

## Article

# 3D printed oral theophylline doses with innovative 'radiator-like' design: Impact of polyethylene oxide (PEO) molecular weight

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1 **3D Printed Oral Theophylline Doses with Innovative**  
2 **‘Radiator-Like’ Design: Impact of Polyethylene Oxide (PEO)**  
3 **Molecular Weight**

4  
5

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## 17 A B S T R A C T

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19 Despite the abundant use of polyethylene oxides (PEOs) and their integration as an excipient  
20 in numerous pharmaceutical products, there have been no previous reports of applying this  
21 important thermoplastic polymer species alone to fused deposition modelling (FDM) 3D  
22 printing. In this work, we have investigated the manufacture of oral doses via FDM 3D printing  
23 by employing PEOs as a backbone polymer in combination with polyethylene glycol (PEG).  
24 Blends of PEO (molecular weight 100K, 200K, 300K, 600K or 900K) with PEG 6K  
25 (plasticiser) and a model drug (theophylline) were hot-melt extruded. The resultant filaments  
26 were used as a feed for FDM 3D printer to fabricate oral dosage forms (ODFs) with innovative  
27 designs. ODFs were designed in a radiator-like geometry with connected paralleled plates and  
28 inter-plate spacing of either 0.5, 1, 1.5 or 2 mm. X-ray diffraction patterns of the filaments  
29 revealed the presence of two distinctive peaks at  $2\theta = 7^\circ$  and  $12^\circ$ , which can be correlated to  
30 the diffraction pattern of theophylline crystals. Varying blends of PEO and PEG allowed the  
31 formation of mechanically resistant filaments (maximum load at break of 357, 608, 649, 882,  
32 781 N for filament produced with PEO 100K, 200K, 300K, 600K or 900K, respectively).  
33 Filaments of PEO at a molecular weight of 200-600K were compatible with FDM 3D printing  
34 process. Further increase in PEO molecular weight resulted in elevated shear viscosity ( $>10^4$   
35 Pa.S) at the printing temperature and hindered material flow during FDM 3D printing process.  
36 A minimal spacing (1 mm) between parallel plates of the radiator-like design deemed essential  
37 to boost drug release from the structure. This is the first report of utilising this widely used  
38 biodegradable polymer species (PEOs and PEG) in FDM 3D printing.

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## 40 A R T I C L E I N F O

41 *Keywords:*

42 Personalised medicine, additive manufacturing, complex structures, tablets, patient-specific, structural  
43 design.

## 44        **1. Introduction**

45        Through recent advances in pharmacogenetics the relationship between an individual's  
46        genome, their genetic predisposition to disease and their response to specific medications is  
47        increasingly understood [1]. With an increased focus on patient-centred and stratified  
48        treatment, there is a growing need for a technological solution to provide individual patients  
49        with reliable and safe personalised dosage forms. In the last few years, additive manufacturing  
50        has been proposed as alternative platform for on-demand production of personalised dosage  
51        forms with significant ability to tailor the size, shape, dose as well as drug release pattern [2-  
52        4].

53        Among other commercially available technologies, fused deposition modelling (FDM) 3D  
54        printing offers major advantages, including the low cost of the printer, the absence of finishing  
55        steps and the lack need for powder facilities. These properties position FDM 3D printing as a  
56        very attractive platform for small-scale individualising for solid dosage forms. Recently,  
57        several examples of the use of FDM 3D printing for production of immediate, delayed and  
58        extended drug release have been reported [3, 5-9]. The technology proved efficacy at accurately  
59        titrating coumarin doses in animals [10] and extended drug release in gastro-retentive systems  
60        [11].

61        For the pharmaceutical industry to make a full use of 3D printing, it is essential to adapt  
62        pharmaceutical grade polymers for FDM 3D printing. Previous studies have used cellulose,  
63        methacrylate, acrylic acid or PVP derivatives to produce solid dosage forms [12]. PEO is one  
64        of the most commonly used polymers in pharmaceutical industry. PEO is commercially  
65        available between 100K to 10,000K g/mole and has been extensively used for oral and parental  
66        formulations (Gullapalli and Mazzitelli, 2015). PEOs have been commonly used to produce  
67        extended release tablets in powder compression Moroni and Ghebresellassie, 1995), hot melt  
68        extrusion (Zhang and McGinity, 1999) and in buccal tablets (Apicella et al., 1993). However,  
69        limited reports are available applying this extensively used polymer species to FDM 3D  
70        printing. In rare examples, PEO was used for formation of thin oral film in combination with  
71        other additives [13], or as an additive to methacrylate polymer for 3D printing of tablets [14].

72        In order for a filament to be compatible with the FDM 3D printing process, it requires critical  
73        mechanical and rheological criteria [15]. Previous studies have linked a filament's 3D printing  
74        compatibility with the rheological properties of the backbone polymers: poly methacrylate [8],  
75        PVA [16] and PVP-VA [16, 17]. The availability of PEOs at different molecular weight grades

76 provides the opportunity to test the impact of polymeric molecular weight and rheological flow  
77 properties of a single polymer.

78 In this work, we have investigated the fabrication of oral doses via FDM 3D printing by  
79 employing PEOs as a backbone polymer in combination with PEG as a plasticiser. We assessed  
80 the impact of polymer molecular weight on the mechanical properties of the resultant filaments  
81 and their rheological properties. We have also tested the effect of an innovative radiator-like  
82 design of the solid dosage form on the acceleration of drug release patterns.

## 83 **2. Materials and Methods**

### 84 *2.1 Materials*

85 Theophylline was supplied by Acros Organics (UK). Polyethylene glycol (PEG 6000) and all  
86 grades of polyethylene oxide (PEO) were purchased from Sigma-Aldrich (Dorset, UK).

### 87 *2.2 Preparation of filaments using hot melt extrusion (HME)*

88 Filaments were prepared by mixing polyethylene oxide (PEO molecular weight of 100K, 200K,  
89 300K, 600K, or 900K), Polyethylene Glycol (PEG 6K) and theophylline (Table 1). The  
90 mixtures were extruded using a Thermo Scientific HAAKE MiniCTW hot melt extruder  
91 (Karlsruhe, Germany) after mixing inside the extruder for 5 min at a temperature range of 60-  
92 80°C (Table1) at 35 rpm using 1.5 mm nozzle.

### 93 *2.3 Tablet design and printing*

94 Tablets were designed using Autodesk® 3ds Max Design 2016 software version 18.0  
95 (Autodesk, Inc., USA). *In the CAD design, the radiator-like tablets were structured with increasing*  
96 *inter-plate spacing of 5, 10, 15 or 20 mm whilst the overall dimensions of the design were maintained*  
97 *within the volume of 20×10×6 mm.* The templates were then imported into the 3D printer software  
98 in a stereolithography (.stl) file format. The previously extruded filaments were fed into the  
99 FDM 3D printer equipped with 0.4 mm nozzle size and MakerWare Version 2.4.0.17  
100 (Makerbot Industries, LLC, USA). Tablets were printed using modified settings of the software  
101 as described earlier in our previous work [18]: Replicator 2X; type of filament: PLA; resolution:  
102 standard; temperature of building plate: 40 °C; speed of extruder 50 mm/sec while extruding  
103 and 150 mm/sec while traveling; infill: 100%; height of the layer: 200 µm. The temperature of  
104 the nozzle for each filament is specified in Table 1.

### 105 *2.4 Thermal analysis*

106 Thermal decomposition profiles for PEOs as both received and extruded filaments were  
107 measured using a TA Q500 Thermogravimetric Analyzer TGA (TA Instruments, Elstree,  
108 Hertfordshire, UK). Samples with an average weight of 10 mg were measured from 25°C to  
109 500°C with a heating rate of 10°C/min and a nitrogen gas purge of 40/60 mL/min for  
110 sample/furnace respectively. The thermal behaviour of these samples was measured using a  
111 TA Q2000 Differential Scanning Calorimeter (DSC) (TA Instruments, Elstree, Hertfordshire,  
112 UK). Samples (5 mg) were prepared in aluminium standard pans (40 µL) and sealed with pin-  
113 holed lid. Each sample was heated from -10 to 255°C at 10°C/min under a nitrogen purge of  
114 50 mL/min. Data from TGA and DSC were analysed using a TA 2000 analysis software (TA  
115 Instruments, Elstree, Hertfordshire, UK). All measurements were carried out in triplicate.

116

### 117 *2.5 X-ray Powder diffractometry (XRPD)*

118 An X-ray powder diffractometer, D2 Phaser with Lynxeye (Bruker, Germany) was used to  
119 assess the physical form of theophylline, PEO, PEG and drug loaded filaments. Samples were  
120 scanned from  $(2\theta) = 5^\circ$  to  $50^\circ$  using  $0.01^\circ$  step width and a 1 second time count. The X-ray  
121 wavelength of 0.154 nm was used using a Cu source and a voltage of 30Kv. The divergence  
122 slit was 1 mm and the scatter slit 0.6 mm. Filament emission was 10 mA using a scan type  
123 coupled with a two theta/theta scintillation counter over 60 min.

### 124 *2.6 Hansen solubility parameter*

125 Hansen solubility parameters for the polymer and the drugs were calculated using HSPiP  
126 software (version 5.0.08).

### 127 *2.7 Scanning electron microscopy (SEM)*

128 The topography of the drug-loaded filaments and the 3D printed tablets were examined using  
129 Quanta-200 SEM microscope at 20 kV. Samples were coated under vacuum with a gold coater  
130 JFC-1200 Fine Coater (Jeol, Tokyo, Japan). In addition, photographs of tablets were collected  
131 a Canon EOS-1D Mark IV (Canon Ltd, Japan).

### 132 *2.8 Rheology studies*

133 A shear Physica MCR 501 rheometer (Anton Paar, Germany) was used in oscillation mode  
134 with a parallel plate configuration (plate diameter = 25mm). The gap between the plate and the  
135 base was set at 0.5 mm. Amplitude sweep test was performed to determine the linear

136 viscoelastic region (LVR). Afterwards, frequency sweep tests were performed at a strain  
137 amplitude of 1% (Well within the LVR region) and an angular frequency range from 100 to  
138 0.1 rad/sec. Each sample was tested at three temperatures; 100, 110 and 140°C. The readings  
139 ( $n = 6$ ) were recorded for each frequency decade (18 points in total). The test was only carried  
140 out after the normal force recorded by the device dropped below 1N, which indicates that the  
141 polymer is in a relaxed state. Power law fit was used in the linear shear thinning area of the  
142 obtained rheological data to measure the shear-thinning index ( $n$ ). Elastic ( $G'$ ) and viscous  
143 ( $G''$ ) moduli as well as complex viscosity data were recorded and plotted against the angular  
144 frequency at each temperature.

### 145 *2.9 Tensile strength studies*

146 A tensile strength testing system 5568 (Instron, Buckinghamshire, UK) was used to measure  
147 the breaking stress for filaments with irregular geometry with an average diameter of  
148 approximately 1.8 and 10mm gauge length. The diameter of the samples was measured using  
149 a Vernier micro-caliper for various sections and the average (c.a. 1.8 mm) was programmed  
150 into the software. The deformation rate (extension) was set to 20 mm/min and the data were  
151 collected every 50 msec. A sand paper was used to prevent the slipping of the sample from the  
152 clamp. Samples that showed signs of slipping from the clamp were rejected and all samples  
153 were measured in triplicate. A stress strain graph was plotted for each sample and the breaking  
154 stress was measured.

### 155 *2.10 Drug Contents and in vitro drug release studies*

156 For assessment of theophylline contents, oral doses were dissolved in 500 mL of deionised water and  
157 were stirred consciously for one hour at 40 °C until complete dissolution. Samples were filtered through  
158 a 0.22  $\mu\text{m}$  Millex-GP syringe filter (Merck Millipore, USA) and the concentration of the drug was  
159 determined using a Jenway Spectrophotometer (Bibby Scientific Ltd, UK) at  $\lambda$  max of 272 nm ( $n=3$ ).

160 To study *in vitro* theophylline release for 3D printed tablets, An AT 7 Smart USP II dissolution test  
161 apparatus (Sotax, Switzerland) was used. A dissolution medium of 900 mL 0.1M HCl (pH 1.2) at  
162  $37 \pm 0.5$  °C with a paddle speed of 50 rpm was used for 2 hours. Each experiment was carried out in  
163 triplicate. Samples were collected at 5 min intervals and drug concentration was determined using  
164 UV/VIS spectrophotometer (PG Instruments Limited, UK) at the wavelength of 272 nm and path length  
165 of 10 mm and outcome data were analysed using IDISis software 2012 (Automated Lab, UK).

### 166 *2.11 Statistical analysis*

167 The data were analysed by one-way ANOVA using SPSS Software (22.0.0.2). The level of  
168 attributed significance for comparisons were as follows:  $p > 0.05$  not significant;  $p \leq 0.05$   
169 significant.

170



### 3. Results and discussion

Polyethylene glycol (PEG) and polyethylene oxide (PEO) are two of the most widely used excipients in pharmaceutical products. Both products are also used in other healthcare applications. Both polymers are also biodegradable and suitable to be used as a polymeric biomaterial in tissue scaffolding [19]. PEGs are considered a safe choice to prepare hydrogel sealant for patients undergoing surgery [20] and are also used in the manufacturing of 3D porous scaffolds [21]. Optimisation of pharmaceutical solid dosage forms produced by FDM 3D printing requires a suitable and compatible polymer backbone for the feed filament. Initially, PEGs were first assessed producing feed filaments for FDM 3D printing (as a backbone polymer). However, the hot melt extrusion process only yielded easily breakable PEG-based filaments which lacked the required rheological and mechanical properties to enable for the use of PEGs in FDM 3D printing of solid dosage forms (data not shown). Therefore, a higher molecular weight thermoplastic polymer (PEO), was used for its mechanical and rheological properties while PEG was added as a plasticiser to facilitate the material flow and pore former to accelerate drug release from the dosage form produced by FDM 3D printing.

The thermal properties of PEOs of different molecular weights (100K-900K) were shown to be stable at  $<150^{\circ}\text{C}$  (Fig. 1A). In addition, PEO revealed a minimum moisture content with a weight loss of  $<2\%$  at  $120^{\circ}\text{C}$ . The polymer showed no significant change in thermal degradation following the compounding into a filament with the addition of PEG and theophylline via HME extrusion (Fig. 1B). Poureopolymer melting was observed above  $66\text{-}69^{\circ}\text{C}$  (data not shown) [22]. However, the compounded filament produced in this study showed slightly lower melting points (in the range of  $62\text{-}65.9^{\circ}\text{C}$ ), which could be attributed to the addition of a lower melting point additive (PEG) (Fig. 1C). Thermal profiles also illustrated that theophylline was crystalline within the polymer matrix with the appearance of theophylline melting endotherm known to be at  $\sim 240^{\circ}\text{C}$  [23].

XRD patterns confirmed the crystallinity status of PEO 200K and PEG 6K with the presence of intensity peaks at  $2\theta = 19.1^{\circ}$  and  $23.2^{\circ}$  the appearance of these peaks in the pattern of HME compounded filament suggests that polymers remained crystalline. The diffraction patterns of extruded filaments also revealed diffraction peaks at  $2\theta = 7^{\circ}$  and  $12.9^{\circ}$  (Fig. 3). The later peaks are characteristic peaks in the diffraction pattern of theophylline [7]. This confirms the crystalline structure of theophylline within the polymeric matrix. The diffraction patterns of filaments produced with other molecular weight PEOs (100K, 300K, 600K and 900K), also revealed the presence of crystalline theophylline (Supplementary data, Figs. S1-4).

The Hansen solubility parameter data of the PEO and PEG blend and the drug are shown in Table 2. The difference in solubility parameter between the PEO and PEG blend and the drug ( $\Delta\delta=7\text{ MPa}^{1/2}$ ), indicated a minimal miscibility between these molecules and predicted the presence of theophylline as a solid suspension within PEG/PEO polymeric matrix.

206 The impact of molecular weight on mechanical properties of HME compounded filaments was assessed  
207 using the tensile strength test (Fig. 3A). HME compounded filaments including PEO of 100K molecular  
208 weight showed the least maximum load before break (357N) ( $p < 0.05$ ) and were deemed too fragile. As  
209 the filament breaks instantly upon the application of gear pressure in the FDM 3D printer's head. HME  
210 compounded filaments including PEO of 200K molecular weight were able to be loaded through the  
211 gears of the FDM 3D printer head. However, frequent breakage of the filament due to the pressure of  
212 the gears interrupted the printing process and resulted in printing failure. When HME compounded  
213 filaments containing PEO of higher molecular weight (300K, 600K and 900K), the filaments were able  
214 to withstand higher tension (Fig. 3A). The maximum load at break steadily increased with longer  
215 polymer chains [24]. On the other hand, Young modulus of PEO 100K based filament reveal more  
216 brittle behaviour in comparison to filaments produced with higher molecular weight PEO (Fig. 3B).  
217 The increased plasticity of HME compounded filaments containing higher molecular weight PEO also  
218 allows the filament to withstand more pressure from the gears of the head of the FDM 3D printer and  
219 mitigates the risk of filament breakage. This increase in the strength of the filament can be related to  
220 previous observations of the reduced mobility due to the entanglement of the amorphous parts of the  
221 polymeric chains associated with an increase in the chain length [25]

222 During the FDM 3D printing process, the filament passed through lead to a hot channel that terminates  
223 in a nozzle and while the path is narrowed from 1.75 to 0.4 mm (nozzle diameter), the filament  
224 experiences an increase from room temperature to the printing temperature (110-145 °C). Therefore, it  
225 is essential to study the rheological behaviour of the filament compositions at the temperature of the  
226 printing nozzle. Hence, [complex viscosity under various angular frequency at two representative  
227 printing temperatures \(110 and 145 °C\) were performed](#) (Fig. 4). Complex viscosity of a polymer is a  
228 temperature-dependent material property [26]. Despite the similarity of the melting points across all  
229 PEO grades, the printability of each filament using FDM 3D printing was dependent on the temperature  
230 of the 3D printer temperature (Table 1). The lower complex viscosities of PEO 100K (539.8 Pa.S) and  
231 200K (1385.31 Pa.S) based filaments suggest possible flow from the hot nozzle of the 3D printer (Fig.  
232 5). However, it was not possible to physically test 3D printing using these filaments due to their  
233 incompatibility with the gears of the 3D printer's head (see above). However, HME compounded  
234 filaments including PEO of higher molecular weights allowed consistent flow from the hot nozzle at a  
235 printing temperature of 110 and 145°C for PEO 300K and 600K respectively (Fig. 5). The complex  
236 viscosity of these filaments was in the range of 9000 and 10000 at the corresponding temperature at 1%  
237 angular viscosity. Filament containing higher molecular weight PEO (900K) was observed to have a  
238 high complex viscosity (>22610 Pa.S) and was associated with restricted materials flow in the nozzle  
239 of the 3D printer and obstructed the printing of this particular filament. Further increase in nozzle  
240 temperatures (up to 220°C), did not improve material flow of this specific HME compounded filament.  
241 This may be because increasing temperature above 150 °C is likely to accelerate PEO degradation [27].

242 It can be deduced that a complex viscosity of approximately  $<8000 \text{ Pa}\cdot\text{s}$  is necessary to achieve  
243 sufficient material flow from the FDM 3D printer hot nozzle and successful completion of FDM 3D  
244 printing.

245 The viscoelastic properties of the filaments produced with PEOs of different MW were characterised  
246 through the measurement of the storage  $G'$  and loss modulus  $G''$  (Fig. 6). In general, increasing the  
247 temperature led to a decrease in both storage modulus  $G'$  and loss modulus  $G''$  across different  
248 molecular weights. Filaments containing PEO 100K were noticed to be in a terminal flow zone as  
249  $G'' > G'$ . A higher PEO molecular weight in the filament resulted in less liquid-like flow and a more  
250 elastic behaviour as the polymer was approaching crossover point. Following extrusion from the nozzle  
251 of the 3D printer, the filament loses its microstructure and conforms to the architecture dictated by the  
252 CAD design and slicing engine. This behaviour can be advantageous in FDM 3D printing as it provides  
253 a wide variety of molecular weights to select from while maintaining the same release profile. This  
254 observation needs to be repeated and validated with other drugs that may interact with PEO.

255 Unlike regular caplet design, where filaments are not only fused with lower and upper layers, but also  
256 with side printed layers, the radiator-like design only allows fusion with upper and lower layers, leading  
257 to potentially different mechanical behaviour to solid caplet design. However, it was not possible to  
258 measure the tensile strength of oral doses due to their thin structure, where weak clamping point of the  
259 structures deemed it unsuitable for the test.

260 When theophylline release from capsule-shaped tablets with PEO 600K produced by FDM 3D printing  
261 was assessed (Supplementary data, Fig. S2), a slow release profile was observed. It is likely that the  
262 drug is released through erosion of the polymeric matrix and diffusion mechanisms [28]. The polymer-  
263 rich structure of the caplet hindered drug release. The fast hydration of PEO/PEG based tablets produced  
264 by powder compression was reported to yield a gel-layer upon introduction to dissolution medium that  
265 significantly prolongs drug release [29]. In fact, PEO/PEG blends have been devised to produce tablet  
266 with extended release over 12-24 hours [30]. In such matrix systems, drug release is dependent on the  
267 rate of polymer dissolution [31], which regulates the pattern of drug release and often yields a zero  
268 order pattern [32].

269 In order to accelerate drug release from PEO matrix, an alternative novel design approach of a radiator-  
270 like architecture was evaluated (Fig. 7). The proposed geometry allows 7-8-fold increase in surface-to-  
271 mass ratio of the structure (Table 3). Moreover, the design facilitates water penetration and drug  
272 permeation from the PEO matrix by minimizing the thickness of gel-layer with the use of low-thickness  
273 plates. Four designs with identical overall dimensions but with increasing spaces (0.5, 1.0, 1.5 and 2.0  
274 mm) between the design plates were tested. With increasing inter-plate spacing within the dimensions  
275  $20 \times 10 \times 6 \text{ mm}$ , the number of plates has decreased and resulted in lower printed mass and dose (Fig. 7,  
276 Table 3). A minimum spacing of 1 mm was deemed essential to accelerate drug release from the

277 structure and meet USP criteria for immediate release products (Fig. 8A). Similar drug release was  
278 obtained within the FDM 3D-printable range of PEOs (200K-600K) (Fig. 8B). Following introduction  
279 to the dissolution apparatus, the PEO matrix hydrates and swells leading to significant growth in the  
280 thickness of the radiator plate. Despite similar surface-to-mass ratio of these oral dose designs (Table  
281 3), the 0.5mm spaced design appeared to be slower in comparison with the rest of designs. It is possible  
282 that such swelling in the 0.5 mm-spaced design resulted in plate adhesion, leading to reduction of  
283 contact surface area with the dissolution medium and hence slowing drug release. [The paper provides](#)  
284 [a unique example of how 3D printing and novel design approach can significantly alter the release](#)  
285 [profile of the same formulation. The use of radiator-like design maximised interaction with dissolution](#)  
286 [medium and prevented the formation of thick permission gel layer, which will slow down drug release.](#)  
287 [In the future, such design approach will help to personalise the release profile without the need to](#)  
288 [modify the formulation.](#)

## 289 **Conclusion**

290 This work demonstrates the effect of PEO molecular weight on the compatibility of HME compounded  
291 filaments for FDM 3D printing. A molecular weight of PEO between 300K-600K was shown to have  
292 optimal mechanical and rheological properties for the FDM 3D printing process. A lower molecular  
293 weight of PEO (100K-200K) yielded mechanically incompatible HME compounded filaments and a  
294 larger molecular weight of PEO (900K) contributed to significantly high complex viscosity and  
295 inhibited material flow. The use of a relatively low printing temperature 105-145 °C potentially extends  
296 the applicability of this technology to a wider range of active pharmaceutical ingredients. A novel  
297 radiator-like paralleled plate geometry oral doses containing widely used biodegradable polymer  
298 species (PEOs and PEG) was reported. By using this architecture, it was possible to accelerate drug  
299 release and overcome polymer hindrance of theophylline release through PEO swelling and erosion.  
300 These findings are essential in the development of next-generation personalised drug delivery doses  
301 using specialised polymer/polymer blends purposely optimised for FDM 3D printing.

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411

412 **Supplementary Data**

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