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FEATURES OF TWO-DIMENSIONAL PRINTING OF DOSAGE FORMS IN PHARMACEUTICAL TECHNOLOGY

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This review of the literature describes the main techniques used in the method of two-dimensional printing. Various types of inkjet and rotary printing technologies are presented, as well as features, advantages and disadvantages of various types of two-dimensional printing, such as continuous inkjet or print-on-demand. Features of production and application of 2D printed dosage forms (oral dispersible, mucoadgesive films, etc.) are shown. Examples of used substrates and their production technologies with specified characteristics are given, as well as requirements and formulations of solutions with pharmaceutical substances used in printing. The prospects for development of 2D printing technology and its application, in particular in the form of QR-encoded dosage forms, are described.

Keywords: two-dimensional printing of dosage forms, inkjet printing, rotary printing, oral-dispersible films

Currently, with development of therapeutic drug monitoring methods, it is possible to accurately determine for patients the dosage of many medicines that have a narrow therapeutic "window". In addition, a number of pharmaceuticals have accurate data on the relationship between the concentration of medicines in the blood and the pharmacological effect, which allows you to adjust the drug therapy for each patient individually. In particular, these pharmaceuticals include cytostatics, aminoglycoside antibiotics, anticonvulsants [1,2,4].

In addition to improving the methods of diagnosis and control of drug therapy of patients, the development of personalized medicine requires the implementation of a production method that has the ability to manufacture individual dosage forms (DF). The most promising methods in this direction are two-dimensional (2D) and three-dimensional (3D) printing technologies for production of medicines [1,3]. 2D-printing has a more flexible, cheap, easy-to-implement and easy-to-maintain technology compared to 3D-printing. Versatility and accuracy of placement of liquids with pharmaceutical substance (PS), depending on the application, the relative ease of the process control (using the simplest software), and the repeatability of distribution of volumes of liquids are also noted.

2D-PRINTING TECHNOLOGY

2D-printing is a method of producing personalized dosage forms, often oral films, by applying the solutions with pharmaceutical substance (printed "ink" or impression) to a soluble or biodegradable substrate before use.

2D-printing technologies have several production methods, they can be divided into inkjet printing technologies and rotary printing methods. The most common methods are inkjet printing ones, because they allow you to produce medicines on a substrate, using a small amount of solution with pharmaceutical substance, depending on the requirements of the recipe. In turn, inkjet printing technology is divided into continuous inkjet printing and print-on-demand [5,6].

Due to its relative simplicity, low cost, and high accuracy, print-on-demand is more preferable than continuous inkjet printing in the desktop printer markets, and it is this technology that is most commonly used in 2D-printed dosage forms. Two main technologies of the presented printers are piezoelectric and thermal (or bubble) printing.

Thermal inkjet printing uses short thermal pulses generated by a resistive element for the jet liquid. Each printhead contains a micro-resistor that quickly heats up when electrical impulses are received, forming bubbles of superheated steam, as shown in Fig. 1.

The vapor bubble expands, forcing the liquid out of the nozzle and creating a drop. The vapor bubble then collapses, creating partial vacuum that pulls the liquid out of the solution tank, re-filling the thermal inkjet printing chamber. The temperature on the surface of the resistor can reach 300°C, but such high temperatures only exist for a few milliseconds only near the microresistor. Only 0.5% (by volume) of the sample is affected, so the technology usually does not destroy thermolabile components.

In piezoelectric printing, each nozzle is surrounded by a piezoelectric element,

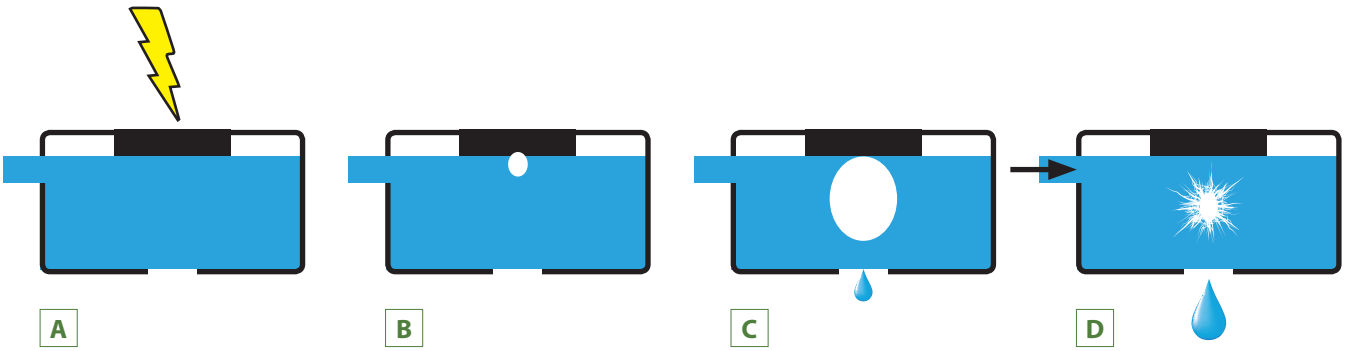

FIG. 1. *Thermal inkjet printing by stages (A) resistor temperature rise; (B) superheated steam bubble formation; (C) bubble growth and droplet deposition; (D) bubble collapse and filling*

usually made of lead zirconate titanate. During the application of voltage to the element, it deforms, creating pressure that leads to the release of liquid. As soon as the element returns to its normal shape, the nozzle is filled again with the solution, ready for repeated ejection (Fig. 2).

Regardless of the technology, inkjet printers emit a precisely controlled volume of solution with the specific coordinates on the substrate. The amount of the precipitated medicine depends on varying the volume of the sprayed solution and /or changing the concentration of the initial solution [14,16].

PREPARATION OF 2D-DOSED DOSAGE FORMS

The main stages of preparation of 2D dosage forms are: preparation of solutions and substrates, determining the size and density of the drawing on the substrate, the printing process and packaging of the dosage forms. The resulting 2D-printed films have an area of approximately 5 to 20 cm^2, in which the pharmaceutical drug is introduced into a matrix containing a hydrophilic polymer. The maximum concentration of medicines is 30–40 mg per dose. Correctly selected or manufactured substrates for printing are very important for preparation of 2D dosage form [3].

SUBSTRATES

Substrates are portable media on which the solution of the medicine is printed. Studies often focus on the practical and technical aspects of 2D printing of specific recipes with less attention to the substrate. However, studies and development of suitable substrates are important tasks, since the nature of the substrate can specify the polymorphic shape of any crystals formed when the solvent evaporates. For example, in the study of Hsu et al. (2013) it was noted that the substrate affected the crystallization of naproxen when printing on various solid amorphous dispersions [15]. In Table 1 the main substrates used according to literature data are listed [10,11,12,14].

Table 1 contains information on the use of a number of different substrates, including food substrates such as sugar sheets, polymer and starch films, and non-food substrates such as paper and acetate films. The use of ready-made food and pharmaceutical substrates, the development and manufacture of new types of them are becoming urgent tasks that should be solved together with the

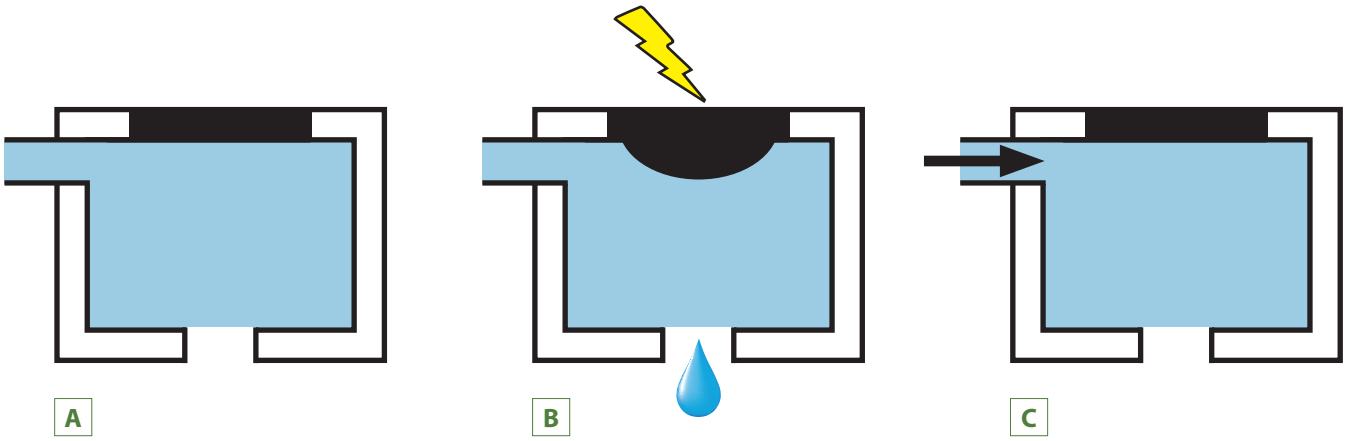

FIG. 2. *Piezoelectric printing: (A) inactive state; (B) movement of the piezoelectric element; (C) re-filling of the chamber*

Table 1

SUBSTRATES USED IN 2D PRINTING OF DOSAGE FORMS

Studies (references)	Substrates
Hirshfield et al. (2014)	Hydroxypropyl methyl cellulose (HPMC) films
Raijada et al. (2013)	Food sugar paper
Sandler et al. (2011)	Uncoated paper, coated paper and polyethylene terephthalate films (PET)
Genina et al. (2013a)	Orodispersible film, waterproof transparent film, cellulose paper
Genina et al. (2013b)	Food paper, PET film, HPC film
Buanz et al. (2011)	Starch film, purified acetate film
Genina et al. (2012)	Uncoated woodfree paper, three times and twice coated paper
Melendez et al. (2008)	PTFE film, coated with clear transparent film
Takala et al. (2012)	Copy and photo paper

implementation of 2D printing technology. The use of various substrates with specified quality characteristics, such as release modification, adsorption, and taste masking, increases interest in substrate manufacturing methods. Some of the substrate preparation technologies are discussed below.

SOLVENT CASTING OF POLYMER FILMS

When casting in a solvent, the substrate is made by casting and distributing a homogeneous layer of a polymer solution on the inert surface. Solution preparation, deaeration, casting or molding, drying, cutting and packaging of substrates are the main six stages of preparing the polymer films by casting in solvent for further 2D printing of dosage forms. As an alternative to film casting, a solvent-free hot melt extrusion method can be used. Substrates (polymer films) obtained in this way are often used for preparation of dosage forms rapidly disintegrated in the oral cavity or compositions for buccal use with prolonged release [13,14].

THE SUBSTRATES OBTAINED BY THE METHOD OF ELECTROSPINNING

Electric spinning (electroforming) is a process that leads to the formation of a polymer fiber as a result of action of electrostatic forces on an electrically charged jet of a polymer solution or melt (Fig. 3).

When electrostatic forces overcome the force of surface tension and charge, the liquid or melt forms a Taylor cone (a cone formed at the tip of a capillary or needle where a jet of liquid polymer is ejected during electrical spinning or spraying). This effect causes the drop to deform and the charged jet to be ejected in the direction of the grounded counterelectrode (drum or plate collector). The solvent evaporates during the transfer of the solution from the ejector to the collector, and finally, continuous solid fibers are collected on a grounded metal drum or plate. Typically, the nonwoven fibrous substrates with random alignment of fibres are obtained by quick whipping during the formation of fibers. However, substrates with parallel aligned fibers can be obtained using other fiber collection methods [14,15].

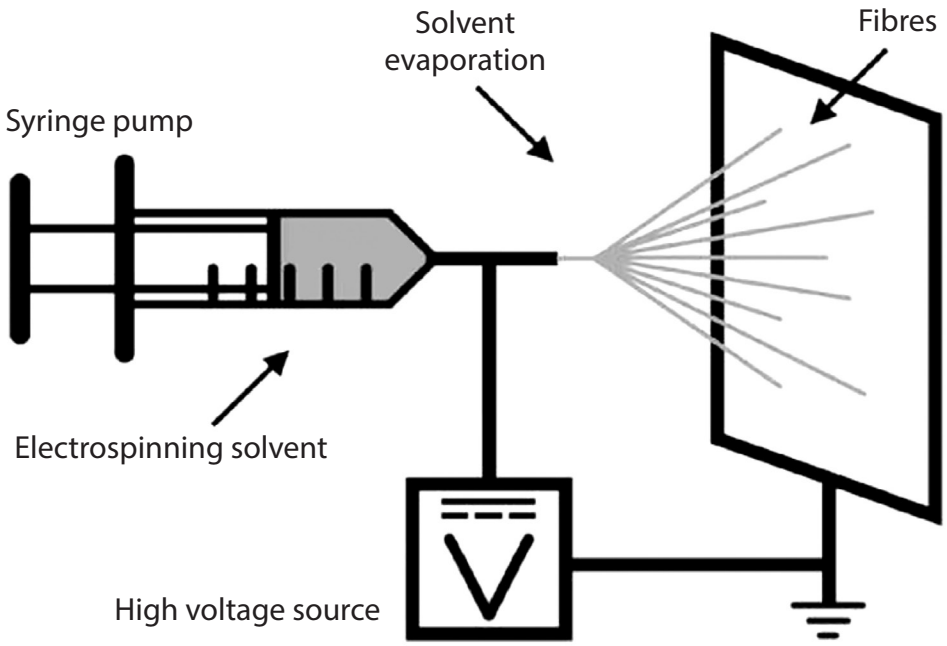

FIG. 3. *Electroforming system*

Electrical spinning is an easy-to-use, but complex-to-standard method in which the formation of fibers strongly depends on the properties of the polymer solution or melt and the parameters and conditions of the electrical spinning process. However, due to the adjustability of the process, electroforming allows you to change and optimize the properties of fibers and substrates for universal use. For example, the diameter, shape, surface topography, and internal structure of electroformed fibers depend to a large extent on the properties of the materials and the polymer solution /melt (molecular weight, concentration, additives, viscosity, surface tension, conductivity), process parameters (applied voltage, solution flow rate, distance between the ejector tip and the collector), and environmental conditions (humidity, temperature). In addition, the fiber morphology depends on the properties of the solvent, such as steam pressure and boiling point, which specify the evaporation rate of the solvent (s) and drying time. By optimizing the composition of the solution/melt and the electrical spinning conditions, it is possible to obtain fiber matrices with modified morphology and structure.

Fiber substrates have a large surface area-to-volume ratio and have the ability to incorporate an increased amount of pharmaceutical substance into their structure, which is an advantage when developing a dosage form. Electroformed substrates can acquire specific properties during the manufacturing process or through subsequent processing, which improves their mechanical strength and elasticity. Electric spinning is an attractive method in the industry due to the simplicity of the process and the possibility of large-scale production. However, this method has significant limitations in production due to the small amount of non-toxic solvents and the problem of ensuring uniformity of electroformed fibers.

In recent years, fiber structural frames containing drug such as antibacterial, anticancer agents, growth factors, and other biologically active molecules for wound healing, chemotherapy, or implants have been thoroughly studied. Electric spinning allows you to produce fibers with a diameter from nano-to micrometers from natural (for example, derivatives of cellulose, chitosan, collagen, gelatin, elastin, silk protein) and synthetic (for example, poly (lactic acid), polycaprolactone,

copolymer of poly (lactide-co-glycolide)) polymers, polymer mixtures, non-polymer materials and multicomponent systems (Fig. 4).

Porous matrices provide increased stability of metastable forms of drug molecules in the structure of substrates and reduce the surface roughness of printed dosage forms. Consequently, the fibrous structure of electroformed substrates demonstrates high suitability for their use in inkjet printing [14,15].

PEPARATION OF SOLUTIONS FOR 2D-PRINTING

The optimized composition of printing solutions is one of the key components of 2D- printed dosage form. "Inks" are divided into solutions with pharmaceutical substances (the most common type for inkjet printing), (nano) suspensions and biofunctional "inks" used in cell engineering. In addition, inkjet printing can be used to form in situ solid dispersions, microcapsules, socrystals, or co-amorphous systems [6,14].

The properties of the solvent and dissolved pharmaceutical substances, excipients, and other additives determine the viscosity and surface tension of solutions, which are critical characteristics for 2D-printing.

The dosage of the printed dosage form directly depends on the concentration of a pharmaceutical substance in the solution. Water-based solutions are preferred due to their non-toxic nature and suitability for thermal inkjet and piezoelectric printing. In aqueous solutions, the concentration of water-soluble pharmaceutical substances can be easily changed to adjust the amount of printed medicine. However, many pharmaceutical substances have certain limitations in solubility. Unlike thermal inkjet printing, piezoelectric printing is applicable for solutions with non-aqueous solvents such as ethanol or dimethylsulfoxide. However, the use of organic solvents should be limited, as this requires the removal of residual solvents after printing. In addition, solvents with low evaporation temperature can cause the nozzle to be clogged and affect the print quality. Therefore, the concentration of solutions strongly depends on the solvent used and/or the addition of solubilizing co-solvents. To modify the viscosity, glycerin, propylene glycol, polyethylene glycols and

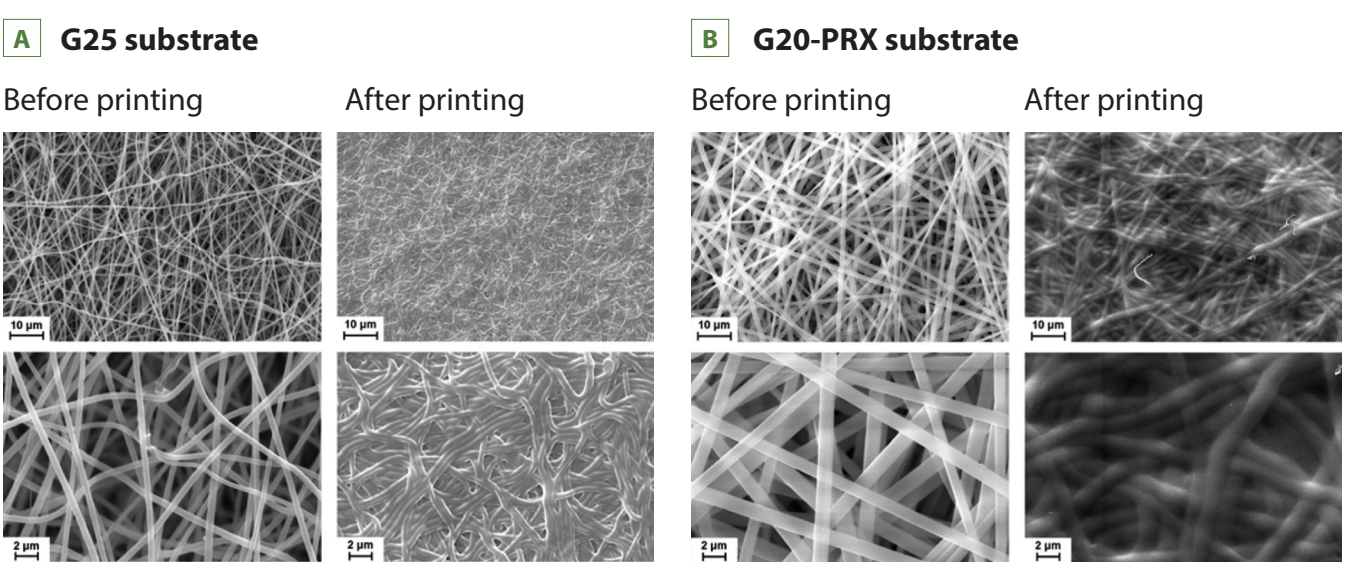

FIG. 4. *Scanning electron microscopy of cross-linked gelatin substrates G25 (A) and gelatin substrates with pyroxicam G20-PRX (B) before and after printing of lidocaine hydrochloride (3000× and 10,000×, from top to bottom) [15]*

Table 2

TYPICAL COMPOSITION OF 2D-PRINTED ORAL DISPERSIBLE FILM

Components	Content
Pharmaceutical substance	5–30%
Water-soluble polymer	45%
Plasticizing agenta	0–20%
Cosolvents	If required
Sweetening agents	3–6%
Excipients as salivants	2–6%
Coloring materials, flavorings, etc.	If required

hydroxypropylcellulose are used, by adding them to various pharmaceutical substances. Other components of solutions include excipients dyeing and masking the taste, the final composition is determined based on the properties of the pharmaceutical formulation and the requirements of the printing system. In general, the resulting composition of 2D-dosage form is shown in Table 2 [3,5,14,18].

TECHNOLOGICAL PARAMETERS OF 2D-PRINTED DOSAGE FORMS

The technological properties of 2D-printed dosage forms are determined by three main aspects: the suitability of the pharmaceutical substances for printing, interaction of solutions with the substrate, and printing parameters. Optimization of printing parameters allows you to provide fine tuning of the printed dosage form within certain limits of the printing system.

When using piezoelectric printing systems, the geometry and behavior of the drop can be optimized by adjusting the applied voltage, waveform, printing frequency, and /or temperature (Fig. 5) [9,16].

However, the influence of these parameters on characteristics of solutions with the pharmaceutical substances has not been systematically studied. The volume, speed and angle of the jet droplet trajectory directly depend on the nozzle diameter (usually 30–60 microns). Creating of smaller droplets allows you to produce 2D-printed films with higher resolution. Inkjet printing is limited by the volume of the applied drop of 1 microL with a corresponding diameter of approximately 12 microns. In this regard, the main problem associated with nonconformity of print quality is clogging of the nozzles. For comparison, the flexography print resolution is approximately 30–75 microns. The accuracy of solution deposition is also determined by the substrate feed system and the overall design of the composition (for example, print pattern, resolution, overlayering).

The assessment of suitability for printing the solutions is based on their physical properties: viscosity, surface tension and density. These properties affect the formation of droplets and the stability of the jet [14,17].

In inkjet printing, optimal viscosity and surface tension ensure uniform spherical droplet formation and solution deposition, avoiding clogging of the nozzles or unwanted leakage. By adjusting these parameters, you can get a trickle of solution drops without tails and satellite drops. In flexographic printing, uniform transfer of solutions to the substrate is achieved using viscous solutions or suspensions with values from 50 to 500 MPa-s.

INTERACTION OF SOLUTIONS WITH THE SUBSTRATE

In 2D-printed dosage forms, where solutions are applied to a supporting matrix, their physical interactions with the substrate affect their own drying mechanism. These interactions can be classified as the spreading of droplets upon

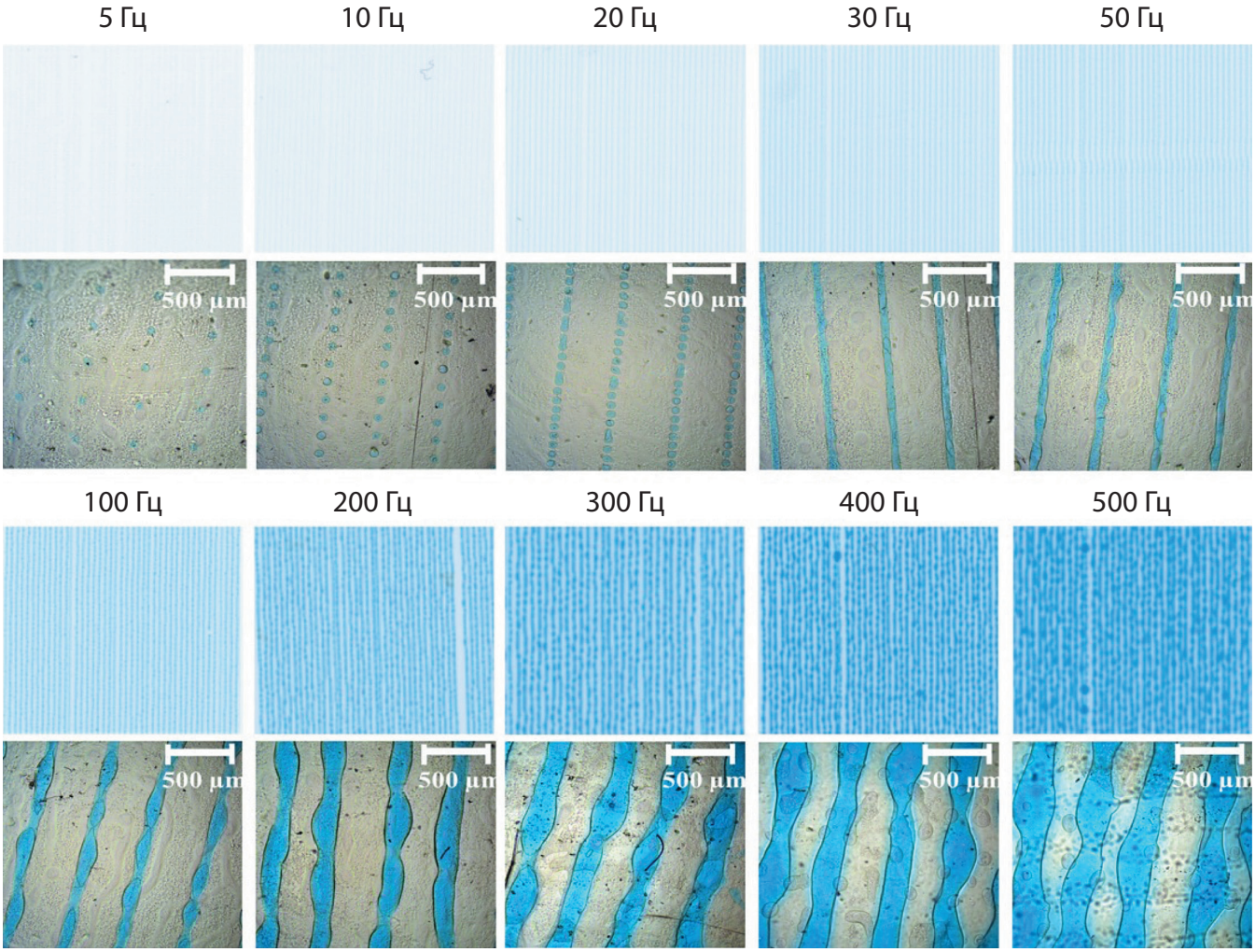

FIG. 5. *2D printing with colored solutions having different frequency of droplet formation*

impact, formation of a pattern on non-porous and porous substrates and solidification of the droplets. After the droplet is ejected from the print head, contact with the substrate is caused by an inertial shock and capillary forces [7]. The contact angle of the droplets determines the shape of the droplet and the printed pattern caused by coagulation. Thus, the pattern of solidified particles varies depending on the wettability of the surface and hydrodynamic flows. Inside the drop, these hydrodynamic flows, including convective flow and surface tension-driven Marangoni flow, attempt to compensate for solvent evaporation during drying. The wettability of the substrate is affected by its roughness, surface energy, and porosity (pore size, volume, and geometry). A reduced distribution over the surface of solutions is observed on porous substrates, but on homogeneous non-porous materials, the droplets tend to merge into larger balls rather than form a uniform layer.

A homogeneous printed pattern is obtained when the dissolved substance is sufficiently distributed during drying. Print quality is degraded due to excessive and/or uneven distribution of solution drops on the substrates. According to the theory of adsorption infiltration, the localization of droplets can be controlled by increasing the affinity of solutions for the substrate, which causes the adsorption retention of droplets on the surface.

Layered systems are produced by printing the multiple layers of ink on top of each other with an intermediate drying stage. Problems with smearing and erosion can be avoided by using printing systems with stationary substrate

holders, by separate solidification of the layers (for example, under UV irradiation or heat treatment), and/or by using porous substrates to increase the absorption capacity. In 2D-printed dosage forms, the penetration of solutions into porous substrates contributes to high accuracy of dosing. When the solution is applied onto impermeable surfaces, the ink layers are combined by re-dissolving, re-suspending, or re-melting the dried layers after applying an additional layer [18–20].

The coated substrates provide additional flexibility for adjusting the characteristics of the surface print. Some studies showed that the hydrophilic coating on porous rice paper makes the surface smoother, but the coating disintegrates or dissolves after printing due to pentration of solutions into the surface layer. In addition, by adding layers of substrate and / or coating, it is possible to change the behavior of pharmaceutical substance release.

Control of the crystal state characteristics of printed solid particles is also of great importance in the development of 2D- dosage forms. During preparation of solid dosed dosage forms, properties of the substrates and interaction of solutions with them affect the solidification and crystallization of printed pharmaceutical substances after the solvent has evaporated. Therefore, additional studies of the interaction of solutions, substrates and the technological process are necessary.

QR-ENCODED SMART DOSAGE FORMS

Personalized 2D-dosage forms themselves represent a very promising area of pharmaceutical technology, but there are many current concepts for the use of two-dimensional printing that expand the possibilities of medicine provision

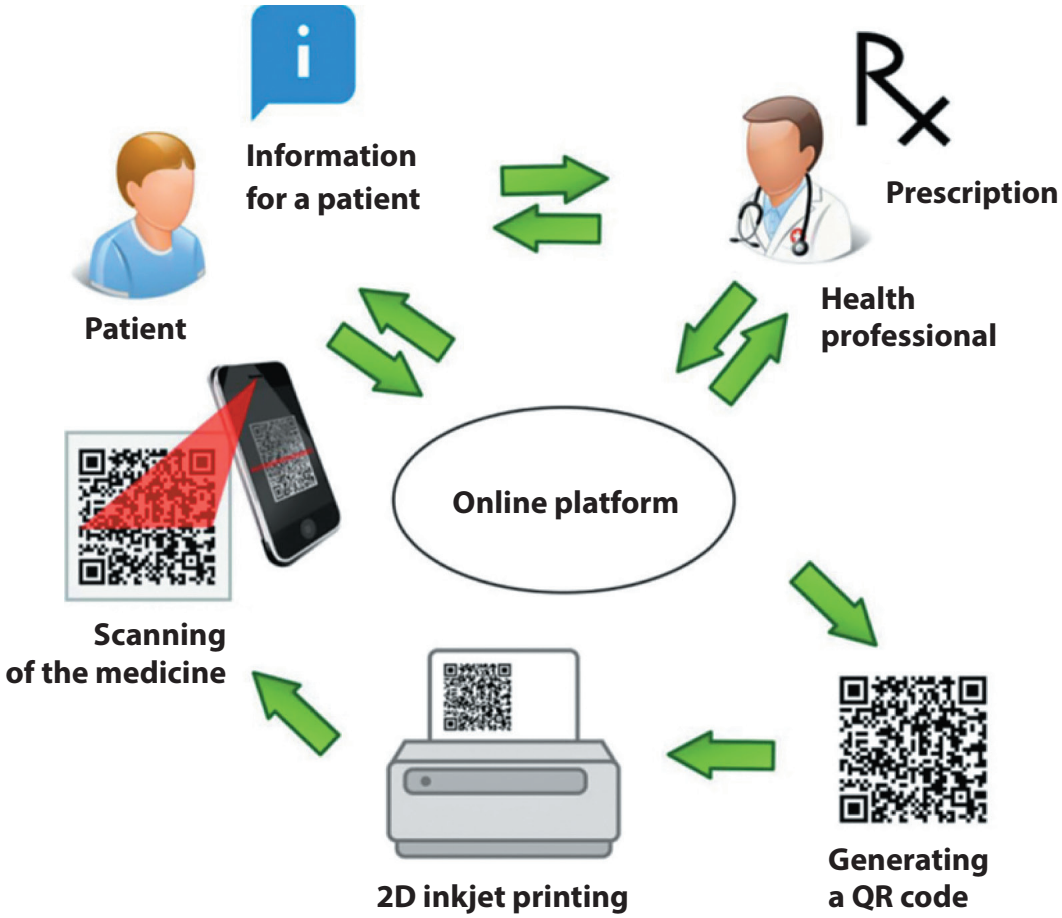

FIG. 6. *Graphical representation of implementation of the idea of QR-encoded dosage form*

for patients. One of these technologies is QR-encoded smart dosage forms.

A QR code is a two-dimensional version of barcode encoding information that can be read using a scanner, such as a smartphone with a QR code reader application. This concept involves combining the individualized medicines with encoding the information in the dosage form itself to ensure that the patient correctly administrate the medicine at the proper time. All necessary information can be included in the QR code in the format specified by national authorities. The possible implementation of the idea is shown in Fig. 6 [8].

This concept has been implemented in some studies. In particular, the University of Copenhagen and ABO University obtained a 2D dosage form as a QR code containing haloperidol [8]. However, the implementation of the concept in practice has multiple difficulties, for example, it is easy to falsify the dosage forms presented in studies, that is, to print QR codes using a regular office printer without pharmaceutical substances in solutions. In addition, the implementation of such coding requires the presence of electronic devices and mobile applications, which is not always feasible. During storage, the QR code may fade or the dye may be transferred. Therefore, in addition to proper packaging for 2D printed dosage forms, the light-, moisture-, and temperature-resistant but edible dyes/pigments should be used. Despite the limitations, 2D printing is being developed and optimized, which in the near future may allow you to arrange the production of innovative medicines to improve the patient adherence to treatment [8,16].

CONCLUSION

2D printing as a method of manufacturing the personalized medicines has a great potential for development in pharmaceutical technology, because it has a number of exceptional advantages, such as simplicity and speed of production, low cost of equipment, high accuracy of dosing, the ability to combine the pharmaceutical substances in a single dosage form. The process proceeds in such a way that after entering the required parameters into the printer software, the required dose can be applied onto a substrate suitable for administration to human within a few minutes. However, medicine production is a complex and regulated process that includes a number of key elements, including ensuring stability, uniformity of dosing, and compliance with regulatory documentation. The 2D printing process must be carried out in good manufacturing practice (GMP) and have appropriate documentation and production conditions. The key stages of the 2D printing process need to be reviewed and adjusted within these production structures and regulatory requirements.

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