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Implementation of Three-Dimensional Printing in Phamaceuticals

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ABSTRACT: Three-Dimensional Printing is a novel technology of additive manufacturing which encompasses the usage of computer science along with pharmaceutics. The technique utilizes a computer design software and programming which ensues a 3-D model where consecutive layers of material are deposited to create a scaffold. Considering the outbreak of bizarre diseases, it was vital to change the traditional approach to something more specific. This invention led to the dawn of individualized therapy which was much necessary as the diversified nature of ailments demanded more specificity in therapeutics.It is ascribed to be one of the most innovatory and influential tools which would completely change the face of pharmaceutical manufacturing style and would bring a new era in regenerative medicine and individualized therapy.

This review entails the majorly used methods of 3DP used in pharmacy along with its salient applications essentially emphasizing on personalized medicine and also the challenges faced by the technique.

I. INTRODUCTION:

Three-dimensional printing (3DP) is an innovative approach, corroborated by Computer Aided Designs (CAD). Among the plethora of discoveries introduced into pharmaceutical and biomedical industry, three-dimensional printing (3DP) is believed to be the most radical and felicitous. This technique serves as amultifaceted tool for pinpoint manufacturing. It serves as a technology for developing specific dosage forms, tissue and organ engineering as well as disease modelling[1].

The term three-dimensional printing was defined by International Standard Organization (ISO) as: "fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology". This technique can be precisely defined as the series of processes involving layer-by-layer engendering of an object using a digital image[2].

The necessity for individualized therapy has been on the table of revolutionary pharmacists for decades due to increasing heterogeneous nature of prevailing diseases creating complication in therapeutics[3].

The idea of 3DP emerged from the early 70's when Pierre A.L. Ciraud introduced the application of powdered material and ensuing layer by layer solidification through the action of high energy beam. In the following decade of early 80's, Ross F.Housholder delineated an idea of sand binding by different materials and Carl Deckard elaborated the method of Selective Laser Sintering (SLS). In 1981, a Japanese doctor, Dr. Hideo Kodama patented an application for rapid-prototyping apparatus but was unfortunately rejected as it did not meet the one-year deadline. He was the first person ever to apply for a patent regarding laser beam resin curing system. Even though his efforts were futile but this idea was still in discussion among the researchers.Finally in 1984, Charles Hull patented stereolithography as the first commercially available rapid prototyping technology.Consequently, 3DP caught attention of various researchers and since then it is an ongoing process of extensive development[3, 4.]

3DP can bolster the process of individualized therapy in an enormous manner not just by enhancing the flexibility of doses, but also reducing the cost, increasing the pace of formulation production, modifying the characteristics pertaining to its release. This article is directed towards the recent applications and accomplishments in the field of pharmacy with the aid of 3DPrinting. Among the various approaches limned in the review, the novel approaches in the formulation of solid dosage forms for individualized therapy are particularly emphasized. As the revolution in pharmaceutical sector is on boom, the 3DP is making the conjectured personalized therapy to be feasible through its applications[5].

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II. METHODS:

The technology like 3DP involves various methods to accomplish the operations which are divided in three categories:Inkjet printing system, Nozzle based printing system and Laser based writing system. The three methods of 3DP gets distributed in various methods among which the article elucidates the methods which are most relevant to the pharma industry and are responsible for the substantial development in the production of pharmaceuticals[6].

The described methods are stated below:

1. Fused deposition modeling.
2. Binder jetting.
3.Selective laser sintering.
4.Stereolithography.

1.Fused deposition modeling (FDM):

The 3DP technology named Fused Deposition Modeling is one of the most popular method among the bunch available. FDM is adaptable with perquisites in exactness of quantity and ability to ingrain different densities of the material filled. The FDM method is known to be a frugal and can bolster the production of convoluted designs. The FDM uses a technology which is known as Hot-Melt Extrusion (HME technology) in which thermoplastic filaments or ink roll are extruded in sequential layers to engender an object. A thermostable drug can be created using HME technology in FDM method, which is otherwise quite precarious when tried using different methods[7, 8].

CAD designs are preceded by selection of filaments and extrusion further layer-by-layer for forming a 3D object limned in CAD design. An enhanced efficiency and the variations in batch-to-batch manufacturing of pharmaceutical product is observed using the FDM method. An increased loading of Metformin HCl onto PVA was observed in the research by Mariam Ibrahim et.al using the Fused Deposition Modeling and various parameters were observed which impacted the dissolution rate[9].The intra-gastric floating of Domperidone drug using hollow tablets made by FDM was observed in research done by Xuyu Chai et.al[10].

2.Binder jetting:

Binder Jetting is a multi-step additive manufacturing process initiated at the Massachusetts Institute of Technology in 90's and was commercialized in year 2010. The technology mainly couples the powdered formulationwith a liquid binder which is used accordingly. This method of Binder Jetting is analogous to that of other methods of 3DP, where the layers of solid metal or ceramic powder/ layers are aligned and jet of liquid binder is then spread or deposited which glues the powder spatially where the CAD indicates to bind them together. The approach of the binder jetting has resulted in a uniform content (isotropic) and an accuracy of binder deposition[11].

The first 3DP based drug to get FDA-approval Spritam (Levitiracetam) is an orally disintegrating drug with a dose variety of 250 mg, 500 mg, 750 mg and 1000mg used for the treatment of epilepsy was engendered using the Binder Jetting method by Aprecia Pharmaceuticals[12]. In an experiment performed by Katstra et.al, projecting the release of the chlorpheniramine maleate was observed to be delayed when binders Eudragit RLPO and Eudragit E-100 were used showing the variation on par with the polymer content; validating the research the mechanical properties of the manufactured tablets were analogous to that of the compressed tablets. However, the post-processing of the Binder Jetting technique like curing, de-powdering, sintering, infiltration, annealing is time consuming, which is one of its drawbacks along with the multistep processes its follows and the abrasion on surface caused along with lower resolution[13].

3.Selective-laser sintering:

As the name suggests, Selective-laser sintering is a process which involves the exposure of Active Pharmaceutical Ingredient (powder) on the powder bed to laser, which incites them to sinter spatially. Following the exposure, the powder tends to bind together on a path directed by the laser, thus fabricating a 3D tablet when performed layer-by-layer. The printer in this process involves a powder bed, a reservoir which contains the material to be fed, which is put forth on the surface of the bed and high-power lasers are then used in a germane manner as described by the geometric details (G-code)[14].

The process sounds relatively fair at the first glance with advantages such as the process doesn't involve the use of solvents, enhancing the speed of manufacturing, the temperature at which the SLS operates is relatively lower, the products produced are of high resolution due to the precision of the application of laser and it can be used to formulate porous tablet with a rapid disintegrating nature, but it also suffers from some disadvantages involving the influence on material which are laser sensitive, furthermore, a consistent flow of powder

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and a layer of specific height is required in printing of ample amount of powder. The practical application of SLS was studied in an experiment by Awad et.al, where the drug pertaining a property of modified release was fabricated using this method. The use of ethyl cellulose was done as a polymer for the fabrication of single mini-printlets where paracetamol was employed as a model drug and use of two polymers, ethyl cellulose-for sustained release and Kollicoat IR (polymer ingrained with PEG & PVA in the ratio of 1:3)for immediate release, was done in case of formulating dual mini-printlets containing paracetamol and ibuprofen[14]; similarly in an experiment performed by Fina et.al, the accelerated release property of drug was observed in an orally disintegrating formulation, where polymer Hydroxypropylmethylcellulose (HPMC E5) and copolymer Vinylpyrollidone-vinyl acetate were mixed separately with paracetamol (5%), as the model drug and Candurin® Gold Sheen as colorant[15, 16].

4.Stereolithography (SLA):

Stereolithography, sometimes also referred as Vat polymerization involves the use of ultraviolet light or a laser. The method is executed by a controlled beam from an ultraviolet-laser source which is made incident on the photocurable resins; the material being photosensitive gets polymerized in a selective manner. The process is applied until the initially fabricated 2D layer gets conglomerated in a desired 3D structure when the process is executed in a layer-by-layer fashion. On the completion of the process, the resin layer which remains uncured can be repudiated back to be cued again or can be removed to attain a desired structure, thus resulting in an enhanced integrity between the layers. The main advantage that bolsters the use of SLA is the enhanced resolution of the cross-linked polymers when compared to other methods of 3DP, without involving the use of high temperature, thus inciting the use of thermolabile drugs. The complex shaped structures (cylindrical, spherical, cubical etc.) gained through application of SLA helps in influencing the property of drug release[17].

The influence on drug release property was projected in an experiment conducted by Martinez et.al, which was fabrication of drug-loaded hydrogels containing ibuprofen with polymer polyethylene glycol diacrylate (PEGDA). They fabricated hydrogels containing 10% w/w ibuprofen and water content with up to 30% w/w and as the outcome, the enhanced drug release profiles was observed, portraying the potential of SLA based 3DP[18].

Analogously, Wanget.al. in an experiment involving paracetamol (acetaminophen) and 4-aminosalicylic acid as the model drugs and PEGDA as a monomer, with diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide as photo-initiator, printed tablets containing polyethylene glycol 300 (PEG300) in the solution and observed that the specific drug release profiles of the tablets with different drug contents was not only independent of the dissolution pH, but rather gets refashioned by the composition of the tablets[19].

APPLICATIONS OF 3DP:

Accustomed Pharmacy was introduced some 200 years ago and through the years it has been on the track of amelioration quite extensively. With having its own advantages, it also has been confined to conventional approaches. 3DP has caused a paradigm shift in the way therapeutics work, by introducing the notion of individualized therapy[20].

3DP has applications in profuse areas but mostly it has turned around the scenario of healthcare industry by introducing some revolutionary dosage forms, such as: microcapsules, hyaluronan-based synthetic extracellular matrices, antibiotic printed micro-patterns, mesoporous bioactive glass scaffolds, nano suspensions, and multilayered drug delivery devices[21]. Backing the notion some of the applications of 3DP are:

1. Personalized Medicine:

The execution of Precision Medicines Initiative in the U.S. in 2015 led to the emphasis on the point that the medical sector is moving away from the ‘one-size-fits-all’ notion and approaching towards individualized therapy[5].

Conventionally, the drugs are manufactured in bulk with a few dosage variety on the basis of majority of population. Evidently, that one dose might not be appropriate for all, as it can range on the basis of patient’s age, weight, genetic profile and disease state. This comprehended that the field of personalized medicine which involves tailored dosing and altering other aspects of the formulation according to the requirement of the patient is necessary[5]. Following are the aspects of the modification of the formulations:

- **TAILORED DOSING:**

Generally, in the field of pediatrics and geriatrics, tailored doses are needed due to the frequent fluctuations in the dose based on the blood

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level (Ex: Drugs with narrow therapeutic index). Consequently, it leads to splitting of formulations to achieve the correct dose which often leads to medication error (over-dosing or under-dosing) and inconsistency.

To circumvent such adversities FabRx designed a personalized medicine 3D printer, the M3DIMAKER which was incorporated into a hospital treating children with an acute metabolic disorder called the Maple Syrup Urine Disorder (MSUD) which involved oral supplementation of isoleucine; the dose of which was tailored according to the blood levels[21].

This innovation led to formulation of variety of dosages, colors and flavors which were assessed for patient acceptability and dose control. This caused a command over target blood concentrations compared with standard therapy.Favorably, 3DP is a highly pliable process which permits easy alteration of dosages as required by the patient by physically altering the tablet dimensions or infill percentage.This study caused a revolution in 3-D printing history and depicted the actual benefits of this approach in the pharmaceutical arena[22].

- **TASTE MAKING:**

In non-compliant patients, taste masking is needed due to the unpalatable nature of the formulation. (Ex: Bitter tasting drugs). Resultantly, it is a real challenge to administer formulations with non-elegant taste to such patients.

So, as a solution Scoutaris et al. 3D printed a taste-masked dosage form called Haribo jelly beans (Starmix) with indomethacin as the chief API which was palatable. It was evaluated for accuracy, content uniformity and rapid dissolution and patient acceptability at the most. It was approved faultlessly as it mitigated the administration of drugs to younger and older patients[23].

- **SIZE AND SHAPE OF TABLET:**

For the patients with regurgitation problems, size and shape of the tablet matters and it affects patient acceptability vigorously. Goyanes et al. used the FDM method to produce 10 different printlet shapes and studied the influence of different shapes of tablets on patient compliance and it was found that torus tablets (donut-shaped tablets) were easiest to swallow. Also, Yu et al.'s study corroborated that the doughnut-shaped drug delivery devices depicted linear drug release capacity on the basis of concentration of the sustained-release polymer[24].

Shin et al. and Tagami et al. discovered the impact of the size of the tablet on the drug release. They came to a conclusion that smaller tablets have quicker drug release due to large surface area whereas larger tablets presented a slower drug release[24, 25].

- **MULTI-DRUG THERAPY:**

With the aging population, polypharmacy is an increasing concern which is causing dosing errors and non-adherence of drugs. 3D Printing provides the flexibility of production of tablets with more than 1 API characterized by different properties. Hence, patients suffering from multiple disorders can be given personalized drug formulation in one multi-dose itself, thereby providing accurate dosing with better patient compliance[26].

Khaled et al. produced a polypill via 3D extrusion-based printing to treat patients suffering from diabetes and hypertension. This medication consists of a captopril compartment joined by a layer of a extended-released compartment of nifedipine and glipizide. After administration of this multi-dose, the joining layer disintegrates rapidly by splitting the formulation into a captopril compartment and a sustained-release compartment of nifedipine and glipizide. With such formulations providing desired drug release profiles, patients with risk of various diseases can be treated concurrently with a single tablet. Also, Gioumouxouzis et al. coupled metformin and glimepiride into the eudragit sustained-release layer and polyvinyl alcohol release layers respectively to develop a multi-drug formulation for diabetes patients[27, 28].

2. Drug Delivery Systems:

- **TRANSDERMAL DELIVERY SYSTEM:**

Transdermal Drug Delivery System (TDD) has been employed in the pharmaceutical sector since 1981 as an alternative for oral and parenteral administration. This system was advantageous for the drugs which gets degraded in the GI tract and eliminates in the first-pass metabolism[29, 30]. Although, there are some limitations like the stratum corneum is restricted to the drugs size <400-500 Dalton, lipophilicity of log P1-3 and potent molecules with elimination half-life <10 hrs and low oral bioavailability. Microneedles are the majorly used apparatus in TDD which are micrometre sized needles (hollow

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or solid) which penetrates only through outermost layers of skin excluding nerve receptors in reticular dermis but this method falls back in certain aspects like deviation in the desired shape and size, drug dissolution and availability of drug at therapeutic level[32].

Recently, a research on microneedle stereolithography was conducted by Cristiane et al. to produce needles with appropriate shape and size, also inkjet printing was executed to coat the microneedles with insulin which depicted rapid in-vitro dissolution of insulin, however,applications of this technology in this particular system is still in the assessment phase[31].

J. Fu et al. successfully manufactured vaginal rings for controlled delivery of progesterone by FDM. Additionally, Goyanes et al. used 3DP and SLA to create a transdermal patch that fits the shape of the individual patient's nose. Also, Lu et al. developed painless transdermal drug injections by creating an array of 25 microneedles made up of fumaric acid that resists the pressure of piercing the skin [29, 30].

- **CELL-DELIVERY SYSTEM:**

3DP technology was able to successfully fabricate 3D mesoporous scaffolds which were used to adjust loading and unloading activity of pharmacologically active substances such as antibiotics, growth factors, etc. Antibiotic-laden delivery systems were formulated that reduces the post-surgery infection. Aldrich et al. developed a 3D-printed scaffold with anti-bacterial activity for treatment of bone infections after craniotomy. After the evaluation, it was found that the local application of anti-microbial provide increased drug delivery than that of intravenous administration and many more scaffolds has been fabricated to corroborate a better and well-regulated antibiotic delivery[33, 34].

Additionally, Anti-HIV drugs including emtricitabine, tenofovir and efavirenz were successfully loaded in a 24-layered rectangular prism-shaped 3DP fabricated controlled release fixed-dose tablets which was able to control the intestinal release of the API[33].

3. Complex Drug Release Profile:

3DP also assisted drug release profiles of various drugs that allows the fabrication of complex geometries. With the utilization of FDM, tablets were developed and injected with paracetamol (APAP)-containing gels. Its assessment concluded that the in-vitro drug release of the tablets can be altered according to the requirement and these release attributes can be managed by using different 3D printed geometries. This study was believed to have a promising potential in further development of patient-centric medicines[26].

As the applications for this notion, a multi-layered bone implant was developed with a distinct drug release profile interchanging between rifampicin and isoniazid in a pulse-release mechanism. In a research, Chlorpheniramine maleate was used to demonstrate that even a minute quantity of drug as small as 10-12 moles can be released at a specific time which was a display of improved accuracy for the minute drug doses as compared to the traditional approach[35].

Skowyra et al. produced prednisolone sustained-release tablets using the FDM printer[36]. Additionally, Melocchi et al. and Chai et al. explored the possibility of sustained-drug release formulations for different prospects[37]. Additionally, Zhang et al. studied the association between the drug release and the shape of 3D printed tablets with the implementation of FDM.The 3D printer was used to develop bilayer tablets with a definite release profile by utilizing hydrated HPMC gel layer[38].

4. Drugs with complex dosage regimens:

Traditionally, administration of medicines with complex dose regimens was meticulous as there was the risk of over-dosing or under-dosing. 3D printing can create a printlet containing the exact dose of the drug as required without any deviation. This has been attained by using FDM to 3D print theophylline which is a narrow therapeutic index drug to treat asthma along with other drugs such as prednisolone and budesonide[5, 8].

5. Rapid Administration and Improved Medicine Access:

3DP can be applied across a surfeit of healthcare services, ranging from community pharmacies to hospital wards to improve medicine access to every part of the society also with the advantage of reduced medicine wastage and accelerated discharge timings. This approach could even be integrated into disaster areas, emergency departments, first response units and military operations where the rapid administration of medication is required at utmost exigency.It could also be integrated with other technological evolution such as cloud-based computing, smart health monitors and various others[5].

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6. Bio-fabricated in-vitro models for study of diseases for therapeutics:

Since the dawn of therapeutics, a lot of experiments have been conducted along with the investment of billions of dollars. In this field animal models have immensely contributed to the exploration of every kind of drug for the pharmacokinetic and pharmacodynamic study but being the drawback animals cannot completely recapitulate the human-pathogen interactions, resulting into dissatisfaction and also failure in clinical trials. Therefore, through 3DP advanced in-vitro models have been developed to create human tissue scaffolds along with the furcation of the microenvironment for the progress in therapeutics. These 3D-printed models can be beneficial as they will represent the most complicated structures in the human and aid in the study of complex organs[20].

Nupura et al. developed a liver-on-chip platform to assess drug toxicity by 3D printing HepG2/C3A Cells. After the assessment of optimum liver function, a hepatotoxic reaction was induced with acetaminophen (APAP), in the bioreactor without APAP treatment metabolism was increased by 78±4 % and in the bioreactor with APAP treatment metabolism was decreased by 63±2 %. It was established that liver-on-chip is responsive to acute toxic drugs and can be used for drug screening[39].

Zhang et al. constructed an endothelialized heart-on-chip via induced pluripotent stem cells. Cardiomyocytes were cultured on a 3D printed scaffold with the sarcomeric α-actinin protein for contraction and connexin-43 for conductivity which made the cardiomyocytes beat strongly. Then they tested the cardiac toxicity of doxorubicin; the beating rates of cardiomyocytes exposed to 10 μm and 100 μm dropped to 70.5% and 1.62%, respectively. It was established that the heart-on-chip has the potential for drug screening[40].

Eventually, some researchers started using 3DP organ models for drug screening. Organovo, a bioprinting company and Roche, a pharmaceutical company used "3D-printed Livers" to test different drug toxicity levels of trovafloxacin. Additionally, Heinrich et al. produced a 3D-printed mini-model of brain that contain Glioblastoma-associated macrophages (GAMs) and Glioblastoma multiform (GBM) to simulate the interactions between the two cell types to test the efficacy of anti-tumour drugs[24].

CHALLENGES IN 3DP:

In the favor of aforementioned applications 3DP is having a huge impact in the evolution of pharmaceuticals. It has shown promising results in various aspects but it also faces many challenges. The 3DP technique is not that archaic as it seems therefore, there is an immense potential of development. It has promising implementation in drug delivery but it falls short when it comes to optimization processes, performance improvement and post-processing. As 3DP is a novel approach, the materials required are limited. Also, it deals with the dearth of expertise among the workforce which is a critical element as for this technology to flourish extraordinarily engineers, managers and executives must understand AM truly. Additionally, lack of standards has an impact on creating the standard operating procedure for the process. 3DP being a high-end process, the equipment costs are very high which might restrict the manufacturing. It also needs brilliant software as the CAD model is the kernel of this whole AM technology but reserved capabilities in data preparation and design restrict the process but it has a lot of scope of development.

3D printer manufacturing has been an area of robust development lately. Most of the manufacturers target to develop the modular systems which can increase the throughput of the process as the German hardware manufacturers, EOS is in the production to increase the productivity of its Laser Pro Fusion Technology. They aim to equip the 3D printer of 1 million diode lasers in the SLS system to accelerate the printing time.

Solely, the operation of bringing a drug to the market costs about a billion dollars so, AM too takes a vigorous amount of time and effort along with a heavy investment. The capital is not only required for the equipment but also for the software, materials, employee training and an appropriate facility to accommodate all this.

These challenges are very much the reason that 3DP is limited to certain prospects but as the ongoing exertion to take a hold of them, it is not a distant vision that 3DP will gain its summit in the pharmaceutical arena[41, 42]. where the tip radius was less than 3.5璷m and 4

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