteins triggiring the coagulation cascade leading to the formation of blood clot. Clotting is initiated by platelet activation as well as by extrinsic and intrinsic pathways. The blood coagulation cascade is shown in Figure 3.5.1. Exposure of blood to biomateral can lead to platelet adhesion, activation and aggregation. Adenosine diphosphate (ADP), in platelets, is believed to trigger the platelet reactions and cause its degranulation. Eventually, activated platelets generate thrombin which results in the formation of a fibrin clot. The extrinsic pathway is usually not activated by contact with materials and involves a tissue factor. The intrinsic pathway on the other hand is initiated by the exposure of blood to nonendothelial surfaces and hence very important for biomaterials. The adsorption of Factor XII (Hageman Factor) upon a biomaterial surface initiates the intrinsic pathway. Factor XII is activated by the adsorption of coagulation proteins

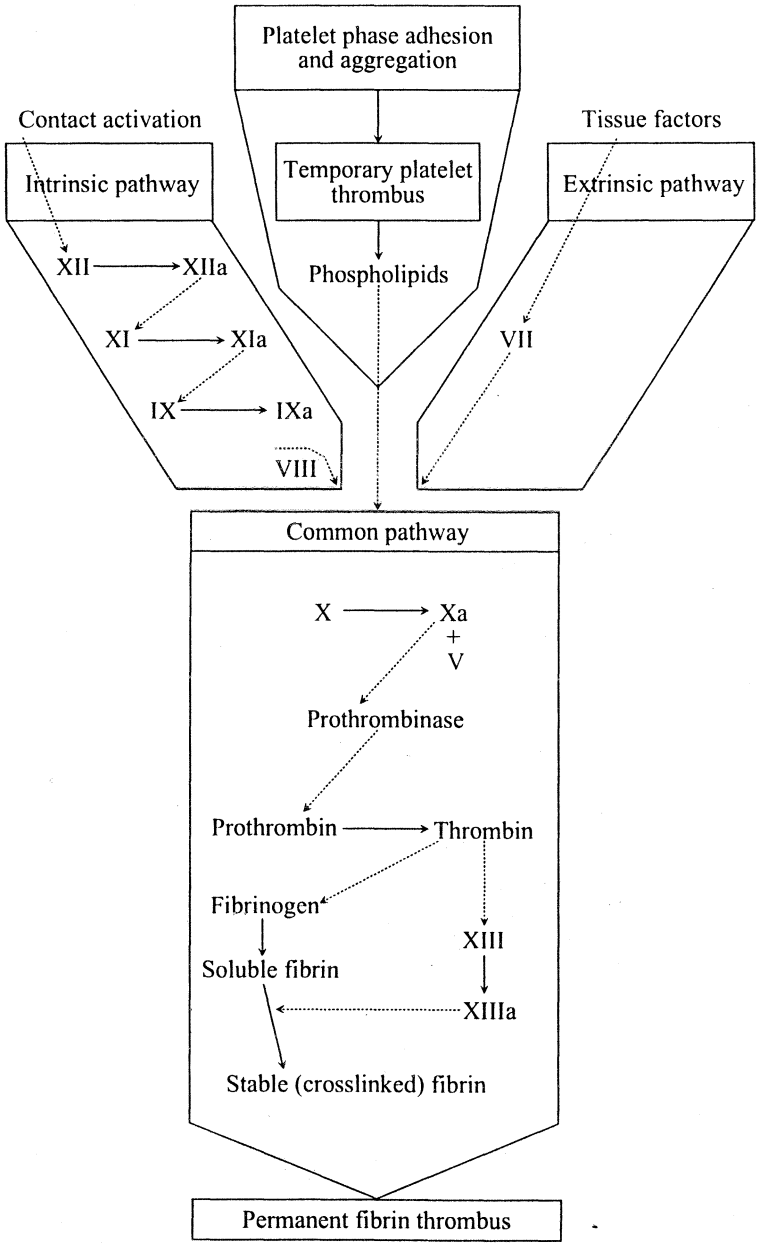


Fig. 3.5.1 Blood Coagulation Cascade (Adapted from Ratnoff, 1981).

including Factor XII itself, FactorXI, prekallikrein, and high molecular weight kininogen (Kaplan *et al.*, 1981). After the activation of cofactors, the coagulation cascade will proceed to produce fibrin. So evaluation of blood compatibility of

materials is a very complex process and hence a multiplicity of test procedures is required to establish the relative thrombogenicity.

The subtle toxicity *i.e.,* toxicity that is difficult to demonstrate on a test animal because it develops slowly at the cellular level may be revealed by studies at the cellular level as represented by tissue culture methods and effect on blood cells. According to Dillingham *et al* (1975), the tissue culture method and haemolysis test are the most sensitive tests for the toxicity evaluation of materials.

Bacterial colonization of biomaterial implant surfaces and subsequent infectious complications are a frequent reasons for the failure of many biomedical devices (Gristina, 1987). It has been reported that up to 45% of hospital-acquired infections are connected with implants or medical devices (Bridgett *et al.*, 1992). Mortality rates of 5-60% have been reported for these infections. Biomaterial related infections prove to be extremely resistant to antimicrobial therapy as well as host defenses and in many cases resolution necessitates the removal of the implanted device. One common early feature of infections of this kind is the deposition and adherence of bacteria to the polymer surface. Subsequent protection of the resultant microcolonies within an enclosed biofilm is believed to contribute towards the persistence of these infecting organisms (Costerton, 1984). Thus bacterial adhesion on the surface is the first and essential step in the pathogenesis of medical device-associated infections (Gristina & Costerton, 1984). The presence of a foreign body greatly augments the chances of infection as the material can act as a scaffold for growth and propagation of bacteria. In animal models, foreign body associated infection was established with no more than 10^2 colony forming unit (CFU) of *Staphylococcus aureus* (*S. aureus*) whereas a dose of $> 10^6$ CFU was

needed to cause skin infection (Zimmerli *et al.*, 1982). Bacterial adhesion is a very complicated process which depends upon many factors such as characteristics of the bacteria, the chemical composition, physical configuration, surface roughness, hydrophilicity or hydrophobicity of the target surface as well as environmental factors such as presence of serum proteins. To inhibit bacterial adhesion and biofilm formation, an interesting approach is to modify the surface of materials in such a way that bacteria are either killed when in contact with surface or prevented from adhering altogether. Surface incorporating antibiotics , silver, materials coated with quaternary amine containing organosilicon salts all have been found to exhibit antimicrobial properties. Alternatively, surface grafting with hydrophilic groups as well as coating with various surfactants have been attempted(Bridgett *et al.*, 1992). Incorporation of hydrophilic polymer such as PEG on hydrophobic polymers has been shown to reduce bacterial adhesion (Humphries *et al.*, 1987; Desai *et al.*, 1992; Park *et al.*, 1998). Incorporation of heparin on the surface of plasticized PVC has shown to reduce bacterial adhesion on the surface (Zdanowski *et al.*, 1997). Studies have shown that endotracheal tubes (Jones *et al.*, 1997) and cerebrospinal fluid shunts made of PVC can produce nosocomial pneumonia and shunt infections (Nomura *et al.*, 1997). Therefore, there is clearly a need to develop PVC based biomaterials which reduce bacterial adhesion to avoid such infections.

In recent years many *in vitro* test models have been developed based on the use of isolated organs, tissues cells or microorganisms for evaluating the various biocompatibility behavior of materials. The *in vitro* methods have advantages like sensitivity, reproducibility, economy and speed compared to *in vivo* method. It can sometimes be faulted in the actual biological conditions but still it can very well be

used as a screening test for selecting materials for biomedical applications. This chapter describes the results of the *in vitro* biocompatibility evaluation of surface modified plasticized PVC described in earlier chapters. The *in vitro* evaluation was carried out with PEG-4000 grafted plasticized PVC, plasticized PVC reacted with sodium sulphide in presence of TBAH and thiosulphate substituted plasticized PVC which appeared to be promising candidates from the point of view of reduced plasticizer migration, ease of surface modification and other physical properties.

3.5.1 Static Platelet Adhesion

Surface induced thrombus formation is one of the main problems in the development of blood-contacting biomaterials. Because platelet adhesion and subsequent activation are mainly responsible for the thrombus formation, ideal biomaterials would be the one which do not allow platelet adhesion at all. Platelet interaction with the surface of materials is perceived as the primary factor in surface-induced thrombosis (Kiaei *et al.*, 1992). The surface composition of a material in contact with blood greatly influences the extent of platelet adhesion and activation (Pelzer & Heimburger, 1986). The *in vitro* platelet adhesion is widely used in the biomaterial field and allows investigation of platelet interactions with the surface. In order to evaluate whether surface modification has any effect on platelet adhesion on plasticized PVC sheets, an *in vitro* platelet adhesion study was carried out with unmodified plasticized PVC sheet and surface modified plasticized PVC sheet (Section 2.2.10.1). Briefly, sheets were immersed in phosphate buffered saline (PBS) overnight at 37°C and exposed to platelet rich plasma (PRP) for 1 h at 37°C. The sheets were then gently washed with PBS to remove weakly

adhered platelets and adhered cells were fixed with 2.5% glutaraldehyde in PBS for 30 min. The fixed sheets were then subjected to critical point drying using liquid carbon dioxide as the transition liquid and sputter coated with gold before examining in SEM. Figure 3.5.2 shows the SEM of unmodified plasticized PVC sheet exposed to PRP for 1 h at 37°C. Lots of slightly activated platelets were seen adherent on the surface of plasticized PVC sheets. This shows the poor blood compatibility of unmodified plasticized PVC sheet. Figure 3.5.3 shows the SEM of PEG-4000 grafted plasticized PVC sheet exposed to PRP for 1 h at 37°C. Virtually no platelets were seen adherent on the surface of PEG grafted plasticized PVC sheet. It is well documented that the incorporation of hydrophilic polymers such as PEG on the surface greatly reduced platelet adhesion (Harris, 1992). The PEG grafted surface shows a textured pattern. Since the sheets after exposing to PRP and fixing with glutaraldehyde was subjected to critical point drying, the grafted surface can be clearly distinguished in the SEM . Thus the *in vitro* platelet adhesion shows that grafting PEG-4000 on the surface of plasticized PVC can increase the antithrombogenicity of the surface. Figure 3.5.4 shows the SEM of plasticized PVC sheet reacted with sodium sulphide in the presence of TBAH, exposed to PRP for 1 h at 37°C. Quite unexpectedly the surface cross-linked sheet also shows significant reduction in platelet adhesion compared to unmodified plasticized PVC sheet. Figure 3.5.5 shows SEM of platelet adhesion on the surface of thiosulphate substituted plasticized PVC sheet. Almost a clear surface was observed in the case of thiosulphate substituted plasticized PVC sheet also. This shows that both the sulphur atoms substituted plasticized PVC sheets shows some extent of improvement in its interaction with platelets.

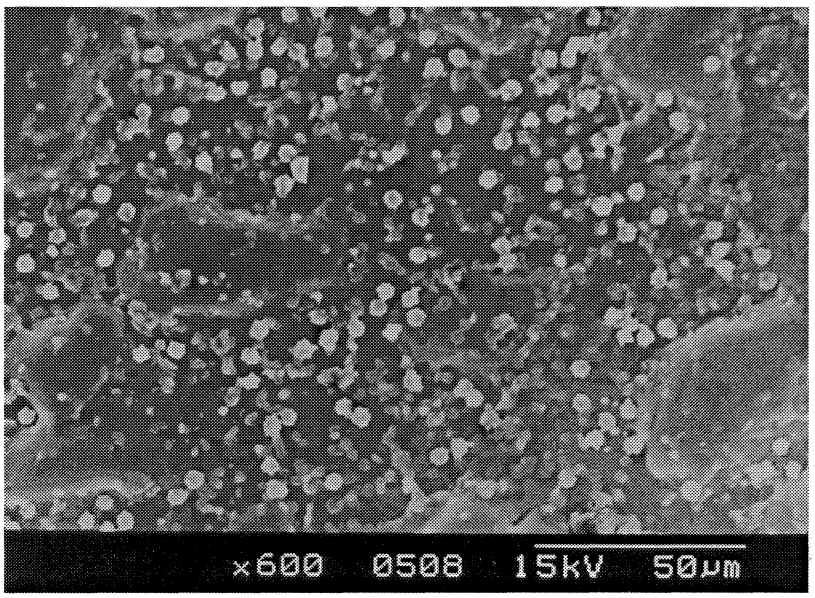


Fig. 3.5.2 SEM showing the adhered platelets on unmodified plasticized PVC sheet.

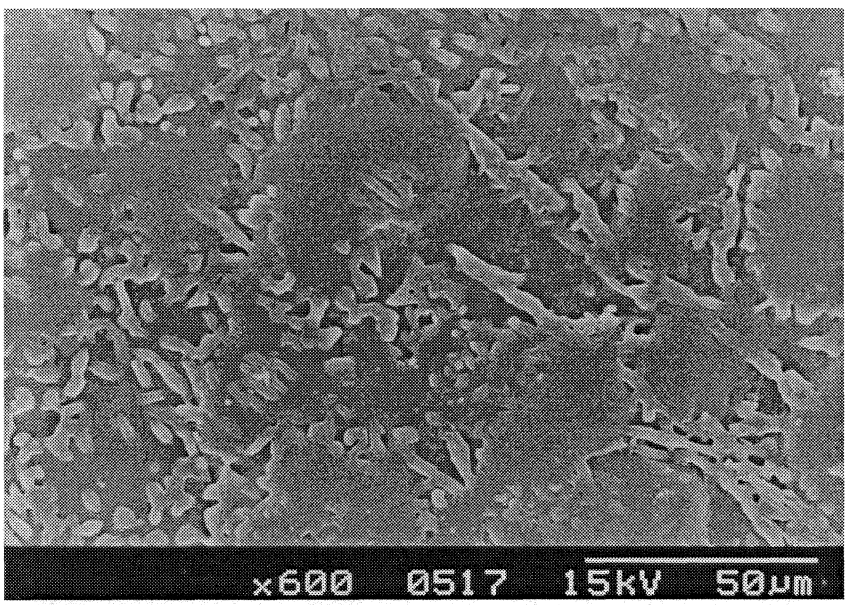


Fig. 3.5.3 SEM of PEG-4000 grafted plasticized PVC sheet exposed to PRP for 1 h at 37°C.

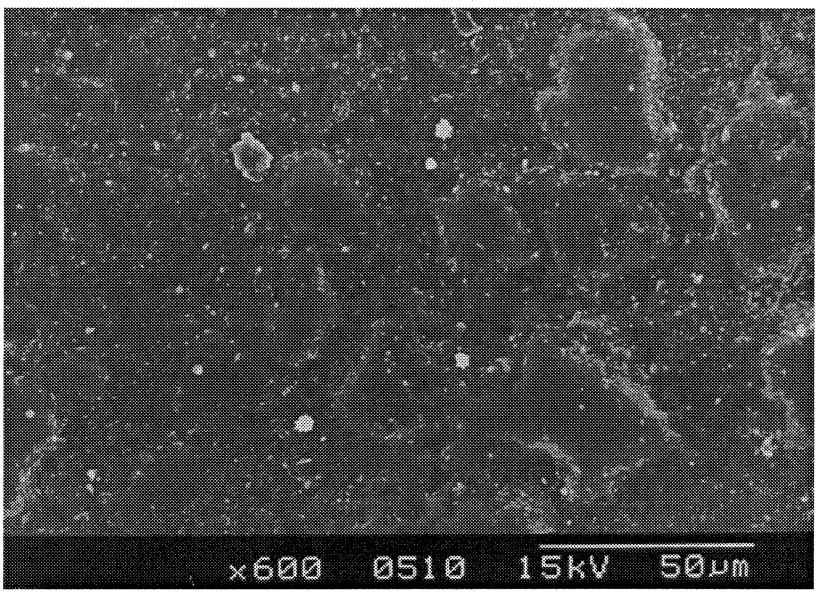


Fig. 3.5.4 SEM of plasticized PVC sheet reacted with sodium sulphide in presence of TBAH at 80°C for 5 h exposed to PRP for 1 h at 37°C.

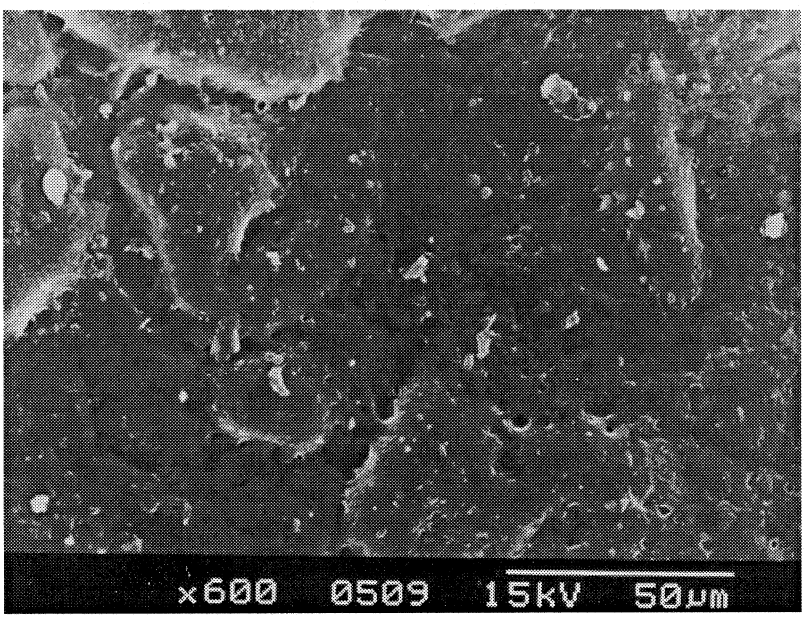


Fig. 3.5.5 SEM of thiosulphate substituted PVC sheet exposed to PRP for 1 h at 37°C.

As discussed above the interaction of blood with artificial surface is highly complex. The blood can interact with surfaces by intrinsic as well as extrinsic pathways, involving protein adsorption, platelet adhesion, activation and aggregation as well as activation of various clotting factors triggering the clotting cascade. So further characterization of the surface modified plasticized PVC by an *in vitro* whole blood clotting test using fresh rabbit blood was carried out.

3.5.2 Whole Blood Clotting Time Assay

The test assesses the activation of the intrinsic blood coagulation system by surface modified and unmodified plasticized PVC sheet. To evaluate the thrombogenicity of materials *in vitro*, the modified Lee-White clotting time test is usually employed. It has some disadvantages such as molding the material to be tested into the shape of tube or a cup like shape and also the end point of clot formation is not definite. So *in vitro* thromboresistant properties of unmodified and surface modified plasticized PVC sheets were determined by a kinetic method developed by Imai and Nose (1972) and further modified by Xianghuai *et al* (1996) (Section 2.2.10.3). Briefly, 0.1 mL fresh rabbit blood is placed in contact with unmodified and surface modified plasticized PVC sheets. At definite intervals, the specimens with blood were transferred into 50 mL distilled water and incubated for 5 min. The red blood cells which had not been trapped in a thrombus were haemolysed and the free haemoglobin was dispersed in water. The free haemoglobin concentration was measured colorimetrically at 540 nm. The absorbance of the solution *vs* time was plotted against the contacting time of blood on the material surface. It has been found that the absorbance of the haemolysed

solution changes with time of contact with the material. Conventionally, the time at which the absorbance decreased to 0.1 is regarded as the clotting time of blood (Xianghuai *et al.*, 1996; Nan *et al.*, 1998). Thus higher the clotting time of blood upon contact with the material, the better the biocompatibility of the material. Figure 3.5.6 shows the blood clotting profiles of PEG-4000 grafted plasticized PVC sheet and that of unmodified plasticized PVC sheet. It can be seen that in the case of unmodified plasticized PVC sheets, the absorbance value falls below 0.1 even within 20 min of contact. The PEG-4000 grafted plasticized PVC sheet on the other hand shows a significant increase in the clotting time. It took more than 70 min for the grafted surface to induce clotting. This is a clear evidence for the better blood compatibility of the PEG grafted plasticized PVC surface. This result corroborates the platelet adhesion studies on PEG-4000 grafted plasticized PVC sheet discussed in section 3.5.1.

Since plasticized PVC sheet surface cross-linked using sodium sulphide as well as by thiosulphate showed a reduced platelet adhesion *in vitro*, further characterization using the whole blood clotting time assay was carried out with these modified surfaces also. Figure 3.5.7 shows the whole blood clotting profiles of sulphide cross-linked plasticized PVC sheet and that of unmodified plasticized PVC sheet. Here not much significant improvement in the clotting time of surface modified plasticized PVC was observed compared to the unmodified plasticized PVC sheet. Figure 3.5.8 shows the whole blood clotting profile of thiosulphate substituted plasticized PVC as well as that of unmodified plasticized PVC sheet. The thiosulphate substituted plasticized PVC shows no improvement in the clotting time of fresh rabbit blood. This shows that even though the *in vitro* platelet

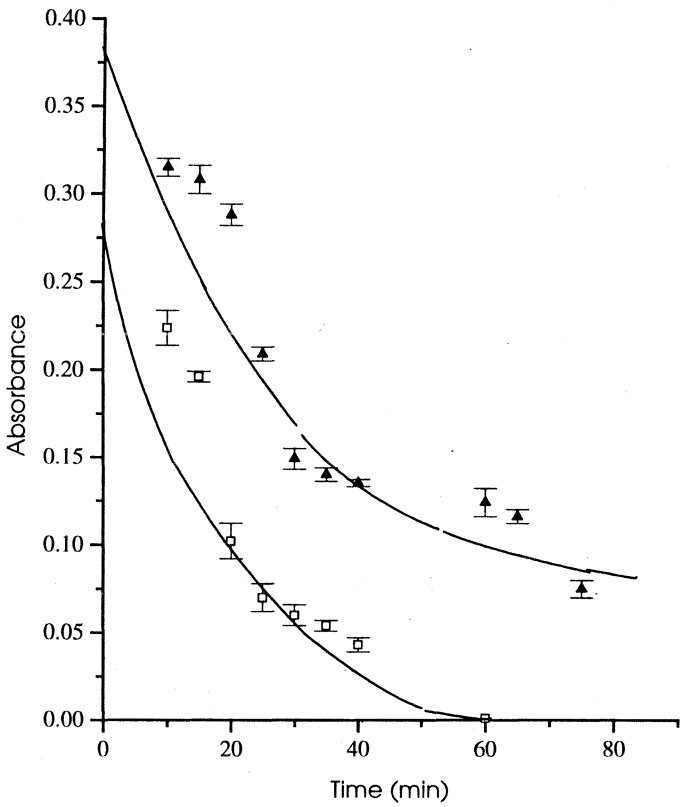


Fig. 3.5.6 Whole blood clotting profile of unmodified plasticized PVC sheet and PEG-4000 grafted plasticized PVC sheet. Unmodified PVC sheet (□) and PEG-4000 grafted PVC sheet (▲).

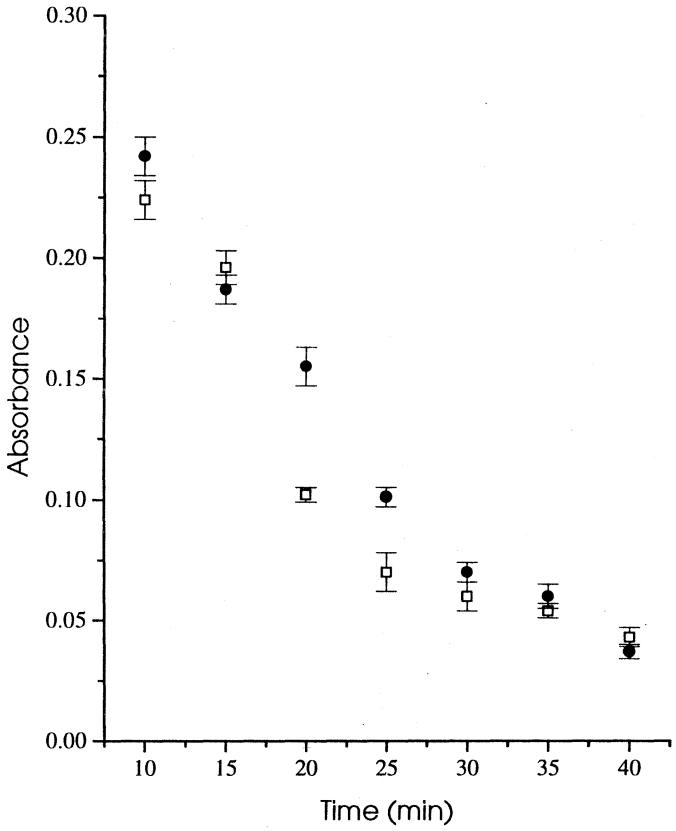


Fig. 3.5.7 Whole blood clotting profile of unmodified plasticized PVC sheet and PVC sheet reacted with sodium sulphide in the presence of TBAH at 80°C for 5 h. Unmodified PVC sheet (□) and PVC sheet reacted with sodium sulphide (●).

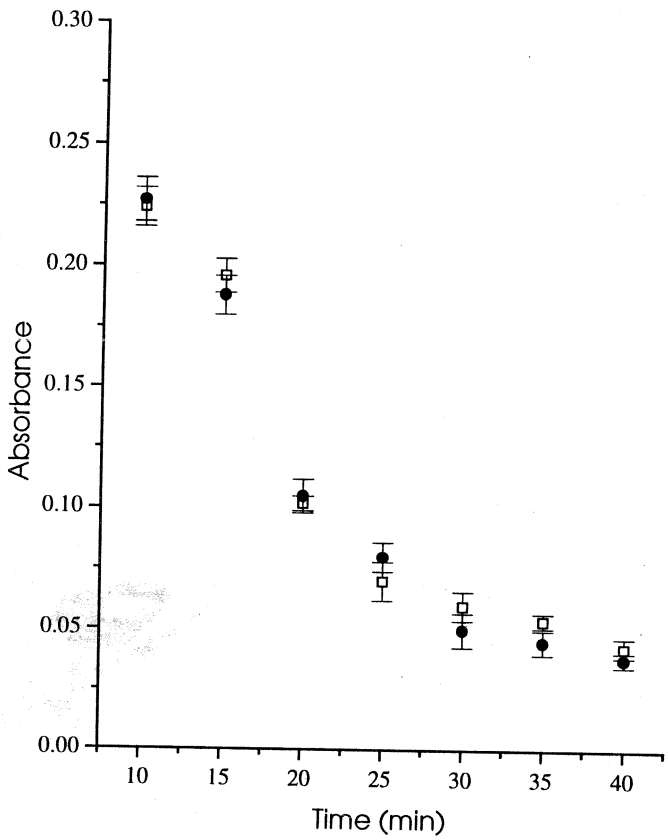


Fig. 3.5.8 Whole blood clotting profile of unmodified plasticized PVC sheet and thiosulphate substituted PVC sheet. Unmodified PVC sheet (□) and Thiosulphate substituted PVC sheet (●).

adhesion on the surface of plasticized PVC sheet reacted with sodium sulphide in the presence of TBAH, as well as thiosulphate substituted plasticized PVC was very low compared to that of unmodified PVC, the antithombogenicity of the surface has not been improved significantly as a result of the surface modification.

3.5.3 Haemolysis Assay

Haemolysis is the premature destruction of red blood cells and the distruction of red blood cells release their free haemoglobin into the plasma (Thompson, 1977). The haemolysis assay is designed to evaluate the haemolytic properties of the materials used in the fabrication of medical devices that may contact blood. In most of the medical applications of plasticized PVC, in the form of blood bags, blood giving and collection sets, transfusion tubings etc, it comes in direct contact with blood. So the evaluation of the haemolytic potential of the surface modified PVC assumes great importance. The test compares the acute haemolysis properties of surface modified and unmodified plasticized PVC sheets with both positive and negative control materials. The test is based upon a plasma haemoglobin spectrophotometric determination. The assay was carried out according to a modified form of the O'Leary method. The haemolytic potential of the material is the measure of the extent of haemolysis that may be caused by the material when it comes in contact with blood. Table XXXI shows the percentage haemolysis of rabbit blood placed in contact with surface modified and unmodified plasticized PVC sheets at 37°C for 60 min (Section 2.2.10.2).

Table XXXI
Percentage haemolysis induced by unmodified and surface modified plasticized PVC sheets

Sample	Haemolysis (%)
Unmodified plasticized PVC	0.583 ± 0.07
PEG-4000 grafted plasticized PVC	0.109 ± 0.008
Sulphide cross-linked plasticized PVC	0.380 ± 0.06
Thiosulphate substituted plasticized PVC	1.88 ± 0.3

*Average of two determinations

Since the medical grade plasticized PVC sheet is used as the control unmodified sheet, the extent of haemolyis is much lower than the permissible level of 5%. The significant observation from this experiment is that, surface modification greatly changes the haemolytic potential of plasticized PVC sheets. The grafting of PEG-4000 on the surface of plasticized PVC greatly reduced the haemolytic potential of the surface. This once again confirmed the better blood compatibility of the PEG grafted plasticized PVC surface, thus corroborating the earlier observations. The plasticized PVC sheets reacted with sodium sulphide in the presence of TBAH shows a slightly lower haemolytic potential compared to the unmodified plasticized PVC sheets. Thiosulphate substituted plasticized PVC sheets on the other hand shows a significant increase in the percentage haemolysis compared to the unmodified plasticized PVC. This shows that the incorporation of thiosulphate groups on the surface greatly increases the red cell toxicity of plasticized PVC.

3.5.4 Cytotoxicity Assay

The cell culture methods take advantage of the sensitivity of cells cultivated *in vitro* towards toxic compounds. Standard cell culture tests were developed for

the biocompatibility evaluation of biomedical devices. One of the most sensitive toxicity testing protocols is based on direct contact of the sample with a cell culture. Since the surface modification of plasticized PVC dramatically changes the interaction with red blood cell, further *in vitro* characterization using fibroblast cells were carried out to evaluate the cytotoxicity of the unmodified and surface modified plasticized PVC sheets. The cytotoxicity evaluation was carried out according to ASTM method (Section 2.2.10.4). Briefly, plasticized PVC sheets (unmodified and surface modified) were placed in direct contact with a monolayer of fibroblast cells for 24 h. The fibroblasts are spindle shaped cells. The cells were evaluated for the general morphology, vacuolization, detachment, cell lysis and membrane.

Comparison of these properties of the cells before and after direct contact with the samples is the basis for the evaluation of a possible toxic effect of the samples. Samples showing greater than 60% cell death were considered to be toxic. Figure 3.5.9 shows the photomicrograph of the monolayer of fibroblast cells in tissue culture plate (negative control). The spindle shape of the cells can be clearly seen from the photomicrograph. Figure 3.5.10 shows the corresponding photomicrograph of fibroblast cells in contact with copper wire (positive control). The cells lost their characteristic shape and became rounded showing cell death. Figure 3.5.11 shows the photomicrograph of unmodified plasticized PVC sheets placed in direct contact with monolayer of fibroblast cells showing the area at the interface between the material and the cells. The cells shows the same morphology and same characteristics which were shown by the negative controls. The medical grade unmodified plasticized PVC employed is thus found to be non-toxic corroborating the lower haemolytic potential. Figure 3.5.12 shows the

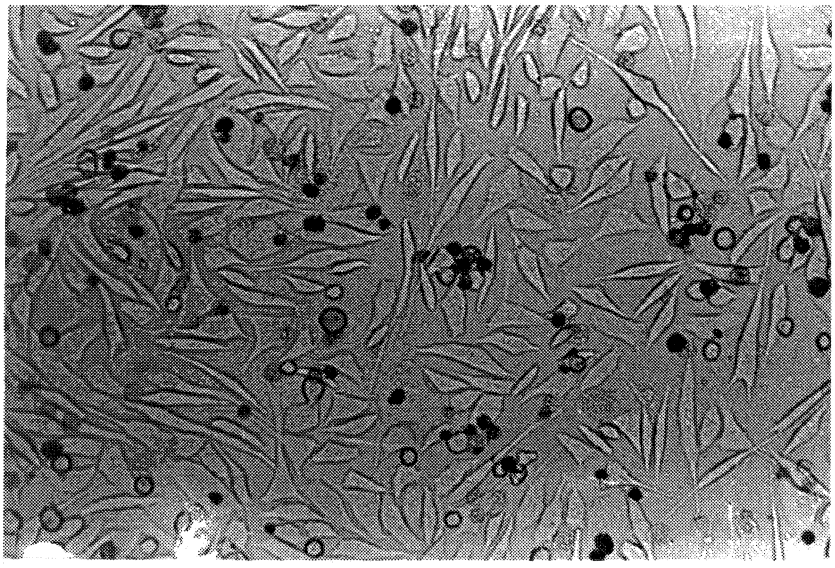


Fig. 3.5.9 Optical photomicrograph of monolayer of fibroblast cells in tissue culture plate (negative control). (×320)

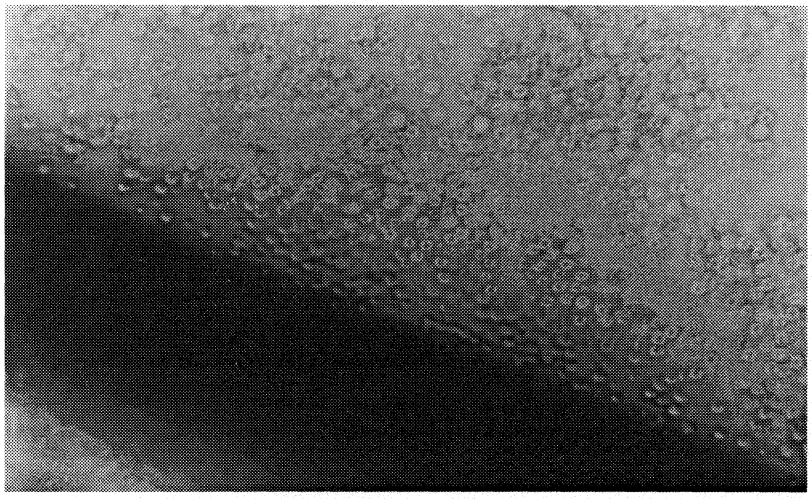


Fig. 3.5.10 Optical photomicrograph of monolayer of fibroblast cells in contact with copper wire (positive control). (×100)

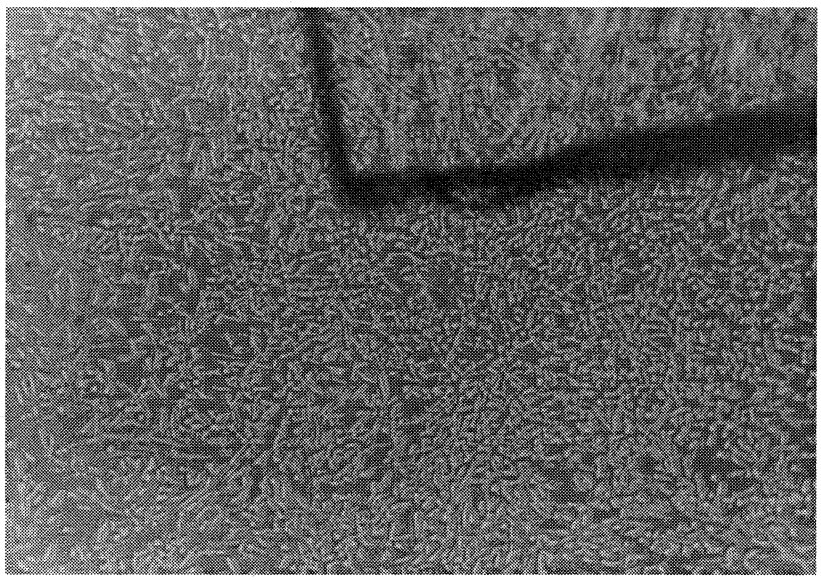


Fig. 3.5.11 Optical photomicrograph of unmodified plasticized PVC sheet in direct contact with a monolayer of fibroblast cells. (×100)

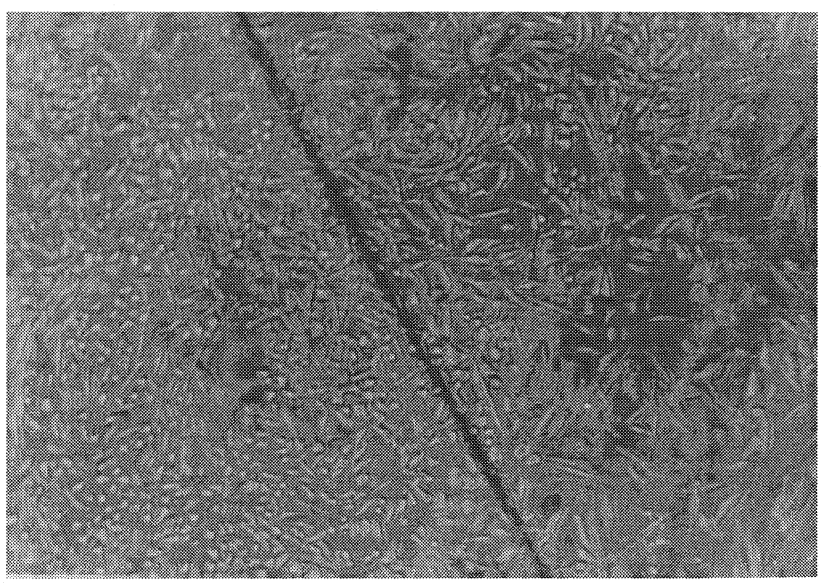


Fig. 3.5.12 Optical photomicrograph of PEG-grafted plasticized PVC sheet in direct contact with a monolayer of fibroblast cells. (×100)

photomicrograph of the interfacial area between the PEG-4000 grafted plasticized PVC sheets and the cells after 24 h of incubation. The cells show the same morphology and characteristics as that of negative control thus confirming the non-toxicity of the PEG grafted plasticized sheet in contact with it. Figure 3.5.13 shows the photomicrograph of the interfacial area between the sulphide cross-linked plasticized PVC sheets and fibroblast cells after 24 h contact. Here also the cells retain the same morphology and characteristic as that of negative control and hence confirming its non-toxic nature. The thiosulphate substituted plasticized PVC sheet on the other hand shows significant difference in its interaction with cultured cells, similar to red blood cells described in section 3.5.3. Figure 3.5.14 shows the photomicrograph of thiosulphate substituted plasticized PVC sheets exposed to monolayer of fibroblast cells. The sheets were found to be cytotoxic. It can be clearly seen that the cells lost the characteristic morphology showing significant cell death upon direct contact with thiosulphate substituted plasticized PVC sheet. This result corroborates the greater haemolytic potential observed with thiosulphate substituted plasticized PVC sheet compared to the unmodified plasticized PVC sheet. The exact reason for this observation is not known at present. Quaternary salts are known to be highly cytotoxic. It has been reported that coating of heparin a sulphonated polymer on polymeric surface greatly reduced cell growth (Nair *et al.*, 1997). The higher toxicity associated with the thiosulphate substituted plasticized PVC may be possibly due to the presence of high concentration of sulphonate groups as well as some quaternary groups on the surface. The results of cytotoxicity assay is summarized in Table XXXII.

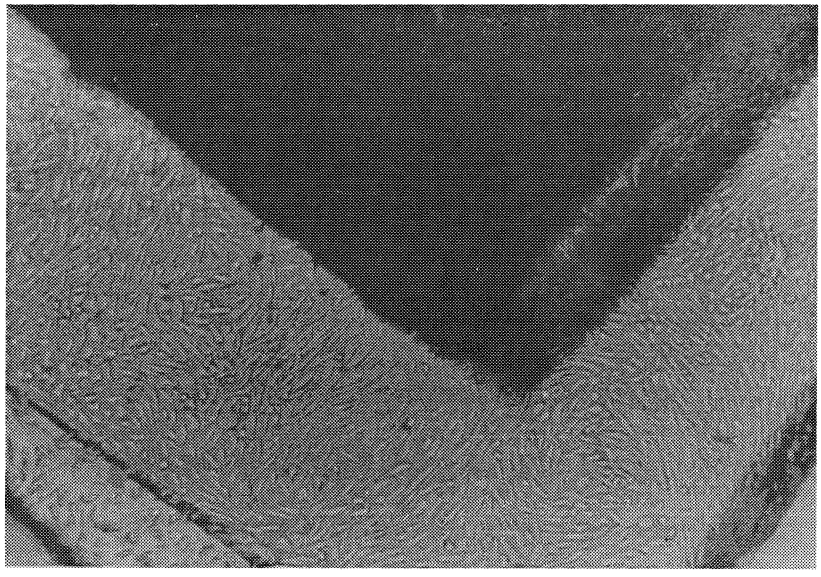


Fig. 3.5.13 Optical photomicrograph of sulphide cross-linked plasticized PVC sheet in direct contact with a monolayer of fibroblast cells. ($\times 100$)

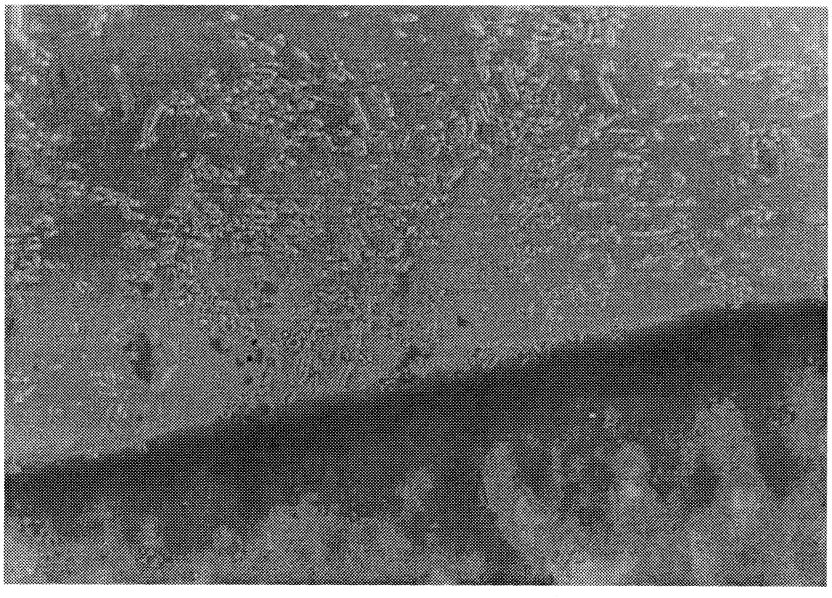


Fig. 3.5.14 Optical photomicrograph of thiosulphate substituted plasticized PVC sheet in direct contact with a monolayer of fibroblast cells. ($\times 100$)

Table XXXII
Results of cytotoxicity assay carried out by direct contact of mouse fibroblast cells with surface modified and unmodified plasticized PVC sheet

Sample	Cell response
Unmodified plasticized PVC sheet	non-toxic
PEG-4000 grafted plasticized PVC sheet	non-toxic
Sulphide cross-linked plasticized PVC sheet	non-toxic
Thiosulphate substituted plasticized PVC sheet	toxic

Among the surface modified plasticized PVC, the PEG-4000 grafted PVC was found to exhibit better blood compatibility compared to the other surface modification as evidenced from the above mentioned *in vitro* tests. So PEG-4000 grafted plasticized PVC tubes were used for further evaluation of blood compatibility using human blood. Figure 3.5.15a shows the SEM of unmodified plasticized PVC tube as well as PEG-4000 grafted plasticized PVC tubes Figure 3.5.15b exposed to anticoagulated whole human blood for 48 h. Briefly, human blood was stored in unmodified and PEG-4000 grafted plasticized PVC tubes at 4°C for 48 h. The tubes were then washed with PBS to remove weakly adhered cells and fixed with 2.5% glutaraldehyde solution in PBS. The fixed tubes were then sputter coated with gold and examined by SEM. Highly activated platelets leading to formation of platelet clumb were seen on the surface of unmodified plasticized PVC tube exposed to whole blood (Figure 3.5.15a). The surface of PEG-4000 grafted PVC tube (Figure 3.5.15b) on the other hand shows almost a clean surface. Grafting of PEG-4000 on plasticized PVC thus greatly improves the blood compatibility of plasticized PVC.

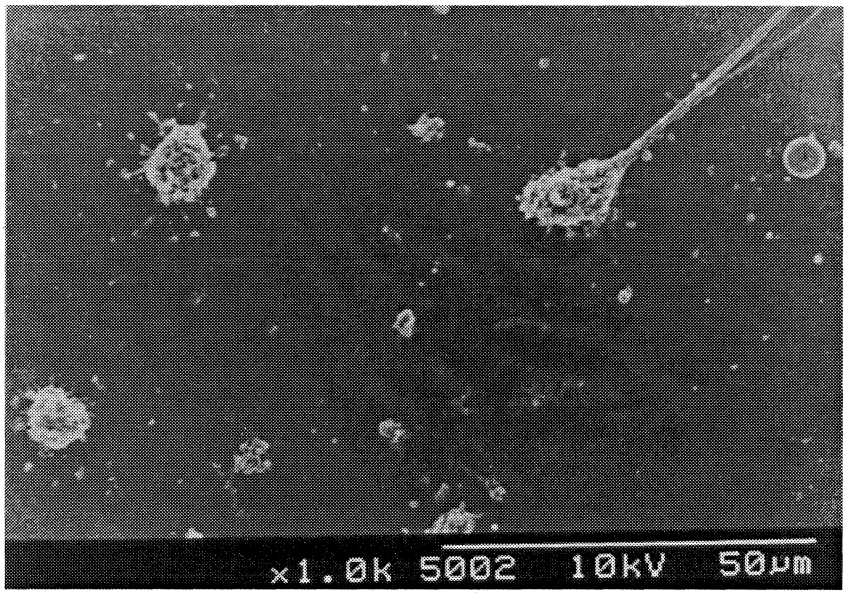


Fig. 3.5.15a SEM of unmodified plasticized PVC tube exposed to human blood for 48 h at 4°C.

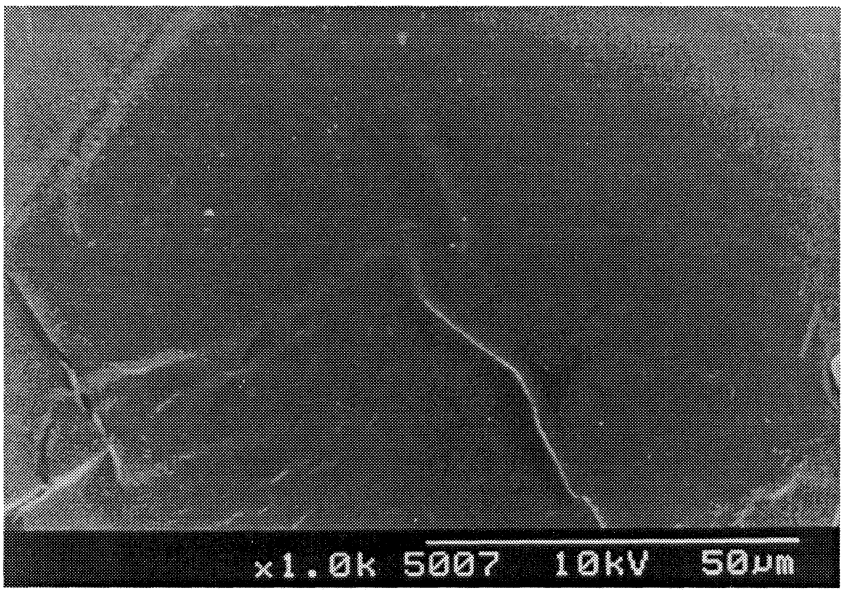


Fig. 3.5.15b SEM of PEG-4000 grafted plasticized PVC tube exposed to human blood for 48 h at 4°C.

3.5.5 Bacterial Adhesion

A gram positive bacteria *S. aureus* was used for evaluating the bacterial adhesion resistance of unmodified and surface modified plasticized PVC sheets. The adhesion of *S. aureus* on unmodified plasticized PVC sheet was found to be significantly high and tended to form microcolonies. The results of *S.aureus* adhesion on unmodified plasticized PVC sheet and PEG-4000 grafted plasticized PVC sheets in tryptone soyabroth (TSB) is shown in Figure 3.5.16. Significant reduction in *S.aureus* adhesion was found with PEG-4000 grafted plasticized PVC sheet compared to unmodified plasticized PVC. The reduction in adherence in the case of PEG grafted PVC may be attributed to the reduced hydrophobic interactions between bacterial cell membranes and the graft surface due to the high hydrophilicity of PEG as well as due to the mobility of the PEG grafted surface. Figure 3.5.17 shows the results of *S . aureus* adhesion on plasticized PVC sheet reacted with sodium sulphide in the presence of TBAH compared to unmodified plasticized PVC sheet. The modified PVC sheet also shows significant reduction in the adhesion of the bacteria on the surface. The reason for the reduction in bacterial adhesion on the modified PVC sheet is not very clear at present. The adhesion of bacteria on the surface is a highly complex process depending on a variety of factors like nature of the bacteria, nature of the surface, nature of the environment etc. Figure 3.5.18 shows the extent of bacterial adhesion on thiosulphate substituted plasticized PVC sheet compared to unmodified plasticized PVC sheet. The thiosulphate substituted plasticized PVC showed no reduction in bacterial adhesion.

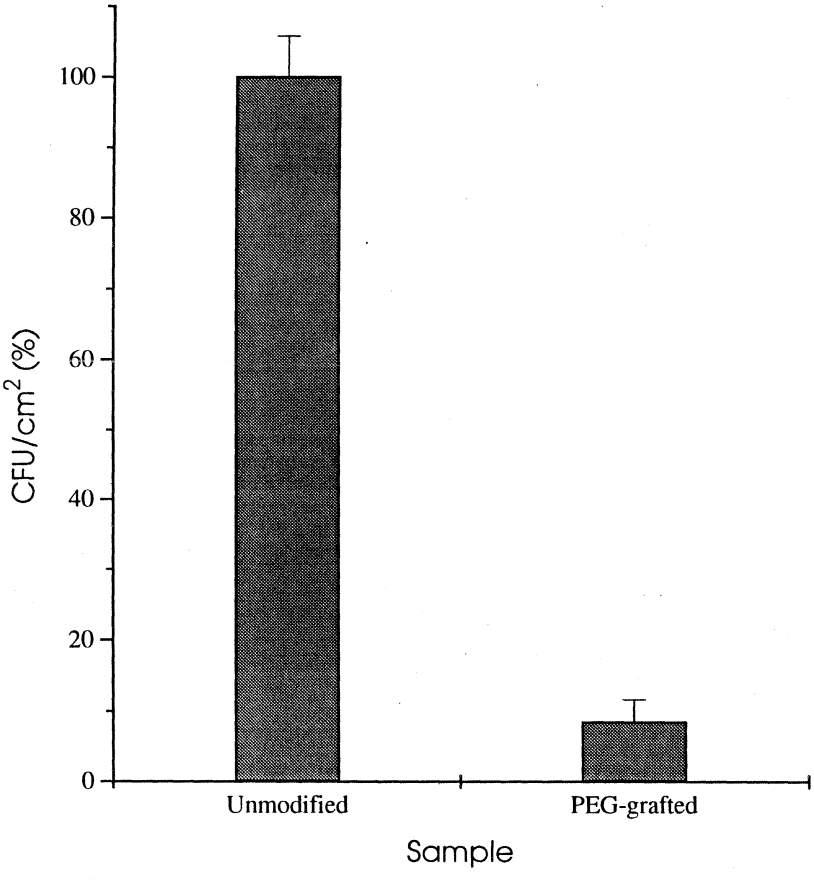


Fig. 3.5.16 Extent of *S. aureus* adhesion on unmodified plasticized PVC sheet and PEG-4000 grafted PVC sheet.

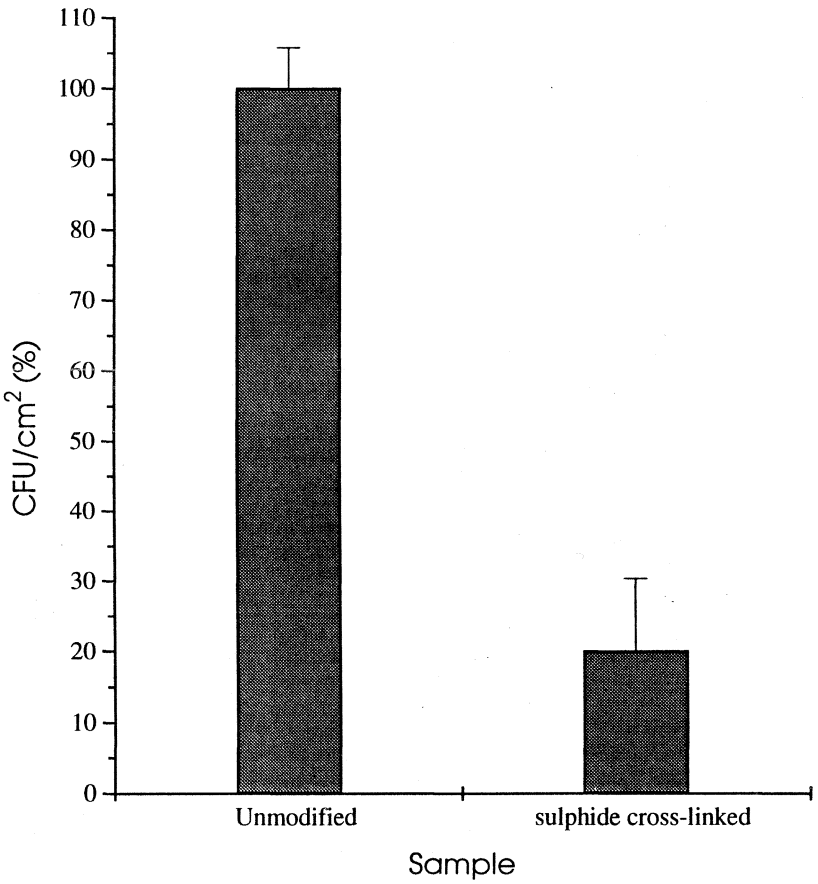


Fig. 3.5.17 Extent of *S. aureus* adhesion on the surface of unmodified PVC sheet and sulphur cross-linked PVC.

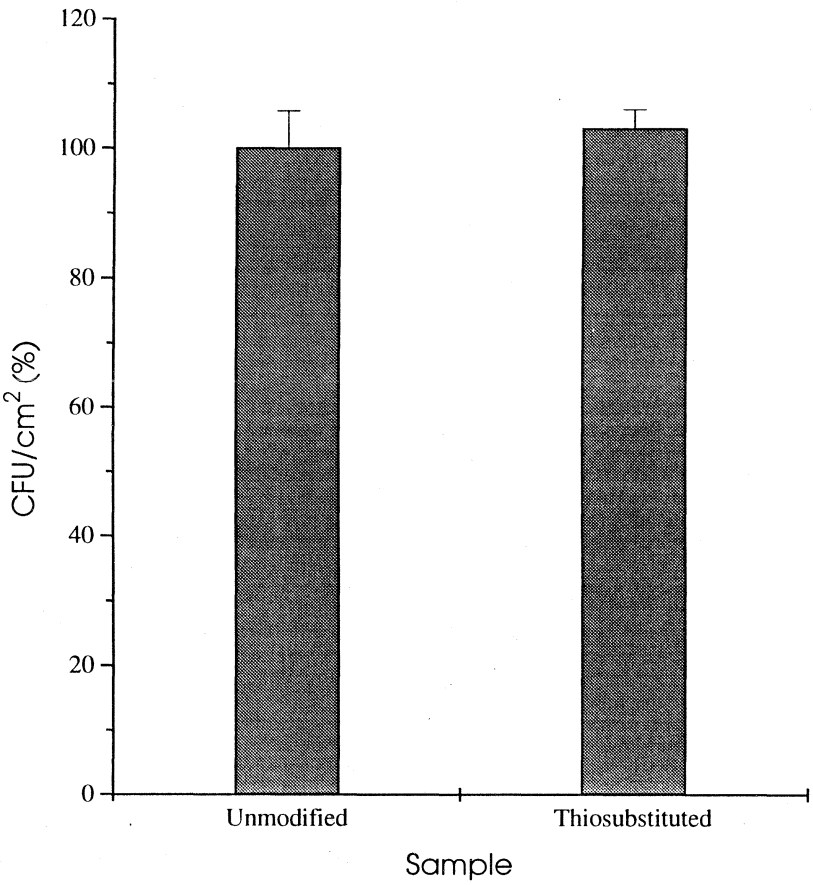


Fig. 3.5.18 Extent of *S. aureus* adhesion on unmodified plasticized PVC sheet and thiosulphate substituted PVC sheet.

The data presented in this chapter throw some light on the blood compatibility as well as the toxicity of the surface modified plasticized PVC compared to unmodified plasticized PVC sheet. It can be seen that grafting of PEG-4000 onto plasticized PVC sheet significantly improves the interaction of PVC with living cells. The antithrombogenicity of the grafted surface is higher than that of unmodified plasticized PVC sheet. The modified surface shows least toxicity with respect to red blood cells as well as towards the fibroblast cells. The adhesion of a gram positive bacteria (*S. aureus*) on the PEG grafted surface was much lower compared to unmodified plasticized PVC sheet. The plasticized PVC sheet reacted with sodium sulphide in the presence of TBAH also shows some improvements compared to unmodified plasticized PVC sheet. Even though the platelet adhesion on the surface was much lower, the antithrombogenicity of the surface was not improved as evidenced from the whole blood clotting time assay. The modified surface was found to be non-toxic as evidenced from the haemolysis and cell culture assay. The adhesion of *S. aureus* on the modified surface was found to be less compared to the unmodified plasticized PVC sheet. The thiosulphate substituted plasticized PVC sheet on the other hand shows significant differences in its interaction with cells as well as blood as such. The antithrombogenicity of the surface was not significant even though sulphonate groups are present on the surface. The modified plasticized PVC was found to be toxic as evidenced from the haemolysis and cell culture assay. The adhesion of *S . aureus* on the surface was also not different from unmodified plasticized PVC sheet compared to the other two modifications.

CHAPTER 4

SUMMARY, CONCLUSIONS AND FUTURE PROSPECTS

SUMMARY, CONCLUSIONS AND FUTURE PROSPECTS

4.1 Summary and Conclusions

Surface modification of polymers has developed into an important way to develop materials having appropriate surface properties and bulk properties. Several techniques have been used for surface modification of polymers. Physico-chemical modifications like coating the surface with other polymers, surface chemical reactions, grafting other polymers on the surface and biological methods like incorporation of biologically active molecules on the surface have all been attempted.

One of the most important problem of plasticized PVC used in medical and related applications is the migration of plasticizer and the associated toxic effects on humans. Extensive studies have been carried out on the phenomenon of plasticizer migration and various attempts have been made to reduce the extent of plasticizer migration from PVC used in medical and related applications.

This work has been devoted to studying the possibility of using surface modification technique to reduce plasticizer migration from plasticized PVC and

improve its biocompatibility. Two different surface modification techniques were attempted, ie., surface confined chemical modification using phase transfer catalysis and grafting a hydrophilic polymer such as PEG onto the surface of PVC. The extent of plasticizer migration resistance of the modified PVC was evaluated. Some of the biocompatibility parameters of the modified surfaces in comparison to unmodified PVC were also examined. The first attempt was to substitute PVC using DTC followed by photocross-linking the surface. The incorporation of DTC groups in PVC as well as photocross-linking the surface were confirmed by IR, sulphur estimation and gel content estimation. There was no significant change in the surface morphology of modified PVC. The optical clarity of the tubes was affected to a certain extent by DTC substitution as well as on photocross-linking. The mechanical properties such as ultimate stress and strain of the sheets were also affected to a certain extent as a result of this modification. The extent of plasticizer migration was evaluated under various conditions of reaction. The optimum concentration of the nucleophile and the catalyst was found to be 0.2 mol dm^{-3} and 0.03 mol dm^{-3} . Among the catalysts examined, the tetrabutylammonium salts were found to be much better and TBAH was the most efficient catalyst for this substitution. The extent of plasticizer migration resistance increased with time of irradiation. When the unmodified plasticized PVC tubes lost almost all its plasticizer in 24 hours in petroleum ether, the 5 h photocross-linked DTC-PVC lost less than 5% of the plasticizer in about 5 days. Both plasticized PVC sheet and tube could be modified by this technique. The physical properties of PVC were found to be adversely affected by the modification. Most importantly, the modified specimens were found to lose their transparency on exposure to atmosphere and

gradually becoming opaque due to moisture absorption from atmosphere. Water uptake experiments performed on modified specimens showed that PVC on DTC substitution absorbed large amounts of water. Although the water absorptivity of the specimens decreased after photocross-linking the surface, still a large amount of water was found to be absorbed thus making them opaque. This property of the modified specimens will be a highly limiting factor in their real-life uses particularly in medical applications.

In another attempt, a dianion such as sulphide ion was attempted for nucleophilic substitution, instead of monoanion like DTC. The logic behind was that a dianion like sulphide ion can directly form a surface cross-linking on plasticized PVC to contain plasticizer migration. There was also no need for subjecting the specimens for either thermal or photocross-linking thus accomplishing the surface modification unambiguously in one single step. Moreover, unlike dithiocarbamates which are toxic in nature, alkali metal sulphides such as sodium sulphide do not exhibit that kind of toxicity. Plasticized PVC was thus reacted with sodium sulphide in the presence of TBAH at 80°C for 5 h. The substitution was confirmed by XPS, gel content estimation as well as by sulphur estimation in the isolated surface cross-linked gel. No significant change in the surface morphology was observed in the modified PVC. The optical clarity of the modified PVC tubes was only slightly affected near the 500 nm region. The surface modified PVC tubes showed much less tendency to absorb water. The modified specimens also did not lose their transparency even on prolonged exposure to atmosphere. This was very important in real life applications. The mechanical properties of the surface modified PVC was only slightly affected.

The optimization of reaction condition was reached by following the extent of plasticizer migration from plasticized PVC reacted with sodium sulphide under various reaction conditions. A catalyst concentration of 0.15 mol dm^{-3} and sodium sulphide concentration of 7 mol dm^{-3} were found to be highly efficient in achieving surface cross-linking. Among the catalysts, tetrabutylammonium salts were found to be highly efficient. The surface modified PVC was found to be highly plasticizer migration resistant in both non-polar and polar extractants. Even after various modes of sterilization such as autoclaving and gamma irradiation, the modified PVC remained migration resistant. Both plasticized PVC tubes and sheets could be feasibly modified by this technique.

Since sulphur nucleophiles such as DTC and sulphide anions were found to be highly efficient in PTC-mediated substitution, another potential nucleophile such as thiosulphate anion was attempted for nucleophilic substitution of PVC. Plasticized PVC on reaction with thiosulphate in the presence of PTC in aqueous medium resulted in the formation of a surface cross-linked PVC. The substitution of the thiosulphate anion on plasticized PVC was confirmed by IR, XPS, sulphur analysis as well as by gel content estimation. No significant change in the surface morphology of the modified PVC was found. The optical clarity of the tubes were not at all affected as a result of this modification. The modified surface became more hydrophilic as evidenced by low contact angle even though the surface showed no appreciable water absorption. The mechanical properties of the modified PVC were slightly affected as a result of modification. A catalyst concentration of 0.15 mol dm^{-3} and a thiosulphate concentration of 3 mol dm^{-3} were found to be optimum for the reaction. Tetrabutylammonium salts (particularly TBAH)

were found to be the most efficient catalysts for the substitution. The thiosulphate substituted PVC showed high migration resistance in non-polar extraction media like petroleum ether and cotton seed oil. Sterilization by autoclaving as well as by gamma radiation did not adversely affect the migration resistance of the modified PVC. The thiosulphate substituted PVC however, showed migration in polar media such as PEG-400 and ethanol-water mixture.

Another attempt was to graft a hydrophilic polymer such as PEG onto the surface of plasticized PVC. The grafting was carried out via Williamson reaction. Different molecular weight PEGs were employed for grafting. Low molecular weight PEGs greatly reduced plasticizer migration from plasticized PVC. The grafting was confirmed by IR as well as by contact angle measurements. The quantification of grafting was not possible as grafting was always followed by plasticizer migration from PVC into the grafting medium. The mechanical properties of the modified PVC were not significantly different from that of unmodified PVC.

Finally, attempts were made to characterize *in vitro* some of the biocompatibility properties of modified PVC in comparison to unmodified PVC. Static platelet adhesion studies carried out on modified and unmodified PVC showed interesting results. Extensive adhesion was seen on the surface of unmodified PVC. PEG grafted PVC showed virtually no adhesion of platelets on the surface. PVC reacted with sodium sulphide as well as thiosulphate showed almost a clear surface. The evaluation of haemolytic potential of the surface showed that PEG grafted PVC showed very low haemoytic potential, PVC reacted with sodium sulphide also showed slightly lower potential compared to unmodified PVC but the thiosulphate

substituted PVC was found to be highly haemolytic. So further characterization of the modified surface was carried out using a whole blood clotting time assay. PEG grafting on plasticized PVC greatly increased the clotting time of fresh rabbit blood. But no significant improvement in clotting profile was found in the case of sulphide modified as well as thiosulphate substituted PVC. This result showed that the antithrombogenicity of sulphide cross-linked and thiosulphate substituted PVC was not very different compared to unmodified PVC. The cytotoxicity evaluation showed that PEG grafted PVC as well as sulphide modified PVC to be non-toxic similar to unmodified PVC but thiosulphate substituted PVC was found to be cytotoxic. The bacterial adhesion studies using S. aureus showed that PEG grafted PVC showed significant decrease in bacterial adhesion. Quite surprisingly, the sulphide cross-linked PVC also showed reduction in bacterial adhesion. But, thiosulphate substituted PVC showed no significant decrease in bacterial adhesion.

4.2 Future Prospects

Among the different methods employed for the modification of PVC with a view of preventing migration of the plasticizer and at the same time improving its biocompatibility, the results obtained with sodium sulphide as the cross-linking agent and PEG as the graft polymer were particularly striking. The extent of plasticizer migration in real-life conditions such as blood and other blood components like serum and plasma stored in bags made from such modified PVC could be further investigated. Since PEG-grafted PVC showed good antithrombogenicity, further detailed studies like protein adsorption, interaction with various cellular components, evaluation of the various parameters such as

pH, etc., of whole blood stored in bags made from PEG-grafted PVC could investigated. Interaction of blood with PVC cross-linked with sodium sulphide and thiosulphate also need to be investigated in detail as they showed reduced platelet adhesion. The reduction in bacterial adhesion of modified PVC needs to be further investigated. Since, the phenomena of bacterial adhesion is a highly complex process depending on the nature of bacteria, the chemical composition, physical configuration, surface roughness, hydrophilicity or hydrophobicity of the target surface etc., further investigation using different strains of bacteria is needed for reaching logical conclusions on the reduced bacterial adhesion shown by some of the modified surfaces in the preliminary study reported in this thesis.

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Appendix A:

Phosphate Buffered Saline (PBS)

Disodium hydrogenphosphate	-	17.972 g
Monosodium hydrogenphosphate	-	5.73 g
Sodium chloride	-	9 g
Distilled water	-	1000 mL

Appendix B:

Acid Citrate Dextrose (ACD)

Trisodium citrate	-	22 g
Citric acid	-	8 g
Dextrose	-	25 g
Distilled water	-	1000 mL

Appendix C:

List of Abbreviations

ACD	-	Acid citrate dextrose
AES	-	Atomic emission spectroscopy
AFM	-	Atomic force microscopy
ATR	-	Attnuated total reflectance
BEAC	-	Benzyltriethylammonium chloride
CPC	-	Cetylpyridinium chloride
DEHP	-	Di-(2-ethylhexyl)phthalate
DMF	-	Dimethyl formamide
DTC	-	Diethyldithiocarbamate
DTC-PVC	-	Diethyldithiocarbamate substituted PVC
FTIR	-	Fourier transform infrared spectroscopy
GA	-	Glutaraldehyde
HPLC	-	High performance liquid chromatography
HTMAP	-	Hexyltrimethylammonium bromide
IR	-	Infrared spectroscopy
LB	-	Langmuir-Blodgett
MEHP	-	Mono-(2-ethylhexyl)phathalate
PBS	-	Phosphate buffered saline
PEG	-	Poly(ethylene glycol)
PEO	-	Poly(ethylene oxide)
PVC	-	Poly(vinyl chloride)
PRP	-	Platelet rich plasma
PTC	-	Phase transfer catalyst or Phase transfer catalysis
SEM	-	Scanning electron microscopy
SIMS	-	Secondary ion mass spectroscopy
STM	-	Scanning tunneling microscopy
TBAB	-	Tetrabutylammonium bromide
TBAH	-	Tetrabutylammonium hydrogen sulphate
TBAI	-	Tetrabutylammonium iodide
THF	-	Tetrahydrofuran
TLC	-	Thin layer chromatography
TSB	-	Tryptone soyabroth
UV	-	Ultraviolet
XPS	-	X-ray photoelectron spectroscopy

Appendix D:

List of Publications

Immobile Plasticizer in Flexible PVC, A. Jayakrishnan and S. Lakshmi, *Nature*, **396**, 638, 1998.

Migration Resistant Blood-Compatible Plasticized Poly(vinyl chloride) for Medical and Related Applications, S. Lakshmi and A. Jayakrishnan, *Artif. Organs*, **22**, 222, 1998.

Photocross-linking of Dithiocarbamate-Substituted PVC Reduces Plasticizer Migration, S. Lakshmi and A. Jayakrishnan, *Polymer*, **39**, 151, 1998.

List of Awards

Very Good Poster Presentation Award - *IUPAC International Symposium on Advances in Polymer Sciences and Technology*, (Macro 98), Chennai, 1998.

Regional Science Fellowship - India, Middle East and Africa, *International Society for Artifical Organs*, Rhode Island, USA, 1997.

Young Scientist Award - *State Committee on Science, Technology and Environment*, Government of Kerala, Cochin, 1996.

Patent

A Process of Grafting Poly(ethylene glycol) onto the Surface of Plasticized Poly(vinyl chloride)., A. Jayakrishnan and S. Lakshmi (Indian Patent Application dated 5-12-1995).