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Review Article

The Application of Polymers in Fabricating 3D Printing Tablets by Fused Deposition Modeling (FDM) and The Impact on Drug Release Profile

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Abstract

A new chapter in the pharmaceutical industry has been created by 3D printing, particularly in the manufacturing of solid preparations. This technology can support the modification of medicine in terms of drug dosage. Furthermore, it is achieved by adjusting the volume of tablets while being designed using the software to meet the required dose. The research aims to review several polymers used in 3D printing through the fused deposition modeling (FDM) technique. The polymers in filament fabrication for 3D printed tablets should be thermoplastic and have the appropriate mechanical properties for further processing steps. This review focuses on studying the characteristics of polymers such as polylactic acid, polyvinyl alcohol, polycaprolactone, polyvinyl pyrrolidone, polyethylene oxide, ethylene vinyl acetate, ethyl cellulose, hydroxypropyl methyl cellulose, and hydroxypropyl cellulose. Additionally, it discusses the effect of these polymers on the drug release profile from the 3D printed tablets.

Introduction

Tablet manufacturing in the pharmaceutical industry is currently produced on a mass scale with an equivalent dose for each unit in one batch. During this era, personalized medicine concepts emerged to accommodate each patient's unique requirements. Dosage, shape, and size of the tablets are several factors changed during the process according to the needs of patients for personalized medicine.[1,2] Personalization will remain difficult as long as the standard approach is employed, as it is inefficient and deemed impractical.[2,3] Therefore, an alternative method such as 3D printing technology is needed to solve the problems of dosage personalization.[4]

3D printing technology is currently being developed in manufacturing solid pharmaceutical preparations. This technology can meet the standard requirements and produce tablets with complex structures, suitable to make any kind of products such as direct consumption and personal products.[3,5] Its use for personalized medicine is relatively inexpensive compared to conventional technology.[6] Spritam®, the first 3D printed tablet that approved by US FDA in August 2015, has been a significant milestone in utilizing 3D printing technology in the pharmaceutical industry.[4]

Fused deposition modeling is one of the techniques in making 3D printing tablets, which is most widely used in producing pharmaceutical preparations since it is simpler and more viable than other techniques.[4] In fused deposition modeling, a filament is needed to print the desired object. The filament is composed of polymeric materials and active pharmaceutical ingredients which are mixed and extruded at a specific temperature. Filament for 3D printing should have thermoplastic characteristics because there is a heating step to soften the filament mass.[7,8] Good mechanical properties should also be possessed by the filaments, such as flexibility, brittleness, and stiffness since these factors can determine whether the filament is suitable for further 3D printing process.[9]

The FDM 3D printing process is started by producing drug-containing filaments generally carried out through the extrusion of polymers with the active ingredient. Furthermore, the shape and size of the pharmaceutical preparation are designed using software according to the required dose then translated to the 3D printer. The filaments produced in the previous step are then used as the material for the 3D printing then printed according to the designed size and shape. After the printing process, all the 3D printed products are gathered and evaluated, as depicted in Figure 1.

Several polymers have been investigated as suitable materials for making the filaments. However, the use of these polymers is limited by several properties that should be possessed. Thermoplastic properties are the main criteria for the polymers to be selected, while others such as non-toxic, biocompatible, and biodegradable characteristics are more beneficial.[10] Filament can be made of natural, semi-synthetic, or even synthetic polymer as the forming materials. Therefore, it is necessary to have a

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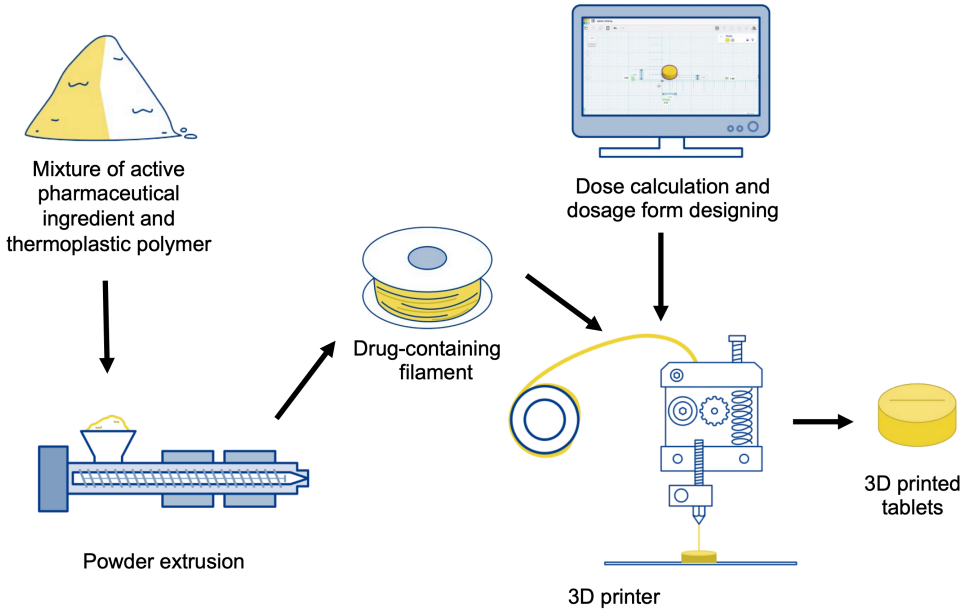

Figure 1. The schematic illustration of 3D printing tablet by fused deposition modeling.

systematic study of polymers with specific characteristics used as the base material for making filaments. This review will discuss the characteristics of filaments formed from polymers like polylactic acid (PLA), polyvinyl alcohol (PVA), polycaprolactone (PCL), polyvinyl pyrrolidone (PVP), polyethylene oxide (PEO), ethylene-vinyl acetate (EVA), ethyl cellulose (EC), hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose (HPC). Additionally, the drug release characteristics of 3D printing technology tablets were analysed.

Characteristics of Polymers for Filament on FDM 3D Printing

The selection of polymers to be used as filament-forming material for FDM 3D printing is based on the specific characteristics possessed by the polymer. The following are the unique characteristics that polymers should have.

Thermoplastic

The polymers used as the filament constituent should have thermoplastic properties.[7] The properties are usually performed by material with straight-chain molecules that will soften when heated and back to be hard when the temperature is down in a specific temperature range.[8] During the extrusion process, heating is carried out to form filaments.[4] Therefore, the thermoplastic polymer was selected because it has a specific melting point, making it easy to melt when extruded but has a relatively high viscosity to make filaments.[5] The thermoplastic polymers used to make filaments can be amorphous or semi-crystalline polymers.

Good rheological and mechanical properties

The melt filament's viscosity plays a significant role in the FDM 3D printing process. The viscosity can affect the extrusion process of filament in the 3D printing process, and the smoothness of filament's surface as well. Generally, the rough filament surface may clog the extruder's nozzle and 3D printer. At the same time, too low viscosity of filament mass may cause the material to drool out from the extruder and 3D printer nozzle spontaneously.[11] The polymers used as the filament-forming material should provide a good mechanical property such as flexibility, brittleness, and stiffness. The filament should be flexible and hard enough to bend and prevent squeezing by the wheels.[9]

Suitable for pharmaceutical use

The filament-forming polymer should be appropriate for pharmaceutical applications, particularly for internal use. Biodegradable and non-toxic polymers are preferred since they can be degraded in the human body with physiological fluids in the presence or absence of enzymes.[10] The use of polymers in drug delivery systems to 3D printed tablets is directed to biodegradable polymers, since the degradation products are non-toxic, and they can be eliminated from the body through natural metabolic pathways with minimal side effects.[5,10,12] Moreover, biodegradable polymers may not produce toxic degradation products to prevent constant inflammatory effects in the human body. Therefore, biodegradable polymers are safe and suitable for pharmaceutical use.[13]

Filament Criteria for Fused Deposition Modeling

The filament should also meet several criteria in fused deposition modeling to print the object. These criteria include uniformity of diameter, also filament's stiffness and brittleness.[1] The final diameter should be suitable with the nozzle size around 1.75 to 3.00 mm. Filament that does not satisfy these specifications will not be able to fit the print head and should be made with the nozzle to obtain an appropriate diameter. The non-uniformity may results

in a change in the object's shape and failure of printing.[1]

The filament should have certain hardness and elasticity value to be compatible with 3D printer tools. It requires some mechanical properties such as flexibility, brittleness, and stiffness. These are critical properties that need to be measured to determine the suitability of the FDM 3D printing process. The values of breaking distance, stress, and force were used to determine filament flexibility, brittleness, and stiffness.[11] Ideally, filament for FDM 3D printers should have a fracture pressure value of >2,941 g/mm^2 and a distance of >1 mm.[9] As a result, the printing process may be hindered due to the filament breaking when it is inserted into the gear on the 3D printer. However, printing will be problematic if the filaments are extremely elastic since they will flex and come out of the gear.[11] Filament hardness/stiffness can be measured using a texture analyzer with a value that should be around ~1,000 N/m.[1]

The molecular weight of the polymers also influences the hardness of the filament and shows high deformation resulting in more fusion areas. The hardness will be high when the molecular weight of the polymer is significant.[14] Besides, heating in the extrusion process can increase the density of the polymers and the hardness values.[15] Filament fragility is measured using tensile testing with ~0.15-0.2% Pa (10^4).[1] The tensile strength value of the filament is influenced by the extrusion temperature in the formation process. An increase in this temperature can also increase the tensile strength value of the filament.[16]

Use of Polymers in 3D printing Tablets Manufacturing

The following lists are polymers that can manufacture 3D printing tablets using the fused deposition modeling method.

Polylactic acid (PLA)

Polylactic acid (PLA) is a polymer derived from lactic acid, a natural organic acid that is biodegradable and water-insoluble.[17,18] This polymer has several advantages, such as being biocompatible, not expensive, and can be degraded into natural metabolites. Hence, it has become one of the most widely used polymers in clinical applications.[19]

Farto-vaamonde *et al.*[19] reported the manufacture of tablets using PLA filament containing prednisolone and dexamethasone for tissue regeneration. In this study, they used commercial PLA filaments, and both active ingredients were loaded by immersing them in a solution of prednisolone and dexamethasone in the mixture of methanol and ethyl acetate at 50:50 (v/v) for 24 hours at 37°C. The release of the active ingredients was observed very slow, reaching four months for the complete release. Only less than 10% of active ingredients are released in the first two weeks.[19] Therefore, PLA can be used as a matrix for tablets or implants to maintain the drug release over a long period.

However, another study conducted by Boetker *et al.*[18] manufactured 3D printed tablets using PLA. They produced the filaments using PLA and hydroxypropyl methylcellulose (HPMC) polymer combination. This study used nitrofurantoin, a BCS class II drug, as the active substance. Two formulas contain 5% nitrofurantoin varied in the ratio of HPMC and PLA. The first is 20% HPMC and 75% PLA, while the second consists of 40% HPMC and 55% PLA. After the formulation, the effect of the matrix on the drug release was observed.[19] The results showed that in 24 days, there was a difference in nitrofurantoin release from both formulations. As much as 50% of nitrofurantoin is released from the 3D printed tablets containing 40% HPMC and 55% PLA. However, only 30% nitrofurantoin is released from the 3D printed tablets made of filaments containing 20% HPMC and 75% PLA. This shows that adding hydrophilic polymers to the PLA filaments can boost and modify the drug release.[18]

Polyvinyl alcohol (PVA)

Polyvinyl alcohol (PVA) is one of the hydrophilic polymers commonly used in pharmaceutical products. It is deemed safe for use in oral medicinal preparations due to its biodegradability and lack of toxicity. Since PVA expands in water, it has been frequently employed as a matrix for modified-release tablets.[12,20-22] Some studies used PVA as the filament-forming material for making pharmaceutical products through FDM 3D printing. Skowyra *et al.*[21] researched the preparation of extended-release tablets using PVA as filament-forming material containing a BCS class I active ingredient, prednisolone. They used a commercially marketed PVA filament with a diameter of 1.75 mm. The PVA filament was immersed in a solution of prednisolone and methanol under saturated conditions at a temperature of 30°C for 24 hours.[21]

Each filament contains the same dose, with the variance in tablet size. Since the drug's concentration is constant, the tablet size will be proportional to the dose required. Therefore, small tablets will have a greater ratio of surface area and mass contact to dissolution medium to enable fast drug release.[21] The higher concentration of PVA resulted the smaller swelling ratio. Moreover, the porosity of the hydrogel dropped, resulting in a decrease in the amount of water that can be absorbed.[23] This is responsible for the extended-release effect of prednisolone from the PVA matrix.

However, another study conducted by Tagami *et al.*[24] produces tablets containing curcumin using PVA as filament constituent. The tablets were hollowed in design to enhance the volume of water absorbed, resulting in rapid drug release. BCS class II curcumin demonstrated that 100% drug release can be achieved within two hours of incubation.[24]

Instead of incorporating the drug into the filament by the diffusion method, Goyanes *et al.*[25] extruded PVA along with the drug. Paracetamol and caffeine were utilized as model drugs because they are heat-resistant and have varying solubilities, making them ideal for testing. The extrusion temperature used for the filament-forming

process was around 180°C. The resulting filaments were not much different from the polyvinyl alcohol available in market, in term of diameter, physical appearance, and mechanical properties.[25]

In the study, the PVA filaments were prepared with concentrations of paracetamol and caffeine of 5% and 10%, respectively. However, the recovery of each active ingredient produced was 4.3% and 8.2%, and 4.7% and 9.5% for paracetamol and caffeine. This is probably because of some drugs were attached to the surface during the mixing and extrusion process, reducing the filament's content. Both active ingredients were completely dissolved within 2 hours, and drug release from the 3D printed tablets was faster following the increase in drug concentration. This occurred because the amount of PVA, which controls drug release, was less in the tablets.[25]

Polycaprolactone (PCL)

Polycaprolactone (PCL) is a thermoplastic polymer and has high possibility for the delivery of drugs with a low molecular weight due to its rubbery characteristics.[26] It is usually used as a matrix for extended-release drug delivery systems such as implanted devices. Furthermore, it is water-insoluble and degrades very slowly in the human body. This polymer is rarely used in the manufacturing of oral delivery systems because it cannot facilitate drug release in the gastrointestinal tract.[27]

Other factors influencing drug release profile include the concentration and crystallinity embedded on the filament, as well as polymer employed for filament formation. Holländer *et al.*[27] developed 3D printing implants as a controlled release delivery system for indomethacin (5, 15, and 30%) using PCL as the matrix. The release study showed that the indomethacin release from the 3D printing implants containing 5, 15, and 30% of indomethacin was 99.4 ± 2.5%, 87.4 ± 0.4, and 67.6 ± 2.0%, respectively, within 30 days. It reveals that the highest drug release was from the 5% indomethacin implant, while the lowest release was the 15% indomethacin implant. It is probably because the crystallinity of indomethacin, since the indomethacin used in the filament is mainly crystalline, which have slower dissolution rate than that amorphous form.[27]

Polyvinyl pyrrolidone (PVP)

Polyvinyl pyrrolidone (PVP) has been widely used in health and pharmaceuticals application. PVP is a hydrophilic polymer that is very soluble in many water-containing and polar solvents. Also, it has low toxicity properties and is commonly used to increase solubility and enhance drug release.[28,29]

Okwuosa *et al.*[30] did research to make immediate-release 3D printed tablets using PVP filament matrix with theophylline and dipyridamole. Filament prepared only of PVP cannot be printed by FDM 3D printing due to the poor flow rate at the nozzle. They add another non-melting excipient such as talc to improve the PVP filament flow rate, therefore, the process can be continued to manufacture 3D printing tablets. The *in vitro* dissolution study showed that the 3D printing tablets prepared by the talc added PVP filament released 85% theophylline and dipyridamole within 30 minutes. This study reveals that polyvinyl pyrrolidone can be used as a matrix to manufacture 3D printed tablets with an immediate drug release profile.[30]

Polyethylene oxide (PEO)

Polyethylene oxide (PEO) is a thermoplastic polymer widely used in pharmaceutical preparations with good solubility, low toxicity, low price, and biodegradability.[31,32] It has different grades based on molecular weights and is commercially available in 100,000 to 10,000,000 Da.[33] It can increase solubility in drugs, and differences in the molecular weight show the variation of the drug dissolution profile.[34]

Isreb *et al.*[32] used PEO as the filament material to manufacture 3D printed theophylline tablets with a modified design resembling a radiator with a different gap 0.5, 1, 1.5, and 2 mm between plates of "radiator-shaped tablet". The drug release shows that the 0.5 mm gap design was slower than the others. The swelling in the 0.5 mm-spaced design resulted in plate adhesion, reducing contact surface area with the dissolution medium and slowing drug release.[32]

Ethylene vinyl acetate (EVA)

Ethylene vinyl acetate (EVA) is a copolymer consisting of different monomers, ethylene and vinyl acetate. It is biocompatible, non-toxic, insoluble in water, and widely used in extended-release drug delivery systems.[35,36] EVA is a thermoplastic polymer whose crystallinity and melting point are affected by the vinyl acetate content in the copolymer.[36] The properties indicate that it can be used as a filament matrix, but due to its water-insoluble properties, the polymer can only use in implant drug delivery.[35]

Genina *et al.*[35] studied EVA polymer as a new raw material for filaments fabrication in FDM 3D printing. The research was conducted to manufacture 3D printed implants as a controlled release indomethacin delivery system using EVA. The EVA filaments were prepared with indomethacin as a model drug in concentrations of 5% and 15%. The drug release study indicated that 30% and 20% of indomethacin were released from 3D printed implants containing 5% and 15% indomethacin, respectively, within 30 days. According to the results, the indomethacin 3D printed implants reveal the prolong release profiles and the 3D printed implants with lower content of drug could release much more indomethacin.[35] Thus, the EVA copolymer is suitable for use as an implant matrix with manufacturing using 3D printing technology.

Ethyl cellulose (EC)

EC is a water-insoluble thermoplastic polymer used in 3D printing technology for pharmaceutical preparations.[37] The water-insoluble characteristic makes it suitable to be utilized as a matrix in slow-release tablets or modified-

release tablets.

Yang *et al.*[15] conducted a study of slow-released 3D printed ibuprofen tablets using EC as the main constituent of filaments with thirteen formulas varied with 16-24%, and EC was around 50-80%. The filament was prepared by mixing ibuprofen, EC, and release modifier and then extruded at a temperature of 100-120°C at 60 rpm for 10 minutes. The release modifier polymers used were hydroxypropyl methyl cellulose (HPMC), sodium alginate, xanthan gum, and PVA. The filaments had a diameter of 1.75 mm, according to the nozzle size of the 3D printer. Furthermore, the hardness decreased with the increased ibuprofen level in the filaments due to a plasticizing effect.[15]

The release of ibuprofen was observed to each formula which contains 20% (w/w) within 24 hours. The cumulative drug release at (Q_{24h}) composed of EC only was 17.8%, caused by the hydrophobicity and increased density due to heating.[16] On the other hand, the addition of release modifying agents may affect the drug release from 3D printed tablets. The addition of HPMC to EC with the ratio of 1 to 3 results in the 83.0% release of ibuprofen, while sodium alginate with the same ratio resulted in the 83.0% release for 24 hours (Q_{24h}). Each of the formulas added by xanthan gum and PVA shows an incomplete release, and the cumulative release was only 54.3% and 42.0%, respectively. Furthermore, the formula using a mixture of EC (55% w/w) and HPMC (25% w/w) with a ratio of 2.2:1 showed the Q_{24h} of ibuprofen was more than 95%.[15]

According to those drug release modifying agents, HPMC is known to have a significant effect in increasing drug release. It works to increase the drug release by expanding while getting contact with water or by erosion. Even though EC polymers provide a slow drug release effect when used as a matrix, the release can be modified by mixing with the other polymers.[15]

Hydroxypropyl methyl cellulose (HPMC)

HPMC is a non-toxic semi-synthetic polymer derived from cellulose ether used as a hydrophilic matrix in slow-release tablets.[38] It is available in various grades with different physical and chemical properties. It brings many advantages in pharmaceutics, such as emulsifiers, suspending agents, thickeners, film coating material, and the modified-release matrix.[39] The drug release from HMPC matrix occurs in two different ways. Firstly, when the polymer contacts with the dissolution medium, it expands and forms a gel layer, allowing drugs to diffuse through the gel layer. Secondly, when HPMC meets the dissolution medium, it will dissolve completely to release the drug from the matrix.[38]

Kadry *et al.*[39] studied the manufacturing of filaments using HPMC only. They developed multipurpose filaments HPMC for drug manufacturing using 3D printing technology tailored to the needs of patients. This research used a BCS class I drug -diltiazem- as the active substance. Diltiazem and HPMC were mixed and then extruded at a temperature of 135 °C at a speed of 15 rpm, with the diameter of filament set around 1.75 mm.[39]

A tablet design was prepared with a cavity in various patterns to to observe the release profiles. The tablet cavity can be produced by adjusting the infill percentage using computer-aided-design software. The percentage was set in 10-100% with various cavity patterns. The results showed that drug release depends on the percentage of tablet infill. Tablets with an infill of 100% showed the slowest release, which can completely release the drug in 12 hours. Meanwhile, the decrease in infill percentage increases the release duration. Tablets with 10% infill showed the fastest drug release of 100% within 6 hours, which can be affected by the cavity pattern. Tablets with a complex cavity pattern showed a prolonged drug release, while hexagonal and diamond cavities produced the fastest and slowest drug release.[39]

Another study was conducted by Zhang *et al.*[9], where the 3D printed tablets were produced with the sustained-release profile. The filament was composed of paracetamol, Soluplus®, and HPMC in a ratio of 1:2:7. The 3D printed tablets were prepared in two variants, with and without a shell. There were two types of shelled tablets with different thicknesses, which were 0.4 mm and 1.6 mm, respectively. Every kind of tablet, with and without a shell, was prepared with different infill percentages, which were 100%, 80%, and 20% for each of the 3D printing tablets.[9]

The results showed that 3D printed tablets with 0.4 mm shell thickness and infill percentage of 100%, 80%, and 20% had 52.91%, 54.27%, and 79.41% of drug released after 4 hours, respectively. Meanwhile, those with 1.6 mm shell thickness and infill percentage of 100%, 80%, and 20% released up to 71%, 79%, and 66% of drugs in 8 hours, respectively. No shell 3D printed tablets with a 20% infill percentage demonstrated the fastest drug release, since 85% of the drugs were released within one hour.[9]

Zhang *et al.*[9] compared the tablets with the same percentage of infill, where two groups had shells. They found that the no-shell tablet had the fastest drug release profile, while tablets with 1.6 mm shell thickness showed the slowest release profile compared with a 0.4 mm and without a shell. This was caused by the tablet shell, which was relatively thick and became the barrier of the drug to get direct contact with the dissolution medium. Generally, drug release from no-shell 3D printed tablets with an infill percentage of 100% was the fastest.

Hydroxypropyl Cellulose (HPC)

HPC is an ether derivative that can be dispersed in water to form a gel mass,[40] and it is a thermoplastic polymer in nature.[41] This polymer is available on the market with a variety of viscosity and molecular weights in the range 40,000 to 1,150,000 Da.[41] Vo *et al.*[42] used HPC polymers as filament constituents to manufacture gastro-retentive tablets. In that study, HPC with a molecular weight of 850,000 Da was used as filament-forming material, and the diameter formed was 1.7 mm. Tablets were produced in a cylindrical shape with a cavity with the infill percentage

of 50-80% to produce tablets with various floating times in the stomach ranging from 6 to 12 hours. Releasing the drug from the matrix occurs after the polymer expands and forms a gel. The active substance may leave the matrix through the diffusion and erosion processes, allowing the manifestation of a burst effect in the initial phase. Over time, there is a slowdown in drug release from the matrix through a zero-order kinetics.[42]

Discussion

The use of 3D printing technology has been a widely used method in manufacturing solid pharmaceutical preparations. The technology can even produce a narrow therapeutic window drug, because it is easy to change the design and the tablet volume.[43] Among all methods, fused deposition modeling (FDM) is the most used technique since it has several advantages compared to others. It is more cost-effective, easy operation, and has shorter printing stages.[44] However, this method is limited only to thermostable active ingredients since there is a heating step in the process. The time for making tablets is slightly longer than other 3D printing techniques because of the limited printing speed, generally around 90 mm/second.[5,12,45]

The polymer used is also limited only to thermoplastic polymers, which soften when heated and become hardened with reduced temperature. Biodegradable polymers are usually preferable because they can be degraded in the physiological fluids both enzymatically and non-enzymatically.[4] Meanwhile, the thermal stress exposed to 3D printed tablets during the FDM process may increase the possible interactions between polymers and active ingredients. When the drug is incorporated into the polymer, it may create intermolecular interactions such as van der Waals forces and hydrogen bonds.[46]

The polymers used as filament-forming material in these studies are polylactic acid (PLA), polyvinyl alcohol (PVA), polycaprolactone (PCL), polyvinyl pyrrolidone (PVP), polyethylene oxide (PEO), ethylene vinyl acetate (EVA), ethyl cellulose (EC), hydroxypropyl methyl cellulose (HPMC), and hydroxypropyl cellulose (HPC). Some are biodegradable, and are more beneficial to be used in pharmaceutical preparations. The solubility of these polymers also varies due to differences in physicochemical properties. Some polymers such as PLA, PCL, EVA, and EC are water-insoluble, hence, they are commonly used to make very slow-release drug delivery systems. On the other hand, PVA, HPMC, and HPC are more hydrophilic and dispersible in water. The gelling ability is the reason for the wide use in sustained-release drug delivery systems preparation. Meanwhile, PVP and PEO are usually used for immediate-release preparations since they are the most water-soluble among the others.

Choice of polymers used in filament preparation may impact the drug release from 3D printed tablets. Since polymers take the most considerable proportion in formulation, their solubility plays a significant role in drug release. Even though the drugs' solubility also affects their release, the data from the previous studies show that the physicochemical properties of the polymers bring a significant effect to the release. Therefore, several approaches can be adopted to improve the release, such as adding a release modifier, or modifying the design to make it easier for liquids to enter the dosage form. Meanwhile, drug release profile can also be modified by adjusting the percentage of tablet infill and the modification can be used to personalize medication for patients. These polymers application on 3D printed tablets by fused deposition modeling technique are summarized in Table 1.

Table 1. Summary of polymer applications in 3D printed tablet manufacturing by fused deposition modeling.

Polymer	Polymer solubility	Polymer properties	Active ingredient	Release behavior
Polylactic acid	Insoluble in water	Thermoplastic, biodegradable, biocompatible	Nitrofurantoin[18] Prednisolone and Dexamethasone[19]	Sustained release
Polyvinyl alcohol	Soluble in water	Thermoplastic, biodegradable, and non-toxic	5-ASA, captopril, theophylline and prednisolone[12] Paracetamol[20] Prednisolone[21]	Sustained release
Polycaprolactone	Insoluble in water	Thermoplastic	Indomethacin[27]	Sustained release
Polyvinyl pyrrolidone	Very soluble in water and polar solvent	Thermoplastic and biodegradable	Theophylline and dipyridamole[30]	Immediate release
Polyethylene oxide	Soluble in water	Thermoplastic and biodegradable	Carbamazepin[31] Theophylline[32]	Immediate release
Ethylene-vinyl acetate	Insoluble in water	Thermoplastic, biocompatible, and non-toxic	Indomethacin[35]	Sustained release
Ethyl cellulose	Insoluble in water	Thermoplastic	Ibuprofen[15]	Sustained release
Hydroxypropyl methyl-cellulose	Dispersed in water	Thermoplastic and non-toxic	Nitrofurantoin[18] Diltiazem[39]	Sustained release
Hydroxypropyl cellulose	Dispersed in water	Thermoplastic	Theophylline and Ketoprofen[40] Cinnarizine[41]	Sustained release

Personalization aspect that can be achieved with 3D printing technology are not limited only to drug release but also to doses. The ease of design related to dosage and drug release made this method can be tailored to produce the products which meet each patient's needs and make it easier to facilitate personalized medicine. This can be conducted quickly by determining the tablet volume design based on the drug content in the polymer filament. This technology assists pharmacists to modify tablets for patients in any way possible to achieve the expected therapeutic goals. Therefore, the use of 3D printing technology can greatly facilitate health workers in treating patients and reach the therapeutic goals as well.

Besides the outstanding advantage of this technology, it still becomes a challenge for many reasons since more studies are required to solidify the types of filament's formulations. Collaboration with pharmaceutical industries and the government is important to make this happen. Meanwhile, there is still a lack of regulation related to FDM 3D printing method used as the technique in pharmaceutical industries, including the good manufacturing practice (GMP) aspects for manufacturing, good distribution practice (GDP) aspects for maintaining the filaments in the storage, and the regulation in healthcare facilities to produce the 3D printed tablets. As a result, 3D printed tablets made with this FDM 3D printing technique may still be unavailable.

Conclusion

Various natural, synthetic, and semi-synthetic polymers can be used as filament-forming material for fused deposition modelling (FDM) 3D printing. The filament that is successfully fabricated should meet the criteria for further 3D printing process such as suitable diameter (generally around 1.75-3.00 mm), also sufficient mechanical properties which are generally evaluated in terms of brittleness and elasticity. Drug release profile from the 3D printed tablet is very dependent on the type of polymer used as well as the concentration of active substances, but can be modified by adjusting the percentage of tablet infill during the 3D printing. The ease of design regarding dose and drug release provides this technique applicable to facilitate personalized medicine. Moreover, regulatory issue is still becoming the challenge to implement this method for pharmaceutical product preparation on a large scale.

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Author Contributions

SS contributed in conceiving the concept and the manuscript, supervised the work and data analysis, performed critical revision of the manuscript, and gave provision of final approval to the manuscript. YB contributed in establishing the manuscript, searched and reviewed the references, analyzed and revised the manuscript. Meanwhile, AK contributed in constructing the manuscript, reviewed and revised the manuscript. All authors read and gave approval of the final manuscript.

Conflict of Interest

The authors report no conflicts of interest.

References

1. Awad A, Trenfield SJ, Gaisford S, Basit AW. 3D printed medicines: A new branch of digital healthcare. Int J Pharm. 2018;548(1):586-96. doi:10.1016/j.ijpharm.2018.07.024
2. Chen G, Xu Y, Chi Lip Kwok P, Kang L. Pharmaceutical applications of 3D printing. Addit Manuf. 2020;34:101209. doi:10.1016/j.addma.2020.101209
3. Khaled SA, Burley JC, Alexander MR, Roberts CJ. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. Int J Pharm. 2014;461(1-2):105-11. doi:10.1016/j.ijpharm.2013.11.021
4. Norman J, Madurawe RD, Moore CMV, Khan MA, Khairuzzaman A. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. Adv Drug Deliv Rev. 2017;108:39-50. doi:10.1016/j.addr.2016.03.001
5. Goole J, Amighi K. 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. Int J Pharm. 2016;499(1-2):376-94. doi:10.1016/j.ijpharm.2015.12.071
6. Han S, Kathuria H, Jia J, Tan Y, Kang L. 3D printed drug delivery and testing systems — a passing fad or the future? Adv Drug Deliv Rev. 2018;132:139-68. doi:10.1016/j.addr.2018.05.006
7. Melocchi A, Parietti F, Loreti G, Maroni A, Gazzaniga A, Zema L. 3D printing by fused deposition modeling (FDM) of a swellable/erodible capsular device for oral pulsatile release of drugs. J Drug Deliv Sci Technol. 2015;30(Part B):360-7. doi:10.1016/j.jddst.2015.07.016
8. Zaferani SH. Introduction of polymer-based nanocomposites. In: Jawaid M, Khan MM, editors, Polymer-based Nanocomposites for Energy and Environmental Applications: A volume in Woodhead Publishing Series in Composites Science and Engineering. Sawston: Woodhead Publishing; 2018. p. 1-25. doi:10.1016/B978-0-08-102262-7.00001-5
9. Zhang J, Feng X, Patil H, Tiwari R V, Repka MA. Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets. Int J Pharm. 2017;519(1-2):186-97. doi:10.1016/j.ijpharm.2016.12.049
10. Caballero-George C, Marin, Briceño. Critical evaluation of biodegradable polymers used in nanodrugs. Int J Nanomedicine. 2013;8:3071. doi:10.2147/IJN.S47186
11. Zhang J, Xu P, Vo AQ, Bandari S, Yang F, Durig T, et al. Development and evaluation of pharmaceutical 3D printability for hot melt extruded cellulose-based filaments. J Drug Deliv Sci Technol. 2019;52:292-302. doi:10.1016/j.jddst.2019.04.043

12. Sadia M, Sośnicka A, Arafat B, Isreb A, Ahmed W, Kelarakis A, et al. Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. Int J Pharm. 2016;513(1-2):659-68. doi:10.1016/j.ijpharm.2016.09.050
13. Prajapati SK, Jain A, Jain A, Jain S. Biodegradable polymers and constructs: A novel approach in drug delivery. Eur Polym J. 2019;120:109191. doi:10.1016/j.eurpolymj.2019.08.018
14. Harris M, Potgieter J, Archer R, Arif KM. Effect of material and process specific factors on the strength of printed parts in fused filament fabrication: A review of recent developments. 2019;12(10):1664. doi:10.3390/ma12101664
15. Yang Y, Wang H, Li H, Ou Z, Yang G. 3D printed tablets with internal scaffold structure using ethyl cellulose to achieve sustained ibuprofen release. Eur J Pharm Sci. 2018;115:11-8. doi:10.1016/j.ejps.2018.01.005
16. Braconnier DJ, Jensen RE, Peterson AM. Processing parameter correlations in material extrusion additive manufacturing. Addit Manuf. 2020;31:100924. doi:10.1016/j.addma.2019.100924
17. Tagami T, Nagata N, Hayashi N, Ogawa E, Fukushige K, Sakai N, et al. Defined drug release from 3D-printed composite tablets consisting of drug-loaded polyvinylalcohol and a water-soluble or water-insoluble polymer filler. Int J Pharm. 2018;543(1-2):361-7. doi:10.1016/j.ijpharm.2018.03.057
18. Boetker J, Water JJ, Aho J, Arnfast L, Bohr A, Rantanen J. Modifying release characteristics from 3D printed drug-eluting products. Eur J Pharm Sci. 2016;90:47-52. doi:10.1016/j.ejps.2016.03.013
19. Farto-vaamonde X, Auriemma G, Patrizia R, Concheiro A, Alvarez-lorenzo C. Post-manufacture loading of filaments and 3D printed PLA scaffolds with prednisolone and dexamethasone for tissue regeneration applications. Eur J Pharm Biopharm. 2019;141:100-10. doi:10.1016/j.ejpb.2019.05.018
20. Goyanes A, Robles Martinez P, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. Int J Pharm. 2015;494(2):657-63. doi:10.1016/j.ijpharm.2015.04.069
21. Skowyra J, Pietrzak K, Alhnan MA. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. Eur J Pharm Sci. 2015;68:11-7. doi:10.1016/j.ejps.2014.11.009
22. Matijašić G, Gretić M, Vinčić J, Poropat A, Cuculić L, Rahelić T. Design and 3D printing of multi-compartmental PVA capsules for drug delivery. J Drug Deliv Sci Technol. 2019;52:677-86. doi:10.1016/j.jddst.2019.05.037
23. Gupta S, Webster TJ, Sinha A. Evolution of PVA gels prepared without crosslinking agents as a cell adhesive surface. J Mater Sci Mater Med. 2011;22(7):1763-72. doi:10.1007/s10856-011-4343-2
24. Tagami T, Fukushige K, Ogawa E, Hayashi N, Ozeki T. 3D printing factors important for the fabrication of polyvinylalcohol filament-based tablets. Biol Pharm Bull. 2017;40(3):357-64. doi:10.1248/bpb.b16-00878
25. Goyanes A, Kobayashi M, Martínez-pacheco R, Gaisford S, Basit AW. Fused-filament 3D printing of drug products: Microstructure analysis and drug release characteristics of PVA-based caplets. Int J Pharm. 2016;514(1):290-5. doi:10.1016/j.ijpharm.2016.06.021
26. Coombes AGA, Rizzi SC, Williamson M, Barralet JE, Downes S, Wallace WA. Precipitation casting of polycaprolactone for applications in tissue engineering and drug delivery. Biomaterials. 2004;25(2):315-25. doi:10.1016/S0142-9612(03)00535-0
27. Holländer J, Genina N, Jukarainen H, Khajeheian M, Rosling A, Mäkilä E, et al. Three-dimensional printed PCL-based implantable prototypes of medical devices for controlled drug delivery. J Pharm Sci. 2016;105(9):2665-76. doi:10.1016/j.xphs.2015.12.012
28. Kim DH, Kim WK, Woo SJ, Wu C, Kim TW. Highly-reproducible nonvolatile memristive devices based on polyvinylpyrrolidone: Graphene quantum-dot nanocomposites. Org Electron. 2017;51:156-61. doi:10.1016/j.orgel.2017.09.005
29. Surini S, Evangelista CN, Iswandana R. Development of glimepiride solid dispersion using the coprocessed excipients of polyvinylpyrrolidone, maltodextrin, and polyethylene glycol. J Young Pharm. 2018;10(2):s45-50. doi:10.5530/jyp.2018.2s.9
30. Okwuosa TC, Stefaniak D, Arafat B, Isreb A, Wan KW, Alhnan MA. A lower temperature fdm 3d printing for the manufacture of patient-specific immediate release tablets. Pharm Res. 2016;33(11):2704-12. doi:10.1007/s11095-016-1995-0
31. Perissutti B, Newton JM, Podczeck F, Rubessa F. Preparation of extruded carbamazepine and PEG 4000 as a potential rapid release dosage form. Eur J Pharm Biopharm. 2002;53(1):125-32. doi:10.1016/S0939-6411(01)00209-0
32. Isreb A, Baj K, Wojsz M, Isreb M, Peak M. 3D printed oral theophylline doses with innovative ' radiator-like ' design : Impact of polyethylene oxide (PEO) molecular weight. Int J Pharm. 2019;564:98-105. doi:10.1016/j.ijpharm.2019.04.017
33. Crowley MM, Zhang F, Koleng JJ, McGinity JW. Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. Biomaterials. 2002;23(21):4241-8. doi:10.1016/S0142-9612(02)00187-4
34. Yang X, Zhong Z, Huang Y. The effect of PEG molecular weights on the thermal stability and dissolution behaviors of griseofulvin-PEG crystalline inclusion complexes. Int J Pharm. 2016;508:51-60. doi:10.1016/j.ijpharm.2016.05.014
35. Genina N, Holländer J, Jukarainen H, Mäkilä E, Salonen J, Sandler N. Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices. Eur J Pharm Sci. 2016;90:53-63. doi:10.1016/j.

ejps.2015.11.005
36. Schneider C, Langer R, Loveday D, Hair D. Applications of ethylene vinyl acetate copolymers (EVA) in drug delivery systems. J Control Release. 2017;262:284-95. doi:10.1016/j.jconrel.2017.08.004
37. Adeleke OA. Premium ethylcellulose polymer based architectures at work in drug delivery. Int J Pharm X. 2019;1:100023. doi:10.1016/j.ijpx.2019.100023
38. Marani PL, Bloisi GD, Petri DFS. Hydroxypropylmethyl cellulose films crosslinked with citric acid for control release of nicotine. Cellulose. 2015;22:3907-18. doi:10.1007/s10570-015-0757-1
39. Kadry H, Al-Hilal TA, Keshavarz A, Alam F, Xu C, Joy A, et al. Multi-purposable filaments of HPMC for 3D printing of medications with tailored drug release and timed-absorption. Int J Pharm. 2018;544(1):285-96. doi:10.1016/j.ijpharm.2018.04.010
40. Szabó P, Kállai-Szabó B, Kállai-Szabó N, Sebe I, Zelkó R. Preparation of hydroxypropyl cellulose microfibers by high-speed rotary spinning and prediction of the fiber-forming properties of hydroxypropyl cellulose gels by texture analysis. Cellulose. 2014;21:4419-27. doi:10.1007/s10570-014-0391-3
41. Loreti G, Maroni A, Del Curto MD, Melocchi A, Gazzaniga A, Zema L. Evaluation of hot-melt extrusion technique in the preparation of HPC matrices for prolonged release. Eur J Pharm Sci. 2014;52:77-85. doi:10.1016/j.ejps.2013.10.014
42. Vo AQ, Zhang J, Nyavanandi D, Bandari S, Repka MA. Hot melt extrusion paired fused deposition modeling 3d printing to develop hydroxypropyl cellulose based floating tablets of cinnarizine. Carbohydr Polym. 2020;246:116519. doi:10.1016/j.carbpol.2020.116519
43. Haris MS, Azlan NHM, Taher M, Rus SM, Chatterjee B. 3D-printed drugs: A fabrication of pharmaceuticals towards personalized medicine. Indian J Pharm Educ Res. 2020;54:S411-22. doi:10.5530/ijper.54.3s.139
44. Daminabo SC, Goel S, Grammatikos SA, Nezhad HY, Thakur VK. Fused deposition modeling-based additive manufacturing (3D printing): techniques for polymer material systems. Mater Today Chem. 2020;16:100248. doi:10.1016/j.mtchem.2020.100248
45. Zidan A, Alayoubi A, Coburn J, Asfari S, Ghammraoui B, Cruz CN, et al. Extrudability analysis of drug loaded pastes for 3D printing of modified release tablets. Int J Pharm. 2019;554:292-301. doi:10.1016/j.ijpharm.2018.11.025
46. Silva IA, Lima AL, Gratieri T, Gelfuso GM, Sa-Barreto LL, Cunha-Filho M. Compatibility and stability studies involving polymers used in fused deposition modeling 3D printing of medicines. J Pharm Anal. 2022;12(3):424-35. doi:10.1016/j.jpha.2021.09.010