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Perphenazine solid dispersions for orally fast-disintegrating tablets: physical stability and formulation

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Abstract

Aim: The aim of this study was to prepare an orally fast-disintegrating tablet (FDT) by direct compression, containing a poorly soluble drug (perphenazine, PPZ) formulated as a stable solid dispersion. *Methods*: The stability studies of the fast dissolving 5/1, 1/5, 1/20 (w/w), PPZ/polyvinylpyrrolidone K30 (PVP) or polyethylene glycol 8000 (PEG)) solid dispersions, and amorphous PPZ were conducted with differential scanning calorimetry, X-ray powder diffraction, Fourier-transform infrared spectroscopy, small-angle X-ray scattering, and dissolution rate studies. *Results and discussion*: It was found that 1/5 PPZ/PEG was the most stable dispersion under elevated temperature and/or humidity. FDTs containing 60% of mannitol, 15% of calcium silicate, 15% of crospovidone, and 10% of 1/5 PPZ/PEG solid dispersion exhibited fast disintegration times (37 ± 3), sufficient hardness (1.28 ± 0.06 MPa), and fast onset of drug dissolution (34% of PPZ dissolved in 4 minutes), and these properties were found to be retained with storage. Thus, by optimizing the drug/excipient ratio of the solid dispersion and tablet composition, it was possible to produce FDTs that possessed fast disintegration and satisfactory drug dissolution in addition to adequate tensile strength, so that they can be handled and packed normally.

Key words: *Amorphous; dissolution; fast-disintegrating tablets; poorly soluble drug; solid dispersion; stability*

Introduction

There is an increasing interest in developing orally fast-disintegrating tablets (FDTs) because they can permit drug administration in the absence of potable liquids and a rapid onset of drug action. They are also beneficial for individuals who have difficulties in swallowing, a common problem for children and the elderly[1]. Furthermore, the bioavailability of a drug can be increased when the fast disintegration of the tablet is combined with rapidly dissolving drug that is directly absorbed into the systemic circulation[2]. FDTs should disintegrate in less than 3 minutes in the mouth without the need of excess water according to the European Pharmacopoeia[3]. However, there is no specification concerning the hardness of this kind of tablets. In studies with FDTs, it is considered that the disintegration in the oral cavity should occur in less than 1 minute[4] or even less than 30 seconds[5]. To attain such a fast disintegration, the dosage forms are very porous and/or compressed with very low compression forces. Thus, despite the growing popularity of orally FDTs, many formulations still face problems of low mechanical strength, high friability, and they often require special packaging[6]. FDTs can be prepared by a variety of technologies[1], but direct compression is simple and economical. However, it requires optimization of the type and amount of excipients and the compression force to produce tablets, which have both sufficient hardness and rapid disintegration.

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Achieving fast drug dissolution, required for intraoral drug delivery by FDTs, might represent an obstacle for lipophilic drugs[7], such as perphenazine (PPZ), which is a first-generation antipsychotic with low aqueous solubility (i.e., lower than 150 μg/mL at pH 6.8) and a poor dissolution rate[8]. In addition, due to the small volume of saliva in the oral cavity, the therapeutic dose of an intraoral drug must be relatively small and in most cases dissolution enhancers must be incorporated into the preparation[9]. One way to overcome these problems is to use a solid dispersion approach, by which the solubility and dissolution rate of PPZ in the conditions present in the oral cavity (i.e., low amount of saliva and pH 6.2–7.4) was markedly improved in our recent study[8]. Freeze-drying of solutions of PPZ with different amounts of a polymer [polyvinylpyrrolidone (PVP) K30 or polyethylene glycol 8000 (PEG)] in 0.1 N HCl led to an improved PPZ solubility and an extremely fast dissolution rate in a small liquid volume (in 3 mL of a pH 6.8 buffer) compared to crystalline or micronized PPZ. The formation of solid solutions of amorphous HCl salt of PPZ in amorphous PVP or in the amorphized part of PEG were the principal factors enhancing PPZ dissolution and they may also be factors that improve the physical stability of the solid dispersions.

The selection of the solid dispersion to be used as the final candidate for formulation studies of an FDT cannot be solely based on the improvement in dissolution, but the stability of the solid dispersions also needs to be examined because the unstable nature of amorphous solid dispersions might limit their applicability[10]. When exposed to heat and humidity, amorphous materials may crystallize due to the increased molecular mobility and decreased glass transition temperature (T_g)[11]. It may be possible to achieve improved stability by elevating the T_g of the system with sufficient amounts of carrier polymers[10,12–15] or by specific drug–polymer interactions, even with low polymer concentrations[16–18]. However, even a miscible system can phase separate and become unstable if the specific interactions between the components are adversely affected by a third component, for example, water[20]. In addition, there may be difficulties in the processing of solid dispersions into suitable dosage forms, for example, tablets. This is due to their poor flow characteristics, compression difficulties, and the possibility that crystallization/polymorphic transformation may occur during compression or storage[21–24].

Thus, in this present study, physical stability of the solid dispersions with different PPZ/polymer (PVP or PEG) ratios is evaluated by exposing the solid dispersions to high temperature and humidity, after which possible changes in their physical and dissolution properties are determined. Subsequently, an orally fast (i.e., in 30 seconds) disintegrating, direct-compression tablet, having a sufficient tensile strength to be handled and packed normally, is prepared for the solid dispersion with the best performance. Tablet properties and dissolution profiles of PPZ from four different tablet formulations are determined before and after storage at room temperature/60% relative humidity (RH).

Materials and methods

Materials

PPZ United States Pharmacopoeia (USP), PVP K30 (purum), and PEG 8000 (Sigma Ultra) were purchased from Sigma Aldrich (Sigma-Aldrich Chemie, Steinheim, Germany). Mannitol (Pearlitol 400 DC, Roquette Frères, Lestrem, France) was used as a tablet excipient. Crospovidone (CP) (Polyplasdone XL-10, ISP Technologies, Inc., Calvert City, KY, USA) and calcium silicate (CS) (Rxcipients FM 1000, Huber Engineered Materials, Havre de Grace, MD) were used as disintegrants. All other materials used were of analytical grade.

Preparation of the solid dispersions

PPZ/PVP and PPZ/PEG solid dispersions with drug–polymer-weight ratios of 5/1, 1/5, and 1/20 and amorphous PPZ were prepared by freeze-drying from 0.1 N HCl solutions. The preparation procedure is described in detail elsewhere[8].

Tablet formulations of the solid dispersions

Tablet preparation

Four different formulations, containing either 1/5 PPZ/PEG or 1/5 PPZ/PVP solid dispersion, mannitol, and disintegrants (CS and/or CP) were prepared (Table 1). Each formulation contained 10% (w/w) of the solid dispersion, that is, each tablet had 4 mg of PPZ. The powder mixtures were prepared in a mortar and they were compressed into tablets with a compaction simulator (PCS-1, PuuMan Ltd., Kuopio, Finland). Compression profiles were double-sided sine waves. The tablets were cylindrical, with a diameter of 10 mm and a mass of 200 mg. Compaction forces are presented in Table 1.

Tablet properties

Tablet volumetric dimensions and masses were measured 24 hours after compression with a micrometer screw (Digitrix, NSK; Osaka, Japan) and an analytical

Table 1. Formulation compositions, compression forces, and resulting porosity (n = 50) of the FDTs containing 10% (w/w) 1/5 PPZ/PEG or 1/5 PPZ/PVP solid dispersion. In addition, mass uniformity [$n = 50 \pm$ SD (before) and $n = 20 \pm$ SD (after)], tensile strength ($n = 6 \pm$ SD), disintegration time (n = 6 ± SD) of the tablets before and after storage at 21°C/60% RH are shown.

	Formulation			
Property	1	2	3	4
Solid dispersion	1/5 PPZ/PEG	1/5 PPZ/PEG	1/5 PPZ/PVP	1/5 PPZ/PVP
Mannitol (%, w/w)	60	60	60	60
Calcium silicate (%, w/w)	30	15	30	15
Crospovidone (%, w/w)	—	15	—	15
Compaction force (kN)	5	10	5	10
Tablet porosity (%)	29	19	32	22
Fresh tablets				
Mean weight (mg)	199.6 ± 0.5	200.5 ± 0.6	198.7 ± 0.5	198.4 ± 1.0
Tensile strength (MPa)	0.40 ± 0.04	1.28 ± 0.06	0.62 ± 0.07	1.58 ± 0.06
Disintegration time (seconds)	104 ± 17	37 ± 3	>120	58 ± 2
After storage				
Mean weight (mg)	199.0 ± 0.4	200.4 ± 0.5	200.9 ± 0.5	204.8 ± 1.1
Tensile strength (MPa)	0.70 ± 0.11	1.11 ± 0.04	1.73 ± 0.14	1.29 ± 0.07
Disintegration time (seconds)	>120	36 ± 4	>120	68 ± 4

balance (A200S, Sartorius, Germany). The tablet porosities were calculated as follows:

$$\varepsilon = 1 - m/(\rho_t V) \quad (1)$$

where ρ_t is the true density and m and V are the weight and the volume of the tablet, respectively. The densities of the tablet components were determined in five parallel measurements with a multi pycnometer (Quanta Chrome, NY, USA) using helium as the measuring gas. Crushing strengths of tablets (n = 6) were measured with a universal tester (CT-5 tester, Engineering Systems, Nottingham, England), operating at a constant crosshead speed of 1 mm/min. The tensile strengths of the tablets were calculated according to Fell and Newton[25]. Disintegration times for the tablets were determined on a petri dish without agitation by immersing the tablet in 20 mL of distilled water and recording the time passing until the tablet had visually disintegrated.

Stability studies

Gravimetric hygroscopicity

The moisture sorption of the solid dispersions was evaluated by using an automated gravimetric analyzator (Hygroscopicity Measurement Apparatus, HMA-8, PuuMan Ltd., Kuopio, Finland). After storage in a silica dessicator, the samples were placed in aluminium pans into the HMA chamber for one week, during which the relative mass change was monitored by a microbalance (Sartorius MC 5, Sartorius AG, Goettingen, Germany). The conditions used were 25°C/33% RH and 25°C/53% RH. Temperature in HMA was kept constant by Peltier elements and humidity was produced with saturated salt solutions (i.e., NaI for 33% RH and NaBr for 53% RH).

Storage at accelerated conditions

Fresh samples of solid dispersions were exposed to the following conditions: 40°C/75% RH and 40°C/~5% RH (silica) for 4 weeks after which the Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray powder diffraction (XRPD) measurements and dissolution studies were conducted for the solid dispersions and the results were compared with the results of the freshly prepared samples[8]. A total of 20 tablets from each formulation were stored at room temperature (21°C)/60% RH for 4 weeks. After that, tablet weights, crushing strengths, and disintegration times were measured, DSC measurements were conducted, and dissolution profiles of PPZ were determined.

Fourier transform infrared spectroscopy. Possible changes in the drug–polymer interactions occurring during storage were studied with a Nicolet Nexus 870 FTIR spectrometer (Thermo Electron Corp, Madison, WI) equipped with an Attenuated Total Reflectance (ATR) accessory (Smart Endurance, Single-reflection ATR diamond composite crystal). For each spectrum, 32 scans were performed at a resolution of 4 cm^{-1}. Three spectra for each sample were measured and their average spectra were calculated.

Differential scanning calorimetry. Thermal behavior and possible changes in the physical properties of the solid dispersions after storage were studied with a

Table 2. DSC cooling/heating programs for freeze-dried PPZ, the solid dispersions with drug–polymer ratio of 5/1, 1/5, and 1/20, the PPZ/PEG physical mixtures and prepared tablet formulations.

Sample	Phase 1 (heating)	Phase 2 (cooling)	Phase 3 (heating)	Temperature modulation
Freeze-dried PPZ, 5/1 PPZ/PVP solid dispersion	From 0°C to 125°C, 10°C/min	—	—	—
5/1 PPZ/PEG physical mixture and solid dispersion	—	at –40°C 10 minutes	From –40°C to 55°C or to 125°C, 10°C/min	—
1/5 and 1/20 PPZ/PEG physical mixture and solid dispersion	—	at –75°C 30 minutes	From –75°C to –10°C or l to 125°C, 10°C/min	—
1/5 and 1/20 PPZ/PVP solid dispersion	From 0°C to 200°C, 1°C/min	—	—	Amplitude ±1°C, frequency 1 minute
Powder mixture and prepared tablet (formulations 1–4)	From 25°C to 150°C, 10°C/min	—	—	—

Mettler Toledo DSC823[e] equipped with an intercooler (Mettler Toledo, Schwerzenbach, Switzerland) and an autosampler (Mettler Toledo, TS080IRO, Sample Robot, Schwerzenbach, Switzerland). DSC measurements were also conducted on the tablet formulations before and after tabletting to study possible changes in the physical properties of the formulations during tabletting, and after the tablets had been stored at 21°C/60% RH for 4 weeks. The cooling/heating programs when measuring the melting points (T_m) and glass transition temperatures (T_g) for the different samples are shown in Table 2. Sine-wave temperature modulation was used in the case of 1/5 and 1/20 PPZ/PVP formulations to separate the overlying water evaporation endotherm from the other thermal events (such as glass transition). The samples were weighed (weight range 2–11 mg) with an analytical balance (Mettler Toledo AT261, Mettler Toledo Ag, Greifensee, Switzerland) and analyzed in sealed 40-μL aluminium sample pans (Mettler Toledo, Schwerzenbach, Switzerland) with a pierced lid. Measurements for each material were performed in triplicate. H_2O, In, Pb, and Zn were used for temperature scale and enthalpy response calibration; however, for the temperature-modulated runs no further calibration was done, thus the obtained ΔCp values were only relative values. Results were analyzed with STAR[e] software (Mettler Toledo Schwerzenbach, Switzerland). Melting points were determined as onset values and the glass transition temperatures as midpoint values. In the case of temperature-modulated measurements, the T_g values were determined from the reversing heat flow signal as midpoint values.

X-ray powder diffraction. XRPD for the samples stored in 40°C/75% RH was performed using a Philips PW 1830 diffractometer (Philips, Amelo, The Netherlands) with Bragg–Brentano geometry (θ–2θ). The radiation used was nickel-filtered CuKα, which was generated using an acceleration voltage of 40 kV and cathode current of 50 mA. Instead, for the samples stored in 40°C/silica, a Philips PW1050 diffractometer (Philips, Amelo, The Netherlands) was used, which made it possible to conduct the measurements at ~5% RH (the measurement chamber contained silica). In that case, the acceleration voltage was 45 kV and the cathode current was 35 mA. The samples were placed into copper sample holders and scanned over 2θ range of 3°–30°, with the step size being 0.04° and counting time 3 seconds per step. Because of conducting the measurements with different equipments, quantitative comparison of the diffraction patterns was not possible.

Small-angle X-ray scattering. Small-angle X-ray Scattering (SAXS) was used for studying the distribution of the drug and the polymers in 1/5 and 1/20 PPZ/PVP and PPZ/PEG solid dispersions after 4 weeks of storage under conditions of room temperature (21°C)/60 % RH. The measurement procedure and equipment are described in detail elsewhere[8].

Dissolution studies

The dissolution behavior of the solid dispersions was evaluated by dissolution tests conducted in a small volume (3 mL) of dissolution medium (pH 6.8 phosphate buffer). The dissolution test procedure has been described in detail elsewhere[8]. The dissolution profiles of PPZ from the prepared tablet formulations were determined using the USP XXVIII rotating basket method, with a rotation speed of 50 rpm (Sotax AT 6 dissolution tester, Sotax AG, Basel, Switzerland). The dissolution medium was 500 mL of phosphate buffer pH 6.8, maintained at 37 ± 0.5°C. Three parallel tablets from each formulation were tested. In these studies, the amount of dissolved PPZ was determined by high-performance liquid chromatography (HPLC) as described elsewhere[8].

Results

Physical properties of the solid dispersions after storage in accelerated conditions

The amount of moisture absorbed by the freeze-dried PPZ and the solid dispersions was followed for one week by exposure to RH of 33% and 53% at 25°C with HMA. With PVP solid dispersions, the amount of absorbed water increased with increasing polymer content, being 3%, 6%, and 6% at 33% RH and 7%, 11%, and 12% at 53% RH for 5/1, 1/5, and 1/20 dispersions, respectively. For PEG solid dispersions an opposite behavior was seen, as the amount of absorbed water was 2%, 1%, and 0.3% at 33% RH and 8%, 3%, and 1% at 53% RH for 5/1, 1/5, and 1/20 dispersions, respectively. The amount of moisture absorbed by freeze-dried PPZ was 0.2% at 33% RH and 10% at 53% RH. At the end of the experiments under both conditions, it was observed that freeze-dried PPZ, 5/1 PPZ/PEG, and 5/1 PPZ/PVP had deliquesced. Thus, it was decided not to attempt the 4-week storage test under conditions of 40°C/75% RH with these materials. Deliquescence was observed also with the 1/5 and 1/20 PPZ/PVP solid dispersions during the storage at 40°C/75% RH. Based on this behavior, one must conclude that deliquescence might be a shared contribution of amorphous PPZ HCl salt form and PVP. Thus, the dissolution and the physical properties could not be studied for these materials after 4 weeks of storage at 40°C/75% RH.

Dissolution rate of perphenazine from the dispersions after storage

The dissolution rates (in 3 mL of pH 6.8 buffer) of freeze-dried PPZ and PPZ/PVP solid dispersions were found to be changed after storage at 40°C/silica gel compared to fresh samples (Table 3). The dissolution of 1/5 and 1/20 PPZ/PVP was considerably poorer that encountered with the fresh solid dispersions. The dissolution rate of PPZ from 1/20 PPZ/PVP had in fact declined back to the level of crystalline PPZ, that is, 2% PPZ dissolved in 4 minutes[8]. In addition, there was a reduction in the dissolution rate of freeze-dried PPZ (51% of PPZ dissolved in 4 minutes) whereas the dissolution was slightly improved for 5/1 PPZ/PVP (59% of PPZ dissolved in 4 minutes).

In the case of PPZ/PEG solid dispersions, the dissolution profiles were also found to be somewhat different than the profiles of fresh samples (Table 3). After storage at 40°C/silica gel, 1/5 PPZ/PEG formulation still had the best dissolution properties (i.e., 64% of PPZ dissolved in 4 minutes). The dissolution of 5/1 PPZ/PEG had remained almost unchanged, but there was a reduction in the dissolution rate of 1/20 PPZ/PEG. After storage at 40°C/75%, the dissolution of PPZ from 1/5 and 1/20 PPZ/PEG had further declined.

Evaluating drug–polymer interactions after storage by FTIR

The stabilizing interactions between the OH-group of PPZ (band at ~3400 cm^{-1}) and the carbonyl group of PVP (band at ~1665 cm^{-1}) and with the OH-group of

Table 3. The amount (%) of PPZ dissolved in the freeze-dried PPZ and from the solid dispersions of PPZ before and after storage at 40°C/silica or 40°C/75% RH ($n = 3 \pm$ SD.).

		% of PPZ dissolved at time t (minutes)					
Dispersion	Storage	$t = 0.25$	$t = 0.5$	$t = 0.75$	$t = 1$	$t = 2$	$t = 4$
freeze-dried PPZ	[a]40°C /silica	72 ± 21	72 ± 3	78 ± 8	77 ± 12	61 ± 12	61 ± 9
		40 ± 6	52 ± 1	57 ± 11	52 ± 5	66 ± 3	51 ± 6
5/1 PPZ/PVP	[a]40°C /silica	22 ± 8	26 ± 5	32 ± 5	39 ± 13	42 ± 5	44 ± 9
		41 ± 1	50 ± 5	56 ± 3	55 ± 4	56 ± 3	59 ± 3
1/5 PPZ/PVP	[a]40°C /silica	35 ± 3	36 ± 5	46 ± 6	60 ± 10	75 ± 11	86 ± 6
		9 ± 2	10 ± 3	10 ± 3	12 ± 2	13 ± 1	15 ± 1
1/20 PPZ/PVP	[a]40°C /silica	10 ± 1	15 ± 2	18 ± 1	20 ± 1	24 ± 3	37 ± 3
		1.7 ± 2.1	1.2 ± 0.3	1.3 ± 0.3	1.1 ± 0.2	1.4 ± 0.1	2.4 ± 0.3
5/1 PPZ/PEG	[a]40°C /silica	26 ± 6	33 ± 4	36 ± 5	–	36 ± 3	38 ± 3
		22 ± 5	25 ± 1	38 ± 5	45 ± 4	43 ± 9	57 ± 3
1/5 PPZ/PEG	[a]40°C /silica	79 ± 8	83 ± 6	82 ± 5	98 ± 6	98 ± 6	96 ± 16
	40°C /75% RH	68 ± 4	64 ± 3	68 ± 2	68 ± 7	67 ± 3	64 ± 3
		47 ± 8	52 ± 5	46 ± 8	44 ± 3	49 ± 5	56 ± 11
1/20 PPZ/PEG	[a]40°C /silica	72 ± 2	76 ± 2	75 ± 1	107 ± 1	73 ± 7	77 ± 8
	40°C /75% RH	48 ± 2	47 ± 7	54 ± 4	56 ± 6	63 ± 4	53 ± 1
		39 ± 1	50 ± 1	53 ± 6	45 ± 1	54 ± 3	53 ± 2

[a]Fresh sample, data reproduced from reference Laitinen et al.[8]

– = not measured.

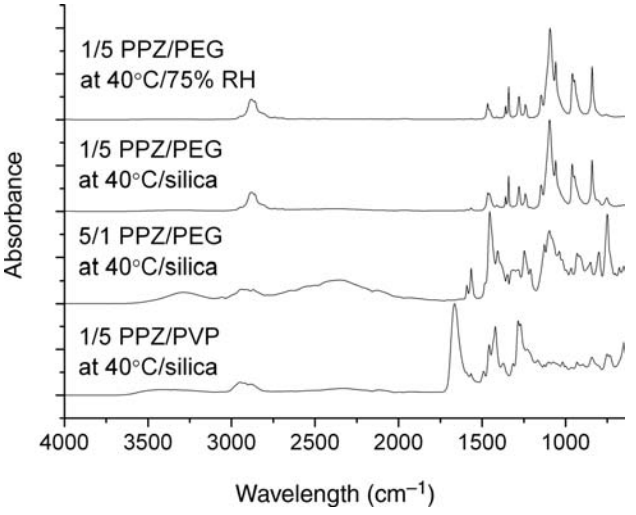

Figure 1. The FTIR spectra of 1/5 PPZ/PVP, 5/1 PPZ/PEG, and 1/5 PPZ/PEG solid dispersions after storage at 40°C/silica and 1/5 PPZ/PEG solid dispersion after storage at 40°C/75% RH.

PPZ and the ether oxygen of PEG (band at ~ 1095 cm^{-1})[8] were found to remain unchanged in all of the PPZ/polymer solid dispersions stored at 40°C/silica gel (e.g., spectra shown in Figure 1). Only in the case of 1/5 PPZ/PEG had the broad OH-band at ~3300 cm^{-1} become lower after storage (Figure 1). Furthermore, small shifts of the band indicating HCl absorption (2400 cm^{-1}) were detected in the case of 5/1 PPZ/PVP, 5/1 PPZ/PEG, and freeze-dried PPZ (spectrum of 5/1 PPZ/PEG shown as an example in Figure 1). Also, the band at 2880 cm^{-1} (C-H stretching) had become lower in the case of 5/1 PPZ/PEG and the peak at 3320 (OH) was shifted toward a lower wave number (i.e., 3290 cm^{-1}, Figure 1). These shifts were probably attributable to the reduced water content of the samples.

In contrast, a break down of the stabilizing drug–polymer interactions after storage of 1/5 and 1/20 PPZ/PEG at 40°C/75% was observed by FTIR (Figure 1). The OH band at ~3300 cm^{-1} had become split into two separate bands, indicative of a break down of the interaction between the ether group of PEG and OH-group of PPZ, possibly leading to crystallization of PPZ. The shift of the C-O absorption band from 1097 to 1093 cm^{-1} also supports this hypothesis. However, these changes could not be observed in the spectrum of 1/20 PPZ/PEG (not shown).

Evaluating changes in the physical state of the materials after storage by DSC

Crystallization during 4 weeks of storage could have occurred for 1/5 PPZ/PEG in both conditions, because no T_g was observed after storage (results for samples stored at 40°C/silica gel shown in Table 4). Also for 1/20 PPZ/PEG crystallization was possible, but no conclusions can be drawn, because no T_g could be observed even in the fresh sample. However, no melting endotherms of PPZ could be observed, because of the dissolution of the possibly crystalline PPZ into the melted PEG. Instead, in the case of 5/1 PPZ/PEG, the T_g was slightly lowered, but the ΔCp value had remained the same after the storage at 40°C/silica gel. The melting temperature of PEG in solid dispersions was slightly elevated during the storage at both conditions (Table 5). The ΔH values of the PEG melting had become elevated back to the level of ΔH of the physical mixtures in the case of 1/5 and 1/20 PPZ/PEG solid dispersions (Table 5), which might indicate phase separation and crystallization of the amorphous part of PEG during storage. Instead, ΔH of 5/1 PPZ/PEG did not revert back to the level of the physical mixture (Table 5).

In contrast, the PPZ/PVP solid dispersions displayed no evidence of crystallization after the storage at 40°C/silica gel, because the glass transitions were visible in all formulations (Table 4). There was an increase in the ΔCp values of 1/5 and 1/20 PPZ/PVP after storage for which no explanation was found. Interestingly, the freeze-dried PPZ seemed to remain at least partially

Table 4. Glass transition (T_g) and heat capacity (ΔCp) values ($n = 3 \pm$ SD) for freeze-dried PPZ and the solid dispersions of PPZ before and after the 4 weeks of storage at 40°C/silica gel.

Sample	T_g (°C) before storage[a]	ΔCp (J/gK) before storage[a]	T_g (°C) after storage at 40°C/silica gel	ΔCp (J/gK) after storage at 40°C/silica gel
Freeze-dried PPZ	53.8 ± 2.5	0.82 ± 0.24	62.3 ± 0.3	0.10 ± 0.06
5/1 PPZ/PVP	58.9 ± 0.6	0.68 ± 0.14	60.09 ± 0.8	0.46 ± 0.10
1/5 PPZ/PVP	155.1 ± 2.4	0.17 ± 0.08	151.4 ± 0.3	0.30 ± 0.01
1/20 PPZ/PVP	170.3 ± 1.4	0.13 ± 0.03	165.7 ± 1.6	0.26 ± 0.02
5/1 PPZ/PEG	22.2 ± 0.7	0.48 ± 0.03	15.6 ± 1.0	0.47 ± 0.04
1/5 PPZ/PEG	−44.9 ± 0.2	0.02 ± 0.01	nd	nd
1/20 PPZ/PEG	nd	nd	nd	nd

[a]From Laitinen et al.[8]
nd = not detected.

Table 5. The melting points (T_m °C) and enthalpies (ΔH/ J/g) ($n = 3 \pm$ SD) of PEG in the prepared solid dispersions of PPZ in PEG before and after the 4 weeks of storage at 40°C/silica gel and 40°C/75% RH.

Sample	T_m(°C), ΔH (J/g)[a] of PEG in physical mixture[b,c]	T_m(°C), ΔH (J/g)[a] of PEG in solid dispersion[c]	T_m(°C), ΔH (J/g)[a] of PEG after storage at 40°C/silica gel	T_m(°C), ΔH (J/g)[a] of PEG after storage at 40°C/75% RH
5/1 PPZ/PEG	59.7 ± 0.1, 165 ± 20	62.9 ± 0.1, 9.4 ± 2	64.0 ± 0.4, 3.6 ± 0.7	—
1/5 PPZ/PEG	59.3 ± 0.1, 198 ± 7	61.4 ± 1.2, 157 ± 6	60.8 ± 0.7, 190 ± 10	62.7 ± 1.6, 190 ± 5
1/20 PPZ/PEG	59.4 ± 0.1, 193 ± 1	61.2 ± 0.3, 168 ± 2	61.0 ± 0.2, 196 ± 2	63.3 ± 0.3, 194 ± 1

[a]ΔH is corrected for the amount of PEG in the mixture.
[b]ΔH of pure PEG is 186 ± 3 J/g.
[c]From reference Laitinen et al.[8]
— = not measured.

amorphous, because no melting endotherm of PPZ was detected and T_g was observed after the storage at 40°C/ silica gel, although the T_g temperature was slightly increased (due to loss of moisture) and its ΔCp value had declined (Table 4).

Evaluating changes in the physical state of the materials after storage by XRPD

No diffraction peaks specific to PPZ were observed in the diffraction patterns of the freeze-dried PPZ and PPZ/PVP solid dispersions stored at 40°C/silica gel (Figure 2). The humps observed at 11° and 22° in the case of PPZ/PVP formulations were attributed to the presence of PVP as their intensity increased with increasing PVP content. However, in the case of PPZ/ PEG formulations, the evaluation of possible crystallization of PPZ was complicated by the partial overlapping of the diffraction peaks of PPZ and PEG. In the case of the 5/1 PPZ/PEG formulation, no peaks attributable to crystalline PPZ were observed after storage at 40°C/silica gel (diffractogram not shown). In the case of 1/5 and 1/20 PPZ/PEG, new diffraction peaks with respect to the diffraction patterns of the fresh solid dispersions were

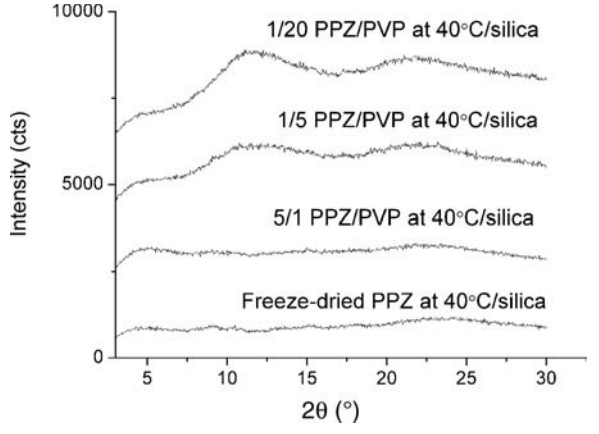

Figure 2. The X-ray diffraction patterns of freeze-dried PPZ, 5/1 PPZ/PVP, 1/5 PPZ/PVP, and 1/20 PPZ/PVP solid dispersions stored at 40°C/silica gel.

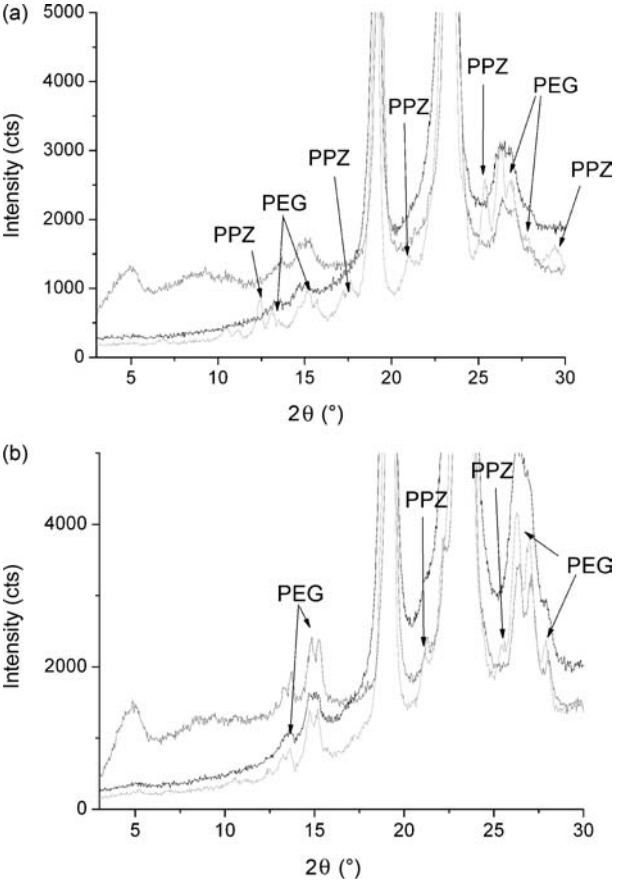

Figure 3. The enlarged X-ray diffraction patterns of the solid dispersions before (black line) and after storage at 40°C/silica gel (gray line) and 40°C/75% RH (light gray line): (a) 1/5 PPZ/PEG; (b) 1/20 PPZ/PEG. The arrows indicate the characteristic PPZ and PEG diffraction peaks. The data of the fresh samples are reproduced from Laitinen et al.[8]

observed after the storage at 40°C/75% (Figure 3a and b). With 1/5 PPZ/PEG, these diffractions of low intensity appeared at 2θ of 10°, 18°, 21°, 25°, and 29° and with 1/ 20 they appeared with even lower intensities. These peaks correspond to the characteristic diffractions of PPZ, which do not overlap with PEG diffractions. However, also the

characteristic PEG diffractions at 2θ of 12–13°, 15–16°, 26–27° seemed to appear sharper and slightly more intense in the diffractograms after storage at 40°C/75% (Figure 3a and b) than in the case of fresh solid dispersions. This might be evidence of the increased PEG crystallinity, also observed with DSC (Table 5).

Instead, after storage at 40°C/silica gel, no new diffraction peaks attributable to crystalline PPZ were observed, but sharpening of the PEG diffraction peaks was still visible (Figure 3a and b). Thus, an increase in PEG crystallinity might have occurred, as observed with DSC (Table 5), but despite that, PPZ had remained amorphous under these conditions.

Determination of the drug size distribution in the polymer matrices after storage by SAXS

It is possible that the drug particle size in a solid dispersion can increase during storage due to phase separation and crystallization of the drug[26]. This possibility was studied by determining the size distribution of the different electron density regions of the solid dispersions before and after the 4 weeks of storage at 25°C/60% RH by SAXS (Figure 4a and b). In the case of PVP formulations (Figure 4a), minor changes in the shape of the pair density distribution curves could be seen, as the maxima had been shifted from 24 nm to 26–27 nm and from 89 to 70 nm (in the case of 1/20 PPZ/PVP). However, similar shifts were visible with the freeze-dried PVP. In the case of PEG formulations (Figure 4b), the shape of the curves remained similar before and after the storage, that is, the maxima were found to be exactly the same in both the fresh and stored samples (i.e., 26 and 80 nm). Thus, no increase in the size of the inhomogeneity regions of the solid dispersions had occurred during storage and phase separation and crystallization was considered unlikely to have taken place under these conditions.

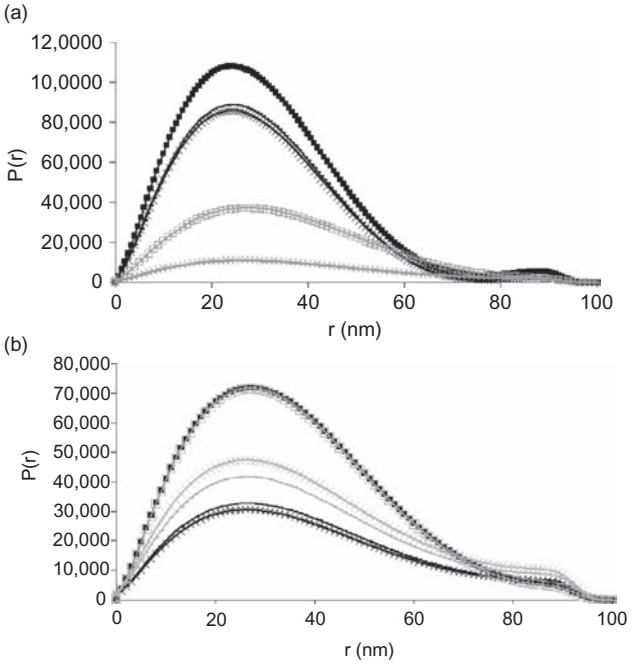

Figure 4. Pair density distribution functions of (a) freeze-dried PVP (□) and 1/5 (×) and 1/20 PPZ/PVP (–) solid dispersions stored at 25°C/60% RH for 4 weeks compared to the fresh samples (similar symbols in black); (b) freeze-dried PEG (□) and 1/5 (×) and 1/20 PPZ/PEG (–) solid dispersions stored at 25°C/60% RH for 4 weeks compared to the fresh samples (similar symbols in black), determined from SAXS measurements. The data of the fresh samples are reproduced from Laitinen et al.[8]

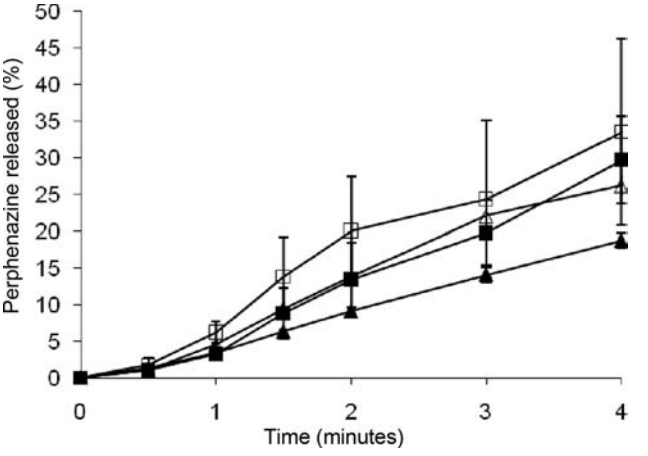

Figure 5. Dissolution properties of the tablet formulations containing 1/5 solid dispersions of PPZ with PEG [formulations 1 (■) and 2 (□)] and PVP [formulations 3 (▲) and 4 (△)]. Formulation compositions are presented in Table 1.

Fast disintegrating tablet formulations of the solid dispersions

Tablet properties

The 1/5 PPZ/PEG solid dispersion was formulated as a FDT. For comparison, similar tablets were prepared with the 1/5 PPZ/PVP solid dispersion. The formulation codes, contents, and the properties of the prepared tablets are shown in Table 1. The weight variation with all of the formulations was very minor (i.e., less than 0.5%), that is, all tablets fulfilled the requirements of European Pharmacopoeia[3] (Table 1). Figure 5 shows the dissolution properties of PPZ from the tablet formulations. Formulation 2 released PPZ fastest (34% in 4 minutes), followed by formulations 1, 4, and 3, respectively. Thus, PPZ was released faster from the formulations containing 1/5 PPZ/PEG than from the formulations containing 1/5 PPZ/PVP, which is in accordance with the dissolution rate results obtained with the solid dispersions (Table 3). The tensile strengths of formulations 2 and 4 (containing CP and CS) were higher than formulations

1 and 3 (containing only CS) due to the higher compression force (Table 1).

Formulation stability

It is well known that processing, such as tabletting, of amorphous drugs may lead to drug crystallization[27]: Therefore, DSC measurements (temperature programs in Table 2) for the powder mixtures before tabletting and prepared tablets were conducted with all tablet formulations, to evaluate possible phase transformations. The thermograms of compressed tablets displayed no new thermal events (e.g., melting endotherm of PPZ) compared to the thermograms of the powder mixtures with all the formulations (results not shown). Thus, it appeared likely that PPZ might still be present in an amorphous form in the tablets.

The prepared tablets (n = 20) were stored for 4 weeks at room temperature 21°C/60% RH. After storage, the dissolution properties of the tablets, the tablet mass, tensile strength, and their disintegration time were determined and DSC measurements were performed. The dissolution properties of formulations 1 and 2 (Figure 6), compared to the dissolution of original tablets (Figure 5), had remained similar (or had become somewhat faster) throughout the storage, with formulation 2 still being the fastest releasing formulation. The dissolution of PPZ was slightly slower from formulation 4 and considerably slower from formulation 3 after storage (Figure 6). These changes in dissolution properties were probably attributable to the changes in the properties of the tablets occurring during storage. Table 1 shows that the weight of the tablets containing 1/5 PPZ/PEG (formulations 1 and 2) had remained constant during the storage, but instead, the weight of the tablets containing 1/5 PPZ/PVP (formulations 3 and 4) had increased. This is clearly attributable to the hygroscopicity of 1/5 PPZ/PVP, observed in the stability studies with the solid dispersions. The tensile strength values had increased with formulations 1 and 3 but decreased with formulations 2 and 4. The increase in tensile strength led to an increase in disintegration time with formulation 1. The disintegration time of formulation 2 had remained the same whereas that of formulation 4 increased despite the decrease in tensile strength, which might explain the slightly slower dissolution.

The DSC thermograms of the tablets after storage (not shown) displayed no evidence of new thermal events when compared to the thermograms of the freshly prepared tablets. In the case of formulation 3, this indicates that crystallization of PPZ from the 1/5 PPZ/PVP was unlikely to have occurred during storage, instead the solid dispersion might have deliquesced and this would have led to the increase in tensile strength.

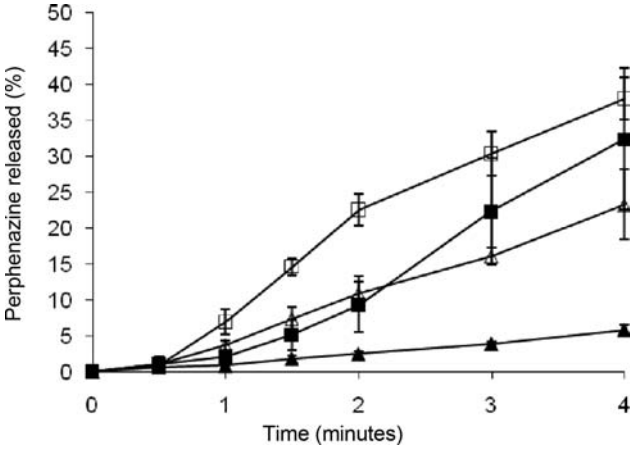

Figure 6. Dissolution properties of the tablet formulations containing solid dispersion 1/5 of PPZ with PEG [formulations 1 (■) and 2 (□)] and PVP [formulations 3 (▲) and 4(△)] after storage at 21°C/60% RH. Formulation compositions are presented in Table 1.

Discussion

Stability of the solid dispersions

As a consequence of the 4 weeks of storage at accelerated conditions (40°C/silica or 40°C/75%), decline in the dissolution rate of PPZ from the solid dispersions was observed (Table 3). Slowing of the dissolution rate of PPZ from 1/5 and 1/20 PPZ/PEG after storage at 40°C/75% might be explained by the breakdown of the stabilizing drug–polymer interactions, which was observed by FTIR (Figure 1), and the subsequent crystallization of the amorphous part of PEG into a higher-melting modification of PEG (Table 5). This led to at least partial crystallization of PPZ, which was observed by XRPD (Figure 3). A similar PEG transformation to the higher-melting modification on storage has been observed previously[26,28]. Furthermore, only a few compounds have been reported to form amorphous solid dispersions in PEG[29,30]. Their physical stability is known to be poor because of the inability of the crystalline PEG to stabilize the amorphous drug and dissolution rate of drugs (in sink conditions) has been claimed to slow down because of the increase in the amount of crystalline drug in the solid dispersions during storage[13,28,31]. However, in general the capacity of PEG to create a local microenvironment allowing more rapid dissolution compensates to a large extent for the transformation of the drug from amorphous into crystalline state[28], which here probably prevented the dissolution rate from reverting back to the level of crystalline PPZ. However, the dissolution of PPZ from 1/5 and 1/20 PPZ/PEG had somewhat declined also after storage at 40°C/silica (Table 3), even though PPZ had remained

amorphous (Figure 3a and b) and FTIR demonstrated that the hydrogen-bonding interactions between PPZ and PEG were stable (Figure 1). However, PEG had crystallized similarly as in higher humidity conditions (Table 5). Thus, it is possible that the ability of crystalline PEG to preserve the supersaturated PEG during dissolution is not as good as that of amorphous PEG[32,33]. However, it should be noted that the dissolution properties after storage were still much better than those of the crystalline PPZ with all PPZ/PEG formulations. No phase separation or crystallization of PPZ and/or PEG was detected in SAXS measurements (conducted after 4-week storage at 25°C/60% RH for 1/5 and 1/20 PPZ/PEG, Figure 4b), where the distribution of PPZ and PEG areas were unchanged compared to fresh samples.

A significant decline in the dissolution rate of PPZ from the 1/5 and 1/20 solid dispersions with PVP stored at 40°C/silica was seen (Table 3), although the solid dispersions were found to be physically stable due to the antiplasticizing effect of PVP (observed by DSC and XRPD, Table 4 and Figure 2) and stabilizing hydrogen-bonding interactions (observed by FTIR, Figure 1). The SAXS measurements (after storage at 21°C/60% RH, Figure 4a) supported the observation that PVP was able to stabilize amorphous PPZ in 1/5 and 1/20 PPZ/PVP solid dispersions. A small decline in the dissolution rate of drugs has been observed in other studies with PVP solid dispersions under storage, despite the physical stability of the solid dispersion[34,35]. On the contrary, the dissolution rate of PPZ from 5/1 PPZ/polymer solid dispersions was even slightly improved (Table 3) during storage at 40°C/silica. This phenomenon has been claimed to be attributable to improved hydrogen bonding between the drug and polymer due to increased molecular mobility during storage at elevated temperatures[36]. In addition, freeze-dried PPZ remained stable during storage at 40°C/silica (Table 4, Figure 2) but its dissolution rate became slightly slower (Table 3). The stability might be due to HCl salt formation, increasing the T_g of the drug[8] and it might promote the stability of PPZ also in the solid dispersions, because the stability of some solid dispersions has been attributed mainly to the physicochemical properties of the amorphous drug[30,37].

However, even though the freeze-dried PPZ, 5/1 PPZ/PEG, and all PPZ/PVP solid dispersions were found to be physically stable under storage conditions of 40°C/silica, the decline in their dissolution rate and observed deliquescence at relatively low RHs were the main reasons for discarding them from the formulation study. Deliquescence is a first-order phase transformation from solid to solution that occurs at a RH value that is specific to the crystalline solid in question. Deliquescence may affect the shelf life, quality, and functionality of end products that contain deliquescent ingredients and thus processing and storage conditions of these materials may be difficult to control[38,39]. With respect to the 1/5 and 1/20 PPZ/PEG solid dispersions, 1/5 dispersion possessed faster dissolution rate before and after storage, and lower bulk mass of the dose, and thus it was selected as the candidate for the tablet formulation study. Furthermore, oral absorption of PPZ has been shown to be enhanced by sublingual administration of 1/5 PPZ/PEG powder in rabbits.[40]

Performance of the orally fast-disintegrating formulations

In this study, producing direct compressed tablets that have both sufficient hardness and rapid disintegration was achieved by the combination of mannitol and disintegrants (CS and/or CP). The tablets were designed to have a disintegration time of 30 seconds in a small liquid volume and sufficient strength (i.e., tensile strength ≥ 1 MPa,[6,41]) in order to be handled and packed normally. Mannitol was selected to be the tablet excipient because it has favorable characteristics in intraoral preparations, such as pleasant taste and "mouth feel," and it is suitable for direct compression[42]. In addition, mannitol is nonhygroscopic and may thus be used with moisture-sensitive ingredients[42]. However, high mannitol quantities might increase the disintegration time[43]. CP was selected to be used as a disintegrant at levels 15% or 30% (w/w). There is a competition between mannitol and CP for the water penetrating into the tablet and thus the disintegration is hindered by the dissolution process of mannitol, that is, swelling of CP will have less effect on the destruction of the tablet matrix, compared with tablets containing more insoluble material and hence, the disintegration effect of CP becomes poor[44]. Thus, CS was used as a disintegration together with CP in two formulations, because it is known to produce tablets that retain their fast disintegration properties in spite of having been subjected to a higher compression force in the presence of a single or combination of superdisintegrants[45].

Formulations 2 and 4 (containing CP and CS) possessed appropriate hardness (i.e., ≥ 1 MPa, Table 1). Interestingly, despite higher tensile strength, the disintegration times of the formulations 2 and 4 were considerably shorter than those of the formulations 1 and 3, which was due to the favorable combination of the two disintegrants (CS and CP, Rxcipients, 2006)[45]. Furthermore, formulation 2, containing 10% of 1/5 PPZ/PEG, 60% of mannitol, 15% CS, and 15% of CP displayed fast disintegration in 37 seconds even though it had a tensile strength as high as 1.3 MPa (Table 1). The disintegration time was 20 seconds shorter than the disintegration time of the similar formulation 4, containing 1/5 PPZ/PVP. This is probably due to the lower tensile strength of formulation 2 than that of formulation 4, which in turn might be attributable to the ability of the solid dis-

persion to resist deformation under the compaction force, which in this case was better with PPZ/PEG, leading to formation of weaker tablets[46]. In general, in the case of fast-dissolving tablets containing a drug formulated as a solid dispersion, the disintegration times reported have been from 60 to 780 seconds[47–49]. Although the different measurement methods complicate comparison of the disintegration times, at least with formulations 2 and 4 the times can be considered as relatively good (Table 1), as the measurement was carried out in a small liquid volume (20 mL) and without stirring.

Furthermore, the formulation 2 had the best PPZ dissolution properties, that is, 34 % of PPZ released in 4 minutes (Figure 5), which is similar or even better compared to drug dissolution reported for other FDT formulations containing PEG dispersions[49,50]. Thus, the dissolution rate of PPZ from the solid dispersion and disintegration time of the tablet seemed to be crucial if one wishes to guarantee fast dissolution of PPZ from the tablet.

In the stability studies, slight decrease in tensile strength was observed with formulations 2 and 4 (Table 1), which could be attributable to several factors. The tensile strength during storage at high RH can decrease due to moisture uptake with a subsequent weakening of the binder bridges[51]. Formulations 2 and 4 contained CP, and a similar behavior has been observed before for this excipient[21]. In contrast, an increase in tensile strength might occur when the sorbed moisture causes recrystallization of a tablet component[6,51,52]. In the case of formulation 3, a relatively large increase in tablet mass was seen and thus, the subsequent large increase in tensile strength might be attributable to crystallization of PPZ from PPZ/PVP formulation, or deliquescence of PPZ/PVP due to the sorbed moisture and subsequent filling of the pores of the tablets[24,37], which would also account for the poorer dissolution of PPZ from the tablet after storage.

From the stability study results it can be concluded that formulation 2 maintained its performance during storage at 21°C/60% RH (Table 1, Figure 6). Thus, in this study, a simple tabletting procedure and formulation was found to be suitable for preventing the change in dissolution of PPZ from formulations containing 1/5 PPZ/PEG (i.e., formulations 1 and 2). In contrast, in the case of formulations containing 1/5 PPZ/PVP, the formulations were not able to protect the solid dispersion from physical changes caused by ambient moisture.

Conclusions

This study showed that it is possible to prepare an FDT by direct compression, containing the active ingredient (PPZ) formulated as a solid dispersion and possessing sufficient mechanical strength, rapid disintegration time and satisfying drug dissolution. After an evaluation of the fast-dissolving PPZ/polymer solid dispersions, 1/5 PPZ/PEG was selected for the formulation evaluation since it was least sensitive to elevated storage temperature and humidity, possessed the best dissolution properties before and after the storage at accelerated conditions, and had a suitable bulk mass of the dose (equivalent of 4 mg of PPZ). The FDT formulation containing 10% of 1/5 PPZ/PEG, 60% of mannitol, 15% of CS, and 15% of CP displayed fast disintegration and had sufficient tensile strength, to permit normal handling and packaging. Furthermore, a rapid and immediate onset of the release of PPZ (i.e., 34% of PPZ in 4 minutes) was seen with this simple formulation, which also maintained its performance during the 4 weeks of storage at 21°C/60% RH.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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