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3d-Printing- An Emerging Trend In Medicinal Field With A New Future Potential

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Abstract: Starting from its introduction and implementation, 3D printing has not only mesmerised the researchers but also many health professionals. The process of 3D printing is impressive and appealing but it comprises punctilious administration and selective process in order to achieve prudent and expected result. This review article gives historical information about 3D printing and their current application and future trends. Also, the importance is being given to the acknowledgement of best fit product and ways to reduce faults and misapplication. The primary benefits of 3D printing are production of lot of medicines, each with specific dosages, shapes, sizes, and release features. In the period of personalized medicine, new platform required to produce the formulations with less toxicity, and to produce required action. This technology enables a flexible process for tailored dosing and drug combinations required. This review mainly focuses on the introduction, principle involved in 3D printing and focused on its working and types of materials used in creating the 3D objects. Moreover, and specifically this review articles showcases the use of 3d printing in the field of pharmaceutics and medicinal applications. **Keywords: - 3D, AM, Spritam, CAD, STL, FDA, MIT, Prototyping,**

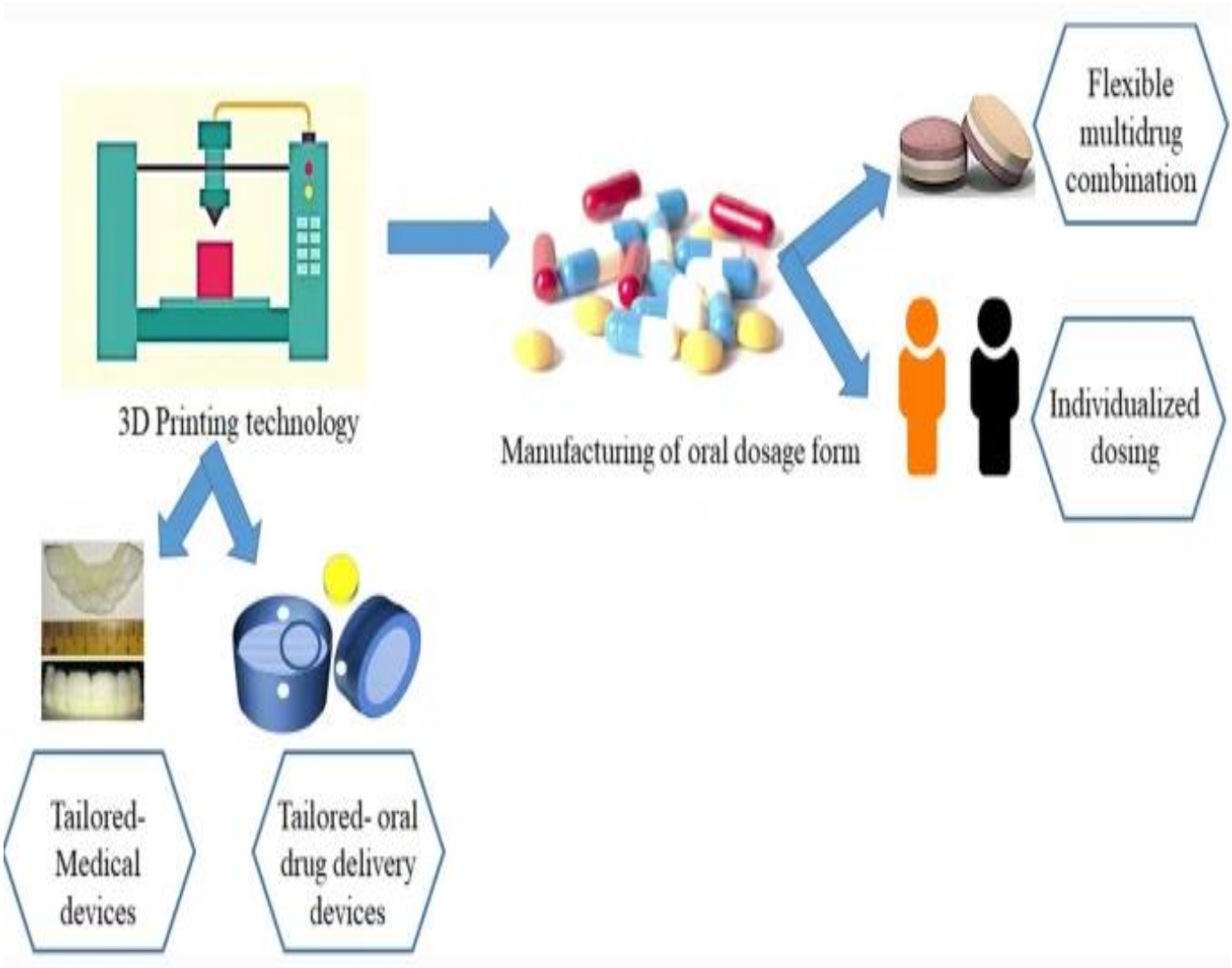
Introduction: - As the term (3D)-Three-dimensional printing was used to showcase the layer by layer deposition of binder material by the inkjet printer heads, onto a powder bed.3d printing was mainly informed so as to rapidly replace so as to give inexpensive and economical substitute to industrial prototyping process.as it has become now the first choice of industries for prototyping thus, it is also said as Rapid prototyping (RP). [1] It was first described by Charles Hull as "stereo lithography" in 1986 and is an influential unique technology. It uses "STL file format" to interpret the data in CAD (Computer aided design) file. The same facts and recorded instructions are communicated to the 3D printer by electronic means. The instructions comprise the parameters like shape, size, texture and thickness of the object to be printed. The 3d Printers produces 3D drug products from digital file. The 3DP technology is unparalleled, flexible, rapid and with exceptional manufacturing capability of pharmaceutical drug products of desired quality. [9] The system was first developed at the (MIT) Massachusetts Institute of Technology (1992) and is centred on CAD models that are manipulated by a terminal computer system. [7] Today people have noticeably understood the tremendous potential of 3D printing and therefore are said as third, fourth and fifth industrial Revolution. [4] Nowadays rapid development and reproduction of 3D printing technology in medicinal field is being broadly used in researches, teachings orthotics, prosthetics for personalised implantations, tissue printing and pre-surgery tissue 3D modelling. [3] New possibilities in 3D printing may open up opportunities for Medicinal research followed Pharmaceutical applications. This technology impacts pharma business model. Pharmaceutical drug research and development (R&D) could be developed extremely by 3D printing. It could add a whole new dimension of possibilities to personalized dose and personalized medicine. [2] Some 3DP technologies suitable for pharmaceutical manufacturing and their applications in the improvement of dosage forms, indicating the opportunity of 3DP technology in regular marketable fabrications and the same is been presented in this review.

Advantages of 3DP in Pharmaceutical Drug Delivery: -In comparison to the processes of conventional pharmaceutical product manufacturing, 3DP therapeutic windows, deals with a lot of striking qualities resembling [21] -

- High rate of production because of its fast functioning systems,
- low-cost of production, mainly due to labour free work
- Capacity to customize products i.e. ability for the production of 28 minor batches of personalised dosage forms at a time straight at the point of care where, not just the dose is viewed as the design of the tailored medications but also the patient's distinct characteristics, preferences and needs. This is not possible by means of conventional manufacturing procedures as the same has bulk manufacturing of
  dosage forms intended for desire actions on the majority of the patients [29]
- Wastage of materials is minimised
- Capability of achieving high drug-load with much-desired accuracy and correctness mainly for strong drugs that are useful in minor quantities,
- Speedy fabrication of samples,
- The safety, efficacy, and availability of medicines is improved
- It enables compliance to wide types of active pharmaceutical ingredients including poorly water-soluble, proteins and peptides, also drug with narrow

WHAT IS 3D PRINTING:

When Looking by important perception from 2D paper printing, 3DP is additive manufacturing (AM) technology, where layer by layer accumulation of material is done in order achieve a desired shape. 3D printing can be said as a sunshade term for a variety of technologies like objects, medical device, drug products, human organ, biomaterials other inactive ingredients, Building materials, and complex things. [5] The pharmaceutical manufacturing of drug products has gained quite consideration currently. And owing to its several characteristic benefits above the conventional technologies, including the personalization and customization of medications with independently accustomed dosages, the ability to engineered multifaceted, precise and accurate solid dosage forms on request. Various drug delivery systems have been developed using 3DP technology, such as oral, pills, implants, immediate release (IR), controlled released tablets, microchips, and multiphase release dose formulation. The personalized dosage forms are on demand and desired to prevent excessive adverse effects, simplify the dosing frequency and attain personalized release profiles. The fabrication of tailored drug delivery systems has got quite support due to implementation of surfacing 3DP technologies. [6] Furthermore, it has the potential to reduce the risk of failure at the later stages of new drug development process, as this technique can be deployed to fabricate more predictable drug screening platforms. [10] The first 3D printing technique used in pharmaceutics was achieved by inkjet printing a binder solution onto a powder binding, therefore the particles together thanks to the semi-liquid binding solution. The process was continuously repeated until the final desired structure was obtained. This first happened in the early 90's at the MIT (Massachuset Institute Technology)



FDA approved tablets named "Spritam" (Levetiracetam) as the first 3D printed drug and in summers of 2016 Aprecia Pharmaceuticals released it in the market. [11] 3D printers are used to print various porous scaffolds with controlled chemistry, interconnected porosity and

special shapes. These prints are biodegradable and proved to be ideal for drug delivery abilities. [22] Some of the highly complex structures

incorporating living cells can be created by this technique and has gained popularity and applicability in cancer treatment. [23]

EXAMPLES OF BIOMATERIALS [8]:

Table No.1: Biomaterials used in the various medical applications of 3D Printing

Sr.No	Materials	Current explored applications
1	Polyester textile	Vascular graph's and heart stents
2	Polyurethane	Pacemaker lead insulation
3	Silicones	Ophthalmological devices, Soft tissue augmentation
4	Poly (methyl methacrylate) PMMA	Bone cement
5	Carbon	Heart valves
6	Stainless steel	Stents and orthopaedic implants
7	Titanium alloys	Dental implants, spinal cages, heart valves, fracture plates

Historical journey of 3D printing in medicinal field:

The initial try-out was conducted on 3D printing by printing multi-delivery device in year 1996. Methylene blue and alizarin yellow dyes were placed in device in 3D form and its conformation, microstructure were operated and was prepared in controlled release form. A square shaped design of polyethylene oxide (PEO) was printed and dyes were localised in the square. And a bottom and top sheet of Polycaprolactone was printed to cover it in order to avoid diffusion. This device exhibited a multiphasic release profile of dyes. [24] A cellulose tablet was formulated using cationic methacrylic ester (Eudragit E-100). Also Eudragit RLPO was used to formulate controlled release profiles tablets. It was concluded from the dissolution studies in stimulated intestinal fluid that drug release time was increased as the binder concentration within tablet increased. [25] Diclofenac tablet was designed comprising of its 2 sections with different binders in both sections resp. And first section was made-up using E-100 which is sensitive to the low pH inside gastric fluid and release inside stomach whereas Eudragit L-100, sensitive above 6-pH value thus, got release in intestine. [26] highly dissolving tablet were made with dense layers at top, bottom and lateral layers and the inside of pill was filled with loose residue along with binder for increasing the stability. 23.5 s was the disintegration time noted with in-vitro dissolution and found released within 2 min. [27] Also, manifold drug release profile tablets was formulated comprising of three different drugs in it – Captopril, Glipizide and Nifedipine. The formulation was evaluated for dissolution and was establish that Captopril showed 0^0-order release of an osmotic pump while, Glipizide and Nifedipine showed both 1^0-order release or Korsmeyer-Peppas release kinetics, according to the excipient ratio used. [25]

Types of 3D printing technologies that are utilized on large scale these days are:

I. **Fused deposition modelling (FDM)-**

Fused Deposition Modelling Printers are most inexpensive and thus common than the Selective Laser Sintering type. The print heads used by FDM printers have similarity to an inkjet printer. [12] Though, beads of heated plastic are released instead of ink from the print head during movement and structuring the thin layers of object. The process is repeated continually to shape each layer precisely, regulating the amount and position of each. This is because the material is heated to fuse and create bonds to the layers below. [17] The computer-aided model is used by 3D printer or information is scanned after which it extrudes or links molten thermoplastic polycarbonate, in a layered manner, in accordance of building objects from lowermost to topmost. The melted plastic layers rapidly chain by one other, hence it enables easy creation of very complex parts that are simple to produce. The resulting aspects of the finished objects can be used as in combination of several materials such as acrylic or wax. [13] Thus FDM has also been broadly used for commercially available pre-processed filaments (for easy and rapid processing) with different types of polymeric materials such as acrylonitrile butadiene styrene (ABS), polylactic acid (PLA), thermoplastic polyurethane (TPU) polyvinyl alcohol (PVA) and high impact polystyrene (HIPS). FDM enables the production of complex objects with high accuracy and using different substances and materials via using multi-nozzle printing systems. [30] It may have enhanced features such as multiple Print heads depending on the complexity and cost of a Fused Deposition Modelling printer. FDM printers can use a variety of plastics. [12] In fact, 3D parts printed by FDM are frequently made from the thermoplastics that are used in old-style injection moulding, so they have similar permanency, robustness and mechanical properties. [17] This method can be used for manufacturing solid dosage forms such as fast dissolving tablets, multi layered tablets and zero order release tablets in medicinal field. Fabrication of a tablet of prednisolone loaded with poly vinyl alcohol (PVA) filaments with extended release was done by utilising Fused deposition modelling technique. [25]

II. **Selective Laser Sintering (SLS)** –

The Selective Laser Sintering (SLS) is another technology used by today's 3D printer is and also known as Powder bed fusion. The powders used are generally nylon (PA), polymer materials. It is similar to Binder jetting (BJ) 3DP but except that instead of a liquid binder to cement the layers, it uses laser radiation to sinter (superficial melting) or fuse the powder materials to form a 3D object. [28] Though throughout this process of Selective laser sintering (SLS), tiny particles of plastic, glass or ceramics are merged by heat from a high motorized laser beam to form a solid. The laser is traced transversely over powder bed according to filed data and the powder inside the powder bed is firmly compacted. The laser moves in the X and Y direction and, on completion of one layer, the powder bed drops in the Z direction then the levelling drum (roller) levels the powder above the surface of the bed to form the design required. These process repeats itself until the printing of whole object. The object is then left to be cooled down. On completion of the process the powder bed is removed from the machine. Major advantages of SLS is that it does not require any structural support for complex parts unlike required in both Stereolithographic and FDM. because of this advantage it helps to save material and ultimately reduces production cost.

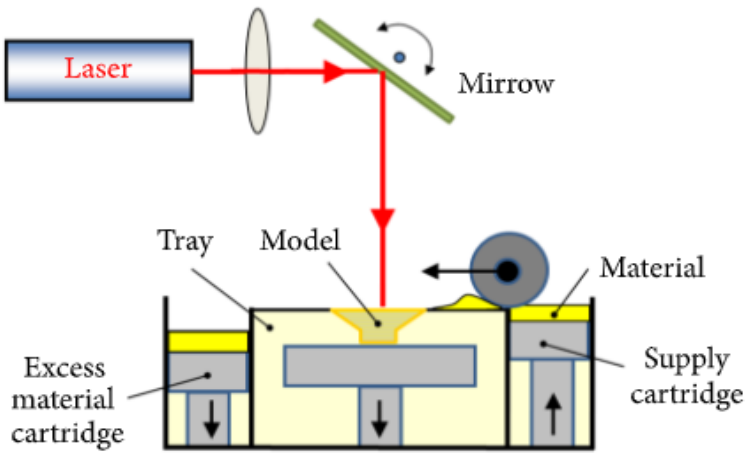


Fig.: Selective Laser Sintering

It generally prints very long-lasting parts [14] SLS offers good control over internal microstructure forming a porous single object. However, the technology has limited sintering speed and sometimes the printed objects show shrinkages or deformations due to thermal heating from laser irradiation. [33] SLS is extensively utilized for printing tailored products like hearing aids, prosthetics and dental retainers. Moreover, objects printed with SLS don't necessitate any moulds or additional tools making it opportune for any user to print complex parts or principally delicate object. [14] The technology has recently been engaged in preparation of modified release tablets of acetaminophen, immediate and the feasibility of the process for the pharmaceutical field has been proven. [34]

III. **Laser-Steriolithography (SLA)-**

Stereolithography (SLA) was first developed by Dr. Hideo Kodama in 1981, as the oldest additive manufacturing (AM) technology. According to his study, it a fast and cheap way of restructuring models in 3D area and as a substitute to holographic methods. [15] Charles W. Hull, patented the first commercially available SLA printer in year 1986. Facilitation of rapid prototyping plastic parts was their main aim. [16] The principle is based upon photosensitive monomer resin, which forms a polymer and solidifies upon exposed to ultraviolet (UV) light. The reaction created by UV light takes place only on the surface of material. [18] Scanning speed, laser control, exposure time, the selection of resin and the quantity of polymer and photo initiator are some key parameters of the SLA method. [31] SLA offers excellent effectiveness, high level of accuracy, adaptability and resolution (0.2 µm), making SLA a superior technique in comparison to other 3DP technologies. [32] SLA has far exceeded its earlier applications in modelling and prototyping and can be applied in manufacturing of highly complex and individually designed geometries. The material is also no longer limited to conventional polymer and even metallic or ceramic specimens is possible. [19]

IV. **Laminated object manufacturing (LOM)-**

Laminated object manufacturing is also called sheet lamination method. It is basically an automated laser cutting and sheet by sheet layering of product. The exclusive feature of this technology is its ability to manufacture complex geometrical parts with low cost of fabrication and operating time. Starting from 1980s, LOM process has been considered many times and arose with encouraging results. [20] LOM has low resolution but is economical and quicker thus useful than most printing methods.

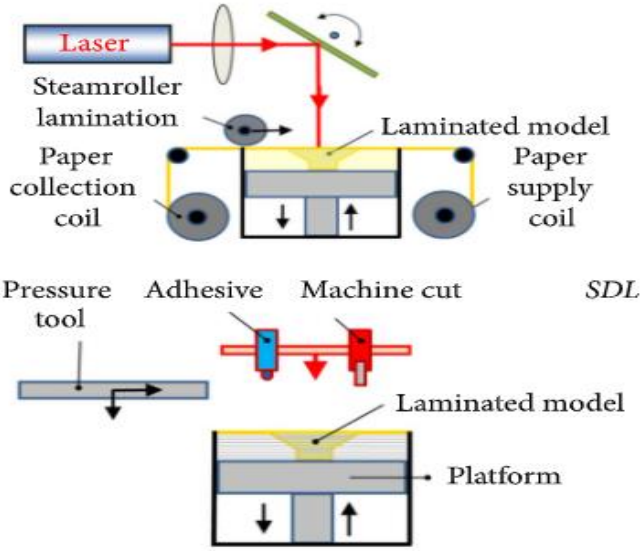


Fig.: Laminated object manufacturing (LOM) technique.

V. **Extrusion method:**

It belongs to Additive manufacturing category. In Extrusion method, from the automatic tap(nozzle), material is extruded onto the substrate. Same as powder bed deposition, but it does not have powder bed and thus necessitate higher grade backing material. Semisolids, molten polymers, suspensions and pastes are the materials that can be extruded. [47]

VI. **Powder bed fusion method:** It is sub category of Additive manufacturing and as the name indicates, it involves the fusion or binding of low melting point with high melting point binders. The laser beam supplies the heat required for the binding. It is a rapid process, but comparatively more complex than extrusion method. [44]

VII. **Material jetting method:**

Of the seven basic additive manufacturing (AM) processes, material jetting is the AM technology that is next to printing text and images on paper. That is because the print heads engaged in material jetting are analogous to those which are used for inkjet printing, but instead of dispensing ink, droplets of material that create a 3D object layer-by-layer are deposited in material jetting. It gives some different advantages above other AM technologies, but then has its drawbacks also. In these the photosensitive material is being jetted and so it is treated through ultraviolet (UV) light instantly after its deposition. Since the layers are thin (approx. 16-30 micron), the material is totally dried when the part is done building. And so, there is no further need of thermal post processing as is case of parts made by various vat photo polymerization practises. [45]

VIII. **Vat Photo Polymerisation Method:**

Vat photo polymerisation method comprises the polymerisation reactions between the liquid resins upon coming in contact of high energy light source or UV. Thus, it needs photopolymerizable raw material specifically for pharmaceutical engineering. So 3D printing of photopolymerizable hydrogels is an example of drug delivery application. [46]

IX. **Direct energy deposition method:**

In direct energy deposition method, the laser or electron beam energy sources are utilised in melting of raw materials sources as they are deposited. The material that cannot be extruded such as powder or other raw materials are used in this method. [41]

X. **Binder deposition method:**

It belongs to category Additive manufacturing technology. In this process, the inkjet printers spray formulation of drug or binder onto the powder bed in the form of small droplets at optimum speed. The liquid formulation is the binder which is available in the printer whereas the API and excipients are the powder bed. The API in the form of solution or suspension can also be jetted onto the powder bed. [43]

XI. **Inkjet printing method:**

In this 3D printing method, blend of active pharmaceutical ingredients and excipients are precisely sprayed on the substrate in the form of droplets based on two techniques, that is, drop on demand and continuous. In continuous printing, the droplets stream

is constantly sprayed on substrate or otherwise, when not in use it is turned near the waste line. But, in first drop on demand method, the necessary amount of droplets is sprayed on the substrate and when not in use, then are closed. This renders it more useful and stops waste that cannot be achieved in constant jet printing. [39]

XII. Direct inkjet writing method:

It helps in designing a complex 3D shaped tablet or any other object without the necessity of any costly equipment or tools. This enables produce of improved sized assemblies and shapes. A computer-controlled steps is acquired by this method in which ink nozzle moves accordingly to create product with controlled 3D shapes and size. Various ink designs such as are polymer melts, gels, colloidal suspension, waxes, dilute fluids, etc. are employed in direct writing techniques. The solvent and temperature phase change technique or gelation and liquid evaporation methods are utilised later on to for the solidification of these inks. [40]

XIII. Pen based 3d printing:

In pen based 3d printing process, with the help of hand-held device (pen), the process is physically does organising of the layer by layer assembly. [41]

XIV. Zip dose method:

This technique was developed by MIT in late 1980's. In this method the layers of powder are bind together by using aqueous fluids. A high dose and rapidly disintegrating tablets are formulated by utilising this method. Zip Dose technology, is the world's first and only FDA approved, commercial scale 3DP. It has the fastest fast-melt capability available, with significant higher dose loads and extra taste masking choices. It also enables a new world of influential formulation results for NCE (New chemical entity) product candidates in Phase I or Phase II development and testing. Zip Dose Technology helps patients and caregivers including physicians and nurses who need medications with easily administration. Zip Dose thus overcomes patient's challenge and difficulty during swallowing, by allowing delivery of high dose of drugs up to 1000 mg loads, in a fast disintegrating form. Zip dose enables unique digitally coded layering and zero-compression processes. Zip dose technology produces rapidly disintegrating formulations of medications by combining the precision of 3D printing and formulation science. [38]

Fig.: Tablets made using Zip dose method

XV. **Thermal inkjet printing method:**

In thermal inkjet printing method type of printers consist of a regulator that generates heat upon induction of current, and it then heats the aqueous fluid ink till conversion into vapour form which passes out of a nozzle, resulting into droplet form. As degradation of the heat sensitive material happens due to the involvement higher temperatures, as a result of this factor, pharmaceutical applications of this method is reduced. [42]

CURRENT CHALANGES:

Despite the enormous potential, 3DP technology shows numerous technical issues and regulatory hurdles to be overcome in order to achieve significant adoption in the pharmaceutical field for LBDDS. This section highlights the current outstanding technical challenges (including formulation and processing parameters), regulatory challenges and the material issues of lipid species that are needed to be overcome in order to develop the real potential of 3DP in the pharmaceutics. General challenges affecting all the 3D printed formulations include, the reproducibility, especially for nozzle based 3DP technologies (i.e. binder jetting and semi-solid extrusion based), as the printing process goes through multiple start-stop steps throughout printing of single or multiple objects. Additionally, many 3DP technologies (i.e. inkjet, binder jetting and semi-solid extrusion) require post-processing treatment which can obviate the apparent benefits of 3DP technology in the first place. The appearance of the final product can impact on the patient compliance as sometimes the deposition of the layers is imperfect and may be visible. [35] Sometimes the production of highly porous structures can lead to poor mechanical resistance such as higher friability values. However, this can be improved by creating more resistant shell structures in a core-shell tablet design. The optimisation of processing parameters and the selection of materials are basic to ensure the quality of the printed products. [36] Furthermore, post-treatment processes such as drying duration, rate and method can affect the properties and appearance of the final product. This is of significant importance in powder based, inkjet and extrusion-based 3D printing which all require post-operative drying. [37] Some of the issues like quality control of printed dosage forms, legal and regulatory matters, cost-effectiveness, availability of materials and equipment needed to produce medicine of better quality, if solved in future, would ascertain the success of the 3D printing in this area.

Conclusion:

The evolution and implementation of the different 3DP technologies are rapidly happening in many manufacturing areas. 3DP has enabled the preparation of complex dosage forms with accurate deposition of materials, with greater geometric flexibility. These features can improve control, consistency and safety of low dose but potent active mixtures. The commercialisation of 3DP printed innovative dosage forms is challenging, yet is innovative technology and will make a momentous impact on the present pharmaceutical industry. In production of customized product, the 3DP drug delivery systems and medical devices serves as a striking tool. Since few years the concept of 3D printed drug formulation quickly evolved and was focused to improve therapy by patient centric medication.
Formulation flexibility that is otherwise difficult to achieve with the conventional technological processes is possible with use of These technology. AM permits preparation of different kinds of dosage forms with high quantitative and qualitative precision of API excipients ratio, in totally new manner with comparison to old-style pharmaceutical manufacturing. The 3D printing thus serves opportunity to create multifunctional drug delivery systems, multidrug devices and drug inventions for tailored therapies with accelerated release characteristic. Consequently, future research should prioritize the development of paediatric and geriatric dosage forms in personalized dosing and specific drug formulations to ensure desired therapeutic efficacy. Considering all the advantages, AM needs to face few challenges like regarding to design parameters control, biocompatibility of printed material, performance and sterilization. Furthermore, the fragile nature of printed objects, particularly cell based collectively with complex nature of prepared structures needs well prearranged process. However, it can be concluded that in future, 3DP can raise the standard of Pharmaceutical formulations by producing tailored and efficient dosage forms and devices.

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