

Application of 3D Printing in Pharmaceutical Sciences, and Evaluation of Administration Routes for Drug-Loaded Composites

Khatami, Mohamad; Doniavi, Ali; Allahyari, Saeideh; Feizollahi, Mahsa; Abazari, Amir Musa; Fotouhi, Mohamad

DOI

[10.34172/PS.2022.49](https://doi.org/10.34172/PS.2022.49)

Publication date

2023

Document Version

Final published version

Published in

Pharmaceutical Sciences

Citation (APA)

Khatami, M., Doniavi, A., Allahyari, S., Feizollahi, M., Abazari, A. M., & Fotouhi, M. (2023). Application of 3D Printing in Pharmaceutical Sciences, and Evaluation of Administration Routes for Drug-Loaded Composites. *Pharmaceutical Sciences*, 29(3), 283-297. <https://doi.org/10.34172/PS.2022.49>

Important note

To cite this publication, please use the final published version (if applicable).
Please check the document version above.

Copyright

Other than for strictly personal use, it is not permitted to download, forward or distribute the text or part of it, without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license such as Creative Commons.

Takedown policy

Please contact us and provide details if you believe this document breaches copyrights.
We will remove access to the work immediately and investigate your claim.



Application of 3D Printing in Pharmaceutical Sciences, and Evaluation of Administration Routes for Drug-Loaded Composites

Mohamad Khatami¹, Ali Doniavi², Saeideh Allahyari³, Mahsa Feizollahi⁴, Amir Musa Abazari¹, Mohamad Fotouhi⁵

¹Department of Mechanical Engineering, Faculty of Engineering, Urmia University, Urmia, Iran.

²Department of Industrial Engineering, Faculty of Engineering, Urmia University, Urmia, Iran.

³Department of Pharmaceutics, School of Pharmacy, Ardabil University of Medical Sciences, Ardabil, Iran.

⁴Neurosciences Research Center, Tabriz University of Medical Science, Tabriz, Iran.

⁵Microlab, Faculty of Civil Engineering and Geosciences, Delft University of Technology, Delft 2628 CN, the Netherlands.

Article Info

Article History:

Received: 20 Aug 2022

Accepted: 27 Nov 2022

ePublished: 9 Dec 2022

Keywords:

-3D printer

-Administration

-Composite

-Drug

Abstract

3D printing is a novel approach in the pharmaceutical field, but its usage has not been fully established. This method can promote drug therapy and overcome some traditional treatment challenges in different ways that are discussed in this paper. "One-size-fits-all", Large-scale production, and less patient and physician acceptability are some limitations that we will encounter in traditional therapy. Three-dimensional printing of pharmaceutical products is a versatile technology that needs specific attention. Droplet-based, extrusion-based, and laser-assisted 3D printers are three main techniques that can be used in this field. The limitations and advantages of this method have been discussed, highlighting potential innovative pathways towards the possibility of drug carriers' usage in ink formulas. The administration pathway of drug-loaded composites is another critical issue in drug treatment strategies that have been discussed here. Oral drug delivery as a convenient method of systemic drug administration with significant patient preference is introduced as the most prevalent pathway that has been studied about 3D printed medicines. Finally, essential ethics and future directions of 3D printing in the pharmaceutical and healthcare industries are outlined.

Introduction

The 3D printing (3 dimensions, x, y, and z) concept emerged almost 50 years ago, and its development in the pharmaceutical field has increased significantly. This manufacturing process offers the potential to create new methods for personalized therapies. Recent advances in this field have overcome the challenges and limitations of traditional disease treatments. Therefore, the introduction of 3D printers, and food and drug administration (FDA) approved excipients for appropriate fabrication of dosage forms would be necessary. The main aspect of this review is to demonstrate the possibility of drug carriers' application in 3D printing processes. Drug delivery systems (DDSs) have been researched widely for incorporation of various drugs in pharmaceutical fields; but, their usage in 3D printing has been limited to a few studies on liposomes and cyclodextrins (CDs). Different dosage forms with multiple shapes can be fabricated by the 3D printing method, and it may affect drug release and administration pathways.¹ These products have been explored for various drug delivery purposes through different administration

pathways that are fully discussed in this paper. 4D printing processes with additional time dimension may also be applied for the proper delivery of active agents in the near future. There have been some published reviews about bioprinters, their types,²⁻⁴ and applications in medical fields such as implants.⁵ But in this review, the authors focus on pharmaceutical fields where traditional drug therapy challenges, types of 3D printers, and ink formulas are briefed and discussed. In addition, this paper provides two topics that were not covered in previous reviews; the possibility of nanocarriers' usage in the manufacturing process, and the classification of drug-loaded composites based on their administration pathways. Thoroughly, this review covered a general overview of the 3D printers' application in pharmaceuticals by providing innovative concepts for researchers.

Background: Current Challenges in Conventional Drug Delivery

Conventional drug delivery is associated with some challenges that are discussed below (Figure 1). The

*Corresponding Authors: Saeideh Allahyari, E-mail: s.allahyari@arums.ac.ir & Amir Musa Abazari, E-mail: am.abazari@urmia.ac.ir

©2023 The Author(s). This is an open access article and applies the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>). Non-commercial uses of the work are permitted, provided the original work is properly cited.



Figure 1. Current challenges accompanied by conventional drug therapies.

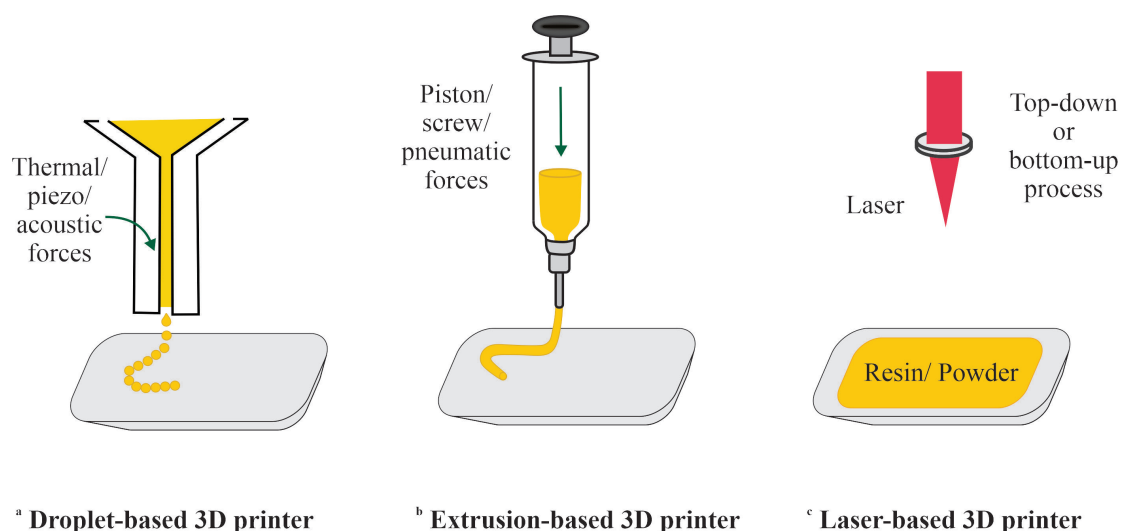
“One-size-fits-all” strategy or general dosage form can be considered as one of the main challenges. The administered dose might fall outside the optimum dose and can result in tablet splitting, compounded medications, and poly-pill prescriptions.^{6,7} A large-scale manufacturing unit is also required for traditional drug preparation. This process is a cost-effective, time-consuming, and labor-intensive procedure that can be regarded as another challenge.^{5,7} Less physician acceptability because of dosage inflexibility is another limitation of current therapy.⁷ All these limitations may lead to patients’ disinclination and create an urgent need for overcoming toxicities and adverse effects among individuals with different genetics and co-existing

problems.^{7,8} 3D printing technology might facilitate the generation of customized therapy for individuals by providing flexibility and free-form geometries.⁷ Personalized medicine may cover a better drug design with few side effects, although it is necessary to establish specific guidelines for ease of implementation.

3D Printers’ Usage in Pharmaceutics

Types of common 3D printers in the pharmaceutical field

Figure 2 shows different common types of 3D printers have been used in pharmaceutics. In the following, the process principles are discussed.



^a Droplet-based 3D printer

^b Extrusion-based 3D printer

^c Laser-based 3D printer

Figure 2. Common types of 3D printers in pharmaceutics. a: Droplet-based 3D Printer, b: Extrusion-based 3D Printer, c: Laser-based 3D Printer.

Droplet-based 3D Printer

Droplet-based 3D Printer (DBP) was first introduced in 1980,⁹ and it works based on three forces: thermal, piezo, and acoustic^{9,10} (Figure 2a). Moreover, drop-on-demand is also classified into drop-on-drop, and drop-on-solid deposition subtypes.³ Inkjet-based printers, the most common printer in pharmaceuticals,¹¹ can eject the ink onto the supporting substrate by the mentioned forces.^{9,12} The deposited substrate can be solidified using different mechanisms such as cross-linking, pH, and ultraviolet (UV) radiation.⁹ Therefore, critical factors in this printing process may be classified into droplet size, patterns, deposition rate, and usage of safe volatile solvent.^{13,14} The volume of droplets would be in the range of pL <1 to pL >300, and can be ejected ~50 µm wide, containing one or two cells in line.⁹ The ejection rate would also range from 1 to 10,000 droplets per second.⁹ This 3D printer offers a fabrication technique that is relatively low cost, high speed, and high resolution with the advantage of compatibility with various materials.⁹ Besides, non-uniformity of droplet size and nozzle clogging would be considered limitations of this method.^{9,10} In addition, the clogging through aqueous formulations would be decreased to some extent using moisturizing agents such as polyethylene glycol (PEG), propylene glycol, or glycerol.¹¹

Extrusion-based 3D Printer

Extrusion-based 3D Printer (EBP) is the most common technology among other methods in pharmaceuticals, and it was first developed in the early 2000s.¹⁵ Its ink is a continuous filament works based on piston, screw, or pneumatic forces⁹ (Figure 2b). The type of applied force would be mainly dependent on the rheological behavior

of substances. Most materials with different viscosities (ranging from 30 mPa·s to 6×10^7 mPa·s) can be printed by this method. Simultaneous deposition of multiple materials can be considered as another advantage of this technology.⁹ Here, it should be considered that the filament characteristics and nozzle clogging are essential factors to be analyzed.^{9,12} Elasticity, stiffness, and the homogeneous dimension of the filaments are other vital factors that should be optimized.¹² Fused deposition modeling (FDM), which operates based on extruding a thermoplastic filament through a high-temperature nozzle, can be categorized as the major subtype of EBP³ and is suitable for the rapid fabrication of small-scale unit composites.¹⁶

Laser-based 3D Printer

The first idea of laser-based, laser-assisted, or laser-direct-write originated in 1984 by Charles Hull,¹⁷ and was named stereolithography as a patent in 1986.¹⁸ This technique can be classified into two main subtypes: stereolithographic (resin reservoir) and powder bed selective laser sintering,³ as shown in Figure 2c. The basics of this technology can be categorized into laser-guided direct writing and modified laser-induced forward transfer systems, which are “weakly focused beam” and “focused laser pulses”, respectively.¹⁵ The resolution of a laser-based 3D Printer (LBP) depends on many factors, including laser energy, pulse frequency, thickness, viscosity of the layer, the air gap between the donor and collector slide, and the wettability of the substrate slide.⁹ In addition to these parameters, the high cost of LBP should be considered as another limitation.^{9,15} At the same time, the main advantages of this method are the elimination of nozzle clogging and printing materials with various viscosities and high resolution;⁹ on the other

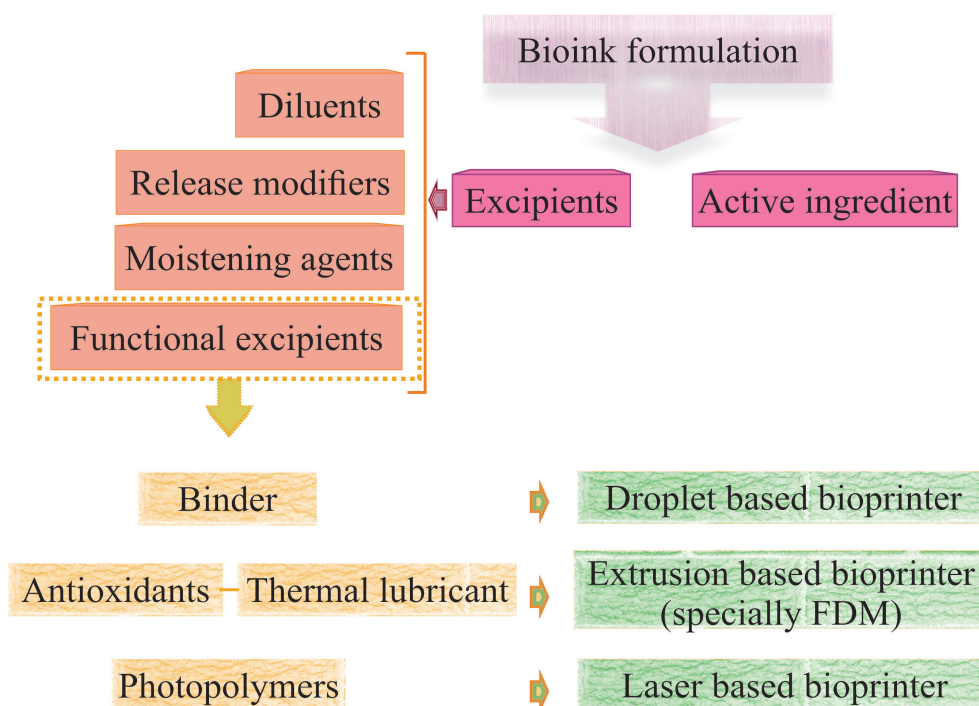


Figure 3. General ink formulas of the three leading 3D printers in the pharmaceutical field.

hand, less drug degradation through this method should be considered as another potential characteristic when compared with FDM.¹⁹

Overall, the inkjet ingredients (active pharmaceutical ingredient and inactive excipients) are almost the same, and some functional excipients may differ among the mentioned 3D printers that have been demonstrated in Figure 3.

Advantages and limitations of 3D printing in pharmaceuticals

Besides considering some advantages, 3D printing may encounter some limitations regarding medical applications. Printing different dosage forms with freedom and flexible design for individuals may be considered the main advantages of this strategy when compared with conventional therapy.^{13,14} On the other hand, this single-step technology is associated with less amount of material waste, and there is no need for full attendance of the operator; therefore, it may be considered a cost-effective process in which the required dosage form would be designed promptly if needed.^{14,18}

There are also several limitations in terms of machines, materials, safety, and copyright issues to this novel manufacturing process (Figure 4). Commercial availability of printers and materials would be considered the main limitation since one printer or one material does not fit in all the pharmaceutical processes.^{2,5} Nozzle obstruction, speed, motion, automation, and cleaning capabilities are other critical factors.^{2,14,18} Job security may also be in danger due to the reduction in manufacturing operators.¹⁸ Furthermore, although 3D printing can minimize wastage as compared to the alternative methods, the production and emission of harmful gases through polymer heating may result in other challenges, such as serious health risks.²⁰

Pharmaceutical Ink Formulations for 3D Printing FDA-Approved Excipients

Pharmaceutical excipients are inert substances other than active pharmaceutical ingredients that should be applied appropriately in drug delivery systems. Conventional excipients have been thoroughly studied for their role in current pharmaceutical applications, but developing appropriate excipients for 3D printing is an ongoing and demanding research area. Different FDA-approved excipients can be used in 3D printing processes^{21,22} (Table 1), but their usage would be different based on the printer type. Polylactic acid (PLA), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), and tribasic calcium phosphate (TCP) are the most commonly used excipients for FDM.^{23,24} Among cellulosic polymers, ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC) are often used as sustained release modifiers. Moreover, PVA and eudragit® E show immediate release in pharmaceutical formulation,²³ whereas PLA and eudragit® L/S can be applied as delayed-release matrix.^{23,25} Release modifiers can also show different characteristics depending on factors such as temperature, molecular weight, degree of crystallinity, and mechanical stability.^{23,26} The ratio or concentration of excipients is another critical factor that may affect the properties of solid-dosage pharmaceuticals.^{22,27} Some compounds with antioxidant properties are used mainly in filaments for FDM to protect drugs against thermal degradation. Lignin and cysteine are used in FDM and LBP, respectively.^{3,28} Besides, moistening agents may affect the solubility,²² thermostability,²³ and integrity of ink ingredients. The use of lubricant as another excipient may also increase the fluidity and reduce the friction between surfaces. However, it may have a negative effect on the toughness of the samples in excess amounts.²⁹

Drug carriers and inks

The application of 3D printing in novel DDSs plays an

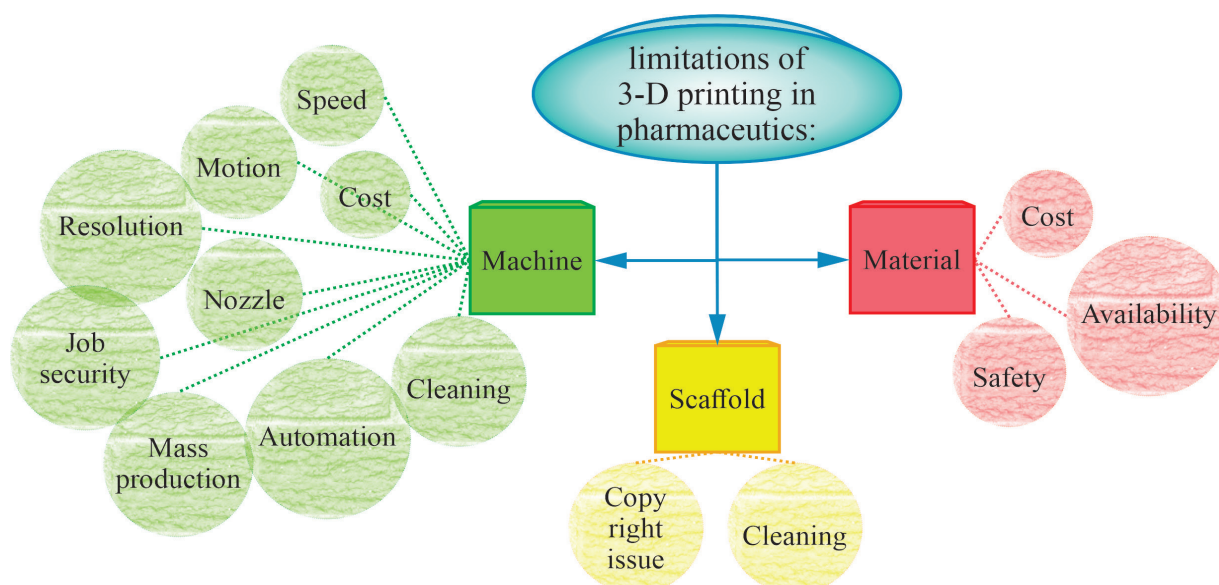


Figure 4. Limitations associated with 3D printing in pharmaceutical drug delivery systems.

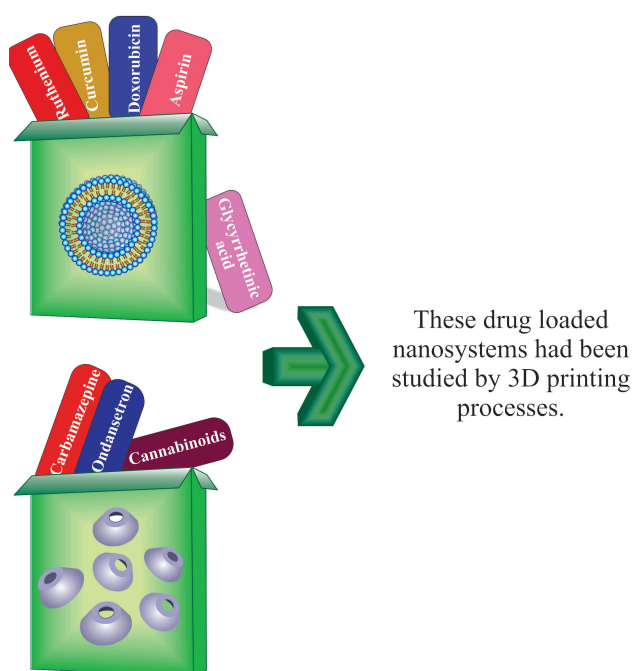
Table 1. Common pharmaceutical-grade FDA-approved excipients used for 3D printing.

Role of excipients	FDA-approved excipients
Diluents/fillers	D-sucrose, Dextrin, Lactose, Pregelatinized starch, MCC, Sorbitol, TCP, Talc, Mannitol and EVA
Release modifiers	HPC, HPMC, EC, PLA, PVA, PVP, Carbopol®, Eudragit® (E, L, S, RL, RS), Poloxamer 407, PLGA, HPMCAS, MCC, Primojel® (Sodium starch glycolate), and CD (HP-βCD)
Moistening agent	Kollidon®, and Triacetin
Binder	HPMC, EC, CMC-Na, PVP, PEG, and DMSO
Antioxidants	Cysteine
Thermal lubricant	Kollidon®, TEC, TBP, Magnesium stearate, and PEG (6000)
Photopolymer	Irgacure 2959, Irgacure TPO, PEGDA, and Envision TEC

active role in improving the efficacy of drug therapy,³⁰ and may exert significant therapeutic potential for loaded drugs. These carriers may be incorporated before or after the scaffold printing. Liposome an available drug vehicle in the market,³¹ can also be used in 3D printing technology (Figure 5). Ruthenium-loaded PEGylated liposome was incorporated into the scaffold, which was printed by extrusion of the filament-like emulsion ink.³² The results revealed the long-term and slow sustained release of ruthenium with uniform distribution of loaded liposomes into the microscopic structure of the composite. The authors used the scaffold for implantation into the bone defect after osteosarcoma resection. Liposomal curcumin, which was incorporated onto the calcium phosphate scaffolds (printed by binder jet printer), was also applied as a potential bone graft substitute. They observed a significant (96%) decrease in *in-vitro* osteosarcoma cell proliferation after 11 days of incubation in the presence of liposomal curcumin compared with controls (3DP scaffold and 3DP scaffold with only delivery vesicle).³³ Another study applied an EBP for printing patches incorporating

PEGylated liposomal doxorubicin. Doxorubicin release was controllable and dependent on the patching shapes and cross-linking density.³⁴ Polycaprolactone (PCL) composites containing aspirin-loaded nano-liposomes enhanced the osteogenic activity in human mesenchymal stem cell line and nude mice when compared with bare scaffold.³⁵ 18- α -Glycyrrhetic acid (18- α -GA) with anti-inflammatory and antioxidant activities on the skin, formulated into ethanolic liposomes to increase its diffusion through the skin barrier. Here, the GA-liposome was prepared by a microfluidic 3D printing and ethanol injection method. The first approach showed smaller particle sizes with improved encapsulation efficiency % (EE%). Overall, the results observed that liposomal vesicles made by a 3D printed PLA microfluidic chip (via FDM) could permeate through skin mimicking membranes almost 8x times more than its saturated solution³⁶ (Table 2).

Cyclodextrins, as another widely used carrier in the pharmaceutical field^{27,30,37} can be used in the ink formula of 3D printers.³⁸ A wet mass containing carbamazepine hydroxypropyl β -cyclodextrin (HP- β CD) was taken to be printed by semisolid EBP.³⁹ The results highlighted the HP- β CD usage in printlet production with suitable physical and drug release properties for oral delivery of poorly water-soluble drugs. Pectin-based films containing cannabinoid- β CD complexes were also fabricated by EBP, indicating the prolonged and complete release of drugs in simulated colonic fluid at the time scale of 360 min (compared with release in simulated gastric and intestinal mediums).⁴⁰ Orodispersible printlets containing ondansetron- β CD were fabricated using the selective laser sintering method. This 3D printed formulation was compared with a commercial ondansetron orally disintegrating tablet (Vonau® Flash). The results observed that 3D printed printlets had almost the same disintegration time and release rate independent of the mannitol content.⁴¹ Among bio-derived molecules, CDs are good candidates both for their complexation abilities^{37,42} and their suitable inks for various 3D printers (Table 2).

**Figure 5.** Drug-loaded nanocarriers that have been used in 3D printing.

Administration Pathways for 3D Printed Composites

A detailed list of the 3D printed drug models is summarized in Table 3. The authors have classified the research data based on the administration pathways and discussed the main findings.

Table 2. Drug-loaded nanocarriers that were used in 3D printing.

Carrier	Active agent	Droplet-based 3D printer		Extrusion-based 3D printer		Laser-based 3D printer		Year	Ref.
		Stage of carrier incorporation		Stage of carrier incorporation		Stage of carrier incorporation			
		Incorporated in 3D printer ink	After scaffold printing	Incorporated in 3D printer ink	After scaffold printing	Incorporated in 3D printer ink	After scaffold printing		
Liposome	Ruthenium				*			2019	32
	Curcumin		*					2019	33
	Doxorubicin				*			2020	34
	Aspirin		*					2019	35
	Glycyrrhetic acid			*				2020	36
HP- β CD	Carbamazepine			*				2019	39
CD	β CD	Cannabinoids			*			2020	40
	β CD	Ondansetron				*		2020	41

Oral drug delivery, as a convenient method of systemic drug administration with patient preference^{30,43} attracted researchers' attention greatly. In a study, 4-aminosalicylic acid (4-ASA) and paracetamol (acetaminophen) were evaluated as 3D printed tablets.¹⁹ Both drugs were successfully loaded into stereolithography (SLA) printed tablets with a loading percent of 5.69% and 5.40% for paracetamol and 4-ASA, respectively. The authors demonstrated that the ratios of polyethylene glycol diacrylate (PEGDA)/PEG 300 would play an essential role in drug release rates. So, the reduction in PEGDA concentration promoted the dissolution rate because of a lower degree of cross-linking in the printed matrix. In another work, researchers used four model drugs with different physicochemical properties and various melting points (acidic: 5-aminosalicylic acid (5-ASA) and captopril, basic: theophylline and neutral: prednisolone). They used TCP as a thermally stable filler in the range of 20-50% for fabricating tablets through FDM printing. Efficient drug content was observed for all the mentioned drugs (above 88%), but captopril content was dropped after the thermal processes.²⁴ 5-ASA (prescribed for inflammatory bowel disease) was also studied using FDM 3DP for fabrication of modified-release tablets and was compared with 4-ASA, which is used for tuberculosis.⁴⁴ Slight differences in their chemical structures were reported, which affected their efficiency, melting points (278°C and 130°C for 5-ASA and 4-ASA, respectively), and solubilities.^{44,45} The results revealed that FDM 3DP was not appropriate for 4-ASA with 50% degradation during the process, with 210°C as the printing temperature.

A combination of several medicines in a single dosage form (polypill) was fabricated by 3D printing technology with different release profiles through multi-structured methods.^{46,47} Programmed concentration profiles with core-shell, multilayer, and gradient structures were

examined by Haring *et al.*⁴⁷ A combination of delayed, pulsed, and constant temporal release profiles revealed programmed drug therapy by 3D printed technology. Subsequently, another research group designed two-compartment polypills containing caffeine and vitamin B analogs in a core-shell design with different release profiles.⁴⁸ Multi-active tablets were also analyzed using room temperature EBP containing captopril (osmotic pump compartment), nifedipine, and glipizide (sustained release part). The obtained data confirmed that the physical separation resulted in no detectable interaction between the components.⁴⁹ Another multi-component formula contains sustained (pravastatin, atenolol, and ramipril) and immediate (aspirin and hydrochlorothiazide) release compartments. The polypill concept was designed for a cardiovascular treatment via a specific solid dosage form.⁵⁰ Rapid release of haloperidol, from a 3D printed tablet containing a 1:1-mixture of Kollidon® VA64 and Affinisol™15 cP, was also seen at pH 2 and 6.8 within two hours for urgent treatment.⁵¹

Goyanes *et al.*⁵² showed that using a multi-nozzle 3D printer, a multilayer device embedding separate formulations could be fabricated. They used this method comprising a caplet containing acetaminophen and caffeine in each compartment layer separately. The results also confirmed that the release profile could be manipulated by designing various multi-component devices, drug solubility, and percentage of drug loading.⁵³ Acetaminophen was also printed using the FDM method in tablet shapes by incorporating into the hypromellose acetate succinate and hydroxypropyl methylcellulose with delayed and zero-order release properties, respectively.^{16,54} FDM 3DP can also print PVA tablets containing paracetamol in different shapes. The results revealed that the drug release depended on the tablets' surface area to volume ratio.⁵⁵ The width and length of the channel and infill percentage should be

considered as other critical factors that impacted the release of hydrochlorothiazide and fluorescein from FDM printed dosage forms, respectively.^{56,57} Goyanes *et al.*⁵⁸ studied the budesonide loaded in PVA filaments using an FDM printer. They compared drug release with two commercial budesonide products, Cortimex® (Uceris®) and Entocort®, with a more delayed and rapid release, respectively. In contrast, the printed product started to release the drug in the mid-small intestine and continued throughout the distal intestine and colon. Another comparative study was done about guaifenesin between 3D printed bilayer tablets with the commercialized Mucinex®. Based on the work, it was concluded that EBP allows for higher drug loading (up to 600 mg) with immediate and sustained release.⁵⁹ The FDM technology also proved the fabrication of a pH-responsive drug release system through gastric-resistant tablets. Here, the authors used a core-shell design for incorporating theophylline, budesonide, and diclofenac sodium.⁶⁰ These works revealed the possibility of manufacturing multi-component drug delivery systems to suit individual patient's needs.

The release profile modulation of formulas can be done by choosing an appropriate polymer. Noticeably different release behavior of felodipine from 3D printed discs was because of distinctive excipients. Therefore, Eudragit EPO and Soluplus® based dispersion showed bulk and peeling style disintegration During *in-vitro* dissolution testing.⁶¹

Here, it is essential to say that the drug loading process can be done through the filament soaking method. Tagami *et al.*⁶² showed that the type of organic solvent, temperature, time, and drug concentration significantly affect the drug incorporation amount, greatly. They found almost 5% of curcumin could be loaded into the PVP filaments through this procedure.⁶² Drug loading can also be done by post-loading procedure. In a study about fluticasone-eluting 3D printed rings, drug was incorporated into the ring by pre and post-loading methods. The results revealed that the different loading processes would affect the drug release kinetics since post-loaded fluticasone exhibited ~2-fold increase in burst release within the first 24 and more significant zero-order kinetics than the pre-loaded rings.⁶³

The reported polymers could also be used as coatings for different dosage forms. Melocchi *et al.*⁶⁴ used disks as simple models for evaluating the performance of various polymers as coating shells. They successfully printed polymers as 600 mm thick disks by FDM and reported different categories as slow, immediate, delayed, and pulsed release profiles.

Children, as a sensitive group, need to adapt drug dosage forms based on their requirements. Therefore, by specializing in the color and shape of drugs, their preference may increase to some extent. Gummy oral dosages containing lamotrigine and ranitidine were successfully printed by EBPs with no drug degradation.^{65,66}

Chewable 3D printed formulations were used in pediatric patients suffering from Maple syrup urine disease. Isoleucine printlets were designed to be chewed and swallowed without needing food or water. These

formulations attracted good acceptability with high preference for their different flavors and colors. The results revealed that the mean and median blood concentration of isoleucine was maintained in the target range of 200 – 400 µM after administration.⁶⁷

Besides the oral administration, there are also local drug delivery systems that can be used for drug-loaded 3D-printed composites. This method has been recognized as a promising method for localized drug delivery which minimizes the associated side effects of the systemic administration pathways.

The topical administration of an anti-acne drug was studied using a personalized nose-shaped 3D printed system. Here, salicylic acid was loaded into the nose-shaped printed device, which was fabricated by FDM and SLA. The results demonstrated that SLA printing results in a high resolution with no drug degradation, but FDM devices revealed faster diffusion of salicylic acid within three hours.⁶⁸

A limited number of polymers with specific characteristics can also be used as an intrauterine system. They should be non-swellable and non-biodegradable with a prolonged degradation rate. Ethylene-vinyl acetate (EVA)⁶⁹ and Poly (ε-caprolactone)⁷⁰ can be introduced as potential ingredients for intrauterine 3D printed DDSs. Diffusion of indomethacin from produced T-shaped prototypes was significantly affected by diffusion. Their results also indicated that higher drug loading (30%) resulted in lower dissolved drug on 30 days, and poorer quality of DDS would be achieved (compared with 5% and 15%).⁷⁰

The process of drug incorporation in implants can be introduced as another method for local delivery. This method, although provides low doses of drugs, effective and sustained delivery would be provided at the targeted site compared to the conventional methods. A 3D printed patch composed of poly(lactide-co-glycolide) (PLGA), PCL, and 5-fluorouracil was used for suppressing the growth of the subcutaneous pancreatic cancer xenografts in mice. The authors demonstrated that the implant shapes could alter the drug release rate by influencing the surface area.⁷¹ Another 3D-printed subcutaneous rod based on EVA was fabricated for 5% and 15% indomethacin delivery. They found the appropriate EVA grade as a matrix for medical devices.⁶⁹ Local slow-release implants containing isoniazid were fabricated using poly(L-lactide) (PLLA) in three different tablet shapes: columnar, doughnut, and multilayer doughnut. The results proved that the structure.

Ethics in Pharmaceutical 3D Printing

There have been some vital ethical challenges in the 3D printing of pharmaceutical dosage forms. Therefore, several essential questions associated with this era need to be answered before starting the process. Copy print and design rights include the central part of legal regulations.⁸³ The safety of excipients is also another critical parameter that should be considered. So, by selecting the target

and porosity of these biocompatible implants influenced drug release.⁷² PLGA disks containing 30% nitrofurantoin showed inhibition of planktonic growth of *Staphylococcus aureus* over seven days. This effect was concentration-dependent, in which 10% nitrofurantoin samples did not inhibit bacterial growth.⁷³ Nitrofurantoin release from printed disks was dependent on the content of drug-loaded⁷³ or water-soluble excipients (Metolose[®]).⁷⁴

Drug-eluting formulations in contact lenses and patches can also be introduced as other models of local treatments. This unique approach for personalized therapy provided controlled release of different commercialized drug formulations such as timolol

maleate.^{75,76}

3D printed rectal suppository may be introduced as another valuable tool in creating a complete treatment. Artesunate was prepared as a suppository for childhood malaria in three types. Artesunate/PEG formulation was inserted into the PVA suppository shell to improve the thermostability of this drug in a tropical climate. The PVA shell, which was printed by the FDM method had an orifice on top that the drug-containing mixture was inserted into the core of it. Obtained data demonstrated that the 3D printed suppository remained unchanged in their visual appearances and amounts of artesunate.⁷⁷

Table 3. Printed drug-loaded composites in pharmaceutical research.

Administration pathway	Drug	BCS	Composite shape	Type of printer	Main polymers	Final drug loading (%EE or %degradation)	Drug release profile	Year	Ref.		
Oral	4-aminosalicylic acid	-	Tablet	SLA	PEGDA	At least 91.8 %	Controlled release	2016	19		
	Acetaminophen	III				At least 95.1 %					
	5-aminosalicylic acid	IV				94.22%					
Oral	Captopril	I	Tablet	FDM	Eudragit E, TCP	88.53%	Immediate release	2016	24		
	Theophylline	I				96.51%					
	Prednisolone	I				93.04%					
Oral	5-aminosalicylic acid	IV	Tablet	FDM	PVA	No reduction	Modified release	2015	44		
	4-aminosalicylic acid	-				Almost half drug degradation					
Oral	Captopril	I	Polypill	EBP (Room temp.)	D-mannitol	-	Zero-order	2015	49		
	Nifedipine	II				HPMC				-	First-order
	Glipizide	II				-					
	Pravastatin	III				-					
Oral	Atenolol	III	Polypill	EBP	HPMC 2208, Lactose	-	Sustained release	2015	50		
	Ramipril	II				-					
	Aspirin	I				Sodium starch glycolate, PVP K30				-	Immediate release
	Hydrochlorothiazide	IV				-					
Oral	Guaifenesin	I	Bilayer tablet	EBP	HPMC 2208, Carbopol [®] 974P NF	Up to 600 mg (Tablet weight: 650 to 730 mg)	Sustained release	2014	59		
						Pharmacel [®] 102, Primojel [®]	Immediate release				
Oral	Haloperidol	II	Tablet	FDM	Kollidon [®] VA64, Affinisol [™] 15cP, and HPMCAS	At least 96.9%	Rapid release	2018	51		
Oral	Acetaminophen	III	Caplet	FDM	PVA	No degradation	Dependent to the macrostructure of device, drug content and solubility	2015, 2016	52,53		
	Caffeine	I									

Table 3. Continued.

Oral	Fluticasone	II	Ring	Digital Light Processing	PCL ₇₀₀ -DMA	Pre-loaded: at least 7.13 mg/g ring Post-loaded: at least 6.84 mg/g ring	Sustained zero-order	2021	63
Oral	Furosemide	IV	Disk	FDM	EC, Eudragit®RL PEO, Kollicoat®IR Eudragit® L, HPMCAS hydrophilic cellulose derivatives, PVA, Soluplus®	Not reported.	Very slow release Immediate release Delayed release (Enteric soluble) Pulsatile release	2016	64
Oral	Lamotrigine	II	Gummy	EBP	Gelatin, HPMC	No degradation	85% drug release within 15 min (for most formulations)	2021	66
Oral	Ranitidine	III	Gummy	EBP	Corn starch, Carrageenan, Xanthan gum, Gelatine	LE: 99.90%	Various release profiles (dependent to the formulation)	2020	65
Chewable printlets	Isoleucine	-	Tablet	EBP	Sucrose, Pectin, Maltodextrin Flex EcoPLA™	Max. 0.64% degradation	rapid release within 5 min	2019	67
Topical	Salicylic acid	I	Nose-shaped	FDM SLA	PCL PEGDA PEG	1.6% degradation 0.8% degradation 0.1% degradation	53 µg/cm ² within 3 h 187 µg/cm ² within 3 h 229 and 291 µg/cm ² within 3 h	2016	68
Intrauterine	Indomethacin	II	T-shaped device	FDM	PCL	Dependent on the amount of drug loading (at least: LE: 73.6%)	Higuchi square root model	2016	70
Intrauterine	Indomethacin	II	T-shaped device	FDM	EVA	-	Korsmeyer–Peppas	2016	69
Implant	5-Fluorouracil	III	Square, Circular and Oval	EBP	PLGA, PCL	LE: 101.2%	Controlled release (over 4 weeks)	2016	71
Implant	Indomethacin	II	Subcutaneous rods	FDM	EVA	-	Korsmeyer–Peppas	2016	69
Implant	Isoniazid	I and III ^a	Tablet	FDM	PLLA	-	Slow release	2014	72
Implant	Nitrofurantoin	II	Disk	EBP	PLGA	-	Controlled release (dependent to drug loading)	2015	73
Implant	Nitrofurantoin	II	Disk	EBP	PLA	-	Controlled release (dependent to Metolose® content)	2016	74
Ophthalmic	Timolol maleate	I	Lens	FDM	EVA copolymer–PLA	-	sustained release over 3 days	2021	75
Rectal	Artesunate	II	Suppository	FDM	PVA	LE: 12%	Zero order	2020	77

^a Borderline of I and III class

ingredients among the FDA-approved excipients, the related rights would be guaranteed.

Additionally, staff-specific safety needs to be taken into consideration since some printer machines may cause significant harm to humans. The ultimate effect of UV light exposure in LBP may danger the health and cause DNA damage.⁸⁴ Protection against hazardous chemicals should be avoided in manufacturing processes, primarily through FDM-associated methods.⁸⁵ Accordingly, practical evaluation should be considered to avoid ethical and legal-related problems. Overall, regarding the complexity of 3D printing in pharmaceutics, it is necessary to write and optimize good manufacturing practice (GMP) guidelines to validate the required safety standards.

Future Perspective

3D printing has been progressed in the pharmaceutical field to impact the improvement of drug delivery pathways. In this review, we highlighted this technology's usage in the pharmaceutical industry and drug delivery. Although this technology holds great promise in drug therapy, but some modifications can be made to its progress. Nanocarriers such as liposomes and cyclodextrins may be applied in the 3D printing through improvements in drug characteristics. Furthermore, this review may open a door in the pharmaceutical field and attract researchers' attention in applying nanocarriers for 3D printing strategies. In this way, not only the pharmacokinetic properties of a loaded drug will be controlled, but also a new ink formula may be introduced into the research field. Although 3D printing is in advancement in pharmaceutics, but 4D printing technology has emerged and developed to create innovative personalized dosage forms. Compared with 3D printing, the 4D printing process includes a fourth dimension, namely "time"⁸⁶ in which by using smart materials their properties will be changed under particular stimuli.⁸⁷ Although this novel process has been rarely used in pharmaceutical fields, there is no doubt that its development in medicine will create more suitable and adaptable dosage forms.

Conclusion

In summary, conventional drug therapy accompanied with some limitations that may overcome by using 3D printing strategy. There are three common types of 3D printers that may be applied in pharmaceutical researches. The expansion of excipient usage will also give opportunities of various drug formulations through different administration pathways. Application of drug nanocarriers in combination with ink formulas or after the manufactured composites, may lead to an increase of 3D printing application in pharmaceutics. Thoroughly, this strategy may represent innovative ways of drug delivery in near future.

Author Contributions

Mohamad Khatami: Writing - Original Draft. Ali Doniavi: Conceptualization, Investigation. Saeideh Allahyari:

Conceptualization, Investigation, Writing - Original Draft. Mahsa Feizollahi: , Writing - Original Draft. Amir Musa Abazari: Conceptualization, Investigation. Mohamad Fotouhi: Writing - Review & Editing.

Conflict of Interest

The supports from Faculty of Engineering, Urmia University and Faculty of Pharmacy, Ardabil University of Medical Science are greatly acknowledged. The authors have also no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

1. Shi K, Salvage JP, Maniruzzaman M, Nokhodchi A. Role of release modifiers to modulate drug release from fused deposition modelling (FDM) 3d printed tablets. *Int J Pharm.* 2021;597:120315. doi:10.1016/j.ijpharm.2021.120315
2. Kačarević ŽP, Rider PM, Alkildani S, Retnasingh S, Smeets R, Jung O, et al. An introduction to 3d bioprinting: Possibilities, challenges and future aspects. *Materials (Basel).* 2018;11(11):2199. doi:10.3390/ma11112199
3. Mathew E, Pitzanti G, Larrañeta E, Lamprou DA. 3d printing of pharmaceuticals and drug delivery devices. *Pharmaceutics.* 2020;12(3):266. doi:10.3390/pharmaceutics12030266
4. Hong N, Yang G-H, Lee J, Kim G. 3d bioprinting and its in vivo applications. *J Biomed Mater Res Part B.* 2018;106(1):444-59. doi:10.1002/jbm.b.33826
5. Trenfield SJ, Awad A, Madla CM, Hatton GB, Firth J, Goyanes A, et al. Shaping the future: Recent advances of 3d printing in drug delivery and healthcare. *Expert Opin Drug Deliv.* 2019;16(10):1081-94. doi:10.1080/17425247.2019.1660318
6. Dumpa N, Butreddy A, Wang H, Komanduri N, Bandari S, Repka MA. 3d printing in personalized drug delivery: An overview of hot-melt extrusion-based fused deposition modeling. *Int J Pharm.* 2021;600:120501. doi:10.1016/j.ijpharm.2021.120501
7. Wallis M, Al-Dulimi Z, Tan DK, Maniruzzaman M, Nokhodchi A. 3d printing for enhanced drug delivery: Current state-of-the-art and challenges. *Drug Dev Ind Pharm.* 2020;46(9):1385-401. doi:10.1080/03639045.2020.1801714
8. Khan FA, Narasimhan K, Swathi CSV, Mustak S, Mustafa G, Ahmad MZ, et al. 3d printing technology in customized drug delivery system: Current state of the art, prospective and the challenges. *Curr Pharm Des.* 2018;24(42):5049-61. doi:10.2174/1381612825666190110153742
9. Peng W, Datta P, Ayan B, Ozbolat V, Sosnoski D, Ozbolat IT. 3d bioprinting for drug discovery and development in pharmaceutics. *Acta Biomater.* 2017;57:26-46. doi:10.1016/j.actbio.2017.05.025

10. Koçak E, Yıldız A, Acartürk F. Three dimensional bioprinting technology: Applications in pharmaceutical and biomedical area. *Colloid Surface B*. 2021;197:111396. doi:10.1016/j.colsurfb.2020.111396
11. Khan FA, Narasimhan K, Swathi CSV, Mustak S, Mustafa G, Ahmad MZ, et al. 3d printing technology in customized drug delivery system: Current state of the art, prospective and the challenges. *Curr Pharm Design*. 2018;24(42):5049-61. doi:10.2174/1381612825666190110153742
12. Zeeshan F, Madheswaran T, Pandey M, Gorain B. Three-dimensional (3-d) printing technology exploited for the fabrication of drug delivery systems. *Curr Pharm Des*. 2018;24(42):5019-28. doi:10.2174/1381612825666190110111525
13. Samiei N. Recent trends on applications of 3D printing technology on the design and manufacture of pharmaceutical oral formulation: A mini review. *Beni-Seuf Univ J Appl*. 2020;9(1):12. doi:10.1186/s43088-020-00040-4
14. Jamróz W, Szafraniec J, Kurek M, Jachowicz R. 3D printing in pharmaceutical and medical applications – recent achievements and challenges. *Pharm Res*. 2018;35(9):176. doi:10.1007/s11095-018-2454-x
15. Ozbolat IT, Moncal KK, Gudapati H. Evaluation of bioprinter technologies. *Addit Manuf*. 2017;13:179-200. doi:10.1016/j.addma.2016.10.003
16. Goyanes A, Fina F, Martorana A, Sedough D, Gaisford S, Basit AW. Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing. *Int J Pharm*. 2017;527(1):21-30. doi:10.1016/j.ijpharm.2017.05.021
17. Ali A, Ahmad U, Akhtar J. 3D printing in pharmaceutical sector: An overview. Ahmad U, Akhtar J. editors. *Pharmaceutical Formulation Design*. London: IntechOpen; 2020.
18. Bhusnure DO. 3d printing & pharmaceutical manufacturing: Opportunities and challenges. *Int J Bioassay*. 2016;5:4723-38. doi:10.21746/ijbio.2016.01.006
19. Wang J, Goyanes A, Gaisford S, Basit AW. Stereolithographic (SLA) 3d printing of oral modified-release dosage forms. *Int J Pharm*. 2016;503(1):207-12. doi:10.1016/j.ijpharm.2016.03.016
20. Wojtyła S, Klama P, Śpiewak K, Baran T. 3D printer as a potential source of indoor air pollution. *Int J Environ Sci Technol*. 2020;17(1):207-18. doi:10.1007/s13762-019-02444-x
21. <https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download>.
22. Tian P, Yang F, Yu LP, Lin MM, Lin W, Lin QF, et al. Applications of excipients in the field of 3d printed pharmaceuticals. *Drug Dev Ind Pharm*. 2019;45(6):905-13. doi:10.1080/03639045.2019.1576723
23. Azad MA, Olawuni D, Kimbell G, Badruddoza AZM, Hossain MS, Sultana T. Polymers for extrusion-based 3d printing of pharmaceuticals: A holistic materials–process perspective. *Pharmaceutics*. 2020;12(2):124.
24. Sadia M, Sośnicka A, Arafat B, Isreb A, Ahmed W, Kelarakis A, et al. Adaptation of pharmaceutical excipients to fdm 3d printing for the fabrication of patient-tailored immediate release tablets. *Int J Pharm*. 2016;513(1):659-68. doi:10.1016/j.ijpharm.2016.09.050
25. Lu M. Novel excipients and materials used in fdm 3d printing of pharmaceutical dosage forms. Maniruzzaman M, editor. *3D and 4D printing in biomedical applications*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA; 2018. p. 211-37. doi:10.1002/9783527813704.ch9
26. Seoane-Viaño I, Trenfield SJ, Basit AW, Goyanes A. Translating 3d printed pharmaceuticals: From hype to real-world clinical applications. *Adv Drug Deliver Rev*. 2021;174:553-75. doi:10.1016/j.addr.2021.05.003
27. Allahyari S, Valizadeh H, Roshangar L, Mahmoudian M, Trotta F, Caldera F, et al. Preparation and characterization of cyclodextrin nanosponges for bortezomib delivery. *Expert Opin Drug Deliv*. 2020;17(12):1807-16. doi:10.1080/17425247.2020.180637
28. Weisgrab G, Guillaume O, Guo Z, Heimel P, Slezak P, Poot A, et al. 3d printing of large-scale and highly porous biodegradable tissue engineering scaffolds from poly(trimethylene-carbonate) using two-photon-polymerization. *Biofabrication*. 2020;12(4):045036. doi:10.1088/1758-5090/abb539
29. Zhang Q, Cai H, Zhang A, Lin X, Yi W, Zhang J. Effects of lubricant and toughening agent on the fluidity and toughness of poplar powder-reinforced polylactic acid 3d printing materials. *Polymers (Basel)*. 2018;10(9):932. doi:10.3390/polym10090932
30. Allahyari S, Esmailnezhad N, Valizadeh H, Ghorbani M, Jelvehgari M, Ghazi F, et al. In-vitro characterization and cytotoxicity study of flutamide loaded cyclodextrin nanosponges. *J Drug Deliv Sci Tec*. 2021;61:102275. doi:10.1016/j.jddst.2020.102275
31. Kiaie SH, Mojarad-Jabali S, Khaleseh F, Allahyari S, Taheri E, Zakeri-Milani P, et al. Axial pharmaceutical properties of liposome in cancer therapy: Recent advances and perspectives. *Int J Pharm*. 2020;581:119269. doi:10.1016/j.ijpharm.2020.119269
32. Ye L, Wang J, Liao C, Li S, Fang Y, Yang Z, et al. 3d printed composite scaffolds incorporating ruthenium complex-loaded liposomes as a delivery system to prevent the proliferation of mg-63 cells. *Macromol Mater Eng*. 2019;304(11):1900295. doi:10.1002/mame.201900295
33. Sarkar N, Bose S. Liposome-encapsulated curcumin-loaded 3d printed scaffold for bone tissue engineering. *ACS Appl Mater Inter*. 2019;11(19):17184-92. doi:10.1021/acsami.9b01218
34. Liu J, Tagami T, Ozeki T. Fabrication of 3d-printed fish-gelatin-based polymer hydrogel patches for local delivery of pegylated liposomal doxorubicin. *Mar Drugs*. 2020;18(6):325. doi:10.3390/md18060325

35. Li Y, Bai Y, Pan J, Wang H, Li H, Xu X, et al. A hybrid 3d-printed aspirin-laden liposome composite scaffold for bone tissue engineering. *J Mater Chem B*. 2019;7(4):619-29. doi:10.1039/C8TB02756K
36. Tiboni M, Benedetti S, Skouras A, Curzi G, Perinelli D, Palmieri G, et al. 3d-printed microfluidic chip for the preparation of glycyrrhetic acid-loaded ethanolic liposomes. *Int J Pharm*. 2020;584:119436. doi:10.1016/j.ijpharm.2020.119436
37. Allahyari S, Trotta F, Valizadeh H, Jelvehgari M, Zakeri-Milani P. Cyclodextrin-based nanosponges as promising carriers for active agents. *Expert Opin Drug Deliv*. 2019;16(5):467-79. doi:10.1080/17425247.2019.1591365
38. Allahyari S, Zahednezhad F, Khatami M, Hashemzadeh N, Zakeri-Milani P, Trotta F. Cyclodextrin nanosponges as potential anticancer drug delivery systems to be introduced into the market, compared with liposomes. *J Drug Deliv Sci Tec*. 2021;67:102931. doi:10.1016/j.jddst.2021.102931
39. Conceição J, Farto-Vaamonde X, Goyanes A, Adeoye O, Concheiro A, Cabral-Marques H, et al. Hydroxypropyl- β -cyclodextrin-based fast dissolving carbamazepine printlets prepared by semisolid extrusion 3d printing. *Carbohyd Polym*. 2019;221:55-62. doi:10.1016/j.carbpol.2019.05.084
40. Andriotis EG, Monou P-K, Louka A, Papaefstathiou E, Eleftheriadis GK, Fatouros DG. Development of food grade 3d printable ink based on pectin containing cannabidiol/cyclodextrin inclusion complexes. *Drug Dev Ind Pharm*. 2020;46(10):1569-77. doi:10.1080/03639045.2020.1791168
41. Allahham N, Fina F, Marcuta C, Kraschew L, Mohr W, Gaisford S, et al. Selective laser sintering 3d printing of orally disintegrating printlets containing ondansetron. *Pharmaceutics*. 2020;12(2):110. doi:10.3390/pharmaceutics12020110
42. Allahyari S, Valizadeh H, Zakeri-Milani P. Polymeric nanoparticles and their novel modifications for targeted delivery of bortezomib. *Pharm Sci*. 2020;26(4):363-9. doi:10.34172/ps.2020.21
43. Palassi S, Valizadeh H, Allahyari S, Zakeri-Milani P. Preparation and in vitro characterization of enoxaparin nano-liposomes through different methods. *Adv Pharm Bull*. 2021;11(2):295-300. doi:10.34172/apb.2021.042
44. Goyanes A, Buanz ABM, Hatton GB, Gaisford S, Basit AW. 3d printing of modified-release aminosaliclylate (4-asa and 5-asa) tablets. *Eur J Pharm Biopharm*. 2015;89:157-62. doi:10.1016/j.ejpb.2014.12.003
45. Sawarkar SP, Deshpande SG, Bajaj AN, Nikam VS. In vivo evaluation of 5-ASA colon-specific tablets using experimental-induced colitis rat animal model. *AAPS PharmSciTech*. 2015;16(6):1445-54. doi:10.1208/s12249-015-0331-z
46. Tan YJN, Yong WP, Low HR, Kochhar JS, Khanolkar J, Lim TSE, et al. Customizable drug tablets with constant release profiles via 3d printing technology. *Int J Pharm*. 2021;598:120370. doi:10.1016/j.ijpharm.2021.120370
47. Haring AP, Tong YX, Halper J, Johnson BN. Programming of multicomponent temporal release profiles in 3D printed polypills via core-shell, multilayer, and gradient concentration profiles. *Adv Healthc Mater*. 2018;7(16):10. doi:10.1002/adhm.201800213
48. Goh WJ, Tan SX, Pastorin G, Ho PCL, Hu J, Lim SH. 3d printing of four-in-one oral polypill with multiple release profiles for personalized delivery of caffeine and vitamin b analogues. *Int J Pharm*. 2021;598:120360. doi:10.1016/j.ijpharm.2021.120360
49. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3d printing of tablets containing multiple drugs with defined release profiles. *Int J Pharm*. 2015;494(2):643-50. doi:10.1016/j.ijpharm.2015.07.067
50. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3d printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. *J Control Release*. 2015;217:308-14. doi:10.1016/j.jconrel.2015.09.028
51. Solanki NG, Tahsin M, Shah AV, Serajuddin ATM. Formulation of 3d printed tablet for rapid drug release by fused deposition modeling: Screening polymers for drug release, drug-polymer miscibility and printability. *J Pharm Sci*. 2018;107(1):390-401. doi:10.1016/j.xphs.2017.10.021
52. Goyanes A, Wang J, Buanz A, Martínez-Pacheco R, Telford R, Gaisford S, et al. 3d printing of medicines: Engineering novel oral devices with unique design and drug release characteristics. *Mol Pharm*. 2015;12(11):4077-84. doi:10.1021/acs.molpharmaceut.5b00510
53. Goyanes A, Kobayashi M, Martínez-Pacheco R, Gaisford S, Basit AW. Fused-filament 3d printing of drug products: Microstructure analysis and drug release characteristics of PVA-based caplets. *Int J Pharm*. 2016;514(1):290-5. doi:10.1016/j.ijpharm.2016.06.021
54. Zhang J, Yang W, Vo AQ, Feng X, Ye X, Kim DW, et al. Hydroxypropyl methylcellulose-based controlled release dosage by melt extrusion and 3d printing: Structure and drug release correlation. *Carbohyd Polym*. 2017;177:49-57. doi:10.1016/j.carbpol.2017.08.058
55. Goyanes A, Robles Martinez P, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3d printed tablets. *Int J Pharm*. 2015;494(2):657-63. doi:10.1016/j.ijpharm.2015.04.069
56. Goyanes A, Buanz ABM, Basit AW, Gaisford S. Fused-filament 3d printing (3dp) for fabrication of tablets. *Int J Pharm*. 2014;476(1):88-92. doi:10.1016/j.ijpharm.2014.09.044
57. Sadia M, Arafat B, Ahmed W, Forbes RT, Alhnan MA. Channelled tablets: An innovative approach to accelerating drug release from 3d printed tablets. *J Control Release*. 2018;269:355-63. doi:10.1016/j.jconrel.2017.11.022
58. Goyanes A, Chang H, Sedough D, Hatton GB, Wang J, Buanz A, et al. Fabrication of controlled-release

- budesonide tablets via desktop (fdm) 3d printing. *Int J Pharm.* 2015;496(2):414-20. doi:10.1016/j.ijpharm.2015.10.039
59. Khaled SA, Burley JC, Alexander MR, Roberts CJ. Desktop 3d printing of controlled release pharmaceutical bilayer tablets. *Int J Pharm.* 2014;461(1):105-11. doi:10.1016/j.ijpharm.2013.11.021
 60. Okwuosa TC, Pereira BC, Arafat B, Cieszyńska M, Isreb A, Alhnan MA. Fabricating a shell-core delayed release tablet using dual fdm 3d printing for patient-centred therapy. *Pharm Res.* 2017;34(2):427-37. doi:10.1007/s11095-016-2073-3
 61. Alhijaj M, Belton P, Qi S. An investigation into the use of polymer blends to improve the printability of and regulate drug release from pharmaceutical solid dispersions prepared via fused deposition modeling (fdm) 3d printing. *Eur J Pharm Biopharm.* 2016;108:111-25. doi:10.1016/j.ejpb.2016.08.016
 62. Tagami T, Kuwata E, Sakai N, Ozeki T. Drug incorporation into polymer filament using simple soaking method for tablet preparation using fused deposition modeling. *Biol Pharm Bull.* 2019;42(10):1753-60. doi:10.1248/bpb.b19-00482
 63. Prasher A, Shrivastava R, Dahl D, Sharma-Huynh P, Maturavongsadit P, Pridgen T, et al. Steroid eluting esophageal-targeted drug delivery devices for treatment of eosinophilic esophagitis. *Polymers.* 2021;13(4):557. doi:10.3390/polym13040557
 64. Melocchi A, Parietti F, Maroni A, Foppoli A, Gazzaniga A, Zema L. Hot-melt extruded filaments based on pharmaceutical grade polymers for 3d printing by fused deposition modeling. *Int J Pharm.* 2016;509(1):255-63. doi:10.1016/j.ijpharm.2016.05.036
 65. Herrada-Manchón H, Rodríguez-González D, Alejandro Fernández M, Suñé-Pou M, Pérez-Lozano P, García-Montoya E, et al. 3d printed gummies: Personalized drug dosage in a safe and appealing way. *Int J Pharm.* 2020;587:119687. doi:10.1016/j.ijpharm.2020.119687
 66. Tagami T, Ito E, Kida R, Hirose K, Noda T, Ozeki T. 3d printing of gummy drug formulations composed of gelatin and an hpmc-based hydrogel for pediatric use. *Int J Pharm.* 2021;594:7. doi:10.1016/j.ijpharm.2020.120118
 67. Goyanes A, Madla CM, Umerji A, Duran Piñeiro G, Giraldez Montero JM, Lamas Diaz MJ, et al. Automated therapy preparation of isoleucine formulations using 3d printing for the treatment of msud: First single-centre, prospective, crossover study in patients. *Int J Pharm.* 2019;567:118497. doi:10.1016/j.ijpharm.2019.118497
 68. Goyanes A, Det-Amornrat U, Wang J, Basit AW, Gaisford S. 3d scanning and 3d printing as innovative technologies for fabricating personalized topical drug delivery systems. *J Control Release.* 2016;234:41-8. doi:10.1016/j.jconrel.2016.05.034
 69. Genina N, Holländer J, Jukarainen H, Mäkilä E, Salonen J, Sandler N. Ethylene vinyl acetate (EVA) as a new drug carrier for 3d printed medical drug delivery devices. *Eur J Pharm Sci.* 2016;90:53-63. doi:10.1016/j.ejps.2015.11.005
 70. Holländer J, Genina N, Jukarainen H, Khajeheian M, Rosling A, Mäkilä E, et al. Three-dimensional printed pcl-based implantable prototypes of medical devices for controlled drug delivery. *J Pharm Sci.* 2016;105(9):2665-76. doi:10.1016/j.xphs.2015.12.012
 71. Yi H-G, Choi Y-J, Kang KS, Hong JM, Pati RG, Park MN, et al. A 3d-printed local drug delivery patch for pancreatic cancer growth suppression. *J Control Release.* 2016;238:231-41. doi:10.1016/j.jconrel.2016.06.015
 72. Wu G, Wu W, Zheng Q, Li J, Zhou J, Hu Z. Experimental study of plla/inh slow release implant fabricated by three dimensional printing technique and drug release characteristics in vitro. *Biomed Eng Online.* 2014;13:97. doi:10.1186/1475-925x-13-97
 73. Water JJ, Bohr A, Boetker J, Aho J, Sandler N, Nielsen HM, et al. Three-dimensional printing of drug-eluting implants: Preparation of an antimicrobial polylactide feedstock material. *J Pharm Sci.* 2015;104(3):1099-107. doi:10.1002/jps.24305
 74. Boetker J, Water JJ, Aho J, Arnfast L, Bohr A, Rantanen J. Modifying release characteristics from 3d printed drug-eluting products. *Eur J Pharm Sci.* 2016;90:47-52. doi:10.1016/j.ejps.2016.03.013
 75. Mohamdeen YMG, Tabriz AG, Tighsazzadeh M, Nandi U, Khalaj R, Andreadis I, et al. Development of 3d printed drug-eluting contact lenses. *J Pharm Pharmacol.* 2022;74(10):1467-76. doi:10.1093/jpp/rgab173
 76. Tagami T, Goto E, Kida R, Hirose K, Noda T, Ozeki T. Lyophilized ophthalmologic patches as novel corneal drug formulations using a semi-solid extrusion 3d printer. *Int J Pharm.* 2022;617:121448. doi:10.1016/j.ijpharm.2022.121448
 77. Persaud S, Eid S, Swiderski N, Serris I, Cho H. Preparations of rectal suppositories containing artesunate. *Pharmaceutics.* 2020;12(3):222. doi:10.3390/pharmaceutics12030222
 78. Li Q, Wen H, Jia D, Guan X, Pan H, Yang Y, et al. Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing. *Int J Pharm.* 2017;525(1):5-11. doi:10.1016/j.ijpharm.2017.03.066
 79. Skowrya J, Pietrzak K, Alhnan MA. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3d printing. *Eur J Pharm Sci.* 2015;68:11-7. doi:10.1016/j.ejps.2014.11.009
 80. Okwuosa TC, Stefaniak D, Arafat B, Isreb A, Wan KW, Alhnan MA. A lower temperature fdm 3d printing for the manufacture of patient-specific immediate release tablets. *Pharm Res.* 2016;33(11):2704-12. doi:10.1007/s11095-016-1995-0
 81. Nukala PK, Palekar S, Patki M, Patel K. Abuse deterrent immediate release egg-shaped tablet (egglets) using

- 3d printing technology: Quality by design to optimize drug release and extraction. *AAPS PharmSciTech*. 2019;20(2):12. doi:10.1208/s12249-019-1298-y
82. Pietrzak K, Isreb A, Alhnan MA. A flexible-dose dispenser for immediate and extended release 3d printed tablets. *Eur J Pharm Biopharm*. 2015;96:380-7. doi:10.1016/j.ejpb.2015.07.027
83. Kirillova A, Bushev S, Abubakirov A, Sukikh G. Bioethical and legal issues in 3d bioprinting. *Int J Bioprint*. 2020;6(3):272. doi:10.18063/ijb.v6i3.272
84. Gilbert F, O'Connell CD, Mladenovska T, Dodds S. Print me an organ? Ethical and regulatory issues emerging from 3d bioprinting in medicine. *Sci Eng Ethics*. 2018;24(1):73-91. doi:10.1007/s11948-017-9874-6
85. Mak SL, Tang WF, Li CH, Chiu WH, Lau HK, editors. A critical review on hazardous chemical emissions and particle from fused decomposition modelling (FDM) machine. 2019 IEEE International Conference on Industrial Engineering and Engineering Management (IEEM); 15-18 Dec. 2019.
86. Firth J, Gaisford S, Basit AW. A new dimension: 4d printing opportunities in pharmaceuticals. In: Basit AW, Gaisford S, editors. *3d printing of pharmaceuticals*. Cham: Springer International Publishing; 2018. p. 153-62.
87. Zhang Z, Demir KG, Gu GX. Developments in 4d-printing: A review on current smart materials, technologies, and applications. *Int J Smart Nano Mater*. 2019;10(3):205-24. doi:10.1080/19475411.2019.1591541