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Review Article

3D Printing Pharmaceuticals: Current Status and Future Opportunities

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The current processes for the dispensing and manufacturing of pharmaceutical preparations can be traced back over several centuries or in some cases B.C. Even today's large-scale manufacturing processes performed in modern production facilities are fundamentally unchanged from processes utilized more than a century ago. Modernization of pharmaceutical manufacturing has been moving forward incrementally over the past decade through the implementation of process analytical technology (PAT) and continuous manufacturing, but the methods used in the actual production of tablets and capsules remain the same. However, the application of three-dimensional (3D) printing technology to drug delivery, pharmaceutical product development, and manufacturing has brought forth a paradigm shift in pharmaceutical preparation and manufacturing. Through this revolutionary design and production process, 3D printing has greatly expanded the possible types of dosage form designs, allowing the customization of drug release and delivery in ways not previously possible, potentially leading to a new ecosystem including novel drug delivery, digital process development and manufacturing, virtual regulatory audit, and agile product distribution.[1]

3D printing is a process that creates a three-dimensional object layer by layer using a digital file converted from computer-aided design (CAD). 3D printing was invented in 1984 but the first application to the fabrication of pharmaceuticals was in 1993.[2,3] The first 3D-printed pharmaceutical product, Spritam was approved by the U.S. Food and Drug Administration (FDA) in 2015, demonstrating the feasibility of this new technology to produce a product meeting regulatory requirements for commercial sale. This approval spurred both pharmaceutical scientists in academia and industry to invest more time and resources in this burgeoning field. This increased interest is evident from the surge in both patent applications and publications regarding the use of 3D printing in pharmaceuticals. In applying 3D printing technology to pharmaceuticals, scientists have taken two complementary but different approaches to patient care. One approach has focused on personalized dosing using tailor-made small-scale manufacturing closer to the point of care (e.g., in a hospital or pharmacy) and the other approach has been to develop end-to-end technology platforms for pharmaceutical product development and commercial-scale manufacturing.

Of the seven categories of 3D printing methods as defined by the American Society for Testing and Materials,[4] six have been investigated for feasibility in pharmaceutical applications. Although all six methods can theoretically be used in pharmaceutical preparations, the materials and side products generated, such as free radicals generated in vat polymerization, in the 3D printing process have limited the application of some methods in pharmaceuticals. The most commonly used 3D printing method to date for research and exploratory efforts in producing pharmaceuticals has been fused deposition modeling (FDM).[5] Much of the early conceptual work was performed using this method. However, challenges in forming drug-containing filament using pharmaceutical excipients for 3D printing, such as obtaining the proper mechanical properties of the filament and obtaining sufficient drug loading, have limited the application of this method in the production of pharmaceuticals. With respect to personalized dosing applications, extrusion-based 3D printing methods, such as FDM, semi-solid extrusion,[6] and direct powder extrusion,[7] have been most commonly utilized. For commercial-scale manufacturing, powder inkjet binding,[8] melt extrusion deposition,[9] and screen printing methods[10] are the most amenable and have been used in large-scale production.

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The application of 3D printing technology to pharmaceuticals provides an unprecedented opportunity to create novel dosage forms, such as tablets and implants, with not only unique external shapes and appearances but also sophisticated internal structures as well. The free-form formation of 3D printing allows the manufacturing process to produce any shape and structure based on a CAD design at will without the need for special tooling or equipment changeover. The ability to customize the internal structures of the dosage forms enables programmed drug delivery through control of rate, mode, onset time, and location of drug release while reducing critical variables in the formulation development process. The internal structure can vary from a simple highly porous structure to a layered structure or even multiple independent compartments with different geometric shapes. Complementing this high degree of customizability, the recently developed 3D Printing Formulation by Design process[11] allows for controlling drug release characteristics through dosage form structure control, transforming the dosage form design and development process from trial and error to a predesigned process with less variability.

Although not always immediately appreciated, 3D printing is inherently a lean and continuous process. Therefore, manufacturing processes based on 3D printing can be naturally designed as a continuous manufacturing process. Due to this capability, continuous manufacturing with PAT implementation and in-line packaging allows for much faster product release. Furthermore, 3D printing manufacturing production lines are also inherently digital through the software and equipment control implemented, further supporting process analytic technology and production record-keeping to facilitate regulatory compliance.

Currently, personalized dosing using 3D printing technologies is undergoing early-stage evaluation through demonstration projects in Europe,[12] China,[13] and Singapore.[14] Although the personalized dosing practice can be implemented via the extemporaneous compounding pathway or hospital-based preparation, the regulatory requirements for widely deploying 3D-printed personalized dosing are not clearly defined at this time in Europe, China, or the United States. One of the biggest challenges to the implementation of 3D printing in personalized dosing is assuring the quality of such personalized products. To address these issues, both U.S. Pharmacopeia (USP) and the U.S. FDA have organized several forums for discussing and setting standards. For large-scale commercial manufacturing of pharmaceuticals with 3D printing, the products follow the usual regulatory approval pathways. In addition to the one approved product, Spritam, several investigational new drug (IND) applications for 3D-printed drug products have received

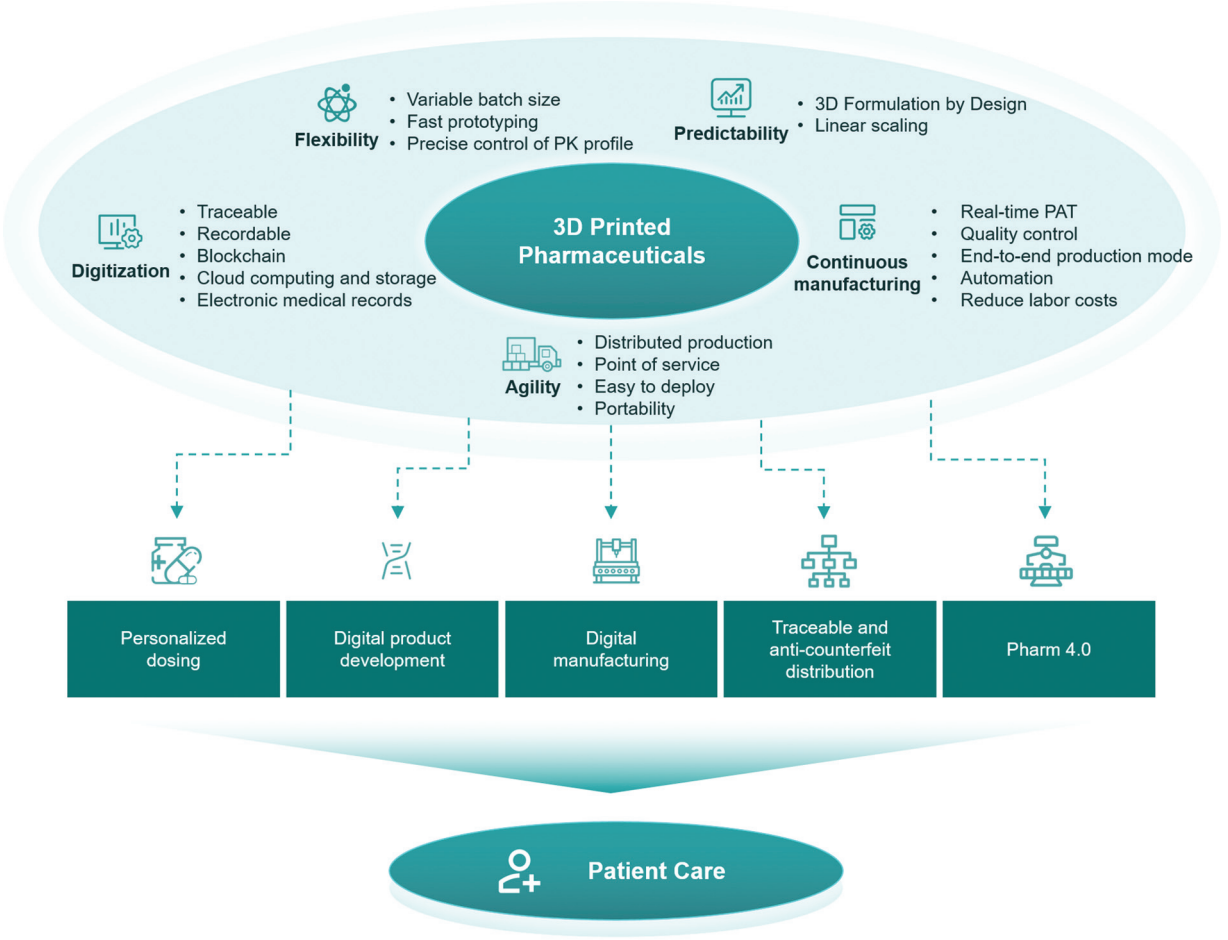

Fig. 1 3D printing pharmaceuticals and its future.

clearance in both the United States and China for conducting human clinical trials.

This flurry of IND submissions suggests that more large-scale manufactured 3D-printed pharmaceutical products will enter clinical use soon. These products provide unique drug release characteristics that conventional dosage forms cannot produce or are too difficult or costly to produce. Personalized dosing will continue to be either exploratory or of limited application until pharmaceutical scientists, the medical community, government agencies like the FDA, and standard-setting bodies such as USP come together to develop quality standards, practice guidance, and criteria for implementation. Both industrial-scale production lines and personalized dosing instrumentations will continue to be refined and adapted specifically for pharmaceutical applications. For elaborated review articles on 3D printing technologies for personalized dosing, drug delivery, product development, and manufacturing, readers are encouraged to follow the references.[1,9,11,15,16]

The future of 3D-printed pharmaceuticals is brighter than ever when considering its potential long-term impact on patient care outcomes and health care in general. 3D printing is inherently digital by nature, which leads to a digital process starting from dosage form structure creation by CAD through pharmaceutical product development, and manufacturing. As the pharmaceutical industry and medical communities adopt this technology in pharmaceutical production and clinical uses, the use of 3D-printed products will increase in a manner analogous to how the implementation of electronic media in the publishing industry began slowly but eventually became equal to or greater in use than traditional print media. Through education of the medical community, prescribing habits may change and more personalized dosing occurs with dosage forms and doses customized for individual patients. 3D printing technology can also integrate with other technologies either currently in practice or under development to leverage the benefits afforded by 3D printing technology such as digitization, flexibility, fast prototyping, small batches, linear scaling, and predictability to create a new pharmaceutical ecosystem. This new ecosystem could encompass product development, manufacturing, distribution, dispensing, and patient care through the incorporation of real-time PAT, electronic medical records, cloud computing and storage, blockchain, and the Pharm 4.0 framework (►**Fig. 1**). It would not be unrealistic to envision that 3D printing pharmaceutical systems could operate anywhere in the world controlled by a central control center that provides and records all digital production parameters. The small footprint of 3D printing production systems could even allow the system to fit into one or two shipping containers that can be loaded on a truck or ship to be deployed to a point of service both on a production scale or personalized dosing pharmacy operations, including in emergencies. As a new technology with numerous unique advantages, there is no limit to what this technology could evolve to become and change the face of health care.

Conflict of Interest
None declared.

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