Impact of processing methods on the dissolution rate of artemether from two non-ordered mesoporous silicas

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Abstract

Poor aqueous solubility is often linked with a poor dissolution rate and ultimately, limited bioavailability of pharmaceutical compounds. This study describes the application of mesoporous materials (Syloid 244 and Syloid AL1) in improving the dissolution rate of a drug with poor aqueous solubility, namely artemether, utilising different processing methods including physical mixing, co-grinding and solid dispersions prepared by solvent evaporation and the lyophilisation technique. The prepared formulations were extensively characterised for their solid-state properties and the drug release attributes were studied. Differential scanning calorimetry and X-ray diffraction confirmed conversion of crystalline artemether into a disordered and amorphous form, while no intermolecular interactions were detected between artemether and silica. Both silica grades enhanced the dissolution rate of artemether in comparison with drug alone, for example from 17.43% (± 0.87 %) to 71.55 % (±3.57 %) after 120 mins with lyophilisation and Syloid 244 at a 1:3 ratio. This enhancement was also dependant on the choice of processing method, for example, co-ground and lyophilised formulations prepared with Syloid 244 at 1:3 ratio produced the most extensive dissolution, thus endorsing the importance of materials as well as choice of formulation method.

Keywords: Artemether; amorphous; co-grinding; dissolution; lyophilisation; mesoporous silica; solid dispersion.

1. Introduction

Despite several possible options for routes of administration, the oral route is most preferable, mainly because of patient ease in ingesting drugs and for economic reasons. Nevertheless, orally administered drugs must dissolve in biological fluids before reaching the target site. It is estimated that more than 70 % of investigational new drugs exhibit poor aqueous solubility and limited dissolution (Kawabata et al., 2011), thus causing difficulty for pharmaceutical researchers with regards to formulation, i.e. to ultimately make them available at the bedside (Lipinski, 2002). Poor aqueous solubility impedes *in vivo* efficacy of drugs by presenting limited bioavailability, a poor pharmacokinetic-profile, increased subject-to-subject and inter-species variation, all of which results in potential drug candidates being rejected from formulation in suitable dosage forms (van de Waterbeemd, 1998). In recent years, various techniques have been proposed to address the poor solubility issue including physical and chemical approaches, such as modification of crystal habits (Blagden et al., 2007), lipid formulations (Humberstone and Charman, 1997), cyclodextrin complexations (Challa et al., 2005), salt or co-crystal formations (Elder et al., 2013), use of solubilising agents, pro-drug formation (Fleisher et al., 1996), solid dispersions (Brough and Williams, 2013; Shahzad et al., 2013), micronisation and nanosization (Chaumeil, 1998; Chen et al., 2011; Müller et al., 2001). All of these methods and techniques have certain benefits and limitations; such as the selection of an appropriate method depends upon the physicochemical properties of the active pharmaceutical ingredient (API).

The poor aqueous solubility of most APIs is believed to be a result of their high lattice energy within the crystalline structure (Thomas et al., 2014). Thus, any technique involving reduction in lattice energy, by converting from a crystalline to amorphous state, may significantly enhance solubility and dissolution. However, purely amorphous drugs are rarely formulated commercially as such in dosage forms, rather they are blended with amorphous excipients, which stabilise the amorphous form of the drug during storage and inhibit recrystallisation during the dissolution phase (Van den Mooter, 2012). The amorphous solid dispersion (ASD) is an interesting approach that can increase apparent solubility without causing a concomitant decrease in apparent permeability as seen with other solubility enhancing techniques, for example, co-solvent solubilisation which improves solubility yet permeability and bioavailability are compromised (Ueda et al., 2012).

Highly porous and amorphous mesoporous silicas are gaining notable attention because of their potential application in medicine, biosensors, drug-delivery, catalysis, thermal energy storage and imaging (Giraldo et al., 2007). Mesoporous silica has a pore diameter of

2-50 nm and classified as ordered and non-ordered, both of which are used as potential carriers for enhancing solubility and dissolution of poorly soluble drugs (McCarthy et al., 2016; Qian and Bogner, 2012; Xu et al., 2013). Mesoporous silica materials are nontoxic, biocompatible and biologically safe. Furthermore, amorphous silicas are degradable in living tissue and excreted from the body as orthosilicic acid (Martin, 2007). Mesoporous materials can be used in their native form or following modifications, including purpose-built functionalisations that have resulted in desireable pharmaceutical properties, thus improving both *in-vitro and in-vivo* profiles of drugs (Vinu et al., 2005).

Structurally, ordered silica has a more uniform and intricate pore structure in comparison with non-ordered mesoporous silica (Hussain et al., 2017). However, they possess a similar surface chemistry, consisting of siloxane and silanol groups (Zhuravlev, 2000) that may associate with the loaded substances to form hydrogen-bonds (Bahl and Bogner, 2006). The advantages of mesoporous materials as drug delivery vehicles can be attributed to their large effective surface area and pore volume, which are known to contribute towards greater drug loading, prevention of premature degradation and promotion of tuned and fast drug release (Xu et al., 2013). The amorphicity of drug in silica solid dispersions is simply a result of adsorption on the surface of silicates (Watanabe et al., 2001; Waters et al., 2013) and confinement/entrapment/capillary condensation of drugs in mesopores (Waters et al., 2013). Once drug is loaded in mesopores, the drug can stay in an amorphous or molecularly dispersed state as a result of spatial constraints of the silica pores that inhibits drug nucleation and crystal growth (Laitinen et al., 2013; Prinderre, 2015). Drug loading methods also account for the enhanced performance of formulations prepared with mesoporous silicas (Qian and Bogner, 2012).

Herein, we report the effect of processing methods on the drug release behaviour of a poorly water-soluble compound, namely artemether, from mesoporous silica. Artemether (Fig.1) is a crystalline drug used as an antimalarial agent that kills malarial parasites by alkylating biomolecules through free radical formation (Meshnick, 2002). Artemether also has the potential to kill cancerous cells (Humphreys et al., 2016). Two grades of silica were employed in preparing formulations encompassing four different methods, namely physical mixing, co-grinding, solvent evaporation and lyophilised solid dispersions. Formulations were extensively characterised using a variety of analytical tools in order to study solid-state properties. This was followed by an investigationof drug release behaviour inan acidic dissolution media in the hope that modifications to the formulation will enhance the drug release profile.

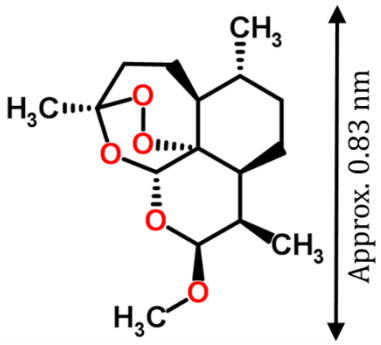

Fig. 1: Chemical structure of artemether

2. Materials and methods

Artemether with a minimum purity of 98 % was received as a gift sample from Hamaz Pharmaceuticals (Multan, Pakistan). Grace Discovery Sciences (Pune, India) generously gifted Syloid® 244 FP and Syloid® AL1/63FP silica. Ethanol was sourced from Sigma-Aldrich (Dorset, UK). Distilled water (prepared at an in-house facility) was used throughout the experiments.

2.1.Physical mixing of drug with silicas

Artemether was tumble mixed with two different Syloid silica samples (Syloid 244 and Syloid AL1) at 1:0.5, 1:1 and 1:3 drug to silica ratios for 5 minutes to ensure homogenous mixtures were achieved. The physical mixtures (PM) were stored in airtight containers until further use.

2.2.Co-grinding of drug with silicas

Samples initially underwent tumble mixing, as described in Sec. 2.1. Following this, samples were subjected to moderate unidirectional grinding in a pestle and mortar for 10 minutes to hopefully achieve complete (or partial) amorphisation of artemether. The co-ground (CG) mixtures were sieved through a number 60 mesh and stored in airtight containers until further use.

2.3.Solvent evaporated and lyophilised solid dispersions

Solid dispersions were prepared by solvent evaporation and lyophilisation techniques. For solvent evaporated (SE) solid dispersions, an accurately weighed quantity of artemether was dissolved in 10 mL of ethanol. To this solution, each silica at a specified drug to silica ratio (1:0.5, 1:1 and 1:3) was added and the mixture was left stirring for 10 minutes.

Afterwards, the mixtures were oven dried at 40 °C to ensure removal of residual ethanol, i.e. until samples reached a constant weight. The resultant dry powder was sieved through a number 60 mesh and the solid dispersions were stored in airtight containers until further investigation.

For lyophilised dispersions (FD), a weighed quantity of drug was dissolved in a 10 % v/v ethanol-water mixture until a clear solution formed. Silica samples were then introduced to the solution at specified drug to silica ratios (1:0.5, 1:1 and 1:3). Each mixture of Syloid 244 and Syloid AL-1FP, at three drug to silica ratios, was frozen at -10 °C , followed by lyophilisation (EYELA Freeze-Dryer FD-550) at -42 °C and vacuum of ~0.100 mBar, in order to completely remove the solvent. The resultant freeze-dried mixtures were gently triturated and then passed through a sieve no. 60 before storing in airtight containers (Ansari et al., 2015).

2.4.Characterisation of formulations

2.4.1. Differential scanning calorimetry (DSC)

Thermal analysis of the samples was conducted using DSC (SDT Q600, TA Instruments, USA). Accurately weighing 2-8 mg samples were placed in flat-bottomed aluminum crucibles. The crucibles were crimped and pierced before placing in the DSC . Samples were heated from 30 °C to 300 °C at a heating rate of 10 °C/min under a dry nitrogen purge flowing at 40 mL/min.

2.4.2. X-Ray powder diffraction (XRD)

XRD patterns of formulations were obtained using an X-Ray Diffractometer (PANalytical X'Pert Pro powder, The Netherlands) equipped with a CuKα radiation source (1.5406 Å) with a generator voltage and current of 30 kV and 10 mA, respectively. Samples were mounted on plate holders and the diffraction patterns were measured in ambient conditions by scanning in the 2θ range of 5-50 ° with a step size of 0.02.

2.4.3. Attenuated total reflectance-Fourier transform Infra-red spectroscopy (ATR-FTIR)

The infrared spectrum of pure artemether and formulations were obtained through ATR-FTIR spectrophotometry (Agilent technologies Cary 600 series) by scanning from 400-4000 cm^{-1} wavelength range at 2 cm^{-1} resolution in the transmittance mode. The instrument calibration was occasionally repeated during these operations.

2.4.4. Scanning electron microscopy (SEM)

The morphology of formulations was analyzed using SEM (JSM-5910, JEOL, Japan). Samples were lightly spread over specimen stubs after sputter coating with gold and images at different magnifications were captured at an accelerating voltage of 10-15 kV energy.

2.5.Spectrophotometric quantification of artemether

Spectrophotometric quantification of artemether (ART) was performed using the World Health Organisation (WHO) prescribed method (WHO, 2016). Briefly, accurately weighed 50 mg samples of ART were dissolved in sufficient dehydrated ethanol to produce a final volume of 100 mL. 20 mL of this solution was diluted to 100 mL with hydrochloric acid/ethanol (1 mol/L) mixture to achieve an artemether concentration of 100 μg/mL. This solution was heated at 55 °C for 5 h in a water bath and allowed to cool to room temperature. Sufficient quantities were withdrawn from the stock solution to make a series of dilutions with HCl/ethanol (1 mol/L), to achieve concentrations of 50, 40, 20, 10, 5, 3.125, 1.56, and 1 μg/mL. The absorbance of dilutions was measured at 254 nm using a UV spectrophotometer (HALO DB-20, Dynamica, Australia) and a calibration plot was constructed.

2.6.*In-vitro* dissolution studies

Dissolution studies were performed on pure artemether, physical mixtures, co-ground mixtures and the solid dispersions prepared by solvent evaporation and lyophilization using USP type II dissolution apparatus. A 20 mg drug equivalent sample of each formulation was added to the dissolution bath filled with 500 mL of freshly prepared 0.1N HCl solution (pH 1.2). The temperature of the bath was set at 37 °C (±0.5 °C) and the paddles were rotated at 50 rpm. At predetermined time intervals of 5, 10, 15, 20, 25, 30, 60 and 120 minutes, 5 mL samples were withdrawn with a syringe fitted with a 0.45μm syringe filter, and immediately replenished with 5 mL of fresh 0.1N HCl solution to ensure perfect sink conditions existed throughout the experiment. The withdrawn samples were analysed using a UV-spectrophotometer set at a wavelength of 254 nm. All experiments were repeated in triplicatewhereby drug release was quantified based on a series of standard solutions at known concentrations.

3. Results and discussion

3.1.Solid-state characterisation

Solid-state properties of pure artemether and formulations were studied using a variety of analytical tools including DSC, XRD, ATR coupled FT-IR and SEM. These

powerful analytical tools were used to help characterise various physical and chemical properties of artemether in the formulations.

DSC thermograms of pure artemether and selected physical mixtures, co-ground mixtures, solvent evaporated and lyophilised solid dispersions prepared with two grades of mesoporous silica are presented in Fig.2. Artemether is a crystalline compound having a melting point of 86 - 90°C (WHO, 2016). DSC thermograms of pure artemether showed an endothermic melting peak appearing at 90 °C followed by a larger and broader exothermic peak appearing at 172 °C. The appearance of the melting peak confirmed the crystallinity of artemether. All formulations prepared at 1:0.5 drug to silica ratios showed characteristic artemether melting peaks without any polymorphic transition (DSC data not shown for 1:0.5 and 1:1 ratios). However, there was a gradual decrease in the intensity of the melting peak with increasing silica content in the formulations, and no melting peak was detected when the silica content reached a maximum (1:3 drug to silica ratio), as exemplified in Fig. 2. The melting point depression, and even disappearance, could be a result of complete pore confinement of artemether within the mesopores of both silica grades, or the drug may have transformed to an amorphous form (Salonen et al., 2005; Xu et al., 2013). The approximate diameter of an artemether molecule is 0.83 nm, as shown in Fig.1. This is sufficiently smaller than the average pore diameter of 16 nm for Syl 244 and 2.9 nm in the case of Syl AL1. Thus, pore confinement of drug is inevitable and attenuation of the melting peak in DSC thermograms confirms this. In the case of physical mixtures, the absence of a melting peak possibly relates to drug adsorption on the silica surface in an amorphous form. This phenomenon has been seen in a previous study whereby a highly hydrophobic drug, namely gemfibrozil, showed almost no melting peak at the highest drug to silica ratio (Hussain et al., 2017). The change in the physical state of drug can also be explained on the basis of possible interaction of silanol groups present on the surface of mesoporous silica with the functional groups of drug that may have resulted in hydrogen bonding between them, thus reducing the drug's crystallinity and promoting amorphicity (Gupta et al., 2002).

We were also interested to see how co-grinding may affect the thermal properties of artemether. The co-ground samples showed a prominent decrease in the peak intensity with increasing silica content, and the melting peak was even absent in the 1:3 co-ground mixtures. This was a result of the reduction in particle size of artemether from grinding. This opens up another possibility of drug being entrapped within the mesopores, or maybe adsorbed on the silica surface, in molten form from shear grinding force. The exact mechanism is still enigmatic, thus warrants further study.

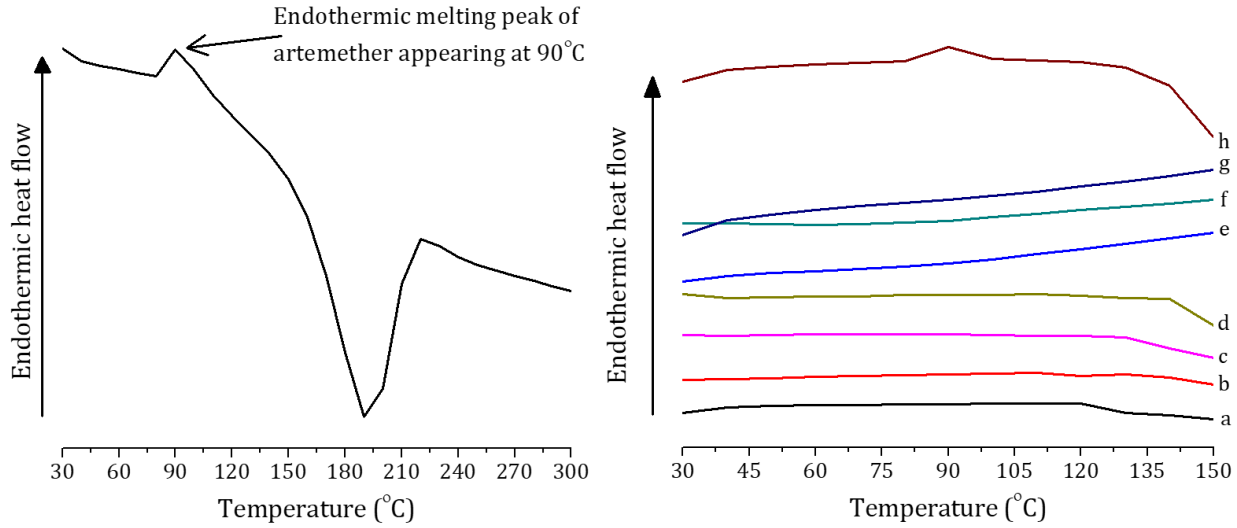

Fig. 2. DSC thermograms of artemethe (left) and selected formulations (right) with two grades of silica i.e. a) Syl 244 PM(1:3), b) Syl AL1 PM(1:3), c) Syl 244 CG(1:3), d) Syl AL1 CG(1:3), e) Syl 244 SE(1:3), f) Syl AL1 SE(1:3), g) Syl 244 FD(1:3), and h) Syl AL1 FD(1:3).

Wide-angle X-ray diffraction is a robust technique to identify crystallinity of a material. The XRD pattern of pure artemether and the formulations (PM, CG, SE and FD) formulated with Syl 244 and Syl AL1 at ratios of 1:0.5 and 1:3 are presented in Fig. 3. The pure artemether displayed several diffraction peaks appearing at 9.72°, 10.23°, 17.91°, 19.55°, thus confirming the crystalline nature of the drug. In comparison to pure artemether, all the samples including PM, CG, SE and FD prepared with either Syl 244 or Syl AL1 displayed drug peaks at the lowest silica content (1:0.5), indicatingartemether was predominantly in its crystalline form. However, the diffraction peaks were absent in the formulations with a higher silica content (1:3). This confirms the conversion of crystalline drug into a more disordered or amorphous form, and possibly the drug may have become entrapped in the pores. The XRD results are in complete agreement with the DSC results (Fig. 2). However, formulation Syl AL1 FD(1:3) showed a diffraction peak with reduced intensity, which means the drug might have recrystallised on the surface of Syloid AL1 silica. This could be attributed to the large surface area (605 m^2/g) and small pore size/volume (2.9nm/0.3cm^3/g) of Syl AL1 as compared with Syl 244 (Hussain et al., 2017). The recrystallisation of drug is also reflected by a small melting peak that appeared in the freeze-dried sample (Syl FD(1:3), as can be seen in Fig. 2h.

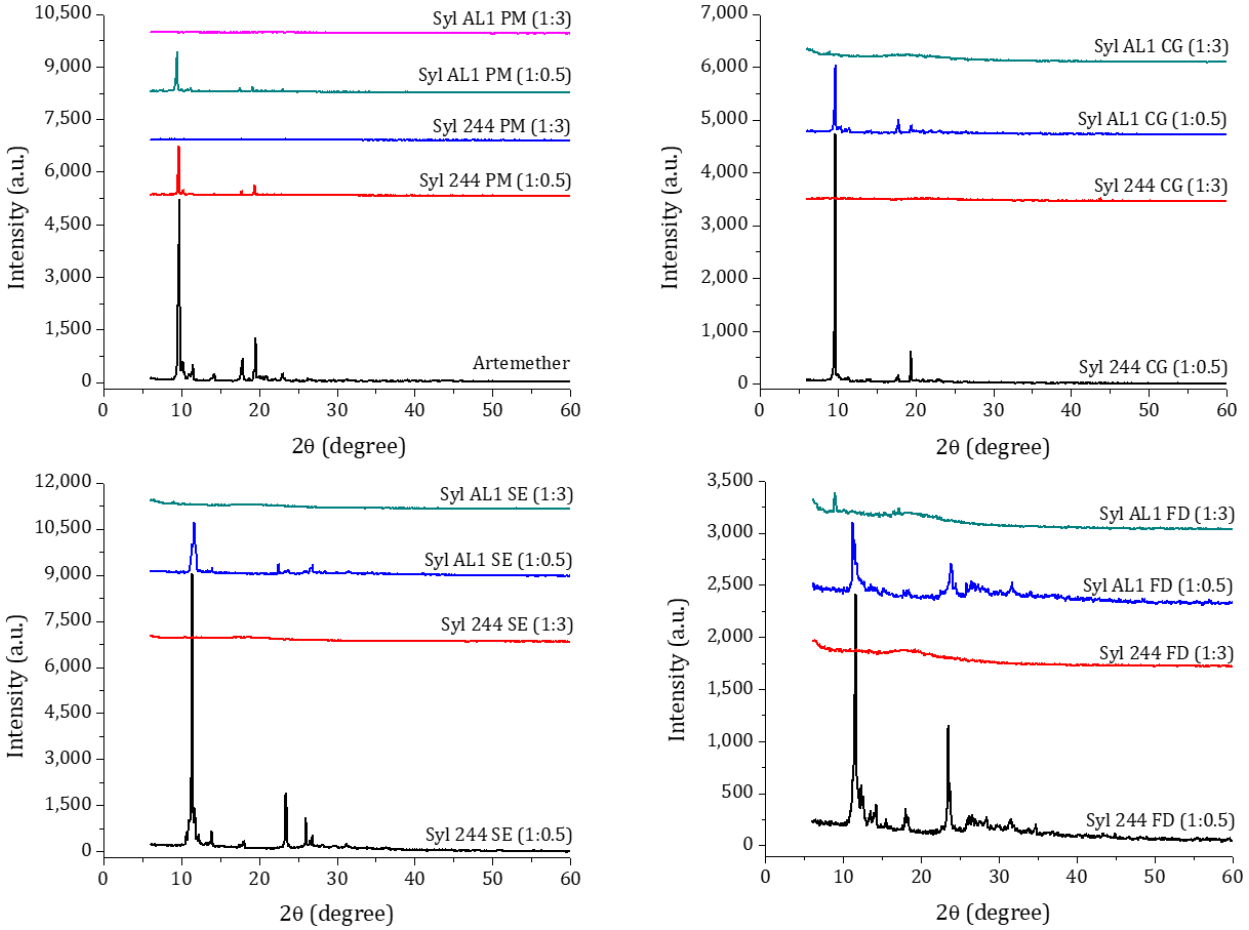

Fig. 3. XRD patterns of ART and formulations using physical mix method and co-grinding method.

The stability of formulations were assessed under stressed conditions for three months, and no significant change in the XRD and DSC patterns were observed (data not shown), thus endorsing the stability of formulations.

Infrared spectroscopy is helpful in elucidating possible drug-excipient interactions, and was therefore applied to this study to investigate interactions between artemether and Syloid silica in various formulations. Fig. 4 illustrates FT-IR spectra of pure artemether, PM, CG, SE and FD formulations at 1:1 drug to silica ratios. Characteristic artemether peaks were observed at 1250.4 cm^{-1} for C-O stretching vibrations, 1450.1 cm^{-1} for C-H bending, 1024.9 cm^{-1} and 1277.8 cm^{-1} for C-O-C stretching vibrations, and a peak at 1121.5 cm^{-1} for C-O-O-C bending vibrations, which is an endoperoxide bridge and responsible for pharmacological activity of artemisinins. In the functional group region, four characteristic peaks of C-H

stretching vibrations appeared at 2938.4 cm^{-1}, 2915.1 cm^{-1}, 2874.8 cm^{-1} and 2845.6 cm^{-1}. FT-IR spectra of Syloid showed a silanol bending band appearing at 950 cm^{-1}, which remains unshifted in the IR spectra of formulations, thus endorsing no observable intermolecular interaction. On the other hand, characteristic artemether peaks with much reduced intensities were observed without a shift in the IR spectra of formulations, thus, it is plausible that the drug was efficiently loaded into mesoporous silica in a partial or completely amorphous form.

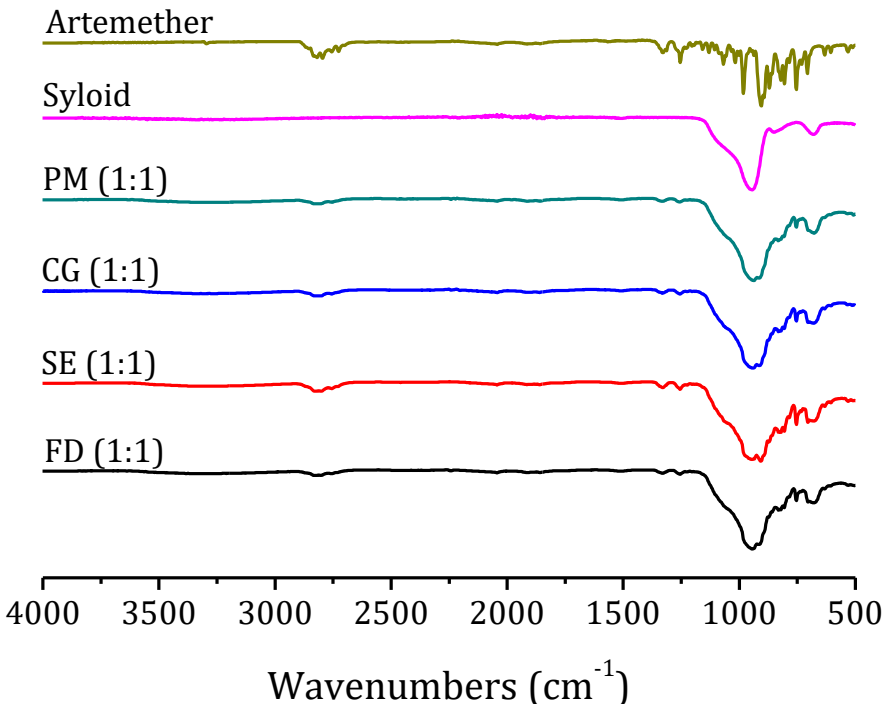

Fig. 4. FT-IR spectra of artemether, Syloid, and selected formulations.

SEM images were taken to assess the surface morphology of silica and formulations (CG, SE and FD) and the images are presented in Fig. 5. Artemether is a crystalline compound as can be seen in Fig. 5(A), SEM image courtesy of Fule and co-workers (Fule et al., 2013). Co-ground mixtures prepared with Syl 244 or Syl AL1 (1:3) showed an even distribution of silica particles with artemether particles reduced in size Fig. 5D and G. The drug appeared to be more amorphous in the solvent evaporated (Fig. 5E) and freeze-dried (Fig. 5F) solid dispersions prepared with Syl 244, as confirmed with DSC and XRD results. Apart from pore confinement of drug into Syl AL1 silica, small crystals of drug also appeared to be adsorbed on the surface of Syl AL1 solid dispersions prepared by the solvent evaporation and lyophilisation methods, as depicted in Fig. 5H and I. This could be a

consequence of the small pore diameter/volume and larger surface area of Syl AL1 compared with Syl 244.

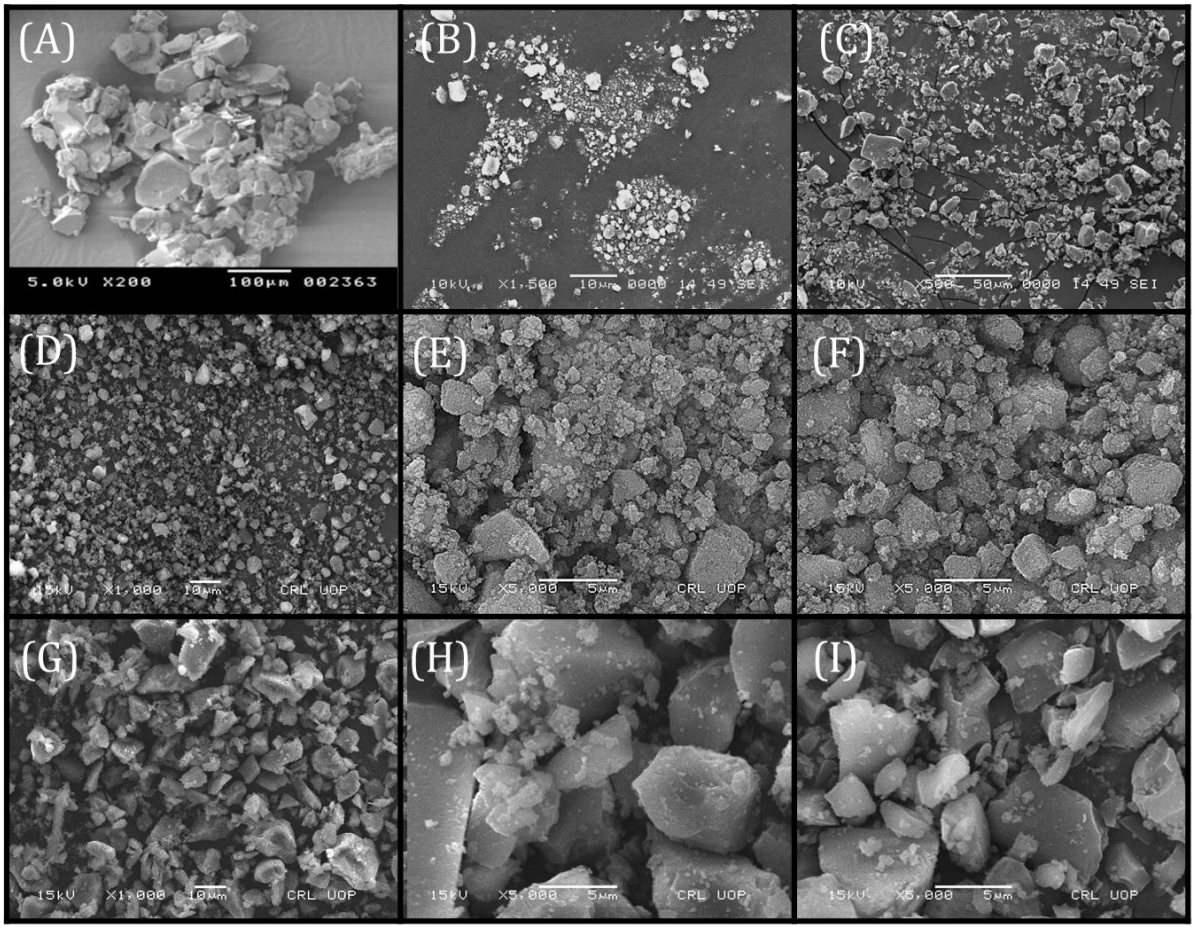

Fig. 5. SEM images of (A) artemether, (B) Syloid 244, (C) Syoid AL1, (D) Syl 244 CG(1:3), (E) Syl 244 SE(1:3), (F) Syl 244 FD(1:3), (G) Syl AL1 CG(1:3), (H) Syl AL1 SE(1:3), and (I) Syl AL1 FD(1:3).

3.2.In-vitro dissolution studies

In-vitro dissolution studies are designed for the biopharmaceutical screening of formulations. As oral formulations are required to disperse in the stomach contents, dissolution measurement in acidic media can provide a good initial estimate of dissolution extent and rate enhancement. The *in-vitro* dissolution profiles of pure artemether, physical mixtures, co-ground mixtures, and solvent evaporated and lyophilised solid dispersions are presented in Fig.s 6 and 7. Overall, the amounts of silica and the processing method appeared to influence the dissolution rate of artemether. Pure artemether only dissolved 17.43% (± 0.87

%) in the dissolution media over the course of 120 minutes. Whilst a significant increase in the dissolution of artemether was observed with both silica grades and with each processing method.

Physical mixtures (PM) with Syl 244 released more drug (33.98 ± 1.6 %) for 1:0.5 ratio, whilst 1:1 and 1:3 ratios released 58.32 % (± 2.91 %) and 57.70% (± 2.88 %) of drug in the course of 120 min, respectively. For co-ground samples (CG), drug release after 120 min was 35.72% (± 1.78 %) for 1:0.5 ratio, 54.28% (± 2.71 %) for 1:1 ratio, and 71.01% (± 3.55 %) for 1:3 ratio. In the case of solvent evaporated solid dispersions (SE), 33.55 % (± 1.68 %) drug was released from the 1:0.5 ratio, 23.90 % (± 1.19 %) from the 1:1 ratio, and 30.48 % (± 1.52 %) from ?. For lyophilised solid dispersions (FD), the extent of drug release after 120 min was 32.56 % (± 1.63 %), 31.76 % (± 1.58 %) and 71.55 % (± 3.57 %) for 1:0.5, 1:1 and 1:3 ratios, respectively. Overall, drug release was superior from Syl 244 processed formulations, compared with pure artemether. Syl 244 CG(1:3) and Syl 244 FD(1:3) formulations produced the greatest release, followed by the Syl PM(1:3) formulation. More interestingly, an initial burst release was observed with CG(1:3) and FD(1:3) formulations with more than 50 % of drug released in the first 30 min of dissolution. This initial burst release of drug could stem from the fact that drug may have adsorbed on the surface or confined in the external pores present on the surface of silica. Whilst slower and sustained release is expected when the drug is entrapped deep in pores (Xia et al., 2012). The later phenomenon was evident in the solvent evaporated solid dispersions, and the drug release was slower and in a more controlled fashion.

The second silica grade, namely Syloid AL1 considered in this study also enhanced artemether dissolution, however, to a lesser extent as compared with Syloid 244. More importantly, the extent of drug release gradually decreased with increasing silica content in the case of PM and CG samples. With physical mixtures, the greatest drug release achieved was 40.50 % (± 2.02 %) for Syl AL1 PM(1:0.5), while 32.27 % (± 1.61 %) and 20.93 % (± 1.04 %) drug release was achieved for 1:1 and 1:3 ratios after 120 mins. Co-ground sample at 1:05 ratio released about 32 % of drug in 120 min dissolution run, which further decreased to 31 % and 22 % for 1:1 and 1:3, respectively. However, the opposite trend was observed in the solvent evaporated and lyophilised solid dispersions, with an exception of Syl AL1 SE(1:1), which produced the greatest drug release (55.74 ± 2.78%) after 120 mins. Drug release increased from 32 % to 48 % with increasing Syl AL1 content in the case of lyophilised solid dispersions (FD). Greater dissolution was achieved with SE and FD formulations in comparison with PM and CG, this could stem from the fact that surface adsorption and pore

confinement is likely to be higher with loading methods involving organic solvents. When the formulation comes in contact with the polar solvent (the dissolution medium), the drug leaves the surface of silica more abruptly owing to interactions between polar solvent molecules and silanol groups available on the silica surface (Charnay et al., 2004; Fernández-Núñez et al., 2009).

Overall, a superior drug release was achieved with both silica grades as compared with pure drug. The contributing factors in enhancing the drug release are possibly the extent of drug's amorphicity and the surface properties including the pore size, pore volume and available surface area. With Syloid 244, drug release was much higher and faster as compared with Syloid AL1. The Syloid 244 silica has a much smaller particle size than Syloid Al-1 silica, therefore diffusion of solvent/dissolution media into pores is expected to be more rapid as path length is shorter, thus quickly dispersing nanosized drug molecules, resulting in enhanced dissolution (Limnell et al., 2011).

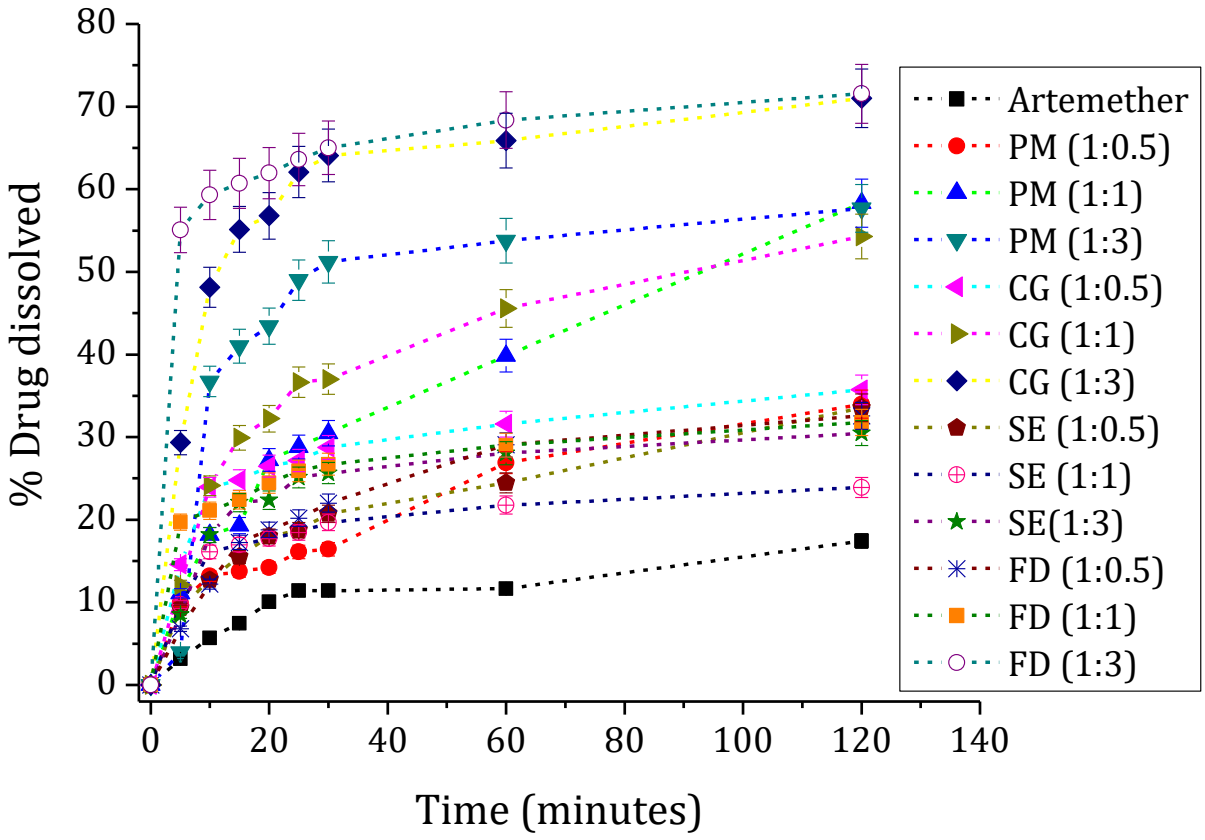

Fig. 6. Dissolution profiles of artemether and Syloid 244 processed formulations

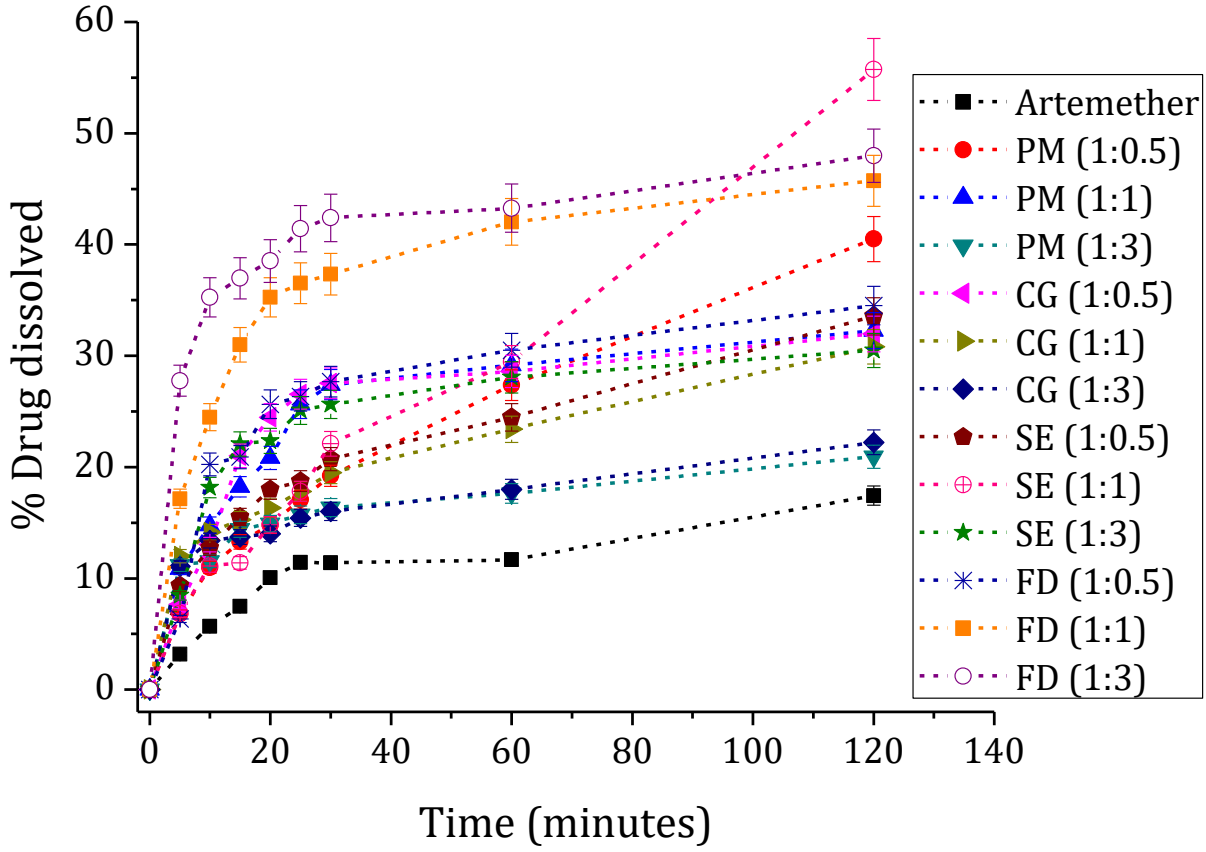

Fig. 7. Dissolution profiles of artemether and Syloid AL1 processed formulations

3.3. Kinetic release mechanism

To understand the kinetic mechanisms of drug release from porous silica particles, Higuchi and Krosmeyer-Peppas kinetic models were fitted to the dissolution data (Peppas, 1985). The best-fit model was selected based on regression coefficient (R^2) value and the corresponding *n* value in Krosmeyer-Peppas model defined the mechanism (Fickian/non-Fickian or anomalous). Krosmeyer-Peppas was found to be best model describing the drug release mechanism in our study. Fickian diffusion was the main kinetic mechanism of drug release in the case of Syl 244 PM(1:0.5) and Syl 244 PM(1:1). The remaining formulations displayed a non-Fickian diffusion, or anomalous, drug release behaviour.

4. Conclusions

In this manuscript, we report the impact of processing methods on the dissolution of a poorly aqueous soluble drug, namely artemether, utilising two grades of silica. Various formulations were created including physical mixtures, co-ground mixtures, solvent evaporated and lyophilised solid dispersions. The formulations were extensively

characterised for their solid- state properties and *in-vitro* dissolution behaviour was studied. Interestingly, the processing method utilised and the type of silica appeared to influence the physicochemical properties of artemether. With increasing silica content, the drug amorphicity increased as confirmed by DSC and XRD, whilst intermolecular interactions were absent as confirmed by FT-IR. SEM images confirmed uniform mixing of artemether with silica, whereas some crystalline drug was also visualised in solvent evaporated and lyophilised solid dispersions prepared with Syloid AL1. Both silica grades (Syloid 244 and Syloid AL1) increased the dissolution rate of artemether; however, this enhancement was more prominent with Syloid 244. The co-ground mixture and lyophilised dispersion prepared at 1:3 ratio using Syloid 244 enhanced drug dissolution the most. On the contrary, dissolution decreased with increasing concentration of Syloid AL1 for physical and co-ground mixtures. The drug release mechanism was found to be predominantly non-Fickian. Overall, a more controlled and precise drug release can be achieved through a judicious choice of excipients and processing methods.

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Conflict of interest

Declared none.

References

Ansari, M.T., Hussain, A., Nadeem, S., Majeed, H., Saeed-Ul-Hassan, S., Tariq, I., Mahmood, Q., Khan, A.K., Murtaza, G., 2015. Preparation and characterization of solid dispersions of artemether by freeze-dried method. BioMed research international 2015.

Bahl, D., Bogner, R.H., 2006. Amorphization of indomethacin by co-grinding with Neusilin US2: amorphization kinetics, physical stability and mechanism. Pharmaceutical research 23, 2317-2325.

Blagden, N., De Matas, M., Gavan, P., York, P., 2007. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Advanced drug delivery reviews 59, 617-630.

Brough, C., Williams, R., 2013. Amorphous solid dispersions and nano-crystal technologies for poorly water-soluble drug delivery. International journal of pharmaceutics 453, 157-166.

Challa, R., Ahuja, A., Ali, J., Khar, R., 2005. Cyclodextrins in drug delivery: an updated review. Aaps Pharmscitech 6, E329-E357.

Charnay, C., Bégu, S., Tourné-Péteilh, C., Nicole, L., Lerner, D., Devoisselle, J.-M., 2004. Inclusion of ibuprofen in mesoporous templated silica: drug loading and release property. European Journal of Pharmaceutics and Biopharmaceutics 57, 533-540.

Chaumeil, J., 1998. Micronization: a method of improving the bioavailability of poorly soluble drugs. Methods and Findings in Experimental and Clinical Pharmacology 20, 211-216.

Chen, H., Khemtong, C., Yang, X., Chang, X., Gao, J., 2011. Nanonization strategies for poorly water-soluble drugs. Drug discovery today 16, 354-360.

Elder, D.P., Holm, R., de Diego, H.L., 2013. Use of pharmaceutical salts and cocrystals to address the issue of poor solubility. International journal of pharmaceutics 453, 88-100.

Fernández-Núñez, M., Zorrilla, D., Montes, A., Mosquera, M.J., 2009. Ibuprofen loading in surfactant-templated silica: Role of the solvent according to the polarizable continuum model. The Journal of Physical Chemistry A 113, 11367-11375.

Fleisher, D., Bong, R., Stewart, B.H., 1996. Improved oral drug delivery: solubility limitations overcome by the use of prodrugs. Advanced Drug Delivery Reviews 19, 115-130.

Fule, R.A., Meer, T.S., Sav, A.R., Amin, P.D., 2013. Artemether-soluplus hot-melt extrudate solid dispersion systems for solubility and dissolution rate enhancement with amorphous state characteristics. Journal of pharmaceutics 2013.

Giraldo, L., López, B., Pérez, L., Urrego, S., Sierra, L., Mesa, M., 2007. Mesoporous silica applications, Macromolecular symposia. Wiley Online Library, pp. 129-141.

Gupta, M.K., Tseng, Y.-C., Goldman, D., Bogner, R.H., 2002. Hydrogen bonding with adsorbent during storage governs drug dissolution from solid-dispersion granules. Pharmaceutical research 19, 1663-1672.

Humberstone, A.J., Charman, W.N., 1997. Lipid-based vehicles for the oral delivery of poorly water soluble drugs. Advanced drug delivery reviews 25, 103-128.

Humphreys, C., Cooper, A.J., Barbu, E., Birch, B.R., Lwaleed, B.A., 2016. Artemisinins as potential anticancer agents: uptake detection in erythrocytes using Fourier transform

infrared spectroscopy and cytotoxicity against bladder cancer cells. Journal of clinical pathology, jclinpath-2016-203721.

Hussain, T., Waters, L.J., Parkes, G.M., Shahzad, Y., 2017. Microwave processed solid dispersions for enhanced dissolution of gemfibrozil using non-ordered mesoporous silica. Colloids and Surfaces A: Physicochemical and Engineering Aspects 520, 428-435.

Kawabata, Y., Wada, K., Nakatani, M., Yamada, S., Onoue, S., 2011. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. International journal of pharmaceutics 420, 1-10.

Laitinen, R., Löbmann, K., Strachan, C.J., Grohganz, H., Rades, T., 2013. Emerging trends in the stabilization of amorphous drugs. International journal of pharmaceutics 453, 65-79.

Limnell, T., Santos, H.A., Mäkilä, E., Heikkilä, T., Salonen, J., Murzin, D.Y., Kumar, N., Laaksonen, T., Peltonen, L., Hirvonen, J., 2011. Drug delivery formulations of ordered and nonordered mesoporous silica: comparison of three drug loading methods. Journal of pharmaceutical sciences 100, 3294-3306.

Lipinski, C., 2002. Poor aqueous solubility—an industry wide problem in drug discovery. Am Pharm Rev 5, 82-85.

Martin, K., 2007. The chemistry of silica and its potential health benefits. The Journal of nutrition, health & aging 11, 94.

McCarthy, C.A., Ahern, R.J., Dontireddy, R., Ryan, K.B., Crean, A.M., 2016. Mesoporous silica formulation strategies for drug dissolution enhancement: a review. Expert opinion on drug delivery 13, 93-108.

Meshnick, S.R., 2002. Artemisinin: mechanisms of action, resistance and toxicity. International journal for parasitology 32, 1655-1660.

Müller, R., Jacobs, C., Kayser, O., 2001. Nanosuspensions as particulate drug formulations in therapy: rationale for development and what we can expect for the future. Advanced drug delivery reviews 47, 3-19.

Peppas, N., 1985. Analysis of Fickian and non-Fickian drug release from polymers.

Prinderre, P., 2015. Mesoporous dosage forms for poorly soluble drugs. Google Patents.

Qian, K.K., Bogner, R.H., 2012. Application of mesoporous silicon dioxide and silicate in oral amorphous drug delivery systems. Journal of pharmaceutical sciences 101, 444-463.

Salonen, J., Laitinen, L., Kaukonen, A., Tuura, J., Björkqvist, M., Heikkilä, T., Vähä-Heikkilä, K., Hirvonen, J., Lehto, V.-P., 2005. Mesoporous silicon microparticles for oral drug delivery: loading and release of five model drugs. Journal of Controlled Release 108, 362-374.

Shahzad, Y., Sohail, S., Arshad, M.S., Hussain, T., Shah, S.N.H., 2013. Development of solid dispersions of artemisinin for transdermal delivery. International journal of pharmaceutics 457, 197-205.

Thomas, W.Y.L., Nathan, A.B., Hui, H.W., Chow, S.F., Wan, K.Y., Albert, H.L.C., 2014. Delivery of Poorly Soluble Compounds by Amorphous Solid Dispersions. Current Pharmaceutical Design 20, 303-324.

Ueda, K., Higashi, K., Limwikrant, W., Sekine, S., Horie, T., Yamamoto, K., Moribe, K., 2012. Mechanistic differences in permeation behavior of supersaturated and solubilized solutions of carbamazepine revealed by nuclear magnetic resonance measurements. Molecular pharmaceutics 9, 3023-3033.

van de Waterbeemd, H., 1998. The fundamental variables of the biopharmaceutics classification system (BCS): a commentary. Eur J Pharm Sci 7, 1-3.

Van den Mooter, G., 2012. The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. Drug Discovery Today: Technologies 9, e79-e85.

Vinu, A., Hossain, K.Z., Ariga, K., 2005. Recent advances in functionalization of mesoporous silica. Journal of Nanoscience and Nanotechnology 5, 347-371.

Watanabe, T., Wakiyama, N., Usui, F., Ikeda, M., Isobe, T., Senna, M., 2001. Stability of amorphous indomethacin compounded with silica. International Journal of Pharmaceutics 226, 81-91.

Waters, L.J., Hussain, T., Parkes, G., Hanrahan, J.P., Tobin, J.M., 2013. Inclusion of fenofibrate in a series of mesoporous silicas using microwave irradiation. European Journal of Pharmaceutics and Biopharmaceutics 85, 936-941.

WHO, 2016. The International Pharmacopoeia, Monographs for Antimalarials. Geneva : World Health Organization, Dept. of Essential Medicines and Pharmaceutical Policies, [2016].

Xia, X., Zhou, C., Ballell, L., Garcia-Bennett, A.E., 2012. In vivo Enhancement in Bioavailability of Atazanavir in the Presence of Proton-Pump Inhibitors using Mesoporous Materials. ChemMedChem 7, 43-48.

Xu, W., Riikonen, J., Lehto, V.-P., 2013. Mesoporous systems for poorly soluble drugs. International journal of pharmaceutics 453, 181-197.

Zhuravlev, L., 2000. The surface chemistry of amorphous silica. Zhuravlev model. Colloids and Surfaces A: Physicochemical and Engineering Aspects 173, 1-38.