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BisGMA and TEGDMA Elution from Two Flowable Nanohybrid Resin Composites: An *In vitro* Study

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Authors' contributions

This work was carried out in collaboration between both authors. Author AW designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author AW also managed the literature searches, analyses of the study performed the spectroscopy analysis and author MNH managed the experimental process. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: The aim of our study was to evaluate the amount of release of BisGMA and TEGDMA from two commercially available enamel replacement composites; Tetric N-Flow™ and G-aenial Universal Flo™ over a period of 24 hours after polymerization with a standard LED Curing Unit.
Methods and Materials: Two flowable nanohybrid composite materials; Tetric N-Flow™ (Ivoclar Vivadent AG, Liechtenstein) and G-aenial Universal Flo™ (GC, India) were investigated and grouped into two groups. Ten samples from each group were prepared by inserting the material into a standardized Teflon mould of size 2x2x2 mm. Each sample was cured with a LED curing unit for 20 seconds and was stored in 2 ml of Ethanol at room temperature. After 24 hours, the samples were removed from the storage medium (ethanol) and prepared for measurements. A reverse phase HPLC unit was used to detect the release of BisGMA and TEGDMA monomers from the prepared samples. The acquired measurements were obtained after testing them in a High Liquid Performance Chromatography Unit. The data obtained was statistically analyzed and the results revealed significant amount of release of TEGDMA as well as BisGMA.

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Results: G-aenial Universal Flo™ showed significant release of both TEGDMA as well as BisGMA as compared to Tetric N- Flow™. The increase was by 0.5 units.
Conclusion: Significant amount of release of TEGDMA as well as BisGMA was seen in both the composite materials after HPLC Unit analysis. This can help in the evaluation of cytoxicity to the soft tissues in the oral environment.

Keywords: BisGMA; flowable composites; HPLC unit; monomer elution; TEGDMA.

1. INTRODUCTION

The most widely accepted restorative materials among clinicians for restorations are light activated resin based composites [1,2]. Control of contour during restoration, increased color stability, increased polymerization and rapid setting compared to chemically activated materials are some of the primary advantages [3]. However inadequate polymerization which results with high residual monomers is one of the common drawbacks [3]. The main bulk of scientific and manufacturing effort during the past years has been focused on the improvement of the filler fraction of composite materials. This fine tuning has resulted in an overall improvement in their aesthetics, physical properties and handling characteristics. According to various studies done previously; oxygen prevents polymerization of monomers by formation of an inhibition zone when the surface of the resin comes in contact with air [4,5].

'Fibre-reinforced composites' and 'Nanocomposites' have been marketed to meet this perceived need, although most of these composite resins consist of a mixture of Dimethacrylates; various methacrylate monomers such as BisGMA Bis[4-(2-hydroxy-methacryloxypropoxy)phenyl]propane), UDMA(urethane dimethacrylate), in combination with co-monomers of lower viscosity such as TEGDMA (triethylene glycol dimethacrylate) [6]. The percentage of filler content by weight of flowable composites is 50% to 70%. This is less than that of traditional hybrid composite resins (70% to 80%) which lowers their viscosity and enhances their handling properties [6].

The monomers and co-monomers in composite materials polymerized through radical chain reactions are responsible for major clinical disadvantages such as polymerization shrinkage leading to micro-leakage phenomenon [6].

Pulpal reactions are also seen when composite materials are placed in deep cavities very close to the pulp. Also BisGMA have been found to cause time and concentration dependant cytotoxity to various cell lines including human gingival and pulp fibroblasts and human THP-1 and peripheral blood monocytes [7,8]. It also has a high affinity for erythrocytes [9]. Many in vitro studies have revealed that TEGDMA is cytotoxic in various cell cultures. It can easily penetrate membranes and react with intracellular molecules [6].

One of the alternatives to overcome polymerization shrinkage is the use of a Light Emitting Diode Curing Unit. It is a highly efficient source of light with a narrow spectral range of light [2]. The Quartz Tungsten Halogen on the other hand produces inadequate polymerization. This could be attributed to the bulb and filter ageing [10,11].

The clinical success of composite materials however depends not only on the physical and chemical properties of the materials; but also on their biological safety. Some authors evaluated the amount of release of monomers from methacrylate based nanocomposites at different electron beam radiation dosages and different storage times. Two dental nanocomposite materials were used and cured for 20 seconds. Regardless of the dose of electron beam radiation, the material or storage time, a higher amount of BisGMA was released compared to TEGDMA. After 24 hours leaching of monomers was maximum in non-irradiated samples and minimum in samples irradiated at dose of 3kGy.Among irradiated samples, maximum leaching of monomers was seen in samples irradiated at 5kGy followed by 1kGy, except in case of BisGMA monomers from restorative nanocomposites. After 1 week there was decrease in leaching of monomers, except in case of TEGDMA monomers from restorative nanocomposites where an increase in leaching was seen [12].

Another study was conducted by other authors to determine the monomer release from two flowable composite materials after different polymerization and storage times. HPLC unit was

used to determine the monomer elution of BisGMA and TEGDMA. Monomer elution was evaluated after 24hours and 7 days and after curing with a LED curing Unit and a QTH Curing Unit. Regardless of polymerization time, the material or storage time, a higher amount of BisGMA was released compared to TEGDMA. No significant difference was found between samples polymerized for 20, 30 and 40 seconds [6].

In the present study; two nanohybrid flowable composites; Tetric N –Flow™ (Ivoclar Vivadent, Liechtenstein) and G-aenial Universal Flo™(GC, India) were used. According to the manufacturers, nanocomposites undergo less polymerization shrinkage.The aim of this study was to evaluate the amount of release of TEGDMA as well as BisGMA from two flowable dental nanohybrid composites after being cured by a LED curing unit when stored at a storage period of 24 hours.

2. MATERIALS AND METHODS

Two composite materials namely G-aeniel Universal Flo™, (GC, India) and Tetric- N Flow™ (Ivoclar Vivadent AG, Liechtenstein) were used. Both these composites are flowable nanohybrid composites used for enamel replacement. Tetric N-Flow™ comprises of Dimethacylates (<40% BisGMA, TEGDMA and UDMA), inorganic fillers, ytterbium trifluoride, initiators, stabilizers and pigments. G-aenial Universal Flo™ comprises of Dimethacrylates (UDMA, Bis-MEPP and TEGDMA), Silicon dioxide, Strontium glass, pigments and photoinitiators. The advantage G-aenial Universal Flo™, (GC, India) has is that the surface particles are treated with glass giving it more flexural strength than Tetric- N Flow™ (Ivoclar Vivadent AG, Liechtenstein) These two composites were grouped into 2 groups. Ten samples from each group were prepared.

All 20 samples were standardized using a teflon mould of dimension 2x2x2 mm. The mould was positioned on a transparent plastic matrix strip placed on a glass plate. After inserting the material into the mould, a transparent plastic matrix strip was placed on top of them to avoid oxidation of the superficial layer. Each sample was cured with a LED Elipar Freelight 2 (3M ESPE, Germany) curing unit for 20seconds. The distance between the light source and the sample was standardized by using a 1cm glass plate.

Immediately after curing, the specimens were immersed in 2 ml of Ethanol (Hayman limited, Eastways Park, Witham, Essex, CM88YE, and England). These samples were stored at room temperature for a time period of 24 hours. After 24 hours the samples were measured using the HPLC (SHIMADZU, Model SPD 20A, Shimadzu Corporation, and Kyoto, Japan) Unit at the Department Of Biotechnology, NMAM Institute of Technology, Nitte. A reverse phase HPLC unit was used to detect the release of monomers. The separation of monomers took place at a stationary phase with a CC 125/4 Nucleodur 100-5 C18ec HPLC-Column. The detection was performed at a wavelength of 254nm at a flow rate of 1mL/min .For the analysis of extracted residual monomers a reference standard of TEGDMA (Sigma Aldrich Chemical Co., USA) and BisGMA (Sigma Aldrich Chemical Co., USA) were purchased. 20 µl from the solution was injected into the HPLC syatem and standard chromatograms were obtained for both the monomers individually.

The results were statistically analyzed using Student-t Test based on the data obtained. SPSS (Statistical Package for Social Science) software version 15 was used.

3. RESULTS

The retentive time of TEGDMA in Tetric® N-Flow and G-aenial Flo™ were 16.1323 and 16.615 units respectively after 24hrs following immersion in ethanol (Fig. 1). The release was between 15.8-16.7 units on the x axis (Fig. 2).

The retentive time of BisGMA in Tetric® N-Flow and G-aenial Flo™ was 17.413 and 17.92833 respectively after 24hrs following immersion in ethanol (Fig. 1). The release was between 17-18 units on the x axis (Fig. 3).

The retentive time of BisGMA and TEGDMA in G-aenial Universal Flo™ was higher compared to Tetric® N-Flow by 0.5 units. Our results confirmed more release of both TEGDMA and BisGMA from the nanocomposite. Although G-aenial Universal Flo™ claims to be BisGMA free, BisGMA release was seen in significant amounts. This could be owed to the presence of BisMEPP (Bisphenol A Ethoxylate Dimethacrylate) present instead of BisGMA.

		Category	N	Mean	Std. deviation	t	df	Sig. (2-tailed)
BIS GMA	Retentive Time	TETRIC N FLOW	3	17.413	0.492232	-1.136	4	0.319
		G-AENIAL FLOW	3	17.92833	0.611991			
	Area	TETRIC N FLOW	3	318339.3	271005.8	-0.687	4	0.53
		G-AENIAL FLOW	3	491552	342452.8			
	Height	TETRIC N FLOW	3	15353.67	13617.89	0.756	4	0.492
		GAENIAL FLOW	3	9046.67	4823.239			
	Area %	TETRIC N FLOW	3	4.874667	0.309267	-1.413	4	0.231
		G-AENIAL FLOW	3	9.311333	5.430846			
	Height %	TETRIC N FLOW	3	9.647667	2.279515	0.099	4	0.926
		G-AENIAL FLOW	3	9.366	4.389001			
TEGDMA	Retentive Time	TETRIC N FLOW	3	16.13233	0.106566	-2.605	4	0.06
		G-AENIAL FLOW	3	16.615	0.302675			
	Area	TETRIC N FLOW	3	1685612	2335025	1.017	2.002	0.416
		G-AENIAL FLOW	3	314740.7	50255.86			
	Height	TETRIC N FLOW	3	38389.67	43169.03	1.147	2.022	0.369
		G-AENIAL FLOW	3	9719	3217.949			
	Area %	TETRIC N FLOW	3	20.41633	18.90469	1.192	2.16	0.348
		G-AENIAL FLOW	3	7.149667	3.77982			
	Height %	TETRIC N FLOW	3	21.98133	14.39773	1.393	2.192	0.288
		GAENIAL FLOW	3	10.12367	3.158622			

Fig. 1. Depicts the retentive time of the monomer release of BisGMA and TEGDMA from Tetric N-Flow and G-aenial Universal Flow respectively

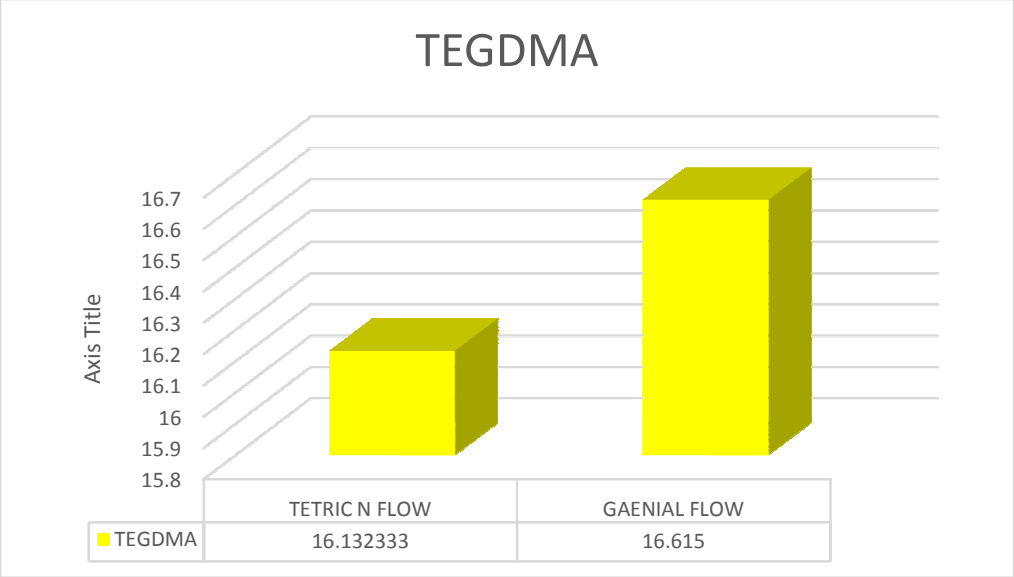

Fig. 2. This graph depicts the retentive time of TEGDMA release from Tetric N-Flow and G-aenial Universal Flo respectively

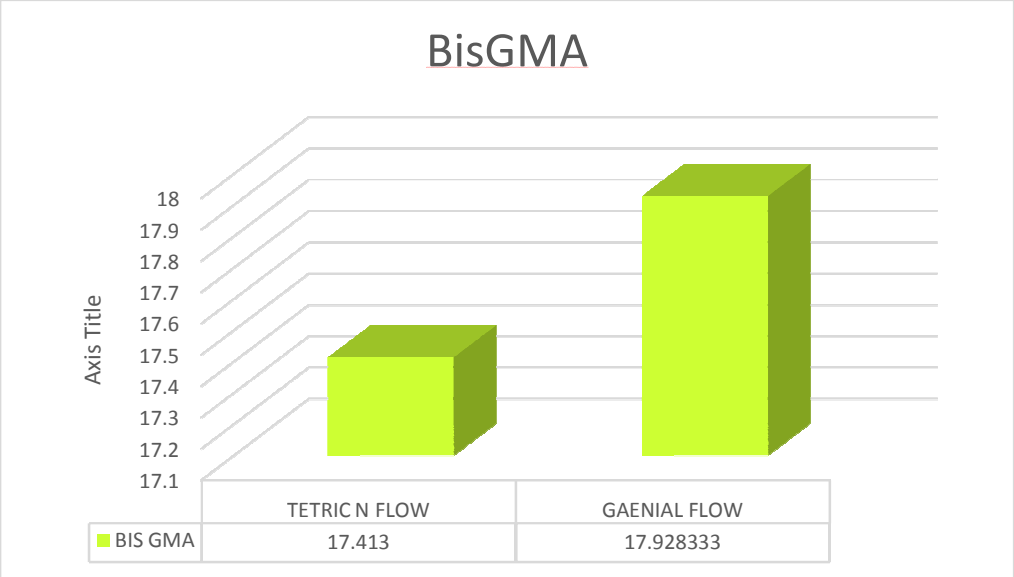

Fig. 3. This graph depicts the retentive time of BisGMA release from Tetric N-Flow and G-aenial Universal Flo respectively

4. DISCUSSION

Better aesthetics and improved adhesion to enamel and dentine has increased the use of resin-based restorative materials. These materials are used in a wide variety of applications in dentistry including prosthodontics, orthodontics and preventive dentistry other than their use in restorative dentistry. However the concern of polymerization shrinkage still prevails. Various unreacted components may be released from these resin based composites in the oral envirommment [13]. These components may be oligomers, or residual monomers and they can affect the biocompatibility of these materials [14].

Several attempts have been made by manufacturers in order to overcome the problem

of polymerization shrinkage through the development of new monomer systems, including the so called “Expanding Monomers”, based on Spiro-orthocarbonate molecules, epoxides systems (oxiranes, siloranes) [6]

Flowable composites as well as nonocomposites have also been developed to meet these needs. In nanocomposites, nanofillers of sizes ≤ 100nm [15] are added and distributed in a dispersed form or as clusters. For enhancing mechanical properties, nanocomposites were reinforced with nanofibers or nanoparticles. For reducing polymerization shrinkage, the resin matrix is modified by using methacrylate and epoxy functionalized nanocomposites based on silsesquioxane cores or epoxy-resin-based nanocomposites [16].

This has led to an increased use of flowable as well as nanocomposites in dentistry. The release of these monomers has been considered as a source of wide variety of adverse biological reactions including local and systemic toxicity, pulp reactions and allergic affects [17]. Elution of monomers occurs by the diffusion of the resin matrix. Its degradation or erosion over a period of time can also be one of the reasons [17,18]. These unpolymerized monomers can be released from dental composites into the pulp by means of dentinal microchannels [19,20] or directly into the oral cavity [21,22].

The factors that contribute to the elution of monomers are the chemistry of the solvent, the size and chemical composition of the elutable species and the extension of the polymerization reaction, rapid immersion and duration used for immersion. Enamel replacement composites are likely to release monomer into the oral cavity than into the pulp as they form the superficial most layers.

The National Institute of Occupational Safety and Health has classified TEGDMA as being irritating to various tissues [23].

Some authors reported that the strong haemolytic potency of BisGMA was due to its chemical structure with a high hydrolytic nature [9].

In most studies the cytotoxicity ranking of the basic monomers has been found to be the following: BisGMA > UDMA > TEGDMA >>> HEMA [13,24,25,26,27].

The aromatic BisGMA is slightly more cytotoxic than the aliphatic monomer UDMA [24,26] Cell toxicity was observed at BisGMA concentrations of 50 pg/ml and higher [28].

100% ethanol was used as a solvent as it has shown maximum ability to extract residual monomers. BisGMA and ethanol have the same solubility parameter [29,30] Ethanol has an ability to penetrate and swell the polymer chains which in turn facilitate the release of entangled free monomers from the set composites [31,32,33]. It is available in small amounts in a hydrophilic environment and is not readily soluble in water. Yet is has been used as a representative acrylate compound for studying the toxic mechanisms of resin monomers on biological tissues [34] BisGMA from dental materials has also shown synthetic estrogenic affects [35].

TEGDMA is easily released from polymerized composites into aqueous media and accounts for most of the unreacted double bonds [36]. Due to its lipophilic nature; it can penetrate the cytosol and membrane lipid compartments of mammalian cells [23].

According to some studies, 85-100% of monomers eluted are eluted within 24 hours [31].

More recently, using the more sensitive methodology of HPCL have shown that monomer elution continued beyond 24 hours for resin based composites and resin mixtures.[21, 37] In another study, TEGDMA was released more within 24hours when Esthet X-Flow and Tetric N Flow were compared after a storage period of 7 days [6]. Tetric N Flow showed more release of BisGMA after 7days storage period [6]. This finding was in agreement with the findings of some authors who showed that elution of bisGMA continued to increase compared to TEGDMA even after 7-28 days [38].

Another study measured the release of TEGDMA and BisGMA from two commercially available composite resins; Filtek Z 250 (3M ESPE, Germany), Leaddent (Leaddent, Germany) and two fissure sealants; Helioseal F (3M ESPE, Germany) Enamel Loc (Premiere Rev, USA) over 1, 3 and 7 days after polymerization with standard quartz-tungsten halogen Coltolux II (QHL) (Coltene Switzerland) and a standard blue light emitting diode Elipar Freelight 2 (3M ESPE, Germany). After HPLC analysis LED 20 second group showed the highest release of monomers at 1, 3 and 7 days in sealant groups. Halogen 40

seconds group resulted highest release of monomers for Leaddent at all time intervals [2].
A study was conducted by some authors to investigate the elution of monomers (BisGMA), (TEGDMA), (UDMA), and (BPA)] from two light-cured materials (nanohybrid and ormocer) and from a chemically cured composite material, after different curing times (0, 20, 40 and 80 seconds) and different storage periods (24 hours, 7 days, 28 days, and 1 year after curing). The samples were analyzed using Liquid Chromatography Tandem Mass Spectrometry (LC–MS/MS) after storage in ethanol. The amount of monomers released from the nanohybrid and the chemically cured composite was significantly higher than that released from the ORMOCER. For the nanohybrid, less monomer was released after increasing the curing time. For the ormocer, 80 seconds of curing resulted in a higher degree of monomer release. Elution of TEGDMA was significantly decreased after storage for 28 days and 1 year. A similar amount of BisGMA was released at each storage time-point analyzed, even after 1 year. This study showed that ormocer released a very small amount of monomers compared with the other materials [39].

In the present study G-aenial Universal Flo™ and Tetric N-Flow™ were investigated. Both the materials are flowable nanohybrid composites and enamel replacement materials. These materials were chosen to measure the amount of monomer release and to evaluate the cytoxicity to the soft tissues in the oral environment. TEGDMA and BisGMA were identified by the retention time in the HPLC Unit. This study was in accordance with the study conducted by previous authors [6]. HPLC analysis is a standard method used for the determination of monomer elution from resin based composites [2,12,40,41].

5. CONCLUSION

The present study revealed release of significant amounts of TEGDMA and BisGMA within 24hours of storage in Ethanol. The retentive time of TEGDMA and BisGMA in G-aenial Universal Flo™ samples was higher by 0.5 units. Although G-aenial Universal Flo™ claims to be BisGMA free; BisGMA monomer was released when the samples were tested for the presence of BisGMA. This could be attributed to the presence of BisMEPP (Bisphenol A Ethoxylate Dimethacrylate) present in the composite instead of BisGMA. BisMEPP belongs to an ethoxy group while BisGMA to a propoxy group [42] of methacrylates.

The manufacturers recommend 20 seconds polymerization time with a LED curing Unit and say that it is enough to achieve polymerization of a 2mm thick composite restoration. However even after curing for 20 seconds, significant amounts of monomer were leached out after 24 hours.

Further studies in material science regarding the value retention properties of composites needs to be done and more light should be shed on the clinical precautions for using resin based composites.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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