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Comparison of fenofibrate - mesoporous silica drug-1 loading processes for enhanced drug delivery 2 3 Robert J. Ahern¹, John P. Hanrahan², Joseph M. Tobin², Katie B. Ryan¹ and Abina M. Crean^{1,*} 4 ¹School of Pharmacy, University College Cork, Ireland, ²Glantreo Ltd, Environmental Research Institute, University College Cork, Ireland, 5 6 *Corresponding Author, Address: The Cavanagh Pharmacy Building, School of Pharmacy, 7 College Road, University College Cork, Ireland, 8 Telephone: +353 (0) 214901667, Email Address: a.crean@ucc.ie 9

10 Abstract

11 Loading a poorly water-soluble drug onto a high surface area carrier such as mesoporous 12 silica (SBA-15) can increase the drug's dissolution rate and oral bioavailability. The loading 13 method can influence subsequent drug properties including solid state structure and release 14 rate. The objective of this research was to compare several loading processes in terms of drug 15 distribution, solid state form and drug release properties. A model poorly water-soluble drug 16 fenofibrate was loaded onto SBA-15 using; (i) physical mixing, (ii) melt, (iii) solvent 17 impregnation, (iv) liquid CO₂ and (v) supercritical CO₂ methods. Physical mixing resulted in 18 heterogeneous drug-loading, with no evidence of drug in the mesopores and the retention of 19 the drug in its crystalline state. The other loading processes yielded more homogeneous drug-20 loading, the drug was deposited into the mesopores of the SBA-15 and was non-crystalline.. 21 All the processing methods resulted in enhanced drug release compared to the unprocessed 22 drug with the impregnation, liquid and SC-CO₂ producing the greatest increase at t=30 min.

23

Keywords: SBA-15, fenofibrate, supercritical CO₂, poorly water-soluble, amorphous, drug loading, mesoporous silica, drug release

26

27 **1.0 Introduction**

28 It has been long established that increasing the effective surface area of a poorly water-

29 soluble drug in contact with the dissolution medium can enhance drug dissolution (Bruner,

30 1904, Nernst, 1904). This can be achieved by loading drug on silica-based ordered

31 mesoporous materials (OMMs) which are characterised by high surface areas, large pore

32 volumes, narrow pore size distributions (5 - 8 nm) and ordered unidirectional pore networks.

33 These properties allow for homogeneous and reproducible drug-loading and release

34 (Manzano et al., 2009, Vallet-Regi et al., 2007, Vallet-Regi et al., 2001).

35 Many publications have focussed on understanding the key properties of OMMs that

36 influence drug-loading and dissolution rate enhancement. It has been reported that the surface

area determines how much drug can be loaded onto OMMs and OMM particle size has an

38 impact on drug release rate, with larger silica particles resulting in slower drug release

39 because of the longer mesopore length (Chen et al., 2012). The pore volume influences the

40 amount of drug loaded, especially if the drug is dissolved in a solvent that can carry it into the

41 mesopores (Vallet-Regi et al., 2007). Larger pore sizes encourage greater drug release rates

42 (Horcajada et al., 2004), while pore geometry has also be shown to affect drug-loading and

43 release (Izquierdo-Barba et al., 2005). Stabilisation of amorphous drug for up to 12 months

44 has also been ascribed to the mesopores of the OMM (Mellaerts et al., 2010, Shen et al.,

45 2010). The silica surface can be functionalised with organic groups to encourage greater

drug-loading by creating stronger bonding between the silica surface and drug (Manzano et
al., 2008), and to extend drug release (Vallet-Regi et al., 2007).

48 Despite the body of literature evaluating the different properties of OMM affecting drug-

49 loading and release, there seems to be a lack of clarity regarding the optimum processing

50 method to load drug onto the OMM and the subsequent implications for drug delivery.

51 Various loading methods have been employed including physical mixing (Song et al., 2005,

52 Qian and Bogner, 2011), solvent based methods that either involve the suspension of the

53 OMM in a drug-solvent solution (Andersson et al., 2004, Izquierdo-Barba et al., 2005,

54 Charnay et al., 2004) or impregnation of the OMM by dropwise addition of a concentrated

55 drug solution (Mellaerts et al., 2008a, Van-Speybroeck et al., 2008). Some researchers have

56 mixed the drug and silica and heated the resultant mixture to below (Tozuka et al., 2005) or

57 above the drug's melting point (Aerts et al., 2010, Mellaerts et al., 2008a, Shen et al., 2010).

58 Alternative loading methods such as supercritical CO₂ (SC-CO₂) (Ahern et al., 2012,

59 Sanganwar and Gupta, 2008) have also been proposed to load drug onto OMMs. The high

60 densities of liquid and SC-CO₂ should permit a large amount of drug to be solubilised, while

61 the high diffusivity of the SC-CO₂ should facilitate ready access to the mesopore network

62 (Fages et al., 2004, Pasquali and Bettini, 2008, York, 1999).

To our knowledge this is the first study to directly compare physical mixing, melt, solvent impregnation and CO₂ based drug-loading methods in terms of the subsequent impact on drug – OMM properties, in particular drug distribution, solid state properties and drug release. To our knowledge, this is also the first study to enhance drug dissolution by loading drug onto OMM using a liquid (near-critical) CO₂ loading method. The model OMM in this study was SBA-15 and fenofibrate was employed as a representative Class II drug as defined by the biopharmaceutics classification system (BCS) (Amidon et al., 1995). It is highly lipophilic

70 (log P = 5.3) (Wishart et al., 2008) and practically insoluble in water (< 0.8 μ g/ml) (Jamzad 71 and Fassihi, 2006).

72

73 **2.0 Materials and methods**

74 2.1 Materials

75 Fenofibrate was supplied by Kemprotec Ltd. (United Kingdom). CO₂ was supplied by Irish

76 Oxygen Ltd. (Ireland). Hydrochloric acid (HCl), dichloromethane (DCM), potassium

bromide (KBr), phencyclidine hydrochloride (P-123) and tetraethyl orthosilicate (TEOS)

78 were supplied by Sigma-Aldrich Ltd. (Ireland). Sodium dodecyl sulphate (SDS) was

79 supplied by Fisher Scientific Ltd. (Ireland).

80

81 2.1.1 Preparation of SBA-15

SBA-15 was synthesized according to the method outlined in literature (Zhao et al., 1998).
Briefly, 200 g of tri-block polymer (P123) was dissolved in 1.6 M HCl solution and was
heated to 40 °C to completely dissolve the polymer, after which 607 ml of 98% TEOS was

added to the solution. The solution was stirred for 24 h at 40 °C and dried for a further 96 h at

60 °C. The SBA-15 was recovered by filtration, washed with deionised water to remove any

87 remaining ethanol and HCl, prior to calcination at 550 °C for 14 h to remove the polymer

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88 template.

89

86

90 2.2 Drug-loading methods

91 Drug-silica samples were prepared with a ratio of 1 mg drug per 3 m^2 mesoporous silica. In

92 each case approximately 400 mg of drug was combined with 2 g mesoporous silica and

93	processed according to the methods detailed below. All samples were prepared in triplicate.
94	Following preparation, a portion of each drug-silica sample was placed in screw-capped
95	plastic tubes (Sarstedt AG, Germany) and stored in a desiccator at ambient temperatures prior
96	to analysis. The remaining part was stored under accelerated storage conditions at 75%
97	relative humidity (RH) and 40 $^{\circ}$ C prior to analysis to assess stability (FDA, 2003).
98	
99	2.2.1 Physical mixing
100	Drug-mesoporous silica physical mixes were prepared by blending the drug and SBA-15 for
101	30 min at 100 revolutions per minute (rpm) using an AR402 Erweka blender (Erweka GmbH,
102	Germany).
103	
104	2.2.2 Melt method
105	The melt method involved heating the drug above its melting point (>80 °C) and relied on its
106	molten viscosity to distribute the drug on the mesoporous silica surface. The drug was
107	manually combined with the mesoporous silica to increase the homogeneity of drug
108	distribution. The sample was maintained above 80 °C for 24 h using an E-series binder oven
109	(Erweka GmbH, Germany) and thereafter cooled to ambient temperature.
110	
111	2.2.3 Solvent impregnation
112	Samples were prepared according to the method reported by Mellaerts and co-workers
113	(Mellaerts et al., 2008a). Approximately 8 ml of a concentrated solution of fenofibrate (50
114	mg/ml) in DCM was added dropwise to the mesoporous silica; after each addition the powder
115	was intensively ground with a pestle. Thereafter, the sample was dried at 40 $^{\circ}$ C for 48 h under
116	vacuum (100 Pa).
	Page 5

117 **2.2.4 Liquid and SC-CO₂ loading**

118 The drug and mesoporous silica were combined in a high-pressure reactor (BC 316), (High 119 Pressure Equipment Company, USA) and stirred using a magnetic stirring. The cell was 120 heated to 25 °C using heating tape and maintained constant for the duration of the experiment 121 using a temperature monitor (Horst GmbH, Germany). The reactor cell was filled with liquid CO₂. A high pressure pump (D Series Syringe Pump 260D, Teledyne ISCO, USA) was then 122 123 used to pump additional CO_2 to a final processing pressure (27.58 MPa). At the end of the 124 experiment the cell was depressurised rapidly by venting the CO₂. The SC-CO₂ loading 125 process followed a similar procedure, except that the cell was heated to 40 °C.

126

127 **2.3 Physicochemical characterisation**

128 **2.3.1 Porosity analysis**

Surface area and pore size analysis by nitrogen (N₂) adsorption was carried out using a Gemini VI surface area and pore size analyser, (Micromeritics, USA). The samples were degassed for 24 h at 50 °C in a FlowPrep 060 sample degas system, (Micromeritics, USA) prior to analysis. During analysis, liquid N₂ at -196 °C maintained isothermal conditions. The pore volume along with pore width were calculated using the Barrett-Joyner-Halenda (BJH) adsorption correlation (Barrett et al., 1951). Each individual fenofibrate-silica processed sample was analysed in duplicate.

136 Comparison of the measured pore volume of the drug-silica samples with the theoretical pore

137 volume provides some indication of the location of the drug in the samples. The theoretical

- 138 pore volume (P.V.) of the processed fenofibrate-silica samples can be determined based on
- 139 the relative mass fractions of silica and drug present in the sample and their respective pore
- 140 volumes. As fenofibrate is a non-porous material its pore volume can be ignored and thePage 6

141	theoretical pore volume (P.V.) of the processed fenofibrate-silica samples was calculated			
142	according to Eq. 1.			
143				
144	Theoretical P.V. = $(P.V{(MS)} \times M_{(MS)})$ (1)			
145				
146	P.V. $_{(MS)}$ refers to the pore volume (cm ³ /g) of unprocessed SBA-15. M $_{(MS)}$ refers to the mass			
147	fraction of mesoporous silica in the fenofibrate-silica sample. The mass fraction of drug			
148	present in the fenofibrate-silica samples was determined by thermogravimetric analysis			
149	(TGA) as described in Section 2.3.2. Eq. 1 was employed based on the assumption that there			
150	was no chemical or physical interaction between silica and fenofibrate in the fenofibrate-			
151	silica samples.			
152	The percentage difference between the theoretical and measured pore volumes (% ΔPV) was			
153	calculated using Eq.2			
154				
155	% $\Delta PV = ((\text{theoretical P.V.} - \text{measured P.V.}) / \text{theoretical P.V.})*100\%$ (2)			
156				
157	2.3.2 Thermogravimetric analysis			
158	Thermogravimetric analysis (TGA) was carried out using a TGA 500, (TA Instruments Ltd.,			
159	United Kingdom). Samples in the weight range 2 to 10 mg were loaded onto tared platinum			
160	pans and heated from ambient temperature to 900 °C, at a heating rate of 10 °C.min ⁻¹ under an			
161	inert N2 atmosphere. All samples were analysed in triplicate. The moisture present in the			
162	samples was calculated from the weight loss between ambient temperature and 100 $^{\circ}$ C and			
163	the drug quantity was calculated from the weight loss between 100 to 900 °C, corrected for			
164	the weight loss over the same temperature range for silica only (Hillerström et al., 2009,			
	Page 7			

165	Van-Speybroeck et al., 2009). TGA thermograms were analysed using Universal Analysis
166	2000 software, (TA Instruments Ltd., United Kingdom). Drug-loading efficiency was
167	calculated using Eq. 3.
168	
169	Drug-loading Efficiency (%) = (actual drug loaded/theoretical drug loaded) x 100% (3)
170	
171	The theoretical drug-loading was based on mass fraction of drug and silica used to prepare
172	samples.
173	
174	2.3.3 Differential scanning calorimetry
175	Differential scanning calorimetry (DSC) was carried out using a DSC Q1000, (TA
176	Instruments Ltd., United Kingdom) operated in modulated mode. DSC was used to measure
177	the glass transition temperature (T_g) , melting point (T_m) and enthalpy of melting of
178	fenofibrate and fenofibrate-silica samples. Samples in the weight range 3 to 5 mg were
179	weighed on a MX5 microbalance (Mettler Toledo International Inc., USA) into Tzero
180	aluminium pans (non-hermetic) (TA Instruments Ltd., United Kingdom). The samples were
181	heated from -40 to 120 °C at a heating rate of 3 °C.min ⁻¹ with modulation frequency of 1
182	$^{\circ}$ C.min ⁻¹ every 60 s. An inert atmosphere was maintained using a N ₂ flow rate of 50 ml.min ⁻¹ .
183	A refrigerant cooling system, the RCS 40 (TA Instruments Ltd., United Kingdom) was used
184	to cool samples below ambient temperature. Analysis of DSC thermograms was conducted
185	using Universal Analysis 2000 software, (TA Instruments Ltd., United Kingdom).
186	
187	
188	

189 2.3.4 Powder X-ray diffraction

Powder x-ray diffraction (pXRD) was performed to determine changes in the solid state structure of fenofibrate after processing with silica. Analysis was performed at ambient temperature using a Stadi MP diffractometer, (Stoe GmbH, Germany) operating in transmission mode with a linear position-sensitive detector, an anode current of 40 mA, an accelerating voltage of 40 kV and Cu K α 1 X-radiation (λ = 1.5406 Å) typically over a scan range of 3.5 to 60 ° 2 θ , scanning in steps of 2 ° for 90 s per step. Samples were held between acetate foils during analysis.

197

198 2.3.5 *In vitro* fenofibrate release

199 The dissolution and release rates of unprocessed fenofibrate and processed fenofibrate-200 mesoporous silica samples were measured in a dissolution medium composed of 0.1 M HCl 201 and 0.3% (w/v) SDS under sink conditions at 37 °C. The dissolution apparatus employed was 202 a USP Type II (paddle method) with a dissolution volume of 900 ml and paddle stirring 203 maintained at 100 rpm. A fixed weight of fenofibrate (15 mg) or a mass of drug-silica sample 204 containing an equivalent mass of drug was added to the dissolution medium. Samples were 205 withdrawn at defined time points and replaced with fresh media to ensure a constant 206 dissolution volume. Samples withdrawn were filtered through a 0.2 µm syringe filter 207 (Sarstedt AG, Germany) prior to analysis by RP-HPLC as described below.

208

209 2.3.6 RP-HPLC analysis

210 RP-HPLC analysis was performed using an Agilent 1200 series HPLC system with a UV/VIS

211 detector (Agilent Technologies, USA). A reversed-phase column Kinetex C-18 column (150

212 mm x 4 mm) with internal pore width 2.6µm (Phenomenex Ltd., United Kingdom), a mobilePage 9

213 phase of acetronitrile and water (70:30) at a flow rate of 1 ml.min⁻¹ and an injection volume 214 of 5 μ l were employed. The wavelength for fenofibrate detection was set at 286 nm. The 215 retention time for fenofibrate was 4.5 min.

216

217 **<u>3.0 Results</u>**

218 3.1 Drug-loading

219 Similar loading efficiencies of greater than 90% were determined for the impregnation, liquid 220 and SC-CO₂ methods, Table 1. Values greater than 100% were determined for the physical 221 and melt samples. However large intra-batch variabilities were evident in these samples that 222 may be attributed to segregation during preparation due to density differences between the 223 mesoporous silica and fenofibrate. In the case of both the physical and melt samples, poor 224 mixing resulted in heterogeneous distribution of drug throughout the silica substrate. The low 225 variability in drug-loading for the impregnation, liquid and SC-CO₂ processed samples was 226 indicative of more homogeneous drug distribution. All loading methods, with the exception 227 of the physical mix, involved the disruption of the drug solid particles by melting or 228 dissolution. For the melt samples, drug distribution was reliant on the viscosity of molten 229 drug and the degree of drug and silica mixing. Drug dissolution in a solvent in the 230 impregnation, liquid and SC-CO₂ samples facilitated more uniform drug distribution in these 231 samples.

232

233 **<u>3.2 Porosity analysis</u>**

234 Changes in silica porosity after drug-loading can assist in understanding how the drug is

235 distributed throughout the silica sample. Mesoporous silica starting material had a very large

236 pore volume (>0.50 cm³/g) and displayed the type IV adsorption-desorption isotherm and H1 237 hysteresis loop (Fig.1a) characteristic of mesoporous materials, (Sing et al., 1985). These 238 characteristics were retained post drug-loading (Fig.1), which indicated that silica was still 239 mesoporous. With the exception of the physical mix, all drug loaded samples showed marked 240 reductions in the mesoporous silica pore size and volume. The closure point (P/P_0) of the 241 hysteresis loop was reduced for all samples, with the exception of the physical mix (Fig.1), 242 indicating a reduction in pore sizes (Izquierdo-Barba et al., 2005). The greatest reduction was 243 observed for the sample prepared by the melt method. The pore size distribution in relation to 244 the pore volume for the various samples is shown in Fig 2. Only a slight change in pore size 245 distribution was seen for the physical mix (Fig.2a). Both impregnation and liquid CO2 246 samples show similar reductions in pore size; interestingly the SC-CO₂ sample showed a 247 lower reduction in pore size compared to these samples. The melt sample showed the greatest 248 spread of pore sizes (Fig.2b).

249 The reduction in pore volume (% ΔPV) calculated with Eq.2 were used to quantitatively 250 compare the reductions in pore volumes of the processed samples compared to the theoretical 251 pore volume. The % Δ PV values are shown in Table 1. The % Δ PV of the physical mix was 252 negligible showing that the presence of the drug had little effect on the silica pore volume in 253 these samples. One-way ANOVA followed by the Tukey test showed that all the other 254 samples had a significantly higher % ΔPV compared to the physical mix (p < 0.05) indicating 255 that processing by these methods resulted in a reduction in the silica pore volume due to drug 256 deposition into the silica mesopores and blocking of the mesopores. Despite having similar 257 loading efficiencies, impregnation and liquid CO_2 samples had a significantly higher % ΔPV 258 values compared to the SC-CO₂ samples (p < 0.05).

259

260 **3.3 Solid state analysis**

Powder XRD and DSC analysis of samples was undertaken to determine whether the loading methods resulted in differences in fenofibrate solid state behaviour. The pXRD diffractogram of the fenofibrate crystalline starting material was in accordance with that previously reported (Heinz et al., 2009). The pXRD diffractograms of drug-silica samples, with the exception of the physical mix, showed no peaks indicating that the drug in these samples was in a noncrystalline state (Fig.3).

The melting point for the starting crystalline fenofibrate agreed with the reported T_m of 79 – 267 81 °C (Heinz et al., 2009). Thermal events in the temperature range -20 to -12 °C were noted 268 269 during DSC analysis of the silica starting material (Fig.4a). This behaviour was previously 270 reported as the melting point of frozen water confined in the mesopores of mesoporous silica 271 (Kittaka et al., 2011). Endothermic thermal events in the same range -20 to -12 °C were noted in all drug-silica samples regardless of the method of the loading. As fenofibrate's $T_{\rm g}$ was 272 reported in this temperature region at -20 °C, (Heinz et al., 2009) it was not possible to 273 274 conclusively detect the T_g of amorphous fenofibrate in any of these drug-silica samples. 275 A large melting endotherm with an onset of 78 °C was visible in DSC thermogram of the 276 physical mix, while there was a slight melting endotherm in the melt sample, indicative of the 277 presence of residual crystalline drug (Fig.4b). The absence of melting endotherms in the 278 impregnation, liquid and SC-CO₂ samples (data not shown), supported the pXRD results that 279 the drug was in a non-crystalline state in these samples.

280

281 **3.4** *In vitro* drug release

282 The release of drug from the silica carrier is a key performance indicator to consider when

283 employing OMM for drug dissolution enhancement. The *in vitro* release of drug from drug-Page 12 284 silica samples and the dissolution of the starting fenofibrate are shown in Figure 5. Utilising 285 mesoporous silica as a carrier material improved the drug dissolution rate for all processed 286 samples. The physical mix showed a slower rate of drug release compared to all of the other 287 loading methods. The release profiles of drug from the impregnation, liquid and SC-CO₂ 288 loaded samples were similar according to the difference (f_1) and similarity (f_2) factors (Moore and Flanner, 1996) and the modified difference factor f_1 (Costa and Sousa-Lobo, 2001). Drug 289 290 was released in a rapid manner in the first 20 min. After 20 min the drug release levelled 291 between 70 - 80 % and did not increase between 20 and 120 min. The release from the melt 292 sample was different in nature to the impregnation, liquid and SC-CO₂ samples according to the f_1 , modified f_1 , and f_2 values. One-way ANOVA followed by the Tukey test at each 293 294 individual time point showed significant differences between the physical and melt release 295 profiles from 5 to 20 min compared to the other samples. After 30 min, the melt release was 296 not significantly different to the impregnation, liquid and SC-CO₂ samples release, according 297 to one-way ANOVA. The physical mix had a significantly less release across all time points 298 (p < 0.05).

In the case of physical mix and melt samples, the variability in drug release at each time point was high in contrast to the other samples reflecting the heterogeneous drug-loading in these samples referred to previously in Section 3.1. The similarity of the drug release profiles for the melt, impregnation, liquid and SC-CO₂ samples indicated that the deposition behaviour of drug in the mesopores did not affect its release.

304

305 3.5 Stability analysis

306 The presence of amorphous drug in the processed samples potentially posed a risk to the drug

307 solid state stability of these formulations. Recrystallization of unstable amorphous forms can Page 13 308 adversely affect drug properties such as dissolution performance. The solubility and 309 dissolution enhancement associated with the amorphous form (Hancock and Parks, 2000) can 310 be lost if there is re-crystallisation occurs While it has been reported that the OMMs can 311 stabilise non-crystalline drug forms (Mellaerts et al., 2010, Shen et al., 2010), the influence of 312 loading method on stability has not been reported. After 12 months accelerated storage at 40 313 °C and 75% RH, there was no evidence of re-crystallisation of the amorphous drug in the 314 pXRD diffractograms of the melt, impregnation, liquid and SC-CO₂ samples (Fig.6). 315 Interestingly, the pore volume of the physical mix sample post storage was reduced compared 316 to the as prepared sample; a significant increase (p < 0.05) in % ΔPV was determined (Table 317 1) according to one-way ANOVA followed by the Tukey test. The reduction of the pore 318 volume was evident in the decrease of size of the larger pores size (Fig.7). The pore volume 319 and size of the melt, impregnation liquid and SC-CO₂ samples remained unchanged post 1 320 month storage.

After storage for 1 month, there was some improvement in drug release from the physical mix samples (Fig.8); the f_1 , modified f_1 , and f_2 values showed a difference between the profiles. One-way ANOVA analysis followed by the Tukey test across each time point showed a significant increase in drug release post storage compared to the as prepared sample (p < 0.05). Long term storage for up to 12 months did not enhance the drug release rate of the drug in the impregnation, liquid and SC-O₂ samples (data not shown).

327

328 **4.0 Discussion**

329 The results of this work highlight the influence of the loading process employed on drug

330 distribution on the mesoporous silica structure. The physical mixing and melt methods

employed resulted in heterogeneous distribution of drug throughout the MESOPOROUS 332 SILICA due to blending difficulties arising from differences in density between the drug and 333 silica. The impregnation, liquid and SC-CO₂ methods obtained samples with drug 334 homogeneously dispersed throughout the mesoporous silica surfaces similar to that reported 335 previously (Ahern et al., 2012, Van-Speybroeck et al., 2009). This was facilitated by 336 dissolution/ of the drug in the solvent.

331

337 Changes in the porosity of silica post processing also highlighted differences in drug 338 distribution resulting from different loading methods. For all loading methods examined, the 339 mesoporous silica retained its type IV adsorption isotherm indicative of its mesoporous 340 nature. Similar findings have been reported previously (Mellaerts et al., 2008b, Morere et al., 341 2012, Moritz and Laniecki, 2012). The deposition of the drug molecules inside the 342 mesoporous silica mesopores resulted in some of the pores being fully or partially filled with 343 drug molecules, which prevented the adsorption and condensation of the N₂ molecules in the mesopores during subsequent pore volume measurement. Ukmar and co-workers reported 344 345 that indomethacin loaded onto MCM-41 and SBA-15 using a solvent impregnation method 346 formed a condensed phase that could block passage of the mesopore channels (Ukmar et al., 347 2011).

348 The melt method resulted in the greatest reduction in pore size and largest reduction in pore 349 volume. This behaviour was attributed to the molten viscosity of drug preventing deep 350 penetration of the mesopores and causing blockage of mesopores. Mellaerts and co-workers 351 utilised a melt method to load itraconazole and ibuprofen onto SBA-15; the subsequent 352 itraconazole-SBA-15 surface area, pore volume and size were similar to the SBA-15, while 353 for ibuprofen-SBA-15 the surface area, pore volume and size were reduced (Mellaerts et al., 354 2008a). Therefore, the distribution of drug in samples prepared using melt methods is Page 15

355 strongly dependent on the drug's molten viscosity, while the ability to form a homogeneous 356 mixture of drug and silica prior to the melting step of the process depends on the density of 357 the powders and method of blending. The decrease in pore size observed was evidence of the 358 drug coating/lining the inside of the mesopores and was also observed by Mellaerts and co-359 workers (Mellaerts et al., 2008a).

360 Due to the greater diffusivity and extremely low surface tension of SC-CO₂ compared to 361 solvents in a liquid state, there appears to be deeper drug penetration of the silica (Belhadj-362 Ahmed et al., 2009). This is reflected in the lower reduction of pore volume and pore size observed for the SC-CO₂ samples compared to the impregnation and liquid CO₂ samples, 363 364 despite all samples having similar drug-loading. From these data it appears that although the 365 drug deposition causes a narrowing of the pore network, it does not preclude N₂ access during 366 measurement to the same extent as in the melt, impregnation and liquid CO₂ samples. It was 367 previously reported that increasing the amount of drug loaded using SC-CO₂ loading 368 correlated with a reduction in pore volume (Ahern et al., 2012). In this work, it is also 369 apparent that the processing method has an important influence on the distribution of drug 370 and subsequent porosity of samples with similar drug-loading.

371 Loading fenofibrate onto SBA-15 using the impregnation, liquid and SC-CO₂ processes

372 resulted in the drug changing from the crystalline to a non-crystalline state. This is in

373 agreement with previous reports showing the crystalline to non-crystalline transition observed

374 when processing drugs with OMMs (Miura et al., 2010, Nishiwaki et al., 2009, Tozuka et al.,

375 2005, Tozuka et al., 2003). Qian and co-workers demonstrated that crystalline to amorphous

transitions occurred in physical mixes of drug and silica via a vapour phase-mediated

377 pathway for drugs with a relatively low vapour pressure (Qian and Bogner, 2011). The

378 physical mixing conditions investigated in this study did not result in any detectable

amorphization of fenofibrate, perhaps due to the relatively high vapour pressure offenofibrate.

Azais and co-workers studied the confinement of ibuprofen in MCM-41 mesopores (35 and 381 382 116 Å) using solid state nuclear magnetic resonance. They reported that the ibuprofen in the 383 mesopores was not in a crystalline or amorphous state at ambient temperature (Azais et al., 384 2006), and proposed the concept of the drug existing as a molecular dispersion in the silica 385 mesopores. The drug loaded onto SBA-15 by the impregnation, liquid and SC-CO₂ processes 386 appeared to be in a molecularly dispersed state as no Tg or Tm was observed. However as 387 highlighted in Section 3.3 frozen water in the pores of mesoporous silica may have 388 confounded the detection of the T_g for fenofibrate in these samples. In the melt sample, there was a small endotherm detected in the DSC thermogram around the drug's melting point, 389 390 which would indicate that some of the drug was still crystalline. 391 It has been previously reported that fenofibrate existed in an amorphous state post loading 392 onto silica. Van-Speybroeck and co-workers impregnated SBA-15 with fenofibrate and detected the drug T_g at – 20 °C, this was ascribed to the higher drug load (higher ratio of drug 393 394 weight to silica surface area) which promoted drug-drug interactions (Van Speybroeck et al., 395 2010a). Sanganwar and Gupta reported the presence of residual crystallinity post processing 396 of fenofibrate with aerosil using SC-CO₂ (Sanganwar and Gupta, 2008). However, this may 397 be due to the non-porous nature and hence lower surface area of aerosil and again, a 398 relatively higher drug weight to silica surface area ratio. Other studies of drug-loading SBA-399 15 using an impregnation process have also reported that the drug was molecularly dispersed 400 as there was no Tg or Tm observed (Mellaerts et al., 2010, Mellaerts et al., 2008a, Van 401 Speybroeck et al., 2010b).

402 Fenofibrate in melt, impregnation, liquid and SC-CO₂ prepared samples was stabilised in the 403 non-crystalline form after 12 month storage under accelerated storage conditions. Fenofibrate 404 is very unstable in its amorphous form; it has a T_g of -20 °C, its recrystallization temperature 405 is 40 °C and its reduced temperature scale is 0.6 (Zhou et al., 2002), hence amorphous 406 fenofibrate is difficult to isolate due to its rapid recrystallization at ambient conditions. 407 Therefore the prolonged stability at accelerated storage conditions must be attributed to its 408 co-processing with SBA-15. These results correspond with those published by Mellaerts and 409 co-workers who reported that itraconazole was maintained in the amorphous form for up to 410 12 months after processing with SBA-15 (Mellaerts et al., 2010). Shen and co-workers 411 published similar findings with respect to ibuprofen co-spray-dried with SBA-15 (Shen et al., 412 2010). The ability of SBA-15 to stabilise drugs in a non-crystalline state has previously been 413 discussed. Qian and co-workers reported that the enthalpy of adsorption of a compound on 414 mesoporous silica can lower the Gibbs free energy and cause spontaneous phase 415 transformation of the molecule from a crystalline to an amorphous state (Qian and Bogner, 416 2011). Another important factor to the stabilisation of the amorphous form is the effect of 417 nanoconfinement on drug recrystallization. A drug cannot re-crystallize when 418 the space in which it is confined does not exceed the drug molecule width by at least a factor 419 of 10 (Rengarajan et al., 2008, Sliwinska-Bartkowiak et al., 2001). 420 There was a limited improvement in drug release rate in the physical mix sample, which was 421 previously reported by Miura and co-workers, when they physically loaded the drug K-832 422 onto the silica material sylysia 350 (Miura et al., 2010). The drug release from the 423 impregnation, liquid and SC-CO₂ samples was rapid and similar. The enhanced rate of drug 424 release was attributable to the more homogeneous distribution of the drug throughout the 425 silica, which spread the drug through all of the available surface area. It has been long Page 18

established that drug release rate can be enhanced by increasing the effective drug surface
area in contact with the dissolution medium (Brunauer et al., 1938). The increased wettability
of the drug after drug-loading (Wang et al., 2006) and the non-crystalline nature of the drug
which has a higher Gibbs free energy compared to the crystalline form (Craig et al., 1999,

430 Yu, 2001) were also contributing factors.

431 The extent of drug release from the physical sample increased after 1 month storage. It has 432 been proposed that water may react with mesoporous silica during storage which causes an 433 increase in the extent of drug release. Itraconazole loaded on mesoporous silica prepared 434 using a solvent impregnation method and stored at 25°C and 97 % RH showed an increase in 435 the extent of drug dissolution post storage (Mellaerts et al., 2010). In this work, the extent of 436 drug release did not improve post 12 months storage for the solvent impregnation, liquid and 437 SC-CO₂ samples. Similar findings were presented by Shen and co-workers who subjected a 438 co-spray dried ibuprofen / SBA-15 sample to 12 month, storage at 40 °C and 75% RH (Shen 439 et al., 2010). The influence of moisture uptake on the release of drugs loaded on mesoporous 440 silica appears to vary with the loading method and warrants further investigations.

441

442 **5.0 Summary**

The method of loading drug onto SBA-15 was shown to influence drug distribution which is evident by the differences in pore size and volume observed for the samples prepared. With the exception of the physical mix and melt samples, solid state and release properties were similar for all processed samples. All processing methods except the physical mix sample, loaded fenofibrate into the SBA-15 mesopores where it was stabilised in a non-crystalline state for 12 month at 75% RH and 40 °C. Drug release rates were increased for all samples, 449 but depended on loading method. While different loading methods may result in differences

- 450 in drug distribution these differences were not shown to result in differences in solid state
- 451 stability or drug release in the case of the impregnation, liquid and SC-CO₂ processed
- 452 samples.
- 453

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- 458

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- 642 643

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647

648 Supporting Data

- 649 **Table 1**
- 650 Comparison of drug-loading efficiency and % ΔPV before and after storage for all processed
- 651 drug SBA-15 samples

Processing Method	Loading Efficiency (%)	% ΔΡV	% ΔPV, 1 month storage
Frocessing method	(n = 9)	(n = 6)	(n = 6)
Physical Mix	106.26 (±42.83)	1.88 (±5.41)	15.29 (±6.08)
Melt Method	103.90 (±30.22)	36.84 (±5.63)	35.09 (±3.89)
Impregnation	92.55 (±5.14)	33.12 (±2.26)	44.40 (±15.92)
Liquid CO ₂	93.25 (±5.35)	32.06 (±1.66)	33.68 (±3.66)
SC-CO ₂	91.98 (±6.34)	19.64 (±5.30)	21.27 (±4.16)

652



654 Fig.1 N2 adsorption/desorption isotherms of (a) unprocessed SBA-15, physical mix and melt method samples and (b) unprocessed SBA-15,

655 impregnation, liquid and SC-CO₂ processed samples.

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Fig.2: Pore size distribution of unprocessed SBA-15, physical mix, melt, impregnation, liquid

- and SC-CO₂ processed samples.



675 Fig.3 pXRD diffractograms of (a) physical mix and melt method samples and (b) impregnation, liquid and SC-CO₂ processed samples.



682 Fig.4 DSC thermograms of (a) unprocessed SBA-15 and (b) physical mix and melt samples with evidence of fenofibrate melting endotherm



685 Fig.5 Release profiles of (a) unprocessed fenofibrate, physical mix and melt method samples and (b) impregnation, liquid and SC-CO₂ processed

686 samples

687





Fig.6: pXRD diffractograms of melt, impregnation, liquid and SC-CO₂ processed systems

- 690 post 12 month accelerated storage.
- 691





693 **Fig.7:** Pore size distribution of physical mix sample as prepared and after 1 month storage



Fig.8: Release profile of physical mix sample as prepared and post 1 month storage













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