AL-Bahir
Journal for Engineering and Pure Sciences
BJEPS

Volume 3 | Issue 1 Article 7

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Recommended Citation
Hossain, Khan Rajib; Jami, Marzan Mursalin; Shyeed, Abu; Khatun, Khadiza; Hasan, Kamrul; Cobra, Khadijatul; and Ahmed, Firoz (2023) "Application of 3D Printing in Medicine: Technologies and Challenges," *Al-Bahir*: Vol. 3: Iss. 1, Article 7.
Available at: https://doi.org/10.55810/2313-0083.1036

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REVIEW

Application of 3D Printing in Medicine: Technologies and Challenges

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Abstract

With the rapid development of 3D printing technology, its application scope has involved various fields such as aerospace, the automobile industry, medical treatment, food and others. The US Food and Drug Administration (FDA) approved the release of "levetiracetam instant tablets," made with 3D printing technology. This means that 3D printing could be used to mass-produce drugs. This article reviews the principles, advantages, and challenges of 3D drug printing technologies: stereolithography, inkjet printing, powder-liquid bonding, and fused deposition, and looks forward to their future development in the preparation of solid preparations of medicine. With the continuous development of computer control, 3D printing industrialization and medicine excipients, and other technical fields, the application of 3D printing technology in the pharmaceutical industry will become more and more extensive.

Keywords: 3D printing, Challenge, Rapid prototyping, Technologies of medicine, Application

1. Introduction

3D printing technology, also known as rapid prototyping technology and additive manufacturing technology [1], is a technology that directly shapes computerized three-dimensional design models by layer-by-layer [2,3] accumulation of special materials. Industrial-grade 3D printing technology has only been around for more than 30 years. Still, with the fast growth of computer science and materials science, it can now make complex objects without increasing costs, with no assembly, zero-time delivery, unlimited design space, no-skill manufacturing, and low-cost materials. 3D printing technology has been applied in many fields, such as aerospace, the automobile industry, medical treatment, and food [4–6]. 3D printing is used in medicine to make medical models, biological tissues and organs, and solid medicines [7]. From 2000, when W.E. Katstra et al. [8] used powder delivery 3D printing technology to prepare chlorpheniramine maleate tablets, to 2015, when the US FDA approved the world's first 3D printing technology to prepare "levetiracetam instant tablets" [9] (Fig. 1) on the market, 3D drug printing has triggered a new wave of research by scientists at home and abroad [10,11]. There are few studies on applying 3D printing technology to medicine preparations. The team led by Peihong Chen et al. used 3D printing technology for the first time to prepare and evaluate the quality of quick-acting gastric floating oral disintegrating tablets for feasibility [12]. This article is based on the principles and features of 3D drug printing technology. It will discuss and analyze the

Received 9 May 2023; revised 29 May 2023; accepted 30 May 2023.
Available online 14 July 2023

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https://doi.org/10.55810/2313-0083.1036

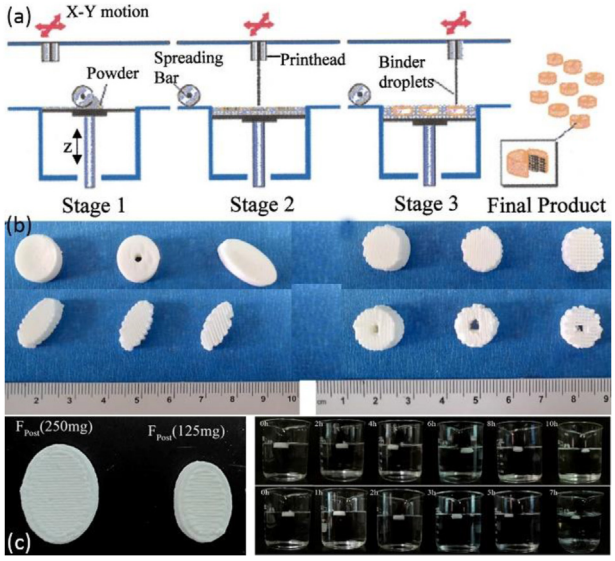

Fig. 1. Images of (a) binder 3D printing process [8], (b) printed solid tablets with three geometrical shapes made using the method described; cylinder lattice tablets that have different infill percentages (from left to right: 100%, 75%, and 50%); torus lattice tablets with different infill percentages (from left to right: 100%, 75%, and 50%); oval lattice tablets with different infill percentages (from left to right: 100%,75%, and 50%) [9], and (c) 3DP gastric floating tablet appearance: the 125 mg and 250 mg tablets in pictures, The floating states of the 3DP gastric floating tablets in the acetate buffer solution were studied for buoyancy, tablet with 250 mg and with 125 mg [12].

pros, cons, and future of the technology's use in solid medicine preparations to give ideas for making new medicine preparations (see Table 1).

The pharmaceutical industry also accepts the impact of various new technologies, such as 3D printing technology, in drug discovery, formulation development, and manufacturing, which exhibit unique advantages. Additive manufacturing is another name for 3D printing. This is how the computer turns a two-dimensional image into three-dimensional data. Specific molding equipment prints and superimposes materials layer by layer, finally turning the blueprint on the computer into a real thing [13]. People have called 3D printing technology the fourth industrial revolution because it changes people's lives. In the current medical environment, 3D printing technology provides a new way for children who must strictly regulate their dosage and drug combinations. The development of scientific preparations has injected new vitality. Oral solid immediate-release preparation is a solid preparation that can disintegrate rapidly after taking it. It allows drugs to be absorbed quickly and has high bioavailability. It works best for medicines that must start working quickly [14]. Compared with traditional tableting, powder 3D printing is a non-compressive production process. The ready-made preparation has a loose, porous structure that makes it easy for liquids to get inside, helps it break apart, and speeds up the release of the active ingredients. 3D Printed drug, levetiracetam is a microporous tablet that can be used immediately and dissolves in the mouth. It was made with powder-based 3D printing technology. It helps people with epilepsy with difficulty swallowing high-dose traditional tablets (1000 mg). Deng-Guang Yu et al. [15] also used 3D powder printing technology to make fast-dissolving tablets of tofu fruit glycoside and acetaminophen for their research in China. The experimental results showed the disintegration times of the two kinds of fast-disintegrating tablets. They are 19.8s and 23.4s, respectively, and can be fully released within 2 min. The hardness, disintegration time, and friability can all meet the relevant regulations of the 2015 edition of the "Chinese Pharmacopoeia." At the same time, scholars have further studied the premise of ensuring the mechanical strength and release speed of the preparation, increasing the drug loading of the preparation, and reducing the number of single doses taken by patients. Shaban A. Khaled et al. [16] used paracetamol as a model drug and successfully prepared immediate-release tablets with a drug loading of up to 80% (w/w) using semi-solid extrusion (SSE). The tablets broke up completely in 60 s, releasing the drug in 5 min. This proved that 3D printing could make high-dose immediate-release preparations that meet USP standards. At the same time, Qijun Li et al. team [17] further found that when the tablet fill rate was 50%, levetiracetam tablets with a drug loading of up to 96% (w/w) could be prepared by using SSE, and the drug was released within 2 min. It can release 97.45%. This research is a breakthrough in semi-solid extrusion 3D printing technology for high-drug-loaded preparations. Also, it shows that 3D printing can be used for high-drug-loaded immediate-release preparations. Scholars are also interested in devices that work quickly and have specific properties and in traditional remedies that immediately work. Julius Krause et al. [18] proposed a pressure-controlled drug delivery system; targeted drug release is achieved through the pressure response to different parts of the gastrointestinal system. The drug delivery system uses brittle polymers. Gelatin, Cellulose, PLLA, EVA, RS is used to make the shell of a capsule, and a preparation that looks like a capsule is made by changing the wall thickness of the capsule shell. The in vitro bio-related pressure results show that it can be used as a pressure-responsive drug delivery system to deliver drugs to the gastrointestinal tract. Targeted position, the capsule shell is broken under a specific pressure to achieve rapid and precise drug release.

Table 1. Summary of 3D printing technologies in the pharmaceutical field.

Material status	Technology Name	Mechanism	Advantages and disadvantages	Applications	Material
Liquid	Poly Jet printing technology (PJP), Nanoparticle jetting (NPJ)	Cooling or heating, solvent evaporation, UV polymerization Ejected material Deposition, solidification	High printing accuracy; environmental protection; no post-processing required; low mechanical performance; expensive; complex structures require printing support; high temperature treatment is required	Fickian Diffusion Based Fenofibrate Tablets 15	Wax-like substances, such as: white beeswax [45]
	Stereolithography (SLA), Digital light processing (DLP)	Selectively transform liquid resin into a solid using a light source such as a laser	High printing accuracy; potential toxicity; requires post-processing and printing support; mechanical properties decline over time, fastest 3D printing technology; precision and finish are limited by pixel size;	3D-printed nose-shaped anti-acne transdermal patch 16	Liquid photosensitive resin: polyethylene glycol diacrylate (PEGDA), polyethylene glycol (PEG) [46–49]
Solid	Binder jetting (BJ) technology, Color Jet printing (CJP) technology	Jetting of liquid binders to selectively agglomerate powders	Fast printing speed; support printing of multiple materials; low mechanical properties of the product; post-processing is required; Full color printing is possible on the basis of BJ technology	Spirtam (Levetiracetam) - the first FDA-approved 3D-printed drug 17	Solid powder: mannitol, lactose, etc.; liquid binder: water, polyvinylpyrrolidone (PVP) [34, 50–51]
	Selective laser sintering, SLS) technology Selective laser melting (SLM) technology	Solidification by melting or sintering powder with laser or other heat source	No printing support is required; high printing accuracy; the raw material can be recycled; the particle size of the raw material affects the precision; the mechanical performance of the product is low; Requires high-performance laser components; high energy consumption; low efficiency	Rapid-release acetaminophen orodispersible tablets 18	Hypromellose (HPMC) [52, 53], vinylpyrrolidone-vinyl acetate copolymer [54], etc
Semi-solid	Fused deposition modeling (FDM) technology, Semi-fluid extrusion (SSE) technology	The material is in a semi-solid state and solidifies after extrusion deposition	The machine is cheap and easy to obtain; supports printing of multiple materials; speed and precision are limited; complex structures require printing supports; Low temperature printing; post-processing is required	Rapidly disintegrating aripiprazole-loaded filaments containing nifedipine, Controlled-release tablets of captopril and glipizide 19	Thermoplastic material: polyvinyl alcohol PEG 6000, microcrystalline cellulose (MCC), HPMC, D-mannitol, etc [55–57].

2. 3D printing techniques

The beginning of this technology dates back to the 1980s when Charles Hull created the foundations for the development of 3D printing [19–21]. It was also he who, in 1993, created the first printed object and invented stereolithography, the first technique and key to the future development of 3D printing technology [22]. There has been significant development of different techniques for 3D printing.

2.1. Stereolithography (SLA)

Charles Hull [23] created this as his initial method. This technique is based on the solidification of a photosensitive liquid polymer. Liquid polymer solidification occurs a source of irradiation, by processes of photopolymerization and projection of light or laser [24,25], which provide the energy that is needed for this chemical reaction to occur, resulting in the union of the molecules, which gives rise to a reticulated structure. In Fig. 2, we can see a schematic of a printer that works with this technique.

Due to their potential applications in biomedicine, multiple materials can be used as polymers, such as corneal implants, drug delivery forms, contact lenses, etc. Another use of CAD in biomedicine is to make anatomical models from CAD files and images from magnetic resonance imaging (MRI) or tomography (Tomography), both of which are used to diagnose medical conditions [28].

2.2. Fused deposition modeling (FDM)

One of the best-known 3D printing techniques is fused deposition modeling. Using a thermoplastic filament [29], this method builds each layer with a print head that lays down the material and heats it before it sticks together. The head moves along the x and y-axes, while the surface where the material is deposited moves along the z-axis. Since there is movement in all three directions, 3D objects can be made [30]. Fig. 3 shows a diagram of the printing process using the FDM technique.

Its application in personalized medicine is based on the fact that some polymers can be loaded with active ingredients. In addition, we find biocompatible and biodegradable materials that can be used in medicine and pharmacy, such as lactic acid-based polymers such as PLA (polylactic acid) and PLC (polycaprolactone). Both polymers have a low melting point, thanks to which they do not lose their bioactivity [32] when melted for the manufacture of medicines, and with the advantage that they are eliminated through the body's excretory pathways. When put to use, FDM printing technology is used to make devices that are unique to each patient. In addition, some of the polymers can be loaded with active ingredients, such as antibiotics, for applications in personalized medicine.

2.3. Binder jetting (BJ)

This is the technique we will focus on in the literature review. We also called it "Drop-on-Solid" (DOS). Within binder jetting technology, different techniques exist to perform it. We can see a schematic of the printer itself in Fig. 4. BJ was invented at the Massachusetts Institute of Technology in 1993. Over the years, and up to the present, various companies have developed the technology and machines to apply it [33].

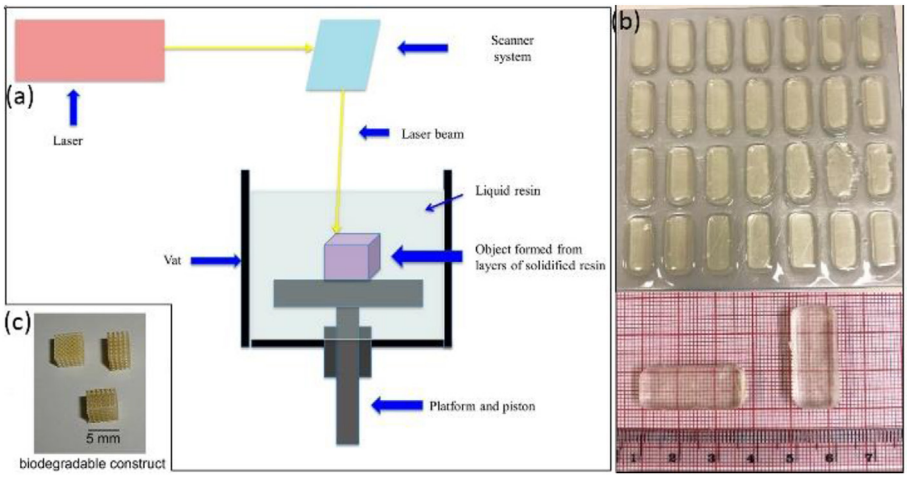

Fig. 2. Scheme of the (a) printer technique for stereolithography (SLA) [11], (b) a complete batch of SLA 3D-printed dosage forms (n = 28); a single dosage form [26], and (c) the printed of creating biodegradable structure using stereolithography [27].

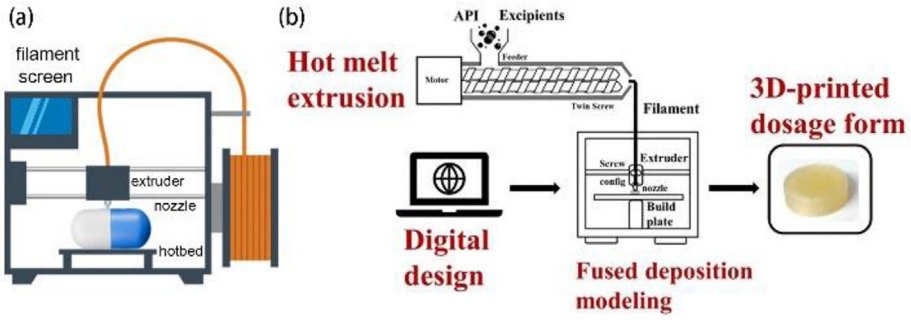

Fig. 3. Schematic overview of the (a) most commonly used 3D printing techniques: Fused Deposition Modeling (FDM), and (b) procedure for using hot melt extrusion and fused deposition modeling combined [31].

The binder jetting method involves putting a binder solution's layers on a powder bed. This liquid will cause the dust particles to stick together, and in this way, a three-dimensional object is formed layer by layer. A heat source is unnecessary since the binding agent is in charge of joining the particles. So, you can only use two things: the powder, which is the base for printing, and the binding liquid, which holds the powder together between the layers and within them [34].

The printer makes a powder bed on the build platform during the printing process, where the liquid binder will be spread. As the authors have said, the object is created layer by layer. By using a counter-rotating roller to deposit a layer of powder, the printer then applies the binder liquid, fusing the powder, and as a result, we get a 2D pattern of this first layer [33]. The platform moves vertically downward to form successive layers [35]. The Silcer software will move the head along the x-y axis [36] based on the model that was made in CAD. This process is repeated with each layer until we finally have the object created [33]. This process is schematized in Fig. 4.

They are usually fragile pieces, so subsequent processing of the object is necessary. Depending on what is sought, it will be processed to achieve different final properties. The quality of the final product depends on both the material and the bed formation process, as well as the processing it undergoes [33]. One of the advantages of this technique over others is that it can process almost any powder. Since heat application is unnecessary, thermolabile materials can be used. It is a method used in many areas of science, and its use in biomedicine is becoming more important at the moment. This method of manufacturing the first 3D-printed drug has received FDA approval [37].

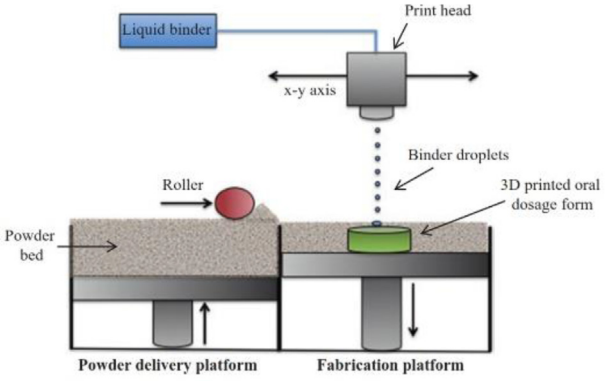

Fig. 4. Schematic view of basic Binder Jet Printing Process [34].

There are different possibilities to incorporate an active principle in the process. It can be put in the liquid binder or added to the powder to make the bed, though the powder is more of a support than a binder. In case a higher concentration of the drug is required, it can be added to both components. The manufacturing process with BJ is similar to the wet granulation process, widely used in the conventional manufacturing of medicines, specifically tablets [38]. Different printing methods are used when 3D printing technology is used in different fields. Since 3D printing is an example of additive manufacturing, melting solid materials into liquids and making them solid again is more flexible and easier to control. Most 3D printing technologies go through a process of melting the base material. However, 3D printing technology for pharmaceutical formulations requires more gentle molding techniques to avoid damage to the active ingredients of the drug and render the drug ineffective. 3D printing has made many complicated preparations possible by allowing the design of three-dimensional structures and prescriptions. According to different 3D printing manufacturing principles, the combination of material combination and structural design can realize flexible control of drug release mode. Regarding immediate-release formulations, laser sintering and binder jetting can hold powders loosely, but their bonds are weaker than those made by mechanical compression forces. It makes very

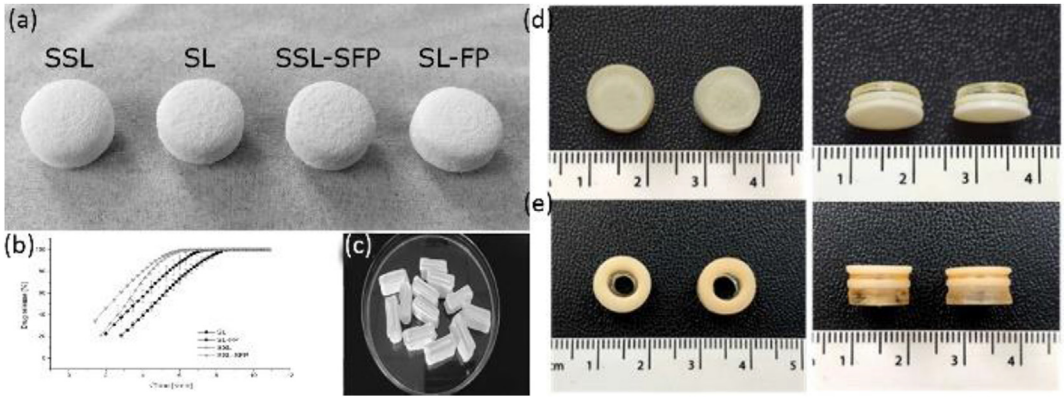

Fig. 5. (a) 3D-printed medicines based on SL, SL-FP, SSL, and SSL-SFP are the final dosage forms, (b) dissolution data plotted as a square root of time (n = 3s) [60], (c) Using SLA, SLS, and FDM, 3D prints a controlled release bilayer tablet [63], and (d–e) Type I polypill printlets (cylinder shape) and Type II printlets (ring shape), respectively. Since the Type III formulation was visually identical to the Type II formulation, the resin formulation was printed using SLA [61].

porous structures and can let dispersible tablets dissolve quickly [39]. Regarding sustained and controlled release preparations, various 3D printing technologies can regulate drugs' in vivo and in vitro release behavior at multiple levels by adjusting the internal structure, shape, and prescription combination [40,41]. In addition, the strong ability of 3D printing technology to create compartments has great advantages for treating complex diseases requiring multiple drug combinations, such as type 1 HIV infection, hypertension, tuberculosis, and type 2 diabetes [42]. Using the multi-chamber structure, drugs can be stored and delivered separately [43]. A partitioned and step-wise delivery system can also be made based on the gastrointestinal tract's pH level and enzyme activity.

In addition to the preparation process, 3D printing technology has other applications. For example, Atheer Awad et al. [44] first reported using 3D printing technology to prepare watches. Face design with braille and moon graphics, the mouthpiece for the visually impaired Cavity-disintegrating tablets that allow patients to identify the drug from its original packaging.

3. 3D-printed medicine

In recent years, various 3D printing techniques have been developed. Different fields have been finding more ways to use and apply these technologies over the past few years. This growth has reached the fields of medicine and pharmacy, where it has many uses, such as making prosthetic parts, implants, anatomical models that fit the patient's body, designing and making drugs, making new dosage forms and ways to release them, customizing medicines, and so on [58,59].

This leads to personalized medicine based on making more accurate, safe, and effective drugs because they are made with a specific dose for each person and taken as prescribed. With the ability to change the amount of the active ingredient, it is possible to make a single dosage form with more than one active ingredient (Fig. 5a), just like in traditional medicine. In this case, the advantage over traditional manufacturing is that the active ingredients and dosage can be changed to fit the needs of each person. As the authors have said, these are dosages and combinations of established principles. This application is exciting for poly medicated patients. These cases usually have various pathologies; for each one, a drug is in a pharmaceutical form, so they have a complex medication administration. This can lead to medication errors and a lack of adherence to treatment. It should be added that most cases of polymedicating people are elderly patients, and this circumstance can be an added factor before the problems reported with taking the medication [60].

To remedy this problem, what is known as “polypills"—a single dosage form containing all or most of the active ingredients—with its adjusted dose, which each patient has prescribed [61] (Fig. 5d and e). What is sought with the polypills manufactured by 3D printing is to combine in a single oral pharmaceutical form (since this is the form most accepted by patients) the different active principles that the patient has prescribed, in a dosage customized for him and with the appropriate release profile.

Studies have been carried out with polypills with various combinations of principles assets manufactured by 3D printing. An example of this is the combination of antihypertensive drugs with hypoglycemic agents. Diabetes and high blood pressure

are usually found together, which makes this combination interesting. In the case of the study carried out by Shaban A. Khaled et al. [62], using the 3D printing technique of extrusion at room temperature, they manufactured a polypill containing captopril, nifedipine, and glipizide. It was also found that captopril had a different release profile in the same pill than nifedipine and glipizide. The first one had a release kinetics of order 0, meaning the release was slow and constant, no matter how many drugs were in the drug. The last two, on the other hand, had Kinetics of order 1, which means that the release did depend on the amount of drug.

Today, applying 3D printing technology in pharmacology is a reality, although it is still at the beginning of its development. In 2015, the Food and Drug Administration (FDA) approved the first drug manufactured by 3D printing, called Spritam®, a tablet whose active ingredient is levetiracetam, an antiepileptic. It was printed using the Drop on Solid (DOS) technique, a modality of the Binder Jetting technique, being marketed in 2016 [63] (Fig. 5c).

3.1. The development of pharmaceutical manufacturing towards small-batch personalized customization

According to the pharmacokinetics study, the drug release rate is related to the geometric shape of the solid preparation, and a change in the geometric shape of the preparation will affect the drug release [9] 3D printing lets you change the shape in many ways, and the design of the preparation's geometric shape and internal structure can control and change how the drug is released [64,65]. Alvaro Goyanes et al. [66] used FDM to prepare tablets with different shapes (cube, pyramid, cylinder, sphere, and torus). The experimental results showed that in the process of drug release dominated by matrix erosion, the geometric shape significantly impacts drug release; the larger the surface area to volume ratio, the faster the drug release. Muzna Sadia et al. [67] team made a multi-channel preparation (Fig. 6a) to learn more about how shape affects drug release. It looked at how the tablet channel's width, length, and alignment affect how the drug gets out. The results showed that in formulations with the same alignment, the drug release rate increased as the channel width increased; tablets with shorter (8.6 mm) but more channels released more drugs than tablets with fewer but longer (18.2 mm) channels. Drugs are released more quickly, which may be related to changes in fluid flow resistance in the channels. Mary Kyobula et al. [68] used beeswax as excipients and fenofibrate as a model drug (Fig. 6c). The release of drugs can only be changed by controlling the size and surface area of the holes in the honeycomb structure with 3D printing. This allows for

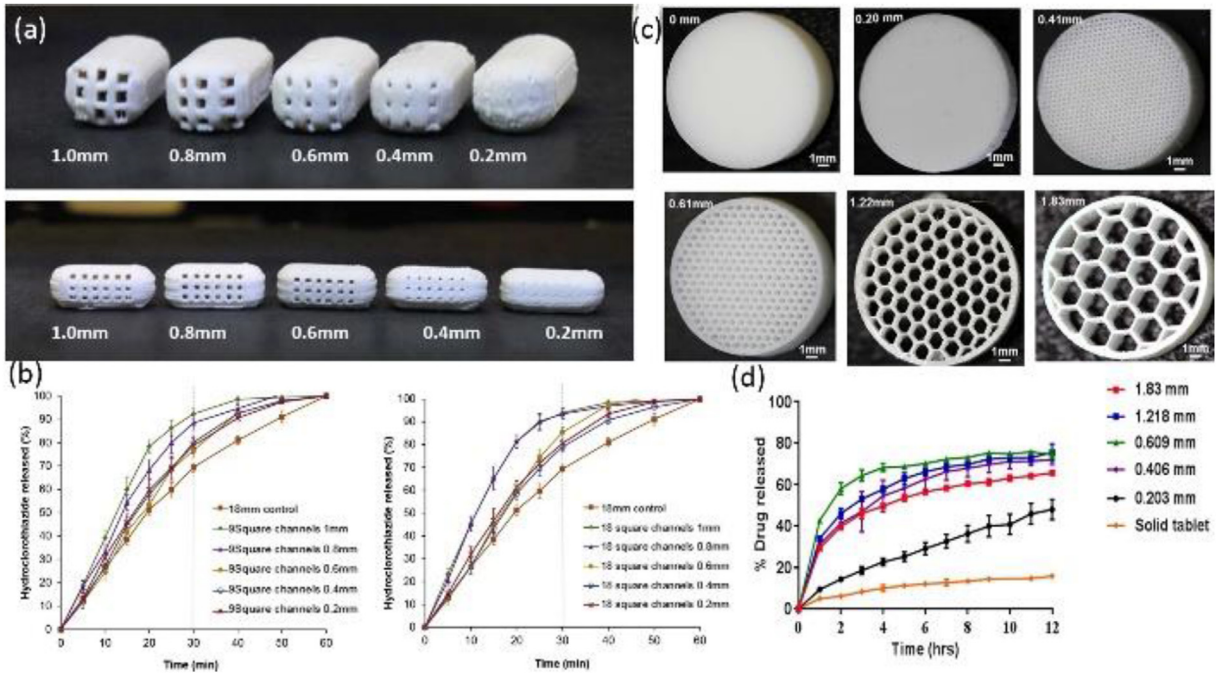

Fig. 6. (a) Drug caplet illustrations that were 3D printed have decreasing channel sizes—9 long channels (top) and 18 short channels (bottom), (b) The USP II dissolve test in stomach media (0.1 M HCl, pH 1.2, 50 rpm) examined the effects of channel width and orientation on the dissolution release pattern from hydrochlorothiazide methacrylate tablets [67], (c) photographs of the printed solid tablet and tablets that resembled honeycombs and had cells that varied in size from 0.20 mm to 1.83 mm, and (d) Drug release predictions and in vitro release investigations. a) Dissolution profiles for tablets with constant weight and printed solid tablets that resemble honeycombs [68].

variable and predictable drug release—a predicted profile. The experimental results reveal that in the process of drug release when the pore size is as large as 0.41 mm, the drug release rate is positively correlated with the surface area; when the pore size is smaller than 0.41 mm, the drug release rate slows down with the increase of the surface area, which is The reason is that the too-small pore size is not conducive to the wetting of the liquid and forms a blocking effect on the flow of the fluid, which is not conducive to the release of the drug.

Also, 3D printing can be used to change the complex shapes and properties of solid preparations at the same time. It makes it easier to control and change how drugs are released. After drying, the floating sustained-release tablet (Fig. 7a) has a low density. They were changing the rate at which the tablet is filled, and the drug's eight-hour sustained-release makes it float well. Fu et al. [69] further utilized the FDM system prepare a drug delivery device with a complex structure (Fig. 7b), which has independent air chambers and drug-loading chambers, and the tablets obtained by the direct compression method are loaded into the drug-loading device (single-network and double-network), achieving a sustained drug release of 72 h and maintaining a stable floating during the drug release. At the same time, the shell structure of the drug-loading device can be designed to affect the change of the osmotic pressure in the core, thereby controlling the release rate of the internal active drug and preparing a 3D-printed solid preparation with delayed and long-acting sustained release. In addition, Wu et al. [70] combined magnetic targeting with 3D printing to prepare a biphasic drug delivery system with magnetic targeting capability (Fig. 7c), which loaded ibuprofen on both sides of the membrane, respectively. And acetamido, the middle is connected by poly beta lactone containing magnetic nanoparticles, folded and loaded in the capsule shell for easy administration. With the help of an external magnetic field, the composite film can release drugs in the intestines in a targeted and slow way. It has a lot of potential uses in both personalized and combined medicines. In a word, adjusting how a drug dissolves can be done using 3D printing to prepare with different three-dimensional structures. When the application is combined with the new idea of preparation, it makes it easier to make new dosage forms with specific pharmacokinetic properties or precise drug release for different parts of the digestive tract (see Fig. 8).

3.2. Applications to the pharmaceutical industry

Currently, the pharmaceutical industry makes medicines in large-scale production with set doses. With 3D printing, a new way of approaching the production of medicines is possible. It allows the application of precision medicine, which involves deciding which treatment is best for the patient based on specific data. Precision medicine goes hand in hand with personalized medicine, that is, making an individualized dose adjustment for each patient depending on her needs [71–73]. Putting 3D printers in hospitals would be a big step forward for personalized medicine. Still, several things could be improved, such as the high cost of installing the printers, the need for qualified personnel, and the complications in the quality control of medicines since they would require non-destructive techniques [74].

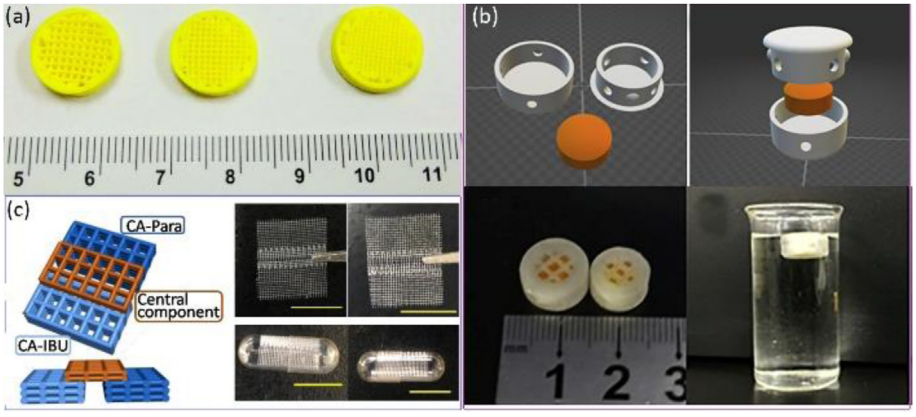

Fig. 7. (a) A gastric floating tablet prepared by extrusion-based dual-nozzle 3D printer [17] (b) Illustrations of two Tablet in devices (TiD) systems, biphasic drug delivery system with magnetic targeting capabilities the in vivo investigation further confirmed TiD systems' long-term stomach retention, TiD systems filled with iron plates were created [69], and (c) prepared gastric floating drug delivery device with an independent gas reservoir and drug loading chamber and images of printed composite membranes with different folding component layers [70].

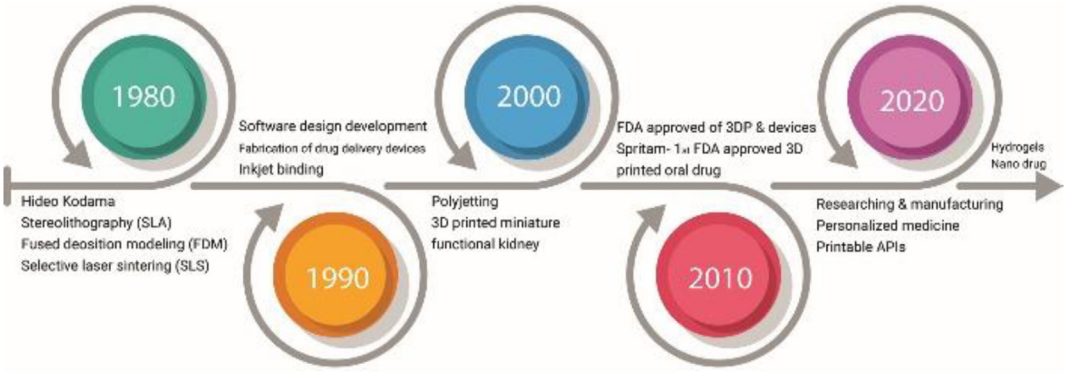

Fig. 8. Illustration of a timeline of the significant stages and major events in the development of 3D printing.

There are some specific fields of medicine in which medicine specialists can find exciting applications. For example, it would make it easier to give doses to children based on their weight, stage of development, rate of growth, etc. Also, in cancer treatments, the dosage is adjusted to the needs and evolution of the process. Another application for binder jetting in the pharmaceutical industry is manufacturing dosage forms with modified release profiles. This app is still developing [75–77].

3.3. Advantages of 3D printing technology in medicine preparations

Sustained-release medicine preparations have the advantage of maintaining the effective concentration of the drug for a longer period and avoiding fluctuations in blood drug concentration or severe adverse reactions. Layered tablet compression technology is currently a common technique for the preparation of sustained-release preparations of medicine. According to the difference in physical and chemical properties, the ingredients in the prescription are grouped and processed in layers. Different blockers are added, and various pressures are applied to compress them into several layered tablets [78]. The preparation of multilayer tablets usually uses tablet presses. However, due to technical limitations, there currently needs to be more equipment capable of producing multilayer tablets with more than 3 layers, which limits the application of layered tablet technology in preparing sustained-release medicine preparations. Using 3D printing to make multilayer, slow-release medicines solve the technical problems when tablets are compressed by hand. According to the drug design model, it can prepare multilayer tablets with more than 3 layers. In addition, 3D drug printing technology can design different drug shapes according to drug release characteristics. Goyanes et al. designed and printed five different shapes of tablets with a fixed surface area: cube, pyramid, column, torus, and sphere [79]. The results of the dissolution test showed that the geometry played a significant role in determining the drug release profile. When the surface area of the 3D-printed tablet was kept constant, the drug release rate was the fastest from the pyramid-shaped tablet, followed by the torus, cube, sphere, and finally, the cylinder. 3D drug printing technology has a lot of benefits when it comes to controlling the release of drugs by changing their shape. It can also make accurate mixtures of medicines, which fits with the "monarch, minister, assistant, and envoy" theory of compatibility.

Compound solid preparations are made up of many parts, and the amount of each medicine in the prescription differs. The drug may include a microdose of precious or toxic medicinal materials for different diseases. The raw and auxiliary materials are made into the designed dosage form in solid medicine preparations through pulverization, mixing, screening, drying, and molding [80]. Each process affects the uniformity of the preparation to varying degrees. The uneven dosage of drug unit preparations will cause a waste of precious medicinal materials and may even cause the drug to be ineffective or toxic. 3D drug printing technology is used in solid medicine preparations. To ensure the accuracy of a single drug dosage, quantitative pumps, and high-precision stepping motors can regulate the amount of drug supply. You can use more than one quantitative pump head to replace raw materials for compound preparations. The mixing process between micro-dosage medicinal materials further improves the accuracy of micro-dosage addition. The same ones used in the preparation can be used regarding the excipients' traditional manufacturing of FDA-approved drugs. Thanks to the manufacturing process, this is very similar to the conventional wet granulation process [81,82].

Some excipients must be in the powder, others in the binding liquid, and others can appear in both phases. Diluents, disintegrants, sweeteners, and lubricants may be found in the powder. Among the diluents, the most common are lactose and mannitol. Pregelatinized starch is an example of something that uses it as a disintegrant. As a sweetener and flavoring agent, for instance, in the Spritam, the mint aroma was used, both naturally and artificially. And finally, silicon dioxide and magnesium stearate are used as lubricants. The binder polymer is going to be what makes the particles stick together. This Polymer can go both in the powder and dissolved in the printing liquid. The location will depend on its characteristics and viscosity. The amount of binder will influence the final product's mechanical resistance since it improves the quality of the union between the dust particles [83]. The components of the binding liquid must be soluble in each other. If there is an insoluble substance, it must have a colloidal particle size, that is, between 10 and 100 nm, since, otherwise, it could sediment and cause obstruction of the print head. In addition, it would make the product obtained not uniform [84–86].

The active principle can be incorporated into the binding liquid and dust. It will depend on the solubility of the drug, its stability in each of the components, and the dose since, if we look for a more significant drug load, it can go in both phases. If we are looking for lower doses, and it is soluble in the binding liquid, it is here where it will be incorporated. In the case of the powder, it will contain the drug when it is insoluble, heat labile, and we are looking for a higher dose.

3.4. The development vision and existing problems of 3D printing medicine preparations

People imagine that future 3D printing technology has many advantages. Still, it has only been 30 years since 3D printing technology appeared, and our understanding of it needs to be more thorough. There are still many practical problems to be solved in the rigorous pharmaceutical field. Only one FDA-approved 3D printing drug is on the market, and the development and application of other products and clinical policies still need to be clarified. As a new technology, 3D-printed medicines must meet the standards for making and controlling medical products and equipment already in place. Since many things can affect the quality and safety of computer-designed dosage forms, proper rules are needed to keep patients and operators safe [87], so that 3D printing technology can be used to make personalized medicines in a safe and effective way.

Drug production supervision methods need to be improved and supplemented. The current "Measures for the Supervision and Administration of Drug Production" say that the drug supervision and management department is in charge of management tasks like reviewing, licensing, supervising, and inspecting the conditions and processes of drug production at pharmaceutical companies. However, the popularization of 3D drug printing in the future will change the production process of drugs from large pharmaceutical factories to a large number of digital files. The focus of drug production supervision will also shift to the review and error correction of these digital files.

On August 3, 2015, after the 3D-printed fast-dissolving tablet Spritam (levetiracetam) developed by Pennsylvania-based Aprecia Pharmaceuticals was approved for marketing, the company invested another 25 million US dollars in building a 3D pharmaceutical preparation platform [88]. However, 3D drug printing technology is still in the laboratory research stage in my country. Although 3D printing has a significant low-cost advantage compared with traditional design concepts and ideas in the product design and development stage, because 3D drug printing technology still has an extensive research space and potential in terms of mechanism, feasibility, and diversification, R&D on processes and equipment requires more R&D investment.

As 3D drug printing technology keeps improving, more and more people want personalized medicine. This means how drugs are made and sold in the future will differ from how they are made and sold now. With constant improvements in design and efficiency, 3D printers of different sizes and capacities can be put in a place that is easy for patients to access. Hospitals can manufacture medicines in their pharmacies without having to store a large number of medicines. In the future, even families can have a medicine printer to print out medicines adapted to their diseases—drugs for love. Once the supply chain has this kind of flexibility and scalability, suppliers and consumers will enjoy the low cost and low price brought by improving operational efficiency.

There are many types of printers on the market, but there need to be more special printers for medicine. Most of the printers used are transformed from food and biological printers. Second, the technical skills of the people involved must be improved to improve the 3D printing preparations. All operators who help with preparation and production must be trained, and clinicians are included in this training. Set up multi-level management authorities for the 3D printing process to ensure the

safety of preparations during the printing process, and traces can be followed when there are problems with the safety of the clinical medication.

Currently, materials, technology, and quality control are the main factors hindering the development of 3D-printed pediatric preparations. As a new type of preparation process, more than 3D printing is needed to develop and store new materials. It is essential to study in depth how further processing affects the stability and compatibility of APIs. Getting 3D printing into clinical practice is also challenging because there are few ways to check quality in real-time. Sarah J. Trenfield et al. [89] devised a way to test the quality of the active ingredients in 3D-printed drugs without damaging them by using near-infrared spectroscopy. This non-destructive testing method of near-infrared spectroscopy has promoted the development of online testing 3D printing pharmaceutical supporting technology.

Modern medicine's solid preparations are made in factories, and some are made on intelligent assembly lines. This has made the process much more efficient. For example, the methods of extracting, concentrating, refining, drying, mixing, granulating, tableting, and making medicine tablets have been combined into a single production line. However, as an emerging pharmaceutical technology, 3D drugs printing's low work efficiency is one of the bottleneck problems. For the integrated molding process of monomers, the workflow is completely fixed, and it is impossible to carry out the production line production of traditional graded manufacturing and flow assembly. So, a critical part of using 3D drug printing technology to make solid preparations of traditional Chinese medicine [90] is to make the work go faster, which is a big challenge. The array printing head makes creating multiple products simultaneously in a single process possible. This makes 3D drug printing more efficient. As electromechanical and control technology continues to improve, 3D drug printing technology can be used in industry.

The application of 3D drug printing technology in medicine preparations is an inheritance and an innovation of the conventional theory of dialectical medicine application. In clinical medicine, doctors usually write different prescriptions for each patient based on their health and clinical symptoms. This is done to make sure that each patient gets the correct dose of the right drug. On the other hand, traditional medicine preparations have many problems, like making decoctions, carrying them, and storing them. Modern medicine preparations, such as medicine tablets, powders, granules, etc., have greatly improved the convenience of taking and carrying them. Still, the preparation of a large number of excipients to the process increases the dose taken by the patient. The physical effect of the molding process has some impact on how the preparation breaks down and dissolves. After the Chinese herbal medicine powder or Chinese medicine extract powder is put in the raw material box of the 3D printer, the printing path and driver program designed by the computer can be used to make a custom product for the specific patient based on the prescription given by the clinical doctor of Chinese medicine. Compared with traditional preparations, both the accuracy of the compatibility ratio and the accuracy of the dosage have been improved [91].

4. Conclusion

3D-printed medicines are still in their infancy. It is hoped that as the legal framework, rules, and policies continue to get better in the future, along with the introduction and development of other integrated technologies, the ethical, safety, and practical problems that 3D-printed medicines face in the clinical setting, such as sex, will be slowly solved. Once the ideal printing platform is established, it will only be a matter of time before 3D-printed medicines take over children's drug shelves.

In the future, the application of 3D drug printing technology will have many advantages, especially for medicine preparations with sustained and controlled release, medicine preparations containing precious or toxic medicines, and volatile oils, which provide a new research idea for innovative medicine preparations. The research and development of new medicine should adhere to the guidance of treatment pharmacological theory, constantly and rationally absorb and utilize modern science and technology. Although the country has the first 3D-printed drug on the market, the comprehensive popularization of 3D drug printing technology still faces many challenges. It is necessary to strengthen technical theory and applied research continuously. With the continued development of computer control, industrialization of 3D printing, medicine excipients, and other technical fields, the 3D printing technology of traditional medicine will continue to improve and mature, and 3D printing will be used more and more in the pharmaceutical industry of medicine.

So far, the applications have made many improvements to dosage, oral disintegration, etc., which opens up many possibilities in pharmaceutical technology. These improvements translate into a series of advantages both in the technological field of manufacturing as well as drug administration to patients:

- Case of development of personalized medicine
- Ease of administration in certain patients
- Improvement of adherence to treatment

Research and development of this technology should focus on making it less annoying and more useful in the pharmacy field while minimizing the problems it causes. We must point out the deficiencies in the legal framework and, therefore, the need to develop regulations regarding this technique. Guidelines are needed to regulate the technical aspects and establish standards in the drug manufacturing process by 3D printing, the requirements that the final product must meet, the tests that must be overcome, regulations regarding dispensing medicines manufactured with 3D printing, etc.

Acknowledgments

I am grateful for all of the following individuals for their expertise and help in all areas of the study we conducted as well as for their support in preparing the manuscript.

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