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APPLICATION OF 3D PRINTING IN PAEDIATRIC TABLETS: ENHANCING PERSONALIZED DRUG DELIVERY

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ABSTRACT

Pediatric patients are considered a special category of patients in pharmacotherapy who are still facing challenges in terms of dose accuracy, palatability, and formulation availability. The traditional approach of preparing tablets based on fixed-dose theories has failed to address the individual needs of paediatric patients at different developmental stages. Three-dimensional printing has been considered a game-changer in the pharmaceutical industry by providing the opportunity for the development of accurate-dose tablets with improved palatability and child-friendly formulations. This review critically discusses the major 3D printing technologies that are being used for the development of tablets for paediatric patients, such as fused deposition modeling, semi-solid extrusion, selective laser sintering, stereolithography, and binder jetting/inkjet printing. The review will cover the pharmacokinetic rationale for the development of personalized paediatric formulations, approaches to improve acceptability and compliance in the paediatric population, materials and excipients, QA issues, and the current regulatory situation with input from the FDA and the EMA. The review will also cover the major clinical feasibility trials, including the development of the first-ever personal formulations for epilepsy, adrenal insufficiency, hypothyroidism, and metabolic disorders. Finally, the challenges facing the field will be discussed in the context of the future of the field.

KEYWORDS: 3D printing, additive manufacturing, paediatric dosage forms, personalized medicine, fused deposition modeling, tablet printing, dose individualization, point-of-care manufacturing.

1. INTRODUCTION

The individualization of pharmacotherapy has always been regarded as the cornerstone of safe and effective practice, especially in the paediatric population. It is important to realize that children are not simply small adults, as the rapidly changing physiology from the neonatal period, through infancy, early childhood, and into adolescence, produces dramatically different pharmacokinetic and pharmacodynamic profiles that require weight-based, age-adjusted approaches to drug dosing.[1] However, the global pharmaceutical industry has, until now, been based on the development of standardized, adult-focused drug products, with the result that the phenomenon of therapeutic orphans in the paediatric population remains a persistent problem, with children frequently being prescribed unlicensed, off-label medicines, often derived from adult medicines through the process of extemporaneous compounding, including the practice of tablet splitting, which is known to be inaccurate in terms of dosing, with patient safety implications.[2]

Three-dimensional (3D) printing, also called additive manufacturing (AM), is a disruptive, patient-centric technology that holds promise to transform the pharmaceutical manufacturing landscape. Unlike conventional processes, which have traditionally focused on maximizing productivity for mass production of similar products, 3D printing enables layer-by-layer construction of pharmaceutical materials using computer-aided design files, creating complex, highly customized drug products at the point of use.[3] 3D printing gives pharmaceutical professionals unparalleled control overdose, tablet size, surface area-to-mass ratio, drug release, and even cosmetic factors such as shape, color, and taste, all of which are critical factors in paediatric medication compliance.[4]

The most important regulatory milestone in the field of pharmaceutical 3D printing was achieved in 2015 by the United States Food and Drug Administration (FDA), which approved Spritam® (levetiracetam), the world's first commercially available 3D printed tablet using Aprecia Pharmaceuticals' proprietary ZipDose® technology for printing pharmaceuticals in the form of a tablet using a binder jetting method.[5] Spritam® can rapidly dissolve in the mouth after a small amount of liquid is taken. This is particularly useful for people suffering from epilepsy, especially children, as they have difficulty swallowing tablets. Although Spritam® is not designed for individualized drug delivery, this approval is an important milestone in the field of pharmaceutical 3D printing as it proved that this technology is able to meet stringent requirements for drug safety, quality, and efficacy.[6]

The global need for better paediatric medicine formulations is significant in scope. The initiative "Make Medicines Child Size," launched by the World Health Organization in 2007, has brought international attention to this issue, and the European Union's Pediatric Regulation (No. 1901/2006) has provided incentives for pharmaceutical companies to design medicines that are age appropriate.[7] However, the availability of age-appropriate drug formulations is still abysmally low, especially in neonates, infants, and patients with rare diseases that require ultra-low doses and high individualization. In this background, 3D printing emerges as a promising solution that is increasingly being supported by preclinical and clinical data that prove its feasibility, accuracy, and patient acceptability.[8]

This review is a comprehensive critical analysis of the status of 3D printing in the manufacture of paediatric tablets, with a specific focus on technologies that offer easy and individualized dosage in the paediatric population. We will discuss the pharmacological rationale for individualized dosing in the paediatric population, the major 3D printing technologies and their pharmaceutical applications, materials and excipients, clinical evidence of feasibility and acceptability, and a vision of the future of 3D printing in the practice of paediatrics.

2. Pharmacological Rationale for Personalized Pediatric Dosing

2.1 Developmental Pharmacokinetics

Pediatric pharmacokinetics differs from that in adults in a fundamental way and is a constantly changing process throughout development. Children are not just small adults; they differ in a significant way in their ability to absorb, distribute, metabolize, and excrete drugs. This is especially true in neonates and infants and gradually decreases with age to resemble that in adults in adolescence.[9] The gastrointestinal absorption of a drug is altered by differences in gastric pH, which is higher in neonates, gastric emptying time, and intestinal motility. The volume of distribution of a drug is altered by age-related differences in body composition due to a higher percentage of total body water in neonates and a lower percentage of fat content compared to adults.[10]

Hepatic metabolism, which is mainly carried out by the cytochrome P450 enzyme family, is subject to considerable ontogenic development. Several isoforms of these enzymes, including CYP3A4, which is the most abundant isoform in adult liver tissue, are present at very low levels at birth, gradually increasing throughout childhood [11]. Likewise, renal clearance is subject to developmental changes, with filtration rate increasing during the first few years of life. Thus, while the same milligram-per-kilogram dose administered to a neonate, toddler, school-age child, or adolescent can have quite different concentration-time profiles, uniform dosing of all paediatric patients, as would be required if using fixed, commercially available formulations, is pharmacologically incorrect and potentially hazardous.[9]

The two most used approaches for individualization of paediatric doses are based on the concept of dose per unit weight (mg/kg) and dose per unit body surface area. However, studies have shown that there are considerable limitations of the allometric scaling approaches. For example, the data on pharmacokinetic modeling have shown that the dose per unit weight does not take into account the disproportionate maturation of drug metabolizing enzymes and renal functions, which can lead to overdosing or under-dosing in certain age groups.[1] This, in turn, stresses the need for formulations that are not only age-appropriate but also easy to customize for precise dosing, as 3D printing enables.

2.2 Limitations of Current Approaches to Pediatric Dosing

In practice, if an appropriate paediatric dosage form is not available, various approaches, each with considerable drawbacks, have been adopted by health professionals and caregivers. Tablet splitting or crushing is one of the most common methods, which is associated with considerable inaccuracies in dosing, especially if a modified-release formulation is used, where the drug release mechanism is completely abolished.[12] Liquid preparations, which are often extemporaneously prepared by compounding pharmacies, offer flexible dosing, but stability, microbiological risk, taste, and dosing inaccuracies during administration by caregivers have been reported.[2]

The extemporaneous compounding of individualized medications by pharmacists using APIs and excipients does not have the quality assurance system in place as in industrialized medicine. Compounded medications may not be subject to the same level of scrutiny as licensed medications, leading to concerns about batch-to-batch variability, sterility, and appropriate dosing.[13] The precise calculation and administration of paediatric doses have also been identified as an important source of medication errors in inpatient and outpatient care. Studies have shown that medication errors in the preparation of paediatric medications may occur in as high as 27% of cases, leading to failure or even life-threatening toxicity.[4]

Another aspect of formulation design, related to age-appropriate formulation, is the developmental stage of the child and their ability to swallow medication. Children under 6 years of age would not be appropriate candidates for tablet or capsule formulations, while older children could take smaller tablets. Children are notoriously sensitive to taste, and palatability is a critical factor affecting medication compliance. Medications that children do not wish to take, or take reluctantly, are considered clinically worthless, irrespective of their pharmacology.[8] Three-dimensional printing techniques provide solutions to all these issues.

3. Three-Dimensional Printing Technologies for Pharmaceutical Tablets

Several technologies for 3D printing have been studied for pharmaceutical applications, and they have their own pros and cons in relation to paediatric tablet formulation. The major technologies are discussed below in relation to their paediatric tablet formulation applications.

3.1 Fused Deposition Modeling (FDM)

Fused Deposition Modeling (FDM) is currently the most researched 3D printing method for pharmaceutical uses, which is also called Fused Filament Fabrication (FFF). In FDM, a drug-loaded thermoplastic polymer filament is melted and extruded layer-wise on a platform to form a 3D dosage form using a heated nozzle.[14] Generally, the filament is prepared using a process called hot melt extrusion (HME) where a drug is uniformly dispersed within a polymer matrix. FDM printers are inexpensive, readily available, and enable the production of tablets with intricate internal structures, which can potentially control drug release profiles.[15]

For paediatric use, it has several significant benefits. It allows for adjustment of drug content and/or dosage by adjusting tablet geometry, percent infill, and/or number of deposited layers without changing filament composition to enable a single filament to be used to produce a variety of doses.[16] Mini tablets with a diameter of 2-3 mm have been shown to be acceptable to infants and young children when administered in small numbers and have been produced by FDM with excellent dose uniformity.[17] It allows to produce orodispersible tablets that disintegrate quickly in the oral cavity without the need for water consumption, which is a significant advantage for children that have difficulties swallowing.[18] It also allows to produce tablets that have defined profiles for immediate or extended release by adjusting infill and/or wall thickness, which has potential benefits for individualized pharmacotherapy based upon each patient’s pharmacokinetics profile.[14]

Significant challenges related to FDM include the need for drug thermal stability in the HME process (usually between 100-200°C), which is a limitation for the APIs used. The polymers need to meet the requirements of the process (melt viscosity, adhesion, flexibility) and the pharmaceutical requirements (GRAS, safety of the material). The PolyPrint consortium, a group of European pharmaceutical scientists and engineers, has contributed significantly to the characterization of the quality aspects and parameters of FDM-based pediatric drugs and the need for GMP printer design.[19]

3.2 Semi-Solid Extrusion (SSE)

Semi-solid extrusion (SSE), which is also called pressure-assisted syringe printing or micro-extrusion printing, uses ambient or low temperatures and involves the use of pneumatic or mechanical pressure to push semi-solid pharmaceutical pastes or gels out of a nozzle. The absence of high temperature in this process makes it especially attractive for thermolabile APIs and for incorporating aqueous drug solutions into formulations.[20] This process has

been used to manufacture various types of paediatric dosage forms such as chewable tablets, gummies, and orodispersible films with incorporated taste-masking agents in the formulation itself.

One of the notable examples of SSE technology being effectively applied to personalized paediatric medicine was published by a group of scientists at Vall d'Hebron University Hospital in Barcelona, who successfully applied SSE 3D printing technology to create personalized chewable hydrocortisone formulations for paediatric patients with adrenal insufficiency—a chronic disorder requiring lifelong low-dose steroid replacement therapy, for which there are currently no commercial paediatric formulations available.[21] The 3D-printed printlets contain varying doses of hydrocortisone, ranging from 1 to 6 mg, in three different flavor and color options, which can dynamically modulate doses using specialized software. This study can be considered a landmark in the application of 3D-printed paediatric medicine. Another study has also shown the effectiveness of SSE technology in 3D printing flavored ibuprofen mini tablets, which have shown excellent palatability as determined through a sensory panel test.[22]

3.3 Selective Laser Sintering (SLS)

Selective laser sintering (SLS) is a process in which a focused laser beam is used to fuse pharmaceutical powders in a layer-wise fashion to form a tablet in a desired shape without the use of a binder or a solvent. SLS allows for the formation of porous and disintegrating tablets that are appropriate for use in orodispersible forms.[23] The process is advantageous from a manufacturing viewpoint as it does not require a solvent and is a one-step process. In SLS technology, it is possible to have high drug content in a tablet and control tablet geometry precisely, which allows for the formation of tablet shapes that are appealing to children, such as animals, stars, and cartoon characters.

Studies have shown that SLS can create mini-tablets and ODTs of a variety of model drug compounds with high CU and controlled release profiles. However, it is important to note that SLS requires that the drug substance has sufficient thermal stability (laser heating can occur), as well as access to appropriate pharmaceutical-grade polymers that can be melted at laser wavelengths. In addition, equipment costs are high compared to FDM/SSE technology, as well as potential powder bed contamination issues in a GMP context.[3]

3.4 Stereolithography (SLA) and Digital Light Processing (DLP)

Stereolithography (SLA) and digital light processing (DLP) use ultraviolet or visible light to cure photopolymerizable resins, creating highly detailed three-dimensional structures. Dosage forms created using SLA/DLP have intricate designs with submillimeter precision, allowing for complex drug release structures. This method enables quick prototyping of innovative tablet formats. However, the pharmaceutical application of SLA/DLP is restricted by the availability of biocompatible, photocurable polymers, which is a limited class of materials, and photo initiator residue safety issues.[24] This method could potentially have niche uses in creating paediatric dosage forms with unique design features or clinical trial materials.

3.5 Binder Jetting and Inkjet Printing

The technology upon which binder jetting, as seen in Spritam®, is based involves depositing binding solutions or drug-impregnated ink onto a powder bed or substrate to form a tablet. ZipDose technology, as seen in Spritam, results in a very porous tablet that has extremely fast disintegration times, which occur within a matter of seconds after a sip of liquid. This is particularly important in paediatric epilepsy treatment.[5] Techniques such as drop-on-demand (DOD) inkjet printing allow for exact quantities of drug-impregnated ink to be deposited onto a substrate, resulting in an

extremely high degree of precision, which is particularly important in paediatric medicine, as small dosage variances can have a large impact on treatment efficacy. Inkjet-printed orodispersible films and tablets have shown to have a high degree of precision compared to other dosage forms.[25]

4. Formulation Design and Excipient Considerations for Pediatric 3D Printing

4.1 Active Pharmaceutical Ingredient (API) Integration

The proper integration of APIs into 3D printable formulations demands consideration of various physicochemical properties of APIs, such as thermal stability, which is a significant factor in FDM; solubility; particle size; and API-excipient interactions. In FDM, it is important that the API be thermally stable at HME processing conditions and that it be compatible with the chosen polymer system. APIs that are unstable under heat conditions, such as biologic agents, proteins, and vitamins, are more appropriate for low-temperature SSE or binder jetting techniques.[3] The drug loading must be optimized to provide adequate mechanical properties to the filaments in FDM, while in SSE, viscosity and extrudability of the semi-solid paste are important considerations.

One of the advantages of 3D printing technology in pediatric dosing is that it allows for the creation of a wide range of drug concentrations within a dosage form known as 'printlets' through a simple adjustment in the number of layers in a 3D-printed dosage form, allowing a pharmacist to prepare individually dosed tablets for patients ranging in age from pediatric to adult without having to prepare multiple dosage forms.[8] Research has shown that it is possible to create tablets containing levetiracetam in a varying amount through a variation in the number of layers in an SSE tablet, which meets European Pharmacopoeia specifications.[26]

4.2 Polymers and Excipients

Polymeric carriers have a dual function in pharmaceutical 3D printing, where not only do they offer structural support, but they also affect drug release profiles. For FDM, various polymeric materials such as polyvinyl alcohol, hydroxypropyl methylcellulose, polyethylene oxide, methacrylic acid copolymers (Eudragit series), and polylactic acid have shown promise. Each of these materials imparts unique characteristics to the printed formulations.[15] For SSE, hydrophilic polymers such as hydroxypropyl methylcellulose, carrageenan, and gelatin have been used as semi-solid bases. However, while choosing a polymer, excipient toxicity needs to be considered, especially in paediatric formulations, as paediatric patients, especially neonates and infants, are highly prone to excipient-induced toxicity due to their immature metabolic enzyme system and high relative surface area of absorption.[27]

The plasticizers used to decrease polymer and increase the flexibility and printability of the FDM filament include polyethylene glycol (PEG), triethyl citrate (TEC), and glycerol. Disintegrants such as croscarmellose sodium and sodium starch glycolate are incorporated into the formulation to ensure rapid disintegration in the mouth, which is a significant factor in orodispersible paediatric formulations. The use of mannitol as a filler material has been shown to have a significant effect in improving the disintegration times of ODTs printed by FDM by increasing tablet porosity.[28]

4.3 Palatability, Taste Masking, and Child-Friendly Design

Palatability is arguably one of the most important but least appreciated factors in medication compliance in children. Children have an extremely developed sense of taste and an innate dislike for bitter-tasting medications, which include most drugs. Poor palatability is among the top reasons for medication refusal, incomplete medication regimens, and

clandestine drug disposal in paediatric populations.[8] Traditional pharmaceutical processing technology does not offer many opportunities for taste masking beyond coating, which may not be possible for certain drug products. Three-dimensional printing technology allows for close integration with taste-masking concepts in drug product design.

The strategies successfully applied in the formulation of paediatric formulations include the following: (1) direct incorporation of sweeteners such as sucrose, sorbitol, and stevia and flavors such as strawberry, orange, chocolate, and vanilla into the formulation for printing; (2) the formulation of core-shell tablet architecture in which the bitter API is embedded in a palatably flavored shell; (3) the formulation of polymer matrices that delay drug release in the oral cavity to decrease bitterness perception; and (4) the formulation of tablets in shapes that are appealing to paediatric populations, such as stars, hearts, and cartoon characters.[29] A notable study by Karavasili et al. showed an excellent taste evaluation in the formulation in which strawberry and orange flavor were incorporated into micro extrusion-printed chewable ibuprofen tablets. Panelist assessment confirmed effective bitterness masking and improved aroma perception in the formulation.[22] Chocolate-based chewable prednisolone formulations printed using the SSE method have also shown high palatability score results in paediatric acceptability studies.

5. Clinical Evidence and Pediatric Applications

5.1 Epilepsy and Neurological Conditions

Pediatric epilepsy, accounting for 1–2% of paediatric patients, is one of the most pharmacologically demanding paediatric disorders, especially due to the low therapeutic index of many antiepileptic drugs (AEDs) and the requirement for precise dose titration according to body weight [31]. Levetiracetam, one of the most popular first-line AEDs, requires dose escalation over a period of weeks during the beginning of treatment, thus requiring multiple different dose levels. Currently, only fixed-dose tablets and liquids of levetiracetam are available, causing considerable inconvenience to patients and their caregivers. SSE 3D printing technology has shown promise in the preparation of levetiracetam ODTs of various dose levels, all meeting European Pharmacopoeia uniformity requirements, with dissolution times of 3 minutes, thus addressing dose titration issues in paediatric patients.[26] The quick disintegration profile ensures that there is no problem of swallowing, which is a known issue with paediatric patients suffering from various neurological impairments, often requiring AED therapy.

5.2 Endocrine and Metabolic Disorders

Children suffering from AI need lifelong hydrocortisone replacement therapy with precise amounts, usually less than 5 mg/dose, which cannot be safely achieved by dividing adult-strength commercial tablets. The clinical study of SSE-printed personalized hydrocortisone "printlets" for paediatric AI, carried out at Vall d'Hebron University Hospital, Barcelona, showed the potential of printing stable formulations with accurate doses of hydrocortisone, ranging from 1–6 mg.[21] These "printlets" were flavored and color-coded to enhance compliance, thus facilitating accurate administration by caregivers. Bioequivalence of SSE-printed formulations was already shown for sildenafil citrate "printlets" in healthy adult subjects, while SSE-printed levothyroxine sodium "printlets" were shown to be bioequivalent to division of tablets, enhancing disease management in infants with transient hypothyroxinaemia.[21]

Rare inborn metabolic disorders, such as phenylketonuria (PKU) and homocystinuria, demand highly individualized nutritional and pharmacotherapeutic regimens, where the dose is determined by intricate metabolic monitoring data, which vary continuously. Rodriguez-Pombo et al. have conducted a paediatric clinical study on 3D printed paediatric personalized medicines for rare metabolic disorders, showing that SSE-printed formulations can administer precise

individualized doses not possible with conventional formulations, with high acceptability results in paediatric patients.[32]

5.3 Oncology

Pediatric cancer patients are one of the most vulnerable and pharmacologically challenging patient groups in medicine.

The chemotherapeutic agents administered in paediatric oncology are often extremely toxic with narrow therapeutic indices and require dose individualization based on body surface area calculations that change as the patient grows during treatment. In addition, some chemotherapeutic agents are not formulated in a form that is appropriate for paediatric use. A scoping review by Ahmed et al. explored the potential of 3D printing in developing personalized pharmaceutical dosage forms for paediatric cancer patients and noted that although substantial preclinical evidence supports this potential application, only six clinical evidence-based studies were identified that meet study criteria, and none were specifically designed to evaluate this potential in paediatric oncology patients.[33] The authors noted that "urgent clinical trials need to be conducted in this understudied patient group and that 3D printing has tremendous potential in addressing some of the most important unmet needs in this patient group."

5.4 Point-of-Care and Hospital Pharmacy Applications

Outside of these therapeutic area uses; the general concept of point-of-care (POC) 3D printing is considered a paradigm shift in the delivery of personalized pharmaceuticals. Here, pharmaceutical companies or compounding centers offer validated, clinically characterized materials for 3D printing, such as filaments, inks, or semi-solid pastes, together with digital prescription files, while hospitals or compounding pharmacies offer the actual 3D printing services to create personalized pharmaceuticals on a "as needed" basis.[34] Compounding pharmacies in the Netherlands and United Kingdom have already initiated the use of semi-solid extrusion printing platforms to routinely manufacture individualized paediatric pharmaceuticals, following emerging national regulatory guidelines.[22]

The potential benefits that may be obtained from POC 3D printing in hospital pharmacies include the absence of the need to hold large quantities of various strengths of a drug; the capacity to manufacture any required dose within a range just-in-time; a substantial decrease in dosage errors in comparison to manual compounding or tablet splitting; and the potential to react promptly to dose changes during a review process [34]. A smartphone-based 3D printing process that has been designed by FabRx researchers allows for the manufacture of variable tablets by users in a simple manner, which may eventually be extended to community pharmacies and homes, thereby making personalized medicines for pediatric patients more accessible.[35]

6. Quality Assurance and Technical Challenges

6.1 Dose Accuracy and Content Uniformity

Therefore, it is essential to maintain dose accuracy as well as content uniformity in 3D-printed tablets to ensure patient safety, especially in paediatric patients, as an error in dosage can have a greater impact on this population. For FDM technology, tablet dose accuracy can be ensured through precise control of drug loading in the filament as well as filament extrusion during 3D printing. Maintaining uniformity in filament dimensions, such as diameter, as well as drug distribution along the filament, is also essential, as an alteration in filament diameter of 0.1 mm can affect dose accuracy to a considerable extent [19]. Analytical tools such as inline NIR as well as Raman spectroscopy have been suggested to monitor filament as well as tablet content in real time during 3D printing.[28]

For binder jetting and inkjet printing, the accuracy of the dose is dependent on the accuracy of the deposition of the drops, the volume of the drops, and the binder concentration. These factors are highly controllable using digital technology, with inkjet printing formulations achieving a coefficient of variation in the dose uniformity of less than 2%, which is more accurate than the process of conventional compounding.[25] The accuracy of the SSE tablets is dependent on the consistency of the syringe pressure, the nozzle size, and the rheology of the semi-solid formulation. Studies have validated the accuracy of the SSE printing process in meeting the uniformity of content and uniformity of mass as specified in the European pharmacopoeia.[21]

6.2 Physical Stability and Shelf Life

The physical stability of 3DP tablets in terms of resistance to environmental moisture and temperature excursions and mechanical stress during handling and transportation must be established for a pharmaceutical product. It has been observed that 3DP dosage forms are more porous than conventionally compressed dosage forms and may be more prone to moisture and physical stability issues during storage. Storage conditions and requirements for packaging and accelerated stability testing for 3DP tablets must be developed and validated. It has been observed that storage under controlled humidity conditions (<40% RH) retains the disintegration properties of FDM-printed ODTs.[28] In addition to physical stability, chemical stability in terms of drug stability in the polymer and detection of degradation products from thermal processing must be a quality attribute.[14]

6.3 Printer Validation and GMP Compliance

However, the integration of 3D printing in the pharmaceutical manufacturing process in the GMP environment poses great challenges, both from the engineering and the regulatory points of view. In fact, the existing pharmaceutical manufacturing equipment is designed for controlled, validated, and reproducible processes, while the 3D printing process is inherently variable, with several process factors, such as temperature, print speed, layer thickness, infill density, nozzle design, etc., influencing the final product quality. The development of GMP-capable 3D printers with validated process controls, cleaning, and cross-contamination prevention, as well as real-time process monitoring, is still in the development phase.[19] The PolyPrint consortium has published detailed quality considerations for the development of GMP-capable FDM 3D printers, including the design of the print head, the filament feeding system, as well as in-process analytical tools.[19]

However, cleaning and cross-contamination prevention are particularly difficult to achieve in those technologies involving contact with drug-containing materials such as filaments, pastes, and inks. FDM print heads' internal geometry is difficult to clean, which has sparked concerns regarding API carryover between different formulation types. Single use print nozzle inserts and separate printer systems for each formulation have been suggested as a viable solution for a multi-product POC pharmacy setup.[34]

7. Regulatory Landscape and Compliance Considerations

7.1 Current Regulatory Frameworks

The regulatory landscape for 3D-printed pharmaceuticals remains to be a rapidly changing field. FDA approval of Spritam® in 2015 through their Emerging Technology Program (ETP) set a precedent that 3D-printed pharmaceutical products can indeed be assessed through existing regulatory frameworks (21 CFR Parts 210 and 211) but also underscored the challenges of applying conventional quality standards to a technology that is fundamentally new.[6] In 2017, FDA released draft guidance on "Technical Considerations for Additive Manufactured Devices" (for medical

devices) as well as broader guidance on emerging technology applications, which identified 3D printing as a high-priority technology innovation area.[5]

The European Medicines Agency has developed a guideline on pharmaceutical development of medicines for paediatric use (EMEA/CHMP/QWP/180157/2004), and a legislative framework has been developed through the EU Paediatric Regulation to incentivize paediatric drug development.[7] Furthermore, the EMA has taken a proactive approach to engaging with the point-of-care pharmaceutical manufacturing model through their Innovation Task Force. In the UK, a public consultation on POC manufacturing has been initiated by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2021. However, there is a lack of a clear regulatory path for personalized 3D-printed medicines, particularly in a POC hospital pharmacy context, in any jurisdiction.[36]

7.2 Challenges in Regulatory Harmonization

One of the main challenges associated with the regulation of 3D-printed PMs is the dichotomy between traditional pharmaceutical regulatory principles (batch manufacturing, batch testing, specification of fixed-dose forms) and 3D printing technology (individual product manufacturing, digital prescription, flexible dosing). Traditional release testing of individually printed patient-specific doses is not feasible due to high cost and time factors associated with it. However, new regulatory strategies such as digital prescription validation, real-time in-process control, and quality system risk models need to be developed but have not been formally established.[37]

Intellectual property issues introduce another dimension of complexity to this problem. The digital nature of 3D-printed pharmaceutical products, wherein the formulation of a drug is encoded digitally in a prescription file that can be electronically sent to a 3D printer anywhere in the world, has important implications regarding how pharmaceutical companies' intellectual property rights to their formulation information can be protected from unauthorized 3D printing.[35] Regulatory harmonization efforts are also complicated by a wide gap between the maturity levels of regulators in different parts of the world; while regulators such as the FDA and EMA are beginning to develop frameworks, regulators in many developing countries are just beginning to become involved in 3D printing technology.[36]

7.3 Ethical and Patient Safety Considerations

Personalized paediatric medicines using 3D printing technology also pose ethical issues. For instance, issues of informed consent for the involvement of patients in the early clinical trials, equitable access to POC printing technology among healthcare systems, and the management of risks in the case of printing errors are significant issues that need careful consideration.[33] The protection of patient information, given the patient's personal information contained in the dosing information for the personalized medicines, and the liabilities in the case of harm arising from the use of a pharmacist-printed medicine are also important issues that need clarity. Comprehensive clinical trial designs for the clinical testing of 3D printing medicines at the POC, covering the clinical, ethical, and legal issues, have been proposed as a framework for the clinical translation of 3D printing medicines.[38]

8. Future Perspectives

8.1 Artificial Intelligence and Pharmacokinetic Modeling Integration

Achieving the full potential of individualized paediatric pharmacotherapy using 3D printing technology will necessitate the integration of sophisticated computational tools with the 3D printing platforms. Population pharmacokinetic and

physiologically based pharmacokinetic models already allow for the prediction of drug concentration in individual paediatric patients based on parameters such as age, weight, organ function status, and genotype. Future possibilities include the ability of decision support systems to calculate optimal doses for individual patients and generate digital prescription records containing the required tablet design and drug loading details, which can be transmitted directly to a validated printing platform in the pharmacy for automated execution as part of an overall system for data-driven automated personalized medicine manufacture.[35] AI-assisted formulation development will help speed up the search for optimal excipients and printing parameters for newly developed APIs, vastly reducing the time required for drug discovery through to availability of accessible individualized paediatric pharmacotherapy.

8.2 Decentralized Manufacturing and Global Access

The current 3D printing technologies available for pharmaceutical use are mainly limited to high-income group academic medical institutions and specialized compounding pharmacies in Western nations. However, it may be argued that the need for personalized paediatric medicines is most pronounced in low- and middle-income nations due to high rates of errors in measuring doses, lower availability of paediatric formulations, and high incidence of paediatric illnesses. A powerful and cost-effective system for SSE or FDM-based 3D printing technologies, coupled with user interfaces and centrally designed open-source digital formulation files, may be instrumental in facilitating decentralization in low- and middle-income nations for personalized paediatric medicine production.[35] The WHO has started to explore and investigate the notion of 3D printing as a facilitating technology in ensuring equitable access to essential medicines.

8.3 Multi-Drug Polypills and Combination Therapy

This is especially true in paediatric patients with long-term conditions such as HIV/AIDS, tuberculosis, epilepsy, and heart disease, which often require a combination of drugs to be taken simultaneously. The management of such a complex multi-drug regime has been identified as a significant problem in paediatric patients and caregivers, with non-adherence levels being directly proportional to the pill burden. 3DP has a distinct advantage in that it allows for the creation of "polypills" that have a combination of APIs in separate compartments or with different release profiles within a single dosage form that may be capable of being developed into a single daily tablet that is tailored to a patient's combination and quantity of drugs.[39] This is a frontier area that has been shown to be achievable at a proof-of-concept level but requires significant development work to be completed in order for it to be translated into a clinical application in paediatrics.

8.4 Biodegradable and Bioinspired Dosage Forms

Current emerging research is also looking into bio-inspired/biodegradable materials that can be used in pharmaceutical 3D printing, such as plant-based polymers, natural gums, and biodegradable synthetic polymers, which have a better environmental profile compared to their petroleum-based counterparts, such as thermoplastics. When considering paediatric formulations, formulations using food-grade materials with established paediatric safety profiles, such as carrageenan, pectin, and gelatin, may have a competitive advantage.[30] Edible pharmaceutical 3D printed dosage forms that mimic popular paediatric foods such as gummies, chocolates, and candies offer a new frontier of creativity in paediatric medication design, blurring the line between food and medicine, which could potentially change the face of paediatric medication.

9. CONCLUSIONS

Three-dimensional printing is at the forefront of a revolution in paediatric pharmaceutical manufacture. The basic flaw in current conventional and adult-dose fixed-dose pharmaceutical products for use in the pharmacologically heterogeneous and developmentally changing paediatric patient population has been long understood but inadequately addressed. 3D printing technologies such as fused deposition modeling, semi-solid extrusion, and binder jetting have emerged as technically viable and clinically proven answers to the main issues in paediatric pharmacotherapy: individualized dosing precision, enhanced palatability and patient acceptability, age suitability of dosage form design, and point-of-care manufacture.

The evidence reviewed in this section indicates that 3DP formulations in paediatrics have shown promise in delivering accurate doses and content uniformity within pharmacopoeia specifications; that formulation in a flavor and form that is more acceptable to children is important; that translation in areas such as epilepsy, endocrine disorders, and rare metabolic disorders is ongoing; and that compounding pharmacies are increasingly utilizing these technologies in a routine clinical setting. However, challenges abound in that the regulations are still evolving and not harmonized; GMP printing systems are still in development; long-term stability data are limited; and cost-effectiveness and scalability of POC printing in a healthcare system have not been fully explored.

The way forward will demand continued collaboration among disciplines, from pharmaceutical scientists and clinical pharmacologists, paediatricians, pharmacists, and regulators, through bioethicists and engineers, united by a shared commitment to the idea of ensuring that the right child receives the right drug in the right dose, in the right form, at the right time. 3D printing technology, with continued innovation and proper guidance from regulators, indeed holds the promise of making truly personalized pharmacotherapy for children a reality.

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