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The Application of 3D Printing in the Formulation of Multilayered Fast Dissolving Oral Films

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ABSTRACT

Fast-dissolving oral films (FDFs) provide an alternative approach to increase consumer acceptance by advantage of rapid dissolution and administration without water. Usually, FDFs require taste-masking agents. However, inclusion of these excipients could make developing the formulation a challenging task. Hence, this work employed fused-deposition modeling three-dimensional printing to produce single-layered FDFs (SLFDFs), or multilayered FDFs (MLFDFs) films, with taste-masking layers being separated from drug layer. Filaments were prepared containing polyethylene oxide (PEO) with ibuprofen or paracetamol as model drugs at 60°C. Also, filaments were produced containing polyvinyl alcohol and paracetamol at 130°C. Furthermore, a filament was prepared containing PEO and strawberry powder for taste-masking layer. FDFs were printed at temperatures of 165°C (PEO) or 190°C (polyvinyl alcohol) with plain or mesh designs. High-performance liquid chromatography and mass spectroscopy analysis indicated active ingredient stability during film preparation process. SLFDFs had thicknesses as small as 197 ± 21 μm, and MLFDFs had thicknesses starting from 298 ± 15 μm. Depending on the formulation and design, mesh SLFDFs presented disintegration time as short as 42 ± 7 s, and this was 48 ± 5 s for mesh MLFDFs. SLFDFs showed drug content uniformity in the range of 106.0%-112.4%. In conclusion, this study provides proof-of-concept for the manufacturing of FDFs by using 3D printing.

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Introduction

Fast-dissolving oral films (FDFs) provide the opportunity to administer medicines and avoid first-pass metabolism.[1] FDFs may also be used in children,[2,3] patients with dysphagia,[4] and elderly patients.[5] Although certain products such as paracetamol are available as oral suspension, these contain additives and sugar, which may not be advisable for children.[6] In addition, administrating oral liquid formulations to children is challenging by using syringes.[7] These concerns are triggers for the development of more number of FDF formulations.

FDFs are manufactured by hot-melt extrusion or solvent-casting methods, with the latter process being popular.[8,9] The application of hot-melt extrusion process is growing due to its solvent-free, continuous production, and less chance of drug instability as the result of not using solvents.[8] In the formulation of FDFs, rapid dissolution/release of the drug is required, and at the same time, masking the drug taste is extremely important. Although there are handful of sweeteners and taste-masking agents, the presence of another ingredient in the mixture of formulation may significantly affect the physicochemical properties of the resulting paste/film. Consequently, further formulation adjustments/improvements are needed.[9] Moreover, there are challenges in the development and manufacturing of FDFs. These include achieving desired FDF weight uniformity, chemical stability of active ingredient/excipients during manufacturing process, increasing film thickness due to the die swell phenomena, and the nonhomogenous flow of powder/paste in the extrusion chamber.[8,10,11]

Three-dimensional (3D) printing has been employed in the development of complex oral dosage forms,[12-19] and at commercial scale for the production of Spritam® fast dissolving tablet.[20,21] Hence, 3D printing may become an option to develop and manufacture desired FDFs by overcoming limitations of current FDF manufacturing techniques. In particular, fused-deposition modeling 3D printing (FDM 3D) is closer to the hot-melt

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extrusion process. FDM 3D has been employed to develop various oral drug delivery systems.[17,22-28]

Conventional FDM 3D printers use filaments to produce the desired objects. In this equipment, the filament passes through a narrow tubing system and rotating pulleys/gears in the 3D printer head. Here, the filament is heated and extruded through a nozzle with narrow diameter (typically 0.4 mm). FDM 3D printers can produce objects with reproducible dimensions, in particular when filaments are used with uniform diameters (low diameter tolerance).[17] If there is an inconsistency in diameter of the filament (being too wide or too thin), either the printed object would have irregular dimensions and weight or the extruder would fail to print. Hence, FDM 3D could potentially allow manufacturing FDFs with reproducible dimensions and physicochemical properties. In addition, FDM 3D provides the opportunity of laminating more than one layer in a film. Then, these hypotheses have been examined in this article. In the present work, FDM 3D was employed to produce 3D FDFs with taste-masking layers being printed on the drug-containing layer and also to create mesh design of FDFs to reduce disintegration time. This property of 3D FDFS was compared to a commercially available FDF.

Materials and Methods

Materials

Paracetamol, polyvinyl alcohol (PVA, Mw 89,000-98,000, 99+% hydrolyzed), polyethylene oxide (PEO) Mw 100,000 Da, PEO Mw 200,000 Da, poly (ethylene) glycol (PEG) Mw 4000 Da, and PEG Mw 30,000 Da were purchased from Sigma-Aldrich (Dorset, UK). Ibuprofen was supplied by BASF SE (Ludwigshafen, Germany). Starch was obtained from BDH Chemicals (Poole, England). Sodium starch glycolate was purchased from Shin-Etsu (Tokyo, Japan). Croscarmellose sodium was acquired from FMC Europe N.V. (Brussels, Belgium). Sodium lauryl sulfate (SLS) was supplied by Janssen Pharmaceuticals (Beerse, Belgium). Freeze-dried strawberry powder was purchased from Healthy Suppliers (Hove, UK). Solvents were of analytical grade.

Preparation of Filaments

The compositions of formulations are illustrated in Table 1. Drug and excipients were ground using pestle and mortar to form fine powder and then mixed together for 15 min using a turbula mixer (Type 2B; WAB, Muttenz, Switzerland). The contents were transferred to a single-screw Noztek Pro Filament Extruder (Noztek, Shoreham, UK) with the temperatures set at 60°C for PEO and 130°C for PVA. The nozzle die diameter was 1.6 mm. The extruder was placed at a height, which provided constant gravity pull on the extrudate to achieve straight filaments with uniform diameter. As the filament was extruded, the diameter was measured every 5-10 cm using a digital vernier caliper (RS Pro, Corby, UK) to ensure uniformity of the filament. The optimum diameter was between 1.60 and 1.80 mm. If the digital vernier caliper measurements indicated that the filament diameter became greater than this range, then an object with the weight of 1 gram was added to the first part of the extruded filament to increase the gravitational force on the extrudate. This was to maintain the desired diameter of the filament. The optimum diameter of the filament was crucial for using in the 3D printer (section 3D Printing of FDFs). Preliminary studies showed that PEG with molecular weight of 30 kDa produced brittle filaments and only PEO 100 and 200 kDa produced suitable filaments. Based on these observations, PVA with large molecular weight was considered. In addition, it was found that SLS improved drug release rate from films containing PEO. Starch and super disintegrating agents (i.e., sodium starch glycolate and croscarmellose) were added to the formulations to aid disintegration of films.

3D Printing of FDFs

The films were printed using an FDM Wanhao Duplicator 4 Desktop 3D printer (Jinhua, Zhejiang, China), and SolidWorks 3DCAD (Dassault Systèmes SolidWorks Corp., Waltham, MA) was used to design the film. The printer head included extruder nozzle with diameter of 0.4 mm. The shapes of the films are provided in Table 1. The circular films were designed with the diameter of 20 mm and thickness of 0.2 mm. The square films were designed with the length of 20 mm (the same width) and the height of 0.2 mm. Mesh films were printed as square shape, to reduce the complexity of designing films. MakerWare software (version 2.2.2.89; MakerWare, Brooklyn, NY) was used to export the design into the printer. Printer extrusion parameters were 40% infill for PEO films and 100% infill for PVA films, 2 shells, 0.10 mm layer height, extruder temperature 165°C for PEO films and 190°C for PVA films, extruder speed 70 mm/s for PEO films and 90 mm/s for PVA films, and with traveling speed of 60 mm/s for PEO films and 150 mm/s for PVA films. The infill of 40% or 100% was chosen to achieve high density films with suitable mechanical strengths and adherence to the surface of 3D printer bed. Although hexagonal infill was the infill pattern, preliminary studies indicated that the infill pattern started to appear after printing first few layers on the printer bed. Sticky masking blue tape (3M™) was used to facilitate the adhesion of printed films on the printer bed. The printer bed

Table 1
The Weight Percentage Compositions of Various Ingredients in 3D Printed FDF Formulations

Formulation	PEO 100 k	PEO 200 k	PVA	Starch	Sodium Starch Glycolate	Croscarmellose	Ibuprofen	Paracetamol	SLS	Texture	Shape	Number of Layers
A	58	–	–	20	–	–	20	–	2	Plain	Circle	1
B	–	58	–	20	–	–	20	–	2	Plain	Circle	1
C	–	40		18	–	–	40	–	2	Plain	Circle	1
D	–	45	–	–	10	2	–	42	1	Plain	Circle	1
E	–	–	80	–	–	–	–	20	–	Plain	Circle	1
F	–	–	63	–	–	7	–	30	–	Plain	Circle	3 (2 taste-masking layers[a])
G	–	–	73	–	7	–	–	20	–	Mesh	Square	1
H	–	–	73	–	–	7	–	20	–	Mesh	Square	2 (one taste-masking layer[a])

[a] Taste-masking layer = PEO 100 k (80%), freeze-dried strawberry powder (20%).

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