Development of Biocompatible Resins for 3D Printing of Direct Aligners

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The objective of this study was to develop biologically compatible resins with optimum safety profiles and physical properties that can be used for long periods inside the mouth, and to attempt to use these resins in a 3D printing process to produce direct aligners for use in mouthpiece orthodontics. Low toxicity water-soluble monomers (1M) were used to develop 3D printer-compatible biocompatible resins (polymers) that have no skin reactivity, carcinogenicity, or reproductive toxicity. Cytotoxicity testing (LDH test), proliferation testing (WST1 test), and mechanical testing were also performed. We attempted to use these resins to produce direct aligners. We successfully produced acrylic-epoxy hybrid light-curing resins that have optimal safety profiles composed of water-soluble monomers alone. The results of cytotoxicity testing and proliferation testing showed that all the water-soluble monomers used for 3D printing (3D-1M) exhibited low cytotoxicity, but the cell survival rates suggested that the composition ratio of the raw materials may be an issue. The results of mechanical testing demonstrated that the 3D-1M met the mechanical strength requirements for base polymers used in orthodontics. We successfully produced direct aligners using these biocompatible resins. However, their middle sections were fragile, suggesting that their physical properties must be improved if they are to be used in aligners. We intend to improve the mechanical properties of these monomers, and perform safety testing for approval as Class-II controlled medical devices.

Keywords: 3D printer, CAD/CAM, Orthodontics, Aligner, Biocompatible resin

1. Introduction

In recent years, 3D printers have become widely applied in medicine [1–5]. Three-dimensional digital data obtained from X-ray CT and MRI equipment potentiate simulations utilizing 3D biological models, allowing for the planning and execution of safer surgical procedures [6,7].

Data digitization through computer aided design (CAD)/computer aided manufacturing (CAM) has been applied in the field of digital dentistry. Digitization has also introduced new trends for general prosthetic treatment [8–10]. In traditional prosthetic treatment, dental models are produced, and prosthetics are created with the aid of technicians upon dental impression and bite registration obtainment. However, Duret proposed a manufacturing system for crown bridges utilizing optimal impressions in 1971 [11]. Furthermore, in 1985, Mörmann and colleagues from Switzerland successfully developed the CEREC system (Siemens AG, Germany) through successful application with ceramic inlays [12]. The CEREC system allows for shortening of the manufacturing process spanning obtainment of cavity optical impressions from the chairside, the cutting of ceramic blocks, and preparation of inlays, onlays,
crowns, and laminate veneers with ample clinical applicability [13]. The inclusion of CAD/CAM crowns for premolars (in 2014) and some molars (in 2016) into the National Health Insurance coverage further increased the demand for these new systems.

Similarly, CAD/CAM has been applied in orthodontics. Given that many people are uncomfortable with wearing orthodontics in Japan, they forgo orthodontic treatment or would undergo treatment only if the orthodontics are less noticeable. Thus, in recent years, less obtrusive orthodontic mouthpieces have been developed for clinical use. These are treatments using custom-made transparent and detachable aligner-shaped orthodontics. The merits of mouthpiece orthodontics are that they are less noticeable, they can be removed for facilitated plaque control, they can be used for patients with metal allergies, and they do not require bracket bonding, wire bending, and ligation, allowing for easy application by non-orthodontists. In 1997, the Invisalign System [14,15] was developed as an application of the CAD/CAM technology for aligner orthodontics production (Fig. 1). The Invisalign mouthpiece is customized and tailored to each patient based on 3D data obtained from comprehensive examinations. Using the 3D simulation software ClinCheck (Fig. 2), the orthodontist composes a treatment plan on the computer screen and determines the required numbers and shapes of aligners over the duration of the treatment. All aligners are then manufactured at the same time prior to treatment initiation, which was an unprecedented manufacturing process at the time. Aligners are produced by first using a 3D printer to create 3D dental models based on the treatment plan. Subsequently, aligner sheets are shaped via suction molding of the 3D dental model, and this sheet is further cut out by a robot and polished. The produced aligners are individually packaged for each 2-week step in the treatment plan and are delivered in approximately 4–6 weeks. In 1998, the US Food and Drug Administration (FDA) approved Invisalign as a medical device, which was introduced in the US in 1999 and in Europe in 2001. Thereafter, Align Technology Japan was launched in 2002, resulting in the official commercialization of Invisalign in Japan starting in 2006. As of August 2018, in Japan, mouthpiece orthodontics other than Invisalign utilizing CAD/CAM technology have been widely used including TRANSCLEAR (GC ORTHOLY), ASO Aligner (ASO International), and Clear Aligner (Wada Precision Dental Laboratories). However, modern day aligners are manufactured via thermoplastic resin molding of dental models produced by 3D printers. If the aligners can be directly produced with a 3D printer (hereafter direct aligner), this breakthrough will improve the efficiency of the manufacturing process along with introducing flexibility to their shapes and thicknesses. However, light-curing resins used in existing 3D printers are brittle and are not well suited as materials for aligners. Furthermore, they comprise bisphenol A and lipid-soluble heavy metal antimony compounds, and are thus a biohazard triggering skin and mucosa irritation. If the safety concerns and physical properties of the resins are resolved, these aligners can be directly manufactured using 3D printers.

![Fig. 1. Unobstrusive orthodontic aligner produced by Invisalign®.](image1)

![Fig. 2. Screenshot showing the ClinCheck® software interface.](image2)

In the present study, we developed biocompatible resins with optimal safety profiles and physical properties that can be inserted in the mouth for a long time and attempted to manufacture direct aligners. The biocompatible resins are made of materials conforming to ISO10993 (biocompatibility) and can be installed in a 3D printer. In Japan today, ingredients are biocompatible if they can be used for skin contact (over 30 days) and short-term mucosa contact (up to
Therefore, only devices such as the dental implant surgical guides for short-term use in the mouth are biocompatible, and no biocompatible resins exist for aligners and other orthodontics that remain in the mouth for over 24 h.

2. Experimental

2.1. Development of biocompatible resins for 3D printing

In the present study, we used water-soluble monomers with confirmed safety data sheet (SDS) information and a median lethal dose (LD50) of over 2,000 mg/kg to develop 3D printer-compatible biocompatible resins (polymers) that have no skin reactivity, carcinogenicity, or reproductive toxicity. Table 1 shows a comparison of the SDS values for the resin in the present study developed by Okamoto Chemicals (3D-1M) and existing 3D printer resins. Since the polymerization of monomers (resin formation) is distinct from chemical reactions, no changes are made to the basic structure or the additive properties of the polymerized components (compound properties are equivalent to the sum of the individual components). While some exceptions exist, we proceeded with development by individually testing for cellular toxicity.

As the selection criteria for monomers revolved around safety, we used epoxy resins for tensile strength and toughness and supplemented this low-sensitivity light-curing resin with highly sensitive acrylic monomer photoreactions as a general approach.

2.2. Cellular toxicity (LDH-Test) and proliferation (WST1-Test) studies

Cellular toxicity experiments measured cytotoxicity with the LDH-Test, and cellular proliferation experiments measured cell survival with the WST1-Test. Samples were treated with Okamoto Chemical manufactured 3D printer resin (3D-1M: 1,2,A-D) and the negative and positive indicator polyethylene films. Samples 1,2,A-D were different in the composition ratios of the individual components. Both LDH-Test and WST1-Test were

| SDS Information | Okamoto Chemicals Resin (3D-1M) | NextDent (Ortho Rigid) | Detax (Freeprint ortho) | Stratasys (MED610) |
|-----------------|---------------------------------|------------------------|------------------------|-------------------|
| Low Risk        | • Skin irritation                | • Skin irritation       | • Skin irritation       | • Toxic when swallowed |
|                 | • Toxic for aquatic organisms   | • Flammable liquid and gas |                       | • Can cause skin allergic response |
|                 |                                 |                        |                        | • Respiratory system irritation |
| High Risk       | • None                          | • N/A                  | • N/A                  | • Severe eye damage |
|                 |                                 |                        |                        | • Organ damage |
|                 |                                 |                        |                        | • Very high toxicity to living organisms |

**Table 1. SDS Information.**

| Oral Toxicity LD<sub>50</sub> | >2,000 mg/kg High safety | • N/A | • N/A | • 1,314 mg/kg |

| Biocompatibility | — | IIa(EU) | IIa(EU) | IIa(EU) |
conducted at 24 h and 72 h timepoints at 37 °C and 5% CO₂ culture conditions.

2.3. Mechanical experiments
We evaluated bending strength, bending modulus, Izod impact strength, heat deflection temperature, water absorption rates, and water solubility of the Okamoto Chemical resin (3D-1M:1) for mechanical experiments. We used existing Ortho Clear data from NextDent for comparison.

2.4. Attempt to manufacture direct aligners
In this study, we used stereolithography (DLP based) in our study. Specifically, we designed 0.7 mm, 1.5 mm thickness aligners based on dental models using dental CAD software (exocad GmbH, Germany). We used the biocomposite resin (3D-1M, Okamoto Chemicals) to manufacture direct aligners using DLP 3D printers (MiiCraft 125, Young Optics Inc., Taiwan) (Fig. 3). MiiCraft125 is a bottom-up format 3D printer with 405-nm wavelength, 2 mJ/cm² energy usage, 65-μm XY resolution, and 125 × 70 × 120 mm model volume. This printer type emits high levels of energy allowing for curing of materials in a short amount of time. Water soluble epoxy hybrid resins require approximately 5 times the amount of energy used for general DLP-based materials, lengthening the manufacturing process and potentially leading to productivity issues. This printer type contains a high energy light source allowing for efficient curing of materials and maintenance of productivity.

3. Results
3.1. Development of biocompatible resins for 3D printing
We succeeded in the production of acrylic-epoxy hybrid light-curing resins that have optimal safety profiles composed of water-soluble monomers alone (Patent 6042523).

3.2. Cellular toxicity (LDH-Test) and proliferation (WST1-Test) studies

Fig. 3. DLP 3D printer (MiiCraft 125, Young Optics Inc., Taiwan).

Fig. 4. Results for cellular toxicity (LDH-Test) and proliferation experiments (WST1-Test).
The results of cellular toxicity (LDH-Test) and proliferation (WST1-Test) experiments for the developed 3D-1M resin (1,2,A-D) are shown in Fig. 4. PK is a negative indicator (no cellular toxicity) whereas NK is a positive indicator (has cellular toxicity). All LDH-Test results with 3D-1M showed equal levels of toxicity as PK for 24 and 72 h culture timepoints. On the other hand, WST1-Test results showed low values for 1,D at the 24 h timepoint and for 1,A,D at the 72 h timepoint.

3.3. Mechanical experiments

Results for mechanical experiments for 3D-1M:1 and NextDent (Ortho Clear) along with the requirements of ISO20795-2 for base polymers used in orthodontics are shown in Table 2. Based on the data, 3D-1M:1 adhered to the requirements set forth by ISO20795-2.

Table 2. Mechanical experiment results.

|                        | Okamoto Chemicals (3D-1M: 1) | NextDent (Ortho Clear) | Requirement ISO 20795-2 |
|------------------------|-----------------------------|------------------------|-------------------------|
| Bending Strength (MPa) | 96.2                        | 70                     | ≥ 50 MPa                |
| Bending Modulus (MPa)  | 3,110                       | 1,596                  | ≥ 1,300 MPa             |
| Izod Impact Strength (J/m) | 39                        | –                      | –                       |
| Heat Deflection Temperature (°C) | 51.5              | –                      | –                       |
| Water absorption rate (μg/mm³) | 12                     | 58                     | ≤ 65 μg/mm³             |
| Water solubility (μg/mm³) | 2                          | 4.6                    | ≤ 5.0 μg/mm³            |

3.4. Attempt to manufacture direct aligners

Direct aligners were manufactured using the DLP 3D Printer by using the resin material 3D-1M:1 (Fig. 5). As a result, we succeeded in manufacturing aligners with thicknesses of 0.7 mm, 1.5 mm. However, upon application of pressure from various angles, we found that they were particularly fragile at the middle position.

4. Discussion

4.1. Development of biocompatible resins for 3D printing

In the present study, we used water-soluble monomers with confirmed safety data sheet (SDS) information and a median lethal dose (LD50) of over 2,000 mg/kg to develop 3D printer-compatible biocompatible resins (polymers) that have no skin reactivity, carcinogenicity, or reproductive toxicity. As a result, we succeeded in manufacturing acrylic-epoxy hybrid light-cured resin for 3D printing using water-soluble monomers alone with optimal safety profiles (Patent 6042523, Patent Publication 2018-076455). Given that epoxy monomer photoreactions are slower than those of their acrylic counterparts and the relatively high-sensitivity antimony photoinitiators were not used in this study, we creatively combined epoxy monomers to make their photoreactions more sensitive. Furthermore, we found that the combination of epoxy and acrylic monomers along with photoinitiators results in a higher sensitivity (in this case epoxy resin photosensitivity) and tensile strength than each component alone. Defining sensitivity is
challenging but for the current study, we compared sensitivities corresponding to the solidification of a 200 μm surface on top of a 2 mm coating. The sensitivities of the epoxy monomer alone, the acrylic monomer alone and the epoxy-acrylic hybrid resin were 550, 20, and 400 mJ/cm², respectively. Therefore, while compounds displaying optimal safety profiles lacked in sensitivity and physical properties, we found that safety, sensitivity, and physical properties can all be satisfied by reevaluating combinations of monomers and photoinitiators.

4.2. Cellular toxicity (LDH-Test) and proliferation (WST1-Test) studies

The light-cured resins required in the creation of objects by DLP-based and other 3D printers contain bisphenol A, antimony, isocyanate, and other biohazardous substances. There are particular concerns about the effects of bisphenol A on infants and young children [16,17]. In the present study, we used water-soluble monomers with confirmed safety data sheet (SDS) information and a median lethal dose (LD50) of over 2,000 mg/kg to develop 3D printer-compatible biocompatible resins (polymers) that have no skin reactivity, carcinogenicity, or reproductive toxicity. Cellular toxicity (LDH-Test) and proliferation experiments (WST1-Test) results show that all 3D-1M samples show low cytotoxicity, but certain composition ratios of raw materials could affect cell survival. Because the biocompatible resins developed in this study do not contain bisphenol A or other hazardous substances, they could potentially be used in dentistry as 3D-printer light-cured resins. However, a few issues still remain, and further improvements are required to develop materials that do not cause problems with cell proliferation.

4.3. Mechanical experiments

The Japanese Industrial Standards (JIS) and the International Organization for Standardization (ISO) have produced standards for orthodontic base polymers (JIS T 6528, ISO20795-2), but there are no standards for materials for use as orthodontic aligners. To meet the specifications of ISO20795-2, the base polymers used for orthodontic devices must have flexural strength of at least 50 MPa and a flexural modulus of at least 1,300 MPa (1.3 GPa). In a study of orthodontic device biocomposite resins for use with 3D printers, Kakami [18] stated that despite the large amount of water absorption, the mechanical properties were considered to be sufficient for use as a Hotz plate.

In this study, mechanical experiment results demonstrate that 3D-1M satisfied orthodontic base polymer requirements for mechanical properties. However, their mechanical characteristics and safety must be confirmed before they can be used for aligner-type orthodontic devices. Our results suggested that further studies are required to establish their safety by assessing the mechanical properties of existing aligner-type orthodontic devices and conducting comparative studies.

4.4. Attempt to manufacture direct aligners

Currently available commercial 3D printers include fused deposition modeling (FDM), material jetting, powder sintering, and stereolithography (laser based/SLA and DLP based) [19,20]. FDM involves melting thermoplastic resin (mainly ABS), pushing it out from the nozzle, and depositing the resin to build the model. It is generally associated with high durability and heat resistance, and thus is suitable for the construction of prototypes, jigs, and simple structures. However, since it is formed by the melting and deposition of resin, layer boundaries are noticeable, so it is not particularly suitable for models that require smooth surfaces. Material jetting involves the UV-curing of acrylic resins sprayed from inkjet heads. It is particularly useful for applications requiring accuracy such as the construction of high-resolution, smooth surface models. Based on the printer type, one can mix various materials of choice. However, the use of UV-cured resin means that the completed model often deteriorates under sunlight. Development is particularly challenging since one cannot use highly polymerized and viscous material. Powder sintering involves laser sintering of powdered thermoplastic resin of 25-μm particle size. This format allows for the manufacturing of high-resolution and highly durable models, and since one can use metallic components, it is well suited for the manufacturing of the final product and casting. The product surface is often rough and grainy, so it requires several steps before finalization in comparison to UV-curing resin types. Given the lack of support, heavy products can often sink so one needs to take caution in the weight and the manufacturing process of the product. Upon completion of manufacturing, the product can be gradually cooled to prevent shrinking. Cooling time is 24–48 h on average. Carbon dioxide or electron lasers of 50–100 W power are used and galvano mirrors are used for
printing. Manufacturing takes place in a nitrogen-filled chamber requiring a nitrogen generator. Given the use of powdered material, one needs to create an environment suitable for this purpose which adds operation and maintenance costs. Transparent components cannot be manufactured. Stereolithography (Laser based/SLA) involves building each layer at a time by shining 365-nm wavelength UV laser on one-component light-curing epoxy resins. This type of 3D printing allows for the creation of high resolution smooth surfaced models. By using an Fθ lens, a large area can be printed using a spot size of the same diameter, potentiating creation of large models in one step. However, keeping approximately 100–300 kg light-curing resins in large containers at a constant temperature of 25–30 °C is a particularly poor storage condition for UV-curing resins. Therefore, one needs to be cautious of change over time under these conditions during development. Stereolithography (DLP based) involves shining light using a projector from under the UV-curing resin one layer at a time. The DLP system is rapid in comparison to laser exposure formats given the fact that the resin is cured in both the XY directions at once. The product is made with high accuracy with a high-resolution structure and distinct edges. The range of model sizes is limited by the resolution of the DLP chip, so scaling up using this method is difficult. Material is used as needed to the model so long-term storage of these materials is relatively easy. Given its low energy requirement, the DLP system is energy-efficient and does not require specific environments for production and replaceable parts are cheap allowing for lower maintenance costs.

In the present study, we attempted to manufacture direct aligners via 3D printers that create high resolution, high accuracy structures with distinct edges (DLP stereolithography). However, the middle section was particularly fragile and requires further improvement in physical properties to successfully be used as aligners.

5. Conclusion

We succeeded in developing biocompatible resins for 3D printers that do not use materials toxic to humans and the environment. We further succeeded in manufacturing direct aligners.

In the future, we plan to improve mechanical properties in such a way that both strength and flexibility are maintained. Furthermore, we plan to perform safety experiments required for approval by the Pharmaceutical Affairs Act as a Class-II controlled medical device.

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