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3D Printing Methods for Pharmaceutical Manufacturing: Opportunities and Challenges: A Review

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Abstract: 3D printing, or additive manufacturing, has gained considerable interest due to its versatility regarding design as well as in the large choice of materials. It is a powerful tool in the field of personalized pharmaceutical treatment, particularly crucial for pediatric and geriatric patients. Polysaccharides are abundant and inexpensive natural polymers that are already widely used in the food industry and as excipients in pharmaceutical and cosmetic formulations. Due to their intrinsic properties, such as biocompatibility, biodegradability, non-immunogenicity, etc., polysaccharides are largely investigated as matrices for drug delivery. Although an increasing number of interesting reviews on additive manufacturing and drug delivery are being published, there is a gap concerning the printing of polysaccharides. In this article, we will review recent advances in the 3D printing of polysaccharides focused on drug delivery applications[6].

Background: 3D printing (3DP) is an emerging technique for fabrication of a variety of structures and complex geometries using 3D model data.Newmethods of 3D printing such as powder bed fusion, fused deposition modeling (FDM), inkjet printing, and contour crafting (CC). Being advantageous in terms of less waste, freedom of design and automation, 3DP has been evolved to minimize incurred cost for bulk production of customized products at the industrial outset. Due to these reasons, 3DP technology has acquired a significant position in pharmaceutical industries. Numerous polymers have been explored for manufacturing of 3DP based drug delivery systems for patient-customized medication with miniaturized dosage forms[4].

Conclusion: Despite several advantages of 3DP in drug delivery, there are still a few issues that need to be ad- dressed such as lower mechanical properties and anisotropic behavior, which are obstacles to scale up the technology. Polymers as a building material certainly plays crucial role in the final property of the dosage form. It is an effort to bring an assemblage of critical aspects for scientists engaged in 3DP technology to create flexible, complex and personalized dosage forms[3].

1. Introduction

Drug delivery refers to approaches, systems, technologies and formulations for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect. The concept of drug delivery has greatly evolved over the years from immediate-release oral dosage forms to targeted-release drug delivery systems. Indeed, the necessity of controlling the drug release profile to modulate the absorption, the distribution, the metabolization and the elimination of the drug rapidly appeared as a key factor for improving product efficacy and safety as well as to increase the compliance of the patients. In the drug delivery area, versatile therapeutic systems intended to yield customized combinations of drugs, drug doses and release kinetics have drawn increasing attention, especially because of the advantages that personalised pharmaceutical treatments would offer[2].

Three dimensional printing (3DP) technology is a novel technique for rapid prototyping, which constructs solid objects by deposition of several layers in sequence. The introduction and application of 3D printing have promoted enormous innovations in many diverse fields, including aerospace industry, architecture, tissue engineer, biomedical research and pharmacy. It seems that 3D printing technology will lead a new epoch of the next industrial revolution based on its versatility and diversity. Along with development and progress in science and technology, the 3D printing technology gets mature enough so that anyone can apply it with open-source software at a relative lower material cost.The recent introduction of the first FDA approved 3D printed[1].

1.1 Scope

3DP is gaining increasing attention in pharmaceutical formulation development as an effective strategy to overcome some challenges of conventional pharmaceutical unit operations. For instance, the conventional manufacturing unit operation involving milling, mixing, granulation and compression can result in disparate qualities of the final products with respect to drug loading, drug release, drug stability and pharmaceutical dosage form stability .3D printing technology has enabled unprecedented flexibility in the design and manufacturing of complex objects, which can be utilized in personalized and programmable medicine. In this report are shown some advantages, limitations, challenges and perspectives of 3D printing in the elaboration of drug delivery[1].

1.2 Advantages and Limitations

Various techniques for 3D printing, such as fused deposition modeling (FDM), binder deposition, inkjet printing, material jetting, powder bed fusion, photopolymerization, pen-based 3D printing and molding, have been reported in the literature. Fused Deposition Modeling (FDM) 3D printing has been recently attracted increasing research efforts towards the production of personalized solid oral formulations. However, commercially available FDM printers are extremely limited with regards to the materials that can be processed to few types of thermoplastic polymers, which often may not be pharmaceutically approved materials nor ideal for optimizing dosage form performance of poor soluble compounds.

Such a technique holds huge potential for the manufacturing of pharmaceutical products and is currently under extensive investigation. Challenges in this field are mainly related to the paucity of adequate filaments composed of pharmaceutical grade materials which are needed for feeding the FDM equipment[3].

1.3 Challenges and perspectives

The technological advancements in the pharmaceutical field are constantly improving and provide various possibilities for meeting the needs of personalized drug therapy. The three-dimensional (3D) printing technology has endless potential in the fabrication of patient-specific drug delivery devices (DDD) and dosage forms as the technological development is progressing. Moreover, the rapidly evolving research on 3D printed DDD has enabled us to determine several challenges related to the manufacturing and marketing of personalized drug delivery systems. The 3D printing has enabled the fabrication of prototypes of DDD with varying complexity and shows that customization of drug products is possible. There is potential to improve patient-specific drug therapies of the future using printing technologies. The technological advancements, new scientific concepts, interdisciplinary work and defined regulatory guidelines will continue to support and strengthen the prospects of 3D printing as an option in the manufacture of medical products. Three-dimensional printing (3DP) is a unique prototyping technology that has advanced over the past 35 years and has the great potential to revolutionize the field of drug delivery with its inherent advantages of customizability and the ability to fabricate complex solid dosage forms with high accuracy

and precision. 3DP can fabricate solid dosage forms with variable densities and diffusivities, complex internal geometries, multiple drugs and excipients. 3DP can successfully address the issues relating to the drug delivery of poorly water-soluble drugs, peptides, potent drugs and the release of multi-drugs, etc. However, there are some problems that restrict the applications of 3DP in commercial market, such as the selections of suitable binders, excipients and the pharmaco-technical properties of final products [1].

3D printing encompasses a range of differing techniques, each involving advantages and open issues. Particularly, solidification of powder, extrusion, and stereo lithography have been applied to the manufacturing of drug products. The main challenge to their exploitation for personalized pharmacologic therapy is likely to be related to the regulatory issues involved and to implementation of production models that may allow to efficiently turn the therapeutic needs of individual patients into small batches of appropriate drug products meeting present quality requirements[2].

1.4 Findings

It is evidenced that through its versatility, speed of production and precision, the use of three-dimensional printing for the elaboration and distribution of controlled drugs plays a key role in the current pharmaceutical industry, considering that drugs can be designed according to the patient's need. The fused deposition modeling (FDM) technique and hot melt extrusion (HME) of filaments for 3DP still excels in relation to the other printing techniques, such as binder deposition, inkjet printing, material jetting, powder bed fusion, photopolymerization, pen-based 3D, printing and molding have been gaining more and more space. The use of 3DP in pharmaceutical formulation development is an effective strategy to overcome challenges of conventional pharmaceutical unit operations, since the conventional manufacturing operation can result in disparate qualities of the final products with respect to drug loading, drug release, drug stability and pharmaceutical dosage form stability. 3DP offers significant potential benefits in the field of drug delivery and pharmaceutical/medical device manufactured[1].

2. Evolution

Three-dimensional (3D) printing was developed more than 30 years ago to manufacture 3D objects based on a digital design. This layer-by-layer process enables a fast and cheap design cycle for the preparation of personalized medication. The term 3D printing was coined as an umbrella term and encompasses a number of processes, and in many reviews the main types were described in detail. Three-dimensional printing gave the means to the manufacture of a high-quality product within minutes in an easy manufacturing cycle. This on-demand manufacturing was time and material saving. Not to mention the fact that 3D printers could conquer the traditional manufacturing regime of 'one size fits all'. As 3D printing was based on a computer-aided design (CAD), it provided the ability to quickly create and produce a flexible and innovative product. Personalized medication carried the opportunity to create drug delivery systems for patient's requirements. Furthermore, 3D printing gained access to the creation of unique dosage forms and achieving more complex drug release profiles. The image could be made to meet the patient's individual needs regarding their age, weight, organ function, and severity of disease. The application of 3D printing technology might be an alternative way to construct effective, customized active pharmaceutical ingredient (API) combinations for the patient immediately. The 3D printing technique opened up the opportunity for the development of tailored single and multi-drug products at the point-of-care[5].

In recent years, many comprehensive publications have been presented on the different designed drug dosage forms. As Moulton et al. highlighted, this kind of process created the opportunity for the manufacturing of controlled and modified release of the APIs, enabled the delivery of poorly watersoluble drugs, increased drug stability, and reduced the used API amount without compromising the efficacy [2]. In

2018, two distinct research groups summarized the recent achievements in the manufacturing of pharmaceuticals but as a rapidly developing area the achievements vary from year to year [3]. Mohapatra et al. gathered together the newest publications in recent years and grouped the research based on the type of 3D printing [1].

The available reviews mostly focus on one or multiple drug dosage forms manufactured by one type of 3D printing technology. Cunha-Filho et al. discussed the fabricated drug delivery systems by fused deposition modeling (FDM) 3D printing [3]. While Gueche et al. summed up the oral dosage forms created by selective laser sintering (SLS) and Wang et al. described the stereolithographic (SLA) constructed oral dosage forms . Inkjet printing of pharmaceuticals was summarized . In more and more research, three-dimensional bioprinting was used which is a new era of 3D printing tech- nologies where researchers aim to build living tissue models [1].

During the last decades multiple research groups were established to fabricate drug delivery systems. FabRx Ltd. is one of the most innovative start-up companies, which is a biotech company, designed to produce 3D-printed medication [2]. Regarding the diverse drug dosage forms, different reviews summarized the achievements. For example buccal patches were analyzed in the work of Shirvan et al. [2], implants in the work of oral dosage forms in the work of Khatri et al. and transdermal delivery systems (TTS) in the work of Economic development.

The aim of this work was to provide a comprehensive image on how the manufacturing of the different drug delivery systems started and where the experiments are headed now. The chosen drug delivery systems were divided into subgroups based on the type of the drug delivery system and the tables summarized the most important research in the last 20 years in chronological order.

2.1 The 3D Printing of Drug Delivery System's evolution.

2.1.1 Tablets

The first publication of a 3D-printed tablet dates back to 1996 when solid samples were created with a desktop printer from PCL and PEO polymers containing blue and yellow dyes. Based on the results, complex drug delivery regimes could be created with this technique, such as the release of multiple drugs or multiphasic release of a single drug. This study demonstrated several simple examples of such devices and several construction methods that could be used to control the release of the drugs.

In the early 3D printing articles, droplet binding was used for the manufacturing of the samples when the used binder was not necessarily polymer but some other auxiliary material, e.g., Eudragit® or mannitol. The authors concluded that with this method adequate oral dosage forms can be manufactured which exhibit erosion or diffusion release mechanisms . At the beginning of the research, the most important question for the authors was the type of the chosen additive manufacturing process, the used printing parameters, immediate- or delayed release tablet manufacturing, and first- or zero-order kinetic profile manufacturing[8].

Gbureck et al. used a unique technology for the manufacturing of the drug delivery system. Firstly, they created the sample with a 3D bioceramic powder printing process and then the used antibiotics were adsorbed during a week to fabricate the tablets . Yu et al. produced an acetaminophen containing matrix tablet using a desktop 3D printer. The middle drug-containing regions of the tablets were formed by depositing the binder liquid containing release-modulation materials onto the automatically spread powder layers.[3]

Tablets with a novel design approach of caplets with perforated channels were fabricated by Sadia et al. to accelerate drug release from FDM 3D-printed samples.The experimental arrangement was to use different channel widths, lengths, and alignments. Based on the results, the parameters should be carefully considered in addition to surface area when optimizing drug release from samples. The incorporation of short channels could be adopted in the patterns of dosage forms built from polymeric filaments.[2]

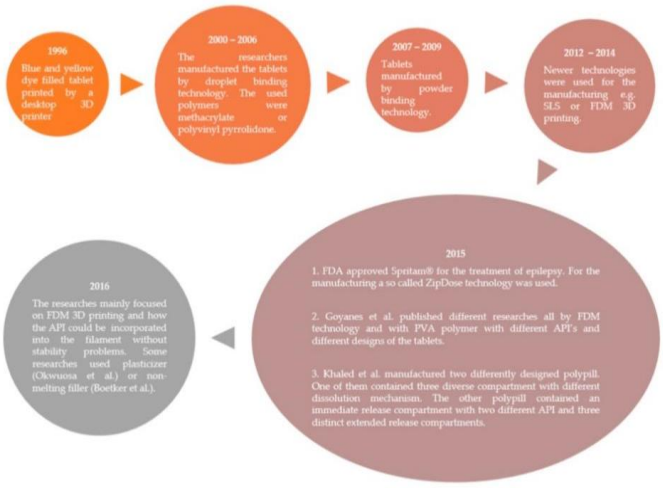

Figure 1.Flowchart on described tablet manufacturing methods, Mein breakthroughs between 1996 and 2016.

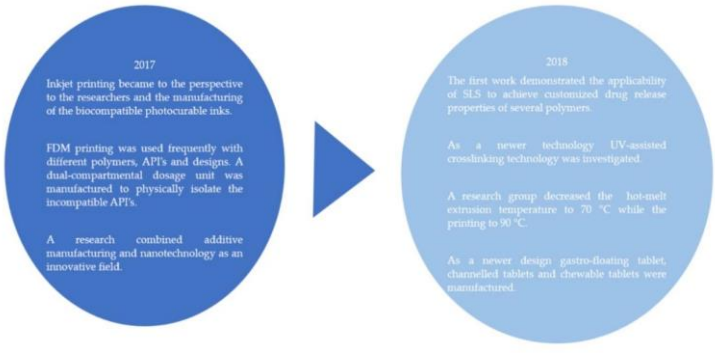

Figure 2.Flowchart on the described tablet, manufacturing methods and main breakthroughs in 2017 and 2018.

Figure 3.Flowchart of the described tablet manufacturing methods and main breakthroughs since 2019.

2.1.2 OrodispersibleFilms(ODFs)

The first 3D-printed oral film was printed by thermal inkjet printing where the used API (salbutamol sulfate) was dissolved in the aqueous solution, the ink cartridges were filled with this solution, and it was printed onto a commercial potato starch film. The authors concluded that this process was suitable for the manufacturing of aqueous drug so- lutions into thin polymer films but the viscosity and API stability had to be controlled [2].

In another work, the aim was to evaluate the applicability of orodispersible films (ODFs), porous copy paper sheets, and water impermeable transparency films (TFs) which contained rasagilinemesylate (RM) as a low dose active pharmaceutical ingredient. Flexible doses of the API were obtained by printing several subsequent layers on top of the already printed ones, using an off-the-shelf consumer thermal inkjet (TIJ) printer[8] .

A research group manufactured the drug dosage form with a special 3D printing method which incorporated two different methods: piezoelectric- and solenoid valve-based inkjet printing technologies to allow the dispensing of an extensive range of fluids. The research demonstrated the opportunity to 3D print a wide range of formulations for the patient needs. The fabrication avoided the risk of drug degradation by ink heating and of substrate damage (by contact printing) and the manufacturing scheme avoided the emergence of defects .

Vakili et al. used inkjet printing to create orodispersible films, which contained propranolol hydrochloride. The drug delivery systems were designed with escalating doses of propranolol hydrochloride on three different substrates and three unalike area sizes were used through the 3D printing with thermal inkjet printing technology. A thin sweetener coating layer of saccharin was successfully included in the final dosage form to increase the patient compliance among pediatric patients [10].

Aripiprazole-containing orodispersible films were fabricated with FDM technology from PVA by Jamróz et al. The aripiprazole in the sample is fully amorphous due to the two-step hot-melt extrusion process (filament fabrication and 3D printing) and the high concentration of PVA polymer helped to maintain the amorphous form [9]

2.1.3 Implants

Levofloxacin-containing PLA implants were designed with inkjet printing. The manu- factured samples were 10 mm in width and rounded. In this research, a complex release profile was demonstrated in the 100-day monitoring period when one pulse of release appeared from the 5th to 25th day, and another pulse began at the 50th day and ended atthe 80th day, with a lag time of 25 days between the two pulses, wherein a steady state of release was observed at about 5 μg/mL [10].

Rifampicin and isoniazid-containing multi-layered concentric cylindrical implants were fabricated against tuberculosis. The multi-layered concentric cylinder was divided into four layers from the center to the periphery and the APIs were distributed individually into the different layers in a specific sequence of isoniazid–rifampicin–isoniazid–rifampicin. The dissolution tests proved that the API liberation takes place orderly from the outside to the center and the peak concentrations were between 8 and 12 days. In this study, a programmed release multi-drug implant with a complex construction was fabricated by 3D printing [7].

A research group prepared dexamethasone-containing tailored drug delivery plat- forms where two distinct designs—structure A: rolled and sealed; structure B: layer- by-layer—were extrusion printed. As the API liberation was continuous for more than 4 months, these samples could be used as implants .

Genina et al. manufactured intrauterine device and subcutaneous rods from ethy- lene vinyl acetate (EVA) copolymer with FDM printing. The samples were containing indomethacin as a model API and with the device the drug dissolution was over 30 days. A long-acting 3D-printed implantable system was built[9].

2.1.4 TTS

Anti-acne drug loaded masks/patches were fabricated by Goyanes et al., but as this system provides transdermal delivery, we decided to subgroup the research here. In the research, salicylic-acid-containing filaments were used for the FDM 3D printing but the API showed significant thermal degradation. The manufacturing by SLA contained a higher amount of drug and showed no drug degradation, so the researchers found this method more adequate [5].

Yi et al. manufactured a 3D-printed biodegradable patch with a versatile shape and incorporated a high drug concentration for the achievement of a controlled drug release profile. The patches composed of poly(lactide-co-glycolide), polycaprolactone, and 5-fluorouracil were the antitumor agent. With the use of 3D printing technology, the geometry of the patch and the drug release kinetics could be manipulated. The patches were flexible, and released the drug over four weeks with minimized side effects [7].

A research group developed an electro hydrodynamic (EHD) printing technique to fabricate antibiotic-containing patches using polycaprolactone (PCL), polyvinyl pyrrolidone (PVP), and their composite system (PVP-PCL). Drug loaded 3D patches possessed perfectly aligned fibers giving rise to fibrous strut orientation, variable inter-strut pore size, and controlled film width (via layering).[6]

2.1.5 Microneedles

In the early research of Ovsianikov et al., a placebo microneedle was developed by femtosecond laser two photon polymerization 3D printing technology. In 2013, an amphotericin B containing microneedle was created by the combination of visible light dynamic mask micro stereolithography, micro molding, and piezoelectric inkjet printing. Based on the results, the printing process was found to be a scalable approach that could be used to incorporate pharmacologic agents, even with complex solubility profiles, within microneedles . The same researchers fabricated miconazole-containing microneedles with the same technology but with a special polymer called Gantrez® AN 169 BF (poly(methyl vinyl ether-co-maleic anhydride)). The manufactured sample had potential use in transdermal treatment of cutaneous fungal infections [5].

A dacarbazine-containing drug delivery system was produced which could be used for the therapy of skin cancer locally. For the manufacturing, a special 3D printing process was used named as multi-material micro stereolithography (μSL). First, the microneedle array was built and then the API was added with blending due to the crosslinking effect of the polymer .

Insulin polymeric layers on metal microneedles were constructed by Ross et al. The dissolution profiles showed rapid insulin release rates in the first 20 min, suggesting that solid-state insulin delivery via microneedles was feasible [4].

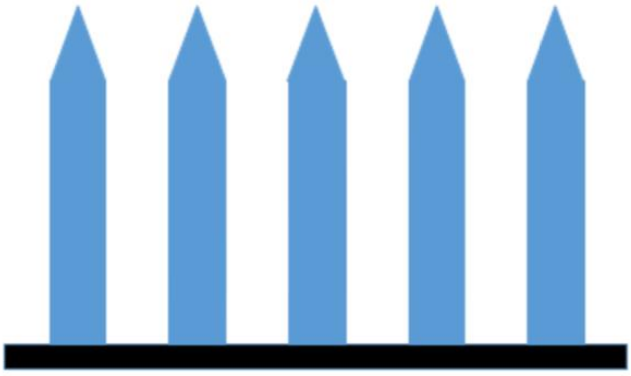

Figure 4.Cross-sectional design of the micro needle array.

2.1.6 Vaginal drug delivery system in 3DP

Even though this subsection consists of numerous drug delivery systems, we would like to discuss them together for easier accessibility.

The article of Genina et al. was already discussed in the section of implants because two distinct type of drug delivery systems were fabricated: intrauterine device (IUD) and subcutaneous rods.

Bioadhesive vaginal films were produced by Varan et al., where the used APIs were paclitaxel and cidofovir, which had antiviral efficacy and used for the treatment of cervical Cancer locally[6].

2.1.7 Micro and nanoscale Dosage form

Another area that concerns the researchers is the possible manufacturing of micro and nanoscale drug delivery systems. In a study, a poorly soluble model drug was used to construct a 10% folic acid containing nanosuspension and the printing was performed on an inkjet-based microdosing dispenser head. In the research, the authors found this method adequate for the incorporation of poorly soluble drugs to increase the oral absorption [3].

Scoutaris et al. produced poorly soluble felodipine and PVP-containing solution for inkjet printing. Based on the authors' research, inkjet printing could be used to prepare this novel drug dosage form consisting of micro-sized dried deposits from sprayed picolitre droplets containing a drug on a substrate. The novelty of the work was that a scalable dosage form could be produced whereby many droplets could be produced to achieve a dissolution profile equivalent to conventional bulk dosage formulations [10].

In another study, rifampicin and PLGA-containing inks were fabricated for micro- pattern printing on a glass or titanium carrier. This research combines special ink for- mulations in microscale range and the author's idea was to use these micro-patterns in orthopedicsurgeries .

Paclitaxel-containing PLGA inks were created for piezoelectric inkjet printing where four different shapes were printed. Microparticles with diverse geometries exhibited non-similar drug release rates mainly due to nonidentical surface areas [6].

Some studies on the manufacturing of micro and nanoscale systems can be found . The research was classified based on the publication year and then in alphabetical order. In the first column, the type of the drug delivery system was described.

3. 3D printing landscape

3.1 Processes of Inkjet printing.

3D printing is a Cutting-edge technology that is helping designers to re-think the design for leadership development, new customized for- mulations, etc. This is accomplished through shortening the design cycle of developing new ideas and concepts, receiving valuable input, and improving the design to make decisions[7].

In this technique, an idea is reversed into a prototype using 3D computer-aided design (CAD) files, allowing for the production of digi- tally controlled and personalized products .

Virtual 3D design of an object is prepared using digital elegant soft- ware like Onshape, Solid works, Creo parametric, Autocad, Autodesk Tinker cad, BRL-CAD, Free CAD, Open SCAD, Wings3D, 3D Slash, Sketch UP, Fusion 360, etc . Using MeshLab, Google SketchUp, plugin, STL-viewer, and Netfabb Studio software, this advanced model is then adapted to (.STL) digital file format, which stands for standard tessella- tion language or stereolithography . Slicing is the ahead interaction of changing over the 3D model into a stack of flat layers. Slicing is done using slicing software like Matter Control, UltimakerCura, Slic3r, Octo Print, idea Maker, etc. Slicing software depicts these layers as straight developments of the 3d printer extruder fixation laser or same. By slicing the design into a sequence of 2D horizontal cross-sections with the help of specialist slicer software installed in the 3D printer, the standard tessellation language (STL) file is turned into a G file. The next step is to choose a suitable material for 3D printing. Filaments consisting of various materials are used in 3D printers. 3D printers use filaments as their “ink”. 3D printing may be done using a wide variety of materials like plastics, ceramics, resins, metals, sand, textiles, biomaterials, glass, food and lunar dust, etc. When the model is loaded into the computer, it sends instructions to the 3D printer for layer-by-layer material deposi- tion. By extruding molten plastic through a small nozzle, a 3D printer works. It moves accurately in response to computer commands. Afterprinting one layer, the printer waits for it to dry before printing the next layer on top[8].

3.2 Pharmaceutical applications of 3D printing

As 3D printing innovation is getting more open to drug researchers and the first 3D printed tablet Spritam was endorsed by FDA in Aug 2015; utilizing 3D printing technology to foster drug items has acquired critical interests in the drug industry and academic. Drug utilization of 3D printing has two expected bearings to carry the drug item improvement to unfamiliar regions, one is the assembling of medication conveyance frameworks with refined constructions and the other one is customized medication. 3DP has been witnessed wide application in pharmaceutical fields due to its potential advantages like enhanced productivity, com- plex drug release profile, multiple dosing, single-step process with low cost and customization/ personalization of drug delivery. This modernized technology is very useful tool for more precise drug dispensing with the tailored release of drug to address the unique need of the individual patient. Moreover, personalized medicine is an unprecedented opportu- nity of 3D printing to cater the challenges for treatment of heterogeneous diseases. Various formulations including oral solid dosage forms, im- plants, microneedle and hydrogel etc. with suitable examples are described below[9].

3.3 Oral solid dosage forms

Tablets have been broadly inspected for the possibility of 3DP ad- vancements in drug fabricating. By and large, tablets delivered by 3DP techniques can be ordered into two gatherings: single API tablets and various API tablets. Particular instances of every class are portrayed in the following two areas, individually.

At first, 3DP innovation was applied to manufacture straightforward quick delivery (IR) tablets including a solitary API[10].

4. Challenges of 3D printing on formulation development

Despite the implicit advantages of 3DP technology in formulation development, the technical difficulties and complications imparting applications of 3DP are the availability of excipients, development of printing software and instruments, optimizing the mechanical properties of products, and the regulatory landscape. Relatively limited availability of excipients is the major hindrance for designing specialized dosage forms. Non-toxic, biodegradable, biocompatible and stable excipients are highly essential to the wide application of 3DP in formulation development. Further, with the increment of the more complex structure of dosage form, continuous updating of modeling and slicing software intended to design and inform its production must be required. The mechanical equipment, operating procedures, and control system need to be updated and optimized to prevent clogging or promote product uniformity. At present, 3D printers used in pharmaceutical formulation preparation do not meet good manufacturing practice (GMP) standards and thus need to be validated to ensure the product meets the required safety standards. The physicochemical parameters such as the viscosity and surface tension of the adhesives, fineness of the nozzle influence the performance of the products. Further, the quality control parameters of the dosage form are to be ensured to make the prepared formulations reproducible. In addition, post-printing processes such as drying methods, drying time, and drying temperature may also affect the appearance and quality of the products which are most important for 3D printing technologies based on DOP, FDM and SSE. Thus, it's essential to ameliorate the mechanical behaviour of products by optimizing printing outfits such as computer control programs, refining of adhesive nozzles and optimizing printing process parameters. In terms of regulation, many questions are surrounding how 3D-printed pharmaceuticals can be monitored and evaluated for quality. The FDA issued its final guidance on technical considerations for the regulation of 3D-printed medical devices in 2017; however, it may not apply to all 3D-printed medical devices as a separate assessment of safety and effectiveness may be required, espe- cially for personalized products. In instances where products are customized to the patient, the question of whether 3D printing is classed as a manufacturing process or compounding would also impact regula- tory guidance. Additionally, though the FDA authorized the first 3D- printed tablets, no regulations or guidelines regarding 3D-printed med- icines are currently available. There remain several regulatory chal- lenges, such as how the performance of 3D-printed pharmaceuticals should be measured or their quality controlled, though the FDA's Office of Testing and Research is currently working [9].

5. CHALLENGES FOR IMPLEMENTING 3D PRINTING

Though 3D printing seems possible advantageous in every field of health care medicine, the restrictions are yet obvious due to certain aspects. Few challenging domains include safety concerns, regulatory perspective, fabrication materials, technological difficulties, and anti-counterfeiting [4].

Safety is the greatest concern during drug manufacturing. During the 3D printing fabrication method, the smaller airborne particles may result which leads to certain respira- tory problems to the manufacturers. The regulatory perspec- tive of any formulation or medical device is also a major step to leap. FDA published “Technical Considerations for Additive Manufacturing of Medical Devices” in 2017 to offer significant regulative suggestions, and prerequisites for the authorization of three-dimensional pharmaceutical materials and biomedical devices . As a result of this, many medical devices found its way into the market by facing challenges. But the only pharmaceutical product approved by the regulatory body was Spritam. Moreover, the fact is still unclear whether the guidelines fit all processes and parame- ters or the final product alone[6].

Fabricating materials should also comply with the regulatory guidelines. Despite the fact that bioinks must have desirability with drugs and other excipients of formulation, it is also compatible with the human body. Bioink's safety is also considered to an extent to defend it from generating any harmful toxic substance throughout the shelf-life . Due to losing framework of guidelines, many counterfeit devices with improper quality and safety attributes find its place in the market. These fake and unauthorized replicas of indigenous products are often misleading patients with substandard devices[5].

6. CONCLUSION

Additive manufacturing is extending beyond its tradi- tional function, and is now used in a wide range of sectors ranging from lightweight engineering to energy technologies, medicine, and far more. 3D bioprinting is one of the most potential technologies for producing cell-loaded scaffolds which could further differentiate and proliferate. The rise of personalized implants and multiactive medicine is a great leap in technology. The patient-specific medicines cut short many harmful sides of the conventional dosage forms. Biopolymers involved in the fabrication also proved to improve the drug efficiency and potentiation. Albeit the printers and biomate- rials used are exorbitant, technology is improving steadily, and prices will drop to the point where it will be ideal for even large-scale production. This breakthrough provides increased advantages to medical students, practitioners, and patients. With the rising use of implants and prostheses for a diverse population, the quality of life is improved in comparison to conventional treatment procedures. We can expect the greater stable technology with further more improved characteristics in the pharma culture. The cell lines incorporated should be mechanically stable over the period with adaptable biological character still being a hurdle for a full stretch. The functionality and characteristics of bioprinted tissue-like constructions may be evaluated using machine learning. With the advancement and maturation of 3D bioprinting, deep learning is expected to play a large role in improving the process and product quality.

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