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Pharmaceutical development and preliminary clinical testing of an oral solid dispersion formulation of docetaxel (ModraDoc001)

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ABSTRACT

For use in chronic oral chemotherapeutic regimens, the potent anticancer drug docetaxel needs a solid oral dosage form. Because docetaxel has a very low permeability and a very low aqueous solubility (biopharmaceutical classification system class IV), a pharmacokinetic booster was combined with a newly developed solid dispersion formulation to improve the oral bioavailability of docetaxel.

The best performing solid dispersion was a 1/9/1 w/w/w ternary mixture of docetaxel, polyvinylpyrrolidone (PVP)-K30 and sodium lauryl sulphate (SLS). In a phase I clinical trial, with ritonavir as pharmacokinetic booster, the docetaxel premix solution (TAXOTERE) was pharmacokinetically evaluated against the solid dispersion formulation filled into hard gelatin capsules (ModraDoc001 15 mg capsules).

There were no significant differences between the pharmacokinetic parameters of docetaxel after administration of docetaxel premix solution or ModraDoc001 15 mg capsules, although there was a trend towards a higher and more variable exposure to docetaxel after oral administration of docetaxel premix solution (513 ± 219 vs. 790 ± 669 ng h/mL).

The low inter-individual variability of docetaxel exposure (44%), the dosing accuracy, and the absence of ethanol and polysorbate are major advantages of ModraDoc001 15 mg capsules over docetaxel premix solution.

1. Introduction

Cancer is still one of the leading causes of death in the Western World. Despite the development and introduction of new anticancer agents, taxanes remain the cornerstone of adjuvant and metastatic chemotherapy against solid tumors. Taxanes belong to the class of anti-mitotic agents and block the disassembly of microtubules, thereby inhibiting vital mitotic functions and cell proliferation. The most widely used taxanes are paclitaxel and its structural analog docetaxel.

Docetaxel is registered for the treatment of breast, non-small cell lung, prostate, gastric, and head and neck cancer. The recommended dose of 75–100 mg/m^2 docetaxel is administered via intravenous (IV) infusion (SPC TAXOTERE).

Because of its mechanism of action continuous exposure to docetaxel could improve its effectiveness against cancer (Bruno et al., 1998; Engels et al., 2005). Continuous exposure can be reached by chronic IV administration of docetaxel. Chronic IV administration is, however, costly and inconvenient for patients. Furthermore, the current IV formulation can induce severe hypersensitivity reactions after IV administration, most probably related to polysorbate 80, one of the excipients. Hence, to enable chronic administration of docetaxel a different administration route is warranted.

The most suitable administration route for chronic administration is the oral route. General advantages of the oral administration route and oral dosage forms are convenience, ease of use and lower costs. Furthermore, it is possible to administer oral dosage forms on an outpatient basis or at home. The combination of these advantages will lead a higher quality of life during treatment (Bardelmeijer et al., 2000).

Unfortunately, the bioavailability of docetaxel after oral administration is less than 10%. The low oral bioavailability of docetaxel is caused by its very low solubility (Gao et al., 2008) and permeability (Engels et al., 2005). Therefore, docetaxel is classified as a Biopharmaceutical Classification System (BCS) class IV drug (Amidon et al., 1995). The very low permeability of docetaxel is partly due to active excretion by P-glycoprotein pumps and for a much larger extent to extensive metabolism by CYP3A4 enzymes in the gut wall and liver (van Waterschoot et al., 2009). We have shown that the apparent oral bioavailability of the docetaxel premix solution

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increased to 131 ± 90% by concomitant administration of ritonavir, a strong CYP3A4 inhibitor (Oostendorp et al., 2009). Ritonavir is an excellent pharmacokinetic booster and is licensed for this use in several anti HIV regimens.

The docetaxel premix solution is, however, not suitable for regular clinical use, because of the bad taste, limited storage stability (only 8 h), high ethanol content and poor dosing accuracy (Aventis Pharma S.A. and European Medicines Agency). Moreover, the lack of a stable, easy to use, patient convenient oral formulation hampers the further development of oral docetaxel chemotherapy.

Although a typical solid oral dosage form could fulfill these demands, the very low solubility of docetaxel, which is approximately 5 μg/mL (Gao et al., 2008), poses a major pharmaceutical development challenge. The low solubility will inevitably lead to low dissolution rates from typical solid oral dosage forms (capsules, tablets); which will negatively affect the oral bioavailability of docetaxel. Therefore, docetaxel needs a special formulation to achieve a higher solubility and dissolution rate. We chose to combine our successful boosting strategy (Oostendorp et al., 2009) with a solid dispersion formulation.

A solid dispersion formulation consists of a crystalline or amorphous drug that is molecularly dispersed in a hydrophilic matrix or carrier (Chiou and Riegelman, 1971; Leuner and Dressman, 2000; Serajuddin, 1999). The large surface area of the drug particles, the presence of a highly soluble carrier and the higher solubility of the amorphous state are responsible for the high dissolution rate of drugs from solid dispersion formulations. Solid dispersion formulations have successfully improved the dissolution and bioavailability of a number of low-soluble drugs (e.g. griseofulvin, tacrolimus, everolimus, ritonavir and lopinavir) (Janssens and van den Mooter, 2009). There have also been attempts to develop solid dispersions of docetaxel, but these formulations were not able to improve the dissolution rate of docetaxel to such an extent that applications in an oral formulation would be feasible (Chen et al., 2008).

The goal of this study was to develop an oral solid dosage form containing a solid dispersion of docetaxel with a high solubility, high dissolution rate, and a high oral bioavailability. We used various carriers (PVP, PEG, and HPMC), surfactants and weight ratios to produce solid dispersions and compared them to physical mixtures with the same compositions. All formulations were examined by modulated differential scanning calorimetry (MDSC), Fourier transform infrared spectroscopy (FT-IR) and X-ray diffraction analysis. Maximum solubility, time to precipitation and equilibrium solubility were measured in a small-scale dissolution test; dissolution rates and duration were examined with a pharmacopoeial dissolution test. The best performing solid dispersion was filled into hard gelatin capsules and compared to the docetaxel premix solution in a phase I clinical trial with six human subjects.

2. Materials and methods

2.1. Materials

Docetaxel anhydrate was purchased from Scinopharm Taiwan (Taiwan). Various grades of polyvinylpyrrolidone (PVP K12-K90) and polyvinylpyrrolidone vinyl acetate copolymer (PVP-VA) were kindly supplied by BASF (Ludwigshafen, Germany). Tert-butanol (TBA), sodium lauryl sulphate (SLS) and dimethyl sulfoxide (DMSO) were purchased from VWR (Amsterdam, The Netherlands). Water for Injection (WfI) was obtained from B. Braun (Melsungen, Germany). Cetylpyridinium chloride (CPC), polysorbate 80, sorbitan monooleate and various grades of polyethylene glycol (PEG 1500–20,000) were purchased from Sigma–Aldrich (Zwijndrecht, The Netherlands). Hydroxypropyl-β-cyclodextrin (HP-β-CD) was supplied by Roquette (Lestrem, France). Hard gelatin capsules were purchased from Capsugel (Bornem, Belgium).

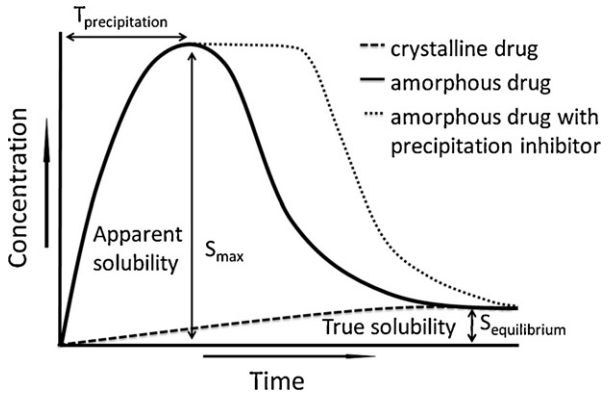

Fig. 1. Concentration vs. time curves of a drug in its crystalline and in its amorphous state. The amorphous drug reaches its maximum solubility, the apparent solubility, (S_{max}) in the supersaturated state. This supersaturated state can only be maintained for a limited period of time ($T_{precipitation}$), after which precipitation occurs. The equilibrium solubility ($S_{equilibirum}$) is reached when the entire excess drug in solution has precipitated. The equilibrium solubility of the amorphous drug equals the maximum solubility of the crystalline drug, i.e. the true solubility of the drug.
Adapted from Brouwers et al. (2009).

2.2. Methods

2.2.1. Preparation of docetaxel formulations

Docetaxel, carriers and surfactants were mixed with mortar and pestle to produce physical mixtures (PM). To produce solid dispersions (SD), docetaxel, carriers and surfactants were dissolved in TBA/WfI mixtures (40/60 v/v). The solutions were transferred to stainless steel boxes (Gastronorm size 1/9) and freeze-dried (Lyovac GT4, GEA Lyophil GmbH, Hürth, Germany) according to a method previous developed by van der Schoot et al. (2007).

An amount of SD or PM powder equivalent to 10–15 mg drug was gently grinded with mortar and pestle and encapsulated with a manual capsulation apparatus into size 0 hard gelatin capsules.

2.2.2. Dissolution testing

Maximum solubility (S_{max}), time until precipitation ($T_{precipitation}$) and equilibrium solubility ($S_{equilibrium}$) (see Fig. 1) were determined with a small-scale dissolution test. Briefly, an amount of powder equivalent to approximately 6 mg docetaxel anhydrate was added to a 50 mL beaker containing 25 mL of WfI. Temperature was kept at 37 °C and the medium was stirred at 720 rpm.

Dissolution of capsules was tested according to the European Pharmacopoeia (PhEur 7.0) with a type 2 (paddle) dissolution apparatus (Erweka, Heusenstamm, Germany). The medium consisted of 500 mL WfI for the test formulations and of 500 mL simulated intestinal fluid without pepsin (SIFsp) (USP 34) for the final formulation. Medium temperature was kept at 37 °C and stirred at 75 rpm. The duration of the dissolution test of the final formulation was 4 h to detect possible recrystallization of docetaxel from the supersaturated solution (Siewert et al., 2003).

Samples were collected at various time points, filtrated using a 0.45-μm filter and diluted 1:1 v/v with a 1:4 v/v mixture of methanol and acetonitrile. All samples were subsequently analyzed on a reversed phase HPLC system with UV detection (RP-HPLC–UV) developed by Huizing et al. (1995).

2.2.3. X-ray powder diffraction

X-ray powder diffraction measurements were performed with an X'pert pro diffractometer equipped with an X-celerator

(PANanalytical, Almelo, The Netherlands). Samples were placed in a 0.5 mm deep metal sample holder which was placed in the diffractometer. Samples were scanned at a current of 50 mA and a tension of 40 kV. The scanning range was 10–60° 2θ, with a step size of 0.020° and a scanning speed of 0.002° per second.

2.2.4. Modulated differential scanning calorimetry (MDSC)

MDSC measurements were performed with a Q2000 differential scanning calorimeter (TA Instruments, New Castle, DE, USA). Temperature scale and heat flow were calibrated with indium. Samples of approximately 10 mg powder were weighed into Tzero aluminium pans (TA instruments, New Castle, DE, USA), hermetically closed and placed in the autosampler. Each sample was equilibrated at 20.00 °C for 5 min, after which the sample was heated to 190.00 °C at a speed of 2.00 °C/min. Modulation was performed every 60 s at ±1.00 °C.

2.2.5. Fourier transform infrared spectroscopy (FT-IR)

Infrared spectra were recorded from 400 to 4000 cm^{-1} with a resolution of 2 cm^{-1} with a FT-IR 8400S Spectrophotometer equipped with a golden gate® (Shimadzu, 's-Hertogenbosch, The Netherlands). A total of 64 scans were averaged into one spectrum.

2.2.6. Residual solvents

Residual water was determined with the Karl Fischer method using a Metrohm 758 KFD Titrino (Herisau, Switzerland). Samples of approximately 50 mg were dissolved in 5 mL of preconditioned methanol. The titrant was standardized with 30 mg of WfI.

Residual TBA was determined with gas chromatography (GC) analysis using a method developed by van der Schoot et al. (2007) Samples of approximately 50 mg powder were dissolved in 5.0 mL of DMSO.

2.3. Clinical study

2.3.1. Study design

The pharmacokinetic parameters of docetaxel after administration of docetaxel premix solution and ModraDoc001 15 mg capsules were determined in 6 patients with advanced cancer in a randomized cross-over study. The study was designed as a proof-of-concept study with a small number of patients; although its statistical power is limited it will give a good indication of the performance of the novel formulation. Each patient received weekly 30 mg of docetaxel concomitantly with 100 mg of ritonavir. Docetaxel premix solution was given in week 1 or 3, while ModraDoc001 15 mg capsules were given in week 2 and 3 or in week 1 and 2, respectively.

The docetaxel premix solution contained 10 mg/mL docetaxel (as trihydrate) in a solution of 25.00% v/v polysorbate 80, citric acid, 9.75% v/v ethanol 95% and 65.25% v/v water for injections (SPC TAXOTERE). Each docetaxel capsule contained 15 mg docetaxel and consisted of a hard gelatin capsule filled with freeze-dried solid dispersion powder. The freeze-dried solid dispersion powder contained 1/11 w/w docetaxel (as anhydrate), 9/11 PVP-K30 w/w and 1/11 w/w SLS (ModraDoc001 15 mg capsules, Slotervaart Hospital Amsterdam, The Netherlands). Ritonavir was administered in soft gelatin capsules containing 100 mg ritonavir per capsule (NORVIR; Abbott, Illinois, USA). Both the docetaxel premix solutions as well as the ModraDoc001 15 mg capsules were administered orally with 100 mL tap water. Vital signs (blood pressure, heart rate, and temperature), weight and the WHO performance were monitored throughout the course of the study.

The study was approved by the Medical Ethics Committee of the Netherlands Cancer Institute (NKI-AvL) and written informed consent was obtained from all patients prior to study entry.

2.3.2. Pharmacokinetic and bioanalysis

Blood samples were drawn in lithium-heparinized tubes at baseline and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 h after docetaxel intake. All blood samples were immediately placed on ice and centrifuged within 1 h at 1500 × *g* for 10 min at 4 °C. Plasma was stored at or below −20 °C until analysis. Docetaxel levels in plasma were quantified by use of high-performance liquid chromatography with tandem mass spectrometric detection (LC–MS/MS), as described by Kuppens et al. (2005). Non-compartmental pharmacokinetic analysis and statistical analysis were performed using R version 2.10.0 (R Development Core Team, 2009). A Wilcoxon signed rank test was used to evaluate the differences between the two formulations.

3. Results and discussion

3.1. Preparation and testing of docetaxel solid dispersion formulations

In principle, solid dispersion is prepared by a variety of methods, such as spray drying, melt extrusion and freeze-drying (Leuner and Dressman, 2000). We chose to use freeze-drying, because the low operational temperatures minimize the risk of thermal degradation of docetaxel, and more importantly, reduces the crystallization ability of the amorphous phase. Because docetaxel is practically insoluble in water, TBA was used as co-solvent. TBA mixes easily with water and can easily dissolve both hydrophilic and hydrophobic components. In addition to this, TBA increases the vapour pressure of TBA/water mixtures, thereby increasing the drying rate, and reducing the drying time (Wittaya-Areekul and Nail, 1998). Solubility tests showed that docetaxel concentrations up to 10 mg/mL could be reached in 40/60 v/v water/TBA mixtures in the presence of various carriers and surfactants. We therefore chose to use the 40/60 v/v water/TBA mixture to prepare the freeze-dried docetaxel formulations.

To facilitate the formation of a supersaturated solution preventing crystallization of the amorphous active component inside the solid dispersion during storage or upon contact with water is essential. Therefore, active component molecules have to be physically separated from each other by the solid dispersion excipients (Serajuddin, 1999; van Drooge et al., 2004). Preferably the solid dispersion excipients will also prevent crystallization once the drug has dissolved by acting as a parachute to prolong the period of supersaturation (Guzmán et al., 2007). Moreover, production of the most optimal solid dispersion starts with a careful selection of the solid dispersion excipients.

To assess the performance of a solid dispersion and its excipients adequately it is essential to perform dissolution tests at a target concentration that lies well above the equilibrium solubility of the drug. At this target concentration, formation of a supersaturated solution takes place and the three dissolution parameters most important to the performance of solid dispersions can be determined: maximum solubility (S_{max}), time until precipitation ($T_{precipitation}$), and equilibrium solubility ($S_{equilibrium}$) (Fig. 1).

We chose to use a target concentration of 200 μg/mL, which is approximately 40 times the equilibrium solubility of docetaxel trihydrate (Gao et al., 2008). Moreover, to reach the target concentration docetaxel has to form a supersaturated solution. Because standard European and United States Pharmacopoeial methods use dissolution medium volumes of 500–1000 mL, large amounts of docetaxel are needed to reach the target concentration of 200 μg/mL. To allow dissolution testing with small amounts of docetaxel, a small-scale dissolution test was set up which used only 25 mL of dissolution medium. At various time points the docetaxel concentration was measured, the highest average concentration was labeled S_{max}, the average docetaxel concentration after 60 min

Table 1
Components, weight ratios, and preparation methods of docetaxel formulations.

Formulation	Components	Weight ratio (w/w/w)	Formulation method
A	Crystalline docetaxel	1/0/0	Pure drug
B	Amorphous docetaxel	1/0/0	Freeze drying
C	Crystalline docetaxel, PVP-K30 and SLS	1/9/1	Physical mixing
D	Amorphous docetaxel, PVP-K30 and SLS	1/9/1	Physical mixing
E	Docetaxel, PVP-K30 and SLS	1/9/1	Freeze drying
F	Docetaxel, PEG 1500 and SLS	1/9/1	Freeze drying
G	Docetaxel, HP-β-CD and SLS	1/9/1	Freeze drying
H	Docetaxel, PVP VA 64 and SLS	1/9/1	Freeze drying
I	Docetaxel, PVP-K12 and SLS	1/9/1	Freeze drying
J	Docetaxel, PVP-K17 and SLS	1/9/1	Freeze drying
K	Docetaxel, PVP-K90 and SLS	1/9/1	Freeze drying
L	Docetaxel, PVP-K30 and SLS	15/5/1	Freeze drying
M	Docetaxel, PVP-K30 and SLS	2/3/1	Freeze drying
N	Docetaxel, PVP-K30 and SLS	1/4/1	Freeze drying
O	Docetaxel, PVP-K30 and SLS	1/19/1	Freeze drying

was labeled $S_{equilibrium}$, and the last time point before a more than 10% decrease in docetaxel concentration was labeled $T_{equilibrium}$.

The discriminative power of the small-scale dissolution test could be adjusted by changing the target drug concentration (i.e. the level of supersaturation), medium temperature, and or stirring speed, because formation of and precipitation from the supersaturated state depends on these parameters (Brouwers et al., 2009).

3.2. Formulation type, carrier type, carrier chain length and docetaxel weight ratio

Docetaxel formulations differed on four variables: formulation method, carrier type, carrier chain length, and docetaxel weight ratios. The properties of the tested docetaxel formulations are given in Table 1 and the dissolution parameters are shown in Fig. 2.

Crystalline and amorphous docetaxel had different S_{max} values but comparable $T_{precipitation}$, and $S_{equilibirum}$ values (Fig. 1: formulations A and B). Both physical states of docetaxel have a higher apparent solubility than docetaxel trihydrate and are very unstable in solution. Therefore, excess docetaxel will precipitate out of the supersaturated solution until its solubility reaches the equilibrium solubility of docetaxel trihydrate. The equilibrium solubility ($S_{equilibrium}$) of the pure drug formulations was slightly higher than the equilibrium solubility of docetaxel reported by Gao et al. (2008) (5.9 μg/mL vs. 4.93 μg/mL), this could be due to the shorter equilibration time (60 min vs. 48 h) and/or the higher medium temperature (37 °C vs. 25 °C) used in our experiments. In addition to this, FT-IR analysis showed that the precipitated docetaxel was indeed docetaxel trihydrate, proving that the solutions were approaching their equilibrium state (data not shown).

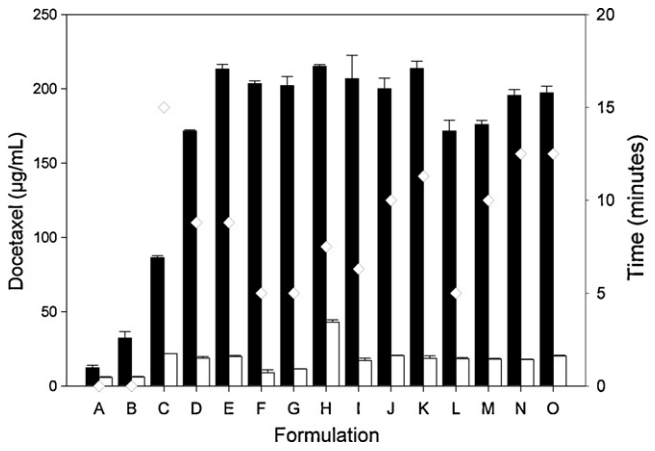

Fig. 2. Dissolution parameters of docetaxel formulations. S_{max} (closed bars) and $S_{equilibirum}$ (open bars) are plotted on the left *y*-axis (docetaxel in μg/mL); $T_{precipitation}$ (open diamonds) is plotted on the right *y*-axis (time in minutes).

Apparently the physical mixture excipients, PVP and SLS, were able to inhibit the rapid precipitation of docetaxel, thereby enabling the measurement of higher S_{max} values (Fig. 2: formulations C and D). Incorporation of amorphous docetaxel into a solid dispersion even further improved the S_{max} value of docetaxel compared to the physical mixture formulation (Fig. 2: formulation E).

It is likely that the difference in S_{max} values between the two formulations was caused by the method of preparation. The physical mixture is produced by physical mixing amorphous docetaxel with the excipients, while the solid dispersion is produced by dissolving and subsequently freeze-drying of docetaxel and the excipients. The latter method will probably lead to a higher mixing efficiency and a higher degree of physical separation of the amorphous docetaxel molecules. This is of prime importance, since crystallization can only occur when a sufficient amount of amorphous molecules are in contact with each other (Brouwers et al., 2009). Most probably part of the amorphous docetaxel in the physical mixture crystallized immediately upon contact with water, thereby limiting the amount of docetaxel available for dissolution and subsequently reducing the S_{max} value (van Drooge et al., 2004).

The tested carriers covered a wide range of types and sizes and had been successfully applied in other solid dispersion formulations. The small-scale dissolution tests showed no significant differences in the S_{max} of docetaxel between the various carriers types (Fig. 2: formulations E–H) or various chain lengths (Fig. 2: formulations I–K). There was however a trend towards higher S_{max} values at lower docetaxel weight ratios (Fig. 2: formulations L–O).

Apparently a minimal amount of carrier molecules is needed to physically separate the amorphous docetaxel molecules and prevent rapid crystallization (Fig. 2: formulation E vs. L). Furthermore at a lower mixing efficiency, more carrier molecules are needed to physically separate the amorphous docetaxel molecules and reach equal S_{max} values (Fig. 2: formulation D vs. M). These findings further strengthen the hypothesis that the amorphous state of docetaxel, the mixing efficiency, and the degree of physical separation of the amorphous docetaxel molecules determine the S_{max} of docetaxel. Additional experiments revealed that at a docetaxel/carrier/surfactant ratio of 2/3/1 w/w/w differences in S_{max} were detected between PVP-K30 and HP-β-CD, suggesting that the carrier type also plays a role in the degree of physical separation of amorphous docetaxel molecules (data not shown).

$T_{precipitation}$ was the highest for the PVP containing carriers (including PVP-VA) (Fig. 2: formulations E–H) and increased with increasing carrier chain length (Fig. 2: formulations I–K) or decreasing weight ratios of docetaxel (Fig. 2: formulations L–O). For both

PVP and SLS inhibition of drug precipitation from supersaturated solutions has been described (Lindfors et al., 2008; Overhoff et al., 2008). Our experiments showed, however, that higher amounts of PVP led to higher values of $T_{precipitation}$ and vice versa. It is therefore most likely that PVP was responsible for the inhibition of docetaxel precipitation, and not SLS. Furthermore, additional tests revealed that SLS alone was not able to prevent docetaxel precipitation (data no shown).

The proposed mechanisms by which PVP inhibits drug precipitation are: shielding of drug molecules by PVP molecules (Ziller and Rupprecht, 1988), formation of hydrogen bonds between drug and PVP molecules (Raghavan et al., 2001), increase of viscosity of the dissolution medium (Brouwers et al., 2009). Because the chemical structure of docetaxel possesses several hydrogen donor and acceptor sites, the latter explanation could play a role in the inhibition of docetaxel precipitation by PVP. It is, however, more likely that the shielding of drug molecules by PVP or the increase in dissolution medium viscosity was the most important factor, because an increase in PVP chain length increased the $T_{precipitation}$ value.

$S_{equilibrium}$ differed only between the various carrier types (Fig. 2: formulations E–H). The findings that the formulation type, carrier chain length and docetaxel weight ratio had little or no influence on the $S_{equilibrium}$ value further suggest that direct interactions between the carrier and docetaxel are responsible for the increase in $S_{equilibrium}$.

3.3. Surfactant type and weight ratio

The amount and type of surfactant were varied to further optimize the docetaxel/PVP-K30 solid dispersion formulation. The selection of the surfactants was based on the three surfactant classes: anionic, non-ionic and cationic; and a broad range of HLB-values. Because it was found that the surfactants primarily influenced the dissolution rate, the standard European Pharmacopoeial type II dissolution method (paddle (EDQM 2011)) was used to test the performance of hard gelatine capsules filled with solid dispersion formulations.

The experiments showed that addition of a surfactant to the solid dispersion formulation increased the dissolution rate of docetaxel, while decreasing the variability in the dissolution rate of docetaxel. This suggests that the improved wettability of the solid dispersion formulation, and especially of the hydrophobic drug, resulted in a more homogenous and complete dissolution of docetaxel (Fig. 3). The initial slow dissolution rate between 0 and 5 min could be attributed to the dissolution of the hard gelatine capsule shell.

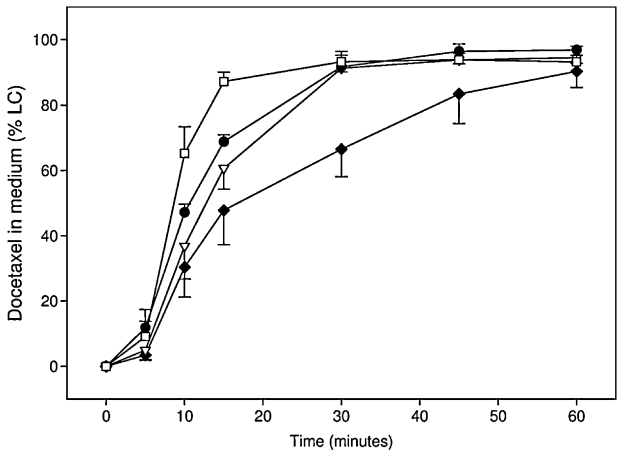

Fig. 3. Dissolution curves of capsules filled with freeze-dried solid dispersion formulations of docetaxel, PVP-K30 and SLS. Filled diamonds: no SLS; open triangles: 4/1 w/w docetaxel/SLS; closed circles: 2/1 w/w docetaxel/SLS; open squares: 1/1 w/w docetaxel/SLS. The dissolution rate of docetaxel increases when the amount of SLS relative to the amount of docetaxel increases.

The difference in dissolution rates between the four surfactant types were in line with their HLB-values: higher HLB-values led to a better wettability of the solid dispersion and a higher dissolution rate of docetaxel. We found no relation between the dissolution rate of docetaxel and the respective surfactant classes (data not shown).

3.4. X-ray powder diffraction, MDSC and FT-IR

We compared the X-ray powder diffraction spectra, the MDSC thermograms and FT-IR spectra of the three formulation types (Table 1: formulations A–E) to examine their physical properties and find an explanation for the observed differences in solubility (see Fig. 4a–c). The characteristic X-ray powder diffraction peaks of crystalline materials were present in the X-ray diffraction spectra of crystalline docetaxel and its physical mixture (Fig. 4: formulations A and C). Properties characteristic to amorphous materials, such as the presence of a glass transition temperature (T_g) and the absence of X-ray powder diffraction peaks, were seen in the X-ray powder diffraction spectra and MDSC thermograms of amorphous docetaxel and its physical mixture (Fig. 4: formulations B, D and E). These findings, combined with the higher solubility of amorphous docetaxel, prove that crystalline docetaxel is rendered amorphous after dissolution and subsequent freeze-drying.

Table 2
Stability results ModraDoc001 15 mg capsules.

	Start	Two years at 2–8 °C, dark	Two years at 25 °C/60% RH
Docetaxel peak purity (%)	99.99	100.0	99.20
Docetaxel dissolved at t = 30 min (%)[a]	97.0 (4.1)	97.5 (6.0)	96.7 (4.9)
Docetaxel dissolved at t = 60 min (%)[a,b]	96.5 (4.0)	96.8 (5.1)	96.6 (3.2)
Docetaxel dissolved at t = 240 min (%)[a,b]	95.2 (4.8)	97.1 (5.2)	92.9 (5.6)

[a] Values are means and coefficients of variation (%).
[b] Time points were included to detect possible recrystallization of docetaxel from the supersaturated solution (Siewert et al., 2003).

Table 3
Pharmacokinetic parameters of 30 mg docetaxel (p.o) administered concomitantly with 100 mg ritonavir (p.o).

	T_{max} [a] (h)	C_{max} [a] (ng/mL)	AUC_{0-24} [a] (ng h/mL)
Docetaxel premix solution	1.7 ± 0.3 (18%)	185 ± 155 (84%)	790 ± 669 (85%)
ModraDoc001 15 mg capsules	1.9 ± 0.85 (44%)	105 ± 53 (51%)	513 ± 219 (43%)

[a] Values are means ± standard deviation and coefficients of variation (%) of 6 patients. T_{max}, timepoint at which the maximum concentration is reached; C_{max}, maximum concentration; AUC_{0-24}, area under the concentration vs. time curve between 0 and 24 h.

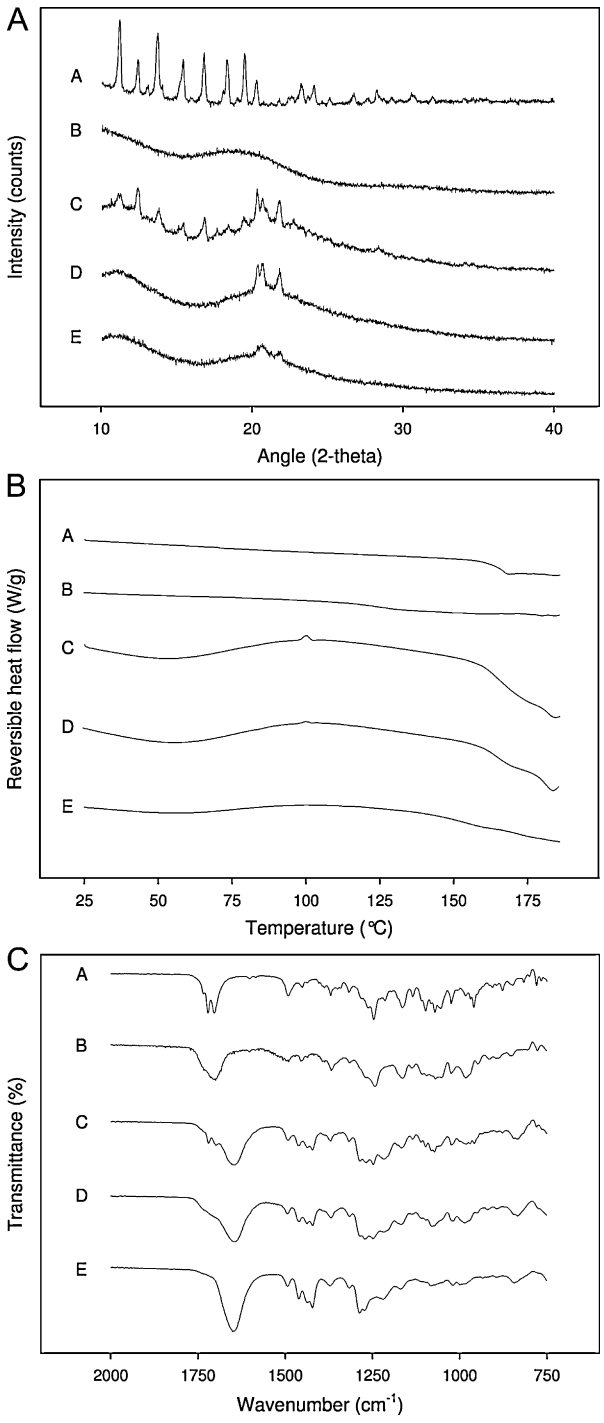

Fig. 4. X-ray diffraction spectra (a), reversed heat flow DSC thermograms (b) and FT-IR spectra (c) of five different docetaxel formulations. A: Crystalline docetaxel; B: amorphous docetaxel; C: physical mixture of 1/11 w/w crystalline docetaxel, 9/11 w/w PVP-K30 and 1/11 w/w SLS; D: physical mixture of 1/11 w/w amorphous docetaxel, 9/11 w/w PVP-K30 and 1/11 w/w SLS; E: freeze-dried formulation of 1/11 w/w docetaxel, 9/11 w/w PVP-K30 and 1/11 w/w SLS.

In addition to this, differences between the X-ray powder diffraction spectra and FT-IR spectra could be related to mixing efficiency of both docetaxel and SLS. The X-ray powder diffraction peaks of SLS, around 21° 2θ, were sharper and larger in the spectra of the physical mixtures than in the spectra of the freeze-dried solid dispersions (Fig. 4a: formulations C, D and E). These findings were confirmed by the FT-IR spectra: the blunt peak of docetaxel near 1700 cm^{-1} (Fig. 4c: formulations D and E), and the SLS peaks around 3000 cm^{-1} (data not shown) were lower in the spectra of the freeze-dried solid dispersion than in the spectra of the physical mixture. It is very likely that the higher mixing efficiency of docetaxel and SLS causes the reduction in intensity. These findings provide a physical basis for the higher solubility of the docetaxel solid dispersion formulation observed in the small-scale dissolution tests.

3.5. Formulation selection

The results of our experiments clearly showed that of the three tested formulation methods, freeze-drying was the best. We therefore continued with testing different carrier types, carrier chain lengths, and docetaxel weight ratios to find the optimal solid dispersion composition.

The results of these experiments showed that PVP-K30, PVP-K90 and PVP VA 64 were all good carrier candidates. We chose to use PVP over PVP VA 64 because we believed that the ability to maintain the supersaturated state was more important than higher equilibrium solubility after precipitation. The docetaxel/carrier/surfactant ratio of 1/9/1 w/w/w was selected because lower docetaxel weight ratios would limit the maximum amount of docetaxel per dosage form. Because it proved to be not practical to produce PVP-K90 solid dispersions on a larger scale, we continued the surfactant tests with PVP-K30.

These test showed that addition of SLS, in a weight ratio of 1/1 w/w to docetaxel, led to the most optimal solid dispersion formulation. In conclusion, for the clinical study we selected the freeze-dried solid dispersion formulation of docetaxel with a docetaxel/carrier/surfactant weight ratio of 1/9/1 w/w/w in which we used PVP-K30 as carrier and SLS as surfactant.

Quality control testing of the clinical formulation showed a very rapid dissolution in USP SIF_{sp} (United States Pharmacopeia Convention), after which docetaxel remained in solution for at least 4 h (Siewert et al., 2003). Residual solvents were below their respective specifications and the capsules conformed to the test for uniformity of dosage units. During 24 months of storage at 2–8 °C and at 25 °C/60% RH the formulation was subjected to dissolution and assay tests; in this period no significant changes in chemical or physical properties were found (see Table 2).

3.6. Clinical Study

Six evaluable patients were included in the clinical study. All patients received ModraDoc001 15 mg capsules on two occasions, and docetaxel premix solution on one occasion. Fig. 5 shows the mean concentration time curves of docetaxel after oral administration of 30 mg docetaxel. Docetaxel was administered as ModraDoc001 15 mg capsules ($n = 6$), or administered as docetaxel premix solution ($n = 6$), both in combination with 100 mg ritonavir.

The relevant pharmacokinetic parameters (T_{max}, C_{max} and AUC_{0-24}) are shown in Table 3 (mean and coefficient of variation (CV)). There were no significant differences between the pharmacokinetic parameters of docetaxel after oral administration of docetaxel premix solution and ModraDoc001 15 mg capsules, although there was a trend towards higher and more variable exposure to docetaxel (AUC_{0-24}) after oral administration of docetaxel premix solution.

Despite the small sample size and of the limited statistical power, the results show that docetaxel reaches clinically relevant concentrations after oral administration of ModraDoc001 15 mg capsules. Furthermore, the docetaxel concentrations after administration of ModraDoc001 15 mg capsules are similar to the docetaxel concentrations after administration of docetaxel premix solution. Even more, in contrast to the docetaxel premix solution; Modradoc001 15 mg capsules have an acceptable taste, two-year

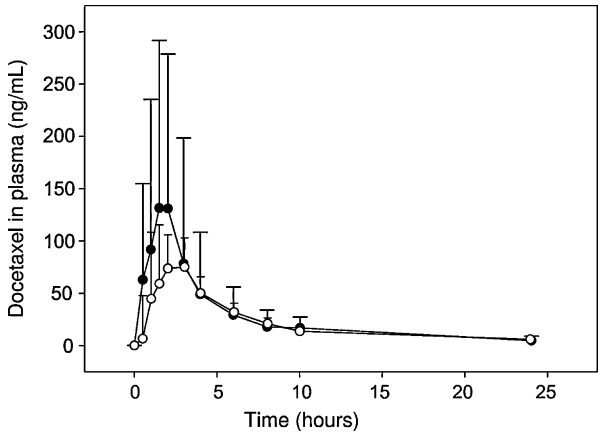

Fig. 5. Concentration vs. time curves of docetaxel (p.o) administered concomitantly with 100 mg ritonavir (p.o). Plotted data are mean and SD values of six patients. Open circles and small error bars: ModraDoc001 15 mg capsules (p.o); Closed circles and wide error bars: docetaxel premix solution (p.o). There were no significant differences between the pharmacokinetic parameters of docetaxel after oral administration of docetaxel premix solution and ModraDoc001 15 mg capsules.

storage stability at room temperature, an excellent dosing accuracy, and contain neither ethanol nor polysorbate 80. Moreover, the ModraDoc001 15 mg capsule formulation is a stable, easy to use, patient convenient oral formulation that enables the further development of oral docetaxel chemotherapy.

4. Conclusions

We developed a ternary solid dispersion formulation of 1/9/1 w/w/w docetaxel, PVP-K30 and SLS. The solid dispersion formulation had a higher solubility and dissolution rate compared to pure drug and physical mixture formulations. Stability tests showed that our formulation was stable at 2–8 °C and at 25 °C/60% RH for at least 2 years.

A clinical study revealed that the combination of ModraDoc001 15 mg capsules and ritonavir led to clinically relevant docetaxel concentrations (Oostendorp et al., 2009) with a low inter-individual variability. Other advantages of the new formulation are its ease of use and the absence of polysorbate 80 and ethanol. Moreover, the successful development of ModraDoc001 15 mg capsules is a major step in the development of oral docetaxel chemotherapy.

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