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Comparison of fenofibrate – mesoporous silica drug-loading processes for enhanced drug delivery

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Abstract

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

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

1.0 Introduction

It has been long established that increasing the effective surface area of a poorly water-soluble drug in contact with the dissolution medium can enhance drug dissolution (Bruner, 1904, Nernst, 1904). This can be achieved by loading drug on silica-based ordered mesoporous materials (OMMs) which are characterised by high surface areas, large pore volumes, narrow pore size distributions (5 – 8 nm) and ordered unidirectional pore networks. These properties allow for homogeneous and reproducible drug-loading and release (Manzano et al., 2009, Vallet-Regi et al., 2007, Vallet-Regi et al., 2001). Many publications have focussed on understanding the key properties of OMMs that 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 impact on drug release rate, with larger silica particles resulting in slower drug release because of the longer mesopore length (Chen et al., 2012). The pore volume influences the amount of drug loaded, especially if the drug is dissolved in a solvent that can carry it into the mesopores (Vallet-Regi et al., 2007). Larger pore sizes encourage greater drug release rates (Horcajada et al., 2004), while pore geometry has also been shown to affect drug-loading and release (Izquierdo-Barba et al., 2005). Stabilisation of amorphous drug for up to 12 months has also been ascribed to the mesopores of the OMM (Mellaerts et al., 2010, Shen et al., 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).

Despite the body of literature evaluating the different properties of OMM affecting drug-loading and release, there seems to be a lack of clarity regarding the optimum processing method to load drug onto the OMM and the subsequent implications for drug delivery.

Various loading methods have been employed including physical mixing (Song et al., 2005, Qian and Bogner, 2011), solvent based methods that either involve the suspension of the OMM in a drug-solvent solution (Andersson et al., 2004, Izquierdo-Barba et al., 2005, Charnay et al., 2004) or impregnation of the OMM by dropwise addition of a concentrated drug solution (Mellaerts et al., 2008a, Van-Speybroeck et al., 2008). Some researchers have mixed the drug and silica and heated the resultant mixture to below (Tozuka et al., 2005) or above the drug's melting point (Aerts et al., 2010, Mellaerts et al., 2008a, Shen et al., 2010).

Alternative loading methods such as supercritical CO₂ (SC-CO₂) (Ahern et al., 2012, Sanganwar and Gupta, 2008) have also been proposed to load drug onto OMMs. The high densities of liquid and SC-CO₂ should permit a large amount of drug to be solubilised, while the high diffusivity of the SC-CO₂ should facilitate ready access to the mesopore network (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

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

2.0 Materials and methods

2.1 Materials

Fenofibrate was supplied by Kemprotec Ltd. (United Kingdom). CO₂ was supplied by Irish Oxygen Ltd. (Ireland). Hydrochloric acid (HCl), dichloromethane (DCM), potassium bromide (KBr), phencyclidine hydrochloride (P-123) and tetraethyl orthosilicate (TEOS) were supplied by Sigma-Aldrich Ltd. (Ireland). Sodium dodecyl sulphate (SDS) was supplied by Fisher Scientific Ltd. (Ireland).

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

2.2 Drug-loading methods

Drug-silica samples were prepared with a ratio of 1 mg drug per 3 m² mesoporous silica. In each case approximately 400 mg of drug was combined with 2 g mesoporous silica and

processed according to the methods detailed below. All samples were prepared in triplicate. Following preparation, a portion of each drug-silica sample was placed in screw-capped plastic tubes (Sarstedt AG, Germany) and stored in a desiccator at ambient temperatures prior to analysis. The remaining part was stored under accelerated storage conditions at 75% relative humidity (RH) and 40 °C prior to analysis to assess stability (FDA, 2003).

2.2.1 Physical mixing

Drug-mesoporous silica physical mixes were prepared by blending the drug and SBA-15 for 30 min at 100 revolutions per minute (rpm) using an AR402 Erweka blender (Erweka GmbH, Germany).

2.2.2 Melt method

The melt method involved heating the drug above its melting point (>80 °C) and relied on its molten viscosity to distribute the drug on the mesoporous silica surface. The drug was manually combined with the mesoporous silica to increase the homogeneity of drug distribution. The sample was maintained above 80 °C for 24 h using an E-series binder oven (Erweka GmbH, Germany) and thereafter cooled to ambient temperature.

2.2.3 Solvent impregnation

Samples were prepared according to the method reported by Mellaerts and co-workers (Mellaerts et al., 2008a). Approximately 8 ml of a concentrated solution of fenofibrate (50 mg/ml) in DCM was added dropwise to the mesoporous silica; after each addition the powder was intensively ground with a pestle. Thereafter, the sample was dried at 40 °C for 48 h under vacuum (100 Pa).

2.2.4 Liquid and SC-CO₂ loading

The drug and mesoporous silica were combined in a high-pressure reactor (BC 316), (High Pressure Equipment Company, USA) and stirred using a magnetic stirring. The cell was heated to 25 °C using heating tape and maintained constant for the duration of the experiment 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 used to pump additional CO₂ to a final processing pressure (27.58 MPa). At the end of the experiment the cell was depressurised rapidly by venting the CO₂. The SC-CO₂ loading process followed a similar procedure, except that the cell was heated to 40 °C.

2.3 Physicochemical characterisation

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.

Comparison of the measured pore volume of the drug-silica samples with the theoretical pore volume provides some indication of the location of the drug in the samples. The theoretical pore volume (P.V.) of the processed fenofibrate-silica samples can be determined based on the relative mass fractions of silica and drug present in the sample and their respective pore volumes. As fenofibrate is a non-porous material its pore volume can be ignored and the

theoretical pore volume (P.V.) of the processed fenofibrate-silica samples was calculated according to Eq. 1.

$$\text{Theoretical P.V.} = (\text{P.V.}_{(\text{MS})} \times M_{(\text{MS})}) \quad (1)$$

P.V._(MS) refers to the pore volume (cm³/g) of unprocessed SBA-15. M_(MS) refers to the mass fraction of mesoporous silica in the fenofibrate-silica sample. The mass fraction of drug present in the fenofibrate-silica samples was determined by thermogravimetric analysis (TGA) as described in Section 2.3.2. Eq. 1 was employed based on the assumption that there was no chemical or physical interaction between silica and fenofibrate in the fenofibrate-silica samples.

The percentage difference between the theoretical and measured pore volumes (% ΔPV) was calculated using Eq.2

$$\% \Delta \text{PV} = ((\text{theoretical P.V.} - \text{measured P.V.}) / \text{theoretical P.V.}) * 100\% \quad (2)$$

2.3.2 Thermogravimetric analysis

Thermogravimetric analysis (TGA) was carried out using a TGA 500, (TA Instruments Ltd., United Kingdom). Samples in the weight range 2 to 10 mg were loaded onto tared platinum pans and heated from ambient temperature to 900 °C, at a heating rate of 10 °C.min⁻¹ under an inert N₂ atmosphere. All samples were analysed in triplicate. The moisture present in the samples was calculated from the weight loss between ambient temperature and 100 °C and the drug quantity was calculated from the weight loss between 100 to 900 °C, corrected for the weight loss over the same temperature range for silica only (Hillerström et al., 2009,

Van-Speybroeck et al., 2009). TGA thermograms were analysed using Universal Analysis 2000 software, (TA Instruments Ltd., United Kingdom). Drug-loading efficiency was calculated using Eq. 3.

$$\text{Drug-loading Efficiency (\%)} = (\text{actual drug loaded/theoretical drug loaded}) \times 100\% \quad (3)$$

The theoretical drug-loading was based on mass fraction of drug and silica used to prepare samples.

2.3.3 Differential scanning calorimetry

Differential scanning calorimetry (DSC) was carried out using a DSC Q1000, (TA Instruments Ltd., United Kingdom) operated in modulated mode. DSC was used to measure the glass transition temperature (T_g), melting point (T_m) and enthalpy of melting of fenofibrate and fenofibrate-silica samples. Samples in the weight range 3 to 5 mg were weighed on a MX5 microbalance (Mettler Toledo International Inc., USA) into Tzero aluminium pans (non-hermetic) (TA Instruments Ltd., United Kingdom). The samples were heated from -40 to 120 °C at a heating rate of 3 °C.min⁻¹ with modulation frequency of 1 °C.min⁻¹ every 60 s. An inert atmosphere was maintained using a N₂ flow rate of 50 ml.min⁻¹. A refrigerant cooling system, the RCS 40 (TA Instruments Ltd., United Kingdom) was used to cool samples below ambient temperature. Analysis of DSC thermograms was conducted using Universal Analysis 2000 software, (TA Instruments Ltd., United Kingdom).

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 ($\lambda = 1.5406 \text{ \AA}$) 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.

2.3.5 *In vitro* fenofibrate release

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

2.3.6 RP-HPLC analysis

RP-HPLC analysis was performed using an Agilent 1200 series HPLC system with a UV/VIS detector (Agilent Technologies, USA). A reversed-phase column Kinetex C-18 column (150 mm x 4 mm) with internal pore width 2.6 μm (Phenomenex Ltd., United Kingdom), a mobile

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

3.0 Results

3.1 Drug-loading

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

3.2 Porosity analysis

Changes in silica porosity after drug-loading can assist in understanding how the drug is distributed throughout the silica sample. Mesoporous silica starting material had a very large

pore volume ($>0.50 \text{ cm}^3/\text{g}$) and displayed the type IV adsorption-desorption isotherm and H1 hysteresis loop (Fig.1a) characteristic of mesoporous materials, (Sing et al., 1985). These characteristics were retained post drug-loading (Fig.1), which indicated that silica was still mesoporous. With the exception of the physical mix, all drug loaded samples showed marked reductions in the mesoporous silica pore size and volume. The closure point (P/P_0) of the hysteresis loop was reduced for all samples, with the exception of the physical mix (Fig.1), indicating a reduction in pore sizes (Izquierdo-Barba et al., 2005). The greatest reduction was observed for the sample prepared by the melt method. The pore size distribution in relation to the pore volume for the various samples is shown in Fig 2. Only a slight change in pore size distribution was seen for the physical mix (Fig.2a). Both impregnation and liquid CO_2 samples show similar reductions in pore size; interestingly the SC-CO_2 sample showed a lower reduction in pore size compared to these samples. The melt sample showed the greatest spread of pore sizes (Fig.2b).

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

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 non-crystalline state (Fig.3).

The melting point for the starting crystalline fenofibrate agreed with the reported T_m of 79 – 81 °C (Heinz et al., 2009). Thermal events in the temperature range -20 to -12 °C were noted during DSC analysis of the silica starting material (Fig.4a). This behaviour was previously reported as the melting point of frozen water confined in the mesopores of mesoporous silica (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_g was reported in this temperature region at -20 °C, (Heinz et al., 2009) it was not possible to conclusively detect the T_g of amorphous fenofibrate in any of these drug-silica samples. A large melting endotherm with an onset of 78 °C was visible in DSC thermogram of the physical mix, while there was a slight melting endotherm in the melt sample, indicative of the presence of residual crystalline drug (Fig.4b). The absence of melting endotherms in the impregnation, liquid and SC-CO₂ samples (data not shown), supported the pXRD results that the drug was in a non-crystalline state in these samples.

3.4 In vitro drug release

The release of drug from the silica carrier is a key performance indicator to consider when employing OMM for drug dissolution enhancement. The *in vitro* release of drug from drug-

silica samples and the dissolution of the starting fenofibrate are shown in Figure 5. Utilising mesoporous silica as a carrier material improved the drug dissolution rate for all processed samples. The physical mix showed a slower rate of drug release compared to all of the other loading methods. The release profiles of drug from the impregnation, liquid and SC-CO₂ 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 was released in a rapid manner in the first 20 min. After 20 min the drug release levelled between 70 – 80 % and did not increase between 20 and 120 min. The release from the melt 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 individual time point showed significant differences between the physical and melt release profiles from 5 to 20 min compared to the other samples. After 30 min, the melt release was not significantly different to the impregnation, liquid and SC-CO₂ samples release, according to one-way ANOVA. The physical mix had a significantly less release across all time points ($p < 0.05$).

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.

3.5 Stability analysis

The presence of amorphous drug in the processed samples potentially posed a risk to the drug solid state stability of these formulations. Recrystallization of unstable amorphous forms can

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

4.0 Discussion

The results of this work highlight the influence of the loading process employed on drug distribution on the mesoporous silica structure. The physical mixing and melt methods

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

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

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

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

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

Loading fenofibrate onto SBA-15 using the impregnation, liquid and SC-CO₂ processes resulted in the drug changing from the crystalline to a non-crystalline state. This is in agreement with previous reports showing the crystalline to non-crystalline transition observed when processing drugs with OMMs (Miura et al., 2010, Nishiwaki et al., 2009, Tozuka et al., 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 pathway for drugs with a relatively low vapour pressure (Qian and Bogner, 2011). The physical mixing conditions investigated in this study did not result in any detectable

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

381 Azais and co-workers studied the confinement of ibuprofen in MCM-41 mesopores (35 and
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 T_g or T_m 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
389 was a small endotherm detected in the DSC thermogram around the drug's melting point,
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
393 detected the drug T_g at – 20 °C, this was ascribed to the higher drug load (higher ratio of drug
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 T_g or T_m observed (Mellaerts et al., 2010, Mellaerts et al., 2008a, Van
401 Speybroeck et al., 2010b).

Fenofibrate in melt, impregnation, liquid and SC-CO₂ prepared samples was stabilised in the non-crystalline form after 12 month storage under accelerated storage conditions. Fenofibrate is very unstable in its amorphous form; it has a T_g of -20 °C, its recrystallization temperature is 40 °C and its reduced temperature scale is 0.6 (Zhou et al., 2002), hence amorphous fenofibrate is difficult to isolate due to its rapid recrystallization at ambient conditions. Therefore the prolonged stability at accelerated storage conditions must be attributed to its co-processing with SBA-15. These results correspond with those published by Mellaerts and co-workers who reported that itraconazole was maintained in the amorphous form for up to 12 months after processing with SBA-15 (Mellaerts et al., 2010). Shen and co-workers published similar findings with respect to ibuprofen co-spray-dried with SBA-15 (Shen et al., 2010). The ability of SBA-15 to stabilise drugs in a non-crystalline state has previously been discussed. Qian and co-workers reported that the enthalpy of adsorption of a compound on mesoporous silica can lower the Gibbs free energy and cause spontaneous phase transformation of the molecule from a crystalline to an amorphous state (Qian and Bogner, 2011). Another important factor to the stabilisation of the amorphous form is the effect of nanoconfinement on drug recrystallization. A drug cannot re-crystallize when the space in which it is confined does not exceed the drug molecule width by at least a factor of 10 (Rengarajan et al., 2008, Sliwinska-Bartkowiak et al., 2001).

There was a limited improvement in drug release rate in the physical mix sample, which was previously reported by Miura and co-workers, when they physically loaded the drug K-832 onto the silica material sylsias 350 (Miura et al., 2010). The drug release from the impregnation, liquid and SC-CO₂ samples was rapid and similar. The enhanced rate of drug release was attributable to the more homogeneous distribution of the drug throughout the silica, which spread the drug through all of the available surface area. It has been long

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, Yu, 2001) were also contributing factors.

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

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,

but depended on loading method. While different loading methods may result in differences in drug distribution these differences were not shown to result in differences in solid state stability or drug release in the case of the impregnation, liquid and SC-CO₂ processed samples.

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Supporting Data

Table 1

Comparison of drug-loading efficiency and % Δ PV before and after storage for all processed drug – SBA-15 samples

Processing Method	Loading Efficiency (%) (n = 9)	% ΔPV (n = 6)	% ΔPV, 1 month storage (n = 6)
Physical Mix	106.26 ($\pm$ 42.83)	1.88 ($\pm$ 5.41)	15.29 ($\pm$ 6.08)
Melt Method	103.90 ($\pm$ 30.22)	36.84 ($\pm$ 5.63)	35.09 ($\pm$ 3.89)
Impregnation	92.55 ($\pm$ 5.14)	33.12 ($\pm$ 2.26)	44.40 ($\pm$ 15.92)
Liquid CO₂	93.25 ($\pm$ 5.35)	32.06 ($\pm$ 1.66)	33.68 ($\pm$ 3.66)
SC-CO₂	91.98 ($\pm$ 6.34)	19.64 ($\pm$ 5.30)	21.27 ($\pm$ 4.16)

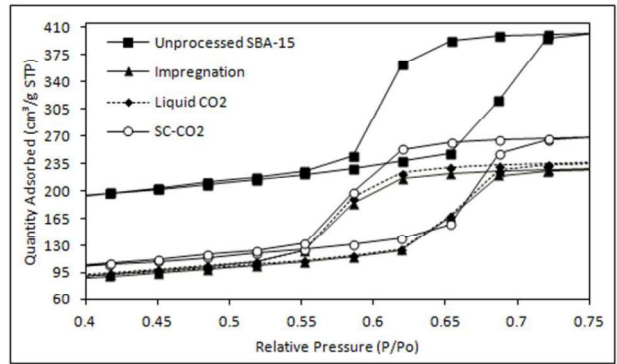
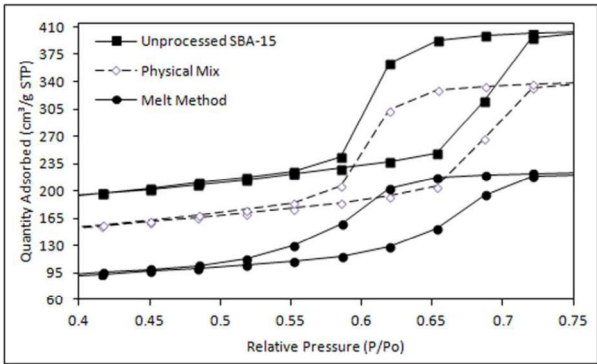


Fig.1 N₂ adsorption/desorption isotherms of (a) unprocessed SBA-15, physical mix and melt method samples and (b) unprocessed SBA-15, impregnation, liquid and SC-CO₂ processed samples.

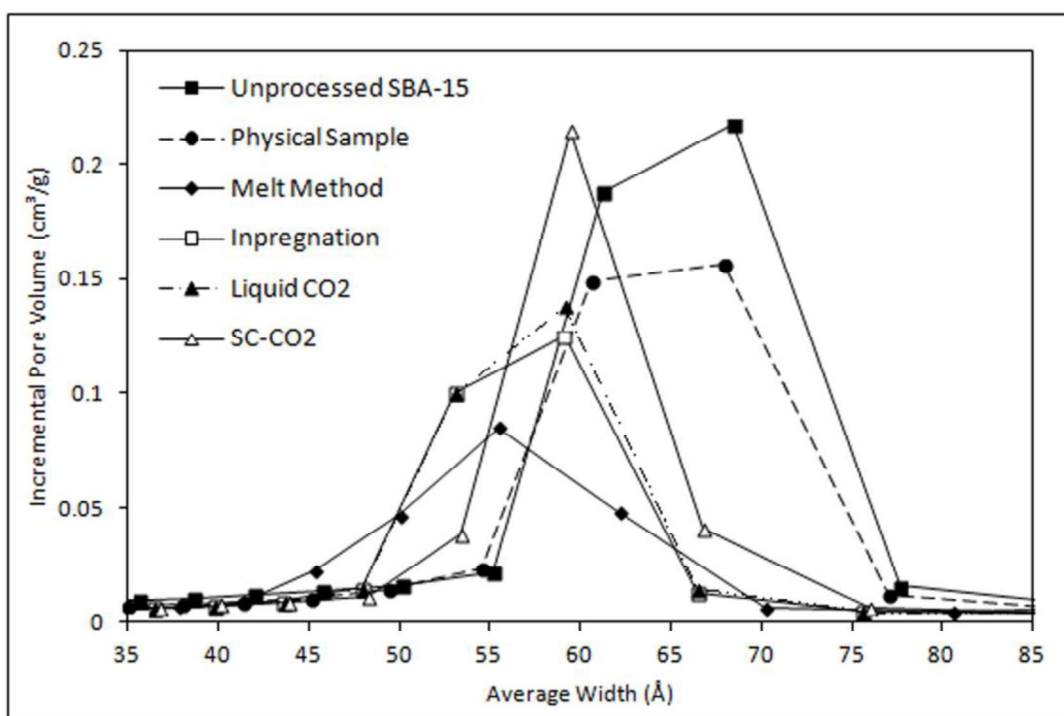


Fig.2: Pore size distribution of unprocessed SBA-15, physical mix, melt, impregnation, liquid and SC-CO₂ processed samples.

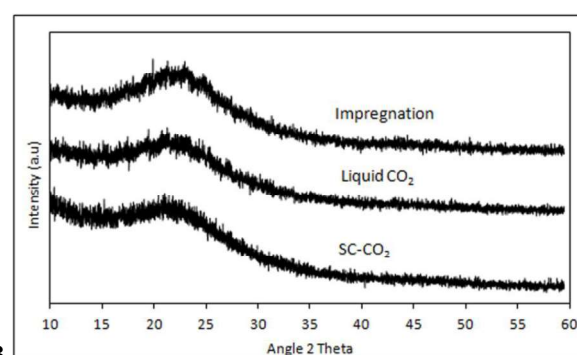
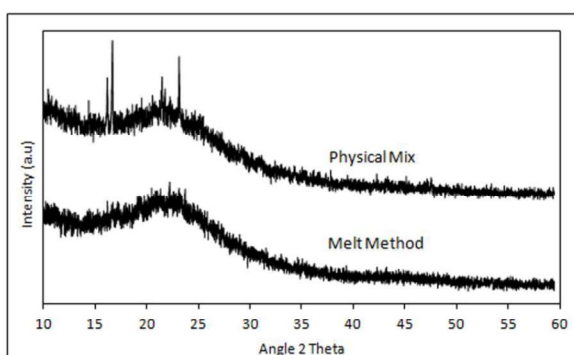
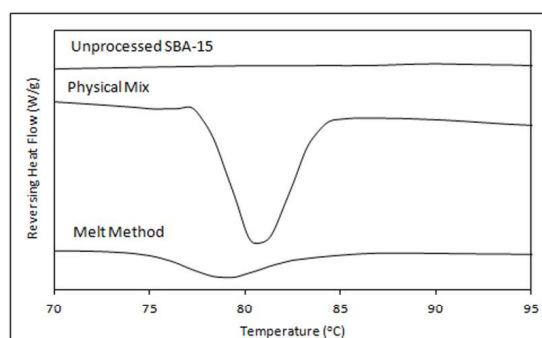
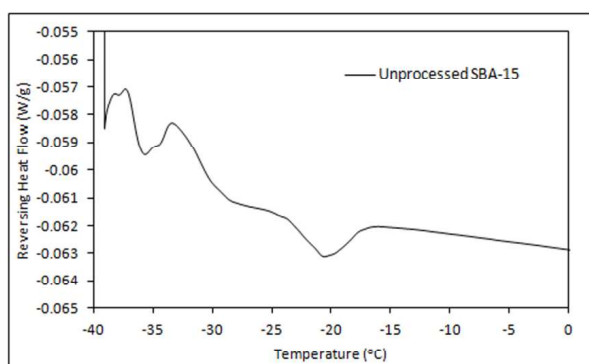


Fig.3 pXRD diffractograms of (a) physical mix and melt method samples and (b) impregnation, liquid and SC-CO₂ processed samples.



681 **A**

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

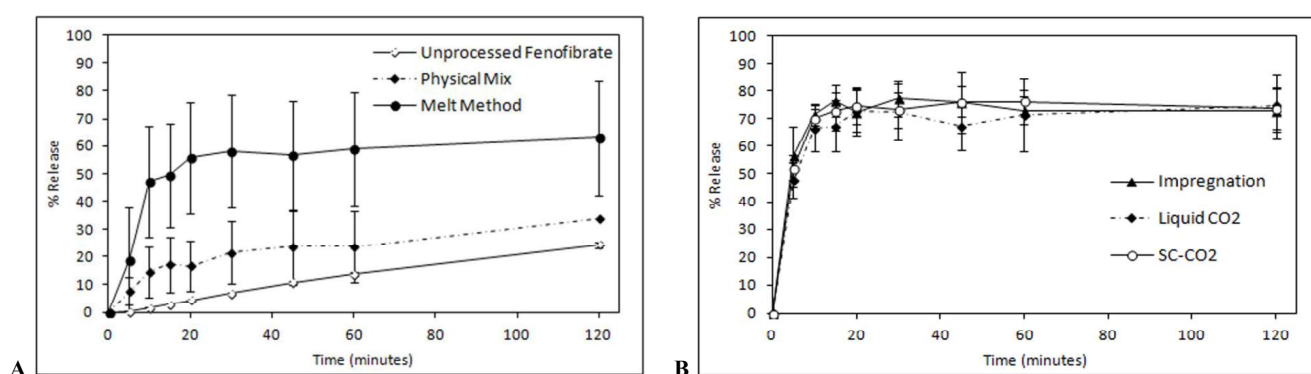
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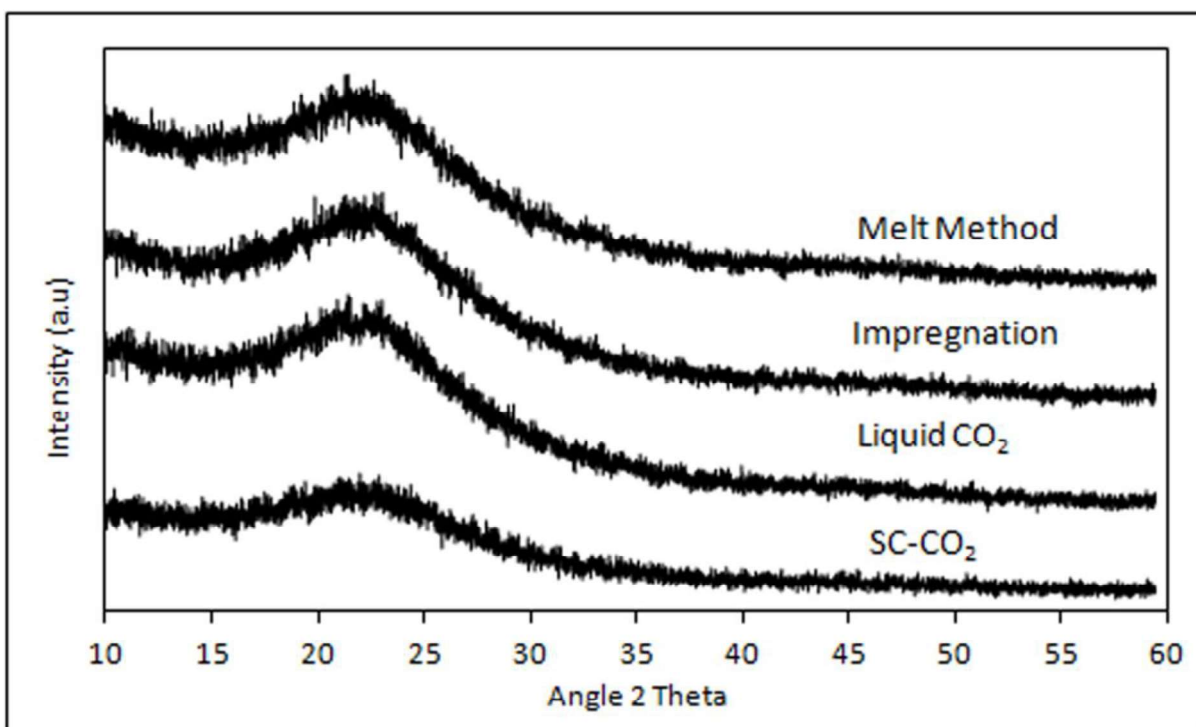


Fig.6: pXRD diffractograms of melt, impregnation, liquid and SC-CO₂ processed systems post 12 month accelerated storage.

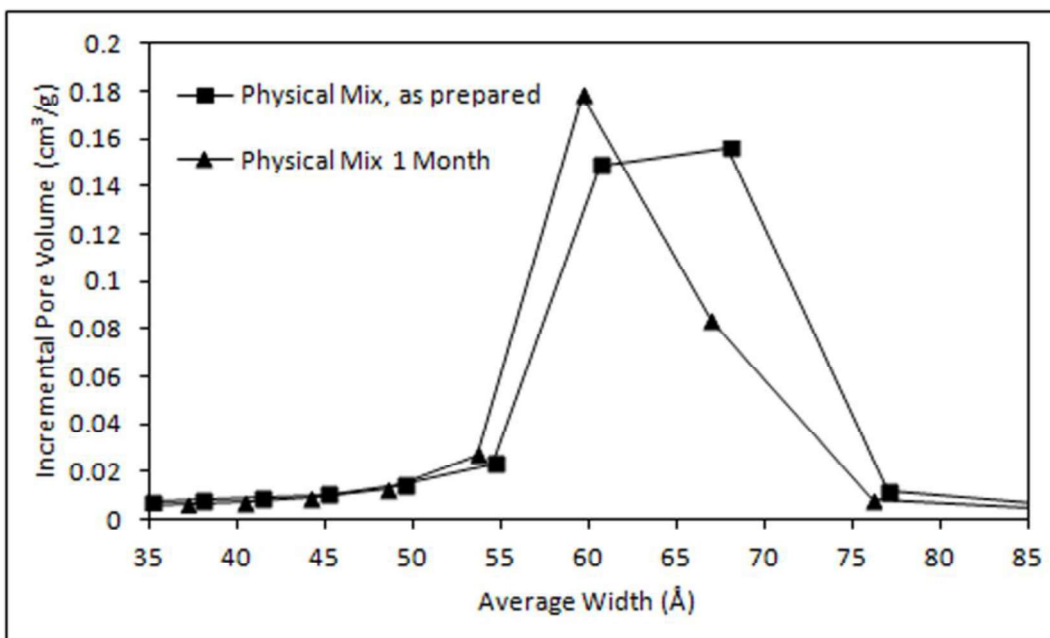


Fig.7: Pore size distribution of physical mix sample as prepared and after 1 month storage

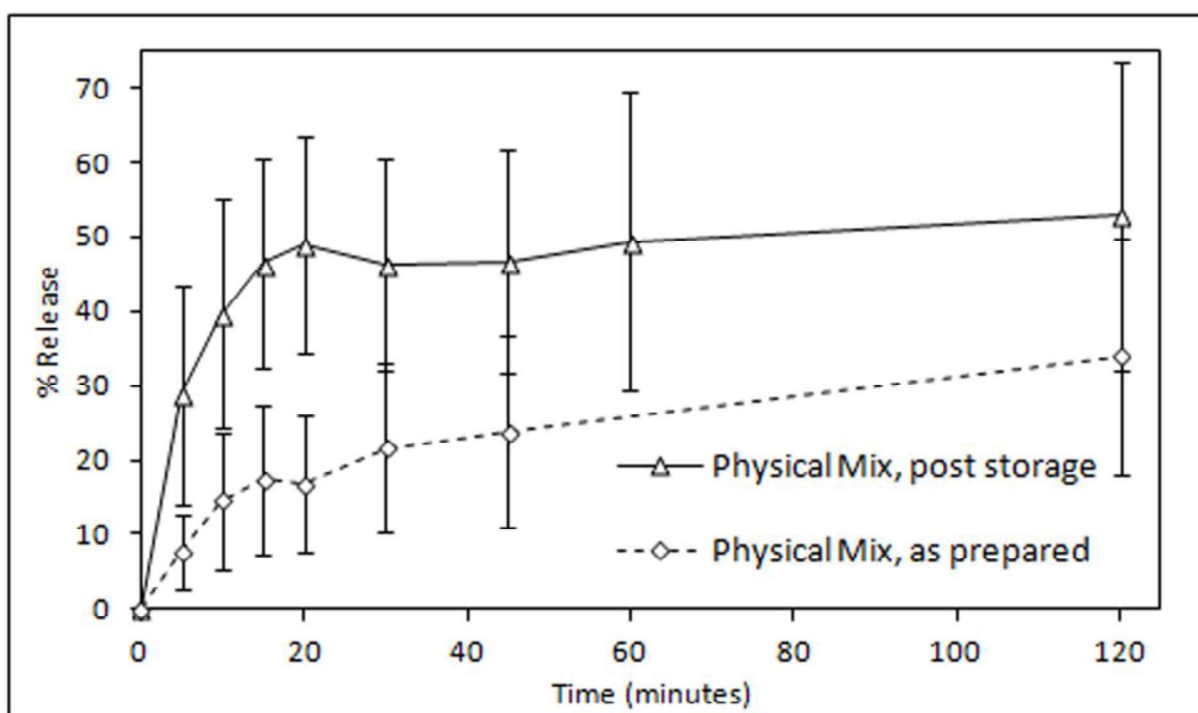
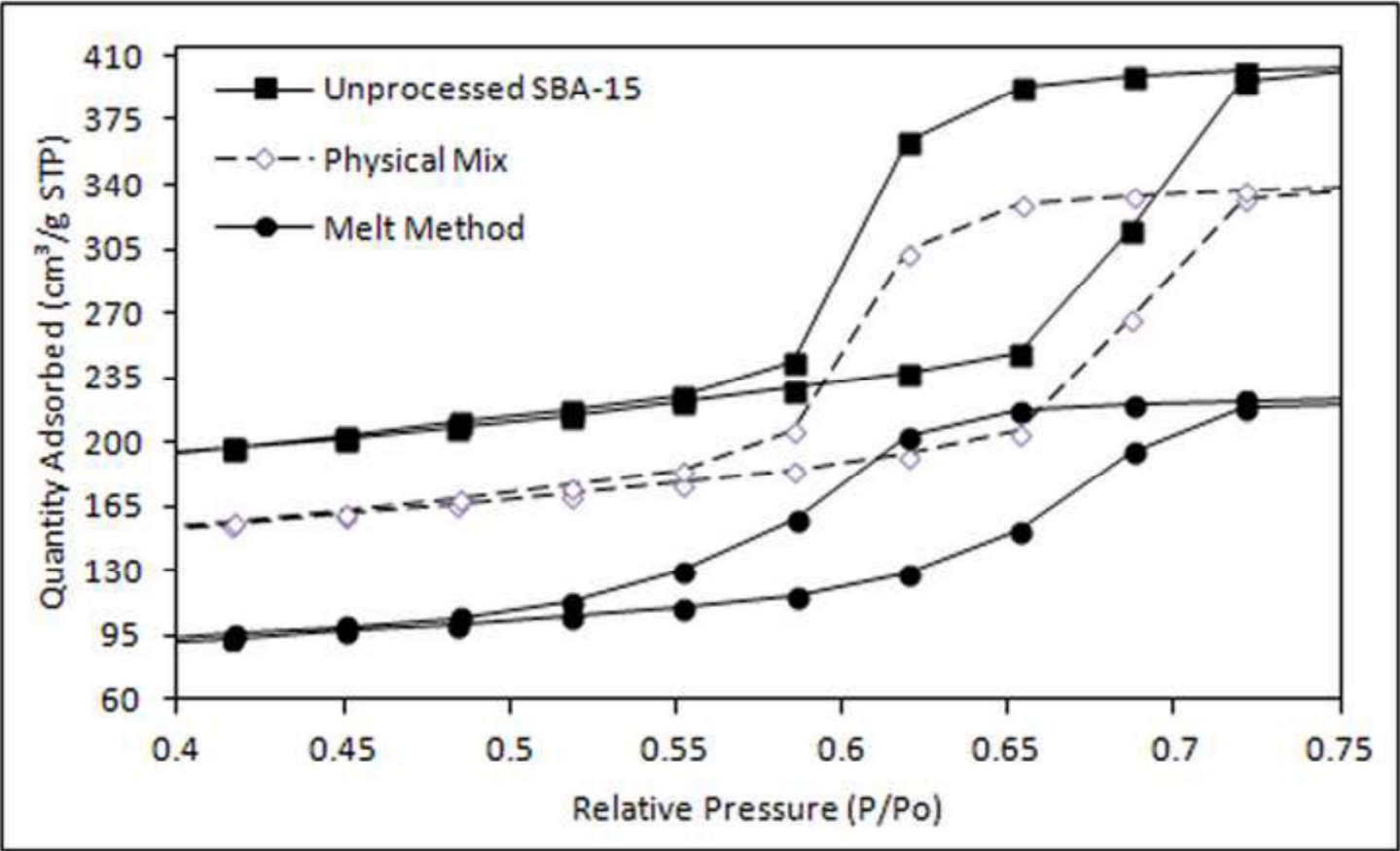
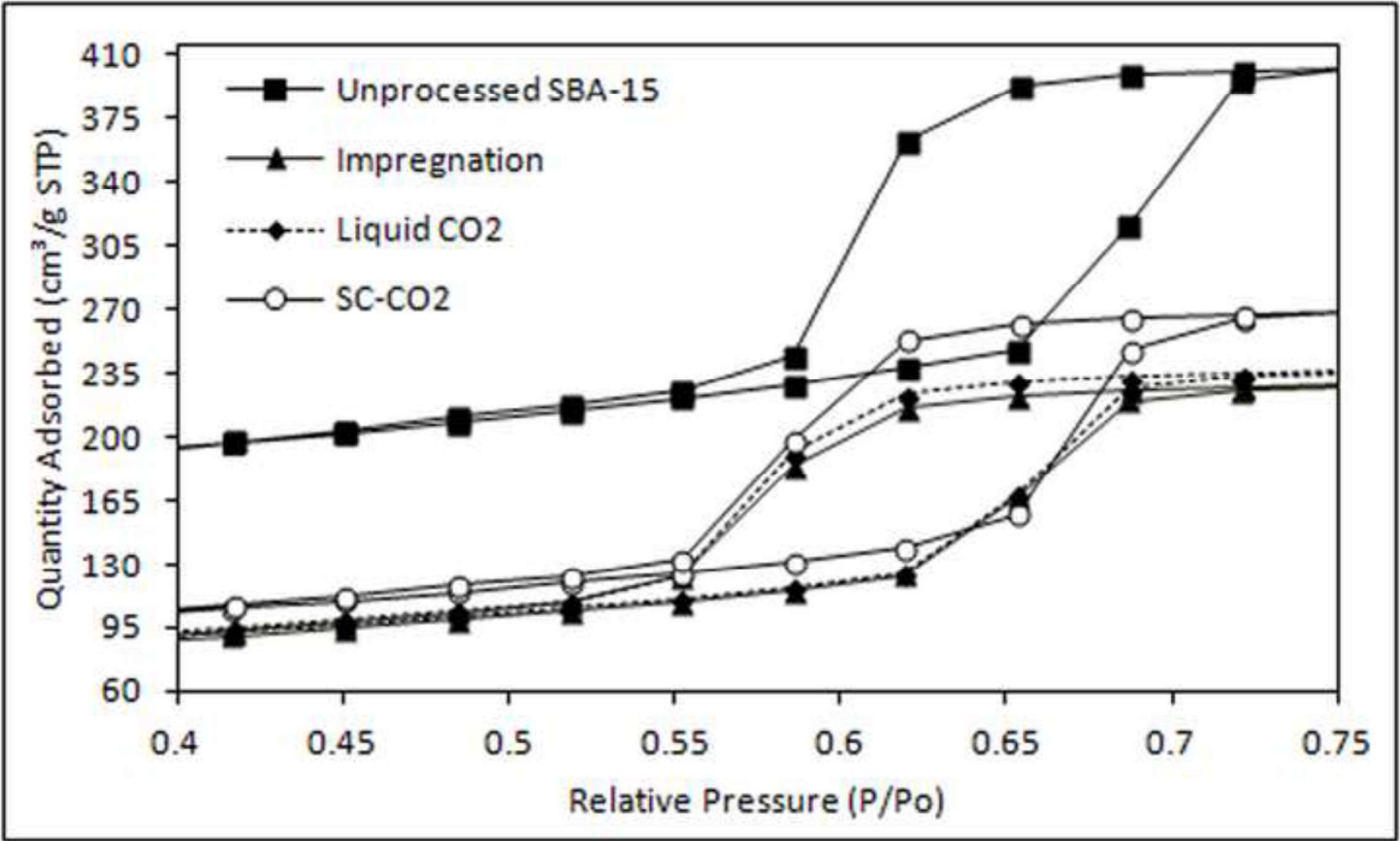


Fig.8: Release profile of physical mix sample as prepared and post 1 month storage

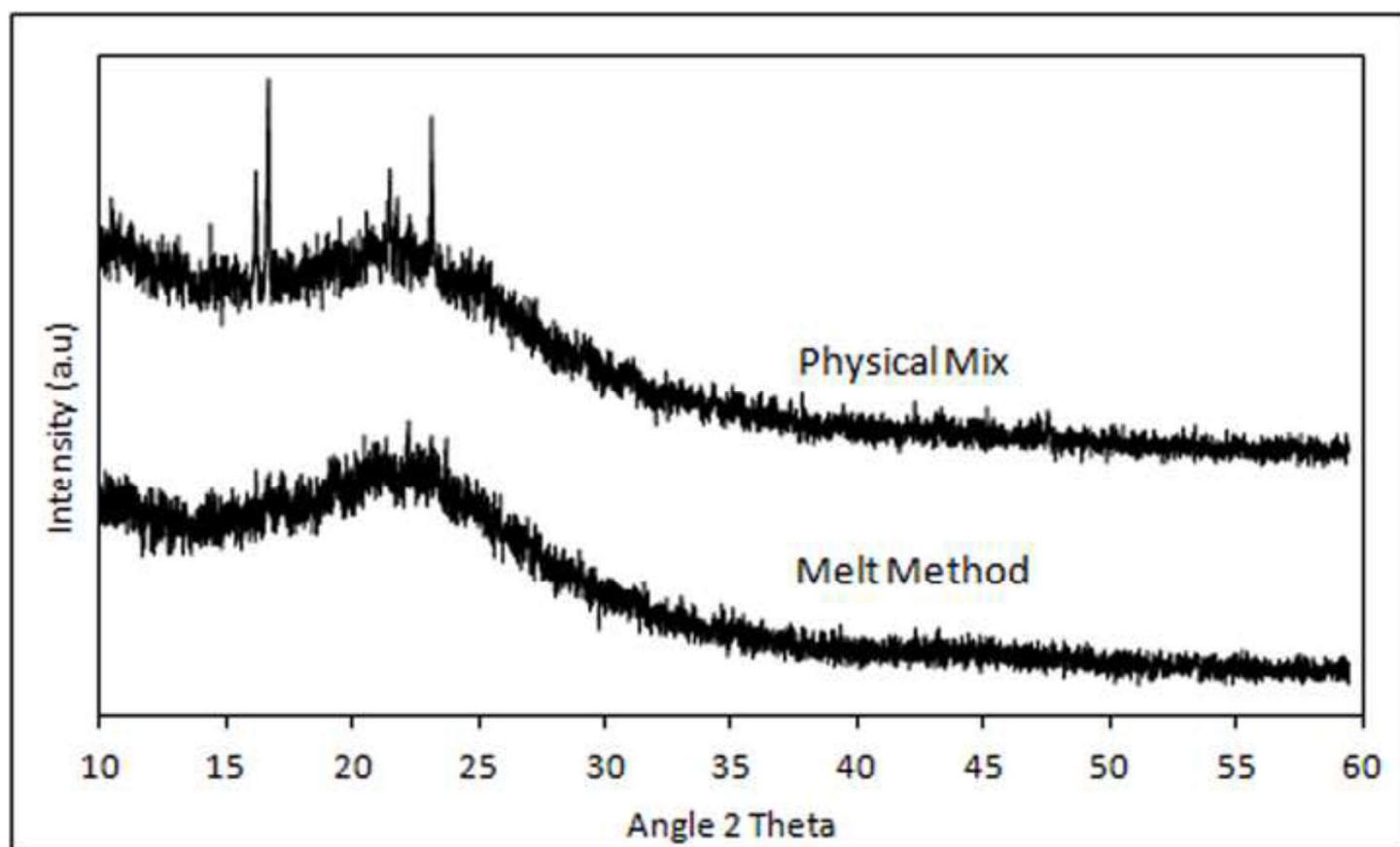
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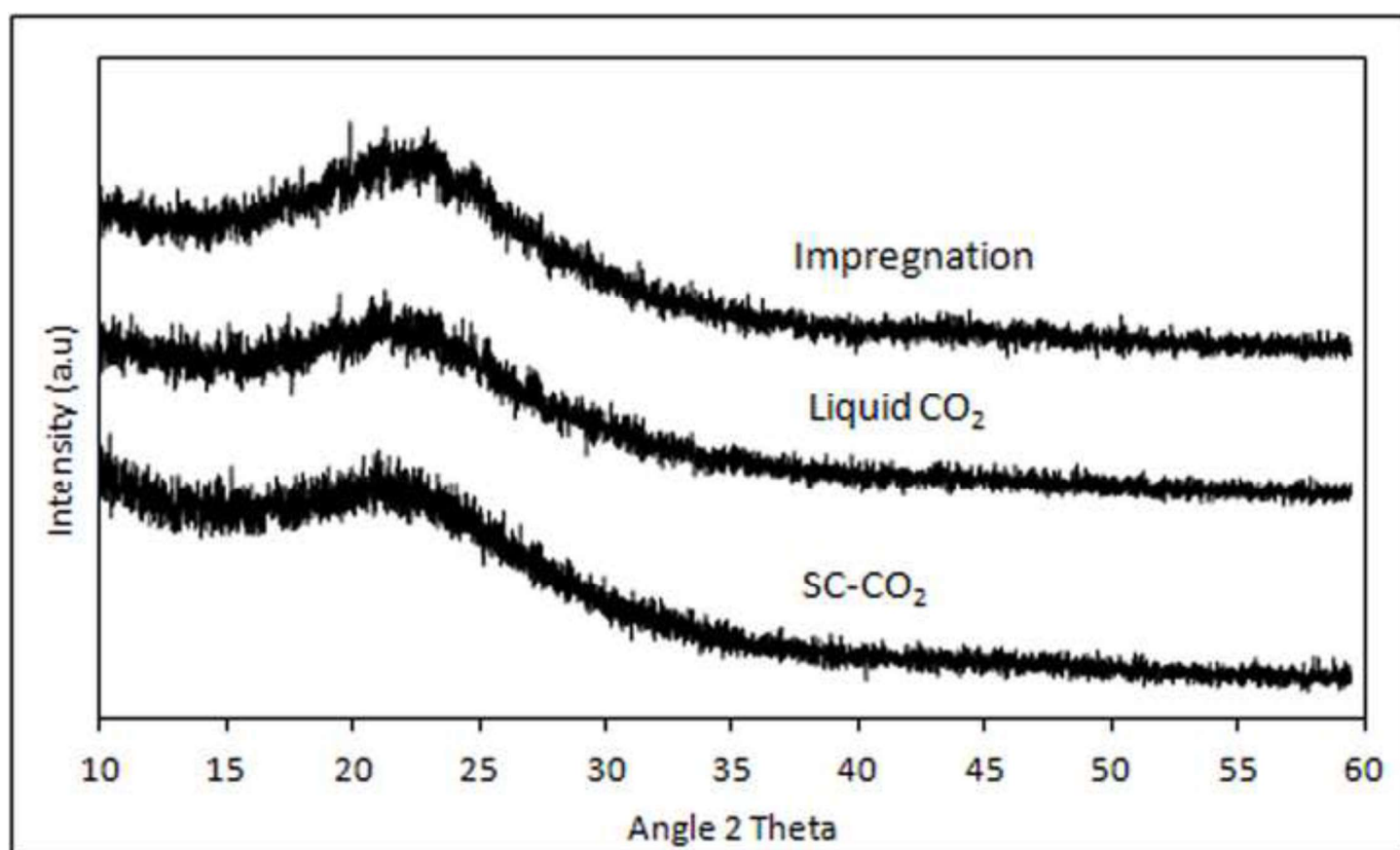
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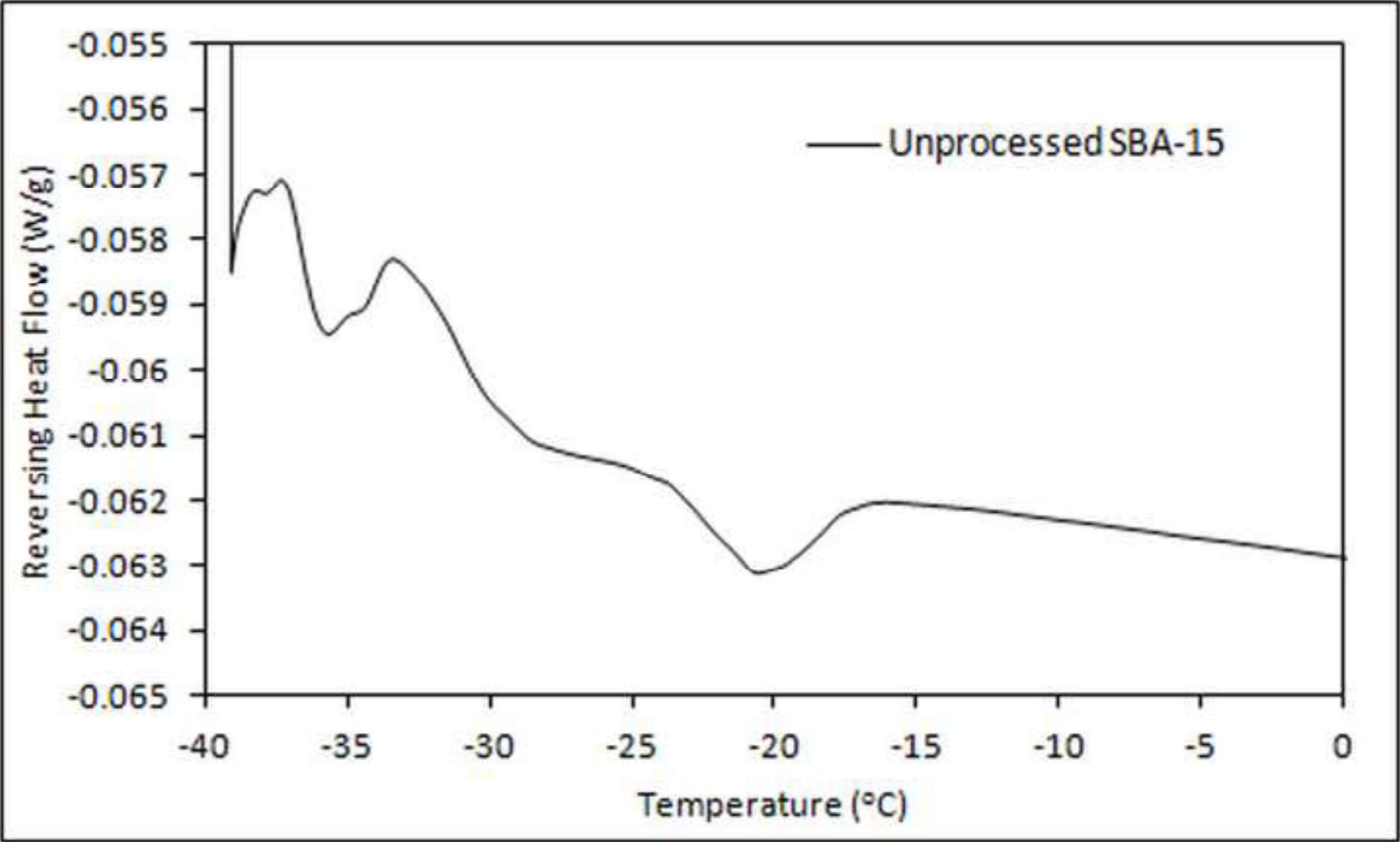
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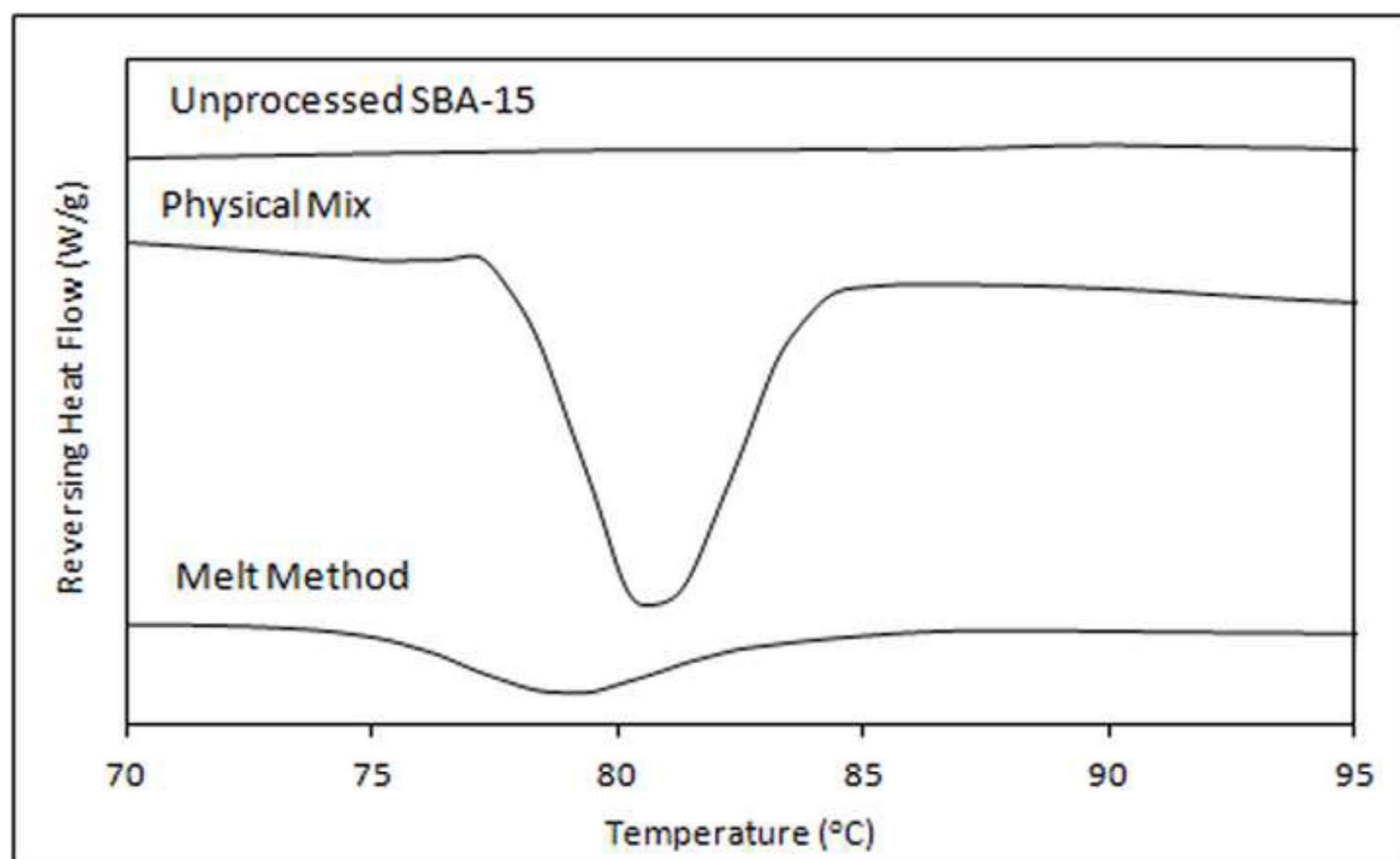
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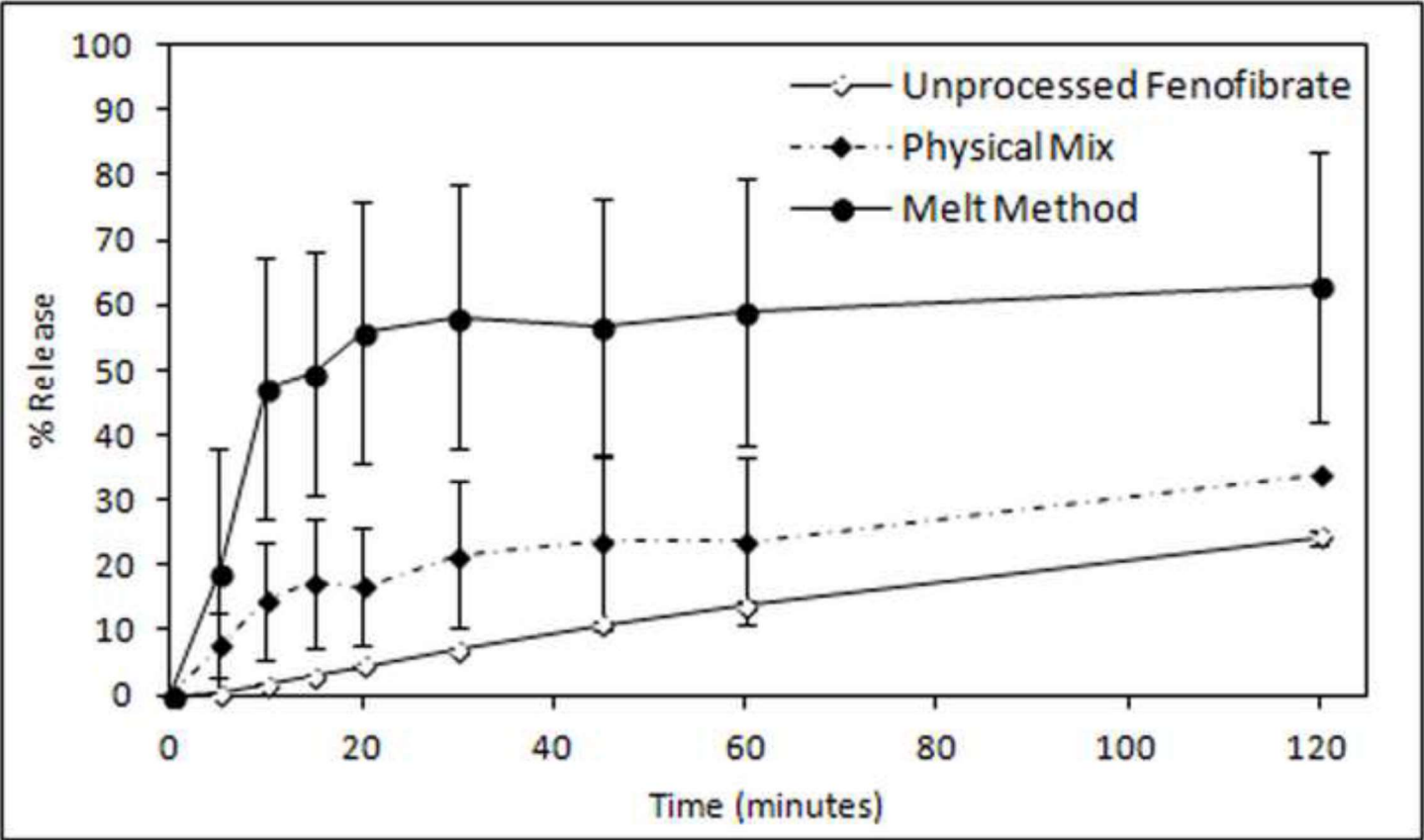
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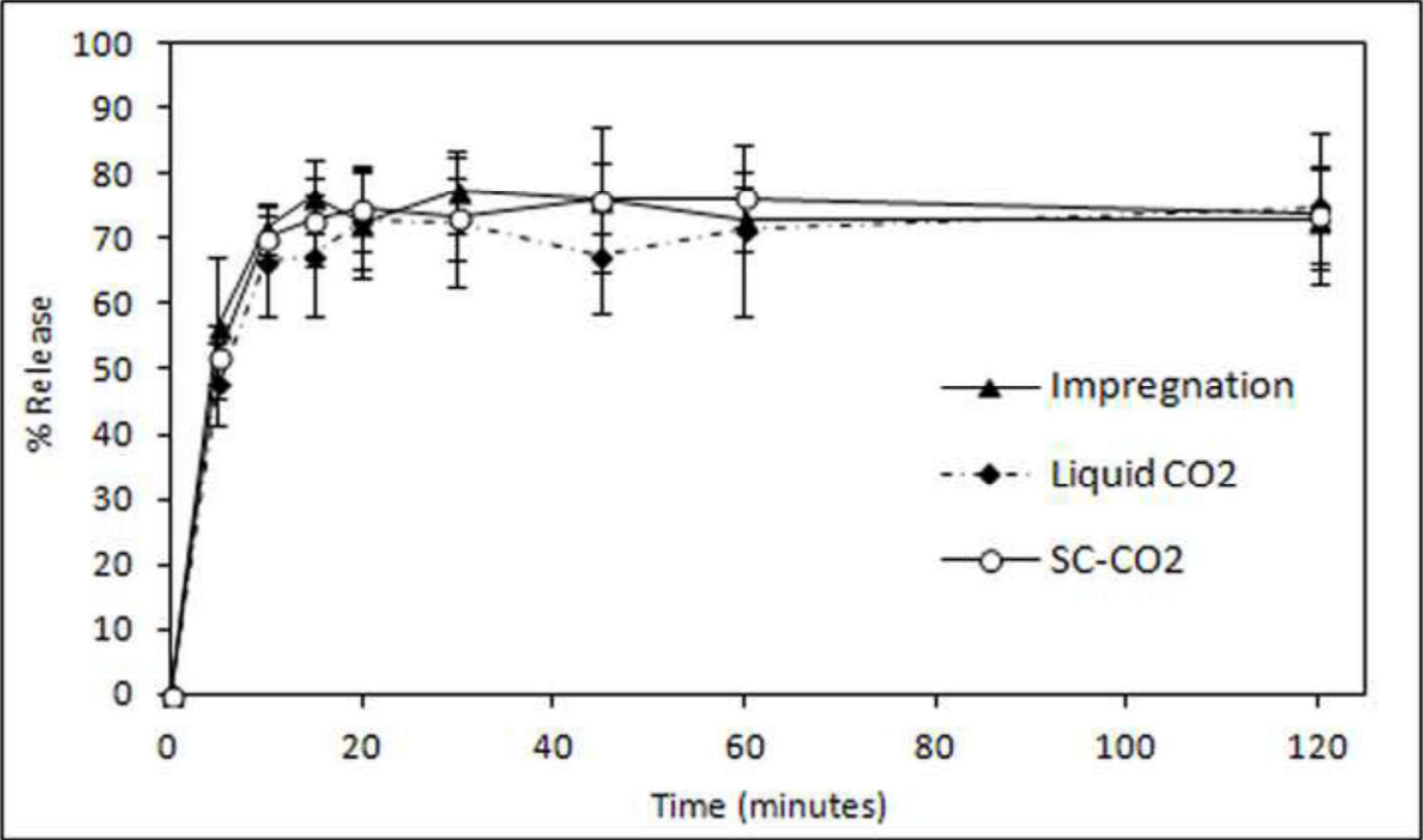
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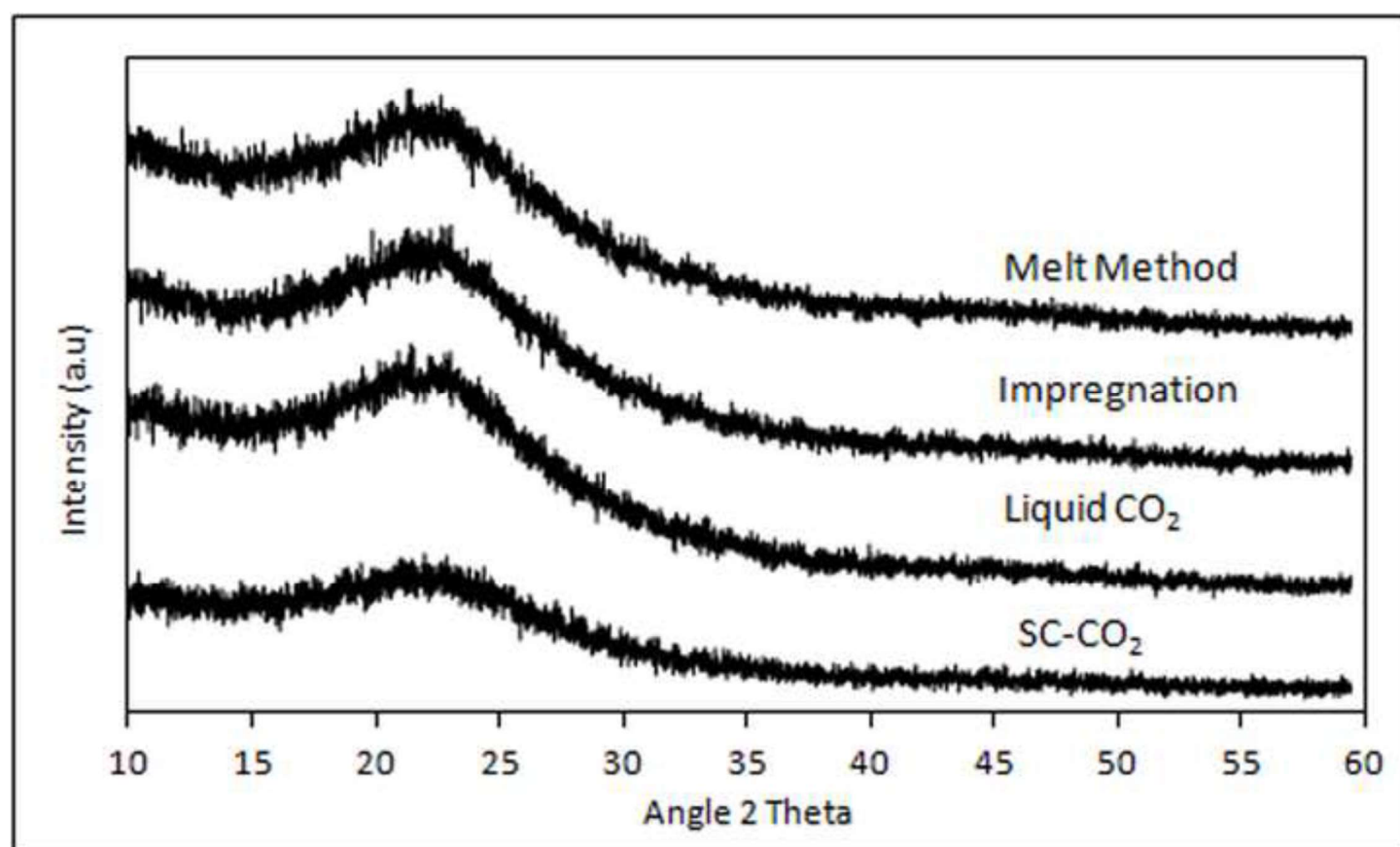
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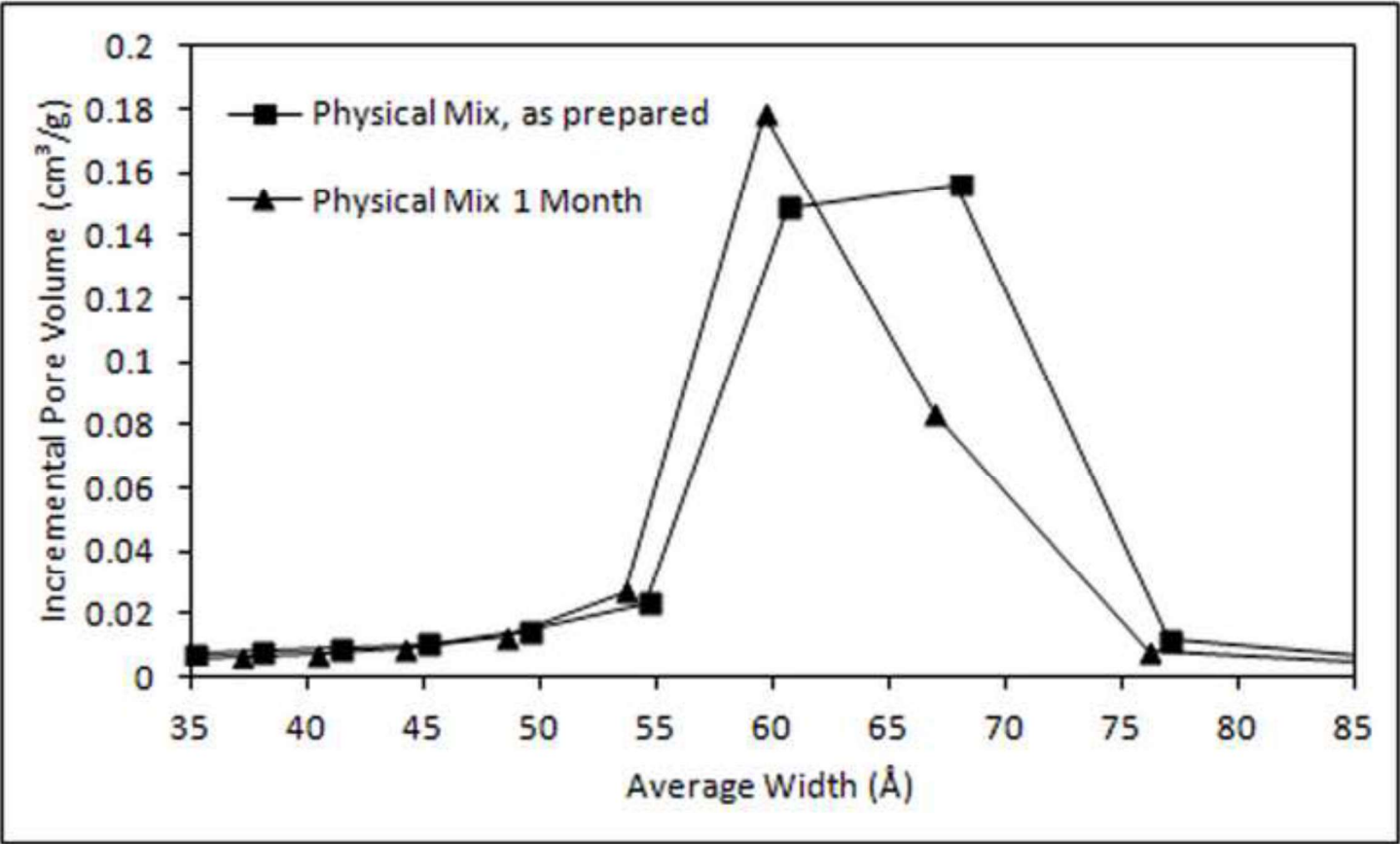
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