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Review Article

Innovation & Challenges of 3D Printing in Pharmaceutics

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ABSTRACT

In the past two decades, 3D printing, which is one of the most rapidly evolving fabrication technologies, has unleashed a flood of innovation. The use of the technology for 3D printing has provided numerous advantages to the pharmaceutical business, especially on a micro-scale. Micro-scale printing of devices and materials has the potential to provide sophisticated techniques for controlled & sustained release, simple delivery, and accurate targeting, which is synthetic analogs for drug development, and future uses in personalized medicine. 3D printing, one of the most powerful and inventive tools accessible today, is employed in the engineering of tissues, diseases modelling, and the precise manufacturing of personalised dosage forms. The application of 3D printing facilitates the development as well as manufacturing of digital medicinal goods. In recent years, there has been substantial progress in the fields of the initial stages preclinical printing using 3D printers and large-scale pharmaceutical manufacturing. Since there are still challenges regarding the issues of scaling up and regulatory authorization, we believe that these kinds of innovations provide intriguing prospects for modern healthcare.

INTRODUCTION

The concept of three-dimensional printing has piqued the curiosity of many people and revolutionized several enterprises. Pharmaceutics is one area where 3D printing has demonstrated enormous promise. Layer by layer, intricate three-dimensional structures may be created using 3D printing technology, providing the pharmaceutical industry with new prospects for personalised therapy, accurate drug release control, and quick production integration (S. Wang et al., 2023). Here's where 3D printing technology comes into play, enabling the creation of personalized dosage forms suited to each patient's specific needs. On the other hand, customized dosage forms with exact medication dosages and release profiles catered to individual patient needs can be created thanks to 3D printing. Both patient compliance and treatment efficacy may be improved by this individualized strategy (Vaz & Kumar, 2021).

The underlying concept of three-dimensional printing is the sequential application of materials

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to turn a computer graphic into a physical object (A. A. Mohammed, Algahtani, Ahmad, Ahmad, & Kotta, 2021). This technique makes it possible to create drug-loaded structures in the pharmaceutical industry with intricate geometries, regulated release profiles, and customised drug dosages, sustained-release formulations, pulsatile drug delivery systems, and other complex release profiles that are challenging to accomplish with traditional manufacturing techniques. This creates opportunities for creating novel drugs and medication delivery methods (Beer et al., 2023). Time-consuming and expensive setup procedures are a common feature of traditional production processes. On the other hand, flexible manufacturing and on-demand production are made possible by 3D printing technology, which does away with the necessity for large-scale manufacturing and shortens lead times (Cui et al., 2021; Mohapatra, Kar, Biswal, & Bindhani, 2022). One major problem in the creation of pharmacological formulations is the poor solubility of medicines. By creating dosage forms with improved drug solubility and dissolution rates, 3D printing provides a way around this problem (Parulski et al., 2022). Pharmaceutical firms can use 3D printing to streamline their supply chains and cut expenses related to distribution and inventory management. This could improve accessibility to medications, lower drug shortages, and increase cost-effectiveness—especially in less developed places or during emergencies (Hossain, Zhumabekova, Paul, & Kim, 2020). The method enables the development of customized implants that are suited to the anatomical needs of specific patients, therefore enhancing surgical outcomes and patient satisfaction. This personalised approach has the potential to have a big impact on sectors such as orthopaedics, dentistry, and reconstructive surgery (Zoabi et al., 2022). By utilising 3D printing technologies, the pharmaceutical business may move towards more customer-focused approaches, improve therapeutic outcomes, and resolve unmet medical needs (Tracy, Wu, Liu, Cheng, & Li, 2022).

2.2 3D Printing Technologies:

Various 3D printing technologies have been used in the field of pharmaceutics to build customised drug delivery systems and personalised therapeutics. Each technology has its own set of benefits and capabilities. Here is an overview of some of the most often utilised 3D printing methods in pharmaceutics:

2.2.1 Selective Laser Sintering (SLS):

To create the desired object, SLS employs a powerful laser that can precisely fuse powdered materials. SLS technique has been utilised in pharmaceutics to generate drug-loaded structures by selectively sintering polymer powders containing the medication. It provides the ability to create complicated shapes with regulated drug release qualities (Awad, Fina, Goyanes, Gaisford, & Basit, 2020).

2.2.2 Digital Light Processing (DLP):

DLP is comparable to stereolithography, in that it uses a digital light projector rather than the laser to specifically cure a photosensitive resin. This technology allows for high-speed printing and has been employed in the pharmaceutical industry to manufacture drug-loaded structures with controlled release features. (Zhang, Hu, Wang, Tao, & Gou, 2020).

2.2.3 Inkjet Printing:

Droplet deposition is used in inkjet printing technology to generate accurate patterns by jetting liquid droplets onto a substrate. In the pharmaceutical industry, inkjet printing has been used to create drug-loaded films, coatings, or microparticles. (Azizi Machekposhti, Mohaved, & Narayan, 2019).

2.2.4 Electron Beam Melting (EBM)

Figure 2.1 depicts Electron Beam Melting (EBM), a 3D printing process that selectively melts metal

particles and forms objects with three dimensions using an electron beam as a heat source. EBM offers unique benefits in terms of fabricating complicated geometries, high-strength metal components, and outstanding material characteristics. EBM has the potential to enhance the development and production of drug delivery systems and medical implants (Munir, Biesiekierski, Wen, & Li, 2020; Sonkamble & Phafat, 2023). EBM allows for the development of complex structures with complicated internal elements and unique shapes. Complex geometries provide an opportunity to improve medication delivery efficiency, patient compliance, and therapeutic effects. EBM specialises in manufacturing metal components with high strength and outstanding mechanical qualities. This is especially useful in the production of implanted devices and medical tools that require strong and long-lasting materials. EBM encourages the application of metal powders such as titanium alloys, cobalt-chromium alloys, and stainless steel, providing material versatility. This adaptability enables the creation of drug delivery systems or implants with particular material features such as resistance to corrosion, biocompatibility, or magnetic capabilities (Mobarak et al., 2023). The capacity of EBM to generate patient-specific implants opens up new avenues in customised medicine. EBM can create personalised implants that precisely match the patient's unique anatomy by utilising patient-specific anatomical data gathered through medical imaging procedures. EBM is well-known for its rapid production and scalability. With the ability to print many components or devices at the same a period of time EBM may speed up the manufacturing process, cutting lead times, and increase overall efficiency in pharmaceutical manufacture (Tamayo, Riascos, Vargas, & Baena, 2021).

Fig. 2.1: Schematic diagram of a standard Electron Bean Melting Technology (Nouri & Sola, 2020)

Challenges:

EBM needs specialise materials with appropriate melting and sintering properties, hence limiting the variety of materials available for pharmaceutical applications. Since EBM machines are expensive, they are out of reach for small-scale pharmaceutical manufacture. Controlling factors such as beam power, scanning speed, and powder layer thickness precisely is difficult and requires optimisation for accurate printing (Mostafaei et al., 2021).

2.2.5 Fused Deposition Modelling (FDM):

Extrusion-based 3D printing, also referred to as fused deposition modelling (FDM), is one of the most widely utilised methods in pharmaceutics. It involves the layer-by-layer application of molten filaments through a nozzle to build the necessary structure. This approach allows for the development of solid drug dosage forms with precise drug distribution and releasing patterns. The FDM technology uses a thermoplastic filament that is melt and extruded through the nozzle, then depositing the substance layer by layer to build the things shown in Figure 2.2. (Henry et al., 2021; Konta, García-Piña, & Serrano, 2017). Here are some of FDM's significant features and prospective uses in the pharmaceutical. FDM enables the use of diverse thermoplastic materials, as well as personalized pharmaceuticals. FDM technology is capable of producing complicated and complex geometries with internal channels or cavities, enabling controlled drug release mechanisms and enhanced treatment effects. FDM's rapid and low-cost prototyping capabilities enable rapid iteration and optimization of drug delivery systems (Cui et al., 2021). FDM can be used to create amorphous solid dispersions, which improve the solubility and bioavailability of medications that are poorly soluble. Through the use of drug-polymer blends

or complexation agents. FDM 3D printing technology has shown promise in pharmaceutical applications: Manufacturing of customised oral dosage forms, such as pills and capsules (Cui et al., 2021; Quodbach et al., 2021).

Challenges:

The limits of FDM in producing high resolution and complex features can have an impact on the quality and precision of printed pharmaceutical dosage forms. Pharmaceutical material compatibility with FDM printers, as well as the availability of acceptable filament material for drug delivery applications, might be a hurdle. To improve mechanical qualities, FDM-printed products frequently require post-processing operations such as smoothing or coating, which can complicate the manufacturing process (Araújo, Sa-Barreto, Gratieri, Gelfuso, & Cunha-Filho, 2019; Quodbach et al., 2021).

Fig. 2.2: Schematic diagram of Fused Deposition Modelling (FDM) (Konta et al., 2017)

2.2.6 Selective Sintering/Electron Beam Sintering (SSE/EBS):

Selective Sintering, commonly known as Electron Beam Sintering (EBS), is a 3D printing process that uses a high-energy electron beam to fuse powdered materials to form three-dimensional objects. SSE/EBS has various advantages, including the ability to produce complicated geometries. The material qualities of printed objects can be precisely controlled with SSE/EBS. It is feasible to acquire desired features such as controlled porosity, mechanical strength, and drug release kinetics by altering sintering parameters such as energy input and powder composition (Gokuldoss, Kolla, & Eckert, 2017). SSE/EBS permits the use of a diverse range of materials, including biocompatible polymers, ceramics, and composites (Skowyra, Pietrzak, & Alhnan, 2015). SSE/EBS allows for the creation of sophisticated drug delivery systems, such as implantable drug reservoirs or biodegradable scaffolds for tissue regeneration (Ashammakhi et al., 2022).

Challenges: Controlling the particle size distribution and achieving homogeneous powder bed density is critical for precise sintering and predictable medication release patterns. The elimination of unsintered powder particles from printed products without compromising their integrity is a difficult task that necessitates precise handling and cleaning processes. SSE/EBS may be incompatible with some medicinal ingredients, limiting their application in certain medication compositions (Tabriz, Kuofie, Scoble, Boulton, & Douroumis, 2023).

2.2.7 Digital Light Processing (DLP)

Digital Light Processing (DLP) is a 3D printing technique that uses a digital light projector to selectively cure a liquid photopolymer resins layer by layer, resulting in three-dimensional objects like that which is seen in Figure 2.3 (Chaudhary et al., 2023; Kadry, Wadnap, Xu, & Ahsan, 2019).

In the sector of pharmaceuticals, DLP has various advantages, such as high resolution, fast printing speed, and the capacity to build complicated structures with fine features. DLP technology allows for high-resolution printing, enabling for the creation of complicated geometries and fine details. This permits the creation of precise drug delivery devices with specific dimensions and drug release properties, such as microneedles, implants, or personalised dose forms (Zhang et al., 2020). DLP printers can print at high speeds because they can cure a complete layer of resin at the same time using digital light projection. This makes DLP technology ideal for large-scale pharmaceutical product manufacture, cutting production time and enhancing efficiency. DLP allows for the construction of complex structures. In personalised medicine, DLP can aid in the manufacturing of drug delivery systems including several active components, such as controlled release formulations or drug-loaded

microparticles. However, current DLP technology research and advances continue to broaden its potential and contribute to the creation of novel drug delivery systems (Kadry et al., 2019).

Challenges:

DLP is based on the photopolymerization process, which necessitates the use of appropriate photo initiators for drug-loaded resins. It can be difficult to find photoinitiators that are both drug stable and have sufficient cure characteristics. The effects of light scattering can limit the resolution and precision of DLP-printed structures, influencing ultimate drug release qualities and dosing accuracy (Al Rashid, Ahmed, Khalid, & Koc, 2021).

Fig. 2.3: Schematic Diagram of Digital Light Processing (DLP) (Kadry et al., 2019)

2.2.8 Selective Laser Sintering (SLS)

Figure 2.4 demonstrates Selective Laser Sintering (SLS), a 3D printing process that uses a high-power laser to carefully fuse powdered materials to form three-dimensional structures. In the area of pharmaceutics, SLS has various advantages, including the capacity to build complicated geometries, use a diverse variety of materials, and establish exact control over drug release. (Balasankar et al., 2023). SLS is able to create pharmaceutical drug delivery systems with specified material properties using a wide range of powdered components such as polymers, ceramics, and metals. SLS technology provides scalability and manufacturing efficiency, making it appropriate for large-scale pharmaceutical product production. SLS enables the inclusion of many active compounds in a single dosage form. The fast prototyping capabilities of SLS allow for rapid iteration and optimisation of drug delivery systems. Nonetheless, current research and advances in SLS technology have the potential to alter medication delivery systems and improve patient care (Balasankar et al., 2023).

Challenges:

Because SLS requires powder materials with adequate melting and sintering qualities, the range of pharmaceutical-grade ingredients is limited. To maintain consistent and regulated release of drug profiles, optimal energy absorption and temperature distribution throughout the sintering process is crucial. It is difficult to remove extra powder from printed products without affecting their structural integrity, which necessitates cautious handling and cleaning processes (Balasankar et al., 2023; W. Han, Kong, & Xu, 2022).

Fig. 2.4: Schematic diagram of a Selective Laser Sintering (Reiff, Wulle, Riedel, Epple, & Onuseit, 2014)

When it comes to pharmaceutics, each 3D printing technology has its own set of benefits and drawbacks. To overcome these obstacles, a mix of technology improvements, materials innovations, and process optimization is required. To address these obstacles and realise the entire potential of 3D printing in the pharmaceutical industry, academics, engineers, and regulatory organizations must work together (Jamróz, Szafraniec, Kurek, & Jachowicz, 2018).

2.2.9 Stereolithography (SLA)

Stereolithography (SLA) is a 3-D printing process that creates three-dimensional objects layer by layer using photopolymerization. It provides distinct advantages in the sector of pharmaceuticals, allowing precise control over the manufacturing process and the manufacture of complicated structures with great resolution. SLA technology enables the production of complicated and extremely detailed structures with high resolution and surface smoothness. SLA technology is particularly adept for generating complicated shapes and intricate interior systems (Lakkala, Munnangi, Bandari, & Repka, 2023; Suresh, Reddy, & Gurram, 2019). SLA systems that have several resin tanks enable the printing of things with diverse materials or characteristics at

the same time. This feature enables the development of drug delivery systems with multiple compartments, combination treatments, or sequential release patterns, broadening the scope of personalised medicine and improving therapeutic efficacy. SLA-based bioprinting has demonstrated potential in the creation of tissue-engineered structures and drug-screening platforms. SLA technology has a high production efficiency, making it suited for both small-scale and large-scale pharmaceutical product manufacture. While SLA technology has several advantages, issues such as material biocompatibility, post-processing processes, and regulatory considerations must be solved before it can be successfully implemented in the pharmaceutical business (Mancilla-De-la-Cruz, Rodriguez-Salvador, An, & Chua, 2022).

Fig. 2.5: Schematic diagram of a Stereolithography (SLA) (Suresh et al., 2019)

2.2.10 Electrohydrodynamic (EHD) Printing

Electrohydrodynamic (EHD) printing, also known as the electrospray printing or electrospinning, is a 3D printing process that uses electrical forces to produce micro and nanoscale structures. EHD printing enables the creation of micro and nanoscale structures with high precision and resolution. EHD printing is versatile in terms of material compatibility. EHD printing works with a variety of materials, including polymers, biopolymers, and composites. Drug delivery systems with tuneable release profiles, such as sustained release, controlled release, or pulsatile release, can be created using EHD printing. Scaffolds for tissue engineering purposes can be created via EHD printing (Cong et al., 2022). EHD printing enables rapid prototyping, enabling for the rapid manufacturing of a smaller scale prototypes for testing and assessment. EHD printing is a developing technology that could have uses in personalised medicine, regenerative medicine, and microencapsulation. Ongoing EHD printing research and development has the potential to broaden its uses in the pharmaceutical business. While EHD printing offers a lot of potential, issues like process scalability, materials stability, and regulations must be addressed before it can be widely used in pharmaceutical manufacturing (Y. Han & Dong, 2018).

Fig. 2.6: Tip assisted Electrohydrodynamic (EHD) (Zou, Yu, Zhou, & Liu, 2019)

When applied to pharmaceutics, each 3D printing technique has its own set of advantages as well as disadvantages, which must be overcome through a combination of technological advancements, material innovations, and process optimisation. Collaborative efforts between researchers, engineers, and regulatory bodies are required to address these drawbacks and unlock the full potential of 3D printing in the pharmaceutical industry (Jamróz et al., 2018; Vaz & Kumar, 2021).

2.3 Advantages and Opportunities of 3D Printing in Pharmaceutical Formulation:

2.3.1 Oral dosage forms

The benefits and opportunities provided by 3D printing in oral dosage forms have enormous potential for personalized medicine, enhanced drug delivery, and patient-centered healthcare. To assure the safety and efficacy of 3D printed pharmaceutical products, however, regulatory considerations, standardization of printing techniques, and quality control must be addressed. As stated in Table 2.1, various 3D Printed oral formulations have been authorized and are currently being researched. (S. Wang et al., 2023).

Table 2.1: List of 3D Printed Oral Dosage Forms

2.3.2 Semisolid dosage forms

3D printing technology provides multiple advantages and potential for the pharmaceutical industry's research and fabrication of semisolid dosage forms. Creams, ointments, gels, pastes, and lotions are examples of semisolid dosage forms which are frequently employed for topical

treatments. Semisolid dosage forms with complicated and customised structures can be created via 3D printing (Jamróz et al., 2018). This involves being able create complicated patterns, surface textures, or multi-layered designs that can improve medication release, skin permeability, and overall therapeutic efficacy. 3D printing in semisolid dosage forms allows for precise control over drug release characteristics. Semisolid dose forms can be developed using 3D printing to target specific locations or depths of the skin. This includes the capacity to develop formulations with desirable sensory characteristics, such as pleasing textures, appealing colors, or pleasant smells, which can promote adherence by patients to the treatment regimen. In the fabrication of semisolid dosage forms, 3D printing technology has the ability to minimise material waste and optimise formulation composition. This can lead to greater long-term cost efficiency by lowering material costs and optimising production processes (Auriemma et al., 2022). The benefits and opportunities provided by the use of 3D printing in semi-solid dosage forms have important implications for personalised medicine, optimised delivery of drugs, and improved patient outcomes. However, problems relating to regulatory considerations, quality control, and printing process standardisation must be addressed to assure the safety, efficacy, and reproducibility of 3D manufactured semisolid formulations (Vaz & Kumar, 2021). Many 3D Printed Semi solid formulations are being researched, as indicated in Table 2.2.

Table 2.2: List of 3D Printed Topical Dosage Forms

2.3.3 Implants

The use of 3D printing technology has transformed the world of implant pharmaceutical formulations, providing several benefits and potential. The benefits and opportunities provided by the use of 3D printing in implant formulations have the potential to revolutionize personalised medicine, enhance patient outcomes, and accelerate the development of innovative implanted drug delivery systems. To assure the safety and efficacy of 3D-printed implants, however, difficulties with regulatory authorization, control of quality, long-term stability, and scalability must be solved (Jamróz et al., 2018). Many 3D Printed Implants are being developed using 3D Printing Technology, as illustrated in Table 2.3.

Table 2.3: List of 3D Printed Implants

2.3.4 Microneedles

Microneedles are needle-like structures that vary in size from just a few hundred micrometres to several millimetres. They are utilised to deliver medications or retrieve bodily fluids. Microneedles can be customised via 3D printing to meet unique drug delivery needs. The versatility of 3D printing allows for the creation of microneedles with specific diameters, geometries, and drug-loading capacity, allowing for customised drug delivery schemes (Aldawood, Andar, & Desai, 2021). Three-dimensional printing in microneedle-based pharmaceutical formulations offers a chance to alter drug delivery by enabling patient-friendly, customised, and efficient therapeutic interventions. To fully realise the potential of 3D printed microneedles in pharmaceutical applications, more research is needed to address problems such as expansion, regulatory considerations, and long-term biocompatibility (Vaz & Kumar, 2021). Table 2.4 lists a few 3D-printed microneedles.

Table 2.4: List of 3D Printed Microneedle

2.4 Challenges of 3D Printing in Formulation Development:

2.4.1 Excipients selection

Developing formulations for three-dimensional printing in pharmaceutics involves various problems that must be overcome for successful adoption. One of the most difficult challenges is selecting appropriate excipients to provide the

necessary qualities of a printed dosage form. Excipients are essential in 3D printing formulations because they contribute to printability, mechanical integrity, medication release, and product stability (Basit & Trenfield, 2022). Excipients must be suitable for the 3D printing method being used. Material qualities like viscosity, rheological behaviour, and melting temperature may be required by different printing processes. During the printing process, the excipients need to be able to achieve the appropriate flow and printability properties. Excipients should have appropriate flow characteristics to allow for successful material extrusion or deposition throughout the 3D printing process. To maintain the stability, potency, and drug release characteristics of the APIs, excipients must be compatible with them. Excipients should be chosen according to their compatible with the printing material along with their biocompatibility. Excipients should allow for precise control of the medication releasing pattern from the printable dosage form. Excipients with varied release mechanisms, such as diffusion, erosion, or osmosis, may exist. The use of suitable excipients can help to achieve the required release kinetics and therapeutic aims (Melnyk & Oyewumi, 2021). Excipients should be chosen in accordance with regulatory criteria and recommendations. It is critical to assess the excipients' regulatory status, safety, and permitted use in pharmaceutical applications. Excipient cost and availability should be taken into account, particularly when considering production on a large scale. Excipients that are easily accessible and cheap can help to improve the economic feasibility and scalability of 3D-printed formulations (Van der Merwe, Steenekamp, Steyn, & Hamman, 2020).Addressing these issues in excipient selection for 3D printing formulations is critical for successful formulation development as well as assuring the safety, efficacy, and quality of the printed dosage forms.

2.4.2 Printing software and instruments

One of the issues is ensuring that the printing software is compatible with the particular technology for 3D printing being utilized. Formats of files and software interfaces may differ depending on the 3D printing technology. It is critical that the printing software utilised supports the specific printing method and has the capability of producing accurate and exact printing instructions (Jandyal, Chaturvedi, Wazir, Raina, & Haq, 2022). It can be difficult to create appropriate 3D designs and models for pharmaceutical formulations. The software utilised should be capable of creating or modifying complicated geometries that meet the precise specifications for the desired dosage form. To accomplish the necessary drug delivery properties, it should give tools for creating drug release patterns, porous architectures, and customised forms (Ahmad, Garg, Mustafa, Mohammed, & Ahmad, 2023). Printing software should assist in selecting and incorporation of appropriate printing materials. It should provide alternates for material libraries or allow for customization of material attributes to satisfy the formulation's requirements. To obtain the appropriate mechanical qualities and drug release patterns, the software should allow for the optimisation of printing parameters like as thickness of layers, infill density, and printing speed (A. A. Mohammed et al., 2021). Validation of the printer is critical to ensuring accurate and repeatable printing results. Calibration of the printing device may provide difficulties, such as nozzles or printing alignment, regulating the temperature, and deposition precision. To produce consistent printing results, the printing instrument must be calibrated and validated. It can be difficult to optimise printing parameters for particular formulas. To achieve the necessary resolution, mechanical qualities, and drug release

characteristics, printer speed, temperatures, thickness of layers, and infill density must be optimised. Iterative experimentation and optimisation are frequently required to determine the best printing parameters (Brion & Pattinson, 2022). Keeping printers in good operating order is critical for consistent and dependable printed outcomes. Machine maintenance, calibration, and part replacement may provide difficulties. Adequate printed instrument knowledge and instruction are essential to ensure proper operation and minimise downtime. It can be difficult to develop quality control methods and standardise the printing process. Maintaining batch-to-batch uniformity, repeatability, and regulatory compliance necessitates stringent quality control techniques. Establishing approval criteria, carrying out during production checks as well as and validating the printing process are all possible challenges (Jin et al., 2021; Tofail et al., 2018).

Addressing these printing software and instrument problems is critical for the effective development and application of 3D printing technologies in pharmaceutics. Collaboration among formulations researchers, engineers, and software developers can assist in overcoming these obstacles and optimizing the printing procedure for pharmaceutical applications.

2.4.3 Mechanical properties of printed dosage forms

The drug formulation development procedure for three-dimensional printing in pharmaceutics involves several obstacles, including mechanical qualities of printed dosage forms. It is critical to achieve the appropriate mechanical characteristics in order to maintain the integrity of the structure, handling, and function of the printed dosage forms. The mechanical qualities of printed dosage forms are greatly influenced by the printing substance used. It is critical to choose materials with appropriate mechanical properties such as strength, flexibility, and elasticity. Finding materials with the appropriate qualities that are additionally suitable for the printing process, on the other hand, can be difficult (Jamróz et al., 2018; Tracy et al., 2022). Achieving uniform distribution of materials and homogeneity across the printed structure is critical for consistent mechanical characteristics. Achieving a homogeneous material blend can be difficult, especially when adding active pharmaceutical agents (APIs) or excipients with varying physical qualities. Inadequate mixing can cause differences in mechanical characteristics throughout a printed dosage form (Tan, Maniruzzaman, & Nokhodchi, 2018; Tracy et al., 2022). The mechanical properties of printed dosage forms can be modified by printing parameters such as the thickness of the layer, infill density, printer speed, and nozzle temperature. Optimising these parameters to attain the desired mechanical properties necessitates iterative experimentation and characterization. Post-processing procedures such as curing, annealing, or cross-linking can be used to improve the mechanical qualities of printed dosage forms. There may be challenges to establishing adequate post-processing procedures that successfully enhance the stability, strength, and durability of the printed structures while maintaining drug integrity. The structural integrity of printed dosage forms is critical for their performance and functioning. During the printing process, there may be difficulties in preventing defects like as warping, cracking, or delamination. To preserve structural integrity, factors such as printed orientation, the structure of support, and printing parameters must be properly optimized (Yankin et al., 2023). Maintaining constant mechanical qualities between batches can be difficult when expanding in the use of 3D printing for large-scale production. Mechanical qualities of printed dosage forms can be affected by changes in printed conditions, equipment, or materials. To achieve batch-to-batch uniformity, stringent quality

control techniques and process validation are required. Collaboration among formulation researchers, materials scientists, and 3D printing specialists can assist in overcoming these obstacles and optimising the printing process to produce the required mechanical characteristics of the dosage forms (Karalia, Siamidi, Karalis, & Vlachou, 2021; Tracy et al., 2022).

2.5 Future Aspects or Perspective: 4D Printing

4D printing is a new technology that is gaining traction in a wide range of industries, including pharmaceutics. Unlike typical 3D printing, which produces static items, 4D printing involves the creation of structures that can alter shape, functionality, or attributes dynamically over time by outside factors such as light, heat, moisture, or pH (Karalia et al., 2021; Shinde, Mane, Vardikar, Dhumal, & Rajput, 2023).The design and manufacture of stimuli-responsive medication delivery systems represents one of the potential applications of four-dimensional printing in pharmaceutics. It is now possible to construct dosage forms that may release medications in controlled quantities based on particular stimuli or environmental conditions by adding smart materials or polymers into 3D-printed structures. 4D-printed implants or capsules, for example, can be designed to respond to physiological changes in the body, releasing medications at the desired spot and time for personalized therapy. The creation of dynamic drug-eluting devices is another intriguing use for 4D printing. These devices can be programmed to change form or release rate in response to external stimuli, resulting in personalised drug release profiles based on the needs of the patient. By providing optimal drug distribution, this allows for personalised therapy and enhanced patient compliance (Gazzaniga et al., 2023; Haleem, Javaid, Singh, & Suman, 2021). Furthermore, 4D printing can be used to create functionalized medication delivery systems with active components embedded in the printed structures. Sensors, actuators, or microfluidic channels, for example, can be placed within 3D-printed devices to track drug release kinetics, modify drug dosage, or provide on-demand drug administration. The introduction of active components into 4D-printed systems improves therapeutic efficacy and allows for precise control over medication release (Vatanparast, Boschetto, Bottini, & Gaudenzi, 2023).

It is crucial to emphasise, however, that widespread use of 4D printing in pharmaceutics confronts significant hurdles. These include the creation of appropriate materials with the needed qualities, the optimisation of printing parameters for complicated designs, and the requirement for durable and dependable triggering mechanisms. Finally, by enabling the development of dynamic, sensitive, and functional drug delivery systems, 4D printing holds significant potential for the future of pharmaceutics (Ramezani & Mohd Ripin, 2023; Vatanparast et al., 2023)

CONCLUSION

In conclusion, the use of 3D printing has transformed the world of pharmaceutics by enabling personalised treatment, precise drug release control, and innovative drug delivery systems. While there are still challenges to be solved, the possibilities and developments provided by 3D printing hold enormous potential to enhance the treatment of patients, improving the effectiveness of therapies, and developing the next generation of pharmaceutical manufacturing. The incorporation of 3D printing technology into conventional pharmaceutical practises is unavoidable as development continues to solve these difficulties. The path from research to application in three-dimensional printing for pharmaceuticals remains an exciting and dynamic field with far-reaching consequences for healthcare's future. Technological, material, and regulatory framework advancements will keep on to stimulate innovation in this industry. With its

dynamic and responsive characteristics, 4D printing integration opens up new possibilities for personalised medicine delivery systems and functionalized devices. However, additional research, cooperation between industries and academia, and guidelines from regulators are required to fully realise the potential of 3D printing.

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FIGURE LEGEND

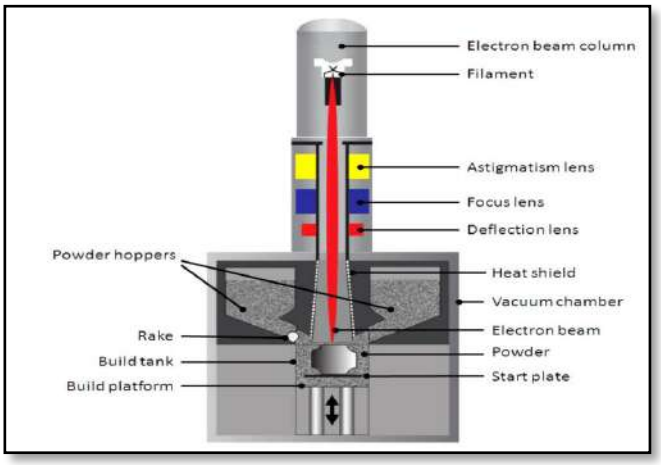

Fig. 2.1: Schematic diagram of a standard Electron Bean Melting Technology (Nouri & Sola, 2020)

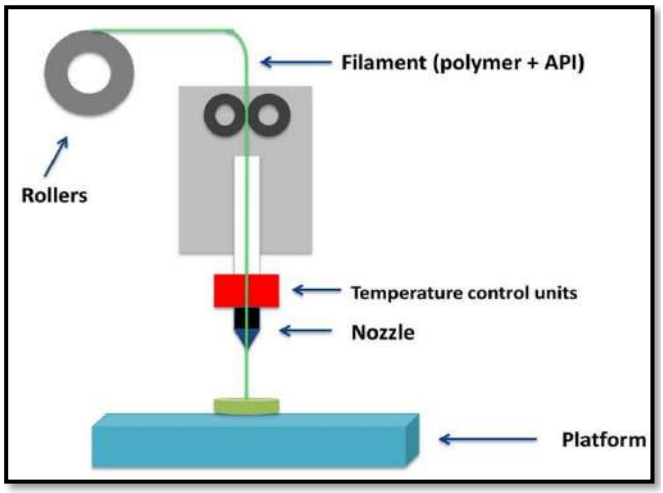

Fig. 2.2: Schematic diagram of Fused Deposition Modelling (FDM) (Konta et al., 2017)

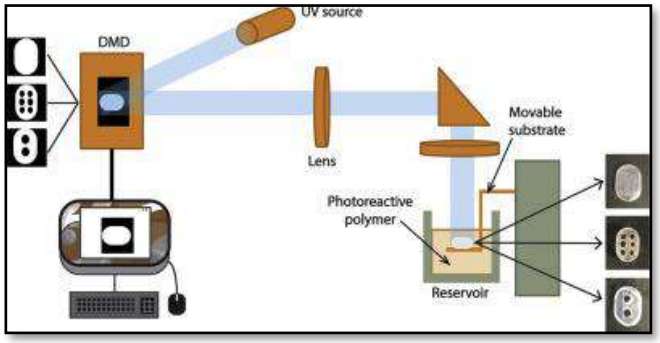

Fig. 2.3: Schematic Diagram of Digital Light Processing (DLP) (Kadry et al., 2019)

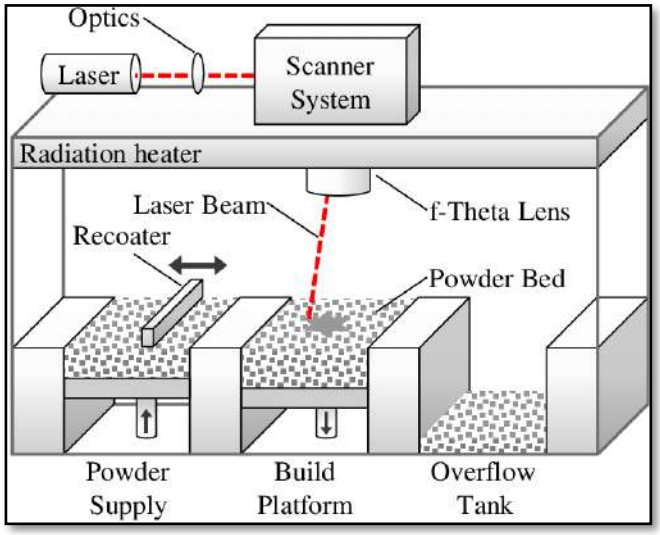

Fig. 2.4: Schematic diagram of a Selective Laser Sintering (Reiff et al., 2014)

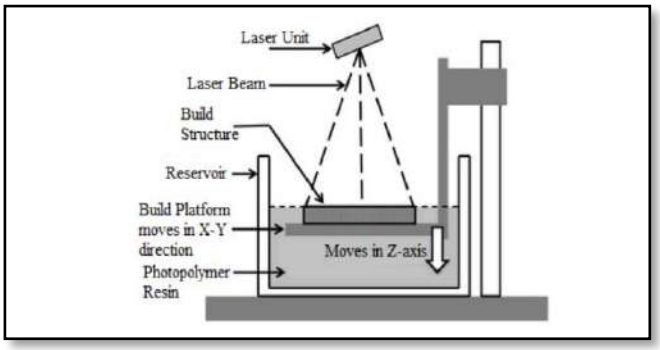

Fig. 2.5: Schematic diagram of a Stereolithography (SLA) (Suresh et al., 2019)

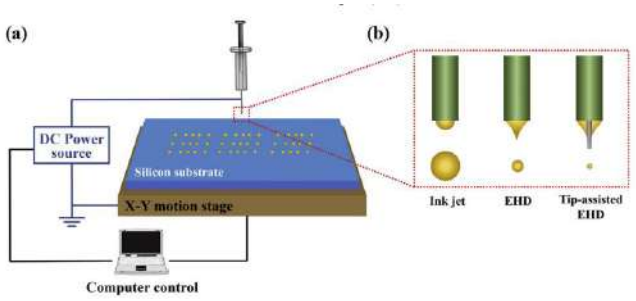

Fig. 2.6: (a) Schematic diagram of Tip assisted Electrohydrodynamic apparatus (EHD) (b) Figure shows comparison between ink-jet printing, electrohydrodynamic (EHD) printing, tip-assisted electrohydrodynamic (EHD) printing (Zou et al., 2019)

TABLE LEGENDS

Table 2.1: List of 3D Printed Oral Dosage Forms

Brand Name	Drug Name	Type of Formulation	Indication	Developer/ Manufacturer	Status	Reference
Spritam	Levetiracetam	Tablet	Epilepsy	Aprecia Pharmaceuticals	Approved in 2015	(Pharmaceuticals, 2015)
-	Furosemide and Sidenafil	Tablet	Erectile Dysfunction	-	Under Research	(Lafeber et al., 2021)
-	Olanzepine	Orodispersible Polymer Film	atypical antipsychotic,	-	Under Research	(Cho, Baek, Lee, & Jin, 2020)
-	Prednisolone	Tablet	Inflammation, Allergies	-	Under Research	(Skowyra et al., 2015)
Spritam	Levetiracetam	Tablet	Epilepsy	Aprecia Pharmaceuticals	FDA approved 1st 3D Printed Tablet	(Mearian, 2016)

Table 2.2: List of 3D Printed Topical Dosage Forms

Drug Name	Type of Formulation	Indication	Status	Reference
Ibuprofen	Topical Gel	Pain and Inflammation	Research	(Fazili, Ward, Walton, Blunt, & Asare-Addo, 2020)
Acyclovir	Topical Gel	Viral Infections	Research	(R. Wang, 2019)
Cryptotanshinone	Niosomal Hydrogel	Acne	Research	(Z. Wang et al., 2020)

Table 2.3: List of 3D Printed Implants

Implant Name	Type of Implant	Application	Status	Reference
Titanium Dental Implant	Dental Implant	Tooth Replacement	Research	(Tedesco et al., 2017)
Auricular Prosthesis	Ear Prosthesis	Facial Reconstruction	Research	(M. I. Mohammed, Tatineni, Cadd, Peart, & Gibson, 2017)
Cranial Implants	Cranial Implants	Craniofacial Reconstruction	Research	(Jindal, Manzoor, Haslam, & Mancuso, 2021)
Acetabular Implant	Hip Replacement	Orthopedic Surgery	Research	(Di Laura, Henckel, & Hart, 2023)
Cervical Cage	Spinal Fusion	Spine Surgery	Approved	(Sheha, Gandhi, & Colman, 2019)
Olanzepine	Subcutaneous Implant	Chronic conditions, such as HIV or schizophrenia	Under Research	(Picco et al., 2023)

Table 2.4: List of 3D Printed Microneedle

Drug Name	Type of Microneedle	Application	Status	Reference
Insulin	Polymeric Microneedle patch	Diabetes Treatment	Research	(Pere et al., 2018)

Cyclosporine A	Dissolving Microneedle Contact lens	Immunosuppression	Research	(Datta, Roy, Garg, & Venuganti, 2022)
Minoxidil	Dissolving Microneedle	slow the progression of hair loss and speed the process of hair regrowth	Research	(Fang et al., 2020)
Acyclovir	topical lyophilized wafer on microneedle	Viral Infection	Research	(Nagra, Barkat, Ashraf, & Shabbir, 2022)