A Review of 3D Printing Technology in Pharmaceutics:

Technology and Applications, Now and Future.

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Abstract:

Three-dimensional printing technology, also called additive manufacturing technology, isused to prepare personalized 3D-printed drugs through computer-aided model design. In recent years, the use of 3D printing technology in the pharmaceutical field has become increasingly sophisticated. In addition to the successful commercialization of Spritam® in 2015, there has been a succession of Tristen’s 3D-printed drug applications that have received investigational new drug (IND) approval from the Food and Drug Administration (FDA). Compared with traditional drug preparation processes, 3D printing technology has significant advantages in personalized drug manufacturing, allowing easy manufacturing of preparations with complex structures or drug release behaviours and rapid manufacturing of small batches of drugs. This review summaries the mechanisms of the most commonly used 3D printing technologies, describes their characteristics, advantages, disadvantages,and applications in the pharmaceutical industry, analyses the progress of global commercialization of 3D printed drugs and their problems and challenges, reflects the development trends of the 3Dprinted drug industry, and guides researchers engaged in 3D printed drugs.

Keywords: three-dimensional printing technology; three-dimensional printed drug; drug delivery medicine research status

1. Introduction

In contrast to the traditional manufacturing techniques of “subtractive manufacturing”, 3D printing is an “additive manufacturing” technology, where a model is constructed using computer-aided design software, sliced, and transferred to a printer, and the 3Dproduct is then constructed layer by layer using the principle of layered manufacturing .

With the research and development of 3D printing technology, many new 3D printing technologies have emerged one after another. As each 3D printing technology uses different materials, deposition techniques, layering manufacturing mechanisms, and final product characteristics, the American Society for Testing and Materials classified 3D printing technologies into seven categories according to their technical principles [3,4], namely material extrusion, binder jetting, powder bed fusion, vat photo polymerization, material jetting,directed energy deposition, and sheet lamination.Three-dimensional printing technology is widely used in automotive, construction,aerospace, medical, and many other fields. In the pharmaceutical sector, research into3D printing technology is currently experiencing a global boom . Compared to traditional preparation technologies, 3D printing offers flexibility in the design of complex3D structures within drugs, the adjustment of drug doses and combinations, and rapid manufacturing and prototyping, enabling precise control of drug release to meet a wide range of clinical needs, a high degree of flexibility and creativity to personalize pharmaceuticals, and a significant reduction in preparation .

Background:

The three-dimensional (3D) printing is paradigm shift in the healthcare sector. 3D printing is platform technologies in which complex products are developed with less number of additives. The easy development process gives edge over the conventional methods. Every individual needs specific dose treatment. ‘One size fits all’ is the current traditional approach that can shift to more individual specific in 3D printing. The present review aims to cover different perspectives regarding selection of drug, polymer and technological aspects for 3D printing. With respect to clinical practice, regulatory issue and industrial potential are also discussed in this paper.

Main body

The individualization of medicines with patient centric dosage form will become reality in upcoming future. It provides individual’s need of dose by considering genetic profile, physiology and diseased condition. The tailor made dosages with unique drug loading and release profile of different geometrical shapes and sizes can easily deliver therapeutic dose. The technology can fulfll growing demand of efficiency in the dose accuracy for the patient Oriented sectors like paediatric, geriatric and also easy to comply with cGMP requirements of regulated market. The clinical practice can focus on prescribing each individual’s necessity of dose.

Conclusion: In the year 2015, FDA approved frst 3D printed drug product, which is initiator in the new phase of manufacturing of pharmaceuticals. The tailor made formulations can be made in future for personalized medications. Regulatory approval from agencies can bring the 3DP product into the market.

The Advantages of 3D Printing Technology in Pharmaceuticals.

1. Personalized Medicine for Special Populations

The health and safety of medication for special populations such as the elderly and children has long been an issue of concern . Children are in a period of growth and development and have a particular reactivity and sensitivity to medication; the elderly have a reduced absorption and metabolism capacity, and the coexistence of multiple diseases and combined medication is very common . Whereas current drug dosages are standardized, there are few specialized drugs for special populations, and children’s medication is often administered by manually breaking tablets, which is not only inaccurate but may also damage the particular structure of the preparation and cause adverse reactions .Three-dimensional printing technology is highly flexible and can be used to print targeted medicines by adjusting model parameters such as size, shape, or fill rate . For paediatric patients, 3D printing technology can be used to produce low-dose personalized medicines suitable for children, and can also be used to improve the appearance and taste of the medicines to increase the compliance of paediatric patients for elderly patients who have difficulty swallowing, 3D printing technology can prepare loose and porous preparations, thus, helping them to take medication; for patients who take multiple drugs at the same time, different drugs can be partitioned and combined into a single tablet to avoid errors or missed drugs, which can increase the safety and effectiveness of medication; in addition, specially shaped preparations can be printed or special symbol scan be printed on the surface of the preparation to provide convenience for patients with visual impairment . The advantages of 3D printing technology for personalized drug delivery provide technical support for people to achieve personalized medicine, and some 3D printed drug companies are moving towards the goal of personalized medicine,such as Fabre in the UK, which prepares personalized drugs for children with maple diabetes, and has placed SSE printers in the pharmacy of a Spanish hospital and conducted clinical trials on the subject .

2. Precise Control of Drug Release

As the most widely used solid oral dosage form, tablets account for 70% of all dosage form production . Traditional manufacturing processes enable tablets to be produced at a lower cost, but they have been less creative in preparation development, with long development times and less ability to manufacture personalized preparations on demand.

Compared to conventional tablets, controlled-release preparations allow for precise control of drug release, avoiding side effects and improving efficacy. However, traditional manufacturing processes pose greater challenges in the development and manufactureof controlled-release preparations due to their limitations. Three-dimensional printing technology is highly flexible and is well suited to the development and manufacture of complex preparations through the combination of different drugs used.

3. Materials Used for 3D Printing Technology in Manufacturing Industry .

Like any manufacturing process, 3D printing needs high quality materials that meet consistent specifications to build consistent high-quality devices. To ensure this, procedures, requirements, and agreements of material controls are established between the suppliers, purchasers, and end-users of the material. 3D printing technology is capable to produce fully functional parts in a wide range of materials including ceramic, metallic, polymers and their combinations in form of hybrid, composites or functionally graded materials (FGMs) [8].

3.1. Metals

Metal 3D printing technology gain many attentions in aerospace, automobile, medical application and manufacturing industry because the advantages existing by this process . The materials of metal have the excellent physical properties and this material can be used to complex manufacturer from printing human organs to aerospace parts. The examples of this materials are aluminium alloys cobalt-based alloys [28], nickel-based alloys ,stainless steels , and titanium alloys . Cobalt-based alloy is suitable to use in the 3D printed dental application. This is because, it has high specific stiffness, resilience, high recovery capacity, elongation and heat-treated conditions . Furthermore, 3D printing technology has capability to produce aerospace parts by using nickel base alloys . 3D-printed object produces using nickel base alloys can be used in dangerous environments. This is because, it has high corrosion resistance and the heat temperature can resistant up to 1200 °C . Lastly, 3D printing technology also can print out the object by using titanium alloys. Titanium alloy with have very exclusive properties, such as ductility, good corrosion, oxidation resistance and low density. It is used in high stresses and high operating temperatures and high stresses, for example in aerospace components and biomedical industry .

3.2. Polymers

3D printing technologies are widely used for the production of polymer components from prototypes to functional structures with difficult geometries . By using fused deposition modelling (FDM), it can form a 3D printed through the deposition of successive layers of extruded thermoplastic filament, such as polylactic acid (PLA), acrylonitrile butadiene styrene (ABS), polypropylene (PP) or polyethylene (PE) [33]. Lately, thermoplastics filaments with higher melting temperatures such as PEEK and PMMA can already be used as materials for 3D printing technology . 3D printing polymer materials in liquid state or with low melting point are widely used in 3D printing industry due to their low cost, low weight and processing flexibility . Mostly, the materials of polymers played important role in biomaterials and medical device products often as inert materials.

3.3. Ceramics

Nowadays, 3D printing technology can produce 3D printed object by using ceramics and concrete without large pores or any cracks through optimization of the parameters and setup the good mechanical properties Ceramic is strong, durable and fire resistant. Due to its fluid state before setting, ceramics can be applied in practically any geometry and shape and very suitable on the creation of future construction and building [37]. According to [38], they said ceramics materials is useful in the dental and aerospace application. The examples of this materials are alumina , bioactive glasses and zirconia . Alumina powder for instance has the potential to be processes by 3D Printing technology. Alumina is an excellent ceramic oxide with a very wide range of applications, including catalyst, adsorbents, microelectronics, chemicals, aerospace industry and another high-technology industry.

Alumina has great curing complexity [38]. By using 3D printing technology, complex-shaped alumina parts with has a high density after sintering and also has high green density can be printed . Furthermore, in successive experiment, Stereolithographic (SLA) machine was used to process glass-ceramic and bioactive glass into dance part. It significantly improving the bending strength of this materials. The increasing of the mechanical strength will open up the potential for apply bioactive glass in relevant clinical structure such as scaffolds and bone. By using Stereolithographic Ceramic Manufacturing (SLCM), it is probable to produce solid bulk ceramics with high densities, very homogeneous microstructure, high compression strength and bending [40]. Meanwhile, zirconia are the main construction materials in nuclear power sectors, using for element tubing. Hafnium-free zirconium is very suitable for this application because it has low susceptibility to radiation and also has low thermal neutron absorption .

3.4. Composites

Composite materials with the exceptional versatility, low weight, and tailorable properties have been revolutionizing high-performance industries. The examples of composite materials are carbon fibres reinforced polymer composites and glass fibber’s reinforced polymer composite . Carbon fibre reinforced polymers composite structures are widely used in aerospace industry because of their high specific stiffness, strength, good corrosion resistance and good fatigue performance . At the same time, glass fibres reinforced polymer composites are widely used for various applications in 3D printing application and has great potential applications due to the cost effectiveness and high-performance . Fiberglass have a high thermal conductivity and relatively low coefficient of thermal expansion. Furthermore, fiberglass cannot burn, and it not affected by curing temperatures used in manufacturing processes, therefore, it is very suitable for use in the 3D printing applicant .

3.5. Smart materials

Smart materials are defined as this material have the potential to alter the geometry and shape of object, influence by external condition such as heat and water . The example of 3D printed object produces by using smart materials are self-evolving structure and soft robotics system. Smart materials also can be classified as 4D printing materials. The examples of group smart materials are shape memory alloys and shape memory polymers . Some shape-memory alloys like nickel-titanium can be used in biomedical implants to microelectromechanical devices application . In the production of 3D printed products by using nickel-titanium, transformation temperatures, reproducibility of microstructure and density is the important issue. Meanwhile, Shape memory polymer (SMP) is a kind of functional material that responds to a stimulus like light, electricity heat, some types of chemical and so on . By using 3D printing technology, the complicated shape of shape memory polymer could be easily and conveniently to produce. The quality evaluation of this material is performed based on

4. The Applications of 3D Printing in Manufacturing Technology

4.1. Aerospace industry

3D printing technology provides unparalleled freedom design in component and production. In aerospace industry, 3D printing technology has potential to make lightweight parts, improved and complex geometries, which can reduce energy requirement and resources [52]. At the same time, by using 3D printing technology, it can lead to fuel savings because it can reduce the material used to produce aerospace’s parts. Furthermore, 3D printing technology has been widely applied to produce the spare parts of some aerospace components such as engines. The engine’s part is easily damaged, which require regular replacement. Therefore, 3D printing technology is a good solution to the procurement of such spare parts [53]. In aerospace industry, nickel-based alloys is more preferred due to the tensile properties, oxidation/corrosion resistance and damage tolerance .

.Automotive industry

Nowadays, 3D printing technology have rapidly changed our industry to design, develop and manufacture new things. In the automotive industry, 3D Printing technique have made phenomena to bring new shines, allowing for lighter and more complex structures in the fast time. For instance, Local Motor had printed the first 3D-printed electric car in 2014. Not only cars, Local Motors also extended the wide range application of 3D printing technology by manufacturer a 3D-printed bus called OLLI. OLLI is a driverless, electric, recyclable and extremely smart 3D printed bus. Furthermore, Ford is the leader in the use of 3D printing technology also apply 3D printing technology to produce prototype and engine parts [55]. In addition, BMW uses 3D printing technology to produce hand-tools for automotive testing and assembly. Meanwhile, in 2017, AUDI was collaborated with SLM Solution Group AG to produce spare parts and prototypes . Consequently, by using 3D printing technology in automotive industry enable company to try various alternatives and emphasize right in the improvement stages, prompting ideal and effective automotive design. At the same time, 3D printing technology can reduce the wastage and consumption of the materials. Moreover, 3D printing technology can reduce costs and time, therefore, it allows to test new designs in a very fast time.

10. Conclusions

This paper reviews the relevant literature on several 3D-printing technologies commonly used in the pharmaceutical industry, elucidating the principles and characteristics of each technology, the dosage forms suitable for each technology, and the development trend; and reporting on the commercialization direction of representative companies or institutions of 3D-printed drugs, their development history, and the breakthrough results achieved, driving the innovation of drug development models. As an emerging technology,the registration and filing path for 3D-printed preparations is unique, while intellectual property rights, drug regulations, and other policies or regulations are still breaking new ground. Overall, this review aims at reflecting the current development status, industrial characteristics, and overall development trends of 3D-printed drugs. We hope that this review can provide a meaningful reference for those who are engaged in related research. It is believed that with continuous efforts, the future of the 3D-printed drug industry is promising and will certainly promote drug preparation technology that is intelligent.