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1 **Injection Moulded Controlled Release Amorphous Solid**
2 **Dispersions: Synchronized Drug and Polymer Release for Robust**
3 **Performance**

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25 **Abstract**

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

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44 **Key words:** Oral Solid Dosage (OSD), Polymer Release, Release Robustness, Poorly Soluble
45 Drug, Polyethylene oxide (PEO), Hot Melt Extrusion (HME), Injection Moulding (IM), Controlled
46 Release, Amorphous Solid Dispersion (ASD).

47

48 **1. Introduction**

49 With the advent of new manufacturing technologies and the need for increased process
50 flexibility and efficiency, the paradigm in the pharmaceutical industry is shifting from batch to
51 continuous manufacturing. Among continuous technologies being applied to pharmaceuticals
52 processing, hot melt extrusion (HME) technology continues to grow in importance mainly due to
53 the advantage of being solvent-free and due to its ability to generate high density pellets that,
54 through selection of suitable excipients, provide potential for improved stability and bioavailability
55 of the finished solid oral dosage form (Breitenbach, 2002; Repka et al., 2018; Repka et al.,
56 2012). One drawback with HME, however is the need for several secondary manufacturing
57 steps to enable a final oral solid dosage form acceptable to patients with variable needs.

58 HME in combination with injection molding (IM) is widely used in the plastics industry to
59 form complex shaped objects with a high degree of dimensional accuracy and reproducibility
60 with the additional advantage of high speed (Bryce, 1996). IM has a long history in the
61 pharmaceutical packaging and medical device field however its use as a technique for
62 manufacturing of solid oral dosage forms was not suggested until the late 1960s (Speiser,
63 1969). Since then, a number of techniques have been explored for producing dosage forms
64 using small scale IM machines, with the main drivers for this research being scalability and
65 patentability (Cuff and Raouf, 1998; Stepto and Tomka, 1987). Additionally, manufacturing of
66 controlled release solid oral dosage forms is possible, providing, for example, delayed release
67 and potential targeting to colon as well as compositions preventing abuse of opioid drugs
68 through introducing protective compartments that are resistant to destruction (Hemmingsen et
69 al., 2011; Zema et al., 2012, Zema et al., 2013). Recently, interest in IM of pharmaceutical
70 tablets appears to have grown, for example Eggenreich et al., 2016, compared tablets directly
71 injection moulded from powder to those first extruded into pellets prior to moulding, and Desai et
72 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-continuously 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 characterized 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 (1×10^5 g/mol) and Polyox WSR 1105 NF (9×10^5 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 tableting powders were
171 weighed and mixed using a diffusion blender (Turbula T10B/ T2F, Willy A. Bachofen Ag,
172 Basel, Switzerland) for 10 min at 32–34 rpm.

173

174 **2.3 Characterisation of Raw Materials, Extruded Pellets and IM Tablets**

175 **2.3.1 Thermal Characterization**

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

181

182 **2.3.2 Raman Spectroscopy**

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

192

193 **2.3.3 AZD0837 Content Analysis**

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

198

199 **2.3.4 In vitro Dissolution of AZD0837 and Polymers**

200 Dissolution testing of IM tablets was performed using USP apparatus II (at 37°C using 900 mL
201 0.05 M Phosphate buffer pH 6.8 and 50 rpm) with a paddle and a basket located at the side in
202 the dissolution bath in a position where the sample is exposed to a laminar flow (Tajarobi et al.,
203 2009; Wingstrand et al., 1990). AZD0837 concentrations were measured with HPLC and
204 polymer concentration was determined with SEC-MALS (Size Exclusion Chromatography
205 coupled to Mass Spectroscopy, Wyatt Technologies, CA, USA). Samples were collected at
206 regular intervals up to 24 hours. At each time point 5mL samples were drawn and the same
207 volume was replaced with phosphate buffer. 100µL of each sample was injected into the SEC
208 system equipped with a TSKgel PWxl column (7.8 mm internal diameter × 30.0 cm length),
209 (TOSOH Corporation, Japan). A mobile phase comprising 0.1M NaCl and 0.02% NaN₃ was
210 used for both formulations. The SEC-RI (SEC with refractive index detector) was coupled to a
211 DAWN HELEOS II 18-angle MALS detector (Wyatt Technologies, CA, USA) and an OptilabREX
212 refractive index detector (Wyatt Technologies, CA, USA) for concentration measurements. SEC-
213 MALS calibration was performed using Pullulan P50 (Skandinaviska Genetec AB, Mw 4.73
214 x10⁴, c = 0.7mg/mL in 0.1M NaCl) and polymer reference standards (in mobile phase). Data
215 acquisition and analysis was performed using Astra software version 6.1.7.17 (Wyatt
216 Technologies, USA). From the concentration of polymer released at each time point and an
217 injection volume of 100 µL, concentration and cumulative % polymer release was calculated.

218

219 **2.3.5 Stressed Stability Study**

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

225 **3. Results and Discussion**

226 **3.1 Material Properties of Raw Materials**

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

$$241 \quad T_{rg} = T_g/T_m \quad (1)$$

242 Where T_g is the glass transition temperature and T_m is the melting temperature. Assuming that
243 viscosity is constant at T_g , materials with higher T_{rg} values would be expected to have a higher
244 viscosity between T_g and T_m and consequently be more resistant to crystallization (Baird et al.,
245 2010). Thus, the closer the T_{rg} value is to 1, the higher the material's GFA. When the
246 classification system is applied to assess the crystallisation tendency of AZD0837 two distinct
247 observations were made. Firstly, its T_{rg} was found to be 0.8 suggesting that the drug substance
248 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).

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 tableting (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

401 **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

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

451 **3.6 Considerations for Robust Release Performance**

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

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

500 **4. Conclusion**

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

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