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Tailormade Drug Delivery System: A Novel Trio Concept of 3DP+ Hydrogel+ SLA

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ABSTRACT

Hydrogels possess three-dimensional polymeric network structure and equipped for retaining extensive measure of water or organic fluids. This quality makes them as exceptional candidate for the simulation of extra cellular matrixes. For this the three dimensional printing (3DP) has evolved as the technique for the formation of the digital models. The 3DP is capable for processing the prescriptions and the therapeutic gadgets. One of the technique known as stereolithographic (SLA) printing has shown promising results in formulating the hydrogel based system for fabrication. The SLA acts by cross connecting the saps to shape the polymer matrices. Due to water captured in the gels it is conceivable to create the pre- wetted, medicate hydrogels and gadgets. The 3DP helps in formation of tailor made drug delivery system as per needs of patients. Many of Bioinks has been tried up for the hydrogel formation such as collagen, gelatin, hyaluronan, silk, alginate, and nanocellulose etc.

Hydrogel printed with riboflavin/ triethanolamine as photoinitiator.

Keywords: 3D Printing, Hydrogel, Steriolithography.

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INTRODUCTION

Personalized medications are recently new advance technique in Pharmaceutical sector. Some medications do not show respond or some show toxic affects with a certain dose, so that to formulate a different dose or different drug delivery system to overcome these side effects. Let us consider if a person required 10 mg but you have only 50 mg you cannot dispense only 10 mg. 3D printing is an advance or more popular technique in a personalized medication. 3D printing mainly focused on the patients need. This method has numerous points of interest, for example, expanding the cost proficiency and the speed of the assembling since a fast prototyping should be possible in only minutes. Notwithstanding, there is as yet a momentous obstruction to guarantee that 3D printed prescriptions have a similar viability, wellbeing and steadiness as the pharmaceuticals customarily fabricated by the Pharmaceutical Industry. It is a major test for the administrative specialists involving extraordinary deterrents with respect to the foundation of rules, laws, quality frameworks and security of utilization and utilization of 3D printed medications[1]. This procedure is

utilized for quick prototyping, which develops strong questions by testimony of a few layers in sequence[2]. In supporting cell adhesion and promoting cell infiltration within their porous matrix, 3D printed scaffolds play an important role[3]. Furthermore, scaffolds are able to provide mechanical support against stressful environments of the human body maintaining sufficient space for the tissue reconstruction and remodeling[4]. Recently, hydrogel is used as a biomaterial in 3D printing because they can be easily modified without complex synthesis steps to replicate the physicochemical properties of most biological tissues[5, 6]. Hydrogel can be display up to 40 fold changes in volume as they swell or shrink in the presence or absence of water respectively and it can be modified the response to various physical and biological stimuli such as temperature, light, pH, ions and biochemical signals[6,7]. These distinctive features make hydrogels excellent environments for cell attachment and proliferation within their hydrated hydrogel polymeric networks, which offer abundant space for cell growth while facilitating the transportation of essential metabolites and nutrients to the engulfed cells[5, 8]. Spritam TM is the top most US FDA validate 3D printed tablet, express the use of 3D printing by binder jetting technique this 3D printed tablet is fastly disintegrated and used in epileptic medications[9]. It is remarkable prototyping innovation that has recent years and to change the field of medication conveyance with its natural favorable circumstances of adaptability and capacity to manufacture complex strong measurement frames with high exactness and precision. 3DP can detail strong measurement frames with various densities and diffusivities, complex inward geometries, numerous medications and excipients. The issues identifying with the medication conveyance of ineffectively water-dissolvable medications (Hydrophobic medications), peptides, powerful medications and the arrival of multi-drugs and so forth can be effectively tended to by the 3DP. The determinations of reasonable binders, excipients and the pharmaco-specialized properties of definite items are a few issues that limit the uses of 3DP in business showcase. Greater progression execution is essential to defeat this circumstance where 3DP innovation can be effectively joined to the novel drug delivery system (NDDS) [10]. In future, to address the issues of individual medications the utilization of different sorts of printing advances offer potential answers for customized drug and custom-made measurement shapes. In addition CADD (Computer aided drug design) plan enables more chances to make appropriate geometries with customized usefulness and distinctive extent of unpredictability to influence the discharge attributes of single or different medication materials to better medicines for patients since difficulties exist. These advancements are growing quick and utilization of adaptable materials to produce new medication conveyance frameworks[11]. This innovation can deal with complex inward structure for example, interior dividers, empty channels, porosity, different material locales and various medication dispersions. Medication conveyance from 3-dimensional (3D) framework is a quickly developing zone in the exploration to accomplish structures wherein sedate solidness is guaranteed and the coveted controlled discharge profile can be achieved. It should likewise to the advancement of fitting manufacture apparatus that permits 3D medicate conveyance frameworks (DDS) to be delivered in a basic, solid and reproducible way[12]. Pamela Robles Martinez et al. (2017) examined that SLA printing was utilized to plan ibuprofen-stacked hydrogels of cross-associated polyethylene glycol diacrylate. They are made up of 30% w/w water and 10% w/w ibuprofen was effectively printed. Dissolution profiles examined that the medication discharge rates rely upon a water content which hydrogel contain more water content the medication discharge is quicker[13].

BENEFITS

- Increased cost efficiency.
- Personalization/customization.
- Democratization of design process.
- Rapid product development.
- Biomimetic and biological recapitulation.
- Micro patterning and organization.

TECHNIQUES FOR 3D PRINTING

There are different procedures which are utilized in 3D printing for example Fused deposition modeling (FDM), binder deposition, inkjet printing, material flying, powder bed combination, photopolymerization, pen-based 3D printing, stereolithographic (SLA) and trim has been accounted for in the documentation[14, 15]. Numerous sorts of 3DP strategies are accessible **(Figure 1)**, Stereolithographic (SLA) printing offers the special component of having the capacity to create protests by cross-connecting pitches to shape arranged polymer frameworks. Since water can be immersed in these lattices it is conceivable on a fundamental level to figure pre-wetted tranquilize stacked hydrogels and gadgets.

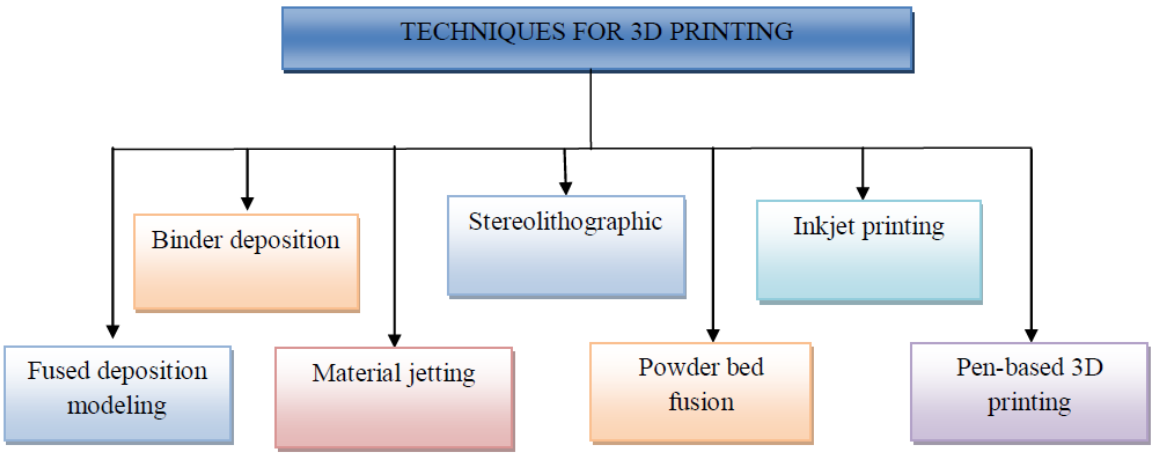

Figure 1: Techniques of 3D Printing

STEREOLITHOGRAPHY TECHNIQUE –

It is a Laser-Based Writing System, in view of the primary gadget developed to make a trio-dimensional item. This procedure was planned by Charles Hull in 1980[16]. SLA printers are comprises of a bright light shaft as a ray that moves the vitality into a fluid photopolymerizable tar (gum) [17]. They are depends on photopolymerization in which free atoms are discharged after the communication between the photoinitiator and UV light[18]. The bright blaze shaft is supported by puzzles; to navigate the surface of the fluid pitch XY development with the end goal to precisely speak to the 3D display already structured **(Figure 2)**[19]. When a film cements, the lifting stage plunges its situation to the tallness of another layer of fluid sap; the maker of the 3D item is done in a films. Thickness of the restored layers in SLA is most essential parameter, which can change the vitality of the UV light to which the tar is uncovered. The gum is a fluid biomaterial prepared to set rapidly upon brightening with the laser light and must be FDA-endorsed for human utilize[18, 20]. SLA emerge the medication and the photopolymer can be blended preceding printing getting to be caught in the set grid. Different focal points of SLA are high goals over alternate methods and that warming is limited amid printing, which takes into consideration the utilization of thermo labile medications not at all like fused deposition modeling (FDM).

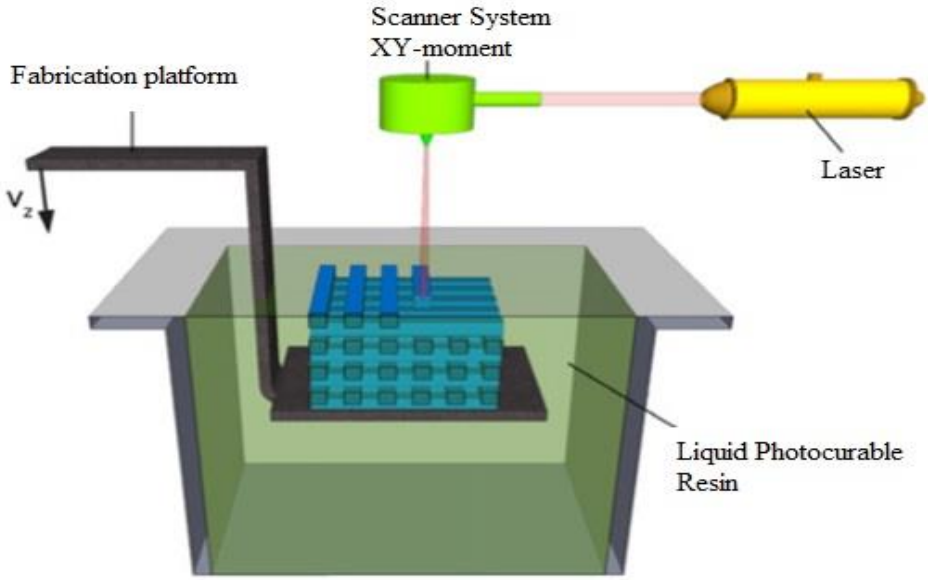

Figure 2: Stereiolithographic apparatus

ADVANTAGES

- Due to more resolution power printing it's good for complex features.
- Cross linking and post processing are used to control the mechanical properties.

PREREQUISITES OF BIOINK FOR 3D BIOPRINTING

Bioink is the most essential segment of 3D bioprinting, its play a vital role in 3D printing. This bioink ought to be exceedingly biocompatible to oblige common or live unit, automatic steady subsequent to printing, including it ought to give big goals amid printing. In 3D bioprinting diverse biomaterials are utilized in bioink however hydrogel is greatest noticeable matter that are utilized as bioink in the bioprinting. They are predominantly because of their capacity to bear occupying cells to alter the compound structures customizable mechanical and ecological characteristics and it can yield a more goals control amid printing. Bioinks for 3D printing capacity to help cell development, printability and so on relies on the determination of bioinks and the properties of the distinctive normal and engineered polymeric biomaterials. Common biomaterials are those polymers which are acquired from a regular asset are called as common biomaterials **(Figure 3)**. These regular materials have differing points of interest over manufactured materials basically identified with the biomimicking of ECM piece or structure, self-gathering capacity, biocompatibility and biodegradation characteristics[21].

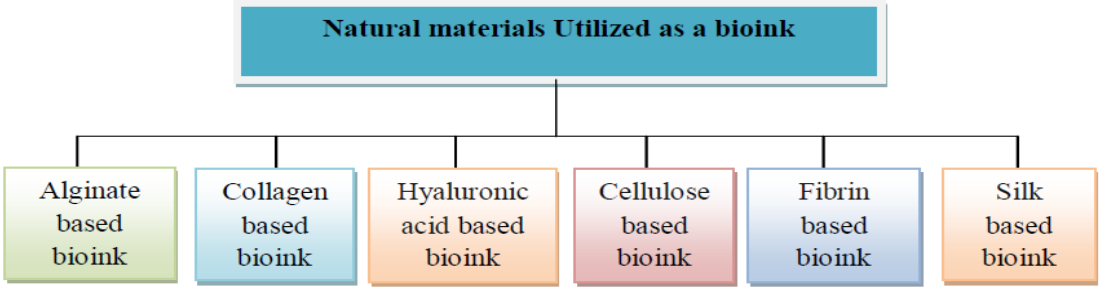

Figure 3: Classification of natural material

Alginate based bioink - Alginate is a characteristic biopolymer got by darker green growth which is effectively accessible. It is also known as alginic acid. The alginate biopolymers can capture water and different atoms by utilizing slim powers and still can enable it to diffuse from back to front because of this trademark property it is perfect for 3D bioprinting bioinks[22,23]. Subsequently, Zhang et al. (2013) to make empty develops utilizing alginate - based bioinks with ligament cells. These vessels-like printable are equipped for transfer air, supplements and biological molecules to build and can bolster cell development[24]. Alginate - form mixed bioink framework that could be straight forwardly apply to print 3D develops[25]. This bioink is a standout amongst the most broadly utilized matter in 3D bioprinting as a result of its various favorable circumstances over alternate hydrogels.

Collagen - based bioinks - Collagen is a fundamental part of ECM or in other words characteristic biomaterials[26,27]. It is utilized as a bioink medium in 3D bioprinting either uniquely or in combination as a result of its great biocompatible properties[26,28]. Collagen crosslinking gives them expanded rigidity and visco-flexible characteristics as compare to the non-crosslinked collagen[27,29]. Gelation or crosslinking of collagen, mandatory at least 30 minutes for gelation at 37 °C. 3D printing is extreme if utilize collagen specifically and consolidating with various review of gelation medium may address this problem. Additionally, the mechanical characteristics of the collagen matters can be expanded by including distinctive polymers in different extents for utilizing it in 3D bioprinting[29, 30].

Hyaluronic corrosive based hydrogel - It is widely used noticeable biomaterials that are utilized in 3D bioprinting for creating 3D structures. The photo crosslinked HA as bioink to get expanded rheological properties by utilizing compound changes. Other regular polymers, HA has low mechanical properties and moderate gelation conduct examined the engineered polymer hydrogels[31]. Ouyang et al. (2016) detailed a HA-based 3D printed manufacture utilizing an auxiliary crosslinking system. They exhibited the potential of the HA-based double cross connected bioinks for 3D bioprinting where it demonstrated no misfortune in mechanical properties in the wake of printing and in addition uncovered great cell grip properties. The cell attachment was improved by the expansion of cell-glue oligopeptides in the hydrogels[32].

Cellulose based Bioink - Carboxymethyl cellulose (CMC) is a semi adaptable polysaccharide acquired from cellulose[33]. For bone recovery, Carboxymethyl cellulose alongside bioactive glass was to create 3D builds with elevated mechanical properties[34]. Marksted et al. (2017) revealed a cellulose nanofibrils and cross-linkable xylans-based inks for 3D printing with high mechanical respectability and astounding printing properties[35].

Fibrin Based bioink - Fibrin hydrogel are gotten from fibrinogen by enzymatic treatment of thrombin. This hydrogel has greater biocompatibility and biodegradation properties; however it has powerless mechanical properties[36]. England et al. (2017), where fibrin was utilized with HA hydrogels to entangled Schwann cells and used to 3D printing.

Silk Based bioink - In Inkjet printing silk fibroin protein with alginate was utilized as bioink material. Silk Based bioink was build with alginate utilizing cross-connected calcium chloride, and buildup of tyrosine of silk fibroin was cross-connected utilizing horseradish peroxidase[37]. Latterly, due to its excellent mechanical properties of spider silk there are widely used as a biomaterial. DeSimone et al. (2017) utilized recombinant arachnid silk proteins in creating 3D printing bioinks.

Gelatin Based Bioink - Gelatin is obtained from a natural polymer collagen and it is a water-soluble protein. There are numerous properties for example amazing biocompatibilities, ecological and nonimmunogenicities in clinical implementation. This 3D bioprinting advances have gone about as the extracellular lattices (ECMs) in organ and job in different pre-characterized physical, synthetic and natural usefulness acknowledgment[38].

APPLICATION OF 3D PRINTING HYDROGEL

Cartilage - Ligaments as a solid and versatile connective tissue that envelops the articulating exterior **(Figure 4)** of the bone in diathrodial joints and is an auxillary part of the rib, confine, ear, nose and other body segments[39]. Ligament structure incorporates 82% of water, exhausted into the collagen fibrils by the hydrophilic irteoglycan complexes; this assumes a vital job in characterizing the tissue stack bearing purpose[40]. As ligament is packed, the extracellular framework is compacted undertake the effluence of water.

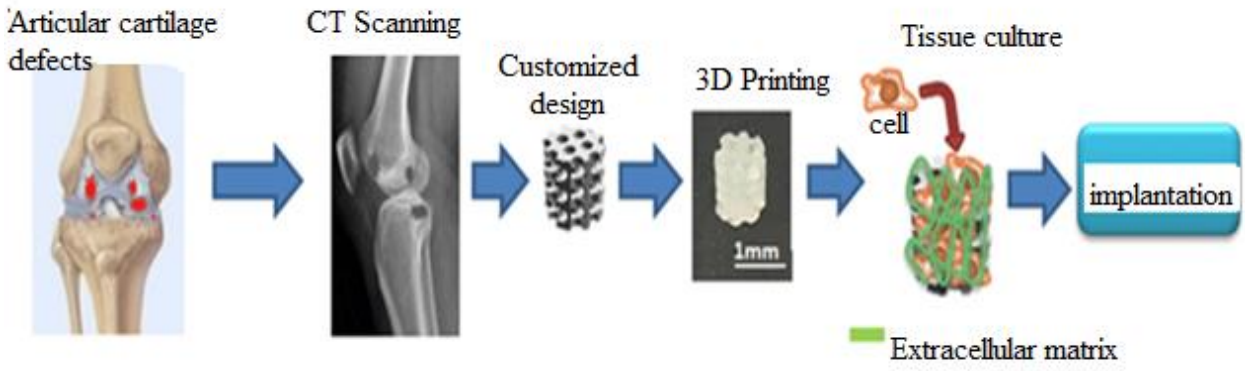

Figure 4: Process of customizing cartilage tissue for cartilage repair

Bone Regeneration - Characteristic biopolymer hydrogels are amazing bioinks for 3D printing, because of their greater biocompatibility bringing about a consistency like the delicate tissue lattice and effortlessly flexible materials qualities for example thickness or gelation kinetics[41].

Osteochondral Tissue Engineering - Hydrogel 3D printing has indicated incredible grant pretend for the creation of redid frameworks in ligament and bone tissue designing. To manufacture 3D builds with composite form by saving cell loaded hydrogels at wanted areas, 3D printing additionally consequence in a favourable method for the creation of inclination frameworks with hydrogels assembles in a various layers[42]. The utilization of 3D printing to the productive recovery of osteochondral tissue to giving a platform that favors joining between the chondral and the rigid stages for osteochondral surrenders repair. 3D printed builds for osteochondral tissue recovery are typically worked in a bilayer design by utilizing diverse bioink details for the subchondral bone and the ligament section.

PATENTS

List of patents on 3D Printing Shown in following Table;

S. No	Publication year	Patent number/ publication number	Title	Inventor	Ref
1.	22.09.2016	WO 2016/149032 Al	Printhead and Method for 3d Printing of Multiple materials	Lewis Jennifer A. *et al.*	43
2	14.12.2016	EP 3 103 638 A1	Water-Washable Resin Formulations for use with 3d Printing frameworks and techniques	Henry L *et al.*	44
3	04.05.2017	WO 2017/074397 A	Forming Three-Dimensional (3d) Printed Electronics	Erickson, Kristopher J *et al.*	45
4	17.03.2016	WO 2016/038356 A	Solid Dosage Form Production	Alhnan AM	46
5	01.10.2015	WO 2015/148521 Al	Composition And Filament For 3d Printer	Paniagua V *et al.*	47
6	13.04.2017	WO 2017/059866 A2	Feedstock for 3d Printing and Uses Thereof	Andersen MO *et al.*	48
7	22.05.2014	WO 2014/078537 Al	Three-Dimensional manufacturing Material Systems for Producing Dental items.	Sun BJ *et al.*	49

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