Published By Guangdong Pharmaceutical University, Guangzhou
Journal of Holistic Integrative Pharmacy
2020,1(2): 109-114

REVIEWS

The new trend of 3D printing drug technology development under the guidance of Holistic Integrative Pharmacy theory

YE Mingzhu[1], RUI Wen[1,2,3*]

[1]*The Center for Drug Research and Development, Guangdong Pharmaceutical University, Guangzhou 510006, China;*

[2]*Key Laboratory of Digital Quality Evaluation of Chinese Materia Medica of State Administration of TCM, Guangzhou 510006, China;*

[3]*Guangdong Engineering & Technology Research Center of Topical Precise Drug Delivery System, Guangdong Pharmaceutical University, Guangzhou 510006, China*

[Abstract] 3D printing technology is an emerging rapid prototyping technology that is widely used in many fields. It is a hotspot of multi-field convergence that coincides with the "Holistic Integrative Pharmacy" concept. This technology has not only revolutionized the manufacturing industry but has also changed all aspects of the medical field. As General Secretary Xi put emphasis on the strategic position of putting peoples' health as a priority, along with giving priority to the development of medical and health services and the establishment of the "Holistic Integrative Pharmacy" alliance in 2017, the integration of pharmaceutical development and modern emerging technologies will become an unstoppable new trend. This paper reviews the development and applications of 3D printing technology in China. In addition, we discuss the prospects and development trends of 3D printing in the field of pharmacy to provide a reference for the research and applications of 3D printing technology.

[Key words] 3D printing; holistic integrative pharmacy; Multi-field convergence; Modern emerging technology

1 Introduction

Pharmacy is a healthcare industry that connects health sciences and chemical sciences and is responsible for ensuring the safe and effective use of drugs. Integrated pharmacy [1] is based on integrated medicine, with a core of "good medicine," "good use medicine," and "Holistic Integrative Pharmacy" with traditional medicine, modern medicine, modern emerging technologies, basic research and application development, and humanities integration. Integrated pharmacy aims to combine the methods and knowledge of various pharmacy-related disciplines, open up discipline barriers, and build a new pharmacy theory and practice system that is more in line with current human health requirements.

3D printing technology, which is also known as 3D rapid prototyping technology or additive manufacturing technology, is a rapid prototyping technology that can produce special shapes or

[Research funding] This work was supported by National Natural Science Foundation of China (No. 81202917; 81573607).

[*Corresponding author] E-mail:gyruiwen@gdpu.edu.

These authors have no conflict of interest to declare.

complex structures directly through a computer-aided design model and computer control[2]. This technology originated in the United States at the end of the 19th century. Following the development of computer and network technologies in the 1980 s, 3D printing technology was born. This technology has been widely used in machinery manufacturing, construction, the food industry, and in the development of biomedical materials and living organs[3]. 3D printing has become a promising technology with broad application prospects[4], but its application in the field of pharmacy is relatively late. This paper summarizes the application of 3D printing technology in the field of pharmacy and discusses its development advantages in the context of integrated pharmacy to provide a reference for the innovation and progress of 3D printing technology in the future.

2 The background of the development of holistic integrative pharmacy

With the development of society and the improvement of people's living standards, society's demand for health has gradually increased. In different regions, different doctors prescribe different drugs, even if there are standard guidelines for each disease, but individual patients are different and their specific needs will be different, therefore guidelines should only be used as a reference. The main purpose of Holistic Integrative Pharmacy is to combine pharmacology with medicine and emphasize the use of personalized medicine. Integration is a magical weapon for solving the current health problems and is an inevitable trend of current developments. Furthermore, integration is in line with the development of things that the human body exists objectively, cells and organs are born with it and follow the objective laws of "successive, long-term," and "spiral rise, wave forward[5]." This regular progressing pace is not much, but there are twists and turns on the way forward; in general, it is moving forward.

With the development of subject research, the pharmacy discipline tends to be precise and accurate, but students are ambiguous or even ignorant of the knowledge outside their respective disciplines. The ultimate goal of pharmaceutical research should be to prepare drugs for clinical use and to save lives. Therefore, the pharmacy-related knowledge of disciplines such as natural medicinal chemistry, medicinal chemistry, pharmaceutical analysis, pharmacology, and pharmacy should be cross-integrated to enhance the pharmacy discipline. A broader understanding will extend the pharmacy professional knowledge chain and improve the knowledge and skills of students in pharmacy services[6]. The purpose of Holistic Integrative Pharmacy is to cultivate high-tech talents that are suitable for social needs and become a powerful force to promote the development of pharmacy in China.

Affected by the traditional pharmacy education model, the current clinical pharmacy education program in China is still dominated by a single subject[7]. It has affected the expansion and deepening of clinical pharmacy work. The idea of Holistic Integrative Pharmacy is the key to solve such problems. The purpose of Holistic Integrative Pharmacy is to integrate pharmacy-related fields and practices, not just to obtain the amount of "A + B = C" but the change is to achieve a qualitative leap of "A × B = D." Combined with the status of pharmaceutical development in China, in line with the new trend of new drug research and development, and under the advocacy of academician Fan Daiming, the "China Integrated Pharmacy Alliance" was established on December 11, 2017 at the Guangdong Pharmaceutical University. The purpose of this alliance was to study medicine and teach "Holistic Integrative Pharmacy" concepts[8], which promoted the comprehensive development of Holistic Integrative Pharmacy.

3 The current status of 3D printing technology in the field of pharmacy in China

The number of applications for 3D printing is growing rapidly[9]. The scientific and technological achievements brought by this emerging technology have gradually penetrated into the pharmaceutical field in China and have played an important role in drug synthesis, pharmaceutical preparations, drug analysis, new drug research, and promoting medical treatments, thus promoting the progress and development of the health industry. In 2015, the US FDA approved the world's first "lesilacetam instant tablet", and 3D printed drugs triggered a boom in domestic and foreign experts[10]. However, 3D printing technology is applied differently in various fields. For example, the 3D printing technology for pharmaceutical preparations requires more gentle molding technology to avoid the destruction of active ingredients of the drug, which would cause the drug to fail[11]. The team of Professor Chen Yanzhong of China used 3D printing technology for the first time to prepare and evaluate the quality of rescue heart-disintegrating tablets. These results showed that 3D printing technology is feasible for the preparation of quick-acting heart-saving orally disintegrating tablets [12].

3.1 3D printing technology for the application of drug synthesis

Using 3D printing technology, Shi et al.[13] designed a polymorphic siloxane biomimetic nano-silver composite material to meet different wound healing requirements. Morphological observations of polyformaldehyde siloxane biomimetic nano-silver composites (i PDMS/AgNPs) by scanning electron microscopy and energy spectroscopy were performed. Cytotoxicity was measured using the CCK-8 method and anti-adhesion and antibacterial properties of the two commonly used drug-resistant bacteria (staphylococcus aureus and escherichia coli) were explored. A mouse with a full skin thickness excision wound was used to observe the effect of i PDMS/AgNPs on the rate of wound healing, neonatal epithelial length, and granulation tissue thickness. Scanning electron microscopy and energy spectrum observation confirmed the presence of nano-silver, indicating that i PDMS/Ag NPs nano-silver composites were successfully prepared. The results of the CCK-8 assay showed that the i PDMS/AgNPs had no obvious toxic effects on fibroblasts. Anti-adhesion and bacteriostatic experiments showed that the i PDMS/Ag NPs membrane was effective against the adhesion of Staphylococcus aureus and Escherichia coli and inhibited their growth (P<0.05). The mouse wound model study showed that the prepared composite membrane significantly improved the wound healing rate, increased the length of regenerated epithelium and increased the thickness of granulation tissue (P<0.05). These results showed that the prepared i PDMS/AgNPs are biocompatible and have effective anti-adhesive properties and antibacterial activity. Furthermore, i PDMS/AgNPs can effectively promote epithelial regeneration and granulation tissue growth in vivo, thus accelerating wound healing. Frederik Kotz [14] had further demonstrated that 3D printing is a versatile technique that can be used for surface structuring of polymers to enhance their wetting performance. Such micro/nanostructuring is important to selectively enhance wetting surface patterns that are versatile for chemical arrays and droplet synthesis.

3.2 The application of 3D printing technology in pharmaceutical preparations

To study the effects of different shapes on drug release, Yan et al.[15] applied 3D printing to pharmaceutical preparations and printed the composite hydrogel in three different shapes using a hot melt extrusion 3D printer. The results of this rheological analysis showed that under acidic or alkaline conditions, the cumulative release rate of bovine serum albumin (BSA) in three different shapes of

hydrogel patches is between 49% and 89%. These results suggest that there are significant differences in the cumulative release rates of circle, cube, and rectangle dosage forms. Further, the hydrogel prepared by 3D printing has a good rigidity and is suitable for the application of drug delivery systems. The prepared hydrogel has a sustained release effect, but at the same time, tablets of different shapes have different release rates. Therefore, 3D printing has good prospects of application in drug delivery systems. Zhang[16] explored the feasibility of using 3D printing technology to prepare individualized, controlled-release aspirin tablets and used traditional tablet presses to suppress the immediate release of aspirin in sustained release bilayer tablets as a controlled preparation. The physicochemical properties (sheet weight difference, friability, hardness, and thickness) and release profile of the tablets produced by two different methods were examined. The results showed that the physicochemical properties of the two tablets were within the scope of the pharmacopeia and the tablets of different shapes printed by the 3D printer had different release profiles, whereas the release printed double-layer tablets were released in a higher amount than the other tablets.

3.3 Application of 3D printing in the development of new drugs

Zhao et al. [17] used cell 3D printing technology to prepare a cell chip for the screening tumor drugs. A cell chip containing multiple interdigitated electrode arrays was constructed using 3D printing technology, along with HO-8910 ovarian cancer cells and human liver mesenchymal stem cell HMSC-H tissue model; these cells were assembled on the cell chip, and processes of cell growth, attachment, proliferation, and apoptosis, along with the effects of drugs on cell activity were measured by detecting cell impedance changes in the tissue model. The anticancer drugs cisplatin and cyclophosphamide were tested for the killing and hepatotoxicity of tumor cells, and cyclophosphamide, a drug that requires secondary metabolites of the liver to produce antitumor drugs, was selected. Studies have shown that the cell chip model constructed using 3D printing technology has great application prospects in the field of new drug screening.

4 The new developing opportunities of 3D printing under the guidance of holistic integrative pharmacy

As a sunrise industry in the 21st century, 3D printing technology has brought new vitality and hope to the continuous growth of China's pharmaceutical industry and is an excellent breakthrough for the rise of the pharmaceutical industry in the world's medical forest. Under the influence of integrated pharmacy, the development of 3D printing pharmacy, nurturing emerging industries, and innovating medical needs will not only bring a more complete health care system to the public but also provide huge benefits for pharmaceutical companies and governments.

4.1 The impact of "holistic integrative pharmacy" theory on the development of 3D printing drugs

Holistic integrative pharmacy is a theory and practice system that integrates pharmacy with traditional medicine, modern medicine, modern emerging technologies, basic research, application development, and humanities. It integrates the methods and knowledge of multiple pharmacy-related disciplines and emphasizes the return to the whole in the development of each subject. In the process, it returns to the whole[1] and 3D printing technology coincides with this concept. 3D printed drugs are digitally systemized from the computer-aided design system and they are widely used in many fields such as drug design and analysis. Elizabeth[18] research showed the biomechanical effects and mechanical properties of 3D-printed

ankle-foot orthotics (AFOs) were comparable to traditionally manufactured AFOs. Developing novel AFO's using 3D printing has many potential benefits including stiffness and weight optimization to improve biomechanical function and comfort. Moreover, 3D printing may help to develop personalized medicines according to the needs of patients, and accurately print medicines of different specifications, sizes, and doses[19]. On the basis of this fine division of labor application and following the concept of holistic integrative pharmacy, it is finally possible to return to the whole, thereby producing medicines that meet people's expectations. This makes raw materials simpler, increases production efficiency, and allows for a larger production scale. The process is simpler, and the production site is reduced. This process of optimization and development is itself a great practice for the Holistic Integrative Pharmacy theory and system. We believe that 3D printing drug technology can deliver more vitality in the new era of integrated pharmacy.

4.2 The advantages of developing 3D printed drugs under the guidance of holistic integrative pharmacy

Although current 3D printing drug technology has a wide range of applications in many fields of drug research and development, its own technology is still in the stage of "excessive expectations". The public's concern for it is not in line with the current industry technology development reality. The 3D printing technology is widely used only in Europe and the United States[20]. Although its technical characteristics may have a great impact on the research and production of future drugs, the technology is still in the research and development stage. Furthermore, the theoretical system and development concept are not mature enough, which will undoubtedly have a great impact on the direction of its future development. The concept of integrated pharmacy has laid a strong theoretical foundation for the development of 3D printing drug technology. It advocates the organic integration of knowledge and practice in the field of pharmacy and the idea of deepening its development level has played a leading role in the industry. As a key direction for the future development of the pharmaceutical industry, 3D printing drug technology will also be rooted in the context of technological development and laying the foundation for greater integration of new technologies, such as pharmacy and 3D printed rugs.

4.3 The new trend of 3D printing drug technology development under the guidance Holistic Integrative Pharmacy

Combined with the >10-year development of 3D printing technology and the applications of 3D printed drugs, 3D printing might provide one of the techniques for personalized medicine and on-demand manufacturing[21-22]. The development of 3D printing drug technology will gradually diversify in the future, and the practicality will become stronger over time. With the continuous optimization and practice of integrated pharmacy theory and system, its guiding role in the development of 3D printing drug technology is becoming more evident, and the technology is continuously being improved. As far as the current use of the technology is concerned, the future development trend will be closer to individualization, rapidness, and scale; moreover, 3D printing will gradually become a technology that is inseparable from drug production, research and development, and analysis. Experts at the French Plastic Surgery Hospital said that vascularization is a major limiting factor in the large-scale construction of 3D printing. Once the obstacles to vascularization are overcome, it might be possible to print organs and composite tissues of any size. The morphological analysis shows that the printed organs can reduce the receptor site rejection reaction[23]. It is foreseeable that in the future drug development process, most pathophysiological experiments can be avoided by computer simulation.

In this way, materials, manpower, and time[24] spent in production and quality control can be saved, and the production process can be standardized. Lean management ensures production and quality in R&D, production, quality control, and quality inspection. Multi-chromatography and wide-area 3D printing technology integration is a new development trend under the guidance of integrated pharmacy.

References

[1] Guo J, Chen G, Su XB,et al. Integrated pharmacy-A new era of pharmaceutical education development[J]. *Pharmaceut Edu*, 2018, 34(3):1-5 (in Chinese).

[2] Xiao YF, Wang B, Lin R. Progress in personalized medicine for 3D printing [J]. *Chin Pharmacol J*, 2017, 52(2):89-95 (in Chinese).

[3] Chen GN, Shu H, Yu P, et al. Application of 3D printing technology in the field of pharmacy[J]. *Chin Pharmacol J*, 2016, 51(16):1353-1359 (in Chinese).

[4] Wang QS, Han GC, Yan SQ, et al. 3D Printing of silk fibroin for biomedical applications[J]. *Materials*, 2019, 19(3):1-19.

[5] Fan DM. The connotation and extension of integrated pharmacy[J]. *Med Philos (A)*, 2017, 38(1):7-13 (in Chinese).

[6] Lu Y, Lu DM, Li CL, et al. Construction practice of the "one body two wings" curriculum system for pharmacy majors in medical colleges[J]. *Basic Medical Edu*, 2018, 20 (11):967-969 (in Chinese).

[7] Song YS, Zhang Y, Fang TT. Construction of quality evaluation system for clinical pharmacy graduate students' practical ability training[J]. *Chin J Med Guide*, 2018, 20(11):700-704 (in Chinese).

[8] Fan DM. My opinion on integrated medical education[J]. *Famous Forum*, 2018, 9(1):1-8 (in Chinese).

[9] Attaran M. The rise of 3D printing: The advantages of additive manufacturing over traditional manufacturing[J]. *Bus Horiz*, 2017, 60(5):677-688.

[10] Wang XC, Wu ZF, Pei ZZ, et al. 3D printing technology and its application prospect in solid preparations of traditional Chinese medicine[J]. *Chin J Pharma Indus*, 2017, 48(8):1093-1098 (in Chinese).

[11] Wang X, Zhang C, Ping QN. Research progress of 3D printing technology in High-end drug preparations[J]. *J Chin Pharma Univ*, 2016, 47(2):140-147 (in Chinese).

[12] Lin QF, Yang F, Fan KY, et al. Preparation of 3D printing fast-acting Jixin orally disintegrating tablets[J]. *J Guangdong Pharm Coll*, 2016, 32(1):1-4 (in Chinese).

[13] Shi GQ, Luo X, Chen XW, et al. Study on 3D printed polyformaldehyde siloxane biomimetic nano-silver composites and their properties[J]. *Med J Chin People's Liberation Army*, 2018, 43 (10):840-848 (in Chinese).

[14] Susanna F, Nils G, Martin W, et al. Three-Dimensional (3D) printing of polymer-metal hybrid materials by fused deposition modeling[J]. *Materials*, 2017, 10(10):1199-1208.

[15] Yan JX ,Wang Y, Zhang X, et al. Snakegourd root/ Astragalus polysaccharide hydrogel preparation and application in 3D printing[J]. *Int J Biol Macromol*, 2019:309-316.

[16] Zhang HZ. Development of 3D printed aspirin immediate release slow release double layer tablets[D]. Hangzhou:Hangzhou University, 2018.

[17] Yang W, Yu H, Li G, et al. Mask-free fabrication of a versatile microwell chip for multidimensional cellular analysis and drug screening[J]. *Lab Chip*, 2017, 17(24):4243-4252.

[18] Ho CY , Ho LK , Jong RH , et al. Ankle-Foot orthosis made by 3D printing technique and automated design software[J]. *Appl Bionics Biomech*, 2017, 2017:1-6.

[19] Palo M, Holländer J, Suominen J. 3D printed drug delivery devices: perspectives and technical challenges[J]. *Expert Rev Med Devices*, 2017, 14(9): 685-696.

[20] Lan T. Risk control research of 3D printing technology[D]. Beijing:Beijing Institute of Technology, 2015.

[21] Norman J, Madurawe RD, Moore CM, et al. A new chapter in pharmaceutical manufacturing: 3D-printed drug products[J]. *Adv Drug Deliv Rev*, 2017(108):39-50.

[22] Khaled SA, Alexander MR, Wildman D, et al. 3D extrusion printing of high drug loading immediate release paracetamol tablets[J]. *Int J Pharm*, 2018, 538(1/2):223-230.

[23] Ma F, Zhu T, Xu F, et al . Neural stem/progenitor cells on collagen with anchored basic fbroblast growth factor as potential natural nerve conduits for facial nerve regeneration[J]. *Act Bio*, 2017, 50:188-197.

[24] Ruban O, Pidpruzhnykov Y, Kolisnyk T. Excipient risk assessment: possible approaches to assessing the risk associated with excipient function[J]. *J Pharm Invest*, 2017, 48(4):421-429.