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Research paper

Dissolution enhancement of the anti-HIV drug UC 781 by formulation in a ternary solid dispersion with TPGS 1000 and Eudragit E100

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ABSTRACT

The present research deals with the improvement of the dissolution properties of the anti-HIV drug UC 781. A ternary solid dispersion consisting of a high amount of TPGS 1000 and exhibiting good powder properties with respect to flowability was developed. Eudragit E100 was selected as a polymer based on supersaturation studies. DSC analysis of solid dispersions containing drug doses from 0 to 80% w/w revealed eutectic phase behaviour of the ternary TPGS 100–Eudragit E100–UC 781 mixture. The release of UC 781 in a medium simulating the gastrointestinal lumen was markedly enhanced, reaching a release of 70% w/w after 4 h. XRD results pointed to the presence of crystalline drug in the solid dispersion. The presence of UC 781 in the dispersion had an influence on the TPGS 1000–Eudragit E100 carrier, favoring folding of the polyethylene glycol chains in TPGS 1000. Moreover, the addition of UC 781 to the binary polymer–surfactant mixture was physically expressed by an increase in fluidity of the samples up to a drug load of 50% w/w. NMR was used to investigate this phenomenon, revealing a shielding and/or deshielding effect of the carrier on aromatic C atoms and methyl groups in UC 781. Polyethylene glycol chains present in TPGS 1000 seemed to play a role in this process. In addition, combining UC 781 with the TPGS 1000–Eudragit E100 mixture led to the appearance of TPGS 1000 clusters with a glass transition temperature well below the T_g's of the pure compounds.

1. Introduction

UC 781 is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), belonging to the class of thiocarboxanilide derivatives [1–4]. Its chemical structure is shown in Fig. 1. Although it is regarded as a potent inhibitor of HIV-1 replication, which makes it a potential candidate for HIV-1 treatment, an oral dosage form of the drug has not yet been developed. This can be explained by the fact that UC 781 suffers from low aqueous solubility leading to insufficient bioavailability after oral intake [5]. Since permeability in the gastrointestinal lumen is adequate, UC 781 is classified as a class II compound by the Biopharmaceutical Classification System, as described by Amidon et al. [6]. Several methods have been developed to improve dissolution-limited absorption, among which the formulation of a solid dispersion by coprecipitation of a drug in a carrier or by co-melting is a popular strategy [7–9]. The drug can be dissolved in the matrix or it can be homogeneously dispersed as fine particles in an amorphous or crystalline carrier. The carrier prevents aggregation of individual drug particles and decreases their particle sizes, thus increasing the surface area from which dissolution can take place. In addition, it can create a micro-environment in which drug solubility is higher as a consequence of an altered pH or an increased concentration of wetting or solubilising agent solubility [10–13]. A solid dispersion formulation process may transform the physical state of the drug, often resulting in improved dissolution rates if conversion of the drug to its amorphous state occurs. Amorphous drugs are however thermodynamically unstable and tend to recrystallise in time [14]. To stabilise amorphous drugs, carriers often comprise a polymer that reduces molecular mobility and thus prevents or impedes nucleation and crystal growth. This is expressed by an increased glass transition temperature (T_g) of compatible drug–polymer blends as compared to the T_g of the drug (Table 1).

The present research focuses on the development of a new carrier system for UC 781. There is a great need for new carrier systems to be used upon formulating solid dispersions. Although extensive research has been done on solid dispersion formulations, focus has been predominantly on binary blends while more complex carriers remain to be explored. In this study, a surfactant was combined with a polymer in order to improve powder properties in terms of flowability and bulk density thus facilitating downstream processing to solid dosage forms. A carrier system made up

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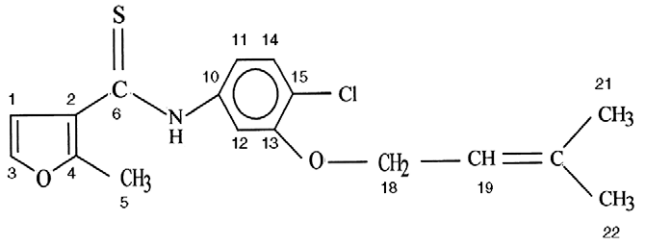

Fig. 1. Chemical structure of UC 781.

Table 1
Measured and calculated values of the heats of fusion of binary Eudragit E100–TPGS 1000 mixtures

Eudragit E100–TPGS 1000 ratio	Experimental heat of fusion (J/g)	Experimental heat of fusion (J/g)	Calculated heat of fusion (J/g)
50/50	47.5	49.9	52.7
40/60	61.6	63.5	63.3
35/65	65.6	66.3	68.5
30/70	71.4	70.9	73.8
20/80	83.2	85.7	84.4

Calculated values are based upon the experimental heat of fusion of TPGS 1000 (105.4 J/g) and the percentage of TPGS 1000 in the binary blend.

of a polymer and a surfactant may show interesting results with respect to drug dissolution. Surfactants lower the solid–liquid surface tension of poorly soluble drug particles and have the potential to maintain a supersaturated solution upon dissolution of a drug. Moreover, a polymer can further enhance stability of a supersaturated solution and prevent drug nucleation and precipitation.

This study focuses on the development of a new ternary solid dispersion to improve the dissolution properties of UC 781. TPGS 1000, a promising surfactant with respect to enhancing drug release, will be combined with a polymer, capable of stabilising a UC 781 supersaturated solution [15,16]. A polymer will therefore be selected based on a supersaturation screening study.

Considering the low melting point of TPGS 1000 and hence its waxy nature, formulating a solid dosage form of a carrier containing a high amount of the surfactant is a challenge. Nevertheless, to improve drug solubility to a maximal extent, a carrier comprising a high amount of surfactant is preferred.

2. Materials and methods

2.1. Materials

UC781 was kindly supplied by the Rega Institute (Leuven, Belgium). Eudragit E100 was obtained from Röhm (Germany) and TPGS 1000 was purchased from Eastman (Wales, UK). Sodium chloride, potassium hydroxide and sodium hydroxide were purshased from BDH (Poole, England). Hydrochloric acid (1N) was purchased from VWR International (Fontenay Sous Bois, France). Trisodium phosphate and methanol were obtained from Acros Organics (Geel, Belgium). Dichloromethane and acetonitrile were purchased from Fisher Scientific (Leicestershire, UK). Polyvinylpyrrolidone K25 (PVP K25), polyvinylpyrrolidone–covinylacetate 64 (PVP-VA64), hydroxypropylmethylcellulose 2910 (HPMC 2910), Poloxamer 188 and Kollicoat IR were a gift from BASF (Ludwigshafen, Germany). Polyethylene Glycol (PEG) 6000 and PEG 10000 were obtained from Acros Organics (Geel, Belgium).

2.2. Methods

2.2.1. Preparation of solid dispersions and physical mixtures

Physical mixtures of UC781 were prepared by mixing the drug with TPGS 1000 and Eudragit E100 during 2–4 min in a mortar until a homogeneous mixture was obtained. The resulting mixture was stored at 25 °C under vacuum for one week.

Binary and ternary solid dispersions were prepared by spray-drying. The appropriate amounts of polymer and TPGS 1000 (binary dispersions at varying ratios) or Eudragit E100, TPGS 1000 and UC 781 (ternary dispersion at a Eudragit E100–TPGS 1000–UC 781 ratio of 72-18-10) were dissolved in dichloromethane so that the total concentration of solid in solution was 6.6% w/v. The solutions were spray-dried using a Büchi Mini Spray Dryer B191 (Büchi Labortechnik AG, Flawil, Switzerland) with a fixed set of adjustable parameters (inlet temperature: 22 °C, feeding rate: 1.85 ml/min, air flow: 400 l/h, power of aspirator: maximum). The dispersions were further dried at 25 °C under vacuum for one week and stored in a desiccator at room temperature.

2.2.2. Solid dispersion flow properties

Flow properties and compressibility of the resulting formulations were studied by determining their Carr's indexes and Hausner ratios. A Carr's index (CI) is determined as

$$CI = D_t - D_0/D_t$$

where D_t is the tapped density of the powder (500 taps) and D_0 is the fluff powder density (only 10 taps). The powder's Hauser ratio (HR) is expressed as

$$HR = D_t/D_0$$

2.2.3. Supersaturation experiments

Hundred microliters of a 0.833% w/v solution of UC781 in methanol was added to 10 ml polymer solution, which consisted of 0.5% w/v, 2% w/v or 5% w/v PVP K25, PVP–VA 64, HPMC 2910, PEG 6000, PEG 100000, Kollicoat IR, Poloxamer 188 or Eudragit E100 in simulated gastric fluid. The concentration of UC 781 was determined at several time points to investigate the ability of the polymers to keep UC 781 dissolved. All samples were diluted with an equal amount of methanol after filtration using 0.45 μm pore size membrane filters (Millipore) prior to HPLC analysis (see Section 2.2.5).

2.2.4. Dissolution studies

UC 781 dissolution from solid dispersions was studied using a dissolution bath SR8 (Analis, Namur, Belgium) at 37 °C and a paddle speed of 100 rpm (USP29, paddle method A). The release medium consisted of 750 ml simulated gastric fluid (SGF, standard USP solution) containing 0.1% w/v Tween 80. After 2 h, 250 ml of 0.2 M tribasic sodium phosphate solution was added and the pH was adjusted to 6.8 ± 0.05 using 1 N hydrochloric acid or 2 N sodium hydroxide if necessary. An amount of solid dispersion containing 2.15 mg UC781 was added to the reaction vessel as the experiment was started. Samples of 2 ml were collected after 5, 10, 30, 60, 90, 120, 130, 150, 180 and 240 min using a syringe and were replaced with the same volume of release medium. The samples were subsequently filtered using 0.45 μm pore size membrane filters (Millipore). Experiments were performed in triplicate. All samples were analysed with HPLC.

2.2.5. HPLC analysis

The concentration of UC 781 was determined using an isocratic HPLC method. The HPLC system consisted of a LiCroGraph L-7100 HPLC pump, a L-7200 autosampler equipped with a 100 μl loop,

a UV detector model L-7420 set at 297 nm, and an interface D-7000, all from Merck-Hitachi (Darmstadt, Germany). The column was a Chromolith Performance RP-18e 100 × 4.6 mm (Merck KgaA, Darmstadt, Germany). A mobile phase of acetonitrile: water (55:45 v/v) was used at a flow rate of 1.0 ml/min. 80 μl samples were injected onto the column. The standards for UC 781 measurements were prepared in methanol and were diluted with water at a ratio of 1/1, prior to analysis. UV signals were monitored and peaks were integrated using the D-7000 HSM software.

2.2.6. Thermal analysis

DSC measurements on binary polymer–surfactant mixtures were carried out using a Perkin Elmer DSC-7 differential scanning calorimeter, equipped with a liquid nitrogen subambient accessory (Perkin Elmer, Norwalk, CT, USA). Samples were weighed in aluminium pans (Perkin Elmer, Norwalk, CT, USA) and heated from 10 to 100 °C at a heating rate of 10 °C/min under nitrogen gas purge. Calibration was carried out using indium and *n*-octadecane as reference materials. Data were treated mathematically using the Pyris Software version 3.6 (Perkin Elmer, Norwalk, CT, USA).

MTDSC measurements on ternary mixtures were carried out using a Q2000 Modulated DSC (TA Instruments, Leatherhead, UK) equipped with a refrigerated cooling system (RCS). Data were analysed mathematically using Thermal Solutions software (TA Instruments). Dry nitrogen (5.0) at a flow rate of 50 mL/min was used as the purge gas through the DSC cell. TA Instruments aluminium open pans were used for all calorimetric studies. The mass of the empty sample pan was matched with the mass of the empty reference pan within ±0.1 mg, the sample mass varied from 2 to 6 mg. The temperature scale and the enthalpic response were calibrated with an Indium standard; heat capacity was calibrated using a sapphire disk. Validation of temperature and enthalpy measurements using the same standard materials showed that deviation of the experimental value from the reference value was <0.5 °C for the temperature measurement, and <1% for measurement of enthalpy at 80 °C. The amplitude used was 0.212 °C, the period was 40 s, and the underlying heating rate was 2 °C/min. The samples were analysed in the range from −70 to 165 °C. Glass transition temperatures were analysed in the reversing heat flow and melting peaks were investigated upon in the total heat flow.

2.2.7. X-ray powder diffraction

Drug crystallinity was measured by X-ray diffraction using a X'celerator detector 3015/20 (Almelo, The Netherlands). A small sample was placed in a capillary spinner PW 3063/00 and was exposed to CuKα (λ = 1.540598 Å) radiation from a PW 3373/10 tube and high tension X-ray generator 3 kW with PW 3085/40 0.04 rad soller slits, a focussing mirror CuW/Si 3086/75 and a Ni 0.02 mm filter. Diffraction patterns were obtained on an X'pert Pro PANalytical X-ray powder diffractometer equipped with a Pw 3050/60 goniometer. The data were collected in step scan mode in the region of $4° \leqslant 2\theta \leqslant 40°$ with a step size of 0.02° and a dwell time of 2 s. Each sample powder was carefully loaded in a glass sample capillary. The diffractograms were analysed using the X'pert data collector program (version 2.2 c, 2007). The experiments were carried out at room temperature.

2.2.8. ^{13}C CP MAS Nuclear Magnetic Resonance

The ^{13}C CP MAS NMR spectra were recorded on a Bruker DSX400 spectrometer (9.4 T). 24000 scans were accumulated with a recycle delay of 10 s. The samples were packed in 2.5 mm Zirconia rotors, and were spun at 6000 Hz. Tetramethylsilane was used as shift reference. A line broadening factor of 30.0 Hz was applied to the spectra.

3. Results and discussion

3.1. Selection and characterisation of a carrier

The non-ionic surfactant tocopheryl polyethylene glycol succinate 1000 or TPGS 1000 has shown in previous studies to possess the capacity to markedly enhance the solubility of poorly water-soluble drugs [15,16]. This can be ascribed to its wetting and solubilising properties that lead to a supersaturated solution of the drug. Because of its low melting point (T_m = 39 °C), TPGS 1000 is very sticky at room temperature, which makes it less suitable as a carrier. Powder properties can however be enhanced by adding a polymer to the carrier system. Moreover, a polymer may prevent precipitation of the drug from a supersaturated solution. The capacity to stabilise a supersaturated solution will therefore be the basis for the selection of a polymer in a screening study. The supersaturation degree, expressed as the percentage of UC 781 remaining in solution after 2 h, was determined by measuring the concentration of UC 781 in 2% w/v polymer solutions after the addition of a methanolic solution of the drug. A 2% w/v solution of Eudragit E100 was able to keep 65.2 ± 2.2% w/v of UC 781 in solution after 2 h (Fig. 2). All other polymer solutions showed inferior stability of the supersaturated UC 781 solution as compared to Eudragit E100 in 0.5% w/v, 2% w/v and 5% w/v polymer solutions. Moreover, it is clear from Fig. 3 that the beneficial effect of Eudragit E100 on UC 781 supersaturation is concentration dependent.

Thermal properties of various spray-dried mixtures of Eudragit E100 and TPGS 1000 were investigated by Differential Scanning Calorimetry (DSC) in order to analyse the compatibility of the surfactant and the polymer. Moreover, a thorough understanding of the binary carrier mixture ensures a correct interpretation of DSC data of the ternary dispersion. Thermograms of the pure compounds as well as blends of different TPGS 1000/Eudragit E100 ratios are shown in Fig. 4. Pure Eudragit E100 is amorphous in nature and exhibits a glass transition at 43.7 °C. The glass transition temperature of pure TPGS 1000 is about −7.5 °C, depending on its thermal history [17]. However, no glass transition is detectable in the DSC thermograms of the TPGS 1000–Eudragit E100 mixtures. In addition, the melting peak of TPGS 1000, which can be ascribed to the melting of its ordered polyethylene glycol (PEG) chains, perseveres through all investigated blends. Its position however shifts to lower values upon adding the polymer, indicating that Eudragit E100 favors folding of the polyethylene glycol chains. Anyway, the occurrence of the melting peak points to phase separation of semi-crystalline TPGS 1000 at all investigated surfactant/polymer ratios. A separate amorphous Eudragit E100 phase can however not be detected, since its T_g (43.7 °C) is situated close to the melting temperature of TPGS 1000.

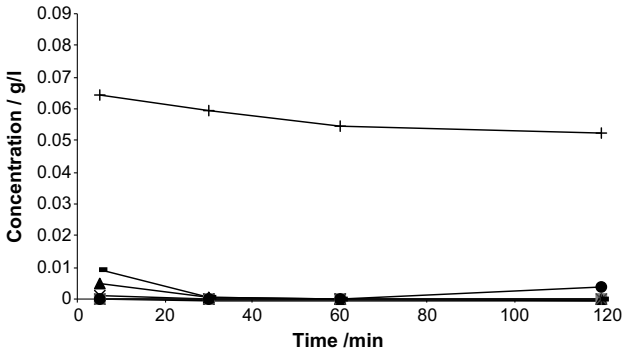

Fig. 2. Supersaturation of UC 781 in SGF containing 2% w/v PVP K25 (♦), PVP VA64 (■), HPMC 2910 (▲), PEG 6000 (×), PEG 100000 (●), Kollicoat IR (∗), Poloxamer 188 (−) or Eudragit E100 (+).

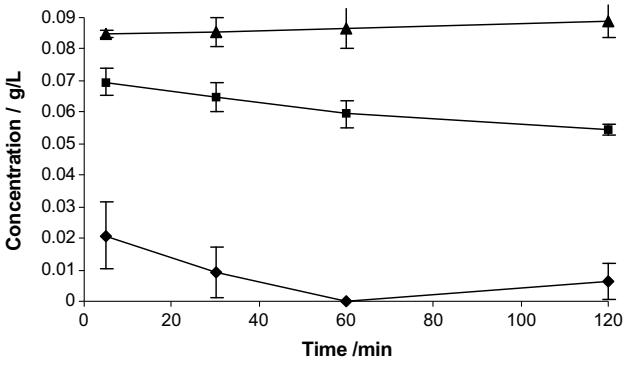

Fig. 3. Supersaturation of UC 781 in SGF containing 0.5% w/v Eudragit E100 (♦), 2% w/v Eudragit E100 (■), or 5% w/v Eudragit E100 (▲). Error bars indicate the standard deviation (n = 3).

An optimal TPGS 1000–Eudragit E100 ratio was selected based upon powder properties, which are described by the Carr index and Hausner ratio of the placebo spray-dried mixtures. UC 781 was not included in this phase due to a limited amount of UC 781 available for this study. A Hausner ratio below 1.2 and a Carr index below 16 generally represent powders with acceptable flowability. Higher values point to poorly flowing powders since initial bulk and tapped densities will be more similar in free flowing powders as compared to poorly flowing powders. Table 2 lists the Carr index and Hausner ratio of TPGS 1000/Eudragit E100 ratios of 50/50, 60/40, 70/30, 80/20 and 90/10 w/w. At TPGS 1000 concentrations of up to 70% w/w, Carr indexes are well below the maximal value of 16, pointing to acceptable flowability, although a Hausner index of 1.21 is obtained at a surfactant concentration of 70% w/w. A blend containing 80% w/w TPGS 1000 and 20% Eudragit E100 exhibits a Carr index and a Hausner ratio value of 16.2 and 1.19, respectively, while further increasing the surfactant concentration to 90% w/w results in poor flow properties. Based on these results, a 80/20 w/w ratio of TPGS 1000/Eudragit E100, representing a maximum amount of surfactant while still exhibiting acceptable flow properties, was selected as a carrier system for the formulation of a solid dispersion.

Table 2
Carr indexes and Hausner ratios of various TPGS 1000–Eudragit E100 concentration ratios

Concentration ratio of TPGS 1000/Eudragit E100	Carr index	Hausner ratio
50/50	14.3	1.12
60/40	8.57	1.09
70/30	12.8	1.21
80/20	16.2	1.19
90/10	22.8	1.29

3.2. Solid dispersion characterisation

3.2.1. Influence of UC 781 on thermal transitions

The impact of UC 781 on thermal transitions of the carrier was investigated by MTDSC. DSC thermograms of solid dispersions at varying drug loads can exhibit two main endothermic events, as is shown in Fig. 5. The first endotherm can be ascribed to melting of the carrier, more precisely of the polyethylene glycol chains present in TPGS 1000. This is also shown in Fig. 4. The second peak represents the melting of drug crystals. Pure UC 781 exhibits a melting peak at 128.72 °C (Fig. 5).

The endothermic events of solid dispersions containing 0–100% w/w UC 781 was plotted in a temperature vs. concentration diagram, depicted in Fig. 6. The phase diagram points to eutectic behaviour of which only one arm is visible. The latter can be explained by the fact that the region at which eutectic melting and melting of the excess carrier crystals occurs is very narrow (T_{m1}). Thus, at carrier concentrations above the eutectic composition, only one transition is shown in DSC results. Upon addition of UC 781 to the binary carrier, the position of the carrier's melting peak shifted to lower values (39.1 °C at 0% w/w UC 781 to 27.3 °C at 50%

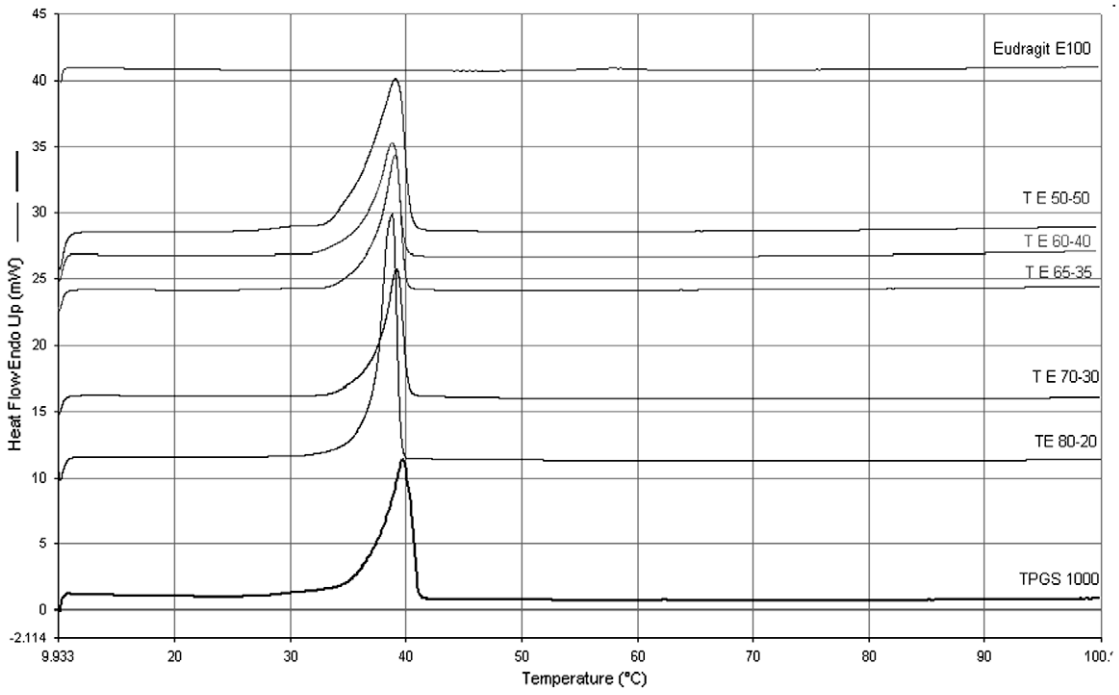

Fig. 4. Heat flow curves of Eudragit E100, TPGS 1000 and combinations of both of varying concentration ratios: 80% TPGS 1000 and 20% Eudragit E100 (TE 80–20), 70% TPGS 1000 and 30% Eudragit E100 (TE 70–30), 60% TPGS 1000 and 40% Eudragit E100 (TE 60–40), 50% TPGS 1000 and 50% Eudragit E100 (TE 50–50).

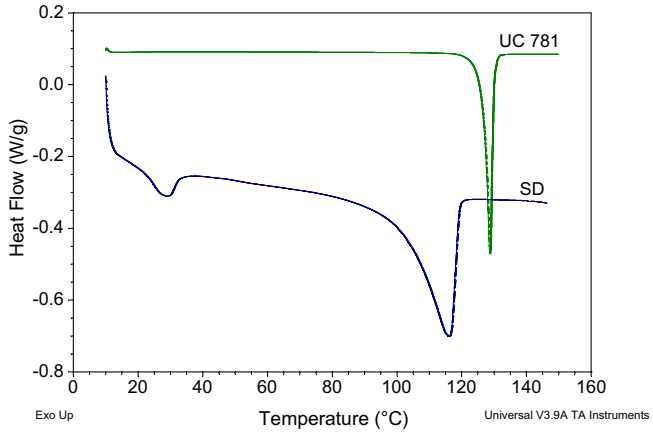

Fig. 5. Heat flow vs. temperature curves of UC 781 and a solid dispersion comprising 60% w/w UC 781 and 40% w/w carrier. The carrier is made up of 80% w/w TPGS 1000 and 20% Eudragit E100.

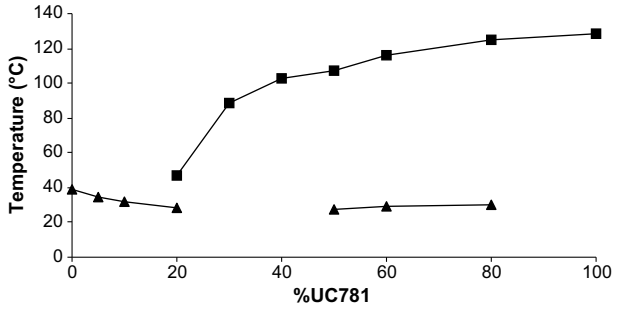

Fig. 6. Phase diagram of the ternary TPGS 1000–Eudragit E100–UC 781 system. (▲) represents T_{m1} and (■) represents T_{m2}.

w/w UC 781), indicating that the drug favors folding of the polyethylene glycol chains present in the carrier system. At UC 781 concentrations above the eutectic composition, the presence of excess drug crystals is expressed by the second melting endotherm (T_{m2}). Upon lowering the drug dose from 100% w/w to 20% w/w, the endotherm broadened due to gradual dissolution of UC 781 crystals in the carrier melt. The same phenomenon had been discussed in previous studies [5,20,21].

As opposed to an amorphous dispersion, which contains the drug in an amorphous state, a eutectic mixture comprises an intimate mixture of crystalline carrier and crystalline drug, hence a two phase system. The drug particle size is markedly reduced, thus possibly enhancing dissolution of UC 781 from the matrix.

At drug loads of 30% w/w and 40% w/w, the first endotherm remarkably disappears, accompanied by an increased fluidity of the samples. The latter caused the baseline to fluctuate in DSC thermograms. In order to investigate the increased fluidity, solid state ^{13}C CP MAS NMR was performed, thereby enlightening the presence or absence of drug–carrier interactions. Since the fluidity of the samples was maximal for solid dispersions containing 30% w/w and 40% w/w UC 781, ^{13}C NMR spectra of dispersions comprising between 20% and 50% w/w drug were recorded. A ternary blend containing 20% w/w was waxy in nature whereas a powder was obtained at a drug load of 50% w/w. If interactions between drug and carrier would occur, the electron density at the interacting C atoms will change, which would be reflected in chemical shift variations.

Fig. 7A shows chemical shifts between 10 ppm and 40 ppm in the case of the pure drug and solid dispersions containing 20% w/w, 30% w/w, 40% w/w and 50% w/w UC 781. As compared to pure UC 781, the chemical shifts of the C atoms of the drug at a drug dose of 50% w/w remained unchanged. In contrast, ^{13}C CP MAS NMR spectra of formulations containing 20%, 30% and 40% w/w UC 781 reveal peak doubling at ppm values of 14, 18 and 26. This points to a shielding and deshielding effect of TPGS 1000 and/or Eudragit E100 on C21, C22 and C3 carbon atoms of the drug (Fig. 1). The extent of this effect decreases upon lowering the amount of carrier in the solid dispersions (2 shoulders in the NMR spectrum of 40% w/w UC 781, separate peaks in the spectra of 20% w/w UC 781 and 30% w/w UC 781). In addition, various carbon atoms of the aromatic ring of UC 781 (C 10, 11, 14 and 15] and of the furan ring of UC 781 (C 2 and 3) also undergo changes in their chemical shifts, expressed as a broadening of the peaks in the ^{13}C CP MAS NMR spectra at ppm values of about 120, 125, 130, 137 and 140 (Fig. 7B). Unfortunately, the inversed effect of the drug on the carrier excipients could not be detected in CP MAS NMR spectra of TPGS 1000 and Eudragit E100. This can be explained by the fact that the latter are large compounds, which means that the change in chemical shift can be reduced by spreading the difference in electron density over a high amount of bonds. Only very weak signals were recorded from TPGS 1000 and Eudragit E100 by ^{13}C CP MAS NMR. However, it is clear form Fig. 7C that UC 781 does interact with TPGS 1000 since changes in chemical shifts to lower ppm values occur upon addition of UC 781, correlating to carbon atoms of the polyethylene glycol chain of the surfactant.

3.2.2. Drug release

UC 781 release from solid dispersions containing 10% w/w drug was measured for 4 h in simulated gastric fluid. Two hours after starting the experiment, phosphate buffer was added to the medium and the pH was adjusted to 6.8, thus further mimicking the in vivo situation.

As could be expected from the drug's low aqueous solubility, pure UC 781 shows a limited dissolution with only 37.1 ± 8.5% drug dissolved after 4 h (Fig. 8). Formulation of the drug in a TPGS 1000/Eudragit E100 solid dispersion leads to a tremendous increase in dissolution rate: ca 50% w/w of the drug was dissolved after only 5 min (Fig. 8). A plateau is reached after 30 min representing a drug release of almost 80%, which persists until phosphate buffer is added. This can be related to the fact that Eudragit E100 dissolves only at low pH values, thus lowering UC 781 dissolution once the pH of the medium is changed to 6.8. Nonetheless a plateau is re-established after 4 h when up to 70% w/w UC 781 has dissolved in the release medium.

A physical mixture of the same composition can also significantly increase UC 781 dissolution as compared to the dissolution of pure UC 781. After 4 h, 58 ± 1.1% w/w UC 781 was dissolved in the release medium. This can be attributed to the wetting and solubilising effect of the binary carrier, locally increasing drug solubility and impeding the aggregation of drug particles.

3.2.3. Physicochemical characterisation

X-ray powder diffraction (XRD) was performed in order to elucidate the physical structure of the drug in the solid dispersion formulation. UC 781 reveals many distinct reflections in its diffractogram, pointing to its highly crystalline nature (Fig. 9). Various diffraction peaks of the drug crystals can be traced in the spectrum of the physical mixture, e.g. at $2\theta = 7.45$, 10.02, 12.5 and 21.11. These peaks are even present in XRD spectra of the solid dispersion formulation, although with lower intensity. This reveals the presence of drug crystals in both formulations. Diffraction peaks at $2\theta = 7.45$ and 14.6 grow in time, as shown by the spectra of the solid dispersions after one and ten months, suggesting UC 781 recrystallisation. The crystalline character of

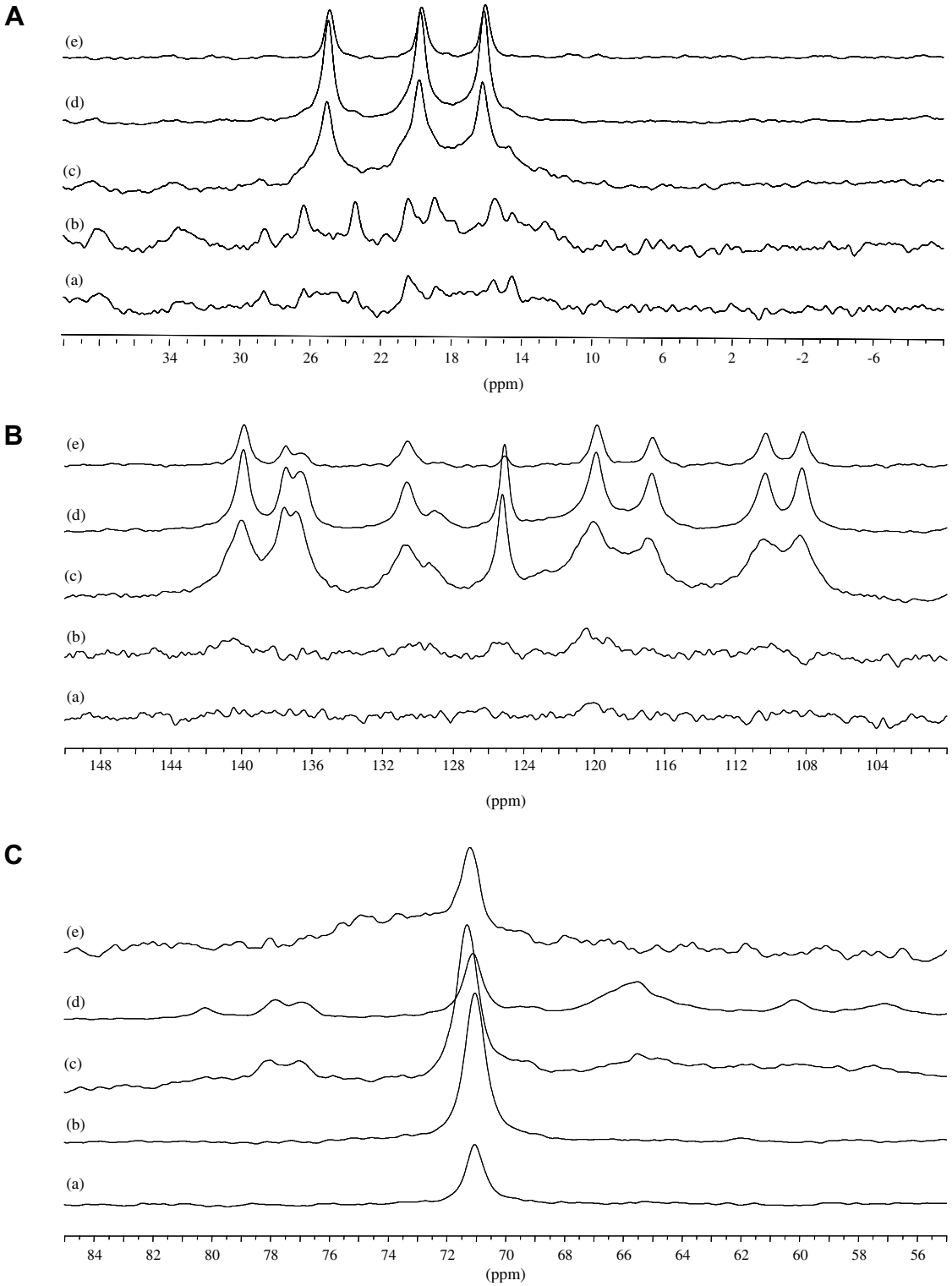

Fig. 7. ^{13}C CP MAS NMR spectra between 40 and 10 ppm (A), 150 and 100 ppm (B) and 85 and 55 ppm (C) of ternary TPGS 1000–Eudragit E100–UC 781 dispersion containing 20% w/w UC 781 (a), 30% UC 781 (b), 40% w/w UC 781 (c) and 50% w/w UC 781 (d). (e) The ^{13}C CP MAS NMR spectrum of pure UC 781.

TPGS 1000 is expressed by its diffraction spectrum, showing 2 diffraction peaks with the highest intensity at $2\theta = 19.14°$ and 23.34°, corresponding to lattice spacings of 4.63 and 3.81 Å, respectively. Identically positioned diffraction peaks can be clearly detected in XRD spectra of the solid dispersion and the physical mixture, ruling out the possibility of the drug interfering with the lattice spacing in TPGS 1000.

MTDSC thermograms of the solid dispersion and the physical mixture are depicted in Fig. 10. The first endotherm (at 39 °C) can be attributed to the melting of TPGS 1000 polyethylene glycol chains, as previously described. Surprisingly, the solid dispersion undergoes a glass transition at −49.3 °C. Since this is considerably lower than the glass transition of Eudragit E100 (42.9 °C), TPGS 1000 (−7.5 °C) or amorphous UC 781 (−7.5 °C) [5,17,18], the T_g

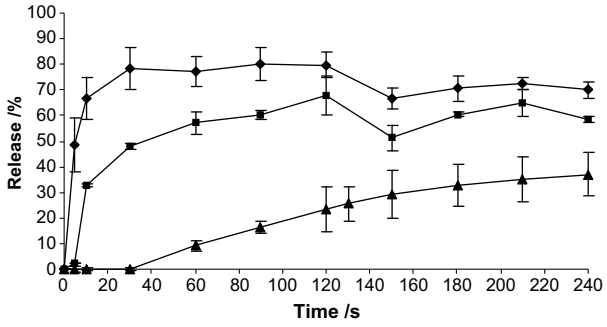

Fig. 8. Release of UC 781 in simulated gastric fluid (SGF) containing 0.1% w/v tween 80. After 2 h, 0.2 M tribasic sodium phosphate was added and pH was adjusted to 6.8. (■) represents release of UC 781 from a Eudragit E100–TPGS 1000 physical mixture, (♦) describes the release of UC 781 from a Eudragit E100–TPGS 1000 solid dispersion. The release of pure drug is indicated by (▲). Error bars indicate the standard deviation ($n = 3$).

can hardly be related to any anti-plasticing effect of the carrier. The relatively low glass transition temperature is also physically expressed by the more waxy nature of the solid dispersion formulation as compared to the corresponding binary TPGS 1000/Eudragit E100 blend. In addition, the DSC thermogram of the physical mixture reveals a glass transition at −27.0 °C, which is less pronounced as compared to the solid dispersion formulation, thus resulting in improved powder properties.

In order to further investigate this phenomenon, solid dispersions containing UC 781 in a concentration range of 5–60% w/w were prepared and transitions occurring in a temperature region of −90 °C up to 160 °C were analysed by DSC. Endothermic transitions are shown in Fig. 11 and listed in Table 3 and reveal glass transitions at temperatures well below the T_g values of the pure excipients. The absence of a glass transition in DSC thermograms of a binary mixture of 80% w/w TPGS 1000 and 20% w/w Eudragit E100 reveals that UC 781 is required for this phenomenon, although the position of the glass transition does not seem to be related to the concentration of the drug. A similar phenomenon has been described by Janssens et al. upon formulation of itraconazole in a TPGS 1000-based carrier, where it was concluded that amorphous TPGS 1000 clusters are created upon addition of the drug showing varying glass transitions, depending on the thermal history of the samples [18].

4. Conclusion

In this research, dissolution of UC 781 is enhanced by formulation in a solid dispersion, attaining a drug release of 70% w/w after 4 h. The formulation consisted of TPGS 1000, which was combined with Eudragit E100 to improve the powder's flowability. Moreover, Eudragit E100 increased UC 781 supersaturation, thereby enhancing drug dissolution. The formulation's phase diagram pointed to eutectic behaviour. Although UC 781 did not seem to affect the lattice spacing of TPGS 1000 polyethylene glycol chains, the drug did influence the binary TPGS 1000–Eudragit E100 blend: besides the effect of UC 781 on the distribution of polyethylene glycol folding forms, the addition of the drug also led to an increased fluidity of the ternary mixture up to a drug load of 40% w/w. It was clear from NMR experiments that several carbon atoms of the aromatic ring and free methyl groups of UC 781 experienced shielding and/or deshielding upon exposure to the carrier. The polyethylene glycol chain of TPGS 1000 played a definite role in this process. The increase in fluidity of the TPGS 1000–Eudragit E100 blend upon addition of UC 781 was also enhanced by the fact that an extremely low glass transition temperature occurred when UC 781 was added to the binary polymer–surfactant mixture, which could be explained by the presence of amorphous TPGS 1000 clusters showing varying glass transitions, depending on the thermal history of the samples. In this respect, the carrier was not able to prevent crystallisation of UC 781 in the solid dispersion formulation.

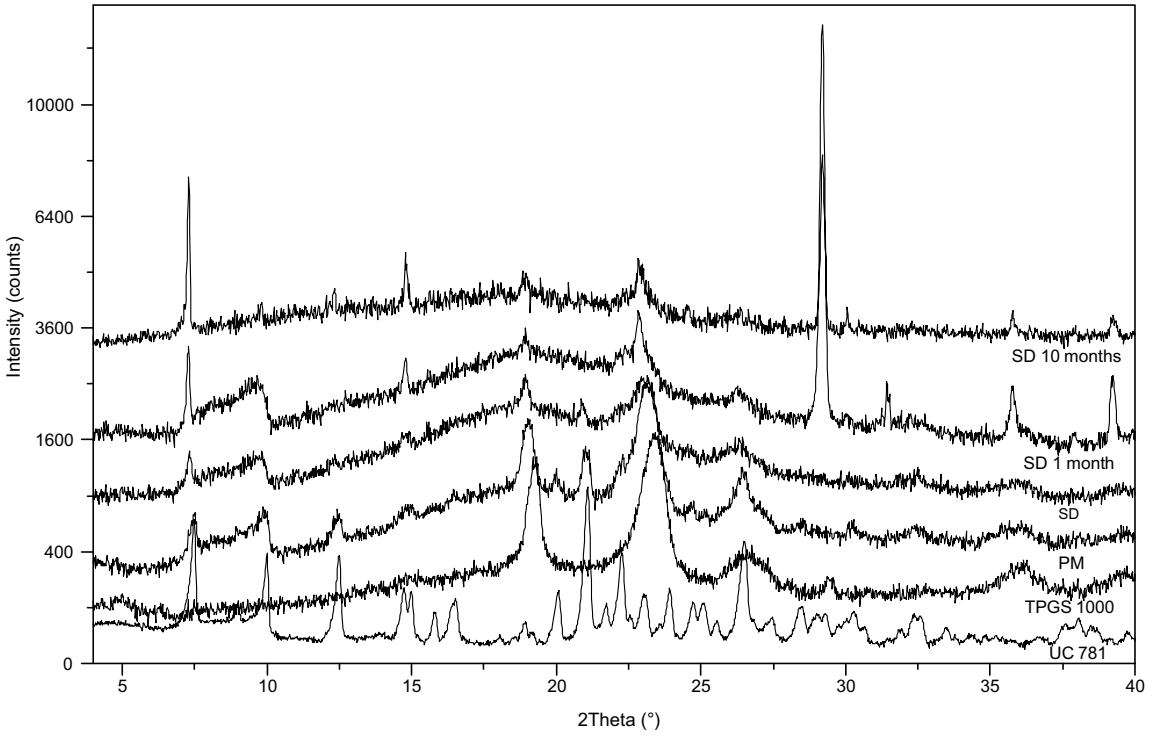

Fig. 9. X-ray diffraction patterns of UC 781, TPGS 1000, physical mixture (PM) containing 10% w/w UC 781 and 90% w/w carrier and solid dispersion (SD) containing 10% w/w UC 781 and 90% w/w carrier after 1 day, 1 month and 10 months.

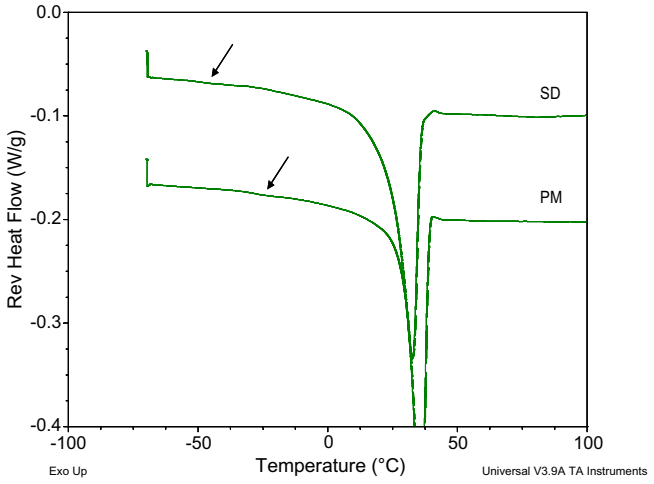

Fig. 10. Reversing heat flow curves of a ternary solid dispersion (SD) and physical mixture (PM) consisting of 18% w/w Eudragit E100, 72% w/w TPGS 1000 and 10% w/w UC 781. Arrows indicate T_g's.

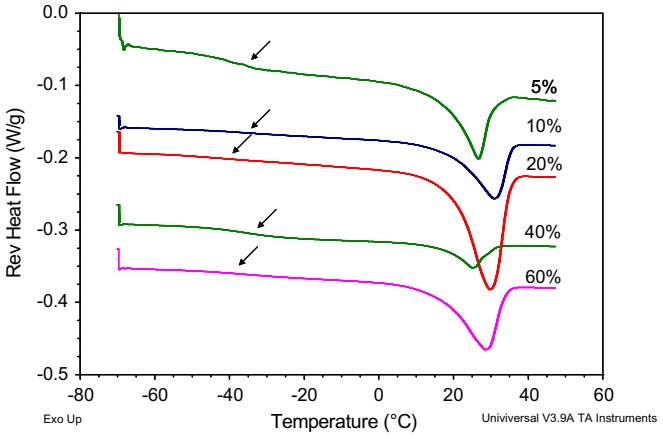

Fig. 11. Reversing heat flow curves of solid dispersions containing UC 781, Eudragit E100 and TPGS 1000. The Eudragit E100/TPGS 1000 ratio was kept constant at 20/80, and the drug dose varied between 0% and 60% w/w (percentage UC 781 is indicated in the figure). Arrows indicate T_g's.

Table 3
Glass transition temperatures of solid dispersions containing UC 781, Eudragit E100 and TPGS 1000 at various drug doses

% w/w UC 781 present in the solid dispersion	0	5	10	20	40	60
T_g/°C	/	−35.5	−36.9	−44.6	−35.3	−37.6

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