RESEARCH ARTICLE

A Novel Process for Improving the Drug Loading of Highly Water-Soluble High-Dose Drug in FDM 3D Printed Tablets

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ABSTRACT

Background: 3D printing technologies, also known as additive manufacturing technologies, are gaining importance in pharmaceutical research and manufacturing. These technologies are widely used in automobile, plastic, and material fabrication industries. In the recent past, pharmaceutical industries are actively working to increase the applicability of these technologies in commercial manufacturing. On the other hand, clinics and hospitals are ready to adopt these technologies due to their versatility such as flexibility, individual customization, and low-cost investment. FDM 3D printing technology is one of the widely used technologies for the manufacturing of finished products. However, this technology has limitations such as drug loading, scale-up issues, and regulatory requirements. The present study focused on developing a suitable solvent system along with a drug-loading method to increase the industrial applicability of this technology.

Methods: Metformin, a high-dose, highly soluble drug, was selected as a model. Solvents such as water, ethanol, and methanol and their combinations were explored. Saturation solubility and drug loading in both PVA filaments and printed tablets were tested for drug loading. The solvent ratio of ethanol/methanol/water (8:1:1) was selected. The different infills of 10, 25, 50, 75, and 100% were printed using PVA filaments and were subjected to drug loading using soaking and solvent curing methods.

Results: The soaking method has resulted in poor drug loading as well as layer separation and swelling of the polymer. The solvent curing method has a maximum drug loading of 91.9% w/w without physical deformities of the tablets. Moreover, the solvent curing method is a scalable process with less process time, and hence this method could be useful for both large-scale commercial manufacturing as well as customized formulations for personalized therapies.

Conclusion: This method could be used for manufacturing thermoliable drug products and moderate-dose drug substances. Based on the research outcomes, we propose a novel, scalable, and rapid solvent-curing method for drug loading in the FDM 3D printing technique.

Keywords: Metformin, 3D printing, Drug loading, Tablet, Immediate release.

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INTRODUCTION

Most of the approved drug products are manufactured and commercialized using conventional manufacturing technologies, which are also known as subtractive manufacturing technologies.[1] These technologies involve the mass manufacturing of drug products with a limited number of fixed strengths and, hence, not suitable for personalized medicine.[2] Moreover, the requirement for large-scale manufacturing capabilities, shipping, distribution, and associated expenses result in a healthcare burden for the nation and/or region. Apart from this, therapeutic failure in the clinical setting remains a major issue.[3] For the incidence, 70% of patients in the UK don't have optimal therapeutic and clinical outcomes and 90% of the drug products have the desired clinical performance in only 30 to 50% of the patient population.[4,5]

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The emergence of additive manufacturing technologies, also known as 3D printing technologies, has several distinct advantages, such as personalized therapies, on-demand manufacturing, patient-centric drug products (dose, color, flavor, texture, shape, size, etc.), and personalized tailor-made therapies.[6] A wide variety of pharmaceutical dosage forms, such as tablets, oral dispersion films, transdermal patches, sterile implants, and microneedles, have been developed using 3D printing technologies.[7] 3D printing technologies can be integrated into healthcare settings, including hospitals, pharmacies, specialty clinics, and emergency wards. Despite several advantages, regulatory sciences have yet to evolve to adopt these technologies in real-time clinical practices.[8] Currently, many regulatory agencies are actively working to develop the regulatory framework to adopt these technologies to improve global healthcare.[9]

Fusion deposition method (FDM) 3D printing technology is a simple and scale-able process for manufacturing tablets.[10] However, most of the polymers explored as matrix components in 3D printing using FDM are hydrophilic, and hence, these polymers have either high aqueous solubility or swelling index. Therefore, the use of water as a solvent for drug loading of highly soluble drugs is limited due to high solubility and swellability. In contrast, the use of pharmaceutically acceptable solvents like ethanol, methanol, etc., have low solubilization capacity of highly soluble drugs for drug loading and, hence, results in poor loading efficiency. Hence, optimization of a suitable solvent system is essential to achieve the desirable drug loading for commercially scale-able technologies.

Most of the recent literature uses a soaking method as a prime choice for drug loading; the limitation of this method includes poor drug loading efficiency and a tedious and non-scaleable process.[11–14] Hence, this method has limited possibilities for commercial large-scale manufacturing. The search for alternative methodologies is a prerequisite to ensure the commercial applicability of FDM 3D printing technology as a method of choice for manufacturing tablets. The present investigation aims to focus on the development of a suitable solvent system and process to improve the drug loading efficiency that facilitates the application of FDM 3D printing technology as a choice of method for manufacturing tablets.

MATERIAL AND METHODS

Materials

Metformin (MET) gift sample received from Aarti Drugs Ltd (India), polyvinyl alcohol (PVA) filament (AquaSolve –PVA) of 1.75 mm thickness was purchased from Form Futura 3D printing material (The Netherlands). All solvents were reagent grades bought from Merck (India).

Methods

Drug excipient compatibility studies

Drug-excipients and drug-process compatibility studies were carried out, and the details were reported in our previously published report.[15]

Solubility studies

The solubility of MET in different processing solvents was determined in saturated conditions. The solvents used in the solubility studies were water, methanol, ethanol, and their mixtures. A 3 g of MET was added in 5 mL of solvent with different ratios (as mentioned in Table 1). Samples were incubated at 25ºC in a rotary shaker (Remi RS 18 plus rotary shaker, Remi India, Mumbai, India) for 6 hours. The rotor was kept at 50 rpm throughout the experiment. The sample was collected and filtered in ambient room conditions and filtered through a syringe filter (Sterile, PVDF, 0.45 µ, 25 mm diameter). Samples were diluted to obtain the concentration within the linearity range. The absorbance was determined by using a UV spectrophotometer (UV-1900i, Shimadzu, Japan) at λ_{max} of 233 nm and the concentration was calculated using a linear equation. All the samples were analyzed in triplicate.

Drug loading in PVA filament by soaking method

Drug loading in PVA filament was done using the soaking method. The different solvents and their combinations (Table 2) were used to obtain the drug loading. Each PVA filament was cut into small lengths (2 cm) and dipped into a saturated solution under constant shaking of 50 dpmat 25ºC in a rotary shaker (Remi RS 18 plus rotary shaker, Remi India, Mumbai, India). The filament samples were recovered at intervals of 15, 60, and 120 minutes and each filament was dissolved in 50 mL of water. A UV spectrophotometer determined the amount of MET per filament at 233 nm (UV-1900i, Shimadzu, Japan).

Designing of 3D printing tablets

The design of 3D tablets was carried out using Autodesk Inventor Professional 2023 software. Figure 1 illustrates the optimized design of the 3D tablet, which was saved in .stl format. Figure 2 consists of Simplify 3D software used for setting different infill conditions with defined porosity. The different parameters such as temperature, design, number of tablets, and dimension were selected and this file was converted into G code format. PVA filament was used for printing 3D tablets using an FDM 3D printer (version 1.1., 3D cubic, Surat, Gujarat, India). The process parameters for printing were printing nozzle: T_{print} = 220 °C, $T_{platform}$ = 60°C, Infill = 10, 25, 50, 75, and 100%, layer height = 0.2 mm, printing speed = 70 mm/s, travel speed = 90 mm/s, number of shells = 2. FDM 3D printed tablet design is shown in Figure 3. The printed 3D tablets were evaluated for their pharmaco-technical properties. The tablets were packed in 100 CRC HDPE bottles and kept at ambient conditions (Shreeji Polymers, Ujjain, India).

Drug loading in tablets by soaking method

Drug loading of different infills such as 10, 25, 50, 75, and 100% tablets, was carried out using an optimized solvent system. Briefly, 500 mg of MET was dispersed in 3 mL volume of the solvent to obtain the final drug concentration of 166.7 mg/mL in the suspension. Tablets were incubated in the drug solution and recovered from the solvent chamber at different time intervals of 15, 30, 60, and 120 minutes. The recovered tablets were dried

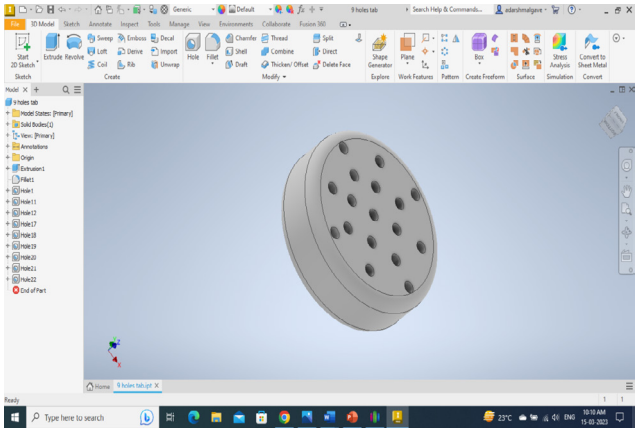

Figure 1: Autodesk software is used in designing differently-shaped tablets.

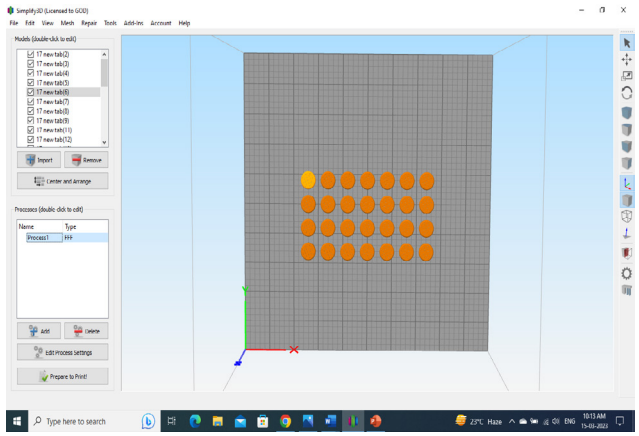

Figure 2: Simplify 3D software for slicing tablets and for infill conditions

at 80ºC using a hot air oven (100 L, UR Biocoction, Kolkata, India) for 6 h to remove the solvent. Dried tablets were stored in ambient conditions using 100 CRC HDPE bottles (Shreeji Polymers, Ujjain, India).

Drug loading by solvent curing method

Tablets with 10, 25, 50, 75, and 100% infill as shown in Figure 4, with some pores for diffusion were used for the passive loading of the tablets. The drug solution was prepared by using the optimized solvent system and 500 mg of the drug was dispersed in 3 mL of solvent composition, 300 µL was accurately measured (100–1000 µL, catalog number: 4641100, Finnpipette, Thermoscientific, USA) and used for passive loading in each tablet with a targeted drug loading of 50 mg/tablet. The tablets were used to dry in a hot air oven (100 L, UR Biocoction, Kolkata, India) at 80°C for 6 hours. The tablets were stored in 100 CRC HDPE bottles (Shreeji Polymers, Ujjain, India) in ambient conditions till further evaluation.

Pharmaceutical Characterization

Weight variation and dimensions

Ten tablets were randomly chosen and weighed individually using a weighing machine (Analytical scale, Model: BSA 223S-CW, Sartorius, Germany). Ten tablets were picked randomly and their dimensions using a tablet tester (Tablet tester, Model: EHT5PR, Electrolab, India) were recorded. The tablet's weight variation and dimensions data are reported in (Table 3).

Table 1: saturation solubility study of met in different solvent ratios

S. No	*Solvent ratio*	*Solubility (mg/5 mL), n = 3*					
		Ethanol: methanol		*Ethanol:water*		*Methanol:water*	
		Mean	*%RSD*	*Mean*	*%RSD*	*Mean*	*%RSD*
1	5:0	BLQ	-	BLQ	-	409.8	15.9
2	4:1	141.2	44.1	275.5	10.9	505.5	7.3
3	3:2	226.7	17.9	743.6	2.9	873.8	4.3
4	2:3	234.8	21.2	1073.3	3.5	1175.0	1.3
5	1:4	316.2	19.6	1368.3	2.5	1390.7	2.0
6	0:5	409.8	15.9	1502.7	0.6	-	-

Table 2: Effect of different solvents on loading of drug in PVA filament

Solvents 15 minutes	*Drug loading (µg of drug per mg of filament)*			*Observations*
	1h	*2h*		
Water 100%	42.2	55.8	-	Poor drug loading, filament completely dissolved after 2 hours
Ethanol 100%	56.1	65.6	91.3	Maximum drug loading
Methanol 100%	28.0	37.5	39.5	Poor drug loading, relatively less than ethanol, swelling, and loss of filament shape
Ethanol: Water (1:1)	37.0	67.8	64.1*	Poor loading, filament partially dissolved after 2 hours
Ethanol: Water (9:1)	44.5	58.5	56.5*	Poor loading, filament partially dissolved after 2 hours
Methanol: Water (1:1)	56.8	-	-	Poor loading, filament completely dissolved after-hour.
Methanol: Water (9:1)	57.3	59.0	71.6	Poor drug loading, swelling of the filament after 2 h

n = 3; for each sampling point one filament was used for estimation of drug content, *drug loss due to solubilization of the filament

Drug content

Six tablets were individually weighed and each tablet was transferred into 50 mL volumetric flasks. The solutions were kept in an incubator shakerat25 ± 0.5°C with a shaking speed of 100 rpm for 120 minutes to ensure the complete extraction of MET. The obtained solutions were diluted to the required concentration and the absorbance was measured at 233 nm (UV-1900i, Shimadzu, Japan). The uniformity of dose per tablet was calculated and the results are shown in (Table 3).

In-vitro dissolution studies

USP dissolution testing apparatus I (basket) was used to perform the dissolution study (Disso 14000 SMART, Labindia, India). A 900 mL of 0.1 N HCl was used as a dissolution

Table 3: Pharmaceutical characterization.

Pharmaceutical Properties	Mean	%RSD
Weight variation* (mg)	702	1.13
Uniformity of the dose* (%)	91.9	0.73
Dimensions* Diameter/Thickness (mm)	14.6/5.69	0.34/1.58
$DE^{**}_{30\ min\ (\%)}$	59.79	24

*n = 10; **n = 6

Table 4: Tablet with different infill and loading by the soaking method

Tablet infill (%)	Drug loading (mg) at different time points				Observation
	15 minutes	30 minutes	1 h	2 h	
10	-	-	-	-	Floating
25	1.99	2.23	2.42	3.80	Layers separated
50	1.50	1.52	2.25	3.87	Layers separated
75	1.78	2.16	2.51	4.28	Layers separated
100	1.66	2.26	2.49	4.76	Layers separated

n = 3; for each sampling point one tablet was used for the estimation of drug content

media and the temperature was maintained at 37 ± 0.5°C with an agitation speed of 100 rpm. Each 5 mL sample was withdrawn and replaced with preconditioned dissolution media at predetermined intervals of 5, 10, 15, 20, 25, and 30 minutes. The collected samples were filtered immediately through a 0.45 µ filter and analyzed using a UV spectrophotometer at 233 nm after appropriate dilutions. The percent drug release was calculated using PCPDisso (version 3.0)software.

RESULTS AND DISCUSSIONS

Saturation Solubility Studies

MET solubility in different solvent ratios is shown in (Table 1). The solubility of MET in water was found to be 1.5 g/mL, whereas, 409.8 µg/mL in methanol. MET is insoluble in ethanol and the solubility was found to be below the limit of quantification. Methanol has a low solubilization capacity of MET and a higher evaporation rate with a boiling point of 64.7ºC. Moreover, methanol is classified as a class II solvent and the maximum permissible limit for pharmaceutical usage is 3000 ppm.[16] Therefore, the absolute use of methanol as a solvent for drug loading is ruled out. Both PVA and MET have high solubility in water. Therefore, using water as a solvent for drug loading is limited. However, we have performed solubility studies in water to understand the magnitude of solubility enhancement of the water in the presence of other pharmaceutically acceptable solvents such as ethanol and methanol. The solubility studies were performed in binary solutions of ethanol/water and methanol/water systems. The results of solubility studies revealed that binary solutions were not suitable for drug loading. Hence it was decided to optimize the solvent ratio, which provides better drug loading. Further, feasibility studies were carried out for a selection of the solvent system for drug loading which is reported in sections 4.2 and 4.3.

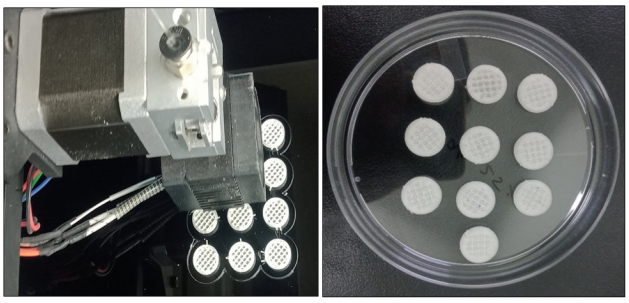

Figure 3: Tablet design using FDM 3D printer.

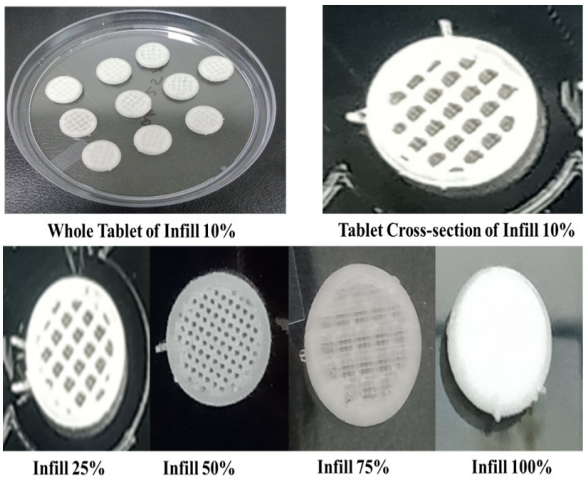

Figure 4: Tablets designs with different infill conditions.

MET-loaded PVA Filament

The drug loading into the PVA filament was carried out using ethanol, water, and methanol and their combinations. Unlike saturation solubility studies, extreme ratios (i.e., 1:1 to 1:9) were chosen based on bracketing design. The drug was suspended in a solvent system, except water. (Table 2) provides the solvent composition and key observations. The maximum drug loading of 91.3 µg/mg was achieved with ethanol as solvent. The drug-loaded filaments are illustrated in Figure 5. It reveals that there is swelling of the filaments during the drug loading process. The swelling patterns of the filaments were indirectly correlated with drug loading efficiency. The drug has poor solubility in ethanol and the visual swelling index was low. Hence high drug loading capacity of ethanol could be due to the high partition of the drug in polymer filament compared with methanol. The low solvent penetration of the polymer in ethanol might be the reason for the low swelling index. The highest human dose as a single-unit tablet dosage form is 1500 mg.[17] Based on the maximum drug loading; 136.5 mg could be formulated as a single-unit tablet with a total theoretical tablet weight of 1636.5 mg. The lowest dose of MET in adults is 500 mg and hence it is practically difficult to adopt the soaking method as a choice for commercial manufacturing. Hence, it is necessary to develop an alternative process for maximizing the drug loading, which could be possible for commercial manufacturing. Therefore, fine-tuning

of solvent systems with high ethanol content is required for optimal loading. Further optimization of the solvent system was performed and the solvent system consisting of ethanol, methanol, and water ratio of 8:1:1. This solvent system was selected for drug loading of 3D printed tablets.

Designing and Printing of Tablets

The designing of tablets was performed using Autodesk software with different infill conditions such as 10, 25, 50, and 100%. Figure 4 shows the representative images of unloaded tablets. The average production time is 20 min/tablet/nozzle as programmed in software. However, the production capacity for commercial manufacturing could be increased by the use of commercial-scale 3D printers. The printed tablets are non-stick and have no production-related defects. All the infill tablets had good morphological and mechanical properties, which were suitable for drug loading. These tablets were used for drug loading using drug solutions with different methods such as soaking method and solvent curing methods.

Drug Loading by Soaking Method in Tablets with Different Infill Conditions

Drug loading was done at different infills of tablets using the optimized solvent ratio of 8:1:1 (ethanol: methanol: water). During the drug loading the separation of layers was found in all fill weights, which are shown in Figure 6. The observations are enumerated in (Table 4). The drug loading of tablets ranged between 3.80 mg to 4.70 mg/tablet and the extent of drug loading was directly related to the polymer concentration. The maximum reported drug loading with absolute ethanol was 0.08% in 3 days of soaking time.[18] First of all, the soaking method is not a preferred method for large-scale manufacturing; however, a significant reduction in soaking time may enhance the chance for commercial manufacturing possibilities. Drug loading time is a critical bottleneck. Hence, in our study, it was decided to keep 120 minutes as a drug loading time. Based on the reported literature and our observations, it is not possible to achieve the desired drug loading of different drugs using a soaking method of less than 120 minutes. Hence it is desired to have an alternative process methodology for drug loading in 3D printed tablets.

Loading of a Drug by Solvent Curing Method

The printed tablet with an infill of 10% was used for drug loading by solvent curing method. A 91.9% drug loading was observed, tablets with different infill volumes of 25, 50, and 75% were unable to achieve sufficient drug loading because of insufficient porosity of the tablets. About 300 µL of the solvent system consisting of 50 mg of the drug was used for drug loading. This is due to the high suspension volume, which results in spilling out of the fluid from the tablet during the drug loading process, especially with low-infill tablets (i.e., >10%). Figure 7 shows the maximum loading of the drug in a 10% infill condition. After drug loading, these tablets were dried and used for further characterization. FDM 3D printing technology offers the highest degree of flexibility to manufacture versatile sizes and shapes of dosage forms. However, drug loading in

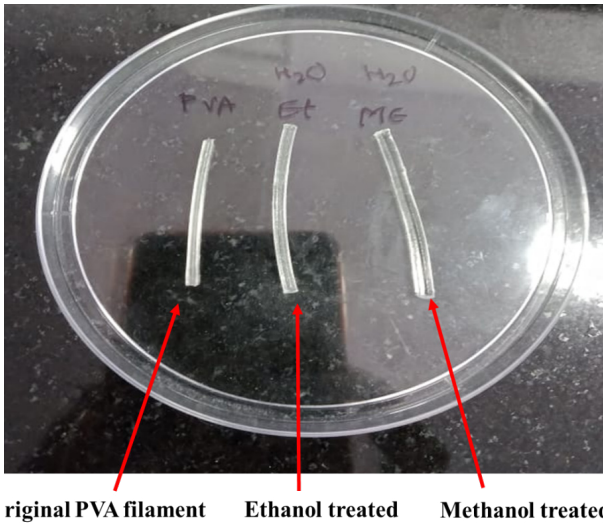

Figure 5: PVA filament after dipping into different solvents

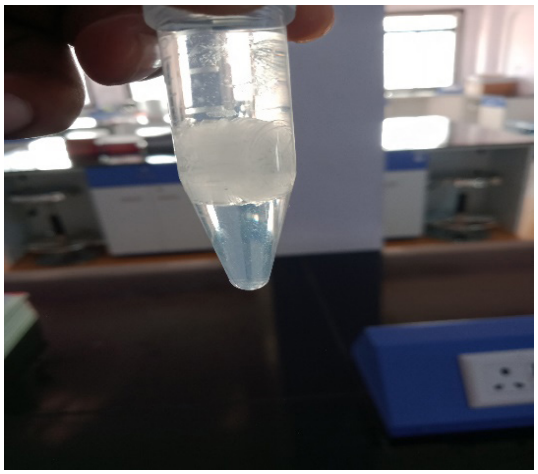

Figure 6: Layer Separation of tablet after 120 min due to solvent ratio of 8:1:1.

finished products remains a major issue to be addressed. The present study focused on developing the process for drug loading of 3D printed tablets using MET as a high soluble high-dose model drug. The use of FDM 3D printing technology for high-dose drugs is limited because of insufficient drug loading. Single-screw and twin-screw extrusion techniques prepared metformin sustained-release drug-loaded filaments. However, the use of these techniques is limited for thermostable drugs, and hence, the search for alternative technology for drug-loading is mandated to utilize the FDM 3D printing technology in routine commercial plants.[19] We have explored the solvent curing method, which utilizes low thermal stress for the evaporation of solvents, ease of manufacturing, and possibilities for commercial scale-up. However, the maximum drug loading of 91.9% (45.9 mg/tablet) was achieved. Hence, it could be difficult to use this novel solvent-curing method as a choice in the commercial manufacturing of high-dose formulations. The observations from this present investigation demonstrate that the novel solvent curring method could

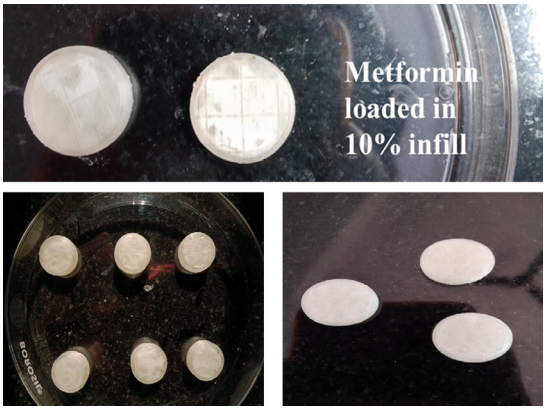

Figure 7: Drug loading of tablets in 10% infill condition using solvent curing method.

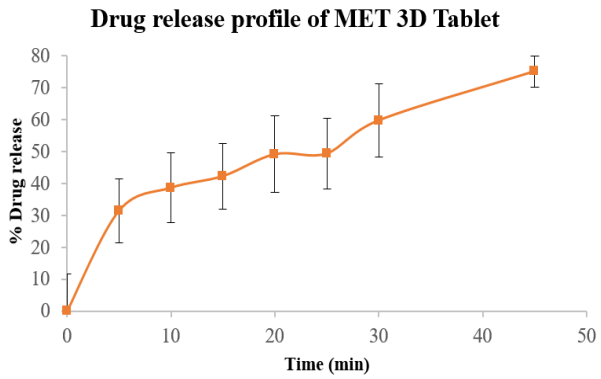

Figure 8: The drug release profile of MET 3D tablets.

have potential industrial applicability for manufacturing low/moderate doses of thermosensitive molecules using the FDM 3D printing technique.

Drug release Studies

Figure 8 illustrates the dissolution profile of FDM 3D printed tablets with 10% infill. The cumulative drug release at 45 minutes was about 72.83%. MET is a strong base and it is a HCl salt. Met has pH-independent high solubility and hence, nature, volume, and hydrodynamics have less influence on drug release profile. The drug dissolution criteria for the quality control test is> 85% in 30 minutes. However, the USP monograph recommends that 75% in 45 minutes.[20] MET being a BCS class III compound, BCS-based biowaiver could be explored for the development of a generic product. Based on biowaiver guidelines, 85% of the drug should dissolve in 15 minutes.[21] Hence, the developed product failed in dissolution studies. Moreover, the %RSD was higher than the approved regulatory limit. The probable reason for lower drug release could be due to the gelation of the polymer in dissolution media, which limits the retardation of the drug release. Further optimization of the formulation components to get the desired release profile for both immediate release and prolonged release formulation. The proposed manufacturing process also provides a degree of freedom for formulation scientists to optimize the drug release by the addition of surfactant, wetting agent, and controlled-release polymer in drug-loading solvent. Based on the preliminary findings obtained from pharmaceutical characterization data, the proposed novel method of drug loading could be useful for manufacturing both immediate-release and prolonged-release tablets using the FDM 3D printing technique.

CONCLUSION

The present study aimed to enhance the industrial applicability of the FDM 3D printing technique for manufacturing tablet dosage forms. The key issues, such as solvent selection and drug loading were bottlenecks for adopting this technique for commercial manufacturing. The solvent composition was optimized to get better tableting properties as well as to consider scale-up probabilities. Saturation solubility studies were carried out to optimize the solvent ratios. Tertiary solutions are more suitable than single and solvent systems. The traditional drug loading method was replaced with a solvent curring method, which enhances drug loading. The proposed novel method was compatible with heat-sensitive molecules and also reduced the manufacturing time. Moreover, personalized therapies in clinical settings and commercial manufacturing are also possible with the proposed method. However, being the proof-of-concept study, our aim was a feasibility assessment of this process rather than product development, and hence, some of the pharmaceutical characterizations didn't fall within the range of approved regulatory limits. But there are fair possibilities for fine-tuning these parameters well within the limit.

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