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Review Article

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

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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

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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.

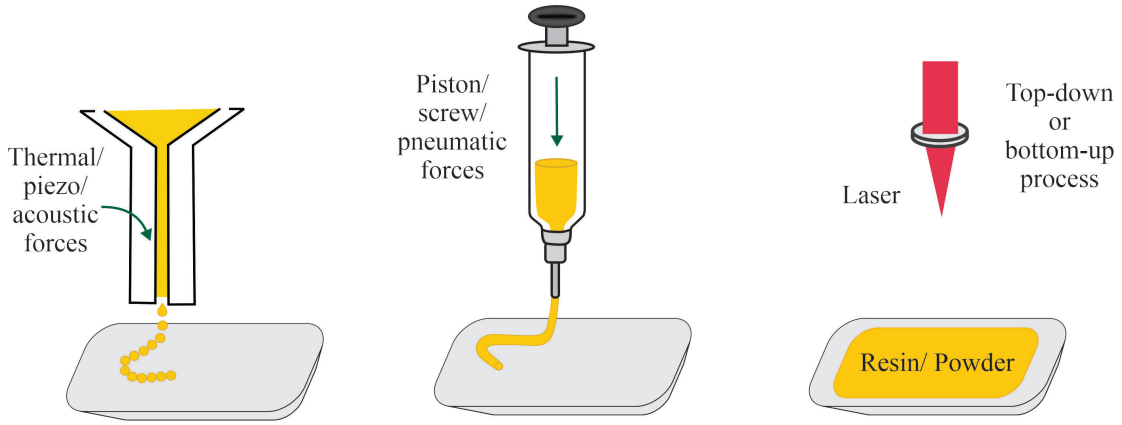

Figure 2. Common types of 3D printers in pharmaceutics. a: Droplet-based 3D Printer, b: Extrusion-based 3D Printer, c: Laser-based 3D Printer.

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 pharmaceutics,[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 pharmaceutics, and it was first developed in the early 2000s.[15] Its ink is a continuous filament works based on piston, screw, or pneumatic forces[9] (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 EBP[3] 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

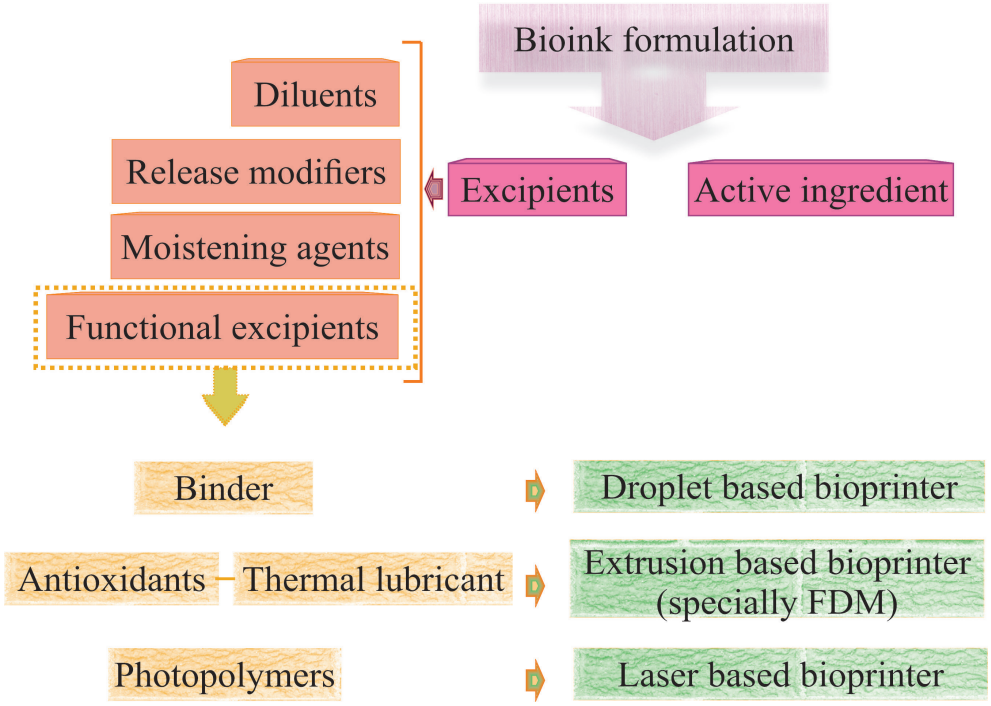

Figure 3. General ink formulas of the three leading 3D printers in the pharmaceutical field.

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 pharmaceutics

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 and cartridge 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

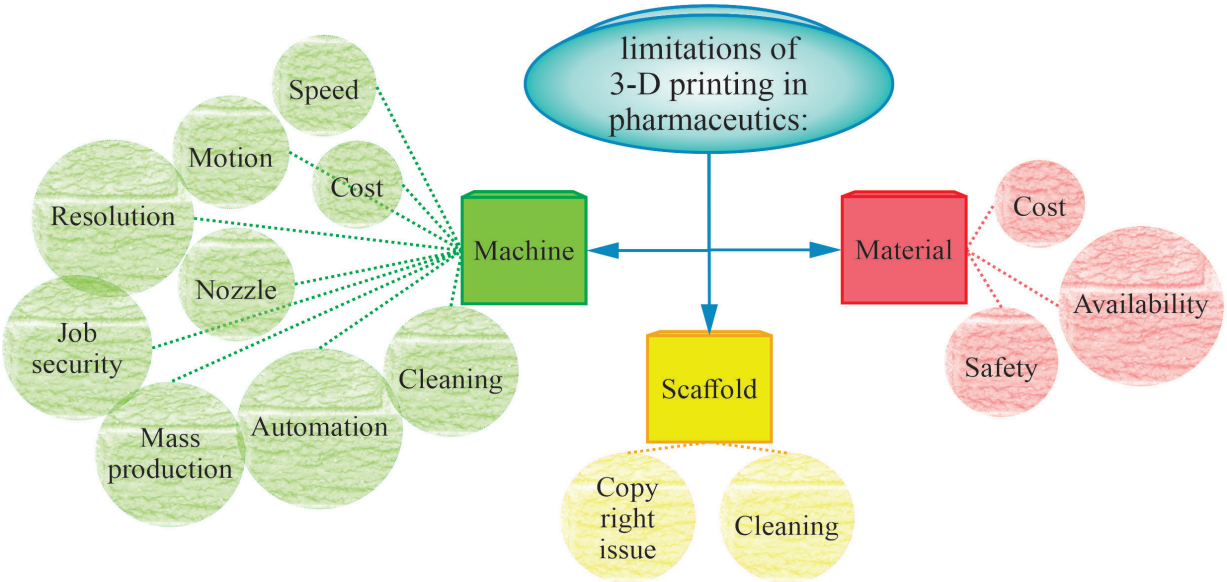

Figure 4. Limitations associated with 3D printing in pharmaceutical drug delivery systems.

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

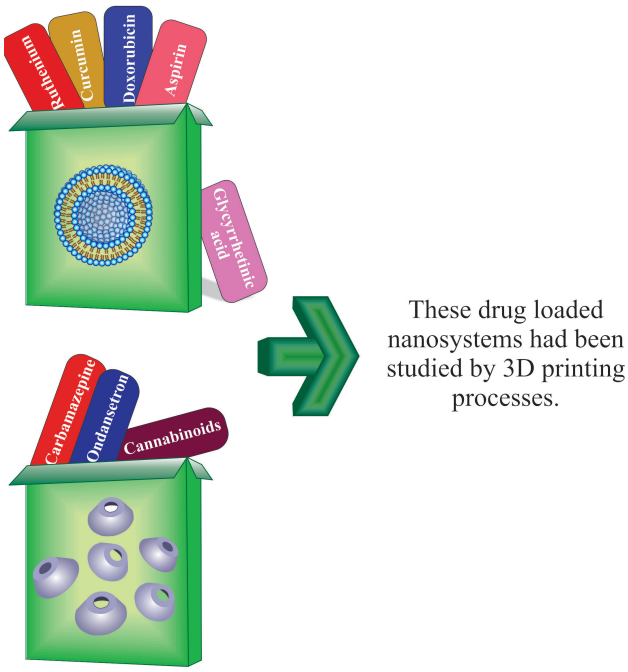

Figure 5. Drug-loaded nanocarriers that have been used in 3D printing.

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-Glycyrrhetinic 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 solution[36] (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-βCD) was taken to be printed by semisolid EBP.[39] The results highlighted the HP-βCD usage in printlet production with suitable physical and drug release properties for oral delivery of poorly water-soluble drugs. Pectin-based films containing cannabinoid-βCD 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] Orodispersable printlets containing ondansetron-βCD 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).

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
		Glycyrrhetinic acid			*				2020	36
CD	HP-βCD	Carbamazepine			*				2019	39
	βCD	Cannabinoids			*				2020	40
	βCD	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, Cortiment® (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-loaded[73] 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 to730 mg)	Sustained release	2014	59
					Pharmacel® 102, Primojel®		Immediate release		
Oral	Haloperidol	II	Tablet	FDM	Kollidon®VA64, Affinsiol™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	Acetaminophen Phenylephrine HCl Diphenhydramine HCl	III I I	Tablet	EBP	Eudragit®, PEG	-	Constant and/or sustained release	2021	46
Oral	Metformin hydrochloride Glyburide Acarbose	III II III	Pollypill	Micro-EBP	Pluronic F-127	Not reported.	programmable temporal release profiles	2018	47
Oral	Vitamin B1 Vitamin B3 Vitamin B6 Caffeine	III I I I	Pollypill	EBP (room temp.)	Craft Blend R30M	No detectable degradation	Immediate released	2021	48
					Craft Blend R4H		Slow release		
Oral	Acetaminophen	III	Tablet	FDM	HPMCAS	No degradation	Delayed release	2017	16
					HPMC	No degradation	Zero-order release	2017	54
					PVA	0.2% degradation	Controlled release (based on erosion)	2015	55
Oral	Fluorescein	III	Tablet	FDM	PVA	0.01% degradation	Dependent to the infill percentage	2014	56
Oral	Hydrochlorothiazide	IV	Caplet	FDM	Eudragit E	-	Immediate release (dependent to channel size)	2018	57
Oral	Budesonide	II	Caplet	FDM	PVA	0.04% degradation	Sustained release	2015	58
Oral	Felodipine	II	Disc	FDM	Eudragit EPO	94.62%	Almost sudden drug release	2016	61
					Soluplus®	95.75%	Slow drug release		
Oral	Glipizide	II	DuoTablet	FDM	PVA	External layer: 0.02% degradation Internal layer: 0.63% degradation	Controlled release (Korsmeyer–Peppas)	2017	78
Oral	Prednisolone	I	Tablet	FDM	PVA	88.7–107%	Extended release (Up to 24 h)	2015	79
Oral	Dipyridamole Theophylline	II I	Caplet-shaped tablet	FDM	PVP	101.18% 99.56%	Immediate release	2016	80
Oral	Metformin hydrochloride	III	Egg-shaped tablet	FDM	PVA	Not reported	Immediate release	2019	81
Oral	Theophylline	I	Tablet	FDM	Eudragit RL, RS	91–96% (in Eudragit RL based tablets)	Extended release (Over 16 h)	2015	82
					Eudragit E, HPC SSL	-	Immediate release		
Oral	Theophylline Budesonide Diclofenac sodium	I II II	Tablets	FDM	PVP, Methacrylic acid co-polymer	At least 84.68% 96.41% 90.47%	Delayed release	2017	60
Oral	Curcumin	IV	Tablets	FDM	PVP	-	Controlled release (dependent to drug content)	2019	62

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, Carra-geenan, Xanthan gum, Gelatine	LE: 99.90%	Various release profiles (dependent to the formulation)	2020	65
Chewable printlets	Isoleucine	-	Tablet	EBP	Sucrose, Pectin, Malto-dextrin	Max. 0.64% degradation	rapid release within 5 min	2019	67
Topical	Salicylic acid	I	Nose-shaped	FDM SLA	Flex EcoPLA™ 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 PLA	- -	Controlled release (dependent to drug loading) Controlled release (dependent to Metolose® content)	2015 2016	73 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

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