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3d Printing in the Pharmaceutical and Biomedical Industries

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Abstract: Additive manufacturing, also known as 3D printing, has the potential to transform manufacturing in pharmaceutical and biomedical industries. It is a highly customizable processing technique that can be applied to polymers and other bio-materials. These days 3D printing with novel materials has appealed to the industries as material have been designed to have synergistic properties. In the Pharmaceutical Industries, working with low quantities with accuracy, precise spatial control can be achieved by employing this technique, which allows us to prepare intricate compositions and 3D geometries are possible. With this technology, customization of dosage form is possible. As per the patient needs, the dosage form can be designed with multiple active pharmaceutical ingredients and desired release profiles. 3D printing also finds it applications in the Biomedical field, as it offers great precision and control of the internal architecture and complicated structures found in biological tissues and organs. Advances in past few years have assisted 3D printing of biocompatible polymers and supporting components into complex 3D functional biological tissues scaffolds and living organs. The adaptability of interactions enables the more simplistic manufacturing of complex parts with tailored structures. The potential for polymers to generate well-defined parts, tissues scaffolds, and complex compositions for drug delivery provides an unparalleled route for developing next-generation 3D printed materials having applicability in the pharmaceutical and biomedical industry.
Keywords: 3D Printing, Biocompatible Polymers, Drug Delivery, Artificial Organs.

Introduction:

3D printing is an additive manufacturing (AM) technique, in which a structure is built by depositing material in layers to produce a 3D structure [1]. Additive manufacturing is a subset of rapid prototyping of material, which includes techniques to fabricate models and prototypes faster as there is no requirement for molds etc. to be made for casting [2]. The use of 3D printing techniques has been steadily growing over the last 35 years in pharmaceutical and biomedical industry. 3D printing technology is expected to revolutionize the pharmaceutical and biomedical industry[3].Tissue and organ fabrication, customized prosthetics, implants, and pharmaceutical dosage forms, drug delivery, and discovery are a few examples of the applications of 3D printing that have been explored[4].

There has been extensive research going on in the area of drug delivery and recently the FDA has approved an orally dispersible 3D printed tablet, Spritam (levetiracetam) and there are many more to get approved in the future. Manufactures have a business incentive in shifting from conventional solid dosage form manufacturing to 3D printing due to disadvantages that the currently practiced methods have such as complex, costly and slowly supply chains, decreasing manufacturing and inventory waste, higher labor cost and initial capital required to set up a manufacturing unit[5]. Also, the benefits of 3D printing drug solid dosage forms include, customization and personalization of the dosage form , precise control over the spatial distribution of an active pharmaceutical ingredient (API) within a solid dosage form, ability to produce complex geometries, deposit very small amounts of API, cost-effectiveness, the ease of designing and manufacturing, and allow for the quick fabrication of varying compositions or preparation of varying dose strengths [3,6–13]. Although AM has recently proven to have significant and exciting applications, regulatory and scientific challenges still remain and this technique will require more time and research to improve and overcome this problems[10–12,14].

3D printing finds a lot of application in the biomedical industry as well, several devices, including orthopedic devices, patient-matched implants, surgical guides, and maxillofacial implants and restorative devices can now be fabricated by using this technique. Research laboratories have been successfully able to 3D printed prototypes of medical products such as cartilage and bones, liver, dental and craniofacial spaces, tracheal splints, cardiac myocytes, blood vessels, and pancreatic tissues. Just like 3D printing drug delivery dosage forms, this technology also faces similar challenges[15].
This review highlights the polymeric material properties, 3D printing techniques and polymeric materials that is used for 3D printing of drug delivery systems, organs and biomedical devices.

Table 1. Acronyms of the additive manufacturing techniques

Polymer-based additive manufacturing (AM)	Acronyms
Stereolithography apparatus	SLA
Digital light projection	DLP
Continuous liquid interface production	CLIP
Selective laser sintering	SLS
Selective heat sintering	SHS
Big area additive manufacturing	BAAM
Fused filament fabrication/fused deposition modeling	FFF/FDM
Laminated object manufacturing	LOM

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3D printing process and materials:

3D printing of advanced multifunctional systems including living biological systems as well as life simulating synthetic systems from polymeric materials.

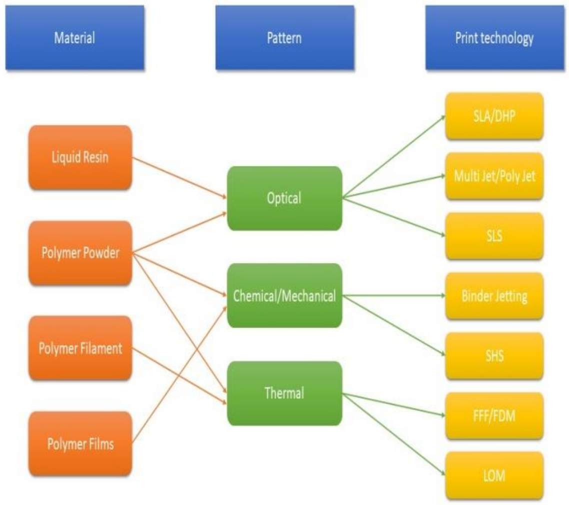

Figure 1: Polymer materials used with specific building methods in 3D printing.

Production of 3D parts can be divided into three major categories – formative manufacturing, additive or subtractive manufacturing . While preformed polymeric materials in powder, filament and film form are used in 3D printing. Several additive manufacturing also utilizes the active polymerization of photo-sensitive resins[16]. The increasingly large number of 3D printing processes can be categorized into diff erent criteria, ranging from the application to the initial condition of processed polymeric materials or the physical principle underlying the layer wise solidification process[17].

The range of polymers used in 3D printing includes thermoplastics, thermosets, hydrogels, elastomers, functional polymers, composites, polymer blends, and biological systems[18]. Characteristics of polymeric material design, building methods, additives, and process parameters as they lead to boosting processing speed and ameliorating precision, functionality, surface properties, stability, chemical and mechanical properties addressed .The polymeric materials used for drug delivery and printing of tissues and organs should be :

1. Physiologically inert: The material been used should be biocompatible and shouldn't cause harm to the patient's body.
2. Physically and Chemically stable with drug: The material should react with the drug. If this occurs then their reacted product may not show any activity inside the body.
3. Free Microbial Burden: The material shouldn't have a microbiologic load as it might adversely affect the patient.
4. No adverse effect on the bioavailability of the drug: The bioavailability of the drug shouldn't be affected by the polymer being used so that the concentration of the drug stays in the therapeutic range and continues to have biological activity in the patient's body.
5. Excellent thermomechanical and surface properties.

The 3D printing design software and the hardware for the AM will continue to improve, conventional and specialized applications of 3D polymer printing will continue to develop with further growth in pharmaceutical and biomedical industry.

Overview of 3D Printing in Drug Delivery:

By using 3D printing technique lower operating costs can be achieved and creates personalized drug delivery systems on demand according to the patients' needs with lower side eff ects. Instant desktop manufacturing can prove to be live saving in cases of emergencies and treatments of elderly people. AM eliminates the issue on shelf stability as well, as the dosage is made on demand.

SLS is used to fabricate implants and drug carriers, which can be loaded with drugs in a treatment. A MIT lab pioneered digital fabrication of resorbable ingredient release devices by means of AM[19]. Binder jetting was used to produce dye model systems consisting of sandwich structures with designed porous poly(ethylene oxide) inside and dense PCL sheets outside. CAD-mediated variations of device compositions and architectures enabled controlled polymer resorption by means of either erosion or diff usion control. Extrusion-based AM methods such as FDM employ drug loaded filaments of biocompatible polymers such as PVA[20−25], poly(ethylene-co-vinyl alcohol)[26], and PCL[27]. The choice of thermoplastics for pharmaceutical FDM is rather limited because elevated melting temperatures cause drug decomposition. To improve both process ability and filament formation of polymers approved for drug release application, polymers such as Eudragit and Soluplus were melt blended together with other polymers such as poly(ethylene oxide)28 and used in core/shell extrusion[29]. FDM of PVA filaments, loaded with 4% paracetamol, aff orded geometries such as 3D printed-cubes, pyramids, cylinders, and spheres, many of which were not readily available by conventional powder compaction[30]. Drug release from such tablets depends on the surface area to volume ratio.

AM fabricated drug-loaded tablets with tailored release characteristics were demonstrated using PEGDA as monomer with TPO as photoinitiator and 4-aminosalicylic acid and paracetamol as model drugs[31]. In AM with drug release stimuli responsive and programmable materials, hydrogels play an important role. Polymer are excellent carriers of drug and are able to achieve desired release rate kinetics.

Overview of 3D printing in biomedical industry:

3-D printing has found widespread applications in tissue engineering, organs engineering and biomedical devices. Major limitation to this technology is that the foreign substance(polymer) has to be biocompatible and biodegradable. 3D bioprinting offers great precision and control of the internal architecture and outer shape of a scaffold and allows mimicking complicated structures found in biological tissues. Recent advances in technology have led to 3D printing of

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biocompatible materials, cells, and supporting components into intricate living tissues.

“Bioprinting” is a broader based term referring to any methods for printing (2D or 3D) with biological ingredients (in particular viable cells) to build functional tissue and organs. 3D bioprinting is possible with a range of diff erent AM methods, and research is growing at an extraordinarily rapid pace. The development of 3D bioprinting over the last 15 years represents a milestone in tissue engineering, regenerative medicine, drug discovery, and biological evaluation of substances without requiring animal testing. The field is beyond the scope of this Review, and the reader is thus urged to consult several comprehensive reviews for further information. Bioprinting is an advance from the AM of biocompatible and biodegradable porous supports as scaff olds for subsequent cell seeding, because viable cells are implemented directly into the 3D printing process. Thus, bio systems mimicking the extracellular matrix and functional tissue are printed directly, which moreover is a form of printed 3D cell culture. In May 2003, Boland et al. filed a patent claiming ink jet printing of viable cells, stating that at least 25% of the cells remain viable after incubation for 24 h at 37 °C.By 3D printing of cell patterns implementing more than one cell type into a one-step multimaterial 3D printing process, 3D bioprinting is far superior to previous multistep patterning processes and micro array printing. In principle, by patterning and assembly of hydrogels, biopolymers, and cells, 3D bioprinting enables CAD/CAM fabrication of functional 3D tissue including hard and soft tissues, which can vary from bones to blood vessels and even living organs.32,33. The development of bioinks as carriers for viable cells plays a key role in 3D bioprinting and was addressed by recent comprehensive review.

Conclusion:

As the growth of the 3D printing technology continues, commercial factors such as manufacturing costs, which include raw-material costs, production speed and volume, energy costs, are now being carefully evaluated alongside that involved with more traditional manufacturing processes 34,35. The properties, performance, lifetimes and recycling potential of printed parts must also be considered. The ability to locally create customizable, precise, working models for individuals as well as business incentives such as predictable low cost and fast turnaround times are captivating factors that will lure the manufacturers to adopt this technology. 3D printing utilizes almost all thermoset or thermoplastic as building material eliminating post processing steps is a must for improving 3D printing technology. The rise of AM has been intrinsically tied to improvements in the understanding of structure, property and processing of these polymers. As the health care industry moves towards customizable medicine as per ones needs and synthetic organ, 3D printers are expected to replace the conventional manufacturing techniques.

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