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RESEARCH WORK

Bisphenol A released and ultrastructural changes in dental composite resins.

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ABSTRACT

Dental composite resins may release bisphenol-A or similar molecules affecting patient health and the environment.
This study measured bisphenol-A release from three commonly used in patients composite resins (Filtek™ Z350 XT, Filtek™ P60, Filtek™ Bulk Fill) immersed in three liquid mediums (artificial saliva, 0.001 M lactic acid and 15% ethanol) and assessed the changes in the surface micromorphology.The released BPA was measured by HPLC at basal time (t=0), 1 h, 1 d, 7 d and 30 d. Topographic analysis of specimens was performed by scanning electron microscopy (SEM). The data were analyzed using one-way ANOVA and Tukey post-hoc test ($P < 0.05$).
BPA in solution increased significantly in the three DCRs immersed in 0.001 M lactic acid at all times. SEM micrographs of the specimen in 0.001 M lactic acid disclosed more structural defects than others.
The surface of the three composite resins was morphologically affected by their immersion in all solutions. SEM evidenced that the dental materials underwent erosion and cracks with filler particles protruding from the surface. The morphological changes in tested dental materials produced by exposure to these solutions are potentially dangerous to patients by causing caries, infections, and partial loss of dental material.

KEY WORDS
Dental composite resin; BPA; Endocrine disruptor; Scanning electron microscopy; Liquid Chromatography.

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INTRODUCTION

Dental composite resins (DCR) consist mainly of inorganic filler particles and an organic resin matrix based on various monomers[1,2]. Its formulations contain one or more base monomers, crosslinking dimethacrylates, such as bisphenol A diglycidyl methacrylate (bis-GMA; CAS 1565-94-2), bisphenol A ethoxylate dimethacrylate (bis-EMA; CAS 41637-38-1), triethylene glycol dimethacrylate (TEGDMA; CAS 109-16-0), and Urethane dimethacrylate (UDMA)[1]. In dentistry, bisphenol-A (BPA) is used as a raw material in synthesizing several resin monomers and may be found as an impurity in dental materials[3-6]. The most frequently used monomers synthesized from BPA include bis-GMA, bis-EMA, and bisphenol A dimethacrylate (bis-DMA; CAS. 3253-39-2)[7].

A significant amount of research has evaluated the release of monomers into the oral cavity and the potential hazardous effects due to monomer release or filler leachability from conventional resin composites[5,8-10]. The potential for cytotoxic, genotoxic and oestrogenic effects of the eluted monomers and degradation products (TEGDMA, HEMA, BPA, Bis-GMA, among others) raised our concerns[10-14] significantly. Adverse health effects such as diabetes[15], coronary artery disease[16], obesity[17], disorders of the immune system[18], reproductive disorders[19], behavioural and cognitive alterations[11], metabolism disorders, modifications in reproductive function (male and female), changed the age of pubertal onset[20], breast cancer[21] and carcinogenesis in the prostate[22] are associated with exposure to low doses of BPA. The European Food Safety Authority (EFSA) proposed a new safety standard of 0.04 nanograms per kilogram of body weight per day, compared to the previous interim standard of 4 micrograms (4,000 nanograms) per kilogram per day. The US Food and Drug Administration (FDA) considers a safe level of 50 micrograms (50,000 nanograms) per kilogram daily[23].

Previous studies suggested that the liberation of monomers induces damage to the DCR surface by physical and chemical causes[24,25]. The micromorphology of the DCR surface after being immersed in artificial saliva, ethanol or acid solution revealed damage with degradation of the organic matrix evidenced by erosion like pores and cracks to a big lagoon with filler particles protruding from the surface[25-28].

Therefore, the purpose of this study was (i) to measure BPA release from three composite resins immersed in artificial saliva, 0.001 M lactic acid and 15% ethanol by high-performance liquid chromatography and (ii) to assess the changes in the surface micromorphology of composite resins.

We hypothesized that three DCR commonly used in Chilean patients produces significant BPA release over time. The second hypothesis implies that these DCR immersed in 0.001 M lactic acid and 15% ethanol

release more BPA than those exposed to artificial saliva. The third hypothesis points out that BPA releases produce changes in the surface morphology over time.

METHODS

Specimen preparation

DCR Filtek™ Z350 XT (3M ESPE, St. Paul, MN, USA), Filtek™ P60 (3M ESPE, St. Paul, MN, USA) and Filtek™ Bulk Fill (3M ESPE, St. Paul, MN, USA) were tested. Table 1 shows the composition of these resins. Twenty-seven disc-shaped specimens, 7 mm in diameter and 2 mm in thickness, were prepared for each DCR using a customized cylindrical stainless-steel mold. The mold was positioned on a transparent plastic strip on a glass plate and then filled with composite material. Specimens were built up in 2-mm-thick increments. Then each side of the specimens was light-cured for 40 seconds (20 seconds on the top side + 20 seconds on the bottom side) using a Led light lamp model D-lux (Diadent, Group International, Europe 8v, AS Almere, The Netherlands) with an intensity of 1100 mW/cm^2 close to the specimen surface. A radiometer (HE) was used to control the power of the curing unit before and after the light exposition.

Immersion of specimens in treatment solutions

Twenty-seven specimens from each group were subdivided into three subgroups. Specimens of each DCR were individually immersed in a glass vial containing 20 mL of storage media artificial saliva (Farmacia Ahumada, Santiago, Chile; pH 6.9), 0.001M lactic acid (Merck; pH 4) and 15% ethanol (Merck KGaA, Darmstadt, Germany; pH 5). The immersion periods for each group were baseline time, one h, 1 d, 7d and 30 d at 37 ºC. 1 mL of each sample saved after immersion was placed in individual containers and immediately frozen at -20 ºC until BPA quantification.

Extraction Procedure

We carried out the liquid-liquid extraction by adding 1 mL of dichloromethane (Optima, Fisher Scientific) to samples, mixing in a Vortex for 30 seconds, and leaving them to decant until reaching two phases. After work, 400 µL of the lower phase was emptied into a new vial. The organic phase was evaporated entirely under a nitrogen stream and reconstituted with 100 µL of a mobile phase of acetonitrile (ACN, LiChrosolv®, Merck): water at 60:40.

HPLC analysis

BPA (Sigma-Aldrich, Steinheim, Germany) was used as the reference standard to identify the monomer peaks in the chromatograms. Ten thousand ppm of BPA was dissolved in methanol (stock solution). The stock solution was stored refrigerated at 8±2 °C until use. Calibration curve used several dilutions of stock solution (1000, 100, 10, 1, 0.8, 0.6, 0.3, 0.2, 0.1 ppm). The validation of the analytical method followed Małkiewicz et al. procedure[29].

HPLC identified and quantified residual monomers. We used a Shimadzu (Nexera, Kyoto, Japan) equipped with a quaternary pump (LC-30AD), a communication module (CBM-20A), and a degasification unit (DGU-205R). It also had an autosampler (SIL-30AC), oven (CTO-20AC) and a diode detector UV-VIS (SPD-M20A). It used a Phenomenex C-18 column, 5 µm particle size, 250 mm long and 4.6 mm in diameter; it performed at 40 ºC, with an injection volume of 10 µL at 210 nm. We worked with two mobile phases: ultrapure H2O (mobile phase A) and acetonitrile at 1.0 mL/min (mobile phase B). The gradient elution was: 60% to 90% B during 4 min, then 90% to 100% during 1 min and maintained during 4 min, then 100% to 60% during 0.1 min and maintained during 8 min.

SEM Analysis

Scanning electron microscopy (SEM) is widely used in materials science to characterize surface roughness. We studied the surface aspects of DCR before and after the experimental protocol using SEM. The specimens were mounted on metallic stubs, sputter-coated with gold (SPI-Module Westchester, USA), and examined with SEM (JEOL, JSM 6380 LV, Tokyo, Japan). Specimens were photographed at x100, x1000, x2000 and x4000.

Statistical analysis

The BPA concentration released from DCR was analyzed using a one-way analysis of variance (ANOVA). Tukey's post hoc comparison allowed us to determine differences at a significance level defined at $P < 0.05$. We used GraphPad Prism software 5.03 (GraphPad Software, San Diego, CA, USA) for statistical analysis.

RESULTS

Artificial saliva immersion

HPLC chromatograms revealed that BPA was undetectable for Filtek™ Z350 XT, Filtek™ P60, and Filtek™ Bulk Fill immersed in artificial saliva at baseline time, one h, 1 d, 7 d and 30 d.

Lactic acid immersion

Figure 1 shows BPA released from Filtek™ Z350 XT, Filtek™ P60 and Filtek™ Bulk Fill composite resins immersed in 0.001 M lactic acid. The amount of BPA began to be quantifiable by HPLC on the first day (1.494±0.217 ppm) of Filtek™ Z350 XT fully immersed in lactic acid. By the end of the experiment (30 d), BPA concentration reached up to 4.219±1.072 ppm. The BPA released in this solvent by Filtek™ Z350 XT was the highest of all tested DCR.

For Filtek™ P60, BPA concentration constantly increased over days. At 30 d, BPA concentration reached 1.472±0.186 ppm, a third of the concentration found for Filtek™ Z350.

On the other hand, BPA released from Filtek™ Bulk Fill was low up to 7 d of exposure (Figure 1). At 30 d, the BPA concentration was 1.416 ± 0,187 ppm. Thus, the maximum concentration of BPA released from Filtek™ Bulk Fill was similar to BPA found for Filtek™ P60.

The results obtained from one-way ANOVA and Tukey's test showed that the BPA concentration increased significantly in the three DCR tested in 0.001 M lactic acid at the immersion times of 1 d, 7 d and 30 d.

Moreover, results exhibit a significant increase of BPA released at 30 d in 0.001M lactic acid from Filtek™ Z350 XT and Filtek™ Bulk Fill compared to BPA released at one h, 1 d, and 7 d, as is shown in Figure 1.

There was a significant difference in the BPA released in 0.001 M lactic acid at 30 d from Filtek™ Z350 XT compared with Filtek™ P60 and Filtek™ Bulk Fill.

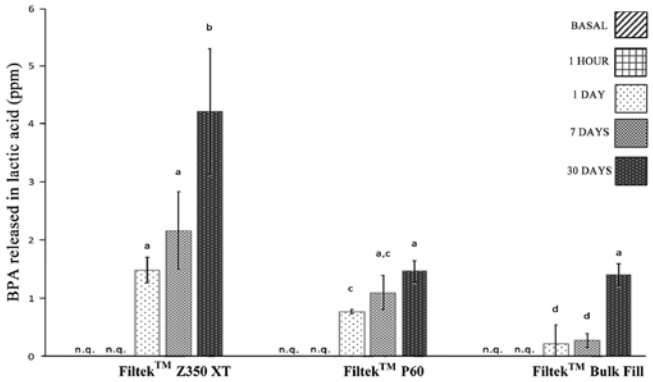

Figure 1. BPA concentration in 0.001 M lactic acid solution from Filtek™ Z350 XT, Filtek™ P60 and Filtek™ Bulk Fill at basal time, 1 h, 1 d, and 7 d and 30 d. Different letters indicate significant differences among dental composite resins. Multiple comparisons of means were performed using Tukey's test ($P < 0.05$) significance level. n.q.: no quantified.

15% ethanol immersion

Released BPA from the three DCR into the 15% ethanol had a similar trend in lactic acid, although BPA concentrations in ethanol solutions from Filtek™ Z350 XT and Filtek™ P60 were much higher at 1 d, 7 d and 30 d, as shown in Figure 2. Furthermore, in all tested times, BPA concentrations from Filtek™ Z350 XT were two-fold higher than from Filtek™ P60 and three-fold from Filtek™ Bulk Fill.

Specimens obtained from Filtek™ Bulk Fill fully immersed in ethanol solution revealed BPA concentrations lower than the quantification limit of the HPLC-DAD method.

The results obtained from one-way ANOVA and Tukey's test showed that the BPA concentration increased significantly in the three resins tested immersed in 15% ethanol at the immersion times of 1 d, 7 d and 30 d, as is shown in Figure 2.

Additionally, results revealed a significant increase of BPA released at 30 d in ethanol from Filtek™ Z350 XT and Filtek™ P60 compared to BPA released at one h, 1 d, and 7 d. However, there was no significant difference for BPA removed from Filtek™ Bulk Fill.

Filtek™ Z350 XT in 15% ethanol immersion after 30 d shows a significant increase of BPA released compared to Filtek™ P60 and Filtek™ Bulk Fill.

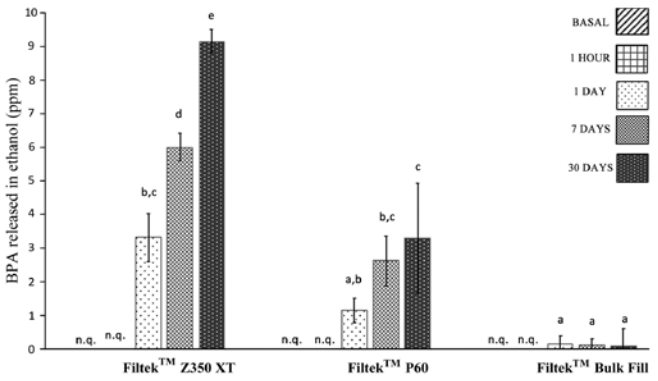

Figure 2. BPA concentration in 15% ethanol from Filtek™ Z350 XT, Filtek™ P60 and Filtek™ Bulk Fill at basal time, 1 h, 1 d, and 7d and 30 d. Different letters indicate significant differences among dental composite resins. Multiple comparisons of means were performed using Tukey's test ($P < 0.05$) significance level.

SEM Analysis

Representative superficial micro-topography of DCR (control, Figure 3A-C) and DCR immersed in artificial saliva, 0.001 M lactic acid and 15% ethanol after 30 d of storage are presented in Figure 3D-L. Control SEM images of Filtek™Z350 XT showed irregular shaped filler particles (Figure 3A). Filtek™ P60 had round-shaped small and medium particles (Figure 3B). Filtek™ Bulk Fill contained mostly spherical fillers (Figure 3C).

After immersion in artificial saliva (Figure 3D-F), the surface of the three DCR shows matrix decomposition with different degrees of erosion. Damage on the composite resin surface was more evident for Filtek™ Z350 XT (Figure 3D) than for Filtek™ P60 and Filtek™ Bulk Fill. Several filler particles protruded from the surface and voids, suggesting particle loss and blankness. Filtek™ P60 showed an irregular surface due to the loss of the superficial layer, with spheres protruded, small pits and laminar structures perpendicular or oblique to the surface (Figure 3E). Filtek™ Bulk Fill exhibited the least harm with slight surface changes such as fewer uniform surfaces with resin removal, dislodged particles, cracks, tiny pores and protruding filler particles (Figure 3F).

A high level of degradation of the organic matrix is evident after 30 d of immersion in 0.001M lactic acid (Figure 3G-I). The DCRs had the filler particles exposed to the surface. Filtek™ Z350 XT has the most altered surface structure with significant loss of the superficial globular layer, extensive lagoons, cracks and pits (Figure 3G). The Filtek™ P60 specimens (Figure 3H) appeared similar to those immersed in artificial saliva but had a greater disintegration degree. The presence of filaments and protruding spheres can be seen more clearly. Filtek™ Bulk Fill showed loss of the surface layer, exposing small polymeric chains detached from the composite bulk that gives an irregular appearance; it is also possible to appreciate several protruding particles, voids and cracks (Figure 3I).

SEM micrographs of composites surface after immersion in 15% ethanol (Figure 3 J-L) presented more structural defects than those immersed in artificial saliva but less than those immersed in 0.001 M lactic acid. Filtek™ Z350 XT revealed several holes, cracks, roughness and protruding particles, confirming a process of surface changes with the erosion of the matrix (Figure 3J). Filtek™ P60 showed an irregular surface with resin removal, dislodged and protruding filler particles, and voids (Figure 3K). Filtek™ Bulk Fill presented a surface having lots of protruding filler particles, tiny pits and voids (Figure 3 L).

DISCUSSION

Dental resin materials are one of the primary sources of BPA in patients. Pure BPA is not a component of DCR. Still, the synthesis of dental resin materials widely uses some derivatives of BPA. For example, bisphenol A diglycidyl methacrylate (bis-GMA), bisphenol A dimethacrylate (bis-DMA), polycarbonate-modified bis-GMA (PC bis-GMA), ethoxylated Bisphenol A glycol dimethacrylate (bis-EMA), and 2,2-bis[(4-methacryloxy polyethoxy) phenyl]propane (bis-MPEPP)[2,4]. BPA could be released from DCR as an impurity in synthesizing resins (monomer trapped in polymers matrix) or by chemical reaction under particular conditions[5,6].

The main goal of the current in vitro study was to measure the BPA released from Filtek™ Z350 XT, Filtek™ P60 and Filtek™ Bulk Fill immersed in artificial saliva, 0.001M lactic acid and 15% ethanol. According to the first hypothesis, Filtek™ Z350 XT, Filtek™ P60, and Filtek™ Bulk Fill release BPA over time. This hypothesis was partially accepted since BPA was not

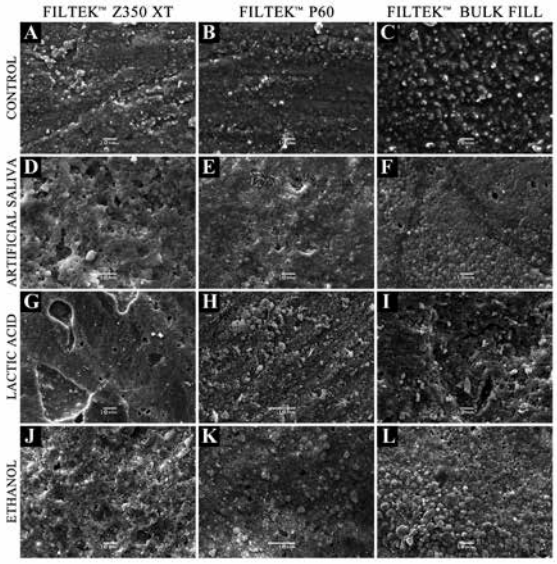

Figure 3. SEM micrographs of dental composite resins: the first column is Filtek™ Z350 XT, the second column is Filtek™ P60, and the third column is Filtek™ Bulk Fill. Control corresponds (A-C), (D-F) artificial saliva, (G-I) 0.001M lactic acid, and (J-L) 15% ethanol.

detected in any DCR from artificial saliva. BPA released over time from tested DCR agreed with Małkiewicz et al.[29] and Marzouk et al.[30].

The second hypothesis was entirely accepted since a significant difference in BPA concentration was quantified in 0.001M lactic acid and 15% ethanol for all DCR.

Hydrophilic materials, such as bis-GMA and TEGDMA, featured higher degradation by water -or aqueous solutions- sorption and solubility than hydrophobic materials, such as bis-EMA and UDMA[31,32]. The organic phase of Filtek™ Z350 XT contain bis-GMA, UDMA, TEGDMA and bis-EMA, Filtek™ P60 has bis-EMA, UDMA and TEGDMA, and Filtek™ Bulk Fill contain AUDMA, UDMA and DDMA. Differences in composition summarized in Table 1 may explain their behavior in releasing BPA.

Hydrogens attached to oxygen or nitrogen can engage in intramolecular and intermolecular hydrogen bonding interactions depending on the monomer structure. The strength of any specific hydrogen bonding interaction generally increases in relationship with the basicity of the lone pair acceptor and the acidity of the hydrogen bond donor[33]. The OH groups, such as in bis-GMA, bis-EMA and TEGDMA, or NH groups, such as in UDMA, can form hydrogen bonds with ether or carbonyl functional groups affecting the hydrophilic character associated with the corresponding polymers. Hydrophilic matrix favored water sorption and subsequently higher matrix softening[26]. Water sorption initially caused a softening of the polymer resin component by swelling the network and reducing the frictional forces between the polymer chains. However, irreversible damage to the dental material by forming microcracks may follow this outcome. DCR may also overcome hydrolytic degradation with scission of the ester linkages, releasing free monomers -such as BPA- and gradual deterioration of the infrastructure over time[8].

The amount of BPA released strongly depended on the immersion media. When ethanol penetrates the polymer network, it causes an expansion of the structure, allowing the release of unreacted monomers and causing the breakup of the linear chains of the polymer[34]. Furthermore, Rehman et al.[8] reported that DCR stored in ethanol significantly reduced the mechanical properties of DCR -tensile strength- compared to artificial saliva, in agreement with our outcomes. Recently, De Nys et al.[35] reported that BPA eluted continuously in pure ethanol from all four tested composites for one year. BPA elution was higher when ethanol was used as an extraction solution than pure water. Although De Nys's findings align with ours, they use pure ethanol and water, moving away from an in-vivo situation.

Our finding agrees with Prado et al.[36], who reported that the sorption and solubility of composites tested were higher in the alcohol-containing immersion media. They also pointed out that hydrophobic matrices, such as bis-EMA and UDMA, present in the composition of evaluated resins, are also susceptible to chemical reactions by alcohol.

Alrahlah et al.[37] studied various dental monomers' physical and mechanical properties after storage in ethanol. TEGDMA added to Bis-GMA enhanced the hydrophilicity characters of the composite resin, which further increased the undesirable water sorption and polymerization

Table 1: Information and composition of the dental composite resins.

Product	Filler Content (% volume)	Shade	Resin (Organic Matrix)	Translucency (%)	Filler	Manufacture
Filtek™ Z350 XT.						
(Nanofiller. Anterior and posterior)	63.3	A3	Bis-GMA Bis-EMA UDMA TEGDMA	35	Zirconia- Silica. Nanocluster (0.6-1.4 µm) and silica nanoparticles (5-20 nm)	3M ESPE, St Paul, MN, USA
Filtek™ P60						
(Microhybrid. Posterior)	61.0	A3	Bis-EMA UDMA TEGDMA	37	Zirconia- Silica. Nanoparticles, aluminum oxide nanoparticles (0.01–3.5 µm)	3M ESPE, St Paul, MN, USA
Filtek™ Bulk Fill (Nanofiller. Posterior)	58.4	A3	AUDMA UDMA DDMA	43	20 nm silica, 4–11 nm zirconia, ytterbium trifluoride filler consisting of agglomerate 100 nm particles.	3M ESPE, St Paul, MN, USA

Bis-GMA: Bisphenol-A Glycidyl Methacrylate. **Bis-EMA:** Ethoxylated BisPhenol-A Glycidyl methacrylate. **UDMA:** Urethane Dimethacrylate. **TEGMA:** Triethylene Glycol methyl ether methacrylate. **TEGDMA:** Triethylene Glycol dimethacrylate. **AUDMA:** Aromatic Urethane Dimethacrylate. **DDMA:** 1,12-Dodecanediol dimetacrylate

shrinkage. TEGDMA, on the other hand, showed high solubility and water sorption and reduced mechanical properties, despite the highest conversion, favoring low-molecular-weight oligomers releasing[38]. TEGDMA and bis-GMA, bis-EMA and UDMA, are present in Filtek™ Z350 XT. SEM images of Filtek™ Z350 XT (Figure 3J) confirmed significant ultrastructural changes after immersion in ethanol.

Lemon et al.[33] reported that bis-GMA engaged in strong hydrogen bonding interactions, but UDMA hydrogen bonding was weakest. UDMA had a higher degree of conversion (DC) and lower water sorption than bis-GMA and TEGDMA. Additionally, TEGDMA has higher hydrophilicity than UDMA. Therefore, the higher the DC, the higher the polymerization shrinkage, the better the mechanical properties, and the lower the water sorption and monomer releasing[39]. This observation agreed with our results since SEM images of Filtek™ Bulk Fill (Figure 3L) -composed of UDMA and AUDMA- showed significant less ultrastructural alteration within tested DCR.

According to Losada et al.[40], each lactic acid molecule has three potential H bond acceptor atoms and two H bond donor atoms to form H bonds between DCR. In contrast, the hydrogen bonding in ethanol is limited because there is only one hydrogen with a sufficient positive charge. Although we expected more releasing of BPA from specimens immersed in lactic acid, our results showed the opposite. Despite this, SEM images revealed a high level of degradation of the organic matrix after 30 d of immersion in 0.001M lactic acid (Figure 3G-I). The filler particles seem to be more exposed in DCR tested. Consequently, we suggest that 0.001M lactic acid diluted other compounds in addition to BPA.

There is limited information about the degradation effect of DCR immersion in lactic acid; nevertheless, studies reported that the pH affects BPA released and provokes ultrastructural changes in dental materials. Turssi et al.[41] stated a significant increment in roughness in all restoratives investigated after the pH-cycling regimen exposition. Pulgar et al.[42] found that BPA, bis-DMA, BADGE, and bis-GMA, among other aromatic components, were leached from composites and sealants; they also observed that the elution of BPA increased as the pH became alkaline. In the current study, pH values of 15% ethanol (pH=5) and 0.001M lactic acid (pH=4) are similar to explain our outcomes.

All the resins tested that released BPA contained BPA derivatives in their composition except Filtek™ Bulk Fill. It is possible but unlikely that BPA detected in Filtek™ Bulk Fill could come from contamination, or the manufacturer has not mentioned all the ingredients in the safety data sheet.

DCR surface study by SEM shows that there were ultrastructural changes such as loss of the surface layer, presence of porosities of various dimensions ranging from small like honeycombs to large undercuts, and exposure of the polymeric matrix. The damages were significant in DCR fully immersed in 0.001 M lactic acid and 15% ethanol. These observations were consistent with the findings of another research groups[25-28]. Consequently, the third hypothesis was entirely accepted since the surface morphology of DCR changed by their immersion during 30 d in study solutions.

CONCLUSION

In conclusion, the artificial saliva samples from Filtek™ Z350 XT, Filtek™P60 and Filtek™ Bulk Fill did not contain BPA; however, we detected but did not identify other compounds. BPA released from Filtek™ Z350 XT immersed in 0.001 M lactic acid, and 15% ethanol was significantly higher compared with Filtek™ Bulk Fill and Filtek™ P60.

SEM study demonstrated that their immersion into artificial saliva, lactic acid, and ethanol affected the surface of composite resins.

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STATEMENT OF CLINICAL RELEVANCE

BPA and similar monomers liberation induce damage to DCR surface by physical and chemical causes. Identifying micromorphology of commercial DCR after immersion in artificial saliva, ethanol, or lactic acid solutions help technician and patients to choose a safe DCR consciously.

CONFLICTS OF INTEREST

The authors certify that they have NO affiliations with or involvement with any organization or entity with any financial interest (such as honoraria, educational scholarships, participation in speakers bureaus, membership, employment, consulting, stock ownership, or other equity interest); and testimony from experts or patent license agreements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

ETHICS APPROVAL

No ethical approval was required for this study.

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