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Research paper

Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG6000 prepared by spray drying

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Abstract

Solid dispersions of PEG6000 and loperamide—a poorly water-soluble agent—were prepared by spray drying. Their physicochemical properties were evaluated immediately after preparation. The dissolution was higher than that of pure crystalline loperamide. DSC- and XRD-measurements revealed that in the dispersions, loperamide is partially present in the crystalline state. A eutectic state diagram was obtained. The samples containing 20% loperamide were stored under different conditions (40 °C and 0% RH, 25 °C and 52% RH, 4 °C and 0% RH) to investigate their stability as a function of time. The dissolution properties deteriorate upon storage at high temperature (40 °C and 0% RH) and in conditions of higher relative humidity (25 °C and 52% RH). The DSC-curves clearly indicate an increase in the amount of crystalline compound under these conditions. From these observations it could be concluded that loperamide, which is partially crystalline and partially amorphous in the freshly prepared samples, continues to crystallize under these conditions, resulting in progressively poorer dissolution properties.

Keywords: Solid dispersions; Dissolution properties; Differential scanning calorimetry; Stability; Physicochemical properties; PEG6000; Loperamide

1. Introduction

Loperamide (4-(4-chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-1-piperidinebutanamide) is a poorly water soluble drug used in the treatment of diarrhoea (solubility <1 mg/100 ml). It is commercially available as a hydrochloride salt under the trade name Imodium® (Janssen Cilag, Berchem, Belgium) in order to overcome the problem of poor solubility and hence poor oral bioavailability.

The aim of this study was to use loperamide as a model compound to explore another route to tackle this problem, i.e. the use of solid dispersions. They are defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix at solid state, prepared by the fusion, solvent or solvent-fusion method [1–4]. These systems provide the possibility of (a) reducing the particle size of the drugs to (nearly) a molecular level, (b) locally increasing the saturation solubility and/or (c) of transforming the drug from the crystalline to the (partially) amorphous state.

The first two characteristics have a clear influence on the dissolution rate according to the well-known Noyes–Whitney relation [5]:

$$\frac{dM}{dt} = \frac{AD(C_s - C_t)}{h}$$

where dM/dt is the dissolution rate, A the specific surface area of the drug particle, D the diffusion coefficient, h the diffusion layer thickness, C_s the saturation solubility and C_t the instantaneous drug concentration.

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The last factor (c) is beneficial since dissolution of an amorphous substance does not require energy to break up the crystalline lattice [6]. This is often the rationale for the preparation of dispersions in which the drug is present in the amorphous state. However, the amorphous state corresponds to a high energy state, is physically metastable and prone to crystallization, especially when stored relatively close to the glass transition temperature (T_g) [7]. The addition of a miscible polymer with a high T_g leads to dispersions with a higher T_g value in comparison to the pure amorphous drug, thereby increasing the physical and chemical stability of the system. Moreover, miscibility between the drug and the carrier at a molecular level leads to the highest level of particle size reduction.

The enhanced dissolution properties of eutectic mixtures in which the drug is present in the crystalline state, can be explained by increased wettability and creation of a microenvironment where the solubility of the drug particles is increased due to a high concentration of carrier in the surrounding solution. In addition, a mixture with a eutectic composition is characterized by a small size of the drug crystals [4,8].

In this investigation, polyethylene glycol 6000 (PEG6000) was used as the carrier. This is a polymer with a low glass transition temperature. Different values for this T_g can be found in the literature: Ford [9] reports a value of −50 °C, whereas Craig [10] reports a T_g at −17 °C. The polymer is usually present in the (partially) crystalline state. PEG6000 is known to form lamellar crystals of once-folded, twice-folded and fully extended chains [11]. In these folded modifications, some amorphous PEG is rejected from the crystals at the surface of the lamellae in order to make the folds in the polymer chains. From a thermodynamic point of view, the extended form is the most stable one with the highest melting point since here, the lamellae are thicker and the volume to surface ratio is higher when compared to the folded modifications [12].

Only two publications have been found describing solid dispersions in which PEG is completely amorphous. Homogeneous, amorphous dispersions could be obtained with ritonavir, but only over a limited composition range [13]. Phase-separated dispersions in which both the drug and the carrier are amorphous, could be prepared from PEG4000 and bendroflumethiazide [14].

The large majority of papers dealing with solid dispersions of PEG, report phase separated systems in which the polymer is present in the semi-crystalline state (mostly eutectica and monotectica) while the drug is crystalline, amorphous or a mixture of both. Physical stability will especially be an issue in the two latter cases. Since the polymer forms a separate phase, it cannot stabilize the metastable amorphous state of the drug as was being described previously.

In this study, dispersions of loperamide and PEG6000 were prepared over a broad composition range by spray drying. Physicochemical characterization of the dispersions was performed on the freshly prepared samples as well as on samples stored under different conditions.

2. Materials and methods

2.1. Materials

The molecular structures of the components of the solid dispersions are given in Fig. 1. The polymer was purchased at Clariant Benelux NV (Louvain-la-neuve, Belgium) whereas loperamide was available from Janssen Pharmaceutica (Beerse, Belgium). It had a purity of 99.8%. All other reagents were of analytical or HPLC grade.

2.2. Preparation of solid dispersions by spray drying

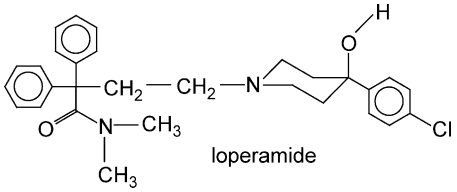
The solid dispersions were prepared by spray drying of solutions in dichloromethane with an overall concentration (drug + polymer) of 5% w/v using a Büchi Mini Spray Dryer B191 (Büchi Labortechnik AG, Flawil, Switzerland). Solutions containing 5, 10, 20, 30, 40, 50, 60 and 80% w/w of loperamide relative to the total amount of solids were spray dried using a fixed set of adjustable parameters of the equipment (evaporation temperature: 50 °C, feeding rate: 7.5 ml/min, air flow: 400, power of the aspirator: maximum). After spray drying, the dispersions were dried at 40 °C under vacuum until constant weight.

2.3. Stability study

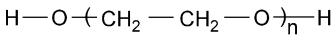
After the drying procedure the dispersions containing 20% of loperamide were stored under the following conditions:

40 °C, 0% RH (installed with P_2O_5)
25 °C, 52% RH (installed with a saturated solution of $Mg(NO_3)_2.6H_2O$)
4 °C, 0% RH (installed with P_2O_5)

The samples were analyzed after 1, 6 and 12 months.



loperamide



PEG6000

Fig. 1. Molecular structures of PEG6000 and loperamide.

2.4. Methods

2.4.1. Headspace gas chromatography (GCS)

Head space gas chromatography was used to identify and quantify the presence of residual organic solvents in the dispersions. The measurements were performed using a Varian 3800 gas chromatograph (Varian gas chromatograph CP3800, Walnut Creek, CA, USA) with splitter injector, FID detector and a headspace sampler (Tekmar Dohrmann 7000, Cincinnati, OH, USA) Approximately 100 mg of the sample was dissolved in 2 ml of 1,3-dimethyl-2-imidazolidinone in a 22 ml headspace vial. Two 50 m silicagel columns (CP-SIL 5 CB: ID 0.32 mm, 5 mm and CP-WAX 52 CB: ID 0.32 mm, 1.2 mm) were used. Nitrogen was used as a carrier gas. The injector was held at 230 °C and the FID detector at 270 °C. The oven temperature was changed from 40 to 220 °C during the analysis.

2.4.2. Thermogravimetric analysis (TGA)

Thermogravimetric analysis was used to determine the total amount of volatile substances (organic solvents + water). The measurements were performed with a TA Instrument Hi-Res TGA 2950 (TA Instruments, New Castle, Delaware, USA) and data station TA2100. Approximately 10 mg of sample was weighed in an aluminum pan of 30 μl and heated from room temperature at a heating rate of 20 °C/min. The end point was set at 300 °C.

2.4.3. High performance liquid chromatography (HPLC)

The exact drug content of the dispersions was determined using a Merck Hitachi pump L7100, a Merck Hitachi autosampler L7200 and a Merck Hitachi UV-detector L7400 (Merck, Darmstadt, Germany). A Hypersil BDS-C18 (3 μm, 4.0 × 100 mm) column (Agilent, Palo Alto, CA, USA) was used. All measurements were performed at room temperature, the flow rate was set at 1 ml/min, the injection volume was 10 μl and the detection wavelength was 220 nm.

An isocratic method was applied, using a 70/30 (v/v) mixture of 1 mM tetrabutylammonium hydrogen sulfate in water and acetonitrile.

2.4.4. Dissolution measurements

The binary solid dispersion with a dose of 200 mg of drug was directly added to 600 ml of a buffer with pH 4.5 (37 °C). This buffer was prepared by dissolving 5.7788 g of citric acid monohydrate and 8.0095 g of $Na_2HPO_4 \cdot 2H_2O$ in demineralized water up to a volume of 1 l. Dissolution was assessed using a paddle rotating at 50 rpm (USP II apparatus, VanKel UK 7000, Cary, NC, USA). The release was followed for 1 h. The concentration of the pharmaceutical compounds was quantified at predetermined time intervals using UV with fiberoptics (Dicon Fiberoptics, GP700, Richmond, CA, USA) controlled by Zeiss software (Zodiac Version 2.0 software, Zeiss, Jena, Germany) and measured using Hellma cuvets with a 1 cm path (Hellma, Mullheim, Germany). The concentration of loperamide was measured at a maximum wavelength of 259 nm.

2.4.5. ADSC-measurements (temperature modulated DSC)

The ADSC-measurements (DSC-measurements with temperature modulation) were performed on a Mettler-Toledo DSC822^e equiped with an intercooler and the results were analyzed with the STAR^e software version 6.10 (Mettler-Toledo, Schwerzenbach, Switzerland). Mercury and indium were used to calibrate the temperature scale and enthalpic response. The calibration of temperature and enthalpy was validated at least weekly, using the same standard materials. Deviation of the experimental value from the theoretical one was less than 0.3 °C for temperature measurement and less than 2% for enthalpy measurement.

The samples (approximately 10 mg) were analyzed in sealed 40 μl aluminum sample pans (Mettler-Toledo, Schwerzenbach, Switzerland) with a pierced lid to allow removal of water and other volatile substances from the melt. The following modulation parameters were used: underlying heating rate: 2 °C/min, amplitude: 0.212 °C and period: 40 s. Measurements were performed at least in duplicate.

2.4.6. X-ray powder diffraction measurements (XRD)

X-ray powder diffraction was performed at room temperature with a Philips PW Diffractometer (beam 173 mm). Monochromatic Cu K_α-radiation ($\lambda = 1.5406$ Å) was obtained with a Ni-filtration and a system of diverging, receiving and scattering slides of 1°, 0.2 mm and 1°, respectively. The diffraction pattern was measured with a voltage of 45 kV and a current of 20 mA in the region of $4° \leq 2\theta \leq 60°$ and a step scan mode of 0.02° per second.

3. Results and discussion

3.1. Chemical analysis of dispersions after preparation

HPLC-analysis was used to determine the exact content of loperamide in the dispersions. This proved to be in good agreement with the theoretical values.

GCS-analysis revealed that the drying procedure was adequate. All the levels of residual solvent were below or equal to 0.1%. From the TGA-experiments, the total amount of volatile substances could be determined. The quantity of water was calculated as the difference between the weight loss and the amount of residual solvent. It is clear that the amount of water increases with increasing drug loading.

The results of these experiments are summarized in Table 1.

3.2. Physicochemical analysis at time zero

The XRD-spectra of the dispersions exhibit clear diffraction peaks from the polymer. Peaks typical for

Table 1
Chemical characterization of the solid dispersions

Theoretical content of loperamide[a]	Experimental content of loperamide[a]	Organic solvents[a]	Water
5	4.97	–[b]	0.13
10	9.97	–[b]	0.18
20	19.87	–[b]	0.30
30	30.23	0.01	0.23
40	40.19	0.02	0.41
50	48.82	0.03	0.44
60	60.47	0.12	0.50
80	81.86	–[b]	0.85

[a] All quantities are expressed as % w/w.
[b] Quantities below 0.005% cannot be detected.

the loperamide monohydrate crystal are also visible but are much more shallow. Only the most intense diffraction peaks of the drug crystals can be traced in the spectra (e.g. at $2\theta = 17.8$ and 20.1). Some of the spectra are depicted in Fig. 2. The fact that loperamide forms monohydrate crystals can explain the increasing water content in the dispersions as the drug loading increases (see Table 1).

As far as the thermal transitions in these samples are concerned, no T_g's could be registered. If (part of) the sample were amorphous, the experimental T_g's would have to be situated in the temperature range $-50 \rightarrow 68.7$ °C or $-17 \rightarrow 68.7$ °C, which are the T_g-values of pure PEG6000 and loperamide. This T_g for PEG6000 was not determined experimentally but taken from the literature [9,10].

The formation of a completely miscible and amorphous solid dispersion would result in one intermediate T_g-value. In the event that phase separation had taken place during preparation leading to the formation of two amorphous phases, two T_g's should be detected corresponding to the pure amorphous substances (i.e. at -50 or -17 and 68.7 °C).

This is clearly not what is being observed in the DSC-curves.

Fig. 3 comprises some DSC-curves. They clearly exhibit 2 endothermic events.

All the melting temperatures have been plotted in a temperature versus concentration diagram depicted in Fig. 4. This phase diagram corresponds to a eutectic behavior of which only one arm (from loperamide) is visible.

Below the eutectic temperature (T_{eu}), two phases coexist: crystalline drug and crystalline PEG6000. Upon heating a sample with the eutectic composition, at T_{eu} all the crystals will melt and a solution with the eutectic composition will be formed. This eutectic melting takes place around 55 °C. From Fig. 4 the eutectic composition can be estimated to correspond approximately to $w_{PEG6000} = 0.9$.

Samples with a higher drug loading than the eutectic composition (to the left of this eutectic point in Fig. 4) also exhibit eutectic melting at T_{eu}. At this point all PEG-crystals melt together with a part of the drug crystals until a liquid phase with the eutectic composition has been achieved. This corresponds to the first endothermic event in the DSC-curves. When the temperature is increased above T_{eu}, a two phase equilibrium is being established between a liquid phase and crystalline drug. The composition of this liquid phase changes with temperature following

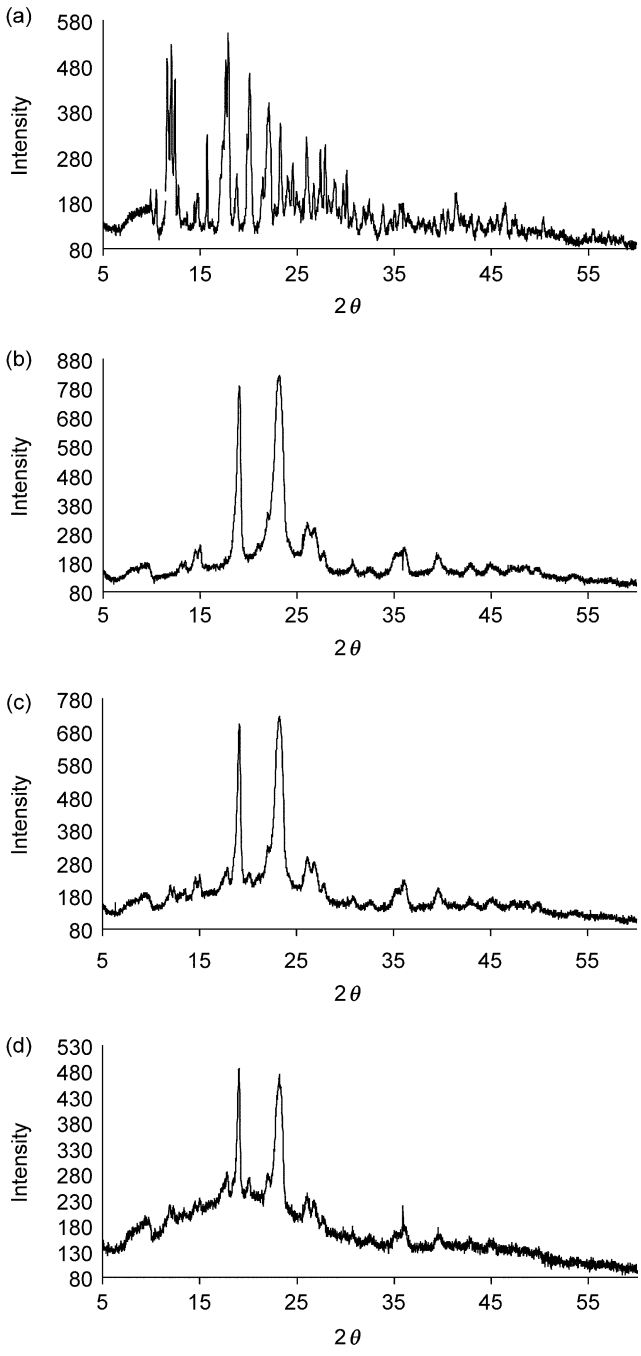


Fig. 2. XRD-spectra (intensity (arbitrary units) as a function of 2θ) of the pure substances and dispersions containing 20 and 60% of drug recorded immediately after preparation. (a) pure loperamide; (b) pure PEG6000; (c) dispersion containing 20% of drug; (d) dispersion containing 60% of drug.

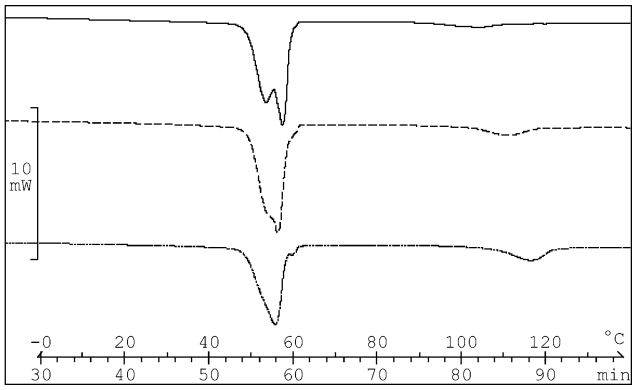


Fig. 3. Total heat flow curves of dispersions containing 40 (upper curve), 50 (middle curve) and 60% (lower curve) of loperamide in PEG.

the liquidus of loperamide. The drug melts and dissolves gradually, causing the second endotherm in the DSC-curves (Fig. 3).

Dispersions with a lower drug content than the eutectic composition, undergo eutectic melting at T_{eu}. All drug crystals melt together with a part of the PEG-crystals leading to a liquid phase with the eutectic composition. Upon further heating, the excess of carrier crystals will melt. The temperature region in which these two phenomena occur (eutectic melting and melting of the excess of PEG-crystals) is very narrow. The liquidus corresponding to the melting point depression of PEG6000, is not visible in the phase diagram (Fig. 4) since it is situated very close to the eutectic melting temperature, resulting in an overlap of both phenomena (eutectic melting and melting of PEG6000) in the DSC-curves.

At the eutectic temperature a three phase equilibrium exists between crystalline PEG, crystalline drug and a liquid with the eutectic composition. According to thermodynamics, a three phase line (horizontal line at T_{eu}) forms the boundary between three two phase regions: (1) solid PEG and solid drug, (2) solid drug and a liquid phase and (3) solid PEG and a liquid phase. Even though this last region is too small to detect, it is definitely there.

As eutectic melting corresponds to an invariant situation according to the phase rule (2 components and 3 phases in a condensed system implicating a constant pressure), the melting temperature should be determined as for a pure substance (also an invariant situation). Therefore the onset temperature of the eutectic melting endotherm should be plotted in the phase diagram. These are marked as ■ in Fig. 4. They show, however, a tendency to decrease as the amount of PEG decreases and are not really constant. This is caused by the fact that the shape of this melting peak alters with composition as can be seen in the DSC-curves (Fig. 3) and will be discussed below. Hence, as a compromise not only the onset temperatures corresponding to this signal but also the peak maxima (indicated by ▲) are included in the state diagram, even though this is thermodynamically not completely correct. These points are more constant over the whole concentration range.

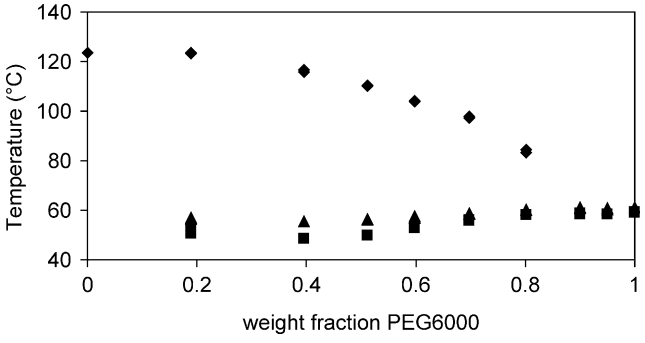


Fig. 4. Phase diagram of the binary loperamide/PEG6000 system. ■ T_{m1} onset; ▲ T_{m1} max; ♦ T_{m2} max.

The melting at the eutectic temperature corresponds to the melting of (at least a part of) the PEG6000-crystals, which can explain the multiple character of the melting peak (see Fig. 3). The contribution of the different forms (once or twice folded and extended) is being reflected in the shape of the melting peaks. The DSC-curves illustrate how the distribution of the PEG-chains over the different crystals is being influenced by the drug loading. An increasing amount of drug favors the formation of crystals of extended PEG-chains. Dordunoo [15] reported a similar dependence whereas the opposite relationship has been found in other dispersions [16,17]. Verheyen [18] found both in dispersions of diazepam and PEG6000, depending on the preparation method of the dispersions.

Based upon the knowledge of the heats of fusion of the pure components (188 J/g for PEG and 150 J/g for loperamide) and the estimated eutectic composition ($w_{PEG6000} \approx 0.9$), the melting enthalpies that are involved in the two melting processes could be calculated. Comparison of the experimental and calculated heats of fusion showed that the second endotherm is smaller than expected (see Table 2).

This can be caused by two phenomena or a combination of both. Some undetectable melting might take place. The gradual melting of drug in the eutectic liquid might start so

Table 2
Heats of fusion of loperamide (second endotherm)

Content of loperamide	$\Delta H_{m\ theor}$ (J/g sample)[a]	$\Delta H_{m\ exp}$ (J/g sample)[b]
10	0	0
20	16.7	5.8
30	33.3	0.6
40	50.0	8.5
50	66.7	12.3
60	83.3	21.5
80	116.7	22.1

[a] These values were calculated based upon the following data: w_{drug} at the eutecticum; 0.1, ΔH_m PEG 188 J/g and ΔH_m drug, 150 J/g.

[b] These values were obtained by integration of the second endothermic peak in the DSC-curves. Each measurement was performed twice and the average value is listed.

slowly that the accompanying endothermic effect is so shallow that it is not detected. A second phenomenon that might be responsible for the low heats of fusion is the presence of amorphous drug. The amorphous drug might form clusters or might be intimately mixed with the amorphous part of the folded PEG chains. Both options have severe repercussions on the physicochemical stability. Most polymers that are being used for the preparation of solid dispersions, have a high T_g. Hence, the formation of a mixed phase of drug and polymer would favor the physicochemical stability since the polymer acts as an anti-plasticizing agent. The drug molecules are molecularly dispersed and due to the high T_g, practically all mobility in the sample seizes [7]. On the contrary, PEG has a very low T_g. Mixing loperamide with the carrier leads to a lower T_g than the value of the pure drug. The molecular mobility increases, resulting in poorer physicochemical stability. The influence of storage was investigated and will be a topic of discussion in Section 3.3.

Dissolution experiments were performed on the dispersions containing 10, 20 and 40% of loperamide immediately after preparation and drying and compared to the dissolution rate of pure, crystalline drug. The dissolution curves are represented in Fig. 5. The dissolution curve of a dispersion containing 20% of drug in HPMC2910 is also included.

The data illustrate a clear increase in dissolution rate for all the dispersions in comparison to the pure compound. The dispersions containing PEG exhibit improving dissolution characteristics as the amount of carrier is increased.

As discussed in Introduction, several phenomena might be at the origin of increased dissolution rate in solid dispersions: decrease of the amount of crystalline drug in the dispersions, reduction of the particle size and/or creation of a better micro-environment for dissolution of the drug by the presence of the carrier.

The decrease in the amount of crystalline drug in the dispersions cannot account for the differences in the dissolution curves of 20% dispersions in PEG, HPMC and the pure drug. In the dispersion with HPMC, the drug is completely amorphous and homogeneously mixed with the polymer (unpublished results), whereas in the dispersion with PEG the crystallinity of the drug is reduced in comparison to the pure compound but still far from zero. Hence, if the crystallinity of loperamide were the critical or determining factor, the dissolution rate would increase in the following order: pure drug $<20\%$ in PEG $<20\%$ in HPMC. The same phenomenon has also been observed by other scientists [19–21].

During the dissolution of the PEG-dispersions in the dissolution medium, the drug will be released in an aqueous phase with a locally high PEG concentration. The predominant feature responsible for the good dissolution properties of the PEG-dispersions seems to be the creation of a micro-environment with an enhanced solvent quality. The addition of PEG leads to an increase of the 'C_s'-parameter in the Noyes–Whitney equation. The fact that part of the drug is in the amorphous state is only of additional value in this case.

3.3. Stability study

For the stability study, one of the dispersions (containing 20% of drug) was investigated after storage for 1, 6 and 12 months under different conditions: 40 °C–0% RH, 25 °C–52% RH and 4 °C–0% RH

Depending on the storage conditions, the DSC-measurements reveal changes of three characteristics: (1) shape of the melting peak of PEG, (2) the melting point of the drug and (3) the heat of fusion of loperamide.

At time zero, the melting peak of PEG clearly has a dual character. This dual character is practically unchanged in the samples stored at 4 °C, whereas in samples stored at 25 and 40 °C the double character of this melting peak is reduced. This is illustrated in Fig. 6 where the total heat flow curve recorded immediately after drying is depicted, together with the curves obtained from samples stored under the different conditions. This change in shape is the result of a change in distribution of the PEG crystals over the different crystal modifications. Storage at high

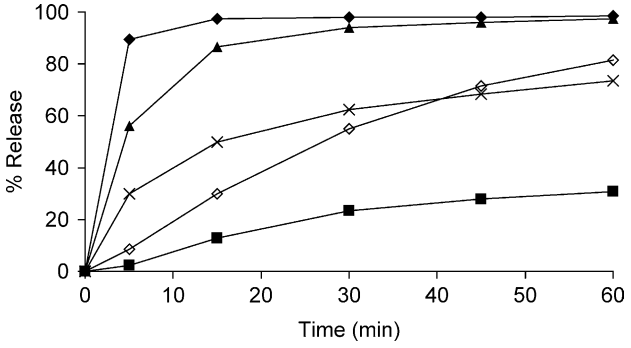


Fig. 5. Dissolution profiles of freshly prepared samples. ■ pure crystalline drug; ◇ 20% loperamide in HPMC; ♦ 10% loperamide in PEG6000; ▲ 20% loperamide in PEG6000; × 40% loperamide in PEG6000.

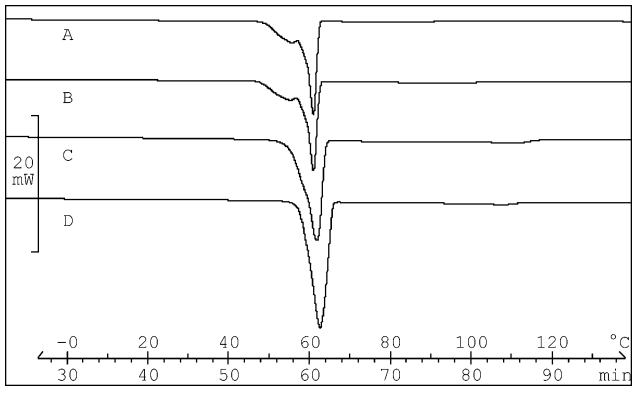


Fig. 6. Total heat flow curves of the 20% dispersion obtained immediately after preparation (A), and after storage for 6 months at 4 °C–0% RH (B), 25 °C–52% RH (C), 40 °C–0% RH (D).

Table 3
Effect of storage on the melting characteristics of loperamide

Time/condition	T_{m2} (°C)	ΔH_{m2} (J/g sample)
After preparation	83.9	5.8
40 °C/0% RH		
1 month	86.7	9.9
12 months	91.9	11.5
25 °C/52% RH		
1 month	87.9	9.0
12 months	87.9	8.5
4 °C/0% RH		
1 month	85.7	7.1
12 months	86.6	6.4

temperature (40 °C, 0% RH) or high humidity (25 °C, 52% RH) led to an unfolding of the polymer chains. Similar phenomena were observed by Dordunoo [15] in dispersions of triamterene and temazepam in PEG.

Furthermore the peak maximum of the second melting peak corresponding to the melting of drug, is influenced by the storage conditions. The impact of storage is not very high but it can be concluded that the more crystalline drug is present in the dispersion, the higher its melting point is. Table 3 includes the melting temperatures of the drug under the different storage conditions.

Not only the melting point, but also the heat of fusion has increased upon storage indicating that the dispersions are not stable (see Table 3). In particular, the samples stored at 40 and 25 °C show crystallization of a considerable amount of drug.

These results point towards incomplete crystallization of drug in the freshly prepared samples as the explanation for the small heats of fusion of the drug (Table 2).

This stability study clearly established that PEG cannot ascertain a good stability in this type of dispersion. A part of the drug which was present in the amorphous state immediately after preparation, crystallizes upon storage.

The dissolution curves that were recorded are depicted in Fig. 7.

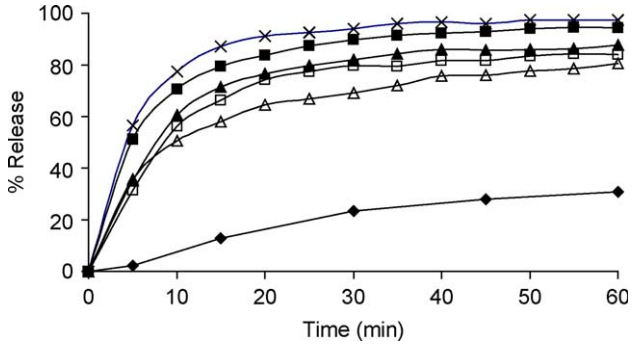


Fig. 7. Influence of the storage conditions on the dissolution properties of loperamide from a 20% w/w dispersion. ♦ pure drug; × 20% dispersion immediately after preparation; ■ dispersion after 1 month at 40 °C–0% RH; □ dispersion after 6 months at 40 °C–0% RH; ▲ dispersion after 1 month at 25 °C–52% RH; △ dispersion after 6 months at 25 °C–52% RH.

It is clear that the dissolution properties deteriorate upon storage at 25 and 40 °C. There is a clear relation between this dissolution study and the calorimetric results: the extent to which the dissolution properties deteriorate is linked to the crystallinity of the drug. It is, however, clear that the dissolution properties are still much better than those of the pure drug.

The capacity of PEG to create a local micro-environment in which the drug dissolves faster, compensates to a large extent for the transformation of the drug from the amorphous into the crystalline state.

Since it is generally assumed that there is some kind of correlation between the dissolution curves of 'immediate release' dosage forms obtained in an in vitro study and the oral absorption/bioavailability in an in vivo situation, this would imply that a decrease of the dissolution properties of the dispersions upon storage can potentially lead to a reduced uptake of the drug from the gastro-intestinal tract. Hence, when developing a solid dispersion one should perform a stability study to elucidate which conditions result in no or only a minor decrease of its physical structure, in order to stay within the limits of the specifications for the dissolution of the dosage form. In this case, storage at 4 °C and 0% RH might be adequate to store the formulation.

4. Conclusion

This study clearly revealed that the preparation of solid dispersions of PEG6000 with loperamide by spray drying, led to enhanced dissolution properties. The DSC and XRD-measurements clarified the physical state of both the drug and the carrier in the samples. A eutectic system was obtained in which the contribution of the PEG crystals over the different modifications (folded and extended) was concentration-dependent. The drug existed in a partially crystalline and partially amorphous state.

Upon storage, both the carrier and the drug were affected. Storage at relatively high temperature and/or humidity led to unfolding of the PEG chains and crystallization of the drug. The crystalline PEG cannot stabilize the amorphous part of the loperamide since it is phase-separated from the drug. What's more, also the amorphous folds of the carrier (even when mixed with the drug) cannot secure the amorphous drug from crystallization due to its low T_g-value.

These changes led to a deterioration of the dissolution properties, although they are still better than those of the pure drug. The enhanced solubility characteristics can be attributed mainly to the ability of PEG to create a better micro-environment for the dissolution of the drug. The physical state of the drug (crystalline or amorphous) is of less significance for the loperamide/PEG6000 system.

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