THE RECENT APPROACHES IN NANO-TECHNOLOGY WITH APPLICATIONS OF 3-D PRINTING (3DP) IN DIVERSE ADVANCED DRUG DELIVERY SYSTEM (DDS)

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Abstract

Three-dimensional (3-D) printing is elevating various growth in production viewpoint both at nanoscale and macro-scales. 3-D printing is being scouted for numerous bio-pharmaceutical administration and creation of nano-medicines employing supplementary production methods and shows assurance in capability in satisfying the demands for a patient-based customized approach. The previous outcome features the accessibility of novel natural bio-materials and finely designed polymeric substances, which can be created as unique 3-D printed nano-materials for numerous bio-pharmaceutical administrations as nano-medicines. Nano-medicine is described as the utilization of nanoscience in fabricating nano-materials for various pharmaceutical utilization, comprising identification, cure, scan, stopping, and management of diseases. Nano-medicine has also displayed a huge effect in the creation and evolve an accurate drug. In contrary the "one-size-fits-all" benchmark for the traditional drug is a personalized, structured, or accurate drug considering the variation in numerous characteristics, comprising genetics and pharmacokinetics of various victims, which have exhibited better outcomes over traditional cures. This article highlights the approaches advancements in the design and development of customized-made nano-medicine employing 3-D printing science.

Keywords: 3-D Printing (3DP), Nano-Medicines, Drug delivery system (DDS), Tissue engineering, Detection and Diagnosis.

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INTRODUCTION

Three-dimensional printing (3-DP) invention was introduced in earlier than the last 20 years. It has provided a satisfactory information for the production method of numerous production that can be monitoring, aviation, medicament, drugs, environmentally and automobiles, and also in inventions [1]. The three-dimensional printing is a proto-typing invention that is used for 3-D products production on a programmed stage for creating purpose and, in a stratified style for a pharmaceutical object and product. The 3-D Printing invention commonly used for the production of the drugs designed for patient's healing needs (e.g., medicine release profiles, dosage, and medicine).

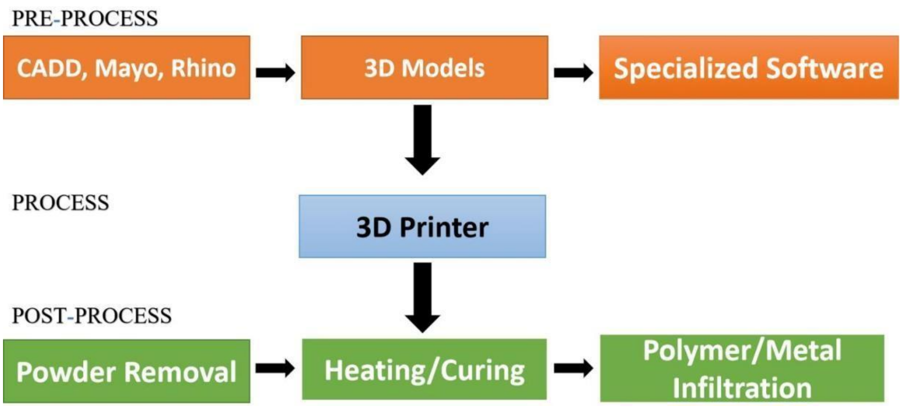

Figure 01. The various process involving in 3D Processing of Model

A) Pre – Process:

The prior use of **computer-aided drug design** (CADD) appeals to create, find out, and optimize new, secure, and powerful medications for patients while reducing patient infection is prime goal. Identify a chemical substance that is both chemically and geometrically ideal for a specific receptor on a protein target while keeping the physiology of the patient in mind is the goal of medication design. The prior principle for 3-D designing is completely dependent on **Lipinski's Rule of five**.

CADD can design 3-D models with specific software (DDDPlus (Dose Dissolution and Disintegration Software), GASTROPLUS (simulation software for drug discovery and development), for Ligand interactions and molecular dynamic (AutoDock, Schrodinger, Glide, Prime, Jaguar, Macro model, Gold (genetic optimization for ligand docking), Biosuite; for molecular modeling and structural activity relationship, Maestro, ArgusLab) [2].

B) Process:

In processing part, 3-D printers have been used that can be FDM (Fused Deposition Modelling), SLS (Selective laser sintering), SLM (Selective laser melting), SLA (Stereolithography apparatus), Gel extrusion, Ink jet printer and many more. Charles Hull in 1984 created history in 3-D printing era by introducing stereolithography. In 1992, Bill Clinton step forward by introducing the world's first Stereolithographic Apparatus (SLA) machine. In mid-1992, world's first Selective Laser Sintering (SLS) machine was created that hits a laser at a powder instead of a liquid [8].

FDM (Fused Deposition Modeling) Fused deposition modelling (FDM) 3-D printing, generally called as fused filament fabrication (FFF), that is a material excursion additive manufacturing (AM) method. The final physical objects are employed with thermoplastic polymers as filaments. Uniting a large installed base of 3-D printers for worldwide, FDM is the one of the widely employed science among various industries, and mostly the prime process is to think about the 3-D printing. The instrumentation of FDM is mentioned **(Fig. 02).**

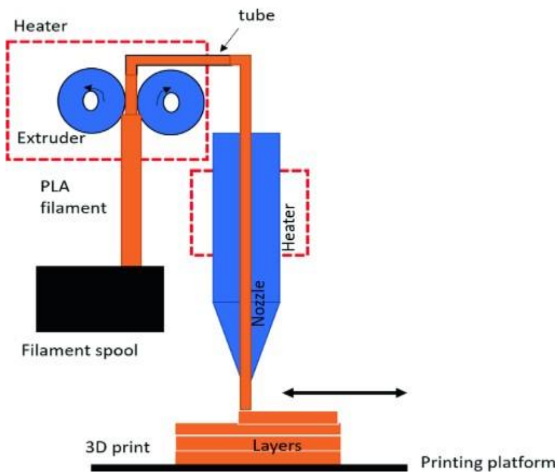

Figure 02. FDM 3D Model Representation for 3D nanotechnology applications

The various types of material employed in FDM as well as the other various techniques which are given in the **Table 1**, below section:

Table 1: The list of materials used in the different techniques

S No.	3-D Printing Technique	Material Employed
01.	FDM (Fused Deposition Modelling)	ABS, Polycarbonate and ULTEM™ 9085 Resin
02.	Stereolithography (SL)	Polypropylene, ABS (*Acrylonitrile Butadiene Styrene*) And Polycarbonate
03.	Binder Extrusion Printing	Gypsum, sand, ceramics, metals or polymers in granular forms.

The materials are given in above (**Table 1**) that plays a vital role in the preparation of 3D model in the nano-medications.

C) Post-Process:

In post-process, extrusion of powder by heating to get rid of extra polymer that are used for the formulation of 3-D models. In this process thermo-responsive hydrogels are employed.

Thermo-responsive hydrogels have been surveyed recently in 3-D bioprinting utilization has excellent printing with required form, and can be adjusted easily by the sol-gel phase by changing temperature by that fast gelation is obtained. Few are also presents a alleviated cell compatibility and optimum climate for cell growth, so they are entirely inspected mainly in tissue engineering for designing of 3D form that presents in commonly microenvironment and vascularization [2].

Numerous thermo-responsive hydrogels along with particular biological characteristic, technique dependent on source, polymer series extend structure, and gelation technique that can be employed in 3-D printing. Few of the thermo-responsive hydrogels with their utilization are discussed in **Table 2**.

Table 2: List of Thermo-responsive gels in 3-D printing

Hydro responsive Hydrogel	Gelation Mechanism	Gelatin Temperature	Technique	Con. Used in 3D Printing (%w/v)	% Cell Viability	Application	Reference
Agarose	Photo polymer ized gelation	<32°C	Pneumatic and mechanism extrusion	1-5%	>70% (Day 7)	VE	[3]
Amino-terminated PNIPAAm hydrogel	Thermal and photo triggered	Room temperature	Pneumatic extrusion	10-20%	98% (Day 7)	CTE	[4]
Collagen	Cross linking	~37°C	Pneumatic dispensing system	0.1-3%	>94% (Day 1)	CTE	[5]
p (HPMA m-lactate)-PEG Hydrogel	TG and photo polymerization	21-40°C	Pneumatic dispensing	25- 35%	~85% (day 3)	CTE	[6]
5-8% Meth acylated gelatin (GelMA)/ gelatin	TG followed by photo cross linking	15-25°C	3D bioink printing system		92.9 ± 2.6	TES	[7]

Vascularization engineering- VE, Tissue engineered scaffold- TES, Cartilage tissue engineering- CTE, and Thermal gelation -TG

Nanotechnology is the science deals with material and matter that are in the range of particle size of nanometers (1nm=10^{-9}m). The term 'nano' came from Latin word, which means dwarf. Nanotechnology deals in characterization, design and application of numerous structures, devices systems by managing the shape and size on nanometric scale. Pharmaceutical Nanotechnology improves the effect of nano science to pharmacy as devices, and as nano materials like diagnostic, imaging, drug delivery, and biosensor materials (Carbon). These nanoparticles have a characteristic feature that make them influenced with numerous fields of technology, comprising of different food, industrial, biomedical, cosmetic, textile, and agriculture [9].

THE APPLICATIONS OF 3D PRINTING (3DP): BASED NANO-MEDICINES

Drug delivery systems based on 3-D printing offer a number of advantages like customized medicine sustain delivery that can be personalized based on purposes. Beyond this, 3-D printing include simple methodology for economically friendly manufacturing that is easily ascend able. A summarized of numerous 3-D printing manufacturing employed in additional production of nano-medicines is mentioned in Table 3. Recently, health care systems are employing 3-D printing in preclinical and clinical setup for personalized dosage forms-for example, tablet, capsule, dentistry, tissue/organ regeneration. This section discusses the existing medical application of 3D printing with potential for translation purposes [10].

Table 3: The List of Techniques in printing including with example and dosage form

Sr. No.	Technique for Printing	Drugs Used in Model	Dosage Form
01.	3-D extrusion printing	Atenolol, Ramipril, Aspirin, Pravastatin, Hydrochlorothiazide	Multiactive solid dosage forms
02.	Fused filament 3-D printing	Fluorescein	Tablet
03.	3-D printing	Isoniazid	Tablet implant
04.	FDM 3-D printing	Prednisolone	Extended- release tablet
05.	FDM 3-D printing method with HME and fluid- bed coating	Budesonide	Tablet
06.	FDM 3-D printing	Acetaminophen and furosemide	HME filaments
07.	FDM 3-D printing	5- Aminosalicylic acid and 4-amino salicylic acid	Modified release drug loaded tablets
09.	Extrusion- based printer	Nifedipine, Glipizide and Captopril	Multiactive tablet
10.	3-D scanning and 3-D printing	Salicylic acid	Anti-acne filament
11.	Electrohydrodynamic printing	Tetracycline hydrochloride	Patterned microscaled structure
12.	SLA 3-D printing	4-aminosalicylic acid Paracetamol	Modified release tablet

Note*: FDM- fused deposition modelling; HME- Hot-melt extrusion; SLA- Stereolithography

1) Drug delivery applications

In industries, 3-D Printing appears to have exclusively applicable in the pharmaceutical industry, as the production flexibility of 3-D Printing allows the manufacturing for personalize medication ondemand and in-house. The capability of HME and FDM 3-D Printing also leads us to many research chances for the creation of novel drug delivery systems [11]. Research on the production of 3-D printing has been conducted worldwide still, in drug delivery system the 3-D printing is not discussed exclusively [12]. Almost all research are based on the 3-D printing of tablets and pills that can be used as personalized remedy [13]. Moreover, personalized medication is vital for precision medicine. Some other innovative 3-D printing drug delivery systems are being observed that will ensure 3-D printing as drug outcome to move from laboratory testing to clinical benefits. The primary-in-vivo of a 3-D printing on oral drug delivery device that is personalized and is wearable [14]. Still this was a prototype study, it is taken as huge step toward the 3-D printing as it is lacking it's personalized drug delivery devices that have fully been tested in humans. Most research have been performed in vitro as well as in vivo in vertebrates, shown results that drug delivery devices based on 3-D printing still have suspects to be get changed from the laboratory testing to clinical trial. Although, Liang et al. has used an FDM printer successfully to create a mouthprotector in which the drug release rate and design can be custom-build as per the patient's needs. The various drug delivery done with the utilization of 3DP in various DDS as shown in the given **Table 4.**

Table 4: The various drug delivery systems in 3D nanotechnology, with their description and example of disease

Drug Delivery System	Description	Example of Disease
Nanoparticles	Small particles that can be used to deliver drugs to specific sites in the body. They can be made of different materials, such as polymers, lipids, or metals.	Cancer, diabetes, and rheumatoid arthritis
Nanocarriers	Nanoparticles that are specifically designed to carry drugs to target cells. They can be targeted to specific receptors on the cell surface, or they can be made to accumulate in certain tissues.	Cancer, Alzheimer's disease, and HIV/AIDS
3D-printed (3DP) drugs	Drugs that are printed in three dimensions to create a specific shape or structure. This can be used to improve the delivery of drugs to specific sites in the body, or to create drugs that are more stable or biocompatible.	Cancer, cystic fibrosis, and Parkinson's disease
Nanorobots	Nanomachines that can be used to deliver drugs to specific sites in the body. They can be programmed to move through the body and release drugs at specific locations.	Cancer, cardiovascular disease, and stroke

The fibre used for 3-D printing were combination of biopolymer polylactic acid (PLA) and polyvinyl alcohol (PVA) loaded with drug having property of anti-inflammatory by HME. The design and shape of the mouthprotector were acquired through mucosal scans of the mouth. For human clinical application, three types of custom-made mouthprotector were tried on on each participant. The outcome demonstrated the release rate of drug was mostly effected by the polymer configuration instead of the geometry, infill pattern, design, or shape of the 3-D printing device. The observation has shown a great probability for stretching our limits from conventional to other systems, like as implants and stents [14]. Multimaterial 3-D printing for the creation of a novel implants biomedical electronic that gives the potential of better advanced and diagnostics therapeutic response [15].

Implantable devices does not necessarily need any such invasive process as it is administered orally as a gastric-resistant electronic that is capability of wire-free communication through Bluetooth. These devices can be used to observe physiological variables in existing time and liberation of drug in a controlled pattern as per the need. The materials employed to assemble this device were rigid elastomeric polymers that reveals robustness against the vigorously hostile gastric surrounding. The electronic device itself is collapsible so that it can be cured into a capsule made by gelatin for drug delivered via oral route. When the capsule is dissolved in the gastric medium, the device swells to a defensive system. This transformed biomedical e-device is an evidence that can help in understanding a next generation of automated therapeutic strategies and distinct diagnostic.

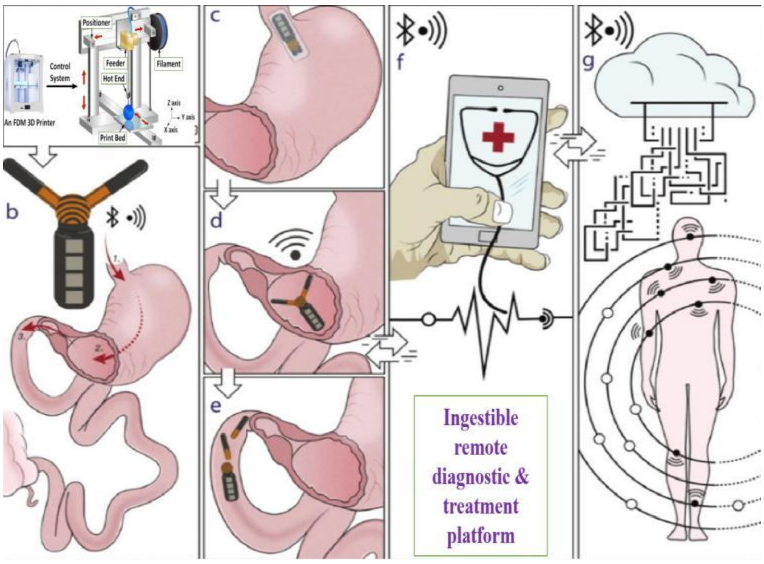

Figure 03. Implantation device based on Bluetooth via oral route of administration

A) IMPLANTS DRUG DELIVERY

Personalized implant planing can be completed by the help of the techniques of 3-D printing. Cause that reduced the requirement of tailored implants are (a) individual diverged optimum size, as observed, and (b) upgrading into the movement and attachment of contributors. Moreover, biopolymer take part in evolution of devices and implants that cures further advantage of broadly adopted in target based upon drug-delivery system (DDS). Detailed explanation of implant apparatus designed employing 3-D printing are mentioned in **Table 5** [16].

Table 5: Implant devices designed using 3D printing

Devices	Description	Reference
Micro-implants	Micro-implants are highly accurate targeting device which has fine results in tissue function restoration and tissue regeneration. Production technique for micro-implants can be elective laser sinistering (SLS), binder jetting and material extrusion methods (e.g., semisolid extrusion and FDM).	**[16]**
Observational working on micro-implants	Including many drugs by planned drug release profiles. A prolonged release was seen by scaffold printing, produced by employing a material extrusion method. By comprising numerous layers of distinct medicine, produced by binder jetting with a goal of releasing two drug simultaneously (dual-pulsed).	**[17]**
Micro-swimmer Devices	Micro-swimmer device mechanism is based on 3 phase, i.e., filling, transport, and liberation. At its individual phase, microscale configuration donates in a notable way. Filling is completed on mechanical trapping, surface chemistry, or passive ingestion in syringes or arms. Method for transportation is based on the theory of engineering based on organs or targeted tissues. Stimuli reacts to chemical, thermal, and magnetic is based on transportation and release mechanism. Micro-swimmers, on sensation or excitation of a stimulus, moves towards demanded administration by centralizing on geometry, and has the way by in vivo vascular systems. Including all technique, magnetic actuation is well known, as the it is noninvasive.	**[16]**

Micro-implants are a highly particular target based device that has been developed for tissue function restoration and tissue regeneration [16]. A scaffold was made by a 3-D printing material extrusion technique, which includes a extended release profile [17]. Adding many layers of numerous drugs in a multi-drug implant, produced with 3-D printing technology binder jetting, to get release of two drug simultaneously for curing bone tuberculosis [18]. 3-D printing methodology is being investigated in spine operation, especially for vertebral skeleton model printing. Because of its relatively low cost and simplicity, it is adopted by both patients and doctors. Moreover, 3-D printing is also being investigated to prepare and design a trace template that can ensure an inner fixation screw that can lead its action.

Implementation of 3-D printing is been investigated in production of medical apparatus as it ensures customization of medical and implants apparatus and can make sure minor invasive detection [19]. Unquestionably, clinical demand for 3-D printing is gigantic, and it can be used in the plan of medical devices and customized implants, as recommended by preliminary research.

B) *TUMOR TARGETED DRUG DELIVERY*

Tumor drugs has numerous puzzle in stretching the target active centre. Their collection may lead to several noxicity in numerous non-cancerous parts. Employing traditional systems like intravenous (IV) injection or oral dosage forms also have drawbacks due to it's poor solubility of drug, that may lead to a hurt the cancer patients.

3-D printing science involving polymers like PCL and PLGA for scaffolds production to deliver tumor and antibiotics. They are created as patches with regular shape and results in release of drug for four weeks with proper release kinetics, that can alleviate patient's compliance [20].
Titanium implants were employed 3-D printing technology to create a distinct micro- and nano-surface (tubular arrays) landscape for bone that has to be made and local anticancer drug delivery of apoptosisinducing ligand (Apo2L/TRAIL) and doxorubicin. These 3-D nano-surfaces can be

investigated for local chemotherapy of secondary as well as primary bone cancers along with fracture support.A 3-D printed micro-fluid fragment for delivery of integrated chemo therapeutics. These fragments consists of multi-passage helical form for combining the chemotherapeutic solutions in whirlwind fashion.The blended result of the tumor elements results in the additive cytotoxic effect on cells of A459 [21]. 3-D printed micro-needles were manufactured by biodegradable resin using SLA. These micro-needles were employed as in vivo cancer alleviated studies and results in noticeable alleviation of cancer weight [22]. 3-D printed calcium phosphate podiums with calculated porosity were prepared for encapsulation for curcumin in a liposome. Curcumin liberated from the 3-D printing scaffold results in remarkable cytotoxicity regarding in vitro bone tumor cells, since it promotes healthy bone cell proliferation and viability [23].

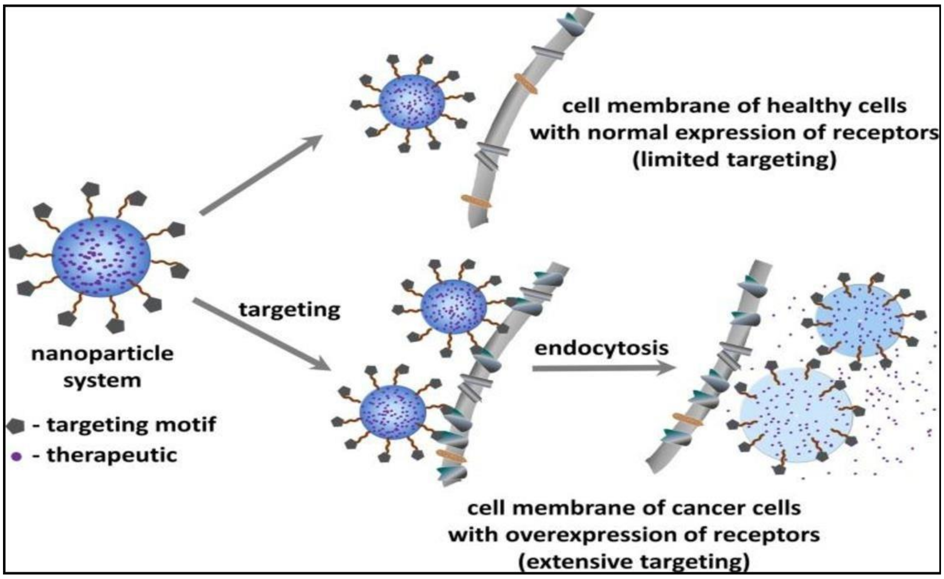

Figure 04. The Cancer treatment with the utilization of Nanotechnology 3D Printing representation

Cure for complex and fatal disease like tumor need planning a modish customized and engineered therapeutic system, that can be made feasible in the upcoming days by employing nanotechnology with 3-D printing.

C) *PEPTIDE DELIVERY*

Micro-needles that has micron-needle arrangement on model surface, elevates skin penetration of bioactive compound. All the micro-needles can be more beneficial to deliver various macro-molecules via skin despite of traditional patch. Modern development in greatly resolve 3-D printing technique, that can create tiny structures, thus gives a vast implementation of the printing in production for microneedles. Whereas conventional method of micro-creation are confined only by micro-needles with basic shape, the latest 3-D printing methods permits micro-needle creation that has greater complex and complex shape [24].

A preparation of polymeric micro-needle patches of a bio-compatible character by using the SLA technique to fulfil insulin via skin. Bio-acceptable resins were photo-polymerized to produce microneedles of pyramid and cone shape, that lead via inkjet (IJ) print with covering of insulin preparation. The created micro-needles have a improved penetration mechanical strength and capacity. They liberation of insulin was quite quick with a time lag of 30 min disregard of the geometry of the microneedle [25]. Operating micro-SLA, a preparation of micro-needles made by poly (propylene fumarate) by inducing tumor remedy for curing dermal carcinoma. To enhancing adjusting viscosity and mechanical strength, they combined diethyl fumarate along with poly (propylene fumarate). The micro-needles liberates anticancer remedy, dacarbarzine, for duration of five weeks [26].

Extra-short peptides can be used in composing of bio-printing appeals as bioinks. The extra-short peptide components has the features to gather itself as hydrogel possessing nano-fibrous topographic geometry, that detects favour collagen and hence imitates tissue extracellular form native geometry. Contemplating a sample, extra-short peptide hydrogel displays bio-adaptability by continuing with intestinal epithelial cells (Caco2) and stem cell 3-D culture oregano-typic culture. There was detention for potency of embryonic stem cell, that can be enveloped in extra-short peptide hydrogels, at the same time Nanog and Tra-I-60, Tra-I-81, Oct4, were employed as tag of pluripotency.

Here are distinct human being with mesenchymal stem unit that was existing into adipogenic lineage from peptide hydrogelson subjected to a estabilished culture environment. The peptide hydrogels perhaps also provide relevant nano-topographyand a 3-D micro-surrounding to assist primary cell organo-typic culture through with stem cell 3-D culture [27].

D) DENTAL DRUG DELIVERY

3-D printing with other 3-D methods donates to the dental production. These productions have been employed to give orthodontic administration, such as dental scaffolds, surgical drill guides, aligners, and orthodontics. Almost all of the dental apparatus are patient restricted and 3-D printing materializes the demand for customization and individualization needs as per industry (**Fig. 05**). 3-D printing can be employed to give personalized application, lined up for geriatric to fabricate the friendly fit that gently shifts the teeth. This technique reduces treatment time and is comfortable also.

Another research on 3-D printing application on orthodontic cure was for the application of intra-oral scan data of the individual to fabricate CAD models of patient-customize brackets, to operate a customized positional guides and arch. A DLP 3-D printer was then employed to fabricate the bracket structure, which was concurrently employed for orthodontic cure.

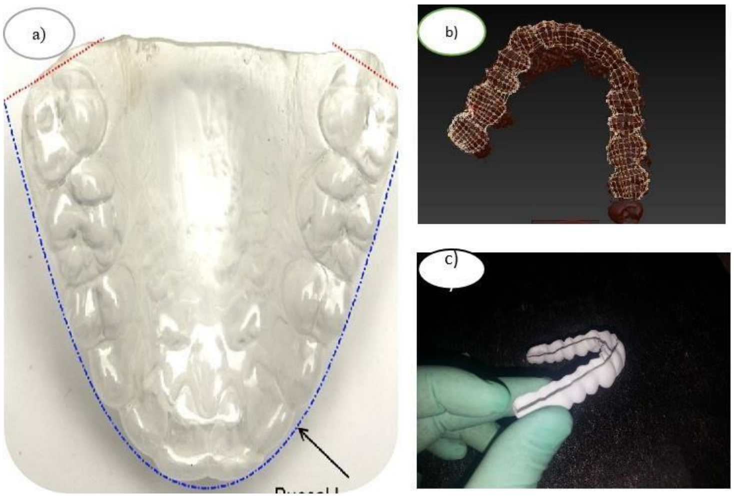

Figure 05. 3-D printed mouthguard a) taking the picture of teeth b) picture on computer c) 3-D customized mouthguard

While 3-D printing has been assured in fabrication of patient-customized cost-effective models, the grades seems to be minor as to the conventional stone replica. A step-wise study contrast the precision of 3-D printing orthodontist prosthesis to traditional stone replica, displaying that 3-D printer replica have alleviated quality. In another research, 3-D printing was also employed to fabricate dental implant adjacently. Two sort of material were employed for 3-D printing, stainless steel and plastics. Likewise, the outcome displays that 3-D printing plastic adjacent was not perfect due to it's poor mechanical strength and threading issues. The metal implants seems to be of greater suited as compare to traditional machined implants, but after fabrication there is still a need for even surfaces. Hence, the needs to improve for precise is needed for 3-D printing method in this particular area. The standard of 3-D printing might not be prefect for few of the dental uses, it can be employed in a form of tool for the evolution of novel and innovative dental implants. A novel smart brace that is effective in betterment of dental orientation has been fabricated by 3-D printing. The 3-D printed braces are comprise nontoxic batteries and flexible along with near-infrared LEDs [28].

This customized 3-D printing dental system elevates bone rejuvenation through LED, along with enamel health-care shield. These smart arrangement can alleviate the burden and cost on the healthcare technique in the future.

2) *WOUND HEALING*

There is greater request subsist for customized innovative devices for evolving extra produced structure for wound healing. Nanoscience-based prospective have potent capability to make a number of challenges aligned with recent pharmaceutical orientation, but their protection is a huge question till now. However these prospective has antimicrobial nano-particles active substances as carrier which elevate healing of wound, they are yet tough to fabricate at production scale. They were also antibacterial patient-customized wound dressings fabricated by PCL induced in silver, copper and zinc. Metal-packed filaments were produced through employing hot-melt extrusion; ear and nose 3-D replica were fabricated. Wound dressings has extended release of numerous bactericidal and metals features.

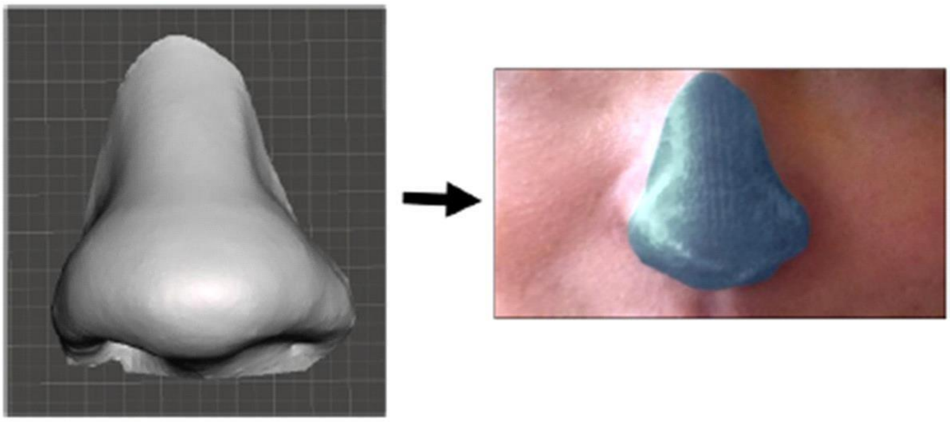

Figure 06. 3-D scan of an individual nose that is covered to be created by employing 3-D printing of Cu-polycaprolactone (PCL)

The 3-D printing of hybrid scaffolds, which were based on integrated poly (ethylene glycol) (PEG) and pericardium model, were produce to encourage wounds healing for vascular grafts assisted with damaged vessel substitution followed by surgical remodeling. Alleviation of swelling indicated by macrophages was seen on embracing analogous pericardium within PEG model, that can change the scaffold model. Researchers have induced purposed nano-sized cellulose for production of 3-D bioplotters with customized tissue, manufactured at centimeter range and optimized with methylcellulose/alginate hydrogel. The technique is employed for rejuvenation remedy in fats and cartilage by a supplementary choice to control defect in tissue. A victory revealed in 3-D printing for dermal application using LbL mechanism.

3-D nano-bioprinting lay outs a notable upper hand of similarity with human dermis, which restores physical size, geometry, shape, and formation [29]. 3-D printed compound of zinc oxide (ZnO) nanoparticles along with photo stimulant was summarized inside hydrogel (alginate) for antimicrobial effect to aid healing of wound. 3-D printed fabrication discloses remarkable amplified structural stability and larger pore sizes contrast to manually recorded specimen.

Bacterial resistance examination on Staphylococcus epidermidis reflects certain incorporation of ZnO nano-particles into gels alleviated bacterial development with contrasted into clear alginate gels. Cell potential of STO-fibroblast cells was favourable influenced with incorporation of ZnO nanoparticles into alginate gels [29]

03) ***TISSUE ENGINEERING AND REGENERATION***

Tissue engineering promotes bio-compatible implant fabrication for substitution of awry or injured tissues. This area employees bio-compatible developing factors, materials, and live cells to produce implants assist with common development of tissues. The calculative production permits the creation of numerous 3-D printed replica that mock the microscopic web of connective tissues. One can find a numerous quality of 3-D printing in the department of tissue engineering, one of them reside in its capacity to supply configuration for complicated shapes by precisely putting out the materials in 3-D area.

Add-on production provides a improved utensil in production of implants aid in bone regeneration. Controlling critical-size bone flaw is still a dare. There is no surety of bone incorporation if there is fillers for macro bone flaws that are needed for bone grafts. The current surgical operations includes vascularization for bone grafting, which is adverse and exclusively technical, or to carry out “Masquelet policy”, that needs a lot of operations and also elevates the morbidity. Add- on to production gives appropriate implant solutions encouraging vascularization and bone rejuvenation. Porosity is an essential property for encouraging bone development. 3-D printing furnish a program for producing porous scaffolds and high resolution from various materials like ceramics and metals [30]. Applying and printing of acellular PCL/HAP scaffolds within rabbits, that were druged by the modifying β3 (TGF β3) growth factor. Following the utilization, it reveals a complete articular surface recreation for proximal humeral joints [30]. A PCL trachea preinted by employing FDM, that was coated along with mesenchymal stem cells (MSCs) and fibrin, reveals neo-cartilage constructed and united along with local tracheal tissue. Researchers are inspecting 3-D printing to acquire a scaffold of demanded polyvinylpyrrolidone nano-topographyin, by fabricating suspension of calcium phosphosilicate nanoparticles with sizes scaling between 20 to 100 nm.

Utilization of 3-D printing in the modelling of nano-medicines could be useful in developing micro- and nano-scale scaffold with demanded results such as osseous integration, as needed in engineering of bone tissue, and also authorize the blueprint of configuration of scaffold contest with customized shape of flaws [30].

4) *IMPLICATION IN COVID-19*

Worldwide undetermined emerging due to epidemic COVID-19, which produced a global emergency. COVID-19 outcome in dare and disturb in providing of numerous sorts of drugs crisis apparatus, due to the ceasing of organization and convince. In this duration, 3-D science possibility was utilized to supplying the necessary drugs and checking apparatus, personal protective equipment (PPE), crisis dwellings, visible aids, and customized attachments. 3-D science was also employed for coaching health management employee with a envisioned tape describing the technique of utilizing PPE kits and supplementary drugs gadget [31-34]. Table 6 represents the detail of PPE kits/masks (respirators) blueprint and production employing 3-D printing for securing through COVID-19. A Scientist inspects an alternative answer by producing an acquire for the Flyte helmet, by that it can be transformed into PPE [32].

Duplicate of anatomy organ parts precisely was achieved via 3-D printing of ample of drug twin employed to coach the drug front warriors for COVID-19 swab checking. 3-D printing can be employed for the creation of nacho-pharyngeal swabs and to encounter the needful for excess requirement of swabs [35].

Table 6: The 3-D printers employed for PPE kits/ mask (respirators)

Face Mask	Description	Reference
3-D printed helmets for arthroplasty remodel in PPE	A creative answer was suggested with modification of the quality helmet technique stated the scarcity of strong aircleaner for inhalation and the possible scarcity of N-95 respirators. The idea of innovating a 3-D printing prospective is to produce an adaptor for the Flyte helmet to access the transformation to PPE.	**[32]**
3-D printer for mask adaptor	Equipped for a parted section of a N-95 inhalation, that kept the N-95 clarification quality and as a result numerous respirators. Keeping the N-95 quality needs a new respirator adaptor layout that follows to the face and adheres throughout every elements of the filter and respirator.	**[33]**
3-D printed respirator for a orthopedic injury in Level-I	Employing of 3-D printing potential to assemble 3-D printed face respirator for orthopedic injury supplying the cleaners that were almost parallel to the clarification matter that is set-up in N-95 respirators.	**[34]**
Clinical inhalation assist equipment	Throughout the outburst of COVID-19 in Italy, there was enormous shortage of respirators. The Venturi-based flaps are vital part of that inhalation assist apparatus, that were hard to multiply. The epidemic circumstances involve the utilization of 3-D printing to construct flaps for facilitate the confined material. The non modified Venturi flaps were normally reachable by "GrabCAD" customer. So most of the layout of flaps employing 3-D printing attains fragment of stimulated oxygen (FiO2) levels at oxygen providing auxiliary rate. There can be a need of printing science for securing airtight box after that replica porosity is changed to FiO2 levels.	
The Lowell producing Respirators	The Lowell produces respirators provide an upper hand on printing by omitting assistance and replaceable front cleaner blue print. The respirator employees sponge padding on the interior side. The foaming substance is re-utilized and upgraded discrete comfort, but the choice of germ-free technique must be reviewed carefully.	

5) DIAGNOSIS AND DETECTION

The last few decades, drug picturing has been announced as one of the growing science employed in the medical wellness quarter. 3-D perspective of interior parts and tissues along with suitable picture for exploration is vital for doctors in detection of infection. 3-D medical science monitors in three steps: image obtain, image post-process, and 3-D printing. Currently, extra production took part in detection that include CAD with capability to be changed to 3-D printed designs [36]. Moreover production science are economically fair, thus can be employed in creation of analytical apparatus and devices for detection. 3-D printed micro-fluidic apparatus has a bulk of delightful purpose to be served in 3-D printing for detection. This science is now applicable for automated as well as non-automated detection. Well known whip hand is by micro-fluidic apparatus is capacity to handle lesser mass [37]. Conformations has been made that 3-D printing can act as helping apparatus for currently accessible detectors like PCR, and improve by blue tooth recognizing via mobile [36]. The various applications of Nano 3D in various infectious and other as below followings:

1. ***Cancer detection:*** Nanoparticles that are coated with antibodies can be used to target and deliver drugs to cancer cells. This approach is being used to develop new cancer therapies. Nanoparticles that can emit light can be used to image cancer cells in vivo. This approach is being used to develop new diagnostic tools for cancer. Nanoparticles that can interact with specific molecules can be used to detect the presence of biomarkers that are associated with cancer. This approach is being used to develop new diagnostic tests for cancer [35-37].
2. ***Infectious disease detection:*** Nanoparticles that are coated with antibodies can be used to detect the presence of bacteria or viruses in blood or other fluids. This approach is being used to develop new diagnostic tests for infectious diseases.
   Nanoparticles that can emit light can be used to image bacteria or viruses in vivo. This approach is being used to develop new diagnostic tools for infectious diseases. Nanoparticles that can interact with specific molecules can be used to detect the presence of biomarkers that are associated with infectious diseases. This approach is being used to develop new diagnostic tests for infectious diseases.
3. ***Biomarker detection:*** Nanoparticles that can interact with specific molecules can be used to detect the presence of biomarkers that are associated with a particular disease. This approach is being used to develop new diagnostic tests for diseases such as Alzheimer's disease and cancer.
4. ***Tissue engineering:*** Nanoparticles can be used to create scaffolds for tissue engineering. This approach is being used to develop new treatments for injuries and diseases. Nanoparticles can be used to deliver drugs or genes to specific tissues or cells. This approach is being used to develop new therapies for diseases such as cancer and heart disease [34-38].
5. ***Drug delivery:*** Nanoparticles can be used to deliver drugs to specific tissues or cells. This approach is being used to develop new drug delivery systems that are more effective and less toxic than traditional methods.

The use of 3D nanotechnology in detection and diagnosis is still in its early stages, but it has the potential to revolutionize these fields. Nanoparticles offer a number of advantages over traditional methods, such as their ability to target specific tissues or cells, their small size, and their tunable properties. As research in this area continues, it is likely that 3D nanotechnology will become increasingly used in diagnosis and detection of diseases.

Detection apparatus along with automated and many loops can also be produced via 3-D printing. One more new altered category of 3-D printing is 3-D bioprinting, that includes encloses of chemicals and biostructure like tissues, cells, and proteins in printable bio-ink mixture [38]. For detection of infection like AIDS; ELISA is employed; as it is situated on the concept of antigen–antibody interactivity. 3-D printing policy can improve the potency of the above as “3-D well” has a greater external area than a traditional decreased plate and provide fine responsiveness; as, detection can be carried out without any trouble and fastly [39].

CURRENT REGULATORY REGULATIONS AND PROGRESS

The regulatory landscape for 3D nanotechnology is still evolving, as there is no one-size-fits-all approach. Different countries and organizations have different regulations in place, and these regulations are constantly being updated as new information becomes available.

- **In the United States**, the Food and Drug Administration (FDA) is responsible for regulating the safety and effectiveness of medical devices that use nanotechnology. The FDA has not yet developed specific regulations for 3D printed medical devices, but it is expected to do so in the near future. In the meantime, the FDA is using its existing regulatory framework to assess the safety and effectiveness of these devices on a case-by-case basis.

- **The Environmental Protection Agency (EPA)** is responsible for regulating the environmental impact of nanomaterials. The EPA has developed a number of guidelines for the safe handling and disposal of nanomaterials, but it has not yet developed specific regulations for 3D printed products that use nanomaterials.
- **The Occupational Safety and Health Administration (OSHA)** is responsible for protecting workers from exposure to hazardous materials. OSHA has developed a number of regulations for the safe handling of nanomaterials in the workplace, but it has not yet developed specific regulations for 3D printing.

In addition to these government regulations, there are also a number of voluntary standards that have been developed for 3D nanotechnology. These standards are developed by industry groups and organizations such as the **International Organization for Standardization (ISO)**. The ISO has developed a number of standards for 3D printing, including standards for the safety of nanomaterials used in 3D printing.

The Food and Drug Administration (FDA) from U.S. passed the firstly ever prescribed 3-D created drug 'Spritam (Levetiracetam)' in July 31, 2015, below the Section 505b (2) and is employed to serve limited convulsions, myoclonic convulsions and mainly generalized stimulant-clonic convulsions. Lots of 3-D printing drug apparatus have been certified via 510k track so far that occular apparatus, orthodontist crowns, bone plate, skull plates, backbone platting system, facial surgery, and surgical apparatus. FDA has prepared hard and fast benchmarks for the selling and acceptance of 3-D Printed commodities.

FDA's one of the lab CDER Workplace of Medication Standard has adopted a scientific plan to inspect the utility of current science like 3-D creation in manufacturing of drugs and medical protection commodities. The federation government of U.S. have manifested an Emerging Technology Team (EET) inside the FDA which focuses in scientific revolution in outlining and creation. The prime dare in accepting the 3-D printer for distribution of medical preparation when required is lagging in enforcing the good manufacturing practices. Recently there is no statements made for 3-D creation mechanism in Schedule M of Drug and Cosmetic Act, 1945 [38-39]. So the question can enter you mind during production and distribution of medicine for quality check Along with this, there is a shortage of preciseness for about the method should be employed as per the regulatory guideline if 3D printing science is employed as producing when required for customized commodities. The various challenges and opportunities in the regulation of 3D nanotechnology as below following:

Challenges:

- The lack of clear regulatory guidelines is making it difficult for companies to develop and market 3D printed products that use nanotechnology.
- There is a lack of understanding of the potential risks and benefits of 3D nanotechnology.
- There is a lack of data on the environmental impact of 3D nanotechnology [39].

Opportunities:

- The development of clear regulatory guidelines could help to facilitate the development and commercialization of 3D nanotechnology.
- The regulation of 3D nanotechnology could help to ensure the safety of consumers and workers.
- The regulation of 3D nanotechnology could help to protect the environment.

The regulatory landscape for 3D nanotechnology is still evolving. There is a growing recognition of the need for regulation in this area, and it is expected that clear guidelines will be developed in the near future [40-41]. This will help to facilitate the development and commercialization of 3D nanotechnology while also ensuring the safety of consumers, workers, and the environment.

CONCLUSION

This manuscript is mainly focused on the utilization of 3-D printing combined with the technique of nano-medicines and improvements in NDDS. Moreover, we also analyzed the 3-D based nanomaterials and its dynamic use in customized medication, with ponder of regulatory outlook. Recently, the 3-D based drug delivery science is in tot stage, but in the upcoming world it may come out as a potent science with replenishment at trading level to get customized release profiles. The destiny of achieving improved drug or therapeutics to get present patient's satisfaction. The main aim of this paper is a give neat representation and elaborate 3-D based technology futuristic. A broad scale of nano composite biomaterials is obtainable for producing 3-D composite drugs and reassuring its closeness. While described, 3-D printing has anticipated its capability within target-based delivery, tissue engineering, wound healing, diagnosis and detection, and else. These requisitions discussed are restricted by preclinical uses, and this is because of regulatory provisions and secure bio-compatibility work within human being.

REFERENCE

1. Palmara, G.; Frascella, F.; Roppolo, I.; Chiappone, A.; Chiadò, A.J.B. Functional 3D printing: Approaches and bioapplications. Biosens. Bioelectron. 2021, 175, 112849.
2. Pal, Rahul & Pandey, Prachi & Chanana, Arsh & Singh, Ravindra & Waheed, Saman & Katiyar, Aparna. (2023). Recent Approaches on 3D Printing (3DP) in Pharmaceuticals as Dominance Role in Traditional Formulation. 8. 989.
3. Bertassoni, L.E.; Cecconi, M.; Manoharan, V.; Nikkhah, M.; Hjortnaes, J.; Cristino, A.L.; Barabaschi, G.; Demarchi, D.; Dokmeci, M.R.; Yang, Y.; et al. Hydrogel bioprintedmicrochannel networks for vascularization of tissue engineering constructs. Lab Chip 2014, 14, 2202–2211.
4. Kesti, M.; Müller, M.; Becher, J.; Schnabelrauch, M.; D'Este, M.; Eglin, D.; Zenobi-Wong, M. A versatile bioink for threedimensional printing of cellular scaffolds based on thermally and phototriggered tandem gelation. Acta Biomater. 2015, 11, 162–172.
5. Rhee, S.; Puetzer, J.L.; Mason, B.N.; Reinhart-King, C.A.; Bonassar, L.J. 3D Bioprinting of Spatially Heterogeneous Collagen Constructs for Cartilage Tissue Engineering. ACS Biomater. Sci. Eng. 2016, 2, 1800–1805.
6. Censi, R.; Schuurman, W.; Malda, J.; di Dato, G.; Burgisser, P.E.; Dhert, W.J.A.; van Nostrum, C.F.; di Martino, P.; Vermonden, T.; Hennink, W.E. A Printable Photopolymerizable Thermosensitive p(HPMAm-lactate)-PEG Hydrogel for Tissue Engineering. Adv. Funct. Mater. 2011, 21, 1833–1842.
7. Yin, J.; Yan, M.; Wang, Y.; Fu, J.; Suo, H. 3D Bioprinting of Low-Concentration Cell-Laden Gelatin Methacrylate (GelMA) Bioinks with a Two-Step Cross-linking Strategy. ACS Appl. Mater. Interfaces 2018, 10, 6849–6857.
8. Athalye, M., & Popat, S. 3D Printing Revolutionising Nanotechnology.
9. Pandey, Prachi & Pal, Rahul & Chanana, Arsh & Singh, Ravinder. (2023). BIOLOGICAL SYNTHESIS OF METAL BASED NANOPARTICLES INCLUDING BACTERIA AND FUNGI. 79-89. 10.36673/AJPAMC.2022.v10.i03.A11.
10. Ujjwal, Rewati & jain, kreeti & Shukla, Rahul & Yadav, Awesh & Flora, Swaran. (2021). 3D Printing in Development of Nanomedicines. Nanomaterials. 11. 420. 10.3390/nano11020420.
11. Pandey, M. et al. 3D printing for oral drug delivery: a new tool to customize drug delivery. Drug Deliv Transl Res (2020) 10, 986–1001
12. Mathew, E. et al. Three-dimensional printing of pharmaceuticals and drug delivery devices. Pharmaceutics (2020) 12, 1–9
13. Thakkar, R. et al. Novel on-demand 3-dimensional (3-D) printed tablets using fill density as an effective release-controlling tool. Polymers (Basel) (2020) 12, 1872
14. Liang, K. et al. 3D printing of a wearable personalized oral delivery device: a first-in-human study. Sci Adv (2018) 4, 1–12
15. Kong, Y.L. et al. 3D-printed gastric resident electronics. Adv Mater Technol (2019) 4, XXX– YYY.
16. Kjar, A.; Huang, Y. Application of Micro-Scale 3D Printing in Pharmaceutics. Pharmaceutics 2019, 11, 390.
17. Pal, R., Pandey, P., Rai, B., Koli, M., Chakrabarti, M., Thakur, P., ... & Saxena, A. CHITOSAN: AS HIGHLY POTENTIAL BIOPOLYMER OBTAINABLE IN SEVERAL ADVANCE DRUG DELIVERY SYSTEMS INCLUDING BIOMEDICAL APPLICATIONS. environmental science, 3, 4.
18. Zhu, M.; Li, K.; Zhu, Y.; Zhang, J.; Ye, X. 3D-printed hierarchical scaffold for localized isoniazid/rifampin drug delivery and osteoarticular tuberculosis therapy. Acta Biomater. 2015, 16, 145–155.
19. Pal, Rahul & Pandey, Prachi & Kumar Maurya, Vishesh & Saxena, Archita & Rizwan, Mohammad & Koli, Manju. (2023). Optimization And Formulation of Doxorubicin (DOX) Loaded Liposome Well-Used in Chemotherapy Involving Quality by Design (QBD): A Transitory Research. European Chemical Bulletin. 12. 4491-4510. 10.48047/ecb/2023.12.si5a.0355.
20. Wu, W.; Zheng, Q.; Guo, X.; Sun, J.; Liu, Y. A Programmed Release Multi-Drug Implant

Fabricated by Three-Dimensional Printing Technology for Bone Tuberculosis Therapy. Biomed. Mater. 2009, 4, 065005.

21. Handa, M.; Sharma, A.; Verma, R.K.; Shukla, R. Polycaprolactone based nano-carrier for coadministration of moxifloxacin and rutin and its In-vitro evaluation for sepsis. J. Drug Deliv. Sci. Technol. 2019, 54, 101286.
22. Chen, X.; Chen, H.; Wu, D.; Chen, Q.; Zhou, Z.; Zhang, R.; Peng, X.; Su, Y.C.; Sun, D. 3D printed microfluidic chip for multiple anticancer drug combinations. Sens. Actuators B Chem. 2018, 276, 507–516.
23. Maher, S.; Kaur, G.; Lima-Marques, L.; Evdokiou, A.; Losic, D. Engineering of Micro- to Nanostructured 3D-Printed DrugReleasing Titanium Implants for Enhanced Osseointegration and Localized Delivery of Anticancer Drugs. ACS Appl. Mater. Interfaces 2017, 9, 29562–29570.
24. Sarkar, N.; Bose, S. Liposome-Encapsulated Curcumin-Loaded 3D Printed Scaffold for Bone Tissue Engineering. ACS Appl. Mater. Interfaces 2019, 11, 17184–17192.
25. Park, B.J.; Choi, H.J.; Moon, S.J.; Kim, S.J.; Bajracharya, R.; Min, J.Y.; Han, H.-K. Pharmaceutical Applications of 3D Printing Technology: Current Understanding and Future Perspectives. J. Pharm. Investig. 2018, 49, 575–585.
26. Pere, C.P.P.; Economidou, S.N.; Lall, G.; Ziraud, C.; Boateng, J.S.; Alexander, B.D.; Lamprou, D.A.; Douroumis, D. 3D Printed Microneedles for Insulin Skin Delivery. Int. J. Pharm. 2018, 544, 425–432.
27. Lu, Y.; Mantha, S.N.; Crowder, D.C.; Chinchilla, S.; Shah, K.N.; Yun, Y.H.; Wicker, R.B.; Choi, J.W. Microstereolithography and characterization of poly (propylene fumarate)-based drugloaded microneedle arrays. Biofabrication 2015, 7, 045001.
28. Jain, P., Kathuria, H., & Dubey, N. (2022). Advances in 3D bioprinting of tissues/organs for regenerative medicine and in-vitro models. *Biomaterials*, *287*, 121639.
29. Nguyen, Tung & Jackson, Tate. (2018). 3D technologies for precision in orthodontics. Seminars in Orthodontics. 24. 10.1053/j.sodo.2018.10.003.
30. Cleetus, C.M.; Primo, F.A.; Fregoso, G.; Raveendran, N.L.; Noveron, J.C.; Spencer, C.T.; Ramana, C.V.; Joddar, B. Alginate hydrogels with embedded ZnO nanoparticles for wound healing therapy. Int. J. Nanomed. 2020, 15, 5097.
31. Ahangar, P.; Cooke, M.E.; Weber, M.H.; Rosenzweig, D.H. Current Biomedical Applications of 3D Printing and Additive Manufacturing. Appl. Sci. 2019, 9, 1713.
32. Tino, R.; Moore, R.; Antoline, S.; Ravi, P.; Wake, N.; Ionita, C.N.; Morris, J.M.; Decker, S.J.; Sheikh, A.; Rybicki, F.J.; et al. COVID-19 and the Role of 3D Printing in Medicine. 3D Print. Med. 2020, 6, 11.
33. Erickson, M.M.; Richardson, E.S.; Hernandez, N.M.; Bobbert, D.W.; Gall, K.; Fearis, P. Helmet Modification to PPE With 3D Printing During the COVID-19 Pandemic at Duke University Medical Center: A Novel Technique. J. Arthroplast. 2020, 35, S23–S27.
34. Imbrie-Moore, A.M.; Park, M.H.; Zhu, Y.; Paulsen, M.J.; Wang, H.; Woo, Y.J. Quadrupling the N95 Supply during the COVID-19 Crisis with an Innovative 3D-Printed Mask Adaptor. Healthcare 2020, 8, 225.
35. Thomas, C.N.; Schroder, L.K.; Cole, P.A. Ten Days to Implementation of 3D-Printed Masks for a Level-I Orthopaedic Trauma Practice During the COVID-19 Pandemic. J. Bone Jt. Surg. Am. 2020, 102, e95.
36. Wang, Y., Ahmed, A., Azam, A., Bing, D., Shan, Z., Zhang, Z., ... & Rehman, M. (2021). Applications of additive manufacturing (AM) in sustainable energy generation and battle against COVID-19 pandemic: The knowledge evolution of 3D printing. *Journal of Manufacturing Systems*, *60*, 709-733
37. .Mahmoudi, Z., Sedighi, M., Jafari, A., Naghieh, S., Stefanek, E., Akbari, M., & Savoji, H. (2023). In situ 3D bioprinting: A promising technique in advanced biofabrication strategies. *Bioprinting*, e00260.Zhao, W., Hu, C., & Xu, T. (2023). In vivo bioprinting: Broadening the therapeutic horizon for tissue injuries. *Bioactive Materials*, *25*, 201-222.
38. Zarrintaj, P., Seidi, F., Azarfam, M. Y., Yazdi, M. K., Erfani, A., Barani, M., ... & Mozafari, M. (2023). Biopolymer-based composites for tissue engineering applications. *Composites Part B: Engineering*, 110701.Lipson, H.; Kurman, M. Fabricated: The New World of 3D Printing, 1st ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2013
39. Taylor, A. A., Freeman, E. L., & van der Ploeg, M. J. (2021). Regulatory developments and their impacts to the nano-industry: A case study for nano-additives in 3D printing. *Ecotoxicology and Environmental Safety*, *207*, 111458.

40. Chen, Z.; Li, Z.; Li, J.; Liu, C.; Lao, C.; Fu, Y.; Liu, C.; Li, Y.; Wang, P.; He, Y. 3D Printing of Ceramics: A Review. J. Eur. Ceram. Soc. 2019, 39, 661–687.
41. Mashari, A.; Montealegre-Gallegos, M.; Knio, Z.; Yeh, L.; Jeganathan, J.; Matyal, R.; Khabbaz, K.R.; Mahmood, F. Making Three-Dimensional Echocardiography More Tangible: A Workflow for Three-Dimensional Printing with Echocardiographic Data. Echo Res. Pract. 2016, 3, R57– R64.