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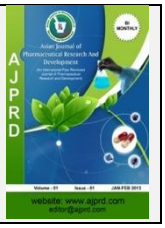

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Review Article

Review on 3-D Printed Drug Delivery Systems

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ABSTRACT

Pharmaceutical of the field of sciences, 3D printed delivery of drug systems (DDS) arerevolutionizing field. With the using of additive printing techniques, these technologies enable the creation of complex, patient-specific drug delivery devices with specialized geometries, dosage schedules, and controlled release profiles. Since 3D printing may be used to customize drug formulations, dosage forms, and the mixing of many medications into a single device, it is a promising technique for improving therapeutic efficacy and decreasing side effects. This article discusses the application of several 3D printing methods include stereolithography (SLA) and fused deposition modelling (FDM) and selective laser sintering (SLS), in the production of implants, drug-loaded matrices, and devices for targeted or sustained drug release. Furthermore, challenges such as material.

Key Words: Printing of 3D; Delivery of Drug Systems; Tablet; Implant; TTS; Microneedle

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INTRODUCTION

Printing of Three-Dimensional Technology in Pharmaceuticals developed the printing of 3D over thirty years ago to produce objects of 3D from a digital design. In a short and economical design cycle, bespoke pharmaceuticals can be prepared thanks to this layer-by-layer process. [1]. Three-dimensional printing allowed a straight forward manufacturing cycle to quickly manufacture a high-quality product.

This manufacture was done on demand, saving time and materials. The "one size fits all" manufacturing model may also be subverted by 3D printers [2]. 3D printing, which is based on computer-aided design (CAD), allowed for the rapid creation and production of a creative and adaptable product [3]. Personalized medication enabled drug delivery methods customized to the patient's requirements. Furthermore, more complex medication release profiles and personalized dosage forms were made feasible by 3D printing. [4]. Alternatively 3D printing technology could be used to quickly create efficient, patient-specific active pharmaceutical ingredient (API) combinations [5]. The printing of 3D technology has made it feasible to create personalized one and more -drug formulations at the point-of-care Recently years have seen a large number of in-depth articles on the many developed pharmacological dosage forms.[6]. According to Moulton et al. this kind of method allowed for the production of regulated and modified release APIs, the delivery of medications that were poorly soluble in water, enhanced drug stability, and reduced the quantity of API required without compromising efficacy. Giving a comprehensive overview of the history of the development of the different drug delivery methods and the present status of the testing was the aim of this work. The most important studies carried out during the previous 20 years were presented in chronological order in the tables, and the drug delivery methods were separated into smaller categories on their nature.[7]

ADVANTAGES

Advantages of 3D-Printed Delivery of drug Systems

Printing of 3D delivery of drug systems offer several advantages over traditional systems, including:

1. Personalized medicine: printing of 3D makes it possible to create drug delivery systems that are specifically matches to the requirements of each patient [8].

2. Accurate control over drug release: 3D printing enables the creation of intricate structures that can precisely and reliably regulate medication release [9].
3. Improved bioavailability: printing of 3D drug delivery devices can be made to make medications more bioavailable, which will increase their effectiveness [10].
4. Decreased side effects: By regulating the release of medications in a targeted and sustained manner, printing of 3D delivery of drug systems may be made to minimize negative effects [11].

DISADVANTAGES

Material Limitations

1. Limited material options: Currently, there are limited material options available for printing of 3D delivery of drug systems, which can limit their functionality and biocompatibility [12].
2. Material degradation: Some materials used in printing of 3D can degrade over time; can be also affect the stability and efficacy of drug delivery system [13].

Manufacturing Challenges

1. Scalability: 3D printing can be a time-consuming process, which can make it challenging to scale up production [14].
2. Reproducibility: Ensuring reproducibility of printing of 3D delivery of drug systems can be challenging due to variations in printing parameters and material properties [15].
3. Quality control: Ensuring the quality of printed 3D delivery of drug systems can be challenging due to the complexity of the printing process [16].

APPLICATIONS

1. Oral solid dose forms: Customized oral solid dosage forms, like pills and capsules, can be made by 3D printing [17].
2. Transdermal patches: Customized transdermal patches for drug delivery through the skin can be made by 3D printing [18].
3. Implants: Custom implants that distribute medications in a targeted and sustained way can be made using 3D printing [19].

Future Perspectives

Drug delivery devices that are 3D printed have the potential to completely transform the pharmaceutical sector. Nonetheless, a number of issues must be resolved, such as repeatability, scalability, and regulatory frameworks [10]. To fully realize the printing of 3D medicine delivery systems and to overcome the obstacles to their development and commercialization, more research is required.

3D-PRINTING DRUG DELIVERY SYSTEM

TABLETS

Solid samples made of PEO and PCL polymers tinted azure and yellowish were produced on a desktop printer to create the first 3D tablet, which was published in 1996. The findings imply that this method may be applied to develop complex drug delivery plans, such as the release of multiple medications or the phased release of a single agent. This study illustrated a number of basic examples of such devices as well as a number of construction techniques that might be applied to regulate the medications' release [20]. Gbureck et al. used a novel technique to distribute the medication device. Researchers used a 3D bioceramic powder printing procedure to manufacture the sample, which was then adsorbed with the used antibiotics for a week in order to create the tablets [21]. Yuet al. used a desktop 3D printer to create a matrix tablet that contained acetaminophen. The binder liquid with release-modulation components was deposited on top of the autonomously distributed powder layers to generate the intermediate drug-containing portions of the tablets (Figure 1) [22]. Two years later, the same researchers made the decision to develop a drug delivery system using the same printing method, polymer, and API. To create a distinctive dissolving process, the layers were arranged vertically this time rather than horizontally.

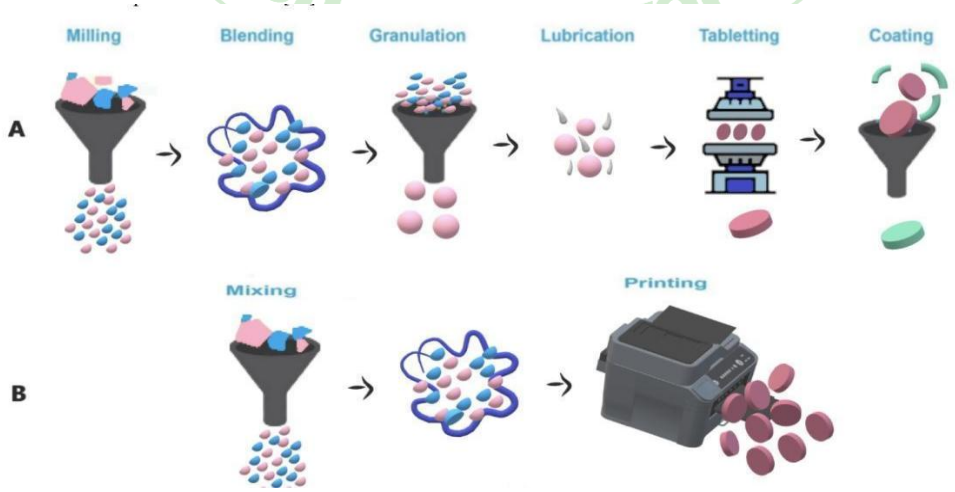


Figure1: Shows a cross-section of the matrix tablets containing acetaminophen according to the authors' figure.

Different compartments are labelled with different colours [23]. Extrusion-based desktop 3D printing was used to Make guaifenesin-containing controlled release bilayer tablets.The purpose of the samples was to show how to produce somewhat complicated formulations that might replicate the release profile of a tablet that is sold commercially [24].

In 2015, Goyanes et al. released four publications discussing the use of PVA filament and FDM 3D printing to manufacture tablets for various uses. In one article, five and four amino acid and salicylic acid were added to commercially manufactured PVA filaments in an ethanolic medication solution. 0.06% and 0.25% weight/weight were the final drug loading values for the APIs, in turn. This fragment was created in a nonidentical style using different fill percentages (Figure two). The dissolving experiments showed that the releasing processes depended on the percentage of infill used as well as the API itself [25].

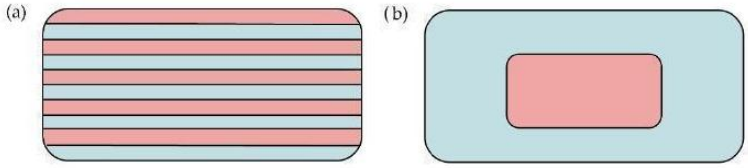


Figure 2: A cross-section of the Goyanes et al. article's produced pharmacological dosage forms. Sectioned Duo Caplet (caplet in caplet) and (a) sectioned multilayer tablet [26] A RegenHU extrusion-based 3D printer created a polypill with unique fillable ink cartridges for the creation of materials comprising semi-solid API.HPMC produced three distinct API-containing inks for this study: glipizide, captopril, and nifedipine. Three different departments housed the three APIs. The drug was released by diffusion from the formulas containing glipizide and nifedipine, and by diffusion from the formulation containing captopril. Osmosis Figure 3 displays the samples' schematic image.[27]

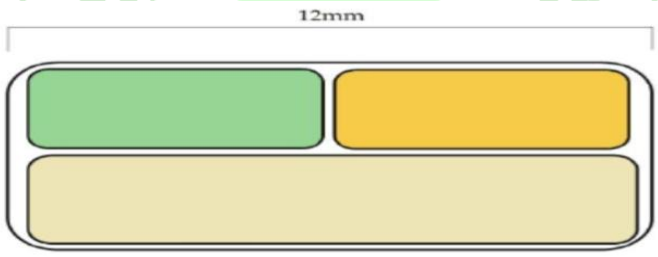


Figure 3: Polypills containing formulations of atenolol, pravastatin, and ramipril in three distinct prolonged release compartments and ASA and HCT in the upper immediate release compartments are shown in cross-section. Because of the original "cake slice" design, the three sections were all the same size but could be seen in this way.[28]

In Okwuosa et al.'s work, hot-melt extrusion was used to create a filament that included 10% API. PVP was utilized as an API for theophylline or dipyridamole, as a polymer, and as an excipient plasticizer. Following construction, these filaments were FDM printed 3D .This study is innovative since it used thermostable filler (talc) for extrusion, allowing for lowertemperature printing at about 110 °C without compromising how reliable the utilized APIs are [29].

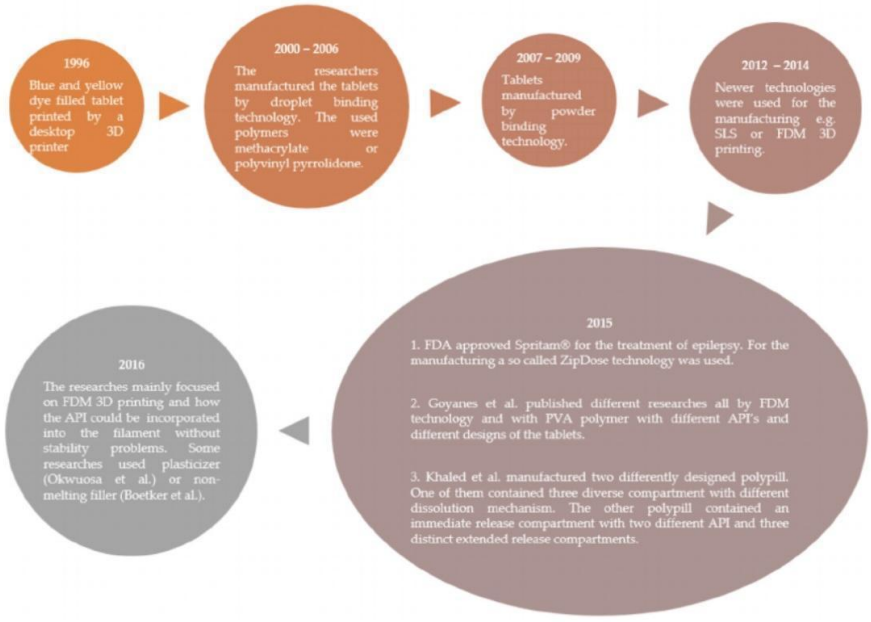


Figure 4: Pharmaceutics 5 of 301, 2022, 14, 1312 Figure 5 shows a flow chart of the key innovations and tablet production techniques from 1996 to 2016 [34–37, 39–42].For inkjet 3D printing, Acosta-Vélez reported creating a biocompatible photocurable pharmaceutical polymer that might be used to create hydrophilic active pharmaceutical components. More precisely, norbornene moieties were used to functionalize hyaluronic acid. This conjugate conducted a polymerization reaction with the help of Eosin Y, a source of visible light, and poly(ethylene) glycol dithiol. Ropinirole HCL was added to the created bioink, which was subsequently poured onto a blank preform tablet using a piezoelectric nozzle before being polymerized. By depositing a The study confirmed the feasibility of inkjet printing for the rapid production of tablets using photocurable bioink designed for hydrophilic APIs.[30]

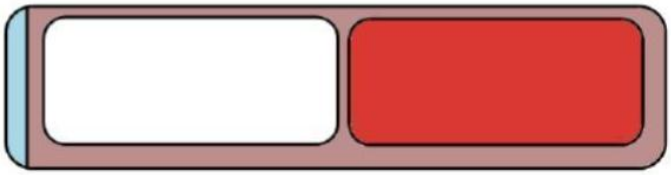


Figure 5: In comparison, Genina et al.'s dual-compartmental dose form is displayed. The brown polymeric cap was 3D printed and sealed with a blue cover after isoniazid (white) and rifampicin (red) were hot-melted extruded. [31]. Hollander et al. investigated the printability of poly (dimethyl siloxane) (PDMS) using a semi-solid extrusion printer and UV-assisted crosslinking technology that uses UV-LED light in order to create drug delivery systems. Prednisolone was used as a model drug in samples with varying pore diameters and API concentrations. Structures with varying release rates could be produced by adjusting the surface area/volume ratio. The study discovered that combining UV-LED crosslinking with printing of 3D was a viable technique and an intriguing substitute for making temperature-sensitive controlled release devices that include prescription drugs. [32] Kollamaram et al. sought to lower the FDM printing temperature in order to create low-melting, thermolabile medications. Ramipril was used as the model low meltingpoint medication (109◦C) in the investigation of two instant release polymers, KollidonVA64 and Kollidon 12PF. The printing temperature was adjusted to 90°C, and the drug-loaded filaments—which included 3w/w% API—were extruded at 70°C. This study demonstrated how this approach might be modified for drugs with lower melting temperatures by selecting and using novel excipients.[33]

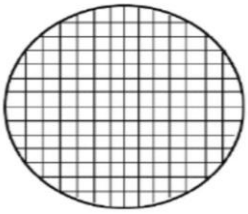


Table1:

Year	Type of printing	Type of polymer	Type of APl
2019	SLS Direct single-screw Powder extrude Specially adapted 3D Printer FDM FDM FDM FDM Bioplotter 3D printer FDM	Kollidon vA64 HPC Pectin HPMC PEO Eudragit RS100 HPMC Polyplasdone PVA	Diclofenac Itraconazole Isoleucine Carvedilol Theophylline Acetaminophen Acyclovir Diclofenac sodium Paracetamol
2020	SLS SLS FDM Semisolid 3D extrusion FDM Direct powder extrusion DLP,SLS,SSE,FDM FDM SLS	Kollidon VA64 Kollidon VA64 HPMC HPMC HPC,EC PEO PVA, PEGDA HPC MCC	Ondansetron Paracetamol Theophylline levetriacetam Theophylline Tramadol Placebo Cinnarizine Clindamycin
2021	Pressure-assisted Microsyringe Direct powder extrusion SLS SSE FDM FDM	PEG400,PEG6000 Kollidon VA64 PVPA Emulsion gel PEG1000 PEGDA	Depagliflozin Praziquantel Ropinirole Fenofibrate Paracetamol, Phenylephrine HCL Warfarin NA+
2022	FDM SLA SLS	Polyvinyl alcohol Polyethylene glycol Polypropylene	Amlodipine Atorvastatin Cl Metformin HCL
2023	FDM SLA SLA	Polyvinylpyrrolidone Polyethylene oxide Polyvinyl alcohol	Acetylsallicyclic acid Lisinopril Omeorazile Magnesium
2024	FDM SLA SLS	Polypropylene Polyethylene glycol Polyvinylpyrrolidone	Albuterol So_4 Clopidogrel so_4 Simvastatin

CAPSULES:

In 2015, Melocchi et al. produced the first capsule ever made using 3D printing. In order to produce HME created hydroxypropyl cellulose filaments, which were then 3D printed, to create swellable abrasive capsules for the pulsatile oral delivery of medications [34]. Basit et al. created four distinct polymer-based capsules in 2018 to study rats' gastrointestinal habits. The polymers chosen for usage with FDM technology of 3Dprinting were acetate succinate, hydroxypropyl cellulose, ethylcellulose, and PVA-PEG. Two types of CT exams were conducted after radioactive tagging with fluorodeoxyglucose (18F-FDG) to track the mobility and disintegration of the produced capsules.Within 60 minutes of oral administration, PVA-PEG copolymer and HPC devices broke down the EC constructs, while HPMCAS-based systems did so 420 minutes later. The rats' gastrointestinal tracts did not break them down. In 2021, studies on customized drug administration advanced as patient safety and treatment effectiveness increased. Given that the currently manufactured gelatin capsules with animal collagen protein release drugs too quickly and have limitations, Gaurkhede et al. have created capsules that will provide customized medical interventions. Using 3D printed capsule shells composed of poly(vinyl) alcohol (PVA) and 5–25% hydroxypropyl methylcellulose (HPMC), the distribution of acetaminophen was examined. Additionally, these shells provide a gelatin capsule substitute that is quicker to decompose and doesn't need the use of animals. It was also observed that a correspondingly higher amount of HPMC was added to the blend, acetaminophen side effects decreased, and release and dissolution were delayed [35] In a study published in 2021, Rossi et al. examined a treatment technique based on time-dependent release while producing and characterizing multi-compartment capsules from FDM-processed PVA. Three different types of reservoirs: one, two, and three were the three varieties of capsules produced. The dissolving times ranged from about 180 to 390 minutes. To find out how high temperatures might impact the polymer, in vitro thermal evaluations were conducted using curcumin as a pharmacological model. The homogeneity of the dimensions was further evaluated using optical microscopy. Findings indicated potential for deploying minimally modified 3D-printed devices as medication delivery devices [36]..Inkjet printing and fused deposition modelling were utilized to build capsules made of various polymer compositions. Three components made up the capsules: two hollow sections with cylindrical closed ends and rounded open ends, and a central section that functioned as a partition and connection. The hollow parts differed in wall thickness and shape. The results showed that within two hours of loading the samples with the model APIs, They might be released in pulses by the apparatus [37].

IMPLANTS:

To treat tuberculosis, multilayered concentric cylindrical implants containing isoniazid and rifampicin were created. From the centre to the outskirts, the multi-layered concentric cylinder was separated into four layers, and the APIs were added to each layer in the precise order isoniazid–rifampicin. The dissolving experiments demonstrated that peak concentrations occurred between 8 and 12 days and that the API liberates in an orderly fashion from the periphery to the core. In this study, a complex, multi-drug, programmed release implant was created using 3D printing. [38]. A study looked at how the polymers utilized affected the drug release profile of a simulated drug called quinine. The samples' dissolving profiles were impacted by the polymers—PCL, PLLA, EC, and Eudragit®RS. Eudragit RS and EC showed the slowest relative drug release, releasing less than 5% of quinine in 78 and 100 days, respectively, whereas PCL showed the fastest, with the dissolved API quantity being over 76% in 51 days. [39] The study's goal was to show how 3D printing technology could be used to create patient-specific fixation devices that enable targeted drug distribution. 3D printing was used to create fixation instruments, such as screws, pins, and bone plates that were filled with methotrexate and gentamicin.

TSS:

Transdermal drug administration, sometimes referred to as transdermal therapeutic systems (TTS), is gaining traction in pharmaceutical drug design and offers a strong substitute for traditional oral and hypodermic insertion drug delivery modalities [40]. Both medicine and cosmetology make extensive use of microneedles (MNs), a unique invasive TDD technique [41]. Although it is unable to provide an additional stimulus for drug transfer in tissue, MNs create a micro-scale canal into the dermis that permits the delivery of hydrophilic and macromolecules to the skin [42]. In 2022, a 3D-printed ultrasonic MN device will be used to get around this restriction. It has been demonstrated that ultrasound delivered by MNs significantly increases modelling efficiency and reduces tissue damage caused by MN insertion by identifying a driving factor behind drug use penetration into the stratum corneum [43]. Because machine learning algorithms can precisely forecast the optimal procedure features, the application of artificial intelligence (AI) in the context of three-dimensional printing (3DP) removes the requirement for specialized knowledge [44]. Using DLP printing technology and artificial intelligence (AI) algorithms, soluble MN patches were successfully produced to distribute lipophilic API, with Ibuprofen (IBU) serving as the prototype medicament. Techniques using artificial intelligence improved printing accuracy and decreased needle mishaps. Following skin permeability tests, mechanical durability testing revealed that IBU MNs successfully created porosity on human cadaver skin, preserving drug permeability for 72 hours [45].BPMNAs, or biodegradable polymeric microneedle arrays,a painless and secure delivery of drug technique, can provide prolonged drug delivery and a high drug charging capacity when used in conjunction with a drug reservoir [46]. FDM used injection volume-filling techniques and polylactic acid (PLA) for 3D printing, while Khosraviboroujeni et al. created a BPMNA employing the medication is estradiolvalerate. for the reservoir. Methylene blue staining, histological examination, and penetration tests revealed that 3D PLA MNAs that were manufactured may pierce the skin without damaging blood vessels or dermal nerves [47].

To promote healing and wound renewal, new coatings with appropriate bactericidal and biocompatible properties have been developed [48]. In addition to its well-known natural antibacterial properties, manuka honey (MH) offers positive physiological effects that may be helpful when it comes to wound care after regeneration [49].The study carried out in

2023 concentrated on creating and testing antibacterial bandages using A three-dimensional representation of manuka gelatin that offered regulated porosity, excellent shape accuracy, and structural stability. The bandages are made from a blend of gelatin and 3D Manuka materials, and the addition of honey made printing easier and improved the product. Additionally, it has been demonstrated that the patches have antimicrobial properties and enhance angiogenesis promotion [50].

MICRONEEDLES

Here's a detailed overview of the evolution of printed 3D delivery of drug systems microneedles:

Early Developments (2000s)

1. Initial Research: Researchers began exploring the microneedles are used for the delivery of the transdermal drug, including the use of printing of 3D technologies [51].
2. Simple Geometries: Early 3D printing technologies limited the creation of simple geometries, such as microneedles with basic shapes [52].
3. Material Restrictions: The creation of intricate microneedle designs was hampered by the small selection of materials that could be 3D printed [53].

Advancements (2010s)

1. Improved Printing Technologies: Advances in 3D printing technologies, such as Stereolithography (SLA) and Fused Deposition Modelling (FDM), enabled the creation of complex microneedle geometries [54].
2. Customized Microneedles: Researchers developed customized microneedles with specific designs and materials, demonstrating the potential for personalized medicine [55].
3. Controlled Release: Researchers investigatedusing printing of 3D to produce microneedles with controlled release profiles, including sustained and pulsatile release

Current State (2020)

1. The application of advanced materials is being investigated by researchers. such as nanoparticles and hydrogels, to enhance drug delivery
2. Precision Medicine: 3D printing enables the creation of personalized microneedles customized to meet the needs of each patient
3. Commercialization: Companies are beginning to commercialize 3D printing technologies for pharmaceutical applications

Future Directions

1. Integration with Other Technologies: 3D printing will be integrated with other technology like the Internet of Things (IoT) and artificial intelligence, to enhance drug delivery
2. Widespread Adoption: 3D printing will become a widely accepted technology for pharmaceutical applications, transforming the industry
3. Personalized Medicine: 3D printing will enable the creation of personalized microneedles tailored to individual patients' needs, revolutionizing the field of personalized medicine

Applications

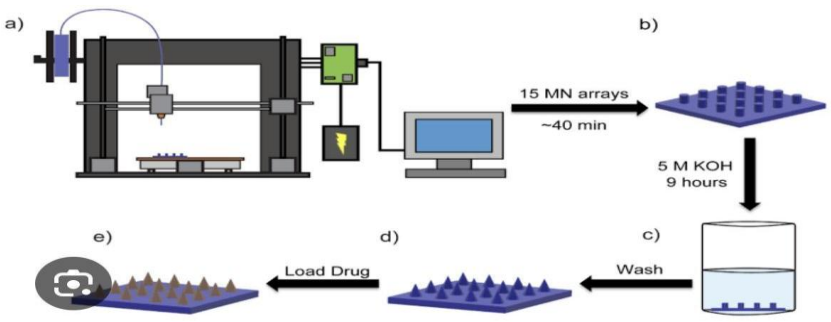
1. Vaccine Delivery: Microneedles can be used for vaccine delivery, improving immunization efficacy
2. Cancer Treatment: Microneedles can be used for targeted delivery of cancer therapeutics
3. Pain Management: Microneedles can be used for delivery of pain relief medications
4. Dermatology: Microneedles can be used for delivery of dermatological treatments

Benefits

1. Improved Efficacy: Microneedles can improve drug efficacy by increasing permeability and reducing degradation
2. Reduced Pain: Microneedles can reduce pain associated with traditional injections
3. Increased Patient Compliance: Microneedles can increase patient adherence because of their user-friendliness

Challenges

1. Scalability: 3D printing technologies need to be scaled up for commercial production [20].
2. Regulatory Frameworks: Regulatory frameworks need to be established to govern the development and commercialization of 3D-printed microneedles
3. Cost: 3D printing technologies need to be cost-effective for widespread adoption.



CONCLUSIONS

To sum up, 3D printing is a cutting-edge and fascinating method in the medication manufacturing sector. That can change things totally the healthcare sector. The automated layer-by-layer technique of On-demand production of complex, personalized items is made feasible by three-dimensional printing.The number of publications has increased annually during the past ten years. The first and only printing of 3D medication was FDA-approved in 2015.confirming the technology's viability for commercial use. Over the past 20 years, numerous research teams have sought to make drugs safer, more efficacious, and more tolerable. And offer tailored treatment to those who need it most by using 3D printing to create various drug dosage forms, such as rectal suppositories, tablets, capsules, and implants.

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