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Review Article

Printing The Future Of Medicine: Unraveling The Potential Of 3d Printing In Drug Delivery System

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ABSTRACT

The notion of personalized medicine for individual patients has been present for some time but has recently garnered significant attention. There is considerable interest in 3D printing technology due to its broad applications in the pharmaceutical industry and various healthcare sectors. This review provides a detailed yet focused exploration of 3D printing technology, the polymers used, outlining its application in drug delivery and its role in the pharmaceutical product development process. The primary methods of material layering in 3D printers include inkjet, extrusion, or laser-based systems, each discussed in this review along with their applications in drug delivery. Recent research in the field of pharmaceutical 3D printing for drug delivery is also highlighted. Alongside the promising opportunities, the review addresses the technical and regulatory challenges hindering the implementation of this technology in the pharmaceutical and healthcare sectors, proposing potential measures to overcome these obstacles.

INTRODUCTION

3D printing is a layer-by-layer production of 3D objects from digital design. 3D printing can used to print 3D skin, drug and pharmaceutical research, bone and cartilage, replacement tissues , organ, printing for cancer research and lastly models for visualization, education, and communication. It includes a variety of technologies for manufacturing, all based on digitally controlled depositing of materials. They have a significant role in personalized medicine, as this technology has become a promising solution for the production of small quantities of medicines at the appropriate dose and drug release [1].

Recently 3D printing has gained power over pharmaceutical industry as it has been approved by

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FDA in August 2015. Spritam (levetiracetam) is the first 3D printed drug approved by FDA, this has increased intrest among researchers and pharmaceutical companies. The method of Spritam fabrication has given the formulation the ultrafast disintegration property which is difficult to produce using the conventional tablet manufacturing technology. [2]

The 3D printing technique is an add-on manufacturing method that is based on the principle of deposition/solidification of successive layers to produce the digitally designed 3D shape. There are three main systems of 3D printing to produce pharmaceutical formulations and they are laser based writing systems, printing-based inkjet systems, and nozzle based deposition systems [1]. This review will provide a broad in scope on the most recent advances of 3D printing in healthcare, covering the current and future applications in drug delivery and medicine.

Current 3D printing technologies

Various computer software's like auto CAD (computer-aided design), 3D Slash, SketchUp, Fusion 360, and Solid works can be used to design 3D objects.

1.Inkjet based 3D printing system

The concept of inkjet printing for 3D objects originated from traditional desktop inkjet printers, where ink droplets are deposited on paper. This principle is applied to 3D printing with various functional materials serving as inks on edible polymeric substrates. Inkjet printing is divided into CIJ(continuous inkjet printing) and DOD (drop-on-demand) types.

CIJ involves a continuous ink flow through an orifice, controlled by piezoelectric transducers and an electrostatic field.

In DOD printing, droplet formation responds to signals, using less ink than continuous inkjet printing. Two types of print heads, thermal and piezoelectric, are employed, with piezoelectric heads being advantageous for drug delivery due to their room temperature operation and compatibility with various solvents. DOD inkjet printing is further classified into drop-on-liquid and drop-on-solid printing. Drop-on-liquid printing, also known as drop-on-drop deposition, creates layered structures through thermal evaporation, suitable for high drug loading and customized drug delivery. This technique overcomes limitations associated with conventional microstructure preparation methods like spray drying and solvent evaporation.

Drop-on-solid printing, also known as drop-on-powder deposition, entails placing a liquid droplet onto a powder bed, creating a solid structure through powder fusion. The liquid droplets serve as binders to powder particles or can independently form a solid bed by drying with complete solvent evaporation. This deposition method is utilized to design controlled drug delivery systems for a diverse range of pharmaceutical ingredients. The first FDA-approved 3D printed commercial product, "Spritam," utilized the drop-on-solid deposition technique

The active pharmaceutical ingredient (API) can be incorporated into the powder bed or the binder ink, enabling high drug loading. Release rate control polymers like ethyl cellulose and Eudragit can be employed as binder inks for formulating controlled release and targeted drug delivery systems. Achieving color printing involves formulating inks of different colors, enhancing patient compliance, especially for geriatric and pediatric patients. However, drawbacks include product friability and brittleness due to high porosity, stability concerns from organic solvent use, and challenges in ink preparation leading to nozzle blockage.

2.Extrusion based 3D printing system

The extrusion-based 3D printing method is extensively studied for drug delivery purposes. This method is divided into PAM-based (pressure

assisted microsyringe) and FDM-based (fused deposition modeling) printing techniques.

The PAM technique utilizes semisolid materials or pastes, also known as the SSE (semi solid extrusion) technique. The PAM-based 3D printer consists of a syringe extruder system, a compressor, and a computer with 3D design and slicing software. The material is filled into a syringe, mounted in the extruder, and pressured by an air pump to extrude through various-sized nozzles. The horizontal movement of the printer head deposits layers, and the printer stage descends for layer-by-layer construction. CAD and slicer software design slice the 3D object, generating G-code for printing parameters. Optional heating elements in the extruder and printer stage facilitate material heating or melting and solvent evaporation during layer formation. Optimizing PAM printing involves adjusting material consistency for smooth nozzle extrusion, ensuring no gritty particles to prevent nozzle blockage. Organic and inorganic solvents are used in paste preparation, with careful consideration of solvent evaporation rates to avoid blockage or delays in layer drying.

Printer parameters like pressure, speed, nozzle shape, and diameter are influenced by material consistency and viscosity. High viscosity may necessitate high pressure and a large nozzle, while low viscosity may require lower pressure and a smaller nozzle. Material extrusion rate, nozzle size, and applied pressure determine layer size and thickness, essential for designing 3D object shapes. Material viscosity also affects printing speed; highly viscous materials can't be printed quickly, and low viscous materials can't be printed slowly without affecting layer geometry. The PAM-based 3D printing method is compatible with various pharmaceutical-grade excipients, preparing paste at room temperature for heat-sensitive materials, enabling high drug loading. However, drawbacks include the use of organic solvents, potentially impacting API stability and drying speed of printed layers. This technique has lower printing resolution compared to others, influenced by nozzle size and layer formation.

FDM, another form of extrusion-based technique, has undergone extensive research for tailored drug delivery applications. In this method, material is supplied to the printer as a filament and melted, then extruded through a heated nozzle. The molten material solidifies rapidly to create a layer, and as the printer stage descends, it enables the formation of a new layer. By repeating this process, the 3D design is realized. For FDM-based 3D printing, the critical step is preparing the filament. Converting pharmaceutical-grade materials into printable filaments poses a major challenge in employing this technology for pharmaceutical dosage form production. A hot-melt extruder (HME) is employed to melt the plastic polymer and extrude it through a hot orifice, forming filaments. To print a dosage form with FDM, the polymeric mixture is either made into a filament and soaked in an API-containing solution or the API is mixed with the polymer before the HME step. The filament is then mounted on the printing head and extruded through a heated nozzle to build the 3D shape layer by layer. Optimizing the printing temperature is crucial for an efficient and continuous printing process. The formed filament must possess favorable properties to withstand thermal and mechanical stresses during printing, ensuring the creation of desired 3D geometries. Maintaining the nozzle head temperature higher than the filament melting temperature prevents blockage, while the printer stage temperature should be lower to allow resolidification of the printed material. The plasticity, rigidity, and brittleness of the filament directly impact the printing process and the quality of the printed object.

The primary advantage of FDM printers lies in their affordability across various applications. In drug delivery, the benefits include the absence of

organic solvents, eliminating the need for post-processing, offering robust mechanical strength, and achieving better printing resolution, particularly compared to PAM. Generally, FDM printing results in slow drug release formulations due to the inherent properties of the printed materials, making disintegration challenging. However, adjusting the in-fill pattern and percentage allows for customization of drug dose and release. The major limitation of this technique is the high processing temperature during filament formation and extrusion, rendering it unsuitable for thermos-sensitive APIs and low-temperature grade polymers.

3.Laser based 3d printing

The laser-based 3D printing method utilizes high-energy light, such as a UV laser beam, focused on the material surface to create layers and form the 3D shape. There are two types of laser-based 3D printing techniques based on liquid and powder solidification: stereolithography (SLA) and selective laser sintering (SLS)

In SLA, the laser targets the top layer of photosensitive polymeric liquid resins. The high-energy focus solidifies a precise area through the polymerization of the liquid, forming a solid layer. The reservoir containing the liquid resin descends to enable the laser to shape the subsequent layer, building the 3D shape. SLA can be used to fabricate drug-loaded hydrogels and create microstructures for transdermal drug delivery applications.

The key advantage of the SLA technique is the exceptional high resolution of the printed object, reaching up to 0.2 mm. This stands out in comparison to other methods where a resolution between 50−200 mm is achievable. The resolution and layer thickness depend primarily on the intensity and duration of laser beam exposure.

A major drawback hindering the application of this technique for dosage form preparation is the lack of FDA-approved photo-polymeric liquid resins. Additionally, the use of photosensitive resins introduces instability to the printed material, and there's a risk of cytotoxicity due to the leaching of entrapped photoinitiator molecules and monomers in the 3D structure.

SLS, a powder solidification technique, involves sintering a bed of powder material below the polymeric material's melting temperature using a laser beam. This causes the melting and fusing of the polymeric material, forming a layer. The stage is then lowered, and a new powder bed from the feed compartment is exposed to the laser beam, creating a layer-by-layer 3D structure. The layer thickness and resolution depend on the laser focus, intensity, speed of laser travel over the stage, and particle size of the powder mixture.

The advantage of SLS lies in its single-step printing process with high resolution and no need for organic solvents or post-printing drying. However, this technique has limitations, including API degradation due to the laser sintering melting process, a restricted selection of photosensitive polymers, and the inability to print hollow structures. [2]

4. Other forms of Additive Manufacture

4.1 Digital Light Processing (DLP)

Digital Light Processing (DLP) is an alternative 3D printing method resembling SLA but utilizing resin. Instead of a laser-focused UV beam, DLP employs UV light from a projector to cure each layer of the 3D printed object. Madzarevic et al. used DLP 3D printing technology to prepare ibuprofen tablets. Eleven formulations were created, revealing that increased water content enhances printing time. Two artificial neural networks (STATISTICA 7.0 and MATLAB R2014b) were employed to assess how components and printing parameters influence ibuprofen release. This study underscores that a well-suited artificial neural network enables the recognition of input-output relationships in DLP printing of pharmaceuticals.

4.2 Stencil Printing.

Wickstrom et al. introduce a novel printing method not previously utilized in pharmaceutical production. The study aimed to assess the feasibility of generating drug-containing polymer inks for the production of flexible dosage forms, ensuring acceptable content uniformity and mass. Haloperidol (HAL) discs were printed using a prototype stencil printer, employing polyester as the stencil material. The stencil geometry defined the dose, allowing dose adjustments by modifying aperture areas and stencil heights. Therapeutic HAL for 6–17 year-old children, meeting mass and content uniformity requirements, was successfully produced. The HAL dose was achieved using 16% hydroxypropyl methylcellulose (HPMC) and 1% lactic acid. Results indicated that the printed drug was amorphous, maintaining a pH above 4. Disintegration studies demonstrated that orodispersible discs had disintegration times below 30 s. Consequently, the study concluded that the innovative method of batch wise stencil printing could serve as a viable approach for pharmaceutical production.

4.3 Embedded 3D Printing (e-3DP)

Embedded 3D printing represents an innovative approach in Additive Manufacturing (AM), involving the extrusion of a viscoelastic ink into a solidifying reservoir through a deposition nozzle following a predefined path. Rycerz et al. presented one of the pioneering applications of e-3DP in the pharmaceutical domain by creating chewable oral dosage forms with dual drug loading. Paracetamol and ibuprofen were the chosen drugs, suspended in a locust gum solution and embedded within a gelatin-based matrix material. Printing occurred at an elevated temperature of 70 ◦C, followed by solidification at room temperature. The dosage variation in the printed forms was achieved by specific adjustments to the printing patterns. The study examined the rheology, printing speed, and needle size of the embedded phase. This proof-of-concept study highlighted the potential of e-3DP for printing oral dosage forms with diverse materials, enabling personalized dosing and unique geometries for innovative pediatric oral dosage forms.[3]

Polymers Employed in 3D Printing for Crafting Personalized Drug Delivery

Polyvinyl Alcohol (PVA).

PVA is a synthetic thermoplastic polymer characterized by its high solubility in water, low solubility in ethanol, and limited solubility in various organic solvents. It lacks odor and exhibits favorable mechanical properties achieved through either partial or complete hydrolysis of polyvinyl acetate, involving the removal of acetate groups. To prevent nozzle blockage, the formulated ink consisted of aqueous PVA solutions combined with a humectant such as glycerin or monopropylene glycol. Additional inks were prepared by combining high and low molecular weight PVAs. The molecular weight plays a crucial role in inkjet printability due to its impact on ink viscosity. Inks derived from high molecular weight PVA remained colorless and exhibited excellent stability over a six-month period. However, it was observed that all inks displayed a blend of pseudo-plastic and thixotropic behavior at low shear rates and Newtonian behavior at higher shear rates.

Poly lactic acid (PLA).

PLA stands out as a biodegradable polymer that holds the Generally Recognized as Safe (GRAS) designation from the United States Food and Drug Administration (FDA), making it suitable for diverse medical applications. These applications include regenerative medicine, drug delivery systems, wound management, stent applications, fixation devices, and tissue engineering. The primary production methods for this polymer revolve around direct and ring opening polymerization. PLA boasts several advantages,

such as the absence of toxicity or carcinogenic effects on humans, and it doesn't metabolize into harmful degradation products. Commercially available for Stereolithography (SLA) and Fused Deposition Modeling (FDM) printing, PLA's widespread use in various human, animal, and cell-based studies makes it a popular choice for biomedically relevant polymer printing.

Poly caprolactone (PCL).

PCL stands as a semicrystalline hydrophobic polymer, and its crystallinity augments as its molecular weight decreases. PCL is currently under evaluation as a biodegradable material for printing scaffolds. In a study conducted by Beck et al., 3D printed tablets composed of PCL and Eudragit RL100, loaded with polymeric nanocapsules, were generated using an FDM printer. To assess the impact of tablet filling, the FDM printer operated at a 90 mm/s extruding speed with a 100% infill percentage, while Eudragit filaments featured a 50% infill percentage. Results indicated that Eudragit exhibited higher drug content and drug loading compared to PCL, likely attributed to its superior swelling indices. Additionally, Eudragit tablets demonstrated a faster release rate than PCL tablets.

Gelatin Methacryloyl (GelMA).

GelMA is an economical biomaterial derived from denatured collagen, chemically modified by introducing methacrylate groups. This photocrosslinkable material utilizes photopatterning techniques to create specific topographies or engineer 3D architectures in GelMA-based scaffolds. Photopatterning involves using light in various forms to imprint patterns into materials.In a study by Fan et al., a two-step photopatterning process was employed to construct spatially defined 3D microgels based on GelMA, designed to capture single neurons at specific locations within the microconstructs. The engineered GelMA hydrogels supported the spread of single neurons after cultivation, offering a practical tool for studying axonal development.

Nanocellulose.

Nanocelluloses, comprising cellulose nanofibrils (CNF) and cellulose nanocrystals (CNC), are derived from cellulose using physical, chemical, enzymatic, or combined methods. These emerging natural and sustainable nanomaterials possess remarkable properties, including high strength, extensive surface area, and versatile surface chemistry. CNF is recognized as a highly appealing biodegradable reinforcing component in composite materials. Its abundance of hydroxyl groups, flexibility, and tendency for fibril entanglement contribute to the facile formation of hydrogels. The high zero shear viscosity and robust shear thinning of CNF hydrogels make them suitable inks for 3D printing. CNC, known for its high specific strength and sustainability, proves effective in reinforcing matrices with minimal loadings. Its high crystallinity and ability to transfer mechanical stress from a deformed matrix are key attributes. Wang et al. demonstrated that BAPOs (Bis (acyl) phosphane oxides) attached to CNC transformed a conventional mono-functional monomer into a polymeric network without the need for additional cross-linkers. This innovative approach was subsequently employed in 3D printing to create free-standing 3D structured objects. [2,7]

Customized drug formulations created through the utilization of 3D printing technology

3D printing technology allows the creation of personalized dosage forms, considering individualized release rates, profiles, and mechanisms.

Tablets

Immediate release tablet

Obtaining an immediate release tablet involves preparing a portion of the drug along with a hydrophilic polymer, with or without plasticizers. The hydrophilic polymer, can be converted into

filaments for use in an FDM-based 3D printer. Okwuosa et al. created immediate release tablets using theophylline and dipyridamole, employing PVP as the polymer, triethyl citrate (TEC) as the plasticizer, and talc as the filler in the ratios of 10%, 50%, 12.5%, and 27.5% by weight, respectively. The results indicated that, with a 10% loading, over 90% of both drugs dissolved within 30 minutes, demonstrating the efficacy of 3D printing in formulating immediate-release tablets.

Pulsatile Drug Release Tablets

A capsular design known as Chronocaps, based on a pulsatile delivery system, has been created using 3D printing. Capsules with variable thickness can be produced through the injection molding technique, utilizing hydrophilic polymers to achieve a varied time lag. Melochhi et al. investigated the performance of such capsular devices produced through both 3D printing and injection molding techniques. They observed that 3D printed devices exhibited a lag phase before drug release, yet the morphological changes were comparable to those in the system produced through injection molding. Consequently, it was concluded that 3D printing can serve as an alternative to the injection molding technique.

Monolithic Sustained -release Tablets

Sustained-release tablets containing 5-aminosalicylic acid were developed using polyvinyl alcohol (PVA) filaments loaded with the drug. These filaments were created by loading the drug from its ethanolic solution onto commercially available PVA filaments. The drug loading observed in the filament was 0.06% w/w for 5-aminosalicylate and 0.25% w/w for 4-aminosalicylate. Dissolution studies conducted revealed that tablets with 90% infill exhibited 100% release over a 4-hour period. Decreasing the % infill accelerated the drug release. Additionally, it was noted that 50% of 4-aminosalicylate degraded during tablet preparation due to the high extrusion temperature (210 °C) for PVA filament. Consequently, this method may not be suitable for thermolabile drugs. Exploring alternative polymers with lower extrusion temperatures could help mitigate drug degradation caused by high temperatures.

Biphasic Release Tablets

Khaled et al. employed 3D printing to create bi-layered tablets of guaifenesin for comparison with the commercially available bi-layer tablet Mucinex®. The bi-layered tablet consisted of an immediate release and a sustained release layer. The immediate release layer was printed using a paste containing guaifenesin powder, HPMC 2910 as a binder, and microcrystalline cellulose (MCC) and sodium starch glycolate (SSG) as disintegrants. The sustained release layer was printed using a paste containing hydroxypropyl methylcellulose (HPMC 2208) and poly(acrylic acid) (PAA). A 3D printer (Fab@Home) with two printing heads was used for tablet manufacturing. A formulation with 14% w/w of HPMC 2208 as the hydrophilic polymer, along with 2% w/w as a binder, exhibited a faster dissolution profile but was not significantly different from that of Mucinex®. Increasing HPMC 2208 resulted in a decreased dissolution rate due to the formation of a thicker gel barrier on hydration, reducing drug release. However, the prepared printed tablets had half the hardness compared to the marketed product, leading to comparable friability.

Fast Disintegrating Tablets

Yu et al. devised a fast-disintegrating tablet that incorporates loose powder in the core, encased by a printed binder region. The creation of a hollow core region for depositing the loose powder involved printing binder solutions in three phases: printing a solid circular region to form a base, adding several layers of rings to create a cavity, and concluding with a solid circular region to cover. The disintegration time of such tablets was determined to be 21.8 seconds, with a hardness of 54.5 N/cm², and a friability of 0.92%.

Transdermal delivery system

3D printing technology has been utilized to produce patches and microneedles for the TDD system.

Patches

The drug-storing patches, characterized by a multi-layered structure, facilitate a consistent drug flux to the skin, allowing for prolonged and continuous delivery. Two distinct design strategies have been employed for these patches: the 'reservoir patch,' and the 'matrix patch'. The 3D-printed transdermal patch was manufactured with Form2 SLA technology with a Class 1 resin evaluated according to ISO 10993-1.SLA-printed patches present important characteristics, such as low printer costs, printing inks, and fast manufacturing times. [9]

Microneedles

In 2012, Innoture Limited published a patent for a 'Method of producing a microneedle or micro implant'. According to the patent, the apparatus generates arrays of microneedles by depositing the first portion or droplet of a substance onto a first surface and subsequently depositing multiple portions or droplets of the substance onto the initial portion, forming a solid needle. It is evident that Innoture Limited has employed Drop-on-Solid (DoS) and Drop-on-Demand (DoD) strategies to create a base on a suitable substrate and then gradually form the microneedle shaft as one drop is deposited layer by layer and solidified upon others. The company has introduced a microneedle patch called Radara® Targeted Skincare, used for cosmetic purposes to deliver hyaluronic serum for skin rejuvenation.

Photopolymerization-based 3D printing technologies also find numerous applications in TDD. Boehm et al. employed micro-stereolithography (DLP) to craft micromolds, from which they derived microneedles for various studies. Additionally, microneedle arrays can be directly printed through DLP processes and subsequently subjected to coating procedures. Gittard et al. devised microneedles using DLP with an acrylate-based polymer via a Perfactory III SXGA+ system printer, potentially applicable in wound healing. These arrays were then coated with silver and zinc oxide films using pulsed laser deposition, imparting them with antimicrobial properties. Similarly, devices containing microneedles were manufactured in a cross shape to secure the skin during wound healing.[4]

Pulmonary drug delivery

Pulmonary drug delivery employs 3D printing as an emerging technology to create medical devices and models for treating respiratory diseases. These 3D printed prototypes, including lungs, aid medical specialists in comprehending diseased conditions, potentially enabling improved diagnosis and treatment. This approach contributes to the development of personalized inhaled medicines through 3D printing techniques.

Morrison et al. demonstrated the use of 3D printing in pulmonary treatment by creating bioresorbable airway splints for pediatric patients with tracheobronchomalacia. These customized 3D printed splints effectively reduced airway collapse, offering an alternative for treating life-threatening diseases.

The application of 3D printing extends to medical device development for asthma and breathing problems. A "sneezometer," created using 3D printing technology, measures airflow and sneeze speed more precisely and rapidly than conventional spirometers. This device aids in determining airflow rates in patients with asthma, facilitating improved treatment through the creation of advanced design inhalers using 3D printing technology. An ergonomically designed 3D printed asthma inhaler enhances the effectiveness, convenience, and user-friendliness of standard inhalers available on the market.

Intrauterine drug delivery

In the realm of intrauterine drug delivery, 3D printing methods are utilized to create personalized drug delivery devices and implants. This technology enables the fabrication of devices with customized sizes and shapes for both local and systemic administration of active pharmaceutical ingredients (API) through the intrauterine route.

Fu et al. applied FDM-based 3D printing to create customized-shaped vaginal rings loaded with progesterone. Utilizing PLA and polycaprolactone as polymers, the drug-loaded filament was transformed into vaginal rings with various shapes (O, Y, and M). Among these, the O-shaped rings exhibited higher drug release characteristics due to increased surface area and geometrical features, showcasing the potential for developing personalized contraceptive devices through 3D printing.

Similarly, an intrauterine device incorporating progesterone and 5-fluorouracil was fabricated using selective laser sintering. The device, produced at different laser powers (3 W and 5 W), demonstrated synergistic effects in treating endometrial and ovarian cancers. The 3D printed device with 3 W laser power exhibited higher drug release attributed to increased porosity and rapid diffusion. The release kinetics varied, with progesterone showing zero-order release and 5-fluorouracil exhibiting an initial burst followed by sustained release for over 35 days.[2]

Applications of 3D printing

In the field of medicine, 3D printing stands out by providing unique advantages not easily achievable through alternative methods. The additional merits, such as cost-effectiveness, simplified production techniques, and increased collaborative opportunities, further enhance its appeal. The current applications of 3D printing in healthcare can be categorized into five main areas: dentistry, fabrication of tissues and organs, utilization of anatomical 3D models for surgical training, pharmaceutical applications, and the development of patient-specific medical devices like prosthetics and implants. Each of these aspects will be discussed in detail, highlighting the existing uses and the potential for 3D printing to revolutionize manufacturing in the medical domain.

1. In Personalized Drug Dosing

The objective of personalized drug delivery is to offer an effective product with increased suitability and reduced side effects.

- Spritam®

Spritam® stands as the first FDA-approved 3D printed drug, featuring levetiracetam, an antiepileptic drug. Comparative pharmacological activity with conventional tablets was observed, but solubilization time was notably decreased. Marketed by Aprecia Pharmaceuticals, it utilizes the ZipDose technique based on powder bed fusion, employing a layer-by-layer production method. The tablet dissolves rapidly with minimal water, accommodating a dosage capacity of up to 1000mg of API.

- Multiactive Dosage Forms

Khaled et al. devised a tablet containing nifedipine, captopril, and glipizide with distinct controlled release profiles through room temperature extrusion-based 3D printing. The research group also introduced a polypill containing five drugs in a single tablet, offering immediate release of aspirin and hydrochlorothiazide and sustained release of atenolol, pravastatin, and ramipril. This is particularly beneficial for polymedicated elderly patients.

- Cancer Treatment

Conventional chemotherapy faces challenges in reaching therapeutic concentrations at tumor sites due to poor drug solubility. 3D printing addresses this with patches loaded with 5-fluorouracil, poly (lactic-co-glycolic) acid, and PCL, successfully printed and implanted directly into pancreatic cancer. These patches maintained drug release for

four weeks with subsequent biodegradation in the body, demonstrating the potential of 3D printing in cancer treatment.

2.In dentistry

In the realm of dentistry, 3D printing has found widespread use across various applications, from crafting surgical models for orthodontics to manufacturing replacement teeth. An exemplary case of 3D printing's impact on dentistry is exemplified by Invisalign®, transparent orthodontic devices produced through 3D printing that offer an alternative to traditional metal braces for teeth straightening.

A compact intraoral camera could scan misshapen teeth directly. The digitized scan could then be transmitted to a local 3D printer for on-site retainer production, ushering in a "digital dentistry" era. Recognizing the increasing demand for 3D printers tailored to dentistry, manufacturers like Stratasys have introduced specialized semi-solid extrusion printers, such as CrownWorx TM and FrameWorx TM, designed for crafting custom crowns and bridges.

Moreover, researchers have explored the capabilities of light-curing 3D printing technologies to create patient-specific dentures with unique antibacterial properties. Additionally, recent studies have highlighted the potential of 3D bioprinting to generate patient-specific composite tissues for tooth tissue engineering. Specifically, researchers have developed a fibrin-based bio-ink for printing human dental pulp stem cells, achieving over 88% cell viability through micro-pattern printing.[5]

3.Anatomical models for surgery

In the realm of surgery, 3D printing offers diverse applications, notably in the modeling of tumors and other anomalous tissue structures in vitro. Recent advancements in 3D printing have facilitated more detailed reconstructions of tumor features, encompassing cellular proliferation, migration, blood vessel organization, and metastases. The rapid prototyping of such constructs has been extensively explored in cardiovascular, radiology, and surgical oncology fields. It has proven valuable for observing fracture fixations in bones, enhancing surgical staff preparation and planning before procedures. This extends to the realm of transplantation, with a case study exemplifying the use of CT scanning to image a pediatric patient's airway, subsequently generating a 3D printed tracheal splint. This application is beneficial both in modeling and practical utilization, supporting surgical interventions by generating splints, guiding templates for bone resection, and developing suturing devices.

Moreover, 3D printing has ventured into the realm of targeted tumor therapies, exemplified by chemotherapy-impregnated mesh devices. These devices can be tailored to fit a specific tumor that might be surgically challenging. This groundbreaking approach has been prototyped in animal models for pancreatic cancer, featuring a patient-customized 3D printed bio absorbable implant targeting the tumor site and releasing drugs at constant therapeutic levels over a four-week period.

4.Medical devices

Innovatively, 3D printing extends its applications to the creation of drug-containing nose masks, precisely customized for acne treatment. In this research, a 3D scanner captured the patient's nasal features, generating a personalized 3D design to craft a mask tailored to the individual. Building upon this, Muwaffak et al. conducted a similar study, employing 3D printing to produce anatomically tailored wound dressings infused with antimicrobial agents like zinc, silver, and copper, mimicking the shapes of noses and ears. This personalized adaptation of masks not only ensured optimal positioning of the dressings on wounds but also offered advantages over traditional flat dressings.

5.Tissue and organ bioprinting

The growing need for bioprinting tissues and organs is underscored by the rising demand for organ transplants. Recent strides in 3D printing technology have penetrated the domain of regenerative medicine, transforming the printing of biological materials from a fantastical notion into reality. Bioprinters now demonstrate the capability to print not only stem cells but also construct organs and blood vessels meticulously, facilitating the creation of tissues suitable for human use on-demand. This is achieved through automated, laser-calibrated print heads. This transformative capability has the potential not only to eliminate the reliance on cadaveric or live-donor transplants, which often carry the risk of rejection due to tissue or cellular incompatibility with the recipient host, but also to enable elective transplantation in areas such as aging and regenerative medicine. [4,5]

Benefits and Challenges of 3D Printing in Drug Delivery and Medicine

In the pharmaceutical industry, cost-effectiveness emerges through customized drugs, potentially reducing doses and expenses based on individual therapeutic profiling. The rapid on-demand production of objects and devices stands out, showcased in the creation of easily processed 3D printed in vitro models.

Despite the promising applications in medicine, the feasibility of clinical use poses challenges. Regulatory requirements and safety considerations, inherent in the evolving field of 3D printing, need careful navigation. While printing and processing speeds have advanced, they still lag behind optimal levels for scale-up manufacturing. However, recent FDA guidance on additive manufacturing devices signals progress in addressing technical considerations. The potential for 3D printing in personalized medicines, medical devices, and regenerative tissues is a compelling and tangible prospect, with discussions involving the use of stem cells for bioprinting regenerative tissues through 3D printing.[8]

CONCLUSION

In today's modern lifestyle, the reliance on medications has increased, leading to personalized medicine gaining significance. The substantial growth in 3D printed formulations through various techniques offers controlled and accurate dosages. Researchers have utilized 3D printing for multiple dosage forms, drug devices, polypills, and transdermal drug delivery, providing cost-effective and safe solutions. The technology holds promise in producing biological tissue scaffolds and treating chronic diseases. Pharmaceutical companies stand to benefit from decreased market competition and increased revenue. The spatially designed devices and formulations enabled by 3D printing could revolutionize medical and pharmaceutical research, paving the way for dramatic advances in healthcare.

However, the healthcare sector, known for its resistance to change, faces challenges due to regulatory guidelines and clinical standards. These factors present technical and quality control hurdles. While these regulations prioritize patient safety, they often impede the path of technological progress. As the evidence supporting 3D printing accumulates, there is a growing need for action to translate the theoretical advantages of 3D printing into tangible benefits for patients in the real world.

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