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A Review On:3D Printing In Pharmaceutical Industry

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ABSTRACT: 3D printing is the manufacturing of 3 dimensional objects with a basic principle of additive manufacturing (AM). Several layers of suitable materials are formed with help of predefined parameters which are designed using computer-aided design (CAD) software. 3D printing became popular in healthcare as well as R&D back in 1980s because of faster & accurate results and cheap manufacturing cost. Knowing its potential and diversified manufacturing procedures, pharma industry has also started adapting 3D printing technology for manufacturing purpose. The main focus of our study is to evaluate the potential of 3D printing in novel drug delivery system (NDDS) and other pharmaceutical manufacturing processes. Binder jet printing, fused deposition modelling (FDM), semi-solid extrusion (SSE), selective laser sintering (SLS), and stereolithography (SLA) are common types of 3D printing used in pharmaceutical industry. Despite of all numerous advantages of 3D printing, the use of this technique on a large scale still remains a challenge due to several barriers like quality control, regulatory guidelines, limited access etc.

Keyword : 3D Printing, excipients, drugs.

I. INTRODUCTION:

3D printing is a computer-aided design (CAD) used to create three-dimensional objects through a layering and is also called as additive manufacturing (AM). 3D printing involves layering materials, like plastics, composites or bio-materials to create objects that range in shape, size, rigidity and color. This 3D printing technology has extreme flexibility in what can be printed. They can also create objects like phone cases or bike handles, using a hybrid rubber/plastic powder. Some 3D printers even have the ability to print with carbon fiber and metallic powders for extremely strong industrial products. This technology is extremely accurate and fast and a promising tool for the future of manufacturing. Many 3D printers are also useful to create prototypes in R&D processes to make it faster and cheaper. Since last few years, 3D printers are also being used in healthcare industry.(1)It takes a combination of top-of-the-line software, powder-like materials and precision tools to create a three-dimensional object from scratch. (1)

Evolution of 3D printing in healthcare:

The adoption of 3D printing in healthcare started back in 1980s at Boston Children's Hospital, Harvard Medical School. The team of researchers built by hand replacement urinary bladders for seven patients by constructing scaffolds from collagen and synthetic polymer, then layering the scaffolds with cells from the patients and allowing them to grow into functioning organs.(2)The trials were a successful and all the patients were healthy even after seven years. But the process of constructing the scaffolds by hand was time-consuming and onerous. Hence, Anthony Atala, MD, one of the research fellows in the trial, thought of automating the process.

When Dr. Atala led the newly formed Wake Forest Institute for Regenerative Medicine (WFIRM), WFIRM researchers began conducting experiments in rudimentary 3D printing using a basic inkjet desktop printer, under his guidance and in addition to that Dr. Atala built on this work, developing machines capable of printing customized scaffolds for human organs. WFIRM scientists have since successfully engineered several categories of tissues and organs by hand in the lab and implanted them in patients in small, clinical trials. Research on 3D printing of tissues and organs continues and is not yet ready for clinical use. (3)(6) In the past decade, the medical 3D printing technology has developed much more beyond manufacturing of scaffolds and expanded itself in printing dental implants, parts of medical devices, surgical instruments, medicines and so on.

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(3) More than 30,000 patents about 3D printing are reported to have been published just in the U.S.(4) In general, each 3DP technology follows a common process for printlet production, (i) Design (ii) Develop and (iii) Dispense. By following these points 3D printer can then be filled with the drug loaded feedstock after implementation of favorable design along with development of the required conditions and properties. Formulations are prepared in a layer-by-layer fashion, which are then ready for 'dispensing'. This method of production varies depending on the printing platform selected.(5)

3D printing in pharmaceuticals:

Pharmaceutical industry is an essential part of healthcare segment. Since last few years, more focus is put forth on development of novel drug delivery system. 3D printing could play an important role in NDDS and beholds a great potential in manufacturing advanced treatment regimens. There are many existing studies which have used 3D printing to overcome the current challenges in drug delivery as well as improving the pharmacokinetic and pharmacodynamic properties of the drug.

Out of seven main categories of 3DP technologies, within pharmaceuticals, five main 3DP technologies have been researched; binder jet printing, fused deposition modelling (FDM), semi-solid extrusion (SSE), selective laser sintering (SLS), and stereolithography (SLA). (5)

Recently, different pharmaceutical-grade feedstock materials for creating tablet-like dosage forms were studied using a binder jet 3D printing method. The pharmaceutical-grade powders were repeatedly spread onto a build plate, followed by inkjet printing a liquid binder to selectively bind the powders in a predetermined pattern designed by computer aided design (CAD) software. The physical properties of the pharmaceutical-grade powders and binders were characterized against standard feedstock materials to select appropriate powder and binder materials for subsequent printing experiments. (13) Additionally, a quick screening was also done to assess different powder-binder combinations and to select a powder type for further printing experiments with different binders.**Indomethacin** was used as a model drug to study effectiveness of binder jet 3D printing as a process to make tablet-like dosage forms using common excipients. Binder Viscosity and Surface Tension Characterization, The Ohnesorge (Oh) number and the minimum velocity calculations, Powder Particle Size and Flowability Characterization etc. physicochemical characteristics were studied.

The drug loading efficiency of **Amitriptyline HCl** was evaluated using a binder-jet 3D printing process by incorporating the drug in ink, and quantifying the printability property of ink solutions. (14) Amitriptyline HCl was used as a model drug because of its higher stability and aqueous solubility in the ink solution. Four different concentrations (5, 10, 20, 40 mg/mL) of API inks and one excipient mixture were selected for the study. The API inks were characterized and evaluated with regards to their printability/ jettability property, whereas the excipient mixture and printed tablets were evaluated through pre-formulation characterization. Additionally, their structure, hardness, content uniformity, and in vitro release patterns were also evaluated. (14)

In another study, a pre-screening test was developed for the binder-jet 3D printing process (BJ3DP) which has been validated using statistical analysis. The **pre-screening test** or drop test has been adapted from the **wet granulation field** and modified later on to be used for tablet manufacturing in BJ3DP. Initially, eight powders and ten water-based binder solutions were introduced in the preliminary test to understand the **powder-binder interactions**. Based on the preliminary test results, powder and binder combinations were then used for 3D printing. The key parameters such as mechanical strength and shape factors of the drop test agglomerates and 3D printed tablets were then compared using multiple linear regressions. Few dimensionless parameters were also introduced in this study to capture the printability properties of the powders.(15)

Fused deposition modeling (FDM) is another 3D printing technique based on the deposition of successive layers of thermoplastic materials following their softening/melting. FDM is currently under investigation and beholds a great potential in 3D printing of pharmaceuticals if more research is done on it. (16)

In an experiment filaments suitable for 3D printing of capsules, modified release dosage forms, tablets etc. were successfully produced by using FDM technique of 3D printing. Here the possible number of pharmaceutical polymers (ethylcellulose, polyethylene oxide, Eudragit1 L, polyvinyl alcohol etc.) were evaluated as starting materials for fabrication via **hot melt extrusion** of filaments suitable for FDM processes. By using a twin-screw extruder, filaments based on insoluble,

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promptly soluble, enteric solubleand swellable/erodible polymers were successfully produced, and the possibility of employing them for printing 600mm thick disks was demonstrated. (16)

In another study FDM was used to develop novel **core-shell gastroretentive floating pulsatile** drug delivery systems using a hot-melt extrusion and direct compression method. **Hydroxypropyl cellulose (HPC)** and **ethyl cellulose (EC)-based filaments** were fabricated and were utilized as feedstock material for printing shells in FDM 3D printing. The directly compressed theophylline tablet was used as the core. The tablet shell to form pulsatile floating dosage forms with different geometries (shell thickness: 0.8, 1.2, 1.6, and 2.0 mm; wall thickness: 0, 0.8, and 1.6 mm; and % infill density: 50, 75, and 100) were successfully designed, printed, and evaluated. (17)

3D printing was used for the production of viable tablets capable of satisfying regulatory tests and matching the release of standard commercial tablets. In this experiment, Hydroxypropyl methylcellulose (HPMC 2208) (MethocelTM K100M Premium) and poly(acrylic acid) (PAA) were used as a hydrophilic matrix for sustained release (SR) layer. HPMC 2910 was used as a binder while microcrystalline cellulose (MCC) and sodium starch glycolate (SSG) were used as disintegrants for immediate release (IR) layer. Guaifenesin bi-layer tablets (GBT) were used as a model drug. (7)

To explore the potential of FDM 3D printing in pharmaceuticals, another experiment was done to formulate immediate release pharmaceutical tablets with various model drugs. In this experiment a nonmelting filler was mixed with methacrylic matrix to facilitate FDM 3D printing and the impact of the nature of filler, compatibility with the gears of the 3D printer and, and polymer: filler ratio on the 3D printing process was studied. A specially developed filament based on pharmaceutically approved methacrylic polymer (Eudragit E) and thermally stable filler, TCP (tribasic calcium phosphate) was optimized. Four model drugs (with different physicochemical properties were included into ready-to-use mechanically stable tablets with immediate release properties.(8)

Fused-deposition 3-dimensional printing (FDM 3DP) was used to produce modified-release drug loaded tablets in a study. Two aminosalicylate isomers namely 5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA), were selected as model drugs. Commercially produced polyvinyl alcohol (PVA) filaments were loaded with the drugs in an ethanolic drug solution. A final drug-loading of 0.06% w/w and 0.25% w/w was achieved for the 5-ASA and 4-ASA strands, respectively. 10.5 mm diameter tablets of both PVA/4- ASA and PVA/5-ASA were subsequently printed using an FDM 3D printer, and varying the weight and densities of the printed tablets was achieved by selecting the infill percentage in the printer software. (9)

The feasibility of using a fused deposition modelling (FDM) based 3D printer was investigated to fabricate extended release tablet using prednisolone loaded poly(vinyl alcohol) (PVA) filaments and to control its dose. **Prednisolone** was loaded into a PVA-based (1.75 mm) filament at approximately 1.9% w/w via incubation in a saturated methanolic solution of prednisolone. The physical properties of the drug were evaluated using differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). In addition to that, the Dose accuracy and in vitro drug release patterns were assessed using HPLC and pH change flow-through dissolution test. (10)

Binder jet printing is another most successful three-dimensional printing (3DP) technology in the pharmaceutical industry to date. In 2015, the binder jet process was adapted as an alternative mass manufacturing technique to enable the production of Spritam® (the first 3D printed tablet) approved by the Food and Drug Administration (FDA).(11)

Understanding the rheology of the polymer and API–polymer mixtures is necessary for successful 3D printing of dosage forms or printed structures. The process perspective for polymers on extrusion-based 3D printing was summarized in a study.The comparison of 3D printing with the traditional direct compression process, the necessity of rheology, and the characterization techniques required for printing were elaborated in the study. (12)

When it comes to selective laser sintering (SLS) printing, it has remained least explored for pharmaceutical applications. There are several challenges in adopting a SLS method for fabrication of personalized medicines. Solvent-free nature, availability of FDA approved thermoplastic polymer/excipients (currently used in hot melt-extrusion process), minimal/no post-processing step, etc. are some of the advantages of the SLS

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printing process. Thermal stability of drug and excipients is one of the major barriers in adoption of SLS in 3D printing. A review was conducted to provide an overview of the SLS printing method, excipient requirements, process monitoring, quality defects, regulatory aspects, and potential pharmaceutical applications. (19)

FDA recently approved a 3D-printed drug product in August 2015, which is indicative of a new chapter for pharmaceutical manufacturing. This review article summarizes progress with 3D printed drug products and discusses process development for solid oral dosage forms. (11)

II. DISCUSSION:

3D printing has a great potential in the pharmaceutical industry and it could be a game changer for the traditional manufacturing procedures of pharmaceutical formulations. Out of the common types of 3D printing techniques, FDM is one of the most promising technique for manufacturing pharmaceutical dosage forms with improved quality, pharmacokinetics, dosage form design, geometrics, physicochemical properties etc. Additionally, studies have shown that use of FDM can help to produce drug delivery systems of diverse dosage forms ranging from capsule shells to immediate release tablets. The paucity of adequate filaments composed of pharmaceutical grade materials needed for feeding the FDM equipment still remains a challenge.

Another promising 3D printing technique is binder jet 3D printing and it has also been used for successful manufacturing of an FDA approved drug.Whereas when SLS printing is considered, there is much research needed to explore novel and effective formulation aspects.

Applications and challenges:

When the application aspects of 3D printing in pharma industry are considered, the technique can be used for the preparation of orally disintegrating formulations, preparation of compound formulations, preparation of high drug loading formulations, preparation of special and customized geometric shapes and improving drug release by regulating geometric shapes and so on.(20)

Manufacturing of personalized medicine is another application of 3D printing in pharma. However, extensive research is still necessary to make the 3DP techniques industrially feasible for dosage form formulation. Nowadays, only one FDA-approved product is on the market. The printable products must comply with the current regulatory standards and quality control aspects. Due to the large number of the factors affecting the quality of computationally designed dosage forms and safety of their use, the appropriate regulatory requirements are very desirable. Till the date, there are no valid regulations for use of 3DP in manufacturing of pharmaceuticals. There is a strong need to make some regulations for this particular group of manufacturing methods. (18)

Early-Phase Drug Development, dose flexibility, reduced labor and resource investment unique characteristics, personalized medicines, personalized medicines in geriatric and pediatric patients, medicines with complex dosage regimes and rapid administration and improved medicine access (5) are some the other applications of 3DP in pharmaceuticals. (5)

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CONCLUSION :

The aim of our study was to evaluate the potential of 3DP in pharmaceutical industry. Several existing experimental aspects and literatures on 3DP were studied throughout this review. If we evaluate and compare the work done by researchers, it can be seen that in addition to current applications, 3DP has yet to be fully explored to implement its use on a large scale in pharma industry. The techniques used currently are fast and cheap, but are not much reliable if considered

Additionally, availability as well as compatibility of suitable polymers and other pharmaceutical parameters are huge challenges in 3DP. As far as the regulatory challenges are concerned, there is a need to set suitable quality control parameters, manufacturing as well as safety guidelines to ensure the quality of products.

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