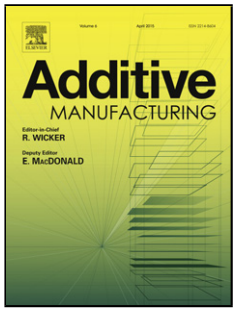

Chemical composition and degradation products in additively manufactured methacrylates for dental devices

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CHEMICAL COMPOSITION AND DEGRADATION PRODUCTS IN ADDITIVELY MANUFACTURED METHACRYLATES FOR DENTAL DEVICES

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Highlights

- Novel methods for characterizing biomedical photopolymers

- Photocured methacrylates are relatively different in compositions
- Ethanol-treatment may enhance biocompatibility of methacrylates
- Liquid resins reveal different material chemistries after polymerization

ABSTRACT

In additive manufacturing (AM) or three-dimensional printing (3DP), crosslinked polymers can be synthesized from multifunctional monomers and telechelic oligomers by photochemical reactions, so liquid to solid phase change takes place within a fraction of a second at ambient temperature. Despite the potentials of AM or 3DP offering speed, biocompatibility is an issue of concern due to the complexities of the manufacturing process including postprocessing. For instance, photochemical reactions rarely proceed to completion hence could lead to accumulation of residual monomer and degradation products, and consequently cause local and systemic side effects in high doses. In this novel study, we evaluate an array of commercially available and proprietary methacrylates for dental devices i.e., denture bases (>60% Bis-EMA and 15-25% proprietary methacrylic oligomer), orthodontic appliances (>70% proprietary methacrylic oligomer, <20% glycol methacrylate and <5% pentamethyl-piperidyl sebucate) and implant surgical guides (≥75% Bis-EMA and 30-50% diurethane dimethacrylate, mixture of isomers) using headspace gas chromatography-mass spectrometry. The qualitative data indicate that a substantial proportion of chemical compounds observed in photocured samples decreased with applied treatment possibly due to ethanoic-aqueous interactions. Also, in the absence of the extensively studied methyl methacrylate, the presence of other potentially toxic acrylic esters and degradation products in the materials emphasizes the need for standards revision to reflect the current trends in biomaterials used in additive manufacturing. While quantitative analysis of the individual compounds is beyond the scope of this study, it lays

the foundation for further work taking into consideration that resin formulations are constantly evolving to meet the requirements for medical devices.

KEYWORDS: Additive manufacturing; Chemical composition; Degradation products; Methacrylates; Dental devices.

1 INTRODUCTION

In additive manufacturing (AM) or three-dimensional printing (3DP), crosslinked polymers can be synthesized from multifunctional monomers and telechelic oligomers by photochemical reactions, so liquid to solid phase change takes place within a fraction of a second at ambient temperature [1]. The chemical process in which light is used to initiate and propagate the polymerization reaction is referred to as photopolymerization [2]. Photopolymerization is considered to be the most effective way to transform solvent-free liquid resins into solid polymers, at ambient temperature [1]. Compared to thermally-activated polymerization, it is more economical and offers a myriad of practicalities in imaging, microelectronics, graphic arts, printing plates, photoresists, laser direct imaging, computer-to-plate technology, holographic optical elements and dentistry, to name a few [3]. Despite the potentials of offering significant benefits in terms of speed in 3DP, there are inherent challenges with the manufacturing process. For instance, as light from the illumination source penetrates the sample, it is absorbed by the initiating species, causing a decrease in light intensity with depth into the sample. The change in light intensity also influences the polymerization rate and double bond conversion of the materials [4]. For acrylic polymers processed by free-radical polymerization, photochemical reactions rarely proceed to completion hence leads to accumulation of residual monomer and degradation products in their polymer network [5], which are known to cause local and systemic side effects in high doses [6-10]. In light of this, analysis of residual monomer has been the topic of many studies [11]. Nonetheless, there is the gap in knowledge concerning this subject for

materials in 3DP. In this paper, we characterize dental methacrylates for composition and degradation products using headspace gas chromatography-mass spectrometry (GC-MS). This analytical method was chosen due to the current limitations of those specified in the standards for dental devices with emphasis on residual methyl methacrylate [12, 13]. Sample preparation was informed by toxicological data from previous studies [14-16]. Considering the propensity of ethanoic-aqueous interaction to alter the physicochemical characteristics and biological performance of acrylic devices [17], we hypothesized that treated methacrylates (by immersion in ethanol) will contain fewer chemical compounds than non-treated counterparts.

2 MATERIALS AND METHODS

2.1 Sample preparation

Three different methacrylates were examined: liquid photopolymer resin, postcured disks (PC) that where built according to manufacturing parameters (Table 1 and Figure 1) recommended for dental devices, and postcured disks treated with ethanol (PCE).

PCE samples were soaked in ethanol absolute (Purity≥ 99.9%, Merck KGaA, Darmstadt, Germany) for 3 minutes, rinsed five times with LC-MS grade water (Merck KGaA, 64271 Darmstadt, Germany) and air-dried for 2 hours at ambient temperature [14-16]. One batch of PC samples were built in-house from Dental SG (DSG) [18] V1 resin (Formlabs Inc. 35 Medford St. Suite 201, Somerville, MA 02143, USA) by reverse stereolithography (SL) [19] using the recommended Form 2 3D printer (Laser specifications: 405nm violet laser and 250mW laser; Laser Spot Size: 140 microns; Layer thickness, Δz: 50μm). Prior to UV postcuring in LC-3DPrint Box (Vertex-Dental, B.V. Centurionbaan 190, 3769 AV Soesterberg, The Netherlands) [20], the "green" samples were rinsed twice in isopropanol

(Purity 99.5%, Acros Organics ENA23, zone1, Janssen Pharmaceuticalaan 3a, B-2440 Geel, Belgium). The other two batches being E-Denture (ED) [21] and E-Guard (EG) [22], were built with EnvisionTec's digital light processing (DLP) technology (Brüsseler Str. 51, 45968 Gladbeck, Germany) [23] using Perfactory DDP 4M 3D printer (Z-height: 67.98mm; Voxel: 100μm; Light power: 180 Mw/dm^2). These samples were supplied in postcured (2x100 flashes in Otoflash G171 (NK-Optik GmbH, Isarstr. 2, D-82065 Baierbrunn, Germany) form by the manufacturer.

2.2 Test procedure

Prior to analysis, photocured samples were stored in a refrigerator at -20°C to maintain their monomeric content and examined alongside liquid photopolymer resins. For ED and EG liquid resins, comparable NextDent Denture [24] and Dental LT Clear [25] resins were analysed, respectively. During headspace GC-MS, the photocured samples were frozen in liquid nitrogen at minus 196 °C and ground into powder before placed in GC-Shimadzu TQ8040 GC-MS/MS (Shimadzu Corporation, Tokyo, Japan). The GC column used was Agilent J&W DB5-MS 30m 0.25mm ID 0.25um film thickness. Test parameters were, column oven temperature at 40.0 °C, injection temperature at 250 °C, column flow rate at 1.16 mL/min, split ratio of 5.0 and a total run time of 15 minutes. To ensure consistency in our test procedure, we analysed the ambient air in the laboratory (as a sample blank). This helped to establish the impurity level of each methacrylate sample.

Table 1 Physical and chemical properties of photopolymers examined

Material indication and composition	Physical properties of postcured material
Dental SG (Formlabs Inc. 35 Medford St. Suite 201, Somerville, MA 02143, USA) is a Class I material for surgical guides and diagnostic models. Hazardous ingredients (w/w%) are ≥75% Ethoxylated bisphenol A dimethacrylate; 30-50% Diurethane dimethacrylate, mixture of isomers; <10% 2,4,6-Trimethylbenzoyl Diphenylphosphine oxide [18].	Flexural strength: ≥ 50 MPa Flexural modulus: ≥1500 MPa Hardness shore D: ≥ 80D Charpy impact strength unnotched: 12-14 kg/m^2 [20]
E-Denture (Brüsseler Str. 51, 45968 Gladbeck, Germany) is a Class IIa material based on acrylic esters and is indicated for 3DP of denture bases. Hazardous ingredients are >60% Ethoxylated bis-phenol A dimethacrylate; 15-25% Methacrylic oligomer; <2,5% Phenyl bis (2,4,6-trimethylbenzoyl)-phosphine oxide. [21].	Flexural strength: 85 MPa Flexural modulus: 2100 MPa Water sorption: 32 µg/mm^3 Water solubility: 1.6 µg/mm^3 Brookfield viscosity at 23°C: 1.0-1.5 Pa•s Residual monomer: 1% Hardness shore D: 80-90 [26]
E-Guard (Brüsseler Str. 51, 45968 Gladbeck, Germany) is a Class I material based on acrylic esters and is indicated for 3DP of splints and retainers. Hazardous ingredients are >70% Methacrylic oligomer; <20% Glycol methacrylate; <5% Pentamethyl-piperidyl sebucate; <2,5% 2,4,6-Trimethylbenzoyl Diphenylphosphine oxide [22].	Flexural strength: 80.9 MPa Flexural modulus: 2123 MPa Water sorption: 27.8µg/mm^2 Water solubility: 1.4µg/mm^2 Elongation at break: 3.81% Charpy impact strength unnotched: 13.3 kJ/m^2 Colour: RES-01-3013 Clear [27]

Figure 1: Surface topography of E-Denture (A), E-Guard (B) and Dental SG (C) methacrylates. Imaging was carried out with Olympus AX70 Fluorescence Microscope, Monochrome FViewII Peltier cooled digital camera (Olympus. Tokyo, Japan) and running Analysis Software (Soft Imaging Solutions, Münster, Germany).

3 RESULTS

GC-MS data presented in Tables 2-4 are of chemical compounds observed consistently in three or more polymeric samples (n=4) in each group. The retention time [RT/min] reported is the time taken for the analyte to pass through the chromatography column.

3.1 Dental SG methacrylate

GC-MS data for DSG in Table 2 shows ethylbenzene and toluene as chemical compounds observed in liquid photopolymer resin and PC samples whereas in PC and PCE samples, 2-ethoxyethyl methacrylate, cyclomethicone 5, cyclomethicone 6, octyl acrylate and d-limonene were produced as new chemical compounds.

3.2 E-denture methacrylate

Table 3 shows dimethadione and ethylbenzene as chemical compounds observed in all samples. In addition, 6 new compounds i.e., 1-methoxy-2-propanol, 2-ethoxyethyl methacrylate, benzaldehyde, cyclomethicone 5, cyclooctanol and spiro [2,4] hepta-4,6-diene were observed in PC samples as against 3 (isobornyl acrylate, 1-methoxy-2-propanol and octyl methacrylate) in PCE samples.

3.3 E-guard methacrylate

In Table 4, dimethadione and o-Xylene were observed in all EG samples. PC samples recorded additional 12 new compounds for which only 1-methoxy-2-propanol and 2,2,4-trimethyl-1,3-pentanediol diisobutyrate were observed in PCE samples.

Table 2 Chemical composition of Dental SG representative materials

Liquid photopolymer	RT [min]	Post-cured	RT [min]	Post-cured and ethanol treated	RT [min]
1,1,2,3-tetramethylcyclopropane	4.352	2-Ethoxyethyl methacrylate	8.105	1-Methoxy-2-propanol	1.955
2-Hydroxyethyl methacrylate	8.238	Glycol Dimethacrylate	9.683	2-Ethoxyethyl methacrylate	8.111
3,3-Dimethyl-1-hexene	10.82	Cyclomethicone 5	9.854	Cyclomethicone 5	8.555
Crotonic anhydride	11.18	Cyclomethicone 6	9.548	Cyclomethicone 6	9.548
Cyclooctatetraene	6.302	D-Limonene	7.855	Octyl Acrylate	9.588
Dimethadione	6.132	Mesitaldehyde	9.726	D-Limonene	7.855
Ethyl methacrylate	3.892	Octyl Acrylate	9.586	p-Xylene	5.975
Ethylbenzene	5.971	Toluene	3.323	3-Ethoxy-1,1,1,7,7,7-hexamethyl-	10.34
Hexyl Methacrylate	10.01	Ethylbenzene	5.975	3,5,5tris(trimethylsiloxy)tetrasiloxane	
n-Hexyl acrylate	8.341	Texanol	9.962		
Octyl Acrylate	9.584	o-Xylene	5.816		
Toluene	3.320	2-butoxyethanol	6.610		
Vinyl crotonate	11.14	m-Xylene	5.969		
2-Propenoic acid, 5-methylene-6-heptenyl	10.12	2,7,10-Trimethyldodecane	9.625		
		Propanoic acid, 2-methyl-, 3-hydroxy-2,2,4-trimethyl pentyl ester	10.07		

Table 3 Chemical composition of E-Denture representative materials

Liquid photopolymer	RT [min]	Post-cured	RT [min]	Post-cured and ethanol treated	RT [min]
1,5-Heptadien-3-yne	3.321	1-Methoxy-2-propanol	1.903	1-Methoxy-2-propanol	1.888
1-Decene	7.484	2-Ethoxyethyl methacrylate	8.114	Isobornyl acrylate	10.12
1-Ethyl-3-methylcyclopentane	5.257	Benzaldehyde	7.234	Octyl methacrylate	9.588
2-Hydroxyethyl methacrylate	8.243	Cyclomethicone 5	8.556	Dimethadione	6.132
3-Hexen-2-one	4.276	Cyclooctanol	7.619	Ethylbenzene	6.303
3-Methyl-5-propylnonane	9.622	Dimethadione	6.141		
Glycol Dimethacrylate	9.678	Ethylbenzene	5.799		
But-3-enyl 2-methylprop-2-enoate	7.190	Spiro [2,4] hepta-4,6-diene	3.337		
Cyclobutylcarboxylic acid	6.439				
Dimethadione	6.128				
Ethyl Methacrylate	3.866				
Ethylbenzene	5.788				
Glycidyl methacrylate	8.841				
Methyl Isobutyl Ketone	2.813				
M-Ethyltoluene	7.269				
N-Butyl methacrylate	7.376				
o-Xylene	5.971				
p-Xylene	6.311				

Table 4 Chemical composition of E-Guard representative materials

Liquid photopolymer	RT [min]	Post-cured	RT [min]	Post-cured and ethanol treated	RT [min]
2,6,11-Trimethyldodecane	9.602	1-Methoxy-2-propanol	1.921	1-Methoxy-2-propanol	1.931
2,6-Dimethylundecane	9.117	2,2,4-Trimethyl-1,3-pentanediol	9.590	2,2,4-Trimethyl-1,3-pentanediol	11.07
2,7,10 Trimethyldodecane	9.461	diisobutyrate		diisobutyrate	
2-Butyloctan-1-ol	7.562	Benzaldehyde	7.235	o-Xylene	5.968
2-Hydroxyethyl acrylate	6.905	Dimethadione	6.136	Dimethadione	6.133
2-Hydroxypropyl acrylate	7.207	Pelargonaldehyde (Nonanal)	8.440		
3-Methyl-1-hexanol	6.428	Texanol	10.07		
5,5-Dimethyl-1-hexene	7.466	Cyclomethicone 6	9.549		
Glycol Dimethacrylate	9.244	2-Ethoxyethyl methacrylate	8.112		
Dimethadione	6.129	o-Xylene	5.807		
Dodecane	8.381	Octyl Acrylate	9.590		
Ethyl Methacrylate	3.856	2-Hydroxyethyl methacrylate	7.715		
Ethylene Glycol Monoacetate	5.702	2-Propyl-1-pentanol	7.833		
Glycidyl acrylate	8.696	Farnesane	9.047		
Glycidyl methacrylate	8.186				
Mesityl Oxide	4.178				
Methyl Isobutyl Ketone	2.790				
o-Xylene	5.969				
p-Xylene	6.306				
Toluene	3.323				

4 DISCUSSION

Although liquid photopolymer resins in 3DP are usually composed of photoinitiators, mono-or-multifunctional monomers and functionalized oligomers [28], their exact ingredients are proprietary. Additional assessment by Fourier transform infrared spectroscopy in Figure 2 shows a degree of similarity between DSG and ED methacrylates. The GC-MS data shed light on the likely composition of the representative materials and compounds that may be categorized as residual monomer and degradation products: the former being unreacted chemical compounds in the liquid resins while the latter represent chemical compounds resulting from the breakdown of the photocured materials including those produced by consecutive chemical reactions [29]. The GC-MS data also corroborate the absence of residual methyl methacrylate (MMA) in our preliminary assessment of DSG (Table 5) as per standards requirements [12, 13] using gas chromatography with flame ionization detector (GC-FID).

Table 5 Quantitative analysis [1] of Dental SG samples for residual methyl methacrylate

	(µg /mL) cMMA	MMA in sample solution (µg) mMMA	Residual monomer % mass fraction	Mean [2] residual monomer
Green or non-postcured	1.12	55.9	0.009	0.01%
	1.4	69.9	0.011	
	0.65	32.7	0.005	
Postcured without ethanol treatment	0.99	49.55	0.008	0.01%
	1.01	50.5	0.008	
	0.97	48.5	0.007	
Postcured with ethanol treatment	0.99	49.35	0.007	0.01%
	1.00	50.05	0.008	
	1.02	51.2	0.008	

[1] Standard solutions for GC-FID analysis yielded an r^2 = ~0.996. Experiment was carried out on polymeric samples (n=3) in GC-2010*plus* (Shimadzu Corporation, Tokyo, Japan). Test parameters were, injection port temperature at 250°C; FID detector temperature at 300°C; initial temperature at 50°C (2 minutes hold), 25°C/min ramp to 75°C (no hold), 150°C/min ramp to 290°C (hold 2.07 minutes) and 6.50 min total run time. Column gas flow rate, 1.37mL/min. Split injection: 10:1. Restek Rxi-1MS column: 30.0m length and 0.25mm inner diameter.

[2] Residual MMA detected in DSG samples was relatively low compared to 2.2 % threshold in the standards.

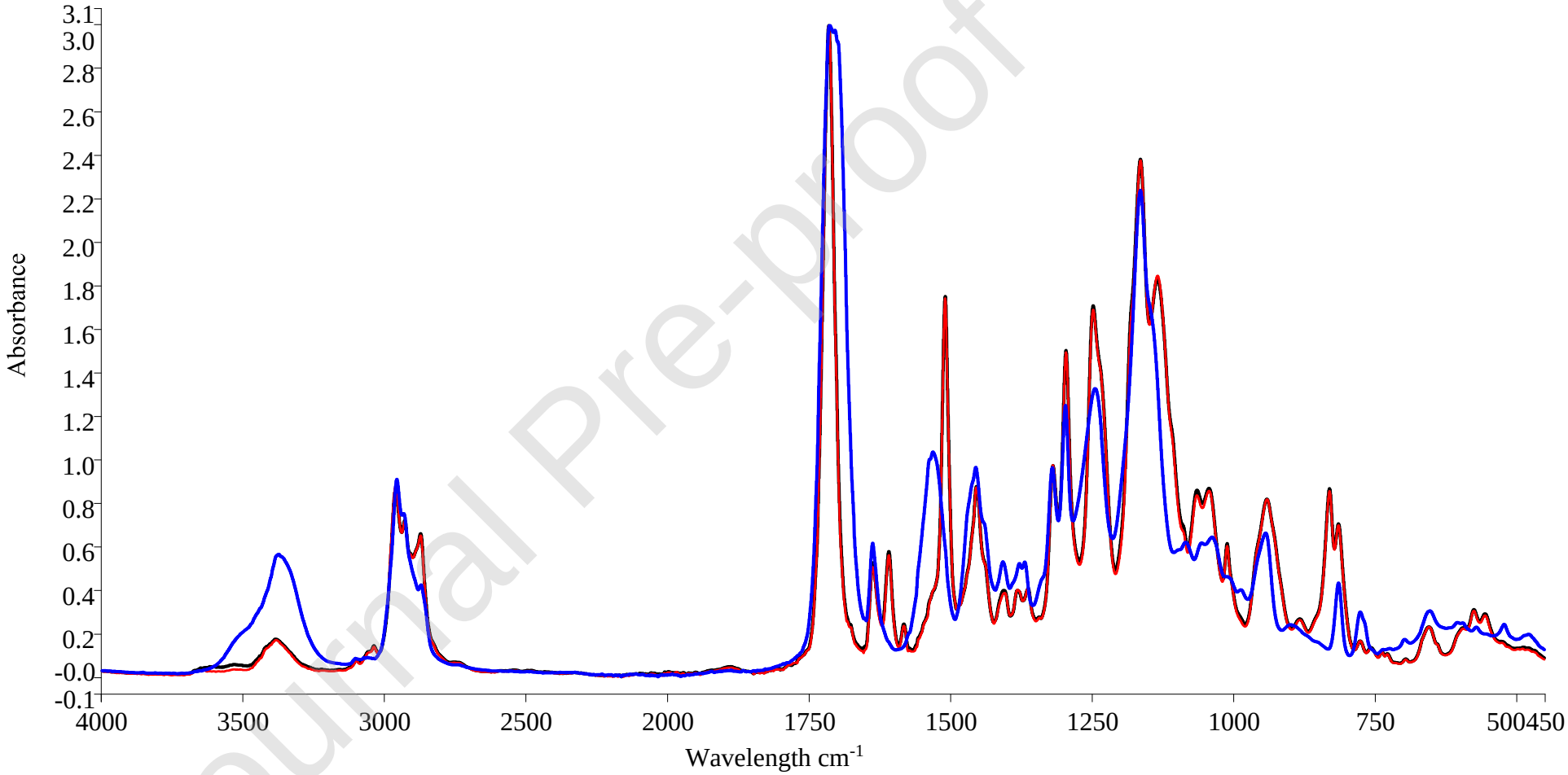
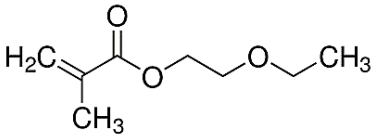
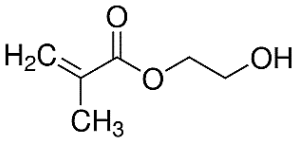


Figure 2: Absorbance spectra of liquid photopolymer resins. Spectra was obtained from Perkin Elmer Spectrum Two FT-IR with Universal ATR (PerkinElmer, Inc. 940 Winter Street Waltham, MA 02451 USA) using 4 cm^{-1} spectral resolution, 4 scans and 4000 - 450cm^{-1} range. Note: Dental SG (**Black**) and E-Denture (**Red**) show similar absorbance spectra in contrast to E-Guard (**Blue**).

Degradation products observed in the polymeric samples include potentially toxic acrylates and methacrylates that have been biologically assessed using different test models [30-34]. Among other test models used in the biological evaluation of chemicals and medical devices, cell-based phenotypic assays are usually employed as initial toxicity screens [35]. Acute systemic toxicity tests, on the other hand, are used to assess toxicity resulting from different types of exposure (e.g., oral, dermal, and/or inhalation) in animal species [36, 37]. Non-animal *in vivo* assays such as fish embryo acute toxicity tests [38] are also gaining in popularity as they offer economy, ease of quantifying multiple toxicity endpoints [15] and fulfil the pertinent aim to replace, reduce or refine the use of animals for the purposes of research or hazard identification [39]. For illustrative purpose, Table 6 shows toxicity data obtained from different test models or bioassays for 2-Ethoxyethyl methacrylate (monomethacrylate with functional groups) and 2-Hydroxyethyl methacrylate (an alkyl ester with a hydroxyl group) [31]. The extrapolation of these toxicity data to human responses are discussed in relevant literature and reference sources [40].

Table 6 Data obtained from different toxicity test models or bioassays

Methacrylate monomer	Toxicological information
 2-Ethoxyethyl methacrylate	Formula: $C_8H_{14}O_3$ Molecular weight: 158.19 g/mol CAS-No.: 2370-63-0 Log P: 1.40 [34] IC_{50} (mmol/L) 2.72 [31] LC_{50} (Pimephales promelas): 27.7 mg/l - 96 h [34]
 2-Hydroxyethyl methacrylate	Formula: $C_6H_{10}O_3$ Molecular weight: 130.14 g/mol CAS-No.: 868-77-9 Log P: 0.42 [41] IC_{50} (mmol/L) 10.07 [31] LC_{50} - Pimephales promelas (fathead minnow) - 227 mg/l - 96 h [34] LC_{50} (Oryzias latipes): > 100 mg/l - 96 h LD_{50} (Oral - Rat - male and female): 5564 mg/kg LD_{50} (Dermal - Rabbit - male): > 5000 mg/kg [41]

IC_{50} is the concentration of inhibitor in the cell culture medium, required to inhibit a protein's transporting activity by 50% [42]. **LC_{50}** (lethal concentration 50) is the concentration of a chemical which kills 50% test animal population. **LD_{50}** (lethal dose 50) is the dose of a chemical which kills 50% of sample population [43].

By undergoing the postcuring process methacrylate conversion could be increased in additively manufactured materials. This is evident in our analysis of "green" DSG versus UV post-illuminated counterpart (Table 7). Similarly, chemical compounds in PC methacrylates reduced with ethanol-treatment possibly due to ethanoic-aqueous interaction [15] that induced swelling in the polymer chains and triggered insoluble substances to diffuse in the ultrapure water rinse after immersion in ethanol [17]. In previous biological assessment of similar materials using zebrafish embryo bioassays, ethanol-treated methacrylates were deemed to be less toxic than non-treated methacrylates [16, 44]. Nonetheless, caution is required in the use of an organic solvent as excessive diffusion into polymer networks can adversely affect the structural integrity [45] of acrylic polymers, which are also associated with low thermal resistance, glass transition temperature and physical properties [46].

Table 7 Effect of UV post-illumination on methacrylate conversion in DSG

Green or non-postcured DSG	RT [min]	Postcured DSG	RT [min]
2,4,5-Trimethylbenzaldehyde	9.726	2-Ethoxyethyl methacrylate	8.105
2-Ethoxyethyl methacrylate	8.106	Glycol Dimethacrylate	9.683
2-Ethylhexyl acrylate	9.209	Cyclomethicone 5	9.854
2-Hydroxyethyl methacrylate	7.731	Cyclomethicone 6	9.548
4-tert-Butylcyclohexene	7.613	D-Limonene	7.855
Glycol Dimethacrylate	9.682	Mesitaldehyde	9.726
Crotonic anhydride	9.759	Octyl Acrylate	9.586
Cyclomethicone 4	7.366	Toluene	3.323
Cyclomethicone 5	8.557	Ethylbenzene	5.975
Decamethyltetrasiloxane	7.975	Texanol	9.962
Dimethadione	6.134	o-Xylene	5.816
D-Limonene	7.855	2-butoxyethanol	6.610
Dodecamethylpentasiloxane	8.756	m-Xylene	5.969
Ethyl methacrylate	3.856	2,7,10-Trimethyldodecane	9.625
Ethylbenzene	5.796	Propanoic acid, 2-methyl-, 3-hydroxy-2,2,4-trimethyl pentyl ester	10.07
Hexamethyldisiloxane	1.820		
n-Hexyl acrylate	8.346		
Octyl Acrylate	9.588		
o-Xylene	5.973		
Pentadecane	8.387		
Tetradecane	9.046		
Toluene	3.322		

5 CONCLUSION

In the absence of MMA specified in the standards for dental devices, the study confirms the presence of other potentially toxic acrylic esters thus underscoring the need for standards revision to reflect the current trends in biomaterials used in additive manufacturing. Whereas quantitative analysis of the individual compounds is beyond the scope of this study, it lays the foundation for further work taking into consideration that resin formulations are constantly evolving to meet the requirements for medical devices. In this regard, it is recommended that additively manufactured devices are characterized qualitatively and quantitatively for chemical composition and if necessary, the throughput of potentially toxic ingredients in biological assays, prior to their approval for clinical use. Further work to assess the physico-chemical-mechanical effects of ethanol treatment on photopolymers will equally enhance academic reflection on the subject of biocompatibility. Finally, the GC-MS technique employed in the study offered ease of identifying unspecified and potentially toxic chemical compounds and could be considered as an initial screening tool for non-traditional materials.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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