

Received: 2017.10.03  
Accepted: 2018.01.16  
Published: 2018.07.07

# Analysis of Base Monomer Elution from 3 Flowable Bulk-Fill Composite Resins Using High Performance Liquid Chromatography (HPLC)

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Source of support:** Departmental sources

**Background:** The aim of this study was to evaluate the elution of BisGMA, UDMA, TEGDMA, and HEMA monomers from flowable bulk fill composite resins with different resin matrix compositions, polymerized in 4-mm-thick layers, into 3 elution media.





**Material/Methods:** Three bulk-fill (SDR® (SDR), X-tra base (XB) and BEAUTIFIL-Bulk Flowable (BF)) resin-composites were tested. Cylindrical samples were immersed in 100% ethanol, 75% ethanol, and distilled water. The concentrations of the monomers were measured using the HPLC method (Agilent Technologies 1200 Series) after 1 and 24 h, as well as after 3, 7, 14, and 21 days.

**Results:** After polymerization of the tested resins, there was elution of the BisGMA, UDMA, TEGDMA, and HEMA monomers from the SDR and BF composites, but none of the tested monomers could be detected eluting from XB. The highest penetrations of the polymerized SDR and BF composites were observed in the 100% ethanol solution. This extraction medium eluted the highest amounts of free monomers. Some eluted monomers were not described in the composites Material Safety Data Sheets.

**Conclusions:** The elution of the residual monomers depended on the resin composition and the materials filler/resin matrix ratio. In composite materials, toxicity assessment should be carried out, and should consider both the material composition as given by the manufacturer, and also the residual monomers that elute from the polymerized material. The elution concentration and time of monomers from composites depended on the solvent used. The highest penetrations of the polymerized SDR and BF composites were observed in the 100% ethanol solution, and this extraction medium eluted the highest amounts of free monomers. The 75% ethanol was a more aggressive medium than water in terms of monomer elution from bulk fill composites.

**MeSH Keywords:** **Chromatography, High Pressure Liquid • Composite Resins • Methylmethacrylate**

**Full-text PDF:** <https://www.medscimonit.com/abstract/index/idArt/907390>

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## Background

Resin-based composites (RBCs) are complex mixtures that generally consist of an organic resin matrix, reinforcing inorganic filler, and a silane-coupling agent that connects the filler and resin matrix. The polymerizable matrix contains 1 or more base monomers such as bisphenol A glycol dimethacrylate (BisGMA) and/or urethane dimethacrylate (UDMA), diluent co-monomers such as ethylene glycol dimethacrylate (EGDMA), diethylene glycol dimethacrylate (DEGDMA), and/or triethylene glycol dimethacrylate (TEGDMA), and various additives such as photoinitiators, co-initiators, polymerization inhibitors, and photostabilizers [1]. Resin-based composites have evolved significantly since they were first developed, particularly in an effort to improve their strength and wear resistance and to decrease polymerization shrinkage. To increase the durability of composite fillings, a technique was developed in which cavities were filled using layers of composite material of up to 2 mm in thickness. The first flowable composite was introduced into clinical practice in 1996 [2]. Since then, a method for decreasing the shrinkage stress of composite fillings has involved placing a lower-density RBC at the bottom of the cavity [3–5]. However, unsatisfactory mechanical properties and the high polymerization shrinkage of such lower-density composites did not allow for their use in thick layers, which could potentially hasten the time-consuming layering procedure [5]. Thus, a new class of flowable materials called bulk-fill flowable RBCs was developed [6,7]. The first of these to enter clinical practice was SureFil® SDR® Flow (Dentsply International, York, PA), which was introduced in Europe in February 2011 under the name SDR® (Dentsply International). The point of difference of this bulk-fill material was that it could be placed in 4-mm-thick layers instead of the conventional incremental placement of 2-mm-thick composite layers [7–11]. Flowable bulk-fill composites have since been extensively developed. Clinical studies advocate the use of bulk-fill flowable RBCs as a base for composite fillings [12–14].

One of the most common drawbacks of flowable bulk-fill composites, like all RBCs, is incomplete polymerization. In clinical application, a considerable amount of residual dimethacrylate monomer can remain in the polymerized resin composite [15]. Such monomers can elute from polymerized dental methacrylate-based materials either into the oral cavity or diffuse into the pulp through dentinal tubules [16]. The leaching of monomers can impact the structural stability and biocompatibility of the material. Solubility influences the resistance to degradation in the oral cavity. This could at least partially account for clinically-observed failures, including decreased wear resistance and hardness, and increased tendency to discoloration. Leachable monomers are also thought to contribute to a wide range of adverse biological reactions. Several *in vivo* and *in vitro* studies have demonstrated that the basic

RBC monomers – BisGMA, UDMA, TEGDMA co-monomer, and 2-Hydroxy-ethyl-methacrylate (HEMA) – exhibit systemic and local toxic properties, including cytotoxic, genotoxic, mutagenic, and allergenic effects [17–21]. These studies have indicated that the cytotoxicity ranking of these basic monomers is BisGMA >UDMA >TEGDMA >HEMA [17–21].

Leaching of monomers from composite resin is a diffusion-rate-dependent process that is influenced by many parameters. Ferracane reported that it is affected by the content of the leachable compound, which is in turn affected by the polymerization rate of the RBC (e.g., energy density of delivered light, and thickness of the RBC layer) [15,22]. The size and chemical composition of the leachable compound, including the polymer matrix composition, filler particle type and content, and resin porosity and homogeneity, can all affect leaching [23]. The chemistry of the solvent can also significantly affect leachate elution [15]. Various solvents have been used in studies evaluating leaching of monomers. The solvents can be divided into 2 main groups: (1) water or aqueous mixtures such as artificial saliva, human saliva, water-based buffer solutions, and cell culture media; and (2) different organic extraction media such as ethanol- or methanol-based, including their aqueous mixtures, acetone, acetonitrile, tetrahydrofuran, and chloroform [19,24–29]. The choice of extraction medium type depends on the research purpose. According to ISO specification, distilled water is an extraction medium for resin-based filling materials, which simulates a humid, intraoral environment containing both saliva and water [30]. This medium is often used in studies on monomer leaching [25,28,31]. Ferracane noticed that fluids in the oral cavity exhibit extraction features that lie between more aggressive organic solvents and water [15]. Therefore, the US FDA recommends the use of a 75% ethanol/water solution as a fluid with properties corresponding to oral cavity conditions, and this solvent has also been used in many studies. [28,29,32–34]. Ethanol, because of its solubility parameter which matches that of BisGMA, is able to penetrate the matrix and expands the space between polymer chains, and soluble substances, such unreacted monomers, may diffuse. Ethanol, as a weathering agent, is an important variable as it can mimic and accelerate, by continuous exposure, the normal degradation expected clinically from food and saliva. Even though a pure ethanol extraction medium is not relevant clinically, it may allow evaluation of the amount of all alcohol-soluble leachable compounds contained in RBCs because it is a more powerful solvent than 75% ethanol [35]. The monomer concentration leached into this solvent should be close to the total leachable content of unreacted monomer in the resin.

Despite the fact that many studies have investigated the release of residual monomers from composite materials [15,16,20,25–27,36], the literature regarding monomer elution from bulk-fill

**Table 1.** The description of the resin composites used in the study.

Material; manufacturer	Code	Lot No.	Organic matrix	Filler amount (wt%/vol%),	Shade
SDR®; Dentsply International	SDR	384201	Modified UDMA, BisEMA, TEGDMA	68/44	Universal
X-tra base; Voco GmbH Germany	XB	1324388	BisEMA, EBPADA, UDMA, DEGDMA	75/61	Universal
BEAUTIFIL-Bulk Flowable; Shofu Dental GmbH Germany	BF	031403	BisGMA, UDMA, Bis-MPEPP, TEGDMA	73 wt%	Universal

RBCs is limited. To date, only a few papers have been published on the release of monomers from low-viscosity bulk-fill RBCs polymerized in a 4-mm layer [28,29,32,34,35]. A study by Alshali et al. showed that elution of residual monomers from bulk-fill composite resins did not differ from conventional resin composites [29]. Cebe et al. evaluated the elution of monomers from bulk-fill composite resins into 75% ethanol solution [32]. Pongprueksa et al. examined monomer elution from composites with different viscosities from the same manufacturer into absolute ethanol [35]. Lempel et al. evaluated the degree of conversion and BisGMA, TEGDMA, and UDMA elution from flowable bulk-fill composites into 75% ethanol [34]. The low-viscosity bulk-fill resin composites, like all RBCs, are a diverse group of resin-based composites, with resin matrix based on different monomers. While a few studies have investigated monomer elution behavior of the first, low-viscosity bulk-fill composite – SDR® (Dentsply International) – with matrix based on UDMA/BisEMA formula, the monomer elution from X-tra base (Voco GmbH Germany) is less known, with no monomer elution study published on use of Beautifil-Bulk Flowable (Shofu Dental GmbH, Germany) [28,29,32,34].

The present study was designed to investigate the 4 monomers elution concentration range that could be obtained with 100% ethanol (maximum elution of monomer), an ethanol/water mixture and distilled water, which may be more clinically relevant, from 3 flowable bulk-fill composite resins with different resin matrix compositions. The composite resins were polymerized in 4-mm-thick layers over 6 different time periods. The elution of monomers was determined using high-performance liquid chromatography (HPLC).

The null hypotheses tested were that: (i) after polymerization of the bulk-fill composite resin, there would be an elution of the BisGMA, UDMA, TEGDMA, and HEMA monomers into the solution; (ii) the elution of the residual monomers would depend on the resin composition of the tested material; and (iii) the eluted monomer concentration would depend on the type of extraction medium.

## Material and Methods

Three flowable bulk-fill resin composites were tested. Descriptions of the materials used in this study are presented in Table 1. From each resin-based composite, 15 samples were prepared.

### Sample preparation

Samples were prepared using forms that afforded standardized cylindrical samples with a diameter ( $\phi$ ) of 5 mm and a height of 4 mm. The forms were positioned on a transparent plastic strip lying on a glass plate, and were then filled with composite material. Samples were built up in 4-mm-thick increments. After filling the mold with composite, a transparent plastic strip was placed on top of the composite to prevent the formation of an oxygen-inhibited superficial layer. Every sample was then polymerized according to the manufacturer's recommendation. Samples were cured with a dental curing unit (G-Light, GC), which had a light intensity of 1000 mW cm<sup>-2</sup> and a tip diameter of 7 mm. The light was positioned directly on the top of the plastic strip on top of each mold. Curing was performed only on 1 side of the sample, to mimic clinical conditions. The intensity of the curing light was measured using a manual radiometer (Spring 2K Light Meter, SPR-SP3K, Spring Health Products Inc., Norristown, PA). Immediately after irradiation, 5 samples of each material were randomly immersed into different storage media. Storage media included 100% ethanol (Gradient Grade, Merck), 75% ethanol/water solution, and distilled water (Direct-Q 3 UV system, Millipore, Billerica, MA). Each sample was immersed in 0.5 mL of the extraction medium. The samples were all placed in an Eppendorf® Thermomixer Compact at 37°C. The extraction medium was renewed after 1 and 24 h, and after 3, 7, 14, and 21 days. The samples were protected from light during the whole procedure. The extraction medium removed at each time point was used to prepare samples for HPLC analysis.

### HPLC analysis

HPLC analysis was performed using an Agilent Technologies (Santa Clara, CA) 1200 Series system consisting of a 4-channel

**Table 2.** The description of substances evaluated in the study.

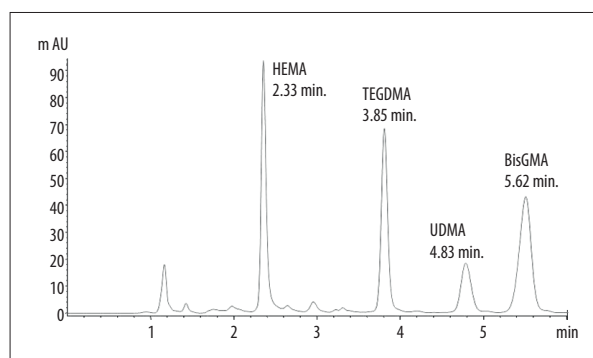
Reference substance (Abbreviation)	Compound	Function	Molecular ion, m/z	RT (min)	CAS#, manufacturer
BisGMA	Bisphenol-A-glycerolate-dimethacrylate	Monomer	512.59	5.62	1565-94-2, Sigma-Aldrich, St. Louis, MO
UDMA	Urethane-di-methacrylate	Monomer	471	4.83	72869-86-4, Sigma-Aldrich, St. Louis, MO
TEGDMA	Triethyleneglycol-di-methacrylate	Co-Monomer	286.32	3.85	109-16-0, Sigma-Aldrich, St. Louis, MO
HEMA	2-Hydroxy-ethyl-methacrylate	Co-Monomer	130.14	2.33	868-77-9, Sigma-Aldrich, St. Louis, MO

CAS# – Chemical Abstract reference number.

gradient pump (G1311A) with a vacuum degassing module (G1322A), an automated dosing system (G1367C), a DAD SL detector (61315C), and a column thermostating compartment (G1316B). Separation was conducted using a reverse phase column (LiChrospher 100 RP-18, column  $\phi$  4 mm, particle  $\phi$  5  $\mu$ m). The column was protected using a LiChroCART 4-4 pre-column. The mobile phase was 70% acetonitrile (Gradient Grade, Merck) and 30% water (Direct-Q 3 UV system, Millipore). The mobile phase flow rate was 5 mL min<sup>-1</sup>, and the column temperature was 23°C. The absorbance was measured at a wavelength of 205 nm. Chromatograms were analyzed using HP Chemstation (Agilent Technologies) software. On-column injection of 10- $\mu$ L samples was performed every 23 min with a triple needle rinsed in 50% acetonitrile in water. All measurements were performed once for each sample. The concentrations of the BisGMA, UDMA, TEGDMA, and HEMA monomers were evaluated (Table 2). An HPLC chromatogram of available reference monomers and their retention times is shown in Figure 1. The monomer concentration was calculated using linear regression analysis of the results from the calibration curve. A calibration curve for each monomer was constructed using the external standard method (Figure 2). The limit of quantification was about 0.5  $\mu$ g mL<sup>-1</sup> for the BisGMA and UDMA monomers, and 0.3  $\mu$ g mL<sup>-1</sup> for the TEGDMA and HEMA monomers. Concentrations below these levels could not be quantified. Identification and quantitative analysis of monomers in the analyzed samples was performed by comparing the elution time and integrated ultraviolet (UV) absorption peak area of the eluates with those of the reference compounds (Figures 1, 3).

### Statistical analysis

Statistical analysis was performed using STATISTICA for Windows 9.0 (StatSoft, Inc.). To evaluate differences between values, the following non-parametric tests were used: Friedman's ANOVA, Wilcoxon's matched-pair test, ANOVA Kruskal-Wallis, and U Mann-Whitney. A probability (*P*) of less



**Figure 1.** HPLC chromatogram of a mixture of reference monomers (monomer – retention time): HEMA – 2.33 min., TEGDMA – 3.85 min., UDMA – 4.83 min., BisGMA – 5.62 min.

than 0.05 was considered significant, and a probability of below 0.01 was considered highly significant.

### Results

Analysis of the HPLC chromatograms revealed that substances other than the examined monomers were also released from the composite resins into each solvent. Their presence was observed up to an analysis time of 6 min in the distilled water eluates. Incubation of the samples in ethanol extraction media also led to elution of substances other than the tested monomers. Those substances were observed in chromatograms at up to 23 min of analysis time, and were also observed throughout the entire analysis period of this study (up to 21 d). Table 3 shows the quantities of eluted monomers (Table 3A – BisGMA, Table 3B – UDMA, Table 3C – TEGDMA, Table 3D – HEMA) from 3 composite resins after incubation in 3 different solutions.

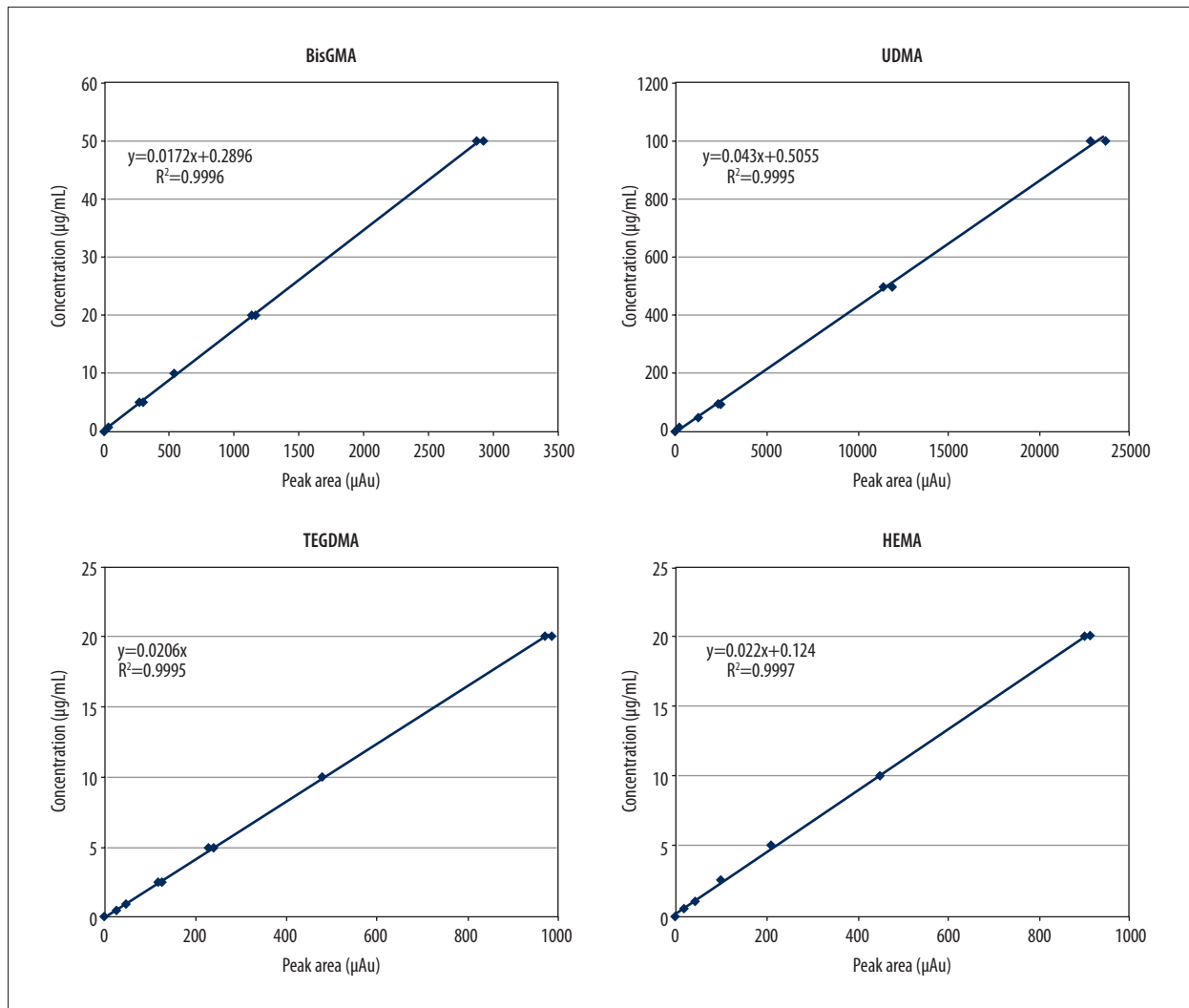


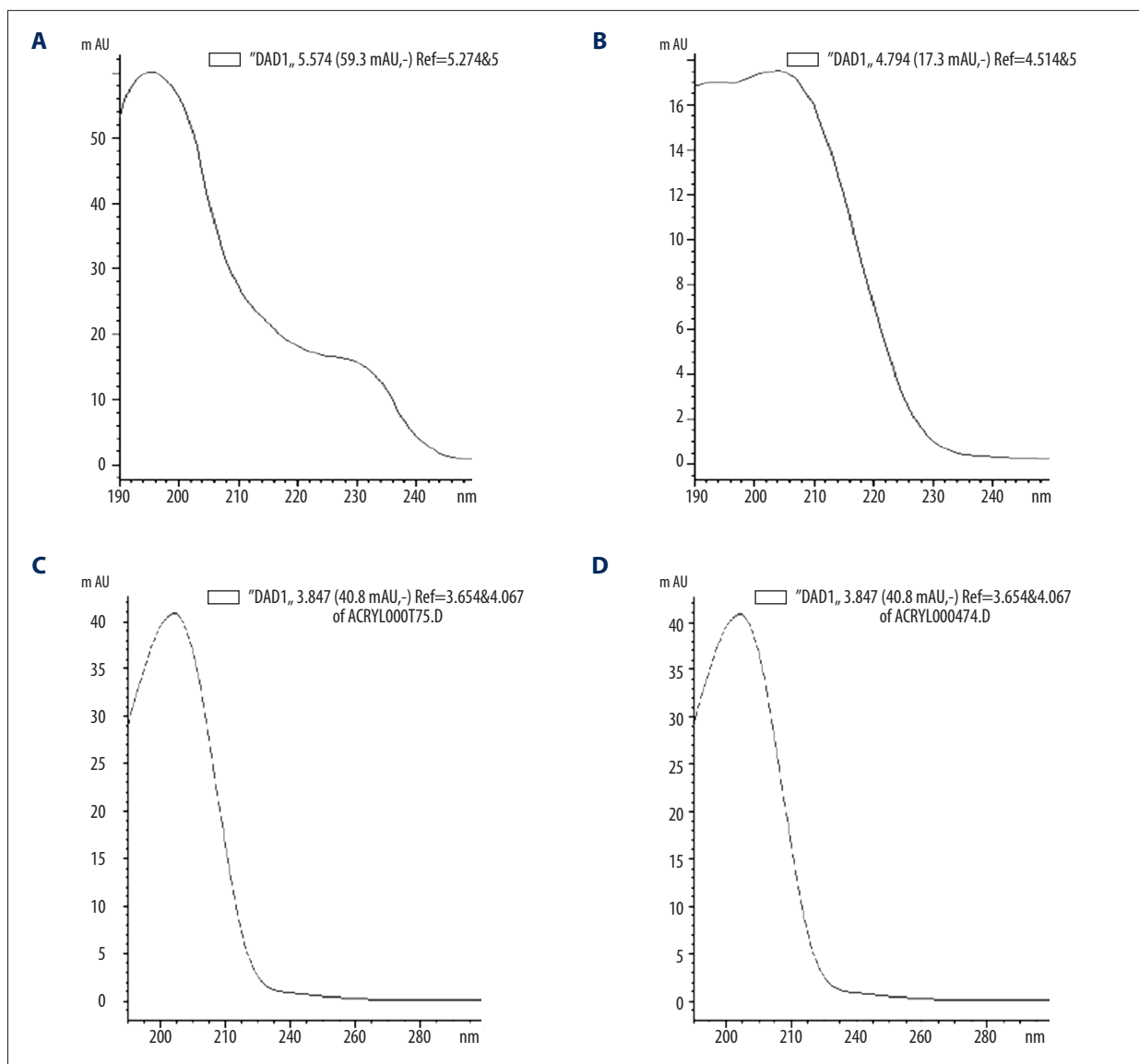
Figure 2. HPLC calibration curves for BisGMA, UDMA, TEGDMA and HEMA monomers.

### BisGMA

No BisGMA monomer was detected in any XB eluates. The BisGMA monomer was also not detected in any distilled water eluate. The BisGMA monomer was eluted from the SDR and BF composite resins into 100% and 75% ethanol solutions. The cumulative concentrations of BisGMA eluted into ethanol solutions from BF after 24 h and 21 d were higher ( $P < 0.01$ ) than those from SDR. The highest elution from BF was detected after 1 h (70% of total elution) and 24 h (almost 90% of total elution) of incubation, and elution was nearly complete after 7 d. The monomer elution from SDR was more constant (13% of total elution after 1 h) and was almost the same at each tested period. For both composite resins, monomer elution decreased with elution time ( $P < 0.05$ ).

### UDMA

The UDMA monomer was not detected in any XB eluates. From SDR and BF, the trend in monomer concentration of the eluate was 100% ethanol > 75% ethanol > distilled water ( $P < 0.05$ ). The cumulative concentrations of eluted UDMA after 24 h and 21 d were higher ( $P < 0.01$  for ethanol solutions,  $P < 0.05$  for distilled water) from SDR than from BF in each tested solution. Similar to the BisGMA monomer, the highest UDMA monomer elution from BF was observed after 24 h of incubation (70–80%), and elution was nearly complete after 7 d. UDMA monomer eluted from the SDR composite resin was detected at each tested time point. For both composite resins, monomer elution decreased with elution time ( $P < 0.05$ ).



**Figure 3.** UV-Vis absorption spectrum of the BisGMA (A), UDMA (B), TEGDMA (C) and HEMA (D) monomers.

### TEGDMA

The TEGDMA monomer was not detected in any XB eluate. In the eluates of the SDR and BF resins, TEGDMA was detected in all tested solutions. The trend in elution time was 100% ethanol >75% ethanol >distilled water. For the SDR composite resin, monomer elution decreased with elution time ( $P<0.05$ ) and was almost complete after 14 d in 100% ethanol and after 3 d in 75% ethanol and distilled water. For the SDR composite, the differences in the eluted monomer concentrations among the solvents (100% ethanol >75% ethanol >distilled water) were statistically significant ( $P<0.05$ ). For the BF composite, residual TEGDMA elution also decreased with elution time ( $P<0.05$ ), but the monomer concentrations in the different elution media were similar. For both composite resins, the cumulative

concentration after 24 h constituted about 80–90% of the total monomer elution.

### HEMA

The HEMA monomer was not detected in any XB eluate. In the SDR eluates, HEMA was detected in all tested solutions, with the trend in elution time being 100% ethanol >75% ethanol >distilled water. For the SDR composite resin, monomer elution decreased with elution time ( $P<0.05$ ). The highest amount of eluted HEMA was observed within 1 h after polymerization, with the cumulative concentration after 24 h being 70–80% of the total elution. In the BF eluates, the HEMA monomer was detected only in ethanol eluates, and its elution was almost complete after 1 h.



**Table 3A.** The quantity of eluted BisGMA monomer from three composite resins after incubation in three different solutions. Mean BisGMA release ( $\mu\text{g/mL}$ ) from composite resins samples was measured after 1 h, and 1, 3, 7, 14 and 21 days. Means with same superscript symbol do not differ significantly. The others means show statistically significant ( $P<0.05$ ,  $P<0.01$ ) differences.

Immersion time	BisGMA ( $\mu\text{g/mL}$ )								
	Extraction solution								
	100% ethanol			75% ethanol			Distilled water		
	SDR	XB	BF	SDR	XB	BF	SDR	XB	BF
0–1 h	0.61 <sup>A</sup> (0.06)	–	9.45 <sup>B</sup> (0.64)	0.52 <sup>A</sup> (0.07)	–	9.74 <sup>B</sup> (0.72)	–	–	–
1–24 h	0.92 (0.04)	–	2.43 (0.21)	0.74 (0.08)	–	1.89 (0.14)	–	–	–
<b>Cumulative conc. after 1d</b>	<b>1.53</b> <b>(0.10)</b>	–	<b>11.88<sup>C</sup></b> <b>(0.85)</b>	<b>1.26</b> <b>(0.15)</b>	–	<b>11.63<sup>C</sup></b> <b>(0.86)</b>	–	–	–
<b>% of the total elution after 24 h</b>	<b>33.7</b>	–	<b>85.6</b>	<b>31.27</b>	–	<b>89.3</b>	–	–	–
1–3 d	0.73 <sup>D</sup> (0.09)	–	1.29 (0.18)	0.67 <sup>D</sup> (0.06)	–	0.88 (0.07)	–	–	–
3–7 d	0.87 (0.11)	–	0.71 (0.09)	0.64 (0.07)	–	0.51 (0.04)	–	–	–
7–14 d	0.82 <sup>E</sup> (0.09)	–	bl	0.78 <sup>E</sup> (0.06)	–	bl	–	–	–
14–21 d	0.59 <sup>F</sup> (0.05)	–	bl	0.68 <sup>F</sup> (0.06)	–	bl	–	–	–
<b>Cumulative conc. after 21 d</b>	<b>4.54</b> <b>(0.44)</b>	–	<b>13.88<sup>C</sup></b> <b>(1.12)</b>	<b>4.03</b> <b>(0.4)</b>	–	<b>13.02<sup>C</sup></b> <b>(0.97)</b>	–	–	–

**Table 3B.** The quantity of eluted UDMA monomer from three composite resins after incubation in three different solutions. Mean UDMA release ( $\mu\text{g/mL}$ ) from composite resins samples was measured after 1 h, and 1, 3, 7, 14 and 21 days. Means with same superscript symbol do not differ significantly. The others means show statistically significant ( $P<0.05$ ,  $P<0.01$ ) differences.

Immersion time	UDMA ( $\mu\text{g/mL}$ )								
	Extraction solution								
	100% ethanol			75% ethanol			Distilled water		
	SDR	XB	BF	SDR	XB	BF	SDR	XB	BF
0–1 h	30.60 <sup>A</sup> (1.20)	–	7.43 (0.24)	30.50 <sup>A</sup> (1.24)	–	1.62 (0.12)	1.76 (0.14)	–	1.0 (0.02)
1–24 h	35.30 (1.14)	–	2.44 (0.08)	18.05 (0.86)	–	2.09 (0.07)	1.33 (0.09)	–	1.47 (0.11)
<b>Cumulative conc. after 1d</b>	<b>65.9</b> <b>(2.34)</b>	–	<b>9.87</b> <b>(0.32)</b>	<b>48.55</b> <b>(2.10)</b>	–	<b>3.64</b> <b>(0.19)</b>	<b>3.09</b> <b>(0.23)</b>	–	<b>2.47</b> <b>(0.13)</b>
<b>% of the total elution after 24 h</b>	<b>41.2</b>	–	<b>83.15</b>	<b>40.5</b>	–	<b>70.41</b>	<b>41.93</b>	–	<b>73.73</b>
1–3 d	23.22 <sup>C</sup> (0.94)	–	1.23 (0.08)	15.49 (0.64)	–	0.94 (0.06)	1.14 <sup>F</sup> (0.08)	–	0.47 (0.04)
3–7 d	26.29 <sup>C,D</sup> (0.86)	–	0.7 <sup>B</sup> (0.04)	19.16 <sup>E</sup> (0.92)	–	0.59 <sup>B</sup> (0.03)	1.11 <sup>F,G</sup> (0.06)	–	0.41 (0.02)
7–14 d	27.05 <sup>D</sup> (0.96)	–	–	22.63 <sup>E</sup> (0.87)	–	–	1.25 <sup>G</sup> (0.08)	–	–
14–21 d	17.39 (0.76)	–	–	14.11 (0.62)	–	–	0.78 (0.07)	–	–
<b>Cumulative conc. after 21 d</b>	<b>159.85</b> <b>(5.86)</b>	–	<b>11.87</b> <b>(0.44)</b>	<b>119.94</b> <b>(5.15)</b>	–	<b>5.17</b> <b>(0.28)</b>	<b>7.37</b> <b>(0.52)</b>	–	<b>3.35</b> <b>(0.19)</b>

**Table 3C.** The quantity of eluted TEGDMA monomer from three composite resins after incubation in three different solutions. Mean TEGDMA release (µg/mL) from composite resins samples was measured after 1 h, and 1, 3, 7, 14 and 21 days. Means with same superscript symbol do not differ significantly. The others means show statistically significant ( $P<0.05$ ,  $P<0.01$ ) differences.

Immersion time	TEGDMA (µg/mL)								
	Extraction solution								
	100% ethanol			75% ethanol			Distilled water		
	SDR	XB	BF	SDR	XB	BF	SDR	XB	BF
0–1 h	7.46 (0.20)	–	3.36 <sup>A</sup> (0.18)	6.49 (1.39)	–	3.27 <sup>A</sup> (0.20)	3.71 <sup>A</sup> (0.28)	–	3.24 <sup>A</sup> (0.16)
1–24 h	4.00 (0.16)	–	1.27 (0.08)	2.69 (0.16)	–	1.07 (0.04)	1.59 (0.22)	–	1.56 (0.11)
<b>Cumulative conc. after 1d</b>	<b>11.46</b> <b>(0.36)</b>	–	<b>4.63</b> <b>(0.26)</b>	<b>9.18</b> <b>(1.55)</b>	–	<b>4.34</b> <b>(0.24)</b>	<b>5.30</b> <b>(0.5)</b>	–	<b>4.8</b> <b>(0.27)</b>
<b>% of the total elution after 24 h</b>	<b>75.1</b>	–	<b>84.5</b>	<b>91</b>	–	<b>86.5</b>	<b>86.5</b>	–	<b>92.7</b>
1–3 d	1.74 (0.08)	–	0.46 (0.04)	0.91 (0.03)	–	0.36 (0.08)	0.83 (0.12)	–	0.38 (0.09)
3–7 d	1.28 (0.06)	–	0.39 (0.06)	bl	–	0.32 (0.06)	–	–	bl
7–14 d	0.78 (0.02)	–	bl	–	–	–	–	–	–
14–21 d	bl	–	–	–	–	–	–	–	–
<b>Cumulative conc. after 21 d</b>	<b>15.26</b> <b>(0.52)</b>	–	<b>5.48</b> <b>(0.36)</b>	<b>10.09</b> <b>(1.58)</b>	–	<b>5.02</b> <b>(0.38)</b>	<b>6.13</b> <b>(0.62)</b>	–	<b>5.18</b> <b>(0.36)</b>

**Table 3D.** The quantity of eluted HEMA monomer from three composite resins after incubation in three different solutions. Mean HEMA release (µg/mL) from composite resins samples was measured after 1 h, and 1, 3, 7, 14 and 21 days. Means with same superscript symbol do not differ significantly. The others means show statistically significant ( $P<0.05$ ,  $P<0.01$ ) differences.

Immersion time	HEMA (µg/mL)								
	Extraction solution								
	100% ethanol			75% ethanol			Distilled water		
	SDR	XB	BF	SDR	XB	BF	SDR	XB	BF
0–1 h	4.56 <sup>A</sup> (0.23)	–	0.44 <sup>B</sup> (0.15)	4.66 <sup>A</sup> (0.37)	–	0.35 <sup>B</sup> (0.08)	0.38 <sup>E</sup> (0.08)	–	bl
1–24 h	3.92 (0.16)	–	bl	1.92 (0.21)	–	Bl	0.34 <sup>E,F</sup> (0.08)	–	–
<b>Cumulative conc. after 1d</b>	<b>8.48</b> <b>(0.39)</b>	–	<b>0.44<sup>C</sup></b> <b>(0.15)</b>	<b>6.58</b> <b>(0.49)</b>	–	<b>0.35<sup>C</sup></b> <b>(0.08)</b>	<b>0.72</b> <b>(0.16)</b>	–	–
<b>% of the total elution after 24 h</b>	<b>67.4</b>	–	–	<b>88.1</b>	–	<b>100</b>	<b>69.2</b>	–	–
1–3 d	1.69 <sup>D</sup> (0.11)	–	bl	0.89 (0.1)	–	bl	0.32 <sup>F</sup> (0.05)	–	–
3–7 d	1.49 <sup>D</sup> (0.12)	–	–	bl	–	–	–	–	–
7–14 d	0.92 (0.08)	–	–	bl	–	–	–	–	–
14–21 d	ND	–	–	–	–	–	–	–	–
<b>Cumulative conc. after 21 d</b>	<b>12.58</b> <b>(0.7)</b>	–	–	<b>7.47</b> <b>(0.59)</b>	–	–	<b>1.04</b> <b>(0.21)</b>	–	–



## Discussion

The elution of BisGMA, UDMA, TEGDMA, and HEMA from 3 bulk-fill flowable composite resins into 3 different elution media was evaluated. The results partially rejected the first null hypothesis that after polymerization of the bulk-fill composite resin, there would be elution of BisGMA, UDMA, TEGDMA, and HEMA residual monomers. For the tested XB composite, resin no eluted monomers were detected when stored in either water or ethanol solutions. This was significantly different from the other materials. SDR and BF composite resins in this study showed a variable extent of elution of the BisGMA, UDMA, TEGDMA, and HEMA monomers into tested media. The results supported the second null hypothesis that the elution of the residual monomers depended on the resin composition of the tested material.

Because of well-documented BisGMA toxicity, this monomer elution is often investigated [17–21,23,24,29,32–36]. BisGMA monomer usually is found in eluates from materials containing this monomer as a component of their resin matrix [33,35,36], which was confirmed in the present study. More BisGMA monomer was detected in eluates from BF, whose resin matrix is based on this monomer, than from SDR. The manufacturer's data indicates that the SDR composite does not contain BisGMA monomer [8]. However, material safety data sheet (MSDS) information is often incomplete and sometimes misleading [37–39]. Manufacturers are obliged to provide information in the MSDS about the main compounds ( $\geq 1\%$ ). Some monomers and additives are present in concentrations below 1%; therefore, no information about them is given. The detected BisGMA from SDR samples also might be impurities of the monomer matrix complex. Cebe et al. reported the detection of BisGMA monomer in 75% ethanol eluate from SDR resin composite, which was confirmed in the present study [32], but a study by Alshali et al. revealed no BisGMA monomer elution from SDR and XB into 70% ethanol solution [29]. The BisGMA monomer, as a hydrophobic base monomer whose solubility parameter matches that of ethanol, shows considerable and continuous elution into non-polar organic solutions (e.g., ethanol-based solution, methanol) [40,41]. In the present study, BisGMA monomer was detected only in ethanol-based eluates, which is consistent with most previous studies [25,42], but some studies have shown that this monomer also elutes in very small quantities in water-based media [24,43,44]. Most of the BisGMA monomer elution (90%) from BF occurred during first 24 h. This contradicts findings of studies that reported rather a lower mean rate of the BisGMA elution (ratio of 24 h to total monomer elution) and a longer elution time of the BisGMA monomer from bulk-fill low-viscosity materials [29]. These differences may be connected with the BF resin structure and the location of the monomer within the polymer network. In polymerized resin, the monomers trapped in

micropores are more susceptible to elution compared with those located inside the microgel [45]. The volume of micropores is higher in more heterogeneous material. Then, the solvent easier penetrates into the matrix, extending the spaces between polymer chains. If a monomer is soluble in a given extraction medium, it can be eluted from the material. Thus, the concentration of eluted monomers and rate of its elution from the material not only depend on the concentration of unreacted monomers, but also on the structure of resins and the location of monomers within the polymer network [45]. In the present study, the eluted BisGMA monomer from BF might be the monomer located on the surface of the tested composite samples, and in places easily accessible for the solvent. The shorter period of BisGMA elution from BF might indicate its lower susceptibility to wear caused by ethanol, compared to SDR, which showed small but continuous monomer elution during the study.

The elution of the UDMA monomer from RBCs has also been often investigated [29,33–35]. However, different kinds of dimethacrylate, called UDMA, with different molecular weight, are used for the production of the resin composites [33,46], but they all are named UDMA. It can therefore be concluded that confusion exists in the literature concerning the UDMA used as a standard and that identified in the tested samples [33,46,47]. According to the material safety data sheet (MSDA), all tested RBCs contain UDMA as a component of their resin matrix. The manufacturer of SDR indicates that the basic monomer of this resin is modified UDMA [8]. It is suggested that this high-molecular-weight compound could represent the sodium adduct of 2 modified UDMA molecules joined by the SDR photoactive group, and that it is SDR-specific [46]. Alshali et al. also reported the detection of a few UDMA monomers with different molecular weights in uncured SDR resin [46]. Modified UDMA monomer was not detected in the present study due to absence of the monomer internal standard. The examined UDMA monomer was the monomer with the 72869-86-4 CAS number (Table 2), and this monomer was detected in eluates from SDR and BF resin composites. SDR and BF resin composites eluted UDMA into 100% ethanol, 75% ethanol, and distilled water. The XB resin composite material did not elute any detectable amount of UDMA. This is partly consistent with other studies, which showed that the XB resin composite also did not release any detectable amount of UDMA into water [29]. However, the studies of Alshali et al. [29] and Lempel et al. [34] showed small amounts of UDMA monomer eluted from XB into 70% ethanol. In the present study, the UDMA monomer elution was connected with elution medium hydrophobicity of the solvent used. UDMA showed a significantly lower rate of elution in 75% ethanol and water than in 100% ethanol. The pattern of the UDMA monomer elution from BF and SDR was similar to the pattern of the BisGMA elution from these resin composites. The concentration of the eluted monomer and

rate of UDMA elution into 75% ethanol and water from SDR composite resin in this study were similar to those obtained by Alshali et al. [29]. In the present study, SDR showed about 13-fold more UDMA elution into 100% ethanol and 24-fold more UDMA elution into 75% ethanol, compared to BF. This might be because there was originally more UDMA content in the SDR resin, but UDMA elution into water from SDR was only 2 times higher than from BF. This might indicate greater SDR susceptibility to ethanol penetration into resin matrix.

TEGDMA monomer is one of the most frequently used diluents in composite materials [1]. It constitutes both SDR and BF resin matrix composition and it was eluted from SDR and BF resin composites in this study. For both materials, most TEGDMA was released after 24 h and decreased with time, with minimal or no more release after 14 d. This is consistent with the other study assessing TEGDMA elution from different bulk-fill RBCs, wherein TEGDMA elution was nearly complete by 1 month [29]. The rather high mean rate of TEGDMA elution and relatively short elution time might be connected with its low molecular mass and the presence of ethylene oxide groups that make this monomer reactive, mobile, and relatively easy to elute from the composite material matrix [15,48,49]. In the present study, TEGDMA monomer eluted into ethanol-based media much easier from SDR resin composite than from BF RBC. It had 3 times higher elution into 100% ethanol and 2 times higher elution into 75% ethanol from SDR than from BF. The elution of this monomer into distilled water from both composite resins was similar, which might indicate that SDR is more susceptible to damage than is BF composite resin, suggesting that SDR has a more heterogeneous matrix composition and lower filler/matrix ratio.

Some compounds in materials are not intentionally added during manufacturing, but are remnants from the syntheses of raw materials [47,50]. The manufacturers' data indicates that the RBCs tested in this study do not contain HEMA monomer, but this monomer was found not only in ethanol-based eluates, but also in water eluates. It is possible that some fraction of the detected HEMA (Table 2) may have been a degradation product from UDMA, which is the main component of SDR and BF. Cebe et al. and Michelsen et al. also detected a small amount of HEMA eluted from composites containing UDMA [32,39]. In the present study, the total HEMA monomer elution from SDR RBC into ethanol solutions was more than 20 times higher than elution of this monomer from BF composite, which might be connected with the originally higher UDMA content in SDR resin.

In the present study, both the eluted monomer concentration and the elution time were influenced by the type of extraction medium. Thus, the third null hypothesis was confirmed. The total amounts of monomers eluted into different

solvents were: 100% ethanol > 75% ethanol > distilled water. This was in agreement with previous studies showing that resin composite monomers eluted into organic solutions of ethanol in significantly higher amounts than into aqueous solutions [15,20,27–29]. Many studies have shown that using ethanol significantly improved elution, and have reported a distinct increase in the amount of each substance detected in these solvents compared to that in water [25,27,28,32,51]. The amount of eluting species ranges between 0.5% and 2% weight in water, 2–6% weight in 70% ethanol, and 10% in methanol [15,26,47]. This was because all dimethacrylate resins are readily soluble in these organic solvents [52]. Our study confirmed that the degree of monomer elution from the SDR and BF bulk-fill composite resins was proportional to the hydrophobicity and swelling capacity of the organic solvent. Both composites showed the highest vulnerability and elution into 100% ethanol. For the clinically relevant solutions, SDR and BF showed higher elution of the UDMA, BisGMA, TEGDMA, and HEMA monomers into 75% ethanol than into distilled water. Monomers that were detected in water extracts were TEGDMA, UDMA, and HEMA. No BisGMA was detected in this medium. This was also in agreement with Alshali et al., who reported more pronounced monomer elution from bulk-fill composites into 70% ethanol solution than into water or artificial saliva [29].

There is no unequivocal data in the literature on the time period necessary for the total elution of unreacted monomers from composite material. Ferracane and Condon reported that 50% of monomers were eluted from the materials during the first 3 h after polymerization, and that 85–100% of monomers were eluted within 24 h [26]. More recent studies using HPLC have shown that monomer elution from RBCs continued beyond 24 h, and that monomer release could be observed over 3, 6, or 12 months [33,36,53]. The saturation of the resin with the extraction medium takes weeks or months to complete, due to the slow diffusion of substances into the cross-linked matrix of the composite resin. However, the monomer elution process itself seems to be completed within a few days because later weight changes are very small and thus not measurable. However, despite further potential monomer elution, the majority of soluble substances could be extracted from the materials within a matter of hours. This was confirmed in the present study. Regardless of the type of extraction medium used, a significant majority of the tested monomers were measured within the first 24 h after the polymerization of the material. Our study also revealed that the elution times of all the tested monomers were longer for ethanol-based solvents than for water. The ethanol can penetrate the resin matrix, increasing sorption, swelling, and plasticization, and expands the space between polymer chains. This facilitates elution of unbound substances not only from places easily accessible for the solvent, but also from the bulk of the RBC. In the present study, the elution times of all the tested monomers were longer for the SDR

resin than for the BF composite resin. Also, the total concentration of eluted monomers was higher for the SDR resin than for the BF resin. Eluted monomers concentration into 100% ethanol was  $192 \mu\text{g ml}^{-1}$  from SDR and almost 6 times lower ( $31.7 \mu\text{g ml}^{-1}$ ) than that of BF. The monomer concentrations in clinically relevant solutions were: 75% ethanol –  $142.34 \mu\text{g ml}^{-1}$  (SDR) and  $23.56 \mu\text{g ml}^{-1}$  (BF); distilled water –  $14.9 \mu\text{g ml}^{-1}$  (SDR) and  $8.53 \mu\text{g ml}^{-1}$  (BF). Among the tested materials, SDR showed the highest vulnerability and monomers elution, with UDMA constituting the main eluate. Considering the filler content, SDR has the lowest filler value among the investigated bulk-fill materials. Together with its low initial monomer/polymer conversion, this may be attributed to the poor cross-link density and heterogeneity of SDR polymer structure, resulting in considerable swelling and opening up of pores and pathways for residual monomers to elute. In a few studies, SDR RBC also showed higher vulnerability and monomers elution in comparison with other RBC [29,34]. The longest monomer elution from SDR may represent the largest risk for biotoxic effects and weakening of the mechanical properties upon elution.

The lower monomer concentration eluted from BF compared to SDR might be connected with the higher filler content in BF (73%) than in SDR (68%). Also, different BF matrix composition based on BisGMA/TEGDMA might make a difference. The BF contains bioactive filler particles, coated with a durable glass ionomer phase before being embedded in the matrix. This technology allows the composite to recharge and release fluoride and also improves the light transmission. Incident light is both diffused by the glass ionomer phase and transmitted straight through the multifunctional glass core of the filler particles, which might cause better matrix cross-linking.

For XB, no eluted monomers were detected when stored in either water or ethanol solutions. This was significantly different from the other materials. The results of the present study

confirmed the Alshali et al. [29] and Lempel et al. [34] study results, showing no or lower monomer elution from XB flowable bulk-fill material compared to the other low-viscosity bulk-fill materials. The lack of detectable eluted species from XB could be partially explained by the material's composition. XB is mainly based on the BisEMA monomer and highly hydrophilic DEGDMA monomer, which were not tested in the present study. Lower XB monomer elution could be also related to the high (75%) filler content of this material. Some reports found a lower absorption rate in composite materials with high filler contents compared to materials with lower filler content [54,55]. Al-Hiyasat et al. reported that the variation in filler/monomer ratio significantly affected the compound release and cytotoxicity of the resin materials [24]. The higher filler content of XB may also increase light scattering, causing a concurrent decrease of translucency for blue light, simultaneously causing better matrix cross-linking [56].

## Conclusions

The elution of the residual monomers depended on the resin composition and the materials filler/resin matrix ratio.

In composite materials, toxicity assessment should be carried out. This should consider both the material composition as given by the manufacturer, and also the residual monomers that elute from the polymerized material.

The elution concentration and time of transition monomers from composites depended on the solvent. The highest penetrations of the polymerized SDR and BF composites were observed in the 100% ethanol solution, and this extraction medium eluted the highest amounts of free monomers. The 75% ethanol was a more aggressive medium than water in terms of monomer elution from bulk-fill composites.

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