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THREE-DIMENSIONAL ADDITIVE PRINTING IN DOSAGE FORM TECHNOLOGY

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Additive technologies (three-dimensional printing) are currently the most developing area in various fields and industries. In pharmaceutical technology, this type of production is closely related to the concept of personalized medicine, where a dosage form with individual characteristics is created on the basis of the patient's personal data. This literature review presents various 3D printing technologies with physical classification of different types of 3D printers. The principle of operation, characteristics, advantages and disadvantages of such types of 3D printing as extrusion printing, powder printing (TheriForm™) and stereolithography are described. Features of the use of three-dimensional printing in such dosage forms as: implants, tablets and transdermal delivery systems (patches with microneedles) are demonstrated. The conclusion is made about the acceptability of three-dimensional printing in pharmaceutical technology, the development prospects and the necessary conditions for formation of a regulatory framework and the implementation of the principles of additive production of dosage forms in everyday practice.

Keywords: 3D printing, additive printing, dosage forms, printers

Currently, the development of pharmaceutical technology is provided in several directions, one of which is the production of personalized dosage forms (DF). This direction is associated with the need for individual pharmacotherapy for patients taking medicines that have a narrow therapeutic window, as well as active pharmaceutical ingredienta (API) that have a proven direct proportional "dose – effect" relationship [2]. In connection with development of the presented direction, it is necessary to create a universal technological mechanism for production of medicines in an individual dosage that corresponds to the metabolism, age, and genetic characteristics of the patient. 3D printing, or additive printing in other words, allows you to produce individual medicines for patients in a wide range of dosages, shapes and sizes, so it is the main technology for creating personalized medicines.

Three-dimensional printing is a form of additive production in which an object is created by successive layer-by-layer deposition or binding of materials [1,3]. Use of additive technologies in the field of the dosage form development was studied and implemented in the form of a 3D-printed orodispersible tablet Spritam® (levetiracetam, USA), which was registered and went on sale in 2016.

The advantages of using additive methods for development and production of dosage forms include the ability to accurately control the spatial distribution of API in the dosage form, create a variety of complex geometric forms of medicines, control the dosage of the minimum number of medicines, and reduce the amount of waste.

Purpose of the review – to highlight the 3D printing methods that are being developed for production of dosage forms, as well as to show the advantages of manufacturing the personalized dosage forms.

CLASSIFICATION OF 3D-PRINTING TECHNOLOGIES

A large number of technologies have been developed for industrial production of three-dimensional structures, but several basic methods are used for pharmaceutical 3D printing. The technologies used can be classified (Fig. 1) based on the origin and running of the main physical processes: extrusion (melting of the filament), dripping (using binding solutions) and laser systems (sintering/curing) [22].

Each method is characterized by the structure of the printed object and the use of material for 3D-printing. In addition, each of them shows certain process characteristics that are preferred for different APIs. The advantages and disadvantages associated with each of the existing approaches can be demonstrated by comparing the dimensional accuracy, mechanical properties, surface roughness, assembly speed, and material cost on several 3D printing platforms [5].

EXTRUSION PRINTING TECHNOLOGY

3D printing by polymer filament extrusion is a semi-liquid material deposition technology known under the brand name Fused Deposition

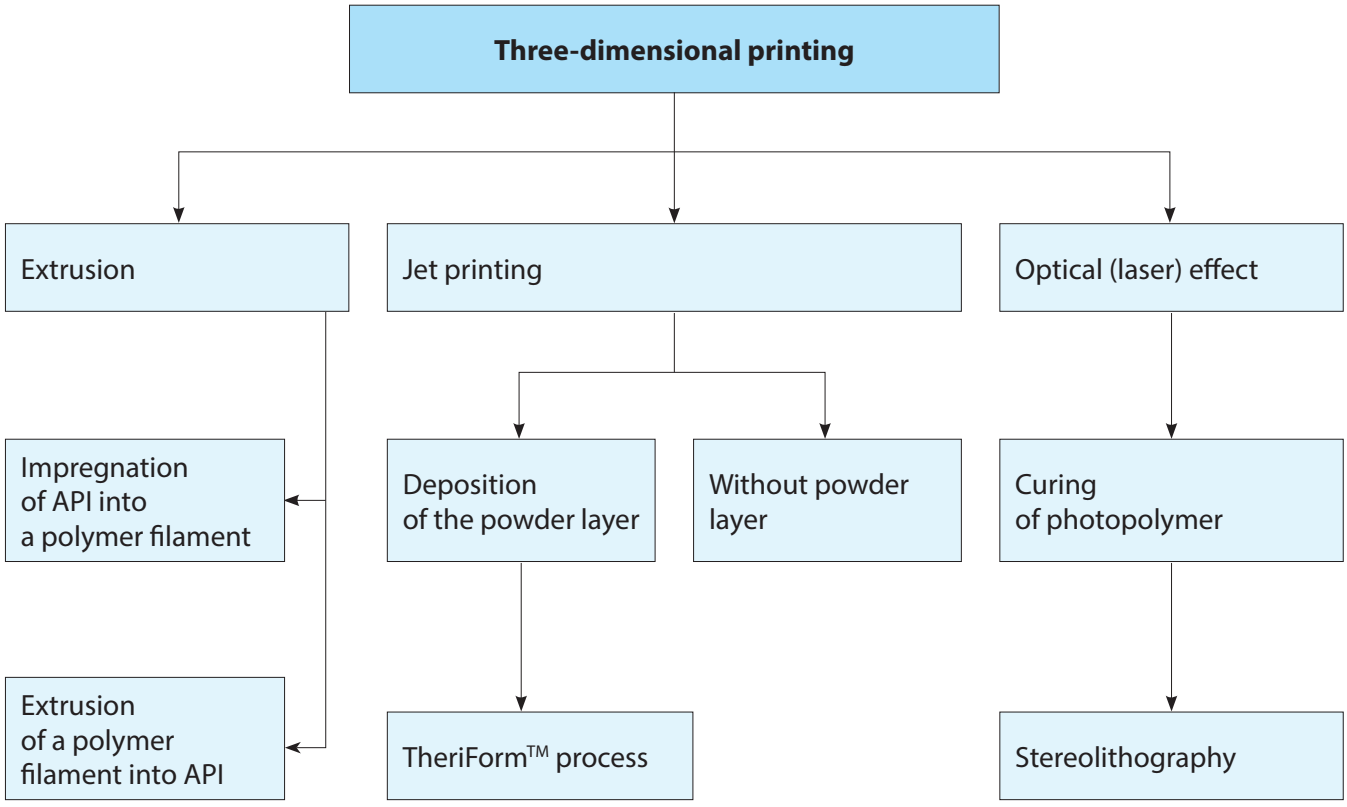

FIG. 1. *Classification of 3D printing methods*

ModelingTM (FDM) [6]. In extrusion printing systems, solid filaments are used that are heated above the material melting point, and then the extrudate is deposited in a continuous flow in layers by means of a movable guidance head. After deposition of one layer in the XY plane, the platform (z axis) is lowered and the procedure is repeated. The presented process continues until the dosage form is created. During thermal melting, the material binds to the underlying layer and solidifies, forming a strong connection between the two layers (Fig. 2).

To improve the interlayer connection, the entire process is performed in a closed chamber that maintains a constant temperature [7].

In 3D extrusion devices, it is possible to place multiple print heads for the use of various excipients and API in a single 3D printed dosage form. If necessary, a second printing head is used to provide a temporary supporting substrate for the manufacture of complex structures with a protrusion, offset, or cavity.

The method of extrusion printing allows you to produce structures with controlled pore size and porosity by changing the amount of deposition of the material, the distance between the filaments and the height interval. The most important criteria for selecting a material for extrusion printing are heat transfer characteristics and rheology, so this method requires certain polymers as filaments.

The main advantage of extrusion printing is that polymer filaments are produced with the specified characteristics by hot melt extrusion.

The extrusion printing process usually requires strict specifications for filaments, for example, the requirements for manufacturing the hydroxypropyl cellulose filaments (Klucel ™ dosage form, Ashland): obtaining uniform filaments with minimum length of 25 cm, round cross-section and the same diameter (1.75±0.05 mm). A smaller diameter of the filament leads to formation of air bubbles inside the 3D-printed dosage form, and too large diameter leads to clogging of the tip [4,12]. The diameter of the extruded filaments depends not only on the diameter of the extrusion head, but also on the process of stress relaxation (swelling)

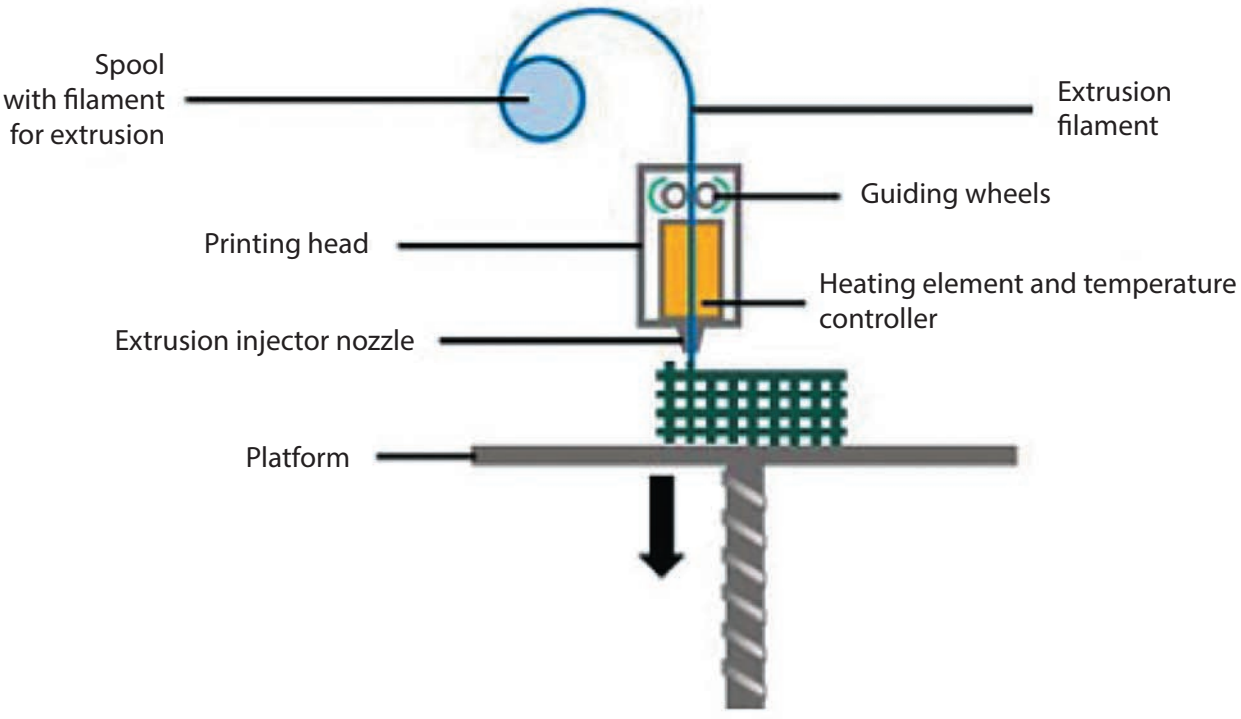

FIG. 2. *3D extrusion printing process diagram*

of polymer and speed of the conveyor belt (Fig. 3). Despite the value of the diameter and dispersion of the filament along the length, the constancy of the diameter is more important than the exact achievement of this value, equal to 1.75 mm.

Suitable polymer materials for an extrusion printer are thermoplastic and melt at sufficiently low heating temperatures (usually below 250°C). They are characterized by rapid solidification due to the high glass transition temperature and retain their shape well.

Despite the influence of the technological process on the physical and chemical properties of the polymer, the main parameters remain unchanged and depend on the nature of the raw material used in extrusion. There are various technological parameters of material processing, such as layer thickness, assembly orientation, 3D object raster projection angle, and raster width, which significantly affect the mechanical properties and characteristics of the polymer thread [12]. Table 1 shows the variables that affect 3D-printed dosage forms.

Initially, acrylonitrile-butadiene-styrene was used as a starting material for creating polymer filaments in extrusion 3D printing, and then such polymers and their mixtures as: polycarbonate, polypropylene, polyphenylsulfone, polyglycolic acid, poly (L-lactic-L-glutamic acid), polycaprolactone, and polydioxanone [10].

The main advantages of the extrusion 3D printing process are that it does not require toxic or organic solvents, and the use of polymer filaments provides continuous low-cost production with high flexibility (variability) of material processing. Despite these advantages, the extrusion printing process is limited by thermolability of the active substance and excipient of filaments used for extrusion and feeding them through the rollers and nozzle. There are also difficulties in calibration of the extrusion filament feed when replacing the polymer material. In addition, dosage forms produced by extrusion printing, due to the variety of interacting technological parameters of the process, show less accuracy in size compared to other methods of additive manufacturing.

FIG. 3: *a – hot melt extrusion of hydroxypropylcellulose (HPC) filaments; b – polymer relaxation (swelling) of HPC after exiting the extrusion head; c – HPC filaments of different diameters (<1.8 mm)*

Table 1

VARIABLES THAT AFFECT THE MECHANICAL PROPERTIES OF 3D-PRINTED DOSAGE FORMS

Process parameters	Equipment parameters	Properties of excipients
Orientation of a dosage form during assembling	Model of a printer	Rheologic properties
Thickness of a layer		Density of raw material
Screen angle of an object projection		
Width of the projection raster	Type of a process	Temperature properties of polymers and other materials
The gap between the projection rasters		
Fill projection	Diameter of extrusion-type injector nozzle	Composition, solubility and concentration of components
Speed of material filling; amount of material		
Extrusion temperature	Software	Diameter of extrusion filaments
Chamber temperature		
Environmental conditions (humidity, etc.)		Uniformity of a filament diameter

POWDER PRINTING – APPLICATION OF DROPS ON THE POWDER (THERIFORM™)

Powder printing under the commercial name TheriForm ™ was developed at the Massachusetts Institute of technology [11]. A special feature of the technology is the use of a liquid binder delivered by an inkjet printhead for layer-by-layer creation of objects from powder. The process starts with uniform distribution of the powder layer on the binding plate (the layer consists of powder with a particle size in the range of 50–100 microns and usually has a thickness of 200 microns) [13]. The inkjet printhead then precipitates drops of liquid binder solution onto the surface of the powder. Two-dimensional cross-section of the wetted powder layer is bonded with binder solution in the required form. Then the support platform is lowered to the depth of the next layer and another even layer of powder is distributed over the surface to print a new cross-section. The process continues until the entire object is completed in the required form in the powder layer. Overhanging structures and pores inside the dosage form are supported by unbound powder during the printing process. After the process is completed, the object is released from the surrounding unbound powder, which is removed from the cavities and pores of the finished structure. This method of 3D printing tends to form porous structures, which may require additional processing to provide the required mechanical strength. The process of powder printing is illustrated in Fig. 4.

Powder printing is characterized by the use of jet heads for distribution of the binder, which are classified according to the principle of ejection of drops of binder. Inkjet printing devices are generally divided into two groups: continuous inkjet printing and on-demand printing. The continuous inkjet printing process creates a continuous stream of charged droplets

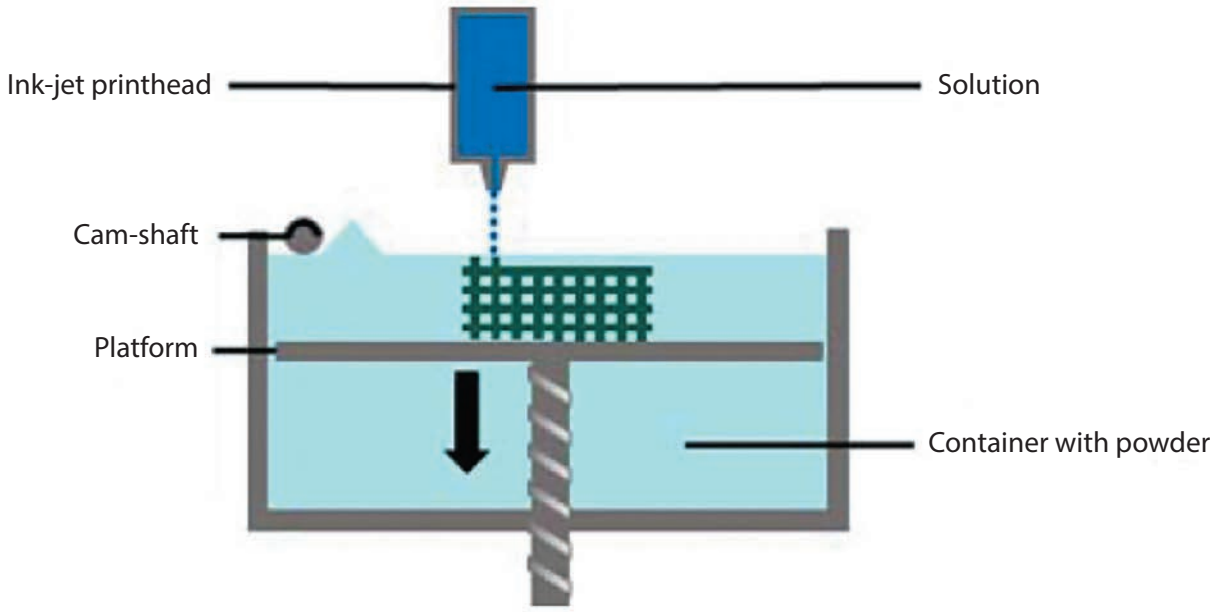

FIG. 4. *Schematic illustration of 3D powder printing*

that are directed by electrostatic plates into the powder layer or deflected into the waste recycling line. When printing on demand, drops of liquid binder are distributed only when the process requires it, which is more economical. In addition, this method is more accurate than continuous inkjet printing, since it is possible to control the volume of droplets in the range of 1–300 µl at their release frequencies up to 10,000 Hz [14]. The production of drops in print heads on demand is achieved using a thermal or piezoelectric method. Thermal printing heads consist of a thin-film resistor that heats up when an electrical pulse is applied. A bubble of superheated steam is formed, which expands and throws a drop out of the print nozzle. The subsequent collapse of the bubble creates partial vacuum into which the fresh binder solution is drawn [17]. Temperatures up to 300°C can be reached on the surface of the resistor, but the exposure time is only a few milliseconds. At the same time, only a small part of the liquid, about 0.5% of the volume, is heated, which minimizes the potential destructive effect on thermolabile components [16]. The formation of drops in a piezoelectric printhead is the result of pressure waves induced by deformation of the piezoelectric transducer. The liquid reservoir is then filled when the piezoelectric material is re-shaped. In contrast to thermal jet print heads, the piezoelectric process is thermally constant and can be performed at any temperature.

As a powdery layer in such systems, pharmaceutical-grade excipients can be used that have sufficient flowability for even distribution across the thickness required for each layer. They should also be easily removed from the cavities and pores of the finished product. In the printing process, combination of powdered excipients is used with a binder that has a sufficiently low viscosity for formation of drops, but at the same time forms strong bonds in the dosage form. For effective and uniform drop flowing out of the print heads, the viscosity of the binder solution should be in the range of 5–20 Pa, and the surface tension should be in the range of 35–40 MJ-1. A number of synthetic polymers, including polycaprolactone, poly (lactic acid – co-glycolide), and polylactic acid, were used with organic solvent-based binders. Natural polymers such as starch, dextran, and gelatin were used in combination with water as a binder. It is also possible to include additional excipients into the

powder layer or binder solution to extend the versatility of the powder printing process.

STEREOLITHOGRAPHIC (LASER) PRINTING – PHOTOPOLYMER- BASED SYSTEMS

Stereolithography is an established 3D printing technology that uses UV or visible light to cure liquid photopolymer resins. Products are created by sequential lighting and curing of thin layers of photopolymers using a laser beam or by projecting a drawing from a digital projector. The product can be built from top to bottom by highlighting the drawing on the top layer of the surface of the bath with polymer resin. As soon as the layer is completed, the platform descends a little deeper and the blade passes over the surface to apply another layer of photopolymer. The new layer of photopolymer is then highlighted with the next layer's drawing. However, you can also build a product from the bottom up. In this case, the resin is placed in a bath made of material that is transparent to ultraviolet radiation, such as polyethylene terephthalate (PET) [14]. The layer drawing is displayed through a transparent window on the lower surface of the resin. The cured layer then rises up by one layer thickness, the liquid resin fills the space under the solid layer and is illuminated by a beam to form the next layer. A schematic representation of these two approaches is shown in Fig. 5

In both cases, the depth of curing of each layer is slightly greater than the vertical step motion. Then unreacted functional groups in the solid layer can be polymerized in a new layer, thus ensuring good adhesion between all the layers of the 3D printing product. At the end of the process, when all the layers are completed, the excess resin is drained and washed away. The finished product is often subjected to the final stage of curing using ultraviolet radiation to ensure complete conversion of unreacted functional groups in the polymer.

Advantages of preparing the dosage form using stereolithography: high accuracy of product construction, ease and speed of 3D printing. However, there are also limitations of the presented method, which consist in a small number of biocompatible photopolymers and

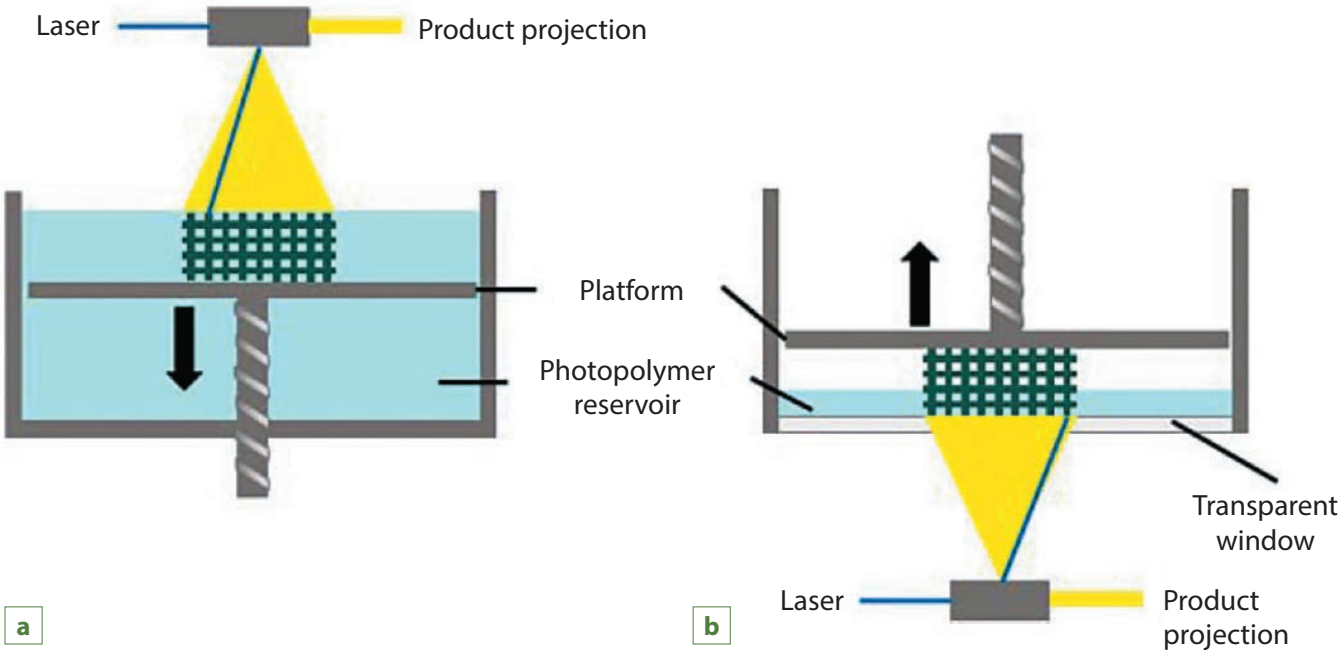

FIG. 5. *Schematic representation of the stereolithography process: a-descending process; b-ascending process*

the impact of physical processes on the active substance. For stereolithography, poly (propylene fumarate), poly (caprolactone-trimethylenecarbonate), poly (D, L-lactic acid), polycaprolactide and polyethylene glycol are used. It is also difficult to include more than one polymer in the dosage form to create modified release [19].

APPLICATION OF 3D PRINTING IN PHARMACEUTICAL TECHNOLOGY. 3D PRINTING OF IMPLANTS

The first dosage form produced with a 3D printer after patenting and publishing a powder-based inkjet printing device were biodegradable implants. Researchers from the Massachusetts Institute of Technology used polyethylene oxide as a polymer matrix and polycaprolactone as a component that restricts the rate of release, and prepared various systems with yellow dyes of the methylene blue and alizarin series as substitutes for the API. Studies have shown the ability to accurately place small amounts of dye solution drops and the ability to create a microstructure with controlled wall thickness depending on the rate of binder deposition and printing speed. Also, three-dimensional printing has shown the ability to control the geometry, surface area, spatial deposition and other technological parameters that affect the kinetics of medicine release. These studies have demonstrated that 3D-printed implants show a more controlled zero-order release than conventional implant manufacturing techniques, such as pressing or injection molding [18].

In 2007, Huang et al. made monolithic levofloxacin implants for comparison with pressed implants, as well as implants with complex structures for immediate and double pulsating release. 3D-printed implants showed a more porous structure than those obtained by pressing, and the part of the implant intended for immediate release of API showed a relatively fast and slightly more complete release than the pressed dosage form. The implants printed with an internal reservoir for active substance, internal and external layers of the dosage form, could, respectively, show an immediate and pulsating release of the medicine. In the study demonstrated, implants achieved the immediate release of up to 400 mg of API and the steady release of 120 mg or less for 90 days. Later, the same group of researchers developed pulse-release implants to deliver two APIs, levofloxacin and rifampicin, with immediate release of levofloxacin on day 1 and delayed release of the internal rifampicin reservoir on day 8 with prolonged release of both APIs up to 6 weeks. This work demonstrated the possibility of creating 3D-printed combined implants with different types of release [19].

3D PRINTING OF TABLETS

The earliest work on obtaining 3D-printed tablets was carried out using three-dimensional printing of the powder layer. In the Massachusetts Institute of Technology the research has been carried out to produce tablets that demonstrate hardness and friability which are comparable with pressed dosage forms by increasing the concentration of polymer/binder, but three-dimensional inkjet printing usually produced more porous and loose tablets. The increased porosity of 3D printed dosage forms is due to incomplete interaction of the binder solution with the powder layer, which leads to the appearance of areas of unbound particles. Aprecia Pharmaceuticals took advantage of the increased porosity of the obtained dosage forms to produce tablets dispersed in the oral cavity. They created a patented ZipDose ® technology based on three-dimensional printing of the powder layer, which makes it possible to dose APIs in a tablet up to 1000 mg. According to the presented technology,

the LP Spritam ® (levetiracetam) for the treatment of epilepsy was put on the market [20].

Despite the existing examples of 3D printing in the production of tablets dispersed in the oral cavity, the main potential of this method lies in the creation of combined dosage forms with modified release. With the help of three-dimensional printing technology, it is possible to produce tablets with immediate, prolonged, delayed and pulsating-released components in the same dosage form by applying different layers or sections containing one or more APIs. In addition, it is possible to use the advantages of creating the tablets that have different geometric shapes and, accordingly, releases. For example, in some studies, to create a specific release profile, tablets were made in a flat-cylindrical shape with a concentric round hole inside, as shown in Fig. 6.

In the presented tablet structure, the upper and lower layers, as well as the side surfaces, contained ethylcellulose to obtain impermeable barriers, while the inner core was made using API of acetaminophen and a binder consisting of 2% ethylcellulose and creating a slower release from the outer surface. Three-dimensional inkjet printing allows you to produce very thin functional barrier layers at the top and bottom, as well as an external surface containing ethylcellulose or other excipients. Theoretically, this technology made it possible to create a dosage form with zero-order release kinetics, since the surface area through which the API passed practically did not change.

Extrusion printing as a method of manufacturing tablets is often used using PVA fibers as a filament. There are known developments with impregnated solutions of aminosalicylates in PVA filaments. At that, non-aqueous (ethanol) solvents were used, since PVA is soluble in aqueous solutions. The solubility of API in the solvent affected the final inclusion of pharmaceutical product into the PVA filaments. Thus, 4-aminosalicylates with lower solubility were impregnated into the filament at 0.06% concentration, and 5-aminosalicylates with higher solubility – respectively, at 0.25% concentration. The presented process was used with prednisone, which demonstrated high thermal stability: it was possible to successfully produce tablets with API content of 88.7–107% of the theoretical value [11].

The inclusion of API into the filament for extrusion printing is also possible at the stage

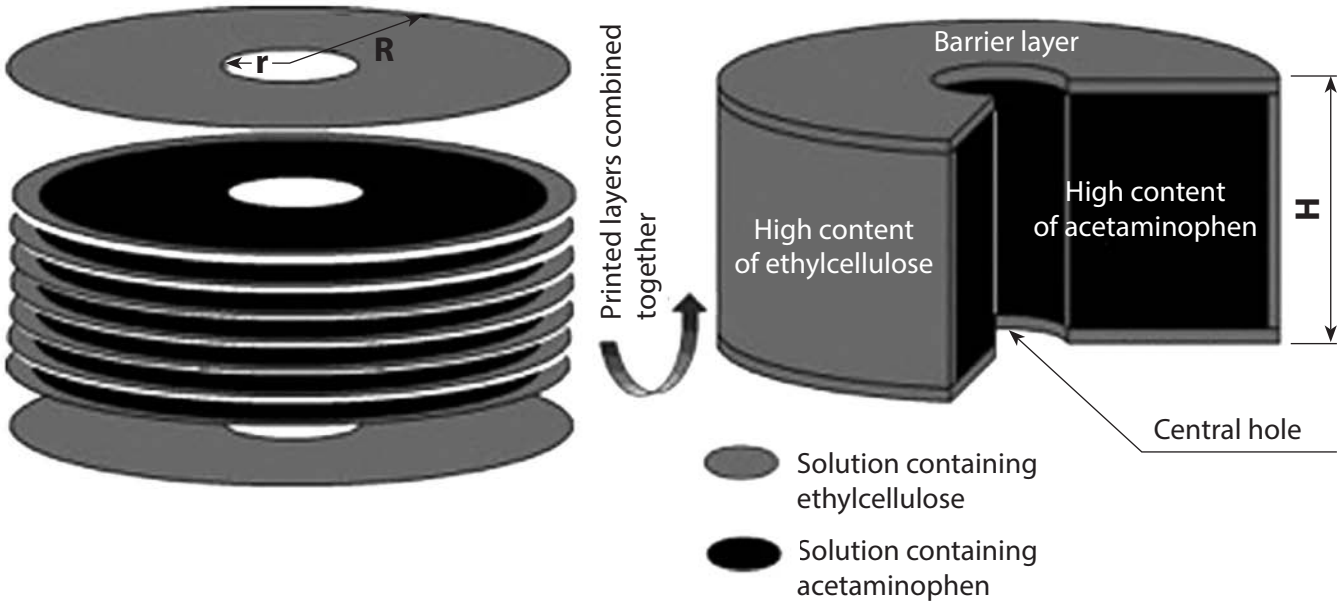

FIG. 6. *A flat cylindrical tablet with a concentric round hole for release with zero order kinetics*

of hot melt extrusion, which allows to increase the content of API in the filament. The literature describes the production of PVA filaments with acetaminophen and caffeine by hot melt extrusion. Filaments with API were used to make multilayer tablets containing acetaminophen in the inner layer and caffeine in the outer layer. The tablet showed the 135 minutes-delayed release of the internal component of acetaminophen and the 50 minutes -extended release of the outer layer. During the hot melt extrusion process, acetaminophen was in an amorphous state, while caffeine remained crystalline. This study showed not only the ability to produce highly concentrated dosage forms with fixed API content, but also the ability to use amorphous solid dispersion to obtain a filament and corresponding increase in the solubility of the medicine [21].

3D PRINTING OF TRANSDERMAL DELIVERY SYSTEMS

Transdermal delivery systems are used to avoid the effect of first passing through the liver or pH- mediated degradation, as well as to ensure compliance with the treatment of chronic diseases such as diabetes. 3D printing methods can be used for manufacturing the multi-layer transdermal patches, in particular, approaches are being developed for printing microneedles filled with API for percutaneous administration. Microneedles usually have height of less than 500 microns and are designed to penetrate the corneal layer (10–15 hours) for API deliver (Fig. 7).

Microneedles should be strong enough to penetrate the epidermis, but not have a hardness that will cause pain or irritation. In addition, biodegradable polymers are preferred for manufacturing microneedles with the tip remaining in the epidermis. Since microneedles have a complex morphology, micro-size, and sufficiently high density per unit of the dosage form, they are difficult to be obtained by traditional methods of coating, but 3D printing technology makes it possible to effectively and relatively simply create patches with microneedles [8].

Researchers from (Boehm et al.) applied additive processes to make microneedles with API. Stereolithography technology was used to create microneedles using poly (methylvinyl ether-alt-maleic anhydride) coated with amphotericin B and filled with miconazole. For the resulting patches,

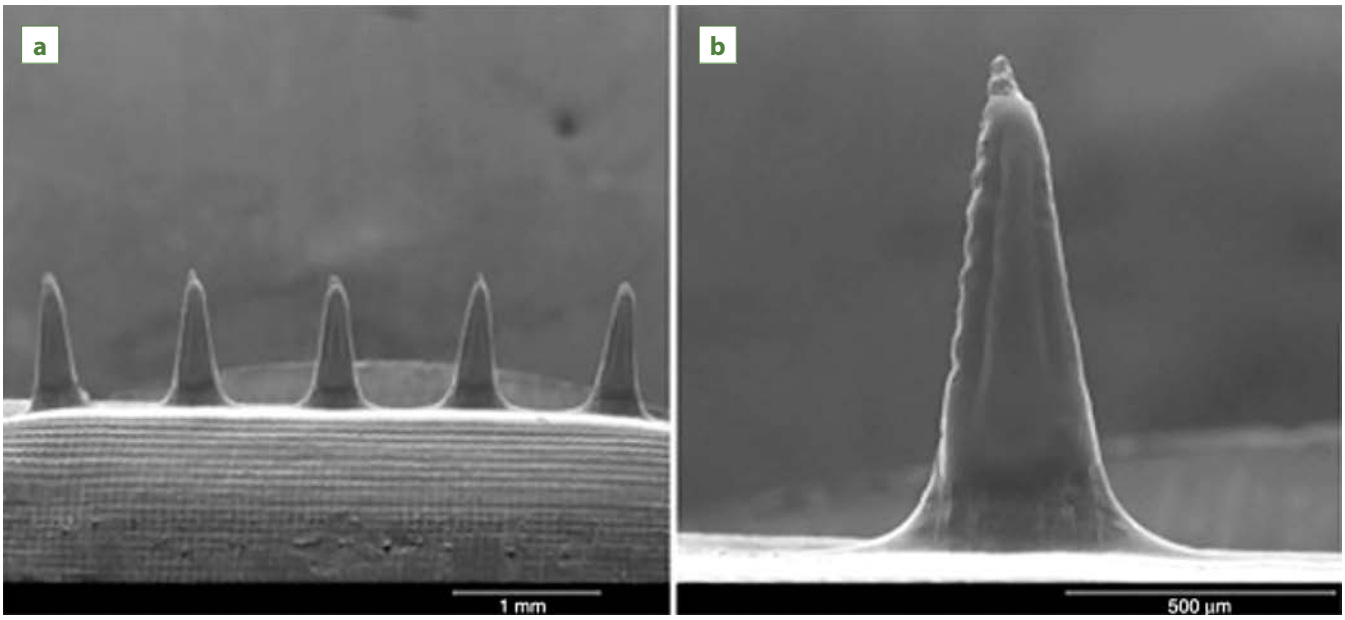

FIG. 7. *Micrographs of (a) an array and (b) a single miconazole-containing needle*

it was demonstrated that the microneedles had good mechanical strength for transdermal administration. However, microparticles coated with solutions of amphotericin B showed some changes in the geometry of the microneedles, since their surface was wetted with amphotericin and it was not possible to apply excipients evenly. Studies with miconazole demonstrated a smaller effect on the structure of the microneedle, since API deposition was concentrated in the upper part of the needle and coated the surface, as shown in Fig. 7 [19,21].

CONCLUSION

Three-dimensional printing is becoming the main tool for manufacturing the dosage form in pharmaceutical technology for personalized medicine, because it allows you to quickly create a wide range of medications with individual dosage. The advantages of 3D printing include a variety of ways to prepare the dosage forms and, consequently, a wide range of technological processes that are suitable for certain properties of API. In addition, certain methods of 3D printing have their own advantages and disadvantages, which allows you to vary the production methods of personalized medications to achieve your goals. The main prospects for the development of 3D printing are observed in production of implantable, solid and transdermal dosage forms. However, despite the development of three-dimensional printing, it is necessary to solve a large number of regulatory, technological and normative tasks that are of paramount importance for implementation of these methods in everyday practice.

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