Dissolution and precipitation behavior of ternary solid dispersions of ezetimibe in biorelevant media

Amani Alhayali, Staffan Tavellin and Sitaram Velaga

Abstract

The effects of different formulations and processes on inducing and maintaining the supersaturation of ternary solid dispersions of ezetimibe (EZ) in two biorelevant media fasted-state simulated intestinal fluid (FaSSIF) and fasted-state simulated gastric fluid (FaSSGF) at different temperatures (25°C and 37°C) were investigated in this work. Ternary solid dispersions of EZ were prepared by adding polymer PVP-K30 and surfactant poloxamer 188 using melt-quenching and spray-drying methods. The resulting solid dispersions were characterized using scanning electron microscopy, differential scanning calorimetry (DSC), modulated DSC, powder X-ray diffraction and Fourier transformation infrared spectroscopy. The dissolution of all the ternary solid dispersions was tested in vitro under non-sink conditions. All the prepared solid dispersions were amorphous in nature. In FaSSIF at 25°C, the melt-quenched (MQ) solid dispersions of EZ were more soluble than the spray-dried (SD) solid dispersions and supersaturation was maintained. However, at 37°C, rapid and variable precipitation behavior was observed for all the MQ and SD formulations. In FaSSGF, the melting method resulted in better solubility than the spray-drying method at both temperatures. Ternary solid dispersions show potential for improving solubility and supersaturation. However, powder dissolution experiments of these solid dispersions of EZ at 25°C may not predict the supersaturation behavior at physiologically relevant temperatures.

Introduction

Supersaturation is becoming an important tool for increasing bioavailability as the number of poorly water soluble compounds increases in drug discovery processes. Supersaturation of an orally delivered drug is reached when its intraluminal concentration exceeds its thermodynamic solubility equilibrium concentration. The need for designing formulations that can create this high intestinal drug concentration is gaining more attention, because the induction of supersaturation in the intestinal lumen will improve intestinal absorption as well as the therapeutic effect.

Solid dispersion technology is an interesting option for achieving supersaturated drug concentrations. The drug is dispersed within a polymer at the molecular level to form an amorphous solid dispersion or solid solution. Methods that have been used to prepare solid dispersions include micronization, melt methods, spray drying and freeze drying, among others. A wide variety of pharmaceutical excipients (including polymers and surfactants) have been used to stabilize the drug in the solid, supersaturated state in vivo.

In ternary solid dispersions, which have been shown to improve the solubility and supersaturation solubility of poorly water soluble and insoluble active pharmaceutical ingredients (APIs), the API is dispersed within a carrier system containing a polymer and a surfactant. The polymer is added to stabilize the system both in the solid state and in solution by preventing precipitation of the drug and phase separation. The surfactant enhances the solubility and dissolution of the API by lowering the surface tension of the drug particles and maintaining supersaturation during dissolution. Surfactants can also act as plasticizers that aid and facilitate thermal processing of the polymer and API.

Ezetimibe (EZ), a cholesterol-lowering drug used in the treatment of atherosclerosis, was chosen as the model drug in this study. It acts by inhibiting the uptake of dietary and biliary cholesterol in the intestine without affecting the uptake of fat-soluble vitamins, triglycerides or bile acids. EZ is a lipophilic molecule with a log \( \text{P} \) (octanol/water) of 4.5. It is very weakly acidic (close to neutral) with a \( \text{pKa} \) of 10.2 (aromatic hydroxyl group) and thus is practically insoluble in water, with a consequently low dissolution rate in the gastric lumen, potentially leading to dissolution-limited bioavailability. In fact, EZ has been classified as a class II drug. A number of formulations and solid-state strategies have been used to improve its solubility and dissolution, including binary solid dispersions, nanocrystals and cocrystals.

In this study, ternary solid dispersions of EZ were prepared using different proportions of the polymer polyvinylpyrrolidone (PVP)-K30 and the surfactant poloxamer 188. Two preparation methods were employed: melt quenching and spray drying. The apparent solubility of EZ from the prepared ternary solid dispersions was studied in two simulated gastrointestinal fluids.
[fasting-state simulated intestinal fluid (FaSSIF; pH 6.5) and fasting-state simulated gastric fluid (FaSSGF; pH 1.6)] in terms of supersaturation at two temperatures: 25°C and 37°C.

The overall objective of the work was to improve understanding of supersaturation phenomena in ternary solid dispersions of EZ in biorelevant media and to investigate the effects of factors such as the preparation process and the temperature of the dissolution medium on the maintenance of supersaturation. The specific aims of the study were (a) to prepare and characterize ternary solid dispersions of EZ using melt-quenching and spray-drying methods, (b) to investigate the powder dissolution and precipitation behavior (supersaturation) of ternary solid dispersions in vitro in simulated gastric (FaSSGF) and intestinal (FaSSIF) fluids at 25°C and 37°C, and (c) to gain insight into the effects of excipients, preparation processes, dissolution media and temperature on the extent and duration of supersaturation in vitro.

Materials and methods

Materials

Ezetimibe and PVP-K30 were purchased from Sigma-Aldrich (Stockholm, Sweden). Poloxamer 188 was a gift from BASF Chemicals (Ludwigshafen, Germany). Simulated intestinal fluid powders for preparing FaSSIF (sodium taurocholate, lecithin, sodium chloride, sodium hydroxide and monobasic sodium phosphate) and FaSSGF (sodium taurocholate, lecithin, sodium chloride and hydrochloric acid) were purchased from biorelevant.com (London, UK). High performance liquid chromatography (HPLC) grade acetonitrile was purchased from Merck Millipore (Solna, Sweden). All other reagents and solvents were of analytical grade. PTFT syringe filters 0.2 μm were used for all the experiments. Very pure deionized water (Millipore, Solna, Sweden) was used throughout the study. All chemicals and solvents were used without further purification.

Preparation of solid dispersions

Melt-quenched (MQ) solid dispersions

Prior to the preparation of solid dispersions, EZ and PVP-K30 were kept in the oven at 100°C for 24 h to remove any adsorbed water from the solids, and differential scanning calorimetry (DSC) analysis was performed on the dried crystalline EZ to ensure its crystalline nature (data not shown). Crystalline EZ, PVP-K30 and poloxamer 188 in different proportions (see Table 1) were accurately weighed and mixed gently for 1–2 min using a porcelain mortar and pestle. The resulting powder mixtures were placed in a preheated oven (BINDER, Tuttlingen, Germany) at 200°C for 5–8 min. After complete melting, the liquid was immediately put in a freezer at –20°C for 1–2 days. The MQ samples were then stored in a desiccator over silica until the day of analysis. Before the analysis, all the formulations were ground and sieved using 125 μm sieves.

Using a similar method, the amorphous form of EZ was prepared for comparison.

Spray-dried (SD) solid dispersions

Crystalline EZ, PVP-K30 and poloxamer 188 in different proportions were accurately weighed and dissolved (equivalent to 2% w/v of solids) in methanol. The solutions were spray dried using a Buchi mini spray dryer B-290 attached to an inert loop B-295 to trap the residual solvents. The processing conditions were as follows: inlet temperature 80°C, air flow 357 L h⁻¹, aspiration 70–80%, feed-flow rate 3 mL/min and outlet temperature 40–50°C. Nitrogen gas was used as the drying gas in a closed-loop experiment. The collected SD powders were stored in a sealed desiccator over silica until the day of analysis.

Scanning electron microscopy (SEM)

The morphology of the particles was examined using a Merlin scanning electron microscope (Zeiss, Oberkochen, Germany) equipped with X-Max 50 mm² X-ray detectors (Oxford Instruments, Abingdon, UK). All the samples were coated with tungsten to increase the conductivity of the electron beam. The instrument voltage was 15 kV and the current was 1 nA.

Solid-state and powder characterization

Thermo-gravimetric analysis (TGA)

The weight loss and thermal degradation behavior of all the formulation components (EZ, PVP-K30 and poloxamer 188) were investigated using a Thermal Advantage TGAQ5000 (TA Instruments, New Castle, DE) connected to a cooling system. Powdered samples (4–7 mg) were placed in the aluminum pans and the furnace was heated from 20°C to 550°C at a rate of 5°C/min. Nitrogen at a flow rate of 50 mL/min was used as a purging gas. Universal analysis software was used to analyze the results.

Differential scanning calorimetry

The thermal behavior of the raw materials and solid dispersions was studied using a DSC Q1000 (TA Instruments, New Castle, DE). The instrument was calibrated before use for temperature and enthalpy using indium. About 1–4 mg of the sample was accurately weighed and placed in a non-hermetic aluminum pan, which was then crimp-sealed. The samples were heated from 25°C to 200°C at a heating rate of 10°C/min under continuous nitrogen purge (50 mL/min). The calorimeter was equipped with a refrigerated cooling system. The data were analyzed using TA analysis software (TA Instruments, New Castle, DE).

Modulated differential scanning calorimetry (MDSC)

MDSC was performed using a Q1000 instrument (TA Instruments, New Castle, DE) for better identification of the glass transition temperature (Tg) through the separation of reversible (i.e. Tg) from nonreversible (i.e. enthalpy recovery, fusion) thermal events. Samples (2–5 mg) were accurately weighed and placed in aluminum nonhermetic pans, which were then crimped. These samples were then heated from 25°C to 200°C at 5°C/min with modulation amplitude of ±0.80°C every 60 s.

Powder X-ray diffraction (PXRD)

PXRD patterns for the crystalline and amorphous EZ and ternary solid dispersions were obtained using an Empyrean PXRD instrument (PANalytical, Almelo, The Netherlands) equipped with a Pixel 3D detector and monochromatic Cu Kα radiation. The tube voltage and amperage were 45 kV and 40 mA, respectively. Powdered

| Table 1. Proportions of different components in the melt-quenched (MQ) and spray-dried (SD) solid dispersions. |
|---------------------------------------------------------------|
| Sample ID | Ezetimibe (%w/w) | PVP-K30 (%w/w) | Poloxamer188 (%w/w) |
| MQ1 or SD1 | 5 | 90 | 5 |
| MQ2 or SD2 | 15 | 80 | 5 |
| MQ3 or SD3 | 10 | 80 | 10 |
samples were loaded into the oval cavity in the metal sample holder and carefully leveled. The experimental settings were as follows: 2/θ ranged from 5° to 40°, step size 0.02° 2/θ. The data were processed using High Score plus Version 3.0 software (PANalytical, Almelo, The Netherlands).

**Fourier transformation infrared spectroscopy (FTIR)**

A Bruker IFS66v/S FTIR spectrometer equipped with a deuterated triglycine sulfate detector was used to obtain the FTIR spectra of the samples. Powdered samples were mixed with KBr and IR spectra were obtained in the diffuse reflectant mode (Kubelka Munk). The following experimental settings were used: 64 scans with a resolution of 4 cm⁻¹, spectral region 400–4000 cm⁻¹.

**In vitro dissolution study**

Excess amounts of the SD or MQ solid dispersions were suspended in 10 mL of FaSSIF and FaSSGF in sealed test tubes and placed in a preheated shaking water bath at a shaking speed of 60 rpm (orbital shaking). The experiments were performed at 25°C and 37°C. The samples were withdrawn after 5, 15, 30, 45, 60, 75, 90, 120, 180 and 240 min and centrifuged (5 min, 17,000×g), then filtered through 0.2 µm PTFE syringe filters to ensure complete separation of the solid phase. The filtrate was diluted adequately with mobile phase and then analyzed by HPLC.

For comparison, the dissolution properties of crystalline and amorphous EZ in FaSSIF and FaSSGF were also studied. The samples were withdrawn at pre-defined intervals following the above procedure. All experiments were done in triplicate.

**High performance liquid chromatography**

The concentration of EZ was determined in an HPLC 1290 series instrument equipped with a quaternary pump and a UV detector (Agilent, Santa Clara, CA). A C-18 Eclipse plus 3 µm (4.6 mm × 100 mm) column was used. The mobile phase consisted of 40:60 (v/v) 0.05% sodium 1-heptane sulfonic acid and acetonitrile. The isocratic method was used, with a flow rate of 0.5 mL/min. The injection volume was 10 µL and the measurements were carried out at a wavelength of 230 nm, in triplicate.

**Results and discussion**

**Preparation of ternary solid dispersions**

Melt-quenching and spray-drying methods were used to prepare ternary solid dispersions. Melting and quenching, one of the oldest methods used in the preparation of solid dispersions, relies on mixing the molten drug with a molten or supercooled polymer followed by rapid cooling or solidification20. With the help of preliminary experiments and prior knowledge, the drug load in the formulations was varied in the range of 5–15% w/w (Table 1). The premixed EZ and excipients were then subjected to melting and quenching. The process temperature of 200°C was based on the melting temperature and thermal decomposition temperatures of the raw materials (see Figure S1). Visually glassy materials of pure EZ and the solid dispersions were obtained. Spray drying is a widely used and efficient method of producing solid dispersions. It is a solvent-based bottom-up method that relies on the rapid evaporation of a solution containing the API and polymers, to yield fine powders20. In addition to formulation variables, process parameters such as the inlet temperature, feed rate, flow rate of atomization air, etc. are known to affect the solid-state and physicochemical properties of the resulting solid dispersions4. In this study, the formulation of EZ, poloxamer and polymer was varied under fixed spray-drying process conditions (Table 1). Dry powders of EZ and solid dispersions were obtained. Figure 1 shows SEM micrographs of crystalline and amorphous EZ and the solid dispersions obtained using the melt-quenching and spray-drying methods. As can be seen, raw EZ is formed as rod/block-shaped crystals. The ground particles of the solid dispersions prepared by melt-quenching were irregular in shape, possibly as a result of micronization of the glassy material, while SD particles were uniform, spherical, porous and aggregated. However, there were no major differences in particle morphology between the different formulations. Further, there were no EZ crystals on the surfaces of the particles (Figure 1). Under fixed process conditions, SD particle formation was not affected by formulation changes.

**Solid-state characterization of materials**

**Thermal analysis**

TGA was used to determine weight loss due to degradation of raw materials and the loss of residual solvents/moisture in the processed samples (MQ and SD). Figure S1 (see supplementary figure) shows the TGA weight loss curves for EZ, PVP-K30 and poloxamer 188. It can be seen that EZ, PVP-K30 and poloxamer lost significant weight, attributed to thermal decomposition at 348°C, 401°C and 453°C, respectively. It is important to know the thermal decomposition temperatures in order to avoid the risk of the API or excipients degrading during the preparation of solid dispersions by thermal methods such as melting and quenching and melting followed by extrusion21. It was invaluable information for the preparation of the solid dispersions in this study.

The final product in solvent-based methods like spray drying may contain residual solvents that can compromise the stability of the solid dispersion. TGA weight loss curves for selected solid dispersions are shown in Figure 2. It is clear that the residual solvent levels are ranging between 3.8 and 5.8% in the MQ and SD solid dispersions, suggesting efficient drying of the MQ solid dispersion product.

DSC analysis results for crystalline EZ, amorphous EZ, PVP-K30 and poloxamer 188 are shown in Figure 3. In the DSC
thermograms for EZ, an endothermic peak corresponding to the EZ melting point \((T_m = 163.4^\circ C)\) was observed. The \(T_g\) for PVP-K30 appeared at \(160.7^\circ C\) and a broad endothermic band was attributed to the sorbed moisture. In fact, the hygroscopic nature of PVP is well known\(^{22}\). Poloxamer 188 showed an endothermic transition at \(54.34^\circ C\) which corresponded to the melting point, confirming its crystalline nature. The thermal behavior of these raw materials was in agreement with that in previous reports\(^{18,21}\). In the DSC thermogram for amorphous EZ, the change in heat capacity at \(60.14^\circ C\) was followed by an exothermic transition at \(129.34^\circ C\) and an endotherm at \(163^\circ C\) (Figure 3(b)). These thermal events were attributed to the \(T_g\), recrystallization and melting points typical of an amorphous material. The DSC thermograms of these ternary solid dispersions had overlapping events, which made interpretation of the results difficult.

MDSC is a powerful tool that separates the total heat flow signal into reversing and non-reversing parts. The reversing heat flow always contains the \(T_g\) while the non-reversing heat flow contains the kinetic transitions, such as crystallization, evaporation, degradation, etc. MDSC was carried out on solid dispersions prepared by melt-quenching and spray-drying methods to separate the \(T_g\) from the dehydration peak. Figure 4 shows the MDSC reversing heat flow thermograms for different solid dispersions. The \(T_g\) was better resolved and a single \(T_g\) (no melting peak for EZ) was observed at \(140–180^\circ C\) for all solid dispersions. This suggests that EZ was molecularly dispersed within the polymer and surfactant, forming an amorphous solid solution\(^{23–25}\). The poloxomer could have increased the solubility of the drug in the polymer, aiding the formation of a solid solution\(^{14,26}\).
Powder X-ray diffraction (PXRD)
Figure 5 shows the PXRD patterns for raw and amorphous EZ and solid dispersions prepared by spray drying. Raw EZ showed several characteristic peaks at 2θ angles of 8.2°, 9.8°, 13.5°, 16.3°, 19.0°, 20.1°, 23.6° and 25.5°, confirming its crystalline nature. The PXRD pattern for crystalline EZ was similar to a previously published pattern. The diffraction peaks completely disappeared in the PXRD pattern of amorphous EZ, resulting in the diffuse hollow pattern distinctive of amorphous materials. All SD solid dispersions (SD1–3) showed diffuse halo PXRD patterns, confirming the amorphous nature of the solid dispersion; i.e. the API was completely dispersed in the polymer and the surfactant matrix. Similar PXRD spectra were obtained for solid dispersions prepared by melt-quenching, confirming their amorphous nature (Figure 5).

Fourier transformation infrared spectroscopy (FTIR)
Diffuse reflectance IR was used to investigate the possible molecular interactions between the drug and polymers in the solid dispersions of EZ.

Figure 4. Modulated differential scanning calorimetry reversing heat-flow thermograms of (a) melt-quenched (MQ) solid dispersion 1, (b) MQ2 and (c) MQ3; and (d) spray-dried (SD) solid dispersion 1, (e) SD2 and (f) SD3 showing the heat capacity (Tg) in the region (140 – 180 °C).

Figure 5. Powder X-ray diffraction patterns of (a) crystalline ezetimibe (EZ), (b) amorphous EZ, and (c) melt-quenched (MQ1) and (d) spray-dried (SD1) solid dispersions of EZ.
IR spectroscopy has been extensively used to study interactions between the components of solid dispersions and to aid understanding of the mechanisms behind stabilization and supersaturation behavior\(^{33}\). Figure 6 depicts the IR spectra for crystalline EZ, amorphous EZ, the physical mixtures of EZ, and selected solid dispersions from melt-quenching and spray-drying methods (MQ2 and SD2 were used as representative solid dispersions in Figure 6). In the IR spectrum of crystalline EZ, a number of characteristic vibrational bands were identified at 3440 cm\(^{-1}\)/C\(_0\), 1728 cm\(^{-1}\)/C\(_0\), 1443.9 cm\(^{-1}\)/C\(_0\), 1398.2 cm\(^{-1}\)/C\(_0\), and 834.8 cm\(^{-1}\)/C\(_0\), which correspond to stretching vibrations of the O–H, C–H and C–O groups (data not shown). Though dilution effects were seen, the IR spectra of the physical mixtures were summations of the individual components, indicating no interactions between the components (Figure 6). In contrast, in the IR spectrum of the MQ solid dispersion MQ2, significant changes were seen: the O–H stretching band in EZ at about 3440 cm\(^{-1}\) had disappeared and a C–O stretch band at 1728 cm\(^{-1}\) had shifted to a lower wave number and broadened. Similarly, changes in the vibrational bands were observed in the IR spectra of the SD dispersions (SD2). These changes in the IR spectra of solid dispersions could be attributed to the formation of strong interactions (H-binding, van der Waals, etc.) between EZ and the PVP. The hydrogen bonding interactions between OH or NH groups on the drug molecules and the carbonyl group on PVP have been cited in many studies previously\(^{31,32}\). These interactions between the API and the excipients are believed to prevent self-association (dimerization) and nucleation of the API phase\(^{31-33}\). The mixing effects on the stretching vibration modes of C\(_{14}\)–O, C\(_{14}\)–C, C\(_{14}\)–N and C\(_{14}\)–F in the range 1200–1730 cm\(^{-1}\) are more prominent in MQ solid dispersions than in SD systems, probably related to the level of miscibility between the components.

### In vitro dissolution study

It is important to optimize the in vitro experimental conditions in studies of the supersaturation behavior of amorphous solids to ensure that they are biorelevant to the in vivo conditions. This study used biorelevant test media, non-sink conditions and orbital shaking. It has been suggested that non-sink conditions are more biorelevant for evaluating the dissolution behavior of supersaturable formulations where the maximum solution concentration is determined\(^8\). The effect of hydrodynamics on the supersaturation/precipitation is poorly understood. In a recent paper, the precipitation rate was shown to be remarkably slower in the shaking model than in the stirring model, emphasizing the importance of the applied hydrodynamic methodology\(^{34}\).

### Effects of process, formulation and temperature on supersaturation in FaSSIF

Figure 7 shows the powder dissolution (concentration versus time) profiles for the prepared solid dispersions in FaSSIF. The solubility of crystalline EZ in FaSSIF (pH 6.5) at 25°C and 37°C was 5.9 μg/mL and 10.1 μg/mL, respectively (Figure 7(a,b)). The apparent solubility (concentration in solution) of EZ from the amorphous form increased and then rapidly decreased at 25°C (Figure 7(a,b)). In contrast, there was no supersaturated concentration at 37°C for amorphous EZ (Figure 7(c,d)). This phenomenon of supersaturation and rapid precipitation is typical of amorphous solids and is described as the “spring” effect\(^3\). For orally administered formulations, the dose-to-solubility ratio has been suggested as an indicator of the precipitation propensity of the drug in the gastrointestinal lumen\(^36\). Drugs with dose-to-solubility (non-ionized) ratios of more than 50:1 have been reported to show a tendency to precipitate in the intestinal environment\(^36\). Evidently, the dose-to-solubility ratio for EZ is about 1000 at a dose of 10 mg, suggesting that the observed precipitation of stable phases is thermodynamically favored in FaSSIF. Interestingly, the “spring” effect disappeared (i.e. there was no increase in solubility) as the temperature of the dissolution experiment was increased to 37°C. This could be explained by differences in the relationship between dissolution and the precipitation/crystallization kinetics of crystalline EZ. It is possible that the crystallization of amorphous EZ was
faster at 37 °C. Similar behavior has been observed with amorphous felodipine and indomethacin in another study.37

Solid dispersions where the drug and polymers are intimately mixed are attractive and widely used formulation strategies to prevent the crystallization of the stable phase and maintain supersaturation of drugs like EZ. In this study, PVP-K30 and poloxomer 188 were selected from the preliminary studies as the precipitation inhibitor and solubilizer, respectively. In fact, PVP has been well established as a crystal growth inhibitor for a range of amorphous drugs.38 In the MQ solid dispersions, solution concentrations of EZ were maintained at about 50–55 mg/mL and no precipitation was observed for at least 240 min at 25 °C (Figure 7(a)). Apparently, the presence of the polymer sustained supersaturation, with solution concentrations about 50 times higher than the equilibrium solubility of EZ, possibly by preventing precipitation of the stable phase. However, no differences in the solution concentrations were observed for different polymer/drug ratios in these solid dispersions. Interestingly, in the SD solid dispersions, supersaturation (with solution concentrations about 70–80 times higher) was followed by desupersaturation at different rates (Figure 7(b)). SD solid dispersions generated higher initial solution concentrations than those generated by MQ solid dispersions, which could be explained by differences in the particle size/morphology and molecular miscibility (Figure 2). This could also mean that solid dispersions result in a greater driving force for crystallization. The desupersaturation curves also show that the lower the polymer-to-drug ratio is in the solid dispersions, the faster the precipitation kinetics will be (Figure 7(b)).

In general, solid dispersions prepared by the melting method showed slightly higher initial concentrations and faster precipitation kinetics at 37 °C than at 25 °C (Figure 7(a,c)), while solid dispersions prepared by the spray-drying method showed direct precipitation in FaSSIF at 37 °C but not at 25 °C (Figure 7(b,d)). The presence of precipitation inhibitors had only a minor effect in maintaining supersaturation at 37 °C. These results are perfectly in line with previous observations on the supersaturation and precipitation behavior of other amorphous drugs in the presence of different polymers.40 The explanation lies in the increase in the rate of dissolution (supersaturation) and precipitation kinetics at higher temperatures. The results suggest that dissolution experiments performed at 25 °C may not be biorelevant and may fail to predict in vivo behavior.41 In the MQ solid dispersions, desupersaturation was dependent on the formulation: higher polymer/poloxomer content resulted in a slower precipitation rate (Figure 7(c)). However, in the SD solid dispersions, precipitation was rapid irrespective of the formulation or polymer content (Figure 7(d)). This suggests that the supersaturation and precipitation behavior of amorphous solids is sensitive to the processing methods, possibly because of the history of the material and the presence of nuclei.42

Effects of process, formulation and temperature on supersaturation in FaSSGF

Figure 8 shows the powder dissolution (concentration versus time) profiles for EZ samples in FaSSGF (pH 1.6). The solubility of crystalline EZ in FaSSGF (pH 1.2) at 25 °C and 37 °C was extremely low: 0.2 μg/mL and 0.1 μg/mL, respectively (Figure 8(a,b)). This extremely low solubility is thought to be due to the un-ionized state of the drug in the dissolution medium. In contrast to its behavior in FaSSIF, amorphous EZ resulted in no increase in initial solution concentrations or supersaturation in FaSSGF. In fact, the method of preparation and the temperature had no effect on this

![Figure 7. Dissolution and precipitation (supersaturation) profiles of ternary solid dispersions of ezetimibe (EZ) in fasted-state simulated intestinal fluid: (a) and (b) melt-quenched (MQ1, 2, 3) and spray-dried (SD1, 2, 3) solid dispersions at 25 °C; (c) and (d) MQ and SD solid dispersions at 37 °C. AMP: amorphous EZ; CRY: crystalline EZ.](image-url)
behavior. This suggests rapid transformation of the amorphous phase into the crystalline phase, possibly as the result of an extremely high driving force for crystallization. Although some increase in the initial EZ concentrations and supersaturation were observed with the MQ and SD solid dispersions in general, the level and extent of supersaturation were much lower in FaSSGF than in FaSSIF at 25°C and 37°C (Figure 8). However, as with FaSSIF, higher polymer/poloxomer content delayed the precipitation kinetics, leading to sustained supersaturation for longer periods. The amorphous form of EZ, which is a poorly soluble and very weakly acidic drug, can show increased solubility (supersaturation) in FaSSIF and FaSSGF. Although PVP and poloxamer 188 were effective in inhibiting/delaying precipitation from the solid dispersions at 25°C, they were ineffective at 37°C, which is the physiologically relevant temperature. The method of preparation also affected the supersaturation and precipitation kinetics. In general, supersaturation was maintained for relatively longer in biorelevant media at both temperatures when MQ solid dispersions were used. It is important to consider these aspects in the design and development of amorphous solid dispersions of poorly soluble drugs.

MDSC, PXRD and FT-IR showed that although we obtained amorphous solid dispersion formulations, these new systems did not remain stable when they were dissolved in FaSSIF and FaSSGF, especially for SD formulations at 37°C.

**Conclusions**

Ternary solid dispersions of EZ containing PVP and poloxamer were successfully prepared by spray-drying and melt-quenching methods. The powders were thoroughly characterized using solid state tools and were found to be predominantly amorphous in nature with Tg values in the range of 140–160°C. FT-IR indicated the presence of interactions between EZ and the excipients. The results indicate that the melting method would be more promising for enhancing the dissolution of EZ from a ternary solid dispersion. Low concentrations of poloxamer 188 are adequate for obtaining the desired improvements in EZ solubility. The apparent solubility of EZ solid dispersions was higher in FaSSIF than in FaSSGF and supersaturation was maintained for an acceptable time, i.e. for the time required for the absorption process to take place. Further, the precipitation kinetics were faster at 37°C than at 25°C in biorelevant media, indicating that dissolution studies currently routinely performed at 25°C may be less relevant. In general, MQ solid dispersions had better supersaturation properties than SD dispersions. This study nicely demonstrated the effects of the formulation, the process, the temperature of the dissolution medium, and the type of biorelevant medium on the supersaturation and precipitation kinetics of ternary solid dispersions of EZ.

**Acknowledgements**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

**Disclosure statement**

There were no conflicts of interest.

**References**

1. Gao P, Shi Y. Characterization of supersaturatable formulations for improved absorption of poorly soluble drugs. AAPS J 2012;14:703–13.
2. Bevernage J, Brouwers J, Clarysse S, et al. Drug supersaturation in simulated and human intestinal fluids representing different nutritional states. J Pharm Sci 2010;99:4525–34.

3. Brouwers J, Brewster ME, Augustjins P. Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? J Pharm Sci 2009;98:2549–72.

4. Dahan A, Beig A, Ioffe-Dahan V, et al. The twofold advantage of the amorphous form as an oral drug delivery practice for lipophilic compounds: Increased apparent solubility and drug flux through the intestinal membrane. AAPS J 2013;15:347–53.

5. Janssens S, Nagels S, De Armas HN, et al. Formulation and characterization of ternary solid dispersions made up of itraconazole and two excipients, TPGS 1000 and PVPVA 64 that were selected based on a supersaturation screening study. Eur J Pharm Biopharm 2008;69:158–66.

6. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000;50:47–60.

7. Modi A, Tayade P. Enhancement of dissolution profile by solid dispersion (kneading) technique. AAPS PharmSciTech 2006;7:87–92.

8. Brewster M, Vancrbruys R, Verreck G, et al. Supersaturating drug delivery systems: effect of hydrophilic cyclodextrins and other excipients on the formation and stabilization of supersaturated drug solutions. Pharmazie 2008;63:217–20.

9. Bevernage J, Hens B, Brouwers J, et al. Supersaturation in human gastric fluids. Eur J Pharm Biopharm 2012;81:184–9.

10. Vancrbruys R, Peeters J, Verreck G, et al. Use of a screening method to determine excipients which optimize the extent and stability of supersaturated drug solutions and application of this system to solid formulation design. Int J Pharm 2007;342:168–75.

11. Shah TJ, Amin AF, Parikh JR, et al. Process optimization and characterization of poloxamer solid dispersions of a poorly water-soluble drug. AAPS PharmSciTech 2007;8:E18–24.

12. Goddeeris C, Willems T, Van den Mooter G. Formulation of fast disintegrating tablets of ternary solid dispersions consisting of TPGS 1000 and HPMC 2910 or PVPVA 64 to improve the dissolution of the anti-HIV drug UC 781. Eur J Pharm Sci 2008;34:293–302.

13. Wang X, Michael A, Van den Mooter G. Solid state characteristics of ternary solid dispersions composed of PVP VA64, Myrj 52 and itraconazole. Int J Pharm 2005;303:54–61.

14. Goddeeris C, Willems T, Houthoofd K, et al. Dissolution enhancement of the anti-HIV drug UC 781 by formulation in a ternary solid dispersion with TPGS 1000 and Eudragit E100. Eur J Pharm Biopharm 2008;70:861–8.

15. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: selection of polymer–surfactant combinations using solubility parameters and testing the processability. Int J Pharm 2007;328:119–29.

16. Shimp MR, Childs SL, Bostrom D, et al. New cocrystals of ezetimibe with l-proline and imidazole. CrystEngComm 2014;16:8984–93.

17. Gulsun T, Gursoy RN, Oner L. Design and characterization of nanocrystal formulations containing ezetimibe. Chem Pharm Bull 2011;59:41–5.

18. Parmar KR, Shah SR, Sheth NR. Studies in dissolution enhancement of ezetimibe by solid dispersions in combination with a surface absorbent. Dissolut Technol 2011;8:55–61.

19. Taupitz T, Dressman JB, Klein S. New formulation approaches to improve solubility and drug release from fixed dose combinations: case examples pioglitazone/glimepiride and ezetimibe/simvastatin. Eur J Pharm Biopharm 2013;84:208–18.

20. Paradkar A, Ambike AA Jadhav BK, et al. Characterization of curcumin–PVP solid dispersion obtained by spray drying. Int J Pharm 2004;271:281–6.

21. Foussteris E, Tarantili PA, Karavas E, et al. Poly (vinyl pyrrolidone)–poloxamer-188 solid dispersions prepared by hot melt extrusion. J Therm Anal Calorim 2013;113:1037–47.

22. Soliman S, Abdel Malak N, El Gazayerly O, et al. Preparation of celecoxib solid dispersions for dermal application: in vitro characterization and skin irritation test. J Drug Deliv Sci Technol 2011;21:509.

23. Patterson JE, James MB, Forster AH, et al. Preparation of glass solutions of three poorly water soluble drugs by spray drying, melt extrusion and ball milling. Int J Pharm 2007;336:22–34.

24. Ambike AA, Madhak K, Paradkar A. Spray-dried amorphous solid dispersions of simvastatin, a low Tg drug: in vitro and in vivo evaluations. Pharm Res 2005;22:990–8.

25. Zhang Y, Luo R, Chen Y, et al. Application of carrier and plasticizer to improve the dissolution and bioavailability of poorly water-soluble baicalein by hot melt extrusion. AAPS PharmSciTech 2014;15:560–8.

26. Newa M, Bhandari KH, Li DX, et al. Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with polyoxamer 188. Int J Pharm 2007;343:228–37.

27. Paoloni L, Patta A, Mangano F. The hydrogen bond with carbonyl groups: theoretical study of the correlation between the X–H stretching frequency shift and the C=O group proper. J Mol Struct 1975;27:123.

28. Mulye SP, Jamadar SA, Karekar PS, et al. Improvement in physicochemical properties of ezetimibe using a crystal engineering technique. Powder Technol 2012;222:131–8.

29. Matsumoto T, Zograf G. Physical properties of solid molecular dispersions of indomethacin with poly (vinylpyrrolidone) and poly (vinylpyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization. Pharm Res 1999;16:1722–8.

30. Khougaz K, Clas S. Crystallization inhibition in solid dispersions of MK-0591 and poly (vinylpyrrolidone) polymers. J Pharm Sci 2000;89:1325–34.

31. Gupta P, Bansal AK. Molecular interactions in celecoxib-PVP-meglumine amorphous system. J Pharm Pharmacol 2005;57:303–10.

32. Taylor LS, Zograf G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm Res 1997;14:1691–8.

33. Doherty C, York P. Evidence for solid- and liquid-state interactions in a furosemide-polyvinylpyrrolidone solid dispersion. J Pharm Sci 1987;76:731–4.

34. Carlert S, Pålsson A, Hanisch G, et al. Predicting intestinal precipitation—a case example for a basic BCS class II drug. Pharm Res 2010;27:2119–30.

35. Amidon GL, Lennernäs H, Shah VP, et al. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 1995;12:413–8.

36. Psachoulias D, Vertzoni M, Goumas K, et al. Precipitation in polymer solutions with poloxamer 188. Int J Pharm 2007;343:228–37.

37. Konno H, Handa T, Alonzo DE, et al. New cocrystals of ezetimibe/simvastatin. Eur J Pharm Biopharm 2013;85:208–18.
dispersions containing felodipine. Eur J Pharm Biopharm 2008;70:493–9.

38. Lindfors L, Forssén S, Westergren J, et al. Nucleation and crystal growth in supersaturated solutions of a model drug. J Colloid Interface Sci 2008;325:404–13.

39. Warren DB, Benameur H, Porter CJ, et al. Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: a mechanistic basis for utility. J Drug Target 2010;18:704–31.

40. Usui F, Maeda K, Kusai A, et al. Inhibitory effects of water-soluble polymers on precipitation of RS-8359. Int J Pharm 1997;154:59–66.

41. Bevernage J, Brouwers J, Brewster ME, et al. Evaluation of gastrointestinal drug supersaturation and precipitation: strategies and issues. Int J Pharm 2013;453:25–35.

42. Greco K, Bogner R. Crystallization of amorphous indomethacin during dissolution: effect of processing and annealing. Mol Pharm 2010;7:1406–18.