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REVIEW ARTICLE / DERLEME MAKALE

AN OVERVIEW OF 3D PRINTING TECHNOLOGIES FOCUSING MULTIDRUG-LOADED 3D PRINTED DOSAGE FORMS

ÇOKLU İLAÇ YÜKLÜ 3D BASKILI DOZAJ FORMLARINA ODAKLANAN 3D BASKI TEKNOLOJİLERİNE GENEL BAKIŞ

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ABSTRACT

Objective: *This review focuses on multidrug-loaded dosage forms produced with three-dimensional printing (3DP) technologies since the confirmation of Spritam®, the first 3D printed dosage form, in 2015.*

Result and Discussion: *The integration of multiple drugs within a single dosage form through 3DP offers substantial flexibility in design, allowing for the customization of dosage, drug release profiles, and geometric structures. These formulations offer significant design flexibility by combining different drugs in a single unit, and have the potential to optimize treatment strategies, especially for diseases requiring multiple drug use. The wide literature search reveals that the most commonly used method is Fused Deposition Modeling (FDM) to obtain 3D printed dosage forms with various geometries, such as multi-compartment capsules or tablets, bi-layered or multi-layered tablets exhibiting different release kinetics, and core/shell structured tablets. Multidrug-loaded 3D-printed dosage forms have significant potential for individualizing fixed-dose combinations and have become a promising tool for advancing personalized medicine and improving therapeutic outcomes for polypharmacy. This innovative approach can optimize therapeutic efficacy, reduce side effects, and improve patient compliance. As research continues to expand, these formulations represent a promising direction for the future of drug development and treatment strategies.*

Keywords: *3DP technology, multidrug-loaded 3D printlets, personalized medicine, polypills*

ÖZ

Amaç: *Bu derleme, 2015 yılında onaylanan ilk üç boyutlu baskılı dozaj formu olan Spritam®'dan bu yana, üç boyutlu baskılama (3DP) teknolojileriyle üretilen çoklu ilaç yüklü dozaj formlarına odaklanmaktadır.*

Sonuç ve Tartışma: *3DP sayesinde, tek bir dozaj formunda birden fazla ilacın entegrasyonu mümkün hale gelmiş olup, bu durum dozaj, ilaç salım profilleri ve geometrik yapılar açısından önemli bir tasarım esnekliği sağlamaktadır. Bu formülasyonlar, farklı ilaçları tek bir ünitede birleştirerek önemli bir tasarım esnekliği sunar ve özellikle birden fazla ilaç kullanımını gerektiren hastalıklar için tedavi stratejilerini optimize etme potansiyeline sahiptir. Geniş literatür araştırması, çok bölmeli kapsüller veya tabletler, farklı salım kinetiği gösteren çift katmanlı veya çok katmanlı tabletler ve çekirdek/kabuk yapılı tabletler gibi çeşitli geometrilere sahip 3D baskılı dozaj formları elde etmek için en yaygın kullanılan yöntemin Eriyik Birikim Modelleme (FDM) olduğunu ortaya koymaktadır. Çoklu ilaç yüklü 3D baskılı dozaj formları, sabit doz kombinasyonlarını kişiselleştirme noktasında önemli bir potansiyel sunmaktadır ve kişiselleştirilmiş tıbbın ilerletilmesinde ve*

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polifarmasiye bağlı terapötik sonuçların iyileştirilmesinde umut vadeden bir araç olarak değerlendirilmektedir. Bu yenilikçi yaklaşım, terapötik etkinliği artırabilir, yan etki riskini azaltabilir ve hasta uyumunu iyileştirebilir. Mevcut araştırmaların ilerlemesiyle birlikte, bu formülasyonlar ilaç geliştirme ve tedavi stratejilerinin geleceği açısından umut verici bir yön sunmaktadır.

Anahtar Kelimeler: *3DP teknolojisi, çoklu ilaç yüklü 3D çıktılar, kişiselleştirilmiş tıp, polipiller*

INTRODUCTION

The pharmaceutical industry continuously conducts research to develop drug formulations that are more effective and safer for treating diseases. The drug research involves many steps, such as discovery of new drugs, assessing their efficacy and safety via clinical trials, and refining existing drugs. Research conducted by the pharmaceutical industry significantly increases the therapeutic options for patients to alleviate the burden of disease, enhance quality of life, and prolong the lifespan.

Three-dimensional printing (3DP) technology turned out the 1980s with Charles Hull generated the first available on the market 3D printer using stereolithography (SLA). Subsequently, Fused Deposition Modeling (FDM) technology was developed at the start of the 1990s. During the same period, two other additive manufacturing technologies came into use: Solid Ground Curing (SGC) and Laminated Object Manufacturing (LOM) which were developed by Cubital and Helisys respectively [1-4]. 3DP is defined as a collection of technologies including rapid prototyping, solid freeform manufacturing, and commonly known as additive manufacturing. Additive manufacturing is equivalent to 3DP and uses a range of advanced printing techniques to build pre-designed 3D digital models layer by layer. The most extensive used 3DP technologies include SLA, FDM, Selective Laser Sintering (SLS), 3D Bioprinting and LOM [5].

3DP in healthcare has serious applications in divers' fields comprising implantable medical device manufacturing (vascular stents, prosthetic valves, orthopaedic implants, artificial joint prostheses, human organs) [6], medical imaging (physical visualization) [7], surgical guides/models [8], pharmaceutical dosage form manufacturing [9,10] and dental applications [11]. The first 3D printed dosage form, Spritam® (levetiracetam), improved by Aprecia Proprietary using the ZipDose Technology platform based on powder bed fusion, was authorised by the United States Food and Drug Administration (FDA) in 2015 [1,12,13].

Conventional pharmaceutical methods impose strict constraints on the drug's parameters, such as its dose, form, dimensions and release profile, and these processes only manufacture drug batches with specific, based on majority of patients to achieve the adequate therapeutic response. This may result in some frequent issues associated with using conventional dosage forms; some patients may require a lower dose, while some others may require a higher dose depending on many factors such as patient's health status condition, genetic traits and body structure are different, and a single specification may not suit all patients [14]. At this point, the use of 3DP technology provides revolutionary originality in dosage form design and enables personalized treatment approaches. Various methods of this technology have been developed to meet the patient-specific requirements expected of drugs, thus providing more customized and efficient treatment opportunities. Some of the potential advantages of pharmaceutical products produced with 3DP technology can be summarized as follows:

- Traditional drug products, such as tablets, usually have a simple and uniform structure and are designed to provide a shelf life of usually around two years. In contrast, 3DP technology offers pharmaceutical companies the opportunity to overcome these limitations enabling the development of complex, personalized, and immediately consumable pharmaceutical products.
- Personalized medicine formulations have the potential to minimize side effects by dose adjustments and make easier treatment processes, especially for pediatric and geriatric populations.
- Drugs manufactured on demand could improve emergency treatment applications and generate new opportunities for bringing novel medications with constrained stability to market [15].
- Orphan drugs which are not on market could be manufactured on demand [16].

This review is planned to give a brief introduction to 3DP technologies commonly used in pharmaceutical manufacturing, then focus on multidrug-loaded 3D printed dosage forms including a

summary of the current literature on these dosage forms. Multidrug-loaded 3D printed dosage forms are a particular most advanced applications that 3DP technology offers to the medicinal field. These formulations allow to formulate various drugs in a one single dosage form and, in addition to the advantages of monolithic (generally for drugs with the same dissolution profile), multilayer (when active substances are chemically incompatible or different dissolution profiles are required within the same dosage form) or multiparticle systems (for use with coated pellets and granules) offered by traditional fixed-dose combinations [17], multidrug-loaded 3D printed dosage forms may offer significant potential in patient-centered treatment strategies. This approach may offer significant advantages in optimizing patients' treatment processes and managing drug interactions. Especially for chronic diseases and complex treatment requirements, such formulations can potentially increase patient compliance and improve treatment efficacy.

A Brief Insight to 3DP Technologies Used in Pharmaceutical Manufacturing

3DP has developed and evolved in parallel with technological advances including powder solidification, liquid solidification, and extrusion-based systems [2]. Figure 1 illustrates a schematic representation of 3DP technologies used in drug formulations.

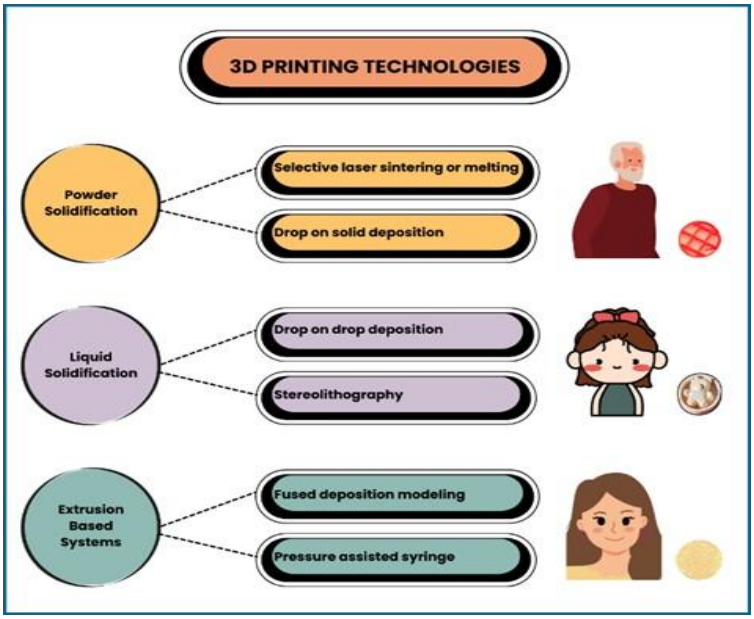

Figure 1. A schematic representation of 3DP technologies used in pharmaceutical formulations

Powder Solidification

The Drop on Solid Deposition (DOS) method, also referred to as binder jetting or drop-on-powder methods, originated at the Massachusetts Institute of Technology (MIT) in the 1980s and was brought to market by Z-Corporation [18]. The production of Spritam® is based on the DOS method. This method can be characterized as a form of wet granulation process where ink droplets or binder are deposited onto thin layers of powder, fusing the powder layers in place. Droplets from the inkjet head are used to bring together the loose powder bed layer. In this method, free powder particles function as a supporting material, preventing the collapse of shapes in the structure. After each step, the object is moved downwards via the movable build platform and a new layer of loose powder is added via the roller or powder spray system. In this process, 3D objects with the intended shape are formed by progressively layering each section. The DOS technique allows for the creation of solid oral dosage forms with elevated drug concentrations and is more convenient for pharmaceutical applications in comparison to other 3DP technologies for reason that powders and binder solutions used as starting materials are already commonly employed in the pharmaceutical sector. However, this method requires some

additional steps, for instance, an extra drying step to eliminate residual solvents and increase the physical strength of the printed structures [2,19,20]. Figure 2 provides a representative image of the DOS 3DP technology.

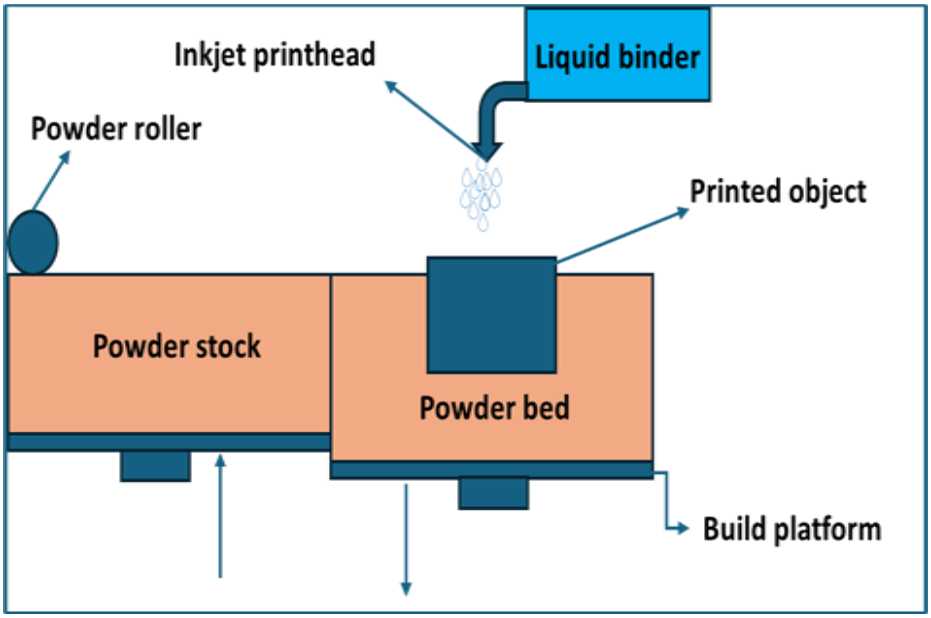

Figure 2. An illustrative diagram of the DOS 3DP technology

Selective Laser Sintering or Melting (SLS/SLM) technique was developed by Carl Deckard in 1984 and is like the DOS method in terms of basic principles. The SLS system comprises three key components: the spreading platform, the powder bed, and the laser system (laser and scanner). In this technique, thermoplastic polymers serve as the primary base material and the surface of the powder is smoothly conveyed to the spreading platform and levelled. The layers are created by lowering the powder bed by one layer thickness, either by sintering (heating to a temperature slightly below the melting point) which fuses the surface of the powder particles, or by melting the polymeric powder layer using a laser beam. This process is repeated to create 3D objects until the entire object is obtained. Once the print is complete, the objects are left embedded in the powder bed, where the bed is slowly cooled to prevent stress. Free powder particles on the build platform serve as a support throughout the process, eliminating the requirement of a secondary support structure. SLS/SLM technology offers a process that requires no solvents, no filaments, no polymerizable monomer/polymer liquid binders and no post-processing. Its solvent-free structure is ideal to produce drug molecules that react to water and organic solvents. The only prerequisite for this method is that the formulation components should be thermoplastic and thermally stable [2,13,21].

Liquid Solidification

The Drop-on-Drop Deposition (DOD) method does not involve a powder bed and are considered as inkjet systems. The ink droplets sprayed from the nozzle are deposited onto thin layers, which are then cured with cooling air or high-energy light. This method requires the use of support material for structures with protruding geometries [2,3].

SLA is the pioneering laser-based printing technology enabling the production of solid objects through the polymerization of liquid resins under ultraviolet (UV) light which developed by Japanese Dr. Kodama in 1980. This 3DP technology implements the formation of 3D objects by triggering the polymerization of photosensitive resin with a high UV laser beam. The laser beam is directed through scanning mirrors, precisely building up layers of the object on the build platform by cross-linking the photosensitive resin. Once each layer is finished, the platform descends by the thickness of one layer.

The heating during the printing process is kept to a minimum, which avoids the thermal degradation of drugs. Additionally, drugs can be integrated into the resin as a solution or suspension prior to printing, ensuring that water solubility does not restrict formulation development. However, the limited availability and toxicity of photo-crosslinkable resins and the high cost of SLA are the major disadvantages of this method [2,3,22-24].

Extrusion Based Systems

Extrusion-based printing is among the most utilized 3DP technologies in pharmaceutical manufacturing. In this approach, a filament or semi-solid material is extruded through a printing nozzle to create 3D objects. The extruded material is deposited in layers according to the shape of the target object, and then these layers are hardened by the cooling process or solidized by evaporation of the solvent [25]. This method can be categorized into two primary types: FDM and Pressure Assisted Modeling (PAM). Since first introduction by Stratasys Corporation in 1992, FDM is one of the most employed methods in the pharmaceutical industry because of its affordability, high product durability, no solvents required and simple equipment. FDM type printers consist of a moving plate and an extrusion head. In FDM printers, drug-loaded filament is pushed through a nozzle, necessitating high temperatures to melt the filament; therefore, pharmaceutical ingredients must be stable in high temperatures. Spinning gears in the print head direct the filament into a heated nozzle, where it melts and then extruded from the nozzle onto the platform, creating 3D structures. The diameter of the filaments used must be compatible with the printer specifications, where the filament requirement can be considered as the restrictive step. Ready to use filaments can be obtained commercially or produced on purpose by Hot Melt Extrusion (HME) method [4,12,26,27]. Figure 3 provides a schematic representation of the FDM 3DP technology.

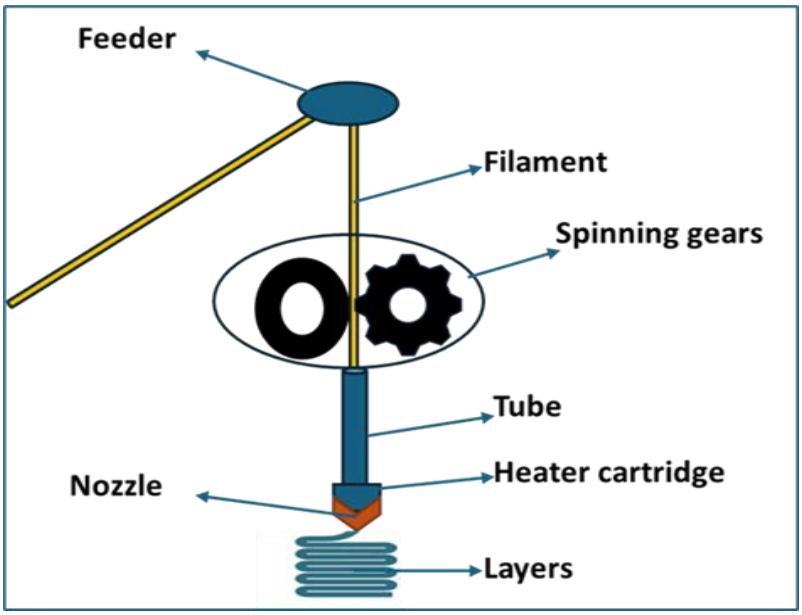

Figure 3. A representative figure of the FDM 3DP technology

Conversely, the PAM method functions at ambient temperature and uses semi-solid materials, eliminating the possibility of active ingredients decomposing in heat. Nevertheless, PAM presents greater difficulty because it demands that the printed materials maintain their shape throughout the deposition process, and post-processing drying of 3D printed products. In the PAM printer, a syringe filled with semi-solid material is placed in an arm that moves above the printing platform. Pressure applied through a pneumatic system, piston, or rotating screw, forces the material through a nozzle, hence creating printed dosage forms. This process is repeated until the desired design is completed and

eventually the 3D object emerges. The rheological characteristics of the semi-solid material employed during printing are crucial. Notably thermally unstable drugs can be easily processed with this method [12,28]. A PAM 3D printer is schematized in Figure 4.

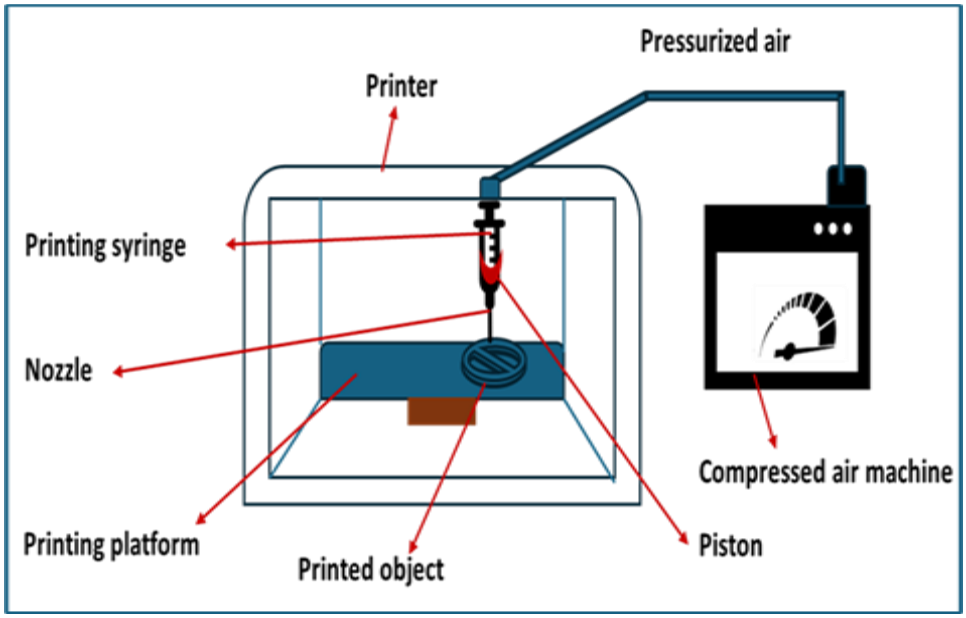

Figure 4. A representative figure of a PAM 3D printer

Multidrug-Loaded 3D Printed Dosage Forms

Combination drug therapies allow targeting multiple biological mechanisms simultaneously providing a superior efficacy compared to single-drug therapies [17,29]. As a fact, the use of multiple prescription medications simultaneously has increased significantly in recent years [30]. Multidrug-loaded dosage forms have the potential to increase patient compliance by simplifying medication management for patients practicing polypharmacy. Combining multiple active ingredients in a single dosage form can reduce dose frequency, improve patient quality of life and the treatment efficiency. Additionally, from an economic perspective, it can reduce the overall cost of medicines by reducing packaging, storage and distribution costs [17]. However, the use of multidrug-loaded dosage forms also has some disadvantages. In particular, standardized dosages that may not fully match the individual treatment needs of each patient may limit treatment flexibility. In addition, the requirement to replace the entire tablet in case of intolerance to a component may complicate the treatment process. Drugs in the same dosage form may cause some *in vivo* incompatibilities in terms of absorption, distribution, metabolism and excretion [17]. Therefore, the use of multidrug-loaded dosage forms should be carefully evaluated according to the specific requirements of each patient, and formulations should be designed accordingly within this framework.

The application of 3DP technologies in manufacturing multidrug-loaded dosage forms stands out as an important development in this field. 3DP can increase treatment flexibility by allowing multidrug-loaded dosage forms to be customized to the individual needs of each patient. By offering combinations specific to each patient, it can lead to better patient compliance and treatment efficacy compared to standard multidrug-loaded dosage forms [31].

After Spritam®'s approval, 3DP technology, which has become increasingly prevalent in the field of drug development, gained significant momentum in the manufacturing of multidrug-loaded dosage forms. With advances in technology, this field has allowed for the emergence of innovative formulations. The main reason for this situation is that different 3DP technologies can be applied to eliminate the deficiencies created by traditional methods in the treatment process. Table 1 showcases

examples of notable multi-drug loaded 3D printed dosage forms developed using 3DP technology since 2015.

Table 1. Examples of multi-drug loaded 3D printed dosage forms developed using 3DP technology since 2015

3DP approach, Year	Therapeutic component/s - Objective of formulation
PAM, 2015	Providing an effective cardiovascular treatment regimen with an immediate-release section bearing aspirin, hydrochlorothiazide and sustained-release sections containing pravastatin, atenolol, and ramipril [32].
FDM, 2015	Production of multilayered capsule-shaped tablets containing paracetamol and caffeine exhibiting modified drug release profiles to meet the necessity of personalized treatments [33].
PAM, 2015	Development of a multi-compartment tablet containing captopril, nifedipine and glipizide for managing diabetic patients with hypertension [34].
FDM, 2017	To develop and produce a flexible capsule-based drug delivery system featuring individual compartments that can be filled with different active ingredients or various doses and/or formulations of a single drug; with paracetamol as the model drug [35].
FDM, 2017	Design and production of oral dual-compartment dosage unit for rifampicin and isoniazid, which are first-line combination drugs for tuberculosis treatment that interact with each other when released simultaneously in acidic medium [36].
FDM, 2018	Production of a bilayer oral solid dosage form containing antidiabetic drugs metformin and glimepiride [37].
FDM, 2018	Integrating the benefits of 3DP with the advantages of fixed-dose combinations by producing bilayer tablets of the antihypertensive drugs enalapril maleate and hydrochlorothiazide [38].
PAM, 2018	Production of most commonly used drugs in diabetes mellitus-metformin hydrochloride, glyburide and acarbose- in polypills of different forms (core–shell, multilayer, and gradient distributions) [39].
PAM, 2019	Developing of a single-step 3DP technology that enables the controlled release of efavirenz, tenofovir disoproxil fumarate and emtricitabine drugs which are used as first-line treatment of HIV-1 [40].
SLA, 2019	Printing of paracetamol, caffeine, naproxen, chloramphenicol, prednisolone and aspirin with different geometries and different compositions of materials [41].
FDM, 2019	Concentric chamber capsule design that can be used when pulse release is needed or when dealing with two distinct active substances (model drugs dronedarone hydrochloride and ascorbic acid) need to be administered simultaneously [42].
FDM, 2019	Production of personalized polypills containing lisinopril dihydrate, indapamide, rosuvastatin calcium and amlodipine besylate for managing cardiovascular conditions [43].
FDM, 2020	Design of a novel hollow composite (two medications contained in individual compartments within the suppository shell) rectal suppository formulation loaded with ibuprofen ionic liquid and domperidone [44].
SLS, 2020	Polypill printing of amlodipine and lisinopril for antihypertensive therapy [45].
FDM - Melt Casting Techniques, 2020	Formulation of a multi-compartment polypill with aspirin and simvastatin for cardiovascular disease prevention (drugs were filled into the polypill compartment using melt casting method) [46].

Table 1 (*continue*). Examples of multi-drug loaded 3D printed dosage forms developed using 3DP technology since 2015

SLA, 2020	Preparation of a multilayer oral dosage form of common antihypertensive drugs (irbesartan, atenolol, hydrochlorothiazide, and amlodipine) [47].
Coaxial bioprinting, 2020	Development of a drug rod (implant) enable to release bevacizumab and dexamethasone by different release kinetics from the same region of the core/shell structure for retinal vascular diseases treatment [48].
FDM, 2021	Manufacture of a bilayer tablet featuring isoniazid and rifampicin for tuberculosis treatment [49].
PAM, 2021	Manufacture of an oral polypill with vitamins B1, B3, B6, and caffeine, designed to provide drug release through two distinct kinetics for personalized supplement delivery [50].
FDM, 2022	Production of a polypill containing pramipexole, levodopa and benserazide enabling to release drugs by varied release kinetics for managing Parkinson's disease [51].
PAM + FDM, 2022	Development of a personalized combi-pill containing tranexamic acid and indomethacin by integrating syringe-based extrusion 3DP with FDM techniques to achieve rapid anti-bleeding and sustained anti-inflammatory effects [52].
FDM, 2022	For antihypertensive therapy, production of core-shell type tablets of fixed-dose combinations of drugs, atorvastatin calcium and amlodipine besylate, as two independent compartments with HME-FDM techniques[53].
FDM, 2022	Producing bilayer tablets of model drugs paracetamol and caffeine citrate [54].
PAM, 2022	Production of cardiovascular polypills containing atorvastatin and metoprolol, to modulate the release of drugs by adjustment of formulation and geometric variables [55].
FDM, 2023	Creation of LEGO®-style compartments for the immediate release of melatonin, with customizable lag times, followed by a controlled release of caffeine for managing sleep disorders [56].
FDM, 2023	Manufacture of polypills incorporating nifedipine, simvastatin, and gliclazide for managing metabolic syndrome [57].
FDM, 2024	Combining artificial intelligence and 3DP technology to create an innovative and personalized capsule containing isoniazid and acetaminophen [58].
FDM, 2024	Developing a gastric floating polypill formulation containing diltiazem, propranolol, and hydrochlorothiazide for hypertension treatment [59].
PAM, 2024	Providing adjuvant chemotherapy with 5-fluorouracil and cisplatin-loaded biodegradable bilayer films [60].

* FDM; Fused Deposition Modeling, PAM; Pressure Assisted Modeling, SLA; Stereolithography, SLS; Selective Laser Sintering

The detailed literature search revealed that dosage forms with various geometries such as multi-compartment capsules or tablets, bi-layered or multi-layered tablets or capsules with different release kinetics, core/shell structured tablets, capsule or rod systems and LEGO®-like compartmental structures could be obtained with different printing techniques. The studies mainly focus on developing multidrug-loaded 3D printed dosage forms for the treatment of diseases that may require the simultaneous use of more than one drug, especially to suggest new treatment strategies for cardiovascular diseases (e.g. hypertension). In addition, multidrug-loaded 3D printed dosage forms have been also investigated for purposes such as antidiabetic effect, analgesic and anti-inflammatory effect, tuberculosis, and HIV treatment. While the availability of different printing techniques (such as SLA, SLS, FDM, bioprinting) in the production of multidrug-loaded 3D printed dosage forms is quite impressive, FDM method is still the most common technique due to its various advantages. In terms of economic aspects, FDM printers

are the most moderate option by far. Additionally, extrusion-based printing techniques are noted to be superior to fabricate more complex structures [17].

There are also studies combining extrusion-based printing with various methods. Fuenmayor et al. [61] developed a manufacturing platform using injection molding (IM) to overcome the low throughput and other limitations of the Fused Filament Fabrication (FFF) process by integrating FFF and IM techniques. In this context, the authors created bilayer tablets with adjustable drug release profiles by incorporating hydrochlorothiazide in the FFF layer and lovastatin in the IM layer. They highlighted this approach as a promising avenue for the mass customization of drug dosage forms. In a similar study conducted by Ebrahimi et al. [62] personalized bilayer tablets loaded with caffeine and paracetamol were produced by integrating Droplet Deposition Modeling (DDM) and IM techniques. In this study, the benefits of both DDM and IM techniques have been integrated for tablet manufacturing.

McDonagh et al. [63] developed two different model formulations, an immediate release erodible system of paracetamol-loaded Eudragit E PO and an erodible/swelling Soluplus system loaded with felodipine using the Arburg Plastic Freeforming (APF) method to achieve simultaneous, delayed, and pulsatile drug release regimes. The direct granule-fed thermal droplet-based 3DP process using APF was thoroughly explained, with the method recommended for pharmaceutical materials unsuitable for other commercial thermal 3DP technologies. Although the tablets produced by the technique successfully provided simultaneous and delayed release profiles, pulsed release could not be achieved due to non-uniform erosion of the tablets under dynamic dissolution conditions.

In addition to multidrug-loaded 3D printed dosage forms, another remarkable field of research is the development of multidrug-loaded 3D printed hearing aids. Lopez et al. [64] detailed the application of 3DP to create hearing aids containing two antibiotics (ciprofloxacin and fluocinolone acetonide). The study, which stated that long-term use of hearing aids causes ear infections, used Kudo 3DSR Flexible resin and Kudo 3DSR ENG hard resin for printing hearing aids by Digital Light Processing 3DP technology. *In vitro* drug release studies demonstrated that both drugs could sustain drug release for over 7 days. The hearing aids also reported to be suitable for sterilization and suggested to be used in the treatment of acute otitis media with tympanostomy tubes. Given that ear anatomy varies from person to person, utilizing 3DP technology for creating drug-loaded hearing aids holds significant potential.

RESULT AND DISCUSSION

In this review, studies conducted on multidrug-loaded 3D printed dosage forms from 2015 to present were systematically examined, and the rising interest on the subject was assessed. The reviewed studies highlighted the promising potential of 3DP technologies in the development of multi-drug loaded formulations and demonstrated how these technologies are increasingly being integrated into drug development processes. 3DP technologies offer substantial benefits in manufacturing of multidrug-loaded dosage forms suggesting great potential, particularly in customizing fixed-dose combinations and the development of patient-specific treatment strategies. 3D printed polypills enable to formulate drugs in the desired doses and combinations for the treatment of diseases that may require more than one drug, such as hypertension and diabetes mellitus. In addition, more complex structures and release profiles can be obtained more effortlessly. However, challenges keep up to date, particularly in optimizing the scale up of the production process, ensuring consistent quality control, and addressing regulatory aspects for 3DP-produced pharmaceuticals. As 3DP technologies continue to evolve, overcoming these hurdles will be critical in enabling wider clinical adoption. While flexibility in the production process offers a great advantage for personalized treatments, creativity in drug design, highlighting patient-specific solutions, and process optimization also increase the future potential of 3DP. In the future, advancements in materials science and printing techniques will likely further expand the application of these technologies in drug development.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

REFERENCES

1. Sultana, N., Ali, A., Waheed, A., Aqil, M. (2023). 3D Printing in pharmaceutical manufacturing: Current status and future prospects. Materials Today Communications, 38, 107987. [CrossRef]
2. Jamróz, W., Szafraniec, J., Kurek, M., Jachowicz, R. (2018). 3D printing in pharmaceutical and medical applications-recent achievements and challenges. Pharmaceutical Research, 35, 1-22. [CrossRef]
3. Souto, E., Campos, J., Filho, S., Teixeira, M., Martins-Gomes, C., Zielinska, A., Carbone, C., Silva, A. (2019). 3D printing in the design of pharmaceutical dosage forms. Pharmaceutical Development and Technology, 24(8), 1044-1053. [CrossRef]
4. Parulski, C., Jennotte, O., Lechanteur, A., Evrard, B. (2021). Challenges of fused deposition modeling 3D printing in pharmaceutical applications: Where are we now?. Advanced Drug Delivery Reviews, 175, 113810. [CrossRef]
5. Hurst, E.J. (2016). 3D printing in healthcare: Emerging applications. Journal of Hospital Librarianship, 16(3), 255-267. [CrossRef]
6. Wang, Z., Yang, Y. (2021). Application of 3D printing in implantable medical devices. BioMed Research International, 2021(1), 6653967. [CrossRef]
7. Jia, G., Huang, X., Tao, S., Zhang, X., Zhao, Y., Wang, H., He, J., Hao, J., Liu, B., Zhou, J. (2022). Artificial intelligence-based medical image segmentation for 3D printing and naked eye 3D visualization. Intelligent Medicine, 2(1), 48-53. [CrossRef]
8. Chen, X., Possel, J.K., Wacongne, C., Van Ham, A.F., Klink, P.C., Roelfsema, P.R. (2017). 3D printing and modelling of customized implants and surgical guides for non-human primates. Journal of Neuroscience Methods, 286, 38-55. [CrossRef]
9. Saydam, M., Timur, S.S., Vural, İ., Takka, S. (2022). Cell culture and pharmacokinetic evaluation of a solid dosage formulation containing a water-insoluble orphan drug manufactured by FDM-3DP technology. International Journal of Pharmaceutics, 628, 122307. [CrossRef]
10. Koçak, E., Yıldız, A., Acartürk, F. (2021). Three dimensional bioprinting technology: Applications in pharmaceutical and biomedical area. Colloids and Surfaces B: Biointerfaces, 197, 111396. [CrossRef]
11. Jaramillo, N., Moreno, A., Ospina, V., Lopera, A., Pelaez-Vargas, A., Cupitra, N., García, C., Paucar, C. (2023). Effect of synthesis on the antimicrobial response of β-TCP/Mg with potential applications in the regeneration of dental tissue: 3D printing of ceramic paste in a β-TCP/Mg/bioglass system. Materials Letters, 350, 134907. [CrossRef]
12. Algahtani, M.S., Ahmad, J., Mohammed, A.A., Ahmad, M.Z. (2024). Extrusion-based 3D printing for development of complex capsular systems for advanced drug delivery. International Journal of Pharmaceutics, 663, 124550. [CrossRef]
13. Charoo, N.A., Barakh Ali, S.F., Mohamed, E.M., Kuttolamadom, M.A., Ozkan, T., Khan, M.A., Rahman, Z. (2020). Selective laser sintering 3D printing–an overview of the technology and pharmaceutical applications. Drug Development and Industrial Pharmacy, 46(6), 869-877. [CrossRef]
14. Zhu, X., Li, H., Huang, L., Zhang, M., Fan, W., Cui, L. (2020). 3D printing promotes the development of drugs. Biomedicine & Pharmacotherapy, 131, 110644. [CrossRef]
15. Norman, J., Madurawe, R.D., Moore, C.M., Khan, M.A., Khairuzzaman, A. (2017). A new chapter in pharmaceutical manufacturing: 3D-printed drug products. Advanced Drug Delivery Reviews, 108, 39-50. [CrossRef]
16. Saydam, M., Takka, S. (2020). Improving the dissolution of a water-insoluble orphan drug through a fused deposition modelling 3-Dimensional printing technology approach. European Journal of Pharmaceutical Sciences, 152, 105426. [CrossRef]

17. Fernández-García, R., Prada, M., Bolás-Fernández, F., Ballesteros, M.P., Serrano, D.R. (2020). Oral fixed-dose combination pharmaceutical products: Industrial manufacturing versus personalized 3D printing. Pharmaceutical Research, 37, 1-22. [CrossRef]
18. Chen, X., Wang, S., Wu, J., Duan, S., Wang, X., Hong, X., Han, X., Li, C., Kang, D., Wang, Z. (2022). The application and challenge of binder jet 3D printing technology in pharmaceutical manufacturing. Pharmaceutics, 14(12), 2589. [CrossRef]
19. Gottschalk, N., Burkard, A., Quodbach, J., Bogdahn, M. (2023). Drop-on-powder 3D printing of amorphous high dose oral dosage forms: Process development, opportunities and printing limitations. International Journal of Pharmaceutics: X, 5, 100151. [CrossRef]
20. Shi, K., Tan, D.K., Nokhodchi, A., Maniruzzaman, M. (2019). Drop-on-powder 3D printing of tablets with an anti-cancer drug, 5-fluorouracil. Pharmaceutics, 11(4), 150. [CrossRef]
21. Awad, A., Fina, F., Goyanes, A., Gaisford, S., Basit, A.W. (2020). 3D printing: Principles and pharmaceutical applications of selective laser sintering. International Journal of Pharmaceutics, 586, 119594. [CrossRef]
22. Deshmane, S., Kendre, P., Mahajan, H., Jain, S. (2021). Stereolithography 3D printing technology in pharmaceuticals: A review. Drug Development and Industrial Pharmacy, 47(9), 1362-1372. [CrossRef]
23. Xu, X., Goyanes, A., Trenfield, S.J., Diaz-Gomez, L., Alvarez-Lorenzo, C., Gaisford, S., Basit, A.W. (2021). Stereolithography (SLA) 3D printing of a bladder device for intravesical drug delivery. Materials Science and Engineering: C, 120, 111773. [CrossRef]
24. Lakkala, P., Munnangi, S.R., Bandari, S., Repka, M. (2023). Additive manufacturing technologies with emphasis on stereolithography 3D printing in pharmaceutical and medical applications: A review. International Journal of Pharmaceutics: X, 5, 100159. [CrossRef]
25. Samiei, N. (2020). Recent trends on applications of 3D printing technology on the design and manufacture of pharmaceutical oral formulation: A mini review. Beni-Suef University Journal of Basic and Applied Sciences, 9(12), 1-12. [CrossRef]
26. Dumpa, N., Butreddy, A., Wang, H., Komanduri, N., Bandari, S., Repka, M.A. (2021). 3D printing in personalized drug delivery: An overview of hot-melt extrusion-based fused deposition modeling. International Journal of Pharmaceutics, 600, 120501. [CrossRef]
27. Rahim, T.N.A.T., Abdullah, A.M., Md Akil, H. (2019). Recent developments in fused deposition modeling-based 3D printing of polymers and their composites. Polymer Reviews, 59(4), 589-624. [CrossRef]
28. Mohammed, A.A., Algahtani, M.S., Ahmad, M.Z., Ahmad, J. (2021). Optimization of semisolid extrusion (pressure-assisted microsyringe)-based 3D printing process for advanced drug delivery application. Annals of 3D Printed Medicine, 2, 100008. [CrossRef]
29. Hatami, H., Mojahedian, M.M., Kesharwani, P., Sahebkar, A. (2024). Advancing personalized medicine with 3D printed combination drug therapies: A comprehensive review of application in various conditions. European Polymer Journal, 215, 113245. [CrossRef]
30. Melocchi, A., Uboldi, M., Maroni, A., Foppoli, A., Palugan, L., Zema, L., Gazzaniga, A. (2020). 3D printing by fused deposition modeling of single-and multi-compartment hollow systems for oral delivery-A review. International Journal of Pharmaceutics, 579, 119155. [CrossRef]
31. Chen, G., Xu, Y., Kwok, P.C.L., Kang, L. (2020). Pharmaceutical applications of 3D printing. Additive Manufacturing, 34, 101209. [CrossRef]
32. Khaled, S.A., Burley, J.C., Alexander, M.R., Yang, J., Roberts, C.J. (2015). 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. Journal of Controlled Release, 217, 308-314. [CrossRef]
33. Goyanes, A., Wang, J., Buanz, A., Martínez-Pacheco, R., Telford, R., Gaisford, S., Basit, A.W. (2015). 3D printing of medicines: Engineering novel oral devices with unique design and drug release characteristics. Molecular Pharmaceutics, 12(11), 4077-4084. [CrossRef]
34. Khaled, S.A., Burley, J.C., Alexander, M.R., Yang, J., Roberts, C.J. (2015). 3D printing of tablets containing multiple drugs with defined release profiles. International Journal of Pharmaceutics, 494(2), 643-650. [CrossRef]
35. Maroni, A., Melocchi, A., Parietti, F., Foppoli, A., Zema, L., Gazzaniga, A. (2017). 3D printed multi-compartment capsular devices for two-pulse oral drug delivery. Journal of Controlled Release, 268, 10-18. [CrossRef]
36. Genina, N., Boetker, J.P., Colombo, S., Harmankaya, N., Rantanen, J., Bohr, A. (2017). Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: From drug product design to *in vivo* testing. Journal of Controlled Release, 268, 40-48. [CrossRef]
37. Gioumouxouzis, C.I., Baklavaridis, A., Katsamenis, O.L., Markopoulou, C.K., Bouropoulos, N., Tzetzis, D., Fatouros, D.G. (2018). A 3D printed bilayer oral solid dosage form combining metformin for prolonged

and glimepiride for immediate drug delivery. European Journal of Pharmaceutical Sciences, 120, 40-52. [CrossRef]
38. Sadia, M., Isreb, A., Abbadi, I., Isreb, M., Aziz, D., Selo, A., Timmins, P., Alhnan, M.A. (2018). From 'fixed dose combinations' to 'a dynamic dose combiner': 3D printed bi-layer antihypertensive tablets. European Journal of Pharmaceutical Sciences, 123, 484-494. [CrossRef]
39. Haring, A.P., Tong, Y., Halper, J., Johnson, B.N. (2018). Programming of multicomponent temporal release profiles in 3D printed polypills via core–shell, multilayer, and gradient concentration profiles. Advanced Healthcare Materials, 7(16), 1800213. [CrossRef]
40. Siyawamwaya, M., du Toit, L.C., Kumar, P., Choonara, Y.E., Kondiah, P.P., Pillay, V. (2019). 3D printed, controlled release, tritherapeutic tablet matrix for advanced anti-HIV-1 drug delivery. European Journal of Pharmaceutics and Biopharmaceutics, 138, 99-110. [CrossRef]
41. Robles-Martinez, P., Xu, X., Trenfield, S.J., Awad, A., Goyanes, A., Telford, R., Basit, A.W., Gaisford, S. (2019). 3D printing of a multi-layered polypill containing six drugs using a novel stereolithographic method. Pharmaceutics, 11(6), 274. [CrossRef]
42. Matijašić, G., Gretić, M., Vinčić, J., Poropat, A., Cuculić, L., Rahelić, T. (2019). Design and 3D printing of multi-compartmental PVA capsules for drug delivery. Journal of Drug Delivery Science and Technology, 52, 677-686. [CrossRef]
43. Pereira, B.C., Isreb, A., Forbes, R.T., Dores, F., Habashy, R., Petit, J.B., Alhnan, M.A., Oga, E.F. (2019). 'Temporary Plasticiser': A novel solution to fabricate 3D printed patient-centred cardiovascular 'Polypill'architectures. European Journal of Pharmaceutics and Biopharmaceutics, 135, 94-103. [CrossRef]
44. Tagami, T., Ito, E., Hayashi, N., Sakai, N., Ozeki, T. (2020). Application of 3D printing technology for generating hollow-type suppository shells. International Journal of Pharmaceutics, 589, 119825. [CrossRef]
45. Trenfield, S.J., Tan, H.X., Goyanes, A., Wilsdon, D., Rowland, M., Gaisford, S., Basit, A.W. (2020). Non-destructive dose verification of two drugs within 3D printed polyprintlets. International Journal of Pharmaceutics, 577, 119066. [CrossRef]
46. Keikhosravi, N., Mirdamadian, S.Z., Varshosaz, J., Taheri, A. (2020). Preparation and characterization of polypills containing aspirin and simvastatin using 3D printing technology for the prevention of cardiovascular diseases. Drug Development and Industrial Pharmacy, 46(10), 1665-1675. [CrossRef]
47. Xu, X., Robles-Martinez, P., Madla, C.M., Joubert, F., Goyanes, A., Basit, A.W., Gaisford, S. (2020). Stereolithography (SLA) 3D printing of an antihypertensive polyprintlet: Case study of an unexpected photopolymer-drug reaction. Additive Manufacturing, 33, 101071. [CrossRef]
48. Won, J.Y., Kim, J., Gao, G., Kim, J., Jang, J., Park, Y.H., Cho, D.W. (2020). 3D printing of drug-loaded multi-shell rods for local delivery of bevacizumab and dexamethasone: A synergetic therapy for retinal vascular diseases. Acta Biomaterialia, 116, 174-185. [CrossRef]
49. Tabriz, A.G., Nandi, U., Hurt, A.P., Hui, H.W., Karki, S., Gong, Y., Kumar, S., Douroumis, D. (2021). 3D printed bilayer tablet with dual controlled drug release for tuberculosis treatment. International Journal of Pharmaceutics, 593, 120147. [CrossRef]
50. Goh, W.J., Tan, S.X., Pastorin, G., Ho, P.C.L., Hu, J., Lim, S.H. (2021). 3D printing of four-in-one oral polypill with multiple release profiles for personalized delivery of caffeine and vitamin B analogues. International Journal of Pharmaceutics, 598, 120360. [CrossRef]
51. Windolf, H., Chamberlain, R., Breitkreutz, J., Quodbach, J. (2022). 3D printed mini-floating-Polypill for Parkinson's disease: Combination of levodopa, benserazide, and pramipexole in various dosing for personalized therapy. Pharmaceutics, 14(5), 931. [CrossRef]
52. Zhang, B., Teoh, X.Y., Yan, J., Gleadall, A., Belton, P., Bibb, R., Qi, S. (2022). Development of combi-pills using the coupling of semi-solid syringe extrusion 3D printing with fused deposition modelling. International Journal of Pharmaceutics, 625, 122140. [CrossRef]
53. Alzahrani, A., Narala, S., Youssef, A.A.A., Nyavanandi, D., Bandari, S., Mandati, P., Almotairy, A., Almutairi, M., Repka, M. (2022). Fabrication of a shell-core fixed-dose combination tablet using fused deposition modeling 3D printing. European Journal of Pharmaceutics and Biopharmaceutics, 177, 211-223. [CrossRef]
54. Zhang, P., Xu, P., Chung, S., Bandari, S., Repka, M.A. (2022). Fabrication of bilayer tablets using hot melt extrusion-based dual-nozzle fused deposition modeling 3D printing. International Journal of Pharmaceutics, 624, 121972. [CrossRef]
55. Alayoubi, A., Zidan, A., Asfari, S., Ashraf, M., Sau, L., Kopcha, M. (2022). Mechanistic understanding of the performance of personalized 3D-printed cardiovascular polypills: A case study of patient-centered therapy. International Journal of Pharmaceutics, 617, 121599. [CrossRef]

56. Tabriz, A.G., Mithu, M.S., Antonijevic, M.D., Vilain, L., Derrar, Y., Grau, C., Morales, A., Katsamenis, O.L., Douroumis, D. (2023). 3D printing of LEGO® like designs with tailored release profiles for treatment of sleep disorder. International Journal of Pharmaceutics, 632, 122574. [CrossRef]
57. Anaya, B.J., Cerda, J.R., D'Atri, R.M., Yuste, I., Luciano, F.C., Kara, A., Ruiz, H.K., Ballesteros, M.P., Serrano, D.R. (2023). Engineering of 3D printed personalized polypills for the treatment of the metabolic syndrome. International Journal of Pharmaceutics, 642, 123194. [CrossRef]
58. Hu, J., Wan, J., Xi, J., Shi, W., Qian, H. (2024). AI-driven design of customized 3D-printed multi-layer capsules with controlled drug release profiles for personalized medicine. International Journal of Pharmaceutics, 656, 124114. [CrossRef]
59. Zgouro, P., Katsamenis, O.L., Moschakis, T., Eleftheriadis, G.K., Kyriakidis, A.S., Chachlioutaki, K., Monou, P.K., Ntorkou, M., Zacharis, C.K., Bouropoulos, N. (2024). A floating 3D printed polypill formulation for the coadministration and sustained release of antihypertensive drugs. International Journal of Pharmaceutics, 655, 124058. [CrossRef]
60. Youssef, S.H., Ganesan, R., Amirmostofian, M., Kim, S., Polara, R., Afinjuomo, F., Song, Y., Chereda, B., Singhal, N., Robinson, N. (2024). Printing a cure: A tailored solution for localized drug delivery in liver cancer treatment. International Journal of Pharmaceutics, 651, 123790. [CrossRef]
61. Fuenmayor, E., O'Donnell, C., Gately, N., Doran, P., Devine, D.M., Lyons, J.G., McConville, C., Major, I. (2019). Mass-customization of oral tablets via the combination of 3D printing and injection molding. International Journal of Pharmaceutics, 569, 118611. [CrossRef]
62. Ebrahimi, F., Xu, H., Fuenmayor, E., Major, I. (2024). Tailoring drug release in bilayer tablets through droplet deposition modeling and injection molding. International Journal of Pharmaceutics, 653, 123859. [CrossRef]
63. McDonagh, T., Belton, P., Qi, S. (2023). Manipulating drug release from 3D printed dual-drug loaded polypills using challenging polymer compositions. International Journal of Pharmaceutics, 637, 122895. [CrossRef]
64. Vivero-Lopez, M., Xu, X., Muras, A., Otero, A., Concheiro, A., Gaisford, S., Basit, A.W., Alvarez-Lorenzo, C., Goyanes, A. (2021). Anti-biofilm multi drug-loaded 3D printed hearing aids. Materials Science and Engineering: C, 119, 111606. [CrossRef]