Seminars in Orthodontics 000 (2024) 1−5

Contents lists available at ScienceDirect

Seminars in Orthodontics

journal homepage:

Unlocking the biological insights of 3D printed aligners: A look at current findings

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A R T I C L E I N F O

Keywords:
Digital orthodontics
3D printing
Clear aligners
Direct printed aligners
Future perspectives

A B S T R A C T

Direct Printing and Direct Printed Aligners (DPAs) are poised to revolutionize contemporary orthodontics and aligner therapy. DPAs made from Graphy's resin (Tera Harz TC-85, Graphy Inc, Seoul, Korea) are currently the only ones being CE and KFDA certified as well as FDA approved. The use of DPAs entails several advantages including increased efficiency of tooth movements due to customized pressure points or zones, a better fit and precision of the clear aligners as well as the ability to produce a wide range of different removable orthodontic appliances in-office. However, biocompatibility and thus safe use is dependent on strict adherence to the production guidelines given by the manufacturers. Alterations to the delicate manufacturing process, involving multiple production as well as post-curing steps, may lead to undesired side effects such as allergic reactions which can be as severe as an anaphylactic reaction. In particular, the vast variety of possible custom-design DPAs poses the risk of exposing patients to cytotoxic materials. Therefore, more research is needed to guarantee patients biological safe use. The latter must also be an orthodontist's major responsibility, particularly when treating children as well as adolescent patients who are still in their developmental stages.

Introduction

Orthodontic therapy has historically relied on traditional methods like removable and fixed orthodontic appliances as well as clear aligners to correct malocclusion. The latter are considered to be more comfortable and hygienic as well as more aesthetically appealing when compared to fixed orthodontic appliances and, thus, represent an increasingly popular treatment method among both orthodontic patients and practitioners.[1,2,3,4] Originally developed for the treatment of simple cases, the clear aligners' constant development continuously increases their spectrum of indications allowing to successfully treat more and more complex cases.[5,6] Its patient population grew considerably over the years: Initially, exclusively recommended for adults, their application has broadened to include an increasing number of teenagers in the mixed dentition and even treatments in early childhood, demonstrating successful outcomes.[4] Traditionally, the clear aligners have been produced in a thermoforming process and are composed of materials like polyurethane, polyethylene terephthalate, polyethylene glycol terephthalate and polyvinyl chloride (TFAs).[7,8]

3D printing represents a relatively new, but rapidly growing and constantly improving process that is expected to revolutionize many orthodontic treatment approaches.[7,8] Due to its increasing popularity and thanks to technological advances, particularly in biomaterials, computer-aided design as well as manufacturing technologies, it is now possible to manufacture direct to print aligners (DPAs) in-office.[9] The extensive history of clear aligner technology, beginning with Kesling's introduction of the tooth positioner in 1945, combined with over 25 years of clinical experience using TFAs (Invisalign®, Align Technology, Santa Clara, CA, USA), has established a solid foundation for the development, application and advancement of DPAs.[10] Digital Light Processing (DLP) is a common printing process, in which liquid resins are selectively light-cured in the 3D printer and appliances are created by photopolymerization.[11] The workflow for designing and printing clear aligners involves intricate steps that must be carefully executed to avoid errors[9,10]: Following intraoral scanning, the quality of which is crucial for accuracy as it directly influences the fit of the DPAs, the generated STL files are imported into orthodontic CAD software.[10] Here, model orientation and model base design as well as segmentation are performed.[10] Furthermore, tooth movements, attachment placement and the virtual design of the aligners are performed.[10] Whereas the initial aligner is designed using drawing tools, all subsequent aligners are automatically generated by the software based on the prescribed tooth movements[10]. Once the design is complete, the virtual aligners are exported and arranged on a virtual platform for 3D printing (Fig. 1).[10]

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https://doi.org/10.1053/j.sodo.2024.10.001

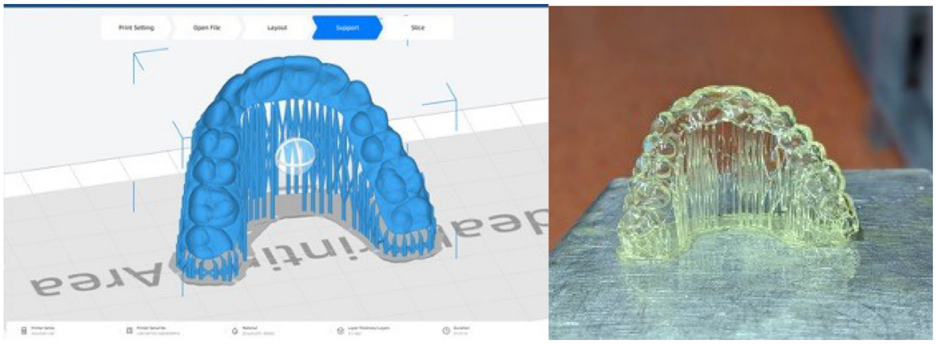

Fig. 1. Digital setup created design & printed DPA with supports

They can be oriented horizontally, vertically or diagonally, with each orientation affecting printing speed, the number of aligners produced as well as the risk of printing failure.[10] A slicing software, which is often provided by 3D printer manufacturers, is then used to add support structures.[10] Printing of the DPAs is recommended in an oxygen-free environment as oxygen is known to inhibit polymerization which, in turn, might affect the DPAs' mechanical properties.[10] After successful printing excess resin is removed by centrifugation which lasts about 6 minutes at 600 rpm.[10] Support structures are manually removed after centrifugation and UV curing takes place.[10] The manufacturer recommends UV curing for 14 minutes using the Graphy Cure THC 2 (Graphy Inc., Seoul, South Korea) in a 95% nitrogen atmosphere.[10] Finally, the DPAs are washed in boiling water for 2 min and polished with rotational brushes.[10] It is important to note that only the finished and ready-to-use DPAs and not the material (Tera Harz TC-85, Graphy Inc, Seoul, Korea) sold by the company itself are certified and approved for patient use. Thus, the orthodontist is the legally accountable person. This fact must be critically reflected, particularly due to the highly precise and susceptible post-processing procedure mentioned earlier.[9] According to the manufacturer Tera Harz TC-85 meets the requirements necessary for dental and orthodontic applications and its biocompatibility was confirmed in several studies.[12,13,14]

Advantages of direct printed aligners

DPAs are expected to transform clear aligner production in the future as they provide several advantages compared to vacuum forming methods: These include a better precision, fit, effectiveness, mechanical resilience and reproducibility.[8,15] Direct 3D printing offers the potential to reduce processing times while simultaneously allowing for customization of aligner properties such as layer thickness or tray dimension.[16] Individual pressure points or zones improving the efficiency of the desired tooth movements as well as enhancing anchorage can be designed.[15] According to Grant et al., adaptations to the labiolingual thicknesses of the DPAs can be used to improve prescribed tooth movements, increase predictability and reduce side effects.[17] This can be achieved by increasing the DPA's thickness on the side of the tooth that trails its intended movement while increasing it on the opposite surface of adjacent teeth.[17] The treatments of open and deep bites with DPAs could also be assisted by adding additional material on the occlusal surfaces of the posterior teeth or the palatal surface of the upper incisors respectively.[10] Thus, the ability to vary the DPA's thickness in different areas should be considered as one of the key advantages when compared to conventional thermoformed aligners. Furthermore, it may enable the reduction of necessary attachments or even allow for attachment-free treatments, which in turn reduces chairside time as well as further improves aesthetics during the entire treatment itself. However, additional research is necessary to allow valid assumptions. Increased efficiency and predictability of prescribed tooth alignments are also facilitated by a greater trueness and precision of the DPAs resulting in a more accurate fit when compared to their thermoformed counterparts.[18] Furthermore, Hertan et al. observed significantly lower and more consistent forces compared to TFAs.[19] Their research indicates that the forces exerted by DPAs are more consistent with the optimal range for orthodontic tooth movement, delivering controlled and biologically compatible forces.[19] This may represent a potential advantage over TFAs.[19] Due to their flexibility and viscoelastic properties, DPAs can also maintain more constant orthodontic forces showing less force decay from repeated insertion and removal over time.[20] Can et al.'s analysis demonstrated no significant changes in the mechanical properties of DPAs following one week of intraoral use, indicating their short-term durability.[21] In contrast, it has been observed that conventional thermoformed aligners (Invisalign®, Align Technology, Santa Clara, CA, USA) show a loss of 50% of their mechanical properties after one week of intraoral use.[10] Additionally, the material demonstrates excellent shape memory properties, suggesting it can recover its original shape after deformation.[20] This could be beneficial for maintaining effective orthodontic force in clinical applications.[20] Graphy's Tera Harz TC-85 further showed superior geometric stability at higher temperatures, indicating potential advantages in clinical practice for hygiene and fit.[20]

We propose that the flexibility in aligner design, which enables the virtual design and subsequent 3D printing of a diverse range of removable orthodontic appliances, represents the second key advantage of DPAs: Functional orthodontic appliances (FOA), similar to the Twin-Block, in which a major increase in layer thickness is used to design thick posterior bite blocks to allow successful Class II treatment, as well as other Class II mechanics comparable to the Mandibular Advancement (MA) tool (Invisalign®, Align Technology, San José, CA, USA) are only two examples to be named (Fig. 2). The effectiveness of these biomechanics has to be carefully evaluated in future research. The production of drilling templates represents a further area of application.

Furthermore, DPAs eliminate the reliance on external third-party manufacturers as the whole manufacturing process can be carried out in-office by the clinician or their technical staff.[9] The number of necessary manufacturing steps is also reduced, shortening the duration of the entire planning and production process.[10] We believe that this also leads to an increased gross revenue. Appliances can be provided to patients much quicker – a factor that, in our opinion, may improve patients' satisfaction and compliance as well as showing marketing benefits.[10] However, it is crucial for orthodontists who serve as manufacturers to assume full responsibility for both the therapeutic outcomes and the biologically safe use of the self-fabricated DPAs in patients. Previous research has demonstrated that the mechanical behavior of DPAs is influenced by the specific 3D printer used.[22] Zinelis et al. observed significant differences in Martens hardness, indentation modulus and elastic index depending on the 3D printer used[22]. Their study comprises five different 3D printers, encompassing both LCD as well as DLP technologies.[22] Generally, DPAs produced by LCD printers demonstrated superior mechanical properties. DPAs' mechanical properties seem highly operator-dependent, depending on the choice of 3D printer and closely related

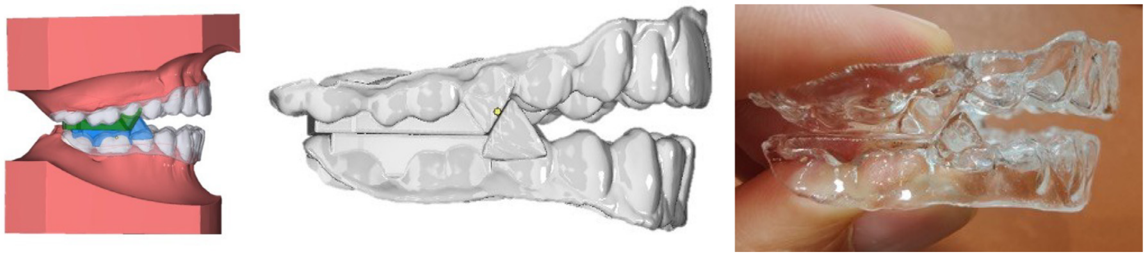

Fig. 2. Example of posterior bite blocks comparable to the MA tool

to the specific production procedures used. This dependency likely extends to the biocompatibility of DPAs, which needs to be investigated in future research projects.[22] 3D printing, as an additive process, generates significantly less waste compared to vacuum forming methods because there is no need to print models that are discarded after thermoforming.[10] From our perspective, particularly complex cases can be strategically planned in phases, while continuously monitoring and adapting new sets of DPAs to the precise intraoral conditions. This may reduce the number of refinements and unnecessary manufactured clear aligners. The entire manufacturing process could be considered significantly more sustainable as well as environmentally friendly - a factor of considerable importance in our modern society.

Concerns and limitations

Biocompatibility is particularly important as obligatory long wearing times of 22 hours per day imply continuous contact of the DPAs with the oral environment including teeth, gingiva and intraoral fluids.[7] In addition, the initial high release flux is continuously sustained throughout the orthodontic treatment, as clear aligners are replaced every 7 to 14 days, making biological safety even more important compared to other dental applications.[7] Consequently, the biocompatibility of the plastic materials used for clear aligner production is an essential requirement and of great importance to prevent undesired side effects such as previously described oral mucosa irritation.[14]

In our clinical experience, we encountered a case of a severe allergic reaction that required hospitalization of the affected patient. For clear aligners produced by thermoforming polyurethane films on 3D printed personalized dental models, there already exist numerous studies on biocompatibility.[23-26] Interestingly, all of these materials exhibit a slight cytotoxicity, which is amplified during the thermoforming process.[24,25] The lack of data concerning DPAs was addressed in a review published by Tartaglia et al., in which TFA's and DPA's technical data and cytotoxicity were compared among other things: As Graphy's Tera Harz TC-85 was not yet on the market at the time of publication, the DPAs included were Accura 60 SLA (3D System) and E-Guard (Envision TEC), both of which are used for retention purposes and not active tooth movements.[8] Their cytotoxicity ranged from slightly to severe.[8] However, the growing interest in DPAs and Graphy's Tera Harz TC-85 has led to further research studies over the past two years that have also been evaluating their biocompatibility, focusing particularly on factors such as cytotoxicity and estrogenicity[12,13]: Here Pratsinis et al. detected neither cytotoxic effects, nor any estrogenic activity and thus suggested good biocompatibility.[13] Nevertheless, the authors acknowledged limitations to their study design such as the inability to fully simulate the oral environment, pointing towards the need for further research.[13] Campobasso et al. also confirmed high biocompatibility and no cytotoxicity, when the manufacturer's protocol is precisely followed.[12] An altered post-curing protocol, however, led to moderate cytotoxicity.[12] Iodice et al. detected that the cytotoxicity of DPAs made from Tera Harz TC-85, regarding fibroblast growth, is comparable to that of Zendura FLX (ZenduraDental, Fremont, United States) which represents a well-established material for TFAs.[14] Furthermore, prolonged UV curing resulted in higher cytotoxicity of the DPAs.[14] These findings support the assumption that the safe use of DPAs made from Graphy's Tera Harz TC-85 is associated with strict adherence to the production guidelines given by the manufacturers.[12,13] However, in our view, given that the process involves multiple steps and a choice of various devices, there is a high risk of errors that could compromise patient safety. Willi et al. analyzed aligner eluents to determine urethane dimethacrylate (UDMA) monomer as well as bisphenol-A (BPA) using liquid chromatography/mass spectrometry[7]. While being BPA free, they detected a considerable variability in UDMA leakage from the samples that could represent a potential health risk for patients.[7] In a further study, Eslami et al. compared the surface roughness and porosity of DPAs and Invisalign aligners (Invisalign®, Align Technology, Santa Clara, CA, USA) before and after one week of intraoral use: Whereas Invisalign aligners showed a significant decrease in these parameters after one week in service, suggesting a polishing effect from intraoral conditions, in DPAs a significantly increased surface roughness and porosity was detected.[27] This raises concerns about the intraoral performance of DPAs, particularly regarding hygiene and maintenance challenges, and highlights the need for further research into the effects of direct printing processes and materials on aligner properties.[27] Furthermore, Shirey et al. showed that the mechanical properties of the 3D-printed resins Material X (Envisiontec, Inc; Dearborn, MI) and OD-Clear TF (3DResyns, Barcelona, Spain) are more significantly affected by moisture compared to those of TFAs.[28] Thus, the impact of moist oral conditions on Graphy's Tera Harz TC-85 needs to be evaluated in future research. Despite the potential advantages of direct printing, such as reduced production time and customization, the technique-sensitive and complex nature of the process poses challenges for consistent aligner quality. Additionally, to our knowledge, information regarding the residual monomer content following the post-curing process is unavailable.

In contemporary society, micro- and nanoplastics increasingly raise concerns regarding human health and environmental safety, owing to their potential harmful impacts.[29] A review article published by Prüst et al. presents a detailed overview of the potential neurotoxic effects of micro- and nanoplastics across various species and in vitro studies: The authors discuss evidence suggesting that these particles can be taken up by organisms like mammals, with some even reaching the brain.[29] The exact extent of brain accumulation and the consequent neurotoxicity, however, remain mostly undiscovered.[29] In spite of research gaps and the demand for further systematic exploration of the neurotoxic effects of different types, shapes and sizes of particles as well as the time of exposure, the existing data suggest that exposure may induce oxidative stress, potentially causing neuronal damage and an increased vulnerability to developing neuronal disorders.[29] Furthermore, exposure can cause inhibition of acetylcholinesterase activity and altered neurotransmitter levels, contributing to observed behavioral changes.[29] Recently, Kopatz et al. proved that nanometer sized plastic particles may successfully cross the blood-brain barrier in mice.[30] Accumulation in the brain was detected as early as two hours post-exposure.[30] The articles highlight the urgent need for further research to clarify the neurotoxic hazard and risk of exposure to micro- and nanoplastics comprehensively.[29,30] However, given the current state of knowledge, the potential risks associated with the use of DPAs should be carefully considered, particularly in children and adolescents who are still in developmental stages

Fig. 3. Delicate production process

Clinical considerations

While direct printing offers potential advantages, such as reduced production time and customization, the technique-sensitive and complex nature of the process − particularly during post-curing − poses challenges for patients' safety and consistent quality of the aligners. Orthodontists considering the incorporation of DPAs into their practice must be aware that Graphy's TC-85 is a fairly new product that is highly toxic prior to proper post-processing, requiring the mandatory use of protective face masks and gloves during its handling (Fig. 3). Establishing protocols for patient selection, treatment planning & DPA production is crucial for optimal results. There is a steep learning curve every practitioner must go through to produce consistent and reliable outcomes when using DPAs as well as properly integrating them into one's own clinical workflows.

Future directions and research opportunities

Besides research exploring the biomechanical properties, in our opinion, it is of great importance to further investigate potential influences on the material's biocompatibility and cytotoxicity: The original digital design, choice of printer, printer settings, cleaning of the aligners after printing and, above all, necessary post-processing actions are only a few variables to be named that might have a significant influence on the material's biocompatibility that should not be underestimated. Post-processing, in particular, involves a number of necessary steps such as curing by UV light in a nitrogen atmosphere, washing in boiling water and complete drying[31]. For each of these steps, it is necessary to precisely determine various factors and clinicians should always adhere to these recommendations when using 3D-printed resin[32]. Furthermore, the benefit of being able to design virtually any kind of customized appliance bears the risk of exposing patients to cytotoxic materials as the standardized production protocol might need adaptations to guarantee biologically safe use in all cases. The latter, to our knowledge, has not been subject to any research so far and, thus, needs to be addressed in upcoming studies.

Conclusion

In our opinion, the ability to produce DPAs in-office using resin instead of thermoformed aligners revolutionizes contemporary orthodontics as well as aligner therapy itself. The transition to DPAs presents challenges, including the need for precise workflow adherence, understanding the mechanical properties of materials, and addressing potential health concerns related to materials used. We believe that DPAs represent the future in aligner therapy, however, orthodontists may only benefit from the various advantages offered by such a state-of-the-art treatment if biological safety for patients can be guaranteed. The latter must always be the orthodontist's primary responsibility and can only be assured when the manufacturer, i.e. the orthodontist, sticks strictly to the manufacturing protocol. Nevertheless, further research on biocompatibility of custom-designed DPAs is needed to assure biological safety in all areas of the broad field of use, which ranges from finishing aligners to hybrid treatments or even entire treatments themselves.

Declaration of competing interest

The authors (C. Erbe & M. Bleilöb) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The author (B. Ludwig) is a Guest Editor for *Special Issue of Seminars in Orthodontics "Hype, Hope or Both"* and was not involved in the editorial review or the decision to publish this article.

CRediT authorship contribution statement

Christina Erbe: Writing − original draft. **Björn Ludwig:** Writing − review & editing. **Maximilian Bleilöb:** Writing − original draft.

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