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ADVANCEMENT IN EXCIPIENTS THAT ARE USED IN ADDITIVE MANUFACTURING(3D PRINTING)

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ABSTRACT

The evolution of additive manufacturing (3D printing) has revolutionized various industries, including pharmaceuticals, by enabling the production of complex, customized, and high-precision structures. A critical aspect of this advancement is the development of novel excipients tailored for 3D printing technologies. Excipients, traditionally used as inert substances in drug formulations, have now been optimized to enhance the printability, stability, and functionality of 3D-printed products. This abstract reviews recent progress in excipient innovation, focusing on materials such as polymers, lipids, and biocompatible composites. Innovations include the modification of polymers like polyvinyl alcohol (PVA) and polyethylene glycol (PEG) to improve solubility and mechanical strength, the use of biopolymers like alginate and gelatin for bioprinting, and the integration of smart excipients capable of responding to environmental stimuli. The paper highlights how these advancements have expanded the capabilities of 3D printing, allowing for the creation of dosage forms with controlled release profiles, enhanced bioavailability, and personalized medicine applications. The implications of these developments suggest a transformative impact on the pharmaceutical manufacturing landscape, paving the way for more efficient, precise, and patient-specific therapeutic solutions.

KEYWORDS: Additive Manufacturing, 3D Printing, Excipients, Polymers, Bioprinting, Pharmaceuticals, Customized Dosage Forms, Controlled Release, Personalized Medicine

INTRODUCTION

The pharmaceutical industry is undergoing transformation and an increased focuson exploring new strategies for drug development and delivery. This shift has sparked interest in optimizing therapies and precision of patient care, particularly through scientific and technological innovations that present opportunities for rare disease treatment and personalized medicine. However, traditional development and manufacturing methods currently in use do not offer the efficiency and speed required to keep up with the industry's evolution.

Moreover, the rising competition between brand names and generics is intensifying market pressure, compelling pharmaceutical manufacturers to seek unique approaches that meet patient demands. As a result, it is crucial for the industry to explore alternative methods to boost productivity and enhance the patient experience.

A significant development in this regard occurred in 2015 with the approval of Spritam, an epilepsy drug which became the first prescription drug to be manufactured using 3D printing (3DP). This additive manufacturing technologyis well-suited for the pharmaceutical industry as it enables greater precision in developing and formulating dosage forms. This underscores a series of potential benefits associated with personalized drug development, including the creation of different strengths to reduce pill weight, improving absorption and compliance through faster dissolution, altered release profiles, and the formulation of combination products. By leveraging these benefits, pharmaceutical companies can not only increase effectiveness and compliance but also contribute to brand sustainability by expanding into other dosage forms and gaining market share. The rapid casting capabilities of this revolutionary manufacturing method can overcome numerous barriers and lead to better patient outcomes within the solid dose market.[1],[2],[3]

Benefits of 3D printing technology in pharmacy practice

1. **Personalized precision medicines:** 3D printing enables the manufacture of personalized medicines, allowing for customized doses, appearance, flavor, dosage forms, and release profiles for each patient, reducing the number of doses required.
2. **Medication adaptability:** Customized shapes and designs can aid diverse patient groups, such as those with vision impairment, by facilitating easy identification of medications.
3. **Pediatric patient benefits:** Personalized flavor masking and appearance of medications can improve compliance in pediatric patients, while 3D printing can create abuse-

deterrent and alcohol-resistant opioids.

4. **Flexibility in Manufacturing/Compounding:** 3D printing allows for the adjustment of drug contents and release profiles for individual patients, offering potential benefits in producing controlled-release dietary supplements and polypills.
5. **Enhanced Accuracy and Flexibility:** 3D printing ensures high accuracy, precision, and uniformity in dosage forms. Formulation changes can be controlled by altering the 3D model or ink deposition instructions, offering a cost-effective and accessible production method for medications[4], [5]

The Evolution of the 3D-Printed Drug Delivery Systems

Three-dimensional (3D) printing has been in existence for over 30 years, allowing for the production of 3D objects from digital designs. This layer-by-layer process enables a rapid and cost-effective design cycle for personalized medication. The term "3D printing" serves as an umbrella term encompassing various processes, and many reviews have provided detailed descriptions of the main types. 3D printing revolutionized the manufacturing process by creating high-quality products quickly and efficiently, saving both time and materials.[6],[7],[8] This approach overcame the traditional "one size fits all" manufacturing regime. Leveraging computer-aided design (CAD), 3D printing enabled the rapid creation and production of versatile and innovative products. Personalized medication offers the potential to create tailored drug delivery systems to meet individual patient needs. Additionally, 3D printing allows for the production of unique dosage forms and the achievement of more intricate drug release profiles, addressing factors such as age, weight, organ function, and disease severity. The application of 3D printing technology provides an alternative method for promptly creating effective, customized combinations of active pharmaceutical ingredients (APIs) for individual patients. This technique also facilitates the development of customized single and multi-drug products at the point of care. In recent years, extensive publications have discussed various designs for drug dosage forms. As this process has created opportunities for the controlled and modified release of APIs, facilitated the delivery of poorly water-soluble drugs, increased drug stability, and reduced the amount of API used without compromising efficacy.[9],[10],[11]

In 2018, two separate research groups reviewed recent advancements in pharmaceutical manufacturing, a field that evolves rapidly and sees varying progress from year to year. Individual or multiple drug dosage forms produced by specific 3D printing technologies. For

example, Many Researchers discussed drug delivery systems made using fused deposition modeling (FDM) 3D printing,while some summarized oral dosage forms created by selective laser sintering (SLS) and described orally administered forms built through stereolithography (SLA). Additionally, increasing research is utilizing three-dimensional bioprinting, a novel 3D printing technology for creating living tissue models. Over the past few decades, several research groups have focused on developing drug delivery systems. An innovative biotech start-up, FabRx Ltd., stands out forits endeavors in 3D-printed medication production.[11]

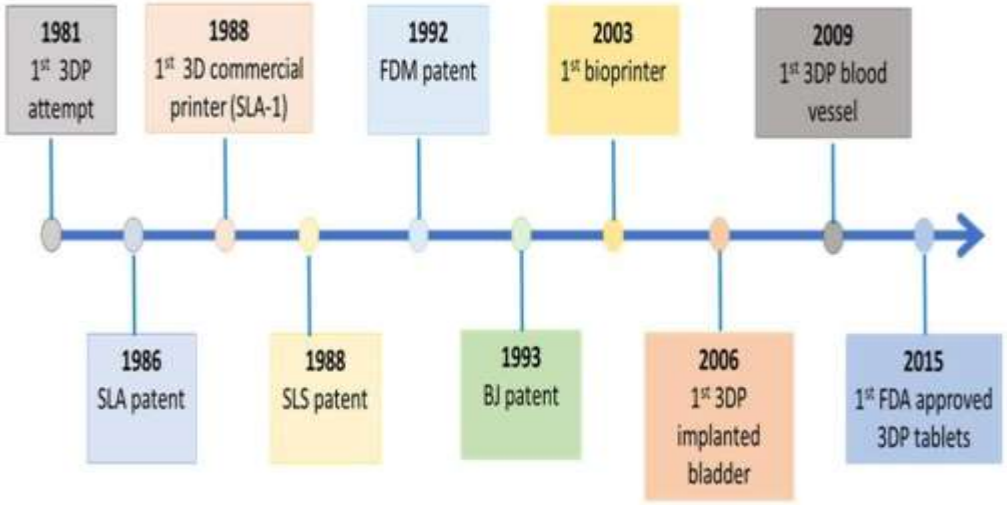

Figure 1: Invention and Development of different 3DP techniques and products.[12]

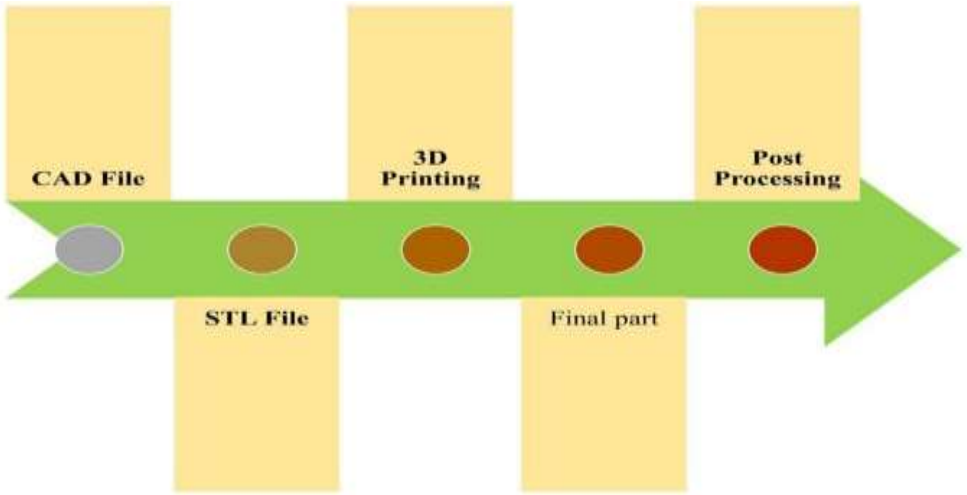

Figure 2: Basic process of 3D printers to create 3D object.[13]

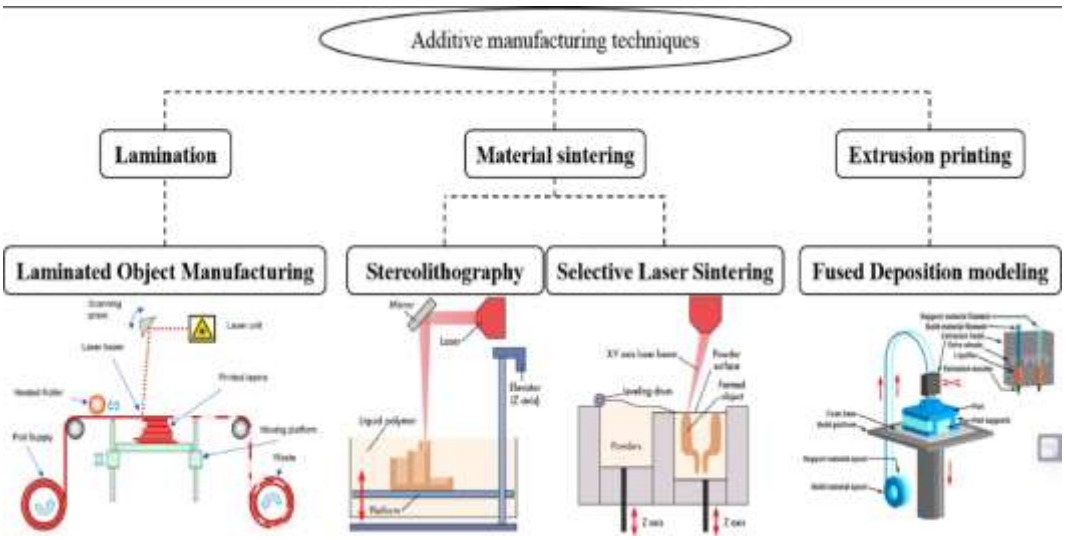

Figure 3: Schematic of AM techniques. [14]

The 3D Printing of Drug Delivery Systems

1. Advancement in tablets

The first reported instance of a 3D-printed tablet dates back to 1996, when researchers created solid samples with a desktop printer using PCL and PEO polymers containing blue and yellow dyes. This method allowed for the creation of complex drug delivery systems, such as the release of multiple drugs or multiphasic release of a single drug. Various construction methods were exploredto control the release of drugs. During the early stages of 3D printing research, droplet binding was used for sample production, where the binder was not necessarily a polymer but another auxiliary material, such as Eudragit® or mannitol. Researchers found that this method could manufacture adequate oral dosage forms with erosion or diffusion release mechanisms. The type of chosen additive manufacturing process, printing parameters, immediate- or delayed- release tablet manufacturing, and the kinetic profile of the tablets were importantconsiderations during this research period.[15], [16]

Some researchers utilized a unique technology for manufacturing drug delivery systems. They initially created the sample using a 3D bioceramic powder printing process and subsequently adsorbed antibiotics over a week to fabricate the tablets. Some produced a matrix tablet containing acetaminophen using a desktop 3D printer. The drug-containing regions of the tablets were formed by depositing a binder liquid containing release-modulation materials onto the automatically spread powder layers. Subsequently, the same investigators employed a similar technique but designed the layers vertically instead of horizontally to create a different dissolution mechanism.

The utilization of extrusion-based desktop 3D printing for the construction of guaifenesin-containing controlled release bilayer tablets was explored, aiming to replicate the release profile of an existing commercially available tablet. Notably, the FDA granted approval for Spritam® in 2015, marking the first and only approval of a 3D-printed drug delivery system for the treatment of epileptic seizures, employing Zip Dose Technology.[17],[18],[19],[20]

2. Zip dose technology

The pharmaceutical industry is exploring novel approaches to drug developmentand delivery to cater to personalized medicine and rare diseases. 3D printing (3DP) has emerged as a promising method due to its precision in creating personalized dosage forms. The approval of Spritam, the first drug manufactured using 3DP, presented significant opportunities to tailor medications to individual needs, such as reducing pill burden and improving absorption. ZipDose, a 3DP technology, addresses limitations of traditional fast-melt platforms, offering a solution for patients with dysphagia by allowing high-dose medications to rapidlydisintegrate with a sip of liquid. Additionally, it overcomes taste-masking challenges, particularly in epilepsy medication like levetiracetam.

The collaboration with the FDA to bring the new levetiracetam dosage form to market demonstrates the potential value of ZipDose compared to traditional orally disintegrating tablet technology. ZipDose's 3DP process uses powder- liquid ink jet printing to create a porous tablet structure, enabling rapid liquid ingress without the use of conventional molding and compression techniques. This innovation has the potential to significantly enhance medication adherence and patient outcomes, especially for individuals with swallowing difficulties andthose requiring high drug loads for conditions like epilepsy time.[17]

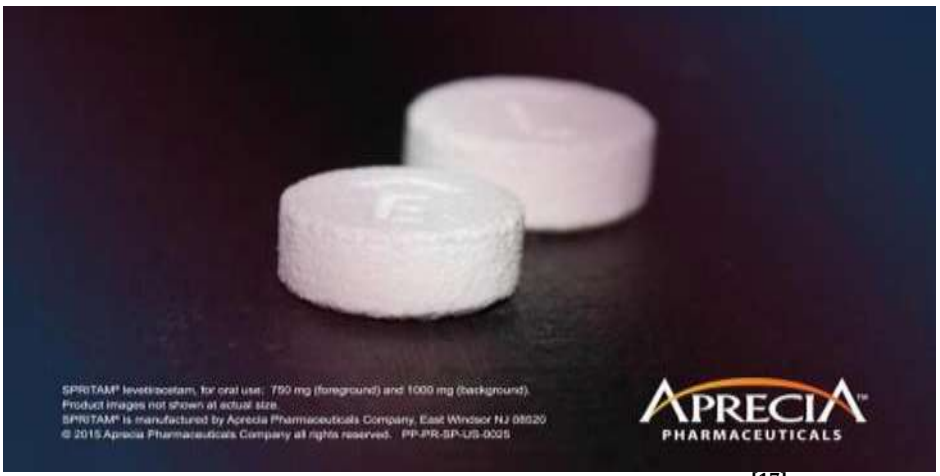

***Figure 4: Aprecia prepared 3D printed tablet.*[17]**

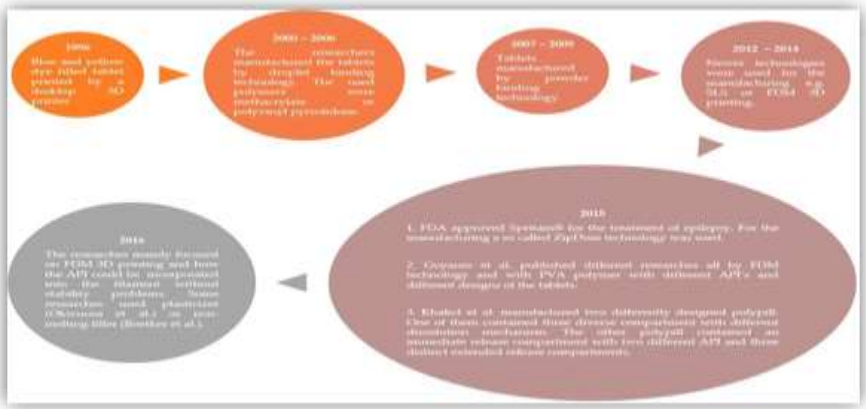

Figure 4: Roadmap from 1996-2016 for development of 3D printing. [15]

Advancement in capsule with use of polymer

A Recent new developed method to 3D print stimuli-responsive core/shell capsules for programmable release of multiplexed gradients within hydrogel matrices. These capsules are composed of an aqueous core, which can be formulated to maintain the activity of payload biomolecules, and a poly (lactic- co-glycolic) acid (PLGA, an FDA approved polymer shell. Importantly, the shell can be loaded with plasmonic gold nanorods (AuNRs), which permits selective rupturing of the capsule when irradiated with a laser wavelength specifically determined by the lengths of the nanorods. This precise control over space, time, and selectivity allows for the ability to pattern 2D and 3D multiplexed arrays of enzyme-loaded capsules along with tunable laser-triggered rupture and release of active enzymes into a hydrogel ambient. The advantages of this 3D printing- based method include (1) highly monodisperse capsules, (2) efficient encapsulation of biomolecular payloads, (3) precise spatial patterning of capsule arrays, (4) "on the fly" programmable reconfiguration of gradients, and (5) versatility for incorporation in hierarchical architectures. Indeed, 3D printing of programmable release capsules may represent a powerful new tool to enable spatiotemporal control over biomolecular gradients.[21]

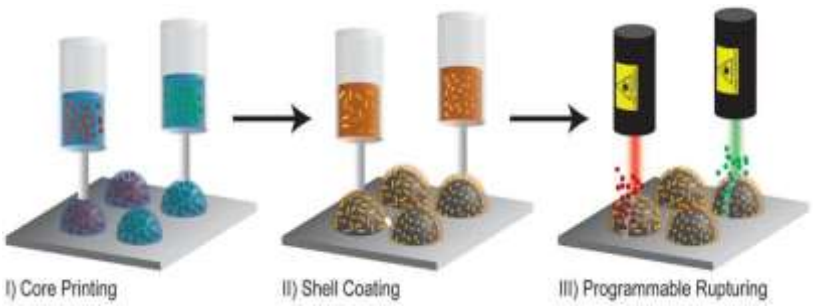

Figure 5: Programmable printing and rupturing of capsules: (I) multiplexed arrays of aqueous cores containing biomolecular payloads are printed directly on a solid substrate;

(II) PLGA solutions containing AuNRs of varying lengths are dispensed directly on the aqueous cores, forming a solid stimuli-responsive shell; (III) the capsules are selectively ruptured via irradiation with a laser wavelength corresponding to the absorption peak of the nanorods.[21]

A key feature in this case that allows the PLGA solution to form uniform shells is that while the polymer solution and aqueous droplet are immiscible, the PVA in the core acts as an emulsifier and allows the polymer solution to fully wet thecore droplet. Additionally, the high volatility and small volume allow the shell torapidly solidify, forming a kinetically stabilized shell structure When the shell was printed from higher concentration PLGA solutions (≥2.5 wt %), the cores were well-encapsulated with minimal passive release. Thus, these high concentration PLGA films hold the highest potential as shell materials for stimuli responsive release studies.[21]

Next advancement is the manufacturing of the 3D-printed capsular devices using hydroxypropyl cellulose-containing filaments produced through hot-melt extrusion, followed by 3D printing. These capsules were designed for oral pulsatile drug release, demonstrating swellable and erodible properties. To construct these capsules, fused deposition modeling and inkjet printing techniques were employed, utilizing various polymer formulations. Each capsulewas comprised of three parts: two hollow sections with a cylindrical closed end and a rounded open end, along with a middle part acting as a joint and partition. The geometry and wall thickness of the hollow parts varied. After being filled with model APIs, the capsules effectively released the model APIs in pulses within a period of 2 hours. This advancement, presented in the pharmaceutical journal Pharmaceutics in 2022, illustrates the potential for 3D printing to revolutionize drug delivery systems by offering customizable and programmable solutions. A research group successfully combined 3D-printed capsules with controlled geometry and the drug release properties of nanocellulose hydrogel to precisely modulate drug release. This innovative method involved filling the capsules with a drug dispersion containing model compounds and anionic cellulose nanofiber hydrogel. The main advantage of this approach is the ability to modulate drug release simply by adjusting the inner geometry of the PLA capsule. Furthermore, since the API did not undergo heating, a wide range of APIs, such as proteins and liposomes, could be utilized. As a limitation, a research group mentioned the API stability and the low amount of pharmaceutical grade polymeric carriers.[18], [19], [20]

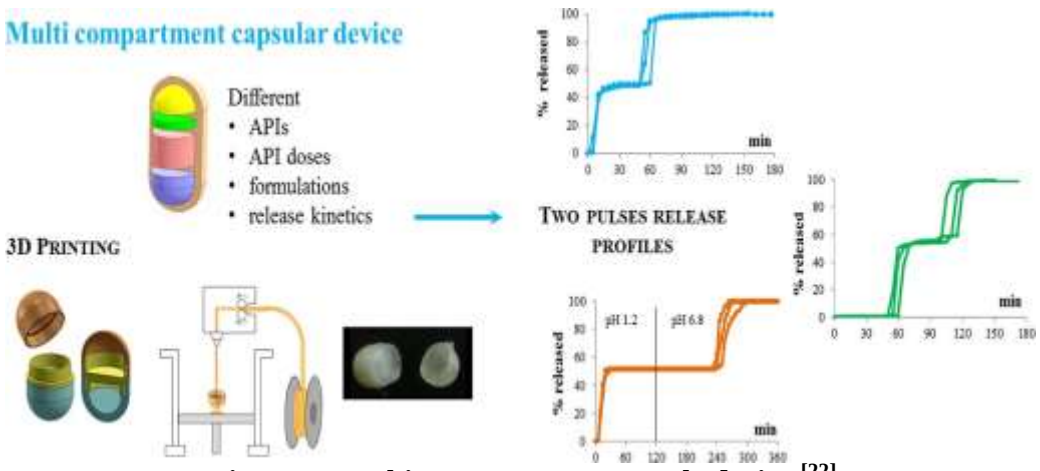

Figure 6: Multi-compartment capsule device. [22]

Yearwise advancement in 3D printed capsule with polymer used

Table 2: Yearwise advancement in 3D printed capsule. [19]-[25]

Year	Type of 3D Printing	Type of Polymer	Type of API
2015	FDM	HPC	no (yellow and blue dye
2016	FDM	EO, PVA, Soluplus,PEG 400 and 8000	Acetaminophen, furosemide
2017	FDM, Inkjet	PLA, PVA, polymer formulations	no (yellow and blue dye)
2018	FDM	PVA-PEG, HPC, EC	
			Fluorodeoxyglucose (18F-FDG)
2020	FDM	PLA	Metoprolol, nadalolol

Advancement in orodispersible films with use of polymers

1. The successful creation of ODFs containing acetaminophen using Klucel™, HPC E5, and Soluplus® as carrier materials is a significant development in pharmaceutical manufacturing. Advanced physicochemical analyses, including Raman mapping, have shown that these ODFs contain drugs in an amorphous state, both in films produced through HME and 3D-printing methods. Interestingly, 3D-printed films displayed a more consistent distribution of amorphous drugs compared to films created using other techniques, suggesting that combining HME and 3DP methods holds promise in improving the physical attributes of formulations and producing ODFs with rapid drug dissolution rates.

2. In addition, an extended drug-release film has been successfully developedby incorporating matrix drug-loaded particles. These microparticles, produced using HME followed by milling, featured diclofenac as the model drug and Eudragit® RS as the matrix former.

The resulting ODF was manufactured by uniformly dispersing the microparticles in the ODF- forming polymer, which consisted of 15% HPMC and 6% glycerol as the plasticizer. Despite challenges related to sedimentation and agglomeration, the incorporation of microparticles up to 500 µm in size led to the creation of ODFs with evenly distributed drugs and satisfactory physical andmechanical properties.[26]

3. These advancements in pharmaceutical formulation and manufacturing hold significant promise for improving drug delivery systems and enhancing the attributes of oral dosage forms. The use of advanced technologies such as HME and 3D printing, as well as innovative approaches for incorporating drug-loaded particles, represents a valuable step forward in the development of ODFs with enhanced drug delivery profiles.3D printing has been applied to create oral films in several innovative ways. For instance, a study utilized thermal inkjet printing to produce the first 3D-printed oral film, highlighting the suitability of the process for manufacturing thin polymer films from aqueous drug solutions,provided that viscosity and API stability are carefully managed.[26]

4. In another example, the use of off-the-shelf consumer thermal inkjetprinters allowed for the production of orodispersible films with flexible doses of the active pharmaceutical ingredient rasagiline mesylate.[28]

5. Additionally, a novel 3D printing approach combined different inkjet printing technologies to dispense a wide range of fluids, demonstrating the potential to tailor formulations to specific patient needs while mitigating the risk of drug degradation and substrate damage.[29]

6. Furthermore, inkjet printing technology was utilized to design orodispersible films containing propranolol hydrochloride, with varying doses and a sweetener coating layer to enhance patient compliance, particularly among pediatric patients.[30]

7. Some Researchers utilize FDM technology to create orodispersible films containing aripiprazole from PVA. The aripiprazole in the sample was successfully rendered amorphous through a two-step hot-melt extrusion process, while the high concentration of PVA polymer aided in maintaining its amorphous form. In another study, benzydamine hydrochloride and HEC were employed to manufacture a printing dispersion. A modified FDM technique was employed, wherein the FDM extruder was substituted with a linear

syringe pump for 3D printing.[31]

Yearwise advancement in orodispersible films

Table 3: Yearwise advancement in orodispersible films in alphabeticalorder.[15]

Year	Type of 3DPrinting	Type of Polymer	Type of API
2011	Thermal inkjetprinting	----	Salbutamolsulphate
2012	Inkjet and flexographic printing	EC	Riboflavin,propranolol
2013	Thermal inkjetprinting	Crospovidone (Kollidon CL-M)	Rasagilinemesylate
2016	Inkjet printing	Sodium picosulphate	Sodium picosulphate
2017	FDM	PVA	Aripiprazole
2018	FDM	PVA, PEO, PEG	Ibuprofen, paracetamol
2019	Semi-solidextrusion	Hydroxypropyl-βcyclodextrin, cellulose	Carbamazepine
2020	Modified FDM	Maltodextrin,HEC	Benzydamine hydrochloride
2021	Multitool 3Dprinter	HPMC	Indomethacin

Advancement in implants with use of polymer

1. As Obesity is high growing disorder especially in young indivisuals. Cappsisin has been utilised as an antiobesity drug which has been formulated as an implant by using polycaprolactone (PCL) as am excipient. Oral films primarily comprise a polymer matrix, which provides film-forming properties with structural integrity. A range of polymers, including but not limited to starch, modified starches, hydroxypropyl methylcellulose (HPMC) (including hypromellose variants E3, E5, and E15), sodium carboxymethyl cellulose (NaCMC), gelatin, hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), pectin, carboxymethyl cellulose (CMC),pullulan, locust bean gum, xanthan gum, guar gum, carrageenan, povidone polymers(polyvinylpyrrolidone, PVP), polyvinyl alcohol (PVA), polyethylene oxide (PEO), maltodextrins (MDXs), and various others have been studied as potential base materials for producing ODFs. The film-forming polymer, which serves as the major component of the ODF, constitutes up to 65% of the weight based on the total dry weight of the film. In some cases, a combination of polymers is employed to enhance the hydrophilicity, flexibility, mouthfeel attributes, and solubility of ODFs. These polymers should be non-toxic, non- irritating, free from leachable impurities, possess excellent wetting and spreadability, have a good shelf life, and should not promote secondary infections in the oral mucosa or dental regions. Additionally, the ODFs should have adequate peel, shear, and tensile strength. Among

oral strips. Table 3 shows a comprehensive overview of the frequently used film- forming polymers, plasticizers, APIs, preparation methods, and the key highlights related to ODFs. The acceptability of ODFs depends upon film composition and the formation process, which affects disintegration, taste, texture, and mouthfeel attributes. The films produced should be transparent and free of air bubbles for aesthetic appeal and stability considerations.[32]

2. Levofloxacin-laden PLA implants were developed using inkjet printing, featuring a unique release profile. During a 100-day monitoring period, twodistinct release pulses were observed, with the first occurring from the 5th to the 25th day and the second from the 50th to the 80th day, separated by a 25-day lag time. A steady state release at approximately 5 µg/mL was maintained.[33]

3. For tuberculosis treatment, multi-layered concentric cylindrical implants containing rifampicin and isoniazid were produced via 3D printing. The individual drug layers were arranged in a specific sequence from the center to the periphery, eliciting controlled drug release with peak concentrations observed between 8 and 12 days.[34] Dexamethasone-containing tailored drug delivery platforms were fabricated using extrusion printing, yieldingcontinuous API release for over 4 months. These implants were designed in two distinct structures, providing versatile options for sustained drug delivery.[33]

4. Intrauterine devices and subcutaneous rods containing indomethacin as a model API were manufactured from ethylene vinyl acetate copolymer using FDM printing, allowing for drug dissolution over 30 days, resultingin long-acting implantable systems.[35] Lastly, for the treatment of osteomyelitis, levofloxacin and tobramycin-containing implants were created utilizing powder-based inkjet printing, resulting in a sustained and programmed drug delivery system with a multi-layered concentric cylinderconstruction.[28]

3D printing technologies offer significant promise for the production of advanced drug implants and personalized macro-porosity implants with tailored drug release characteristics. Commercially available implants often lack treatment personalization and fail to account for individual anatomical variations, age, gender, and disease conditions. A study has highlighted that 3D-printed implants can exhibit complex drug release patterns, setting them apart from conventionally manufactured drug implants. Through 3D printing, it becomes feasible to produce smaller, lessinvasive, and more site-specific implants, offering substantial advantages

over traditional implant manufacturing methods.[33] While the clinical evidence supporting the routine use of 3D-printed customized implants is currently limited, there is a growing expectation that patient-specific implants will attract more attention and become increasingly popular for prophylaxis and treatment of conditions like complicated bone infections and bone tuberculosis. This trend is anticipated to gain traction in the near future as digital and manufacturing technology continues to advance.[36]

CONCLUSION

The utilization of 3D printing for drug manufacturing is an innovative and transformative technology with the potential to revolutionize the healthcare sector. This method involves an automated layer-by-layer process, enabling the production of intricate and personalized products on-demand. Over the past decade, there has been a substantial increase in publications related to 3D printing in drug manufacturing. The FDA's approval of the first and only 3D-printed drug in 2015 highlighted the commercial viability of this technology. Numerous research groups have focused on utilizing 3D printing to create various drug dosage forms, including tablets, capsules, implants, and rectal suppositories. These endeavors aim to enhance the safety, effectiveness, and tolerability of medications, ultimately enabling personalized therapy for patients with specific needs. In summary, 3D printing in drug manufacturing holds great potential for improving the quality and customization of medical treatments.

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