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Title	3D printed oral theophylline doses with innovative 'radiator-like' design: Impact of polyethylene oxide (PEO) molecular weight
Type	Article
URL	https://clock.uclan.ac.uk/28342/
DOI	https://doi.org/10.1016/j.ijpharm.2019.04.017
Date	2019
Citation	Isreb, Abdullah, Baj, Krzysztof, Wojsz, Magdalena, Isreb, Mohammad, Peak, Matthew and Alhnan, Mohamed A (2019) 3D printed oral theophylline doses with innovative 'radiator-like' design: Impact of polyethylene oxide (PEO) molecular weight. International Journal of Pharmaceutics, 564. pp. 98-105. ISSN 0378-5173
Creators	Isreb, Abdullah, Baj, Krzysztof, Wojsz, Magdalena, Isreb, Mohammad, Peak, Matthew and Alhnan, Mohamed A

It is advisable to refer to the publisher's version if you intend to cite from the work.
<https://doi.org/10.1016/j.ijpharm.2019.04.017>

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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

18

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° , 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.

39

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° using 0.01° 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 μm 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 λ 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 ± 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

171 3. Results and discussion

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

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

194 XRD patterns confirmed the crystallinity status of PEO 200K and PEG 6K with the presence of intensity
195 peaks at $2\theta = 19.1^\circ$ and 23.2° the appearance of these peaks in the pattern of HME compounded filament
196 suggests that polymers remained crystalline. The diffraction patterns of extruded filaments also revealed
197 diffraction peaks at $2\theta = 7^\circ$ and 12.9° (**Fig. 3**). The later peaks are characteristic peaks in the diffraction
198 pattern of theophylline [7]. This confirms the crystalline structure of theophylline within the polymeric
199 matrix. The diffraction patterns of filaments produced with other molecular weight PEOs (100K, 300K,
200 600K and 900K), also revealed the presence of crystalline theophylline (Supplementary data, Figs. S1-
201 4).

202 The Hansen solubility parameter data of the PEO and PEG blend and the drug are shown in Table 2.
203 The difference in solubility parameter between the PEO and PEG blend and the drug ($\Delta\delta=7 \text{ MPa}^{1/2}$),
204 indicated a minimal miscibility between these molecules and predicted the presence of theophylline as
205 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.

302

303

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379

380

381 **List of Figures**

382 Figure 1. TGA thermal decomposition profile of: A) raw PEO powder with molecular weights
383 (100K, 200K, 300K, 600K, and 900K), B) hot melt extruded filaments containing 30 %
384 theophylline, 35% PEG 6K, and 35% PEO (100K, 200K, 300K, 600K, and 900K), and C) DSC
385 thermographs of corresponding filaments.

386 Figure 2. Representative XRD diffraction patterns of raw theophylline, PEG 6K, raw PEO
387 200K, and hot melt extruded filament containing 35% PEO200K, 35% PEG 6K, and 30%
388 theophylline (for other grades, see Figure S1 in Supplementary Data)

389 Figure 3. Tensile strength data of A) maximum load at break and B) Young Modulus for hot
390 melt extruded filaments containing 30 % theophylline, 35% PEG 6K, and 35% PEO (100K,
391 200K, 300K, 600K, and 900K).

392 Figure 4 Shear index for filaments containing 30 % theophylline, 35% PEG 6K, and 35% PEO
393 (100K, 200K, 300K, 600K, and 900K) at 110 and 145 °C.

394 Figure 5 Shear rheometer data of complex viscosity for filaments containing 30 % theophylline,
395 35% PEG 6K, and 35% PEO (100K, 200K, 300K, 600K, and 900K) at A) 110 and B) 145 °C.

396 Figure 6 Shear rheometer data of storage modulus and loss modulus for filaments containing
397 30 % theophylline, 35% PEG 6K, and 35% PEO (100K, 200K, 300K, 600K, and 900K) at A)
398 110 and B) 145 °C.

399 Figure 7 (A1) Rendered image and (A2) photograph of radiator-like design. (B1) Top view ,
400 (B 2) side view and (B3) photograph of radiator-like doses based on theophylline :PEG
401 6K:PEO 600K 30:35:35.

402 Figure 8 *In vitro* release pattern of: A) 0.6mm, 1.0mm, 1.5mm, and 2.0mm spaced radiator-
403 like 3D printed tablet containing 30 % theophylline, 35% PEG 6K, and 35% PEO 600K, and
404 B) tablets prepared using filaments composed of 30 % theophylline, 35% PEG 6K, and 35%
405 PEO 600K.

406 **List of Tables**

407 Table 1 Composition, processing temperatures and FDM 3D printing compatibility of
408 theophylline filament based on PEO with different molecular weights.

409 Table 2 Solubility parameter and its components of theophylline and PEO/PEG in MPa^{1/2}.

410 Table 3

411

412 **Supplementary Data**

413 Figure S1a XRPD patterns of 30 % theophylline, 35% PEG 6K, and 35% PEO (100K,
414 200K, 300K, 600K, and 900K.

415 Figure S1b XRPD patterns of: A) raw theophylline, raw PEG 6K, raw PEO 100K, and
416 filament containing 30:35:35 theophylline:PEG 6K:PEO 100K, B) raw theophylline, raw
417 PEG 6K, raw PEO 200K and 30:35:35 theophylline:PEG 6K:PEO 200K.

418 Figure S1c XRPD patterns of raw theophylline, raw PEG 6K, raw PEO 300K, and filament
419 containing 30:35:35 theophylline:PEG 6K:PEO 300K.

420 Figure S1d XRPD patterns of raw theophylline, raw PEG 6K, raw PEO 600K, and filament
421 containing 30:35:35 theophylline:PEG 6K:PEO 600K.

422 Figure S1e XRPD patterns of raw theophylline, raw PEG 6K, raw PEO 900K, and filament
423 containing 30:35:35 theophylline:PEG 6K:PEO 900K.

424 Figure S2 In vitro release pattern of A) theophylline from FDM 3D printed caplet tablet and a
425 radiator-like dose with spacing of 2 mm (theophylline: PEG 6K: PEO 600K 30:35:35).

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