Injection Moulded Controlled Release Amorphous Solid Dispersions: Synchronized Drug and Polymer Release for Robust Performance

Shivprasad Deshmukh[a,d], Anant Paradkar[a], Susanna Abrahmsén-Alami[b],

Rydvikha Govender[b,c], Anna Viridén[b], Fredrik Winge[b], Hanna Matic[b],

Jonathan Booth[d], Adrian Kelly[a] *

[a]Centre for Pharmaceutical Engineering Science, University of Bradford, UK

[b]Pharmaceutical Technology and Development, AstraZeneca Gothenburg, Sweden

[c]Chalmers University of Technology, Gothenburg, Sweden

[d]Pharmaceutical Technology and Development, AstraZeneca, Macclesfield, UK

* Corresponding author A.L.Kelly@Bradford.ac.uk

Abstract

A study has been carried out to investigate controlled release performance of caplet shaped injection moulded (IM) amorphous solid dispersion (ASD) tablets based on the model drug AZD0837 and polyethylene oxide (PEO). The physical/chemical storage stability and release robustness of the IM tablets were characterized and compared to that of conventional extended release (ER) hydrophilic matrix tablets of the same raw materials and compositions manufactured via direct compression (DC). To gain an improved understanding of the release mechanisms, the dissolution of both the polymer and the drug were studied. Under conditions where the amount of dissolution media was limited, the controlled release ASD IM tablets demonstrated complete and synchronized release of both PEO and AZD0837 whereas the release of AZD0837 was found to be slower and incomplete from conventional direct compressed ER hydrophilic matrix tablets. The results clearly indicated that AZD0837 remained amorphous throughout the dissolution process and was maintained in a supersaturated state and hence kept stable with the aid of the polymeric carrier when released in a synchronized manner. In addition, it was found that the IM tablets were robust to variation in hydrodynamics of the dissolution environment and PEO molecular weight.

1. Introduction

With the advent of new manufacturing technologies and the need for increased process flexibility and efficiency, the paradigm in the pharmaceutical industry is shifting from batch to continous manufacturing. Among continuous technologies being applied to pharmaceuticals processing, hot melt extrusion (HME) technology continues to grow in importance mainly due to the advantage of being solvent-free and due to its ability to generate high density pellets that, through selection of suitable excipients, provide potential for improved stability and bioavalilabity of the finished solid oral dosage form (Breitenbach, 2002; Repka et al., 2018; Repka et al., 2012). One drawback with HME, however is the need for several secondary manufacturing steps to enable a final oral solid dosage form acceptable to patients with variable needs.

HME in combination with injection molding (IM) is widely used in the plastics industry to form complex shaped objects with a high degree of dimensional accuracy and reproducibility with the additional advantage of high speed (Bryce, 1996). IM has a long history in the pharmaceutical packaging and medical device field however its use as a technique for manufacturing of solid oral dosage forms was not suggested until the late 1960s (Speiser, 1969). Since then, a number of techniques have been explored for producing dosage forms using small scale IM machines, with the main drivers for this research being scalability and patentability (Cuff and Raouf, 1998; Stepto and Tomka, 1987). Additionally, manufacturing of controlled release solid oral dosage forms is possible, providing, for example, delayed release and potential targeting to colon as well as compositions preventing abuse of opioid drugs through introducing protective compartments that are resistant to destruction (Hemmingsen et al., 2011; Zema et al., 2012, Zema et al., 2013). Recently, interest in IM of pharmaceutical tablets appears to have grown, for example Eggenreich et al., 2016, compared tablets directly injection moulded from powder to those first extruded into pellets prior to moulding, and Desai et al., 2017, performed a mechanistic understanding of the effect of IM process parameters on

73 tablet properties. Other recent studies have explored the use of IM to produce release-
74 controlling capsule shells (Braitico-Vangosa et al., 2019), multi-compartmental capsules (Maroni
75 et al., 2017), tablet coatings (Puri et al., 2018), sustained release tablets (Verstraete et al.,
76 2016) and a hybrid process combining 3D printing and injection moulding (Fuenmayor et al.,
77 2019).

78 For drugs with high solubility, development of extended release (ER) hydrophilic matrix
79 based oral solid dosage forms with predictable performance (in-vitro and in-vivo) is
80 straightforward even at high doses (Siepmann and Peppas, 2000; Timmins et al., 2005; Larsson
81 et al., 2008). This is due to the fact that the release of drug from the swollen matrix for highly
82 soluble drugs is fully determined by the matrix hydration and diffusion. Developing ER
83 hydrophilic matrix tablets based on poorly soluble drugs, on the other hand, comes with many
84 challenges. Here, the release mechanism is primarily determined by the erosion process of the
85 matrix and hence to a large extent by the properties of the polymeric matrix (Larsson et al.
86 2008, Timmins et al. 2014). The result is variability in release rate throughout the gastro-
87 intestinal tract resulting from variable hydrodynamics, mechanical forces and the limited volume
88 of GI-liquid available for dissolution. This results in both inter and intra-patient variability of
89 performance (Grimm et al., 2017; Riethorst et al. 2018; Schiller et al., 2005; Weitschies et al.,
90 2010). As the drug content in the tablet composition increases the release will no longer be
91 exclusively determined by the polymer characteristics, but, to an increasing extent, also by the
92 drug characteristics such as solubility and agglomeration tendency. Knowledge of both drug and
93 polymer release and their synchronisation is a pre-requisite to assuring robust release and to
94 enable prediction (Abrahmsén-Alami et al., 2007; Caccavo et al., 2017; Kaunisto et al., 2011;
95 Tajarobi et al., 2009; Tajarobi et al., 2011). For compositions with high drug content,
96 synchronisation is not always easily achieved. Typically, the polymer release will be faster than
97 the drug release and result in incomplete drug dissolution. In environments with low volumes of
98 dissolution media, such as in the colon, the situation may be further exacerbated, highlighting

99   the need for formulations with advanced control (Amidon et al., 2015; Grimm et al., 2018;

100   Schiller et al., 2005; Sako et al., 1993; Bar-Shalom and Kindt-Larsen, 1991, Sjökvist 1988).

101   Here, the use of the amorphous state of a drug represents an opportunity for increased

102   bioavailability, enabling delivery of higher and more effective doses, although, re-crystallisation

103   or precipitation of an amorphous drug during GI-transit could still jeopardize drug bioavailability.

104   However, by careful selection of the polymeric carrier, the formation of amorphous solid

105   dispersions (ASD) can assure a system with maintained performance throughout the dissolution

106   process (Buckley et al., 2013; Wilson et al., 2018). For immediate release formulations the

107   advantage of tailoring performance through synchronized release of polymer and drug achieved

108   through intimate mixing , eg ASD's, has already been proven (Esnaashari, et al., 2005). For

109   controlled release formulations the prerequisite of synchronized release will be even more

110   important. Therefore, the use of IM to manufacture suitably formulated amorphous solid

111   dispersion solid eroding oral dosage forms with controlled release performance provides an

112   opportunity to produce robust products, optimized with regards to stability, bioavailability and

113   patient acceptability. To our knowledge this field of reasearch has until now rarely been

114   investigated (Pajander et al., 2017).

115   The aim of the work was to explore how melt extruded-injection moulded ASDs can be

116   used to produce solid dosage forms with controlled release and robust performance. In the

117   present work, solid oral dosage forms based on amorphous solid dispersions of a poorly soluble

118   drug (AZD0837) and polyethylene oxide were manufactured semi-continously using HME

119   combined with IM. AZD0837 is used as a model drug in this work and was originally developed

120   by AstraZeneca as an orally available direct thrombin inhibitor with intended use as

121   anticoagulant therapy for the prevention and treatment of thromboembolic diseases (Olsson et

122   al., 2010, Dunér et al., 2012). Early studies indicated that poly ethylene glycol (PEG) is a good

123   solubilizer for AZD0837, hence, it would be expected that PEO would function as an effective

124   ASD carrier (Unga et al., 2009). The physical/chemical storage stability and release robustness

125 of the tablets were characterisized and compared to that of conventional ER hydrophilic matrix

126 tablets of the same composition. To understand the release mechanisms the dissolution of both

127 polymer and drug were studied.

128   The underlying hypothesis behind the approach of using ASDs manufactured by IM to

129 gain predictable controlled drug release performance is that more intimate mixing between the

130 components in a non-porous homogeneous matrix would assure uniform hydration and

131 synchronized release which would reduce the likelihood of drug recrystallisation throughout

132 dissolution - both in vitro and in vivo.

133

134 2. Materials and Methods

135 AZD0837 free base was received from AstraZeneca (Gothenburg, Sweden). The two grades of

136 polyethylene oxide (PEO) polymers used were kindly supplied by Dow, Polyox WSR N10 NF

137 $(1x10^5$ g/mol) and Polyox WSR 1105 NF $(9x10^5$ g/mol). A wider range of molecular weight

138 PEOs were initially evaluated but processability of the above grades was found to be most

139 suited to the injection moulding process.

140

141 2.1 Hot melt extrusion

142 Blends containing AZD0837 and polyethyleneoxide (PEO) WSR were used for the HME. Two

143 blends containing 30% (w/w) AZD0837 (with a nominal 150 mg AZD0837 tablet strength) were

144 prepared: (i) PEO-High PM (containing 70%w/w PEO WSR1105) and (ii) PEO-Low PM

145 (containing 20%w/w PEO WSRN10 and 50%w/w PEO WSR1105). The components required

146 for the batch size of 500 g were weighed and mixed at 32 rpm using a shaker mixer (Shaker

147 Mixer TURBULA® Type T2 C, Switzerland) for 8 minutes. The prepared blends were fed

148 through a loss in weight feeder (Brabender Mini-twin, Thermo Scientific, Germany) into an

149 intermeshing co-rotating hot melt extruder (Pharmalab 16, Thermo Scientific, UK), using the

150   following temperature profile: Zone 1 = 25°C, Zone 2 = 40°C, Zone 3 = 70°C, Zone 4 to Zone 10

151   = 130°C,   a screw rotation speed of 200 rpm and a feed rate of 0.9 kg/hr. The screw

152   configuration (see supporting information) used for this work provided sufficient mechanical

153   shear and residence time to yield homogeneous ASDs. Cooled extruded strands were chopped

154   into 3 mm long cylindrical pellets using a pelletiser (Prism, Thermo Scientific, Germany).

155   Extruder melt pressure and torque values were monitored in real time throughout the run. Those

156   pellets are from hereon denoted PEO-High EX and PEO-Low EX, respectively.

157

158   **2.2 Manufacturing of IM and DC Tablets**

159   The extruded pellets of the two batches using high or low molecular weight PEO were moulded

160   into IM tablets - from hereon denoted PEO-High IM and PEO-Low IM, respectively. Pellets were

161   gravity fed into the IM machine (Roboshot s2000i-5a, Fanuc, Japan) fitted with a twin cavity

162   caplet shaped mould. The optimised process parameters for IM process were as follows;

163   injection speed: 100mm/s, pack time: 20 seconds, mould temperature: 20°C and cooling time,

164   20 seconds. In the process the temperature, shot size and pack pressure were selected based

165   on the rheological properties of the melt to ensure complete filling and effective packing of the

166   material in the mould cavity. Figure 1 shows the picture of the mould cavity design and PEO-

167   High IM tablets manufactured during this work. Directly compressed ER tablets (flat-faced

168   round, 12 mm) of the same weight and composition as IM tablets were manufactured, using a

169   Kilian SP300 single-punch tablet press (Kilian, Germany). Those tablets are from hereon

170   denoted PEO-High DC and PEO-Low DC, respectively. Prior to tabletting powders were

171   weighed and mixed using a a diffusion blender (Turbula T10B/ T2F, Willy A. Bachofen Ag,

172   Basel, Switzerland) for 10 min at 32–34 rpm.

173

2.3 Characterisation of Raw Materials, Extruded Pellets and IM Tablets

2.3.1 Thermal Characterization

The materials, extruded pellets and IM tablets were characterised using a TA instruments DSC Q2000 via a heat-cool-heat cycle. Samples were heated at 10°C/min from 25°C to 150°C and cooled to -50°C at 10°C/min and heated again at 10°C/min to 150°C to observe thermal transitions. The IM tablets were ductile in nature thus it was possible to obtain a cross section from the middle of the tablet using a scalpel from which the sample was taken.

2.3.2 Raman Spectroscopy

The solid-state form of the components of the IM tablets stored at room temperature or stressed conditions (see Results and Discussion for further details) were analysed by FT-Raman spectroscopy using a MultiRAM FT-Raman Spectrometer (Bruker Optik GmbH., Ettlingen, Germany) equipped with an Nd:YAG laser excitation source operating at 1064nm. The laser was defocused at a power of 500mW. OPUS Version 7.5 (Bruker Optik GmbH, Ettlingen, Germany) was used for instrument operation and data acquisition. An average of 256 scans was obtained for each sample to obtain a good signal-to-noise ratio with a resolution of $2cm^{-1}$. AZD0837 and PEO powders were presented to the Raman spectrometer in an NMR tube and IM tablets were mounted directly on a sample holder.

2.3.3 AZD0837 Content Analysis

The drug content of extruded pellets and tablets was measured by dissolving approximately 500 mg of pellets or tablets in 20 mL of methanol followed by dilution with 30 mL of 0.05 M phosphate buffer pH 6.8. The resulting solutions were filtered through 0.22μm PVDF syringe filters and analysed using UV-visible spectrophotometer (V-730, Jasco, UK).

2.3.4 In vitro Dissolution of AZD0837 and Polymers

Dissolution testing of IM tablets was performed using USP apparatus II (at 37°C using 900 mL 0.05 M Phosphate buffer pH 6.8 and 50 rpm) with a paddle and a basket located at the side in the dissolution bath in a position where the sample is exposed to a laminar flow (Tajarobi et al., 2009; Wingstrand et al., 1990). AZD0837 concentrations were measured with HPLC and polymer concentration was determined with SEC-MALS (Size Exclusion Chromatography coupled to Mass Spectroscopy, Wyatt Technologies, CA, USA). Samples were collected at regular intervals up to 24 hours. At each time point 5mL samples were drawn and the same volume was replaced with phosphate buffer. 100µL of each sample was injected into the SEC system equipped with a TSKgel PWxl column (7.8 mm internal diameter × 30.0 cm length), (TOSOH Corporation, Japan). A mobile phase comprising 0.1M NaCl and 0.02% NaN_3 was used for both formulations. The SEC-RI (SEC with refractive index detector) was coupled to a DAWN HELEOS II 18-angle MALS detector (Wyatt Technologies, CA, USA) and an OptilabREX refractive index detector (Wyatt Technologies, CA, USA) for concentration measurements. SEC-MALS calibration was performed using Pullulan P50 (Skandinaviska Genetec AB, Mw 4.73 $\times 10^4$, c = 0.7mg/mL in 0.1M NaCl) and polymer reference standards (in mobile phase). Data acquisition and analysis was performed using Astra software version 6.1.7.17 (Wyatt Technologies, USA). From the concentration of polymer released at each time point and an injection volume of 100 µL, concentration and cumulative % polymer release was calculated.

2.3.5 Stressed Stability Study

The stability performance of IM tablets stored at room temperature (RT) for more than 1 year and for tablets stored under stressed conditions (at 40°C and 75% RH (open) for 19 days) were determined through analysis of drug content, weight, physical form and dissolution performance. For comparison, an analogous study was made for the extruded pellets and IM tablets under ambient condition (RT) within three days after manufacturing.

3. Results and Discussion

3.1 Material Properties of Raw Materials

The melting point and associated melting enthalpy of pure materials as received from the supplier and their physical mixtures were determined and are presented in Table 1. PEO exhibits a sub-0°C glass transition temperature (T_g) and melts in the region of 66-70°C (Abu-Diak et al., 2012; Pajander et al., 2017). Thermal analysis of AZD0837 using DSC showed a melting endotherm at 117.8°C indicating the crystalline nature of the drug substance. The two grades of PEO showed melting endotherms in the range of 66.0 to 69.0°C indicative of the semi-crystalline nature of the PEO (Zhao et al., 2005). The suitability of the drug substance to form an ASD was also considered via the concept of the glass forming ability (GFA) and Glass stability (GS) as proposed by Baird (Baird et al., 2010). GFA of the material is defined as the ability of substances to vitrify on cooling from the melt. GFA accounts for the ease of vitrification of a liquid/melt upon cooling whereas GS accounts for the resistance of a glass towards devitrification upon heating (Baird et al., 2010). One of parameter often used to assess the GFA of organic molecules is the reduced glass transition temperature (T_{rg}) which was first described by Kauzmann (Kauzmann, 1948) and later proposed by Turnbull (Turnbull, 1969) equation 1:

$$T_{rg} = T_g/T_m \qquad\qquad (1)$$

Where T_g is the glass transition temperature and T_m is the melting temperature. Assuming that viscosity is constant at T_g, materials with higher T_{rg} values would be expected to have a higher viscosity between T_g and T_m and consequently be more resistant to crystallization (Baird et al., 2010). Thus, the closer the T_{rg} value is to 1, the higher the material's GFA. When the classification system is applied to assess the crystallisation tendency of AZD0837 two distinct observations were made. Firstly, its T_{rg} was found to be 0.8 suggesting that the drug substance has an excellent GFA, and, secondly, it belongs to class III i.e. no crystallisation was observed

249 upon either cooling from a completely molten state to below T_g or upon subsequent reheating to
250 the melting point (see Figure S1 in supporting information). Therefore it is well suited to
251 amorphous solid dispersion formation.

252   Thermal data, the melting enthalpies in particular, obtained from the analysis of the raw
253 materials on their own as well as in the physical mixtures were studied in conjunction with PEO
254 molecular weights. In Table 1 the estimated crystallinity of PEO grades is reported. It was found
255 that PEO WSR N10 and PEO WSR 1105 exhibited crystallinities of 88.5% and 86.9%
256 respectively, corresponding to amorphous contents of 11.5% and 13.1% respectively. This is
257 consistent with the well-known semi-crystalline nature of PEO (Bogdanov, B. and M. Mihailov ,
258 1985).

259

260 The melting enthalpy (ΔH) of drug substance in the PEO-High PM and PEO-Low PM was found
261 to be 9.1 Jg^{-1} and 1.5 Jg^{-1} respectively, which represent significant differences to the melt
262 enthalpy of pure AZD0837 (89.6 Jg^{-1}). These results suggest some crystalline content was still
263 present in the mixture after the first heating. However, the greater decrease in melting enthalpy
264 (ΔH) of AZD0837 observed in the case of PEO-Low PM suggests that AZD0837 to a larger
265 extent has been solubilised in the PEO above its melting point and remains solubilized (in the
266 amorphous regions of the polymer) upon cooling (Trotzig et al., 2007; Unga et al., 2009).
267 Furthermore, a melting point depression from 117.8°C for pure AZD0837 to 113.2°C was also
268 observed for the PEO-Low PM. This decrease in the melting point of AZD0837 is indicative of
269 greater miscibility and solubility of AZD0837 in PEO-Low PM than in PEO of high molecular
270 weight, where the drug melting point reduced only to 116.5°C (Table 1) (Deshmukh, 2015;
271 Marsac et al., 2006). The % crystallinity of PEO in the physical mixture was observed to be
272 87.7% and 92.5% for PEO-High PM and PEO-Low PM respectively which suggests PEO

273   crystallinity in the physical mixture does not significantly change and exhibits similar %

274   crystallinity when compared to the pure PEO polymers.

275

276   **3.2 Manufacturing using HME and IM**

277   IM is a cyclic process in which molten material is injected into a mould cavity under pressure

278   where it is solidified into a final shape. The process consists of five phases: (i) mould clamping;

279   (ii) injection; (iii) packing; (iv) cooling and plasticisation; (v) mould opening and part ejection.

280   During an injection phase, molten material is injected into the mould cavity at a controlled speed

281   by lateral movement of the screw. A constant pressure is then applied by the screw during the

282   packing phase to allow additional material to flow into the mould cavity during cooling and

283   solidification. This avoids formation of shrinkage marks and voids. Following a sufficient period

284   of cooling, the screw is then rotated and forced backwards to prepare the next shot of the

285   molten material, termed plasticisation. Finally, the mould halves open and the solidified parts

286   are ejected by sliding pins.

287   The HME process variables such as melt temperature, feed rate, screw speed and screw

288   configuration are known to have a possible effect on the homogeneity and quality of ASDs

289   (Repka et al., 2018; Repka et al., 2012). The screw configuration used for this work was kept

290   constant for both the formulations and the other process variables were optimised to obtain

291   homogenous ASDs (see Figure S2 and Table S1 in supporting information). The plasticisation

292   effect of PEO on the drug leads to increased molecular mobility and decreased viscosity of the

293   drug-polymer melt compared to the pure polymer system. During HME, the steady state torque

294   for PEO-High and PEO-Low was observed to be 6.32 Nm and 5.36 Nm, respectively, which

295   indicates, as expected, that the PEO-Low EX system exhibits a lower melt viscosity than PEO-

296   High EX system, which can be attributed to the difference in PEO molecular weights. Likewise,

297 the melt pressure was observed to be 28 bar and 22 bar respectively for PEO-High and PEO-

298 Low suggesting a lower viscosity of PEO-Low melt than the PEO-High.

299 The volume of melt required to form a satisfactory moulded component is termed as the shot

300 size, which is set by in the initial position of the screw. In this study, mould cavity filling was

301 optimised by increasing the shot size in increments of 1 mm, as shown for PEO-High IM tablet

302 in Figure 2. Incomplete filling and inadequate packing of moulded part leads to warping,

303 formation of sink marks and shrinkage, whereas higher pack pressure and packing time can

304 result in an increase part weight due to densification. As shown in Figure 2, a shot size of 16

305 mm was sufficient to fill the mould cavity, however a small amount of pack pressure (300 bar)

306 was essential to produce a fully formed and acceptable IM product.

307

308

309 **3.3 Thermal and Raman Analysis of IM Tablets**

310 The Figure 3A shows that pure crystalline AZD0837 displayed a melting endotherm at 117.8°C

311 but no melting endotherm was observed in either melt extruded or moulded systems, confirming

312 the formation of ASDs in all cases. The melting enthalpies of the PEO obtained in the physical

313 mixture (Table 1) were compared with enthalpies of the melt extruded and IM tablets (Table 2)

314 and a reduction in the melting enthalpy to approximately 50% was observed. This reduction is

315 also associated with a reduction in the crystallinity of PEO-Low EX and PEO-High EX to 46.1%

316 and 45.9%, respectively, after extrusion. When taking the effect of AZD0837 into account, the

317 melting enthalpy and degree of crystallinity of PEO-Low HME and PEO-High HME correspond

318 well to that previously reported for meltprocessed PEO WSR N10 (Trotzig et al., 2007). No

319 further reduction of melting enthalpy and melting temperature was observed though, after

320 injection moulding. Hence, PEO in these systems is to a higher degree amorphous which

321 contributes to its ability to solubilize the drug (Trotzig et al., 2007; Unga et al., 2009).

13

322

323 Raman spectra of the injection moulded solid dispersions were compared to that of the raw

324 materials (Figure 3B). Data is presented to reflect the fingerprint region. Peaks at 327 cm^{-1} and

325 256 cm^{-1} are characteristic of crystalline AZD0837 and their absences in both solid dispersion

326 formulations clearly indicate amorphization of the drug and it complements the obtained DSC

327 data. These peaks were well resolved from PEO peaks at 363 and 279 cm^{-1} (Figure 3B, C-F)

328 and were therefore chosen to identify the presence of crystalline AZD0837 in a region without

329 interfering peaks from raw materials. One consideration is that backscattering Raman

330 measurements constitute a surface analysis of the region of the IM tablets in the laser path.

331 Hence, Raman will not provide information about drug form in the bulk of the tablet. However,

332 absence of crystallinity in the bulk of both PEO-High IM and PEO-Low IM tablets measured by

333 DSC is consistent with complete amorphization of the drug as do the release studies discussed

334 further below (Figure 3A).

335 **3.4 Release Performance of IM and DC Tablets**

336 The in-vitro dissolution of AZD0837 (30% w/w) from IM tablets with polyethylene oxide (PEO) as

337 a matrix-former is shown in Figure 4. Complete release of AZD0837 occurred after 7 to 8 hours.

338 The polymer and drug release are clearly shown to be synchronized for both compositions

339 studied. Even though the PEO-Low IM composition contains a significant amount of low

340 molecular weight PEO (20% w/w PEO WSRN10) the release of drug and polymer is not

341 dramatically faster than that of PEO-High IM. The time to 50% release only decreased from 3.2

342 to 2.9 hours, hence, the effect of increased polymer molecular weight on the release is relatively

343 small in this case (see Table 3). Another important observation to highlight here is that the full

344 dose (nominally 150 mg) is released into the dissolution media (900 mL). This corresponds to a

345 drug concentration of 0.17 mg/ml in the bath at the end of the experiment which is close to the

346 solubility limit of the pure crystalline drug (S_0 = 0.2 mg/mL) indicating that AZD0837 most

347 probably remains in an amorphous state throughout the dissolution process even though sink

348 conditions are not met. The drug release was also studied for hot melt extruded pellets prior to

349 injection moulding (Figure S3 in Supporting Information). Drug release was found to be faster

350 for extruded pellet formulations compared to that of moulded tablets. This is thought to result

351 from a combined effect of the larger surface area available for release from pellets and the

352 possible densification of the composition resulting from higher pressures experienced in the

353 moulding process which would be expected to retard water uptake and subsequent drug

354 dissolution.

355 Direct compressed (DC) compositions containing 30% (w/w) crystalline AZD0837 with the same

356 nominal drug dose (150 mg) were manufactured for comparison with the IM tablets. In Figure 4

357 A & B the dissolution results are plotted together with the corresponding data from the IM tablets

358 using the non-sink dissolution test described above for IM tablets. Significant differences

359 between the two systems are clearly evidenced (Figure 4 and Table 3). Unlike the IM tablets

360 where the drug and polymer release are well synchronized, the drug and polymer release

361 profiles from the DC tablet are poorly synchronized and both drug and polymer dissolution are

362 significantly slower than that of the IM tablets. Also note that the difference in release of PEO

363 between PEO-High and PEO-Low is greater for the DC tablets than for IM tablets (T_{50} ratio 1.4

364 compared to 1.1), Table 3, which is discussed further below. A further observation from the data

365 presented in Figure 4 is that the drug release for DC tablets is incomplete at the end of the test

366 whereas the polymer is released fully. These results are in line with those from a previous study

367 where high dose PEO based IM tablets with carbamazepine in crystalline form did not release

368 the full drug dose (Pajander et al., 2017). Note specifically that the drug release starts to plateau

369 at the point where 100 % of the polymer is released (10 and 15 h for PEO-low DC and PEO-

370 High DC, respectively), hence after this point the pure drug characteristics fully determines the

371 release rate. Due to the immediate faster onset of polymer release observed, as the dissolution

372 process proceeds, the drug release rate becomes, increasingly limited by the reduced matrix

373 hydration rate, caused by the increased concentration of the low solubility crystalline drug in the

374 remaining matrix. Hence the full dose cannot be released under the test conditions used, in

375 which true sink conditions is not fully achieved. Interestingly, such behaviour is not observed

376 under sink conditions as exemplified by the study of Tajarobi (Tajarobi et al., 2011). In that

377 study, drug release was complete for crystalline poorly soluble drugs, and, the difference in

378 release behaviour between physical mixtures containing a poorly soluble crystalline drug and

379 solid dispersions with drug in amorphous form of the same PEO-containing compositions, was

380 minor.

381

382 Figure 5 shows polymer and drug release of the PEO-High IM tablets at varying stirring rate.

383 Upon an increase of stirring rate from 50 to 100 rpm a decrease of the time to 50% released is

384 observed (from approximately 2.9 h to 2.4 h giving a T_{50} ratio of approximately 1.2). The data

385 indicates that the release of poorly soluble drugs formulated as a controlled release amorphous

386 solid dispersion using injection moulding has a release less susceptible to variation in

387 hydrodynamics than ER matrix compositions of poorly soluble drugs made using conventional

388 manufacturing methods with similar polymers including dry powder mixing or granulation before

389 final tabletting (Abrahmsén-Alami et al., 2007; Körner et al., 2005; Wang et al., 2017). However,

390 further studies including direct comparisons would be needed to understand the difference in

391 performance in detail. It is important to note that the polymer and drug release are well

392 synchronized also at the high stirring rate even though the amount of dissolution media was

393 lower in this study (500 mL). In this case, complete dissolution of the drug dose corresponds to

394 a concentration in excess of the crystalline drug solubility and the system will become

395 supersaturated. The observation that complete drug release is observed from the IM tablets

396 under these conditions suggests that drug crystallization is insignificant and that the drug is

397 maintained in an amorphous state throughout the dissolution process. The ability of the IM

398 tablets to achieve comparable dissolution performance under different dissolution regimes with

399 respect to hydrodynamics and volume points to a high release robustness of IM tablets.

400

3.5 Stressed Stability of IM Tablets

402 The stability performance of IM tablets stored at room temperature (RT) and 20% relative

403 humidity (RH) for more than 1 year and for tablets stored under stressed conditions, 40°C and

404 75% RH (open) for 19 days, were determined through analysis of drug content, weight, physical

405 form and dissolution performance. It was found that IM tablets took up water to varying extents

406 after storage at RT and under stressed conditions (Table 4). Surprisingly, the PEO-High IM

407 tablets, in spite of the high polymer hydrophilicity, did not absorb moisture to any measurable

408 amount during storage at RT and low RH. Even under stressed conditions these tablets took up

409 only a small amount of water (~3% w/w). The tablets containing PEO of low molecular weight

410 (PEO-Low) on the other hand absorbed significantly more water at RT and under stressed

411 storage (>10%). In spite of this AZD0837 remained chemically stable during long-term RT

412 storage both in PEO-Low and PEO-High IM tablets (loss of assay < 0.2% for PEO-High and <

413 2% for PEO-Low).

414 To investigate stability against recrystallization during storage, the solid-state form of

415 AZD0837 in IM tablets was probed by Raman spectroscopy after stressed storage and

416 compared to that of IM tablets stored at RT (> 1 year) (Figure 6). In the formulation containing

417 only high molecular weight PEO, no recrystallization was evident after storage (Figures 6A and

418 6B).   In contrast, the formulation containing both high and low M_W PEO revealed minor

419 recrystallisation on storage as shown by crystalline AZD0837 peaks at 327 cm^{-1} and 256 cm^{-1}

420 (Figure 6E). This finding corresponds to the higher uptake of water of the formulation containing

17

421   low molecular weight PEO (Table 3). Water will act both as an anti-solvent for the poorly soluble

422   AZD0837 and facilitate crystallisation of the drug via plasticisation of regions of amorphous PEO

423   polymer (Trotzig et al., 2007). Re-crystallisation of amorphous PEO in the presence of water

424   with the exclusion of solubilised drug is a further mechanism to promote drug crystallisation.

425   Nonetheless, the presence of crystalline drug did not influence drug release, as shown in Figure

426   7. It should be noted however that Raman analysis is sensitive only to a small region of the

427   tablet surface, indicating that the crystallinity observed could be a very minor when compared to

428   total AZD0837 content of the IM tablets.

429   The recrystallization tendency of AZD0837 was also investigated upon hydration of the IM

430   tablets by submerging them in 100 mL of water for 30 minutes prior to analysis (Figures 6C and

431   6F). Interestingly, crystalline AZD0837 peaks that were present at the surface of the dry IM

432   tablet containing low molecular weight PEO were no longer present upon hydration (Figure 6,

433   spectra F) suggesting release of crystalline AZD0837 initially present at the tablet surface into

434   the surrounding medium or that crystallites were not present at the specific surface position

435   probed either before or after hydration.

436   Data on the recrystallization tendency of AZD0837 during storage and wetting revealed

437   that these polymeric carriers in an IM tablet were to a large extent effective in stabilising the

438   drug in an amorphous form during storage and upon hydration.To assure adequate

439   performance AZD0837 dissolution after storage at RT (> 1 year) and after stressed storage was

440   compared. The most important observation from this study is that the dissolution of AZD0837

441   did not change significantly after storage under stressed conditions (Figure 7). Only a very slight

442   increase in release rate is observed for both drug and polymer (very close to the variability of

443   the methodology), as shown in Table 3 and Figure 7. Alternatively, polymer degradation during

444   stressed storage could be suggested. However, previous work using similar process conditions

445   indicate that the polymer molecular weight should not be substantially affected by the process

446   (Pajander et al., 2017). Note here also that only 500 mL dissolution media was used for

447   dissolution testing, indicating, again, that full and robust release is assured even under non-sink

448   conditions also after the IM tablets had experienced a severe challenge with respect to

449   temperature and humidity.

450

3.6 Considerations for Robust Release Performance

451

452   The present study indicates that by formulating controlled release oral solid dosage forms

453   using IM combined with formation of ASD's provide opportunities for drug products with robust

454   release characteristics. Specifically, it is shown that the release profile and rate of release is

455   maintained under variable conditions and after stressed storage. The results of this study

456   indicate that AZD0837 in IM tablets is maintained in an amorphous solid state throughout the

457   dissolution process, and, with the aid of the polymeric carriers (here PEO), also achieves

458   supersaturated concentrations (Bevernage et al., 2013; Saboo et al., 2019). An enabler for the

459   stabilisation in the swollen matrix tablet and in solution is that the polymer and drug release are

460   synchronized throughout the dissolution process. Previous studies have shown similar and

461   synchronized release (polymer/drug) for PEO/PEG based DC tablets containing drugs with

462   relatively low aqueous solubility (butyl-parabens) in both physical mixtures and ASD's when

463   under sink-conditions (Tajarobi et al., 2011). However, the current study shows that it is not

464   possible to achieve synchronized release between polymer and drug under non-sink conditions

465   for physically mixed DC tablets with the drug in its crystalline form. The reason for this behavior

466   is that upon hydration water enters the matrix via hydrophilic polymer channels and the polymer

467   starts to dissolve and translate through the matrix. This highlights the superior robustness of IM

468   tablets compared to physical mixtures in that the formation of an ASD assures intimate mixing

469   and absence of these channels.

470   In general, for physically mixed direct compressed ER matrix systems where the release

471   rate is determined mainly by the erosion of the polymer matrix, a large variation in release rate

472   is observed when the polymer molecular weight is varied (Siepmann and Peppas, 2000). The

473   results for ASD IM tablets in the current work does not show a large variability with molecular

474   weight of the polymer. This diverges somewhat from results presented in the literature for matrix

475   tablets based on direct compressed physical mixtures of PEO of various molecular weights with

476   and without poorly soluble model drugs (Abrahmsén-Alami et al., 2007; Körner et al., 2005;

477   Maggi et al., 2002). The larger effect of polymer molecular weight on release from DC tablets of

478   the current study, however, corresponds well to historical observations. Furthermore, a recently

479   published study reported that for IM tablets with crystalline drugs, an effect of the molecular

480   weight of the PEO on the drug release is observed (Pajander et al., 2017). Hence, the reduced

481   effect of the polymer molecular weight on IM tablets of the present study appears to be related

482   to the formation of an ASD and that the polymer dissolution process is influenced by the

483   hydrophobic drug. Consequently, the release for IM tablets will to a larger extent be determined

484   by the hydration rate of the matrix (Tajarobi et al., 2011; Bar-Shalom and Kindt-Larsen 1991).

485   To clarify further, for ASD's the dissolution mechanism of both polymer and drug substance is

486   determined by characteristics of the combined system. As the content of poorly soluble or

487   sparingly soluble drug in the system increases, the rate of hydration will decrease, for both

488   physical mixtures and ASD's but the intimate mixing between the components in ASD's assure

489   uniform hydration and synchronized dissolution of polymer and drug.

490   The present work highlights the advantages of controlled release ASD IM tablets in that they

491   provide release characteristics that are more robust to several parameters of importance for in-

492   vivo performance. The compositions described in this study were proved to maintain the drug in

493   its amorphous state throughout the full dissolution process also under conditions where the

494   amount of fluid amount available to dissolve the drug was limited (Grimm et al., 2018). In future

studies of these systems it would be important to consider alternative dissolution methodologies to gain a better understanding of the in-vivo behaviour and potential additional advantages compared to tablets manufactured by direct compression (Abrahmsén-Alami et al., 2007 S., Körner, A., Nilsson, I., Larsson, A., 2007, Andreas et al., 2018; Butler et al., 2019; Kostewicz et al., 2014).

4. Conclusion

Melt extrusion combined with injection moulding was found to be an effective methodology to produce controlled release ASD dosage forms with robust performance. A twin-cavity caplet shaped mould was successfully used to produce moulded amorphous solid dispersions of AZD0837 within a PEO matrix. The melt viscosity-lowering effect of AZD0837 on PEO was found to be beneficial for mould filling during injection, resulting in dense controlled release ASD IM tablets where AZD0837 was effectively maintained in an amorphous state under various storage conditions and throughout the complete release duration (8-12 hours). When compared to conventional directly compressed ER hydrophilic matrix tablets of the same composition, controlled release IM ASD tablets were found to exhibit superior dissolution performance. Results indicated that AZD0837 in IM tablets remained amorphous throughout the dissolution process and was maintained in a supersaturated state and hence kept stable with the aid of the polymeric carrier which was shown to be released in a synchronized manner. For ER DC tablets, AZD0837 release was slower and incomplete due to poor synchronization with the polymer release. IM ASD tablets were also significantly more robust to variation in hydrodynamics of the dissolution environment and PEO molecular weight. Controlled release ASD tablets manufactured via HME-IM offer potential to be integrated into a continuous large-scale manufacturing line to achieve predictable controlled release of poorly soluble drugs throughout the gastrointestinal tract.

5. References

Abrahmsén-Alami, S., Körner, A., Nilsson, I., Larsson, A., 2007. New release cell for NMR microimaging of tablets. Swelling and erosion of poly (ethylene oxide). Int. J. Pharm. 342, 105-114. https://doi.org/10.1016/j.ijpharm.2007.05.005

Abu-Diak, O.A., Jones, D.S., Andrews, G.P., 2012. Understanding the performance of melt-extruded poly (ethylene oxide)–bicalutamide solid dispersions: Characterisation of microstructural properties using thermal, spectroscopic and drug release methods. J. Pharm. Sci. 101, 200-213. https://doi.org/10.1002/jps.22748

Amidon, S., Brown, J.E., Dave, V.S., 2015. Colon-Targeted Oral Drug Delivery Systems: Design Trends and Approaches. AAPS PharmSciTech 16, 731-741. https://doi.org/10.1208/s12249-015-0350-9

Andreas, C.J., Rosenberger, J., Butler, J., Augustijns, P., McAllister, M., Abrahamsson, B., Dressman, J., 2018. Introduction to the OrBiTo decision tree to select the most appropriate in vitro methodology for release testing of solid oral dosage forms during development. Eur. J. Pharm. Biopharm. 130, 207-213. https://doi.org/10.1016/j.ejpb.2018.07.003

Baird, J.A., Van Eerdenbrugh, B., Taylor, L.S., 2010. A classification system to assess the crystallization tendency of organic molecules from undercooled melts. J. Pharm. Sci. 99, 3787-3806. http://dx.doi.org/10.1002/jps.22197

Bar-Shalom, D., Kindt-Larsen, T. (1991). Controlled release composition. WO 91/04015

Bevernage, J., Brouwers, J., Brewster, M.E., Augustijns, P., 2013. Evaluation of gastrointestinal drug supersaturation and precipitation: Strategies and issues. Int. J. Pharm. 453, 25-35. http://dx.doi.org/10.1016/j.ijpharm.2012.11.026

Briatico-Vangosa, F., Melocchi, A., Uboldi, M., Gazzaniga, A., Zema, L., Maroni, A., 2019. Effect of Polyethylene Glycol Content and Molar Mass on Injection Molding of Hydroxypropyl Methylcellulose Acetate Succinate-Based Gastroresistant Capsular Devices for Oral Drug Delivery. Polymers, 11, 517. http://dx.doi.org/doi:10.3390/polym11030517

Breitenbach, J., 2002. Melt extrusion: from process to drug delivery technology. Eur. J. Pharm. Biopharm. 54, 107-117. https://doi.org/10.1016/S0939-6411(02)00061-9

547 Bogdanov, B. and M. Mihailov, 1985. Melting of water/poly(ethylene oxide) systems. J. Polym.
548 Sci. Part B Polym. Phys. 23, 2149-2158. https://doi.org/10.1002/pol.1985.180231011

549 Bryce, D.M., 1996. Plastic Injection Molding, Volume I - Manufacturing Process Fundamentals.
550 Society of Manufacturing Engineers (SME), Michigan, pp. 105-116.

551 Buckley, S.T., Frank, K.J., Fricker, G., Brandl, M., 2013. Biopharmaceutical classification of
552 poorly soluble drugs with respect to "enabling formulations". Eur. J. Pharm. Sci., 50, 8-16.
553 http://dx.doi.org/10.1016/j.ejps.2013.04.002

554 Butler, J., Hens, B., Vertzoni, M., Brouwers, J., Berben, P., Dressman, J., Andreas, C.J.,
555 Schaefer, K.J., Mann, J., McAllister, M., Jamei, M., Kostewicz, E., Kesisoglou, F., Langguth, P.,
556 Minekus, M., Müllertz, A., Schilderink, R., Koziolek, M., Jedamzik, P., Weitschies, W., Reppas,
557 C., Augustijns, P., 2019. In vitro models for the prediction of in vivo performance of oral dosage
558 forms: Recent progress from partnership through the IMI OrBiTo collaboration. Eur. J. Pharm.
559 Biopharm. 136, 70-83. https://doi.org/10.1016/j.ejpb.2018.12.010

560 Caccavo, D., Lamberti, G., Barba, A.A., Abrahmsén-Alami, S., Viriden, A., Larsson, A., 2017.
561 Effects of HPMC substituent pattern on water up-take, polymer and drug release: An
562 experimental and modelling study. Int. J. Pharm. 528, 705-713.
563 http://dx.doi.org/10.1016/j.ijpharm.2017.06.064

564 Cuff, G., Raouf, F., 1998. A preliminary evaluation of injection moulding as a technology to
565 produce tablets. Pharm. Technol. 22, 96-106.

566 Desai, P.M., Hogan, R.C., Brancazio, D., Puri, V., Jensen, K.D., Chun, J.H., Myserson, A.S.,
567 Trout, B.L., 2017, Integrated hot-melt extrusion - injection molding continuous tablet
568 manufacturing platform: Effects of critical process parameters and formulation attributes on
569 product robustness and dimensional stability. Int. J. Pharm., 531, 332-342.
570 http://dx.doi.org/10.1016/j.ijpharm.2017.08.097

571 Deshmukh, S.S., 2015. Investigation of injection moulding for novel drug delivery systems. An
572 investigation into the use of injection moulding to produce pharmaceutical dosage forms and to
573 understand the relationship between materials, processing conditions and performance, in
574 particular drug release and stability. Doctoral thesis, University of Bradford. Braford Scholars,
575 2015. https://bradscholars.brad.ac.uk/handle/10454/14302 (accessed 20 Jun 2019).

576 Dunér, K., Hulthe, J., Tranberg, M., 2012. Determination of the thrombin inhibitor AZD0837 and
577 its metabolites in human bile using mixed mode solid phase extraction and LC–MS/MS. J.
578 Chromatogr. B., 904, 29-34. https://doi.org/10.1016/j.jchromb.2012.06.026

579 Eggenreich, K., Windhab, S., Schrank, S., Treffer, D., Juster, H., Steinbichler, G., Laske, S.,
580 Koscher, G., Roblegg, E., Khinast, J.G., 2016. Injection molding as a one-step process for the
581 direct production of pharmaceutical dosage forms from primary powders. Int. J. Pharm. 505,
582 341-351. http://dx.doi.org/10.1016/j.ijpharm.2016.03.034

583 Esnaashari, S., Javadzadeh, Y., Batchelor, H.K., Conway, B.R., 2005, The use of
584 microviscometry to study polymer dissolution from solid dispersion drug delivery systems. Int. J.
585 Pharm., 292, 227-230. https://doi.org/10.1016/j.ijpharm.2004.11.036

586 Fuenmayor, E., O'Donnell, C., Gately, N., Doran, P., Devine, D., Lyons, J.G., McConvillec, C.,
587 Major, I., 2019, Mass-customization of oral tablets via the combination of 3D printing and
588 injection molding. Int. J. Pharm., 569, 118611. https://doi.org/10.1016/j.ijpharm.2019.118611

589 Grimm, M., Scholz, E., Koziolek, M., Kühn, J.-P., Weitschies, W. 2017. Gastric Water Emptying
590 under Fed State Clinical Trial Conditions Is as Fast as under Fasted Conditions. Mol. Pharm.,
591 14 (12), 4262-4271. https://doi.org/10.1021/acs.molpharmaceut.7b00623

592 Grimm, M., Koziolek, M., Kühn, J.P., Weitschies, W., 2018. Interindividual and intraindividual
593 variability of fasted state gastric fluid volume and gastric emptying of water. Eu. J Pharm.
594 Biopharm. 127, 309-317. https://doi.org/10.1016/j.ejpb.2018.03.002

595 Hemmingsen, P.H., Haahr, A.-M., Gunnergaard, C., Cardot, J-M., 2011. Development of a New
596 Type of Prolonged Release Hydrocodone Formulation Based on Egalet ADPREM Technology
597 Using In Vivo-In Vitro Correlation. Pharmaceutics, 3, 73-87.
598 https://doi.org/10.3390/pharmaceutics3010073

599 Kaunisto, E., Abrahmsén-Alami, S., Borgquist, P., Larsson, A., Nilsson, B., Axelsson, A., 2010.
600 A mechanistic modelling approach to polymer dissolution using magnetic resonance
601 microimaging. J Control. Release. 147 (2), 232-241.
602 https://doi.org/10.1016/j.jconrel.2010.07.102

603 Kauzmann, W., 1948. The Nature of the Glassy State and the Behavior of Liquids at Low
604 Temperatures. Chem. Rev. 43, 219-256.

605 Kostewicz, E.S., Abrahamsson, B., Brewster, M., Brouwers, J., Butler, J., Carlert, S., Dickinson,

606 P.A., Dressman, J., Holm, R., Klein, S., Mann, J., McAllister, M., Minekus, M., Muenster, U.,

607 Müllertz, A., Verwei, M., Vertzoni, M., Weitschies, W., Augustijns, P. (2014). In vitro models for

608 the prediction of in vivo performance of oral dosage forms. Eur. J. Pharm. Sci., 57, 342-366.

609 https://doi.org/10.1016/j.ejps.2013.08.024

610 Körner, A., Larsson, A., Piculell, L., Wittgren, B., 2005. Molecular information on the dissolution

611 of polydisperse polymers: Mixtures of long and short poly (ethylene oxide). J. Phys. Chem. B.,

612 109, 11530-11537. https://doi.org/10.1021/jp044332s

613 Larsson, A., Abrahmsén-Alami, S., Juppo, A. 2008. Oral extended-release formulations.

614 Pharmaceutical manufacturing handbook: Production and process. G. Shayne Cox Eds, Johan

615 Wiley & Sons.

616 Maggi, L., Segale, L., Torre, M.L., Ochoa Machiste, E., Conte, U., 2002. Dissolution behaviour

617 of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the

618 controlled release of a water-soluble drug. Dimensionality study. Biomaterials, 23, 1113-1119.

619 https://doi.org/10.1016/S0142-9612(01)00223-X

620 Maroni, A., Melocchi, A., Parietti, F., Foppoli, A., Zema, L., Gazzaniga, A., 2017, 3D printed

621 multi-compartment capsular devices for two-pulse oral drug delivery, J. Control Release. 268,

622 10-18. https://doi.org/10.1016/j.jconrel.2017.10.008

623 Marsac, P., Shamblin, S., Taylor, L., 2006. Theoretical and Practical Approaches for Prediction

624 of Drug–Polymer Miscibility and Solubility. Pharm. Res. 23, 2417-2426.

625 http://dx.doi.org/10.1007/s11095-006-9063-9

626 Olsson, B.S., Rasmussen, L.H., Tveit, A., Jensen, E., Wessman, P., Panfilov, S., Wåhlander,

627 K., 2010, Safety and tolerability of an immediate-release formulation of the oral direct thrombin

628 inhibitor AZD0837 in the prevention of stroke and systemic embolism in patients with atrial

629 fibrillation. Thromb. Haemost. 103, 604-612. http://dx.doi.org/10.1160/TH09-07-0509

630 Pajander, J., Rensonnet, A., Hietala, S., Rantanen, J., Baldursdottir, S., 2017. The evaluation of

631 physical properties of injection molded systems based on poly (ethylene oxide) (PEO). Int. J.

632 Pharm., 518, 203-212. http://dx.doi.org/10.1016/j.ijpharm.2016.12.050

633 Puri, V., Brancazio, D., Harinath, E., Martinez, A.R., Desai, P.M., Jensen, K.D., Chun, J.H.,

634 Braatz, R.D., Myerson, A.S., Trout, B.L., 2018, Demonstration of pharmaceutical tablet coating

635 process by injection molding technology. Int. J. Pharm., 535, 106-112.
636 https://doi.org/10.1016/j.ijpharm.2017.10.062

637 Repka, M.A., Bandari, S., Kallakunta, V.R., Vo, A.Q., McFall, H., Pimparade, M.B., Bhagurkar,
638 A.M., 2018. Melt extrusion with poorly soluble drugs - An integrated review. Int. J. Pharm. 535,
639 68-85. https://doi.org/10.1016/j.ijpharm.2017.10.056

640 Repka, M.A., Shah, S., Lu, J., Maddineni, S., Morott, J., Patwardhan, K., Mohammed, N.N.,
641 2012. Melt extrusion: process to product. Exp. Op. Drug Delivery 9, 105-125.
642 http://dx.doi.org/10.1517/17425247.2012.642365

643 Riethorst, D., Mols, R., Duchateau, G., Tack, J., Brouwers, J., Augustijns, P., 2018, Human
644 intestinal fluid factors affecting intestinal drug permeation in vitro. Eur. J. Pharm. Sci. 121: 338-
645 346. https://doi.org/10.1016/j.ejps.2018.06.007

646 Sako, K., Nakashima, H., Sawada A., T., Okada, A., Fukui, M. (1993). Hydrogel-forming
647 sustained-release preparation. US6699503

648 Saboo, S., Mugheirbi, N.A., Zemlyanov, D.Y., Kestur, U.S., Taylor, L.S., 2019. Congruent
649 release of drug and polymer: A "sweet spot" in the dissolution of amorphous solid dispersions. J.
650 Controlled Release 298, 68-82. https://doi.org/10.1016/j.jconrel.2019.01.039

651 Schiller, C., Frohlich, C-P., Giessmann, T., Siegmund, W., Monnikes, H., Hosten, N.,
652 Weitschies, W., 2005. Intestinal fluid volumes and transit of dosage forms as assessed by
653 magnetic resonance imaging. Aliment. Pharmacol. Ther., 22, 971-979. .
654 https://doi.org/10.1111/j.1365-2036.2005.02683.x

655 Siepmann, J., Peppas, N.A., 2000. Hydrophilic matrices for controlled drug delivery: an
656 improved mathematical model to predict the resulting drug release kinetics (the "sequential
657 layer" model). Pharm. Res. 17, 1290-1298. https://doi.org/10.1023/a:1026455822595

658 Sjökvist, E. and C. Nyström (1988). Physicochemical aspects of drug release. VI. Drug
659 dissolution rate from solid particulate dispersions and the importance of carrier and drug particle
660 properties. Int. J. Pharm., 47(1): 51-66. https://doi.org/10.1016/0378-5173(88)90215-3

661 Speiser, P., 1969. Injection-moulded oral medicament in solid form. US3432592.

662 Stepto, R.F.T., Tomka, I., 1987. Injection-Molding of Natural Hydrophilic Polymers In the
663 presence of water. Chimia 41, 76-81.

664 Tajarobi, F., Abrahmsén-Alami, S., Hansen, M., Larsson, A., 2009. The impact of dose and
665 solubility of additives on the release from HPMC matrix tablets--identifying critical conditions.
666 Pharm. Res. 26, 1496-1503. http://dx.doi.org/10.1007/s11095-009-9861-y

667 Tajarobi, F., Abrahmsén-Alami, S., Larsson, A., 2011. Dissolution rate enhancement of
668 parabens in PEG solid dispersions and its influence on the release from hydrophilic matrix
669 tablets. J. Pharm. Sci., 100, 275-283. http://dx.doi.org/10.1002/jps.22248

670 Timmins, P., Donahue, S., Meeker, J., Marathe, P., 2005. Steady-state pharmacokinetics of a
671 novel extended-release metformin formulation. Clin. Pharm., 44, 721-729.
672 https://doi.org/10.2165/00003088-200544070-00004

673 Timmins, P., Pygall, S.R., Melia C.D., 2014. Hydrophilic Matrix Tablets for Oral Controlled
674 Release. Eds. AAPS Advances in the Pharmaceutical Sciences Series. AAPSPress Springer,
675 London.

676 Trotzig, C., Abrahmsén-Alami, S., Maurer, F.H.J., 2007. Structure and mobility in water
677 plasticized poly(ethylene oxide). Polymer 48, 3294-3305.
678 https://doi.org/10.1016/j.polymer.2007.03.047

679 Turnbull, D., 1969. Under what conditions can a glass be formed? Contemp. Phys., 10, 473-
680 488.

681 Unga, J., Tajarobi, F., Norder, O., Frenning, G., Larsson, A., 2009. Relating solubility data of
682 parabens in liquid PEG 400 to the behaviour of PEG 4000-parabens solid dispersions. Eur. J.
683 Pharm. Biopharm., 73, 260-268. https://doi.org/10.1016/j.ejpb.2009.06.003

684 Verstraete, G., Van Renterghem, J., Van Bockstal, P.J., Kasmi, S., De Geest, B.G., De Beer, T.,
685 Remon, J.P., Vervaet, C., 2016, Hydrophilic thermoplastic polyurethanes for the manufacturing
686 of highly dosed oral sustained release matrices via hot melt extrusion and injection molding. Int.
687 J. Pharm., 506, 214-221. https://doi.org/10.1016/j.ijpharm.2016.04.057

688 Wang, L., Chen, K., Wen, H., Ouyang, D., Li, X., Gao, Y., Pan, W., Yang, X., 2017. Design and
689 Evaluation of Hydrophilic Matrix System Containing Polyethylene Oxides for the Zero-Order
690 Controlled Delivery of Water-Insoluble Drugs. AAPS PharmSciTech 18, 82-92.
691 https://doi.org/10.1208/s12249-016-0498-y

692 Weitschies, W., Blume, H., Monnikes, H., 2010. Magnetic marker monitoring: high resolution
693 real-time tracking of oral solid dosage forms in the gastrointestinal tract. Eur. J. Pharm.
694 Biopharm., 74, 93-101. https://doi.org/10.1016/j.ejpb.2009.07.007

695 Wilson, V., Lou, X., Österling, D.J., Stolarik, D.F., Jenkins, G., Gao, W., Zhang, G.G.Z., Taylor,
696 L.S., 2018. Relationship between amorphous solid dispersion in vivo absorption and in vitro
697 dissolution: phase behavior during dissolution, speciation, and membrane mass transport. J.
698 Control Release, 292, 172-182. https://doi.org/10.1016/j.jconrel.2018.11.003

699 Wingstrand, K., Abrahamsson, B., Edgar, B., 1990. Bioavailability from felodipine extended-
700 release tablets with different dissolution properties. Int. J. Pharm., 60, 151-156.
701 https://doi.org/10.1016/0378-5173(90)90301-J

702 Zema, L., Loreti, G., Melocchi, A., Maroni, A., Gazzaniga, A., 2012. Injection Molding and its
703 application to drug delivery. J. Control Release, 159, 324-331.
704 https://doi.org/10.1016/j.jconrel.2012.01.001

705 Zema, L., Loreti G., Macchi E., Foppoli A., Maroni A., Gazzaniga A., 2013. Injection-molded
706 capsular device for oral pulsatile release: Development of a novel mold. J. Pharm. Sci. 102(2):
707 489-499. https://doi.org/10.1002/jps.23371

708 Zhao, L., Kai, W., He, Y., Zhu, B., Inoue, Y., 2005. Effect of aging on fractional crystallization of
709 poly(ethylene oxide) component in poly(ethylene oxide)/poly(3-hydroxybutyrate) blends. J.
710 Polym. Sci. Pol. Phys. 43, 2665-2676. https://doi.org/10.1002/polb.20552