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3D Printing for Personalized and On-Demand Drug Delivery: The Next Frontier in Pharmaceutics

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ABSTRACT

There has been a change in the pharmaceutical industry as a result of the introduction of three-dimensional (3D) printing technology, which has made it feasible to manufacture oral dosage forms that are both complex and customizable. Powder bed printing and fused deposition modeling (FDM) are two of the most notable practices that have been investigated for the purpose of enhancing the precision and effectiveness of the distribution of medicine. In spite of the fact that FDM-printed oral dosage forms are often robust and won't break easily, the use of thermoplastic polymer matrices makes it challenging to ensure rapid drug release. Within the scope of this work, we evaluated the feasibility of developing fast-dissolving oral dosage forms for FDM by mixing a formulation based on poly(vinyl alcohol) with sugar alcohol. It was a successful method to print sugar alcohol-containing filaments into oral dosage forms with a shape that was defined. Research conducted on the rate of medication release revealed that a dosage form in the shape of a ring that contains 55% maltitol has the potential to release more than 85 percent of the drug in less than 15 minutes. Dogs that were subjected to in vivo testing demonstrated oral absorption that was comparable to that of conventional tablets that dissolve quickly inside the mouth. With the use of 3D computer-aided design (CAD), it is possible to fine-tune the dose and medication release profile via geometric change. This is very beneficial. When it comes to the creation of pharmaceutical dosage forms, 3D printing is becoming an increasingly essential technology, and our findings demonstrate that it has the potential to enhance individualized therapy.

Keywords: *3D Printing, Pharmaceutical Dosage Forms, Fast-Dissolving Tablets, Drug Release Profile, Poly(vinyl alcohol), Computer-Aided Design (CAD)*

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1. INTRODUCTION

There has been a dramatic shift in the pharmaceutical industry due to the advent of three-dimensional printing, or 3D printing. It provides an unparalleled level of freedom in the design and manufacture of oral dosage forms. 3D printing, in contrast to more traditional means of production, enables the fabrication of intricate geometries as well as customizable medicine delivery systems that are suited to the specific needs of particular patients. In a significant development, the Food and Drug Administration (FDA) has authorized Spritam®, the first additively manufactured medication for epilepsy. This approval demonstrated that additive manufacturing can fulfill regulatory criteria while also addressing patient-centric demands [1].

1.1 Technologies in 3D Printing

The pharmaceutical sector has investigated a wide variety of 3D printing techniques, each of which has its own set of advantages and disadvantages. It is difficult to obtain quick medication release when using fused deposition modeling (FDM) to extrude thermoplastic polymers layer by layer in order to construct dosage forms that are both precise and robust [2]. This is because many polymers have a sluggish dissolving tendency. Powder bed printing is an additional method that may be used to generate very porous structures. This is accomplished by affixing layers of powdered medicine and excipient, which enables the pharmaceutical to dissolve more rapidly [3]. SLS, which stands for selective laser sintering, is a process that can be used to make intricate forms that are perfect for applications that need controlled release techniques. Fusing powdered materials into solid structures without the need of support materials is the goal of this technique, which requires the use of laser light [4].

1.2 Advancements in Material Science

The creation of novel materials is very necessary in order to make the prospect of 3D-printed medications a reality. Using polymeric polymers, such as polyvinyl alcohol (PVA), which is commonly used, it is feasible to adapt the release patterns of medications according to the specific needs of the patient [5]. Although the slow dissolving rate of dosage forms is one of the most significant downsides of FDM printing, this issue may be remedied by including sugar alcohols such maltitol into the formulation [6]. With hybrid materials, which blend polymers and excipients, it is feasible to exert more control over the mechanical properties of the drug as well as the kinetics of its release [7].

Figure 1. A schematic showing several dose forms made using 3D printing

1.3 Personalized Medicine and Patient-Centric Approaches

One of the most appealing advantages of this technology is the prospect that it would provide the production of tailored pharmaceuticals via the use of 3D printing. Because of the capability of 3D printing to alter dosage, release patterns, and the combining of many pharmaceuticals into a single composition, it is now feasible to create individualized treatment programs. It is possible that patients who have complex treatment regimens, such as those in the pediatric or geriatric populations, or those for whom regular dosages may not be adequate, might benefit tremendously from making use of this. One of the most important applications of 3D printing in patient-centered healthcare is the creation of customized dose forms. Patients are more likely to comply with treatment plans when these forms are used [8].

1.4 Regulatory and Quality Control Challenges

3D printing might revolutionize the medical business, but there are regulatory and quality control hurdles that are preventing it from reaching that point just yet. In order to ensure that medications that are created via 3D printing are of a satisfactory quality, it is required to design specified methodologies and conduct rigorous validation. Having a consistent quality control system is essential because the diversity of printing parameters may have an effect on the mechanical characteristics and the release of medicine. The establishment of reliable regulatory frameworks and quality control systems is necessary in order to bring dosage forms that have been created via 3D printing to the market. There is reason to be optimistic about the prospects of 3D printing in the pharmaceutical business. The creation of innovative materials with superior mechanical and drug-release features, the incorporation of digital health technology to enable real-time monitoring and personalized modifications, and the development of manufacturing techniques that are economically feasible and scalable are all areas of research that are now being conducted. To fully use 3D printing for pharmaceutical dosage form manufacture, interdisciplinary collaboration among engineers, materials scientists, and healthcare practitioners is very

essential.

2. OBJECTIVES

1. To research and evaluate the latest advancements and applications of 3D printing technology in the manufacturing of pharmaceutical dosage forms.
2. To investigate the challenges, properties of drug release, and potential applications of 3D printing for patient-centered drug delivery and personalized medicine

3. MATERIAL AND METHOD

3.1 Materials

Polysciences, Inc. of Warrington, Pennsylvania, USA, supplied the hydrolyzed poly(vinyl alcohol) (PVA) with a molecular weight of 6,000. The Tokyo, Japan-based Roquette Japan K.K. provided both the maltitol and mannitol. Pearlitol 200SD and SweetPearl P200 are the names of the brands that sell them. We were able to get these substances from the FUJIFILM Wako Pure Chemical Corporation in Tokyo, Japan: xylitol, lactitol (lactitol monohydrate), and sucrose. The erythritol (Erythritol 100M) was supplied by the Aichi, Japan-based B Food Science Co., Ltd. The Tokyo, Japan-based Kanto Chemical Co., Inc. was found to be the sorbitan source in the end. German company BENEO-Palatinit GmbH (Mannheim) supplied the isomalt, which was called Galen IQ720. A trip to Tokyo, Japan's Tokyo Chemical Industry Co., Ltd. was in order to get the triethyl citrate (TEC). Chemically, N2-[(2E)-3-(4-chlorophenyl)-2-propenoyl] is a good example of a pharmacological model. A 2-oxo-2-(4-[6-(trifluoromethyl) pyrimidine-4-yl]oxy piperidine-l-yl)ethyl) is the chemical name for the substance. Both the API and the standard fast-dissolving tablet came from Tokyo, Japan's Astellas Pharma, Inc. The API may be described by the following properties: molecular weight of 617.02, pH of 4.4, logD7.4 of 4.3, PSA of 78.8, and solubility of 5 mg/mL in a pH 1.2 buffer solution. This investigation made use of analytical grade materials.

3.2 Filament preparation and FDM printing of the oral dosage form

The filaments were manufactured by the process of extrusion with hot melt. Twenty grams of the material, including the pharmaceutical component and additional excipients, were hand-mixed in a plastic bag. A conical twin screw extruder (Xplore Conical Twin Screw Extruder, Model MC15; Xplore, Sittard, The Netherlands) was used to manually feed the physical combination into its hopper. The extruder was set at a barrel temperature of 170 degrees Celsius and a screw spinning speed of fifty rotations per minute. In recirculation mode, the screw speed was maintained at 100 revolutions per minute for three minutes each time throughout the extrusion process. Various components of the formulation necessitated adjustments to the extrusion temperature, which ranged from 140 to 170 degrees Celsius. Thanks to the screw's speed at 10 revolutions per minute, the extrudate was able to escape the die after the extrusion process. Xplore, located in Sittard, the Netherlands, manufactured the winding mechanism that was used to wound the extrudate. Here, the extrudate was cooled to room temperature before being wound into filament. By regulating the winding unit's rotational speed, a consistent filament diameter may be produced. The Eagleed commercial FDM 3D printer, made in Wakayama, Japan, by Reis Enterprise, was used to make the oral dosage forms. The printer's nozzle has a diameter of half a millimeter. A hundred percent fill density, fifty millimeters per second for the nozzle travel speed, and one tenth of a millimeter for the layer height were all used during printing. Nozzle temperature was fine-tuned to be between 140 and 190 degrees Celsius, in line with filament formulation.

3.3 Measurement of Rheology

A rheological study was carried out in order to evaluate the viscoelastic properties of the PVA/sugar alcohol mixture. This was accomplished by using a HAAKE Mars 40 rheometer (Thermo Fischer Scientific, Waltham, Massachusetts, United States) that had a diameter of 25 millimeters and a gap of 1 millimeter. Using a running frequency of 1 Hz and a constant strain of 1%, a rheological investigation was conducted on the mixture. The objective of this inquiry was to explore the complex viscosity (η^*) in a manner that was dependent on temperature. The evaluation of the rheological data was carried out with the assistance of a piece of software called HAAKE Rheowin 4 Job and Data Manager, which was produced by Thermo Fisher Scientific in Waltham, Massachusetts, in that country.

3.4 Drug Release Test in Vitro

The drug release test was conducted according to the procedures outlined in the Sixteenth Edition of the Japanese Pharmacopoeia. The conditions included a temperature of 37 degrees Celsius, a paddle speed of 50 revolutions per minute, and 900 milliliters of dissolution test first fluid (pH 1.2) medium containing fifty or one hundred milligrams of drug material. The drug release test was conducted in an environment typical of a sink. In a buffer solution with a pH of 1.2, the API dissolves at a concentration of 5 mg/mL. A UV-Vis spectrophotometer and a dissolution tester (NTR-6100A, Toyama Sangyo Co., Ltd., Osaka, Japan) were used to ascertain the drug concentration in the solution. A wavelength of 285 nm

was used for the absorption measurement.

3.5 In Vivo Dog Oral Absorption Study

The study's animal tests were approved by Astellas Pharma, Inc.'s Institutional Animal Care and Use Committee, and the researchers were very cautious to follow all the necessary protocols to ensure the safety of the animals. The beagle dogs were given the sample orally and then given up to 50 mL of water via a catheter right after. Blood samples weighing 2.5 milliliters were taken at the following intervals for each of the eight time periods: 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours after the oral dose. The plasma was separated from the blood by applying centrifugal force at a force of 1870× g for 15 minutes. In order to gather all of the samples, four dogs were used. Between sixteen hours before to the first dosage and eight hours after the final blood sample, the dogs were fasted. Furthermore, the canines were instructed to hold their water intake for thirty minutes before the drug was given until two hours after the blood collection procedure was finished. A thirty-minute pre- and thirty-and-a-half-minute post-event injection of pentagastrin (0.015 mg/kg) into the muscle was administered to change the stomach's pH [9].

Using a straightforward protein precipitation method, in vivo plasma samples were extracted by combining 0.5 mL of samples with 4 mL of diethyl ether and a carbonate-bicarbonate buffer with a pH of 10. An internal standard was used, which was benzophenone, which was present in methanol at a concentration of 100 µg/mL. The materials were shaken for a period of twenty minutes prior to being subjected to centrifugation at a force of 1630× g for a duration of twenty minutes. We collected the organic phase that was present in the supernatant and then evaporated it before proceeding. After the substance had evaporated, it was redissolved in 500 microliters of mobile phase, which consisted of a mixture of acetonitrile and 0.02 M potassium hydroxide (55,45). After injecting 20 µL of the solution, the next step was to analyze it using an HPLC system with an ODS column (Inertsil ODS-3, 5 µm, 150 × 4.6 mm I.D., GL Sciences, Tokyo, Japan), as described in the manufacturer's instructions. An assay range of 0.2-20 µg/mL was created by setting a detection limit of 0.2 µg/mL. The non-compartmental model was used to ascertain pharmacokinetic parameters. Based on Certara, this device is manufactured by Pharsight Corporation of Mountain View, California, USA.

3.6 Statistical Analysis

For a sample size of three, the results are reported as the mean plus the standard deviation (SD), whereas for a sample size of two, the findings are shown as the mean plus the range. In the canine investigation, the pharmacokinetic properties of the 3D-printed oral dose form were compared to those of the traditional pill using a paired t-test. A p-value of less than 0.05 was used to determine statistical significance.

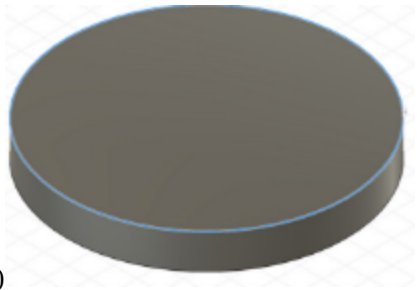
4. RESULT AND DISCUSSION

4.1 Making a 3D-printed Maltitol oral dosage form

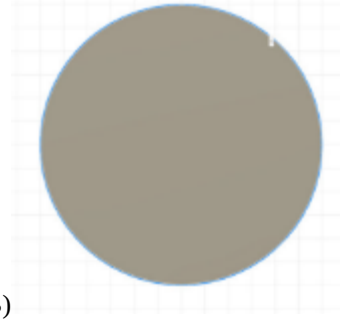
Because of its ability to dissolve in water, we decided to use a low molecular weight polyvinyl alcohol (PVA) as the major base material. This decision was made in light of the fact that the purpose of this study was to design a 3D-printed drug that dissolves rapidly. The incorporation of sugar alcohol into the PVA-based filament was done with the intention of increasing the pace at which the drug was released. We chose maltitol as our sugar alcohol of choice for two reasons: first, to test the feasibility of making filament from a sugar alcohol and PVA mixture; and second, to enhance the printed dosage form's drug release rate via the filament's use.

4.1.1. Printing the Oral Dosage Form and Preparing the Filament with Maltitol

See Table 1 for further information on the physical combination that we made by hand using 35% maltitol. We used the active pharmaceutical ingredient (API) as our model chemical to study the medication release characteristics from printed oral dosage forms. With the use of a conical twin screw extruder, we adjusted the winding procedure to make sure the filament was properly prepared before extruding. Based on the 3D CAD files, a cylindrical object with a 12 mm diameter was manufactured using FDM filament (Figure 2a). The thing had a height of 1.5 mm. The oral dose form may be effectively printed using PVA-filament with or without maltitol. After adding maltitol to PVA-filament, the temperature dropped to 165 degrees Celsius, whereas the temperature of the non-maltitol-containing filament reached 190 degrees Celsius. These findings demonstrate that the formation capability of PVA was unaffected by the addition of sugar alcohol.



(A)



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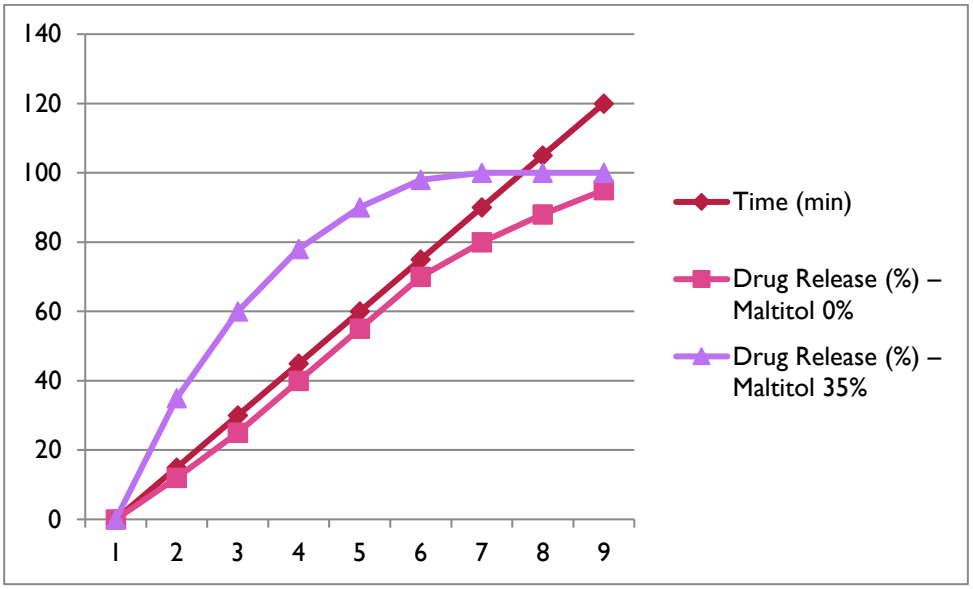


(C)

Figure 2. 3D CAD design of cylindrical dosage form and drug release profiles from PVA filaments with/without maltitol (mean ± range, n=2).

Table 1. Formulation composition and physical properties (thickness, weight) of PVA filaments with/without maltitol (mean ± range, n=2).

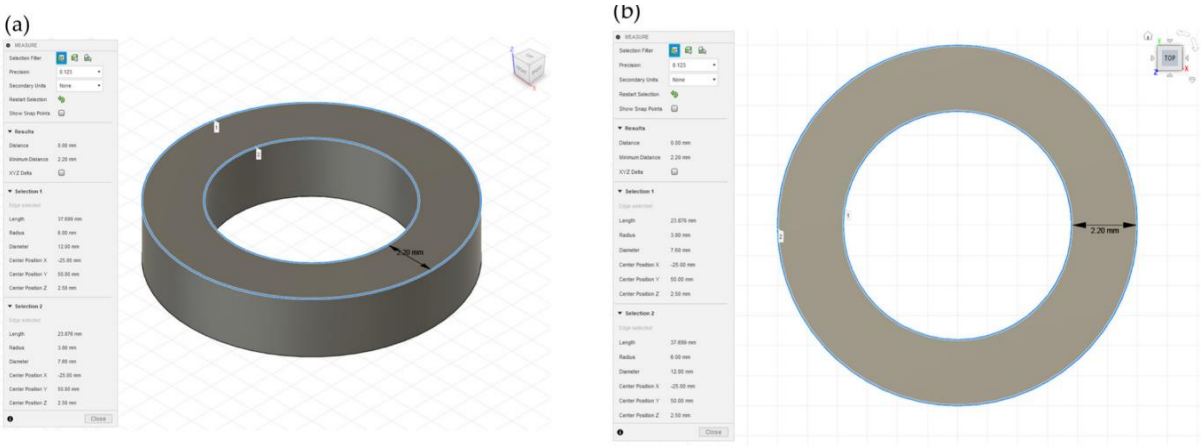
Formulation	Maltitol 0%	Maltitol 35%
API	20	20
PVA	79	40
Maltitol	-	35
TEC	1	5
Thickness (mm)	1.59 ± 0.01	1.56 ± 0.11
Weight (mg)	208.0 ± 0.5	239.2 ± 12.9

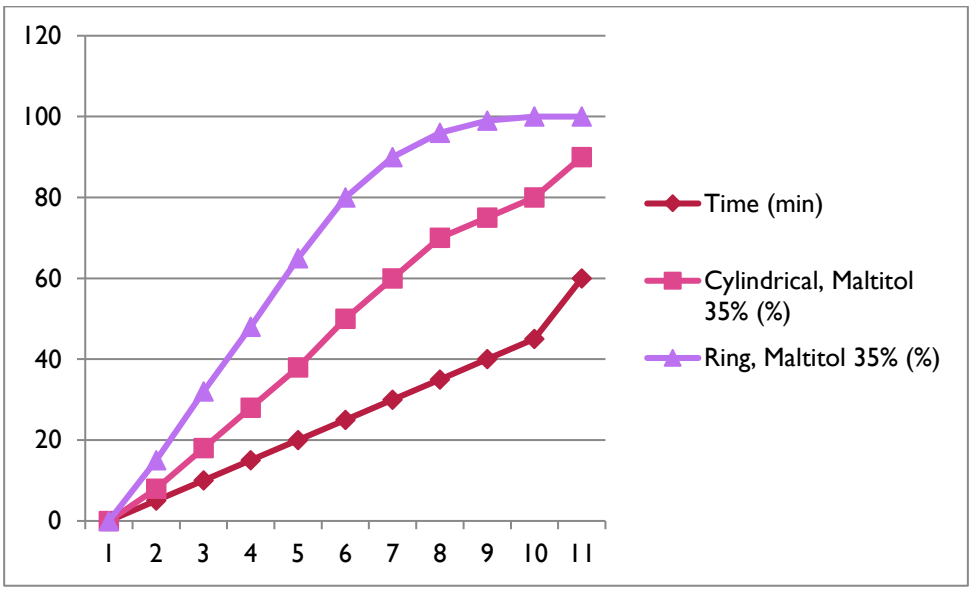
4.1.2. Maltitol-PVA Oral Drug Release Study

Figure 1b shows that both the PVA-filament and maltitol-PVA-filament oral dose forms show signs of drug release. The PVA-filament is used to print both of these mixtures. Our objective release rate is more than 85% of the medication being released within 15 minutes, and even with the addition of maltitol, the medicine was still not released quickly enough. Based on the data collected on the drug release, it seems that the dosage form dissolved completely but did not break down. Since the surface area affects the rate of drug release, we reasoned that it would be conceivable to vary the form of the object [10,11,12].

4.1.3. Changing Oral Dosage Form Shape

When it comes to the advantages of 3D printing, one of the advantages is the simplicity with which the forms of items may be adjusted according to 3D computer-aided design files. As seen in Figure 2a, we remodeled the model such that it is now a ring rather than a cylinder because of our efforts. Ring-shaped products were also effectively manufactured by using maltitol-PVA filament in the production process. The drug release patterns for both the cylinder and the ring are shown in Figure 2b for our viewing pleasure.





(C)

Figure 3. 3D CAD design of ring-shaped dosage form and drug release profiles of cylindrical (mean ± range, n=2) and ring (mean ± SD, n=3) shapes

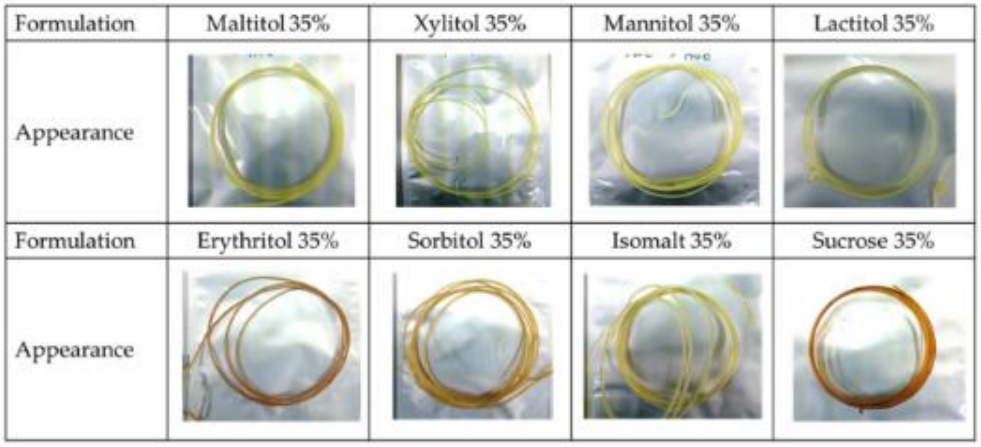
Compared to the cylindrical device, the ring-shaped one delivered the medicine significantly more quickly. When the ring shape is 2.5 mm tall, the cylindrical form (Figure 2a) and the ring shape (Figure 3b) have theoretical surface areas of 283 mm2 and 289 mm2, respectively. For shapes where the volumes are constant, this holds true. Therefore, the fact that the ring-shaped object had a faster drug release rate is more important than the fact that its surface area was really larger than the cylindrical form. in [13] Previous studies have shown that the surface area to volume ratio and the tablet's surface area are closely correlated with the rate of drug release. Since the items remained motionless at the bottom of the container during the drug release test, we reasoned that their bottoms could only have a limited impact on the medicine's release. If

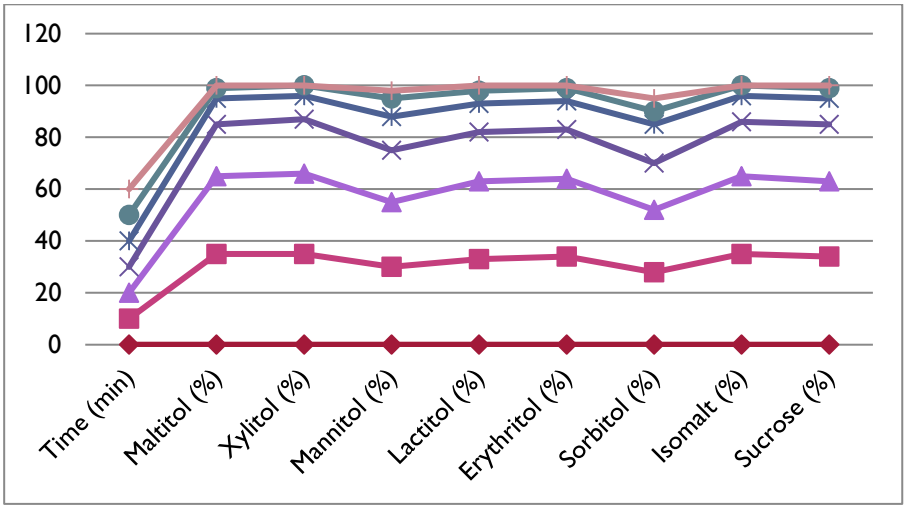
we compare the surface areas of two objects, we find that rings have 222 mm2 of usable space while cylindrical objects have 170 mm2 (not including the base) of surface area. As a result of the printing method increasing the available surface area, the ring-shaped item is believed to have a quicker drug release profile. In comparison, the medication release profile of the cylindrical shape is slower. The shape of the oral dosage form, rather than its formulation structure, may influence the rate of drug release, as we also found. Using 3D printing technology to properly generate oral dose forms is an additional benefit.

4.2. Sugar Alcohol Screening

We were able to confirm that it was feasible to manufacture a PVA filament containing maltitol. One possible use for this filament is to accelerate the dissolution of a printed oral dose form of the medicine. No matter how hard we looked, we couldn't locate a rapid medication release option that met all of our needs. This situation is really appalling. Here, we were able to create filament using xylitol, mannitol, lactitol, erythritol, sorbitol, and isomalt, which is composed of 20% active medicinal component, 40% polyvinyl alcohol, 35% sugar alcohol, and 5% TEC. We were able to do this by conducting a battery of experiments to identify the most effective sugar alcohol [14]. In addition, we used sucrose as a standard since it is a sugar and not an alcohol; at 20 °C, it dissolves quite well (2.1 g/mL). Because of this, sucrose was selected as our benchmark. The surprising thing is that any sugar alcohol, including sucrose, may be utilized to make filaments. Figure 4a shows the overall appearance of these filaments. On average, the 10 tests for each of the sugar alcohols showed an RSD value below 9%, and the filament diameters varied from 1.57 to 1.83 mm, which was highly consistent. As a result, the possibility of using these filaments in 3D printing is not completely nuts. In the course of our research, we discovered that the PVA filament may include any of these sugar alcohols. We also discovered that these sugar alcohol-PVA-filaments, when made using this specific addition ratio and procedure, could be utilized in FDM without any problems. Sugar alcohol and polyvinyl alcohol (PVA) are around 1:1 in ratio.

(a)





(B)

Figure 4. "Appearance of sugar alcohol–containing filaments and drug release profiles of ring-shaped 3D-printed dosage forms (mean ± SD, n=3).

The next step that we took was to use these filaments to print items in the form of rings (Figure 3a). When we adjusted the printing temperatures to match each formulation, we found that all of the filaments were able to do so. The temperatures had been set at 165 degrees Celsius for maltitol, 150 degrees Celsius for xylitol, 140 degrees Celsius for mannitol, 155 degrees Celsius for lactitol, 140 degrees Celsius for erythritol, 155 degrees Celsius for sorbitol, 150 degrees Celsius for isomalt, and 180 degrees Celsius for sucrose. Additionally, the pharmaceutical release characteristics are shown in Figure 4b. In spite of the fact that the sorbitol-based product had a slightly delayed drug release, there was no discernible difference between the sugar alcohols. It is possible that the drug release profile of the printed object that contained sorbitol was altered due to its ability to absorb moisture. This is because sorbitol is one of the sugar alcohols that is most hygroscopic [15], and the drug release rate of the printed object that contained sorbitol was slightly different from that of the other sugar alcohols.

4.3. Rheological Evaluation of the PVA and Sugar Alcohol Blend

In the course of this experiment, the extrusion process was carried out with the assistance of a conical twin screw extruder. As a result of the extruder, melt kneading may be performed in a system that is completely sealed. The closed system makes it relatively easy to get extrudates that are thoroughly mixed, and the equipment is appropriate for applications that are performed on a small scale, such as formulation screening [16]. Continuous procedures are often carried out with the assistance of twin screw extruders in the pharmaceutical business. More often than not, they are equipped with a barrel that contains two screws. The powder mixture is kneaded and extruded as it moves down the barrel, which is propelled by screws that revolve [17]. This occurs after the powder mixture has been fed into a hopper. This process is carried out at all times without the exception. There is a possibility of mixing defects occurring if the components have highly different melting points [18]. This is due to the fact that the materials melt slowly as they go down the barrel. By the same token, materials that have a melt viscosity that is either extraordinarily low or exceptionally high are less favorable to the melting and kneading processes. According to Kolter et al. [19], the complex viscosity of the melted material should be between 1000 and 10,000 Pa•s. This is a prerequisite for the extrusion procedure for the material. It can be shown in Figure 4b that none of the sugar alcohols considerably enhanced the rate at which the medicine was released from the oral dosage forms that were based on PVA and printed. As a result, we decided to stick with maltitol and tested the complicated viscosity of the combination of PVA and maltitol to determine whether or not it may be used once again.

Through the process of hand-mixing, sugar alcohol, PVA, and TEC were combined in the ratio of 35:60:5. We also employed sorbitol, lactitol, and maltitol as supplementary controls in this experiment. Following the melting process at a temperature of 200 degrees Celsius, the viscoelasticity of the mixture was measured using a rheometer as the temperature was lowered [20]. The results of the study are shown in Figure 5. Under all circumstances, the sorbitol-PVA mixture displayed the least difficult viscosity values among the evaluated samples. In spite of the fact that both lactitol-PVA and maltitol-PVA melt at temperatures that are almost identical (Tm: 150 °C and Tm: 148 °C, respectively), there is no difference in the complex viscosities of the two compound combinations above 140 degrees Celsius [C]. The viscosity of the maltitol-PVA complex remained within the optimal extrusion range even when maintained at temperatures varying from 95 to 150 degrees Celsius. However, when the temperature was between 100 and 135 degrees Celsius, sorbitol maintained its optimal range, and lactitol did the same thing when the temperature was between 90 and 115 degrees Celsius [21]. Given that the physical mixture melts slowly in the extruder barrel and that the temperature of the process is dependent on the formulation component that has the highest melting point, it is ideal if the complex viscosity of the melted material falls within a range that is compatible with extrusion, regardless of how high the temperature is. On the basis of these considerations, maltitol seemed to be an excellent sugar alcohol to make use of.

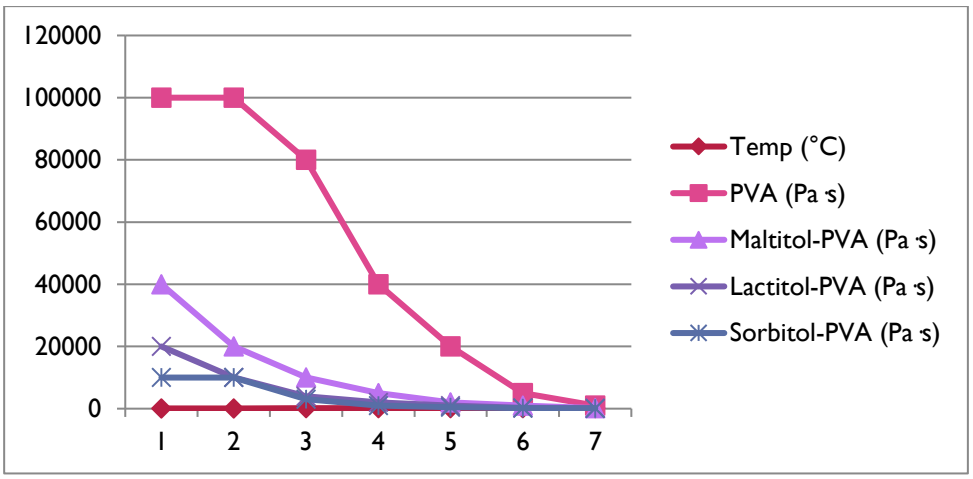


Figure 5. ***Complex viscosity (\|η\|) of PVA and sugar alcohol/PVA/TEC powder mixtures."***

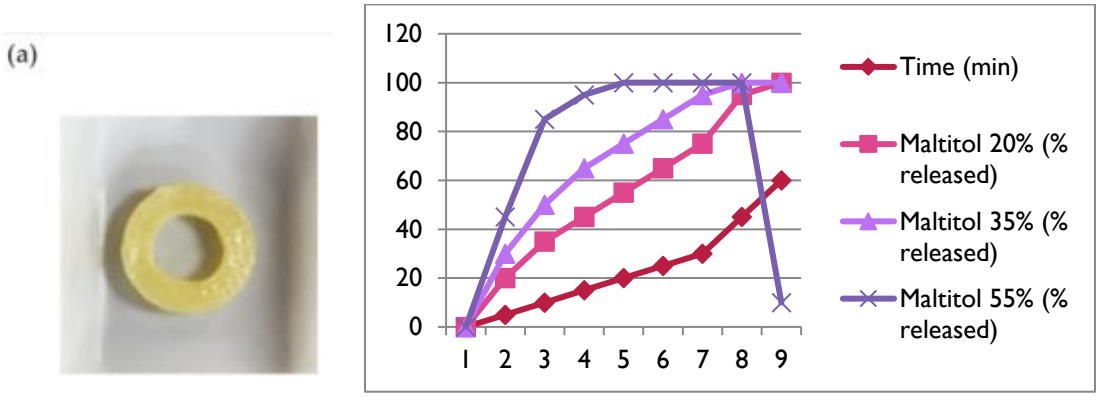
4.4. Impact of Maltitol's Addition Ratio on Filament Formulation

As was mentioned earlier, the incorporation of maltitol into the printed oral dosage form resulted in an increase in the rate at which the medicine was released into the body [22]. There is a possibility that the filament might be produced using 35% maltitol in addition to other components consisting of 20% API, 40% PVA, and 5% TEC. In light of the fact that maltitol is more soluble in water than PVA, it appeared reasonable to increase the addition ratio of this material in order to speed up the release of the drug even more. Using maltitol at a concentration of 55%, we were able to successfully produce a filament. The other components of the filament were 20% API, 20% PVA, and 5% TEC. On the other hand, when we increased the maltitol ratio to 65% (the remaining composition consisted of 20% API, 10% PVA, and 5% TEC), everything became very difficult to prepare. For the purpose of greater precision, the extrudate did not harden rapidly after it was removed from the die of the extruder, and it was not possible to wind it under tension [23]. In addition, 75% maltitol was put in the extrudate. One of the possible explanations for this phenomenon is that when the amount of PVA that is applied is low, the extrudate takes a considerable amount of time to solidify regardless of the temperature. It is necessary to prepare the filament with a certain proportion of PVA in order to circumvent this issue; in this particular case, the percentage was twenty percent. We ended up with three filaments that varied in the amount of maltitol added: 20%, 35%, and 55%. With the help of each filament and a printing temperature of 165 degrees Celsius, we successfully printed a ring-shaped oral dosage form (Figure 3a). Table 2 shows that even though the 3D CAD design was same, the printed object became heavier when the maltitol dosage was raised [24]. This might be because the addition of maltitol altered the filament's density, which would explain the observed behavior.

Table 2. Measurements taken of the printed oral dose form's thickness and weight using different ratios of maltitol to PVA filament. The data show the average plus or minus the standard deviation, with a sample size of 3.

Formulation	Maltitol 20%	Maltitol 35%	Maltitol 55%
Thickness (mm)	2.36 ± 0.09	2.62 ± 0.18	2.59 ± 0.13
Weight (mg)	229.5 ± 2.4	245.6 ± 6.8	263.2 ± 30.3

Figure 6 shows the characteristics of medication release that are linked to different dose forms. It is anticipated that the rate of drug release into the body will be enhanced with an increase in the quantity of maltitol supplied. The 55% maltitol oral dose form released more than 85% of the medicine in about 15 minutes, compared to previous prescription formulations that included 20% maltitol [25]. Earlier versions of the medication had a different percentage of maltitol (40%) and a different rate of drug release (48.7% after 15 minutes). We achieved our goal of creating a 3D-printed oral dosage form that dissolves as fast as traditional tablets, and the drug is released at a pace that is equivalent to that.



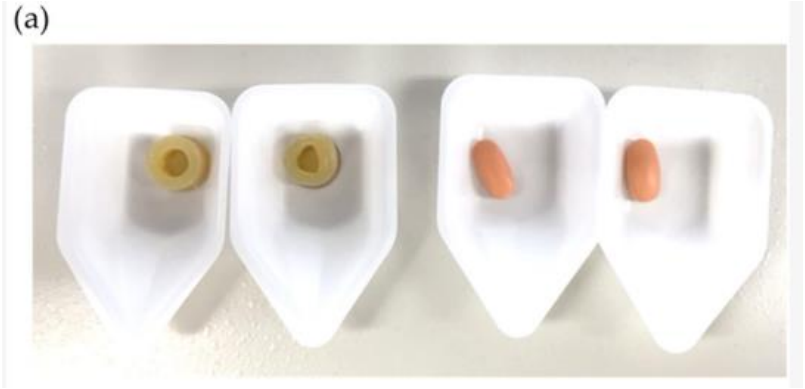
(b)

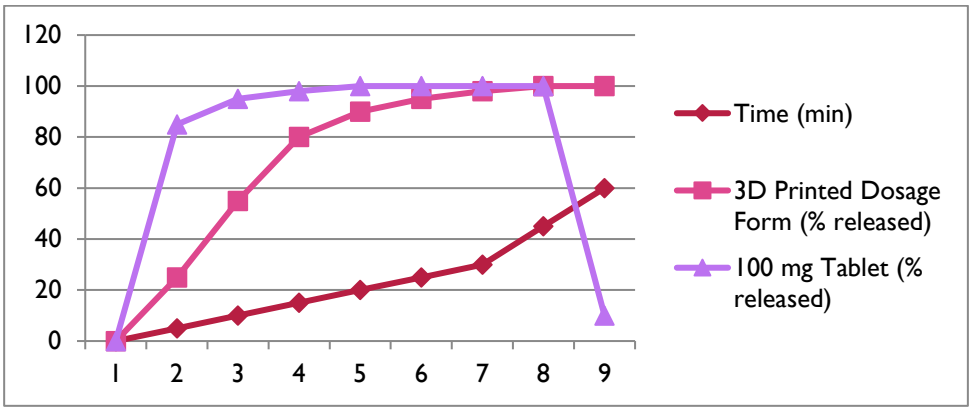
Figure 6. "Appearance and drug release of ring-shaped 3D-printed dosage forms using filaments with varying maltitol content (20–55%, mean ± SD, n=3).

4.5. Test of Oral Absorption in Living Things (Canines)

The FDM-printed oral dosage form with a profile of fast-dissolving was found to be 55% maltitol and 20% PVA. However, after the medicine was released, this form dissolved instead of disintegrating, unlike regular tablets that dissolve rapidly. Determining if this printed item will release a medication as soon in vivo as it did in vitro was also vital for further promoting the employment of FDM for pharmaceutical manufacture. A pharmaceutical component with rapid drug release and a 100 mg tablet formulation was used as the model API in this study [27]. We produced 100 mg of the printed oral dosage form using a filament that contains 55% maltitol (20% active pharmaceutical substance, 20% polyvinyl alcohol,

and 5% triethanol ether) to ensure that it could be absorbed when consumed orally. The oral dose form was designed with a ring shape and a height of 5.2 millimeters (Figure 3b). This allowed for the adjustment of the pharmaceutical component quantity to 100 milligrams. You can see the medication release characteristics for both the traditional 100 mg tablet and the 3D-printed oral dose form in Figure 7b. The 3D-printed oral dosage form demonstrated an 80% drug release in under fifteen minutes, in contrast to the fast-solving quality of the traditional tablet. Figure 6 shows that the printed dosage forms achieved an 85% drug release in only 15 minutes. Consequently, in order to manufacture 100 mg printed dosage forms, we doubled the height and quadrupled the capacity. When the volume (height) was doubled, the surface area only rose by 1.5 times, even though the accessible surface area had risen by 1.7 times [28]. A two-fold increase in height resulted in an increase of 0.85 times the value of the accessible surface area/volume. This means that the drug's release rate from 100 mg 3D-printed oral dose forms may be slower than expected.





(b)

Figure 7. "Appearance and drug release of 3D-printed oral dosage forms vs. conventional tablets (mean ± range, n=2).

When these drugs were administered orally to four beagle dogs, we examined how effectively they were absorbed by their bodies. Figure 8 shows the average blood drug concentrations, and Table 3 shows the Cmax, Tmax, and AUC0-24 hours of the medication. In terms of pharmacokinetic properties, the 3D-printed oral dose form was indistinguishable from the conventional pill. It was found that the AUC0-24 h and Tmax of the oral dosage form that was created via 3D printing were comparable to those of the conventional tablet [29]. It was also observed that the Cmax was considerably higher, however this did not approach the level of statistical significance. It may be deduced from this that the maltitol and PVA oral dosage form that was 3D printed dissolves rapidly both in vitro and in vivo [30].

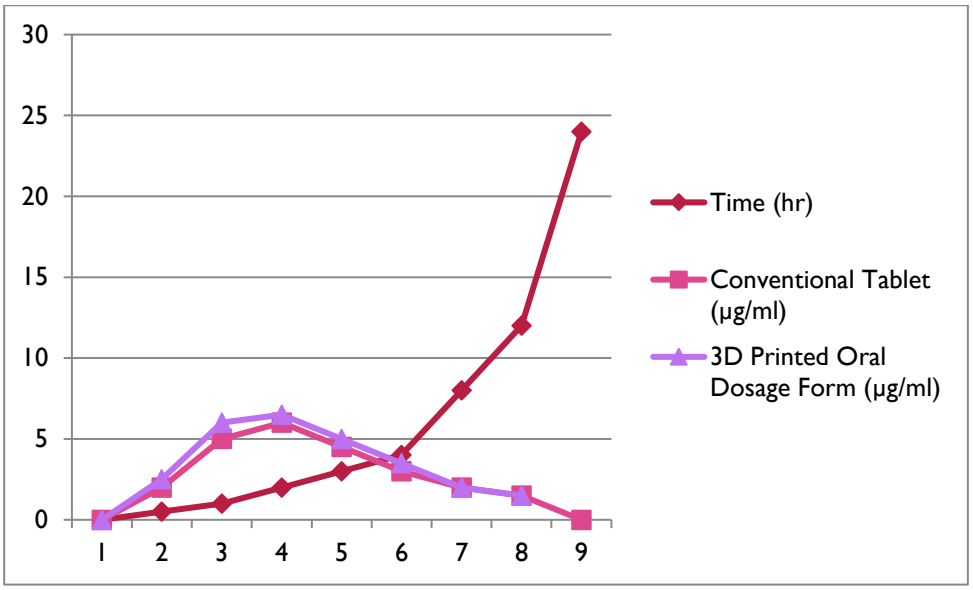


Figure 8. Beagle dogs' plasma medication concentrations following oral tablet and 3D-printed dosage form administration (mean ± SD, n=4)[31].

Table 3. Oral absorption studies pharmacokinetic characteristics in canines [32].

Samples	Cmax (µg/mL)	Tmax (h)	AUC0–24 h (µg·h/mL)
Conventional tablet	4.2 ± 2.2	1.4 ± 0.6	34.0 ± 11.1
3D-printed oral dosage form	5.6 ± 1.8	1.2 ± 0.8	35.1 ± 15.6

5. CONCLUSIONS

The results of this research show that fused deposition modeling (FDM) 3D printing might be a viable option for producing rapidly dissolving oral dosage forms. To achieve this, poly(vinyl alcohol) filaments are enhanced with sugar alcohols. The addition of maltitol accelerated the drug's escape from the container. Furthermore, by adjusting the filament composition and object form, the release profile may be fine-tuned. A ring-shaped oral dosage form made of 3D-printed maltitol discharged over 85% of its medicine content after 15 minutes in laboratory tests. When given orally, the form had an oral absorption rate that was on par with that of regular tablets, which disintegrate rapidly in vivo. According to the research, customizing pharmaceutical release profiles and dose quantities may be achieved by just adjusting the 3D CAD design, without changing the formulation composition. The results of this research show that 3D printing might be a game-changing technique for making medicine dose forms. Since this technology might allow for the creation of customized drugs, it could revolutionize the pharmaceutical sector.

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