Dental Composites – a Low-Dose Source of Bisphenol A?

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Summary

Dental composite materials often contain monomers with bisphenol A (BPA) structure in their molecules, e.g. bisphenol-A glycidyl dimethacrylate (Bis-GMA). In this study, it was examined whether dental restorative composites could be a low-dose source of BPA or alternative bisphenols, which are known to have endocrine-disrupting effects. Bis-GMA-containing composites Charisma Classic (CC) and Filtek Ultimate Universal Restorative (FU) and "BPA-free" Charisma Diamond (CD) and Admira Fusion (AF) were examined. Specimens (diameter 6 mm, height 2 mm, n=5) were light-cured from one side for 20 s and stored at 37 °C in methanol which was periodically changed over 130 days to determine the kinetics of BPA release. BPA concentrations were measured using a dansyl chloride derivatization method with liquid chromatography – tandem mass spectrometry detection. The amounts of BPA were expressed in nanograms per gram of composite (ng/g). BPA release from Bis-GMA-containing CC and FU was significantly higher compared to "BPA-free" CD and AF. The highest 1-day release was detected with FU (15.4±0.8 ng/g), followed by CC (9.1±1.1 ng/g), AF (2.1±1.3 ng/g), and CD (1.6±0.8 ng/g), and the release gradually decreased over the examined period. Detected values were several orders of magnitude below the tolerable daily intake (4 μg/kg body weight/day). Alternative bisphenols were not detected. BPA was released even from "BPA-free" composites, although in significantly lower amounts than from Bis-GMA-containing composites. Despite incubation in methanol, detected amounts of BPA were substantially lower than current limits suggesting that dental composites should not pose a health risk if adequately polymerized.

Key words

Bisphenol A • Dental Composite • Liquid Chromatography • Mass Spectrometry • Release

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Introduction

Bisphenol A (BPA, 2,2-bis(4-hydroxyphenyl) propane) is known for its capability of interfering with hormonal system, thus being termed an endocrine disruptor (Diamanti-Kandarakis *et al.* 2009). The estrogen-like effects of BPA have been known for a long time (Fleisch *et al.* 2010), but BPA is also able to bind to other types of receptors, such as androgen, thyroid, or glucocorticoid (Kolatorova Sosvorova *et al.* 2017, Vandenberg *et al.* 2009). Therefore, its potential negative effects were examined in many studies which proved BPA harmful in animal models. In humans, causality can hardly be proven, but strong associations were found between exposure to BPA and reproductive, developmental, metabolic and other disorders (Rochester 2013, Kolatorova *et al.* 2017, Kolatorova *et al.* 2018a, Kolatorova *et al.* 2018b, Vitku *et al.* 2018). As a consequence, the use of BPA has been limited, and BPA has been replaced in some products by its structural analogues, e.g. bisphenol S (BPS), bisphenol F (BPF) or bisphenol AF (BPAF) (Fig. 1) whose use has not been regulated. However, the metabolism and mechanism of action of BPS and BPF are similar to BPA, resulting in comparable endocrine-disruptive effects (Eladak *et al.*

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2015, Rochester and Bolden 2015). BPAF is considered even more damaging than BPA due to its higher electronegativity and reactivity of the CF_3 moiety (Yang *et al.* 2012).

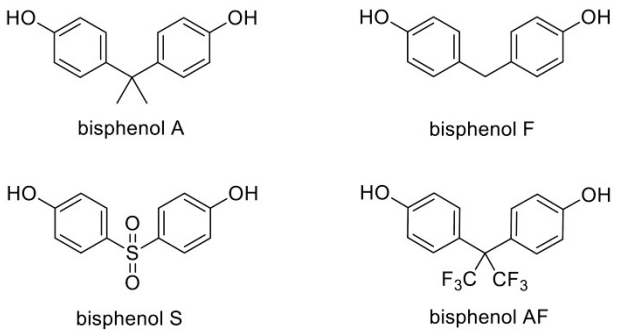

Fig. 1. Bisphenol A and some of its industrially used structural analogues.

BPA is a building block of polycarbonates and is contained in epoxy resins and in other synthetic polymer-based materials. They are widely used as wrappings in food industry, so the dietary intake contributes to daily BPA exposure. Among other sources, the ingestion of dust, dermal absorption of BPA from thermal paper, or release from dental restorative materials are commonly mentioned in the literature (Geens *et al.* 2012). The tolerable daily intake (TDI) has been set to 50 μg/kg body weight, but the European Food Safety Authority (EFSA) has temporarily reduced it to 4 μg/kg body weight in 2015 (EFSA Panel on Food Contact Materials and Processing 2015). Although EFSA estimated that the daily BPA exposure for adults is 1.449 μg/kg body weight, some studies suggest that the dose-response relationship is nonmonotonic (Diamanti-Kandarakis *et al.* 2009, Vandenberg *et al.* 2012); therefore, concerns about long-term low-dose exposure to BPA remain (Birnbaum 2012, vom Saal and Hughes 2005).

While BPA is not a constituent of most dental materials, resin-based materials contain monomers derived from BPA, e.g. Bis-GMA (bisphenol A glycidyl dimethacrylate), Bis-EMA (ethoxylated bisphenol A glycol dimethacrylate), or Bis-DMA (bisphenol A dimethacrylate) (Fig. 2). As a consequence, BPA may be present in these materials in trace amounts as a contaminant from the manufacturing process (Fig. 3), or a degradation product of the monomer hydrolysis (Löfroth *et al.* 2019, Soderholm and Mariotti 1999, Van Landuyt *et al.* 2011). Several studies confirmed the release of BPA from dental materials, but the amounts varied greatly (Löfroth *et al.* 2019), probably due the lack of standard methodology and different types of materials tested. However, it was revealed that monomers with ether linkage of BPA, such as Bis-GMA and Bis-EMA which are used in restorative resin composites and adhesive systems, are less prone to hydrolytic degradation than those with ester bond to BPA like Bis-DMA contained in dental sealants (Fleisch *et al.* 2010, Löfroth *et al.* 2019, Schmalz *et al.* 1999).

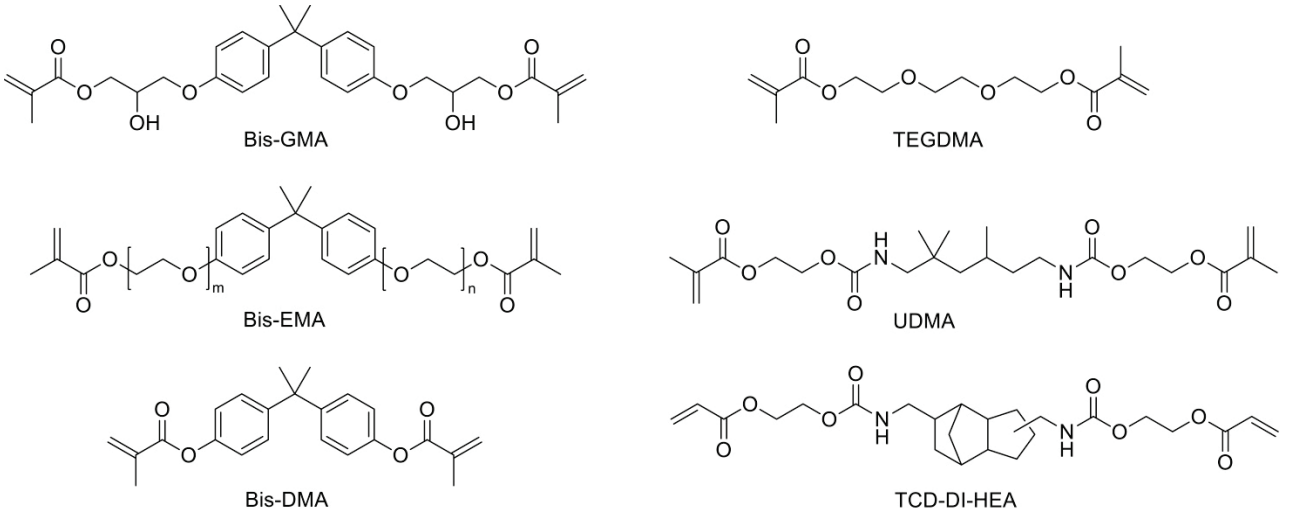

Fig. 2. Dental methacrylate monomers. Bis-GMA is the most common monomer in dental restorative composites, Bis-EMA is its ethoxylated derivative. Bis-DMA is used in dental sealants. TEGDMA, UDMA and TCD-DI-HEA are included as examples of bisphenol-A free monomers used in dental composites. Bis-GMA – bisphenol A glycidyl dimethacrylate, Bis-EMA – ethoxylated bisphenol A glycol dimethacrylate, Bis-DMA – bisphenol A dimethacrylate, TEGDMA – triethylene glycol dimethacrylate, UDMA – urethane dimethacrylate, TCD-DI-HEA – bis(acryloyloxymethyl) tricyclo [5.2.1.02,6] decane.

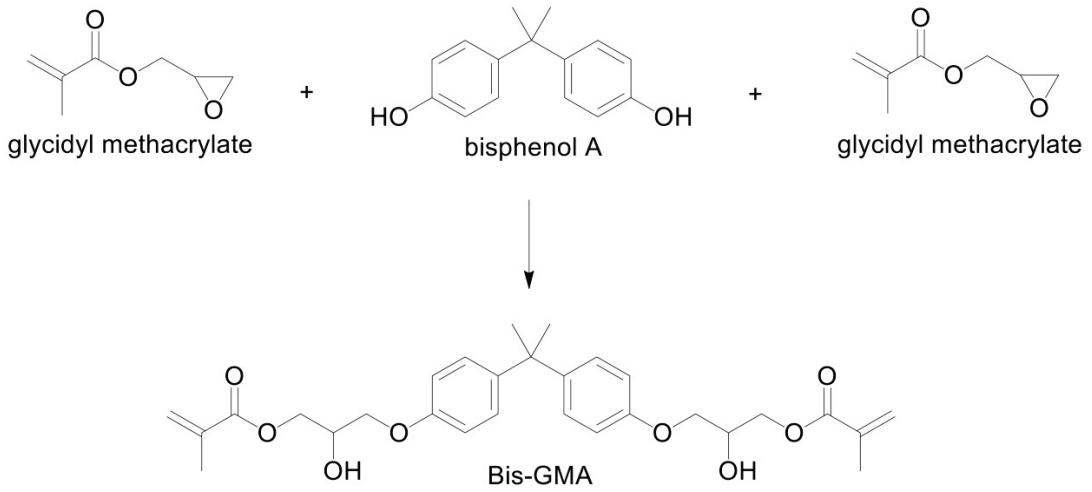

Fig. 3. Synthesis of bisphenol A glycidyl dimethacrylate (Bis-GMA).

In reaction to concerns about the leakage of BPA from dental materials, some "BPA-free" alternatives were introduced. In this study, the release of BPA from two conventional Bis-GMA-containing and two "BPA-free" restorative resin-based composites, which are commonly used as tooth-colored filling materials, was examined using liquid chromatography – tandem mass spectrometry (LC-MS/MS). Derivatization with dansyl chloride (Kolatorova Sosvorova *et al.* 2017) was used in order to increase sensitivity and enable the detection of eventual trace amounts of BPA in materials labeled as "BPA-free". Besides BPA, it was investigated whether alternative bisphenols BPS, BPF, and BPAF were present. Previous studies showed that more BPA was released to organic solutions, so methanol was selected as the elution medium to simulate the worst-case scenario. To determine the kinetics of the release, methanol was periodically changed over the period of 130 days. The null hypotheses tested were 1) that there would be no significant difference in the release of BPA between Bis-GMA-containing and "BPA-free" composites, and 2) that alternative bisphenols would not be detected.

Methods

The resin-based composites tested in this study included Bis-GMA-containing Charisma Classic (CC; Kulzer, Hanau, Germany) and Filtek Ultimate Universal Restorative (FU; 3M, St. Paul, MN, USA), and "BPA-free" Charisma Diamond (CD; Kulzer, Hanau, Germany) and Admira Fusion (AF; Voco, Cuxhaven, Germany). The composites were of A2 shade except for FU whose shade was A2 Dentin. The overview of their compositions is presented in Table 1. Standards of BPA, BPS, BPF, BPAF and deuterated standard of BPA (d16BPA) were purchased from Sigma-Aldrich (St. Louis, MO, USA) as well as acetone, sodium bicarbonate, ammonium formate and dansyl chloride. Standard of deuterated BPS (d4BPS) was synthesized as described in Kolatorova Sosvorova *et al.* (2017). Diethylether, LC-MS grade methanol and water for chromatography were from Merck AG (Darmstadt, Germany). Methanol p.a. was purchased from Lach-Ner (Neratovice, Czech Republic).

Specimen preparation

Cylindrical specimens (6 mm diameter, 2 mm thickness, surface area 94 mm^2, n=5) were prepared in PTFE (polytetrafluoroethylene) molds placed on a glass slide. The materials were applied in one increment, covered with another glass slide to create a flat surface and prevent oxygen inhibition of polymerization, and light-cured from one side for 20 s using the LED polymerization lamp Valo (Ultradent Products, South Jordan, UT, USA) in the "standard" mode (1000 mW/cm^2).

Thirty minutes after polymerization, specimens were pushed out of the molds and transferred to glass test tubes with 2 ml of LC-MS grade methanol. The tubes were closed using caps with PTFE septa and incubated at 37 °C. Methanol was changed after 1, 4, 9, 16, 35, 65, and 130 days to determine the kinetics of bisphenol release. Eluates were poured into new glass test tubes, and test tubes with specimens were rinsed with 0.5 ml of methanol five times. Then, 2 ml of methanol were added, and the test tubes were placed to the incubator. To avoid potential contamination, only glass and metal instruments repeatedly rinsed with methanol were used.

Table 1. Composition of materials used in this study.

Composite material (abbreviation)	Manufacturer (batch number)	Composition
Charisma Classic (CC)	Kulzer, Hanau, Germany (K010733)	Bis-GMA, TEGMA, Ba-Al-F glass fillers, pre-polymerized filler, pyrogenic silica, initiator
Filtek Ultimate Universal Restorative (FU)	3M, St. Paul, MN, USA (N985020)	Bis-GMA, Bis-EMA, UDMA, TEGDMA, PEGDMA, non-agglomerated/non-aggregated silica and zirconia filler, aggregated zirconia/silica cluster filler, initiator
Charisma Diamond (CD)	Kulzer, Hanau, Germany (K010073)	TCD-DI-HEA, UDMA, TEGDMA, Ba-Al-F glass fillers, pyrogenic silica, initiator
Admira Fusion (AF)	Voco, Cuxhaven, Germany (1919447)	no conventional methacrylate monomers, "organically modified ceramics" resin, glass ceramic filler, nano filler, initiator

Bis-GMA – bisphenol A glycidyl dimethacrylate, TEGDMA – triethylene glycol dimethacrylate, Bis-EMA – ethoxylated bisphenol A glycol dimethacrylate, UDMA – urethane dimethacrylate, PEGDMA – polyethylene glycol dimethacrylate, TCD-DI-HEA – bis(acryloyloxymethyl) tricyclo [5.2.1.02,6] decane.

LC-MS/MS analysis

The calibration mixture was prepared by diluting methanol stock solutions of BPA, BPS, BPF and BPAF in methanol. A nine-point calibration curve in the range 0.032-8.0 ng/ml was constructed. The mixture of internal standards, also in methanol, contained d16BPA and d4BPS.

A methanol extract of each sample (700 µl) was spiked with 10 µl of internal standard (IS) mixture and evaporated to dryness under reduced pressure. Quality control samples with known addition of individual analyte as well as calibration curve samples were treated the same way. The derivatization reaction was conducted according to Kolatorova Sosvorova *et al.* (2017) and Vitku *et al.* (2015). Briefly, 50 µl of dansyl chloride in acetone (1 mg/ml) and 50 µl of 100 mM sodium bicarbonate buffer were added to dry residues, vortexed and evaporated under reduced pressure. The dry residues were subsequently reconstituted in 300 µl of methanol and equally diluted with 10 mM aqueous solution of ammonium formate. 50 µl were injected and analyzed by LC-MS/MS.

LC-MS/MS was performed using API 3200 (Sciex, Concord, Canada), a triple stage quadrupole mass spectrometer with electrospray ionization (ESI) connected to ultra-high performance liquid chromatograph (UPLC) Eksigent ultraLC 110 system (Redwood City, CA, USA). Chromatographic separation was performed using a Kinetex C18 1.7 µm (150×3.0 mm) column (Phenomenex, Torrance, CA, USA) equipped with a security guard at a flow rate 0.4 ml/min at 50 °C. A mixture of methanol and water was used as a mobile phase. For detailed information about LC-MS/MS conditions, please refer to Kolatorova Sosvorova *et al.* (2017), Vitku *et al.* (2015). The lower limit of quantification (LLOQ) was 0.042 ng/ml for BPA, 0.055 ng/ml for BPS, 0.044 ng/ml for BPF, and 0.151 ng/ml for BPAF.

Results

BPA was detected in all eluates, whereas alternative bisphenols BPS, BPF, and BPAF were not detected in any of them. Mean concentrations of BPA in eluates (ng/ml) and amounts of BPA released per gram of composite (ng/g) are presented in Table 2 and Table 3, respectively. Figure 4 shows average daily BPA release in ng/g while cumulative curves in Figure 5 illustrate the proportions of total released amount at each time period.

BPA release from Bis-GMA-containing CC and FU was significantly higher compared to "BPA-free" CD and AF. All materials exhibited the largest BPA release during the first day, with the highest amount released from FU (15.4±0.8 ng/g), followed by CC (9.1±1.1 ng/g), AF (2.1±1.3 ng/g), and CD (1.6±0.8 ng/g). Figure 4 illustrates that the average daily elution gradually decreased towards zero over the examined period except for FU, where the elution continued at a steady rate between days 4 and 130. In the case of AF, mean concentrations of released BPA were around or below LLOQ in eluates collected after 9, 16, 35, 65, and 130 days. The highest total amounts of BPA were released from FU (182.6±6.0 ng/g), followed by CC (146.3±7.0 ng/g), CD (8.3±1.5 ng/g), and AF (5.2±1.3 ng/g).

Table 2. Concentrations (mean ± SD in ng/ml) of bisphenol A released from tested composites to methanol between each methanol change.

Composite material	1 day (Day 1)	4 days (Days 2-4)	9 days (Days 5-9)	16 days (Days 10-16)	35 days (Days 17-35)	65 days (Days 36-65)	130 days (Days 66-130)
Charisma Classic (CC)	0.66±0.09	0.54±0.07	0.58±0.07	0.99±0.16	2.17±0.22	2.26±0.26	3.37±0.49
Filtek Ultimate Universal Restorative (FU)	1.01±0.06	0.27±0.14	0.43±0.08	0.57±0.09	1.50±0.33	3.59±0.16	4.64±0.30
Charisma Diamond (CD)	0.11±0.05	0.08±0.02	0.10±0.06	0.05±0.01	0.08±0.05	0.07±0.02	0.16±0.03
Admira Fusion (AF)	0.15±0.01	0.08±0.08	0.03±0.02	0.04±0.01	0.03±0.01	0.02±0.01	0.03±0.01

Table 3. Amounts of bisphenol A released from tested composites to methanol between each methanol change and the total (cumulative) amount of bisphenol A in nanograms per gram of composite (mean ± SD in ng/g).

Composite material	1 day (Day 1)	4 days (Days 2-4)	9 days (Days 5-9)	16 days (Days 10-16)	35 days (Days 17-35)	65 days (Days 36-65)	130 days (Days 66-130)	Total (Days 1-130)
Charisma Classic (CC)	9.1±1.1	7.5±0.7	8.1±0.9	13.7±2.5	30.0±2.1	31.3±3.1	46.6±6.2	146.3±7.0
Filtek Ultimate Universal Restorative (FU)	15.4±0.8	4.2±2.2	6.5±1.2	8.7±1.3	22.8±4.6	54.6±2.0	70.5±6.0	182.6±6.0
Charisma Diamond (CD)	1.6±0.8	1.1±0.3	0.9±0.1	0.7±0.1	1.1±0.7	1.0±0.3	2.3±0.5	8.3±1.5
Admira Fusion (AF)	2.1±1.3	1.2±1.1	0.4±0.3	0.6±0.1	0.4±0.2	0.2±0.1	0.4±0.1	5.2±1.3

Mean specimen mass was 0.145±0.01 g for CC, 0.132±0.01 g for FU, 0.143±0.01 g for CD, and 0.143±0.01 g for AF.

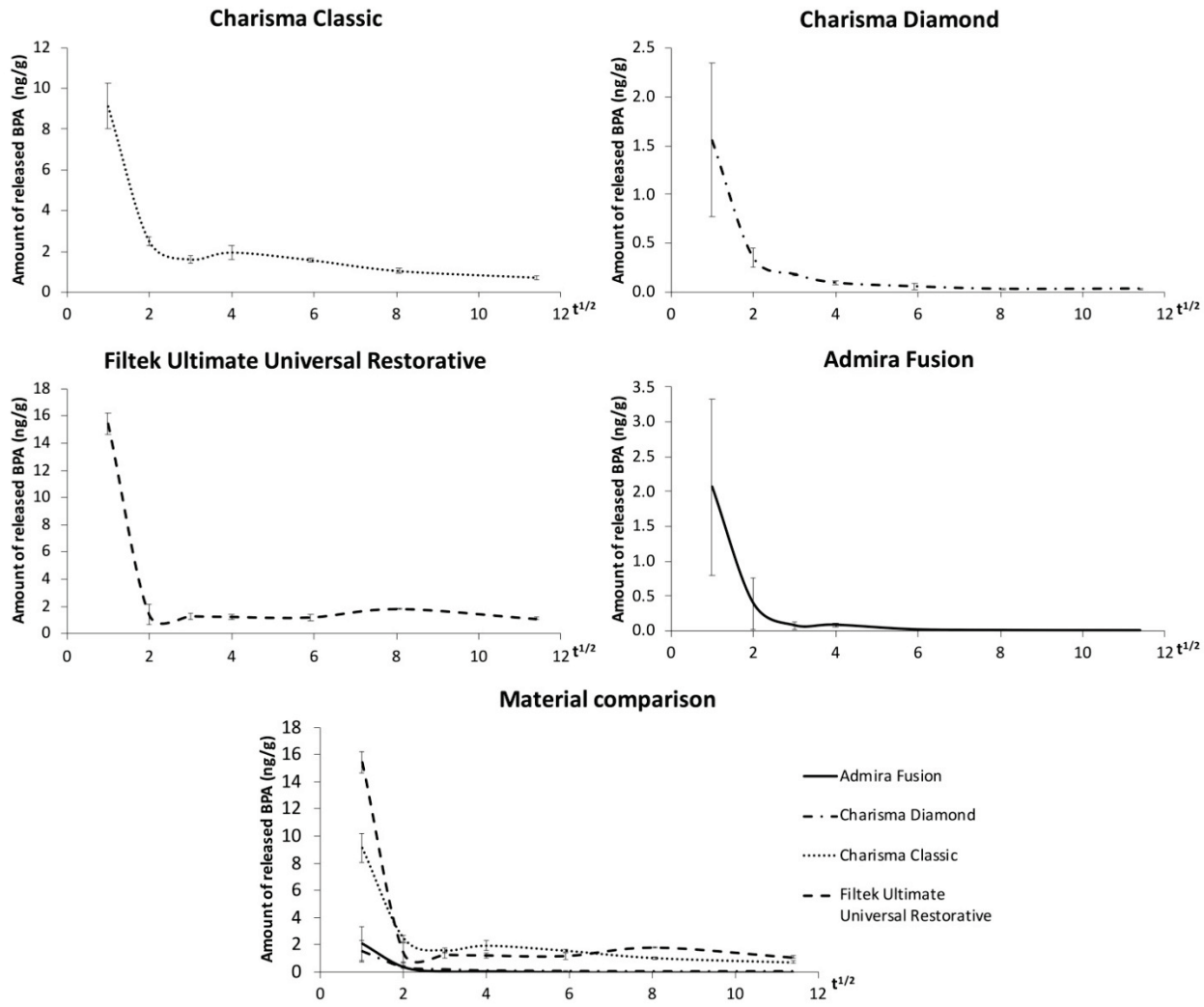

Fig. 4. Average daily release of bisphenol A per gram of composite (ng/g) plotted against the square root of time. The highest BPA release was observed after 1 day and a gradual decrease in daily released amount of BPA followed over the examined period except for Filtek Ultimate Universal Restorative, where the elution continued at a steady rate between days 4 and 130.

Discussion

The release of BPA from dental materials has been assessed in many studies using various analytical methods, mostly HPLC or gas chromatography mass spectrometry (Löfroth *et al.* 2019). However, the amounts of released BPA may often range around or below their quantification limit, which may lead to inaccurate and unreliable results. Moreover, the specificity of these methods may be insufficient, so other leached compounds might confound the results (Hope *et al.* 2016, Noda *et al.* 1999). Therefore, UPLC-MS/MS was used in two recent studies for its higher sensitivity and specificity. Their lower limits of quantification (LLOQ) were 0.1 ng/ml (Becher *et al.* 2018) and 0.25 ng/ml (De Nys *et al.* 2018), respectively, much lower than those of previous studies reviewed by Löfroth *et al.* (2019). The latter study used derivatization with pyridine-3-sulfonyl chloride to improve the detection sensitivity (De Nys *et al.* 2018). In this study, a previously validated LC-MS/MS method using derivatization with dansyl chloride (Kolatorova Sosvorova *et al.* 2017, Vitku *et al.* 2015) was applied. As a result, the LLOQ of BPA was 0.042 ng/ml, allowing for a very sensitive determination of BPA levels even in the "BPA-free" materials. Besides that, the method also enables a sensitive detection of alternative bisphenols BPS, BPF, and BPAF, which have not been examined in dentistry to date.

BPA was detected in all eluates, but Bis-GMA-containing composites FU and CC released significantly higher amounts of BPA than "BPA-free" materials. Therefore, the first null hypothesis had to be rejected. All composites exhibited the highest release during the first day, presumably due to the rapid penetration of methanol

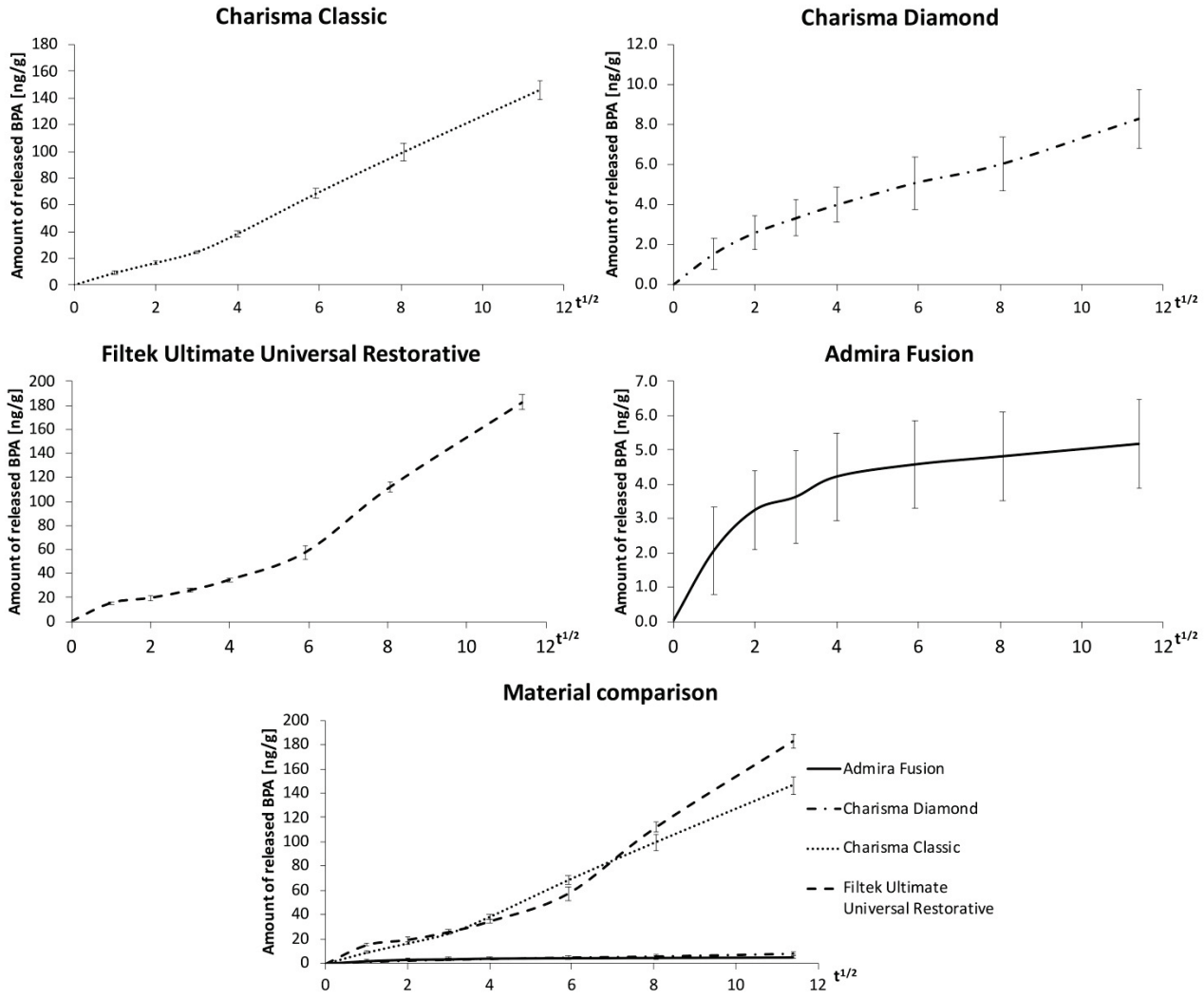

Fig. 5. Cumulative release of bisphenol A per gram of composite (ng/g) plotted against the square root of time. The cumulative amounts of released BPA increased over the examined period. In the case of Admira Fusion, the plateau suggests that the release almost reached its maximum. In contrast, the cumulative curves of other materials indicate that the release would continue beyond the examined period, although at a gradually decreasing rate.

in the composites enabling the release of BPA from their structure. In the Bis-GMA-containing composites, the not entirely polymerized and easily soluble surface layer could contribute to the high initial BPA release, although glass slides were used to prevent oxygen inhibition of the free radical polymerization. The fast release of BPA during the first day could also be related to the fact that the degree of conversion (DC) of the composites was not final before they were immersed in methanol. The post-irradiation polymerization (Leung *et al.* 1983, Pilo and Cardash 1992) is ongoing at a relatively high rate during the first hours after light-curing, and the gradual increase in DC could slow down the release of BPA. In "BPA-free" materials, the released BPA is presumably a contaminant from the manufacturing process.

Compared to previous studies of light-cured dental composites incubated in methanol (Durner *et al.* 2011, Imai and Komabayashi 2000), significantly lower amounts of released BPA were detected in this study. Presumably, this could be caused by differences in specimen preparation and analytical methods. Durner *et al.* (2011) used GC/MS, Imai and Komabayashi (2000) used HPLC, and neither of the studies mentioned the quantification limit. On the other hand, no release of BPA from Filtek Supreme XT (3M, Seefeld, Germany) to 75 % ethanol was detected in a LC-MS/MS study (Polydorou *et al.* 2009). This does not indicate that no BPA was released, but rather that its levels could be below the LLOQ 0.5 µg/ml of the method used. In the two recent studies using UPLC-MS/MS, composites containing BPA-derived monomers incubated in artificial saliva (De Nys *et al.* 2018) and deionized water (Becher

et al. 2018) mostly exhibited a slightly lower leakage of BPA compared to Bis-GMA-containing composites tested in our study. This could be attributed to the fact that the amounts of BPA released to water-based media are significantly lower compared with organic media (Van Landuyt *et al.* 2011).

In this study, the average daily release of BPA decreased markedly after the first day and was steadily decreasing over the 130-day period. This finding is in agreement with previous *in vitro* studies which examined the kinetics of BPA release (De Nys *et al.* 2018, Imai and Komabayashi 2000, Polydorou *et al.* 2009). However, long-term release was examined only by Polydorou *et al.* (2009) who did not detect any BPA after 1-year storage in 75 % ethanol, probably due to the insuffiecient detection sensitivity (LLOQ 0.5 µg/ml). The average daily release of BPA after day 4 did not surpass 2 ng/g of Bis-GMA-containing composites and 0.2 ng/g of "BPA-free" composites. While there are concerns about long-term low-dose exposure to BPA (Birnbaum 2012, vom Saal and Hughes 2005), these values appear to be only a negligible contribution to the daily exposure of 1.449 µg/kg body weight estimated by EFSA.

Alternative bisphenols were not detected in any of the eluates tested, so the second null hypothesis had to be accepted. The use of alternative bisphenols is not common in dentistry, because BPA-derived monomers can be replaced by BPA-free ones, although their physico-mechanical properties might be slightly different. This is in contrast with industry where BPA is an indispensable constituent of various polymers and cannot be easily eliminated, leading to the substitution with its analogues to achieve "BPA-free" products.

This study confirmed that BPA may be released from dental composites; however, the amounts were several orders of magnitude lower than TDI despite the use of methanol for incubation. De Nys *et al.* (2018) stated that the total exposed surface area of full crown restorations of all teeth is 7,372 mm^2, so even in this worst-case scenario, 159 ng of BPA could be released from FU during the first day. For a 70-kg person, that equals to approximately 0.06 % of TDI and 0.16 % of the estimated daily exposure. The released amounts of BPA further decreased over the incubation period of 130 days. Based on the results of this study and the other recent UPLC-MS/MS studies (Becher *et al.* 2018, De Nys *et al.* 2018), it seems that the amounts of BPA released from light-cured resin composites may be lower than previously reported. Although studies evaluating the association between BPA release from dental composites and its adverse effects on human health are scarce, it appears that the contribution of contemporary restorative composites to the daily BPA exposure is only minor if they are properly polymerized.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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