A Review Paper- Impact of 3D Printing in Medical

Rugnesh Patel, Assistant Professor, CSPIT, CHARUSAT, CHANGA, INDIA,

rugneshpatel.me@charusat.ac.in

Abstract: **Additive manufacturing (AM) also known as 3D printing, the applications of 3D printing are vast, the world is moving towards 3d printing, apart from the most obvious applications in the fields of architecture and engineering, now 3D printing is showering its fragrances in medical field too such as surgical models and tools, tooling equipment, medical devices. Three-dimensional (3D) printing is opening new opportunities in medical field by enabling creative problem solving, faster prototyping of ideas, advances in tissue engineering, and customized patient solutions. This progress represents a valuable breakthrough that exhibits many potential uses, such as research on drug release control or live organ printing mechanism. This technology helps to solve the shortage of organs for transplant in the future. Therefore, the purpose of this review paper is to (1) Describe the various AM technologies and process used in medical field (2) Different types of 3D printing applications. (3) Discuss some of the challenges and future developments for 3D printing in medical field.**

Keywords: 3-D printing, Additive Manufacturing, Biomedical engineering, Biomedical Prosthetic-Implants, Rapid Prototyping, Tissue Engineering.

I. INTRODUCTION

What used to take weeks, or even days, to manufacture? Now only takes a matter of hours—this is the transformational potential that additive manufacturing (AM), also often called 3-D printing, brings to the medical device industry. Medical applications for 3D printing are expanding rapidly and expected to revolutionize health care [1]. Medical uses for 3D printing, both actual and potential: organized into several broad categories, including: tissue and organ fabrication; creation of customized prosthetics, implants, and anatomical models; and pharmaceutical research regarding drug dosage forms, delivery, and discovery [2]. Tuomi [3]. Has classified the Additive Manufacturing application in medical into five major areas:

i. Medical Model
ii. Surgical Implant
iii. Surgical Guides
iv. Surgical Aids
v. Bio Manufacturing

Medical 3D printing used in many areas such as biomedical modelling.3DP help for printing organs produces cells, cell-laden biomaterials, and biomaterials individually.

The process used for bio printing organs are:

i. Bio- imaging and CAD creates vascular structural Design- blueprint of organ.
ii. Bio printing process design formation
iii. Isolate stem cells, Differentiate of stem cell in to organ-specific cells
iv. Preparation of bio ink reservoirs with the help of blood vessel cells, organ-specific cells and support medium.
v. Maturogens and Biomonitoring-Bioreactor in clinical phase

3D bio-printing technology is a new medical engineering technology, defined as a special biological printer, which contains active materials including cells, growth factors, and biological material as the main processing content. it can be applicable to the large variety of medical applications including dentistry, general and anatomical models, medical devices, tissue engineering scaffolds, tissue models and drug formulation [4]-[6]. Today, 3D Dental Digital Dentistry labs can 3D print bridges, crowns, orthodontic appliances (crooked teeth and improper bites) and stone models, are becoming a new norm. Surgical applications include medical devices, such as custom orthoses and prostheses (O&P) and surgical instruments, [7] and anatomical models [8].Anatomical models aid pre-surgical planning and education [9].3D printing technology has been adapted to the pharmaceutical field, with a growing focus on developing personalized-dose medicines [4]. 3D printing is also becoming popular in tissue engineering and regenerative medicine. Tissue and organ printing is an emerging area with significantly increasing interest from academia and industry [5], [10]. In addition, bio printing of pre-clinical, patient-specific tissue and disease models for drug testing and high-throughput screening is another emerging area with great potential for developing patient-tailored drugs and reducing the use of animal models [11].

 DOI : 10.18231/2454-9150.2018.0357

ISSN : 2454-9150 Vol-04, Issue-03, June 2018

In today's marketplace, medical device manufacturers, to meet customer needs, is turning to use Additive manufacturing methods like, PolyJet printing, Stereolithography (SLA), and Fused Deposition Modeling (FDM)/ Fused Filament Fabrication (FFF), for a variety of applications. The range of techniques, along with a growing array of engineering and prototyping materials, gives design engineers tremendous flexibility to meet the challenges of this fast-moving industry. These techniques are like Direct Metal Laser Sintering (DMLS), Selective Laser Sintering (SLS), Selective Laser Melting (SLM), and Electron Beam Melting (EBM). [12], [13].

WHAT IS 3D PRINTING?

3D printing often referred as additive manufacturing; this term accurately describes how this technology works to create objects. "Additive" refers to the successive addition of thin layers of materials until the object created from a CAD data file. Each of these layers visible as a thinly sliced horizontal cross-section of the eventual object. In which the materials can uses such as, plastic, metal, ceramics, powders, liquids, or even living cells to produce 3D objects [14], [15], [16]. This technique is also knowns as rapid prototyping (RP), or solid free-form fabrication (SFF); computer automated manufacturing or layered manufacturing [17]. 3D printing enables to produce complex (functional) shapes using less material than traditional manufacturing methods.3D printing starts with a digital file derived from computer aided design (CAD) software [16]. Once a design is completed, and then exported as a standard tessellation language (STL) file, meaning the file translated into triangulated surfaces and vertices. The STL file then sliced into hundreds - sometimes thousands – of 2-D layers. A 3D printer then reads the 2-D layers as building blocks which it layers one atop the other, thus forming a three dimensional object (Figure-1) [1] [18].

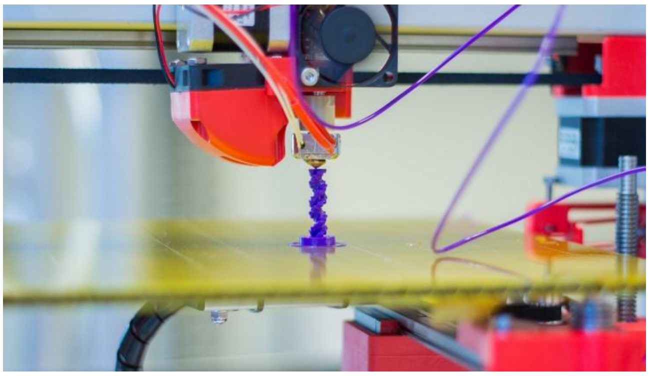

Figure:1, 3D printer Follow the Instructuion to create physical object.,source:Felix 3Dprinter-printer Head

BASIC CONCEPTS OF 3D PRINTING

A CT or CAT scan also known as, “a computerized axial tomography (CT) scan” are special X-ray tests that produce cross-sectional images of the human body using X-rays and a computer [19]. Consider a CT scan, which consists of multiple planar slices: in a certain way, AM (additive manufacturing) might be called its reverse process where digitized images are brought back to the physical world as metal, plastic, ceramic, or composite parts regardless of the complexity of their shape. Most AM processes have layer thicknesses far thinner than slice thicknesses of primary medical imaging methods, thus the radiology step of the production process is crucial for model accuracy [20].

Houtilainen et al [19] compared 3D printing and CT scans very effectively, by saying that, 3D printing is essentially the opposite of CT scans. CT scans allow to look at the inside of the body just as one would look at the inside of a loaf of bread by slicing it, This type of special X-ray, in a sense, takes "pictures" of slices of the body in a computer, whereas 3D printing takes layers of images in a computer and creates an object from them, By these collective impressions,3D printing is capable of creating a level of finesse and detail in its layers that current medical imaging is not capable of delivering [20]. It is important to note that two-dimensional (2D) radiographic images, such as x-rays, magnetic resonance imaging (MRI), or computerized axial tomography (CT) scans, converted in to the template which projected on the two planes of the X-ray images. The projections matched in shape with the X-ray images by the algorithm and the modified projections converted back to a 3D model of complex, customized anatomical and medical structures (Figure 2) [22][23].

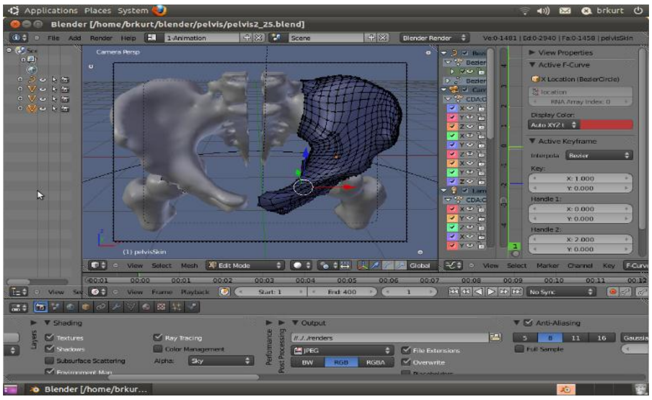

Figure:2, Human Comlieant pelwis model converted to 3D print files to create complex, customized anatomical and medical structures. Source:Make human compliant Pelwis Model(WIP)

HISTORY OF 3D PRINTING

1800s: 3D printing does not officially get started until the late twentieth century, but some elements of the ideas and conceptual foundations stretching back further, which hinted the roots of 3D printing lie in photo-sculpture and topography [24]. In 1859, a French artist named François Willème demonstrates photo-sculpturing method -the world’s first “3D scanning” technology. A few years later, in 1892, inventor Joseph E. Blanther patented a layering method of 3D topographical maps - similar in concept to

 DOI : 10.18231/2454-9150.2018.0357

today's 3D printers [24]. Dr Hideo Kodama grants attempts, describing a photopolymer rapid prototyping system. Which used a UV light to harden photo reactive polymers as part and builds up the model in layers. Those early pioneers called it Rapid Prototyping (RP) technologies [25]. In 1983, Chuck Hull invents stereolithography apparatus (SLA) a process that produced a tangible 3D object from digital data. [26] After rigorous testing and experiment, Hull then founded new technology of 3D Systems in 1986, first commercial RP system, the SLA-1 introduced in 1987 and sold in 1988 [21]. Scott crump filed patent for FDM in 1989 issued in 1992.In terms of commercial operations, Sanders Prototype (later Solidscape) and Z Corporation were set up in 1996, Arcam was established in 1997 [26]. 3D printing technology is growing fast; with the advancement of AM researcher broaden the way of application in various sectors such as aircraft, automobile, even food, construction and medical field.

OVERVIEW OF CURRENT APPLICATIONS

COMMERCIAL USES:

For decades, AM was used in the manufacturing industry primarily for increasing the speed of prototype [14], [16]. Nowadays, with the advances in the available materials, speed, resolution, accuracy, reliability, cost and repeatability of AM technologies have explores different applications and the possibilities in the medical field [26], [27]. In 2012, medical applications of 3D printing." Accounted for 16.4 percent of the total system-related revenue estimated at $121.6 billion, with an annual expected growth rate of 5.4 percent for the AM, market. [28], [29]. Companies that use 3D printing for commercial medical applications: Organovo, Merck, and L'Oréal such industries uses 3D printing to fabricate living kidney, liver tissue [2].Cyfuse Biomedical is another company working on a bioprinter called as Regenova. Utilizing a technique, they call Kenzan; they can print three-dimensional cell structures, for example, human tissue, using cell spheroids in little needle clusters. The firm has already raised $16.5 million and can print biological components such as digestive and urinary organs, cartilage, blood vessels, tubular tissues, and even functional liver [33]. At present, however, the impact of 3D printing in Healthcare rising. In addition, expected to reach $2.3 Billion, Globally, by 2020 [31]. 3D printing has always been a niche market, with a small handful of companies dominating the industry. That said, the industry is rapidly growing as more companies make the leap to enter the market, which is expected to be worth over $30 billion by 2022 [33].

CONSUMER USES:

3D printing technology with the ability to test and revise designs has opened new doors to innovation in consumer products throughout the phases of functional prototyping, design, tooling, and even through series part production. [16], [34] online 3D printing services brings virtual designs to real life, with mass customization; also give designers and makers' the freedom they need: changing the size or material of an object [34], [35].

3D printing offers an alternative solution to traditional design and manufacturing limitations. Simultaneously produce multiple design iterations so, that each, tested for form, fit, and function. At the same time, check ergonomics, and visual appeal, all without any expensive tooling. Reducing costs 3D printing technology to create the most complex geometries quickly and easily. Durable end-use parts are also possible with the additive manufacturing capabilities of 3D printing. Such as guns, body parts, cosmetics, food, forensic &archeology. Astonishing realistic appearance possible in consumer electronics, sporting goods, toys Lego bricks and jewelry [2]. 3D printing used in fashion to create visually stunning dresses and accessories, Iris Van Herpen was the first Dutch fashion designer to present a 3D printed piece on the runways in 2010 at the Amsterdam Fashion Week [33] as well as a unique "smoke" dress unveiled at the 2013 Frankfurt International Motor Show. Lady Gaga wore the world's first flying dress, Volantis, another 3D printed dress, at the 2013 Art Rave. Lulzbot (www.lulzbot.com) provides very pro-open source approach including not just the designs, but also all the documentation even of things like their material testing, RepRap (www.reprap.org) and MakerBot are considered leaders in both open source and the quality of the printers themselves. Another highly regarded company is SeeMeCNC, maker of the highly regarded Rostock Max. [37], [38]. All of these circumstances are driving a new industrial revolution that is going to change the consumer products of the future [34].

COMMON TYPES OF 3D PRINTERS

There are various 3D printing methods; each has their own set of strengths, weaknesses, which offer transformative advantages at every phase of creation – from initial concept design to the production of final products, will define the characteristics of 3D printed structures, and objects [22]. Process selection mainly depends on materials, application and manufacturing capabilities [34]. Total, seven different categories of additive manufacturing processes identified, where only three technologies best suited for medical applications: selective laser sintering (SLS), thermal inkjet (TIJ) printing, and fused deposition modeling (FDM) [34], [39]. Overview of each of these technologies are as follows.

Selective laser sintering (SLS):

SLS also called laser sintering (LS) uses thermoplastic powdered material in the vat, heated to a temperature just below the polymer's melting point. A recoating blade or wiper deposits a very thin layer of the powdered material typically 0.1 mm thick onto a build platform [41]. A CO_2

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laser beam then begins to scan the surface. The laser will selectively sinter the powder and solidify a cross-section of the object. When the entire cross-section scanned, the build platform will move down one layer thickness in height. The recoating blade deposits a fresh layer of powder on top of the recently scanned layer, and the laser will sinter the next cross-section of the object onto the previously solidified cross-sections [41]. These process remain continue until all objects are fully manufactured, Powder, which is not sintered, remains in place to support the object, this material removed after the object is formed for re-use. LS build versatile parts and prototypes with high elongation at break; provide lightweight, heat and chemical resistant solutions. LS can create objects of Polyamide (Nylon), Polystyrenes, Thermoplastic Polyurethane (TPU), Metal [40].

Thermal Inkjet Printing (TIJ):

Thermal ink jet (TIJ) method is non-contact printing technology. Different way of firing method of ink using resistor, piezoelectric and electromagnetic produces tiny drops of ink or other materials in the form of bubble or jet, inkjet printers very simply as a firing squad of nozzles rattling off millions of dots of ink at the substrate on every single second [42]. Tiny heating elements used to eject ink droplets from the print head's nozzles. Most thermal inkjets have print heads containing a total of between 300 and 600 nozzles, each about the diameter of a human hair (approx. 70 microns). These deliver drop volumes of around 8 to 10 picolitres (a picolitre is a million millionth of a liter), and dot sizes of between 50 and 60 microns in diameter [49]. For the biomedical application: tissue-generating, inkjet printing successfully applied which can produced 20um to 90um microsphere of calcium used to produce silica shell, several applications of inkjet dispensing in deposit of living cells, growth factors, hydrogels and other biomaterial s promising the use in tissue engineering and regenerative medicine [42],[43]. The greatest value of inkjet printing due to its high speed, availability, and relatively low costs features encourage researcher to apply in bio printing: tissues and organs [39]. This technique with digital control proves direct repair of tissue, it may also use in drug delivery and gene transection during vascular tissue construction [39].

Fused Deposition Molding (FDM):

FDM technology sometimes referred to as Fused Filament Fabrication, or FFF, In FDM objects built with production-grade thermoplastics [20] by heating a thermoplastic filament to its melting point and extruding the thermoplastic layer by layer on a build stage until the object is finished. The plastic used in FDM are generally ABS (Acrylonitrile ButadieneStyrene),PLA(PolylacticAcid),PC (polycarbonate) and Nylon (Polyamide), but other exotic varieties of materials used like a blend of plastic and wood or carbon [40].There are also several types of support materials including water-soluble wax or PPSF (polyphenylsulfone) [48]. FDM technology is widely spread nowadays in variety of industries such as automobile companies like Hyundai and BMW or food companies like Nestle and Dial. For new product development, model concept, prototyping and in manufacturing development, even in food and drug packaging. This technology considered as simple-to-use and environment-friendly [48].

BENEFITS OF 3D PRINTING IN MEDICAL APPLICATIONS

Customization and Personalization:

3D medical Printing technology brings a new wave of advancement in the healthcare industry & prove to be an asset in developing new medical applications at affordable prices [44]. The main constraint: ability to create custom products and equipment. Personalized implants and tools can decrease the time needed to perform surgery as well as speed up patient recovery time, [45] Commercially available 3D printed medical devices include: Instrumentation (e.g., guides to assist with proper surgical placement of a device),Implants (e.g., cranial plates or hip joints), and External prostheses (e.g., hands) [47]. 3D printed technology allows constructing individual's specific requirements of drug like, the size, dose, appearance and rate of delivery [47].

Productivity and Efficiency:

Earlier, it is very difficult to manufacture complex, organic shape by traditional method, Nowadays AM plays a vital role to create complex designs and print parts potentially limitless. Functionality graded scaffold like bone have porous structure of metal manufactured inexpensively very quickly [48]. AM technology especially provides effective strategies with open sources facilities to designers and engineers to quickly create and iterate designs, more efficiently using realistic prototypes and ultimately reduce time and cost to market. Especially for small prosthetics and implants [54]. The advent of 3D printing stands along with freedom in complexity comes the option to customize a product to almost any requirement (less tooling). It increases lead times and speeds up delivery, with reducing overall waste. It leads to decrease the costs of medical products [44].3D printing is changing the development and manufacturing processes, featuring with create full-size concept models of the parts, or even mass-product the end products, rapid tooling fabrication, functional testing to improve product quality, multi-material composite, innovative products and components on-demand. It results in factory streamline operations to maximize output and reduce overhead costs [44].

 DOI : 10.18231/2454-9150.2018.0357

ISSN : 2454-9150 Vol-04, Issue-03, June 2018

APPLICATION OF 3D PRINTING IN MEDICAL

Implants & Prosthetics:

3D technology allows an artificial prosthetic to be designed and built within 24 hours, and at a fraction of the cost of conventional prosthetic [48]. 3D printing technology is being to use in efficient way to produce patient specific components of prosthetics, such as upper and lower limbs that fit comfortably with the patient's anatomy [51]. This ability to produce complex shapes from a range of multi-materials with low cost has resulted in AM being adapted at worldwide at the locations, even in war torn areas in Syria and Africa, An estimated 30 million people worldwide need prosthetics - such as a hand, arm or leg, In Uganda, 5000 patients waiting for a new limb [49]. To fulfill requirement a team of Canadians and Ugandans are using a 3D printer to speed up the production process [49].Statistics shows, 2.1 million people living with limb loss in the USA, and that number expected to double by 2050. Approx., 185,000 people have an amputation each year [50]. To fulfill demand and supply AM industries provides online-open source platforms (e-NABLE) where, prosthetic models available at free of cost; anyone can design, modify and print from anywhere as per requirement with owned 3D printer. Open Bionics creating the next generation of prosthetic limbs using 3D printing (Figure.3 (a)). 3D Printed prosthetic limbs created using both rigid and flexible materials TPU and PLA to support the varying functionalities of different parts of the hand [51]. Metal 3D printing technology produce patient-specific implants such as hip, knee, shoulder, spinal cage and facial implant based on anatomical data of the patient and requirements of surgeon. The U.S. Food and Drug Administration (FDA) has cleared the first 3D-printed cranial/craniofacial plate implant to be made from titanium. Designed by Brazil-based Bio Architects printed by Sweden-based Arcam's electron beam melting (EBM) technology to combine the precision and customization of 3D printing with the lightweight and high tensile strength of titanium alloys (Figure.3 (b)) [52].

Innovative Manufacturing Cooperative Research Centre (IMCRC) is co-funding AUD$2.36 million cash for Research project called "Just in time implants," New Australian Project Will Use 3D Printing and Robotic Surgery in Bone Cancer Treatment the collaboration will combine advanced manufacturing, robotic surgery, and 3D printing to make custom implants for patients suffering from bone cancer [53]. 3D printed prosthetics composed mainly of plastic materials such as acrylonitrile butadiene styrene (ABS) plastics or for s stronger material, Bridge nylon with other materials like lightweight titanium to increase durability and strength [54].The first 3D printed titanium mandibular prosthesis, successfully implanted in Belgium [55]. FDA approved a 3D printed polyetherketoneketone (PEKK) biocompatible: mechanically similar to bone -skull implant made with most advanced laser sintering, successfully implanted by Oxford Performance Materials (OPM) [55]. An anatomically correct 3D printed prosthetic ear, capable of detecting electromagnetic frequencies, made using silicon, chondrocytes, and silver nanoparticles. Where Implants printed with live cells [54]. CSIRO's Lab 22 manufactured its first 3D printed titanium sternum and rib cage successfully implanted in 54-year-old Spanish cancer patient. (Figure.4) [55].

Figure 3: (a) Open Bionics Prosthetic Limb (b) Cranial/craniofacial plate implant

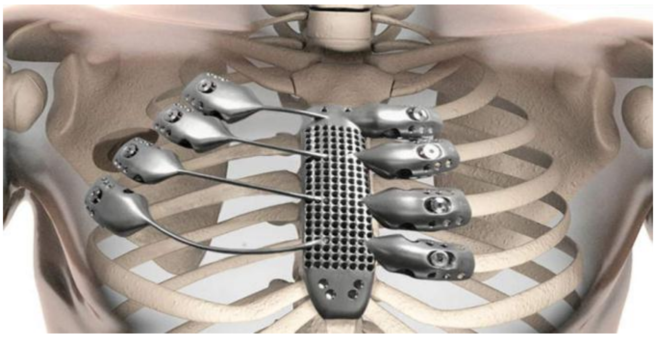

Figure 4: 3D printed Titanium Sternum and Rib cage by CSIRO's Lab 22

Bio printing- Tissues and Organs

The biggest challenging and serious issue in medical field is Tissue or organ failure due to aging, diseases, accidents, and birth [39] United Network for Organ Sharing (UNOS) reported, there is a chronic shortage of human organs available for transplant. Currently, more than 115,398 people are waiting for a transplant [59]. 3D bio printing technologies emerged as an efficient tool for tissue engineering and regenerative medicine by adopting computer-controlled 3D printing and manufacturing [56], [57]. Bio printing promote the restorative and repair of lost function in damaged or diseased tissues and organs by Mixing scaffolds, cells, and biological signaling molecules to recreate functional biological substitutes and mimic native tissues and functions [58]. 3D bioprinting utilize 3D printing techniques to combine cells, growth factors, and biomaterials to produce biomedical parts that excellently reproduce natural tissue characteristics [58].3D bioprinting utilizes the layer-by-layer method to deposit materials known as bioinks to create tissue-like structures that used for transplant [60]. Bioprinters works exactly same as 3D printers, with one key difference. Instead of delivering materials such as plastic, ceramic, metal or

 DOI : 10.18231/2454-9150.2018.0357

ISSN : 2454-9150 Vol-04, Issue-03, June 2018

food, they deposit layers of biomaterial that may include living cells, to build complex structures like blood vessels or skin tissue [61]. Tissues naturally made up of cells (kidney cells, skin cells) taken from the patient's body cultivated until enough to create the bio-ink which is loaded in to the printer cartridge , sometimes adult stem cells used to form cells for particular tissues [61]. By following the medical scans of patient's body precision printer heads deposit cells exactly where they are needed, over the several period of hours, an organic object built up by a large number of very thin layers [61].

Common methods used for 3D bioprinting of cells: inkjet, acoustic, laser, micro valve, tissue fragment, and direct cell extrusion [61], [62]. The traditional tissue engineering strategy; cellular tissue matrices are usually prepared by removing cellular components from tissues via mechanical and chemical manipulation to produce collagen-rich matrices; these matrices tends to slowly degrade on implantation and are generally replaced by the ECM proteins that are secreted by the ingrowing cells [65][66]. Over the traditional tissue engineering strategy, 3D bioprinting offers additional important advantages beyond this 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 [28].

Challenges in -Building Bio printed Organs:

To date, promising results reported, with the successful regeneration of artificial vessels, bones, and ear tissues, but the organs that produced were miniature and relatively simple [1], [16]. Size is the biggest issue to achieving 3D bioprinted organs for transplant, now day's researchers able to print very tiny structures up to about two millimeters in size, but with large size, difficulty to maintain cells go through alive [28]. However, the biggest challenges of building organs with 3D printing faced by researcher to maintain a flat and tubular cell structure of cell types such as human skin and blood vessels, [68] Hollow non tubular organs such as the stomach or bladder, each with more complicated functions and interactions with other organs. Solid organs such as the heart, liver, lungs and kidneys the ultimate goal for bioprinting pioneers [68]. There are several 3D bioprinting techniques to create artificial vasculature, such as using coaxial nozzles to create tubular structures with sacrificial cores, but it is the complex design of vasculature throughout organ that may prove difficult to replicate through 3D bioprinting [67].

Organovo scientists have experimented with building tiny slices of livers by first creating "building blocks" with the necessary cells [61].Organovo has begun working toward that goal by experimenting with 3D-printing blood vessels 1 millimeter or larger in width. The company has also built tissues containing tiny blood vessels about 50 microns or

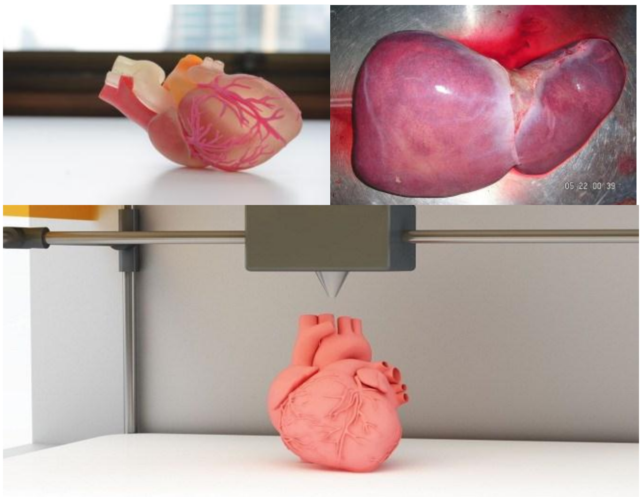

Figure: 5 3D Printed Heart & liver Models by Organovo

Anatomical Models for Surgical Preparation:

Now day's Medical 3D printing changes the surgical approach, 3D printed anatomical models helps medical specialists diagnose ailments, plan for surgery, provide education to the patient, and surgical training is preferable [2]. The individual variances and complexities of the human body make the use of 3D-printed models ideal for surgical preparation [2].The organs' 3D printed replicas reproduce the size, weight and texture of organs, allowing surgeons to rehearse complicated procedures on 3D models [2]. Simulating all surgical steps in advance using prototype models can help to foresee intra-operative complications, which may result in reduced operating time and hence allowing a cost-effective use of operating rooms. The complicated, sometimes obscured relationships between cranial nerves, vessels, cerebral structures, and skull architecture can be difficult to interpret based merely on radiographic MRI- CT scan 2D images. Complex spinal disproportion can be studied better using a 3D model [2]. Pirogov interactive anatomy visualization table-APK is an innovative educational product with unique human anatomy data content [69].For instance, anyone can specify and examine a certain muscle, blood vessel system, nerve-ending level. By selecting and removing parts of 3D images, the human body can be visible from a truly unique point of view: from inside (Figure: 6) Pioneering surgeons Aya shinomiya, Atsushi shindo and his team used 3D printed models in endoscopic end nasaltrans sphenoidal (EeTSS) for pituitary adenoma [82].

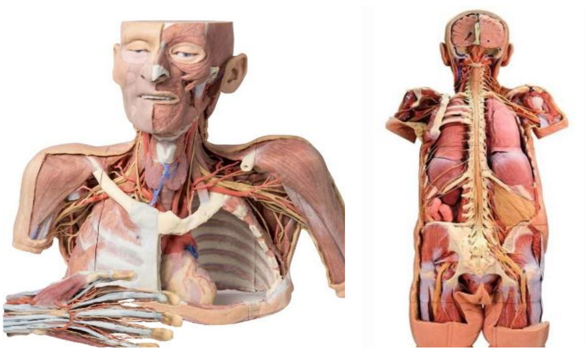

Figure: 6 3D printed model from the Monash University Anatomy Series, produced with a ProJet 4500 printer.

By using preoperative 3D virtual images and life-size multi-material 3D resin, models created by 3D printers for EeTSS simulations, Also for endoscopic transnasal pituitary tumor resection; virtual simulation and 3D model created by 3D printers [82].

Custom 3D- Printed Dosage Forms and Drug delivery Devices:

The technological innovation with advancements in the pharmaceutical field are constantly improving and provide various possibilities for meeting the needs of personalized drug therapy [83]. 3D printing technologies already prove their potential transformative in the fabrication of patient-specific drug delivery devices (DDD) and dosage forms in pharmaceutical research [83].Advantages of 3D printing include precise control of molecular shape, size, and weight, high reproducibility, and the ability to produce dosage forms with complex drug-release profiles [23].

Personalized Drug Dosing:

The purpose of drug discovery should be to increase efficacy evaluates desired effect, safety and toxicity and decrease the risk of adverse reactions in humans, a goal that can efficiently be achieved through the application of 3D printing to produce personalized medications [23], [27]. The capabilities of 3D printing of dispensing low volumes with accuracy, precise spatial control and layer-by-layer assembly allow the preparation of complex compositions and geometries of drug dosage form [84]. The high degree of flexibility and control with 3D printing enables the preparation of dosage forms with multiple active pharmaceutical ingredients with complex and tailored release profiles [84]

3DP can fabricate solid dosage forms with variable densities and diffusivities, complex internal geometries, multiple drugs and excipients. 3DP can successfully address the issues relating to the drug delivery of poorly water-soluble drugs, peptides, potent drugs and the release of multi-drugs, etc. [86].However, there is still a significant barrier to ensure that 3D printed medicines have the same efficacy, safety, and stability as the pharmaceuticals conventionally manufactured by the Pharmaceutical Industry [74].

Unique Drug Dosage Forms:

The 3D printing technologies used for pharmaceutical production are inkjet-based or inkjet powder-based fabrication, Direct-Write, Zipdose, Thermal inkjet (TIJ) printing and Fused Deposition Modelling (FDM). The drug, SPRITAM (levetiracetam), licensed for use with other medicines to treat primary generalized tonic-clonic, myoclonic and partial onset seizures. SPRITAM developed using Aprecia's proprietary ZipDose technology [75]. ZipDose technique developed at the Massachusetts Institute of Technology in 1984. A unique delivery platform serves as the foundation or dispersible formulations of highly prescribed high-dose medications. It creates premeasured, spill-proof unit-doses designed to disintegrate in the mouth with just a sip of liquid. This process binds multiple layers of powder blend using an aqueous fluid to produce a porous, water-soluble matrix that rapidly disintegrates with a sip of liquid [75], [76]. Many researchers developed oral dosage form guaifenesin bi-layer tablets with excellent content uniformity and dosage control using 3D printing technology, which fulfilled the necessities of regulatory standards and matches with the release standards of commercial tablets [77],[78].

Also 3D extrusion printer used to manufacture a multi-active solid dosage form (polypill), were the complex medication regimes combined in a single tablet [78]. A piezoelectric inkjet printer used to manufacture paclitaxel (poly-lactic-co-glycolic acid) loaded polymer micro particles with precise and well-ordered shapes. Micro particles exhibited a two-phase release profiles with an initial burst due to diffusion and subsequent continued release due to degradation of loaded polymer [79]. Researchers have further upgraded this technique by spraying uniform "ink" droplets onto a liquid film that condenses it, which generating micro particles and nanoparticles, such matrices used to supply small hydrophobic molecules and growth factors [23]. Compared with traditional pharmaceutical product manufacturing process, 3D printing provides a lot of attractive qualities, such as, high production rates, ability to achieve high drug-loading with much desired precision and accuracy, reduction of material wastage, amenability to broad types of pharmaceutical active ingredients including poorly water-soluble, peptides and proteins, as well as drug with narrow therapeutic windows [23],[80],[81].

Complex Drug-Release Profiles:

Three-dimensional printing (3DP) is a novel technique in the creation of medications with complex drug-release profiles. Conventional compressed dosage forms generally made from a homogeneous mixture of active and inactive ingredients, hence limited to a simple drug-release profile [82]. However, 3D printers used to fabricate a tablet with a convex drug release profile. A circumscribed sphere with a regular tetrahedron (pyramid) cavity shell model created by a computer-aided design (CAD) program and printed by a 3D printer. A specialized shell with an external round shape and internal regular tetrahedron (pyramid) shape made-up by 3DP, which allows injected medicine to form a tetrahedral shape in the cavity. When the shell dissolved, the drugs progressively exposed to buffer solution. The tablets will dissolved together with the shell from its four corners. The surface area of the drugs will gradually increase the ratio of it to the shrinking diameter of the tablets [83].

 DOI : 10.18231/2454-9150.2018.0357

3D-printed dosage forms can also be made-up in complex geometries that are porous and loaded with multiple drugs throughout, surrounded by barrier coats that control release. [82]. FDM, especially used in pharmaceuticals for the preparation of tablets, in which polymeric filaments with embedded drugs prepared by melt extrusion, and the filaments then pushed through the heated nozzle of a 3D printer by an automated gear system. The molten material is deposited layer-by-layer into the desired shape [82]. Implantable drug delivery devices with novel drug-release profiles created by 3D printing. Dexamethasone printed in a dosage form with a two-stage release profile [84]. Levofloxacin has been 3D printed as an implantable drug delivery device with pulsatile and steady state release mechanisms. Unlike conventional treatments that can affect non-afflicted tissue, these devices implanted to provide direct treatment to the involved area [84].Bone infections are one example where direct treatment with a drug implant is more appropriate than general treatment [82].

Researches available on 3D printing for Cancer Treatment; Difficulties founded in traditional chemotherapy to achieve require therapeutic concentrations at the tumor site. Because most chemotherapeutic drugs have a poor solubility in aqueous media, in adding, antineoplastic usually accumulated in relevant organs such as the liver and heart, causing serious side effects. Thus, local delivery systems would be of great advantage to overcome the deficiencies of conventional chemotherapy. Currently, the production of patches loaded with 5-fluorouracil, poly (lactic-co-glycolic) acid, and PCL have been successfully printed and implanted directly into a pancreatic cancer. The geometry of the patch and the release kinetics manipulated, maintaining the drug release for a total of four weeks. After that period, the patch was biodegraded in the body [84].

FUTURE TRENDS

3D printing is projected to play significant role in the trend toward personalized medicine, through its use in customizing nutritional products, organs, and drugs [16], [26]. 3D printing is predictable to be especially common in pharmacy settings [23]. Instead of taking a generic pill, a pharmacist makes one using a 3D print to match a patient's specific needs that has a time-release function [86]. The manufacturing and distribution of drugs by pharmaceutical companies could be easy to replace by databases of medication formulations to pharmacies for on-demand drug printing [1]. This would root present drug manufacturing and supply systems to change extremely and become more, productive and cost-effective [1].The most advanced anticipated application of 3D printing is the bioprinting of complex organs such as, heart, liver, kidney [16]. Researchers believe practical use of these advances could be 10 to 20 years away from a fully functioning printable heart. However, the future might get here quickly [86].Medical 3D printing technologies used to manufacture artificial veins, muscles, limbs, cells, tissues, skin and other organs. Researchers are experimenting with printing human tissue and organs by layering living cells instead of plastic or titanium [26]. Regenerative medicine researchers at Wake Forest University in Winston-Salem, N.C., are already using human cells instead of polymers to print organs using an advanced Integrated Tissue and Organ Printing System [86].This ability to print human tissue could have a huge impact on such things as pharmaceutical research, organ transplants, surgical operations and reconstructive surgery [86]. The Henry Ford Innovation Institute in Detroit. "They will be able to make a sheet of skin for a burn patient or full ears made out of cartilage." [86].

This will open the door to making feasible live implants, as well as printed tissue and organ models for use in drug discovery [26]. The key challenges for the future of 3D printing in this industry will be to develop new materials and to improve the reactivity to create a made-to-measure implant in only a few hours to save the patient-lives in an emergency [86].

CONCLUSION

To summarize, the medical advances achieved by 3D printing are significant and electrifying, Researchers continue to advance current medical applications that use 3D printing technology and to discover new ones; like bioink material. The 3D printing technology is changing the medical world for the better, with efficient, low cost and rapid fabrication, Hence, conclude that the 3-D printing technology's importance and everyday impact increases gradually, which significantly influence the human's life, the economy and medical society.

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