3D printed 3D printed Polyethylene Oxide (PEO) oral doses with innovative ‘radiator-like’ design

Abdullah Isreb[a], Krzysztof Baj[b], Magdalena Wojsz[c], Mohammad Isreb[d], Mohamed A Alhnan[a,e]*

[a] *School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, Lancashire, UK*

[b] *Faculty of Pharmacy, Medical University of Lodz, Lodz, Poland*

[c] *Faculty of Pharmacy with the Laboratory Medicine Division, Medical University of Warsaw, Warsaw, Poland*

[d] *School of Pharmacy, University of Bradford, Richmond Road, Bradford, UK*

[e] *Institute of Pharmaceutical Science, King's College London, London, UK*

A B S T R A C T

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

A R T I C L E I N F O

Keywords:

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

1. Introduction

The study of genetic polymorphism has shine the light on the effect of various genes on the susceptibility of people to certain diseases and the way they respond to medications (Hamburg and Collins, 2010). Various genes can results in a large difference in the way that people react to medication. Whether they need a larger or a smaller dose and whether they will produce a toxic effect to that drug

Fused deposition modelling (FDM) 3D printing has major advantages over other 3D printing technologies; low cost, the absence of finishing steps and lack the need for powder facilities renders it into very attractive platform for small-scale individualizing for solid dosage forms. Recently, various examples of using FDM 3D printing for production of immediate, delayed and extended drug release have been researched and reported (Goyanes et al., 2015, Li et al., 2017, Tagami et al., 2017, Pietrzak et al., 2015, Sadia et al., 2016, Skowyra et al., 2015a). The system proved efficacy for controlling the dose in animals (Arafat et al., 2018) and extended drug release in gastro-retentive systems (Li et al., 2018).

PEO is one of the most commonly used polymers in pharmaceutical industry. It is commercially available from 100K to 10,000K g/mol and have been extensively used for oral and parental formulations (Gullapalli and Mazzitelli, 2015). Low molecular weight PEO are known to have barely any bioadhesion properties in comparison to a good bioadhesion characteristics for high molecular weight (Apicella et al., 1993). PEO is a thermoplastic homo-polymer and often synthetized using ethylene oxide monomer by catalytic polymerisation. PEO has been commonly used to produce extended release tablets through powder compression (Kim, 1995), (Moroni and Ghebresellassie, 1995), hot melt extrusion (Zhang and McGinity, 1999) buccal tablets (Apicella et al., 1993).

For pharmacy to make full use of 3D printing, it is essential to adapt pharmaceutical grade polymer for FDM 3 printing. Previous attempts have used cellulose, methacrylic and corbopol PVP derivatives to achieve this goal. PEO is one of the most commonly used polymers in pharmaceutical industry. It is commercially available from 100K to 10,000K g/mol and have been extensively used for oral and parental formulations (Gullapalli and Mazzitelli, 2015).

PEO have been assessed for hot melt manufacturing for extended release pattern (Crowley et al., 2002). PEO was combined with ethylene vinyl acetate (EVA) to craft an extended release

system with swelling properties (Almeida et al., 2012). With its miscibility to small molecule (Yang et al., 2013). Limited reports are available applying this extensively used polymer species to FDM 3D printing. In a rare example, PEO was used for formation of thin oral film in combination with other additives (Ehtezazi et al., 2018), or as an additive to methacylate polymer for 3D printing of tablets (Alhijjaj et al., 2016).

In order for the filament to be compatible with FDM 3D printing process, it has to posess critical mechanical and rheological criteria. Previous attempts have linked filament's 3D printing compatibility with the rheological properties of the backbone polymers; poly methacrylate (Sadia et al., 2016), PVA (Boetker et al., 2016) and PVP-VA (Fuenmayor et al., 2018). The availability of PEO with different molecular weight grades provides the opportunity to test the impact of polymeric MW and rheological flow properties of polymer of same chemical nature.

In this work, we have investigated the fabrication of oral doses via FDM 3D printing by employing PEOs as a backbone polymer in combination with polyethylene glycol (PEG). We have employed an innovative design approach of radiator-like architectures with a various inter-block distances and assessed drug release patterns

MATERIALS AND METHODS

2.1 Materials

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

2.2 Preparation of filaments using HME

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

2.3 Tablet design and printing

Tablets were designed using Autodesk® 3ds Max Design 2016 software version 18.0 (Autodesk, Inc., USA). The templates were then imported to the 3D printer's software in a stereolithography (.stl) file format. The previously extruded filaments were fed into FDM 3D

printer equipped with 0.4 mm nozzle size and MakerWare Version Version 2.4.0.17 (Makerbot Industries, LLC, USA) and Tablets were printed using modified settings of the software as described earlier in our previous work (Skowyra et al., 2015b):Replicator 2X; type of filament: PLA; resolution: standard; temperature of building plate: 40 °C; speed of extruder 50 mm/sec while extruding and 150 mm/sec while traveling; infill: 100%; height of the layer: 200 µm. The temperature of the nozzle for each filament is specified in Tablet 1.

2.4 Thermal analysis

Thermal decomposition profiles for polymer as received and extruded filaments were measured using TA Q500 Thermogravimetric Analyzer TGA (TA Instruments, Elstree, Hertfordshire, UK). Samples with an average weight of 10 mg were measured from 25°C to 500°C with a heating rate of 10°C/min and a nitrogen gas purge of 40/60 mL/min for sample/furnace respectively.

The thermal behaviour of these samples was measured using a TA Q2000 Differential Scanning Calorimeter (DSC) (TA Instruments, Elstree, Hertfordshire, UK). Samples of 5 mg weight were prepared in a aluminium standard pans (40 µL) and sealed with pin-holed lid. Samples were heated from -10 to 255ºC at 10°C/min under a nitrogen purge of 50mL/min.

Data from TGA and DSC were analysed using a TA 2000 analysis software (TA Instruments, Elstree, Hertfordshire, UK). All measurements were carried out in triplicate.

2.5 X-ray Powder diffractometry (XRPD)

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

2.6 Hansen solubility parameter

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

2.7 Scanning electron microscopy (SEM)

The topography of the drug-loaded filaments and the printed tablets' were examined using Quanta-200 SEM microscope at 20 kV. Samples were coated under vacuum with a gold coater JFC-1200 Fine Coater (Jeol, Tokyo, Japan)

In addition to that, photographs of tablets were collected a Canon EOS-1D Mark IV (Canon Ltd, Japan).

2.8 Rheology studies

A shear Physica MCR 501 rheometer (Anton Paar, Germany) was used in oscillation mode with a parallel plate configuration (plate diameter = 25mm). The gap between the plate and the base was set at 0.5mm. Amplitude sweep test was performed to determine the linear viscoelastic region (LVR). Afterwards, frequency sweep test were performed at strain amplitude of 1% (Well within the LVR region) and an angular frequency range from 100 to 0.1 rad/sec. Each sample was tested at three temperatures; 100°, 110° or 140°C. The readings (n = 6) were recorded for each frequency decade (18 points in total). The test was only carried out after the normal force recorded by the device dropped below 1N, which indicates that the polymer is in a relaxed state. The power law fit was used in the linear shear thinning area of the obtained rheological data to measure the shear-thinning index (n). Elastic (G') and viscous (G") moduli as well as complex viscosity data were recorded and plotted against the angular frequency at each temperature value.

2.9 Tensile strength studies

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

2.10 In vitro drug release studies

An AT 7 Smart USP II dissolution test apparatus (Sotax, Switzerland) was used to study the *In vitro* drug release studies for 3D printed tablets. A dissolution medium of 900 mL at 37±0.5 °C with paddle speed of 50 rpm were used. The tablets were tested in of a stimulated gastric fluid (0.1M HCl, pH 1.2) for 2 hours. Each experiment was carried out in triplicate in. samples were collected at 5 min intervals by UV/VIS spectrophotometer (PG Instruments Limited, UK) at the wavelength of 272 nm and path length of 10 mm. Data was analysed using IDISis software 2012 (Automated Lab, UK).

2.11 Statistical analysis

One-way ANOVA was employed using SPSS Software (22.0.0.2) to analyse the results. Differences in results above probability level ($p > 0.05$) was considered not significant whilst; ($p<0.001$) were considered very significant and between $p = 0.01$ and 0.05 were considered significant.

2. Results and discussion

Polyethylene glycol (PEG) and polyethylene oxide (PEO) are two of most widely used excipients in pharmaceutical products. They are biodegradable and suitable to be used as a polymeric biomaterial in tissue scaffolding (Bliley and Marra, 2015). PEG is considered a safe choice to prepare hydrogel sealant for patients undergoing cranial surgery (Cosgrove et al., 2007) and is also used in the manufacturing of 3D porous scaffolds (Husár et al., 2014). However, HME yield easily breakable PEGs only based filaments and lack the required rheological and mechanical properties to enable its use in FDM 3D printing (data not shown). Therefore, a thermoplastic polymer (polyethylene oxide, PEO), was used as it has good mechanical and rheological properties while PEG was added as a plasticiser to facilitate the material flow and pore former to accelerate drug release the structure.

The thermal properties of PEOs of different molecular weights (100K-900K) revealed to be stable at <150^{o}C (Figure 2A). In addition to that, the polymer revealed a minimum moisture content with a weight loss of <2% at 120°C. The polymer showed no significant change in thermal degradation following the compounding into a filament with the addition of PEG theophylline via HME extrusion (Fig. 2B). DSC thermal profiles revealed an endotherm of pure polymer melting was observed above 66-69°C (data not shown) (Beech and Booth, 1970). However, the produced filament showed slightly lower melting points in the range of 62-65.9 ^{o}C, which could be attributed to the addition of lower melting point additive (PEG) (Fig 2C). Thermal profiles also illustrated that theophylline was crystalline within the polymer matrix with the appearance of theophylline melting endotherm at ~240°C (Hock et al., 2008).

XRD patterns confirmed the crystallinity status of PEO 200K and PEG 6K with the presence of intensity peaks at 2Theta= 19.1^{o} and 23.2^{o}, the appearance of these peaks in the pattern of HME compounded filament suggests that polymer remained crystalline. The diffraction patterns of extruded filaments also revealed diffraction peaks at 2θ = 7° and 12.9° (**Fig. 3**). The later peaks are distinguished peaks in the diffraction pattern of theophylline (Sadia et al., 2016, Pietrzak et al., 2015, Okwuosa et al., 2016). 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 X. The difference in solubility parameter between the PEO and PEG blend and the drug ($\Delta\delta$=7 MPa$^{1/2}$), indicated a minimal miscibility between these molecule (Table 2) and predicts the presence of theophylline as a solid suspension within PEG/PEO polymeric matrix.

The impact of molecular weight on mechanical properties has been assessed using tensile strength test (**Fig. 4A).** Filament based on PEO 100K showed the least maximum load before break (357N) and were deemed too fragile. Such filament breaks instantly upon the application of gear pressure in the FDM 3D printer head and were incompatible with FDM 3D printing. PEO 200K base filament was was possible to load through the gears of the FDM 3D printer's head. However, frequent breakage of the filament due to the pressure of the gears interrupted the printing process and result in printing failure. When PEO of higher molecular weight (300K, 600K and 900K) was employed as a backbone for the filament, a stronger filament with ability to withstand higher tension was yielded (**Fig. 4A**). The maximum load at break steadily increased with longer polymer chains (Husken and Gaymans, 2009). On the other hand, Young modulus of PEO 100K based filament reveal more brittle behaviour in comparison to filaments produced with higher molecular weight PEO **(Fig. 4B)**. The increase plasticity of the filament can withstand more pressure from gears the head of the FDM 3D printer and reduce the risk of filament breakage. This increase in the strength can be related to the reduced mobility due to the entanglement of the amorphous parts of the polymeric chains due to the increase in the chain length (Kennedy et al., 1994)

During FDM 3D printing process, the filament goes through PTFE lead to a hot channel that ends in nozzle, through this path the temperature of the process is elevated from room to the printing temperature (110-145 ^{o}C) while the path is narrowed from 1.75 to 0.4 mm (nozzle diameter). Therefore, it is essential to study the rheological behaviour of the filament compositions under the temperature of the printing nozzle. Hence, complex viscosity under various angular frequency at two representative printing temperatures: 110 and 145 °C were carried out (**Fig. 5**).

Complex viscosity of a polymer is a temperature-dependant material property (Wissbrun, 1980). Despite the similarity of the melting points across all PEO grades, the printability of the filaments using FDM 3D printing process were dependant on the 3D printer's temperature was employed (Table 1). While the complex viscosities of PEO100K and 200K based filaments of 539.8 and 1385.31 Pa.S suggests flow from the hot nozzle of the 3D printer (**Fig. 6**), it was not possible to test 3D printing using these filaments due to their incompatibility with the gears of the 3D printer's head. However, higher molecular weight filaments (300K and 600K) allowed consistent flow from the hot nozzle at a printing temperature of 110 and 145°C for PEO 300K and 600K respectively (**Fig. 6**). The complex viscosity were 9000 and 10000 at the corresponding temperature at 1% angular viscosity. Filament containing higher molecular weight PEO (900K) was noticed to have a high complex viscosity (>22610 Pa.s). This resulted in restricted materials flow in the 3D printer's nozzle and obstructed the printing of this particular filament. When higher temperature were employed (up to 220 ^{o}C), it was blockage of the nozzle. However, increasing temperature above 150 °C is likely to accelerate PEO degradation (Crowley et al., 2002). It can be deduced that a complex viscosity of approximately <8000 Pa.S is

necessary to achieve sufficient material flow from FDM 3D printer hot nozzle and successful completion of 3D printing.

The viscoelastic properties of the filaments were characterised through the measurement of the storage G` and loss modulus G`` **(Fig. 7)**. In general, increasing the temperature has led to a decrease in both storage modulus G` and loss modulus G`` across different grades. Filaments containing PEO 100K were noticed to be in a terminal flow zone as G`` is higher than that of G`. While higher PEO molecular weight in the filament resulted in less liquid-like flow and a more elastic behaviour as the polymer was getting closer to crossover point. Following extrusion from 3D printer's hot nozzle, the filament loses its microstructure and conforms to the architecture dictated by CAD design and slicing engine.

This behaviour can be advantageous in 3D printing as it provides a wide variety of molecular weights to choose from while keeping the release profile the same. This observation needs to be checked for other drugs that may interact with PEO. It is likely the drug release though erosion of the polymeric matrix and diffusion mechanisms (Shojaee et al., 2015)

Theophylline release from tablet produced with PEO 600K are shown in (Fig. 8A). When caplet was printed using 600K, a slow release profile was noted. This is likely to be related to the erosion mechanism of PEO which regulates the pattern of drug release. In order to accelerate drug release, a novel radiator-like architecture has been employed (**Fig. 9**). The proposed geometry allows significant increase in surface-to-mass ratio of the structure. In addition, the design facilitates water penetration and drug permeation from PEO matrix. Four designs with identical dimensions and increasing spaces (0.5, 1, 1.5 and 2mm) between the design plates were tested. A minimum spacing of 1 mm was deemed essential to accelerate drug release from the structure. It is possible that in the 0.5 mm-spaced radiator design, PEO swelling resulted in plates adhesion, leading to reduction of contact surface area with the dissolution medium and hence slowing down drug release. The MW of PEO appeared to have a minimal impact on theophylline release pattern for the radiator-like structure (Shojaee et al., 2015).

3. Conclusion

Novel radiator-like geometry with inter-connected paralleled oral doses based on widely used biodegradable polymer species (PEOs and PEG) were reported. By adopting this architecture, it was possible to accelerate drug release and overcome polymer hindrance of theophylline release through PEO swelling and erosion. This work also illustrates the impact of MW of PEO on compatibility of filament for FDM 3D printing. An optimal MW of PEO 300K-600K deemed to have favourable mechanical and rheological properties for FDM 3D printing process. While lower MW PEO (100-200K) yielded mechanically, incompatible filament and larger PEO grade (900K) showed significantly high complex viscosity and inhibited material flow. The use of relatively low printing temperature 105-

145 ^{o}C extends the applicability to a wider range of active molecules. These findings are essential in development of next-generation personalised drug delivery doses using specialised polymer/polymer blends purposely optimised for FDM 3D printing.

References

ALHIJJAJ, M., BELTON, P. & QI, S. 2016. An investigation into the use of polymer blends to improve the printability of and regulate drug release from pharmaceutical solid dispersions prepared via fused deposition modeling (FDM) 3D printing. *Eur J Pharm Biopharm,* 108**,** 111-125.

APICELLA, A., CAPPELLO, B., DEL NOBILE, M., LA ROTONDA, M., MENSITIERI, G. & NICOLAIS, L. 1993. Poly (ethylene oxide)(PEO) and different molecular weight PEO blends monolithic devices for drug release. *Biomaterials,* 14**,** 83-90.

ARAFAT, B., QINNA, N., CIESZYNSKA, M., FORBES, R. T. & ALHNAN, M. A. 2018. Tailored on demand anti-coagulant dosing: an in vitro and in vivo evaluation of 3D printed purpose-designed oral dosage forms. *Eur J Pharm Biopharm*.

BEECH, D. R. & BOOTH, C. 1970. Thermodynamic melting point of poly(ethylene oxide). *Journal of Polymer Science Part B: Polymer Letters,* 8**,** 731-734.

BLILEY, J. M. & MARRA, K. G. 2015. Polymeric biomaterials as tissue scaffolds. *Stem Cell Biology and Tissue Engineering in Dental Sciences.* Elsevier.

BOETKER, J., WATER, J. J., AHO, J., ARNFAST, L., BOHR, A. & RANTANEN, J. 2016. Modifying release characteristics from 3D printed drug-eluting products. *Eur J Pharm Sci,* 90**,** 47-52.

COSGROVE, G. R., DELASHAW, J. B., GROTENHUIS, J. A., TEW, J. M., VAN LOVEREN, H., SPETZLER, R. F., PAYNER, T., ROSSEAU, G., SHAFFREY, M. E. & HOPKINS, L. N. 2007. Safety and efficacy of a novel polyethylene glycol hydrogel sealant for watertight dural repair. *Journal of neurosurgery,* 106**,** 52-58.

CROWLEY, M. M., ZHANG, F., KOLENG, J. J. & MCGINITY, J. W. 2002. Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. *Biomaterials,* 23**,** 4241-8.

EHTEZAZI, T., ALGELLAY, M., ISLAM, Y., ROBERTS, M., DEMPSTER, N. M. & SARKER, S. D. 2018. The Application of 3D Printing in the Formulation of Multilayered Fast Dissolving Oral Films. *J Pharm Sci,* 107**,** 1076-1085.

FUENMAYOR, E., FORDE, M., HEALY, A. V., DEVINE, D. M., LYONS, J. G., MCCONVILLE, C. & MAJOR, I. 2018. Material Considerations for Fused-Filament Fabrication of Solid Dosage Forms. *Pharmaceutics,* 10.

GOYANES, A., BUANZ, A. B., HATTON, G. B., GAISFORD, S. & BASIT, A. W. 2015. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. *Eur J Pharm Biopharm,* 89**,** 157-62.

HAMBURG, M. A. & COLLINS, F. S. 2010. The path to personalized medicine. *New England Journal of Medicine,* 363**,** 301-304.

HOCK, C., STRASSBURG, S., HABERLAND, H., ISSENDORFF, B. V., AGUADO, A. & SCHMIDT, M. 2008. Melting-point depression by insoluble impurities: a finite size effect. *Physical review letters,* 101**,** 023401.

HUSÁR, B., HATZENBICHLER, M., MIRONOV, V., LISKA, R., STAMPFL, J. & OVSIANIKOV, A. 2014. Photopolymerization-based additive manufacturing for the development of 3D porous scaffolds. *Biomaterials for Bone Regeneration.* Elsevier.

HUSKEN, D. & GAYMANS, R. 2009. The tensile properties of poly (ethylene oxide)-based segmented block copolymers in the dry and wet state. *Journal of materials science,* 44**,** 2656-2664.

KENNEDY, M., PEACOCK, A. & MANDELKERN, L. 1994. Tensile properties of crystalline polymers: linear polyethylene. *Macromolecules,* 27**,** 5297-5310.

LI, Q., GUAN, X., CUI, M., ZHU, Z., CHEN, K., WEN, H., JIA, D., HOU, J., XU, W., YANG, X. & PAN, W. 2018. Preparation and investigation of novel gastro-floating tablets with 3D extrusion-based printing. *Int J Pharm,* 535**,** 325-332.

LI, Q., WEN, H., JIA, D., GUAN, X., PAN, H., YANG, Y., YU, S., ZHU, Z., XIANG, R. & PAN, W. 2017. Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing. *Int J Pharm,* 525**,** 5-11.

OKWUOSA, T. C., STEFANIAK, D., ARAFAT, B., ISREB, A., WAN, K. W. & ALHNAN, M. A. 2016. A Lower Temperature FDM 3D Printing for the Manufacture of Patient-Specific Immediate Release Tablets. *Pharm Res,* 33**,** 2704-12.

PIETRZAK, K., ISREB, A. & ALHNAN, M. A. 2015. A flexible-dose dispenser for immediate and extended release 3D printed tablets. *Eur J Pharm Biopharm,* 96**,** 380-7.

SADIA, M., SOSNICKA, A., ARAFAT, B., ISREB, A., AHMED, W., KELARAKIS, A. & ALHNAN, M. A. 2016. Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. *Int J Pharm,* 513**,** 659-668.

SHOJAEE, S., EMAMI, P., MAHMOOD, A., ROWAIYE, Y., DUKULAY, A., KAIALY, W., CUMMING, I. & NOKHODCHI, A. 2015. An Investigation on the Effect of Polyethylene Oxide Concentration and Particle Size in Modulating Theophylline Release from Tablet Matrices. *AAPS PharmSciTech,* 16**,** 1281-1289.

SKOWYRA, J., PIETRZAK, K. & ALHNAN, M. A. 2015a. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. *European Journal of Pharmaceutical Sciences,* 68**,** 11-17.

SKOWYRA, J., PIETRZAK, K. & ALHNAN, M. A. 2015b. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. *Eur J Pharm Sci,* 68**,** 11-17.

TAGAMI, T., FUKUSHIGE, K., OGAWA, E., HAYASHI, N. & OZEKI, T. 2017. 3D Printing Factors Important for the Fabrication of Polyvinylalcohol Filament-Based Tablets. *Biol Pharm Bull,* 40**,** 357-364.

WISSBRUN, K. F. 1980. Observations on the melt rheology of thermotropic aromatic polyesters. *British Polymer Journal,* 12**,** 163-169.

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

Filament	**Composition**	**HME**		**FDM 3D Printing Temp. (°C)**	**Compatibility with the gears of FDM 3D printer's head**
		Processing Temp. (°C)	Extrusion Temp. (°C)		
Fil K100	Theophylline:PEG 6K: PEO 100K 30:35:35	60	60	NA*	Too fragile
Fil K200	Theophylline:PEG 6K: PEO 200K 30:35:35	65	65	105	Fragile
Fil K300	Theophylline:PEG 6K: PEO 300K 30:35:35	70	70	110	Compatible
Fil K600	Theophylline:PEG 6K: PEO 600K 30:35:35	80	80	145	Compatible
Fil K900	Theophylline:PEG 6K: PEO 900K 30:35:35	80	80	NA**	Compatible

* Filament were incompatible with FDM 3D printer due to frequent filament breakage.

** Filament were incompatible with FDM 3D printer due to instant nozzle blockage.

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

	δD	**δP**	**δH**	**HSP**
Theophylline	19.7	15.4	10.5	27.1
PEO, PEG	17	10	5	20.3

Where δD, δP and δH are the dispersion, polar, and hydrogen components of solubility parameter and (HSP) Hansen solubility parameter.

Figure 1. (A1) Rendered image of radiator-like oral dose, (A2) the dose is composed paralled plates. photograph of the oral dose with using FDM 3D printing. (B1,B2) rendered image and (B3) photographs of variation of the design with increasing inter-plate spaces were printed.

Figure 2. TGA thermal decomposition profile of: A) raw PEO powder with various molecular weights (100K, 200K, 300K, 600K, and 900K), B) hot melt extruded filaments containing 30 % theophylline, 35% PEG 6K, and 35% PEO (100K, 200K, 300K, 600K, and 900K), and C) DSC thermographs of the same filaments.

Figure 3. representative XRD diffraction patterns of raw theophylline, PEG 6K, raw PEO 200K, and hot melt extruded filament containing 35% PEO200K, 35% PEG 6K, and 30% theophylline.

Figure 4. Tensile strength data of A)maximum load at break for hot melt extruded filaments containing 30 % theophylline, 35% PEG 6K, and 35% PEO (100K, 200K, 300K, 600K, and 900K), and B) Young Modulus of the same filaments.

Figure 5 Shear rhoemeter data of complex viscosity for filaments containing 30 % theophylline, 35% PEG 6K, and 35% PEO (100K, 200K, 300K, 600K, and 900K) at a) 110degrees and b) 145degrees.

Figure 6 Shear rhoemeter data of storage modulus and loss modulus for filaments containing 30 % theophylline, 35% PEG 6K, and 35% PEO (100K, 200K, 300K, 600K, and 900K) at a) 110degrees and b) 145degrees.

Figure 7 In vitro release pattern of: A) theophylline from FDM 3D printed radiator-like tablets with spacing of 0.6mm, 1.00mm, 1.5mm, and 2mm using 35%PEO 600K, PEG 6K, and 30% theophylline, and B) FDM 3D printed tablets prepared using filaments containing 30 % theophylline, 35% PEG 6K, and 35% PEO (200K, 300K, 600K, and 900K).

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

Figure 9 Images of one section of radiator-like structure printed using FDM 3d printer with filament containing 30 % theophylline, 35% PEG 6K, and 35% PEO in comparison to B) zero spacing tablet. C) Impact of spacing effect of the new radiator-like structure in comparison to standard (zero spacing) 3D printed tablets using 30 % theophylline, 35% PEG 6K, and 35% PEO 600K.

Figure S1-1 XRPD patterns of 30 % theophylline, 35% PEG 6K, and 35% PEO (100K, 200K, 300K, 600K, and 900K.

Figure S1-2 XRPD patterns of: A) raw theophylline, raw PEG 6K, raw PEO 100K, and filament containing 30:30:35 theophylline:PEG 6K:PEO 100K, B) raw theophylline, raw PEG 6K, raw PEO 200K and 30:30:35 theophylline:PEG 6K:PEO 200K.

Figure S1-3 XRPD patterns of raw theophylline, raw PEG 6K, raw PEO 300K, and filament containing 30:30:35 theophylline:PEG 6K:PEO 300K.

Figure S1-4 XRPD patterns of raw theophylline, raw PEG 6K, raw PEO 600K, and filament containing 30:30:35 theophylline:PEG 6K:PEO 600K.

Figure S1-5 XRPD patterns of raw theophylline, raw PEG 6K, raw PEO 900K, and filament containing 30:30:35 theophylline:PEG 6K:PEO 900K.