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Mini-Review

Theme: Pediatric Drug Development and Dosage Form Design
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3D-Printed Drugs for Children—Are We Ready Yet?

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Abstract. The first medicine manufactured by three-dimensional (3D) printing was recently approved by the Food and Drug Administration (FDA). The advantages of printing as a manufacturing route enabling more flexibility regarding the dose, and enlarging individual treatment options, have been demonstrated. There is a particular need for flexible drug delivery solutions when it comes to children. Printing as a new pharmaceutical manufacturing technology brings manufacturing closer to the patient and can easily be adjusted to the required dosing scheme, offering more flexibility for treatments. Printing of medicine may therefore become the manufacturing route of choice to provide tailored and potentially on-demand treatments for patients with individual needs. This paper intends to summarize and discuss the state of the art, the crucial aspects which should be taken into account, and the still-open questions, in order to make 3D printing a suitable manufacturing route for pediatric drugs.

KEY WORDS: 3D printing; children; drug delivery; pediatrics.

INTRODUCTION

Printing in Personalized Medicine

Growing awareness in the healthcare industry that individual and tailored therapy solutions are the key features for successful treatment of patients has resulted in new processing technologies, which are presently revolutionizing pharmaceutical manufacturing. As new approaches in medical device development and dosage form design are already taking place in today's research and development domains, investigating the opportunities offered by new technologies in terms of healthcare applications is worthwhile (1).

In 2015, the United States Food and Drug Administration (FDA) approved a 3D-printed tablet, which in turn put the fabrication of drug delivery systems in the spotlight (2). This article will not go into detail about the different additive manufacturing technologies: further detailed information may be found in recent literature overviews (2–5). In brief, the most common techniques involve 3D printing based on fused-deposition modeling (FDM) using a polymer strand as feedstock material (6), or a powder-based layer-by-layer approach, as used in the recently approved 3D-printed tablet Spritam® from Aprecia® (7).

Printing technologies such as 3D printing, also known as additive manufacturing (AM), have recently replaced many conventional manufacturing techniques, especially in the medical and dental field, at a surprisingly fast speed, and health biomaterial-based technologies are expected to follow (8). AM has already been shown to be successful in creating patient-tailored implants, devices, even prostheses, and new tissues (9–11). In addition to being able to manufacture, for example, tailored medical devices such as pulmonary delivery devices, printing of a personalized oral drug delivery system is now possible: if it was possible to print a device according to a patient's need, it must also be possible to print a drug in terms of the required size, dosage, release properties, and shape (12). Printing technologies based on inkjet or flexography technology (3,13,14) have also garnered interest. These well-known techniques established in multiple fields have enabled the deposition of very precise and, in particular, low amounts of drugs onto a suitable edible substrate (15,16). Although these printing techniques may be described more like a 2D approach, the use of polymer-based jettable inks and the application of multiple layers will result in a very fine 3D structure. However, despite being a widely investigated field, the 2D printing of drugs using inkjet technology is limited to rather low-dose applications. Therefore, the seemingly unlimited options, using an additive manufacturing/3D printing approach, offer the opportunity to obtain a variety of dosage forms and doses. With regard to children, in particular, they not only require individual and tailored doses depending on

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their age, weight, and present diseases, or even multimorbidity, but may also have very individual preferences when it comes to taste, shape, and color (17).

Oral Drug Delivery in Children

Oral administration is widely regarded as the most convenient route, compared to other routes such as intravenous or even rectal applications, and usually does not require a professionally trained caregiver. However, as simple as oral drug delivery seems to be at first sight, it can become rather complex when it comes to individual treatment (18–21). Table I summarizes the aspects to be considered when an oral drug delivery system is intended for a child. It may appear obvious that, for some children, minor attributes such as preferences in taste, colors, or shape can significantly influence the success of therapy (22,23). A child may simply reject the dosage form on offer. One might say that it is simply impossible to satisfy all individual preferences, which is where 3D printing that enables high flexibility steps in (12). By developing printable drug formulations—e.g., a printable drug-polymer filament that can be fed into a hot-melt extrusion-based 3D printer (6)—the potential exists for patients to be supplied with tailored dosage forms.

Advantages and Limitations of 3D-Printed Drugs

The production of tailor-made doses and dose combinations is enabled by using flexible 3D designs. Recent studies have described a 3D-printed polypill, involving multiple drugs and defined immediate and sustained release profiles (24,25). Adherence to a prescribed therapy may be challenging when it comes to children. With a flexible printing process, not only can the precise doses and required drug combinations be manufactured, but a child's individual preferences can be met regarding the color or shape of the medicine. A potential scenario would be that the doctor could ask caregivers, or even the children themselves, about the preferred colors or shapes that the medicine should have. This brings the medicine closer to the patient, which is especially beneficial to children if they can have their own personalized product, thereby potentially increasing the success of therapy (26,27).

It has been shown and widely discussed that orally disintegrating dosage forms such as mini-tablets and films are suitable for children (18,19). These dosage forms can most likely also be prepared in a 3D printer. First studies have shown that thin polymer substrates can be manufactured using a 3D printer, which enables a flexible dosing approach by adjusting area, thickness, and infill percentage (28). Mini-tablets of varying diameters could also be prepared in a 3D printing process. Yet to be installed is an intelligent 3D design software, which can be fed with the child's information (e.g., body weight, maximum tablet size that can be swallowed, and dose needed). Such a software design would be beneficial to obtain the dosage form with the necessary dimensions and dose for an individual pediatric patient. This software could ideally also calculate the release kinetics based on the surface area and shape of the dosage form to be printed. In this area, there is still a need for thorough investigation to be able to design a dosage form with the required release profile(s), since the shape and surface area of the printed tablet are known to affect the release profile (29).

Furthermore, the potential of combining two or more drugs in the same dosage form may increase compliance, since the child only would need to take one single 3D-printed dosage form, instead of multiple dosage forms if produced with conventional manufacturing techniques. As earlier described, the advantage of being able to combine instant release and controlled release in the same dosage form enables less frequent administration. Thus, the caregiver can give the medicine to the child in a familiar environment at home in the morning and evening, instead of making daycare employees or teachers accountable for the administration. Adjustable ratios and combinations are further advantages of creating multi-drug dosage forms by means of 3D printing. Changes in therapy can be applied more rapidly by changing the ratios of combined drugs in the design and printing process, compared to conventional tablet manufacturing methods where personalization is very limited or non-existent, due to fairly fixed process methods. Furthermore, available fixed-dose combinations (FDC) can result in under- or overdosing of one component in different pediatric patients, and the cutting of tablets does not always result in accurate doses. The required doses are not only dependent on age but also on body weight and organ development. In a specific case, children with lower body weight could experience underdosing when receiving an antiretroviral drug FDC (30). Knowing these challenges, false and ineffective treatments could be avoided when preparing tailored combinations for a specific pediatric patient.

However, we have to bear in mind that as simple and convenient as these approaches appear, there is still a long way to go. To date, there are no commercially available drug-loaded printable filaments or other formulations, depending on the type of printer, available. The provision of these products will be a prerequisite for the on-demand production of a 3D-printed pill in a doctor's practice, hospital, or pharmacy. Filaments or other printable materials with defined drug loads and release properties, as well as sufficient stability and pharmaceutical quality, have to be developed first. Additionally, it is certain that the printing of different sizes and shapes, along with the infill level or porosity of the printed product, may significantly influence the drug release properties due to changes in surface area (29). Therefore, the design to be printed has to be carefully chosen and evaluated to actually achieve the desired doses and release properties.

Table I. Points to Consider for Pediatric Drug Therapy

Patient-related	Disease-related	Product-related
Age	Influence on physiological functions	Available doses
Weight	Required dose variation	Ratio in fixed dose combinations
Individual preferences	Changes in metabolism	Production site

CHALLENGES AND POINTS TO CONSIDER

General Regulatory Aspects

A variety of medical devices are already being prepared by 3D printing. The FDA provides guidance and investigates suitable printers for the manufacturing of instrumentation, prostheses, and implants, for example (9). In 2016, the United States Department of Health and Human Services, together with other institutions, published a draft guidance on the technical considerations for additive manufactured devices (31). The draft deals with a list of critical aspects, which also apply to dosage forms using printing techniques. An overview is given in Table II. Process validation, acceptance criteria, cleaning and sterilization requirements, and testing of the end product are all crucial to ensure a high-quality product. Prior to printing, it has to be determined whether a standard design is to be used or if the design is patient matched. This raises the question of which type of file format is to be used for the design—for example, if patient data and also computer tomographic images are to be used, and in what file format the resulting 3D design is stored. The material controls are established. Starting materials have to be of defined and suitable quality, but it must also be evaluated whether the materials are recyclable—e.g., unsintered powders or uncured resins—or if any alterations take place during the printing process that influence the material quality.

Furthermore, the classification of printed products plays an important role. Depending on the production site, the medicine may be classified as a hospital formulation or an individual contemporary formulation. The bottom line is that, regardless of where the end product is manufactured—whether it is within industry, in a hospital, or in a pharmacy—the product quality must be ensured. Recently, it was emphasized that 3D printing, as a manufacturing process itself, is not, from a regulatory point of view, going to be a limitation as long as the final product meets the set requirements (32). The approved 3D-printed tablet Spritam®, mentioned above, contains only excipients that would also occur in a conventional tablet (7). Only the production process is different. Therefore, in this case, it can be assumed that the same quality requirements apply as for other orally disintegrating tablets, such as dose uniformity and sufficiently rapid disintegration. To date, a 3D-printed dosage form does not require a unique regulatory pathway (32): dosage forms manufactured by utilizing the 3D printing technique can follow existing approval pathways. In the future, however, it is likely that 3D-printed medicinal products will be defined as a new type of dosage form with their own labeling claims and guidelines.

Table II. Points to consider for additive manufacturing processes (modified according to the Technical Considerations for Additive Manufactured Devices: Draft Guidance for Industry and Food and Drug Administration Staff)

Design	Standard or patient-matched
Software	File format conversion
	Digital design -> Physical product
Material controls	Starting material
	Recycling
Post-processing/ validation and acceptance	Process validation and revalidation
	Acceptance activities
	Cleaning and sterilization
End product	Mechanical testing
	Material characterization
	Biocompatibility

Once the technologies are established and it is clear where the responsibilities lie in terms of the production of starting materials and end products, 3D printing has the potential to become the routine manufacturing route for challenging substances, such as poorly soluble drugs, individual drug combinations, or orphan drugs. Regulatory authorities may offer incentives for the development of pediatric orphan drugs using a printing approach. Especially for orphan drugs, the path from drug discovery toward actual medicine can be realized more rapidly by means of 3D printing, as well as providing accurate and individual treatment for pediatric patients.

Safety and Quality Aspects

Critical safety attributes and questions about how to ensure the quality and safety of a 3D-printed drug are foregrounded when a new innovation—especially a novel manufacturing approach—enters the market. This includes hardware (printers and printheads), software (digital design), and material safety and quality (33). Points to consider are as follows:

- Material safety
- Reliability of material and hardware
- Expected output quality and suitable control tools
- Distribution of tasks and responsibilities

Safety aspects further include the safety of excipients. With new technologies, new excipients may be needed to actually manufacture a tailored pediatric dosage form. In this case, special attention has to be paid to the suitability for children and, in particular, for children of different age groups (17).

Additionally, if the production takes place at the point of care and not in an industrial environment, measures need to be taken to ensure that the operator of the printer—who may be a nurse, a pharmacist, a technician, or even the patient's doctor—is sufficiently trained to produce 3D-printed medicine. Furthermore, it is as yet unclear who ensures the quality and stability of the printed product. It may appear reasonable that retention samples are required to be stored, which becomes particularly important regarding liability aspects. Pathways, responsibility, and liability aspects need extensive evaluation before printed medicine—in particular, on-demand printed medicine—can be put in the market.

Another point, which is not negligible, is the actual printer. The question will be who builds or provides the printer and whether this printer can operate with materials from different pharmaceutical manufacturers.

Production Aspects

Several scenarios about the manufacturing site of 3D-printed drugs have been discussed and the "print-at-home" approach in particular has gained interest and popularity, especially in lay media. Rapid prototyping for research

purposes is an obvious advantage in the pharmaceutical industry and related research. A home fabrication approach, however, appears excellent for other industries, involving toys or household tools and goods, amongst others (34,35), but may be considered unsuitable for pharmaceuticals, and for pediatric medicine in particular, where the high quality of the medicinal product needs to be guaranteed at all times. Therefore, it becomes a question of the right distribution of responsibilities along the production chain of a 3D-printed medicine (Table III). These questions need to be answered first, with models for the material supply, manufacturing, and distribution needing to be established.

Figure 1 provides an overview of potential 3D-printed product lifecycle scenarios, which may be established in the future, including the design and printing in the pharmacy or related institution or company. The scenario on the left shows that the design and the manufacturing (steps 3 and 4) both take place in the pharmacy, which is provided with the materials from industry (step 1) and the patient data and treatment plan from the doctor or hospital (step 2). The scenario on the right indicates that the design of the dosage form according to the doctor's therapy plan (step 1) is still made in the pharmacy (step 2). The actual manufacturing, however, would take place in a contract manufacturing organization (step 4), which could be a compounding pharmacy or other external business. The patient supply is delivered to the pharmacy, where the professionals can again check if the correct printed medicine has been delivered. Depending on the site of manufacture and distribution, the aforementioned question of liability is one of the most important determining factors and will influence future manufacturing pathways.

It should be considered whether the complete production of printed dosage forms as part of an industrial setup is the safest and best approach to take. However, since the 3D printing process of pharmaceuticals is far from established, and given that the current state of the technology cannot compete with the production speed and effectiveness of, for example, a conventional rotary tablet press process, not only is the mass production of 3D-printed pharmaceuticals unsuitable at the present time but the convenience of the tailored on-demand approach, where medicine is manufactured close to the patient, may be lost. Therefore, it becomes even more important in the future to identify the most effective and safest production cycle to maintain the aforementioned advantages of individualized 3D-printed medicines.

Table III. Questions Regarding the Production Chain Life Cycle for a 3D-Printed Medicine for Pediatrics

Aspect	Questions to be answered/responsibilities to be defined
Materials	Who provides the starting material?
	Does the 3D printer need ready-to-use filaments?
Printer	What type of printer will be used?
	Who provides the digital design (3D model) for the medicine?
Printing process	Who operates the printer?
	Does the operator require certified training to use the printer?
	Who decides on the final design of the medicine prior to printing?
Shelf life	How long is the shelf life of the starting material and printed product?
Quality and safety	How can the product quality and safety be ensured at the point of care?
	Are specific acceptance limits required?

Economic Aspects

The economic perspective of conventional dosage forms *versus* 3D-printed ones should not be overlooked. As discussed previously, printed dosage forms may offer advantages in terms of individualized drug delivery solutions, as well as requiring material and business innovations. Furthermore, 3D printing is associated with low cost for small batches compared to conventional manufacturing techniques, making it a cost-effective method for personalized dosage forms and orphan drugs. The aspects of who prints and who provides the printers and printable materials will be a determining factor for the economic aspects of this new way of manufacturing.

When more 3D-printed products enter the market, a cost-benefit analysis will need to be conducted. Benefits for patients and the healthcare system include the partial replacement of non-cost-effective extemporaneous dispensing and on-demand production of only the dose that is actually needed (12). Aspects such as specific drug responses and differences in drug metabolism can be unique in children. By providing pediatric patients with tailored medicines, unnecessary costs incurred by using unlicensed formulations, and potentially ineffective treatments, can be avoided. Once these benefits can be shown in practice, the advantages in terms of insurance and related institutions will become evident.

Once suitable 3D printing technologies and production policies are established, printed medicines may also become a solution for developing countries. Fixed dose combinations of the aforementioned retroviral drugs could be printed at the point of care when the dispensing institution is provided with the adequate starting materials. Children in developing countries could be supplied with tailored on-site manufactured dosage forms.

In respect of new business opportunities, the prevailing model for the mass production of pharmaceuticals, with only limited flexibility in terms of dose levels and drug combinations, could be replaced by a new business model. It should be expected that today's research activities will reveal new suitable materials for the preparation of printed dosage forms, facilitating opportunities for excipient suppliers to expand their palette of materials, as well as opening up the potential for new businesses to provide and produce materials for a specific printing application. New or optimized excipients for pharmaceutical 3D printing may come at a price. The required physicochemical and toxicological properties of a printable material will potentially increase the costs for certain excipients—e.g., when the supplier provides a pre-processed product such as a ready-to-use-mixture (active ingredients, polymer(s), plasticizer, disintegrant, etc.).

Besides the new opportunities for material suppliers and pharmaceutical companies, the printer market will be one to watch in the near future. Printers complying with pharmaceutical quality standards are of significant interest, as are

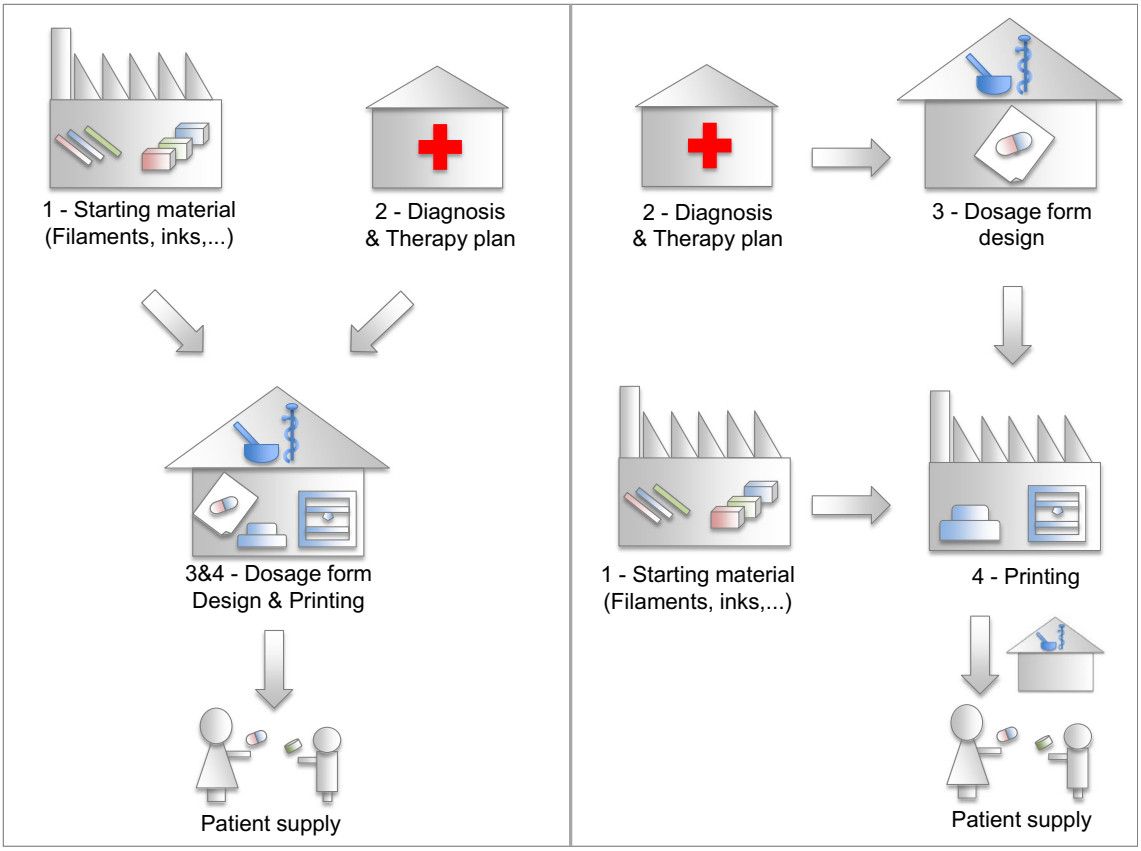

Fig. 1. 3D-Printed medicine on demand: (*1*) provision of starting materials (industry); (*2*) diagnosis and therapy (hospital/doctor's office); (*3*) dosage form design (pharmacy or related institution); (*4*) printing in the pharmacy (*left*) or in industry (*right*)

printers with increased printing speed without compromising the precision of the dosage form. In other words, companies producing high-quality printers—e.g., FDM printers—for pharmaceutical use and on different scales, from small batches for use in hospitals to large industrial scale, can be expected to enter the market. In addition, new service business models are required. This may include qualified training in terms of how to operate and produce high-quality 3D-printed drugs, as well as external services such as contract on-demand manufacturing commissioned by a local hospital, pharmacy, or drug distribution center (Fig. 1).

CONCLUSION

Bringing manufacturing closer to the patient and offering individual treatment solutions mean that 3D printing is a promising technology, particularly in relation to the challenging pediatric patient population, many of whom require different doses and flexible dose adjustments. With this new chapter in pharmaceutical manufacturing, a number of challenges and questions need to be addressed regarding the use of 3D-printed drugs, especially for pediatric patients before we are ready for new products. While there are obvious opportunities for new healthcare and business models in the pharmaceutical environment, this phenomenon also requires new regulatory thinking, pathways, and guidance.

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