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STATE-OF-THE ART TECHNOLOGIES IN PHARMACY

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Modern technologies are being actively introduced into various spheres of human activity, including the pharmaceutical industry. Today, in the process of developing and manufacturing the medicines, new approaches are being explored and applied, such as computer modeling, the creation of modern systems for delivering medicines to organs and tissues, three-dimensional printing of medicines, the use of supercritical fluids at various stages of production, etc. They allow manufacturers to improve the final product, adapt it to the clinical characteristics and needs of patients, as well as optimize the production processes

Keywords: state-of-the art technologies, pharmacy, three-dimension printing

Three-dimensional printing, (3DP) is a form of additive manufacturing (by layer-by-layer building up of raw materials), in which a structure is created by depositing or binding the materials in successive layers to create a 3D object.

3D printing technologies have been used in various industries for several decades. Today, articulation joints and implants for cranio-cerebral and maxillofacial surgery are printed by a 3D printer. Printers print buildings, tools, food, and parts used in aircraft and mechanical engineering. It is known that the annual growth rate of the world market for additive technologies is 15% and by 2025, the market volume is expected to increase fourfold: from 5 to 20 billion dollars per year [1].

In medicine, the use of these technologies began with the production of anatomical models used for the diagnosis and planning of various operations. Then they began to be used in dentistry for the manufacture of individual tooth crowns, dental bridges, etc. After that, they also began to print individual prostheses, orthopedic implants, various cellular tissues, personalized hearing devices and medicines [2].

Three-dimensional printing as a revolutionary method of medicine production is a potential tool for personalized medicine and makes it possible to take into account age, weight, comorbidity, pharmacokinetic characteristics. This approach is especially important for children and elderly patients. Dose adaptation according to pharmacokinetic characteristics and age is a key way to achieve the desired therapeutic effect and improve the balance between efficacy and safety. In addition, changes in color, smell, and even the configuration of dosage forms can significantly increase adherence to treatment in both children and elderly patients. It is worth noting that at the moment, the selection of the dose is mostly based on empirical methods, and therefore the probability of side effects increases significantly. At the same time, the side effects even became part of the therapeutic process [3].

Not only for children and the elderly, it is important to adapt the medicines to individual characteristics but personal approach is also required for the patients who must take 5 drugs a day at the same time. The therapy simplification, which is based on taking a fixed combination in one tablet, improves the patient persistence to the prescribed treatment. By the method of three-dimensional printing, it is possible to create fixed combinations of complex composition with an optimal release profile [3,4].

In production of medicines using 3D printing, the changes are simplified and easily introduced at the design development stage. It is possible to modify the product by releasing a series to meet the customer needs. Also an important advantage of 3D printing technology is the ability to produce complex dosage forms from the point of view of release. For example, it is possible to provide precise location of the active component (one or more) and excipients in the medicine for the purpose of modified release to provide several "sites" with different composition, release rate and mechanism of action [5,6].

There are various types of 3D printing, but only some approaches are most applicable in pharmaceutical technology. For example, printing on the basis of inkjet systems: solid-based deposition (DOS-drop on solid), drip deposition (DOD – drop on drop). Also selective laser melting (SLL – selective laser sintering or melting), semi-liquid material deposition technology (FDM-fused deposition modeling), pressure micro-spraying (PAM-pressure-assisted microsyringe), stereolithography are used (Table. 1) [6,7].

It is necessary to note that the methods presented in Table 1 include such technological processes as bonding, solidification, and melting, which occur at certain temperatures and these temperatures can be significantly higher than under conditions of granulation, microencapsulation, and tableting used in classical medicine

Table 1

THREE-DIMENSIONAL PRINTING METHODS USED TO CREATE MEDICINES

Material used	Method	Processes
Printing with the use of powder	DOS	Bonding of powder particles by liquid: the head of the printer ejects a drop on a solid material.
	SLL	Solidification of the molten powder after exposure to a laser beam
Printing with the use of liquid	DOD	Solidification of dropы: the printer head ejects the drops on one another
	stereo-lithography	Solidification of the photosensitive liquid. The geometric pattern is transferred to photosensitive liquid polymer on a substrate using UV light
Printing with the use of extrusion process	FDM	Solidification of the molten material. The molten thermoplastic polymer thread is extruded by two rollers through a high-temperature nozzle, and then solidified on the assembly platform
	PAM	Extrusion of a viscous semi-liquid material from an extrusion syringe to create the required three-dimensional shape, solidification

production technology. Therefore, the question arises about the introduction of additional requirements for the substance and the determination of critical points in the technological process.

Special attention should be paid to the fact that the first medicine produced using 3D printing for commercial purposes was the antiepileptic drug Spritam (Aprecia Pharmaceuticals), which contains levetiracetam as an active substance.

The drug was approved by the FDA in 2015. In the production of Spritam, the DOS method was used, which made it possible to achieve a porous structure of the tablet, capable of dissolving in the oral cavity in no time. It is important that the dose of levetiracetam in a tablet was 1000 mg and there were technological problems with the production of the orodisperse form of the drug by the traditional way, since the tablet was large, including due to a significant amount of excipients, and did not dissolve properly in the oral cavity [3,6,8].

After the first medicine was "printed", research in this area began to be conducted even more actively. Today, there are a large number of developments for printing various medicines (Table 2).

To date, a large number of studies on the production of medicines using 3D printing are based on the study and development of such medicines based on polymers. The polymers that are most suitable for certain methods of 3D printing of medicines are studied separately. Thus, the technology of three-dimensional modeling uses polyvinyl alcohol (a thermolabile synthetic polymer with high solubility in water, low solubility in ethanol and insoluble in many organic solvents),

Table 2

SOME DEVELOPMENTS OF DOSAGE FORMS PRODUCED BY A 3D PRINTER

Type of 3D-printing	Dosage form	Active substance/ auxiliary polymer	Author
Stereolithography	Hydrogel	Ibuprofen, riboflavin, PEG, diacrylate	Martinez et al.
FDM	Tablets	Felodipine, PEG, Tween 80, Eudragit EPO	Alhijjaj et al.
UV-jet printing	Tablets	Ropinirole, PEGDA	Clark et al.
PAM in combination with UV crosslinking	Tablets	Prednisolone, polydimethylsiloxane	Hollander et al.
FDM	Tablets	Haloperidol	Solanki et al.
FDM and hot melt extrusion	Tablets	Domperidone, hydroxypropyl cellulose	Chai et al.
FDM	Tablets	Hydrochlorothiazide	Sadia et al.
FDM and hot melt extrusion	Suppositories	Indometacin, ethylenevinyl acetate copolymers	Genina et al.
FDM	Tablets	Furadantin, polylactide, HPMC	Boetker et al.

** PEG – polyethyleneglycol, PEGDA – polyethylene glycol diacrylate, HPMC – hydroxypropyl methylcellulose*

polylactide, polycaprolactone, etc. [3]. However, there are studies that also study the «printing» of dosage forms based on lipids, for example, self-emulsifying medicine delivery systems [10].

One of the state-of-the-art processing method used in the pharmaceutical industry is also the use of supercritical liquid at various stages of production. A supercritical solvent is a state of matter in which its temperature and pressure exceed critical parameters. At the critical point, the liquid and gas phases become indistinguishable. Supercritical solvents include: carbon dioxide, n-pentane, ethanol, water, etc. [11]. Using supercritical fluids, the pharmaceutical industry produces nano-and microparticles which are carriers of active pharmaceutical ingredients and systems for prolonged medicine release [12].

Supercritical fluids are also actively used for the micronization of substances. One of the methods of micronization in the production of pharmaceuticals is RESS (Rapid Expansion of Supercritical Solutions): a solution of a substance in a supercritical fluid is sprayed through a nozzle. When the pressure decreases, the solvent converts into a gaseous state, and the dissolved substance is deposited in the form of a fine powder. The use of supercritical fluids provides opportunities for creation of water-soluble, fat-soluble substances, as well as polymers. By changing the temperature, pressure, and configuration of the dispersing nozzle, it is possible to produce powders with the specified particle size [13]. In addition, supercritical fluid technology is an alternative approach for increasing the solubility of water-insoluble substances [11].

In addition, in recent years, the scientific community has focused on the use of biodegradable solvents. They include deep eutectic solvents (DES), which are a mixture of solid compounds, such as choline chloride and sugar, whose melting point is significantly lower than that of individual components [14]. They are characterized by the formation of strong hydrogen bonds and, due to the extremely low vapor pressure, are widely used in polymer chemistry and synthetic organic chemistry, as well as for the extraction of biologically active substances [15,16]

For example, when using a mixture of "urea-choline chloride" and "choline chloride-malonic acid", the solubility of poorly soluble molecules, such as benzoic acid, griseofulfine, danazole and itraconazole, in DES is 5–22000 times higher than in water [17].

It is also worth noting computational simulation as one of the up-to-date methods that is actively used in various industries. Computational simulation is the construction of symbolic and physical models of objects studied in science, created in technology, medicine, art, and other areas of human activity using computers and computer devices [18].

Currently, computational simulation is used to predict the physiological activity, the compatibility of pharmaceutical substances and excipients, and to determine the relationship between the structure and properties of substances. Important advantages of computational simulation, which specify the efficiency of its use by scientists, are the possibility of its repetition for the required number of times, the ability to simulate such experimental parameters that cannot be created in the laboratory, the ability to study fast-flowing processes, the safety of virtual research, which excludes harm to humans and the environment, significant savings and economic benefits compared to in vivo and in vitro experiments. In addition, using the mathematical simulation, scientists study the functioning of various human organs in normal and pathological conditions. So, in 2016, researchers from the University of York for the first time created a three-dimensional model of heart tissue, which is able to pulse like a real heart. Scientists were able to include three types of tissues in this virtual model. This three-dimensional model can be used to predict the toxic effect of the studied medicines on the heart or to study the problems that arise during heart tissue transplantation [19,20].

CONCLUSIONS

Today, everywhere in the world, new processes are being actively introduced into the pharmaceutical industry, speeding up and improving the production process and the final product, as well as introducing the principles of personalized medicine, which in the future can make the production of medicines more accessible and adapted to a specific patient. In this regard, analyzing the possibilities of introducing 3D printers into domestic use, the humanities are faced with the question "Can consumers be trusted with the means of producing an unlimited range of things?". The production and distribution of pharmaceutical products, especially narcotic drugs and strong drugs, should undoubtedly be subject to strict control, which means that the introduction of new processes, such as three-dimensional printing, should be carefully developed and regulated in the future [1]

REFERENCES

1. *O.V. Letunova, N.A. Ermienko, I.Yu. Ermienko, V.G. Sherstyukov. Additive processes and their influence on the market of personalized goods // Collection of articles of the International Scientific and Practical Conference "Economics, Management, Law: current issues and vectors of development". – Petrozavodsk, 2019. – pp. 109–113.*
2. *D.V. Yakovleva, E.V. Verkhoturova. 3D printing processes in the production of pharmaceutical products // Collection of scientific papers under the general editorship of E.G. Privalova "Innovative processes in pharmacy". – Irkutsk, 2019. – pp. 401–404.*
3. *Konta A.A., García-Piña M., Serrano D.R. Personalised 3D-Printed Medicines: Which Techniques and Polymers Are More Successful? // Bioengineering. – 2017. – №4. – Vol. 79.*
4. *Nishimura R., Kato H., Kisanuki K., Oh A., Onishi Y., Guelfucci F., Shimasaki Y. Comparison of persistence and adherence between fixed-dose combinations and two-pill combinations in Japanese patients with type 2 diabetes // Current Medical Research and Opinion. – 2019. – №5. – Vol. 35.*
5. *Hsiao W.K., Lorber B., Reitsamer H., Khinast J. 3D-printing of oral drugs: a new reality or hype? // Expert Opinion on Drug Delivery. – 2018. – №1 (15). – P. 1–4.*
6. *Jamróz W., Szafraniec J., Kurek M., Jachowicz R. 3D-Printing in Pharmaceutical and Medical Applications – Recent Achievements and Challenges // Pharm. Res. – 2018. – №9. – Vol. 35. – P. 176.*
7. *E.V. Blynskaya, S.V. Tishkov, K.V. Alekseev. Processes of three-dimensional printing for the production of dosage forms // Development and registration of medicinal products. – 2018. – №3 (24). – pp. 10–19.*
8. *Norman J., Madurawe R.D., Moore C.M.V., Khan A., Khairuzzaman A.K.M. A new chapter in pharmaceutical manufacturing: 3D-printed drug products // Advanced Drug Delivery Reviews. – 2017. – V. 108. – P. 39–50.*
9. *Diogo J H. 3D-Printing of Pharmaceutical Drug Delivery Systems // Arc.Org. Inorg. Chem. Sci. – 2018. – №2. – Vol. 1.*
10. *Vithani K., Goyanes A., Jannin V. et al. A Proof of Concept for 3D-Printing of Solid Lipid-Based Formulations of Poorly Water-Soluble Drugs to Control Formulation Dispersion Kinetics // Pharm. Res. – 2019. – №7. – Vol. 36. – P. 102.*
11. *Kaur T., Sharma P., Kumar S. Supercritical fluid technology: an innovative approach used to enhance solubility of water insoluble drugs // Journal of Drug Delivery & Therapeutics. – 2017. – №7 (5). – P. 22–26.*
12. *S.E. Bogorodsky, L.I. Krotova, S.A. Minaeva, G.V. Mishakov, V.K. Popov, Yu.B. Basok, V.I. Sevastyanova. Supercritical fluid micronization and encapsulation of ibuprofen*

in microparticles of aliphatic polyesters. // Advanced Materials. – 2013. – №1. – pp. 23–32.

13. *D.Yu. Zalepugin, N.A. Tilkunova, I.V. Chernyshova, V.S. Polyakov. Development of processes based on the use of supercritical fluids // Supercritical fluids: theory and practice. – 2006. – №1. – Vol. 1. – pp. 27–51.*
14. *Abbott A.P. et al. Deep Eutectic Solvents Formed between Choline Chloride and Carboxylic Acids: Versatile Alternatives to Ionic Liquids // Journal of the American Chemical Society. – 2004. №29. – V.126. – P. 9142–9147.*
15. *Dai Y. et al. Ionic Liquids and Deep Eutectic Solvents in Natural Products Research: Mixtures of Solids as Extraction Solvents // Journal of Natural Products. – 2013. – №11. – Vol. 76. – P. 2162–2173.*
16. *Tang B., Zhang H., Row K.H. Application of deep eutectic solvents in the extraction and separation of target compounds from various samples // Journal of Separation Science. – 2015. – №6. – Vol. 38. – P. 1053–1064.*
17. *Morrison H.G., Sun C.C., Neervannan S. Characterization of thermal behavior of deep eutectic solvents and their potential as drug solubilization vehicles // International Journal of Pharmaceutics. – 2009. – №1. – Vol. 378. – P. 136–139.*
18. *URL: https://bigenc.ru/technology_and_technique/text/4010577 (access date 03.06.2020).*
19. *S.O. Losenkova, A.V. Pogrebnyak, Yu.A. Morozov, E.F. Stepanova. Computational simulation as one of the up-to-date methods of forecasting in pharmaceutical technology. // Pharmacy and Pharmacology. – 2014. – №6 (7). – pp. 105–113.*
20. *S.A. Chiryapkin, A.A. Glushko Mathematical simulation in medicine and pharmacy // Rostov Scientific Journal. – 2019. – №3. – pp. 343–351.*

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