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Designing drug delivery systems through additive manufacturing

Deepak Yadav(1, 2 *), Kajal Sonkar(2), Jatin Kumar(1), Amit Chaudhary(1)

Corresponding Author: **Deepak Yadav**

Chitkara University School of Pharmacy, Chitkara University-Himachal Pradesh, HIMUDA Education Hub-Atal Shiksha Kunj, District: Solan, Himachal Pradesh, India-174103

Phone: +91-9878310858
E-mail: deepakyadavphd@gmail.com

Affiliation:

[1]Chitkara University School of Pharmacy, Chitkara University-Himachal Pradesh, HIMUDA Education Hub-Atal Shiksha Kunj, District: Solan, Himachal Pradesh, India-174103

[2]Chandigarh College of Pharmacy, Sector 112, Sahibzada Ajit Singh Nagar (Mohali), Punjab, India-1403

Designing drug delivery systems through additive manufacturing

Abstract

Abstract: Additive manufacturing, also called 3D-printing is an emerging technique for the formulation of drug dosage forms in pharmaceutical formulation. This approach is widely used for its benefits over conventional drug formulations. 3D printing is giving an enhancement to the customization of drugs. This technique is able to carry many different drugs in a single dosage form. Customization is also seen in conventional drug dosage forms, but 3D printing gives more precision as per pharmacological response desired for each individual patient. Moreover, the customisation process is simple and instant production is obtained. Physically incompatible drugs can be added to one drug dosage form by providing barriers of polymers, etc. Here, we have discussed some of the tablets, capsules, transdermal patches, suppositories fabricated by 3D printing by researchers. Different types of techniques under 3D printing have also been discussed which are being used in fabricating the above-mentioned drug dosage forms. 3D printing is being considered in the pharmaceutical field due to its advantages of easy operation, the fewest possible steps, lower labour costs and many other factors. This technique shows the benefits of 3D printing of various desirable drugs.

Keywords: 3-D Printing, Polymer, Dosage form, Customization, Capsule, Transdermal patches, suppositories.

Abbreviations: HCl- Hydrochloric acid, FDM- Fused Deposition Modelling, FDA- Food and Drug administration, CADD- Computer aided drug design, API- Active pharmaceutical agent, SLA- Stereolithography, SLS- selective laser sintering, 3D- Three dimensional

1. Introduction

Modern drug design takes into account cutting-edge concepts, enhancement of drug quality and their manufacturing procedure. Additive Manufacturing (also known as 3D printing) has been seen to gain attention for personalised drug dosage forms containing more than one drug which is purely made by observing an individual's body condition. Prototyping of medicine through 3D printing came into existence recently, mainly for the quality of customised drugs and determined shape and size. Compiling more than one drug has made it economic and patient compliant which has overcome the problems seen in conventional drugs. 3D printing was first used in 1990s [1].

3D printing is a novel method for quickly designing and generating dosage forms by layering the drug in the required form or shape. 3D printing is widely being used in different areas because of its creative use. This method is valued for removing the difficulties associated with conventional dosage forms, which lead to a decrease in the quality of the ultimate drug by undergoing various steps throughout the process of manufacturing. Eventually, these factors influence stability of the drug, loading and release profile. This strategy has made it simpler for us to produce drugs with customised and diverse release rates [2]. 3D printing is giving many benefits. This technique is ready for the scale up of production.

Taking the pharmaceutical field into consideration ‘Spritam’ was the first 3D printed drug dosage form. This was designed to be a dispersible tablet. Additive manufacturing is eliminating the various steps in the manufacture of conventional dosage forms, lowering the labour cost, and other storage expenses of raw drugs or the final product as the final product is fabricated instantly and handed over to the consumer [3]. 3D printing has the major significance in the customisation of drugs. Customisation of the drug can be done following traditional methods, but it is eventually dependent on some factors such as the lifestyle of the patient, response by the body, medical history of the patient, interaction of the drug with other drugs or with food. These factors are expressed differently in each individual. This in turn makes customisation difficult. 3D printing is taking over the traditional customisation of the drug formulation. This technique considers every specification and fabrication of the desired dosage form. 3D printing is able to produce a small amount of drug with accuracy. This process is the least time consuming, including fewer steps in procedure, and replicable results [4]. Customisation is seen to be a prominent factor in drug delivery. According to research, chronic diseases account for a significant portion of the annual mortality rate. One of the reasons for this is that patients are not sticking to the dosage regimen properly, which in turn worsens the condition of the patient. Patients could not follow the regimen due to a large number of doses (more than one tablet or capsules) based on the condition, and frequent dosing. This is seen to be inconvenient to the patient and sometimes the dose is missed, leading to an incomplete course of treatment. 3D printing is able to print combining the required different drugs into one pill. This customisation resolves the problem of taking frequent doses and completion of the course is observed [5].

The FDA's clearance has had a significant influence on scientific study into 3DP technologies, which has resulted in a rapid rise in studies and research with notable outcomes, particularly for the production of tablets[6-13], capsules [14, 15], orodispersible films[16-21], and medical devices [22-25]. These accomplishments have shown the true potential of 3DP as a powerful instrument to realise individualised treatment solutions that are tailored to the demands of individual patients[26]. Focusing on the procedure, 3D printing utilises different techniques. The basic procedure is to first incorporate the drug with the polymer which is the support of printing. Afterwards, designing of the dosage form is done through computer software and a file is exported to the printing cell[27]. The same geometry of the drug is formulated. With this method it is easy to prototype a drug and dosage form which is hardened by air drying for a period of time. Any leftover material found not prototyped can be used again in the starting material [28]. Figure 1 shows some of the benefits of 3-D printing in the pharmaceutical industry.

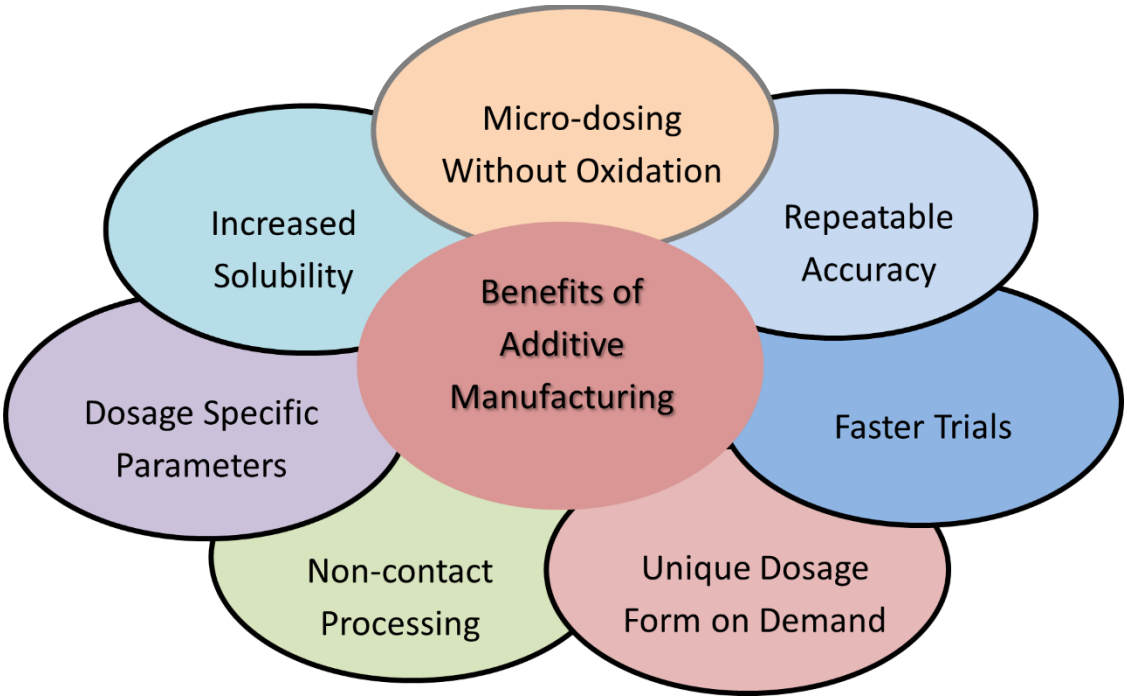

Figure 1. Benefits of additive manufacturing in pharmaceutical dosage form development.

2. History of additive manufacturing

The concept of 3D printing was developed in the 20th century by Pierre A.L. Ciraud who investigated the process of pouring a powdery substance followed by solidifying the entire coating by exposing it to an extremely energised beam. Other research in the field established a way to solidify a powdery layer by a laser method known as the selective laser sintering (SLS) method. Stereolithography (SLA) was first marketed as a technique by Chuck Hull. A patent was registered on fused deposition modelling in the 1980s [1] and also gave the concept of computer designing which works with the 3D printer prior to the prototyping of the final product. The computer helps in the designing of the formulation by selecting the suitable size, shape and release pattern of the drug dosage form. Subsequently, other techniques such as SLS were invented, which works as the powder bed is made of the drug, and exposure to the beam of light causes the hardening of the product. Stereolithography was invented in the same year as the SLS technique[29]. The difference between this method and the SLS method is the beam's intensity. After different techniques where invented, modification to the SLA technique was introduced by adding an inkjet printer to the SLA technique. Here, bio-inks are used (made of polymers) making the loose powder hold together. The development of one of the most used type of techniques was introduced in the 1980s, known as Fused Deposition Modelling (FDM) [30].

3. Techniques used for additive manufacturing of pharmaceutical dosage forms

There are various techniques of 3D printing. The different techniques have shown a variety of advantages to various types of formulations. These different techniques are favourable to a range of drugs which in total can produce the formulation of any sensitive drug. Sensitivity could be towards heat, shape, etc. 3D printed formulations have shown better effects than conventional drug dosage forms[27]. As a result, this approach has given improved dissolution and release patterns. Some of the 3D printing techniques are considered below.

3.1. Stereolithography (SLA)

This is a technique used previously for the fabrication of dosage forms. This is an extensively used technique. The technique is used for regenerative medicine. The mechanism of hardening the product is photo polymerization. SLA uses liquid resin in the production of materials. The technique uses a laser for printing; the intensity of the laser depends on the amount of light, initiators and the polymer used. Due to the use of laser, this technique gives accurate results. The regulated heat of stereolithography facilitates the formulation of drugs that are heat sensitive. It also allows for multitasking because the API can be combined with the polymer prior to production, allowing the API to fit into the polymer's cage [31]. In reported data, the SLA technique has shown its use in making a dosage form containing more than five drugs. Treatment of the disease was seen to be faster compared to the conventional drug delivery system[32, 33].

3.2. Fused Deposition Modelling (FDM)

FDM is a technique in 3D printing which has produced an FDA approved drug. Production of this has prompted interest in 3D printing. Observing the working of FDM, first a basic idea is taken and plotted on a computer via software CADD. The strand of polymer is put into the opening of the FDM machine and ejects out from the nozzle of the machine in a melted state as heating is being given to the polymer in the printer[34]. The strands coming out of the nozzle are then drawn in different axes as the head of the machine is movable, which draws the x and y axes of the plane, and the surface or the slab is being taken down automatically to draw the z axis. This way the 3D projection is made. Further coating layers are added one after another on the surface in any required shape or size. Considering the negatives of this method, some drugs exhibit thermal instability, dosage forms may contain insufficient amounts of the medication, and the finished formulation may alter the product's solubility. One of the most attractive reasons that FDM is used is its economic production[35, 36].

3.3. Selective Laser Sintering (SLS)

This technique has high cost but is being used widely in different fields. The technique uses a laser which causes the hardening of the material as in the stereolithography technique. The difference is that this technique uses an intense laser, and the material which is to be prototyped is in powdered form. Due to the intense laser a large amount of powder is hardened. For the final product, the laser is focused on the material to produce the required geometry of the end product. This process is continued by exposing a new layer of material on the former layer until the required product is achieved [37]. This technique has the benefit of using no solvents. The technique is less time-consuming as it has fewer steps than others and does not require any efforts before the manufacture or time for drying after the production process.

This technique gives the accurate shape or size of the product as printed by the laser. Focusing on some drawbacks, this technique is not suitable for all types of drugs as it utilises an intense laser and some materials used with the drug can spoil the drug. So, this technique is restricted to biomedical devices or other purposes [38, 39]. The FDA's clearance has had a significant influence on scientific study into 3DP technologies, which has resulted in a rapid rise in studies and research with notable outcomes, particularly for the production of tablets, capsules, orodispersible films, and medical devices. These accomplishments have shown the true potential of 3DP as a powerful instrument to realise individualised treatment solutions that are tailored to the demands of individual patients[40].

Selective laser sintering SLS is a 3DP method using a laser that relies on the application of a high-energy beam to solidify powder [27, 39-41]. Each layer is created by sintering using a laser beam that can heat materials just below the melting point after a layer of free powder is placed with a roller [27]. Ceramic powders, thermoplastic powders, and metal powders may all be processed using this method. In the latter scenario, a laser beam is required to melt the powdery bed; this particular method is known as selective laser melting (SLM) [40].

3.4. Inkjet Printing

This technique includes liquid ink. In this technique ink is stored in the container which is then brought into the printer outlet. Pressure is created to move the ink out. Pressure is created via two mechanisms: by heating or by an electric pulse. This leads to the formation of a void in the container and ink moves out of the outlet. Formulation is printed in designed geometry and the printer head is moved in the designated pattern. This way the drug dosage form is obtained [42]. This technique has overcome formulation of drugs which face problems with solubility [43]. The formulation of an API-containing ink with the necessary qualities represents the primary problem, which is frequently overlooked. The ink must be sprayed into precise-sized droplets with a predetermined speed and motion during a generic inkjet-based 3DP process. To enable consistent jetting and homogenous droplet production with few satellites, operational parameters must be carefully defined[44, 45]. The solid state of the loaded API after deposition and, consequently, its bioavailability, might be affected by the solvent used in the ink formulation as well as the rate at which the ink dries [46]. The use of SLS in the manufacture of drug-loaded devices has been severely constrained by drug degradation, of which there are a few examples [31, 47-52]. SLS has however been utilised to treat soft materials in both the bioprinting for tissue engineering and in the food industry [53]. A schematic view of 3D printing methods applied for drug formulation is presented in Fig. 2.

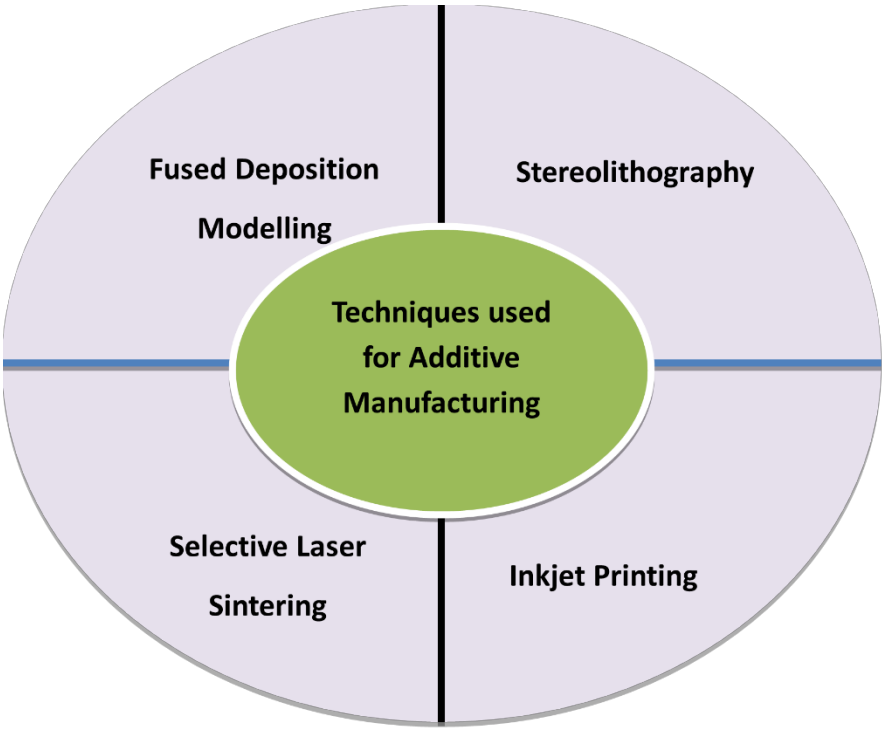

Figure 2. Schematic view of different additive manufacturing techniques used for pharmaceutical dosage form development.

4. The 3D printing methods

The ability to quickly manufacture custom objects that may be used in individualised therapy or medication gives 3D printing techniques increased significance in the pharmaceutical and medical fields. The integration of 3D printing into pharmaceutical technology is focused on creating patient-centered dose forms that are built on structural design. It is still an emerging area of study with the potential to develop freeform, targeted-release medication delivery systems. Oral dosage forms are the focus of much study since they are still the most common and preferred method of delivery[4]. Additionally, several studies are concentrating on topical dose formulations. Examples of 3D-printed items show how various 3D printing processes are being used to create drugs with increasing interest (Table 1).

Table 1. Examples of dosage forms prepared with different additive manufacturing techniques.

Manufacturing method	Dosage form	API	Excipients	Reference
Powder solidification				
Drop on solid	Implant	Isoniazid	Powder: PLLA Ink: Acetone, Ethanol, Water	[54]

	Tablets	Captopril	**Powders:** Maltitol, Maltodextrin, **Ink:** Water Polyvinylpyrrolidone	[55]
Selective laser sintering	Orodispersible tablets	Paracetamol	Hydroxypropyl methylcellulose vinylpyrrolidone-vinyl acetate copolymer	[47]
Liquid solidification				
Stereolithography	Tablets	Paracetamol 4-Aminosalicylic acid	Poly (ethylene glycol) diacrylate, Poly (ethylene glycol) 300, diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide	[56]
	Microneedles	Insulin	Dental SG resin Xylitol, Mannitol, Trehalose	[57]
Drop on drop	Tablets	Ropinirole HCl	Irgacure 2959 Poly (ethylene glycol) diacrylate	[58]
	Tablets	Fenofibrate	White beeswax	[59]
Extrusion based methods				
Fused deposition modelling	Orodispersible films	Aripiprazole	Polyvinyl alcohol	[18]
	Tablets	Theophylline	Hydroxypropyl cellulose, Triacetin, Sodium starch glycolate, Croscarmellose sodium, Crospovidone,	[60]
Extrusion at room temperature	Floating tablets	Dipyridamole	Hydroxypropyl methyl cellulose, Microcrystalline cellulose, Lactose, Polyvinyl pyrrolidone	[61]
	Multi-compartment tablet	Nifedypine, Captopril, Glipizide	Polyethylene glycol 6000, Microcrystalline cellulose, Hydroxypropyl methylcelloluse, D-Mannitol, Lactose, Sodium starch glycolate,	[62]

			Croscarmellose sodium, Sodium chloride, Tromethamine	

5. Drug dosage forms prepared by additive manufacturing

5.1. Tablets prepared by additive manufacturing.

Ukti Bhatt et al, worked on the formulation of immediate release olanzapine tablets. In the conventional technique the process contains more steps in the procedure and many post formulation problems are being seen which affect dissolution and release of the drug. This technique is used as this technique is simple and cheap with a single step, less time consuming, and no solvent is needed in it[63]. The process was done by hot melt extrusion followed by FDM printer aiding software for the designing of drug. Here, first extrusions were made by the hot melt extrusion process by first blending together the polymer, API, and the agents to soften the polymer for improved formulation. The polymer used was hydrophilic which showed better disintegration of the drug. Further, the required environment was maintained with reference to heat, rotation etc. The extrusions made underwent the FDM procedure for printing out in the required geometry. Extrusions were made and compared with the polymer alone and polymer with the drug, comparing the diameter of the strand at each standard length for uniformity. Further characterization was done of the extrusion made, uniformity of the strand which as a result was under the required size and was able to be put into the head of printer and come out of the nozzle[64]. The dissolution study performed has shown good absorption of the drug due to the polymer used, which was hydrophilic and helped the drug release immediately. The total drug was dissolved in a very short time, showing the drug has improved solubility. The entrapment efficiency seen was very good, which results in a uniformly mixed drug. The weight variation recorded was very small and acceptable. To determine the robustness, friability testing was carried out, and the result obtained was in the acceptable range. This demonstrates that the tablets had optimum capability to withstand post formulation conditions as well as during release of the drug [65].

Similarly, Shaban A. Khaled et al. have worked on the formation of tablets containing more than one drug substance. This has given the convenience of taking a single dose which eventually releases different medicament doses at a given time. The dose release will be dependent on the design of formulation (immediate or sustained release). There is still one marketed formulation containing different drugs in it by Cadila Pharmaceuticals with the brand name “Polycap”. Production of this kind of formulation has made it easier to take multiple drugs with advantages including fewer doses to be taken, fewer chances of missing the drugs, or any hindrance in the dose regimen[66]. Here the authors have taken different drugs (such as atenolol used for cardiac disease, pravastatin used to lower lipid level, hydrochlorothiazide used as diuretic, ramipril acting as an ACE inhibitor, aspirin NSAID used as blood thinner) and made different sections for the different drugs. Here, five sections were made, one compartment for each drug. Three sections were separated from two via a lipophilic layer. In the given three sections drugs, like ramipril, pravastatin and atenolol were added and the other two had hydrocholorthiazide[67]. For the preparation of the tablet first designing was done via software to

decide the dimensions of the tablet and other parameters. The design objective was to get the best release profile of each drug. After designing, the tablet was set to be formulated by first taking all the drugs and triturating them for the required time. Then, a lipophilic layer was prepared by using cellulose acetate and other excipients. Temperature was maintained to avoid the obstruction of nozzle while making strands. Sustained release can be obtained by taking all the chemicals required and triturating them. The drugs to be added to the sustained release formulation were triturated and mixed separately, likewise drugs to be added to the two sections for immediate release were triturated for the required time [68]. Then, prototyping of the tablet was done in a set pattern and the powdered ingredients made above were fed in different nozzles. First the sustained release layer was printed on to the surface and the drugs to be released in sustained manner were added to it. Subsequently, the immediate release layer was added on to the sustained release layer. Drying was done for the required time and the prepared dosage form was evaluated further.

Alvaro Goyanes et al. worked on a drug which is acid labile. Here, an API with high solubility and penetrability was selected. Coating was needed to protect the API as done in formulation of conventional drug delivery systems[69]. This process takes more time, and several steps were involved. 3D printing gives an advantage by overcoming these problems. The procedure in the literature describes how first filaments are to be formed which will further be inserted into the printer head for fabrication of tablets. The API was premixed with the polymer and other excipients to protect the drug from acidic conditions. The mix was triturated to decrease the particle size of the powder. The mixed material was ready to be extruded. After the extrusion filaments were produced, the filaments are taken for the fabrication of tablets via 3D printing process using a 3D printer. Prior to this, design was selected including shape, size and other parameters[70]. Design was made and converted to a file. This file was then sent to the printer to programme the production. The desired shape and dimension of tablet was formed layer by layer via an FDM printer. Evaluation was done after the fabrication of tablet. The excipient added had worked efficiently in maintaining the stability of formulation. The drug release pattern was seen to be within the standard range [71].

The author worked on combining two different drugs acting on the same disease. Drugs are selected which act on high blood sugar level. Traditionally these two drugs are recommended to be taken in combination, or a regimen is made where drugs are consumed at different times. Site of action of both drugs are different where one drug is absorbed in the stomach and another in the intestine. By observing the activity of drug, 3D printing was performed. Both the drugs were designed and added to a single pill. Two layers were formed to differentiate both drugs. Polymers added to both the drug layers are selected based on the type of release required. One of the drugs was mixed with polymer giving the release in the stomach, whereas another polymer gave extended release (release in the intestine) [72]. Preparation was done as first filaments for each drug was made. Each API was mixed with the required excipient and triturated in a mortar pestle for size reduction. To one of the drugs, calcium stearate was added with polymer as the drug alone shows the property of die swell and irregular shape of the filament is seen. Once the filament was produced, it was taken for printing. Prior to printing, design was carried out using the computer software and exported to the printer. Filaments were added to the printer head and the formulation was fabricated layer by layer in selected dimensions. Evaluation of formed drug delivery was performed [73].

5.2. Capsules fabricated by additive manufacturing.

In another study the author worked on a pH sensitive capsule containing tablets in it. It has been seen that there are some drugs that degrade when exposed to an acidic medium. So the author and co-workers made a formulation which releases the drug in basic conditions and can be site specific, and additionally, controlled release is also maintained for prolonged effect[74]. Here, the API was taken and mixed with the polymer which helps to protect the acid labile drug from the acidic pH, as the polymer used in the formulation responds to the pH and helps the drug to release in alkaline pH. This formulation has helped the drug to overcome degradation in an acidic medium and increased the therapeutic efficacy of the drug. The polymer shows a mucoadhesive property which eventually allows the drug to be released at the required site (intestine)[75]. After this the mixture was poured drop wise to the solution of calcium chloride giving the suitable environment. The product formed was filtered and dried for few days. Drug loading was calculated by the process of UV analysis. Hot Melt Extrusion is used to form the strand to be used in the printing of the capsule by FDM. A polymer and permeation enhancer is used to produce the filament used in prototyping the vacant cylindrical shell[76]. After the extrusion process, the geometry of the capsule is designed via software. Size and shape of the capsule is decided by considering the drug to be encapsulated in it. Two layers were designed by FDM with different polymers as upper and lower layer and the beads were encapsulated. While incorporating the beads into the capsule the process was paused for a while and beads were added in the required quantity and the drug evenly spread and the part left was printed. Multiple shells were designed to strengthen the impenetrable property[77]. As the shell is light in weight, a coating was given to increase the weight, leading to a high-density capsule. The capsule formed was given an enteric coating to protect the release of the drug in the stomach region by decreasing the penetration of fluid [78].

Similarly, Georgios et al. worked on biomacromolecules as model drugs to show the effect of pH sensitive capsules. Biomacromolecules are substances which cannot tolerate acidic conditions and degrade in the stomach region thus impacting the therapeutic efficacy of the drug. Here, the macromolecule is incorporated in a hydrogel which shows a control release pattern. This is further incorporated in a polymeric capsule which responds to the pH and helps the drug to release at the targeted site[79]. The procedure of production follows as the formulation is produced by FDM. Filaments were produced by an extrusion process containing polymer. All the parameters were taken into consideration such as diameter, nozzle size, temperature etc. for better quality of the product. The geometry of the capsule was designed through CAD software by keeping the size of the capsule the same as that of standard size. Vacant cylindrical capsules were printed by FDM as designed in software. After some structure of the capsule was printed, the printing process was stopped, and the API containing self-assembling hydrogel and buffer was loaded by hand. Printing was resumed to print the remaining part of the capsule. In vitro testing and other characteristics were determined [80].

A.Maroni et al. worked in manufacturing 3D printed capsules having two layers. This customisation was done for patient compliance. Here in each layer two drugs having different therapeutic actions can be adjusted, or the same drug with different concentrations can be added to it. The capsule was designed in such a way that release of drug from the capsule would vary between immediate or extended release. The mechanism of release can be by external stimuli or any other type of suitable mechanism[81, 82]. In preparation, firstly all the polymers to be used are activated by providing the suitable environment. Further formation of filaments was done by a suitable process. Then, dimensions of the capsule were

selected by computer software and the file was converted and exported to the printer through which the formulation was to be printed[83]. Formulation was performed by two techniques. Prototyping was performed with fused deposition modelling and one another technique and a comparison was made. Further characterisation of the formed capsule was performed. It was seen that FDM had given better results than another technique. The FDM technique was seen to produce the formulation in less time. But this technique is only applicable if the production is not extensive [83, 84].

Beatriz C Pereia et al. worked on prototyping a capsule which can encapsulate four types of drugs having different release kinetics. Considering partition for adding four drugs in the same capsule, two different types of partitioning were designed. One was designed having a coaxial arrangement, where four circular compartments were made of different diameters sharing the same axis. Another had four straight side by side compartments. Both dosage forms had extended release in the outer compartments[85]. The inner compartments exhibited fast release. The drug formulation having straight four compartments had an aperture in the inner walls of the compartments which caused immediate release and outer compartments exhibited delayed release, adding the suitable drug in each compartment. In coaxial designed drug formulation, walls thickness was modified for different types of release. Here, in preparation, first the body of the capsule having four compartments was formed by 3D printing, then the API was filled in each compartment. In the last step the remaining part of the capsule was fabricated. Evaluation of the formulation was performed, and all the parameters were within the acceptable range. The drug delivery system was formulated successfully [86].

5.3. Transdermal drug delivery systems by additive manufacturing

3D printing is working well in topical drug delivery. For the preparation of the patch bio-inks are used for prototyping. Bio-inks are the substance used as a material to give structure to the formulation in the printing process which includes polymers. These are inks or gel extruded layer by layer in a specific shape or size on to the surface of printer. Bio-inks are found to be compatible to the body, biodegrade, and feasible to print[87, 88]. The rheology property is to be considered as the flow of the ink is crucial as the ink should have to regain its solid state after extruding through pressure for better strength of the formulation. Some polymers used in the formulation do not have viscoelastic properties causing less intact formulation. To overcome this problem thickeners are added[89]. Lyophilisation is taken into consideration after the final product is obtained, as this technique keeps the formulation intact. The author and co-workers of this study have worked on formulating local delivery patches containing the drug. Here, in preparation, the polymer was taken and mixed with thickeners in different ratios keeping the concentration of polymer fixed. The above solution was mixed for several minutes until mixed properly and a suitable environment and temperature was maintained and kept cool to overcome loss of solvent[90]. The API was loaded to the polymer and thickener mixture. The formed bio-inks were then taken for 3D printing via an extrusion process. The desired structure was formed by extruding the bio-ink layer by layer. The production was held at the required temperature and consideration given to all necessary conditions. The product obtained was lyophilised to yield a better permeability effect, as this process makes the formulation porous. The formed patches underwent different tests, highlighting major characteristics such as mechanical strength. It was seen that adding thickeners at different concentrations showed varied results. Other parameters, like flow of the bio-ink, settlement of the layers etc. were seen to be within range, but the hardness of the formed patches was seen on increased concentration of the thickeners[91].

3D printing has performed successfully in printing a patch which has the ability to stick to the site of action by itself. A 3D printed patch gives an advantage over conventional patches as conventional patches need to be stitched or pasted at the end. Moreover, the release of the drug is seen to be non-specific to the site of injury. This leads to decreased effect of the drug at the site of the injury. This self-sticking patch is mainly designed for nerve injury. The peripheral nerve system is taken into the consideration. It has been seen that injury caused in peripheral nerves causes loss of movement or any sensation. Recovery of the injured part happens by itself, but this is still dependent on the site and extent of the injury. Focusing on the treatment reveals that giving conditions like cellular components helps in boosting the regenerative factors and cures the nerve damage[92]. Taking into consideration all the parameters, patches were designed and prototyped. Here a bandage which shows a self-sticking property was prepared by the mechanism of click chemistry. Macromolecules were used showing self-sticking properties undergoing reaction. Two layers of colloidal gel were formed, with one layer consisting of the gel alone and the other layer containing drug nanoparticles in it. The formed layers were designed in such a way that the formulation gives the better dissolution of the drug. Analysis was performed of the obtained formulation. Release of the drug was seen active on the site of injury and showed potential therapeutic effect. The monomers and other additives were found to be compatible to the body. The patch was seen to dissolve within a few days and did not show any toxicity in the body. The formulation showed successful release of drug and improved recovery of injury of the nerves [93, 94].

5.4 Rectal drug delivery systems by additive manufacturing

Suppositories are used as local as well as systemic drug delivery systems. These are easy to use and are mainly prescribed for paediatric use. Suppositories are made using an oil base. The mechanism is based on the principle that the material used melts at body temperature and releases the API showing its effect[95]. The easy melt of suppositories has the drawback that the drug is sometimes not delivered at the site required. This leads to the loss of concentration at the site of action and reduced therapeutic effect. The other problem with instant melt and release of the drug is lack of prolonged action of the drug. To overcome this problem a suitable polymer with natural elasticity keeps the drug delivery system intact, and prolonged action can be obtained. This will also help the drug to reach the site of action by its thickening its nature and sticking to it[96]. The author worked on the problem and the result showed that suppositories could be made via 3D printing but could not be printed directly. So, moulds are made by 3D printing which help in giving structure to the suppositories as direct printing is difficult [97, 98].

In another study, the author and co-workers showed the successful production of suppositories. The drug chosen for the study is used for treating ulcerative colitis. The drug used shows the potential effect at the target site, but at the same time it is seen to affect the kidneys and some other organs. Taking the disease and site of action into consideration, the API was designed to be incorporated into suppositories and fabricated by the 3D printing process, including the technique of extrusion[99]. The research claims that 3D printing gives the opportunity to produce a personalised suppository by keeping the desired shape and size of the formulation, and the dose could also be decreased if the concentration of the drug is as that of the concentration of blood[100].

In the procedure, the API was dissolved with the oil base in a suitable glassware apparatus. The dissolved material was heated with continuous stirring. The drug and excipient were mixed thoroughly and then added to the syringe for extrusion. The material was kept at rest to cool down to the required

temperature and to attain the required viscosity. The syringe was then connected to the printer head. The desired shape and size of suppositories were fabricated taking all relevant parameters into consideration. The formulation was then kept at the lowest temperature for intact formulation. Before and after the preparation of suppositories, preliminary and post formulation analyses were performed respectively. Release of drug, drug loading, accuracy of the formulation and other formulation and pre-formulation tests were carried out. This experiment was mainly performed to overcome the issue of formulation of suppositories without the requirement for a cast. It was seen that the formulation was produced successfully without a cast via 3D printing. The successful result was achieved because the melting point of the forming suppository material was taken into consideration[101]. The viscosity of the material was kept optimum so it would not be melted, as melted or low viscosity material causes asymmetrical formulation. It should also not be too thick as this will eventually stick the material in the orifice of the printer. The fabrication of suppositories was performed in two positions: upright and parallel to the surface of the build plate. Focusing on the time taken in fabrication of formulation of each position, the upright position was seen to take more time in fabrication compared to the parallel position. However, accuracy of shape and size was seen in the upright position of the suppository as the parallel position produced a curve which is not feasible to be printed. Drug loading was found to be high. Summing up, 3D printing was successful in printing the suppositories and the excipients used with the API have worked well in all aspects [102, 103].

6. Additive manufacturing combined with Nanotechnology

3D printing has been seen to merge with nanotechnology. FDM has played a vital role in the formulation. FDM contains no solvent and is easy to operate. Merging nanotechnology with 3D printing has attracted attention and advancement in formulation as nanoscale drugs show enhanced dissolution, better stability and increased therapeutic effect, and 3D printing is giving the opportunity of a personalized drug. In the preparation procedure followed here nano-capsules were made by adding a suitable polymer to the organic phase and the drug to be loaded was added to the aqueous solution containing a surfactant with constant stirring. A filament was produced by the extrusion process for the tablet making. Four types of filaments were prepared containing two different polymers and by altering the ratio of other ingredients. This was further used in the formation of the tablet by the FDM technique. Designing was done via software deciding the shape, size and other characteristics of the tablet. The tablets printed were then soaked in polymeric nano-capsule [101, 104].

7. Conclusion

3D printing has revolutionized drug delivery systems and medical equipment, enhancing patient-centered medicine-based therapy. This technology allows for the preparation of various dosage forms with high accuracy of API-excipient ratios. It also allows for the construction of multipurpose medication delivery systems and multidrug devices, reducing time and costs of medical treatment, improving surgery success rates, and developing new surgical procedures. 3D printing of highly mimetic models of organs can shorten operation time and reduce intra-operative complications. The use of live cells in biomaterials for implantation, drug screening, disease modelling, and cancer research can also be achieved through 3D printing. Despite its advantages, additive manufacturing faces challenges in sterilization, device performance, control of design parameters, and biocompatibility. 3D printing is particularly beneficial in customizing drugs, ensuring patient compliance and successful course

completion. Overall, 3D printing is an approach for designing and producing drugs with multiple drugs, treating various diseases simultaneously.

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