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# PROJECT COMPLETION REPORT

1. **Project Number** : **6210**

2. **Title of the Project** : Development of a bioactive radiopaque inorganic-organic hybrid resin for dental and orthopedic applications.,

3. **Funding Agency Name** : TDF,SCTIMST

4. **Project Reference Number provided by the Funding Agency**: TDF 6210

5. **Principal Investigator (Name & Address) : Dr.Lizymol P.P. ,Scientist, DEP,DBST,BMTW,SCTIMST (Guide)**

6. **Co-Investigators (Name & Address): V.KalliyanaKrishnan**
7. **Implementing Institution** : SCTIMST

8. **Collaborating Institutions** : NIL

9. **Date of Commencement** : 12-05-2015

10. **Duration** : 2 years6 months

11. **Date of Completion** : **11-11-2017**

12. **Objectives as approved :** . Development of a bioactive radiopaque inorganic-organic hybrid resin for dental and orthopedic applications

* To synthesize inorganic-organic hybrid resins containing radiopacifying agent like zirconia through sol-gel method.
* To characterize the synthesized resins.
* To prepare visible light cure composites using this synthesized resin.
* To evaluate the physio-mechanical properties of the prepared composites.
* To investigate the degradation and remineralisation of these composites.
* To investigate the extent of polymerization shrinkage using various techniques including µ-CT.
* To evaluate the in vitro cytotoxicity of visible light cured dental composites based on these synthesized resins

**13. Deviation made from original objectives if any, while implementing the project and reasons thereof : NIL**

**14. Field/Experimental work giving full details of summary of methods adopted, data collected supported by necessary tables, charts, diagrams and photographs :**

**1. Methodology**

Broadly methodology part is divided into four phases.

**Phase I:**

Synthesize inorganic-organic hybrid resins containing zirconia through sol-gel method using dimethacrylate/tetramathacrylate silane as the starting material. The concentration of inorganic part in the resin is needed to be optimised.

The synthesized resins characterised through Fourier Transform Infra-Red, Fourier Transform Raman and Nuclear Magnetic Resonance spectroscopy. The purity of the synthesized resins checked using High Performance Liquid Chromatography and its molecular weight is evaluated using Gel Permeation Chromatography and its thermal stability is assessed using Thermogravimetric Analysis.

**Phase II:**

Visible light cure composites prepared using the synthesized hybrid resins with fillers like HAP/quartz etc and its physico-mechanical properties will be evaluated for dental applications. Effect of temperature gradient on these composites studied using thermocycling procedure. Radiopacity measured

**Phase III:**

Self cure composites prepared using the synthesized hybrid resins with fillers like HAP/PMMA and its physico-mechanical properties evaluated for orthopaedic applications. Radiopacity also measured as per international standards.

**Phase IV:**

Biological part of the studies include *In vitro* cytotoxicity analysis Cell proliferation, cell viability and antibacterial properties of VLCs carried out.

**I. Synthesis and characterization of resin**

**Synthesis of ormoresin**

Synthesis of calcium containing resins at acidic and basic conditions was carried out. Various batches of ormoresins were synthesized with 0.0, 0.05%, 0.1% ,0.15%, 0.2%, 0.25% and 0.5% $Ca(OH)_2$ using □- Trimethoxy silyl propyl methacrylate

**Synthesis and characterization of radiopaque Zirconium containing inorganic-organic hybrid resin**

Radiopaque zirconium containing pre-polymer was synthesized using a simple single-pot modified sol gel method. Zirconium containing pre-polymer was characterized by FTIR and FT-Raman. Developed photocured polymeric composites using the novel zirconium containing pre-polymer and investigated linear polymerization shrinkage, radiopacity and cytocompatibility of the composite.

## Synthesis and characterization of Filler part for Bone cement application

**Synthesis of Hydroxy apatite**

**Route 1**

**Synthesis of Hydroxy apatite using Calcium hydroxide and ortho phosphoric acid**

**Reagents used**

Calcium Hydroxide (special LR s-d fine), orthophosphoric acid (AR grade), Ammonia solution (25%) (s-d fine).

**Procedure**

0.5 M Calcium hydroxide and 0.3 M ortho phosphoric were prepared in deionised water so as to maintain Ca/P ratio 1.67 .Orthophosphoric acid was added drop wise to vigorously stirred (with magnetic stirrer) Ca $(OH)_2$ solution at room temperature for approximately one hour (pH maintained above 10.5 with ammonia solution).Aged for 24 hours, supernatant liquid decanted,washed with deionised water(2-3 times) and centrifuged . Hydroxy apatite was dried by lyophilisation and sintered at 1200°C and 1300°C for one hour.

**Route II**

**Synthesis of Hydroxy apatite using Calcium nitrate and di- ammonium hydrogen ortho phosphate**

**Reagents used**

Calcium nitrate tetra hydrate (GR, Merck), di- ammonium hydrogen ortho phosphate (ARgrade), Ammonia solution (25%)

**Procedure**

1M calcium nitrate solution and 0.6M di- ammonium hydrogen ortho phosphate were prepared in deionised water so as to maintain Ca/P ratio 1.67.pH of both solutions adjusted to 11 with ammonia solution .Calcium nitrate solution was added drop wise to vigorously stirred (with magnetic stirrer) di- ammonium hydrogen ortho phosphate solution at room temperature for 1 hour. Precipitate obtained was further stirred for 1 hour .Then the reflux process was employed and aged for 24 hours. Precipitate obtained washed with deionised water (2-3times),centrifuged dried at 80°C for 8 hours .Dried powders were crushed using mortar and pestle and calcined in alumina crucible at 800°C for 1 hour.

**Silanation of Hydroxy apatite**

Hydroxy apatite was silanated using 3-trimethoxy silyl propyl methacrylate by the following procedure.12.5 wt % of silane was dissolved in 70: 30 mixture of acetone and water.Hydroxy apatite particles were added and the mixture was heated to 40°C for 3 hours under constant magnetic stirring, followed by further treatment at 60°C for 5 hours.Silanated Hydroxyapatite was kept in hot air oven at 120°C for 2 hours.

**Sintering of Hydroxy apatite**

Hydroxy apatite was sintered at different temperatures (800°C, 1200°C and 1300°C) to evaluate the effect of sintering temperature on the compressive strength of bone cement. Bone cement prepared with hydroxy apatite at 1300°C for one hour exhibited higher compressive strength.

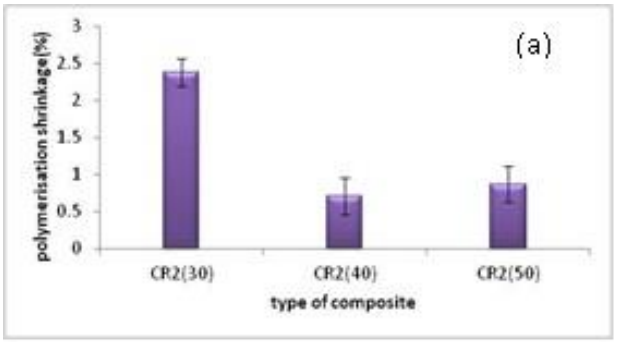
**Characterisation of Hydroxy apatite**

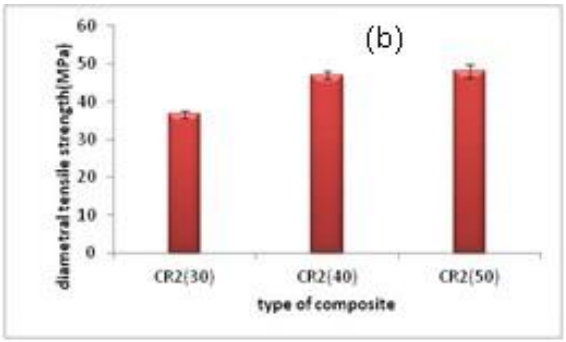
Characterization of Hydroxy apatite was done by Fourier Transform Infrared spectroscopy.

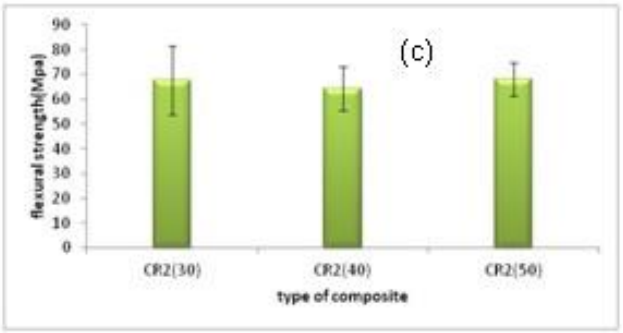
**15. Detailed anaylsis of results : Part of the results are published in the following articles listed in section 19.**

Tetramethacrylate

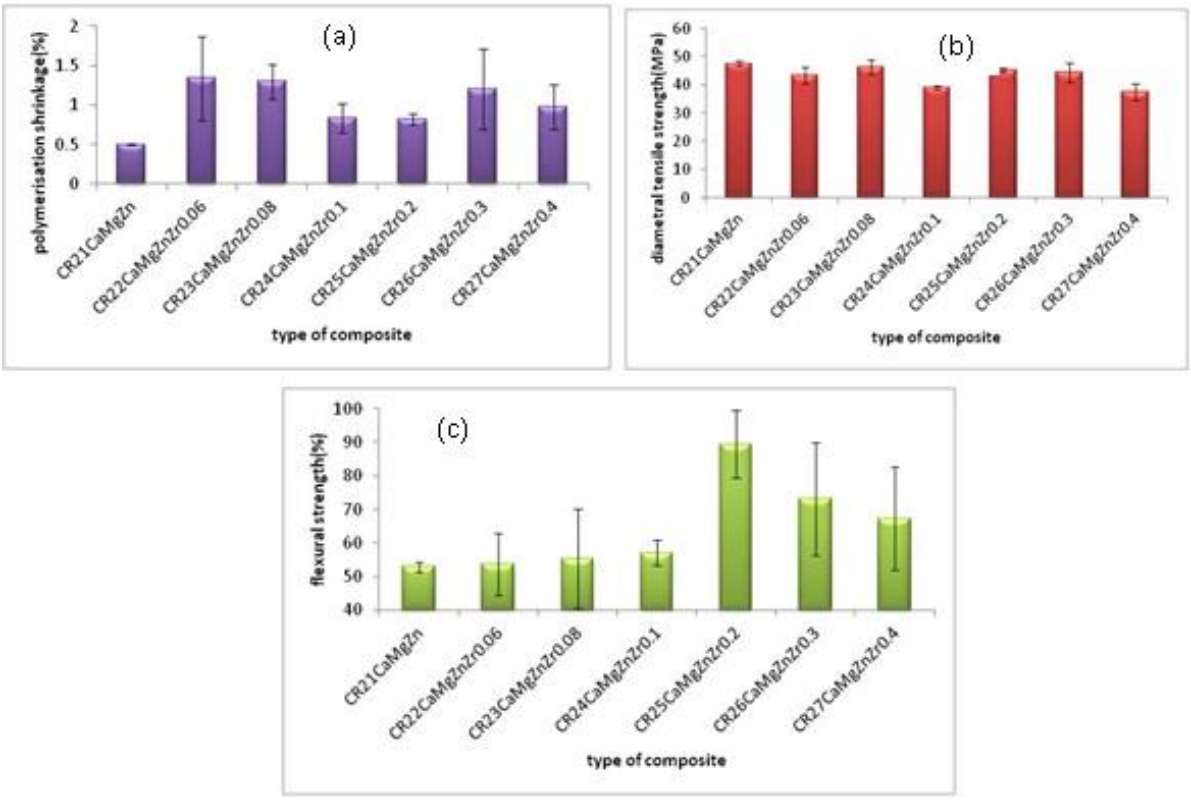
CR21CaMgZn, CR22CaMgZnZr0.06, CR23CaMgZnZr0.08, CR24CaMgZnZr0.1,
CR25CaMgZnZr0.2, CR26CaMgZnZr0.3, CR27CaMgZnZr0.4

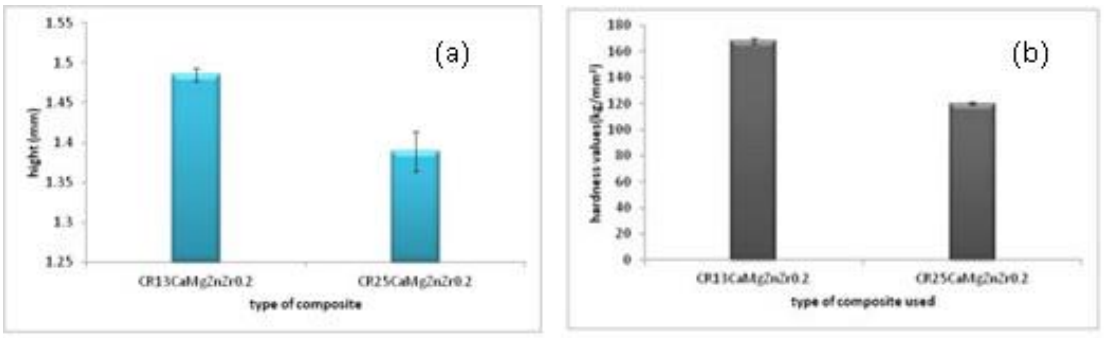



Effect of diluent



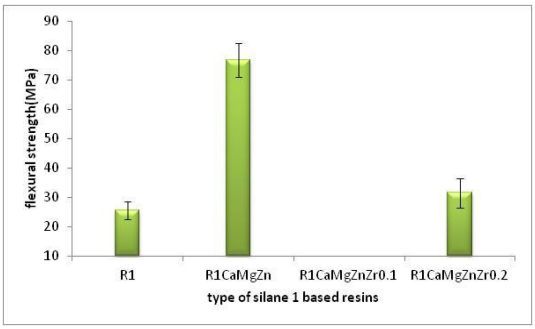



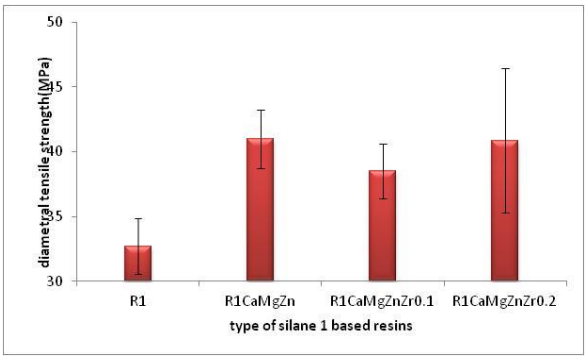

Effect of physico-mechanical properties after optimizing the diluent concentration

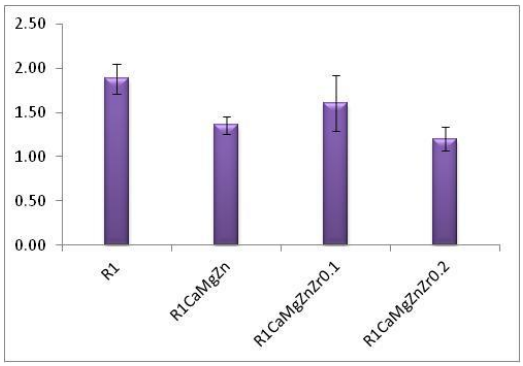
Dimethacrylate

| Resin code | Refractive index |
|---|---|
| **R1** | **1.478** |
| **R11** CaMgZn | **1.4745** |
| **R12** CaMgZnZr0.1 | **1.482** |
| **R13** CaMgZnZr0.2 | **1.4828** |

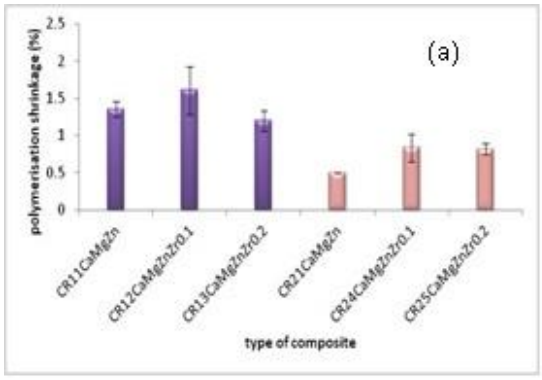
Physico-mechanical properties

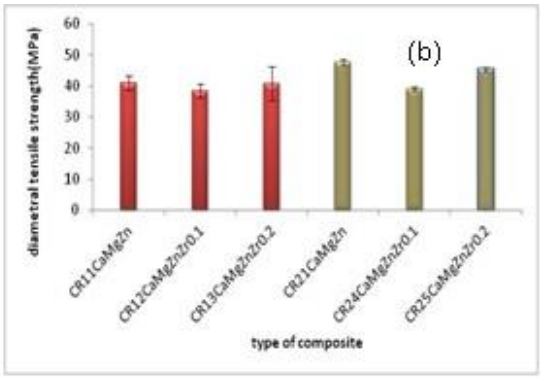


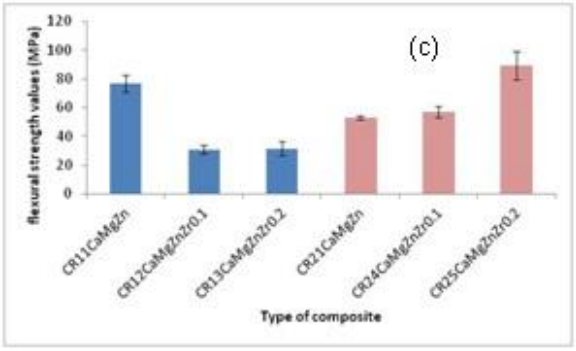




Physico-mechanical properties of VLCs prepared from resin synthesised from silane1 ;(a) polymerisation shrinkage (b)diametral tensile strength (c)Flexural strength

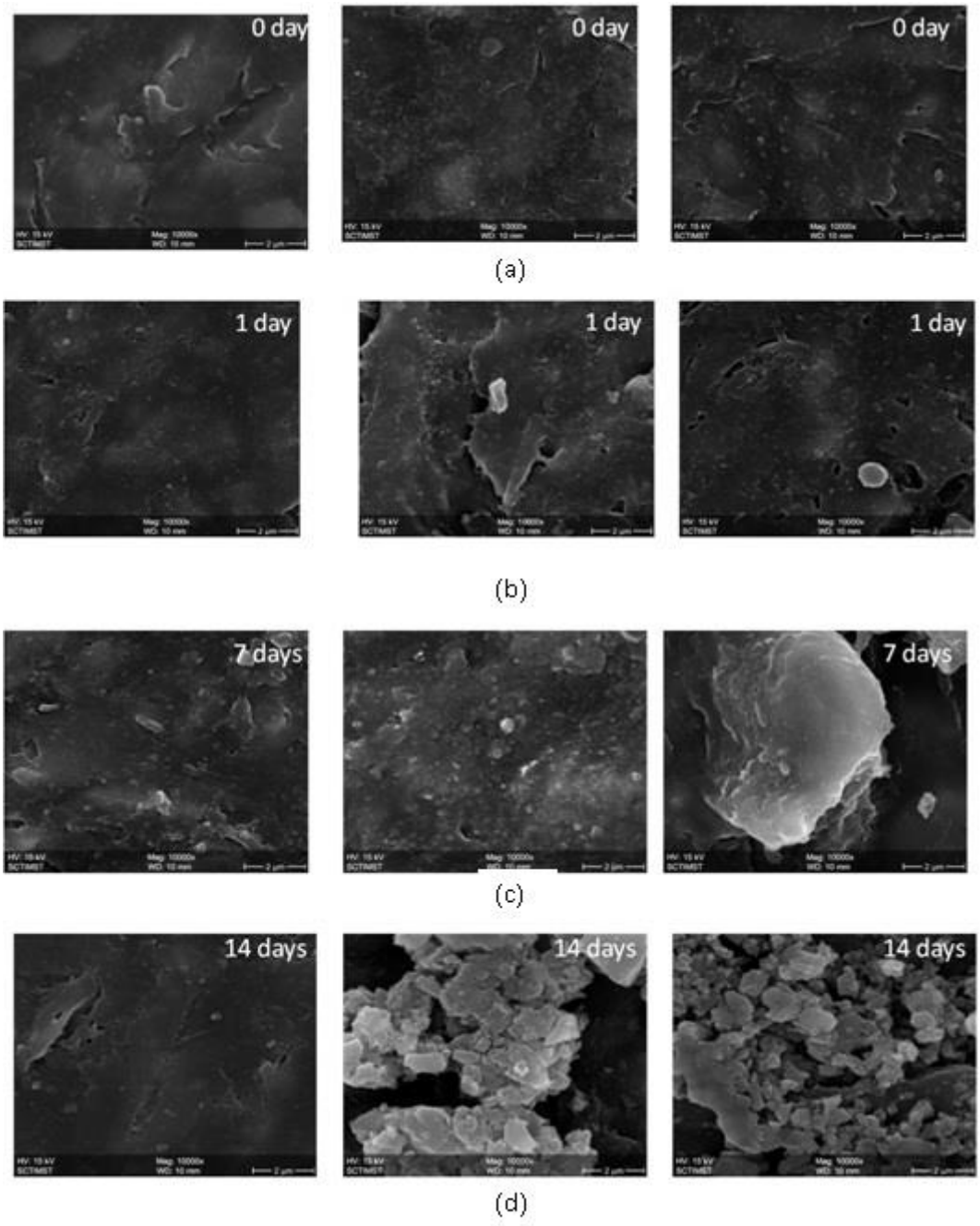


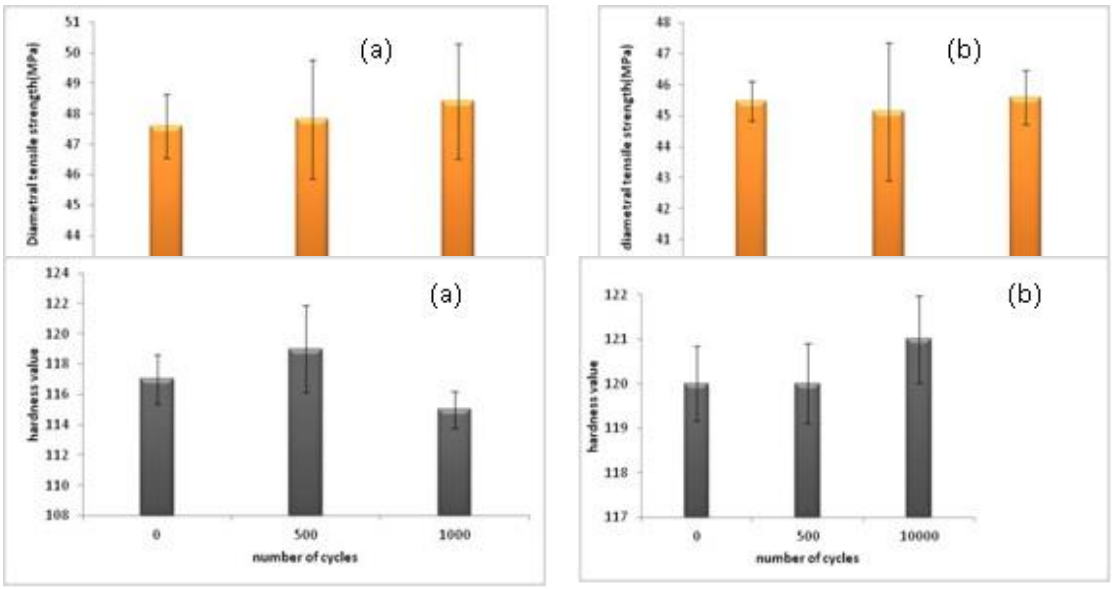

Comparison of VLCs prepared from silane 1 based resins and silane 2 based resins (a) polymerisation shrinkage (b) diametral tensile strength(c) flexural strength

Remineralisation studies



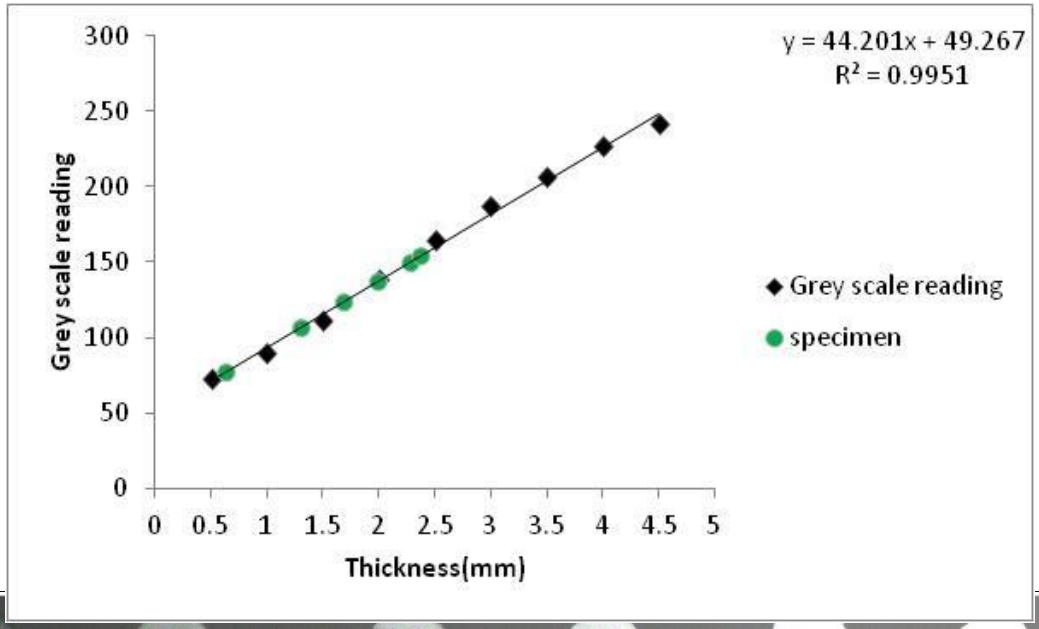

Remineralisation images of (a) Bis GMA (b) CR21CaMgZn and (c) CR25CaMgZnZr0.2

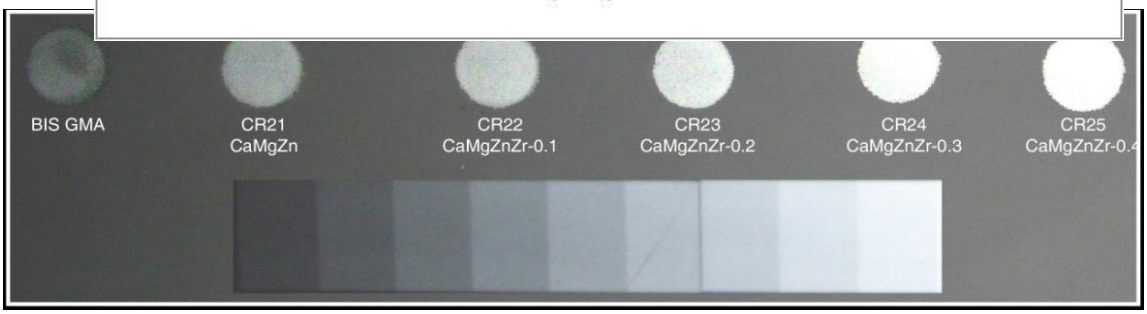
Thermocycling




Comparison of VLCs prepared from silane 1 based resins and silane 2 based resins (a) DTS (b) hardness after thermocycling

Radiopacity of tetramethacrylate



(i)Vibha C, Lizymol P.P* (2017) Development of hydroxyapatite-reinforced biocomposites based on polymerizable multifunctional strontium containing inorganic-organic hybrid resins for biomedical applications. Materials Letters (Featured Letter) 197: 63–66

(ii)Vibha C, Lizymol P.P., Novel bioactive Strontium containing (tetra methacrylate resin) composites for medical applications, Advanced Polymeric Materials for Sustainability and Innovations, Apple Academic Press, CRC Press, Taylor and Francis Group, Hard ISBN: 9781771886338, E-Book ISBN: 9781315102436, 6, October 2, 2018.

(iii).Vibha C., Lizymol P P. Development of bioactive multifunctional inorganic-organic hybrid resin with polymerizable methacrylate groups for biomedical applications‖ in Nanoparticles in Polymer Systems for Biomedical Applications, Apple Publications, ICNT 2016 Hard ISBN: 9781771887038,9, November 2018 .

**16. Summary sheet of not more than 2 pages under following heads :**
**(Title, Introduction, Rationale, Objectives, Methodology, Results, Translational Potential)**

**Title,** Development of a bioactive radiopaque inorganic-organic hybrid resin for dental and orthopedic applications.,

**Introduction,**

Resin composites are tooth-colored materials extensively used in modern restorative dentistry because of their better aesthetics. These materials are composed of a mixture of an organic polymerizable matrix, particulate ceramic reinforcing fillers, molecules promoting and modifying the polymerization reaction, and silane coupling agent connecting the filler and the organic matrix. The polymerization shrinkage associated with these composites creates contraction stresses in the resin composite restoration and internal stress and deformation in the surrounding tooth structure resulting in poor marginal adaptation, postoperative pain, and recurrent carries. This will creates contraction stresses in the resin composite restoration and internal stress and deformation in the surrounding tooth structure resulting in poor marginal adaptation, postoperative pain, leaching of uncured organic monomers causing cytotoxic effects and recurrent carries [18-19]. Only a thorough understanding of the mechanisms that cause shrinkage stress and the techniques that may reduce its effect only gain a better use of resin composite. In recent years, the use of reinforcing inorganic fillers in various forms has been a major approach towards the development of improved dental composites [20-22]. The properties of fillers were made use in most of the studies to impart better properties to dental restoratives[23-30]. Recurrent caries is one of the leading causes of recurrent restoration replacement, it is vital that low-shrinkage composite resins should be developed. Inorganic-organic hybrid resins are new concepts [31] which can be used as monomer matrix in dental restoratives to diminish their polymerization shrinkage and improve abrasion resistance, ease

of processing and biocompatibility [32-33]. This concept is to combine properties of organic polymers (functionalization, ease of processing at low temperature and toughness) with properties of glass like materials (hardness, chemical and thermal stability, and transparency) to generate new/synergistic properties. They are manufactured in a two-step process, the first of which consists of the hydrolysis and polycondensation reaction of organically functionalized alkoxysilanes. Previous studies reported that use of novel di functional and tetra functional inorganic–organic hybrid resins containing alkoxides or mixtures of alkoxides of silicone, aluminum, calcium and titanium can diminish polymerization shrinkage and improve wear resistance [14].

Furthermore, composites that are not adequately radiopaque have been confused as secondary caries in subsequent recall appointments and restored unnecessarily. Thus radiopacity of a composite considered to be an important parameter. So many radiopacifiers were currently available out of these zirconia is reported to be biologically safer [17]. If the radiopacifying agents are compatible with the novel inorganic-organic hybrid resin matrix, it can be applied to orthopaedics also.

The filler does not appear to play a major role in the biocompatibility of the material, despite the organic component. The organic matrix consists of a mixture of various methacrylate monomers, such as 2,2-bis[4- (2-hydroxy-3-methacryloxypropoxy)phenyl]propane (bis-GMA) and urethane dimethacrylate (UDMA) in combination with co-monomers of lower viscosity, such as triethyleneglycol dimethacrylate (TEGDMA), ethyleneglycol dimethacrylate (EGDMA) or diethyleneglycol dimethacrylate (DEGDMA). Dental composite restorative materials also include the flowable resins that have been formulated in a variety of viscosities and compositions to meet the demands of various uses. Biocompatibility ranks as one of the most important properties of dental material. One of the criteria for biocompatibility is the absence of material toxicity to cells, according to the ISO 10993 recommendations. Far from physiological conditions, comparison of material toxic effects in vitro may be of significance and may predict and correlate with in vivo situations. The biocompatibility of a resin-based dental restorative material is predominantly determined by the amount and nature of released organic substances into the oral cavity [34-35] during implantation and even after polymerization [36-37] many cause adverse effects like mucosal irritation, epithelial proliferation, oral lichenoid reaction, hypersensitivity, and anaphylactoid reactions [38]. Leaching compounds can, after dilution by the saliva, enter the intestine [39-41] where, after uptake and metabolization they can form toxic and radical intermediates [42-44]. Possible approaches to increasing the longevity of restorations is to reduce polymerization shrinkage and to promote

biocompatibility of tooth structure [45].

By deducing these three aspects, it is proposed to develop a novel bioactive radiopaque inorganic-organic hybrid resin with low polymerisation shrinkage which will be a promising product in dental as well as orthodontic applications.

**Rationale**

During the last century, much has been learned about the process of dental caries, a localized destruction of tooth tissue by plaque microorganisms that ferment dietary carbohydrates into organic acids which then cause dissolution of tooth mineral. Teeth are constantly going through cycles of mineral loss (when oral pH is below the point at which tooth mineral begins to dissolve) and repair (neutral and/or basic pH conditions that favour the redeposition of mineral). The net loss or gain in mineral over time ultimately determines whether tooth decay (demineralization) will advance, stabilize and/or regress. The major goal of clinical intervention is the preservation of tooth structure and the prevention of lesion progression to the point where restoration is needed.

Dental products account for 30-35% of the total medicinal devices sold in the country and 80-85% of medical devices are imported. The indigenous production is limited to a few. As a result of this and also due the generally high cost of the imported products, there has been a consistent demand for developing indigenous products, which can help bring down the prices and reduce the cost of dental care. There is a wide choice of materials available for restorative dentistry covering a range of requirements which includes silicates, amalgams, glass ionomers, composites, ormocers etc. Polymeric composites are usually used as tooth colored restorative materials [1]. Dental composites habitually consist of organic phase, inorganic phase, and a coupling agent. Coupling agent binds the dispersed glass or silica filler with the resin based restorative material. Commercially available composites are based on bisphenol A glycidyl methacrylate (Bis GMA)/ urethane dimethacrylate (UDMA) / both as resin medium. Resin based composites may ideally provide good sealing of the cavity with no marginal gaps; however, polymerization shrinkage during placement, combined with cyclic mechanical loading during function, may lead to local interface failure and gap development [2]. These marginal gaps can serve as suitable anchorage sites for bacterial colonization [3]. Ineffective bonding with the inorganic filler and organic matrix is one of the main causes for polymerization shrinkage. Dental materials developed for restorative purposes should be able to seal restored interfaces preventing bacterial colonies, better mechanical and bioactivity for its longevity.

Another property to consider is the radiopacity of a composite. Dental materials

should be sufficiently radiopaque to be detected against a background of enamel and dentin, resulting in correct evaluation of restoration in every region and providing the detection of secondary caries, marginal defects, contour of restoration, and contact with adjacent teeth, cement overhangs and interfacial gaps [4-8]. Radiographs are useful not only to evaluate restoration, but also to monitor its long-term stability [9]. The advantages of radiopaque over radiolucent materials are the ease of detection of recurrent dental caries, as well as the observation of the radiographic interface between the materials and tooth substrates. Dental diagnosis relies on radiology, and it is essential to distinguish intraoral placed material, such as composite resin or cement, from surrounding anatomical structures. Radiopacity of the material must be sufficiently different from tooth tissue to be distinguished equally it must be radiopaque enough that it can be distinguished from a void [10].

Possible approaches to increasing the longevity of restorations is to reduce polymerization shrinkage and to promote remineralization of tooth structure [11]. Remineralization of teeth can repair damage of the tooth to a certain degree but damage beyond that cannot be repaired by the body. Enamel itself cannot be re-grown or harden to its original state, but it can self-repair and stay strong if remineralization keeps in step with demineralisation. So the dental restorations having remineralisation ability can enhance its performance in the oral cavity. Recent works in dental biomaterial research targets on the development of bioactive restorations like development of novel dental cements [12], innovative light-curable therapeutic resin-based restorative materials to promote mineral precipitation in mineral-depleted dental hard tissues at the bonding interface [13], etc. Bioactive properties of fillers are made use in most of the studies to impart bioactivity to dental restoratives. However, to date there have been no published studies of dental restorative composites containing bioactive radiopaque inorganic organic hybrid resin as the matrix. Previous studies reported that use of inorganic–organic hybrid resins containing alkoxides of calcium in dental restoratives can diminish polymerization shrinkage and improve wear resistance [14]. The application of bioactive radiopaque inorganic-organic hybrid is not limited to dental restoration but it can extend its application to orthopaedics. During the working phase of the bone cement, polymerization progresses resulting in sudden increase in the viscosity and temperature (it can exceed 100°C) while using methyl methacrylate (MMA) as liquid monomer which one of the drawbacks of bone cement [15]. A liquid monomer working at room temperature is inevitable for *in vivo* conditions. Recent studies have also shown that addition of radiopaque agents in PMMA enhance macrophage-osteoclast differentiation and therefore may contribute to bone resorption which can ultimately lead to loosening of the prosthesis [16]. Thus, an alternative to the traditional

radiopaque agents is needed to improve the performance of the bone cement. Radiopacifying agents that are compatible with the polymer matrix is an alternative route for achieving radiopacity in organic polymers [17]. Thus replacement of existing liquid monomer with a novel bioactive radiopaque resin matrix with low shrinkage working at normal temperature will be a boon to orthopaedics.

## 2. References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innovative light-curable resin-based dental materials containing bioactive micro-fillers. J. Mater. Chem. B.,1: 2624–2638.

**Objectives,** Development of a bioactive radiopaque inorganic-organic hybrid resin for dental and orthopedic applications.,

**Methodology, Modified sol gel process**

**Translational Potential: NIL**

**17. Contributions made towards increasing the state of knowledge in the subject :**
Process for development of radiopaque formulations of composite was optimized

**18. Conclusions summarising the achievements and indication of scope for future work :**

Process for development of radiopaque formulations of composite was optimized

**19. Science and Technology benefits accrued :**

**a. List of research publications with complete details :**

Vibha C, Lizymol P.P* (2017) Development of hydroxyapatite-reinforced biocomposites based on polymerizable multifunctional strontium containing inorganic-organic hybrid resins for biomedical applications. Materials Letters (Featured Letter) 197: 63–66

**Lizymol P. P*.,** Vibha C., Deepu D. R., and Sonalilaxman Waghmare Effect of Zinc Oxide Nanoparticles on Polymerization Shrinkage and Mechanical Properties of ORMO-48, Chapter 11, Bio-Based Polymers and Composites Properties, Durability, and Applications Amadou Belal Gueye (Ed) Hard ISBN: 9781774915325 Apple Academic press, Taylor and Francis group, CRC Press 2023

**Book Chapters**

1. Lizymol P.P., Vibha C, Effect of processing parameters on physico- mechanical properties of visible light cure composites, Functionalized Engineering Materials and Their Applications, Apple Academic Press, Hard ISBN: 9781771885232, E- Book ISBN: 9781771885249, 15, September 11, 2018.
2. Vibha C, Lizymol P.P., Novel bioactive Strontium containing (tetra methacrylate resin) composites for medical applications, Advanced Polymeric Materials for Sustainability and Innovations, Apple Academic Press, CRC Press, Taylor and Francis Group, Hard ISBN: 9781771886338, E-Book ISBN: 9781315102436, 6, October 2, 2018.
3. Vibha C., Lizymol P P. Development of bioactive multifunctional inorganic-organic hybrid resin with polymerizable methacrylate groups for biomedical applications‖ in Nanoparticles in Polymer Systems for Biomedical Applications, Apple Publications, ICNT 2016 Hard ISBN: 9781771887038,9, November 2018 .

**Conference Papers**

1. Vibha C and Lizymol P P "Bioactive radiopaque composites for biomedical applications; in vitro and in vivo studies" in Second International Conference on Advanced Polymeric Materials, Mahatma Gandhi University, Kottayam, 7-9 April 2017.

2. Vibha C and Lizymol P P "Development of bioactive radiopaque composites for biomedical applications" authored in 29th Kerala Science Congress, Mar Thoma College, Thiruvalla, Pathanamthitta, 114, January 28-30, 2017 (Best poster award).
3. Vibha C., Dhanya G R., Lakshmi L., Lizymol P P., Novel bioactiveradiopaque composite for biomedical applications- in vitro and in vivo studies,Science fete, SCTIMST, July 15, 2017.
4. Vibha C, Dhanya G R., Sabareeswaran A., Lizymol P P "Development of bioactive radiopaque composites for biomedical applications" authored in 30th Kerala Science Congress, Government Brennan College, Thalassery, Kannur, January 28-30, 2018.
5. Vibha C, Lizymol PP, In vitro and in vivo bicompatibility studies of novel bioactive radiopaque polymeric composite for biomedical applications, Material Research Society of India, Annual Technical Meeting/Annual General body Meeting-2018, 24 March 2018, IISER Thiruvananthapuram.

6. Vibha C, Praveen Krishna V, Lakshmi L, Lizymol P.P, Effect of inorganic content on polymerization shrinkage and radiopacity of novel inorganic- organic hybrid resins, 28th Kerala Science Congress, University of Calicut, Thenhipalam, Malappuram, January 28-30, 2843-2856, 2016.

**b. Manpower trained on the project :**

| | | | |
|---|---|---|---|
| **i.** | **Research Scientists or Research Fellows** | **:** | **NIL** |
| **ii.** | **No. of PhD's produced** | **:** | **NIL** |
| **iii.** | **Other Technical Personnel trained** | **:** | **1** |
| **c.** | **Patents taken, if any** | **:** | **1** |

**Patents**

**1.** Lizymol Philipose Pampadykandathil, Venkiteswara Kalliyanakrishnan, Vibha Chandrababu (2017). Development of smart bioactive radiopaque dental composites with superior mechanical properties from inorganic-organic hybrid resin. Indian Patent Application Number 201741025621.

**d. Products developed, if any : NIL**

**20. Abstract: (In 300 words for possible publication in ..... Bulletin):NA**

**a. Background:**

**b. Materials:**

**c. Results:**

**d. Conclusion:**

**21. Procurement/Usage of Equipment:**

**a. Details of Equipment: NIL**

| Sl. No. | Name of Equipment | Make/ Model | Cost (Rs.) | Date of Installation | Utilisation | Remarks regarding maintenance breakdown |
|---|---|---|---|---|---|---|
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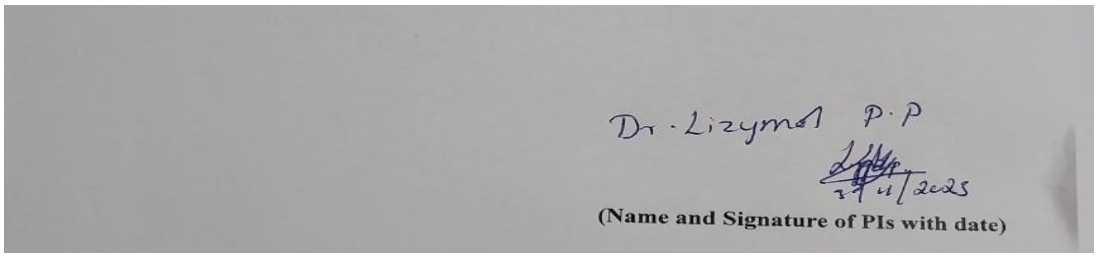
**b. Suggestions for disposal of equipment(s):Not Applicable**




***Routing:*** *Signed copy of "Project completion Report" by PI → root@sctimst.ac.in, rpc@sctimst.ac.in*