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RESEARCH ARTICLE

A comparative study of spray-dried and freeze-dried hydrocortisone/polyvinyl pyrrolidone solid dispersions

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Abstract

Poor water solubility of new chemical entities (NCEs) is one of the major challenges the pharmaceutical industry currently faces. The purpose of this study was to investigate the feasibility of freeze-drying as an alternative technique to spray-drying to produce solid dispersions of poorly water-soluble drugs. Also investigated was the use of aqueous solvent mixtures in place of pure solvent for the production of solid dispersions. Aqueous solvent systems would reduce the environmental impact of pure organic solvent systems. Spray-dried and freeze-dried hydrocortisone/polyvinyl pyrrolidone solid dispersions exhibited differences in dissolution behavior. Freeze-dried dispersions exhibited faster dissolution rates than the corresponding spray-dried dispersions. Spray-dried systems prepared using both solvent systems (20% v/v and 96% v/v ethanol) displayed similar dissolution performance despite displaying differences in glass transition temperatures (T_g) and surface areas. All dispersions showed drug/polymer interactions indicated by positive deviations in T_g from the predicted values calculated using the Couchman–Karasz equation. Fourier transform infrared (FTIR) spectroscopic results confirmed the conversion of crystalline drug to the amorphous in the dispersions. Stability studies were preformed at 40°C and 75% relative humidity to investigate the physical stability of prepared dispersions. Recrystallization was observed after a month and the resultant dispersions were tested for their dissolution performance to compare with the dissolution performance of the dispersions prior to the stability study. The dissolution rate of the freeze-dried dispersions remained higher than both spray-dried dispersions after storage.

Keywords: Poor aqueous solubility, solid dispersions, spray-drying, freeze-drying, amorphous, stability, dissolution

Introduction

Increased understanding of biochemical systems, coupled with the introduction of combinatorial chemistry and high-throughput screening, has led to the introduction of new chemical entities (NCE) with suboptimal physicochemical properties for oral drug delivery[1]. The poor aqueous solubility of many NCE can pose an obstacle to the drug development process[2]. Poor aqueous solubility leads to poor oral bioavailability and can prohibit the development of NCE into preferential oral dosage forms, such as tablets and capsules.

Increasing the dissolution rate of poorly water-soluble drugs through the use of amorphous drug forms is well-documented[3–6]. The amorphous form of drug, compared with its crystalline counterpart, is more soluble owing to its higher free energy arising from the enthalpy and entropy associated with these systems. Due to their higher free energy, amorphous systems are unstable and the instability of amorphous drug systems is a major drawback to their inclusion in commercial drug products[7,8]. In an attempt to stabilize amorphous drug forms, amorphous drugs are often formulated as solid dispersions[4,9–11]. Solid dispersions are systems where drug is dispersed in a carrier material through the application of different processing methods. Carriers selected can stabilize amorphous drugs by retarding their conversion to more stable crystalline forms by increasing the system's viscosity and/or intermolecular interactions[12].

Solid dispersions can be prepared by a range of methods including solvent removal, fusion, milling, and supercritical fluid techniques. A number of studies

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have compared the effectiveness of solid dispersion preparation techniques; however, there is no consensus regarding the effectiveness of different methods for enhancing the dissolution rate and stabilizing the amorphous drug form. The performance of solid dispersions prepared by different methods appears to be highly dependent on the drug and carrier in each case. A study by Patterson et al. compared the physicochemical properties of solid dispersions of carbamazepine, dipyridamole, and indomethacin and polyvinyl pyrrolidone (PVP) prepared by spray-drying, melt extrusion, and ball milling. They concluded that the physicochemical properties of the resultant solid dispersions were dependent on both the method of preparation and the degree of hydrogen bonding between drug and polymer[13]. A study by Betageri and Makarla that compared fusion and freeze-drying techniques to prepare glyburide/polyethylene glycol solid dispersions found the freeze-dried solid dispersions resulted in a 2-fold increase in dissolution rate compared with solid prepared by the fusion method[14]. Van den Mooter et al. compared the dissolution performance of itraconazole–Inutec SPI solid dispersions prepared by spray-drying and melt extrusion and they reported that solid dispersions prepared by melt extrusion showed higher dissolution enhancement compared with dispersions prepared by spray-drying[15].

Although spray-drying is one of the more widely used solvent removal methods used to prepare solid dispersions, freeze-drying is a less frequently exploited technique. Freeze-drying offers a number of advantages due to the minimal thermal stress applied during the preparation. Direct comparisons of solid dispersions prepared by spray-drying and freeze-drying method are limited[16].

The objective of this article is to compare the performance of spray-dried and freeze-dried hydrocortisone/PVP solid dispersions with regard to enhancing dissolution rate and stabilizing the amorphous drug form. The spray-dried dispersions were prepared using two ethanol/water systems (96% v/v ethanol and 20% v/v ethanol) and the freeze-dried dispersions using an ethanol/water system containing 20% v/v ethanol. Organic solvents are commonly utilized to prepare solid dispersions containing poorly water-soluble drugs by a solvent removal techniques such as spray-drying and freeze-drying. A limitation to the use of a single solvent can be the different solubility profiles of drug and carrier. Pandya et al. overcame this issue through the use of co-solvents to dissolve drug and carrier to produce amorphous solid dispersions[17]. Aqueous–organic co-solvent systems have also been used to prepare solid dispersions by freeze-drying[16]. An advantage of the use of aqueous–organic co-solvent systems is their reduced environmental impact. In this study, the performance of spray-dried hydrocortisone/PVP solid dispersions prepared from solutions with high (96% v/v) and low ethanol (20% v/v) content is also compared.

Materials and methods

Materials

Hydrocortisone base was obtained from TNN development Ltd., Dalian, China. PVP, brand name Povidone (Kollidon 17 PF) with an average molecular weight of 9000, was a generous gift from BASF ChemTrade GmbH, Germany. All other chemicals and solvents were of reagent grade and were used without any further purification.

Preparation of solid dispersions

Solid dispersions containing 75%:25%, 60%:40%, 50%:50%, and 40%:60% hydrocortisone:PVP weight ratios were spray-dried and freeze-dried. Hydrocortisone and PVP were dissolved in a sufficient volume of the ethanolic aqueous co-solvent system, either 96% v/v ethanol or 20% v/v ethanol. Solutions were filtered through a 0.45-μm filter prior to drying to remove any dust or particulate matter.

Spray-drying was carried out using a laboratory spray-dryer (Buchi Mini Spray-Dryer B-290, Switzerland). An inlet temperature of 69°C was employed for the 96% v/v ethanol solutions and 100°C for 20% v/v ethanol solutions. The feed rate was 6 mL/min and aspirator setting was 100%. The drying atmosphere was compressed air at a flow rate of 600 L/h.

Freeze-drying was performed using a bench-top freeze-dryer (VirTis BTK4; New York, NY). Hydrocortisone/PVP solutions were frozen at –80°C prior to freeze-drying. Freeze-drying was carried out using a condensor temperature of –76°C and pressure of 0.220 mbar until a dry cake was obtained.

Physical mixtures containing 75:25, 60:40, 50:50, and 40:60 hydrocortisone:PVP were prepared by mixing both components using a mortar and pestle.

Characterization of solid dispersions

Scanning electron microscopy

SEM images of solid dispersions and physical mixtures were acquired using a scanning electron microscopy system (SEM) (Jeol JSM 5510, UK) operated at accelerating voltage 5 kV. Samples were coated with gold in order to increase conductivity of the electron beam.

Powder X-ray diffraction

Powder X-ray diffraction (pXRD) patterns were recorded using a X-ray diffractometer (Panalytical X-Pert MPD, Philips, The Netherlands). The samples were irradiated with monochromatized Cu–Kα radiation (1.542 Å) and analyzed between 5° and 40° (2θ). The voltage and current used were 40 kV and 35 mA. The scan rate was 0.07° (2θ)/sec.

Modulated differential scanning calorimetry

Modulated differential scanning calorimetry (MDSC) studies were performed using a modulated differential scanning calorimeter (Q1000 instrument; TA

Instruments, Crawley, UK) equipped with a rapid cooling system. An indium standard was used to calibrate the heat flow and a sapphire standard was used for heat capacity calibration. Samples were analyzed in Tzero aluminium pans closed with Tzero aluminium lids (TA Instruments) and heated at a constant rate of 3°C/min with a modulation of 1°C/min over a temperature range of 0–300°C. An inert atmosphere was maintained by purging the nitrogen gas at flow rate of 50 mL/min.

Infrared spectroscopy

Infrared (IR) spectroscopy was performed using an infrared spectrophotometer (Spectrum One; Perkin Elmer, Cambridge, UK). Discs of powders for analysis mixed with KBr were prepared on KBr-press (Specac; Specac Ltd., Slough, UK). The spectra were scanned over wave number 4000–450 cm^{-1} and the final spectrum presented was the mean of 32 scans.

Measurement of moisture content

Moisture content was determined by the Karl-Fisher (KF) titration method using a KF-21 Moisture meter (Mitsubishi Chemical Co., Kanagawa, Japan).

BET surface area determination

Each sample for analysis was degassed over night at room temperature prior to nitrogen adsorption measurement. The BET surface areas were calculated from a 20-point nitrogen adsorption isotherm plot. Nitrogen BET isotherms were generated at 77 K on a Micromeritics Gemini VI surface area and pore size analyzer.

Dissolution studies

Dissolution testing was carried out under sink conditions at 37.0 ± 0.5°C using USP apparatus with paddle rotating at 100 rpm. In all cases, a powder sample weight equivalent to 3 mg hydrocortisone was added to the dissolution bath followed by 150 mL preheated deionized water. Dissolution studies were performed in triplicate. One milliliter of filtered sample was withdrawn for every 5 min up to 30 min and replenished with fresh medium. Hydrocortisone content was determined at λ_{max} of 254 nm using a UV/vis spectrometer (Unicam, Leeds, UK).

Stability studies

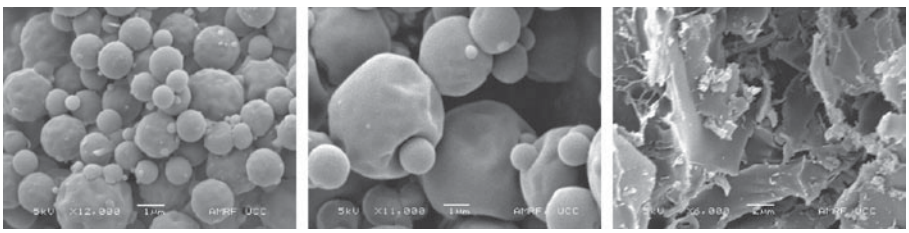
The stability of the solid dispersions was evaluated by following the ICH (Q1A) guidelines for accelerated stability of pharmaceutical preparations. Samples were stored at 40°C and 75% relative humidity (RH) for 1 month. Solid dispersions were evaluated by MDSC, pXRD, and KF titration after storage. Dissolution studies were repeated after storage. Due to the sticky nature of the samples after storage, samples were dried at 30°C for 12 h in hot air oven prior to performing dissolution studies.

Results and discussion

Characterization of solid dispersion amorphous behavior

SEM images of representative hydrocortisone/PVP solid dispersion particles are shown in Figure 1. All hydrocortisone/PVP spray-dried dispersions were spherical, homogeneous particles with no evidence of crystalline drug. The drug appears to be dispersed within the polymer carrier. SEM images of freeze-dried solid dispersions show particles of irregular, flake-like appearance, which is typical for freeze-dried materials[18]. It was not possible to identify discrete drug or polymer particles in these SEM images, indicating a single phase solid dispersion at this level of scrutiny. Representative pXRD patterns of hydrocortisone/PVP solid dispersions are shown in Figure 2A. The powder X-ray patterns of PVP and all hydrocortisone/PVP solid dispersions were devoid of distinctive crystalline peaks, indicative of an amorphous material.

MDSC was employed to compare the non-isothermal behavior of the hydrocortisone/PVP solid dispersions. The PVP starting material MDSC thermogram displayed typical characteristics of an amorphous solid; it was devoid of a melting endotherm and displayed glass transition (T_g) around 142°C. Previously, T_g values ranging from 126°C to 134°C were reported for the grade of PVP utilized, PVP K-17[19]. No hydrocortisone exothermic recrystallization peak or endothermic melting peak was detected for any of the hydrocortisone/PVP solid dispersions, indicating their amorphous nature and excellent stability during the heating cycle of MDSC analysis. Recrystallization exotherms were previously reported



(a) (b) (c)

Figure 1. Representative scanning electron microscope (SEM) images hydrocortisone/polyvinyl pyrrolidone (PVP) spray-dried and freeze-dried solid dispersions; (A) 25% hydrocortisone/75% PVP spray-dried (20% v/v ethanol), (B) 25% hydrocortisone/75% PVP spray-dried (96% v/v ethanol), and (C) 25% hydrocortisone/75% PVP freeze-dried (20% v/v ethanol).

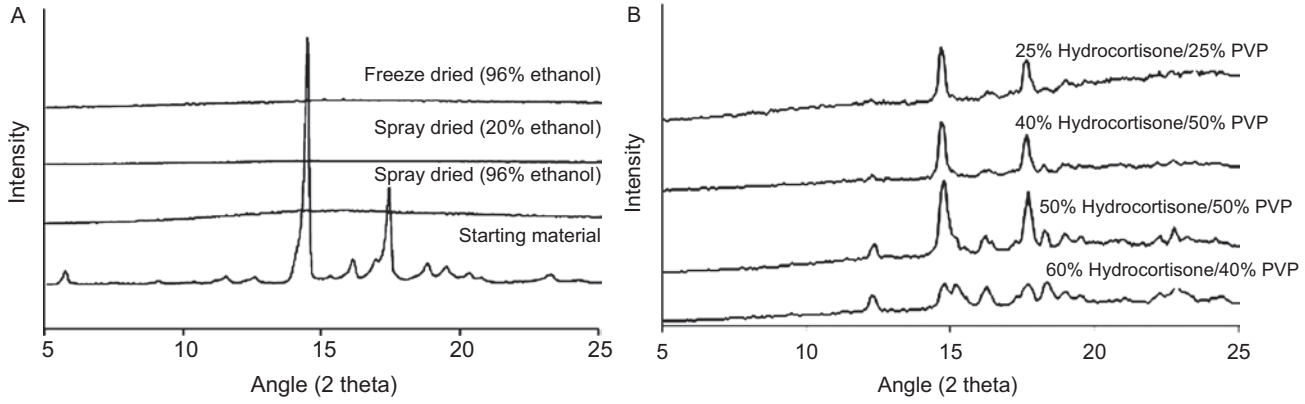


Figure 2. Powder X-ray diffraction patterns; (A) hydrocortisone starting material and processed solid dispersions containing 60% hydrocortisone/40% polyvinyl pyrrolidone (PVP) before storage and (B) hydrocortisone/PVP solid dispersions spray-dried from 20% ethanol solutions after 1 month storage at 40°C and 75% relative humidity.

for hydrocortisone spray-dried alone and for hydrocortisone/PVP solid dispersions with lower levels of PVP[10]. For the solid dispersions prepared in this study, the level of PVP utilized (minimum 40% w/w) appears to inhibit the recrystallization of amorphous hydrocortisone during the MDSC heating cycle. The ΔC_p was in the region of 0.33 J/g °C for all solid dispersions prepared.

T_g values for individual solid dispersions are shown in Figure 3. The effect of polymer content on the glass transition behavior of the solid dispersions was predicted using the classical thermodynamic theories of Couchman and Karasz[20,21]. Using the simplified Couchman–Karasz equation (Equation 1), the theoretical glass transition of the solid dispersions can be calculated[22,23].

$$T_g = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2} \quad (1)$$

where T_{g1} and T_{g2} are the glass transition temperatures of drug and polymer, respectively, w_1 and w_2 are weight fractions of drug and polymer, respectively, and K is a thermodynamic constant, which is obtained by dividing the heat capacity change at T_g of polymer (ΔC_{p2}) by heat capacity change at T_g of drug (ΔC_{p1}). Figure 3 compares the T_g of the solid dispersions studied predicted by the Couchman–Karasz equation with the T_g values determined experimentally by MDSC analysis. The experimental T_g values for all solid dispersions showed a positive deviation from the predicted T_g values. Interestingly, the degree of positive deviation from predicted behavior varied between spray-dried samples and freeze-dried samples. Spray-dried dispersions from solutions containing 20% v/v ethanol showed higher positive deviation compared with corresponding samples spray-dried from 96% v/v ethanol. Freeze-dried solid dispersions with 50% w/w and 60% w/w PVP also showed a positive deviation from predicted behavior but to a lower extent to the spray-dried systems. The behavior predicted by the Couchman–Karasz equation can be observed when the intermolecular attraction forces between the individual phases are stronger than those between two phases. If the

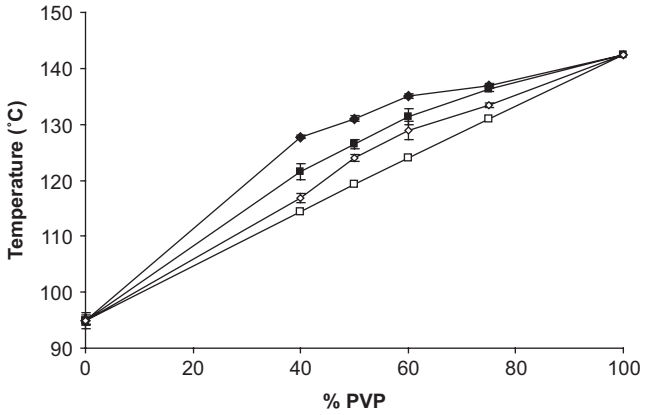


Figure 3. Glass transition temperatures (Tg) of hydrocortisone/polyvinyl pyrrolidone (PVP) solid dispersions with varying ratios of PVP, open squares (□) indicate predicted values calculated using the Couchman–Karasz equation, open diamonds (◊) indicate freeze-dried dispersions from 20% v/v ethanol solutions, black squares (■) indicate spray-dried dispersions from 96% v/v ethanol solutions, and black diamonds (◆) indicate spray-dried dispersions from 20% v/v ethanol solutions; $n=3$ (Y error bars indicate ±standard deviation).

intermolecular attraction between the drug and polymer is stronger than that between individual components, then this leads to decreased chain mobility of polymer molecules thus increased T_g values. PVP has been extensively studied for its ability to interact with drugs in solid dispersions. It was shown to have both strong interactions with certain drug molecules leading to positive deviation from ideal T_g behavior[24], and weaker interactions with other molecules leading to negative deviation from ideal behavior[25]. The apparent strong interactions between hydrocortisone and PVP in the solid dispersions indicated by this positive deviation were further investigated by IR spectroscopy.

Fourier transform infrared spectroscopy analysis

Fourier transform infrared (FTIR) spectra of the hydrocortisone starting material showed characteristic bands that represent hydroxyl, methyl, and carbonyl groups (3431, 1643, and 1713 cm^{-1}). The spectra of the PVP

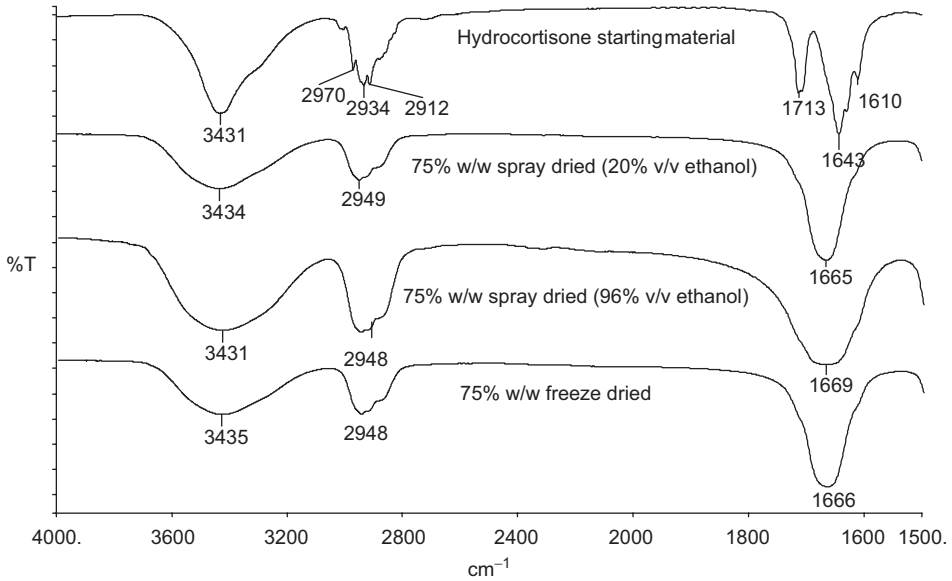


Figure 4. Representative Fourier transform infrared (FTIR) spectra of hydrocortisone and hydrocortisone/polyvinyl pyrrolidone (PVP) solid dispersions, showing the distinctive peaks wave numbers.

starting material showed, among others, important bands at 2955 cm^{-1} (C–H stretch) and 1665 cm^{-1} (C=O). A very broad band was visible at 3448 cm^{-1}, representative of hydrocortisone hydroxyl groups and also due to the presence of water[9]. The C=O group in pyrrolidone moiety of PVP has the ability to form hydrogen-bonding interactions. Interactions between drug and polymer can be observed by a shift in peak wavelengths and a broadening of peaks compared with the pure drug and polymer[26]. This broadening of the peaks can also indicate the conversion of drug to an amorphous form[27]. Poorer resolution of peaks, particularly in the 2940 cm^{-1} (C–H stretch) and 1660 cm^{-1} (C=O stretch) region of the spectra, was evident for all solid dispersions Figure 4. This FTIR behaviour supports the conversion of hydrocortisone to an amorphous form also detected by pXRD and MDSC. As a result of broad peaks in the region of 1660 cm^{-1} (C=O stretch), due to the contribution of PVP and hydrocortisone C=O groups, and in the region of 3440 cm^{-1} (O–H stretch), due to the contribution of hydrocortisone O–H groups and water, it is difficult to detect significant peak shifts in these regions. It was not possible to determine whether the positive deviation from ideal T_g behavior displayed by the solid dispersions in Figure 3 could be attributed to hydrocortisone and PVP intermolecular interactions from the FTIR results obtained.

Influence of moisture on the glass transition temperature of solid dispersions

Although drug/polymer interactions have an influence on the T_g of solid dispersions, the influence of their respective moisture content should also be considered. The moisture content of solid dispersions influences the T_g by acting as a plasticizer[28]. The amount of moisture a powder sample absorbs is also influenced by its surface area; increased surface area results in sample being prone to take up more moisture by adsorption[28]. Hydrocortisone starting material was a crystalline powder with low hydrophilicity and as expected its measured moisture content was low, 0.15% w/w. Due to its amorphous polar nature, the moisture content measured for PVP starting material was higher, 5.68% w/w. The measured moisture content and surface area of all solid dispersions are shown in Table 1.

Table 1. Moisture content determined by Karl-Fisher titration and surface area determined by BET analysis of starting materials and processed hydrocortisone (HC)/polyvinyl pyrrolidone (PVP) solid dispersion samples (average of three different measurements are given, standard deviation given in brackets).

Sample	Surface area (m^2/g)	Moisture content (%)
Hydrocortisone	4.5 (±0.1)	0.2 (±0.1)
PVP	0.3 (±0.0)	5.7 (±0.2)
Spray-dried (20% v/v ethanol)		
60% HC/40% PVP	4.1 (±0.1)	3.3 (±0.0)
50% HC/50% PVP	3.1 (±0.1)	3.6 (±0.2)
40% HC/60% PVP	3.3 (±0.0)	4.6 (±0.3)
25% HC/75% PVP	2.7 (±0.1)	6.0 (±0.2)
Spray-dried (96% v/v ethanol)		
60% HC/40% PVP	3.9 (±0.0)	3.5 (±0.1)
50% HC/50% PVP	2.9 (±0.0)	4.4 (±0.2)
40% HC/60% PVP	2.6 (±0.0)	7.1 (±0.1)
25% HC/75% PVP	2.1 (±0.0)	9.6 (±0.4)
Freeze-dried (20% v/v ethanol)		
60% HC/40% PVP	17.0 (±0.4)	3.1 (±0.2)
50% HC/50% PVP	10.9 (±0.2)	4.5 (±0.3)
40% HC/60% PVP	10.3 (±0.1)	4.3 (±0.3)
25% HC/75% PVP	6.4 (±0.1)	4.6 (±0.2)

Solid dispersions spray-dried from 96% v/v ethanol solutions contained higher moisture content than the corresponding samples spray-dried from 20% v/v ethanol solutions, despite the surface area of solid dispersions spray-dried from 96% v/v ethanol solutions

being lower than the corresponding spray-dried dispersions from 20% v/v ethanol solutions. Therefore, it appears the reduction in T_g values for spray-dried systems from 96% ethanol solutions compared with the corresponding dispersions spray-dried from 20% ethanol (Figure 3) could be attributed to their higher moisture content. Freeze-dried solid dispersions have considerably higher surface areas compared with corresponding spray-dried dispersions, yet freeze-dried solid dispersions with 60% and 75% w/w PVP had significantly lower moisture content than the corresponding spray-dried systems. Freeze-dried solid dispersions with 40% and 50% w/w PVP had similar moisture content to the corresponding spray-dried systems. The moisture content of freeze-dried solid dispersions did not explain their differences in T_g compared with the spray-dried systems. Other factors, in addition to moisture content, appear to be responsible for these differences.

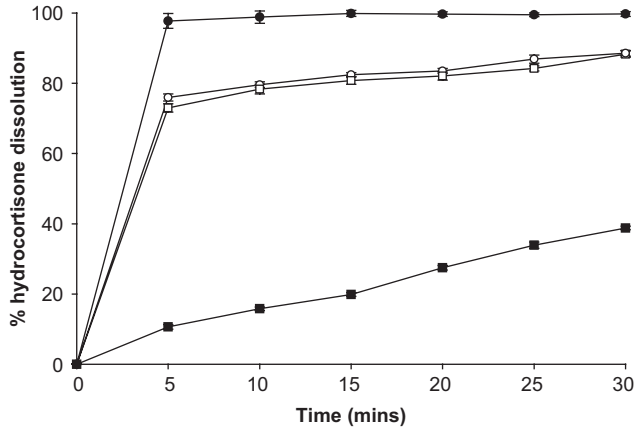


Figure 5. Dissolution profiles of hydrocortisone and hydrocortisone/polyvinyl pyrrolidone (PVP) physical mixtures and solid dispersions with 75% PVP, black squares (■) indicate hydrocortisone starting material, black circles (•) indicate spray-dried dispersions from 20% v/v ethanol solutions, open squares (□) indicate spray-dried dispersions from 96% v/v ethanol solutions, and open circles (○) indicate freeze-dried dispersions from 20% v/v ethanol solutions; $n=3$ (Y error bars indicate ±standard deviation).

All spray-dried solid dispersions showed an increase in moisture content with increase in PVP content (Table 1). The same trend was not observed for the freeze-dried dispersions. The increased moisture content of spray-dried dispersions at the higher levels of PVP compared with the freeze-dried dispersions may be due to an increased presence of PVP at the particle surface. The lower moisture content of freeze-dried dispersions may result in a more uniform distribution of drug and polymer between the surface and bulk of these particles as a result of the method of preparation. Compared with the spray-drying process, molecular migration would be restricted in the freeze-drying process. It has been previously reported regarding the ability of PVP to significantly occupy the surface of the spray-dried PVP/lactose particles[29]. According to this report, PVP composed up to 50% w/w of the surface composition of the composite particles even when the average particle composition is 25% w/w PVP. Electron spectroscopy for chemical analysis (ESCA) was used to investigate the enrichment of PVP on the surface of spray-dried particles. An increased presence of PVP at the particle surface after spray-drying would result in a concentration gradient of PVP within individual particles; higher PVP concentration on the exterior compared with the interior. This proposed behavior could not be detected by the MDSC analysis technique employed in this study. Distinctive

Table 2. Dissolution rates of hydrocortisone starting material and processed hydrocortisone (HC)/polyvinyl pyrrolidone (PVP) solid dispersions in the initial 5 min and % drug dissolution after 30 min before and after the stability at 40°C and 75% relative humidity for 1 month (average of three different measurements are displayed, standard deviation given in brackets).

	Release rate for first 5 min (μg/mL/min)		Hydrocortisone dissolution in 30 min %	
Sample	Before storage	after storage	Before storage	After storage
Hydrocortisone	0.6 (±0.03)	N/D	39 (±0.5)	N/D
Spray-dried (20% v/v ethanol)				
60% HC/40% PVP	3.0 (±0.07)	2.1 (±0.04)	73 (±4.4)	60 (±1.2)
50% HC/50% PVP	3.1 (±0.01)	1.9 (±0.04)	71 (±0.8)	61 (±0.9)
40% HC/60% PVP	3.2 (±0.04)	2.2 (±0.04)	75 (±1.3)	76 (±1.6)
25% HC/75% PVP	4.1 (±0.05)	3.0 (±0.03)	88 (±0.8)	88 (±0.7)
Spray-dried (96% v/v ethanol)				
60% HC/40% PVP	2.7 (±0.06)	2.1 (±0.04)	76 (±3.6)	61 (±1.2)
50% HC/50% PVP	3.0 (±0.15)	3.0 (±0.15)	76 (±6.6)	61(±1.8)
40% HC/60% PVP	3.1 (±0.14)	2.1 (±0.01)	76 (±1.9)	75 (±0.5)
25% HC/75% PVP	3.9 (±0.06)	3.0 (±0.02)	88 (±0.9)	87 (±0.4)
Freeze-dried (20% v/v ethanol)				
60% HC/40% PVP	3.9 (±0.08)	2.6 (±0.14)	87 (±1.1)	73 (±1.8)
50% HC/50% PVP	4.2 (±0.04)	4.2 (±0.04)	91 (±0.8)	73 (±1.2)
40% HC/60% PVP	4.6 (±0.04)	3.4 (±0.08)	100 (±0.2) 25 min*	98 (±1.2)
25% HC/75% PVP	5.2 (±0.11)	3.9 (±0.10)	100 (±0.6) 10 min*	100 (±0.9) 10 min*

N/D indicates not detected.
*Indicates the time 100% dissolution was observed.

glass transition events for the exterior and interior of the particles were not detected. The inability of MDSC to detect differences between the composition of the interior and exterior of the particles may be due to the limitations of the technique and the gradient of PVP concentrations in the particles. The glass transition events observed by MDSC occurred across a temperature range of 5–10°C. The MDSC technique may be unable to resolve individual T_g events within this temperature range. Although the differences in moisture content observed between spray-dried and freeze-dried systems may suggest enrichment of PVP on the surface of spray-dried solid dispersions, this hypothesis could not be proven in this study and warrants further investigation.

Dissolution performance of solid dispersions

All solid dispersions showed an increase in hydrocortisone dissolution rate compared with the starting material (Figure 5 and Table 2). All solid dispersions showed rapid dissolution in the first 5 min, after which a reduction in dissolution rate was observed. The reduction in dissolution rate was attributed to recrystallization tendency of amorphous drug. When amorphous drugs engage in the dissolution, rapid recrystallization of the amorphous form can occur due to the plasticization effect of water[30]. Drug dissolution in the first 5 min was faster for freeze-dried dispersions compared with the spray-dried samples (Figure 5 and Table 2). The faster dissolution rate of freeze-dried dispersions may be partially attributed to the increased surface area observed for these dispersions. Spray-dried systems, irrespective of the solvent system employed, showed similar dissolution rates for corresponding PVP levels. Spray-dried systems with 75% PVP gave the highest increase in dissolution, whereas at lower levels of PVP (40% v/v, 50% v/v, and 60% v/v PVP) no considerable differences in their dissolution rates were observed. Unlike the spray-dried samples, freeze-dried solid dispersions showed a gradual increase in dissolution rate with increase in PVP level. This was expected as increasing the hydrophilic polymer level enhances the wetting capacity of drug in solid dispersions. The differences in dissolution performance of corresponding spray-dried and freeze-dried dispersions may be partially due to the orientation of hydrocortisone and PVP within these particles. This difference may be a result of the processing method employed.

Hydrocortisone recrystallization behavior in solid dispersions

Stability studies were conducted to assess the recrystallization tendency of the amorphous solid dispersions. Solid dispersions were stored at elevated humidity (75% RH) and temperature (40°C) for 1 month and then characterized by MDSC and pXRD to investigate if any solid state conversions occurred during the storage period. Dissolution studies were also carried out after storage to investigate the impact of phase transitions on hydrocortisone dissolution performance. After storage, powder X-ray showed the recrystallization of drug in all solid dispersions. Representative images of pXRD patterns of solid dispersions after storage are shown in Figure 2B.

MDSC analysis of solid dispersions after storage revealed a single clear glass transition temperature for all samples indicating the amorphous content of these samples and an endothermic peak representing the melting of crystalline material in these dispersions. As the PXRD profiles showed the recrystallization of drug, the observed T_g could be attributed to the presence of amorphous PVP alone or remaining amorphous drug/PVP solid solution. There was a general increase in T_g for the solid dispersions after storage, which reflects a reduction in hydrocortisone present in the drug/PVP solid solution phase (Figure 6). Hydrocortisone reduces the T_g of PVP when in a single phase solid solution state.

Changes in the dissolution performance of solid dispersions before and after storage are shown in Table 2. It can be observed that the respective dissolution rates in the first 5 min were decreased considerably for all dispersions after storage. The reduction was similar for corresponding spray-dried dispersions from 20% v/v and 96% v/v ethanol solutions. Dissolution rate reduction can be explained by the increased crystalline content of the drug detected by pXRD and MDSC analysis. However, initial dissolution rates were still higher than the starting material as a result of the remaining amorphous content due to partial recrystallization of drug. Freeze-dried dispersions showed higher dissolution rates compared with corresponding spray-dried dispersions after storage. These higher dissolution rates for freeze-dried samples may be partially attributed to their higher surface areas.

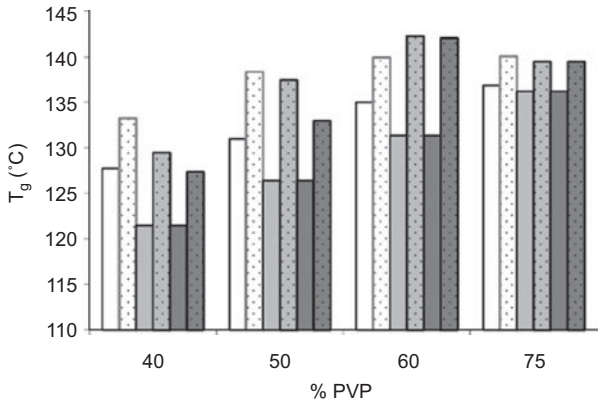


Figure 6. Glass transition temperatures (*T*g) of hydrocortisone/polyvinyl pyrrolidone (PVP) solid dispersions before (undotted bars) and after storage at 40°C and 75% relative humidity for 1 month (dotted bars). ☐ indicates spray-dried dispersions from 20% v/v ethanol, ▒ indicates spray-dried dispersions from 96% v/v ethanol, and ▓ indicates freeze-dried dispersions from 20% v/v ethanol.

Greatest dissolution rates were observed for freeze-dried dispersions with highest PVP content both before and after storage.

Conclusion

Results show that the solid dispersion preparation method had a significant effect on the dissolution performance and recrystallization tendency of amorphous hydrocortisone. Preparation methods investigated influenced the T_g, surface area, and molecular interactions between drug and polymer in resultant dispersions. These properties in turn influenced dissolution rates and recrystallization tendency. Of the two processes studied, freeze-drying was more effective in producing solid dispersions with higher dissolution rates than spray-drying. Increased dissolution rates of freeze-dried dispersions were attributed to increased surface area. Recrystallization tendency was also influenced by the method of preparation. The polymorphic solid state formed appears to be dependent on the PVP level and method of processing. Solid dispersions for 20% ethanol solutions with lower PVP content recrystallized to a range of polymorphic forms. Freeze-drying can be advantageous in terms of dissolution enhancement but the associated production costs should be considered before applying this technology. A reduction in solvent usage, through the use of aqueous solvent mixtures in the preparation of amorphous spray-dried dispersions, also offers a number of economical and environmental advantages.

Declaration of interest

The authors report no declarations of interest.

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