Characterization and Physical Stability of Spray Dried Solid Dispersions of Probucol and PVP-K30

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The main purpose of this study was to obtain stable, well-characterized solid dispersions (SDs) of amorphous probucol and polyvinylpyrrolidone K-30 (PVP-K30) with improved dissolution rates. A secondary aim was to investigate the flow-through dissolution method for in-vitro dissolution measurements of small-sized amorphous powders dispersed in a hydrophilic polymer. SDs were prepared by spray drying solutions of probucol and different amounts of PVP-K30. The obtained SDs were characterized by dissolution rate measurements in a flow-through apparatus, X-ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), particle sizing (laser diffraction) and Brunauer-Emmett-Teller Method (BET) and results were compared with starting material and a physical mixture. The physical stability was monitored after storage at 25°C and 60% RH for up to 12 weeks. The flow-through method was found suitable as dissolution method. All SDs showed improved in-vitro dissolution rates when compared to starting material and physical mixtures. The greatest improvement in the in-vitro dissolution rate was observed for the highest polymer to drug ratio. By means of the results from XRPD and DSC, it was argued that the presence of amorphous probucol improved the dissolution rate, but the amorphous state could not fully account for the difference in dissolution profiles between the SDs. It was suggested that the increase in surface area due to the reduction in particle size contributed to an increased dissolution rate as well as the presence of PVP-K30 by preventing aggregation and drug re-crystallization and by improving wettability during dissolution. The stabilizing effect of the polymer was verified in the solid state, as all the SDs retained probucol in the amorphous state throughout the entire length of the stability study.

Keywords: amorphous, flow-through dissolution, solid dispersion, stability, spray drying, probucol

INTRODUCTION

Low aqueous solubility of pharmacologically active compounds is frequently experienced by the pharmaceutical scientist, complicating the development of delivery systems due to low and variable bioavailability of these compounds. Increased bioavailability for orally administered compounds can be achieved by manipulating the solid state properties of the drug compound and/or by adding excipients to the formulation that lead to an increased solubilization. One well recognized approach is the transformation of a crystalline drug into a high energy amorphous state. However, as the amorphous form normally is thermodynamically unstable...
over time, it tends to revert back to a more stable crystalline state. This means that during processing, testing and storage, the risk of crystallization is always present, and that fact may lower the dissolution rate and consequently affect the bioavailability of the compound upon administration. Various attempts to stabilize the amorphous form have been made. For example the addition of hydrophilic polymers with a high glass transition temperature (Tg), with the formation of a solid dispersion (SD), has been applied to several drugs and has been the subject of intense research (e.g. Yoshioka et al., Ambike et al., Chokshi et al., and Jung et al.).

During development and optimization of drug formulations, dissolution testing is a key method applied in order to screen different formulation approaches. The pharmacopoeias (Ph. Eur., USP) and several guidelines include descriptions of different dissolution testing methods. When dealing with a poorly soluble drug compound, the use of the flow-through apparatus, normally described as apparatus 4 in the Pharmacopoeia, is advantageous as it makes it possible to obtain sink conditions. This may not be possible in the more frequently used methods, i.e. the basket or paddle. Furthermore, the flow through method makes it possible to ensure that a hydrophobic pharmaceutical powder is in contact with the dissolution media and not floating on the top of fluid in the dissolution vessel, a feature often seen for hydrophobic drug particles. The flow-through method has been applied in several studies, employing poorly soluble drug substances, but its use in the evaluation of amorphous SDs introduced to the flow cell as a powder is to our knowledge very limited. Single examples can, however, be found in the literature, e.g. studies by Giunchedi et al. and Emara et al. It is of high value to the formulation scientist to be able to elucidate the dissolution characteristics of SD powders during the early development stage before including other excipients necessary for a capsule or tablet formulation.

In present study probucol is used as a representative compound for a low aqueous soluble drug. Pharmacologically it is a cholesterol lowering agent. It has previously been demonstrated that amorphous SDs can be produced by various methods with probucol using polyvinylpyrrolidone (PVP) as carrier, but the spray drying technique has never been applied. Generally, PVP of smaller molecular weight (K25 and K30) was found to be the best carrier with respect to achieving the highest dissolution, however, the impact of drug to polymer ratio on the dissolution profile has not been reported. Furthermore, the long term stability of the systems has never been evaluated.

The aim of the current study was to characterize stabilized amorphous probucol produced by spray drying method. The stabilizing effect of PVP-K30 in different ratios was evaluated with respect to re-crystallization. A second objective was to evaluate the suitability of the flow-through method for in vitro dissolution measurements of small-sized amorphous powders dispersed in a hydrophilic polymer.

**MATERIALS AND METHODS**

**Chemicals**

Probucol was received from Sigma (St Louis, MO, USA). Polyvinylpyrrolidone K-30 (Povidone) was supplied by ISP Technologies (Texas City, TX, USA) and ethanol 99.9% from De Danske Spritfabrikker (Aalborg, Denmark). The three materials were of Pharmacopoeia grade. Sodium lauryl sulfate (Ph.Eur. 96.6%) (SLS) was purchased from Unichem (Copenhagen, Denmark), polyoxyethylene 20 sorbitan monolaurate (Tween 20) from Applichem (Darmstadt, Germany) and polyoxyethylene 20 sorbitan monooleate (Tween 80) from Applichem (Darmstadt, Germany). Acetonitrile was HPLC grade (VWR International, Leuven, Belgium). The water used in all experiments was obtained from a Milli-Q water purification system (Millipore, Milford, MA, USA).

**Preparation of Solid Dispersions and Physical Mixture**

Samples of probucol in combination with different amounts of PVP-K30 (1:2, 1:3, 1:5, 1:7 and 1:9, w/w) were dissolved in a suitable amount of ethanol 99.9%. The ethanol was subsequently removed by spray drying to obtain the amorphous material. The spray drying was carried out using a SDMicro™ (GEA Niro A/S, Soeborg Denmark) with a pneumatic pump (Watson Marlow, Falmouth, UK) and a pneumatic two-fluid nozzle with a 0.5 mm exit orifice. The spray drying was carried out in a co-current mode under the following set of conditions: Inlet temperature: 90 ± 2°C, process air: 30.0 kg/h, atomization air flow: 1.60 kg/h, feed rate: 2.8 g/min. The inlet temperature, the outlet temperature, the feed rate and the air flow were recorded continuously during each run. A 1:2 and a 1:9 w/w physical mixture (PM) of drug and polymer were prepared by mixing probucol and PVP-K30 in a mortar for 5 min.

**Solubility Measurements**

Excess probucol was weighed into glass centrifuge tubes with teflon-lined caps containing solutions with 1% (w/v) of either SLS, Tween 20 or Tween 80. The tubes were then placed in a stirrer with constant end-over-end rotation, maintained at 37°C for 3 days. At specific time intervals each tube was centrifuged at 4500 rpm for 10 min.
a 1.1 mL sample was taken and transferred to an eppendorf tube and centrifuged at 15,000 rpm for another 10 min. The supernatant (0.25 mL) was diluted with 1 mL ethanol 99.9% and analyzed by high-performance liquid chromatography (HPLC) with UV detection as described in the section: “Analytical Method”. The solubility of probucol was determined in triplicate for each surfactant solution.

**In-Vitro Dissolution Testing**

The flow-through method was employed at 37°C (Sotax CE70 apparatus including a flow cell bath, pump, splitter and collector). The tests \((n = 3)\) were run by the software WinSotax version 2.1.2. The flow cell had a diameter of 22.6 mm, and a flow of 8.3 ± 0.2 mL/min was employed. In the bottom of the flow cell, a rubber glass bead (diameter 5 mm) was placed. On top of the rubber glass bead, 0.2 g of small glass beads (diameter 1 mm) were placed plus a mixture of the test sample/powder (an amount equal to 100 mg probucol) mixed with 4 g of the small glass beads. In the top of the flow cell, a glass fiber filter (Advantec GF-75, 0.2 mL/min was employed). Samples were taken at given time points and diluted appropriately with the dissolution medium. This was done in order to secure that all samples had a probucol concentration below the solubility of crystalline probucol in the dissolution medium. The samples were transferred to HPLC vials and analyzed by HPLC with UV detection.

**Analytical Method**

Samples from solubility and dissolution experiments were analyzed by a reverse-phase HPLC assay method modified from Yagi et al. A HPLC system from Hewlett Packard (series 1100, Palo Alto, CA) was employed and equipped with an autosampler (G1313A), quaternary pump (G1310A) and diode array detector (G1315A) with integration by HP ChemStation software (Rev. A.08.03). The reverse-phase column was a Phenomenex, Luna C18 column (150 × 4.6 mm, 5 μm) with a Phenomenex C18 precolumn (4 × 3 mm). The injection volume was 100 μL and the analyses were carried out at 254 nm. The mobile phase was acetonitril:water 85:15 (v/v). A flow rate of 1.5 mL/min gave a retention time of 24 min.

**Characterization of Spray Dried Powder**

The spray dried powder was characterized by the methods described below. The characterization also includes a 12-week study on stability.

**Stability**

The stability was monitored for up to 12 weeks after storage at 25°C and 60% RH in a Termaks KBP 6395 F climatic cabinet (Bergen, Norway). Periodically (initial, after 1 week, 4 weeks and 12 weeks), samples were removed and the presence of crystallinity was investigated by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

**X-Ray Powder Diffraction (XRPD)**

Two polymorphic forms of probucol have previously been described by Gerber et al. The compound received from the vendor was equal to the high melting form, form I. Form II was prepared as previously described by Gerber et al. by rapid crystallization from a saturated ethanol solution. This was achieved by vacuum evaporation of the ethanol phase at a temperature of 45°C in a vacuum oven (Vacuubrand, Wertheim, Germany).

The crystalline state of probucol in the different samples was evaluated by XRPD. Diffraction patterns were obtained on a PANalytical X’Pert PRO X-ray Diffractometer (Panlytical, Almeo, The Netherlands) in alpha1 configuration equipped with an X-celerator detector. Cu \((λ = 1.5406Å)\) was used as anode material and crystal graphite monochromator, operated at a voltage of 40 kV and a current of 45 mA. The samples were analyzed in the 2θ angle range of 5–40°, and the process parameters were set as follows: step size of 0.045° (20), scan step time of 0.5 s, and time of acquisition of 2 h.

**Differential Scanning Calorimetry (DSC)**

DSC analysis was carried out using a Diamond DSC (Perkin-Elmer, Shelton, USA) with an ULSP-130 cooler unit (ULSP B.V., Ede, The Netherlands). Nitrogen was used as purge gas with a flow rate of 30 mL/min. A heating rate of 50°C/min was used for all samples. Prior to analysis, indium and tin standards were used to calibrate for enthalpy and temperature. Data were treated in the Pyris software version 7.0 (Perkin-Elmer, Shelton, USA).

Samples of approximately 5.00 mg were placed in pin-holed aluminum pans (Perkin-Elmer). After sealing, the samples for the stability study were stored as previously described at 25°C and 60% RH up to 12 weeks. Periodically (initial, after 1 week, 4, 8 and 12 weeks), samples were removed and analyzed. Before analyzing, all samples were dried in a vacuum dessicator over phosphorus pentoxide at 50°C ± 5°C for 24 h in order to minimize the presence of volatile substances. In order to determine the glass transition temperature \((T_g)\) of amorphous probucol, a sample of crystalline probucol was heated to 140°C (50°C/min) and held...
for 1 min. The sample was then cooled to −20ºC and reheated to 200ºC (50ºC/min).

Scanning Electron Microscopy (SEM)

The samples were mounted on stubs with double-faced adhesive tape and sputter coated for 120 sec. with a thin gold-palladium layer in an Auto sputter coater (ES2000, BIO RAD, Watford, UK). Surface topography was analyzed with a scanning electron microscope (JSM 5200, JEOL, Tokyo, Japan). An acceleration voltage of 10 kV and a working distance of 20 mm were used.

Particle Size Distribution

The particle size distribution of the spray dried powders were analysed by laser diffraction. The measurements were carried out using a Malvern Mastersizer S (Malvern Instruments, Worcestershire, UK) with a MS7 magnetically stirred dry sampling system and a 300 mm lens. A pressure of 2 Bar was used in order to disperse the particles. The particle size will be reported as D_{10}, D_{50} and D_{90}.

Brunauer-Emmett-Teller Method (BET)

The specific surface area (SSA) was measured by the Brunauer–Emmett–Teller method (BET) by the use of the Gemini 2375 gas adsorption analyzer (Micromeritics, Norcross, GA, USA). Samples were subjected to helium purge at 30ºC for 5 h prior to analysis using the VacPrep 061 degassing unit (Micromeritics, Norcross, GA, USA). The sample mass used was approximately 2 g. The SSA values were determined to be mass independent below and above 2 g as part of method development. Filler rods were used in the sample cells. Experiments were conducted at −196ºC using a 2.75-l nitrogen dewar. Adsorption was conducted from 0.1–0.5 relative pressure of nitrogen in 0.01 increments. The isotherm was measured in triplicate. All data analyses were conducted using the equipment software version 4.01 (Micromeritics, Norcross, GA, USA).

RESULTS

Choice of Dissolution Medium

The data from the solubility study of probucol in the surfactant solutions are shown in Figure 1. The results indicate that equilibrium was reached after 72 h for all samples. Solubility of probucol in the three tested solutions was measured to 4 μg/mL, 37 μg/mL and 95 μg/mL for 1% SLS, 1% Tween 20, and 1% Tween 80, respectively. Since the highest solubility of probucol was found in 1% Tween 80, this solution was used as dissolution medium in the dissolution experiments.

In-Vitro Dissolution

The in-vitro dissolution results presented in Figure 2 clearly discriminated between the different SDs. Depending on the drug to polymer ratio, increments up to ~ 62 mg probucol dissolved in 60 min was seen. Thus, in order to obtain the greatest improvement in dissolution rate of probucol, a high polymer to drug ratio is required. The dissolution rate of the probucol starting material showed the slowest dissolution rate with less than 1 mg dissolved during the dissolution testing. It is noteworthy that these results show that the presence of PVP-K30 in the physical mixture with probucol did not lead to a significantly increased dissolution rate compared to crystalline probucol (Figure 3). This was observed for both of the investigated physical mixtures (probucol/PVP-K30 w/w% ratio 1:2 and 1:9).

Since the flow through dissolution method often is used in order to obtain sink conditions for poorly soluble substances, a closer look at the specific concentrations at the different sampling times is interesting. The highest concentration levels of probucol were obtained during the dissolution study at the first three time points. These concentrations are shown in Table 1. Concentrations above 95 μg/mL probucol, which is the saturation solubility of crystalline probucol in the dissolution medium, were seen for the three SDs containing the highest level of PVP-K30. All the sampling points from 30–60 min gave a concentration of probucol below 95 μg/mL.
Spray Dried Solid Dispersions of Probucol and PVP-K30

Table 1

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Drug/polymer ratio (w/w%)</th>
<th>1:2</th>
<th>1:3</th>
<th>1:5</th>
<th>1:7</th>
<th>1:9</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td>51 µg/mL</td>
<td>60 µg/mL</td>
<td>220 µg/mL</td>
<td>368 µg/mL</td>
<td>398 µg/mL</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>18 µg/mL</td>
<td>21 µg/mL</td>
<td>116 µg/mL</td>
<td>353 µg/mL</td>
<td>536 µg/mL</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>7 µg/mL</td>
<td>6 µg/mL</td>
<td>39 µg/mL</td>
<td>151 µg/mL</td>
<td>271 µg/mL</td>
</tr>
</tbody>
</table>

Figure 2. Dissolution profiles of spray dried solid dispersions (SD) of probucol and PVP-K30 in drug to polymer ratios of 1:2, 1:3, 1:5, 1:7 and 1:9 (w/w). An amount of powder equal to 100 mg of drug was used. The dissolution medium was 1% tween 80 and error bars show the standard deviation (n = 3).

Figure 3. Dissolution profiles of crystalline probucol and physical mixtures (PM) of probucol and PVP-K30 in ratios of 1:2 and 1:9 (w/w). An amount of powder equal to 100 mg of drug was used. The dissolution medium was 1% tween 80 and error bars show the standard deviation (n = 3).
X-Ray Powder Diffraction (XRPD)

X-ray powder diffraction patterns of various systems of probucol and PVP-K30 are shown in Figure 4. The pattern of probucol as received from supplier showed diffraction peaks at 2θ values of 5.73°, 9.47°, 16.02°, 19.13° and 22.89° (Figure 4a), characteristic of the polymorphic form I of probucol. The formation of the other polymorphic form of probucol after crystallization (form II) was also confirmed by the presence of characteristic peaks for this form at 2θ values of 7.36°, 8.39°, 15.64°, 17.32° and 23.79° (Figure 4a). PVP-K30 being amorphous did not show any peaks (Fig 4a). Although less intense, no changes in the positions of diffraction peaks were observed after physical mixing, indicating that the crystalline form of probucol had not changed (Figure 4a).

Initially, all SDs showed a halo diffraction pattern indicating that probucol was present in the amorphous state in these samples (data not shown). At the end of the stability study, no occurrence of crystals could be observed in any of the SDs (Figure 4b). In contrast, re-crystallization of amorphous probucol without PVP-K30 was evident after 1 day as seen from Figure 4c. According to the X-ray pattern, the re-crystallization process begins with the formation of the polymorph II. Form II of probucol was also the polymorph present after 12 weeks of storage in the climatic cabinet (25°C, 60% RH).

Differential Scanning Calorimetry (DSC)

The DSC profiles of the various samples investigated are shown in Figure 5. The probucol starting material showed an endothermic melting peak at 127°C (Figure 5a) and could therefore be classified as crystal Form I as also demonstrated by X-ray. PVP being an amorphous polymer showed a single Tg with an onset at 163°C (Figure 5a). The thermogram of the physical mixture included both the probucol melting peak and the Tg resulting from PVP-K30 indicating one more time that the crystalline form was not changed after physical mixing (Figure 5a).

Initially, no melting peak for probucol was evident in the thermograms resulting from the SDs, (data not shown). This was also the case after 12 weeks of storage (Figure 5b). Instead a single Tg could be observed depending on the composition. All Tg values were found within the limits of probucol and PVP-K30. A single Tg represents the presence of a single phase. This suggests that within the investigated concentration range, there is complete miscibility between the drug and the polymer.

The unstable nature of the amorphous probucol found by XPRD was confirmed by DSC (Figure 5c), but the timescale is slightly different. When compared to the results from XPRD, the re-crystallization process starts later when evaluated by DSC. The Tg of the amorphous probucol prepared by quench cooling (quench cooled within the DSC) was found at 28°C (Figure 5c). Other authors have reported a melting point of 116°C of the polymorphic form II of probucol. After 4 weeks it is evident that the sample consists of a mixture of the two polymorphs (the melting peak from form I is very small and broad) and the amorphous form (Figure 5c). Conversion towards the polymorph I occurs, but the conversion is not completed within the inspected timescale (12 weeks). Differences in methods regarding the ability to detect and quantify the amorphous contents in pharmaceutical solids have been noticed previously. Furthermore, the amorphous samples were prepared in two different ways. Thus, the samples for the XRPD measurements were prepared by spray drying, whereas the ones for DSC were made by quench cooling. Besides the differences in the preparation methods and the employed characterization methods, the unstable nature of amorphous probucol was verified. Furthermore, the results from the DSC analysis confirmed the stabilizing effect of PVP-K30 on the amorphous probucol.

Morphology

Micrographs of probucol starting material and SDs (1:2, 1:5 and 1:9) are shown in Figure 6. The particles of probucol as received from the supplier were rather irregular in size and shape. The spray drying process resulted in generally spherical particles. Compared to the starting material, the particle sizes of the SDs are much smaller. This reduction in particle size facilitates the dissolution process. The structure of the surface of the different SDs differed depending on the drug to polymer ratio. Thus, increasing the amount of PVP-K30, results in particles with a more folded surface.

Particle Size Distribution

The measured particle sizes (D_{10}, D_{50} and D_{90}) are presented in Table 2. Only minor differences in the particle size were observed between the SDs. Thus, the final size of the particles seems unaffected by the drug to polymer ratio. The particle size distributions were regarded as narrow, as the span, calculated as D_{90}-D_{10}/D_{50}, was below 1.7 for all the spray dried powders.

Specific Surface Area (BET)

The specific surface areas for the SDs are shown in Table 2. The specific surface area of the SD 1:2 particles was considerably higher (more than three times) than the
Figure 4. X-ray powder diffraction spectra of probucol/PVP-K30 systems: (A) Starting materials, physical mixture 1:9 (PM 1:9) and probucol after crystallization; (B) Solid dispersions (SD) after 12 weeks of storage at 25°C/60%RH; (C) Amorphous probucol stored at different timescales at 25°C/60%RH.
Figure 5. DSC profiles of probucol/PVP K30 systems. (A) Starting materials and physical mixture 1:9 (PM 1:9); (B) Solid dispersions (SD) after 12 weeks of storage at 25°C/60%RH; (C) Amorphous probucol stored at different timescales at 25°C/60%RH.
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particles resulting from the other drug to polymer ratios. As the particles are almost similar in size, but much more structured for the higher drug to polymer ratios, these findings suggest that the particles with the low drug to polymer ratio have a hollow interior, that is accessible for the nitrogen gas. An increase in the surface area will normally give an enhancement of the dissolution rate. Solely based on these data, the SD 1:2 should have the fastest dissolution rate of the SDs. This was not found to be the case as seen in Figure 2. Therefore, it can be speculated, if the interior of the particles is accessible for the dissolution media. On the other hand, the impact of an increased surface area on the dissolution rate could be minor when compared to the other contributing effects.

DISCUSSION

Dissolution Media

The extremely low solubility of crystalline probucol calls for the use of additives in the dissolution media in order ensure sink conditions during dissolution testing. Large amounts of ethanol and surfactants have previously been used in the dissolution media in dissolution studies (paddle method) of SDs with probucol. In the present study, the goal was to avoid ethanol and only use a surfactant

Table 2

<table>
<thead>
<tr>
<th>Drug/polymer ratio (w/w %)</th>
<th>Particle size (μm)</th>
<th>Specific surface area (m²/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D₁₀</td>
<td>D₅₀</td>
</tr>
<tr>
<td>1:2</td>
<td>3.2</td>
<td>8.3</td>
</tr>
<tr>
<td>1:3</td>
<td>3.0</td>
<td>7.4</td>
</tr>
<tr>
<td>1:5</td>
<td>3.8</td>
<td>8.5</td>
</tr>
<tr>
<td>1:7</td>
<td>3.3</td>
<td>9.0</td>
</tr>
<tr>
<td>1:9</td>
<td>3.2</td>
<td>8.8</td>
</tr>
</tbody>
</table>

Figure 6. SEM micrographs of probucol/PVP-K30 systems. (A) Probucol as received from supplier, (B) SD 1:2, (C) SD 1:5, (D) SD 1:9. The magnification of the SD (×2000) micrographs was 10 times higher than for probucol (×200).
recommended for dissolution studies in order to increase the solubility of probucol during dissolution testing. The concentration level of the surfactants was 1%, which is above the critical micellar concentration (CMC) for all the surfactants employed.[19,20] Thus, both increased wetting and increased solubility can be expected at this concentration of surfactant. The level of surfactant has previously been employed for drug products with poorly soluble substances and these three surfactants are commonly used for dissolution studies.[21,22]

Dissolution Method Set-up

The following is a discussion on the method set-up used in the present study. The dissolution profiles and the release mechanism in combination with the results concerning the solid state properties are discussed in the section: “The Mechanism behind the Increased Dissolution Rate”. The flow-through dissolution apparatus appeared to be the most suitable for this specific application. Despite the relatively high concentrations of probucol in the first sampling points for some SDs a flow of 8.3 ± 0.2 ml/min was chosen, which is within the recommended flow rate between 4 and 16 ml/min (Ph. Eur.). The problem with small-sized powders with poor wettability is that they tend to form agglomerates and hinder proper wetting during the dissolution measurements. The choice of mixing the samples with the small glass beads prior to loading was made to assure maximum area available for dissolution media and to avoid accumulation of too much undissolved sample on the glass fiber filter in the top of the flow cell. Furthermore, mixing unformulated particles with glass beads in order to avoid wetting problems has been suggested by Langenbucher et al.[23] Other authors have shown that the sample loading method into the flow-through dissolution cells is important when working with poorly wettable powders.[11] Bhattacher et al. tested different loading methods including a homogenous mixing with the small glass beads.[11] They also tested the effect of placing the powder sample in different layers, i.e. either in the middle or at the bottom of the glass beads. Mixing the sample with the glass beads gave the fastest dissolution and the lowest variability in the dissolution profiles. This loading method is, however, not the recommended method in the pharmacopeias for dosage forms. Thus, when testing a dosage unit, a tablet or capsule, it is recommended to place it on top of the glass beads.

The Mechanism behind the Increased Dissolution Rate

The full mechanism behind the improved dissolution rates for amorphous drug compounds stabilized by a hydrophilic carrier is still not fully understood. Comprehensive reviews of the subject have been given by others, e.g. by Leuner and Dressman and Craig.[24,25] SDs of a number of poorly soluble compounds and different ratios of PVP-K30, where the dissolution rate has increased, has previously been reported.[26–28] All the SDs in the present study contained probucol in the amorphous form as indicated by the XRPD and DSC measurements. Therefore, the increased dissolution rate for all the SDs could be due to the increased solubility of the amorphous state (temporary, the solubility of the amorphous state could be higher than the intrinsic solubility of the drug). This effect is assumed to be similar for all the SDs, irrespective of the amount of PVP-K30. Therefore, the presence of probucol in the amorphous state does not explain the different dissolution profiles of the SDs.

SDs are often quite simple formulations consisting of the drug dispersed in one carrier as in present study. Thus, during the dissolution process, these two components dissolve. This dissolution has been suggested to either be carrier-controlled or drug-controlled. For the carrier-controlled, the dissolution is dominated by the properties of the carrier, whereas for the drug-controlled, drug properties such as particle size and physical form can be linked to the dissolution rate.[25] Craig suggested that, in both situations, a concentrated polymer layer will be formed at the dissolving surface. The drug will need to pass this layer on its way to the bulk phase. For the carrier-controlled process, the drug particles will dissolve in this layer and thereby be molecularly dispersed in this diffusion layer. In the case of drug-controlled dissolution, the dissolution into this diffusion layer is slow, and the drug is released as solid particles into the bulk. However, both types of mechanisms may be present simultaneously. It is likely that for the SD with the highest polymer to drug ratio the diffusion layer contain a larger amount of polymer. Thus, the increase in dissolution rate of these SD could be related to an increased solubility of probucol in the diffusion layer at the dissolving surface.[25] Furthermore, the probability of crystallization might be decreased by the presence of polymer, as the polymer hinders the probucol molecules to form seeds. Since probucol is extremely poorly soluble in aqueous solutions, we assume that, during the dissolution of the SDs, both the drug-controlled and the carrier-controlled dissolution processes play simultaneously. For the SDs with the high polymer to drug ratio, it is suggested that there is a higher degree of carrier-controlled dissolution determining the dissolution rate. As can be seen in Table 1, the concentration in the first samples during the dissolution tests is in some cases above the saturation solubility of the crystalline probucol in the dissolution medium. This is seen for the ratios 1:5, 1:7 and 1:9 with increasing
concentrations of probucol as the amount of polymer increases. Unfortunately, it was not possible to measure the dissolution of the amorphous probucol alone due to the fast conversion to the crystalline state seen even in the solid state. Furthermore, since fresh dissolution medium is continuously fed to the test material in the flow through dissolution method, the solubility enhancement due to the presence of PVP-K30 is difficult to quantify.

Other factors that might have an influence on the dissolution rate of the SDs are avoidance of drug particle aggregation and improved wetting. Furthermore, the differences in particle morphology seen in the micrographs could account for some variation in the dissolution profiles. The particle size was approximately the same for all the SDs (7.4–9.0 μm). When compared with probucol starting material and the physical mixtures, this reduction in size will increase the dissolution rate of all the SDs. However, it has not been possible to measure the size of the amorphous probucol particles dispersed within the carrier in the SDs. Neither has it been clarified in the present study, how the probucol particles are distributed inside the SD particles.

Several factors have to be withdrawn when trying to understand the mechanism behind the observed improvements in the dissolution of probucol. To what extent each of the individual parameters contribute to the overall dissolution profile still remains unknown, and additional factors may be involved. However, this study demonstrated that probucol can be incorporated successfully into a SD, which can be characterized by the flow-through dissolution method.

CONCLUSION

The spray drying method could be used to prepare amorphous solid dispersions (SDs) of probucol and Polyvinylpyrrolidone K-30 (PVP-K30). By way of commonly used characterization methods the solid state properties of the SDs were determined. The flow through dissolution method has been demonstrated to be suitable for small-sized hydrophobic powders dispersed in a hydrophilic polymer.

It was found that the PVP-K30 had a stabilizing effect on the amorphous probucol, i.e. re-crystallization was only observed for the pure amorphous probucol and not for any of the SDs in the solid state. All the SDs showed improved dissolution in comparison with starting material and physical mixtures of probucol and PVP-K30. The improved dissolution rate of the SDs was ascribed to the conversion of probucol into its amorphous form, the presence of polymer and the reduction in particle size.

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