3D Printing Nanotechnology in Nano-Medicine

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Abstract **- Three-dimensional printing (3D) is growing numerous advances in manufacturing both at Nano and macro scales. 3D printing is used for various biomedical applications and fabrication of Nano-medicines using additive manufacturing techniques and shows the fulfilling the need for personalized patient treatment. Nano medicine is defined as the application of nanotechnology in designing Nano-materials for different medicinal applications, including diagnosis, treatment, monitoring, and prevention. Nano medicine is also showing a significant impact on the design and development of precision medicine. This article deals with the development and design of Nano medicine using 3D printing technology.**

Index Terms **- NANO MEDICINE; 3D PRINTING ETC**

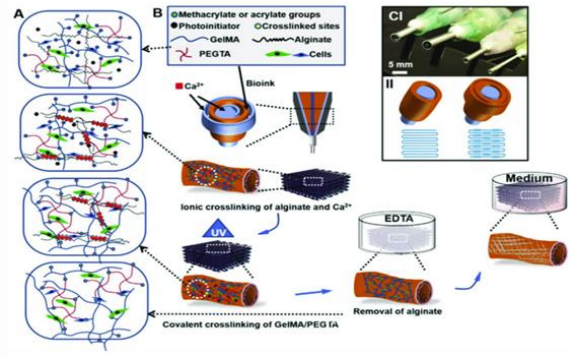
INTRODUCTION

Over the last few years, nanotechnology has been introduced into our daily routine. This revolutionary technology has been applied in multiple fields through an integrated approach. An increasing number of applications and products containing Nanomaterials or at least with Nano-based claims have become available. This also happens in pharmaceutical research Nanomaterials can be applied in Nano medicine for medical purposes in three different areas: diagnosis (Nano diagnosis), controlled drug delivery (Nano therapy), and regenerative medicine. A new area that combines diagnostics and therapy termed theranostics is emerging and is a promising approach that holds in the same system both the diagnosis/imaging agent and the medicine three-dimensional (3D) printing invention has developed over the last 20 years. It has helped provide relevant information for the manufacturing process of various industries, including pharmaceuticals, medicine, ecological monitoring, aviation, automobiles, and the research field. [1] 3D printing in Development of Nano medicines. Jain, K.; Shukla, R.; Yadav, A.; Ujjwal, R.R.; Flora, S.J.S. 3D Printing in Development of Nano medicines [2] Application and Performance of 3D Printing in Nano biomaterials Wenyong Liu, Ying Li, Jinyu Liu, Xufeng Niu, Yu Wang, and Deyu Li [3] 3D Printing in Medicine: Current Challenges and Potential Applications ASHISH, M.TECH • NABEEL AHMAD, Ph.D. • P. GOPINATH, Ph.D. • ALEXANDR VINOGRADOV, Ph.D. [4] How can 3D printing be a powerful tool in Nano medicine? Wei Zhu1, Thomas J Webster2 & Lijie Grace Zhang*, [5] Future Medicine: The Impact of 3D Printing Article in Journal of Nanomaterials & Molecular Nanotechnology · June 2015 DOI: 10.4172/2324-8777.1000163 [6] A. G. Fabrizio Fina, "Selective laser sintering (SLS) 3D printing of medicines," Int. J. Pharm., vol. 529, pp. 285–293, 2017[7]https://www.materialsciencejournal.org/vol18no1/an-overview-on-3d-printed-medicine/ [8]https://www.sciencedirect.com/search?qs=nanomedicine&articleTypes=FLA&lastSelectedFacet=articleTypes [9] Jain, V.; Haider, N.; Jain, K. 3D Printing in Personalized Drug Delivery. Curr. Pharm. Des. 2018, 24, 5062–5071 [10] Konta, A.; García-Piña, M.; Serrano, D. Personalised 3D Printed Medicines: Which Techniques and Polymers Are More Successful, Bioengineering2017 [11] https: //www. eurekaselect.com/node/172024/article/3d-printing-technology-a-new-milestone-in-the-development pharmaceuticals [12]https://www.sciencedirect.com /science/article/pii/S1818087621000167

3D PRINTING IN NANO MEDICINE [1].

3D printing is explored for the manufacture of oral dosage forms of different geometry and size. The starting material for the 3D screen printing process was developed for the controlled release of the model drug paracetamol (acetaminophen). The model screen print unit was used to manufacture different tablets in a single production process. The tablets were manufactured in three different sizes and five designed geometrics, including disk, doughnut, oval, grid, and cuboid. The study of the size and mass of the

individual tablets showed high uniformity inside the different groups of tablets. The action of their physical parameters of formulation, such as breaking force, friability, yield valve, was found to be superior in comparison to conventional tablets. The study of drug release tests performed in artificial gastric media showed that paracetamol release depends on the surface to area volume ratio. Studies of 3D printing enable the potential manufacture of complex oral dosage forms for mass production with more reproducibility. Thermoresponsive polymer poly (N-isopropyl acrylamide)-co-acrylic acid hydrogel was documented and effectively used for different kinds of 3D printing, including 3D single nozzle expulsion printing, 3D coaxial printing, and 3D hybrid printing. Three-dimensional printing with hybrid bionic using three different types of skin-related cells showed relatively high cell viability regardless of cell seeding density, position, or cultivation time. The bioengineered skin made from multi-layered human umbilical vein endothelial cells (HUVECs), 3T3-J2, and HaCat cells, showed external surface keratinisation of the epidemics layers, and sprouting and splitting of the subcutaneous endothelial cells after in vitro air-liquid-interface induction. It is believed that bioengineered skin grafts might be used as potential implants for wound healings. Three-dimensional printing-based design of perusable vascular constructs using cross-linked bio-link is shown diagrammatically in figure 1



NANO MEDICINE AND 3D PRINTING

Nano medicine is nanotechnology applications in various fields of medicine such as site-specific drug delivery, theranostic tools, and drug repurposing. Nano medicine is a relatively recent field, extensively explored for research and innovative ideas by scientists of different disciplines. Nano-materials are also used in combination as a hybrid to explore new possibilities such as dual-targeting, stimuli-responsive release, and theranostic applications. Nano medicine is a promising tool for various theranostic applications in infectious diseases, no fatal communicable diseases such as brain tumours, multidrug resistance (MDR) tumours, infectious diseases, metastatic tumours, and relapsed tumours that are highly challengeable for clinical studies. The crossing of therapeutic agents to the brain, dodging the MDR pathways, inhibiting migratory tumour cells, immunostimulation, antiangiogenic activity, and removing the cancer stem cells. Various nanotechnologies, including nanoparticles (lipid nanoparticles, polymer nanoparticles, and metallic nanoparticles), dendrites, Nano diamonds, Nano crystals, quantum dots, carbon nanotubes, Nano gels, Nano emulsion, etc. due to their extra small size with a confined size distribution, are being explored for designing various Nano medicines. These Nano medicines are also being fabricated using 3D printing technology as precision medicines to satisfy individual specific needs by using apparent surface functional design along with bio conjugation and extreme biocompatibility. Three-dimensional printing provides the ease of ion preparation and tailoring of micro and Nano particles conjugated with functional antibodies in a continuous mixing process with desired features. Pal and co-workers fabricated a bilayer composite for tissue regeneration using a 3D printed layer and Nano fibrous layer. These composites are composed of a dual-pore system including a 3D printed matrix and Nano fibrous layer with a pore diameter of -200 and -20.59µm, respectively. The structural and compositional features conferred the composites with moderate hydrophobicity, providing contact angle for the Nano fibrous layer and 3D printed layer of 64.4^0 and 92.2^0. Additionally, prepared composites showed a tensile strength of 6.12±1.26MPA and a high-water uptake capacity of 95%. These parameters depicted the migration, adhesion of fibrobladst cells, and observation of growth on either surface of the scaffolds. Based on hydrogel, Ceylon and co-workers designed a 3D printed enzymatically biodegradable micro swimmer for theranostic application. The scientists also tested this system in ErbB2 overexpressing SKBR3 breast cancer cells, where magnetic contrast and SPIONs, tagged with anti

ErbB2, were released rapidly due to enzymatic biodegradation of the micro swimmer.

Similarly, multi photon lithography based 3D printing methodology was employed to fabricate carrier free 3D shape designed antigen nanoparticles (ANP). These 3D shape designed ANP were of distant aspects ratios and could elicit shape dependent immune responses. Three dimensional printing can be explored convincingly in the design of safe and effective precision medicines and Nano medicines are complex and challenging to be formulated with conventional top-down and bottom-up approaches.

3DP TECHNIQUES FOR NANO MATERIALS

Two kinds of 3DP techniques are mainly adopted for Nano biomaterials fabrication. One is the inkjet printing with the typical printers such as the NP 2.1(GeSim, Germany) and the Z402 (Zcorp, USA). The other is the Nano imprint lithography with the typical printers such as the EVG620 Nano imprinter and lithography with the typical printers such as the EVG620 Nano imprinter and the 520 hot embossers (EV group, Austria).

BONDING-BASED INKJET PRINTING

MIT developed the bonding-based inkjet printing technology. This procedure deposits a stream of micro particles of a binder biomaterial over the surface of a powder bed, joining particles together where the object is to be formed. A piston lowers the powder bed so that a new layer of powder can be spread over the surface of the previous layer and then selectively joined to it. After the building process, the unbounded powder is removed, and a conventional reinterring process must strengthen the porous model.

According to different working modes, the inkjet printing technique is divided into the drop-on-demand catalogue. Electrical signals are used to control the ejection of an individual droplet and the continuous ejection catalogue in which the ink emerges continuously from a nozzle under pressure. The DOD catalogue comprises the electromechanical (piezo actuated and electrostatic actuated), the electro thermal (thermal actuated), and the electrostatic vacuum. The continuous ejection catalogue comprises the electro field-controlled inkjet and the Hertz continuous inkjet (mutual charged droplet repulsion type).

The bonding based inkjet printing has been adopted for fabricating many tissue modes with micro/Nano biomaterials. Woo et al. employed the 3DP with particulate leaching to create porous scaffolds using polylactide-coglycolide (PLGA) powder mixed with salt particles and a suitable organic solvent. Hepatocytes were successfully attached to the scaffolds. Baca et al. found that the cell viability organisation of bio / Nano interface can be accomplished during the inkjet printing or selective wetting processes allowing patterning of cellular arrays and even spatially defined genetic modification. Cui and Boland used a modified thermal inkjet printer. They demonstrated the feasibility of printing microvasculature with human micro vascular endothelial cells suspension in thrombin solutions onto fibrinogen solutions, which served as the substrate. The printed cells achieved the capacity to interact and proliferate within fibrin channel forming a tubular lining.

BIO INK JET PRINTING

The bio inkjet printing technology was developed along the concepts of cell printing proposed by Yan et al. This process print gets, single-cell, and cell aggregates offering a possible solution for organ printing. To be used for cell printing, the thermal or piezo tip print heads and ink cartridges are modified to allow bionics to be printed. These bio links usually consist of aqueous media, thermo reversible polymers or polymer/ hydrogel precursors combined with living cells.

Laser-assisted cell printing techniques have also been developed. These techniques comprise called laser guidance direct-write (LGDW). The LGDW process was the first reported technique to print viable cells by forming patterns of embryonic chick spinal cord cells on a glass slide. Shortly after this, modified laser-induced forward transfer (LIFT) techniques and modified inkjet printing were also used to print viable cells and proteins, followed by the recently introduced electro hydrodynamic jetting (EHDJ) method.

NANO IMPRINT LITHOGRAPHY

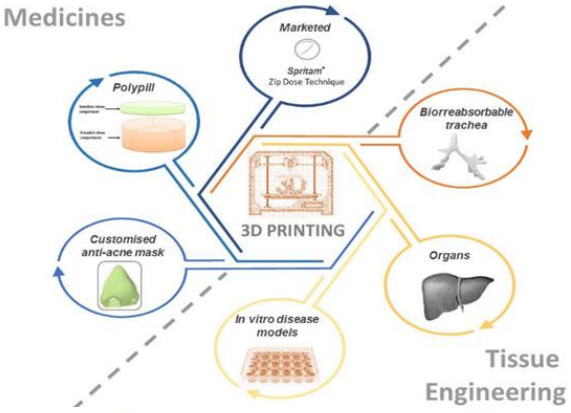
The Nano imprint lithography (NIL) is a fast and cost-efficient technique for fabricating nanostructures. The procedure of NIL is to stack multiple layers of such structures on top of each other that is, a finished double layer of structure is covered with a spacer layer which is planarised using the chemical mechanical polishing so that a second layer can be processed on top. This process is a new and unique possibility to stack structure patterns by transferring structures several times on the same substrate. It can therefore be used to build up 3D Nano biomaterials in a fast and cost-efficient way. Bergmair et al. have fabricated a 3D stacking of gold structures like finest structures using NIL and demonstrated its industrial application valve.

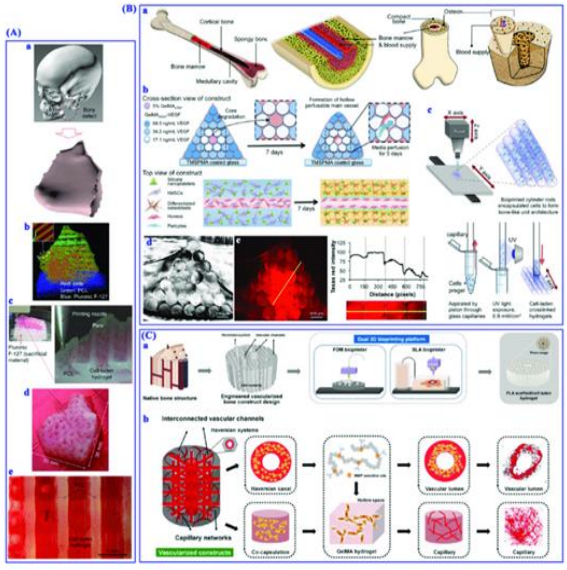
3D PRINTING IN MEDICINE: CURRENT CHALLENGES AND POTENTIAL APPLICATIONS

HISTORICAL PERSPECTIVE [2]

In early 1980s Charles Hull was working on the development of plastic devices utilising photopolymers. Still, the limitations of existing technology (length procedure, less accuracy) motivated him to improve prototype development technology. In 1984 Hull invented apparatus for a new layer-by-layer printing technology named as "stereo lithography". Later in 1986 Hull also founded the company "3D systems" and provided the term STL compatible with the existing CAD software to design the 3D objects. In 1987, SLA-1 3D printer was introduced. In 1988 the company came up with the first commercially available 3D printing (SLA-250).2 In 1989 Deckard a graduate student at the university of Texas introduced another important technology selective laser sintering (SLS).19 In 1992 Scott crump patented another modified 3D printing technology. That is ,fused deposition modelling (FDM).20 In 1993 E.Sachs and M.Cima at Massachusetts Institute of Technology (MIT) developed inkjet printing based "3D printing "for printing complex shapes of polymer, metal, ceramic, plastic, etc. Over the years, different companies (Z Corp, Envision Tec, Solids cape, DTM Corporation, and Objects Geometries) used 3D printers for various commercialised applications. 3D printing in medicine was started in the late 1990s by allowing the printing of various dental implants. A shows the major events and developments in the evolution of both 3D Printing and 3D printing in medicine. In 1999 Attalla et al.at Wake forest Institute for Regenerative Medicine fabricated the first laboratory-grown organ, synthetic 3D urinary bladder scaffold that was further modified with the patient's cells and then transplanted to the patient. This revolutionary procedure directed enormous progress and development in the field of medicine using 3D printing technologies.

Furthermore, in 2002 the same group developed a functioning kidney by directly printing with the cell-seeded bio-ink instead of simply printing a bare scaffold and then coating it with cells. In 2003 Wilson et al. developed inkjet technology-based bio-printing hardware for protein and cell printing. In 2004, Jacob et al. also utilised laser-based technology to deposit mammalian cells onto a biopolymer matrix. Next breakthrough in the industry happened in 2009 when Invetech and Organology developed the first commercial bio printer (NovoGen MMX).In 2010 Binder et al.





3D PRINTING IN PERSONALIZED DRUG DELIVERY [3].

3D Printing technology uses digitally controlled devices for formulating API and excipients in a layer by layers pattern to develop a suitable personalised drug delivery system as per the patient's need. It includes various techniques like inkjet printing and fused deposition modelling, which can be classified into continuous inkjet system and drop on demand. To formulate such dosage forms, scientists have used various polymers to enhance their acceptance and therapeutic efficacy. Polymers like polyvinyl alcohol, poly (lactic acid) (PLA), poly (caprolactone) (PCL) etc. can be used during manufacturing.

3D BIO PRINTING [4]

As it is easy to see, there are more questions than answers in the bioethical and legal issues of 3D bio printing. The lack of answers is because the speed of development of research and the increase of technological capabilities vastly outstrips the speed of our understanding of the moral and legal consequences of their development. There is currently no suitable statutory framework or particular regulatory guidelines governing 3D bioprinting of tissues and organs and their further transplantation in Russia and globally. The problem of ethical evaluation using standard clinical trials or taking into account the current regulatory requirements.

However, before the 3D bio printing technology spreads and becomes clinically available, several scientific research and medical practice regulations should be adopted. First of all, there is a need to develop informed consent for donation, material manipulation, storage, and further use, including commercial and research purposes. Moreover, it is necessary to develop a requirement for the safety, quality, and efficiency of technological procedures and the end products obtained by 3D bio printing taking into account human rights and dignity. Furthermore, it is of great importance to establish committees for the creations and regulation of national guidelines on technical, legal, and ethical issues related to the development and application of 3D bio printing technologies. All patients, including minors and incapable people, need to be legally protected. Last but not least, it is essential to establish regulations of turnover and limits of commercialisation for 3D bio printing technologies of human organs and tissues, as well as possible sanctions for illegal trafficking of artificial organs.

INNOVATION COLOUR JET 3D PRINTING OF LEVETIRACETAM PERSONALISED PAEDIATRIC PREPARATIONS [12]

This study proves that the preparation of colourful cartoon levetiracetam paediatric tablets can be realised by using CJ-3DP. Through the optimisation of formulation and tablet structure, the 3D printed tablets had an admirable appearance and a lower surface roughness, all of which were notably improved compared with the properties of spritam; meanwhile, the 3D printed tablets had solid mechanical properties and immediate release characteristics. Compared with Spritam, the total number and area of pores of the tablets printed in this study were significantly higher with similar porosity. A large number of small holes formed easy-wetting capillary channels when the tablets were in contact with water, which could penetrate the tablet through the capillary channels and wet the whole tablet quickly, resulting in its disintegration. Moreover, this study proves that the dispersion of tablets can be further accelerated by adjusting the internal spatial structure of the model, and the flexible adjustment of drug strengths can be achieved by establishing a dosage model to realise personalised administration.

For CJ-3DP and most inkjet processes in general, the biggest challenge is the development of the ink. In this study, exhaustive experiments were carried out to determine the appropriate link, and the applicability of the formulation to scale up the production was considered. However, different powders and printing heads usually lead to different optimal compositions of the ink. From the view of scale-up production, when using hot-bubble printing heads, the proportion of organic solvent in ink should not be too large to avoid the interlinear fracture of the tablets caused by poor jetting uniformity. Compared with the traditional preparation process, 60 min are required in CJ-3DP to print 120 tablets in this study. Although there is an immediate potential for unit dose fabrication with significantly reduced processing steps, the production efficiency is still low. The use of production printing equipment in the future is expected to increase

production efficiency, but 3D printing equipment still needs to be continuously improved to meet high printing accuracy and efficiency requirements. An attractive characteristic of this technology is that once a stable formulation and processing parameters are obtained, it can be scaled up for commercial production. In the foreseeable future, the development of 3D printing technology in personalised medical preparations for children deserves more attention

3D PRINTING FOR CLINICAL APPLICATION IN OTORHINOLARYNGOLOGY [10]

By integrating 3D printing into issues engineering and materials, it may be possible for otolaryngologists to implant 3D printing functional grafts into patients to reconstruct various tissue defects in the foreseeable future. In this review, we will introduce the current state of 3D printing technology combined with tissue engineering and future directions of bio printing in the field of otolaryngology.

PERSONALISED 3D PRINTED MEDICINES: WHICH TECHNIQUES AND POLYMERS ARE MORE SUCCESSFUL [9]

Regarding the establishment of guidelines, laws, quality systems and safety of use and consumption of 3D printed medicines, it is a tremendous challenge for the regulatory authorities entailing significant obstacles, given the standard requirements by the pharmaceutical sector. However, the perspective of the regulatory authorities is adapting fast to the real world and patient's needs. The FDA developed in 2016 a new guidance entitled "Technical Considerations for additive Manufacturing Devices" to provide the FDA's initial thinking on technical considerations associated with AM processes, and recommendations for testing and the characterisation for devices that include at least one AM fabrication step.

3D BIO PRINTING FOR VASCULARIZED TISSUE FABRICATION [8]

The moderate success of current tissue engineering strategies has been attributed to the current inability to fabricate thick tissue engineering constructs that contain endogenous, engineered vasculature or nutrient channels that can integrate with the host tissue. Successful fabrication of a vascularised tissue construct requires synergy between high throughput, high-resolution bio printing of layer perusable channels and instructive bionic that promotes antigenic sprouting and neovascularisation. This review aims to cover the recent progress in the field of 3D bio printing of vascularised tissues. It will cover the methods of bio printing vascularised constructs, bio-ink for vascularisation, and perspectives on recent innovations in 3D printing and biomaterials for the next generations of 3D bio printing for vascularised tissue fabrications.

TOWARDS ARTIFICIAL TISSUE MODELS: PASTS, PRESENTS, AND FUTURE OF 3D BIO PRINTING

Bio printing has emerged as a promising 3D bio manufacturing technology, enabling precise control over cells and ECM's spatial and temporal distribution. Bio printing technology can engineer artificial tissues and organs by producing scaffolds with controlled spatial heterogeneity of physical properties, cellular compositions, and ECM organisation. This innovative approach is increasingly utilised in biomedicine and can create artificial functional constructs for drug screening and toxicology research and tissue and organs transplantation. Herein, we review the recent advance in bio printing technologies and discuss current markets, approaches, and biomedical applications. We also present current challenges and provide future directions for bio printing research.

3D-PRINTING DRUGS FOR CHILDREN

There is a particular need for flexible drug delivery solutions when it comes to children. Printing as a new pharmaceutical manufacturing closer to the patient can easily be adjusted to the required dosing scheme, offering more flexibility for treatment. Therefore, medicine printing may become the manufacturing route of choice to provide tailored and potentially on-demand treatments for patients with individual needs. This paper intends to summarise and discuss the still-open question to make 3D printing a suitable manufacturing route for paediatric drugs.

3D BIO PRINTING AND THE FUTURE OF SURGERY DIVERSE

The diverse application of bio printing technology has already been demonstrated globally, leading to novel constructs from vessels and composite tissue to organoids and complex cellular and tissue models for drugs, cosmetic and experimental testing. The 3D bio printing market has seen off shoot companies set up to corner a specific sub-set of the production and manufacturing of complex 3D printing tissues; from desktop 3D bio printers and bio inks, to scaffolds preloading with and without growth factors generating a market value in the $US billions. The diversification of this technology and its associated components demonstrate the critical issue with this unique technology and potential difficulty in harnessing its true potential; the lack of "end to end" visibility by any agency.

The translation of 3D printed constructs into clinical practice is challenging. The optimisation of the translational pathway demands concerted efforts from scientists, engineers and clinicians, contextualised within an infrastructure in which an effective supply chain exists. It is no longer sufficient for scientists, clinicians and regulatory bodies to exist in operational silos. There is a need for a collaborative effort to translate this impactful technology into a real-world healthcare setting. To harness the true potential of 3D printing in surgery, surgeons will need to keep abreast of developments in the field, identify niches in which this technology can be applied and encourage its integration into mainstream surgical practice. With incremental advances in 3D printing and bio printing expected over the next century, the impact on the future of surgery could be transformational.

MEDICAL 3D PRINTING FOR THE RADIOLOGIST

Three-dimensional printed models, already entrenched in the nonmedical sciences, are rapidly being embraced in medicine and the lay community. Incorporating 3D printing from images generated and interpreted by radiologists presents particular challenges, including training, materials and equipment, and guidelines. The clinical benefits must balance the overall costs of a 3D printing laboratory. It is expected that the number of 3D-printed models generated from DICOM images for planning interventions and fabricating implants will grow exponentially. Radiologists should, at a minimum, be familiar with 3D printing technologies and materials used to create 3D-printed anatomic models, published applications of models to date, and clinical benefits in radiology. Online supplemental material is available for this article,

PRINCIPLES OF THREE-DIMENSIONAL PRINTING AND CLINICAL APPLICATIONS WITHIN THE ABDOMEN AND PELVIS

3D-printed anatomical models to contribute to personalised medicine, surgical planning, and education across medical specialities and these models are rapidly changing the landscape of clinical practice. A physical object that can be held in one's hands allows for significant advantages over standard two-dimensional (2D) or even 3D computer-based virtual models. Radiologists have the potential to play a significant role as consultants and educators across all specialties by providing 3D-printed models that enhance clinical care. This article reviews the basics of 3D printing, including how models are created from imaging data, clinical applications of 3D printing within the abdomen and pelvis, implications for education and training, limitations, and future directions.

CONCLUSION

- 3D printing has become a useful and potentially transformative tool in a number of different fields including medicine.
- The use of nanoparticles for implanting Nano medicine is also discussed. Nanoparticles based on metals, polymers, lipids, and inorganic are discussed.
- As printer performance, resolution and available materials have increased, so have the application.
- Researchers continue to improve existing medical applications that use of 3D printing technology and to explore new ones.
- The medical advances that have been made using 3D printing are already significant and exciting, but scene of the more revolutionary applications such as organ printing will need time to evolve.

- Additive manufacturing 3D printing is a disruptive technology that highly promises to revolutionise manufacturing and education.
- It also emphasises how Nano medicine is useful for cancer treatment for various body parts.
- There is still a lot of scope of research in the field of Nano medicine foe organ printing, tissue engineering, etc.
- The future of Nano medicine is early detection of pathological or biological changes at the molecular level by using unambiguous imaging methods and less invasive treatment of the patient with individually tailor-made medicines as soon as the disease is in the development stage.

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