

Original Research

Bisphenol A Release from Orthodontic Clear Aligners: An In-Vitro StudySydney Katras ^{1,*}, Dejian Ma ², Ayman al Dayeh ³, David Tipton ⁴

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Abstract

Bisphenol A (BPA) is a widely used synthetic compound that has been identified as an endocrine disruptor. It has been linked to adverse health effects such as developmental defects, infertility in both men and women, cardiovascular disease, and obesity. There has been increased interest in BPA's effects on the developing fetus and data has revealed that doses below the presumed safe dose can produce harmful effects. Orthodontic clear aligner therapy is a popular treatment modality that involves the patient wearing sets of plastic aligners up to 22 hours per day for the duration of treatment. The BPA release from these aligners was rarely investigated. The objective of this study was to detect, quantify, and compare the amount of BPA released by 3 popular brands of orthodontic aligners in artificial saliva, artificial gastric fluid, and ethanol. Equal amounts of SmileDirectClub[®], Invisalign[®], and Essix Ace[®] aligners were placed in sterile glass vials and submerged in 5.5mL artificial saliva,



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artificial gastric fluid, and ethanol. Samples were incubated at 37°C and 1 mL aliquots were removed at various time points. Samples were prepared and analyzed using high performance liquid chromatography tandem mass spectrometry. BPA was released from all three brands of aligners with great variability. Peak BPA concentrations were detected in artificial saliva; Smile Direct Club® produced 5.0 ng/mL after 20 days, Invisalign® released 3.5ng/mL after 24 hours, and Essix Ace® released 6.3ng/mL after 10 days of incubation in artificial saliva. There was no significant difference in BPA concentration between the 3 types of aligners in the 3 media. When comparing time points, there was a significant increase of BPA release in the first 24 hours after incubation compared to the baseline ($p < 0.001$). There is potential BPA release from orthodontic aligners. There was no significant difference in the amount of BPA released between the three types of aligners at any time point. The majority of BPA release occurred during the first 24 hours.

Keywords

Orthodontics; clear aligner therapy; bisphenol A; estrogenicity

1. Introduction

Bisphenol A (BPA) is a widely used synthetic organic compound that can act as an endocrine disruptor due to its estrogen-like activity [1]. BPA is a principal ingredient in the production of polycarbonate plastics and epoxy resins, which are used to make food storage containers, children's toys, and dental materials. The primary source of BPA exposure in humans is thought to be through ingestion of food contaminated with BPA that has leached from containers, as well as dental materials [2, 3].

BPA is a known endocrine disruptor; it has been found to bind to estrogen receptors and have estrogenic effects in laboratory studies. Further, BPA can act as an antiestrogen, blocking the estrogenic response by competing with endogenous 17β estradiol [4, 5]. BPA can also directly bind to androgen receptors, and is possibly antiandrogenic, blocking endogenous androgen action [6, 7]. BPA binds to thyroid receptors and has both agonistic and antagonistic effects on thyroid function [6, 8]. Besides interfering with the actions of hormones [9], BPA increases the risk of cancer, diabetes, heart disease, and hyperactivity in children. It can also produce both male and female infertility [10]. Studies have found that BPA lowers sperm count in workers at the facilities where BPA is in use [11]. It can cause precocious puberty, promote the growth of hormone-dependent tumors, influence metabolic disorders such as polycystic ovarian syndrome, and disrupt glycemic control and increase insulin resistance in type 2 diabetic patients [12].

The first safety standard set by the Environmental Protection Agency in 1988 and adopted by the Food and Drug Administration as a reference dose for BPA was 50 $\mu\text{g}/\text{kg BW}/\text{day}$ [13]. It remained at that level until 2015, when the tolerable daily intake of BPA was reduced to 4 $\mu\text{g}/\text{kg BW}/\text{day}$ [14]. There is evidence that BPA may exert non-monotonic dose-responses, which indicates that even low doses (nanomolar range) of BPA may induce adverse effects although these levels are assumed to be safe. Moreover, the activity level lies within a range that is under the detection limit of most analytical methods.

Clear plastic aligners are a popular form of orthodontic therapy to correct dental crowding. It involves patients wearing sets of aligners for ~22 hrs per day for the course of the treatment. The number of prescribed aligners varies and is dependent on the amount of dental crowding and case complexity. Many cases require over 60 sets of maxillary and mandibular aligners that are changed on weekly or biweekly basis. While these aligner materials are advertised as BPA-free, few studies measured and compared the potential BPA release from these materials.

Solid Phase Extraction (SPE) followed by high performance liquid chromatography/ tandem mass spectrometry (LC-MS/MS) provide a highly sensitive method to detect and quantify BPA. The objective of this study is to investigate the BPA release from three types of commercially available aligners' material: Invisalign®, SmileDirectClub®, and Essix Ace® plastic using SPE followed by LC-MS/MS. The null hypothesis is there is no difference in the amount of BPA released from the three aligners.

2. Materials and Methods

2.1 Materials

2.1.1 Orthodontic Clear Aligner Materials

Unused Invisalign® and SmileDirectClub® clear aligners (Align Technology, Santa Clara, CA and SmileDirectClub, Nashville, TN, respectively) were donated by patients. The Essix Ace® plastic for fabrication of in-house aligners was obtained directly from the manufacturer (Dentsply Sirona, York, PA). The .035" Essix Ace® aligners were thermoformed according to the manufacturers' instructions with a Ministar® vacuum thermoforming system (Model SN 20323, Scheu-Dental GmbH, Iserlohn, Germany) on 3D printed casts. The casts were printed using FormLabs Form 2® printer (FormLabs, Somerville, MA) and cured according to the manufacturer's recommendations.

2.1.2 BPA Release Experiment

All chemical components for artificial saliva, artificial gastric fluid, and ethanol were purchased directly from Sigma Aldrich (MilliporeSigma, Munich, Germany).

2.1.3 Calibration Standards and Sample Preparation for LC-MS/MS

All mobile phase solvents were purchased from Fisher-Scientific (Pittsburgh, PA, USA). Milli-Q water was used for aqueous mobile phase. BPA and BPA-d₁₆ were purchased from Millipore-Sigma for use as external and internal standards, respectively (Sigma-Aldrich, St. Louis, MO).

2.2 BPA Release Experiment

Artificial saliva was synthesized by dissolving the constituent chemical components in water. Briefly, 896 mg KCl, 888 mg NaHPO₄, 420mg NaHCO₃, 298mg NaCl, 1.8mg NaOH, and 15 mg uric acid were dissolved in 1L deionized water and held at room temperature until use. Artificial gastric fluid was produced by adding HCl to normal saline solution until a pH of 1.2 was reached. 200-proof pure ethyl alcohol was used for the ethanol samples. Each of the three types of aligners were cut into sections of 35.0± 1.0mg. A third unbiased party randomized the aligners' sections into glass vials

containing 5.5 ml of artificial saliva (n=8), 5.5 ml of artificial gastric fluid (n=3) and 5.5ml of pure ethanol (n=3) each. The investigators that collected the samples and performed the LC-MS/MS measurements were blinded to the aligner material in each vial. 1.0mL aliquots of artificial saliva (n=3), artificial gastric fluid (n=3), and ethyl alcohol (n=3) were removed from the 5.5 ml stock solutions to establish baseline BPA concentration (T0). The vials were incubated in a water bath at 37.5°C. ~ 1.0mL aliquots were removed at 24hrs (T1), 48hrs (T2), 6 days (T6) 10 days (T10) and 20 days (T20). Samples were sealed and stored at -80° C until analysis.

2.3 Sample Preparation and LC-MS/MS Measurement

Stock solutions of BPA and BPA-d₁₆ (10 mM) were prepared in methanol. Milli-Q water was used in all subsequent dilution to make calibration standards. All the samples (except the samples extracted using ethanol) were processed using solid phase extraction (SPE). The purpose of SPE is to remove salt from the sample solution to minimize the suppression of the target ion signal strength. Briefly, Oasis HLB 3cc cartridge (Waters, Milford, MA) was conditioned with 2 x 2 mL methanol, then equilibrated with 2 x 2 mL Milli-Q water. After that, 0.5 mL sample solution was loaded and subsequently washed with 2 x 2 mL water, and finally BPA was eluted with 2 x 1 mL methanol. The SPE eluate was dried down under a gentle stream of nitrogen gas flow and stored under -20°C. For samples extracted using ethanol, a 0.5 mL sample was directly evaporated to dryness under nitrogen without SPE procedure. For LC-MS/MS measurement, each sample was reconstituted in 100 µL internal standard (BPA-d₁₆) water solution and 80 µL was then transferred to a 96-well plate. A sample aliquot (1 µL) was injected for LC-MS/MS analysis and the amount of BPA released from each sample at designated timepoints was quantified.

The LC-MS/MS system used for BPA quantification was a Sciex (Framingham, MA) 5500 triple quadrupole mass spectrometer, equipped with a Turboionspray™ (electrospray ionization, ESI) interface, and coupled with a Shimadzu (Columbia, MD) Nexera XR HPLC system and SIL-20ACXR autosampler. Separation of analytes was carried out using an Eclipse Plus C18 column of 50 x 2.1 mm i.d., and 5 µm particle size (Agilent Technologies, Santa Clara, CA). The mobile phase consists of Milli-Q water with 5% methanol as mobile phase A, and methanol as B. The combined flow rate was 0.5 mL/min. A gradient time program was applied as following: 0-1 min 20% B; 1-1.5 min 20-90% B; 1.5-2.8 min 90% B; 2.8-2.9 min 90-20% B; 2.9-3.0 min 20% B, and the time program stopped at 3.0 min. Total run time was 4.5 minutes with an extra 1.5 min equilibrate time before each run with 20% mobile phase B. The retention time was 2.45 min for both BPA and internal standard (BPA-d₁₆). A switching valve directed eluent to MS between 2.1 and 2.8 min during the 3 min time program. The flow was directed to waste bottle before 2.1 min and after 2.8 min to avoid unnecessary contamination to the MS ion source and analyzer.

Negative ionization mode was used with typical ion source parameters as following: TurbolonSpray (IS) voltage -4.5 kV, entrance potential (EP) -10 V, declustering potential (DP) -135 V, collision energy (CE) -30 eV for BPA, -36 eV for BPA-d₁₆, and collision cell exit potential (CXP) -7 eV for BPA, -9 eV for BPA-d₁₆. The channel electron multiplier (CEM) was 2100 V, and source temperature was set at 600°C. Dwell time was 200 ms. Curtain gas was set at 20 PSI. Both Gas 1 (nebulizer gas) and Gas 2 (desolvation gas) were 50 PSI. CAD (collision gas) was 8 PSI. Multiple reaction-monitoring (MRM) in negative mode was used for quantification of BPA (227.1/133.1) and BPA-d₁₆ (241.1/142.1). Note that the deuterium atoms of the two hydroxy groups in BPA-d₁₆ are

exchangeable with the solvent once in methanol solution, therefore the precursor mass for BPA-d₁₆ in negative mode was 241.1 Da instead of 243.1 Da. Measurements were performed in duplicate and the results were averaged. The software program Analyst (Version 1.6.3) and MultiQuant (Version 3.0.2) were used to process the analytical data.

2.4 Statistical Analysis

Kruskal Wallis test was used to assess the difference in the amount of BPA release from the Invisalign[®], SmileDirectClub[®], and Essix Ace[®]. Friedman test was used to compare the amounts of BPA released between various time points. Statistical significance was set at 0.05. Statistical analysis was performed using IBM[®] SPSS Statistics (IBM, Armonk, NY).

3. Results

SmileDirectClub[®] aligners showed the least amount of BPA release in ethanol, followed by artificial gastric fluid, and the highest amount of BPA release in artificial saliva, with 5.0 ng/mL detected at T_F (Figure 1A). Peak BPA concentration in artificial gastric fluid occurred at T₆, with a value of 3.1 ng/mL. Invisalign[®] (Figure 1B) showed the highest release of BPA in ethanol at T₁₀ (9.2ng/mL). The highest BPA release in artificial saliva occurred at T₆ with a value of 3.5 ng/mL. Very little BPA was released in the artificial gastric fluid samples. The highest release of BPA in the Essix Ace[®] aligner group (Figure 1C) was seen in artificial saliva with 6.3 ng/mL at T₁₀. Peak BPA release in artificial gastric fluid occurred at T₁, with a value of 3.5 ng/mL. No significant difference in BPA concentration was found between the 3 types of aligners in the 3 media at each of the time points ($p > 0.28$, Kruskal Wallis test). When comparing time points, the difference in BPA concentration was significant ($p < 0.001$, Friedman test). Post hoc analysis revealed that this difference was due to the higher BPA concentration at T₁ compared to T₀. No difference was found between the remaining timepoints.

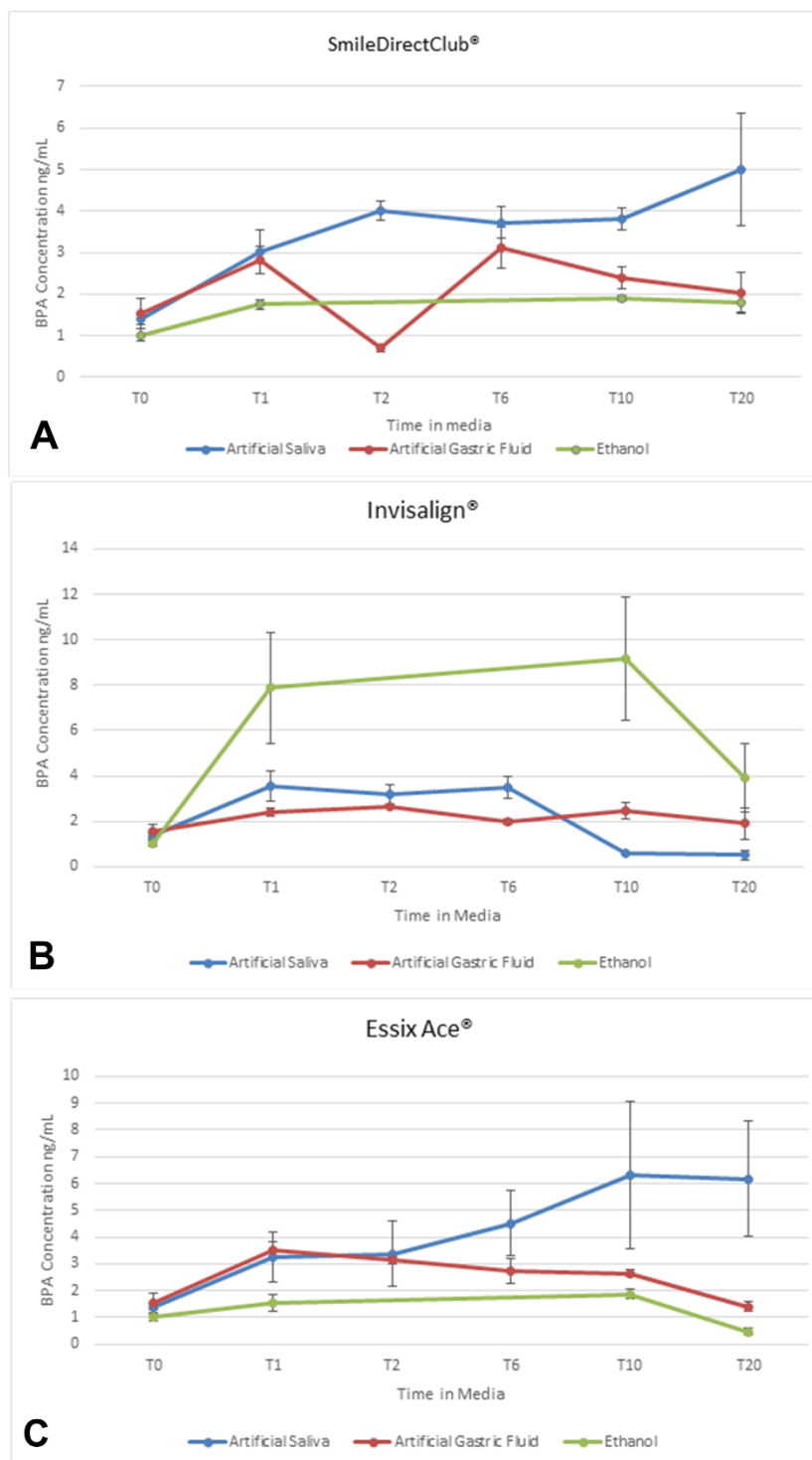


Figure 1 **A** SmileDirectClub® BPA concentration in artificial saliva, artificial gastric fluid and ethanol after 24hrs (T₁), 48hrs (T₂), 6 days (T₆), 10 days (T₁₀), and 20 days (T₂₀). Samples were analyzed using LC-MS/MS. **B** Invisalign® BPA concentration in artificial saliva, artificial gastric fluid and ethanol after 24hrs (T₁), 48hrs (T₂), 6 days (T₆), 10 days (T₁₀), and 20 days (T₂₀). Samples were analyzed using LC-MS/MS. **C** Essix Ace® BPA concentration in artificial saliva, artificial gastric fluid and ethanol after 24hrs (T₁), 48hrs (T₂), 6 days (T₆), 10 days (T₁₀), and 20 days (T₂₀). Samples were analyzed using LC-MS/MS.

4. Discussion

In this study we report on BPA release from three types of orthodontic aligners in three media: artificial saliva, artificial gastric fluid and ethanol. Although the three types of aligners are advertised as BPA-free, small amount of BPA was detected. On average, the aligners in this experiment released 3.6ng/ml (range 1.4-6.3) of BPA in artificial saliva with no difference between the three materials tested. Patients typically wear each set of maxillary and mandibular aligners for 1-2 weeks. The number of aligners needed vary by severity of the case, with most of the comprehensive cases requiring >60 sets of aligners. The average weight of one set of aligners is ~3.6 grams. Thus, according to our results, each set of aligners could potentially release ~1.8 µg (1851 ng) of BPA. Our results are lower than those reported by Kotyk et al [15], who reported, using gas chromatography/mass spectroscopy, ~7.6µg of BPA released from 1 g of Essix Ace® with great variability. They also investigated BPA release from Invisalign, reporting no-detectable value. While differences in sample preparation and the detection methodology between the two studies make comparison difficult, it suggests that more standardized studies are needed to assess BPA release from aligners. In this study we utilized LC-MS/ MS, while Kotyk et al used gas chromatography/mass spectroscopy.

In 2015, the European Food Safety Authority (EFSA) updated and reduced the threshold value for BPA intake to 4 µg/kg BW/day after conducting an exposure assessment. According to that report [12] the average daily intake of BPA amounted to 126 ng/kg BW/day among adults in Europe through diet, which is well below the threshold value for safety. Thus, the BPA released from aligners is well below the safety threshold established by the EFSA. However, a prevailing concern regarding BPA exposure is its ability to bind to the estrogen receptors α (ER α) and β (ER β), through which this endocrine-active substance may affect humans at doses below the presumably safe tolerable daily intake. Several studies have suggested an adverse endocrine disruptive effect by BPA at doses as low as 0.025-0.200 µg/kg/day, such as a decrease in daily sperm production and fertility in males at a dose of 0.2 µg/kg/day [13] stimulation of mammary gland development at 0.025-0.250 µg/kg/day [14, 16] and a decrease in antioxidant enzymes at 0.2 µg/kg/day [17]. In addition to these multi-system health effects being linked to BPA, there is evidence of transcription of proliferation and differentiation-related genes in response to low-dose BPA in activated ER β in oral keratinocytes, which are the first targets of BPA by oral intake [18] showed a sublingual absorption of BPA besides typical digestion, which shows that BPA can diffuse through oral mucosal tissues.

Aligners are typically placed in the oral cavity for 22 hours per day for 1-2 weeks to achieve gradual tooth movement. Once the aligner is passive, the patient moves to a new set of aligners. Aligners in the oral cavity undergo wear, cracking and distortion [19], which can potentially lead to BPA release and swallowing of small particles. The presence of BPA in the saliva of patient wearing either Hawley or Essix Ace retainer was investigated by Raghavan et al. [20]. They reported higher BPA in the saliva of the patients wearing the Essix Ace® retainer 1 hour and 1 week after using the retainers, the values sharply decreased afterwards. While comparing the values reported to those in our study is complicated by the differences in methodology, their findings suggest that BPA released from aligners is absorbed systemically. Eliades et. al. [21] reported on the in-vitro cytotoxicity and estrogenicity of Invisalign® appliances on cultured human gingival fibroblasts. Although their results show minimal effects of Invisalign, the level of BPA used in their study was

not reported. Future studies will need to assess the effects of BPA in dose dependent manner and under *in vivo* conditions that closely resemble the clinical application of the aligners.

The three types of aligners chosen for use in this study were Invisalign®, which is probably the most widely known brand of clear aligner, SmileDirectClub®, a popular direct-to-consumer clear aligner brand, and Essix Ace®, which is commonly used to provide in-house clear aligner therapy. All three types are made with thermoformed plastic on digitally printed resin models and delivered to the patient, who places them in the oral cavity. The three types of media chosen for this experiment were artificial saliva, artificial gastric fluid, and pure ethanol. Clear aligners are subjected to heavy masticatory forces increasing the likelihood that small particles of the plastic are accidentally ingested. We wanted to see if contact with artificial gastric fluid and the highly acidic environment influenced BPA release. Interestingly, there was less BPA released in artificial gastric fluid than in artificial saliva, indicating that there could be a positive correlation between acidity and stability. Ethanol was added to the media set because BPA is soluble in organic solvents and we wanted to determine whether consumption of alcoholic beverages can affect BPA release from aligners. Clinicians instruct their patients not to eat or drink with the aligners in their mouths but compliance varies widely. While a trend for higher BPA release was seen in Invisalign® group, the differences did not reach statistical significance.

There is increasing interest in the adverse effects of fetal exposure to BPA due to its ability to pass through the placenta from mother to baby, and the low endogenous concentration of UDP-glucuronosyltransferase (UGT) in a fetus [1]. Liver UGT activities have an important effect on the removal and detoxification of BPA. UGT in the human fetal liver is present at a concentration five-fold lower than in the adult liver, posing a much higher risk of exposure [1]. In addition, BPA that is removed via fetal UGT is excreted in the urine, increasing the concentration of BPA in amniotic fluid and prolonging exposure [22]. The highest concentrations of BPA have been recorded in the placenta and fetus, with values ranging from 1 to 104 ng per gram of tissue [23]. Fetal exposure to BPA has been linked to obesity, behavioral and mood disorders, cognitive impairment, and sex-specific alterations to the reproductive system [24, 25]. Because women of child-bearing age constitute a major user of clear aligners [26, 27], extra precautions should be taken to reduce exposure to BPA. One of the interesting findings of this study was that most of the BPA release happened during the first 24 hours following incubation. This is comparable to Raghavan et al (2017), who reported sharp increase of BPA in saliva 1 hour after the patient wearing the Essix Ace® retainer. While the limited time points in both studies prevent definitive conclusion, they suggest that most of the BPA release occur within the first 24 hours of wearing the aligners. Thus, a simple activity such as rinsing the aligners or soaking them in deionized water before wearing could significantly decrease exposure.

Our study suffered several limitations, and the clinical implications need to be interpreted with care. First, the study was done *in vitro*. In the oral cavity, constant flow of the saliva might help increase the elimination rate of BPA, limiting its clinical impact. Nonetheless, the presence of BPA in orthodontic aligners suggests that further studies are needed to determine their biologic impact especially in vulnerable population such as pregnant females. Another limitation is the extended time intervals for BPA detection. Initially, we expected that the BPA release will be extended over period of days and the time points were designed accordingly. Surprisingly, most of the BPA release was seen at the first time point (24 hrs). Future studies should assess the BPA release on hourly rather than daily basis as the acute release might result in more impact on the body. Our study was

further affected by our limited knowledge of the plastic fabrication and, except for the in house aligners, the aligners' fabrication. Careful observation of the fabrication process will help to determine whether reduction of the BPA content in the aligners are feasible. We attempted to investigate the products as received by the patient to determine whether the products are clinically safe. Future studies will need to collaborate with the manufacturers to determine the effects of various manufacturing parameters on the final BPA release from the aligners.

5. Conclusions

- There is potential BPA release from the three types of orthodontic aligners investigated
- The amount of BPA released is well below the established safety levels for adult patients
- There was no significant difference in the amount of BPA released between the three sets of aligners in each of the three media.
- The majority of BPA release occurred during the first 24 hours of embedding the aligners

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Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table I: BPA release from SmileDirectClub®, Invisalign®, and Essix Ace® in artificial saliva.
2. Table II: BPA release from SmileDirectClub®, Invisalign®, and Essix Ace® in artificial gastric fluid.
3. Table III: Mean BPA levels (ng/mL) released from orthodontic clear aligners at different time points in ethanol.
4. Figure IIA: BPA release from SmileDirectClub®, Invisalign®, and Essix Ace® in artificial saliva.
5. Figure IIB: BPA release from SmileDirectClub®, Invisalign®, and Essix Ace® in artificial gastric fluid.
6. Figure IIC: Mean BPA levels (ng/mL) released from orthodontic clear aligners at different time points in ethanol.

Author Contributions

Dr. Katras conceived and designed the experiment, performed the experiment, and collected the samples. Dr. Ma prepared the samples, conducted the liquid chromatography tandem mass spectroscopy measurements, and wrote the sample preparation and LC-MS/MS section of the paper. Drs. al Dayeh and Katras performed statistical analysis, interpreted the results, created the graphs and figures, and wrote the manuscript, with the exception of Dr. Ma's contribution. Dr. Tipton provided guidance and insight throughout all stages of the experiment and writing of the manuscript.

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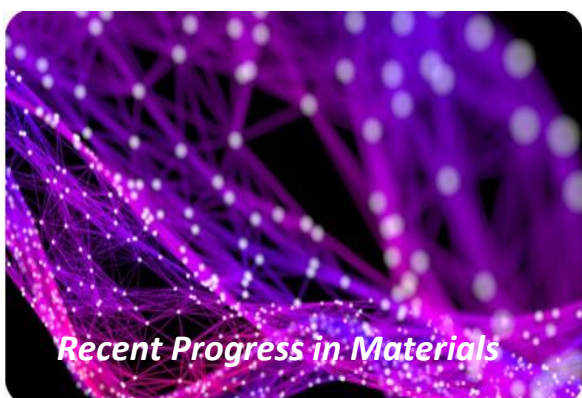
Competing Interests

The authors have declared that no competing interests exist.

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