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Review Article

3D PRINTING: A REVIEW ON THE TRANSFORMATION OF ADDITIVE MANUFACTURING

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ABSTRACT

3D printing and nanotechnology have been two of the most important tools in the development of personalized medical treatments. More recently, their alliance has developed in an effort to create new, flexible, multidisciplinary, and/or medical and drug-wise products. Therefore, a comprehensive review of scientific studies, including 3D printing and nanomaterials on the development of new pharmaceutical methods and medical applications for the treatment and prevention of diseases, is presented here with the help of secondary research from most recent articles. 3D printing, also known as additive manufacturing, has held the power of building a new class of active nanocomposites. With the ability to print a layer of complex 3D objects by layer, additional production of nanomaterials can be used in new ways to significantly control architectural structures of all sizes. The high efficiency of embedded nanomaterials can further extend the power of nanocomposites to structures such as gradients in thermal conductivity, converted photonic emissions, and increased energy and reduced weight. According to the survey done by annual industry, around 50% of the market of 3d printing in the industrial sectors is credited to created prototypes by means of photopolymers. While, Formlabs, Stratasys, HP, Desktop Metal, Ultimaker, Carbon, EOS, Nanoscribe and Markforged are among the top additive manufacturers. This work is hereby an effort to focus on different techniques, merits and demerits, applications, recent advances, relation with nanotechnology along with future aspects.

Keywords: 3D printing, Nanotechnology, Selective laser sintering, Additive Manufacturing, Sheet lamination

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INTRODUCTION

In the present era, 3D printing is a growing sector of technology which is quietly developing applications in the fields of science or art. The term 3D is known as Three-Dimensional Printing. This term is given by the International Standard Organization. The secondary data was collected from different sources like pubmed, google scholar, research gate etc of previous years. In this printing system, we use nozzles, print heads, and other printer technologies [1]. 3D printing is used in a variety of research and innovative fields, including biomedical, tissue engineering, architecture, aerospace, and pharmacy. It also helps in the pharmaceutical industry in various sectors, like pharmaceutical formulation and development, and also helps in pharmaceutical unit operations like milling and mixing. 3D printing technology involves the designing and manufacturing of dense materials, which are used as programmable and personalized medicine [2]. 3D printing, which can play an important role in the formulation of potent dosage forms with controlled or sustained release properties, 3D printing is more active in a personalized dosage form concept called the poly pill Concept. It shows various possibilities for single dosage therapy. 3D printing technology is a modern and firmest prototype method. With this method, solid objects are developed by depositing various layers into a structure. This method develops physical models of buildings with the help of computer-aided design in multiple dimensions. 3D technology shows unique flexibility in manufacturing and designing dense objects and is also used in programmable and personalized medicine [3].

3D printing shows various benefits in the formulation of single or multiple-layer dosage forms with sustained and controlled release properties, and active ingredients play a very important role. It reduces the intensity and number of dose units that are taken by a patient on a daily basis. 3D printing technology shows high activity in personalized dosage form. This opens the prospect of combining all of the medications needed for treatment into a single dosage form unit [4]. Additive manufacturing is the process of forming solid objects by layering them together. This term was introduced in the early 2000s and is called "3D printing" [5]. All 3D technologies have a common principle that is based on layer-by-layer addition of objects [6]. It is defined as the layered manufacturing of solid material in the additive manufacturing literature. While 3D printing is a popular field of engineering, the term "additive manufacturing" is converted into 3D printing due to common principles and which is highlighted by the media. 3D printing and additive manufacturing describe the same manufacturing process, which is based on the same principle [7]. In 3D printing, a computer is a very important instrument which is used to form various layers of material. It is generally used in the formulation of novel drugs, and this technique has also helped in the production of 160 pharma innovations. 3D printing is also involved in regulatory testing and follows the standard system [8, 9]. It is a computer-based technology. Nanotechnology is a complex field that explains the formulation, analysis, and use of various materials at the nano metric scale and also controls their shape and size. [10]. In the fields of pharmaceutics and nanomedicine, the use of nanostructure is very popular as niches that have been evolving in the last 30 y. The nanotechnology field has been defined with a new treatment method with a new policy and given approval for a new drug that has several benefits in the treatment of patients [11]. In 1986, Charles Hull explained the principle of 3D printing [12]. This technology plays an important role in the fields of energy, biotechnology, medical devices and many more [13].

At present time, nanotechnology and 3D printing are two things that are used in the formulation of drug-loaded biomedical products for diagnosis and treatment of disease [14]. The use of nanostructures and nanomaterials to improve the mechanical properties and functions of products [15]. Furthermore, due to their ability to create more complex drug release profiles and exclusive dosage forms, both 3D printing and nanotechnology have been widely used in the expansion and progress of new treatments, resulting in a more relevant and specific medical therapy for the patient [16, 17]. Incorporating nanostructures into porcelain, metal, and polyamide substrates produces composites that can increase the physical qualities of 3D-printed products while also assisting in the personalization of therapies. It offers a promising and forward-thinking approach to the creation of nanomedical solutions [18]. This study updates the state of the science on the use of nanotechnology to 3D print goods for *in vivo* biological and biomedical applications with benefits in the prevention or treatment of illnesses. Firstly, provide a detailed explanation of 3D printing and nanomaterials for pharmaceutical applications [19]. This review also includes a brief but comprehensive discussion of 3D printing and nanomaterials issues with various medical applications [20].

Techniques or types used for 3-D printing

Selection of 3D Printing technique depends upon different properties of the medium which is needed to be printed as damp proof, cheap and in proper atmospheric conditions etc [21]. Different techniques used are binder jetting, material jetting, sheet lamination, light photo polymerization, selective laser sintering, powder bed fusion, material extrusion and direct energy deposition.

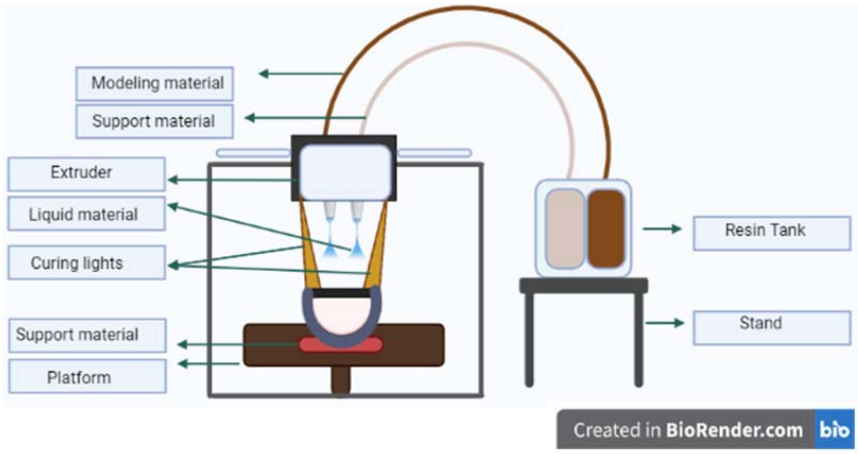

Fig. 1: Binder jetting process [22]

Binder jetting

Binder jetting prints the surface by the powder layer with the help of adhesive. The adhesive is showered over the powdered layer as shown in fig. 1 [22]. A various type of substance can be printed through binder jetting like iron, sands etc. Binder jetting is easy and affordable techniques to print large-size objects [23]. BJ is also called powder bed and inkjet head 3D printing. It was first developed and patented by Sachs *et al.* [24] in 1993. The idea is to extend the standard 2D print to a third dimension. In fact, it uses the mouth of one or more microphones to inject a liquid binding over the powder bed, attaching the powder together. The pipeline runs in a designed way until a thin layer of powder is applied. Eventually, the 3D object was formed by a series of layers [24].

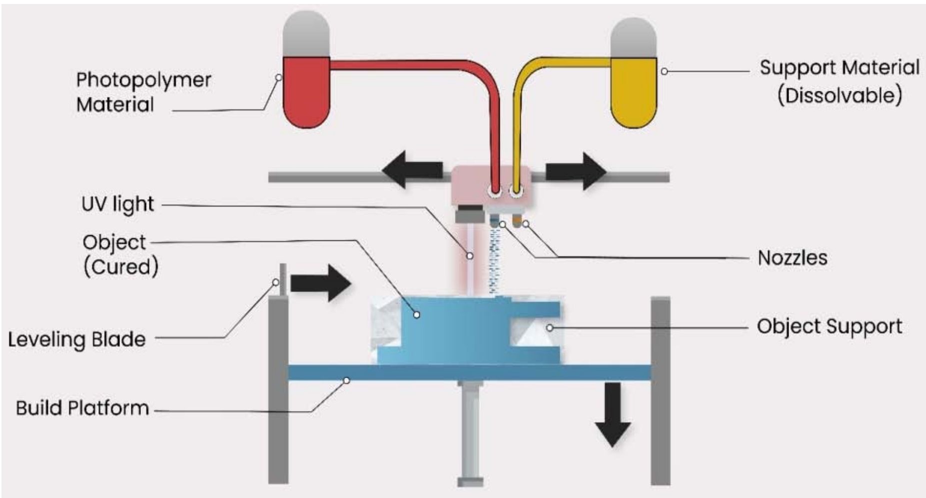

Fig. 2: Material jetting process [25]

Material jetting

Material jetting is another extensively used additive manufacturing technology. In this techniques, the surface is printed by adhesive/liquid photopolymers as shown in fig. 2. The Printing surface is dried with the help of UV light, which form a solid layer. Through this technique, polychromatic objects can be created by spraying mixed combination of different substances. Ink jetting (material jetting) is another 3D polymer printing process for microscale and nanoscale materials. The process was developed on the basis of standard 2D inkjet printing. This process uses liquid-phase or fine-grained materials containing slurries such as ink to form droplets, which form a substrate layer by layer. Murata [26] developed an ink-jetting device capable of producing 1 micron-sized nanodots. Using transition-metal nanoparticles as catalyst ink, a list of carbon nanotubes patterns is printed. Material limitations are the most important challenge for inkjet printing. With the incorporation of high-velocity polymer, the greatest limitation is the formation of droplets [26]. In Margolin's work [26], the concept of acoustic resonance jetting was explained. The use of ultrasonic waves of jetting ink provides gradients with high pressure near the outlet of the nozzle, thus releasing droplets from time to time. However, improvements in ink-jetting performance are limited due to viscous friction or vitrification inside the pipe. Dependence on mechanical properties in the printing of the polymer-jetted segment was studied by KĘSy and Kotli Ski [27].

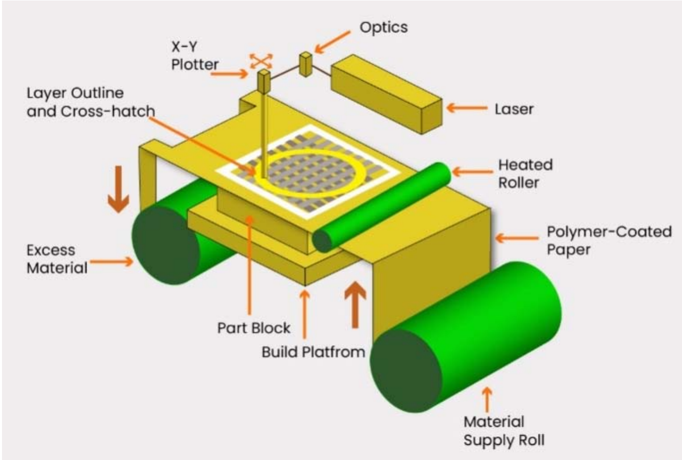

Fig. 3: Sheet lamination process [28]

Sheet lamination

Sheet lamination is the process of additive manufacturing in which any object is designed by linking of sheet material together, as shown in fig. 3 [29]. Laminated object manufacturing (LOM) and ultrasound 3D printing both are the examples of sheet lamination [30]. It is absolutely cost-effective for full-color prints. Generally, LOM is accomplished for the production of wallpaper design [31]. Ultrasonic Additive Manufacturing (UAM) is a ground-breaking method that uses sound to combines layers of metal taken from featureless foil material [32, 33]. LOM is a technique that uses metal sheets as food stocks. It uses a local power source, especially an ultrasonic or laser, to assemble a stack of the precision cut sheet metal to form a 3D object [34, 35]. By using ultrasonic wave and machine pressure on sheet metal stacks at room temperature, the joints of the packed sheets are bound to disperse rather than melt. Stacked sheets are folded layer by layer to form a 3D object without using any colliding power as a heat source [36, 37]. Prior to UC assembly, metal sheets were usually cut according to a geometric pattern [38]. Normal polishing is applied voluntarily during or after the merging process to achieve a detailed finish. The most commonly used production method is Ultrasonic Additive Production (UAP) or Ultrasonic Mixing (UM), introduced and patented by White [39, 40].

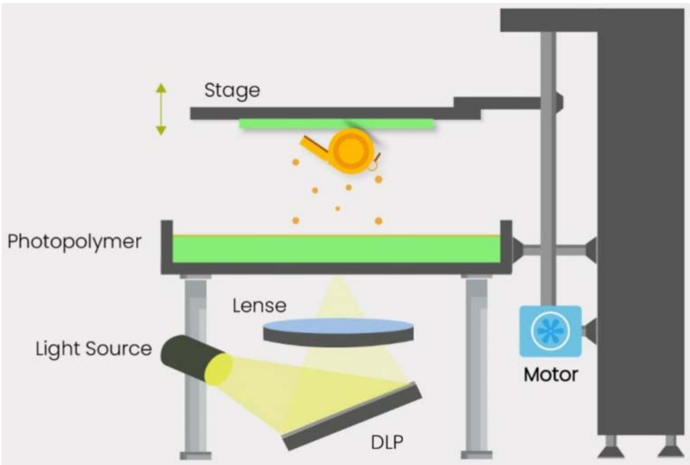

Fig. 4: Stereo lithography process [41]

Light photo polymerization

Stereo lithography (SLA) and digital light processing (DLP) are the advanced methods of additive manufacturing which uses photopolymer, as shown in fig. 4. Drying of photopolymer is processed by laser [42]. If DLP and SLA were compared, the difference only between light sources as it used Arch lamp with liquid crystal display in place of laser. It is faster than stereo lithography because it can cover the whole surface of a photopolymer adhesive vat in a single pass [43]. Contact time, amount of electricity and wavelength are the crucial factor which affect the Vat Photo polymerization. Generally, liquid materials are used, it will solidify when subjected to Ultraviolet (UV) radiation. Photo polymerization is a flawless technique for producing delicate structures with high quality [30]. SLA, also called vat polymerization, is one of the major processes in polymers [44]. It uses an ultraviolet (UV) laser beam to scan and treat the surface of a liquid monomer to form a solid polymer. The laser method is controlled by a computer using a CAD cut model (cutting software converts 3D models into two-dimensional (2D) layers [45, 46]. The elevator controls the liquid monomer tank to move up/down between each layer of the 2D plane cured structure [47]. So a lot of layers form a 3D polymer structure. The operational features of the SLA are influenced by the environment in which the design is made [48, 49]. For example, the sloping areas produced by the SLA process naturally have an unattractive trampled appearance. This texture limit can be improved with better process control algorithms. SLA position control was studied by Lan *et al.* [50].

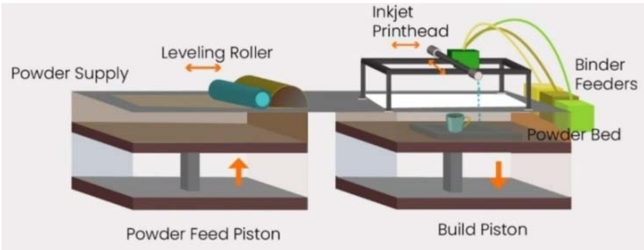

Fig. 5: Selective laser sintering process [51]

Selective laser sintering (SLS)

The selective laser sintering or laser melting method may be utilized with any powdery substance, the material which is used, must be melted first and then solidified by laser light after cooling. Plastics, metals, and ceramic materials are all part of the material spectrum. These techniques are mostly used in dentistry for metallic materials as shown in fig. 5.

A warmed powder is placed in the chamber and then set such that the temperature of the powder does not rise over the raw material's melting point. The benefits of preheating of the powder is that laser doesn't consume more energy to amalgamate the powder particles. As a result, substantial temperature variations are avoided, which may otherwise cause object deformation. After each cycle, high-power CO2 lasers are imposed to the material, resulting in the two-dimensional melting of powder. After that, a thin layer of powder is included to the previous layer by a sharp edge, reducing the installation space by one layer thickness. Because the particles in the tank are not compressed, for the assortment of materials, particle size, shape, density, and temperature sensitivity are important considerations. Round-shaped particles have less rolling resistance than unequal particles. Rough-shaped particles are packed more tightly. Tiny Particles cause processing complications caused by unnecessary cohesion [52, 53]. The temperature of the powder bed before it is heated has an impact on the density of the powder particles [54, 55].

Powder bed fusion

The electron beam melting (EBM), selective laser sintering (SLS), and Selective Heat Sintering (SHS) printing techniques are all involved in the powder bed fusion process [56]. To compound the particles together, laser or electron beam is used [57]. Material like metals, ceramics, polymers, composites, and hybrids can be used for powder bed fusion [58]. Powder-based 3D printing method is most often known as SLS as far as its functioning is concerned; this additive manufacturing is very fast and accurate in nature [59]. To sintering the polymer, a high-power laser is used to prepare 3 D models, especially which are made up of metal plastic and porcelain [60]. SHS technology, on the other hand, is a type of additive manufacturing which produce models through thermal printing that employs a thermal print head over the thermoplastic material [61].

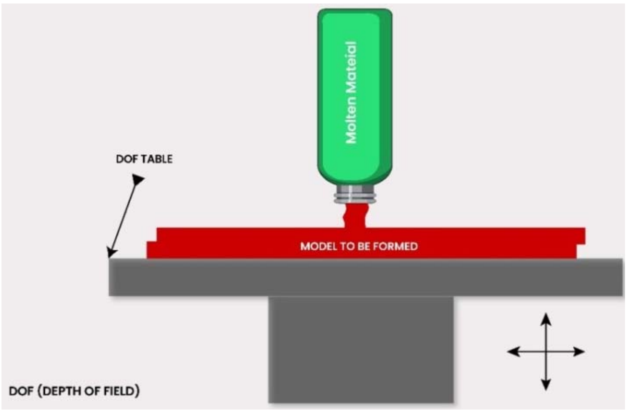

Fig. 6: Material extrusion process [62]

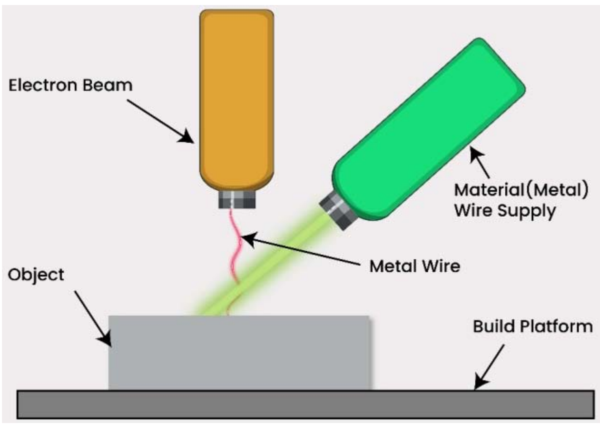

Fig. 7: Direct energy deposition process [67]

Material extrusion

Material extrusion or extrusion printing is a type of additive manufacturing process where the continuous filament is deposited on desired entity, as shown in fig. 6. Similar to inkjet printing, a typical material extrusion printer comprises of an X–Y–Z three-axis motion dais, numerous extrusion nozzles, and auxiliary curing equipment. To achieve the patterns in one layer, the extruded wire is deposited at the intended position with XY axis movement [63, 64]. When one single layer is finished, either the extrusion head or the build platform moves up or down to make room for the next layer to be deposited. These processes are carried out again and again till the designed entity is finished [65, 66].

Direct energy deposition

Another well-developed manufacturing technique is direct energy deposition (DED). Instead of using a powder bed, the DED processes use metal powder flow or metal wire as feedstock, along with energy sources such as laser or electron beam, to melt and deposit the material on the top of the substrate. The DED technique can be divided into two major categories based on the feedstock type [68]. The first category includes methods that were developed from traditional welding, which uses metal wire as a feedstock [69]. The second method was developed by Sandia National Laboratory in 1996 using powder flow as a feedstock, which is named as laser engineered net shaping (LENS) [70]. DED is popular method of AM that concurrently add material and heat input, as shown in fig. 7. Laser beam, electron beam, or plasma arc can all be used to generate heat. Metal powder or wire are used as material feedstock [71]. When compared to powder, wire shows high deposition efficiency as whole part would be, melted and attached to substrate [72, 73].

Fused deposition modelling (FDM)

With FDM technique, printers use a thermoplastic type of fiber and this filament heats up to reach a melting temperature, followed by a layer-by-layer extrusion, thus leading to the construction of a 3-D structure. Uninterrupted access to a given object using horizontal print components [74]. The heat element present in the liquefier head is used to bring the filament to the semi-liquid phase and then to the nozzle in the print area to print the actual part [75]. The most important function of this particular process is to assemble the next layer before it is reinforced, as a pre-assembled can have a significant impact on other structural components [76]. The FDM process has a fair number of benefits and limitations. The simplified process costs and high printing speed are considered to be the most profitable facts, while complex process parameters that directly affect component construction are considered to be a major limitation, and sufficient document works are not available for detailed specifications [77]. Analysis for all parameters. Researchers are now working on this vast area of concern to find a well-designed standard operating system parameter to meet custom requirements [78, 79].

Table 1: Table showing different techniques involved along with principles, advantages and disadvantages

Technique	Principle	Material used	Advantages	Disadvantages	References
Binder jetting	Extrusion of ink and powder liquid binding	Photo-resin or hydrogel	Very good accuracy • Very high surface finishes.	Fragile parts • Slow build process • The grainy or rough appearance • Post-processing is required to remove moisture • Poor mechanical the properties.	[80]
Material jetting	Deposition of the droplets of the photo-curable liquid material and cured	polymer	Multiple jetting heads are available to build materials • Different levels of flexibility • Allows using different coloured photopolymers • More control over the accuracy • High accuracy and smooth surface	Vulnerable to heat and humidity • Lose strength over time • Relatively higher cost compared to others • Sharp edges are often slightly rounded.	[81]
Sheet lamination	Sheet of metals are bonded to form an object	Paper, metals	Low cost. Parts with high strength can be produced. No requirement for post-processing.	Higher wastage of material. It is relatively difficult to build parts with complex cavities.	[82]
Light Photo polymerization	UV initiated polymerization cross section by cross-section	Resin (Acrylate or Epoxy-based with proprietary photoinitiator)	Large parts can be built easily • High accuracy and surface finish • Good for complex built • Simple scalability • Uncured material can be reused	Not well-defined mechanical properties due to the usage of photopolymers • Slow build process • Expensive process • Moisture, heat, and chemicals can reduce its durability • Brittle structure	[83]
Selective laser sintering	Laser-induced sintering of powder particles	Metallic powder, polyamide, PVC	High resolution No support structure is required High strength Less time Complex structures can be easily fabricated	Only metal parts can be printed Finishing or post-processing is required due to its grainy roughness and Difficulty in the material changeover.	[84, 85]
Powder bed fusion	Thermal energy selectively fuses regions of powder bed	Metals, polymers	Support structures can be removed easily. Composites with higher reinforcement of loading can be achieved. Fine resolution Powders that remains unused can be used again	Rough surface finish Low printing	[86]
Material extrusion	Droplets are deposited selectively	Plastic, nylon	Easy to fabricate economically Multi-material capability	Degradation and clogging of nozzle	[87]
Direct energy deposition	Focused thermal energy fuses materials as deposited	powder	Reduces material waste Complex geometries	Low quality and accuracy High production time	[88]
Fused Deposition Modelling	Extrusion of constant filament	ABS, PLA, Wax blend, Nylon	High-speed High quality Used for a wide range of material Durable over time less time	Porous structure for the binder Weak mechanical properties Often required support	[89]

Merits and demerits of 3D printing

Merits of 3D printing

Manufacturing of small-batch is applicable and the procedure can be finished in a single run. 3D printers are inexpensive and inhabit least space plus minimize variations among batches faced in material developed of conventional dosages [90]. An instant and controlled release layer can be united because of the bendable design and production of these dosage forms, it aids in selecting the finest therapeutic agent for a single person [91, 92]. It improves patient compliance in case of multiple dosing regimen [93]. Large amounts of drug can be filled as compared to predictable dosage forms and small doses of potent drugs can be administered accurately. Due to lesser material wastage, it decreases cost of production, as well as poorly water-soluble drugs, can be formulated easily [94]. Provides adequate therapeutic index with personalized medicines for patients centered on their genetic differences, cultural changes, gender, age and environment. It can be suitable for use in mobile military facilities, hospitals and for less stable drugs [95]. One of the most significant profits of 3D printing is enabling dosage personalization. It proves to be valuable in making different dosage forms for clinical trials. Dissolution of poorly soluble Active Pharmaceutical Ingredient (API) is upgraded. Dissolution and disintegration rate can be enlarged either by printing highly porous or hollow arrangements. This increases surface area, either using extrusion approaches ensuing in amorphous dispersions or smooth filling of the inner core with loose powder. Tremendously little amounts of API can be printed, even as small as 3ng. While seeing smaller batches, 3D printing is less luxurious than traditional industrial manufacturing. Less stable APIs could be printed for instant administration, though diverse study suggests connecting simple API fusion with 3D printing [96].

Demerits of 3D printing

Selection of raw material: physicochemical characteristics, printability, print fluid characteristics, thermal conductivity and for human use viscoelastic stuff has to be sensibly inspected besides safety of the raw materials. 3D printing of powder-based requires narrowed or special part to achieve printing, as powder leakage is critical and it can prove to be an occupational threat. In powder-based technique, friability is higher in 3D dosage forms. For good dosage form strength, production technology is important. When it prints at high temperature there are certain manufacturing processes that may not be suitable for thermo labile drugs. When related to conventional tablet compression procedures the 3DP are relatively limited in material colors, selections, and surface finishes [97]. In 3D printing, appropriate materials are still limited for drugs. Steps after processing which include desiccating using microwaves, hot air, or infrared sources, may be needed in some instances when residual solvents are needed to be detached from the final product. Boundaries befall specifically when taking into account the quantity of APIs used and the final product size when it is considered polypills [98].

Medical applications for 3D printing: present and predictable uses

3-D involves several applications as shown in fig. 8, which includes its use in bioink, in drug delivery system, in 3-D vascularized organ, surgical preparations etc.

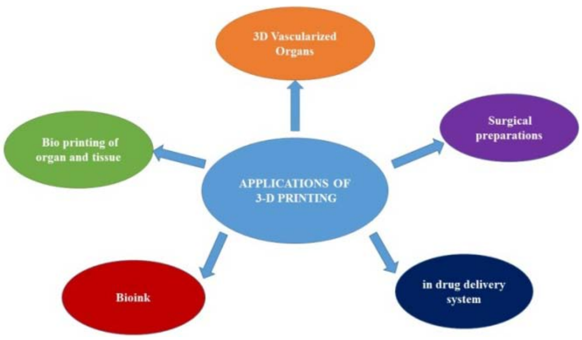

Fig. 8: Applications of 3-D printing

Bioprinting of organ and tissue

The ratio of several death occur either due to accidents, aging, birth defects and ageing can led to create a major problems like failure of tissue and organ. Various therapies has been evaluated, including regenerative medicine and tissue engineering, to get the remarkable solution. The organ printing technology has been used for the production of cells, 3D-like structure of tissue and cell-laden biomaterial, which will helps to provide porosity and strength to the tissues [99].

The process of bioprinting organs may help to design and create the blueprint of the organ, including their vascular cells, isolation of stem cells and then creating the reservoir for bio link, which contains blood vessel cells and other specific organ cells. Further these bio-printed organ cells can be transferred into the bioreactor for transplantation process. The other innovation techniques like laser printers have also used for the process of cell printing, where laser energy helps to excite the cell and control the spatial arrangement in the cellular environment [100]. For example-Researchers have used 3D printers to build the heart valve, knee meniscus, the spinal disk, other cartilage and bone structures, and the artificial ear [101].

Challenges in building 3D vascularized organs

Due to the complex and thickness nature of some organ like the heart, liver and kidney cells are unable to perform their metabolic function due to vascularization. To supply oxygen, growth and nutrients to the cells, bioprinting of functional vasculature should be done to get fabricated organ which can further led to the maturation of the cell. The multiple cell type can led to build the dense and complex organ which simultaneously can build the vascular system for organ function [102]. For example-various 3D printing techniques and building materials have been successfully used to create a simple vasculature as a single channel, as well as complex geometry, such as bifurcated channels or branches [103, 104].

Surgical preparation

In health aspects, during surgery 3D Printing plays vital role in the treatment of patient's specific disease. However, during Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) scan it helps physician to study patients' anatomy more efficiently than the 3D images of MRI [105]. It has been seen that in various cases 3D model gain the sight of a patient's specific history while performing medical operation. This procedure has been utilized to regenerate calcified aorta with the help of 3D printing to remove plaque from presurgery, using a 3D model of shoulder bone growths which helps in constructing a premature infant's airway to study aerosol drug delivery to the lungs and also removing tumour from deep tissue and skull through presurgical treatment [106, 107].

Bioink

In recent studies it has been found that bio link has been used for creating the tissue architectures that contains biochemical and biophysical characteristics. The bio inks usually prepared are generally made up of naturally or either synthetic polymer that shows remarkable printability and biocompatibility [108].

The polymer isolated from the natural source i.e. cells or tissues to formulate bio link shows tremendous effect to shows cellular function like differentiation, proliferation and migration. It has also been observed that bio links containing gelatin, collagen, hyaluronic acid and alginate contains only single protein are limited to use for biochemical and biophysical properties such as glycosaminoglycan, elastin and fibronectin etc. The decellularized extracellular matrix (dECM) works as a promising bio linker to shows a synergistic effect on encapsulated cells. To get the tissue specific cellular behavior it was seen that matrisome protein-containing constituents shows retaining properties in dECM bio ink. However natural polymer shows remarkable property to provide good cell affinity and also to builds cellular structures [109]. Recent research has used a combination of thermoplastic and high viscosity hydrogel bioink to print a muscle-tendon engineering unit where thermoplastics is used to mimic tissue biomechanics and cellular bioinks serve as a cellular source for tissue development. The muscle building component contains thermoplastic polyurethane containing C2C12 myoblasts of the cellular additive, while the tendon component contains PCL and NIH/3T3 fibroblasts. Both thermoplastic structure polymers and bioink-filled cells are printed on the same tri-axis stage with four spatially separated cartridges [110].

3D Printing used in drug delivery system

3D printing has eliminated the various limitation to show customized drug delivery by concerning individual characteristics. Nowadays 3D printing has become the strong strategy technique to eliminate the tradition-based drug delivery with personalized drug delivery using 3D printing as a promising technique to show effective drug delivery routes and better absorption [111].

Oral-based drug delivery system

As oral-based drug delivery system is considered to be the best route of drug delivery for treating several diseases which also give better compliance. Several mechanisms was followed during drug metabolization in the liver and elimination from the kidney. Solubility is one of the important factors which affect the bioavailability during oral administration of the drug. The physiological system of digestive parts plays an important role during drug formulation of oral-based drugs [41-43].

Vaginal-based drug delivery system

The vaginal-based drug delivery system shows the fast onset of drug release during comparison with oral route. As this route will does not involves first pass metabolism for efficient release of drug. This category of drug generally include sustained release of drug which decreases the chances of side effect and finally improves the drug solubility. It has been studied that fluctuation in the therapeutic dose level sometimes led to enhance the adverse effect and also decreased efficacy of the drug. So personalized drug has been introduced to give better absorption and enhance the medical status of the patient [54].

As, Chlorpheniramine maleate was 3D printed on a substrate of cellulose powder in amounts as small as 10 to 12 moles to show that even a small amount of the drug could be released within a specified time. This study showed improved accuracy in very small doses of drugs compared to conventional drugs. Dexamethasone is printed in a standardized dual-release form. Levofloxacin has been published in 3D as an artificial drug delivery tool with pulsatile and steady-state release methods [112].

5. 3-D printing in relation with nanotechnology

3D printing and nanotechnology are two new sciences that are being combined to provide a variety of intriguing new technologies as shown in fig. 9 [55] By merging these two disciplines, it is possible to make significant changes in existing components and develop whole new materials [56]. Nanotechnology based 3D Printed targeted drug molecule provide unique medical approach for developing control release formulation. Simulation of 3D Domain for improving cell function in the field of Tissue engineering and development of small size nanodevices for the diagnostic purposes [113].

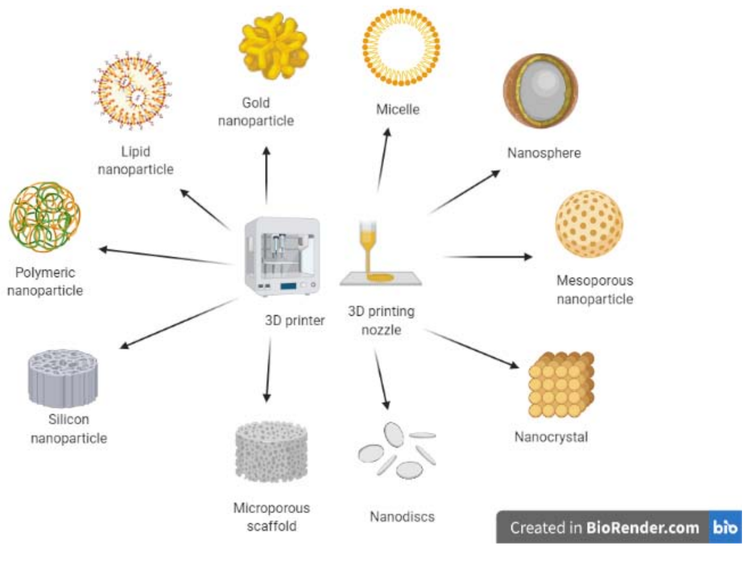

Fig. 9: Interlinking of additive manufacturing with nanotechnology

Nanoscale configured high resolution 3D printing process

3D printing techniques like ink jet printing, fused deposition modeling and selective laser sintering hardly produce the component resolution less than few microns [114]. Currently the technology is more advanced for high-resolution 3D printing, such as Two-Photon Polymerization (TPP), Projection Micro Stereo Lithography (PμSL) which allow fabrication by using UV laser, direct ink writing (DIW) and Electrohydro Dynamic Printing (EHDP) can achieve high resolution [115]. A near-infrared femtosecond laser is used to establish photo resistance for the creation of ultraprecise 3D nanostructures in the TPP-based 3D printing technology and the potential use of TTP technique in the field of medicine is limitless [116].

Nanocomposite development for medical purposes using 3D printing

Hydrogels with functional Poly Di Acetylene (PDA) nanoparticles were 3D printed to construct a 3-D detoxification device. The production of 3-D printed hydrogels is difficult when water-soluble photo-initiators with high UV absorbance are not present [117]. However, Poly (Ethylene Glycol) Diacrylate (PEGDA) hydrogels were successfully printed, with a mechanical strength six times that of a conventional hydrogel. This indicates that the hydrogels that have been produced are robust enough to sustain their own weight, making them ideal for use as an implant and in situ [118].

3D printing nanostructured in tissue engineering

Nanostructured extracellular matrices are found in natural tissues and organs that live in their surroundings; using the nanomaterial for manipulation of artificial scaffolds for tissue regeneration is a one-of-a-kind technology. It is possible to exert simultaneous control over the scaffold's structure and change part dimensions by including nanomaterials into 3D printed constructs like creating nanostructured surfaces [119]. By modifying the Properties of scaffolds in terms of biological and electrical properties, the nanoparticles could increase cell function and allow new tissue creation. When the customized shape of 3D printed nanocomposite scaffolds is used *in vivo* to satisfy the needs of individual patients. Nanomaterials, on the other hand, impact cell fate in order to facilitate tissue formation. Within 3D printed nanocomposites, there is a nano-biointerface and it has an impact on cell-extracellular Metrix interactions. *In vitro* tissue/organ models made from Scaffolds with 3D printed nanostructures could be used to research disease progression and drug discovery [120].

3D printing in nanomedicine for pharmaceutical and medical application

3D printing enables for the fabrication of no discrete tailored dosage forms for specific patients, as opposed to traditional solid dosage forms with discrete dosing. The benefit of 3D printed dose forms is that they may be personalized for every age group with specified gender and to match individual administration needs [121]. Personalized treatment has long been an aim in therapeutics, and it's especially important for children and the elderly. This is owing to the fact that children's physiological and metabolic processes evolve rapidly, but adults may have a variety of co-morbidities [122].

3D printing Nanodevice for diagnostic application

The conductive property of different types of nanomaterials like carbon nanotubes, graphene and metallic nanoparticles is unique that could be used to print electronics for the development of innovative nanodevices for diagnostic applications. The development of electrochemical sensors for cell or tissue analysis viability is a hot topic of research in this regard [123].

Recent advances in manufacturing

Researchers will be able to create items with more advanced features and outstanding mechanical qualities as a result of this. Strong and portable products are required by the aircraft industry and healthcare industries. Matrix hybrid composites are attracting a lot of interest in today's society because they offer excellent mechanical and long-term durability, as well as other thermos electrical structures [124].

Fillers, on the other hand, are only allowed up to a certain point. The filled particles then begin to agglomerate and enhance vacuum formation, resulting in decreased mechanical characteristics [125].

When the shape and size or grain size of the composite material prevent the photocopiers from extracting the material successfully, the binding capacity between the two components is diminished, which supports space structure and has an impact on the product's upper end. The majority of the issues that AM methods face are caused by the process [126, 127].

The treatment of powder and alloys is done layer by layer in 3D printing procedures for combining heat, such as direct metal laser melting SLM and SLA. Temperature fluctuations during treatment may cause straight and parallel structures to fluctuate. It has the potential to improve the printed part's anisotropic nature. Processing speed and anisotropic characteristics during manufacture are also difficulties with other approaches. Despite numerous problems and roadblocks, AM technology has grown in popularity and now offers a wide range of capabilities. Researchers are attempting to develop 3D printing methods to overcome their limitations as compared to traditional production methods in the above-mentioned research. Scientists have gained more rights to study and manage the qualities and performance of goods linked to their successful usage in past years, thanks to the advancement of biodegradable polymers, and have opened up a present time for advanced materials [128].

In medical field

With the employment of AM in the medical field, the future looks good; however, there are no hurdles in the way. Traditional technologies, rather as 3D printing, are more suited to large production. Although injection molding becomes more expensive as manufacturing capacity increases, the cost of extra print output remains the same [129].

While increased production cuts prototype time in half, it takes longer for each item than conventional methods like the injection molding process [130]. It's difficult to increase print speed because there's generally an exchange involving feature modification and deposition rate [131]. High-density printing processes like photolithography, laser cutting, or electrodeposition fusion ejection have increased the cost of materials and the highest amount of processing power required. As a result, additive manufacturing has traditionally been considered suitable for quick experimentation and device design but not for mass production. However, the previously listed parameters are dependent on geometry, which can only be achieved through increased manufacture. As a result, the pharmaceutical business is very interested in developing more products for mass production. Science and technology will continue to be a vital area for further economic growth. Despite the fact that the number of printing materials available has increased dramatically over the last decade [132, 133].

Material standards will continue to constrain and guide the feasibility of new manufacturing techniques for specific applications. Bioink of extrinsic matrix material has the potential to have a significant impact on the area of 3D bioprinted scaffolds when it comes to the construction components [134].

Large-scale solutions may benefit from advancements in material possibilities and printing processes. Other essential considerations include printing, mechanical qualities, and drug loading capacity, despite the fact that this article focuses on solutions [135].

Bone implants, for example, should have mechanical qualities similar to *in vivo* bone strength, and micro-implants investigations have shown mechanical parameters such as Young's modulus [136], compressive strength, and yield stress [137].

Future aspects and challenges

In recent years, additive manufacturing has fetched flexible advances in production technology and has taken us to a wider and more diverse outlook. Though, additional production still has several problems and challenges compared to traditional production methods [138]. Some of the confines confronted by 3D printing are low mechanical properties, material selection, horizontal appearance, production time, vanity and lack of geometric stability after extrusion, and overall cost efficiency [139]. Recently, diverse 3-D printing procedures use a variation of ingredients comprising metals, thermoplastic polymers, ceramics composites, and matrix composites with diverse fillers such as metal nanoparticles, fibers, and various materials that enhance their performance. The choice of materials relies on the method and the requisite structural belongings of the product. The material range of 3D printing materials has augmented, but the processing speed is slower paralleled to conventional production methods like mime or molding. There are numerous features that bound the processing speed. It is a course of applying a layer and the cooling time of the whole layer is dissimilar from the preceding and subsequent layer of laying. This unique cooling generates certain structural differences from the original Computer-Aided Design (CAD) model and reduces the strength between layers [140]. The need for innovation is important in all areas from industrial manufacturers to customer delivery. The acceptance of AM in all aspects of production remains subject to a lack of additional production standards. This issue has been the subject of intense research for hundreds of researchers, scientists, and organizations over the past three decades in order to develop appropriate standards for increased productivity. However, various research teams were working with the utmost integrity to resolve this issue on a large scale in all fields. When we associate the handling time of any AM procedure on average with the standard production method, AM procedure makes a 38 mm cube for about 1 hour while injection modeling can make less identical cubes per minute. Therefore, 3D printing is not suitable for use as a mass-production element of any product [141].

The most popular 3D printing programs for drug delivery and pharmacy are FDM and inkjet printing. Although these technologies provide high precision with costly efficacy, rapid drug delivery, over-the-counter drugs, and large loads of drugs, they suffer from lower productivity compared to traditional medicine methods. In addition, 4D printing is a new concept in the pharmaceutical industry, and limited technologies, namely the writing of direct ink for intravesical drug delivery systems, have been used [142]. In the future, we can witness the use of other 3D printing technologies in the pharmaceutical industry. Another challenge to using AM in the pharmaceutical industry comes from limited biomaterials. For example, sterilization methods used in polymer-based drugs cannot be harsh or use temperatures higher than the glass biopolymer temperature. However, hydrogel rejuvenation has shown great potential for future drug use. Lastly, upgrading technology in this field is a very important shortcoming, which prevents AM technology from providing the mass production of your own specific drugs. Therefore, further efforts are needed to address the problems mentioned above in the future [142].

CONCLUSION

3-dimensional (3D) printing gained significant improvements in production methods for both macro-nanoscales. 3D printing is seen in a variety of biomedical applications and nanomedicine formulations using additional production techniques plus demonstrates auspicious potential in rewarding patient-centered personalized medical needs. The current work provided a brief overview of the AM processes used in production. The resulting components of combinations from different AM techniques are also summarized. Each AM method has its advantages. A major challenge lies in the process of interlayer-related building materials and structures. The success of the desirable mechanical properties can be ensured by the proper selection of the AM strategy and the acquisition of the right obligation. The future scope of AM in compounding is highlighted and opens the boundaries of future research. Preliminary reports indicate that this is due to the discovery of new biomaterials and well-designed polymeric materials, which can be synthesized into 3D printed nanomaterials for use in a range of biomedical presentations like nanomedicine. Contrary to the principle of the "one size fits all" system of conventional medicine, personal or accurate medicine considers differences in a variety of factors, plus genetics and pharmacokinetics of diverse patients, which have revealed better consequences over conventional treatment. Different techniques are shown in this article, along with recent advances and future aspects.

ABBREVIATION

3D-3 Dimensional, LOM-Laminated object manufacturing, UAM-Ultrasonic Additive Manufacturing, SLA-Stereo lithography, DLP-Digital Light Processing, UV-Ultraviolet, EBM-Electron Beam Melting, SLS-Selective Laser Sintering, SHS-Selective Heat Sintering, UAM-Ultrasonic Additive Production, UC-Ultrasonic Mixing, DED-Direct energy deposition, LENS-Laser Engineered Net Shaping, FDM-Fused Deposition Modelling, API-Active Pharmaceutical Ingredient, MRI-Magnetic Resonance Imaging, CT-Computed Tomography, DECM-Decellularized extracellular matrix, TPP Two-Photon Polymerization (TPP), PµSL-Projection Microstereo Lithography, DIW-Direct Ink Writing, PEGDA-Poly (Ethylene Glycol) Diacrylate, EHDP-Electro Hydro-Dynamic Printing, CAD-Computer Aided Design.

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CONFLICT OF INTERESTS

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