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3Dp Technology: An Emerging Trend in Health Care Sector: A Review

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ABSTRACT

In the present review, an attempt is made to understand the effective utilisation of additive manufacturing technology which is also called as 3D (dimensional) printing. It is an innovative and efficient method of creating an object with online monitoring and control. In this process successive layer of material is added one upon other under computer control to create the object three dimensionally. In Pharmacy 3Dp is used in formulation of high doses of drug, orodispersible pills which are easy for administration. It is highly porous pill which is very useful for epileptic patients and patients having problem in swallowing a tablet. High doses nearly (1000mg) can be formulated simply by using drop on demand process and arranging the successive layers. Highly porous nature of the pill disintegrates immediately in 4 sec after coming in contact with aqueous phase. This also helps in developing personalised dosages for patients. USFDA has approved a pill called 'Spritam' (levetiracetam) which is an orodispersable pill made using 3Dp. Bioprinting enables creating various tissues and organs which can help in clinical trials of drugs. Prosthetic implants produced using 3D printing technology are helping differently abled in customising them accordingly. There is a need for post-processing and adherence to strict health and safety protocols. Advances in 3D printing technology can revolutionise and may become the greatest accomplishment in health care.

INTRODUCTION:

Three-dimensional (3D) printing (3Dp) is a rapid prototyping technology that has gained increasing recognition in many different fields. (1)3Dp technology relies on computer aided design(CAD) to achieve un paralleled flexibility, time saving, and exceptional manufacturing capability of pharmaceutical products.(2)Three-dimensional (3D) printing is a manufacturing method in which objects are made by fusing or depositing materials such as plastic, metal, ceramics, powders, liquids or even living cells in layers to produce 3D objects. This process is also referred as additive manufacturing (AM), rapid prototyping (RP) or solid freeform technology (SFF). (3)

There are about two dozen 3D printing processes, which use varying printer technologies, speed, resolution and hundreds of materials. (4)These technologies can build a 3D object in almost any shape imaginable as defined in a computer aided design file.Additive manufacturing refers to a group of technologies that build physical object directly from 3D computer aided design data.

Additive manufacturing begins with computer aided design modelling software that takes a series of digital images of the design or object and sends description of them to a professional grade industrial machine. The machine uses the description as blueprints to create the item by adding material layer upon layer. Layers which are measured in microns are added hundreds or thousands in number until three-dimensional object emerges. Raw materials may be in the form of liquid, powder, sheets which are typically made of plastic and other polymers, metals or ceramics. The numerous additive manufacturing process differs per the materials patterning and fusing layers they employ. Major process includes material extrusion, material jetting, binder jetting, sheet lamination, vat photo polymerisation powder bed fusion and directed energy deposition.The earliest 3D printing technologies first became visible in the late 1980's, at that time they were called Rapid Prototyping (RP) technologies. This is because the processes were originally conceived as a fast and more cost-effective method for creating prototypes for product development within industry.

Approximately 15 percent of U.S. additive manufacturing takes place with in this industry. Additive manufacturing has also been used worldwide to create approximately 30,000 prosthetic limbs, more than half a million dental implants and countless other devices. (5) One of the most well-known applications of additive manufacturing is Orthodontics. The medical industry is the leading user of additive manufacturing. Additive manufacturing is being used to create customised medical devices that closely replicate human form.

In recent years scientists have devices a means of using the patient's body cell to additively manufacture tissues and other human body parts.The pharmaceutical industry is also applying the technology, for example, additive fabricating a single custom made daily pill for each patient eliminates the need to keep track of multiple medications. (6) The purpose of drug development should be to increase efficacy and decrease the risk of adverse reactions, a goal that can potentially be achieved through the application of 3D printing to produce personalised medications.

Oral tablets are the most popular drug dosage from because of ease of manufacture, pain avoidance, accurate dosing, and good patient compliance. However, no viable method is available that could routinely be used to make personalised solid dosage forms, such as tablets. Oral tablets are currently prepared via well-established processes such as mixing, milling, and dry and wet granulation of powdered ingredients that are formed into tablets through compression or moulds. Each of these manufacturing steps can introduce difficulties, such as drug degradation and form change, possibly leading to problems with formulation or batch failures. In addition, these traditional manufacturing processes are unsuitable for creating personalised medicines and restrict the ability to create customised dosage forms with highly complex geometries, novel drug-release profiles, and prolonged stability. (7)

Personalised 3D-printed drugs may particularly benefit patients who are known to have a pharmaco-genetics polymorphism or who use medications with narrow therapeutic indices. Pharmacists could analyse a patient's pharmaco-genetics profile, as well as other characteristics 22such as age, race, or gender, to determine an optimal medication dose. A pharmacist could then print and dispense the personalised medication via an automated 3D printing system. If necessary, the dose could be adjusted further based on clinical response. (8)

3D printing also has the potential to produce personalised medicines in entirely new formulations such as pills that include multiple active ingredients, either as a single blend or as complex multilayer or multi reservoirs printed tablets. Patients who have multiple chronic diseases could have their medications printed in one multi dose form that is fabricated at the point of care. Providing patients with an accurate, personalised dose of multiple medications in a single tablet could potentially improve patient compliance.

Although an ideal scaffold will account for all these factors, challenges still exist with biomaterial selection and 3D shape specificity. Biomaterial commonly used is polymers (synthetic and natural), ceramics, and metals. Each biomaterial has specific material and mechanical properties, processing

methods, chemical properties, cell material interactions, and FDA approval. Common fabrication methods to produce porosity and a range of pore size are gas foaming, solvent casting with particle leaching, freeze drying and electrospinning while the microarchitecture in these methods is well-controlled and understood, the ability to control macro architecture with these methods is limited to 3D shapes and geometries determined by moulds and manual processing. (9,10)

China, Singapore and some countries in Europe have committed hundreds of millions of dollars to develop and commercialise additive manufacturing. China, for example, has been investing in additive manufacturing since the early 1990s and the Chinese government is pledging 1.5billion Yuan ($245 million) to a seven-year project to advance development of the technology. The Asian manufacturing association, (11) Beijing –funded trade group, are promoting wider integration of additive manufacturing by establishing 10 innovation institutes, each starting with a$3.3 million injection of investment. (11) A company in Hefei, Anhui province, is investing 750 million yuan ($125 million), indicating that Chinese business is eager to explore the additive manufacturing technology. (11,12) 3D-printed drugs may particularly benefit patients who are known to have a pharmaco-genetics polymorphism or who use medications with narrow therapeutic indices.

HISTORY OF 3DP:

The beginning of 3D printing was seen in 1980s, the very first patent application for RP technology was filed by a Dr. Kodama, in Japan, in May 1980. Stereolithography uses a .stl(standard triangle language)file format to interpret the data in a CAD file, allowing these instructions to be communicated electronically to the 3D printer. Along with shape, the instructions in the .stl file may also include information such as the colour, texture, and thickness of the object to be printed. (3)

Hull later founded the company 3D Systems, which developed the first 3D printer, called a "stereolithography apparatus." (3) In 1988, 3D Systems introduced the first commercially available 3D printer, the SLA-250. (3)

Many other companies have since developed 3D printers for commercial applications, such as DTM Corporation, Z Corporation, Solids cape etc., basing on Hull's work, as well as advances made by other researchers. Other 3D printing technologies and processes were also emerging during these years, namely Ballistic Particle Manufacturing (BPM) patented by William Masters, Laminated Object Manufacturing (LOM) patented by Michael Feygin, Solid Ground Curing (SGC) patented by Itzhak Pomerantz and 'three-dimensional printing' (3DP) patented by Emanuel Sachs.

And so the early nineties witnessed a growing number of competing companies in the RP market but only three of the originals remain today 3D Systems, EOS and Stratasys. (13,14)

By the early 2010's, the terms 3D printing and additive manufacturing evolved in which they were alternate terms for AM technologies, one being used in popular vernacular by consumer - maker communities and the media, and the other used officially by industrial AM end use part producers, AM machine manufacturers, and global technical standards organisations.

Both terms reflect the simple fact that the technologies all share the common theme of sequential-layer material addition/joining throughout a 3D work envelope under automated control.

Starting from stereolithography many processes were developed making slight changes in the original technique, the materials used also evolved from metals, ceramic, plastic to bio inks.

TECHNIQUES AND TECHNOLOGY

The term additive manufacturing means creating physical objects three dimensionally by adding successive layers of material. In order to create objects in 3D, a digital model of the object has to be created. Additive manufacturing is fundamentally different from existing traditional manufacturing techniques. There are many limitations in traditional manufacturing and many complex structures that require intricate machinery and may take quite lot of time However, these technologies all demand subtraction of material from a larger block whether to achieve the end product itself or to produce a tool for casting or moulding processes and this is a serious limitation within the overall manufacturing process.

For many applications, traditional design and production processes impose a number of unacceptable constraints, including the expensive tooling as mentioned above, fixtures, and the need for assembly for complex parts. In addition, the subtractive manufacturing processes, such as machining, can result in up to 90% of the original block of material being wasted.

In contrast, 3D printing is a process for creating objects directly, by adding material layer by layer in a variety of ways, depending on the technology used.The major requirement for 3D printing technology is a computerised mode of the object to be created i.e. a CAD file or a STL file or a magnetic resonance imaging (MRI) or CT scans. Computer aided drafting or designing (CAD) is the technology used to help in creation, modification, analysis, and optimisation of design through a computer.

3D file → Apparatus+ material → 3D object

- **CAD** computer aided design or also known as computer aided manufacture (CAM) (15)is playing an important role in development of 3D printing technology. The digital file required for the manufacture can be conveniently created using CAD. The 3D printer follows the instructions in the CAD file to build the object. The print head moves in x-y plane to build the base and raises along the z axis to build the object vertically. CAD is an important industrial art extensively used in many applications, including automotive, shipbuilding and aerospace industries, industrial and architectural design, prosthetics, and many more. Computer-aided design (CAD) is the use of computer systems to aid in the creation, modification, analysis, or optimisation of a design. CAD software is used to increase the productivity of the designer, improve the quality of design, improve communications through documentation, and to create a database for manufacturing. (15,16)

- **STL file** also known as standard triangle language and standard tessellation language is widely used in rapid prototyping and computer based manufacturing STL files describe only the surface geometry of a three-dimensional object without any representation of colour, texture or other common CAD model attributes, a file format native to the stereolithography CAD software created by 3D Systems. (17,18,19)The STL format specifies both ASCII and binary representations. Binary files are more common since they are more compact. (20)An STL file describes a raw unstructured triangulated surface by the unit normal and vertices (ordered by the right-hand rule) of the triangles using a three-dimensional Cartesian coordinate system. STL coordinates must be positive numbers, there is no scale information, and the units are arbitrary. Stereolithography machines are 3D printers that can build any volume shape as a series of slices. Ultimately these machines require a series of closed 2D contours that are filled in with solidified material as the layers are fused together. A natural file format for such a machine would be a series of closed polygons corresponding to different Z-values. However, since it is possible to vary the layer thicknesses for a faster though less precise build, it was easier to define the model to be built as a closed polyhedron that can be sliced at the necessary horizontal levels. The STL file format appears capable of defining a polyhedron with any polygonal facet, but in practice, it is only ever used for triangles, which means that much of the syntax of the ASCII protocol is superfluous. To properly form a 3D volume, the surface represented by any STL files must be closed and connected, where every edge is part of exactly two triangles, and not self-intersecting. Since the STL syntax does not enforce this property, it can be ignored for applications where the closure does not matter. The closures only matter insofar as the software that slices the triangles requires it to ensure that the resulting 2D

polygons are closed. Sometimes such software can be written to clean up small discrepancies by moving vertices that are close together so that they coincide. The results are not predictable, but it is -often sufficient. All the digital files are saved in STL format which is used to direct the 3D printer. (21)

- **3D scanner** is a device used to analyse an object and collect the data on its appearance. The collected data is used to construct digital three-dimensional models. The purpose of a 3D scanner is usually to create a point cloud of geometric samples on the surface of the subject. These points can then be used to extrapolate the shape of the subject (a process called reconstruction). If colour information is collected at each point, then the colours on the surface of the subject can also be determined.3D scanners share several traits with cameras. Like most cameras, they have a field of view, they can only collect information about surfaces that are not obscured. While a camera collects the colour information about surfaces within its field of view, a 3D scanner collects distance information about surfaces within its field of view. (22)The "picture" produced by a 3D scanner describes the distance to a surface at each point in the picture. This allows the three-dimensional position of each point in the picture to be identified. For most situations, a single scan will not produce a complete model of the subject. Multiple scans, even hundreds, from many different directions are usually required to obtain information about all sides of the subject. These scans have to be brought into a common reference system, a process that is usually called alignment or registration, and then merged to create a complete model. This whole process, going from the single range map to the whole model, is usually known as the 3D scanning pipeline.Structured-light 3D scanner uses projected light patterns and a camera system to collect the data for a digital 3D file. (22,23)

- **MRI** is a medical imaging technique discovered in 1970-1980s used to determine the anatomy of body with the help of strong magnetic field and radio waves to generate images. Thus, the digital file helps in slicing the object and allowing the 3D printer to place successive layers. This is mainly used in bio printing, face reconstruction and in virtual surgery planning in order to get the anatomy and these 2d images are then converted into 3D images. The magnetic resonance imaging is based on nuclear magnetic resonance (NMR) “certain atoms absorb and emit radio waves when placed in external magnetic field.” In clinical and research MRI, hydrogen atoms are most often used.

- **CT scan** is another medical imaging technique which uses x-rays. It uses a computer processed combination of X-rays taken from different angles to produce tomographic images (virtual slices) of specific areas of scanned object (24) without cutting. These images are also used in bio printing,

virtual surgery planning. The 3D file obtained from the above-mentioned technologies are the guiding principle for the apparatus to print the 3D object layer by layer. The technique used in 3D printing can change with the material used and a wide range of materials from simple powders to complex cells are being used in 3D printing.

TECHNIQUES:

Stereolithography (SL):

This technique of 3D printing also known as resin printing or optical fabrication invented in 1970`s by Japanese researcher. The term stereolithography was coined in 1986 by Charles hull(25). This technique utilises photopolymerization, a process by which molecules link up to form polymer (25) with the help of light or concentrated beam of ultraviolet light focused onto the surface of a vat filled with a liquid photopolymer. The UV light beam is focused onto the surface to draw a pre-programmed design or shape onto the surface of the photopolymer vat creating each layer of the desired 3D object by means of cross linking (or degrading a polymer). The UV laser is used because photopolymers are photosensitive under ultraviolet light. (26) In models featuring an elevator apparatus, (27) an elevator platform descends a distance equal to the thickness of a single layer of the design typically 0.05 mm to 0.15 mminto the photopolymer vat. Then, a resin-filled blade sweeps across a cross section of the layer, re-coating it with fresh material. The subsequent layer is traced, joining the previous layer. A complete 3D object can be formed using this process. Designs are then immersed in a chemical bath in order to remove any excess resin and cured in an ultraviolet oven.

Then the vat is "rocked", flexing and peeling the bottom of the vat away from the hardened photopolymer; the hardened material detaches from the bottom of the vat and stays attached to the rising build platform.

Stereolithography requires the use of supporting structures which attach to the elevator platform to prevent deflection due to gravity and to hold cross sections in place in order to resist lateral pressure from the resin-filled blade or retain newly created sections during the "vat rocking" of bottom-up printing. Supports are created automatically during the preparation of 3D Computer Aided Design models and can also be made manually. (27) With more expensive stereolithography models, these supports must be removed from the finished product manually.

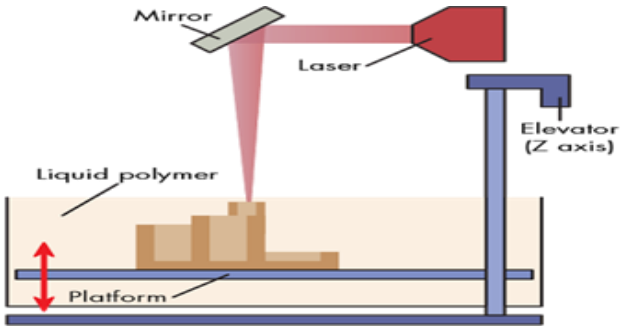

Figure 1: Stereolithography

Selective laser sintering (SLS):

It is a technique of 3D printing which was developed and patented by Dr. Carl Deckard and Dr. Joe Beaman.(28) This technique is mainly useful for powdered materials as a high power laser beam is used to create the 3D objects. The laser selectively fuses powdered material layer after layer by scanning cross sections generated from a 3D digital description. The powder bed is lowers by one layer thickness, a new layer of material is spread and the process is repeated. The fusion of the powdered material is based on the partial melting and full melting. The temperature of the materials is raised slightly below its melting point to make it easier for laser to raise the temperature of selected region to fuse.

This technique is useful for metals, plastic, ceramics, etc. But it is not possible to use thermo-labile substances as they get deteriorated by heat.

Direct metal laser sintering (DMLS): It follows the same technique as selective laser sintering but used to create object with metals and their alloys. In this technique, a high powered nearly 200watt by fibre optic laser is used for fusing the layers. Alloys like stainless steel, bronze and metals like aluminium, cobalt, chromium, etc.

This technique of manufacturing doesn't require any special tooling e.g. casting

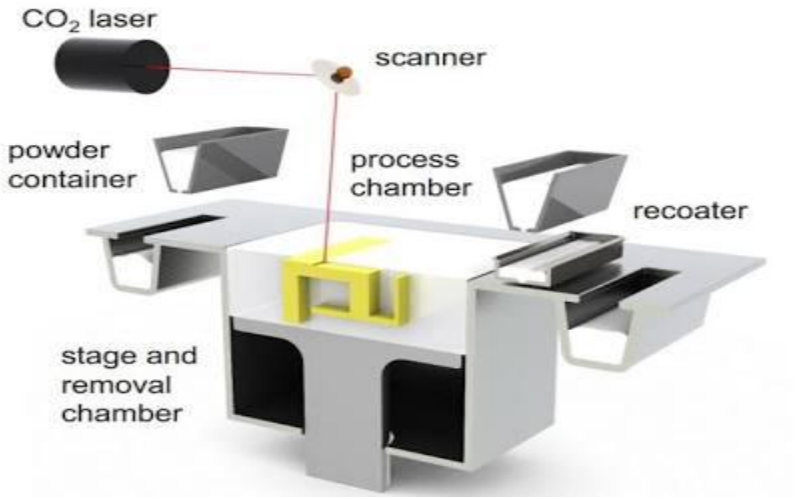

Figure 2: Direct metal laser sintering (DMLS)

Fused deposition modelling(FDM):

The technology was developed by S. Scott Crump in the late 1980s and was commercialised in 1990. The term fused deposition modelling and its abbreviation to FDM are trademarked by Stratasys Inc. (29)

FDM begins with a software process which processes an STL file (stereolithography file format), mathematically slicing and orienting the model for the build process. The materials required to build the object are placed as coils and the coil is unwounded as the material is extruded. Heated nozzles melt the material and extrude them onto the base layer by layer. The nozzles moves both horizontal and vertical directions.The nozzle follows a tool path controlled by CAM. The extruded materials dry immediately when exposed to air, the adhesion between the layers can be made strong when the molten material is exposed to inert gases like nitrogen and argon. (30) Both object and supporting structure can be built simultaneously and once the object is created the soluble support structures can be broken down. Usually, thermoplastics are used in this process because of their flexibility. Acrylonitrile Butadiene Styrene ABS, Polylactic acid PLA, Polycarbonate PC, Polyamide PA, Polystyrene PS, lignin, rubber, (31)among many others, with different trade-offs between strength and temperature properties.

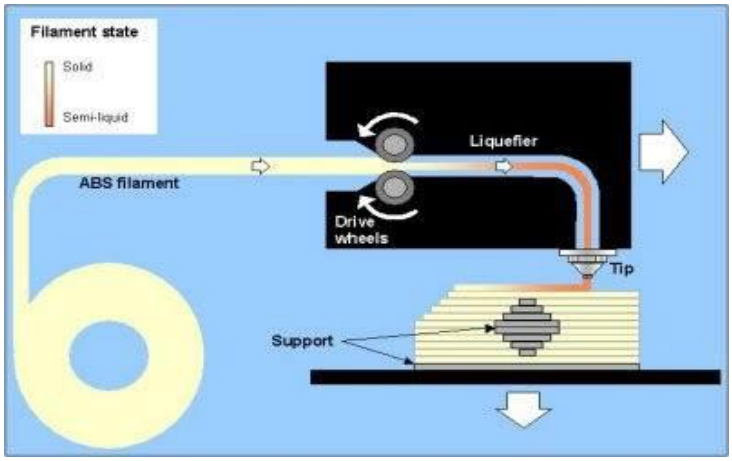

Figure 3: Fused deposition modelling (FDM)

Binder jetting technique:

This technology was first developed at the Massachusetts Institute of Technology in 1993 and in 1995, Z Corporation obtained an exclusive license. (32) It is also known as powdered bed inkjet 3D printing. Binder jetting is an additive manufacturing technique which creates a physical object layer by layer by delivering adhesive liquid from an inkjet head onto the powdered material using digital instructions. Layers of material are then bonded to form an object. The print head strategically drops binder into the powder. The vat containing material lowers and another layer of powder is then spread and binder is added. Over time, the part develops through the layering of powder and binder. Binder Jetting is capable of printing a variety of materials including metals, sands and ceramics. Some materials, like sand, require no additional processing. Other materials are typically cured and sintered and sometimes infiltrated with another material, depending on the application. Hot isostatic pressing may be employed to achieve high densities solid metals. Recently USFDA has approved an or odispersed pill called 'SPRITAM' developed by Aprecia pharmaceutical using zip dose® technology which typically involves binder jetting. This pill is used to treat epilepsy.(33)

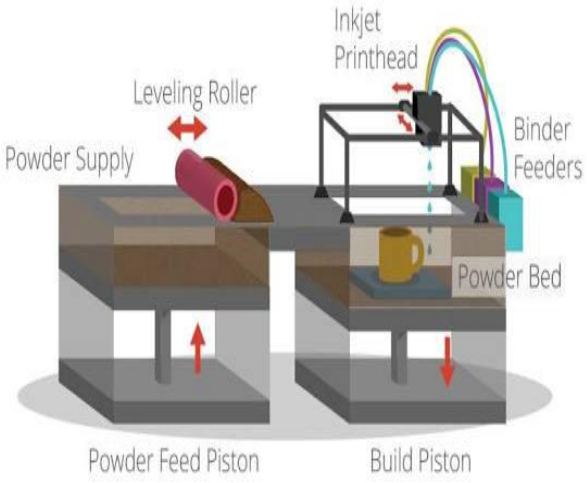

Figure 4: Binder jetting technique

Selective deposition lamination (SDL):

Selective deposition lamination is also called as laminated object manufacturing (LOM), is a rapid prototyping system developed by Helisys Inc. In this system, layers of adhesive-coated paper, plastic, or metal laminates are successively glued together and cut to shape with a knife or laser cutter Objects printed with this technique may be additionally modified by machining or drilling after printing. Typical layer resolution for this process is defined by the material feedstock and usually ranges in thickness from one to a few sheets of copy paper. (34)

"Selective"-Refers to the selective method that the printer uses in depositing the adhesive to bond the sheets of paper. A much higher density of adhesive drops is deposited in the area that will become the part, and a much lower density of adhesive is applied in drops in the surrounding area that will serve as the support. This results in very quick and easy weeding or excavation of the part out of the supporting paper when printing is complete.

"Deposition"-Deposition refers to the method of applying the adhesive in droplets onto a sheet of ordinary paper following the cutting of the profile of the part in that sheet (this process is repeated for each sheet of paper that will be used to create the part).

"Lamination" describes the process of building up successive layers of a substance – in our case, regular office paper – and bonding them to form a durable finished product. And, although prototypes built with our printers are made from ordinary paper, they are incredibly durable! They don't have to be post-processed to make them strong; you can safely use them right out of the

printer. They are not brittle and therefore don't break or shatter when dropped, and if desired, they can be drilled, threaded, tapped or made water resistant with a quick dip in a sealant. (35)

This technique of 3D printing can be used in the manufacture of tetra packs which are being very useful in dairy, pharmaceutical and food packaging.

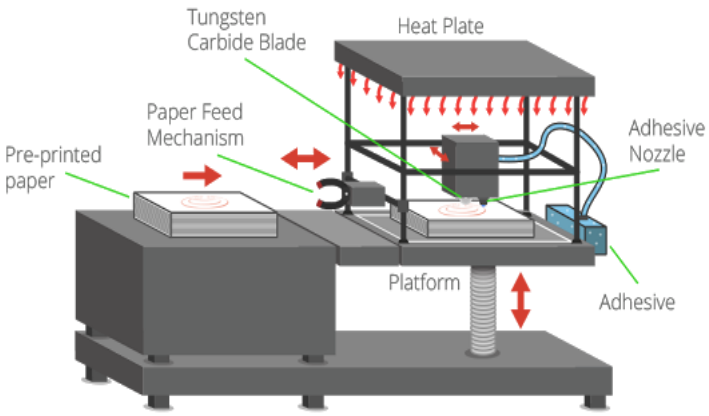

Figure 5: Selective deposition lamination (SDL)

MATERIALS USED IN 3D PRINTING:

The final product in additive manufacturing depends on the materials used because not all materials are suitable for additive manufacturing. Material design and its quality are among the main topics that need to be optimised in AM and are not yet fully adapted to the different procedures of additive manufacturing. The materials used must have strength to retain their shape and should have enough flexibility to print. Materials used are polymers like plastics, metals and their alloys, ceramics, paper, biomaterial and others.

- **Polymers and Resins:**

Wide range of polymers are being used in additive manufacturing because of their natural flexibility. Various polymerised, including acrylonitrilebutadienestyrene (ABS), polycarbonate (PC), poly lactic acid (PLA), high-density polyethylene (HDPE), PC/ABS, polyphenyl sulfone (PPSU) and high impact polystyrene (HIPS). In general, the polymer is in the form of a filament fabricated from virgin resins.

- **Metals and alloys:**

Metals and alloys can be used easily in 3D printing. Metals used can be either in powdered form or as thin filaments. 3D printing of metals is mainly based on the melting point of the metal. Titanium is one of the strongest possible metal materials and has been used for 3D printing industrial applications for some time. Supplied in powder form, it can be used for the sintering/melting/EBM processes.

- **Ceramics:**

A ceramic is an inorganic, non-metallic solid material comprising metal, non-metal or metalloid atoms primarily held in ionic and covalent bonds. This article gives an overview of ceramic materials from the point of view of materials science.The crystallinity of ceramic materials ranges from highly oriented to semi-crystalline, and often completely amorphous (e.g., glasses). Varying crystallinity and electron consumption in the ionic and covalent bonds cause most ceramic materials to be good thermal and electrical insulator (extensively researched in ceramic engineering).With such a large range of possible options for the composition/structure of a ceramic (e.g. nearly all of the elements, nearly all types of bonding, and all levels of crystallinity), the breadth of the subject is vast, and identifiable attributes (e.g. hardness, toughness, electrical conductivity, etc.) are hard to specify for the group as a whole. General properties such as high melting temperature, high hardness, poor conductivity, high moduli of elasticity, chemical resistance and low ductility are the norm, (36)with known exceptions to each of these rules (e.g. piezoelectric ceramics, glass transition temperature, superconductive ceramics, etc.). Many composites, such as fibreglass and carbon fibres containing ceramic materials, are not considered to be part of the ceramic family. (37)

- **Paper:**

Paper is a thin material produced by pressing together moist fibres of cellulose pulp derived from wood, grasses, and drying them into flexible sheets. It is a versatile material with many uses, including writing, printing, packaging, cleaning, and a number of industrial and construction processes.

- **Bio ink:**

Bio inks are the polymers generally containing living cells or biomaterials which are used to provide nutrition and support to the living cells. Alginate bases are extensively used in 3D printing. Alginate is a naturally derived biopolymer from the cell wall of brown algae. Alginates are used because of their ability to form cross linking with divalent cations like calcium. alginate-based bio inks can be blended with other materials such as nano cellulose for application in tissues such as cartilage. (38) Methacrylation of gelatin is a common approach for the fabrication of gelatin scaffolds that can be printed and maintain shape fidelity at physiological temperature. (39)Several companies have been founded with the goal of commercialising and standardising bio inks for research use. CELLINK was the first bio ink company in the world, developing a universal bio ink for all 3D printers. (40)Other companies such as Regenhu has developed standardised bio inks for bone tissue. (41)

APPLICATIONS OF 3D PRINTING IN MEDICINE:

3D printing has been applied in medicine since the early 2000s, when the technology was first used to make dental implants and custom prosthetics. (3,42) Since then, the medical applications for 3D printing have evolved considerably. Recently published reviews describe the use of 3D printing to produce bones, ears, exoskeletons, windpipes, a jaw bone, eyeglasses, cell cultures, stem cells, blood vessels, vascular networks, tissues, and organs, as well as novel dosage forms and drug delivery devices. (43, 44, 45) The current medical uses of 3D printing can be organized into several broad categories: tissue and organ fabrication; creating prosthetics, implants, and anatomical models; and pharmaceutical research concerning drug discovery, delivery, and dosage forms (46). A discussion of these medical applications follows.

1. BIOPRINTING TISSUES AND ORGANS

Tissue or organ failure due to aging, diseases, accidents, and birth defects is a critical medical problem. Current treatment for organ failure relies mostly on organ transplants from living or deceased donors. However, there is a chronic shortage of human organs available for transplant. (42, 43). Organ transplant surgery and follow-up is also expensive. An additional problem is that organ transplantation involves the often-difficult task of finding a donor who is a tissue match. The problem could likely be eliminated by using cells taken from the organ transplant patient's own body to build a replacement organ would minimise the risk of tissue rejection, as well as the need

to take lifelong immune suppressants. (43,47).Therapies based on tissue engineering and regenerative medicine are being pursued as a potential solution for the organ donor shortage.

3D bioprinting offers additional important advantages beyond the traditional regenerative method (which essentially provides scaffold support alone), such as: highly precise cell placement and high digital control of speed, resolution, cell concentration, drop volume, and diameter of printed cells. Organ printing takes advantage of 3D printing technology to produce cells, biomaterials, and cell-laden biomaterials individually or in tandem, layer by layer, directly creating 3D tissue-like structures. Various materials are available to build the scaffolds, depending on the desired strength, porosity, and type of tissue, with hydrogels usually considered to be most suitable for producing soft tissues. (3,48)

Inkjet-based bioprinting is most common. This method deposits "bio ink," droplets of living cells or biomaterials, onto a substrate according to digital instructions to reproduce human tissues or organs. (47)Multiple print heads can be used to deposit different cell types (organ-specific, blood vessel, muscle cells) are necessary feature for fabricating whole hetero-cellular tissues and organs. A process for bioprinting organs has emerged:

1) Create a blueprint of an organ with its vascular architecture;

2) generate a bioprinting process plan;

3) isolate stem cells;

4) differentiate the stem cells into organ-specific cells;

5) Prepare bio ink reservoirs with organ-specific cells, blood vessel cells, and support medium and load them into the printer;

6) Bio print (47)

A bioprinter- three-dimensional printer that uses living cells in suspension as its ink, and injection nozzles that can follow a CT scan blueprint.

Scientists and clinicians began exploring tissue culture for transplant surgery more than 20 years ago. But researchers in the US report in Nature biotechnology that they have harnessed a sophisticated, custom-designed 3D printer to print living muscle, cartilage and bone to repair battlefield injury. The printed body parts so far have been tested only in laboratory animals. But

tested organs have the size, structure and function for human use: once transplanted, they could be colonised by blood vessels and begin to grow and renew themselves normally. The study was backed by the US Armed Forces Institute for Regenerative Medicine.

“It can fabricate stable, human-scale tissue of any shape. With further development, this technology could potentially be used to print living tissue and organ structures for surgical implantation.the 3-D bioprinting method they developed generated a large (100 x 100 centimetres) area of skin in under 35 minutes - including the 30 minutes "required for fibrin gelation."Instead of the cartridges of coloured inks normally associated with printing, the 3-D bioprinter uses biological components. Experts say that these "bio-inks" are the key to the successful 3-D printing of human tissue and organs.

As with their existing plasma-based, manual method, the skin-printing technology that the team from Spain has developed generates two layers of skin: the epidermis and the dermis. It prints the epidermis, including the stratum cornea (the protective outermost layer comprising keratinised cells). Then, it prints the deeper, thicker dermis, complete with fibroblasts that make collagen (the protein that gives skin its strength and elasticity). (49)Humans begin as one fertilised cell but develop into perambulating structures of a hundred trillion cells of around 300 different varieties. In 1998, US scientists announced that they had found a way to isolate and grow human stem cells – the tiny living t that differentiate into blood, brains, skin, bone, sinew and internal organs.

Figure 6: Bioprinting of various organs.

The Wake Forest team spent a decade developing their new bioprinter, called ITOP: Integrated Tissue and Organ Printing System. It uses biodegradable materials to form the shape of the tissue and water-based gels that contain the living cells. (50)

The next challenge was to fabricate potential transplant tissue that would survive for long enough to be used in an operating theatre. So, the "ink" that holds the cells carries nutrients and the printed tissue is latticed with tiny channels so that nutrients, water and oxygen can get to the living cells within the printed organ.

The institute had already made a baby's ear and observed signs of blood vessel growth after an implant. The bioprinter results offer new hope and more confidence of success.

The researchers have printed human-sized ears and attached them under the skin of mice, to observe blood supply and the formation of cartilage tissue within two months. They planted muscle tissue within rats and observed nerve formation within two weeks. And in a five-month test, bio printed fragments of skull implanted in rats had formed bone tissue with its own blood supply. (50,51)

Challenges for bio printed organs

Though there is no FDA approved organ or tissue but researchers in this domain had boosted up because of the successful attempts made by different universities across the globe. There are many challenges beings faced by the developers. The most important hurdle in development is the composition of cell suspension to be used and to maintaining the living conditions for cells. Another problem is that vascularisation of organs. The organs created are alive in laboratory conditions but when transplanted the organ may take time to develop vascularisation. These problems are currently under investigation.

2. PHARMACEUTICAL DRUG DELIVERY:

Fabrication of 3D objects can be achieved through a number of techniques such as inkjet based fabrication, Direct-Write, Zip dose, thermal inkjet (TIJ) printing and Fused Deposition Modelling (FDM).

Compared to conventional pharmaceutical product manufacturing process, 3DP offers a lot of attractive qualities, such as,

(a) High production rates due to its fast operating systems.

(b) Ability to achieve high drug-loading with much desired precision and accuracy especially for potent drugs that are applied in small doses. (8)

(c) Reduction of material wastage which can save in the cost of production.

(d) Amenability to broad types of pharmaceutical active ingredients including poorly water-soluble, peptides and proteins, as well as drug with narrow therapeutic windows.

3DP in pharmaceutical drug delivery is anticipated to excel tremendously in the area of personalised medicines. We have reached an era in pharmacy practice and medicine whereby "one size does not fit all" since medication must be customised to individual patient's needs while taking into consideration differences in genetic profiles, age, race, gender, epigenetic and environmental factors. Also, there are situations where the treatment regimens must be customised to improve patient's adherence to treatment. It is particularly important in treatment of chronic illnesses where patients must follow complicated treatment regimens involving multiple medicines and high frequency of dosing couples with side effects. In all these cases, medicine customisation can be achieved through 3DP technology is possible, development and manufacture of single or multi-drug products with built-in immediate and controlled-release layers that can be tailored to unique patient's situations. As such, we envision that through personalised 3DP medicines, health professionals will have the opportunity to consider a patient's pharmaco-genetics profile before selecting the course of treatment.

"SPRITAM", the first 3D printed pill approved by USFDA. (33)

Complex drug release profiles

Drug release profiles explain how a drug is broken down when taken by the patient. Traditionally manufactured usually have simple drug releases profile. 3D printing makes it possible to print personalised drugs that facilitate targeted and controlled drug release by printing a binder onto a matrix powder bed in layers. This creates a barrier between the active ingredients, allowing researchers to study the variations of the release more closely. Designing and printing drugs first-hand makes it much easier to understand their release profiles. As manufacturers start to understand the full set of opportunities allowing them to make more effective drugs, there will likely be more research and investment into this area in the coming years. Dexamethasone has been printed in a dosage form with a two-stage release profile. (8) Levofloxacin has been 3D printed as an implantable drug delivery device with pulsatile and steady-state release mechanisms. (8) Implantable drug delivery devices with novel drug-release profiles can also be created using 3D printing and fabricated in complex geometries that are porous and loaded with multiple drugs throughout, surrounded by barrier layers that modulate release. (3)

Unique dosage forms

The primary 3D printing technologies used for pharmaceutical production are inkjet-based or inkjet powder-based 3D printing. Whether another material or a powder is used as the substrate is what differentiates 3D inkjet printing from powder-based 3D inkjet printing. (8)

In inkjet-based drug fabrication, inkjet printers are used to spray formulations of medications and binders in small droplets at precise speeds, motions, and sizes onto a substrate. (8) The size of the droplet, speed and spacing are computer controlled. The most commonly used substrates include different types of cellulose, coated or uncoated paper, microporous bioceramics, glass scaffolds, metal alloys, and potato starch films, among others. Investigators have further improved this technology by spraying uniform "ink" droplets onto a liquid film that encapsulates it, forming microparticles and nanoparticles. Such matrices can be used to deliver small hydrophobic molecules and growth factors. In powder-based 3D printing drug fabrication, the inkjet printer head sprays the "ink" onto the powder foundation. When the ink contacts the powder, it hardens and creates a solid dosage form, layer by layer. The ink can include active ingredients as well as binders and other inactive ingredients. After the 3D-printed dosage form is dry, the solid object is removed from the surrounding loose powder substrate. (8)

These technologies offer the ability to create limitless dosage forms that are likely to challenge conventional drug fabrication. 3D printers have already been used to produce many novel dosage forms, such as microcapsules, hyaluronic based synthetic extracellular matrices, antibiotic printed micro-patterns, mesoporous bioactive glass scaffolds, nano-suspensions, and multilayered drug delivery devices. Ink formulations used in 3D drug printing have included a variety of active ingredients, such as steroidal anti-inflammatory drugs, acetaminophen, theophylline, caffeine, vancomycin, ofloxacin, tetracycline, dexamethasone, paclitaxel, folic acid, and others. Inactive ingredients used in 3D drug printing have included: poly (lactico-glycolic acid), ethanol-dimethyl sulfoxide, surfactants (such as Tween 20), Kollidon SR, glycerin, cellulose, propylene glycol, methanol, acetone, and others. (8)

3. HEART STENTS

A coronary stent is a tube-shaped device placed in the coronary arteries that supply blood to the heart, to keep the arteries open in the treatment of coronary heart disease. It is used in a procedure called percutaneous coronary intervention (PCI). Stents reduce chest pain and have been shown to improve survivability in the event of an acute myocardial infarction. (52) These coronary stents are

generally made up of metals like stainless steel in the form of mesh which supports the inner wall arteries and allows the passage of blood. The stents are very delicate and expensive. The use of metals can also cause many problems like clotting. Right now, the vast majority of stents are made from a metal and have off-the-shelf availability in various sizes, the physician has to guess which stent size is a good fit to keep the blood vessel open. But we're all different and results are highly dependent on physician experience, so that's not an optimal solution. (53)

3-D printing technique, called projection micro-stereo-lithography, to fabricate stents using a polymer previously developed. The technique uses a liquid photo-curable resin or polymer to print objects with light. When a pattern of light is shined on the polymer, it converts it into a solid that is then slowly displaced to cure the next layer of liquid polymer. The printing technology allows the team to fabricate a stent that precisely matches desirable design characteristics. (54)

Not only can we customise the stent for a patient's blood vessels, but we can create all new types of patient-specific medical devices that could make the outcomes of surgical procedures better than what they are today.

4. DENTAL IMPLANTS

Crown copings and partial denture frameworks

With the use of intra oral optical scanners or laboratory scanners, it is possible to develop a precise virtual model (55,56)of the prepared tooth, implant position (57)and the dental arch (56,58). In fixed and removable prosthodontics, treatment may be planned and restorations designed in CAD software. This scan data and CAD design may be used to mill or print crown or bridge copings, implant abutments, and bridge structures.

3D printing may be harnessed for the fabrication of metal structures (59)either indirectly by printing in burn-out resins or waxes for a lost-wax process, or directly in metals or metal alloys. (60) The advantage of printing in resin/wax and then using a traditional casting approach is that there is much less post-processing involved than in the direct 3D printing of metals.(61)casting alloys and facilities are also familiar and widely available. Printing directly in metals requires the use of more costly technologies which have their own very specific health and safety requirements, and demand a great deal of post-processing before components may be ready for use.(62)While printing elaborate implant bridge structures 3D printing may be used in conjunction with milling/machining technologies to produce a high precision mechanical connection to the implant –

combining the best attributes of printing – complex geometry with little waste - with milling – high precision mechanical connecting surfaces.

While it may be somewhat wasteful in material, milling has the advantage that the material used is intrinsically homogeneous and unaffected by operating conditions. There is little need for post-processing, and the equipment is considerably less costly. (63)

Invisalign braces are another successful commercial use of 3D printing, with 50,000 printed every day. These clear, removable, 3D-printed orthodontic braces are custom-made and unique to each user. This product provides a good example of how 3D printing can be used efficiently and profitably to make single, customised, complex items.(63)

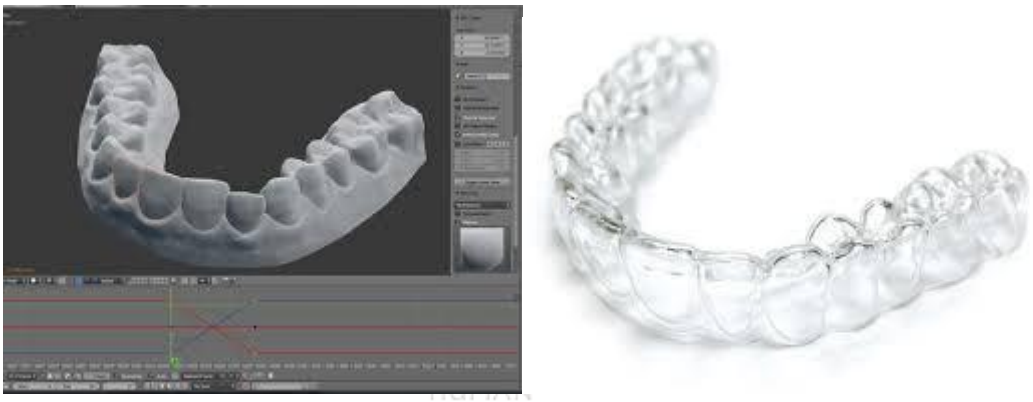

Figure 7: Invisalign braces

Prosthetic implants:

The artificial implants are very useful for physically special individuals but the manufacture of prosthetics is equally difficult and lot of time consuming process the precision and comfort from these prosthetic implants is also less when manufactured traditionally, here 3D printing technology has made its place by its uniqueness. Prosthetics are the artificial or replacement of a body part like limbs, eye, facial, dental crowns, etc. Prosthetics may be removable as in case of most prosthetic limbs. With advances in biomedical research the prosthetics highly advanced prosthetics integrated with body tissues including nervous system are being developed e.g. Like myoelectric prosthetics, the primary function of these limbs is to mimic the appearance and replace the function of the original limb. The myoelectric limbs work in order to have both appearance and functions of natural limbs. The primary disadvantages of this kind of prosthetic are currently their weight and cost, not all could afford this and the growing children have to change their limbs replacing the limb to keep pace with the child's rate of growth until he or she reaches maturity can be a pretty

expensive process. 3D printing technology can solve this problem because of its versatility in manufacturing. Prosthetics made from 3D printing can be easily customised and created to suit the owner. A 3D printed prosthetic limb can usually be made in a day. In comparison, it generally takes weeks or even months to produce and calibrate regular prosthetic limbs. The most important thing is 3D printing being cost effective, organisation called e-NABLE team prints these prosthetics for 50$.

Trails have proved that 3D printed prosthetics are nearly equal to the advanced prosthetics. Previously, surgeons had to perform bone graft surgeries or use scalpels and drills to modify implants by shaving pieces of metal and plastic to the desired shape, size, and fit. This is also true in neurosurgery, Skulls have irregular shapes, so it is hard to standardise a cranial implant. In victims of head injury, where bone is removed to give the brain room to swell, the cranial plate that is later fitted must be perfect. Although some plates are milled, more and more are created using 3D printers, which makes it much easier to customise the fit and design.

There have been many other commercial and clinical successes regarding the 3D printing of prostheses and implants. (46, 44,3)A research team at the BIOMED Research Institute in Belgium successfully implanted the first 3D-printed titanium mandibular prosthesis. (46)The implant was made by using a laser to successively melt thin layers of titanium powders. In 2013, Oxford Performance Materials received FDA approval for a 3D-printed polyetherketoneketone (PEKK) skull implant, which was first successfully implanted that year (46). Another company, Layer Wise, manufactures 3D-printed titanium orthopaedic, maxillofacial, spinal, and dental implants. An anatomically correct 3D-printed prosthetic ear capable of detecting electromagnetic frequencies has been fabricated using silicon, chondrocytes, and silver nanoparticles (3). There is a growing trend toward making 3D-printed implants out of a variety of metals and polymers, and more recently implants have even been printed with live cells. (4)

3D printing has already had a transformative effect on hearing aid manufacturing (44). Today, 99% of hearing aids that fit into the ear are custom-made using 3D printing. Everyone's ear canal is shaped differently, and the use of 3D printing allows custom-shaped devices to be produced efficiently and cost-effectively (44). The introduction of customized 3D-printed hearing aids to the market was facilitated by the fact that class I medical devices for external use are subject to fewer regulatory restrictions.

5. PREOPERATIVE SURGICAL PLANNING

Increasingly, physicians and their partners are recognizing the value that 3D printing offers, not only for developing new medical devices, implants, and prosthetics, but also for the creation of patient specific replicas of bones, organs, and blood vessels. These replicas are made possible through software that converts the patient's own scans such as computerized tomography (CT) and magnetic resonance imaging (MRI) 2D scans into STL files. These files essentially encode each patient's specific anatomic or pathologic features, which then can be fabricated by 3D printers. Use of special printing materials such as photopolymers that produce both hard and soft materials allow the accurate replication of human tissue, calcification, and bone. Physicians and their teams can use these models to improve the diagnosis of illnesses, elucidate treatment decisions, plan, and, in some cases, even practice selected surgical interventions in advance of the actual treatments. The models help physicians understand patient anatomy that is difficult to visualize, especially when using minimally invasive techniques. Models also assist in accurately sizing medical devices. Finally, physicians can use the models to explain an upcoming surgery to patients and their families and to communicate the surgical steps to the clinical team. Traditional preoperative surgical planning using patient imaging (2D scans), 3D reconstructions of patient scans on a computer, and generic physical models to imagine access routes and how particular medical devices would fit in particular anatomies. Since it is difficult to extrapolate all of the necessary information from these methods, adaptations have to be made on the fly during procedures, which adds a major element of uncertainty (IyerStratasys). The use of 3D printed models mitigates this uncertainty and allows physicians to better anticipate problems prior to performing the procedure. (64) 3D visualization of anatomy and pathologic conditions.

ADVANTAGES OF 3D PRINTING:

Additive manufacturing offers numerous advantages for mass customisation. Flexibility, speed and the ability to build objects directly make it an attractive alternative to conventional machining, forging, moulding and casting of customised parts. Additive manufacturing at low volumes is very cost competitive compared to traditional manufacturing. For the production of prototypes that verify form and fit, it is significantly cheaper than other alternative manufacturing methods (injection moulding) and is often competitive for manufacturing one off functional parts. Traditional manufacturing techniques become more cost effective as volumes begin to increase and the high setup costs are justified by the large volumes of productions.

CUSTOMISATION

A major advantage in 3d printing. With just a raw material, a blueprint and a 3d printer, one can print any design no matter how complex it might be. Additive manufacturing also reduces the transportation cost as these objects can be printed anywhere at any point of time.

Cost

The cost of manufacture can be broken down into 3 categories; machine operation costs, material cost and labour costs.

Machine operation costs: Most desktop 3D printers use the same amount of power as a laptop computer. More industrial additive manufacturing technologies consume a high amount of energy to produce a single part, however, the ability to produce complex geometries in a single step results in higher efficiency and turnaround. Machine operation costs are typically the lowest contributor to the overall cost of manufacture.

Material costs: The material cost for additive manufacturing varies significantly by technology. Desktop FDM printers use filament coils that cost around $25 per kg while SLA printing requires resin that retails around $150 per litre. The range of materials available for additive manufacturing make quantifying a comparison with traditional manufacturing difficult. Nylon powder used in SLS costs around $70 per kg while comparable nylon pellets used in injection moulding can be purchased for as little as $2 - $5 per kg. Material costs are the biggest contributor to the cost of a part made via additive manufacturing.

Labour costs: One of the main advantages of 3D printing is the cost of labour. Post processing aside, the majority of 3D printers only require an operator to press a button. The machine then follows a completely automated process to produce the part. Compared to traditional manufacturing where highly skilled machinists and operators are typically required, the labour costs for a 3D printer are almost zero. (65)

Complexity and design freedom

The restrictions imposed by traditional manufacturing on what can be made are generally not relevant for additive manufacturing. Because components are constructed one layer at a time design requirement such as draft angles, undercuts and tool access do not apply when designing parts to be 3D printed. While there are some restrictions on the minimum size features that can be accurately

printed most of the limitations of additive manufacturing around how to optimally orientate a print to reduce support dependency and the likelihood of print failure. This allows designers a large amount of design freedom and means that very complex geometries can easily be created. (65)

Pharmaceuticals:

Reducing the steps in manufacturing of tablets i.e., as the tablet manufacturing involves mixing, filling, compression, ejection, coating of the tablets which introduce a lot of processing problems like blister formation, capping, lamination, peeling etc.,3D printing technology reduce the number of steps involved and also ensures drug content uniformity. 3D printing of pharmaceuticals can be used for creating complex drug release profiles as the 3D printing involves layer by layer manufacture.

TECHNOLOGICAL CHALLENGES:

The additive manufacturing offers tremendous opportunities for the development of new aged manufacturing techniques and instruments, yet has challenges that need to be overcome by learning and exploring the technology. The 3D printing technology has provided a platform for the customised manufacture by globalising the technology which can be easily shared through internet. This arises a serious question of proprietary items as any product can be scanned and printed in any part of the world. This can lead to a serious problem in medical field as the standards, hygiene and environmental conditions in which the object manufactured is very important as this can prove to be dangerous. The overall use of 3d printing technology in manufacturing is less than 2% because of its

- Equipment costs
- Limited materials available
- Post-processing requirements
- Manufacturing costs
- Lack of in-house additive manufacturing resources
- Lack of expertise and/or training among workforce/employees
- Limited repeatability (accuracy from build to build)

- Lack of formal standards
- Lack of proven documentation of additive manufacturing's capabilities
- Software development and capabilities
- Longer production timelines
- Limited recyclability
- Risk of litigation/legal implication
- Data storage requirements. (66)

The equipment's used in additive manufacturing are highly sophisticated and need high maintenance when compared with the traditional machinery used in production. Apart from very high-level machines, costing several million dollars each, 3D printing tends to produce items that are less 'resistant' than classic molded parts. Layer by layer build-up leads to a structural weakness, this can lead to the production of weak and low standard products.

Not all the raw materials used in traditional manufacturing are suitable for the additive manufacturing. The materials used in additive manufacturing must be flexible, thermally stable, light resistant, and strong enough to provide strength to the object being created. They should be able to flow through print heads and solidify immediately after being deposited on the platform. Most additive manufacturing processes use proprietary polymers that are not well characterised, Parts that have been additively manufactured with metals have physical properties that can be quite different from conventional cast metals, for example, they may lack full density, which can compromise fracture toughness and fatigue properties.

The 3D printing should be done in a controlled environment to maintain the purity of the substance being manufactured especially in printing pharmaceutical dosage form though 3d printing might be accurate in printing, the raw materials may get affected by the surroundings.The 3D printed products should undergo post process in order to remove excess materials, support structures and might undergo coating in few techniques. As the technology is being developed in recent past the availability of skilled labour and CAD formatted files are very less.

Another setback is that it cannot benefit from economy of scale. And of course, the 'time to produce' will depend on the number of layers to be printed, and this can last for hours, or even days. Admittedly this is in order and acceptable for prototyping but not for 'mass-production' or rather small series. Speed of printing will remain very dependent on the speed at which the printer-head can extrude the raw material used.

While 3D printers might not need to be retooled in between production runs, the speed at which a 3D printer can assemble an object often pales in comparison to the traditional assembly line. (67)

This is because 3D printing requires each object to be assembled one layer at a time, with each new layer being directly placed on top of the previous one. Even with a "fast" 3D printer, some small objects can take hours to make. (67)

3D printing can lead to legal risks i.e. there are many loopholes in the additive manufacturing technology where intellectual properties are concerned. Many formulas, process, materials used, objects themselves are governed and protected by patents and copyrights, thus there are issues surrounding the scanning using 3d scanner and how much a modification of scanned geometry will affect the original product. There are liability issues concerning the machine, its data and materials used and also liabilities surrounding the manufactured components raising a big question of customer's safety.

"No wastage" using 3D printing is a myth, which has been broken.3D printing definitely reduces the amount of waste produced during processing but the ecological impacts of 3D printing are quite high. 3D printers are not necessarily less wasteful; their waste is not necessarily recyclable; their waste isn't even that important compared to their electricity use.

Even if 3D printers did eliminate transportation of goods, it wouldn't matter much, transport is a tiny part of most products' environmental impacts.

CONCLUSION

In the present scenario medicine 3D imaging and modelling, CAD technologies are hugely impacting on all aspects of development. 3D printing makes it possible to accurately make one-off, complex geometrical forms from this digital data, in a variety of materials, locally or in industrial centres. Even now, nearly everything we make in factories can be made by a 3D printer, but no single technology is sufficient for all our needs. The technology is already widely used in

orthodontics, where high resolution printing in resin is already an entirely practical proposition, and similar technology is being used to print models for restorative dentistry and patterns for the lost wax process which is becoming increasingly important with the rise of intraoral scanning systems. In maxillofacial and implant surgery, it is becoming commonplace and prerequisite to use anatomical models made by any number of different 3D printing techniques to assist with the planning of complex treatments. It is widely acknowledged that surgery may be less invasive and more predictable with the use of surgical guides printed in resins or autoclavable nylon. For many, the real excitement will be in the development of complex and unique dosage forms using additive manufacturing. As pharmaceutical industries play a major role in healthcare sector it is important to upgrade the technology in production of pharmaceuticals. Development of technology should not just concentrate on the bulk production instead precision in production of pharmaceuticals is necessary. Traditional manufacturing of pharmaceuticals in a way lacks precision for e.g.in a batch of tablets the amount of drug present each tablet varies, this leads to change in the drug content uniformity. 3D printing of pharmaceuticals can successfully reduce these problems. 3D printing can be proved beneficial in personalised drug manufacture.

Although 3D printers are becoming more affordable, the cost of running, materials, maintenance, and the need for skilled operators must also be carefully considered, as well as the need for post-processing and adherence to strict health and safety protocols. Despite these concerns, it is clear that 3D printing will have an increasingly important role to play in pharmaceutical sector. The congruence of scanning, visualisation, CAD, milling and 3D printing technologies, along with the professions innate curiosity and creativity makes this an exceptionally exciting time to develop new drug delivery system to provide a better treatment.

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