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A Review On 3d Printing Of Pharmaceuticals

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ABSTRACT

With the use of computer-aided design software, 3D printing technology allows for rapid prototyping and can create solid things with a variety of geometric shapes by sequentially depositing many layers. The customization of medications with individually adjusted doses, on- demand tailored manufacturing, unparalleled flexibility in the design, manufacturing of complex and sophisticated solid dosage forms, and financial benefits are the main advantages of three- dimensional printing (3DP) technology over traditional pharmaceutical manufacturing. A lot of researchers have been working recently to utilize 3DP technology to the production of pharmaceutical products and various drug delivery methods. Several 3DP methods, like as stereolithography, semi-solid extrusion, fused deposition modeling, and selective laser sintering, can be implemented in a variety of customizable and programmable medications. 3DP technology has previously produced sublingual, orodispersible, and fast-dissolving drug delivery formulations. Recently, 3DP was used to produce drug-loaded tablets with modified-release characteristics, doughnut-shaped multilayered tablets with linear release kinetics, and controlled release formulation with different properties.Still, only a small number of 3DP techniques result in relatively porous structures and dose forms with irregular geometries. Current obstacles that may prevent the widespread use of 3DP technology for pharmaceutical products include the cost of transition, facility adaption, obtaining regulatory approval, etc. Intense research is being done to modify the 3DP methodologies in order to get over the shortcomings and present constraints of this technology.

INTRODUCTION

One of the most essential and often used terms in the pharmaceutical sciences is "drug delivery." It is the technique that allows a substance to be safely transported through the body one step at a time to attain the necessary therapeutic efficacy. In order to improve patient compliance, new concepts for medication delivery have evolved over time from the days of traditional oral dosage forms to targeted release drug delivery systems [1-3]. Over the past 10 years, there has been a significant amount of focus on the creation of innovative drug delivery methods and patient- centered pharmaceutical solutions. Three-dimensional

printing (3DP) is regarded as the most innovative and adaptable technique in the pharmaceutical business, according to numerous recent discoveries [4]. Rapid prototyping technology, additive manufacturing, comes after 3DP [5]. It can print three-dimensional things by joining several layers in a certain order that is managed by computer-aided design (CAD) software [6–9]. Quick developments in 3DP technology enable a number of pharmaceutical uses, including as improved drug delivery system design [10,11]. The first dental implants and conventional prosthesis were created using 3DP in the early 2000s. Currently, it can be applied successfully to reduce the chance of failure at various stages of the drug development process [12,13]. 3DP has numerous benefits over traditional pharmaceutical manufacturing technologies, including high drug loading ability, higher efficiency, customized medication with individually adjusted doses, on-demand production, ability to fabricate strong medications with high accuracy and precision, reduce therapeutic window, and cost effectiveness [14,15]. With various dose treatments, the treatment can be tailored for multi-drug therapy by using the 3D printed drug delivery system. Batch-to-batch change, which is frequently seen in the large- scale manufacturing of traditional forms of dosage, can be avoided with this approach [16, 17]. Several drug delivery systems, including oral controlled release systems, multi-layered pills with linear release kinetics, immediate-release tablets, implants, modified releasing dosage forms, pills, and microchips, are made possible by the use of 3DP technology [18–25]. Additionally, a variety of active pharmaceutical components, including as proteins, peptides, and insoluble in water drugs, can be used with this approach [26–29]. The first 3D-printed pill that got approval from the FDA was called SPRITAM, and it contained levetiracetam as the active ingredient [2]. The product was manufactured using the ZipDose technique, which relies on a powder bed fusion system that is used layer by layer [30]. This review aims to evaluate the impact and implications of 3DP technology in pharmaceutical manufacturing, thereby highlighting its significance and future prospects. The study additionally serves to investigate the various 3DP processes and to obtain an in-depth knowledge of the medicinal products that can be created with the method of production.

MATERIAL AND METHODS

The strategy is based on a similar method that is frequently employed for computer-controlled inkjet printing. When using the method in the pharmaceutical industry, normal paper with consumable sheets is utilized as the substrate and medication solutions are used in place of ink [31]. Two approaches can be applied to this system: drop-on-demand (DOD) printing and continuous inkjet (CI) printing. When a high-pressure pump is present, liquid ink is continuously pumped through an aperture with a diameter of 50 to 80 m in CI printing. A piezoelectric crystal is used to break up the liquid ink into droplets at precise intervals, sizes, and speeds. These characteristics can be controlled by the electrostatic field that forms [25]. Ink droplets having a diameter of 10–50 µm and a volume of 1–70 pL are generated during DOD printing [32]. In DOD printing, thermal head and piezoelectric crystal are employed as printer heads. The liquid ink in the DOD printing thermal head is locally heated to as high as 300´C. Bubbles are created as a result, ejecting the ink to print. Nevertheless, only volatile liquids can be used with this thermal head. Furthermore, employing such a high temperature can cause excessive vapor pressure to damage medicinal components and medications [7]. When piezoelectric crystal is used for DOD printing, it quickly changes in shape, which causes a quick change in

volume. To discharge the ink, an auditory pulse is produced [33]. This piezoelectric crystal in DOD printing can be used with a wide range of liquids, in contrast to the thermal head. Additionally, since this DOD printing may operate at ambient temperature, there is no possibility of any medication degradation [7]. Therefore, the piezoelectric crystal works better for pharmaceutical applications when used in DOD printing [32]. Drop-on-solid deposition and drop-on drop deposition are the two kinds of the DOD printing technology that can be distinguished [7]. Powder bed fusion, drop on powder, plaster printing, drop-on-bed deposition, and binder jetting 3DP are some other names for drop-on-solid deposition. With this technology, a 200 m-tall stage is covered with a powdered solid material that is spread out, and then liquid ink is sprayed on the powders as a binder solution. After that, the stage is pulled down, and the prescribed procedure is carried out once more until the successive layers are adhered to to form a 3D structure [7,34]. In the drop-on-drop deposition process, ink droplets with a diameter of 100 m are released from the printer head onto one another to form a solid layer. A high-resolution three-dimensional structure is formed by the layers, whose thickness is less than the size of the ink droplets. Microscopic drug delivery systems can be expertly fabricated using this deposition technique [35,36]. Compared to drop-on-drop deposition, the drop-on-solid deposition approach in DOD printing seems more suitable for the pharmacoprinting of a wide variety of pharmaceuticals. Nonetheless, precisely regulating the dosage combination and medication release pattern is a significant advantage made possible by the inkjet printing technology [25, 37].

Nozzle-based printing system

The shortcomings of the inkjet printing technique, such as its application to only modest therapeutic doses, insufficient hardness, trouble with multiple layer printing, prolonged drying times, and development of a rough surface, have been addressed by the invention of nozzle- based printing systems [25, 38]. Drugs, polymers, and other solid components are combined with the binder solution in nozzle-based printing systems. To create a three-dimensional object, this mixture is then applied through a nozzle, immediately depositing the successive layers [39]. This system falls into two categories: pressure-assisted microsyringes (PAM) and fused deposition modeling (FDM) [35]. Fused Deposition Modeling, or FDM for short, is one of the most studied 3DP systems [40, 41]. In FDM, the medicine is combined with thermoplastic polymers and either melted together using a hot-melt extrusion technique at the proper temperature, or it is mixed and then incubated in a suitable solvent [42]. Subsequently, the liquid material is pushed into filament by means of a high-temperature nozzle, and the resulting layers are immediately solidified and placed onto a plate [20]. FDM has a number of benefits, including an affordable manufacturing process, strong mechanical properties, and adaptability. the kinetics of drug release and the creation of extremely complex medicinal substances. Hot-melt extrusion was used to create floating 3D-printed tablets once the drug-loaded filaments were created [43]. In the recent advancement of medicines, a vast variety of drug delivery systems have been designed using FDM printing technology [44–52]. While it has several benefits for usage in pharmaceutical applications, there are some disadvantages as well, such as the high temperature required for extrusion and the lack of biodegradable thermoplastic polymers with appropriate melt viscosity characteristics [35]. In PAM, the liquid components with the proper viscosity are extruded using a microsyringe [7]. Compressed

air is utilized to release the liquid material from the microsyringe, which can move like an inkjet printer head. PAM aids in the creation of intricate drug delivery systems and microstructured products with a diameter of 5–10 µm or less [53]. Room temperature is required for this 3DP technology to function in a continuous flow. A different method, called piston- assisted microsyringe (PAM2), has been developed that is similar to PAM in that it releases the printing material through a stepper motor rather than compressed air [54]

Laser-based writing system

The photopolymerization theory, which underpins this system, states that when the photoinitiator and UV light successfully interact, free radicals are liberated [14]. A solid freeform production technique based on laser-oriented printing is called stereolithography (SLA). For the purpose of carefully solidifying a liquid resin through photopolymerization, a high-energy ultraviolet light beam in the form of a laser is focused and scanned over the highest area of the resin [55]. Until a solid three-dimensional item is found, the polymerized layers are created and the process is repeated [35]. SLA is an extremely precise method that creates 3D objects with high-quality surfaces. This technique has previously been utilized to produce oral dosage forms of aspirin and paracetamol at concentrations of 5% and 2.5%, respectively. It is also frequently employed in tissue engineering and implant design [56,57].

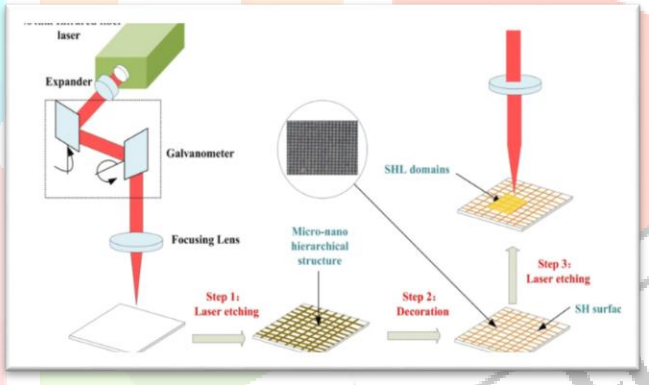

Fig 1. Laser-based writing system

Numerous promising applications of SLA have been identified by research studies, including the ability to produce multi-layered, multi-drug tablets to achieve personalized patient-specific medication and the ability to fabricate dosage forms from 28 different drugs in a single print cycle [56, 58]. Another 3DP approach has been created based on the same digital light projection (DLP) and SLA principle [59]. In comparison to SLA, the DLP process facilitates the creation of 3D objects more quickly and allows for easy modification of the polymerized layer thickness [35, 60]. Using a high intensity laser to melt the powdered raw materials and fuse the powdered materials together is known as selective laser sintering, or SLS [61]. SLS has a number of benefits, including faster printing times, greater strength products, and chemical resistance [35]. SLS has been used to generate a variety of drug delivery methods, including single miniprintlets of paracetamol and dual miniprintlets of paracetamol and ibuprofen, as well as tiny oral dose forms with control released characterized [41]. According to the laser-based writing system, which is widely employed in drug-loaded implants, there are additional techniques such as selective laser melting and electron beam melting [62].

Three-dimensional bioprinting

An innovative method for treating bone abnormalities and fractures is the 3D-bioprinted medication delivery system. Bone healing and repair can occur when simvastatin is released into the system under controlled conditions for a minimum of 20 days [63]. A study successfully demonstrated the system's effectiveness in producing 3D-bioprinted wound dressings with enough antibacterial activity using bio-ink based on pectin [64].

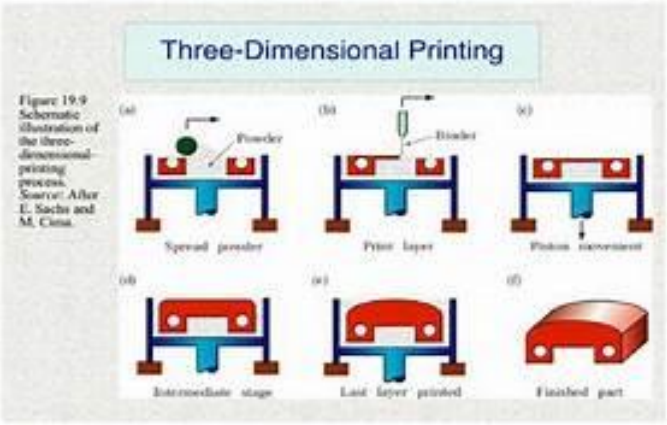

Fig 2. Three-dimensional printing

Embedded 3DP (e-3DP)

e- 3DP is a fast-prototyping technique that involves extruding a viscoelastic ink into a solidifying reservoir along a predefined path using a deposition nozzle. Other 3DP techniques that have been developed but are not frequently used for pharmaceutical applications include laminated object production, stencil printing, multi-jetting modeling, semisolid extrusion printing, and selective heat sintering. But in the near future, a variety of innovative approaches to drug delivery systems will be made possible by the adaptability of the aforementioned techniques and recent advances in material sciences [35, 41].

Fabrication Of Pharmaceutical By Applying 3DP

The majority of the 3DP technology currently in use is used to create transdermal and oral solid drug delivery systems. Still, research is being done to find out how various medication delivery systems' 3D printing protocols might be designed. Following its invention, 3DP technology was initially used to create immediate-release tablets with a single medication. Such tablets were produced using FDM because of its straightforward operating method [66–68]. After the dosage forms were successfully manufactured, other 3D techniques were used for pharmaceutical research and medication creation. Complex pharmacological dosage forms can be manufactured in a standard and straightforward manner thanks to 3DP technology. Thanks to this technology, dosage forms can release medications based on the patients' needs. Using various 3D printing techniques, a wide range of drug release profiles for oral solid dosage forms utilizing one or more active pharmaceutical components (polypill) have been effectively created, as Table 1 [69-82]

illustrates. 3D printing has been used to create high dose (up to 1000 mg) orodispersible tablets, sublingual, and other fast-dissolving formulations that dissolve quickly in the oral cavity [83–86]. The goal of 3DP-based implants is to build intricate macro- and microstructures inside a single system. According to Table 2 [87–90], it has been discovered in recent research that several medications can be put into 3DP-based implants to provide immediate therapeutic efficacy. For almost two months, an implant with an odd number of levofloxacin and an even number of tobramycin layers was able to distribute the medications gradually and continuously. The drug- device combination prevented chronic osteomyelitis in rabbits by maintaining the optimal drug concentration [90]. These days, bone defects can be addressed by creating scaffolds with 3DP technology by combining hydrogel strands filled with vascular endothelial growth factor with calcium phosphate cement [91]. Because of their optimal pharmacological effect, site-selective drug release, and cytocompatibility, 3DP-structured multi-drug implants could be a potential treatment option for pancreatic cancer, bone TB, and other chronic diseases [87,89]. It has been proposed that 3DP-structured biodegradable implants could be beneficial for the efficient local administration of anticancer medications [87].

THEORY

CURRENT CHALLENGES AND FUTURE PERSPECTIVES OF 3DP TECHNOLOGY

For 3DP technology to be widely used in the pharmaceutical business on a broad scale, a few obstacles must be solved. During the fabrication process' post-processing phase, this technology is unable to make the goods accurately enough. To get the desired shape, the product also needs to undergo a finishing process like polishing. Numerous technical and physical aspects of 3D printing, including viscoelastic properties, thermal conductivity, and physicochemical Carefully consider the properties of liquid ink and printability [14]. The dosage forms created using 3DP techniques, particularly powder bed fusion, have more friability than the identical to what is generated by traditional production. The selection of possible colorants and raw materials that are now accessible for 3DP technology.

Application of 3D Printing

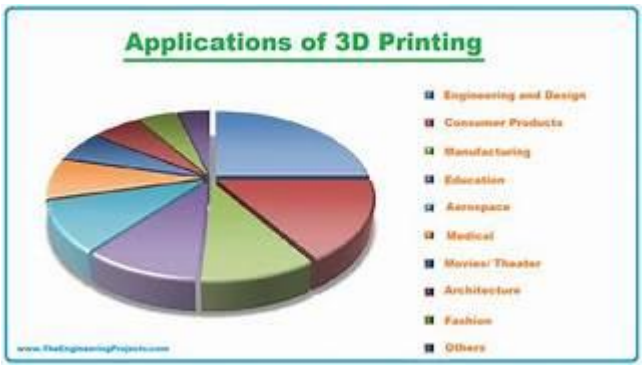

Fig 3. Applications

CONCLUSION

Several 3DP technology approaches enable the creation of extremely complex dosage forms with a variety of geometries, enable the creation of variable doses containing one or more active pharmaceutical components, and provide a broad range of drug release kinetics. It is projected that 3DP technology will be crucial to the shift toward individualized and customized drug delivery. The swift progression and enhanced investigation of 3DP technology will have wide applicability in various drug delivery systems and expedite the metamorphosis of pharmacy practice in alignment with customized medication. It has been observed that the pharmaceutical industry's current state greatly benefits from the use of 3DP technology for medication manufacturing and distribution due to its flexibility, speed of production, and precision. But the pharmaceutical sector has been ready for the fourth industrial revolution, which will see 3DP produce tailored medications across a wide range of industries.

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