Development and clinical application of oral dosage forms of taxanes

ISBN/EAN: 978-90-820193-1-5

Artwork: Bart Nijstad – www.bartnijstad.com
Layout and design: Esther Ris – www.proefschriftomslag.nl
Printed by: Gildeprint drukkerijen - www.gildeprint.nl

Development and clinical application of oral dosage forms of taxanes

Ontwikkeling en klinische toepassing van orale toedieningsvormen van taxanen

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 30 oktober 2013 des middags te 2.30 uur

door

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geboren op 8 december 1979 te Nijeveen

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Printing of this thesis was financially supported by:

Huisartsenpraktijk Kolderveen, Nijeveen, The Netherlands
Utrecht Institute of Pharmaceutical Sciences (UIPS), Utrecht, The Netherlands
The Netherlands Laboratory for Anticancer Drug Formulation (NLADF), Amsterdam, The Netherlands
TEVA Pharmachemie BV, Haarlem, The Netherlands
Boehringer Ingelheim BV, Alkmaar, The Netherlands

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Chapter 1

Introduction

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. Its recommended dose of 60 to 100 mg/m^2 is administered via intravenous (IV) infusion over 1 hour every 3 weeks [1]. Paclitaxel is currently approved for the treatment of ovarian, breast, and non-small cell lung cancer, and Kaposi's Sarcoma. Paclitaxel's recommended dose of 100 mg/m^2 to 175 mg/m^2 is administered via IV infusion over 3 to 24 hours every 2 to 3 weeks [2].

Because of their mechanism of action continuous exposure to docetaxel and paclitaxel could improve its effectiveness against cancer [3-6]. Continuous exposure can be reached by chronic IV administration, however, this is costly and inconvenient for patients. Furthermore, the current IV formulations can induce ethanol intoxication [7] and severe hypersensitivity reactions after IV administration [8, 9]. The latter are most probably related to the respective formulation vehicles, polyoxyethylated castor oil for paclitaxel and polysorbate 80 for docetaxel [1, 2]. Hence, to enable chronic administration of docetaxel and paclitaxel 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 is expected to lead to more patient convenience and a higher quality of life during oral anticancer treatment with taxanes [10].

Unfortunately, docetaxel's and paclitaxel's oral bioavailability is very low which is caused by their very low solubility [11, 12] and very low permeability [6, 13]. Therefore, both docetaxel and paclitaxel are classified as class IV drugs according to the Biopharmaceutical classification system (BCS) class IV [14]. The very low permeability of docetaxel is partly due to active excretion by the drug efflux pump P-glycoprotein (PgP) and to a much

larger extent to extensive metabolism by CYP3A4 enzymes in the gut wall and liver [15]. The low permeability of paclitaxel is mainly attributed to active excretion by PgP and to a lesser extent to CYP3A4 and CYP2C8 metabolism in the liver and gut wall [13]. We were able to overcome the low permeability of docetaxel by concomitant administration of the IV premix solution of docetaxel and the pharmacokinetic (PK) booster ritonavir, a strong CYP3A4 inhibitor [16]. We also succeeded in overcoming the low permeability of paclitaxel by concomitant administration of paclitaxel's IV premix solution and the PgP-inhibitor Cyclosporin A [17].

The IV premix solutions of docetaxel and paclitaxel are, however, not suitable for regular clinical use, because of their bad taste, limited storage stability of 8 to 27 hours, high ethanol content, and poor oral dosing accuracy [1, 2]. Further development of oral docetaxel and paclitaxel chemotherapy was therefore hampered by the lack of a stable, easy to use, patient convenient oral formulation.

Although a typical solid oral dosage form could fulfill these demands, the very low solubilities of both docetaxel and paclitaxel pose major pharmaceutical development challenges. Their low solubility will inevitably lead to low dissolution rates from typical solid oral dosage forms such as capsules and tablets, which will negatively affect the oral bioavailability of docetaxel and paclitaxel.

The aim of this thesis was to develop oral dosage forms of docetaxel and paclitaxel with increased solubilities and dissolution rates in-vitro. The increased solubility and dissolution rate in vitro should result in an improved pharmaceutical availability of docetaxel and paclitaxel in the gastrointestinal tract. In combination with ritonavir, this should lead to clinically relevant exposures to docetaxel and paclitaxel.

The current development status of oral taxane formulations is described in Chapter 2. Apart from an overview of the applied formulation strategies, their potential to reach the market is discussed.

Chapter 3 describes the pharmaceutical development and initial clinical testing of a freeze-dried solid dispersion of docetaxel (ModraDoc001). Various polymers, surfactants, and weight ratios were evaluated to optimize the solid dispersion formulation. After encapsulation in hard gelatin capsules the freeze-dried solid dispersion formulation was compared to the orally administered docetaxel IV premix solution in a phase I clinical study.

The development and characteristics of a freeze-dried solid dispersion formulation

of paclitaxel is described in Chapter 4 (ModraPac001). Based on the solid dispersion of docetaxel, Hanssen solubility parameters, and dissolution screening experiments a capsule formulation of paclitaxel was developed and characterized. Its pharmacokinetic parameters were compared to the orally administered paclitaxel IV premix solution in a phase I clinical study.

The physicochemical characteristics and the stability of the freeze-dried solid dispersion formulations of docetaxel and paclitaxel are evaluated in Chapter 5. In addition, the differences in dissolution profiles of the solid dispersions of docetaxel and paclitaxel and their underlying mechanisms are discussed.

Chapter 6 describes the development of spray drying as a new preparation method for the solid dispersion of docetaxel. Furthermore, the development of a fixed-dose combination tablet of docetaxel and its pharmacokinetic booster ritonavir is described. Finally, the physical and chemical stability of the spray dried docetaxel solid dispersion and tablets are discussed.

A phase I clinical study in which the freeze-dried solid dispersion formulation of docetaxel was compared to the spray dried solid dispersion formulations of docetaxel is described in chapter 7. In addition, the pharmacokinetic parameters of docetaxel and ritonavir administered in single agent formulations were compared to pharmacokinetic parameters of docetaxel and ritonavir administered in a fixed-dose combination tablet.

Chapter 8 summarizes the conclusions and achievements and provides suggestions for further research.

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Chapter 2

Oral formulations of docetaxel and paclitaxel
- a mini review -

J.J. Moes, J.H. Beijnen, J.H.M. Schellens, B. Nuijen

Abstract

To make use of the full potential of the potent anticancer agents docetaxel and paclitaxel patient convenient oral formulations are needed that overcome their low bioavailability. A wide variety of formulations strategies such as lipid based nanoparticles, cyclodextrins, self-emulsifying systems, micelles and solid dispersions have been tested in-vitro and/or pre-clinically.

All reported formulations made use of a dual strategy: improving both the solubility of docetaxel and paclitaxel, and inhibiting the activity of PgP and CYP450. The largest increase in oral bioavailability was achieved by nanoparticle formulations, however this was for a large extent due to increased circulation times of the drug-containing nanoparticles. Using the pharmacokinetic boosters cyclosporine A and/or ritonavir the oral drug bioavailability was increased independent of the formulation strategy.

To date only a few formulations made it to clinical trials and showed comparable pharmacokinetic parameters compared to the orally administered IV formulations. Currently three strategies seem to be in active development. The first strategy is a solid dispersion formulation of docetaxel (ModraDoc) or paclitaxel (ModraPac) combined with the pharmacokinetic booster ritonavir. This strategy is currently at the end of phase I and it's development is described in Chapter 3 to 7 of this thesis. The second strategy, currently under phase II clinical investigation, is a combination of the novel pharmacokinetic booster HM30181A with an unknown paclitaxel formulation. The third strategy is a self-emulsifying system named DHP107. DHP107 is currently evaluated in a Phase III study with patients with metastatic or recurrent gastric cancer after failure of first-line chemotherapy.

Introduction

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 (Figure 1 and 2).

Docetaxel is approved for the treatment of breast, non-small cell lung, prostate, gastric, and head and neck cancer. Its recommended dose of 60 to 100 mg/m^2 is administered via intravenous (IV) infusion over 1 hour every 3 weeks [1]. Paclitaxel is currently approved for the treatment of ovarian, breast, and non-small cell lung cancer, and Kaposi's sarcoma. Paclitaxel's recommended dose of 100 mg/m^2 to 175 mg/m^2 is administered via IV infusion over 3 to 24 hours every 2 to 3 weeks [2].

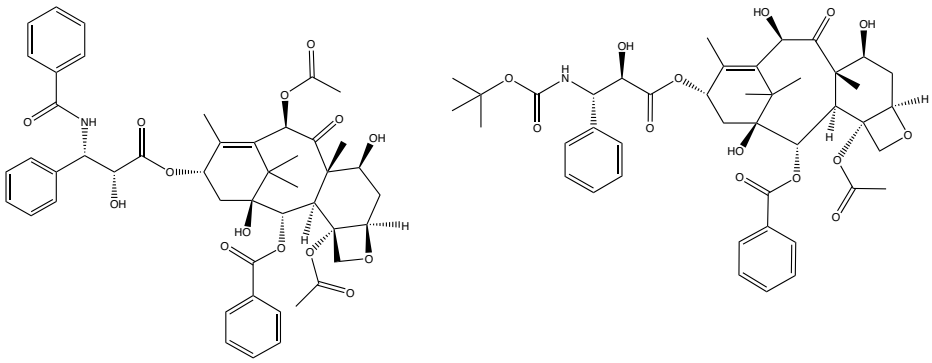

Figure 1: Molecular structures of paclitaxel (left) and its structural analog docetaxel (right)

Because of their mechanism of action continuous exposure to docetaxel and paclitaxel could improve its effectiveness against cancer [3-6]. Continuous exposure can be reached by chronic IV administration, however, this is costly and inconvenient for patients. Furthermore, the current IV formulations can induce ethanol intoxication [7] and severe hypersensitivity reactions after IV administration [8, 9]. The latter are most probably related to the respective formulation vehicles, polyoxyethylated castor oil (Cremophor EL) for paclitaxel and polysorbate 80 (Tween) for docetaxel [1, 2]. Hence, to enable chronic administration of docetaxel and paclitaxel 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 is expected to lead to more patient convenience and a higher quality of life during oral anticancer treatment with taxanes [10].

Unfortunately, docetaxel's [11] and paclitaxel's [12] oral bioavailability is estimated to be below 10% which is caused by their very low aqueous solubility [13, 14] and very low permeability [6, 12]. Therefore, both docetaxel and paclitaxel are classified as class IV drugs according to the biopharmaceutical classification system (BCS) class IV [15]. The very low permeability of docetaxel is partly due to active excretion by the drug efflux pump P-glycoprotein (PgP) and to a much larger extent to extensive metabolism by CYP3A4 enzymes in the gut wall and liver [16]. The low permeability of paclitaxel is mainly attributed to active excretion by PgP and to a lesser extent to CYP3A4 and CYP2C8 metabolism in the liver and gut wall [12, 17].

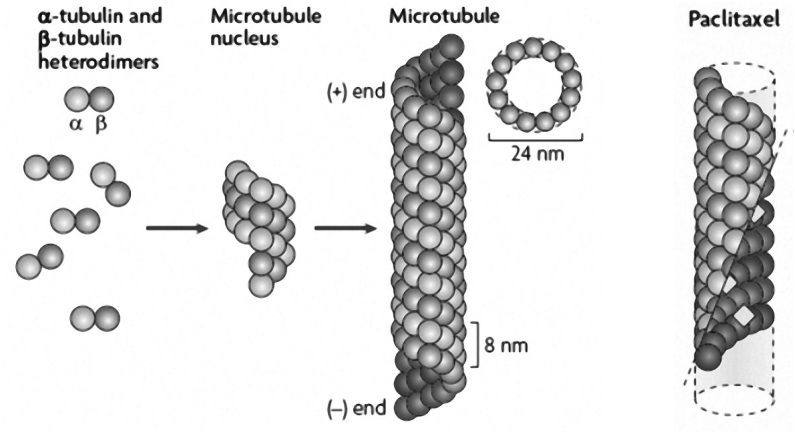

Figure 2: Microtubule formation and the binding sites of paclitaxel. Soluble tubulin dimers, containing one α-tubulin peptide and one β-tubulin peptide, polymerize to form a microtubule nucleus. Additional dimers are added head-to-tail and the resulting microtubules are highly dynamic structures containing a (+) end, characterized by an exposed β-tubulin peptide and a (–) end, characterized by an exposed α-tubulin peptide. Binding site of paclitaxel (diamonds). Although vinca alkaloids, such as vinblastine, bind to microtubule ends, colchicine binds to soluble dimers, which can be incorporated in the microtubules. Taxanes, such as paclitaxel, bind along the interior surface of the microtubules. Adapted from Dumontet et al. [18]

Over the years there have been various attempts to synthesize taxane analogs with increased solubility and decreased affinity for PgP and CYP450 activity. Examples of these taxane analogs are Tesetaxel [19-21], BMS-275183 [22, 23], ortataxel [24], IDN-5390 [25, 26], and milataxel [27], Despite successful pre-clinical studies and initial clinical studies, active oral clinical development of these molecules seems to be halted. Moreover, due to their high variability in PK, unfavorable safety profile or lack of anti-tumor activity it is doubtful whether these taxane analogs will ever reach the clinic for oral anticancer treatment.

Another option to increase the solubility and bypass PgP and CYP450 is the formation of conjugates. Recently, pre-clinical studies with polyethyleneglycol (PEG) and chitosan conjugates of docetaxel [28] and paclitaxel [29, 30] were published with promising increases in oral bioavailability. However, before such conjugates will reach the clinic there are many hurdles from regulatory to quality to be overcome [31].

Since it became clear that PgP and CYP450 are involved in the low oral bioavailability of paclitaxel and docetaxel there has been a lot of interest in improving the oral bioavailability by co-administration of PgP and/or CYP450 inhibitors. Various substances have been evaluated pre-clinically such as cysteine [32], verapamil [33] and its analog KR-30031 [34], curcumin [35, 36], tesmilifene [37], schisandrol B [38], biochanin A [39], silibinin/silymarin [40, 41], naringin [42], flavone [43], quercetin [44], SDZ PSC 833 [45]. Some promising pharmacokinetic boosters have also been evaluated in clinical trials, for instance HM30181A [46], elacridar (GF120918) [47], and ONT-093 [48] which mainly inhibit PgP; ritonavir, ketoconazol, grapefruit juice, and claritromicyn which mainly inhibit CYP450 [49], and cyclosporin A which inhibits both PgP and CYP450 [11, 12]. Recent reviews showed that pharmacokinetic boosting is a feasible strategy to improve the oral bioavailability of docetaxel and paclitaxel [50, 51].

However, most of these studies were performed with the orally administered IV formulations of docetaxel [1] and paclitaxel [2]. Evidently, these formulation were not developed for oral administration and have, as a result, considerable drawbacks such as a poor taste, a poor physical and chemical stability at ambient temperatures, a limited dosing accuracy, and a high contamination risk. Furthermore, the toxicity of the abovementioned excipients Cremophor EL, Tween 80 as well as ethanol attribute to the patient unfriendly nature of the IV formulations. Hence, development of a more suitable oral formulation of paclitaxel and docetaxel is still warranted.

The past 10 years a wide variety of oral taxane formulation strategies have been tested

in-vitro, and a number of pre-clinical and clinical studies have been published. This mini-review will provide a selected overview of the pre-clinical and clinical formulation strategies applied to oral formulations of docetaxel and paclitaxel and will discuss their potential (Table 1). Formulation strategies were classified into four groups: nanoparticles, micelles, self-emulsifying systems, and solid dispersions.

Table 1: Published clinical studies with oral formulations of paclitaxel or docetaxel

Drug	Study	Formulation	Excipients	PK-booster
Paclitaxel	Malingre et al. [52]	Micelles	Polysorbate 80, ethanol	Csa (15 mg/kg)
	Veltkamp et al. [53]	SEDDS (SMEOF#3)	Vitamin E, TPGS 1000, Tyloxapol, ethanol	CsA (700 mg)
		SEDDS (M1)	TPGS 1000, propylene glycol, vitamin E, ascorbyl palmitate, ethanol	CsA (10 mg/kg)
	Veltkamp et al. [54]	SEDDS (M2)	TPGS 1000, Labrasol, sorbitan monooleate, ascorbyl palmitate, ethanol	CsA (10 mg/kg)
		SEDDS (M3)	TPGS 1000, Labrafil M 1944 CS, PEG400, ascorbyl palmitate, ethanol	CsA (10 mg/kg)
	Chu et al. [55]	SEDDS (DHP107)	monoolein, tricaprylin, and Tween 80	None
	Veltkamp et al. [56]	Solid dispersion	polyvinyl acetate phthalate	CsA (10 mg/kg)
	Moes et al. [57]	Solid dispersion (ModraPac001)	PVP-K30, SLS	RTV (100 mg)
Docetaxel	Moes et al. [58]	Solid dispersion (ModraDoc001)	PVP-K30, SLS	RTV (100 mg)

TPGS: d-alpha tocopheryl polyethylene glycol 1000 succinate; PVP: polyvinylpyrrolidone; SLS: sodium lauryl sulfate; CsA: cyclosporine A; RTV: ritonavir;

Bioavailability calculations are complicated when pharmacokinetic boosters and pharmacokinetic modifying excipients are involved [59]. Ritonavir and cyclosporine A, for instance, do not only inhibit PgP and CYP450 in the gut wall they do as well inhibit CYP450 in the liver, thereby effectively decreasing clearance. Furthermore, the formulation vehicle Cremophor EL increases the plasma compartment affinity

an substantially decreases the clearance paclitaxel after IV administration. However, Cremophor EL does not enter the systemic circulation after oral administration[12, 52]. Moreover, therapeutic levels of paclitaxel determined with IV formulations can be different for oral administration as the fraction of free drug differ [60].

In the reviewed articles bioavailability of docetaxel and paclitaxel were reported in three ways: the apparent bioavailability, that is the dose corrected AUC of the oral formulation divided by the dose corrected AUC of the IV administered reference formulation (Taxol or Taxotere); the relative bioavailability, that is the dose corrected AUC of the oral test formulation divided by the dose corrected AUC of the orally administered reference IV formulation (Taxol or Taxotere without PK boosters). The absolute bioavailability, that is the dose corrected AUC of the orally administered test formulation divided by the dose corrected AUC of the IV administered test formulation. Where possible we used the available data to calculate the relative bioavailability to estimate the effect of the formulation and compare the formulations between studies.

Nanoparticles

In general, the term "nanoparticles" refers to particles sized between 1 and 100 nm. However, submicron particles are also commonly referred as nanoparticles in the field of pharmaceutics [61]. The most spectacular increases in oral bioavailability of docetaxel and paclitaxel have been achieved with nanoparticles in pre-clinical studies. To date a number of pre-clinical studies with nanoparticle formulations of docetaxel [62, 63] and paclitaxel [33, 64–69] have been reported.

Some nanoparticles were lipid based [33, 67, 69], others contained cyclodextrins [64, 65], polyanhydride [64, 68], d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS) [63, 66], PEG [68] and/or poly(lactic-co-glycolic acid) (PLGA) [62, 66] as main constituents. Particle sizes ranged from 60 nm [33] to 350 nm [65] with PDI values below 0.2. Drug loads varied from 4% [62] w/w to 50% w/w [64].

The increased bioavailability of docetaxel and paclitaxel in the nanoparticle formulations was attributed to various mechanisms: increased aqueous solubility of the drug due to solubilization of the drug by excipients [63, 65, 67], longer gastrointestinal (GIT) transit times and direct contact due to the mucoadhesive properties of excipients and/or nano-sized particles [63, 64, 66-68], permeability enhancement by excipients [69] and/or small particle size [66, 69], encapsulation of the drug and endocytosis [62, 66, 69], lymphatic uptake [33, 66],

inhibition of PgP and or CYP450 by excipients [33, 65, 67].

The reported apparent bioavailabilities ranged from 9% [68] to 666% [62] and relative bioavailabilities ranging from 2.1 [69] to as high as 120 [62]. These extreme values were caused by reduced clearance of the drug containing nanoparticles which resulted in significantly longer circulation times compared to oral and even the IV reference formulations (Taxol and Taxotere, respectively) [62-64, 66, 68]. Hence, interpretation of the reported bioavailability is difficult due to the different pharmacokinetic profiles of the nanoparticles compared to current IV formulations. Furthermore, as most nanoparticle reach the systemic circulation intact it would be of interest to know the plasma free drug concentration, the fraction that is not incorporated in the nanoparticle.

In conclusion, a wide variety of nanoparticle formulations of docetaxel and paclitaxel have been evaluated pre-clinically. However before these formulations can enter the clinical phase questions related to toxicity of the excipients and the in-vivo drug release need to be addressed [70].

Micelles

Micelles are nano-sized systems (~10–30 nm) formed when a surfactant is placed in aqueous environment above its critical micellar concentration (CMC). The micelles consist of an hydrophobic inner core and a hydrophilic outer core. The hydrophobic inner core segments can incorporate hydrophobic substances and improve their apparent solubility, while the hydrophilic outer core serves as a stabilizing interface between the hydrophobic core and the external aqueous environment [71]. The current IV formulations of paclitaxel and docetaxel are micellar systems consisting of purified cremophor EL (poyoxyethylene castor oil) and ethanol in the case of paclitaxel [2], and of polysorbate 80 and ethanol in case of docetaxel [1].

A critical parameter of micellar formulations for oral administration is the CMC of the surfactant. During oral administration the micellar formulation is diluted due to the fluids in the gastrointestinal tract-fluids which may result in reduced solubilization when the surfactant concentration drops below its CMC. New micellar formulations of paclitaxel with significantly lower CMC values compared to low-molecular weight surfactants were developed to ensure that the micelles remain intact even after severe dilution in the gastrointestinal tract [72, 73]. The relative oral bioavailability of paclitaxel in rats after administration of N-deoxycholic acid-N, O-hydroxyethyl chitosan (DHC) micelles was

3 [72], while pluronic F127 to F188 low molecular weight heparin-all-trans-retinoid acid conjugate micelles increased the relative oral bioavailability of paclitaxel to 17 and 22 [73]. Yoncheva et al. stabilized polymeric micelles of Pluronic F-38 by UV-induced cross linking of pentaerythritol tetraacrylate (PETA); oral administration to mice showed an apparent bioavailaibity of 110% due to longer circulation of the polymeric micelles after absorption [74]. This extreme value is comparable to some of the nanoparticle formulations [62, 64] and is probably caused by the fact that the paclitaxel containing stabilized micelles reach the systemic circulation and display altered pharmacokinetics. The absolute bioavailability of paclitaxel was estimated to be 90% [74].

Explanations for the high oral bioavailability of the pre-clinical micellar formulations were: increased solubility of paclitaxel due to the polymeric micelles [72-74], mucadhesive properties of the excipients or micelles [72, 74], absorption by endocytosis of the intact micelles [73, 74], increased permeability [72, 73], and prolonged circulation times of the micelles [73, 74], inhibition of PgP and/or CYP450 by pluronic copolymers [73, 74].

Bardelmeijer et al. showed that Cremophor EL limited the oral absorption of paclitaxel by entrapment of paclitaxel in micelles [75]. Based on this pre-clinical study Malingre et al. tested a polysorbate 80 / ethanol 1/1 v/v formulation of paclitaxel at 60 mg/m² and showed that the C_{max} 162 +/- 51 ng/mL and AUC 1418 +/- 94 ng · h/mL values of paclitaxel co-administered with CsA at 15 mg/kg were significantly increased compared to the regular Cremophor EL containing formulation [52]. Chu et al. reported similar results with a micellar formulation of Cremophor EL /PEG300/Tween 80/ ethanol 20/49/11/20 v/v/v/v. At a dose of 60 mg/m² paclitaxel and concomitant administration of 10 mg/kg CsA the C_{max} was 185 ng/mL(range 147-350) and the AUC was 1290 (range 1120-1640) ng · h/mL [76]. Although the oral bioavailability of paclitaxel was improved by these formulations they still have the disadvantages of the orally administered IV formulation, such as poor taste, poor dosing accuracy, and high contamination risk. Hence, further clinical application with these formulations is not likely.

Self-emulsifying systems

Part of the lipid based drug delivery systems are self-emulsifying drug delivery systems (SEDDS) which are physically stable, isotropic mixtures of oil, surfactant, co- surfactant and a solubilized drug substance. SEDDS are suitable for oral delivery in soft and hard

gelatin or hard hydroxypropyl- methylcellulose capsules. Depending on the excipient selection and relative composition of the formulation, aqueous dilution will result in spontaneous formation of lipid droplets ranging in size from approximately 100 nm (SEDDS) to less than 50 nm (SMEDDS) [77, 78].

Self-emulsifying formulations of docetaxel [79, 80] and paclitaxel [35, 41, 81-87], have been evaluated pre-clinically by various authors. Vitamin E [41, 82, 83, 87], monoolein [84], myvacet [86], capryol 90 [79, 80, 86], and/or omega-3 fatty acid-rich flax-seed oil [35] were used as oil-components.

Surfactants and co-surfactants used were TPGS 1000 [82, 83, 87], TGPS 400 (85), tyloxapol [87], Cremophor EL [41, 79, 81], Cremophor RH 40 [41, 82] glyceryl dioleate [81]; deoxycholic acid sodium salt (DOC-Na) [35, 82], Labrasol [80, 83], Labrafil [83]; tricaprylin [84], polysorbate 80 [41, 84, 86]); lecithin [35, 86]; Capmul [86], Transcutol [41, 79, 80], and/or ethyl linoleate [41].

As solvents or co-solvent ethanol [81, 85, 87], propylene glycol [82], 1-butanol [86], or PEG 200 [41] were used. Reported droplet sizes after self-emulsifying varied from 2 nm [82] to 1000 nm [86].

The proposed mechanisms by which the taxane SEDDS formulations enhanced the oral bioavailability were lower amounts of cremophor RH [82], increased permeability by membrane fluidity due to oil and surfactants such as DOC Na and Labrasol [35, 79, 80, 82, 86], solubilization of the drug by excipients during GIT transit [41, 79, 80, 82, 85], protection form chemical and enzymatic degradation by encapsulation in the oil droplets [82], mucoadhesive properties of excipients resulting in prolonged GIT transit time [84], enterocyte and lymphatic uptake of lipids particles (Figure 2) [35, 80, 82, 84]; fusion of oil droplets with cell membrame [35, 84], inhibition of PgP by excipients such as Labrasol [80, 83], Transcutol [79, 80], TGPS [82, 83, 85], Cremophor [82], and DOC Na [35]. To further increase the oral bioavailability of paclitaxel some SEDDS formulation were co-administered with the pharmacokinetic boosters CsA [81, 82, 87], curcumin [35] and silymarin [41].

The relative oral bioavailability without concomitant administration of a PK booster ranged from 0.3 [87] to more than 6.5 [80, 83]; with concomitant administration of a PK booster the relative oral bioavailability ranged from 2.5 [82] to 11.3 [81].

One of the concerns of SEDDS for clinical use are the necessary amounts of surfactants and their toxicity [78]. Furthermore, stability and dosing accuracy of the liquid formulation is a challenge, though the latter can be solved by dispensing liquid filled capsules or by solidifying the SEDDS on an inert carrier [80]. Moreover, for other low soluble drugs

there are several approved and marketed SEDDS formulations [70]).

Following the successful pre-clinical results of SMEOF#3 [87] a clinical study was conducted by Veltkamp et al. [53]. SMEOF#3 contained paclitaxel, vitamin E, TPGS 1000, tyloxapol, and ethanol. After oral administration of 160 mg paclitaxel in combination with 700 mg CsA C_{max} was 210 ng/mL (150-350) and $AUC_{0\text{-}inf}$ was 2060 ng · h/mL (1150-3470); the apparent bioavailability was 40% compared to IV Taxol. The novel SMEOF#3 formulation was well tolerated after oral administration at the given dose of 160mg when coadministered with CsA, without induction of relevant gastrointestinal or haematological toxicity [53].

In another clinical study Veltkamp et al. [54] evaluated a drinking solution and two liquid filled capsules. The drinking solution contained TPGS 1000, propylene glycol, Vitamin E, ascorbyl palmitate, and ethanol; the liquid filled capsules contained TPGS 1000, ascorbyl palmitate, ethanol and Labrasol/sorbitan monooleate or Labrafil M 1944 CS/PEG400. After oral administration of 180 mg paclitaxel in combination with 10 mg/kg CsA the exposure to paclitaxel was comparable between the three formulations and also in line with other studies. The authors preferred to use the capsule formulation with Labrafil M 1944 CS/PEG400 in future studies because of the generally better tolerability and safety profile of a capsule formulation above an oral drinking solution, and because of the slightly higher AUC 2670 ng · h/mL (range 1050-3610) of paclitaxel compared to the other liquid filled capsule.

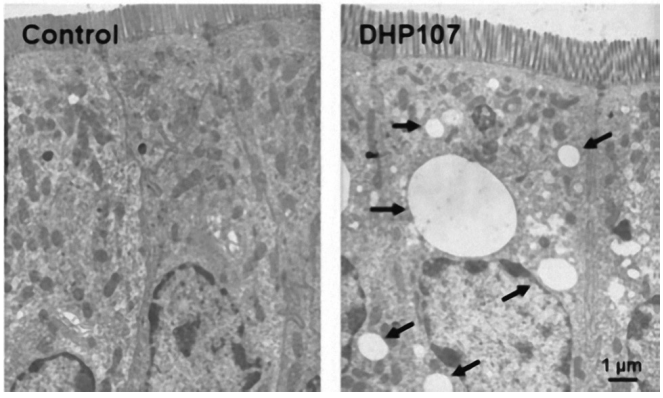

Figure 3: Transmission electron microscopy of intestinal absorptive cells 0.5h after oral administration of control and DHP107. Arrows indicate DHP107 lipid particles in the cytosol. Adapted from Hong et al. [84]

Another SEDDS formulations of paclitaxel that made its way to the clinic is DHP107. It is a semisolid mucoadhesive oral formulation containing 10 mg/mL of paclitaxel in a mixture of monoolein/tricarprylin/polysorbate 80 1/0.5/0.3 v/v/v [84, 88]. Recently, a Phase I dose escalation study of DHP107 was reported by Hong et al. [55]. Above 250 mg/m^2 non-linear pharmacokinetics were observed which was likely due to limited absorption of DHP107 at high dose levels rather than to its increased clearance by dose. At 250 mg/m^2 the C_{max} was 410 +/- 116 ng/mL and the $AUC_{0\text{-}inf}$ was 2150 +/- 254 ng · h/mL. Estimated apparent bioavailability was 9.5% at a dose of 60 mg/m^2 which is lower than the apparent oral bioavailability in mice (12% – 28%) [84]. The authors concluded that DHP107 was safe and feasible in patients with advanced malignancies and advised to limit the dose to 250 mg/m^2 of DHP107 as exposure of paclitaxel reached a plateau. Currently DHP107 is being evaluated in a Phase III study [89].

Solid dispersions

A solid dispersion is the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method [90]. Usually, solid dispersions are two component systems consisting of a hydrophilic carrier in which the active ingredient is incorporated (dispersed) in either a crystalline or an amorphous state. Currently, the term solid dispersion is mostly linked to an amorphous system (amorphous solid dispersion, ASD): a distribution of API in molecular or amorphous form in an (amorphous) inert carrier [91-93]. The improved dissolution rate of a solid dispersion can be attributed to an increased solubility of the drug because of its amorphous state, an increased surface area available for drug dissolution because of the small size of the dispersed particles, and an improved wetting of the drug caused by the hydrophilic carrier. The latter can be further improved by incorporating a wetting agent (e.g. surfactant) in the solid dispersion [91, 94-96].

As solid dispersion excipients are vital for maintaining the amorphous state upon storage and after dissolution [97-99], a careful selection process is needed to select the most suitable excipients. Most often, an extensive experimental screening program is conducted to test all possible excipients.

No pre-clinical studies using solid dispersion formulation of docetaxel or paclitaxel have been reported. Veltkamp et al. [56] evaluated the oral bioavailability of a polyvinyl acetate phthalate based solid dispersion of paclitaxel. After oral administration of 100

mg paclitaxel the apparent oral bioavailability was 13% without CsA and 26% with CsA. With CsA C_{max} was 79 +/- 72 and AUC was 967 +/- 779 ng · h/mL Because of the delayed release profile of paclitaxel from this novel formulation, the authors hypothesized that a split-dose regimen in which CsA is both given before and after paclitaxel administration would further increase the systemic exposure of paclitaxel from this formulation.

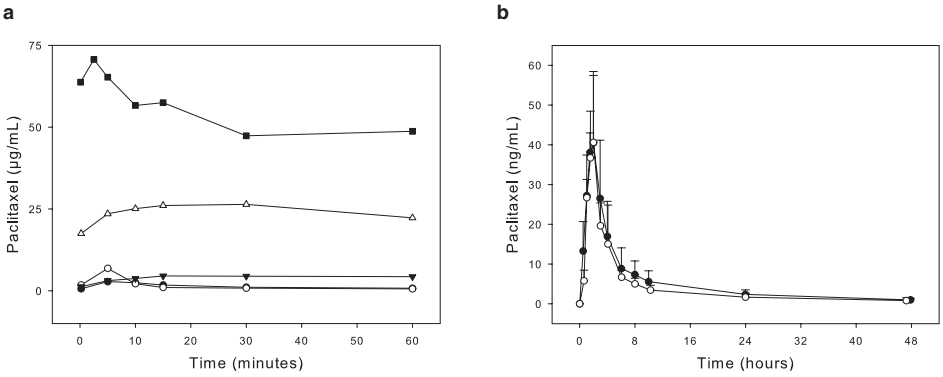

Figure 4: (a) Concentration vs. time curves of five paclitaxel formulations: paclitaxel di-hydrate (C: •); amorphous paclitaxel (D: ○); physical mixture of paclitaxel di-hydrate/PVP-K30/SLS (E: ▼); physical mixture of amorphous paclitaxel/PVP-K30/SLS (F: △); solid dispersion of amorphous paclitaxel/PVP-K30/SLS (G: ■). The amorphous solid dispersion of paclitaxel, PVP-K30 and SLS achieves highest apparent solubility of paclitaxel (C-F vs. G)

(b) Plasma concentration vs. time curves of paclitaxel after oral administration of 30 mg paclitaxel as premix solution (•) or as ModraPac001 10 mg capsule (○), both in combination with 100 mg ritonavir (n=4). No significant differences were found in the T_{max}, C_{max}, and AUC_{0-48} of paclitaxel between the two formulations. Adapted from Moes et al. [57].

More recently Moes et al. used a Modulated Drug Absorption (Modra) concept by combining polyvinylpyrrolidone (PVP) K30/sodium lauryl sulfate (SLS) based solid dispersion formulations of docetaxel (ModraDoc001) [58] and paclitaxel (ModraPac001) [57] with the pharmacokinetic booster ritonavir. Analysis of the solid dispersion formulations by X-ray powder diffraction (XRD), Fourier transform infrared (FT-IR) spectroscopy, and modulated differential scanning calorimetry (mDSC) confirmed the amorphous nature of paclitaxel and docetaxel, and their fine dispersion in the matrix of PVP-K30 and SLS. Furthermore, in-vitro tests showed a major increase in the apparent solubility and dissolution rate of paclitaxel (Figure 4a) and docetaxel. Thirty

milligrams of docetaxel and paclitaxel were concomitantly administered with 100 mg of ritonavir and compared to the orally administered IV formulations Taxol and Taxotere. The apparent bioavailability paclitaxel and docetaxel in the ModraPac001 (Figure 4b) and ModraDoc001 formulations was not significantly different from the orally administered IV reference formulations. Furthermore, the solid dispersion formulations seemed to provide a lower variability in paclitaxel and docetaxel exposure compared to the orally administered IV formulations. Based on these results the ModraDoc001 and ModraPac001 formulations are currently being evaluated in Phase I dose escalation studies [100-102].

Conclusions

A wide variety of formulation strategies have been applied to overcome the low oral bioavailability of paclitaxel and docetaxel. Most published articles concern paclitaxel, although the articles related to docetaxel seem to increase the past few years.

In general the described formulation strategies not only try to enhance the solubility of docetaxel and paclitaxel. They also try to inhibit the activity of PgP and CYP450 to further increase the oral bioavailability. Inhibition of PgP and CYP450 was achieved by concomitant administration of a regular PK booster such as CsA or ritonavir, but also with the excipients present in several nanoparticle and SEDDS formulations. Examples of these expients are TPGS and pluronic copolymers [103-105]. For a number of formulations it was shown that the surfactant type influenced the permeability of docetaxel and paclitaxel [79, 85, 86]. Enhancement of the solubility and dissolution rate of docetaxel and paclitaxel is achieved by size reduction, physical state conversion [57, 58], and solubilization by surfactants, polymers, oils, and cyclodextrins.

Despite their promising results, the nanoparticle formulations are the only one that have not yet reached the clinic, in contrast to the other formulation categories discussed. This is most probably related to the general concerns about polymeric nanoparticles with respect to toxicity and scale-up [70].

Currently, one oral formulation of docetaxel and three oral formulations of paclitaxel are in active clinical development. The first two formulations make use of the Modra concept by combining oral solid dispersion formulations of docetaxel (ModraDoc) and paclitaxel

(ModraPac) with the pharmacokinetic booster ritonavir. This concept has resulted in clinically relevant exposure to docetaxel and paclitaxel in humans. For both docetaxel and paclitaxel clinical studies are currently at the end of Phase I and ready to progress to Phase II. The third formulation, currently under phase II clinical investigation, is a combination of paclitaxel and the novel PgP-inhibitor HM30181 (Oraxol) [46, 106, 107]. Unfortunately, the composition of this formulation nor pharmacokinetic data is publicly available. The fourth oral formulation, currently in phase III testing, is the lipid based paclitaxel formulation DHP107 [55, 84, 89]. DHP107 is developed without a pharmacokinetic booster, however the oral bioavailability of paclitaxel seems to be lower than the ritonavir boosted ModraPac formulation.

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Chapter 3

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

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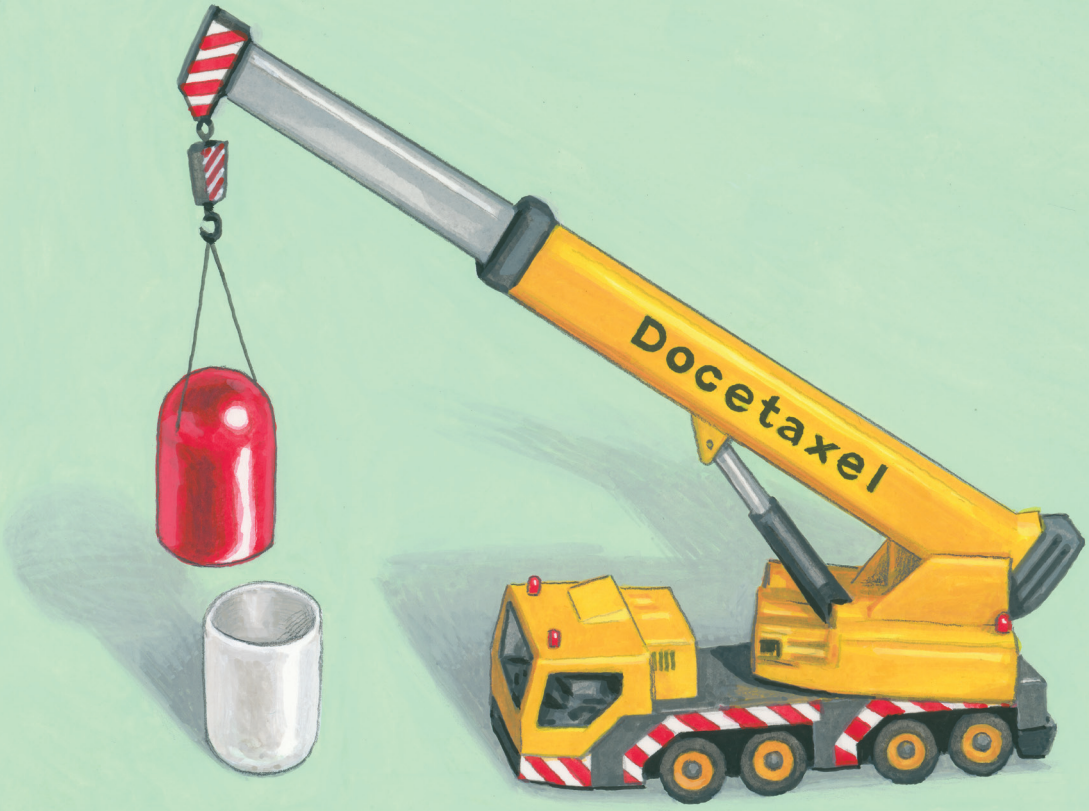

International Journal of Pharmaceutics 2011 (420) 2: 244-250

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 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.

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 to 100 mg/m^2 docetaxel is administered via intravenous (IV) infusion.

Because of its mechanism of action continuous exposure to docetaxel could improve its effectiveness against cancer [1, 2]. 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 [3].

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 [4] and permeability [2]. Therefore, docetaxel is classified as a Biopharmaceutical classification system (BCS) class IV drug [5]). 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 [6]. We have shown that the ap[7]parent oral bioavailability of the docetaxel premix solution increased to 131 ± 90% by concomitant administration of ritonavir, a strong CYP3A4 inhibitor [8]. 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 hours), high ethanol content and poor dosing accuracy [7]. 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 [4], 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 [8] 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 [9-11]. 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) [12]. 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 [13].

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 powder diffraction (XRD) 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.

Materials and methods

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 1500-20000) were purchased from Sigma-Aldrich (Zwijndrecht, The Netherlands). Hydroxypropyl-ß-cyclodextrin (HP-ß-CD) was supplied by Roquette (Lestrem, France). Hard gelatin capsules were purchased from Capsugel (Bornem, Belgium).

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 Beijnen et al. [14]

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.

Dissolution testing

Maximum solubility (S_{max}), time until precipitation ($T_{precipitation}$) and equilibrium solubility ($S_{equilibrium}$) (see Figure 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.

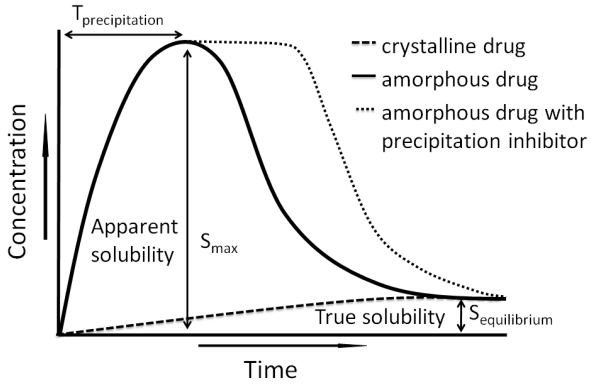

Figure 1: Concentration vs. time curves of a drug in its crystalline and in its amorphous state. The amorphous drug reaches its maximum solubility, the apparent solubility, (S_{max}) in the supersaturated state. This supersaturated state can only be maintained for a limited period of time ($T_{precipitation}$), 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. [15]).

Dissolution of capsules was tested according to the European Pharmacopoeia [16] 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) [17] 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 hours to detect possible recrystallization of docetaxel from the supersaturated solution [18].

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. [19]

X-ray powder diffraction (XRD)

XRD 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

degrees 2-theta, with a step size of 0.020 degrees and a scanning speed of 0.002 degrees per second.

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 minutes, after which the sample was heated to 190.00 °C at a speed of 2.00 °C/min. Modulation was performed every 60 seconds at +/- 1.00 °C.

Fourier transform infrared spectroscopy (FT-IR)

Infrared spectra were recorded from 400 – 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.

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. [20] Samples of approximately 50 mg powder were dissolved in 5.0 mL of DMSO.

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 milligrams of docetaxel concomitantly with 100 milligrams

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 [7]. 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.

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 hours after docetaxel intake. All blood samples were immediately placed on ice and centrifuged within 1 hour at 1500 g for 10 minutes 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 [21]. Non-compartmental pharmacokinetic analysis and statistical analysis was performed using R version 2.10.0 [22]. A Wilcoxon signed rank test was used to evaluate the differences between the two formulations.

Results and Discussion

Preparation and testing of docetaxel solid dispersion formulations

In principle, solid dispersion are prepared by a variety of methods, such as spray drying,

melt extrusion and freeze-drying [11]. 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 [23]. 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 [10, 24]. 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 [25]. 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 ($S_{equilibrium}$) (Figure 1).

We chose to use a target concentration of 200 µg/mL, which is approximately 40 times the equilibrium solubility of docetaxel trihydrate [4]. 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 to 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 minutes 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 [15].

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 Figure 2.

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-ß-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

Crystalline and amorphous docetaxel had different S_{max} values but comparable $T_{precipitation}$, and $S_{equilibirum}$ values (Figure1: formulation 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. (5.9 µg/mL vs. 4.93 µg/mL) [4], this could be due to the shorter equilibration time (60 minutes vs. 48 hours) 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).

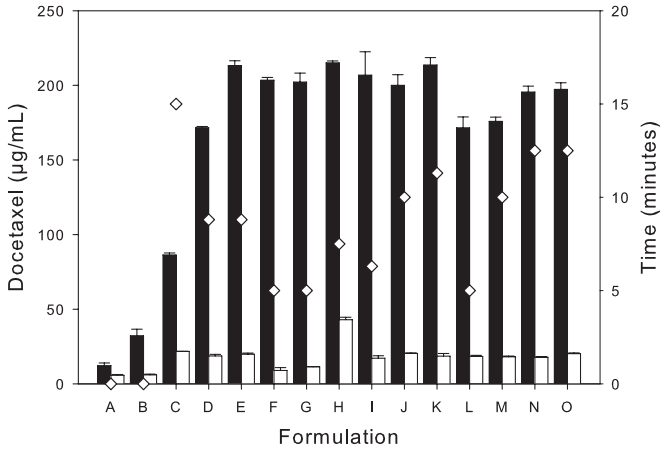

Figure 2: Dissolution parameters of docetaxel formulations. S_{max} (closed bars) and $S_{equilibirum}$ (open bars) are plotted on the left y-axis (docetaxel in µg/mL); $T_{precipitation}$ (◇) is plotted on the right y-axis (time in minutes). All values are means and standard deviations.

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 (Figure 2: formulation 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 (Figure 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 [15]. 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 [24]. 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 (Figure 2: formulation E to H) or various chain lengths (Figure 2: formulation I to K). There was however a trend towards higher S_{max} values at lower docetaxel weight ratios (Figure 2: formulation L to O).

Apparently a minimal amount of carrier molecules is needed to physically separate the amorphous docetaxel molecules and prevent rapid crystallization (Figure 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 (Figure 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-ß-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) (Figure 2: formulation E to H) and increased with increasing carrier chain length (Figure 2: I to K) or decreasing weight ratios of docetaxel (Figure 2: L to O). For both PVP and SLS inhibition of drug precipitation from supersaturated solutions has been described [26, 27]. 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 [28], formation of hydrogen bonds between drug and PVP molecules [29], increase of viscosity of the dissolution medium [15]. 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 (Figure 2: formulation E to 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 $S_{equilibrium}$.

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 [16]) was used to test the performance of hard gelatine capsules filled with solid dispersion formulations.

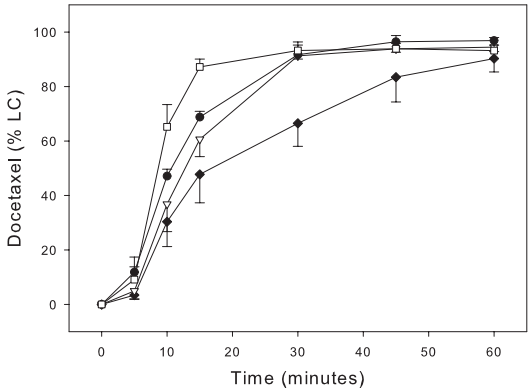

Figure 3: Dissolution curves of capsules filled with freeze-dried solid dispersion formulations of docetaxel, PVP-K30 and SLS. (◆): no SLS; (▽): 4/1 w/w docetaxel/SLS; (●): 2/1 w/w docetaxel/SLS; (□): 1/1 w/w docetaxel/SLS. The dissolution rate of docetaxel increases when the amount of SLS relative to the amount of docetaxel increases.

The 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 (Figure 3). The initial slow dissolution rate between 0 and 5 minutes could be attributed to the dissolution of the hard gelatine capsule shell.

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).

XRD, MDSC and FT-IR

We compared the XRD spectra, the MDSC thermograms and FT-IR spectra of the three formulation types (Table 1: formulation A to E) to examine their physical properties and find an explanation for the observed differences in solubility (see Figures 4a, 4b, and 4c). The characteristic XRD peaks of crystalline materials were present in the XRD spectra of crystalline docetaxel and its physical mixture (Figure 4a: formulation A and C). Properties characteristic to amorphous materials, such as the presence of a glass transition temperature (Tg) and the absence of XRD peaks, were seen in the XRD spectra and MDSC thermograms of amorphous docetaxel and its physical mixture (Figure 4a/b: 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.

In addition to this, differences between the XRD spectra and FT-IR spectra could be related to mixing efficiency of both docetaxel and SLS. The XRD diffraction peaks of SLS, around 21° 2-theta, were sharper and larger in the spectra of the physical mixtures than in the spectra of the freeze-dried solid dispersions (Figure 4a: formulation C, D and E). These findings were confirmed by the FT-IR spectra: the blunt peak of docetaxel near 1700 cm^{-1} (Figure 4c: formulation 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.

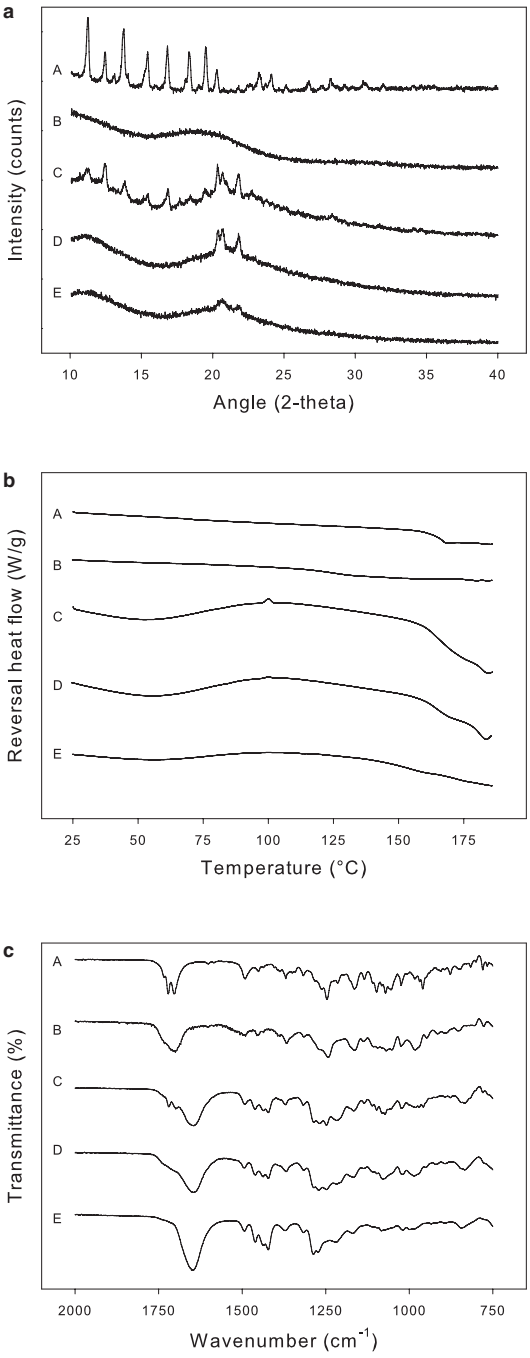

Figure 4. XRD spectra (a), reversal heat flow signals (b), and FT-IR spectra (c) of five different docetaxel formulations. A: Crystalline docetaxel; B: amorphous docetaxel; C: physical mixture of 1/11 w/w crystalline docetaxel, 9/11 w/w PVP-K30 and 1/11 w/w SLS; D: physical mixture of 1/11 w/w amorphous 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.

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.

Table 2: Stability results ModraDoc001 15 mg capsules

	Start	2 years at 2-8°C, dark	2 years at 25 °C / 60% RH
Docetaxel peak purity (%)	99.99	100.0	99.20
Docetaxel dissolved at t=30 minutes (%)[a]	97.0 (4.1)	97.5 (6.0)	96.7 (4.9)
Docetaxel dissolved at t=60 minutes (%)[a,b]	96.5 (4.0)	96.8 (5.1)	96.6 (3.2)
Docetaxel dissolved at t=240 minutes (%)[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 [18]

Quality control testing of the clinical formulation showed a very rapid dissolution in USP SIF_{sp} [17], after which docetaxel remained in solution for at least 4 hours [18]. 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).

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. Figure 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.

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 hours

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.

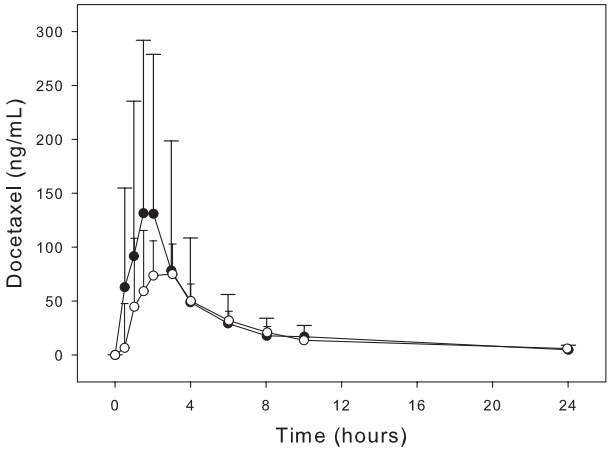

Figure 5: Concentration vs. time curves of docetaxel (p.o) administered concomitantly with 100 mg ritonavir (p.o). Plotted data are mean and SD values of six patients. (○) ModraDoc001 15 mg capsules (p.o); (●) docetaxel premix solution (p.o). There were no significant differences between the pharmacokinetic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

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 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.

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 [8] 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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Chapter 4

Development of an oral solid dispersion formulation for use in low-dose metronomic chemotherapy of paclitaxel

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J.H. Beijnen, B. Nuijen

European Journal of Pharmaceutics and Biopharmaceutics 2013 (83) 1: 87-94

Abstract

For the clinical development of low-dose metronomic (LDM) chemotherapy of paclitaxel, oral administration is vital. However, the development of an oral formulation is difficult due to paclitaxel's low oral bioavailability, caused by its low permeability and low solubility. We increased the oral bioavailability of paclitaxel by combining a pharmacokinetic booster, ritonavir, with a new oral solid dispersion formulation of paclitaxel.

The combined use of Hansen solubility parameters and dissolution experiments resulted in the development of a solid dispersion formulation containing 1/11 w/w paclitaxel, 9/11 w/w polyvinylpyrrolidone (PVP) K30 and 1/11 w/w sodium lauryl sulphate (SLS). Analysis of the solid dispersion formulation by X-ray diffraction (XRD), Fourier transform infrared (FT-IR) spectroscopy, and modulated differential scanning calorimetry (mDSC) confirmed the amorphous nature of paclitaxel, and the fine dispersion of paclitaxel in the matrix of PVP-K30 and SLS. Furthermore, in-vitro tests showed a major increase in the apparent solubility and dissolution rate of paclitaxel. To test the clinical significance of these findings the solid dispersion formulation of paclitaxel (ModraPac001 10 mg capsule) was compared to the paclitaxel premix solution in four patients with advanced cancer.

Although the mean systemic exposure to paclitaxel after oral administration of the solid dispersion formulation was slightly lower compared to the paclitaxel premix solution (190 ± 63.1 ng/mL·hr for vs. 247 ± 100 ng/mL·hr), the systemic exposure to paclitaxel is clinically relevant [1, 2]. In addition to this, the favorable pharmaceutical characteristics, e.g neutral taste, dosing accuracy, and the two-year ambient shelf life, make the ModraPac001 10 mg capsule an attractive candidate for oral paclitaxel chemotherapy. Currently, the ModraPac001 formulation is applied in the first clinical trial with oral LDM chemotherapy of paclitaxel.

Introduction

The intravenous (IV) formulation of paclitaxel (Taxol(r) and several generic products) has been approved for the treatment of various malignancies. Current treatment regimens of paclitaxel are based on the classic dose-intensive chemotherapy theory. According to this theory, the maximum tolerated dose (MTD) will result in the highest anti-tumor activity. An alternative treatment regimen to MTD is low-dose metronomic (LDM) chemotherapy.

LDM chemotherapy consists of administration of anticancer drugs at relatively low doses on a frequent administration schedule with no drug-free periods. Unlike dose-intensive chemotherapy, which is directly aimed at killing the tumor cell, the main target in LDM chemotherapy is the angiogenic capacity of tumor cells. Dose-intensive chemotherapy may not lead to optimal anti-tumor activity, and often exposes patients to severe side-effects. In fact, dose-intensive chemotherapy could reduce the anti-angiogenic capacity of the therapy [3].

Recent studies have shown that LDM chemotherapy of paclitaxel had anti-tumor activity by inhibiting angiogenesis [3], both in vitro and in vivo [1, 4]. A recent phase II study with 96-hour paclitaxel infusions confirmed these findings in humans; unfortunately, the long infusion times resulted in a high incidence of bacterial infections [5]. Moreover, for the successful implementation of LDM chemotherapy of paclitaxel, oral administration of paclitaxel is vital in terms of patient convenience and patient compliance.

However, the oral bioavailability of paclitaxel is limited by paclitaxel's poor aqueous solubility (paclitaxel di-hydrate, 1 μg/mL [6]), its affinity for the drug efflux pump P-glycoprotein (Pgp), and by the extensive presystemic metabolism by cytochrome P450 (CYP) enzymes in the liver and gut wall. Because of its low solubility and permeability, paclitaxel is classified as a class 4 drug in the biopharmaceutical classification system (BCS) [7].

We were able to overcome the low permeability of paclitaxel by concomitant administration of a pharmacokinetic (PK) booster. Initially we used Cyclosporin A, an inhibitor of Pgp, for this purpose [8]. Recently, we found that the systemic exposure to paclitaxel could also be increased by known CYP3A4 inhibitors such as ketoconazole, clarithromycin, and ritonavir [9]. Especially ritonavir (NORVIR(r)) is an attractive PK booster, because it has been approved for use in anti-HIV therapy to enhance the

systemic exposure of other HIV-1 protease inhibitors (e.g. amprenavir, lopinavir and saquinavir) [10].

In our initial studies with oral paclitaxel, we bypassed paclitaxel's solubility problem by using the premix solution of paclitaxel's IV formulation. Evidently, this formulation was not developed for oral administration and has, as a result, considerable drawbacks such as a poor taste, a poor physical and chemical stability at ambient temperatures, a limited dosing accuracy, and a high contamination risk. Furthermore, the toxicity of the excipients polyoxyethylated castor oil (Cremophor EL) and ethanol anhydrous attribute to the patient unfriendly nature of the paclitaxel premix solution. Hence, development of a more suitable oral formulation of paclitaxel was vital to continue our clinical studies into LDM chemotherapy of paclitaxel.

The goal of this study was to develop and clinically evaluate an oral solid dosage form of paclitaxel. We investigated if a solid dispersion formulation was suitable for this purpose. A solid dispersion is the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method [11]. Usually, solid dispersions are two component systems consisting of a hydrophilic carrier in which the active ingredient is incorporated (dispersed) in either a crystalline or an amorphous state. Currently, the term solid dispersion is mostly linked to an amorphous system (amorphous solid dispersion, ASD): a distribution of API in molecular or amorphous form in an (amorphous) inert carrier [12-14]. The improved dissolution rate of a solid dispersion can be attributed to an increased solubility of the drug because of its amorphous state, an increased surface area available for drug dissolution because of the small size of the dispersed particles, and an improved wetting of the drug caused by the hydrophilic carrier. The latter can be further improved by incorporating a wetting agent (e.g. surfactant) in the solid dispersion [12, 15-17].

As solid dispersion excipients are vital for maintaining the amorphous state upon storage and after dissolution [18-20], a careful selection process is needed to select the most suitable excipients. Most often, an extensive experimental screening program is conducted to test all possible excipients. We combined theoretical calculations of Hansen solubility parameters (HSP) with small-scale dissolution tests to develop the most optimal solid dispersion formulation of paclitaxel.

Although originally designed to explain the interactions between solvents and solutes, HSP and the Hildebrand total solubility parameter (δ_{HIL}) are frequently used to explain

the interactions between solid dispersion components [21]. HSP are three parameters describing the different interactions between solvents and solutes, dispersion interactions (δ_D), polar interactions (δ_P), and hydrogen bonding interactions (δ_H) [22]; the square root of the sum of squares of the HSP gives the Hildebrand total solubility parameter [23]. Because of the structural similarities between docetaxel and paclitaxel and our promising results with a solid dispersion formulation of docetaxel [24], we calculated the HSP and δ_{HIL} for paclitaxel and docetaxel, and the solid dispersion components PVP-K30 and SLS. Additional small-scale dissolution tests evaluated various formulation types, weight ratio's, carrier types, and surfactants. X-ray powder diffraction (XRD), modulated differential scanning calorimetry (mDSC), and Fourier transform infrared spectroscopy (FT-IR) were used to characterize the formulations of paclitaxel. Finally, the solid dispersion formulation of paclitaxel, the ModraPac001 10 mg capsule, was compared to the paclitaxel premix solution in a clinical proof of concept study.

Materials and Methods

Materials

Paclitaxel was purchased from Indena (Milan, Italy). Polyvinylpyrrolidone K30 (PVP-K30) was 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). Lactose 200 M and colloidal silicon dioxide were purchased from Spruyt Hillen (IJsselstein, The Netherlands). Hard gelatin capsules were purchased from Capsugel (Bornem, Belgium).

Solubility parameters

We used the Yamamoto molecular break (Y-MB) method in the software program Hansen Solubility Parameters in Practice (HSPiP version 3.1, www.Hansen-Solubility.com) to calculate the HSP and δ_{HIL} of docetaxel, paclitaxel, PVP-K30 and SLS. Ra and $\Delta\delta_{HIL}$ values were calculated for the combinations of paclitaxel-PVP-K30, paclitaxel-SLS, docetaxel-PVP-K30, docetaxel-SLS, and PVP-K30-SLS. Equation 1 gives the relation between Hildebrand total solubility and HSP. Equation 2 defines the affinity of

one compound for another compound in terms of HSP; Equation 3 defines the affinity in terms of the Hildebrand total solubility parameter [22, 23].

Eq. (1): $\delta_{HIL}^{\ 2} = \delta_D^{\ 2} + \delta_P^{\ 2} + \delta_H^{\ 2}$

Eq. (2): $Ra = \sqrt{\left[4(\delta_{D1} - \delta_{D2})^2 + (\delta_{P1} - \delta_{P2})^2 + (\delta_{H1} - \delta_{H2})^2\right]}$

Eq. (3): $\Delta\delta_{HIL} = \sqrt{(\delta_{HIL1} - \delta_{HIL2})^2}$

Preparation of paclitaxel formulations

Paclitaxel formulations were prepared by freeze-drying and/or physical mixing (mortar and pestle). Freeze-drying of paclitaxel formulations was performed in stainless steel boxes (Gastronorm size 1/9) using a freeze dryer (Model Lyovac GT4, GEA Lyophil GmbH, Hürth, Germany) according to a method previous developed by Beijnen et al. [25]. Prior to freeze-drying, all components were dissolved in 60/40 v/v mixtures of TBA/WfI; the concentration of paclitaxel in TBA was 10 mg/mL for all formulations.

The clinical capsule formulation (ModraPac001 10 mg capsule) was produced by mixing an amount of solid dispersion powder equivalent to 10 mg paclitaxel with 110 mg of lactose and 2.2 mg of colloidal silicon dioxide using mortar and pestle. The final powder mixture was encapsulated with a manual capsulation apparatus into size 0 hard gelatin capsules.

Dissolution testing

The performance of the paclitaxel formulations was tested using a small-scale dissolution method. Briefly, an amount of powder, equivalent to approximately 3 mg paclitaxel, was added to a 50 mL beaker containing 25 milliliter of WfI at 37 °C and stirred at 720 rpm by a magnetic stirring bar (non-sink conditions).

Dissolution of the capsule formulation was tested according to the European Pharmacopoeia, using a type 2 (paddle) [26] dissolution apparatus (Erweka, Heusenstamm, Germany) filled with 500 mL Simulated Intestinal Fluid without pepsin (SIFsp) [27]. The medium was kept at 37 °C and stirred at 100 rpm (non-sink conditions).

Samples were collected at various time points, filtrated using a 0.45 μm filter (Millex HV PVDF, Millipore, Billerica, MA, USA) and diluted 1:1 v/v with a 1:4 v/v mixture of methanol and acetonitrile. Samples were subsequently analyzed on a reversed phase HPLC system with UV detection (RP-HPLC-UV) developed by Huizing et al. [28].

X-ray powder diffraction (XRD)

XRD measurements were performed on an X'pert pro diffractiometer equipped with an X-celerator (PANanalytical, Almelo, The Netherlands). Samples of approximately 0.5 mm thick were placed in a metal sample holder, placed in the diffractiometer and scanned at a current of 50 mA and a tension of 40 kV. Scan range was 10-60 degrees 2-theta, with a step size of 0.020 degrees and a scan speed of 0.002 degrees per second.

Modulated differential scanning calorimetry (MDSC)

MDSC measurements were performed on 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 transferred into Tzero Aluminum pans (TA instruments, New Castle, DE, USA), covered with a Tzero lid, and placed in the autosampler. Samples were equilibrated at 20.00 °C, after 5 minutes the samples were heated to 190.00 °C at a speed of 2.00 °C/min. Modulation was performed every 60 seconds at ± 1.00 °C.

Glass transitions (Tg) were determined at the inflection points with Universal Analysis 2000 (version 4.7A, TA instruments, New Castle, DE, USA). The Fox-equation (4) [29] was used to estimate the Tg_{mix} of the solid dispersion formulation.

Eq. (4): $1 / Tg_{mix} = w_1 / Tg_1 + w_2 / Tg_2$

In which W_i is the weight fraction of the i^{th} component, Tg_i is the glass transition temperature of the i^{th} component, and all temperature values are expressed in Kelvin.

Fourier Transform Infrared spectroscopy (FT-IR)

Infrared spectra were recorded from 650 – 4000 cm^{-1} with a resolution of 4 cm^{-1} on a FT-IR 8400S Spectrophotometer equipped with a golden gate (r) (Shimadzu, 's-Hertogenbosch, The Netherlands). The average of 3 spectra, consisting of 16 scans each, was reported.

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 a gas chromatography (GC) analysis method developed by Van der Schoot et al. Samples of approximately 50 mg were dissolved in

5.0 mL of DMSO [30].

Clinical study design

This study was designed as a randomized, open label, proof of concept study. Over a period of two weeks, patients received once a week 30 mg paclitaxel p.o. and 100 mg ritonavir p.o. (Norvir(r); Abbott Laboratories Ltd, Illinois, USA). Paclitaxel was formulated either as a premix solution containing 6 mg/mL paclitaxel, 527 mg/mL polyoxyl 35 castor oil, and 49.7% v/v ethanol anhydrous (Paxene, Norton Healthcare Ltd, London, United Kingdom) or as a solid dispersion formulation (ModraPac001 10 mg capsule, Slotervaart Hospital Amsterdam, The Netherlands). Both ritonavir and paclitaxel were administered in combination with approximately 150 mL tap water.

Patients were randomized into two groups. Two patients received the ModraPac001 10 mg capsules in the first week and the paclitaxel premix solution in the second week; the other two patients received the formulations in the reversed order.

A complete physical examination and a review of the medical history was performed before inclusion. During study, vital signs, WHO performance status, weight, hematology, and blood chemistry were monitored.

The study protocol was approved by the medical ethics committee of the Netherlands Cancer Institute; all patients had to give written informed consent prior to start of the study.

Pharmacokinetic and bioanalysis

The pharmacokinetic profile of both the paclitaxel premix solution and the ModraPac001 10 mg capsule was determined. Blood samples were drawn in lithium-heparinized tubes at baseline and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24 and 48 hours after paclitaxel intake. Samples were immediately placed on ice and were centrifuged within 1 hour at 1500 g for 10 minutes at 4°C. Plasma was stored at or below -20°C until analysis. Paclitaxel was quantified in plasma by use of high-performance liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) described earlier [31].

Individual pharmacokinetic parameters were analyzed using descriptive pharmacokinetic methods and validated R scripts (R version 2.10.0) [32].The areas under the plasma concentration-time curves to the last quantifiable sample point (AUC_{0-t}) were estimated by the linear trapezoidal (absorption phase) and logarithmic trapezoidal rule (elimination

phase). A Wilcoxon signed rank test was used to evaluate the differences between the two formulations.

Table 1: Patient Characteristics

Parameter	N
Sex	
Female	3
Male	1
Age (years)	
Median	54
Range	47 - 63
ECOG performance status	
0	2
1	1
2	1
Pathological diagnosis	
Prostate	1
Breast	1
Gastric	1
Primary unknown	1
Disease stage	
Metastatic	4
No. of Prior treatments (surgery, radiotherapy or chemotherapy)	
2	2
3	-
≥4	2

Results and discussion

Solubility parameters

Although docetaxel and paclitaxel are structural analogs, the compounds differ in physicochemical properties which might affect the characteristics of their formulations. Especially the differences in water solubility (paclitaxel 0.8 μg/mL vs docetaxel 4.9 μg/mL) and the number of hydrogen bond donors (paclitaxel 4 vs. docetaxel 5) could lead to significant differences in the formation, stability, and performance of their solid dispersion formulations [12, 15].

We therefore compared the compatibility of paclitaxel and docetaxel with PVP-K30 and SLS using the Ra and $\Delta\delta_{HIL}$ values derived from the HSP. All combinations had $\Delta\delta_{HIL}$ values below 7.5 $MPa^{1/2}$ (data not shown). These values are promising because Greenhalgh et al. concluded that, in general, $\Delta\delta_{HIL}$ values below 7.5 MPa1/2 indicate good miscibility between components [21]. Furthermore, Ra and $\Delta\delta_{HIL}$ values were lower for the combination of paclitaxel and PVP compared to the combination of docetaxel and PVP. In addition to this, there was a close agreement between the low Ra and $\Delta\delta_{HIL}$ values and the experimental results of the docetaxel formulation [24]. In summary, the low Ra and $\Delta\delta_{HIL}$ values of paclitaxel and PVP, suggests that a solid dispersion formulation of paclitaxel, PVP-K30 and SLS could perform well.

XRD, mDSC and FT-IR

We produced five different formulations of paclitaxel to evaluate the formation, stability, and performance of the solid dispersion formulation: two pure drug formulations, two physical mixture formulations, and one solid dispersion formulation. The physical mixture formulations and the solid dispersion formulation all contained the same components at equal weight ratios: paclitaxel, PVP-K30 and SLS in a weight ratio of 1/9/1 w/w/w. An overview of the paclitaxel formulations is given in Table 2; XRD spectra, mDSC thermograms, and FT-IR spectra are shown in Figure 1.

Table 2: Paclitaxel formulations and their components

Formulation	Description	Components	Weight ratio	Preparation method
A	Carrier	PVP-K30	n.a.	n.a.
B	Surfactant	SLS	n.a.	n.a.
C	Cr PTX	Paclitaxel dihydrate	n.a.	n.a.
D	Am PTX	Amorphous paclitaxel	n.a.	Freeze-drying
E	PM Cr PTX/PVP-K30/SLS	Paclitaxel dihydrate, PVP-K30, SLS	1/9/1 w/w/w	Physical mixing
F	PM Am PTX/PVP-K30/SLS	Amorphous paclitaxel, PVP-K30, SLS	1/9/1 w/w/w	Physical mixing
G	SD PTX/PVP-K30/SLS	Paclitaxel, PVP-K30, SLS	1/9/1 w/w/w	Freeze drying

Cr: crystalline; Am: amorphous; PTX: paclitaxel; PM: physical mixture; SD: solid dispersion

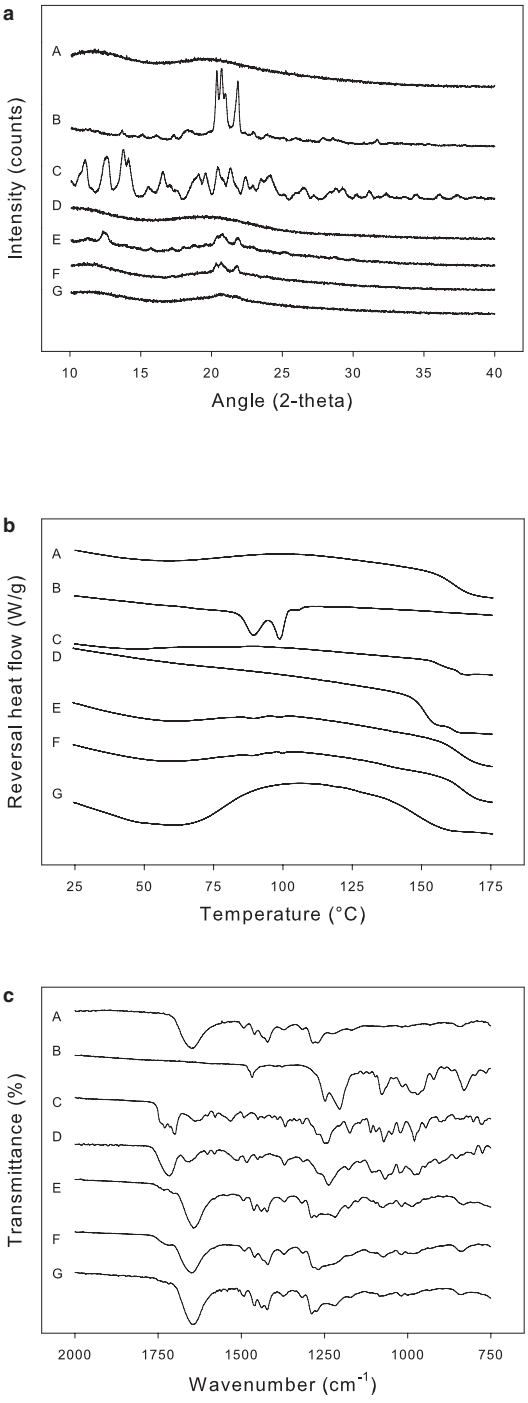

Figure 1: XRD spectra (a), reversal heat flow signals (b) and FT-IR spectra (c) of five paclitaxel formulations and their components. A: PVP-K30; B: SLS; C: paclitaxel di-hydrate; D: amorphous paclitaxel; E: physical mixture of paclitaxel di-hydrate/PVP-K30/SLS; F: physical mixture of amorphous paclitaxel/PVP-K30/SLS; G: solid dispersion of amorphous paclitaxel/PVP-K30/SLS. Freeze drying of paclitaxel di-hydrate results in amorphous paclitaxel (C vs. D); freeze drying of paclitaxel di-hydrate, PVP-K30 and SLS results in an amorphous solid dispersion (E and F vs. G).

Based on the XRD spectra of paclitaxel di-hydrate and freeze-dried paclitaxel, it was concluded that freeze-drying of paclitaxel di-hydrate results in amorphous paclitaxel (Figure 1a: C vs. D). In addition to this, the XRD spectra of the physical mixtures showed peaks characteristic to SLS, paclitaxel di-hydrate and/or amorphous paclitaxel (Figure 1a: A to F). This proved that SLS, paclitaxel di-hydrate and amorphous paclitaxel could be detected in physical mixtures at a weight ratio of 1/11 w/w, which is the weight ratio used in the solid dispersion formulation. However, compared to the XRD spectra of the physical mixtures, the intensity of the SLS peaks was considerable lower in the XRD spectrum of the solid dispersion formulation (Figure 1a: E to G). The XRD analysis of the paclitaxel formulations and their excipients justify the conclusion that freeze-drying of paclitaxel di-hydrate in combination with PVP-K30 and SLS results in a solid dispersion with amorphous paclitaxel. Furthermore, the lower intensity of the SLS peaks in the XRD spectrum of the solid dispersion indicates that SLS, and very likely paclitaxel as well, were more finely dispersed over PVP-K30 in the solid dispersion formulation.

The mDSC thermograms (see Figure 1b) confirmed the results of the XRD analysis. Freeze dried paclitaxel di-hydrate, i.e. amorphous paclitaxel, had a Tg at 151 ° (Figure 1b: D). The glass transition of PVP-K30 at 162 °C (Figure 1b: A), and the characteristic thermal events of SLS, i.e. the endothermic peaks at 89 and 99 °C (Figure 1b: B), were visible in the thermograms of both physical mixtures (Figure 1b: E and F); while they were absent in the mDSC thermogram of the solid dispersion formulation (Figure 1b: G). Additional proof of the formation of a true solid dispersion was the detection of one glass transition at 150 °C (Tg_{mix}) in the thermogram of the solid dispersion formulation (Figure 1b: G). According to the Fox equation (1) [29] full miscibility of PVP-K30 and amorphous paclitaxel will result in a Tg_{mix} of approximately 161 °C. The difference between the experimental and theoretical Tg_{mix} is likely due to the presence of the third component of the solid dispersion formulation, SLS. Indeed, mDSC thermograms of a 9/1 w/w binary mixture of PVP-K30 and SLS showed a decrease in the Tg of PVP-K30 (data not shown). Ghebremeskel et al. also reported a lower Tg of PVP-K30 in combination with SLS [33] and suggested that SLS acted as a plasticizer of PVP-K30. Moreover, the existence of a Tg_{mix} indicates a strong interaction between paclitaxel, PVP-K30, and possibly SLS.

The combined information of the XRD and mDSC analysis was used to explain the

differences in FT-IR spectra of the paclitaxel formulations (see Figure 1c). The transformation from paclitaxel di-hydrate to amorphous paclitaxel was most clearly visible around 1700 cm^{-1}, where the sharp dual peak of paclitaxel di-hydrate turned into a single blunt peak (Figure 1c: C vs. D). These differences were also visible in the spectra of both physical mixtures, indicating that paclitaxel di-hydrate and amorphous paclitaxel could be detected in FT-IR spectra at a weight ratio of 1/11 w/w (Figure 1c: E vs. F). Compared to the FT-IR spectrum of the physical mixture, the blunt peak of amorphous paclitaxel was less intense in the FT-IR spectrum of the solid dispersion (Figure 1c: F vs. G). The latter finding provides another strong indication that freeze-drying results in a more fine dispersion of paclitaxel over PVP-K30 compared to physical mixing.

Dissolution testing

All formulations were tested in a small-scale dissolution test, to determine the influence of their physical properties on the apparent solubility of paclitaxel (S_{app}). The advantage of the small-scale dissolution test is the limited amount of powder necessary to reach a concentration of paclitaxel well above the equilibrium solubility of paclitaxel [24].

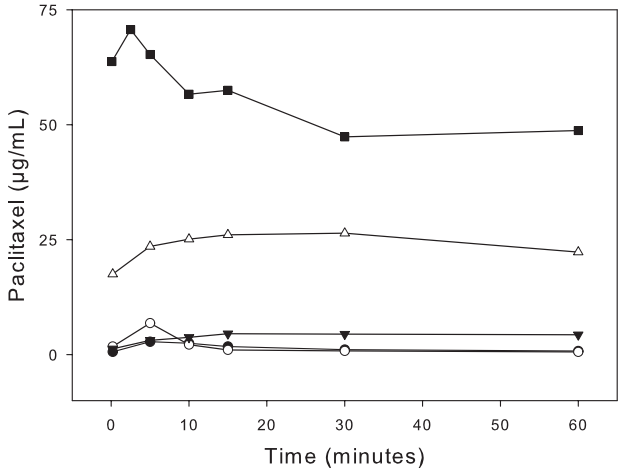

Figure 2: Concentration vs. time curves of five paclitaxel formulations: paclitaxel di-hydrate (C: •); amorphous paclitaxel (D: ○); physical mixture of paclitaxel di-hydrate/PVP-K30/SLS (E: ▼); physical mixture of amorphous paclitaxel/PVP-K30/SLS (F: △); solid dispersion of amorphous paclitaxel/PVP-K30/SLS (G: ■). The amorphous solid dispersion of paclitaxel, PVP-K30 and SLS achieves highest apparent solubility of paclitaxel (C-F vs. G)

The results of the small-scale dissolution test are shown in Figure 2. The solid dispersion formulation performed best; the maximum S_{app} was 70 μg/mL and the S_{app} remained above 50 μg/mL for at least 1 hour (G: ■). Furthermore, at 60 minutes the S_{app} of the solid dispersion formulation was approximately 2 times the S_{app} of the physical mixture containing amorphous paclitaxel (22 μg/mL) (F vs. G: △ vs. ■), and approximately 100 times the S_{app} of amorphous paclitaxel (0.6 μg/mL) (Figure 2: ™) and paclitaxel di-hydrate (0.8 μg/mL) (C: •). The measured Sapp of the latter two are in line with the equilibrium solubility of paclitaxel di-hydrate reported by Liggins et al (1 μg/mL) [6].

The increase in the S_{app} of paclitaxel is caused by several factors. Firstly, the physical state of paclitaxel, the amorphous state of paclitaxel has a higher S_{app} than the crystalline state of paclitaxel (D vs. C: ○ vs. •). Secondly, the solubilizing effect of the excipients, PVP-K30 and SLS solubilize paclitaxel di-hydrate and increase the S_{app} (E vs. C: ▼ vs. •). Thirdly, recrystallization of amorphous paclitaxel is inhibited by PVP-K30 and/or SLS and results in a higher S_{app} of amorphous paclitaxel (F vs. D: △ vs. ○). Fourthly, the solid dispersion preparation method leads to an improved dispersion and physical separation of amorphous paclitaxel, which prevents immediate recrystallization of amorphous paclitaxel upon contact with water and increases the amount of amorphous paclitaxel available for dissolution (G vs. F: ■ vs. △).

Additional dissolution tests with different carriers (HP-β-CD, PVP-K12 and PVP-K17) and drug to carrier ratio's (3:1, 2:3, and 1:3) confirmed the superior performance of PVP-K30, SLS, and the 1/9/1 weight ratio (data not shown).

Although both PVP-K30 and SLS have been named as crystallization inhibitors [34, 35], experiments with docetaxel showed that PVP was responsible for inhibiting recrystallization of docetaxel [24]. Furthermore, the amount of PVP in the formulation is 9 times higher than the amount of SLS, and the HSP calculations predicted a stronger interaction between paclitaxel and PVP than between paclitaxel and SLS. Indeed, additional small-scale dissolution tests in WfI solutions with 0.5% w/v PVP-K30, showed an increase in solubility and time to precipitation of paclitaxel. Moreover, PVP-K30 is primarily responsible for the inhibition of the recrystallization of paclitaxel. Nevertheless, dissolution experiments revealed that SLS is a vital excipient in the solid dispersion formulation of paclitaxel. The improved wetting by SLS significantly increased the dissolution rate of paclitaxel in the initial stages of dissolution and dissolution of paclitaxel from a solid dispersion formulation without SLS took several hours (data not shown).

Clinical formulation

Because of the promising in vitro results, the solid dispersion formulation of paclitaxel was used to produce a clinical capsule formulation, denoted the ModraPac001 10 mg capsule. Quality control and stability testing of the ModraPac001 10 mg capsule showed high peak purity, low residual solvents, and a rapid dissolution of paclitaxel from the capsule formulation. Retests, consisting of a dissolution test and assay, performed after 12 and 24 months of storage at 2-8 °C and at 25 °C / 60% relative humidity (RH) showed no changes in peak purity or release profile of paclitaxel contained in the ModraPac001 10 mg capsule (Table 3). In addition to this, XRD, mDSC and FT-IR measurements on the ModraPac001 SD powder revealed no changes to the amorphous nature of paclitaxel after 24 months of storage at 2-8 °C.

Table 3: Stability results ModraPac001 10 mg capsule

	Start	Two years at 2 – 8 °C, dark	2 years at 25 °C / 60% RH
Paclitaxel peak purity (%) [a]	99.91	99.88	99.56
Paclitaxel dissolved at t=30 minutes (%) [a, b]	93.8 (4.3)	94.5 (4.0)	91.9 (6.5)
Paclitaxel dissolved at t=60 minutes (%) [a, b]	91.9 (5.3)	94.6 (3.8)	91.0 (2.1)
Paclitaxel dissolved at t=240 minutes (%) [a, b]	92.1 (5.2)	90.9 (7.3)	90.1 (4.7)

[a]Values are means and coefficients of variation (%). [b]Time points were included to detect possible recrystallization of paclitaxel from the supersaturated solution [36]. RH: relative humidity

Clinical study

In this proof-of-concept study we compared the exposures to 30 mg paclitaxel after oral administration of the paclitaxel premix solution and the ModraPac001 10 mg capsule; both formulations were co-administered with 100 mg ritonavir. Four patients, 3 males and 1 female with a median age of 51 years, were enrolled in the proof-of-concept study; relevant patient characteristics are listed in Table 1. Patient 2 received ritonavir two hours prior to administration of the paclitaxel premix solution; patient 4 received ritonavir simultaneously with the ModraPac001 10 mg capsules. The mean concentration time curves and the relevant pharmacokinetic parameters are shown in Figure 3 and Table 4. There was a tendency towards a higher maximum plasma concentration and exposure

values after administration of the paclitaxel premix solution. However, no significant differences were found between the pharmacokinetic parameters of paclitaxel of the two treatment regimens.

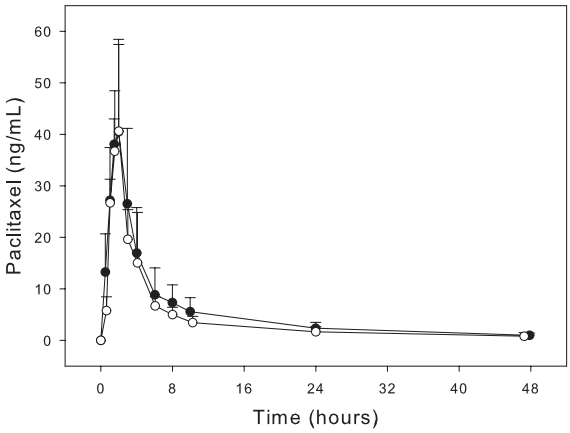

Figure 3: Plasma concentration vs. time curves of paclitaxel after oral administration of paclitaxel premix solution (•) or ModraPac001 10 mg capsule (○), both in combination with 100 mg ritonavir (n=4). No significant differences were found in the T_{max}, C_{max}, and AUC_{0-48} of paclitaxel between the two formulations.

In general both treatment regimens were well tolerated. Adverse events that were possibly related to orally administered paclitaxel, either as paclitaxel premix solution or ModraPac001 10 mg capsule, were: nausea (CTCAE grade 1; n=2), voice changes (CTCAE grade 1; n=2), vomiting (CTCAE grade 1; n=1), myalgia (CTCAE grade 1; n=1), pyrexia (CTCAE grade 2; n=1).

Unfortunately we could not include a treatment regimen without ritonavir. However, in previous studies we investigated the influence of PgP and CYP3A4 inhibitors on the exposure of paclitaxel after oral administration of the paclitaxel premix solution. First we showed that oral administration of paclitaxel was feasible and that the exposure to 60 mg/m^2 paclitaxel was significantly increased by co-administration of 10 mg/kg oral cyclosporine A (CsA, NEORAL $^{(r)}$) (AUC_{0-48} 170 ± 85 ng · h/mL vs. 1450 ± 768 ng · h/mL) [8, 37, 38]. More recently we used a cross-over design to show that the exposure to 100 mg paclitaxel administered as the paclitaxel premix solution was comparable when co-administered with 15 mg/kg CsA or 100 mg ritonavir (AUC_{0-24} 1030 ± 124 ng · h/mL vs. AUC_{0-24} 732 ± 432 ng · h/mL) [9].

Despite the fact that this proof-of-concept study had a limited sample size and statistical power; the pharmacokinetic data suggests that the ModraPac001 10 mg capsule is comparable to the paclitaxel premix solution. More importantly, the exposure to paclitaxel after administration of the ModraPac001 10 mg capsule and ritonavir was in line with our previous studies when the differences in paclitaxel dose are taken into account [8, 9, 37, 38].

Table 4: Pharmacokinetic parameters of 30 mg paclitaxel (p.o) administered concomitantly with 100 mg ritonavir (p.o)

	T_{max}[a] (h)	C_{max}[a] (ng/mL)	C_{48h} (ng/mL)	AUC_{0-48}[a] (ng·h/mL)
Paclitaxel premix solution	1.64 ± 0.44 (27%)	47.5 ± 14.5 (31%)	0.99 ± 0.43	247 ± 100 (41%)
ModraPac001 10 mg capsule	1.91 ± 0.21 (11%)	41.8 ± 15.9 (38%)	0.80 ± 0.72	190 ± 63.1 (33%)

[a]Values are mean ± standard deviation and coefficient of variation (%) of 4 patients. T_{max}: time point at which the maximum concentration is reached; C_{max}: maximum concentration; C_{48h}: concentration at 48 hours; AUC_{0-48}: area under the concentration vs. time curve between 0 and 48 hours

To investigate whether the ModraPac001 10 mg capsule could be used in oral metronomic paclitaxel therapy, we compared the single dose exposure and plasma levels of paclitaxel found in this study with published data. In our study the mean peak plasma concentration (C_{max}) after weekly administration of 30 mg paclitaxel was 41.8 ng/mL (median 37.5 ng/mL); after 24 hours and 48 hours the plasma concentrations were 1.67 ± 0.98 ng/mL and 0.80 ± 0.72 ng/mL respectively. These values are well within the effective range of 0.085 – 8.5 ng/mL (0.1 – 10 nM) predicted by the studies of Wang et al. [1], Merchan et al.[2], and Bhatt et al. [5] and below the myelosuppression threshold of 43 ng/mL (50 nM) established by Gianni et al [39]. Furthermore, in-vitro and pre-clinical studies performed with cremophor EL [40] and the cremophor EL-free, albumin bound formulation of paclitaxel [41] suggested that cremophor EL decreases the antiangiogenic effect of paclitaxel. Hence, the anti-angiogenic plasma levels of paclitaxel will probably be lower in the absence of cremophor EL. Moreover, given that the median half-life of paclitaxel in both treatment regimens was around 14 hours it is very likely that the use of daily or bi-daily dosing will results in effective and non-toxic plasma levels of paclitaxel.

Although, PK boosted oral administration of paclitaxel has demonstrated anti-tumor activity and acceptable toxicity in 3 phase II studies [42-44], further development was hampered by the safety profile of CsA and the unpractical formulations of both CsA and paclitaxel. In the past, we tested several oral formulations of paclitaxel to replace the paclitaxel premix solution: Paxoral® [42], SMEOF#3 [45] and a polymeric paclitaxel formulation [46]. However, the development of all these formulations was terminated due to low systemic exposure, high variability in exposure to paclitaxel and/or unpractical drug administration. Several taxanes were especially designed for oral administration, such as BMS275183 [47], ortataxel (IDN-5109) [48], IDN-5390 [49], and milataxel (MAX-321)[50]. However, due to their high variability in PK, unfavorable safety profile or lack of anti-tumor activity it is doubtful whether these compounds will ever reach the clinic. In recent years there have been new developments, Chu et al used CsA as PK booster in combination with their oral liquid formulation of paclitaxel (Genetaxyl), and found pharmacokinetic parameters similar to our previous results (60 mg/m^2 paclitaxel and 10 mg/kg CsA: $AUC_{0\text{-}inf}$ 1.29 ± 0.19 µg x h/mL and C_{max} 0.185 µg/mL) [51]. Most recently, Hong et al used a different approach to enhance the oral bioavailability of paclitaxel; instead of using a PK booster they used a novel lipid formulation (DHP107). At a dose of 60 mg/m^2 of paclitaxel exposure and maximum plasma levels of paclitaxel were lower compared to our results ($AUC_{0\text{-}48}$ 488.6 ± 166.3 ng · hr /mL; Cmax 131.3 ± 30.9 ng/mL) [52]. Although, the authors claim a favorable toxicity profile due to the absence of cremophor EL and a PK booster, the available data suggests that a large part of the administered paclitaxel remains in the gastrointestinal tract causing diarrhea. It remains to be seen if these side effects will be acceptable during daily administration.
Compared to the above mentioned formulation, the main advantage of the ModraPac001 10 mg capsule is its ease of use, and stability at ambient conditions. These characteristics are of prime importance for outpatient metronomic treatment regimens.

Conclusions

In a clinical proof-of-concept study, we demonstrated that the oral solid dispersion formulation of paclitaxel, the ModraPac001 10 mg capsule, had a pharmacokinetic profile comparable to the paclitaxel premix solution. Furthermore, the ModraPac001 10

mg capsule has favorable pharmaceutical characteristics such as a 24-month stability at ambient conditions and an acceptable taste. Even more the ModraPac001 10 mg capsule allows safe and practical dosing of a highly toxic anticancer agent. More importantly, the plasma levels of paclitaxel are within effective therapeutic range for metronomic paclitaxel therapy. These promising results encourage further investigation of oral administration of paclitaxel by administration of the ModraPac001 10 mg capsule in combination with ritonavir. Currently a dose-escalation study with daily and bi-daily dosing of ModraPac001 capsules is ongoing to find the optimal metronomic dosing schedule.

Acknowledgements

We would like to acknowledge Dr. Steven Abbott for his help with the HSPiP software package.

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Chapter 5

Stability of freeze-dried amorphous solid dispersion formulations used in oral taxane chemotherapy

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Interim analysis

Abstract

To date the successful clinical application of oral taxane chemotherapy is hampered by the low oral bioavailability of paclitaxel and docetaxel. Recently we showed that their bioavailability was increased by combining the pharmacokinetic booster ritonavir with an oral amorphous solid dispersion formulation consisting of docetaxel or paclitaxel, polyvinylpyrrolidone (PVP) K30, and sodium lauryl sulfate (SLS) in a weight ratio of 1/9/1.

In this study we evaluated the physical and chemical stability of the amorphous solid dispersion formulations of docetaxel and paclitaxel using X-ray powder diffraction (XRD), modulated differential scanning calorimetry (mDSC), Fourier Transform Infrared spectroscopy (FT-IR), residual solvent analysis, assay, and dissolution tests.

During storage the amount of water in the amorphous solid dispersions increased, which facilitated the total removal of tert-butanol (TBA) and induced phase separation of SLS. Despite this phase separation both active ingredients remained amorphous and no chemical degradation was observed. Furthermore, it is hypothesized that phase separation of SLS also made way for stronger interactions between docetaxel and PVP which led to an increased stability in solution. Nevertheless, phase separation of SLS also led to a decreased wetting of the PVP based solid dispersion which resulted in a significant change in the dissolution profile after more than 52 weeks of storage at 25 °C /60% RH. By improving the primary and secondary packaging of the amorphous solid dispersion formulations the absorption of water could be reduced which would further increase their pharmaceutical shelf life and increase the ease of use in outpatient treatment.

Introduction

Taxanes belong to the most potent anticancer drugs against solid tumors. Because they inhibit the mitotic cell division by stabilizing microtubules they are ideal candidates for low dose weekly or daily metronomic chemotherapy [1-6]. However, the low oral bioavailability of paclitaxel and its structural derivative docetaxel makes the development of an oral treatment challenging. Their low oral bioavailability is a result of the poor water solubility [7, 8], the active excretion by Pg-P protein pumps, and the extensive metabolism by gastro-intestinal and hepatic CYP3A4 enzymes [2].

Earlier we showed that the oral bioavailability of docetaxel and paclitaxel was increased by concomitant oral administration of the pharmacokinetic booster ritonavir and the intravenous (IV) pre-mix solution [9-11]. Recently, we developed oral amorphous solid dispersion formulations for both active ingredients, the ModraDoc001 and ModraPac001 10 mg capsules. We subsequently showed that concomitant oral administration of the amorphous solid dispersion formulations and ritonavir led to clinically relevant exposure to docetaxel and paclitaxel [12, 13]. To date the ModraDoc001 10 mg capsule has been administered to 97 patients [14, 15] and the ModraPac001 10 mg capsule to more than 21 patients [16] in phase I clinical trials.

The ModraDoc001 and ModraPac001 10 mg capsules contained lactose monohydrate, colloidal silica, and a freeze-dried amorphous solid dispersion (SD) of the active ingredient, polyvinylpyrrolidone K30 (PVP-K30), and sodium lauryl sulfate (SLS) in a weight ratio of 1/9/1 w/w/w. We found earlier that the improved dissolution rate of the amorphous solid dispersions was due to the higher apparent solubility of the amorphous active ingredient, the increased surface area of the finely dispersed active ingredient, and an improved wetting of the active ingredient by the hydrophilic carrier PVP-K30 and the surfactant SLS [12, 13]. Hence it is of prime importance that these characteristics are maintained throughout the pharmaceutical shelf life to ensure a reproducible pharmaceutical availability of the active ingredient.

Solid dispersion excipients are vital to maintain the amorphous state of the active ingredient upon storage and after dissolution [17-19]. The selection process of the excipients should therefore take into account physical and chemical stability, and initial and long term dissolution performance. In principle, crystallization of amorphous substances occurs above the glass transition temperature (Tg). However, molecular

mobility already occurs above the Kauzmann temperature, which is 50 °C below the Tg [20]. In addition to this, the Tg can be substantially lowered by the plasticizing effect of water. Another threat to the stability of amorphous solid dispersion is phase separation of the amorphous solid dispersion components. Phase separation is induced by the absorption of water and decreases the interaction between the hydrophobic drug and the hydrophilic solid dispersion excipients. The decreased interaction could lead to decreased dissolution performance especially if phase separation results in crystallization of the amorphous active ingredient [21, 22]. In conclusion, the two most important factors which influence the physical and chemical stability of amorphous solid dispersion formulations are humidity and temperature.

The goal of this study was to determine the physical and chemical stability of the clinical amorphous solid dispersion formulations of docetaxel and paclitaxel. First we tested the crystallization potential of the pure amorphous active ingredients at 40°C/75 % RH. Next we evaluated the stability of the amorphous solid dispersions at 2-8 °C for more than 24 months. Finally we tested the stability of the final products, ModraDoc001 and ModraPac001 10 mg capsules, stored at 2-8 °C and 25 °C/60% RH. We used modulated Differential Scanning Calorimety (mDSC), X-ray powder diffraction (XRD), Fourier Transform Infrared spectroscopy (FT-IR), residual solvents assays to characterize the amorphous solid dispersion formulations and detect physical and chemical changes during storage. In addition to this we calculated Hanssen solubility parameters (HSP) and performed dissolution tests to explain differences between the amorphous solid dispersions of docetaxel and paclitaxel and to determine their pharmaceutical shelf life.

Table 1: Physical and chemical properties, and solubility parameters of paclitaxel and docetaxel

Property	Docetaxel	Paclitaxel
Molecular weight (g/mol)	807.9[b]	853.9[b]
Melting point °C (K)	232 °C (505 K)[b]	213-216 °C (486-491 K)[a]
Glass transition temperature	148 °C (421 K)[d]	151 °C (424 K)[d]
Crystal forms	Anhydrous, trihydrate	Anhydrous, dihydrate
Water solubility	4.9 µg/mL (trihydrate)[d]	0.8 µg/mL (dihydrate)[d]
Hydrogen donors/acceptors	5/15[c]	4/15[c]
HSP: δ_D, δ^z, δ_H[e]	18.8, 11.9, 17.4	19.7, 8.7, 15.8
$Ra_{PVP\text{-}K30}$ ($HSP_{PVP\text{-}K30}$: 17.5, 8, 15)	5.3	4.5
Ra_{SLS} (HSP_{SLS}: 17.5, 16.8, 16.8)	5.6	9.3
δ_{HIL}	28.2	26.7
$\Delta\delta_{HIL\text{-}PVP\text{-}K30}$ ($\delta_{HIL\text{-}PVP\text{-}K30}$: 24.4)	3.8	2.3
$\Delta\delta_{HIL\text{-}SLS}$ ($\delta_{HIL\text{-}SLS}$: 29.5)	1.3	2.8

[a]Liggins et al. [8]; [b]DrugBank [23]; [c]Pubchem [24]; [d]Own experimental data, [e]Hansen Solubility Parameters (HSP) calculated with HSPiP [25]

Materials and Methods

Materials

Docetaxel anhydrate was obtained from Scinopharm Taiwan (Tainan, Taiwan). Paclitaxel was purchased from Indena (Milan, Italy). Polyvinylpyrrolidone K30 (PVP-K30) was supplied by BASF (Ludwigshafen, Germany). Tert-butanol (TBA), sodium lauryl sulfate (SLS) and dimethyl sulfoxide (DMSO) were purchased from VWR (Amsterdam, The Netherlands). Water for Injection (WfI) was obtained from B. Braun (Melsungen, Germany). Lactose 200M and colloidal silicon dioxide were supplied by Spruyt Hillen (IJsselstein, The Netherlands). Hard gelatin capsules were purchased from Capsugel (Bornem, Belgium).

Preparation of formulations

Production and development of ModraDoc001 and ModraPac001 amorphous solid dispersion formulations was described previously [12, 13]. Briefly, the intermediate products, ModraDocc001 SD powder and ModraPac001 SD powder, were freeze-dried from a solution of the active ingredient, PVP-K30, and SLS at a weight ratio of 1/9/1 w/w/w in a 60/40 v/v mixture of TBA and WfI. The active ingredient was dissolved in TBA at a concentration of 10 mg/mL; excipients were dissolved in WfI at a concentration of 150 mg/mL. After complete dissolution of all ingredients both solutions were mixed and transferred to stainless steel lypophilization boxes (Gastronorm size 1/3). Freeze-drying was done in a Lyovac GT4 freeze dryer (GEA Lyophil GmbH, Hürth, Germany) according to a freeze-drying program developed earlier [26]. The freezing phase started with a freezing ramp from ambient temperature to -35 °C in 1 hour followed by a holding step of 2 hours at -35 °C. Primary drying was performed at -35 °C and 0.2 mbar for 45 hours. Secondary drying started with a heating ramp from -35 °C to 25 °C at 0.2 mbar in 15 hours followed by a holding step at 25 °C and 0.2mbar for 3 hours.

Pure amorphous active ingredients were freeze-dried using the same procedure; physical mixtures were prepared using mortar and pestle.

The final products, the ModraDoc001 10 mg capsule and the ModraPacc001 10 mg capsule, were prepared by mixing an amount of ModraDoc001 or ModraPac001 SD powder equivalent to 10 mg of the active ingredient with 110 mg lactose and 2.2 mg colloidal silicon dioxide. The resulting powder mixture was encapsulated with a manual encapsulation apparatus into size 0 hard gelatin capsules.

Stability study

Amorphous active ingredients were transferred to open flasks and stored at 40 °C /75% RH for 10 days. Samples were weighed and subjected to FT-IR, mDSC, and XRD analysis before and after storage.

ModraDoc001 and ModraPac001 SD powders were stored in glass containers closed with a Polypropylene (PP) lid and stored at 2-8 °C for up to 147 weeks. At various time points the powders were subjected to XRD, mDSC, and FT-IR analysis, residual solvent testing, and small-scale dissolution tests.

ModraDoc001 and ModraPac001 10 mg capsules were individually packaged in transparent Polyethylene Terephthalate (PET) diamond shaped blister strips with label

sealing. The blisters were packaged in white Polypropylene (PP) jars with white screw caps and stored at 2-8 °C and at 25 °C /60 % RH for up to 140 weeks. At various time points stability samples were pulled and the capsules were subjected to dissolution testing, weight measurements, and assay and related substances testing.

Water

The amount of water absorbed by the pure amorphous active ingredients was derived from the weight before and after storage and based on the heat of evaporation in the non-reversal mDSC heat flow signal. The amount of water absorbed was expressed as weight percentage of the initial weight.

Total water in ModraDoc001 and ModraPac001 SD powders 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. Total water was expressed as weight percentage of the total dried weight.

The amount of water absorbed by the ModraDoc001 and ModraPac001 10 mg capsules was derived from the assay values of the active ingredient (Eq. 5) and the weight of the capsules used in the dissolution test (Eq. 6). The amount of water absorbed was expressed as weight percentage of the initial weight.

Eq. (5): $\text{Water}_{\text{assay}}\,(\%\ \text{w/w}) = 100 \cdot (1 / \text{Assay}_0 - 1 / \text{Assay}_t) / (1 / \text{Assay}_0)$

Eq. (6) $\text{Water}_{\text{weight}}\,(\%\text{w/w}) = 100 \cdot [(W_t - W_{caps}) - (W_0 - W_{caps})] / (W_0 - W_{caps})$

In which Assay_t and Assay_0 are the assay values at time=0 and t after production; W_t and W_0 are the total capsule weights at time=0 and t after production; W_{caps} is the weight of an empty capsule.

Residual TBA

Residual TBA in freeze-dried solid dispersion powders was determined with a gas chromatography (GC) analysis method developed earlier; samples of approximately 50 mg were dissolved in 5.0 mL of DMSO. [27]. Total TBA is expressed as weight percentage of the total dried weight.

Assay and related substances

Assay and related substances of docetaxel and paclitaxel were determined using a

previously developed stability-indicating reversed phase HPLC system with UV detection [28]. An amount of powder equivalent to 10 mg of active ingredient or the weighed content of one capsule was dissolved in 100 mL of a methanol/acetonitrile/0.02 M ammonium acetate buffer pH 5 mixture (1:4:5 v/v/v). Docetaxel and paclitaxel were detected at 227 nm. Assay values of ModraDoc001 and ModraPac001 SD powders were reported as weight percentage of total dried weight; assay values of ModraDoc001 and ModraPac001 10 mg capsules were reported as weight percentage of total weight. Chromatographic peak purity was calculated as the percentage of the main peak area relative to the total peak area (Chromeleon 7.2; Dionex Corporation, Sunnyvale, CA, USA).

X-ray powder diffraction (XRD)

XRD measurements were performed on a X'pert pro diffractometer equipped with an X-celerator (PANanalytical, Almelo, The Netherlands). Samples of approximately 0.5 mm thick were applied on a metal sample holder, placed in the diffractometer and scanned at a current of 50 mA and a tension of 40 kV. Scan range was 10-60 degrees 2-theta, with a step size of 0.020 degrees and a scan speed of 0.002 degrees per second.

Modulated differential scanning calorimetry (mDSC)

mDSC measurements were performed on 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 transferred into Tzero Aluminium pans (TA instruments), non-hermetically closed, and placed in the autosampler. Samples were equilibrated for 5 minutes at 20.00 °C and subsequently heated to 190.00 °C at a rate of 2.00 °C/min. Modulation was performed every 60 seconds at +/- 1.00 °C.

Glass transition temperature (Tg), heat capacity difference (ΔCp), and heat of evaporation (ΔH_{vap}) were determined from the reversal and non-reversal heat flow signals using Universal Analysis 2000 (version 4.7A, TA instruments, New Castle, DE, USA). The midpoint of the Tg was reported for each sample. The Fox-equation (Eq. 1) [29] was used to estimate the Tg_{mix} (30).

Eq. (1): $1 / Tg_{mix} = w_1 / Tg_1 + w_2 / Tg_2$

In which w_i is the weight fraction of the i^{th} component, Tg_i is the glass transition temperature of the i^{th} component expressed in Kelvin.

Fourier Transform Infrared spectroscopy (FT-IR)

FT-IR spectra were recorded on a FT-IR 8400S Spectrophotometer equipped with an Attenuated Total Reflectance (ATR) holder (Golden Gate ATR; Shimadzu, 's-Hertogenbosch, The Netherlands). Each spectrum had a range of 650 cm-1 to 4000 cm^{-1} at a resolution of 2 $cm^{-1}$and was the average of 16 individual scans. Pre-treatment and analysis of FT-IR spectra were performed using The Unscrambler X (version 10.3. CAMO software AS, Oslo, Norway). Pre-treatment consisted of averaging individual spectra and standard normal variate (SNV) correction.

Theoretical physical mixture spectra were calculated using a method described by Rumondor et al. [21]. Briefly, spectra of individual components were added after multiplication by a weighing factor. The weighing factor was the ratio of the relative number of carbon bonds of each individual component ($C\text{-}C_{number}$) and the relative intensity of a selected carbon bond ($C\text{-}C_{intensity}$). The weighing factor was calculated using equation 2 to 4:

Eq. (2): $C\text{-}C_{number,i} = (N_a \cdot C\text{-}C_i \cdot w_i / mw_i) / (\Sigma N_a \cdot C\text{-}C_{i\text{-}n} \cdot w_{i\text{-}n} / mw_{i\text{-}n})$

Eq. (3) $C\text{-}C_{intensity,i} = I_i / \Sigma I_{i\text{-}n}$

Eq. (4) Weighing factor = $C\text{-}C_{number} / C\text{-}C_{intensity}$

In which w_i is the weight fraction, mw_i is the molecular weight, $C\text{-}C_i$ is the number of C-C bonds per molecule, and I_i is the peak absorbance intensity at the midpoint of the selected peak of the i^{th} component; N_a is Avogadro's constant of $6.22 \cdot 10^{23}$.

The following parameters were used for the calculations: $Mw_{docetaxel}$ 807.9 g/mol; $C\text{-}C_{docetaxel}$ 29 bonds and peak located at 1243 cm^{-1}; $Mw_{paclitaxel}$ 853.9 g/mol; $C\text{-}C_{paclitaxel}$ 28 bonds and peak located at 1237 cm^{-1}; $Mw_{PVP\text{-}K30}$ 49,000 g/mol; $C\text{-}C_{PVP\text{-}K30}$ 4 bonds and peak located at 1284 cm^{-1}; Mw_{SLS} 288.4 g/mol; $C\text{-}C_{SLS}$ 11 bonds and peak located at 1205 cm^{-1}.

Solubility parameters

We used the Yamamoto molecular break (Y-MB) method in the software program Hansen Solubility Parameters in Practice (HSPiP version 3.1, www.Hansen-Solubility.com) to calculate the HSP and δ_{HIL} of docetaxel, paclitaxel, PVP-K30 and SLS. Although originally designed to explain the interactions between solvents and solutes, HSP and the Hildebrand total solubility parameter (δ_{HIL}) are frequently used to explain the interactions between solid dispersion components [31]. HSP are three parameters

describing the different interactions between solvents and solutes, dispersion interactions (δ_D), polar interactions (δ_P), and hydrogen bonding interactions (δ_H) (25).Ra and $\Delta\delta_{HIL}$ values were calculated for the combinations of paclitaxel-PVP-K30, paclitaxel-SLS, docetaxel-PVP-K30, docetaxel-SLS, and PVP-K30-SLS. Equation 7 gives the relation between Hildebrand total solubility and HSP. Equation 8 defines the affinity of one compound for another compound in terms of HSP; Equation 9 defines the affinity in terms of the Hildebrand total solubility parameter [25, 32].

Eq. (7): $\delta_{HIL}^{\ 2} = \delta_D^{\ 2} + \delta_P^{\ 2} + \delta_H^{\ 2}$

Eq. (8): $Ra = \sqrt{\left[4(\delta_{D1} - \delta_{D2})^2 + (\delta_{P1} - \delta_{P2})^2 + (\delta_{H1} - \delta_{H2})^2\right]}$

Eq. (9): $\Delta\delta_{HIL} = \sqrt{(\delta_{HIL1} - \delta_{HIL2})^2}$

Dissolution testing

ModraDoc001 and ModraPac001 SD powder were subjected to a small-scale dissolution test described earlier [12]. Briefly, an amount of powder, equivalent to approximately 3 to 6 mg of the active ingredient, was added to a 50 mL beaker containing 25 mL of WfI. Throughout the test the temperature was kept at 37 °C and the medium was stirred at 720 rpm. At the end of the small-scale dissolution test the dissolution medium was transferred to 30 mL PP tubes which were shaken continuously at 1200 RPM on a Vibramax 100 shaker (Heidolph Instruments GmbH, Schwabach, Germany). After 48 hours of shaking, samples were withdrawn to determine the equilibrium solubility ($S_{equilibrium}$). Based on the screening curves the maximum apparent solubility (S_{max}) and the time to precipitation ($T_{precipitation}$) were determined. The $T_{precipitation}$ was defined as the last time point before the amount of active ingredient in solution decreased more than 10%.

Dissolution of the ModraDoc001 and ModraPac001 10 mg capsules was tested according to the current European Pharmacopoeia using a type 2 (paddle) [33] dissolution apparatus (Erweka, Heusenstamm, Germany) filled with 500 mL Simulated Intestinal Fluid without pepsin (SIFsp) [34]. Throughout the test the temperature was maintained at 37 °C and the medium was stirred at 100 rpm.

All experiments were at least conducted in duplicate. 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. Subsequent analysis was performed on a reversed phase HPLC system with UV detection [28].

To compare the dissolution curves the difference (f1; Eq. 10) and similarity (f2; Eq. 11) factor were calculated according to Moore and Flanner [35].

Eq. (10): $f1 = \Sigma_{ij} \mid R_{ij} - T_{ij} \mid / \Sigma_{ij} R_{ij}$

Eq. (11): $f2 = 50 \cdot \log \{ [1 + (1/n) \Sigma_{ij} \mid R_{ij} - T_{ij} \mid^2]^{-0.5} \cdot 100 \}$

In which Rij and Tij are the amounts of active ingredient dissolved for the Reference and Test formulation at time=i,j, etc.

Results

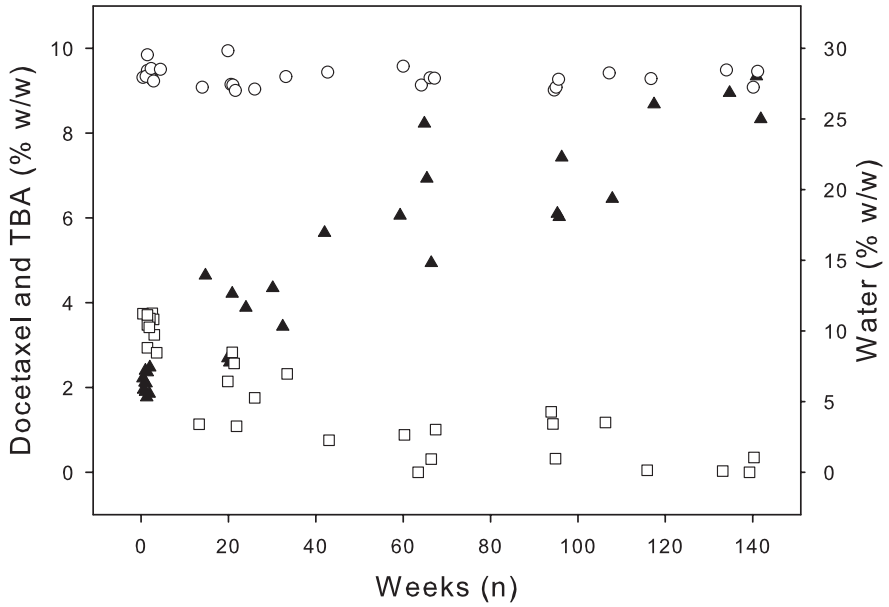

Figure 1: Docetaxel (○),TBA (□), and water (▲) content of ModraDoc001 SD powder vs. number of weeks stored at 2-8°C. During approximately 140 weeks of storage the amount of water increased from 6.3% to 27%, while the amount of TBA decreased from 3.4% to 0.12%. Docetaxel content remained stable at approximately 9.4%.

Chemical and physical stability

Figure 1 shows the amount of residual TBA, the amount of water, and the docetaxel content of ModraDoc001 SD powder vs. the number of weeks stored at 2-8 °C. The amount of residual TBA decreased from 3.4% to 0.12% w/w while the amount of water

increased from 6.3% to 27% w/w. Docetaxel content remained stable at approximately 9.4% w/w and no degradation was observed as the chromatographic peak purity was more than 99.5%. Stability results of ModraPac001 SD powder were comparable to those of ModraDoc001 SD powder for all items tested (data not shown). The amount of water absorbed by the pure amorphous docetaxel was -1.0 % w/w based on the weight measurements and 1.1% w/w based on the mDSC measurements, values for pure amorphous paclitaxel were respectively -0.2% w/w and -0.6% w/w.

After more than 100 weeks of storage the amount of water absorbed by the ModraDoc001 10 mg capsule was 12% w/w at 2-8 °C and 6.4% w/w at 25°C/60% RH. Similar values were obtained for the ModraPac001 10 mg capsule (data not shown).

Physical mixtures of amorphous and crystalline active ingredients were subjected to XRD, mDSC, and FT-IR analysis to test the sensitivity of these methods to changes in crystalline content. All three methods showed clear signal changes with decreasing amorphous content and increasing crystalline content: increasing diffraction peaks in the XRD spectra, decreasing ΔCp values in the reversal heat flow signal of mDSC, and changing peak locations and peak intensities in the FT-IR spectra.

XRD was able to detect in between 5% w/w and 10% w/w of crystalline material, while FT-IR and mDSC were able to detect at least 5% w/w of crystalline material; (data not shown). However, as the amorphous active ingredient only constitutes 9.1% w/w of the amorphous solid dispersion crystallization can only be detected when at least 50% of the amorphous active ingredient in the solid dispersion has crystallized.

Because of the limited detectability of crystallization in the amorphous solid dispersion formulations we tested the crystallization potential of the pure amorphous active ingredients. After 10 days of storage in open containers at 40 °C / 75% RH the XRD spectra showed no diffraction peaks, nor were there significant changes in Tg and ΔCP of docetaxel (0.28 J/(g x °C) at 148 °C) and paclitaxel (0.23 J/(g x °C)) at 151 °C). Furthermore, there were no changes in the FT-IR peak locations or intensities characteristic to crystallization (data not shown).

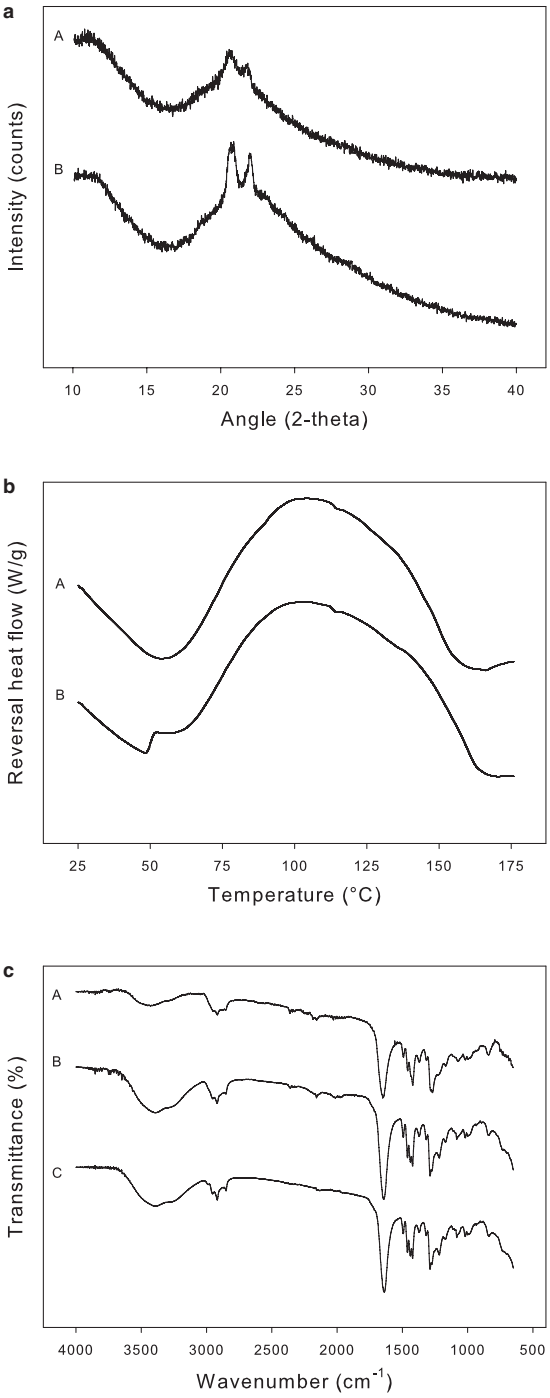

Figure 2: XRD spectra (a), reversal heat flow signals (b), and FT-IR spectra (c) of ModraDoc001 SD powder after less than 21 weeks of storage (A) and more than 139 weeks of storage (B) at 2-8 °C, and a FT-IR theoretical physical mixture spectrum (C). With increasing storage time the characteristic XRD peaks of SLS around 21 2-theta increased in intensity (a), the average Tg_{mix} increased from 150 °C to 160 °C, and the corresponding average ΔCp increased from 0.19 J/g·°C to 0.25 J/g·°C (b). The FT-IR peaks related to water, SLS, and amorphous docetaxel increased in intensity and the carbonyl peak of PVP-K30 shifted to lower wave numbers with increasing storage time (c).

Fig 2a shows the average XRD spectra of ModraDoc001 SD powder after 10 and 139 weeks of storage at 2-8 °C. During storage the intensity of the characteristic SLS peaks at 20.6 and 22.0 2-theta increased and the underlying amorphous halo broadened. It should be noted, however, that the XRD spectra could not be used for quantitative analysis because the increasing amount of water changed the powder characteristics which made it impossible to apply equal sample amounts.

Figure 2b shows the mDSC reversal heat flow signals of ModraDoc001 SD powder after 8 and 142 weeks of storage at 2-8°C. The average Tg_{mix} increased from 150 °C to 160 °C and the corresponding ΔCp increased from 0.19 J/g·°C to 0.25 J/g·°C during storage.

Figure 2c shows the SNV normalized spectra of a theoretical physical mixture and of ModraDoc001 SD powder after 11 and 140 weeks of storage at 2-8 °C. With increasing storage time peaks characteristic to SLS increased in intensity at 2952 cm^{-1}, 2917 cm^{-1}, and 2850 cm^{-1} and a peak characteristic to docetaxel appeared at 2987 cm^{-1} (Figure 2c). The main carbonyl peak of PVP shifted from 1650 cm^{-1} for the theoretical physical mixture to 1642 cm^{-1} after 11 weeks of storage and to 1638 cm^{-1} after 140 weeks of storage. The intensity of the OH regions from 3100 to 3500 cm^{-1} and from 650 to 850 cm^{-1} increased with increasing storage time. XRD, mDSC, and FT-IR analysis of ModraPac001 SD powder yielded similar results (data not shown).

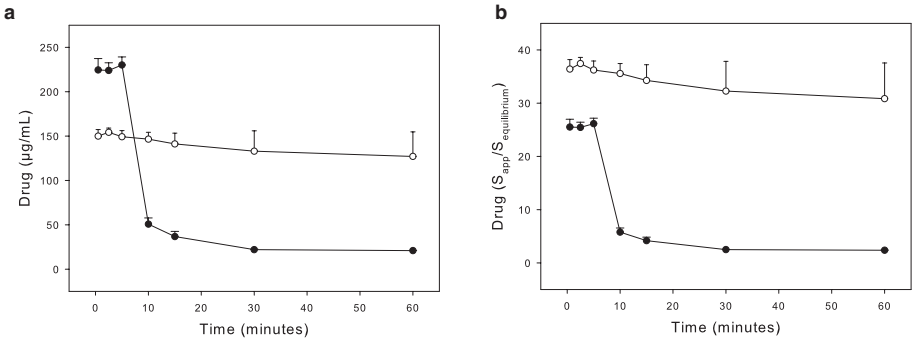

Figure 3: Dissolution profiles of docetaxel (•) and paclitaxel (○) from ModraDoc001 and ModraPac001 SD powder. a: drug dissolved vs. dissolution time; b: degree of supersaturation vs. dissolution time. The S_{max} of docetaxel is higher than paclitaxel (230 vs. 154 µg/mL), while the $T_{precipitation}$ (5 vs. 30 minutes) and the degree of supersaturation (26 vs. 37) of docetaxel is lower.

Dissolution profiles

To gain more knowledge about the differences between the amorphous solid dispersion formulations of docetaxel and paclitaxel the initial dissolution profiles of ModraDoc001 and ModraPac001 SD powder were compared (Figure 3a and 3b). The S_{app} of docetaxel is approximately 1.5 times higher than the S_{app} of paclitaxel (Figure 3a); in contrast the degree of supersaturation (S_{app} / $S_{equilibrium}$) of docetaxel is approximately 1.4 times lower than the degree of supersaturation of paclitaxel (Figure 3b). In addition to this, the $T_{precipitation}$ of docetaxel is approximately 5 minutes while the $T_{precipitation}$ of paclitaxel is approximately 30 minutes. Likewise, the precipitation rate of docetaxel from the supersaturated solution is significantly higher than the precipitation rate of paclitaxel.

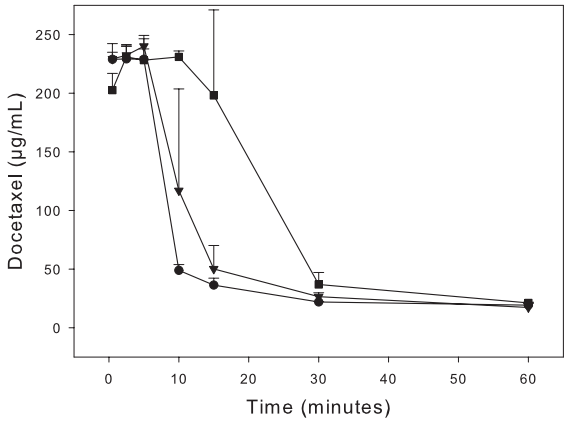

Figure 4: Average dissolution profiles of ModraDoc001 SD powder after 29 (•), 102 (▾) and 144 (■) weeks of storage at 2-8 °C. With increasing storage time at 2-8°C the Tprecipitation docetaxel increased from 5 minutes to approximately 15 minutes.

Figure 4 shows the average dissolution profiles of ModraDoc001 SD powder stored at 2-8 °C for 29, 102 and 144 weeks. With increasing storage time the dissolution rate decreased while the time to crystallization ($T_{precipitation}$) increased from approximately 5 to 15 minutes. On the other hand, for ModraPac001 SD powder no differences were observed between the initial and stability dissolution profile after 128 weeks of storage at 2-8 °C (data not shown). $S_{equilibrium}$ after 48 hours remained 9 µg/mL for docetaxel and increased from 4 µg /mL to 5.5 µg/mL for paclitaxel after more than 120 weeks of storage at 2-8 °C.

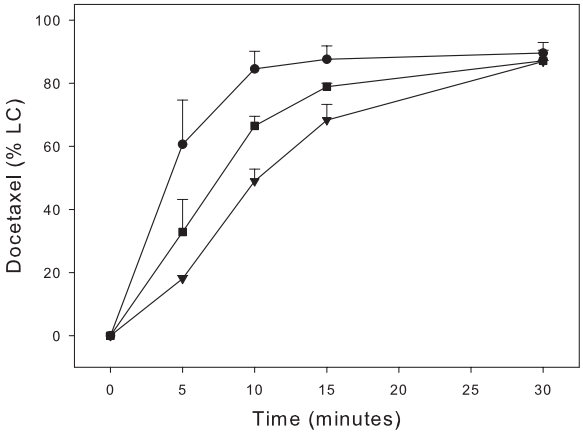

Figure 5: Average dissolution profiles of ModraDoc001 capsules generated after production (•), after 105 weeks of storage at 25 °C/60% RH (▼), and after 109 weeks of storage at 2-8 °C (■). Although all dissolution profiles met the specification of Q=75% at t=30 minutes, the dissolution rate decreased significantly during storage at 2-8° and at 25 °C/60% RH.

Figure 5 shows the average dissolution profiles of the ModraDoc001 10 mg capsule after production, after 109 weeks of storage at 2-8°C, and after 105 weeks of storage at 25°C/60% RH. Upon storage the dissolution rate of docetaxel from the ModraDoc001 10 mg capsule significantly decreased at both storage conditions. However, the decrease in dissolution rate was higher for the capsules stored at 2-8°C. Initial and stability dissolution profiles were compared based on the difference (f1) and similarity factor (f2) in between t5 and t15. Dissolution profiles are considered comparable when f1 is below 15 and f2 is above 50 [35]. At 2-8 °C the stability dissolution profile remained comparable up to 18 weeks of storage, while at 25°C / 60% RH the dissolution profiles remained comparable up to 52 weeks of storage. The ModraPac001 10 mg capsule stability dissolution profile remained comparable up to 26 weeks at 2-8 °C and up to 57 weeks at 25 °C / 60% RH.

Discussion

At first sight the average release rate of TBA from ModraDoc001 SD powders seemed linear (Figure 1). However, when TBA was plotted vs. the amount of water there

appeared to be a two-stage release process. At the start of the stability study the release rate of TBA was approximately 0.32 TBA/water while it was 0.13 TBA/water for the remainder of the study. The initial high release rate of TBA is probably the result of the opening of microregions at a threshold water content [36]; examination of the release plots of individual lots showed that the opening occurred at approximately 6.5% w/w of water. The lower release rate in the second stage was probably caused by gradually increasing diffusion of the remaining TBA with increasing water content [36].

ModraDoc001 SD powder absorbed approximately 20% w/w of water at 0.15% w/w per week and ModraPac001 SD powder absorbed approximately 14% w/w of water at a rate 0.12% w/w per week. The water absorption rate of the amorphous solid dispersion powders was probably rate limited by the diffusion of water vapor into the closed containers. Indeed, additional tests with ModraDoc001 SD powder in open containers at 40°C/75% RH showed water absorbance rates of more than 1.5% w/w per week (data not shown). The limited water absorption of the pure amorphous active ingredients was probably due to the highly hydrophobic nature of the amorphous active ingredients. This is also reflected in the very low water solubility of docetaxel and paclitaxel [7, 8]. Furthermore, PVP-K30 and the active ingredient constitute more than 90% w/w of the amorphous solid dispersion. Hence it was assumed that PVP-K30 absorbed all water in the ModraDoc001 and ModraPac001 SD powders. Likewise we assumed that PVP-K30 absorbed all water in the ModraDoc001 and ModraPac001 10 mg capsules, because the amorphous solid dispersion and lactose monohydrate constitute 99.5% w/w of the capsule content and the latter absorbs practically no water at the tested conditions. Moreover, by correcting the water absorbance value for the weight ratio of PVP-K30 we were able to compare absorbance values of the SD powders and capsules.

The higher water absorbance of the ModraDoc001 and ModraPac001 10 mg capsules stored at 2-8 °C compared to the ones stored at 25 °C/60% RH was probably caused by the high humidity in the refrigerator. Compared to the ModraDoc001 and ModraPac001 SD powders the ModraDoc001 and ModraPac001 10 mg capsules absorbed more water at 2-8 °C: ModraDoc001: 25% w/w vs. 30% w/w and ModraPac001: 17% w/w vs. 29% w/w (PVP-K30 ratio corrected values). These differences are most likely caused by differences in the diffusion rate of water vapor through the primary and secondary packaging. In conclusion, water absorbance by the ModraDoc001 and ModraPac001 SD powders and capsules can be limited by storing at 25 °C/60% RH instead of 2-8°C, and

by improving the primary packaging.

We also compared the water absorbance values of the ModraDoc001 and ModraPac001 SD powders and capsules with reported water absorption values of pure PVP-K30. With values ranging from 39% to 42% w/w, determined after 7 days of storage at 25°C / 75% RH or using dynamic vapor sorption (DVS) [37], it seemed that pure PVP-K30 absorbed more water than PVP-K30 incorporated in the amorphous solid dispersions. Several studies reported that hydrophobic active ingredients hydrophobized PVP in amorphous solid dispersion formulations and subsequently limited the water absorption [30, 38, 39]. The proposed underlying mechanism is the formation of hydrogen bonds between the active ingredient and PVP which would subsequently reduce the amount of free hydrogen bond acceptors of PVP and its ability to absorb water. Although the results suggest possible hydrophobization of PVP by docetaxel and paclitaxel, additional DVS experiments with various drug loads are warranted to confirm this hypothesis.

The results of the mDSC, XRD, and FT-IR analysis of the pure amorphous active ingredients clearly showed that no crystallization occurred after 10 days of storage at 40°C / 75% RH. Furthermore, as there is no or only limited water absorbed by the amorphous active ingredients the risk of a reduced Tg due to the plasticizing effect of absorbed water is very low. Indeed, the Tg's of docetaxel and paclitaxel remained unchanged during the accelerated stability tests. Furthermore, because the Tg's of docetaxel and paclitaxel are around 150 °C it is very unlikely that amorphous paclitaxel or docetaxel will crystallize during storage at ambient temperatures. Even more, in the amorphous solid dispersion the molecular mobility of the amorphous active ingredients will be reduced due to the interactions with PVP thereby further reducing the risk of crystallization. In conclusion, the risk of crystallization of the active ingredients in the ModraDoc001 and ModraPac001 SD powders and capsules is very low despite the high amount of water absorbed.

Nevertheless, the absorbance of water could still negatively influence the stability of the amorphous solid dispersion formulations by inducing phase separation. Indeed, XRD, mDSC, and FT-IR analysis of the ModraDoc001 and ModraPac001 SD powder revealed indications of phase separation. There was a clear trend of increasing XRD peaks characteristic to SLS with increasing storage times and increasing amounts of water absorbed. Furthermore, the 10°C increase of the Tg_{mix} was most probably caused by phase separation of SLS as well. Own experiments and literature data [40] showed

that 10% w/w of SLS incorporated in the solid dispersion was responsible for a 10 °C decrease of the Tg_{mix}. In contrast, 10% w/w of moleculary dispersed amorphous docetaxel or paclitaxel was only responsible for a 1.5 °C decrease of the Tg_{mix}. Hence, a 10 °C increase of the Tg_{mix} can only be explained by phase separation of SLS. Moreover, the XRD results and the increasing intensity of FT-IR peaks characteristic to SLS further strengthen this conclusion.

Crystallization from a supersaturated solution depends on the degree of supersaturation and the S_{app} of the dissolved amorphous active ingredient. Both a higher degree of supersaturation and a higher S_{app} increase the starting point of crystallization, that is the nucleation rate [41]. Despite paclitaxel's higher degree of supersaturation, crystallization of docetaxel starts earlier and progresses significantly faster. This could be due to the higher S_{app} of docetaxel, although it is more likely that PVP-K30 is more successful in preventing recrystallization of paclitaxel than in preventing recrystallization of docetaxel.

The latter explanation would indicate that the interaction between paclitaxel and PVP-K30 is stronger than the interaction between docetaxel and PVP-K30. This is also suggested by the increase of $S_{equilibrium}$ in the presence of PVP-K30 and SLS. $S_{equilibrium}$ of docetaxel increased approximately 1.6 times while the $S_{equilibrium}$ of paclitaxel increased more than 5 times.

The stronger interaction between paclitaxel and PVP was also predicted by the HSP calculations; the Ra and $\Delta\delta_{HIL}$ values of paclitaxel and PVP were lower than the values of docetaxel and PVP (Table 1). Moreover, the higher Ra value of paclitaxel and SLS suggests a much weaker interaction between paclitaxel and SLS compared to docetaxel and SLS. These values might explain the surprising increase of the $T_{precipitation}$ of docetaxel during storage at 2-8°C. We showed earlier that $T_{precipitation}$ increased with increasing PVP chain length and decreasing drug loads [12]. Increase of the PVP chain length upon storage is extremely unlikely as it requires chemical reactions. Also, a decrease in the drug loads is not relevant as no active ingredient is removed, nor is PVP added upon storage. The only remaining explanation would be an increasing interaction between docetaxel and PVP which would have the same effect as a decreased drug load. This hypothesis is supported by the red shift of the PVP-carbonyl peak in the FT-IR spectra. The red shift is generally attributed to strong hydrogen bonding of PVP with water or other substances [42, 43]. Hence, it could be that the red shift is a result of stronger interactions

between PVP-K30 and docetaxel. An explanation for the increased interaction could be that the phase separation of SLS freed up hydrogen bond acceptors of PVP which were subsequently used for hydrogen bond formation with the active ingredient.
It is very likely that the absorption of water during storage also induced phase separation inside the ModraDoc001 and ModraPac001 capsules. The decreasing dissolution rate was therefore probably the result of water mediated phase separation of SLS and subsequent decreased wetting of the PVP-active ingredient complex. The limited effect of the SLS phase separation on the dissolution rate of the ModraDoc001 and ModraPac001 SD powder is explained by the large surface area of the loose powder and the high mixing rate during the small-scale dissolution tests. Despite the decreasing dissolution rate we showed that the dissolution profiles of ModraDoc001 and ModraPac001 10 mg were stable up to 1 year of storage at 25 °C/60% RH ($f1 < 15$ and $f2 > 50$), because the significant decrease in dissolution rate after 1 year of storage is most probably caused by water mediated phase separation of SLS the stability of the ModraDoc001 and ModraPac001 10 mg capsules can be further improved by reducing water absorption. This could be easily achieved by improving the primary and secondary packaging. Furthermore, the stability of ModraDoc001 and ModraPac001 10 mg capsules at room temperature offers a huge advantage for future outpatient treatment.

Conclusions

In this study we evaluated the chemical and physical stability of the clinical oral amorphous solid dispersion formulations of docetaxel and paclitaxel using mDSC, FT-IR, XRD, assays, and dissolution tests. Upon stability the amount of water increased which facilitated the total removal of TBA and induced phase separation of SLS. Despite these changes the active ingredients remained amorphous and no chemical degradation was observed. Furthermore, it was hypothesized that phase separation of SLS made way for stronger interactions between docetaxel and PVP-K30 which led to an increased $T_{precipitation}$. Nevertheless, phase separation of SLS did also led to a decreased wetting of the PVP based solid dispersion which resulted in a significant change in the dissolution profile after more than 52 weeks of storage at 25 °C /60% RH. Furthermore, by improving the primary and secondary packaging of the amorphous solid dispersion

formulations the absorption of water could be reduced which would further increase their pharmaceutical shelf life and increase the ease of use in outpatient treatment.

Acknowledgement

We would like to acknowledge Dr. Steven Abbott for his help with the HSPiP software package.

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Chapter 6

Pharmaceutical development of spray dried oral solid dispersion tablets of docetaxel and ritonavir

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Submitted

Abstract

Oral formulations of the potent anticancer agent docetaxel would enable the development of new treatment regimens potentially with reduced toxicity, increased efficacy, and increased patient convenience. Earlier we showed that the bioavailability of docetaxel increased by combining the pharmacokinetic booster ritonavir with an freeze-dried solid dispersion (SD) capsule formulation of docetaxel, polyvinylpyrrolidone (PVP) K30, and sodium lauryl sulfate (SLS) in a weight ratio of 1/9/1 w/w/w. Our new goal was to develop a scalable manufacturing process for the SD formulation and to combine docetaxel and ritonavir in a fixed dose combination (FDC) tablet.

In this study we compared the physical and chemical properties of spray dried PVP-K30/SLS SD formulations containing docetaxel, ritonavir, or docetaxel/ritonavir. X-ray powder diffraction (XRD), modulated differential scanning calorimetry (mDSC), Fourier Transform Infrared spectroscopy (FT-IR), residual solvent analysis, assay, and in-vitro dissolution tests were used to characterize the SD formulations after storage at 2-8°C; 40 °C / 75% RH; and ambient conditions. Spray-drying resulted in a fully amorphous SD of docetaxel, ritonavir PVP-K30, and SLS. During accelerated stability at 40 °C / 75% RH the absorption of water resulted in phase separation of SLS. In contrast, at 2-8 °C the SD powders were stable for more than 52 weeks. Release rates of docetaxel and ritonavir from the spray dried SD tablets were equal and highly correlated with the release rate of the solid dispersion carrier, PVP-K30. Upon storage the release rates of the fixed-dose combination tablet decreased significantly after 25 weeks, although they remained within specifications.

In conclusion spray drying is a promising manufacturing method for amorphous solid dispersion formulations of docetaxel and ritonavir which produces chemically and physically comparable or better SD powder. The combination of docetaxel as well as ritonavir in one FDC tablet will improve patient convenience and could result in increased exposure to docetaxel compared to single drug formulations.

Introduction

Docetaxel is a highly effective anticancer agent used in the treatment of various solid tumors [1]. Due to its cytostatic mechanism of action docetaxel could be even more effective when administered chronically to patients [2, 3]. Because of its low oral bioavailability docetaxel is currently only available as an intravenous infusion (IV) formulation, which makes chronic administration impractical, patient unfriendly, and expensive. To enable the successful clinical implementation of oral docetaxel chemotherapy we had to combine pharmacological and pharmaceutical strategies to improve docetaxel's oral bioavailability.

The low oral bioavailability of docetaxel is caused by its low solubility [4] and low permeability. The latter is mainly attributed to extensive metabolism by CYP3A4 enzymes in the gut wall and liver, and partly to active excretion by P-glycoprotein pumps [5]. We increased the low permeability of docetaxel by concomitant oral administration of the pharmacokinetic booster ritonavir [6]. However, the IV pre-mix solution still hampered further development of this oral concept. We therefore developed an oral capsule formulation of docetaxel, the ModraDoc001 15 mg capsule, containing a freeze-dried solid dispersion (SD) powder of docetaxel, PVP-K30, and sodium lauryl sulfate (SLS) in a weight ratio of 1/9/1 w/w/w (ModraDoc001 SD powder) [7]. After we had shown that concomitant oral administration of ritonavir and the ModraDoc001 15 mg capsule led to a clinical relevant exposure to docetaxel we continued the phase I dose escalation study with the ModraDoc001 10 mg capsule [8]. Apart from the ModraDoc001 SD powder the ModraDoc001 10 mg capsule contained lactose monohydrate and colloidal silica to improve the powder flow properties and capsulation efficiency of the freeze-dried SD powders. To date the ModraDoc001 10 mg capsule has been administered to 97 patients in two phase I clinical trials [9, 10].

To support future phase II and III clinical trials a new manufacturing method suitable for large scale manufacturing was warranted for the solid dispersions powder. In addition, a fixed-dose combination formulation of docetaxel and its pharmacokinetic booster ritonavir was preferred to further improve patient convenience.

For large scale manufacturing of the SD powder spray drying was chosen over freeze-drying because it is a well-established and industrially scalable method. Furthermore, it can be used in continuous processing, and it is a cheap, fast, and one step process.

Moreover, spray drying allows for control of the size, density and morphology of the particles which aids downstream processing of the SD powder into tablets [11, 12].
Previously we showed that the improved dissolution rate of docetaxel from the freeze-dried SD powder was due to the higher apparent solubility of amorphous docetaxel, the increased surface area of finely dispersed docetaxel, and an improved wetting of docetaxel by the hydrophilic carrier PVP-K30 and the surfactant SLS [7]. Furthermore, because ritonavir is like docetaxel classified as a class IV drug according to the biopharmaceutical classification system [13, 14], it needs a special formulation to improve its solubility. Hence, inclusion of ritonavir into the SD matrix of PVP-K30 and docetaxel was chosen to be the best way forward. However, inclusion of both ritonavir and docetaxel in the SD powder and FDC tablet may not negatively influence their release rates and oral bioavailability. Moreover, it is essential that spray drying produces SD powder that is chemically and physically comparable to the existing freeze-dried product.
In this article we describe the development, physical and chemical characteristics, and stability of spray dried PVP-K30/SLS SD powders and tablets containing docetaxel, ritonavir, or docetaxel and ritonavir. Furthermore, the characteristics and stability of spray dried SD tablets of docetaxel (ModraDoc003 10 mg tablet) and docetaxel and ritonavir (ModraDoc004 10/50 mg tablet) used in the phase I pilot bioequivalence study are described [15].

Materials and Methods

Materials

Docetaxel anhydrate originated from Scinopharm Taiwan (Tainan, Taiwan). Ritonavir was supplied by LGM Pharma (Boca Raton, FL, USA). Polyvinylpyrrolidone K30 (PVP-K30) was purchased from BASF (Ludwigshafen, Germany). Pharmacopoeial grade absolute ethanol, sodium lauryl sulphate (SLS), dimethyl sulfoxide (DMSO), tert-butanol (TBA), potassium dihydrogen phosphate, sodium hydroxide 25%, and hydrochloric acid were purchased from VWR (Amsterdam, The Netherlands). Water for Injection (WfI) was obtained from B. Braun (Melsungen, Germany). Lactose monohydrate 200M and colloidal silicon dioxide was supplied by Spruyt Hillen (IJsselstein, The Netherlands). Granulated lactose (modified lactose monohydrate, SUPERTAB) was obtained from

DMV-Fonterra Excipients (Veghel, The Netherlands). Polyoxyethylene 10-lauryl ether was obtained from Sigma Aldrich Chemie B.V. (Zwijndrecht, The Netherlands). Hard gelatin capsules were purchased from Capsugel (Bornem, Belgium).

Preparation of spray dried API, physical mixtures, and SD powders

The composition and preparation method of all formulations mentioned in this article are listed in Table 1. Spray dried docetaxel, spray dried docetaxel, and spray dried docetaxel/ritonavir mixtures were prepared according to the spray drying procedure used for preparing the SD powders. Physical mixtures were prepared by mixing accurately weighed amounts of the components with mortar and pestle.

Freeze-dried docetaxel (ModraDoc001) and ritonavir SD powder were prepared using a method described previously [7]. Briefly, SD powders were freeze-dried from a 60/40 v/v TBA/WfI solution. Docetaxel or ritonavir was dissolved in TBA at a concentration of 10 mg/mL; excipients were dissolved in WfI at a concentration of 150 mg/mL (see Table 1). After complete dissolution of all components both solutions were mixed and transferred to stainless steel lypophilization boxes (Gastronorm size 1/3). Freeze-drying was done in a Lyovac GT4 freeze dryer (GEA Lyophil GmbH, Hürth, Germany) according to a freeze-drying program developed earlier [7]. The freezing phase started with a freezing ramp from ambient temperature to -35 °C in 1 hour followed by a holding step of 2 hours at -35 °C. Primary drying was performed at -35 °C and 0.2 mbar for 45 hours. Secondary drying started with a heating ramp from -35 °C to 25 °C at 0.2 mbar in 15 hours followed by a holding step at 25 °C and 0.2 mbar for 3 hours.

Spray dried SD powders were prepared by spray drying a 75/25 v/v ethanol/WfI solution. All components were accurately weighed and dissolved in the ethanol/WfI mixture with a total solid concentration of 129 mg/mL (see Table 1). Spray drying was performed on a B290 mini spray dryer equipped with a second aspirator and connected to a B-296 dehumidifier and a B-295 inert loop (Büchi Labortechnik AG, Flawil, Switzerland). A standard nozzle with an inner tip diameter of 0.7 mm and an outer tip diameter of 1.5 mm was used. Inlet temperature was set at 150 °C, N2 gas flow rate was set at 35 arbitrary units, aspirator flow rate was set at 100%, and product feed rate was set at 30%.

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

Formulation	Components	Weight ratio[a] (w/w/w/w)	Formulation method
A	Docetaxel	1/0/0/0	Spray drying
B	Ritonavir	0/1/0/0	Spray drying
C	Docetaxel and ritonavir	0.05/0.95/0/0	Spray drying
D	Docetaxel and ritonavir	0.13/0.87/0/0	Spray drying
E	Docetaxel and ritonavir	0.23/0.77/0/0	Spray drying
F	Amorphous docetaxel, PVP-K30 and SLS	1/0/9/1	Physical mixing
G	Amorphous ritonavir, PVP-K30 and SLS	0/1/9/1	Physical mixing
H	Docetaxel, PVP-K30 and SLS (ModraDoc001 SD powder)	1/0/9/1	Freeze-drying
I	Ritonavir, PVP-K30 and SLS	0/1/9/1	Freeze-drying
J	Docetaxel, PVP-K30, and SLS	1/0/9/1	Spray drying
K	Ritonavir, PVP-K30, and SLS	0/1/9/1	Spray drying
L	Docetaxel, ritonavir, PVP-K30, and SLS	0.05/0.95/9/1	Spray drying
M	Docetaxel, ritonavir, PVP-K30, and SLS	0.13/0.87/9/1	Spray drying
N	Docetaxel, ritonavir, PVP-K30, and SLS	0.23/0.77/9/1	Spray drying
O	Docetaxel, PVP-K30, SLS (ModraDoc003 SD powder)	1/0/9/1	Spray drying
P	Docetaxel, ritonavir, PVP-K30, and SLS (ModraDoc004 10/50 SD powder)	0.17/0.83/9/1	Spray drying

[a]Weight ratio of individual components in standard order: docetaxel, ritonavir, PVP-K30, and SLS

Preparation of tablets and capsules

Tablets containing 10 mg to 50 mg of docetaxel and/or ritonavir were prepared from the spray dried SD powders listed in Table 1. Approximately 60% to 80% w/w of spray dried SD powder was mixed with granulated lactose, 1% w/w colloidal silicon dioxide, and 1% w/w magnesium stearate. Mixing was performed in a 3 L stainless steel bin with a Turbula mixer T10B operating at the highest mixing speed (Willy A Bachofen AG Maschinenfabrik, Muttenz, Switzerland). Tablets were manually compacted on an EK 0 eccentric press (Korsch AG, Berlin, Germany) equipped with oval 6/11, 8/16, or 12/22 mm tooling.

The ModraDoc001 10 mg capsule was prepared by mixing an amount of ModraDoc001 SD powder [7] equivalent to 10 mg of docetaxel with 110 mg lactose and 2.2 mg colloidal silicon dioxide. The resulting powder mixture was encapsulated with a manual encapsulation apparatus (Feton international NV, Brussels, Belgium) into size 0 hard gelatin capsules.

The ModraDoc003 10 mg tablet was prepared by mixing an amount of ModraDoc003 SD powder equivalent to 10 mg of docetaxel with 50% w/w granulated lactose, 1% w/w colloidal silicon dioxide, and 1% w/w magnesium stearate; the mixture was manually compacted using 9 mm round tooling. The ModraDoc004 10/50 mg tablet was prepared by mixing an amount of ModraDoc004 10/50 SD powder equivalent to 10 mg of docetaxel and 50 mg of ritonavir with 70% w/w granulated lactose, 1% w/w colloidal silicon dioxide, and 1% w/w magnesium stearate; the mixture was manually compacted using 14 mm round tooling.

Stability study

The accelerated stability study consisted of storing samples in open container for 10 days at 40 °C /75% RH. Samples were weighed and subjected to FT-IR, mDSC, and XRD analysis before and after storage.

ModraDoc003 and ModraDoc004 10/50 SD powders were stored in glass containers closed with a Polypropylene (PP) lid and stored at 2-8 °C for more than 52 weeks. At various time points the powders were subjected to XRD, mDSC, and FT-IR analysis, residual solvent testing, and small-scale dissolution tests.

ModraDoc003 10 mg tablets and ModraDoc004 10/50 mg tablets were individually packaged in transparent Polyethylene Terephthalate (PET) diamond shaped blister strips with label sealing. The blisters were packaged in white Polypropylene (PP) jars with white screw caps and stored at ambient conditions for more than 52 weeks. At various time points stability samples were pulled and the tablets were subjected to dissolution testing, weight measurements, and assay and related substances testing.

Water

The amount of water absorbed during the accelerated stability study was derived from the sample weight before and after storage. The amount of water absorbed was expressed as weight percentage of the initial sample weight.

Total water in SD powders 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. Total water was expressed as weight percentage of the total dried weight.

Residual ethanol

Residual ethanol in spray dried SD powders was determined with a standard gas chromatographic (GC) analysis method using 2-propanol as internal standard. Samples of approximately 50 mg were dissolved in 5.0 mL of DMSO. Total ethanol was expressed as weight percentage of the total dried weight.

Assay and related substances

Assay and related substances of docetaxel and ritonavir were determined using a modified stability-indicating reversed phase HPLC system with UV detection [16]. An amount of SD powder equivalent to 10 mg of active ingredient was dissolved in 100 mL of a methanol/acetonitrile/0.02 M ammonium acetate buffer pH 5 mixture (1:4:5 v/v/v). Docetaxel was detected at 227 nm; ritonavir was detected at 210 nm. Assay values were reported as percentage of the label claim (LC). Chromatographic peak purity was calculated as the percentage of the main peak area relative to the total peak area (Chromeleon 7.2; Dionex Corporation, Sunnyvale, CA, USA)

Modulated differential scanning calorimetry (mDSC)

mDSC measurements were performed on 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 transferred into Tzero Aluminium pans (TA instruments), non-hermetically closed, and placed in the autosampler. Samples were equilibrated for 5 minutes at 20.00 °C and subsequently heated to 180.00 °C at a rate of 2.00 °C/min. Modulation was performed every 60 seconds at +/- 1.00 °C

Experimental glass transition temperature (TgExp) were determined from the reversal and non-reversal heat flow signals using Universal Analysis 2000 (version 4.7A, TA instruments, New Castle, DE, USA). TgExp was determined at the inflection point using the temperature first derivative of the reversal heat flow singal. The Fox-equation

(Eq. 1) was used to estimate the Tg_{Fox} [17].

Eq. (1): $1 / Tg_{Fox} = w_1 / Tg_1 + w_2 / Tg_2 + w_3 / Tg_3 \; w_4 / Tg_4$

In which w_i is the weight fraction of the i^{th} component, Tg_i is the glass transition temperature of the ith component expressed in Kelvin.

X-ray powder diffraction (XRD)

XRD measurements were performed on a X'pert pro diffractometer equipped with an X-celerator (PANanalytical, Almelo, The Netherlands). Samples of approximately 0.5 mm thick were applied on a metal sample holder, placed in the diffractometer and scanned at a current of 50 mA and a tension of 40 kV. Scan range was 10-60 degrees 2-theta, with a step size of 0.020 degrees and a scan speed of 0.002 degrees per second.

Fourier Transform Infrared spectroscopy (FT-IR)

FT-IR spectra were recorded on a FT-IR 8400S Spectrophotometer equipped with an Attenuated Total Reflectance (ATR) holder (Golden Gate ATR; Shimadzu, 's-Hertogenbosch, The Netherlands). Each spectrum had a range of 650 cm^{-1} to 4000 cm^{-1} at a resolution of 2 cm^{-1} and was the average of 16 individual scans. Pre-treatment and analysis of FT-IR spectra were performed using The Unscrambler X (version 10.3. CAMO software AS, Oslo, Norway). Pre-treatment consisted of averaging individual spectra, standard normal variate (SNV) correction, Savitzky-Golay 1^{st} and 2^{nd} derivative with 15 smoothing points and a 2^{nd} degree polynomal.

Dissolution testing

Tablets were subjected to a dissolution test adapted from the authorized USP pending monograph of lopinavir and ritonavir tablets [18]. Briefly, 500 mL of a 37.7 g/L polyoxyethylene-10-lauryl ether solution in WfI was heated to 37 °C and transferred to a type 2 (paddle) dissolution apparatus (Erweka, Heusenstamm, Germany). The paddle was operated at 75 RPM and each formulation was tested in triplicate. Samples of 1.0 mL were withdrawn at various time points after the dosage form was added to the medium. All samples were filtrated with a 0.45 µm filter (Millex HV, Millipore) and subsequently analyzed on a RP-HPLC-UV system described earlier [16]. Docetaxel was detected at 227 nm; ritonavir and PVP-K30 were detected at 210 nm. The amount of

active ingredient released was reported as the concentration percentage of the final concentration; the amount of PVP-K30 released was reported as the area percentage of the final PVP-K30 peak area.

To compare the dissolution curves the difference (f1) and similarity (f2) factor were calculated according to Equation 10 and 11 [19].

Eq. (10): $f1 = \Sigma_{ij} \mid R_{ij} - T_{ij} \mid / \Sigma_{ij} R_{ij}$

Eq. (11): $f2 = 50 \cdot \log \{ [1 + (1/n) \Sigma_{ij} \mid R_{ij} - T_{ij} \mid^2]^{-0.5} \cdot 100 \}$

In which R_{ij} and T_{ij} are the amounts of active ingredient dissolved for the Reference and Test formulation at time=i,j, etc.

Results

Preparation of spray dried SD formulations

To manufacture fully amorphous solid dispersions using spray drying it is a pre-requisite to dissolve all components. We chose to use a mixture of water and ethanol, because ethanol can easily dissolve docetaxel, ritonavir, and PVP-K30; and water can easily dissolve SLS and PVP-K30. Because docetaxel and ritonavir are practically insoluble in water and because SLS is poorly soluble in ethanol we evaluated their solubility in 60/40 v/v, 75/25 v/v, and 90/10 v/v mixtures of ethanol and WfI. The 75/25 v/v ethanol/WfI mixture was found to be most suitable because SLS, docetaxel, and ritonavir could be dissolved up to 12 mg / mL, and PVP-K30 was freely soluble (> 400 mg/ml).

Total solid content was set at 129 mg/mL to maximize yield and product flow was fixed at 15 mL/min to reach acceptable process times. Inlet temperature and N2 settings were set as low as possible until the drying column remained dry during spray drying 75/25 v/v ethanol/WfI without solutes. Average outlet temperatures were in between 75 °C and 85 °C. Spray dried SD powders had a low density and poor powder flow characteristics, although manual compaction was possible after pre-compaction.

Average water content of the spray dried SD powders (Table 1: I to P) was 3.6 % w/w and average ethanol content was 2.8% w/w. Average content corrected for the residual solvents was 100.7% LC for docetaxel and 96.6% LC for ritonavir; no degradation of either docetaxel or ritonavir was observed.

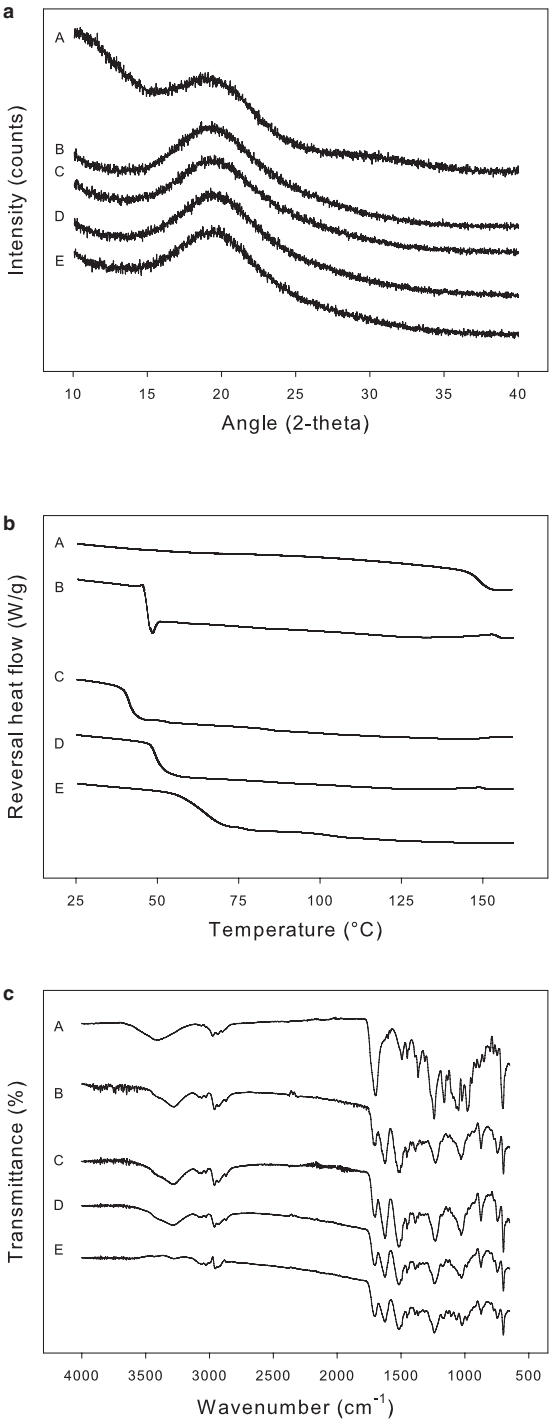

Figure 1. XRD spectra (a), reversal heat flow signals (b), and FT-IR spectra (c) of spray dried docetaxel (A), spray dried ritonavir (B), and spray dried docetaxel/ritonavir mixtures at weight ratios of 0.05/0.95 w/w (C), 0.13/0.87 w/w (D), and 0.23/0.77 w/w (E) (see Table 1). All powders were fully amorphous because no XRD peaks are present (a), all reversal heat flow signals have a single Tg and no melting peaks are present (b). Futhermore, no FT-IR peaks characteristic to crystalline docetaxel and crystalline ritonavir are present (c). With increasing weight ratios of docetaxel the Tg and docetaxel FT-IR peak intensity increases while ritonavir FT-IR peak intensity decreases (b and c).

Characteristics of spray dried docetaxel and ritonavir

No diffraction peaks are present in the XRD spectra of spray dried docetaxel, spray dried ritonavir, or spray dried docetaxel/ritonavir mixtures (Fig 1a; A to E). Nor were any diffraction peaks found in the XRD spectra of spray dried docetaxel or spray dried ritonavir after accelerated stability testing (data not shown).

The mDSC reversal heat flow signals of spray dried docetaxel, spray dried ritonavir and spray dried docetaxel/ritonavir all have a single Tg and no melting endotherms are present (Fig 1b: A to E). The mDSC reversal heat flow signal of spray dried ritonavir has a small endothermic peak after the glass transition, this was probably caused by enthalpic relaxation (Fig 1b: B). The value of the Tg_{Exp} of spray dried docetaxe/ritonavir increased with increasing weight ratios of docetaxel (Fig 1b and Table 2: C to E). After accelerated stability testing no significant changes were observed in the mDSC reversal heat flow signal of spray dried docetaxel. In contrast, the Tg_{Exp} of spray dried ritonavir decreased from 47 °C to 40 °C and a small melting peak appeared at 120°C (data not shown).

Table 2. Experimental and theoretical Tg values of docetaxel and ritonavir formulations

Formulation	Tg_{Exp} (°C)[a]	Tg_{Fox} (°C)	SLS endothermal peaks[g]
A	149[b] / 148[c]	n.a.	n.a.
B	47b / 40[c]	n.a.	n.a.
C	41	51	n.a.
D	49	57	n.a.
E	65	66	n.a.
F	140[a] and 162[a]	n.a.	Yes
G	47[a] and 170[a]	n.a.	Yes
H	150[a]	141[e] / 161[f]	Yes
I	n.d.	129[e] / 147[f]	Yes
J	147[b] / 162[c]	141[e] / 161[f]	No
K	131[b] / 145[c]	129[e] / 147[f]	No
L	130[b]	130[e] / 148[f]	No
M	133[b]	131[e] / 149[f]	No
N	135[b]	132[e] / 150[f]	No
O	148[d]	141[e] / 161[f]	No
P	135[d]	131[e] / 149[f]	No

[a] Tg measured at inflection point; [b] Tg after production; [c] Tg after accelerated stability study; [d] Tg after 60 weeks of storage at 2-8 °C; [e] Calculated using Fox equation with $Tg_{docetaxel}$ = 149 °C; $Tg_{ritonavir}$ = 47 °C Tg_{SLS}= 11 °C (estimated using Fox equation on PVP-K30/SLS SD); $Tg_{PVP-K30}$ = 162 °C; [f] Calculated using Fox equation without SLS; [g] Presence of endothermal peaks related to crystalline SLS in the mDSC non-reversal heat flow after manufacturing; n.a. = not applicable; n.d. = not detectable.

The absorption peaks in the FT-IR spectra of spray dried docetaxel and spray dried ritonavir are broader and less sharp compared to the absorption peaks in the FT-IR spectra of crystalline docetaxel and ritonavir (data not shown). No peaks characteristic to crystalline docetaxel or crystalline ritonavir were observed in the FT-IR spectra of spray dried docetaxel/ritonavir mixtures. The majority of the FT-IR spectra of spray dried docetaxel/ritonavir mixtures is similar to the spray dried ritonavir FT-IR spectrum (Fig 1c: C to E vs. B). At wavenumbers were the spray dried ritonavir spectrum differs from the spray dried docetaxel spectrum an increase in docetaxel peak intensity and a decrease in ritonavir peak intensity is visible with increasing weight ratios of docetaxel (Fig 1c: C vs. E). Peaks characteristic to docetaxel increase at 1365 cm^{-1}, 1240 cm^{-1}; 1166 cm^{-1}, 1108 cm^{-1}, 1066 cm^{-1}, 984 cm^{-1}, 798 cm-1, and 753 cm^{-1}; peaks characteristic to ritonavir decrease at 1454 cm^{-1}, 1388 cm^{-1}, 1230 cm^{-1}, 872 cm^{-1}, and 745 cm^{-1}. The FT-IR spectrum of spray dried docetaxel recorded after accelerated stability testing was equal to the spectrum recorded after manufacturing. The FT-IR spectrum of spray dried ritonavir recorded after accelerated stability testing deviated from the FT-IR spectrum recorded after manufacturing at 1106 cm^{-1}, 1092 cm^{-1}, and 1052 cm^{-1}. However, these spectral changes did not correspond with crystalline ritonavir (data not shown).

Characteristics of spray dried solid dispersions of docetaxel, ritonavir, PVP-K30, and SLS

Peaks characteristic to SLS are present at 20.7 and 22.0 2-theta in the XRD spectra of the physical mixtures and freeze-dried SD powders (Fig 2a: F to I). In contrast, in the XRD spectra of spray dried SD powders no diffraction peaks were present (Fig 2a: L to N).

Individual Tg's of amorphous docetaxel, amorphous ritonavir and amorphous PVP-K30 are present in the mDSC reversal heat flow signals of the physical mixtures (Fig 2b and Table 2: F and G). Freeze-dried and spray dried SD powders have a single Tg in between the Tg of amorphous docetaxel or amorphous ritonavir and the Tg of amorphous PVP-K30 (Fig 2b and Table 2: H to N). In addition, two small endothermic peaks characteristic to SLS were observed in between 75 °C and 100 °C in the non-reversal heat flow signals of the physical mixtures and freeze-dried SD powders; these peaks were not observed in the signals of the spray dried SD powders (Table 2).

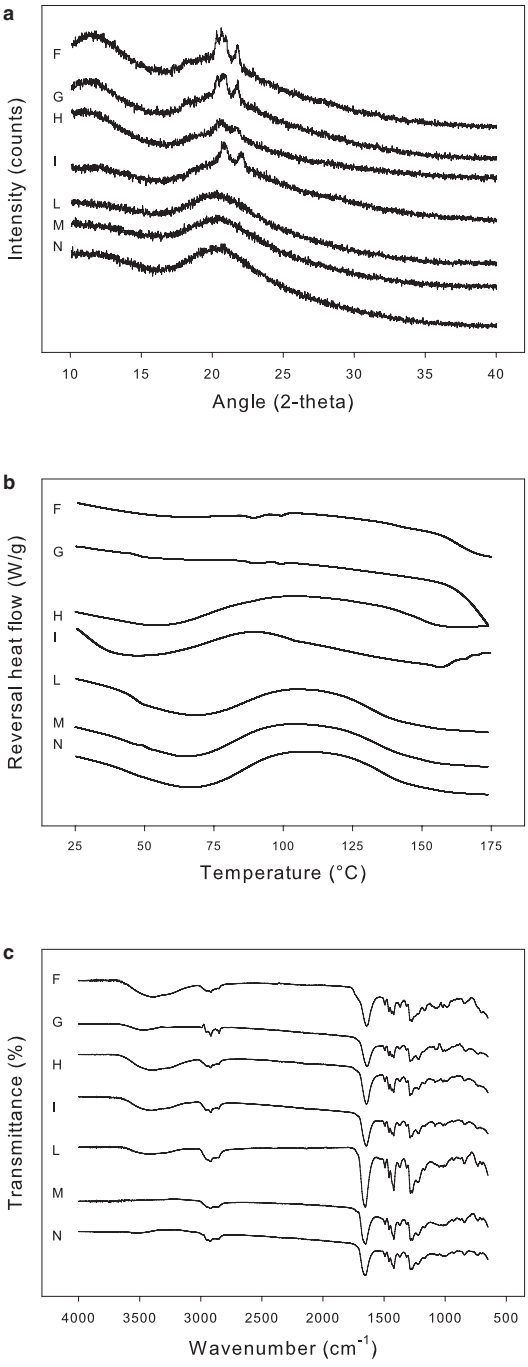

Figure 2. XRD spectra (a), reversal heat flow signals (b), and FT-IR spectra (c) of physical mixtures of amorphous docetaxel (F) and amorphous ritonavir (G); freeze-dried SD powders of docetaxel (H) and ritonavir (I); and spray dried SD powders of docetaxel/ritonavir at weight ratios of 0.05/0.95 w/w (L); 0.13/0.87 w/w (M); 0.23/0.77 w/w (N) (see Table 1 and 2). Physical mixtures and freeze-dried SD powders were not fully amorphous as XRD peaks characteristic to SLS are present around 21 2-theta (a: F to I), and the physical mixtures have two Tg's, one of the amorphous active ingredient and one of amorphous PVP-K30 (b: F and G). In contrast, a single Tg is present in the signals of the freeze-dried and spray dried SD powders (b: H to N). Futhermore, spray dried SD powders were fully amorphous as no XRD peaks are present at all (a: L to N). The intensities of the FT-IR peaks characteristic to SLS around 2900 cm^{-1} are highest in the FT-IR spectra of the physical mixtures and lowest in the FT-IR spectra of the spray dried SD powders.

The intensities of absorption peaks characteristic to SLS at 2954 cm^{-1}, 2917 cm^{-1}, and 2850 cm^{-1} are highest in the FT-IR spectra of the physical mixtures and lowest in the FT-IR spectra of the spray dried SD powders (Fig 2c: F and G vs. L to N). Additional differences between physical mixtures, freeze-dried SD powders, and spray dried SD powders are the absence of a sharp peak at 1438 cm^{-1} and equal peak intensities at 1284 cm^{-1} and 1270 cm^{-1} in the FT-IR spectra of the spray dried SD powders (Fig 2c: F to I vs. L to N). The majority of the spectra of the spray dried docetaxel/ritonavir SD powders is equal to the spectrum of spray dried ritonavir SD powder. With increasing weight ratios of docetaxel peaks characteristic to ritonavir decreased at 1526 cm^{-1}, 1050 cm^{-1}, 874 cm^{-1}, 701 cm^{-1}, and peaks characteristic to docetaxel increased at 1733 cm^{-1}, 1112 cm^{-1}, 1070 cm^{-1}, and 986 cm^{-1} in the spectra of spray dried docetaxel/ritonavir SD powders (Fig 2c: L to N).

Drug release from spray dried solid dispersions tablets of docetaxel, ritonavir, PVP-K30, and SLS

Single agent tablets of docetaxel or ritonavir were prepared from spray dried SD powders J and K; FDC tablets of docetaxel and ritonavir were prepared from spray dried SD powders L, M, and N (Table 1). In-vitro dissolution profiles of spray dried SD tablets containing approximately 42 mg of docetaxel, ritonavir, or docetaxel and ritonavir were compared to the in-vitro dissolution profile of ModraDoc001 10 mg (Fig 3). Almost 100% of docetaxel was released within 20 minutes from the spray dried SD tablets, however, the release rate of docetaxel from the ModraDoc001 10 mg capsule was higher (Fig 3: ▾ vs. •). There were no significant differences between the release rates of docetaxel and ritonavir from the single agent tablets; the release rate of docetaxel and ritonavir from the FDC tablets were equal (Fig 3: ■ and □).

We used the in-vitro dissolution data of all FDC tablets to plot the amount of dcoetaxel released vs. the amount of ritonavir released; the linear fitted trend line had an R^2 of 0.999 and a slope of 0.994. Based on the in-vitro dissolution profiles of all single agent and FDC tablets we plotted the amount of active ingredient released vs. the amount of PVP-K30 released; the linear fitted trend line of this plot had an R^2 of 0.8 and a slope of 0.93.

Stability of spray dried ModraDoc003 and ModraDoc004 10/50 SD formulations

To compare the exposure to docetaxel and ritonavir after administration of the ModraDoc001 10 mg capsule and the spray dried SD tablets a phase I clinical study

with a cross-over design was initiated [15]. Based on the results of the spray drying experiments and the defined dosing level of 40 mg docetaxel and 200 mg ritonavir it was decided to prepare a single agent tablet containing 10 mg of docetaxel (ModraDoc003 10 mg tablet) and a FDC tablet containing 10 mg of docetaxel and 50 mg of ritonavir (ModraDoc004 10/50 mg tablet) [15]. The stability of the ModraDoc003 SD powder (O) and ModraDoc004 10/50 SD powder (P) as well as the ModraDoc003 10 mg and ModraDoc004 10/50 mg tablet were evaluated after more than 52 weeks of storage.

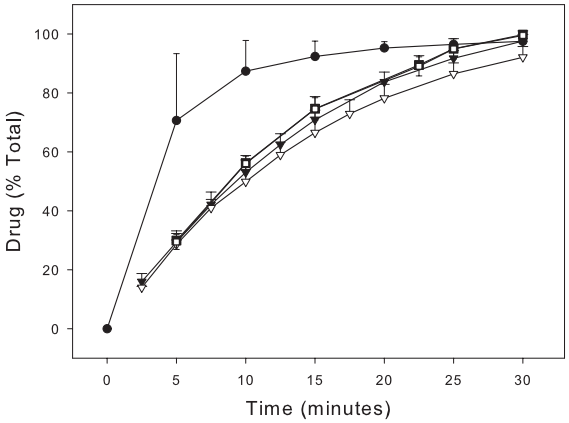

Figure 3: In-vitro dissolution profiles of 10 mg docetaxel (•) from the ModraDoc001 10 mg capsule, 42 mg docetaxel (▼) from a single agent tablet of spray dried docetaxel SD powder (J), 42 mg ritonavir (▽) from a single agent tablet of spray dried ritonavir SD powder (K), 10 mg docetaxel (■) and 32 mg ritonavir (□) from a FDC tablet of spray dried docetaxel/ritonavir SD powder (N). USP type II (paddle) dissolution apparatus, 500 mL 37.7 g/L Polyoxyethylene-10-laurylether in WFI, 37 °C, 75 RPM. Release of docetaxel from the ModraDoc001 10 mg capsule is faster than release from the spray dried SD tablets. Docetaxel and ritonavir are released at equal rates from the single agent and FDC tablets.

After more than 52 weeks of storage at 2-8°C water increased from 5.2% w/w to 6.7% w/w in the ModraDoc003 SD powder and from 5.1% w/w to 9.2% w/w in the ModraDoc004 10/50 SD powder. At the same time ethanol content decreased from 2.5% w/w to 2.2% w/w in the ModraDoc003 SD powder and from 2.4% w/w to 1.8% w/w in the ModraDoc004 10/50 SD powder. No degradation of docetaxel or ritonavir was detected in the ModraDoc003 or ModraDoc004 10/50 SD powders after more than 52 weeks of storage at 2-8 °C. Nor was any degradation of docetaxel or ritonavir observed in the ModraDoc003 10 mg or ModraDoc004 10/50 mg tablet after more than 52 weeks of storage at ambient conditions (data not shown).

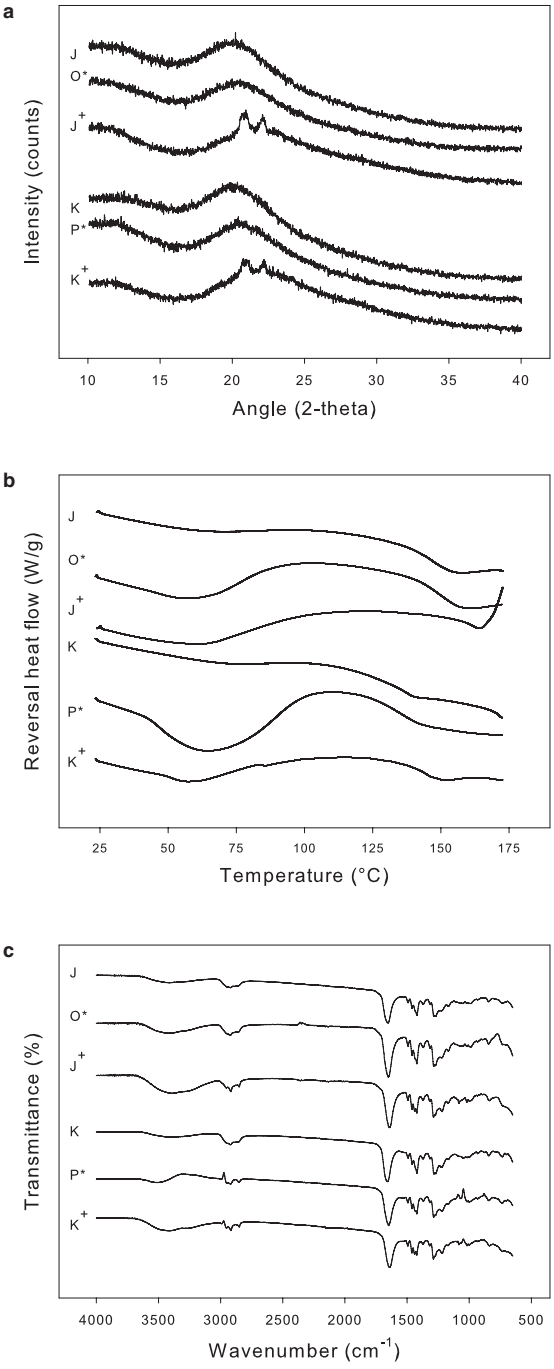

Figure 4: XRD spectra (a), reversal heat flow signals (b), and FT-IR spectra (c) of spray dried SD powders of docetaxel (J) and ritonavir (K) recorded before and after accelerated stability testing (J^+ and K^+); spray dried ModraDoc003 SD powder (O*) and spray dried ModraDoc004 10/50 SD powder (P*) after more than 52 weeks of storage at 2-8 °C. XRD peak characteristic to SLS around 21 2-theta were present after accelerated stability testing of spray dried SD powders (a: J, K vs. J^+, K^+); no XRD diffraction peaks were present in the XRD spectra of ModraDoc003 or ModraDoc004 10/50 SD powder after more than 52 weeks of storage at 2-8 °C. The Tg_{Exp} of the spray dried SD powders of docetaxel and ritonavir increased and approached the Tg_{Fox} without SLS (see Table 2). Increase of the Tg_{Exp} of ModraDoc003 and ModraDoc004 10/50 SD powders was limited after more than 52 weeks of storage 2-8 °C (b). Increase in FT-IR peak intensity and FR-IR peak shifts were less for ModraDoc003 and ModraDoc004 10/50 SD powders after storage at 2-8°C compared to spray dried docetaxel and ritonavir SD powders after accelerated stability testing (c).

The stability of ModraDoc003 and ModraDoc004 10/50 SD powders stored in closed containers at 2-8 °C for more than 52 weeks was compared to the stability of spray dried docetaxel or ritonavir SD powders after accelerated stability testing (Fig 4a, b, c). After accelerated stability testing diffraction peaks characteristic to SLS are present at 20.7 and 22.0 2-theta in the XRD spectra of spray dried SD powders of docetaxel and ritonavir (J and K vs. J^+ and K^+). In contrast after more than 52 weeks of storage at 2-8°C no diffraction peaks were present in the ModraDoc003 or ModraDoc004 SD powder (O* and P* vs. J^+ and K^+).

Tg_{Exp} values of the spray dried SD powders of docetaxel and ritonavir increased approximately 15°C after accelerated stability testing (Fig 4b and Table 2: J and K vs. J^+ and K^+). The Tg_{Exp} of ModraDoc003 SD powder after more than 52 weeks of storage at 2-8°C was comparable to the Tg_{Exp} of the spray dried docetaxel SD powder before storage (Fig 4b and Table 2: O* vs. J). After more than 52 weeks of storage at 2-8°C the Tg_{Exp} of ModraDoc004 10/50 SD powder was in between the Tg_{Exp} values of spray dried ritonavir SD powder determined before and after accelerated stability testing (Fig 4b and Table 2: P* vs. K and K+). Furthermore, the Tg_{exp} was equal to the Tg_{Exp} of spray dried docetaxel/ritonavir SD powder at a weight ratio 0.23/0.77 w/w (Table 2: P* vs. N).

During accelerated stability testing absorption peaks characteristic to SLS increased at 2954 cm^{-1}, 2917 cm^{-1}, 2850 cm^{-1} , 1287 cm^{-1} 1218 cm^{-1}, 1083 cm^{-1}, and the peak at 843 cm^{-1} shifted to 836 cm^{-1}. Docetaxel absorption peaks increased at 1438 cm^{-1}, 1170 cm^{-1}, 1137 cm^{-1}, 1017 cm^{-1};ritonavir absorption peaks increased at 1532 cm^{-1} and 1438 cm^{-1}. The carbonyl absorption peak of PVP shifted from approximately 1652 cm-1 to 1640 cm^{-1} (Fig 4c: J and K vs. J^+ and K^+). The increase in SLS absorption peak intensities was higher after accelerated stability testing of the spray dried docetaxel and ritonavir SD powders compared to the ModraDoc003 and ModraDoc005 10/50 SD powders. Furthermore, the carbonyl peak at 1650 cm^{-1} was not shifted in the FT-IR spectrum of ModraDoc003 SD powder and was only shifted from 1652 cm^{-1} to 1644 cm^{-1} in the FT-IR spectrum of ModraDoc004 10/50 SD powder. Moreover, the intensity of the OH regions in between 3500 cm^{-1} and 3100 cm^{-1}, and in between 850 cm^{-1} and 650 cm^{-1} increased more during accelerated stability testing than during more than 52 weeks of storage at 2-8 °C (Fig 4c: O* and P* vs. J^+ and K^+).

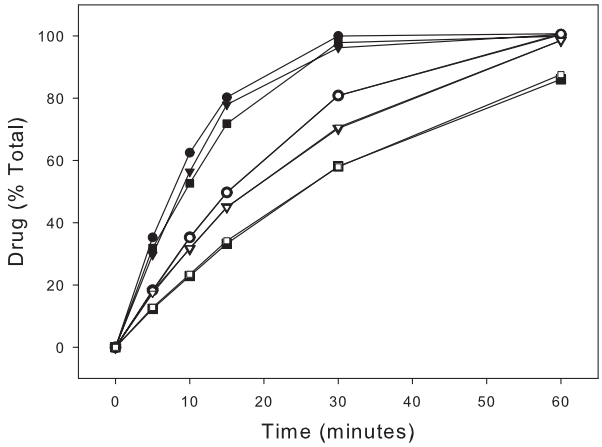

Figure 5: In-vitro dissolution profiles of docetaxel from the ModraDoc003 10 mg tablet (left 3 curves) after 0 weeks (•), 25 weeks (▾), and more than 52 weeks (■) of storage at ambient conditions; in vitro dissolution profiles of docetaxel (• ▾ ■) and ritonavir (○ ▿ □) from the ModraDoc004 10/50 mg tablet after 0 weeks (• ○), 25 weeks (▾ ▿), and more than 52 weeks (■ □) of storage at ambient conditions. USP type II (paddle) dissolution apparatus, 500 mL 37.7 g/L Polyoxyethylene-10-laurylether in WFI, 37 °C, 75 RPM. During storage the dissolution rate of docetaxel from the ModraDoc003 10 mg tablet did not change; the dissolution rate of docetaxel and ritonavir from the ModraDoc004 10/50 mg tablet decreased equally.

Figure 5 shows the in-vitro dissolution profiles of the ModraDoc003 10 mg and ModraDoc004 10/50 mg tablets. After more than 52 weeks of storage at ambient conditions there are no significant differences with the initial release rate of docetaxel from the ModraDoc003 10 mg tablet (Fig 5: • vs. ■). The release rates of docetaxel and ritonavir from the ModraDoc004 10/50 mg tablets decreased significantly after 25 weeks of storage at ambient conditions (Q5-Q30: f1>15, and f2<50). However, the decrease in dissolution rate was the same for docetaxel and ritonavir, hence despite the decreasing dissolution rate the individual release rates of docetaxel and ritonavir remained equal during storage at ambient conditions.

Discussion

Preparation of spray dried SD formulations

The results of the assay and related substances show that the spray drying parameters do no result in chemical degradation of docetaxel or ritonavir. This proves that spray

drying can be used to manufacture chemically stable solid dispersions of docetaxel, ritonavir, PVP-K30, and SLS. Water and ethanol contents are well within acceptable ranges and can probably be further reduced by optimizing the spray drying parameters. However, the chosen spray drying parameters did not produce acceptable powder flow properties, we therefore manually compacted all tablets. The poor powder flow properties are probably related to the small particle size; indicative laser diffraction measurements showed that the average particle size (x50 value) was approximately 10 μm. Ongoing optimization experiments are focused on increasing the particle size and improving the powder flow properties to enable automated tabletting.

Characteristics of spray dried docetaxel and ritonavir

XRD, mDSC, and FT-IR analysis of spray dried docetaxel, spray dried ritonavir, and spray dried docetaxe/ritonavir mixtures showed that all spray dried powders were amorphous after manufacturing. After accelerated stability testing the Tg of amorphous docetaxel was unchanged and no changes were observed in the XRD and FT-IR spectra, hence amorphous docetaxel does not crystallize at the accelerated stability conditions. On the other hand the Tg of amorphous ritonavir decreased from 47 °C to 42 °C and a small melting peak of crystalline ritonavir appeared. Although crystalline ritonavir was not observed in the XRD or FT-IR spectra a small portion of amorphous ritonavir crystallized during accelerated stability testing. Nevertheless, it seems that amorphous ritonavir has a very limited crystallization potential because even when stored around its Tg at high humidity only a very limited amount crystallized. The limited crystallization potential of ritonavir was also observed by Zhou et al. and Law et al. and was attributed to ritonavir's low mobility and large configurational entropy under dry conditions [20, 21]. Moreover, the low crystallization potential of both docetaxel and ritonavir after exposure to 40 °C / 75 % RH make them excellent candidates for inclusion in a solid dispersion formulation. Furthermore, inclusion of ritonavir in a solid dispersion with docetaxel (Tg 149 °C) and/or PVP-K30 (Tg 162 °C) will probably increase its Tg and reduce molecular mobility which will further decrease the crystallization potential of ritonavir and consequently increase the pharmaceutical shelf life of spray dried SD powders containing ritonavir.

The fact that the mDSC reversal heat flow signal of spray dried docetaxel/ritonavir mixtures had single Tg suggests molecular mixing of amorphous docetaxel and ritonavir.

The differences between the TgExp and the TgFox of the spray dried docetaxel/ritonavir mixtures are probably due to the plasticizing effect of residual moisture. More importantly, molecular mixing of docetaxel and ritonavir after spray drying suggest excellent compatibility between docetaxel and ritonavir.

Characteristics of spray dried solid dispersions of docetaxel, ritonavir, PVP-K30, and SLS

XRD and FT-IR analysis revealed no signs of crystalline material in the spray dried SD powders. Even more, all spray dried SD powders had single Tg_{Exp} values; and most of them were in close agreement with the Tg_{Fox} values. This suggests molecular mixing of all SD components including SLS. Because there are no indications of crystalline SLS in the XRD and FT-IR spectra, nor in the mDSC reversal heat flow signal of docetaxel SD powders it is likely that the larger difference between Tg_{exp} en Tg_{Fox} is caused by a poor prediction of the Tg_{Fox} for docetaxel SD powders (Table 2: H, J, O). These results are in contrast with the XRD and FT-IR spectra of freeze-dried SD powders which contained SLS characteristic peaks. Furthermore, the Tg_{Exp} values were higher for freeze-dried SD powders compared to spray dried SD powders. Apparently SLS is not rendered amorphous during the freeze-drying process or its dispersion after freeze-drying is not as complete as after spray drying. It is hypothesized that during the freezing separation of water and TBA occurs which will result in the formation of an SLS rich water phase and a drug rich TBA phase. Due to the rapid evaporation of the WfI/Ethanol solution phase separation is not likely during spray drying, and hence a fully amorphous SD powder is obtained.

Furthermore, the majority of the FT-IR spectra of spray dried SD powders was equal to the FT-IR spectrum of PVP-K30, which suggests a fine distribution of docetaxel, ritonavir, and SLS over the carrier. Apparently spray drying results in an amorphous molecular dispersion of all components. This is a promising result as a molecular dispersion of ritonavir and PVP-K30 will further reduce its crystallization potential during storage and upon dissolution. In addition to this, the molecular dispersion of docetaxel, ritonavir, and PVP-K30 would allow for simultaneous release of the carrier and active ingredients from spray dried SD tablets.

Dissolution of spray dried solid dispersions of docetaxel, ritonavir, PVP-K30, and SLS

The in-vitro dissolution tests showed that the release of docetaxel and ritonavir from the spray dried SD tablets is dependent on release of PVP-K30. In addition, the release rates of docetaxel and ritonavir from the FDC tablets are equal. These results are in line with the physical characteristics of the spray dried SD powders; that is, the molecular dispersion of docetaxel and ritonavir over the carrier PVP-K30. The faster release of docetaxel from the ModraDoc001 10 mg capsule is probably the result of the loose packing of the powder inside the capsule.

In a phase I pilot bioequivalence study the simultaneous release rate of docetaxel and ritonavir from the ModraDoc004 10/50 mg tablet appeared to result in a higher exposure to docetaxel compared to administration of single agent formulations with different in-vitro release rates of docetaxel and ritonavir [15]. Moreover, the simultaneous release rates of docetaxel and ritonavir from the spray dried FDC tablets with various strengths suggests that administration of these FDC tablets will also result in equal or higher exposures to docetaxel. In conclusion, multiple FDC tablet strengths would grealy improve patient convenience while still providing the clinician with the necessary tools to easily apply dose adjustments during oral chemotherapy.

Stability of spray dried ModraDoc003 and ModraDoc004 10/50 SD formulations

During more than 52 weeks storage at 2-8°C the amount of water in the ModraDoc003 and ModraDoc004 10/50 SD powders increased while there was a decrease in the amount of ethanol. This is similar to what we observed for the freeze-dried SD powder of docetaxel (ModraDoc001) in which the amount of water increased from 6.3% to 27% w/w (dried weight) and the amount of TBA decreased from 3.4% to 0.12% w/w (dried weight) during 138 weeks of storage at 2-8 °C (Chapter 5 of this thesis). Release of TBA is known to be promoted by absorption of water (22). This could also be the driving force for ethanol release from the spray dried SD powders, although regular diffusion and evaporation are also key factors. Moreover, the available data suggests that the amount of water absorbed by freeze-dried and spray dried solid dispersions is similar.

Accelerated stability testing of the spray dried SD powders resulted in the appearance of diffraction peaks characteristic to SLS, an increase in Tg_{Exp} values which were in line with the predicted Tg_{Fox} values excluding SLS, and finally increasing FT-IR peak

intensities characteristic to SLS. Moreover, the XRD and FT-IR spectra of spray dried SD powders after accelerated stability testing were comparable to the XRD and FT-IR spectra of freeze-dried SD powders after manufacturing. All these results suggest phase separation and/or crystallization of SLS, this is similar to what we previously reported for the freeze-dried solid dispersions of docetaxel and paclitaxel (Chapter 5 of this thesis). It is likely that the phase separation of SLS is caused by the absorption of water during storage. Therefore air tight packaging and storage at lower humidities are recommended for spray dried SD powders to prevent SLS phase separation.

mDSC, and FT-IR analysis of the ModraDoc003 and ModraDoc004 10/50 powder after more than 52 weeks of storage at 2-8 °C also revealed signs of SLS phase separation. The Tg_{mix} values increased and were roughly in between the Tg_{Fox} values calculated with and without SLS. In addition to this, FT-IR spectra suggested that phase separation of SLS had progressed further in the ModraDoc004 10/50 SD powder than in the ModraDoc003 SD powder. The latter is in agreement with the hypothesis that the phase separation of SLS was induced by water because a higher amount of water was present in the ModraDoc004 10/50 SD powder compared to the ModraDoc003 SD powder after more than 52 weeks of storage (9.2% w/w vs. 6.7% w/w).

The stable dissolution rate of the ModraDoc003 10 mg tablet after more than 52 weeks of storage and the decreased dissolution rate of the ModraDoc004 10/50 mg tablet after 25 weeks of storage at ambient conditions are in line with the physical and chemical analysis performed on the SD powders. Most probably water mediated phase separation of SLS decreased the wetting of the PVP-active ingredient complex which subsequently led to a decreased dissolution rate of docetaxel and ritonavir from the ModraDoc004 10/50 mg tablet. The stability tests at 2-8 °C showed a higher amount of water absorbed by ModraDoc004 10/50 SD powder compared to ModraDoc003 SD powder. Furthermore, the XRD and FT-IR analysis suggested a higher degree of SLS phase separation for ModraDoc004 10/50 SD powder.

It should be noted that despite the decrease, the dissolution rates of docetaxel and ritonavir from the ModraDoc004 10/50 mg tablet were still within specification. Even more, it is not likely that these minor changes in the in-vitro dissolution profile will result in a significantly changed in-vivo performance. Nevertheless, the ModraDoc003 10 mg tablet can be considered stable at ambient conditions for at least 52 weeks; the ModraDoc004 10/50 mg tablet can be considered stable at ambient conditions for at

least 25 weeks. Moreover, primary and secondary packaging of the spray dried SD tablets should become air tight to prevent water mediated phase separation of SLS and subsequently decreased dissolution performance.

Conclusions

Spray drying of docetaxel, ritonavir, PVP-K30, and SLS in an active ingredient/PVP/SLS ratio of 1/9/1 and various docetaxel/ritonavir weight ratios resulted in fully amorphous solid dispersions. XRD, mDSC, and FT-IR analysis suggested a molecular distribution of docetaxel and ritonavir in the PVP-K30/SLS matrix. Compared to freeze-dried solid dispersions SLS is amorphous and/or molecular dispersed over docetaxel, ritonavir, and PVP-K30; this might result in increased dissolution rates in-vivo and in-vitro. In summary, it can be concluded that spray drying produces comparable or better SD powder than freeze-drying. The spray drying process should be optimized to further reduce the residual solvents and, more importantly, optimize the powder flow characteristics to enable automated compaction of spray dried SD tablets of docetaxel and ritonavir.

Release of docetaxel and ritonavir from the single agent and FDC tablets was simultaneous and dependent on the release of PVP-K30. The simultaneous release rate of docetaxel and ritonavir is a huge advantage for clinical applications and might increase the in-vivo exposure to docetaxel [15]. Although water absorption by the spray dried SD powders during storage caused no crystallization of docetaxel or ritonavir it did induce phase separation of SLS which led to a decreased in-vitro dissolution performance. ModraDoc003 10 mg tablets can be considered stable at ambient conditions for at least 52 weeks; ModraDoc004 10/50 mg tablets can be considered stable at ambient conditions for at least 25 weeks. Nevertheless, primary and secondary packaging of the solid dispersion tablets should be improved to prevent water mediated phase separation of SLS and a decreased dissolution performance.

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Chapter 7

Pharmacokinetic evaluation of three oral formulations of docetaxel boosted with ritonavir: two single drug formulations vs a fixed-dose combination tablet

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Drug Delivery and Translational Research 2013 (3) 3: 243-251

Abstract

The ability to deliver the potent anticancer agent docetaxel via the oral route may enable the development of promising new treatment regimens with reduced toxicity, increased efficacy, and increased patient convenience. Recently, we were able to overcome the low oral bioavailability of docetaxel by concomitant administration of the pharmacokinetic booster ritonavir and the design of an oral solid dispersion formulation of docetaxel (ModraDoc001 10 mg capsule). Further research lead to the development of a docetaxel tablet (ModraDoc003 10 mg tablet) and a fixed-dose combination (FDC) tablet of docetaxel and ritonavir (ModraDoc004 10/50 mg tablet). In this clinical proof-of-concept study the exposure to docetaxel and ritonavir was compared between the single agent formulations and the FDC tablet. Six evaluable patients received 40 mg docetaxel and 200 mg of ritonavir once a week according to a cross-over design. No significant differences were found in the exposure to docetaxel and ritonavir between the single agent formulations and the FDC tablet. There was however a tendency towards a higher exposure to docetaxel after the administration of the FDC tablet, which could be an effect of the simultaneous release of docetaxel and ritonavir in the gastrointestinal tract. The FDC tablet of docetaxel and ritonavir is a pharmaceutically and clinically feasibly option in the development of patient convenient oral anticancer therapy with docetaxel.

Introduction

Docetaxel is a highly effective anticancer agent used in the treatment of various solid tumors [1]. Due to its cytostatic mechanism of action docetaxel could be even more effective when administered chronically to patients [2, 3]. However, because of its low oral bioavailability, docetaxel is currently only available as an intravenous infusion formulation, which makes chronic administration impractical, patient unfriendly, and expensive. Hence, for the successful implementation of oral docetaxel chemotherapy an oral formulation of docetaxel is needed that overcomes the low oral bioavailability of docetaxel.

Due to its low solubility and low permeability docetaxel is classified as a class IV drug according to the biopharmaceutical classification system [4]; its oral bioavailability is estimated to be less than 10% [3, 5]. The very low permeability of docetaxel can be mainly attributed to extensive metabolism by CYP3A4 enzymes in the gut wall and liver, and partly to active excretion by P-glycoprotein pumps [6]. We have shown that the oral bioavailability of a docetaxel micellar solution could be increased by concomitant administration of the strong CYP3A4 inhibitor ritonavir [7].

Recently, we increased the oral bioavailability of docetaxel by combining the pharmacokinetic booster ritonavir with the ModraDoc001 10 mg capsule, a newly developed solid dispersion formulation of docetaxel [8]. Subsequent studies with this new formulation confirmed that CYP3A4 inhibition in the liver and gut wall was primarily responsible for the increase in docetaxel exposure; and showed that 200 mg ritonavir led to a higher exposure to docetaxel compared to 100 mg of ritonavir [9]. The ModraDoc001 10 mg capsule contains a freeze-dried solid dispersion powder of docetaxel, polyvinylpyrrolidone K30 (PVP-K30), and sodium lauryl sulphate (SLS), in a weight ratio of 1/9/1 w/w/w (ModraDoc001 SD powder) [8]. To date the ModraDoc001 10 mg capsule has been administered in combination with ritonavir to more than 40 patients in a phase I dose escalation study [10].

Special formulations such as micellar solutions and solid dispersions can increase the pharmaceutical availability of docetaxel. However, over time these formulations cannot prevent docetaxel precipitation or degradation in the gastrointestinal tract [8, 11, 12]. It is therefore essential that the pharmacokinetic booster ritonavir is present to promote rapid absorption of the dissolved docetaxel before the onset of degradation

or precipitation [7]. To date we were not fully able to fulfill this prerequisite, given the available docetaxel and ritonavir formulations. Immediately after oral administration, the docetaxel micellar solution will be available for absorption while the hard capsule shell of the ritonavir formulation will first have to be penetrated before ritonavir can be released. Indeed, administration of the ritonavir formulation 60 minutes prior to administration of the docetaxel micellar solution showed a tendency towards a higher exposure to docetaxel compared to simultaneous administration of both formulations [7]. Moreover, both theory and practice show that the timing and site of the ritonavir release relative to the docetaxel release influence the absorption of docetaxel. Consequently, docetaxel and ritonavir have to be released at the same time at the same site to achieve optimal pharmacokinetic boosting of docetaxel.

Recently, the manufacturing of spray dried solid dispersion powder enabled us to develop two tablet formulations of docetaxel: the ModraDoc003 10 mg tablet and the ModraDoc004 10/50 mg tablet. The ModraDoc003 10 mg tablet is the equivalent of the ModraDoc001 10 mg capsule except for the spray drying of the intermediate product. The ModraDoc004 10/50 mg tablet is a fixed-dose combination (FDC) tablet and contains 10 mg of docetaxel and 50 mg of ritonavir.

The FDC tablet of docetaxel and ritonavir has potentially several advantages over single agent formulations. First of all, patient convenience and adherence is likely to improve due to the reduced number of dosage units and the simplified dosing schedule [13]. Secondly, the FDC tablet eliminates the possibility that docetaxel is administered without its pharmacokinetic booster ritonavir. Finally, simultaneous release of docetaxel and ritonavir could probably increase the exposure to docetaxel and decrease its variability.

The aim of this study was to evaluate the in vitro and in vivo performance of three oral formulations of docetaxel boosted with ritonavir: two single drug formulations of docetaxel, the ModraDoc001 10 mg capsule and the ModraDoc003 10 mg tablet, versus the FDC tablet of docetaxel and ritonavir, the ModraDoc004 10/50 mg tablet.

Patients, Materials and Methods

Materials

Docetaxel anhydrate was obtained from Scinopharm Taiwan (Tainan, Taiwan). Ritonavir was purchased from LGM Pharma (Boca Raton, FL, USA). Povinylpyrrolidone K30 (PVP-K30) was supplied by BASF (Ludwigshafen, Germany). Pharmacopoeial grade absolute ethanol, 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). Lactose 200M and colloidal silicon dioxide were supplied by Spruyt Hillen (IJsselstein, The Netherlands). Granulated lactose (modified lactose monohydrate, SUPERTAB) was obtained from DMV-Fonterra Excipients (Veghel, the Netherlands). Hard gelatin capsules were purchased from Capsugel (Bornem, Belgium). Polyoxyethylene 10-lauryl ether was obtained from Sigma Aldrich Chemie B.V. (Zwijndrecht, The Netherlands).

Preparation of docetaxel and ritonavir formulations

The ModraDoc001 10 mg capsule contained a freeze-dried solid dispersion powder: ModraDoc001 SD powder. ModraDoc001 SD powder consisted of docetaxel, PVP-K30 and SLS in a weight ratio of 1/9/1 w/w/w. Preparation of the ModraDoc001 SD powder was done by freeze-drying. All solid dispersion components were accurately weighed and dissolved in TBA/WfI mixtures (60/40 v/v); the concentration of docetaxel in TBA was 10 mg/mL. The resulting solution was transferred to stainless steel boxes (Gastronorm size 1/9), placed in a freeze-dryer (Lyovac GT4, GEA Lyophil GmbH, Hürth Germany) and freeze-dried according to a method described earlier [14]. The freezing phase started with a freezing ramp from ambient temperature to -35 °C in 1 hour followed by a holding step of 2 hours at -35 °C. Primary drying was performed at -35 °C and 0.2 mbar for 45 hours. Secondary drying started with a heating ramp from -35 °C to 25 °C at 0.2 mbar in 15 hours followed by a holding step at 25 °C and 0.2mbar for 3 hours. The ModraDoc001 10 mg capsule contained lactose monohydrate 200 M, colloidal silicon dioxide, and an amount of ModraDoc001 SD powder equivalent to 10 mg of docetaxel. ModraDoc001 SD powder and capsule excipients were accurately weighed and gently grinded with mortar and pestle. Encapsulation into size 0 hard gelatin capsules was performed on a manual capsulation apparatus (Feton International

NV, Brussels, Belgium).

The ModraDoc003 10 mg tablet contained a spray dried solid dispersion powder: ModraDoc003 SD powder. ModraDoc003 SD powder consisted of docetaxel, PVP-K30 and SLS in a weight ratio of 1/9/1 w/w/w. Preparation of ModraDoc003 SD powder done by spray drying. All solid dispersion components were accurately weighed and dissolved in a 75/25 v/v ethanol/WfI mixture. The resulting solution was spray dried with a B290 mini spray dryer connected to a B-296 dehumidifier and a B-295 inert loop (Büchi Labortechnik AG, Flawil, Switzerland). A standard nozzle with an inner tip diameter of 0.7 mm and an outer tip diameter of 1.5 mm was used. Inlet temperature was set at 150 °C, N2 gas flow rate was set at 35 arbitrary units, aspirator flow rate was set at 100%, and product feed rate was set at 30%. The ModraDoc003 10 mg tablet contained granulated lactose, colloidal silicon dioxide, magnesium stearate, and an amount of ModraDoc003 SD powder equivalent to 10 mg of docetaxel. ModraDoc003 SD powder and the tablet excipients were accurately weighed in a 3 L stainless steel bin and mixed in a Turbula mixer T10B operating at the highest mixing speed (Willy A Bachofen AG Maschinenfabrik, Muttenz, Switzerland). Tablet powder was manually compacted on an EK 0 eccentric press (Korsch AG, Berlin, Germany) equipped with 9 mm tooling.

The ModraDoc004 10/50 mg tablet contained a spray dried solid dispersion powder: ModraDoc004 SD powder. ModraDoc004 SD powder consisted of the active ingredients, PVP-K30 and SLS in a weight ratio of 1/9/1 w/w/w; the active ingredients consisted of docetaxel and ritonavir in a weight ratio of 1/5 w/w. Preparation of the ModraDoc004 SD powder was equivalent to the preparation of the ModraDoc003 SD powder. The ModraDoc004 10/50 mg tablet contained granulated lactose, colloidal silicon dioxide, magnesium stearate, and an amount of ModraDoc004 SD powder equivalent to 10 mg of docetaxel and 50 mg of ritonavir. Preparation of the ModraDoc004 10/50 mg tablet was equivalent to the ModraDoc003 10 mg tablet except for the use of 14 mm tooling.

Ritonavir (NORVIR) 100 mg soft gelatin capsules and ritonavir (NORVIR) 100 mg tablets originated from Abbott Laboratories (Abbott park, Illinois, USA)[15].

In vitro evaluation of docetaxel and ritonavir formulations

All formulations used in the clinical study, i.e. ModraDoc001 10 mg capsules, ModraDoc003 10 mg tablets, ModraDoc004 10/50 mg tablets, ritonavir (NORVIR) 100 mg capsules, and ritonavir (NORVIR) 100 mg tablets, were subjected to a dissolution

test adapted from the USP monograph of lopinavir and ritonavir tablets (16). Briefly, 500 mL of a 37.7 g/L polyoxyethylene-10-lauryl ether solution in WfI was heated to 37 °C and transferred to a type 2 (paddle) dissolution apparatus (Erweka, Heusenstamm, Germany). The paddle was operated at 75 RPM and each formulation was tested in triplicate. Samples of 1.0 mL were withdrawn at 0 (baseline), 5, 10, 15, 30, 60, 120, 180, and 240 minutes after the dosage form was added to the medium. All samples were filtrated with a 0.45 μm filter (Millex HV, Millipore) and subsequently analyzed on an adapted RP-HPLC-UV system originally described by Huizing et al. (17). Of each sample 20 μL was injected on an APEX octyl analytical HPLC column (150 x 4.6 mm ID; particle size 5 μm; Grace Discovery Sciences, Deerfield, IL, United States). Eluens was a mixture of 1/4/5 v/v/v methanol/acetonitrile/0.02M ammonium acetate buffer at pH 5; run time was 20 minutes at a flow of 1.0 mL/min. Docetaxel was detected at 227 nm and ritonavir was detected at 210 nm.

Patient population

Patients with a histological or cytological proof of cancer refractory to current therapies who might benefit from treatment with docetaxel were eligible for the study. Other eligibility criteria included: Age > 18 years; life expectancy > 3 months; no radio- or chemotherapy within the last 4 weeks prior to study entry, however limited radiation for pain reduction as palliative treatment was allowed. Patients had to have a World Health Organization (WHO) performance status ≤ 2, and adequate hematological, renal and hepatic function. Patients were not eligible if they suffered from uncontrolled infectious disease, neurologic disease, bowel obstructions, or symptomatic brain metastases. Other exclusion criteria included concomitant use of known P-glycoprotein or CYP3A4 inhibitors, and chronic use of H2-receptor antagonists or proton pump inhibitors.

The medical ethics committee of the Netherlands Cancer Institute approved the study protocol and all patients gave written informed consent prior to start of the study. The study was registered in the NIH registry www.clinicaltrials.gov under identifier NCT01173913.

Study Design

This study was designed as an open label, pharmacokinetic proof of concept study. In the first three weeks of the study patients received all three docetaxel formulations according

to a cross-over design. Upon entering the study, patients were randomly assigned to one of the six possible treatment sequences of the cross-over design. Pharmacokinetic monitoring was performed for all tested formulations during the first three weeks of the study. After completion of the pharmacokinetic part of the study treatment was continued until the patient no longer had clinical benefit, e.g. progressive disease, or if toxicity led to patient withdrawal.

In the first three weeks patients received once a week 40 mg docetaxel concomitantly with 200 mg ritonavir. After completion of the pharmacokinetic part of the study patients received 80 mg docetaxel in combination with 100 mg ritonavir once a week.

Drug composition and administration

Study drugs were administered on an empty stomach; patients fasted at least 2 hours before drug administration, and at least 1 hour after drug administration. Docetaxel was administered simultaneously with ritonavir; patients received approximately 150 mL of tap water after administration of the study drugs.

In the first three weeks, pre-treatment consisted of 1 mg granisetron (p.o) 1 hour prior to administration of the study drugs. Docetaxel was administered as ModraDoc004 10/50 mg tablet, as ModraDoc001 10 mg capsule or as ModraDoc003 10 mg tablet. Ritonavir was administered as ModraDoc004 10/50 mg tablets, as ritonavir 100 mg capsule, or as ritonavir 100 mg tablet. After completion of the pharmacokinetic part of the study pre-treatment was not specified in the protocol and was provided on an individual basis. Docetaxel was administered as ModraDoc001 10 mg capsule; ritonavir was administered as ritonavir 100 mg capsule or as ritonavir 100 mg tablet

Safety

All observed toxicities were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 3.0 [18].

Sample collection and analysis

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 hrs after administration of the study formulations. Samples were immediately placed on ice and were centrifuged within 1 hour at 1500 x g for 10 minutes at 4°C. Plasma was stored at or below -20°C until analysis.

Docetaxel and ritonavir were quantified in plasma by use of high-performance liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) with labeled analogues as internal standards as described by Hendrikx et al. [19]. Briefly, compounds were extracted from 200 µL human plasma using tertiair-butylmethylether; the solution was subsequently dried and the residue was reconstituted in a 1/1 v/v WfI/methanol mixture. Of each sample 25 µL was injected onto a Zorbax Etend C18 column (150 x 2.1 mm ID; particle size 5 µm; Agilent Technologies, Amstelveen, The Netherlands) protected with an inline filter (0.5 µm). Eluens was a mixture of 7/3 v/v methanol/10 mM ammonium hydroxide in WfI; run time was 9 minutes at a flow of 0.3 mL/min; column temperature was set at 35 °C, and autosampler temperature was maintained at 4 °C. Compounds were detected using positive ionization electrospray tandem mass spectrometry. The lower limit of quantification of the assay was 0.5 ng/mL for docetaxel and 2 ng/mL for ritonavir.

Pharmacokinetic and statistical analysis

The individual pharmacokinetic parameters were analyzed using descriptive non-compartmental pharmacokinetic methods and validated R scripts (R version 2.10.0) [20]. The areas under the plasma concentration-time curves to the last quantifiable sample point (AUC_{0-t}) were estimated by the linear trapezoidal (absorption phase) and logarithmic trapezoidal rule (elimination phase). The areas under the plasma concentration-time curves to infinite time (AUC_{0-Inf}) were calculated by extrapolation. The observed maximum plasma concentration (C_{max}), the time to the maximum plasma concentration (T_{max}), the elimination half-life ($T_{1/2}$), and mean residence time (MRT) were reported. Pharmacokinetic parameters were compared visually and statistically with paired t-tests on the natural-log transformed values of AUC_{0-inf} and C_{max}. To support the design of future bioequivalence studies the bioequivalence ratios for C_{max} and AUC_{0-inf} were calculated according to the current EMA guideline [21].

Results

In vitro performance of docetaxel and ritonavir formulations

Figure 1 presents the initial dissolution profiles of the docetaxel and ritonavir

formulations. The release rate of docetaxel from the ModraDoc001 10 mg capsule was the highest (Q=75% ~ 10 minutes); the lowest release rate of docetaxel was from the ModraDoc004 10/50 mg tablet (Q=75% ~ 30 minutes). The release rate of ritonavir was lowest from the 100 mg tablet (Q=75% >90 minutes); the highest release rate of ritonavir was from the 100 mg capsule (Q=75% <20 minutes). The release rates of docetaxel and ritonavir from the ModraDoc004 10/50 mg tablet were equal; within 60 minutes both docetaxel and ritonavir were completely released from the ModraDoc004 10/50 mg tablet.

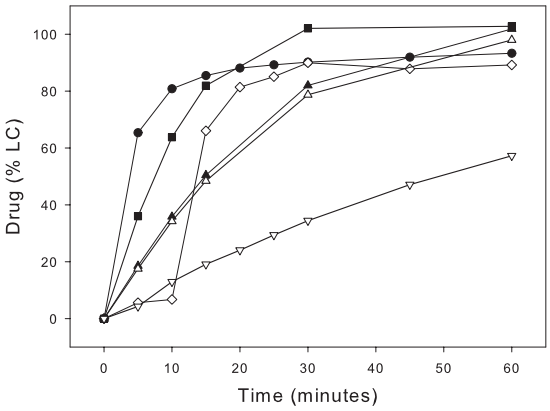

Figure 1: In-vitro dissolution profiles of docetaxel from the ModraDoc001 10 mg capsule (•); ModraDoc003 10 mg tablet (■); ModraDoc004 10/50 mg tablet (▲); and ritonavir from the ritonavir 100 mg capsules (◇); ritonavir 100 mg tablet (▽); ModraDoc004 10/50 mg tablet (△). USP Type II (Paddle) dissolution apparatus, 500 mL 37.7 g/L polyoxyetyle-10-laurylether in WfI, 37°C, 75 RPM (n=3). Docetaxel release is highest from the ModraDoc001 10 mg capsule (Q=75% ~ 10 minutes) and lowest from the ModraDoc004 10/50 mg tablet (Q=75% ~30 minutes). Ritonavir release is highest from the ritonavir 100 mg capsule (Q=75% < 20 minutes) and lowest from the ritonavir 100 mg tablet (Q=75% > 90 minutes). The ModraDoc004 10/50 mg tablet has equal release rates for docetaxel and ritonavir.

Patient characteristics

In total nine patients were included in the study, all of them had metastatic disease. Patient characteristics are listed in Table 1. One patient (patient 3) developed vomiting in the first week, 30 minutes after administration of the study drugs; the patient was therefore excluded from the pharmacokinetic part of the study and continued treatment with 80 mg of docetaxel and 100 mg of ritonavir. Two patients (patient 4 and 5) went off study due to neutropenia (patient 4) and progressive disease (patient 5) before

completion of the pharmacokinetic part of the study. Six patients (patients: 1, 2, 6, 7, 8, and 9) completed the pharmacokinetic part of the study and were therefore evaluable.

Table 1: Patient characteristics

Parameter	N
Number of patients:	
total (evaluable)	9 (6)
Sex:	
Male	5
female	4
Age:	
median (range)	52 (47-72)
WHO status:	
0	3
1	4
2	2
Pathological diagnosis:	
NSCL	4
UCC	2
Mamma	1
Ewing sarcoma	1
Oesophageal	1
Prior treatment:	
Chemotherapy	9
Radiotherapy	6
Surgery	4

Pharmacokinetic and statistical analysis

Figure 2 depicts the plasma pharmacokinetic profiles of docetaxel (Figure 2a) and ritonavir (Figure 2b.) after treatment with the docetaxel and ritonavir formulations. Table 2 lists for each treatment the characteristic pharmacokinetic parameters of docetaxel and ritonavir: Tmax, Cmax, AUC0-Inf, T1/2, and MRT. Paired t-tests revealed no significant differences in the pharmacokinetic parameters of docetaxel between the ModraDoc001 10 mg capsule, the ModraDoc003 10 mg tablet and the ModraDoc004 10/50 mg tablet, nor were there any significant differences in the pharmacokinetic parameters of ritonavir between the ritonavir 100 mg capsule and the ModraDoc004 10/50 mg tablet.

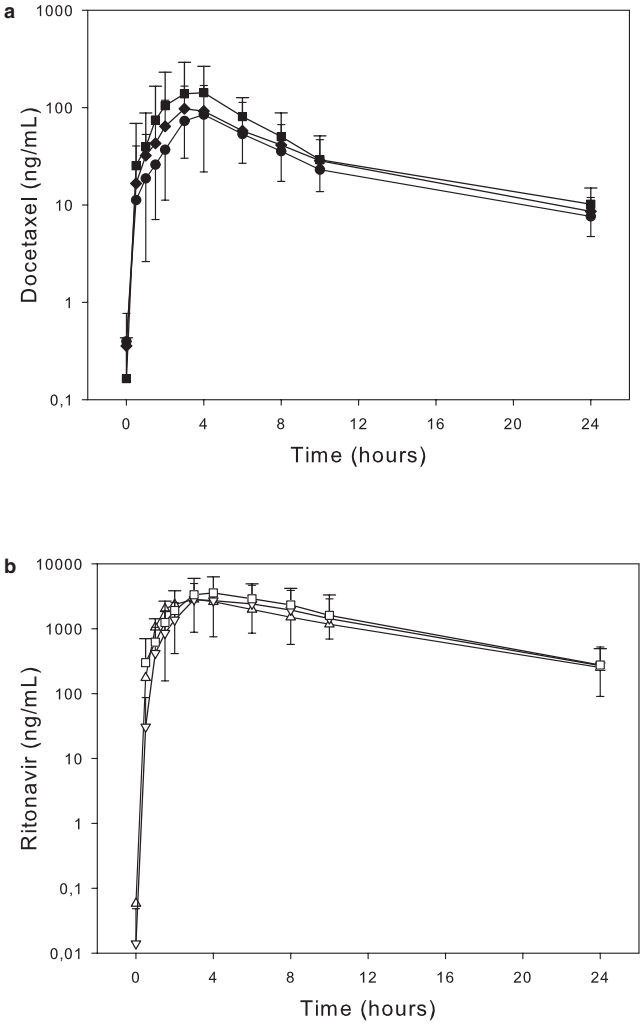

Figure 2: Log plasma concentration of docetaxel (a) and ritonavir (b) vs. time curves of 40 mg docetaxel (p.o.) administered concomitantly with 200 mg ritonavir (p.o.) (n=6, mean and SD).There is no significant difference in the exposure to docetaxel between the single drug formulations (ModraDoc001 10 mg capsule and ModraDoc003 10 mg tablet) and the fixed-dose combination tablet (ModraDoc004 10/50 mg tablet). There is no significant difference in the exposure to ritonavir between the single drug formulation (ritonavir 100 mg capsule) and the fixed-dose combination tablet (ModraDoc004 10/50 mg tablet).

Table 2: Pharmacokinetic parameters of docetaxel and ritonavir formulations after oral administration

Docetaxel	ModraDoc001 10 mg capsule[a]	ModraDoc003 10 mg tablet[a]	ModraDoc004 10/50 mg tablet[a]
T_{Max} (h)	4.2 ± 1.6 (38%)	5.3 ± 2.9 (55%)	3.7 ± 1.4 (37%)
C_{max} (ng/mL)	107 ± 50 (47%)	115 ± 74 (64%)	161 ± 143 (89%)
$AUC_{0\text{-}inf}$ (ng · h/mL)	731 ± 223 (30%)	882 ± 437 (50%)	1144 ± 864 (76%)
$T_{1/2}$ (h)	8.0 ± 2.3 (29%)	8.3 ± 3.4 (42%)	8.1 ± 3.3 (41%)
MRT (h)	11.8 ± 1.9 (16%)	12.6 ± 3.4 (27%)	11.4 ± 3.2 (28%)
Ritonavir	**Ritonavir 100 mg capsule[a,b]**	**Ritonavir 100 mg capsule[a]**	**ModraDoc004 10/50 mg tablet[a]**
T_{Max} (h)	4.2 ± 2.9 (70%)	3.6 ± 1.5 (42%)	4.0 ± 1.1 (27%)
C_{max} (ng/mL)	3383 ± 1901 (56%)	3957 ± 2328 (59%)	3813 ± 2582 (68%)
$AUC_{0\text{-}inf}$ (ng · h/mL)	29122 ± 13761 (47%)	30488 ± 21971 (72%)	35815 ± 29385 (82%)
$T_{1/2}$ (h)	6.8 ± 3.1 (46%)	5.7 ± 1.1 (19%)	5.3 ± 1.3 (24%)
MRT (h)	11.3 ± 4.2 (37%)	10 ± 2.2 (22%)	9.9 ± 2.3 (23%)

[a] Values are means ± standard deviation and coefficients of variation (%) of 6 patients; [b] Two patients received ritonavir 100 mg tablets instead of ritonavir 100 mg capsules; T_{max}, time at which the maximum plasma concentration is reached; C_{max}, maximum plasma concentration; $AUC_{0\text{-}Inf}$, area under the plasma concentration time curve from 0h to infinite time; $T_{1/2}$,elimination half-life; MRT, mean residence time.

Table 3 lists the results of the bioequivalence evaluation of the tested docetaxel and ritonavir formulations. The analysis of variance revealed no significant period or sequence effects for any treatment. The point estimates for Cmax and AUC0-Inf of docetaxel of the ModraDoc004 10/50 mg tablet were respectively 32% and 39% higher when compared to the ModraDoc001 10 mg capsules, and 48% and 30% higher when compared to the ModraDoc003 10 mg tablet. The point estimate for Cmax and AUC0-Inf of ritonavir were 4% and 14% higher for the ModraDoc004 10/50 mg tablet when compared to the ritonavir 100 mg capsule.

Table 3: Statistical bioequivalence evaluation of docetaxel and ritonavir formulations

	ModraDoc003 10 mg tablet[c] vs. ModraDoc001 10 mg capsule[c] (docetaxel)	ModraDoc004 10/50 mg tablet[c] vs. ModraDoc001 10 mg capsule[c] (docetaxel)	ModraDoc004 10/50 mg tablet[c] vs. ModraDoc003 10 mg tablet[c] (docetaxel)	ModraDoc004 10/50 mg tablet[c] vs. Ritonavir 100 mg capsule[d] (ritonavir)
C_{max} [a,b]	0.89 (0.39 - 2.04)	1.32 (0.59 - 2.95)	1.48 (0.64 - 3.44)	1.04 (0.83 - 1.31)
$AUC_{0\text{-}Inf}$ [a,b]	1.07 (0.6 - 1.92)	1.39 (0.95 - 2.02)	1.30 (0.72 - 2.34)	1.14 (0.93 - 1.41)

[a]Values are the differences of the geometric mean and their 90% confidence intervals; [b]C_{max} and $AUC_{0\text{-}Inf}$ are considered bioequivalent when the 90% confidence interval of the difference of the geometric means falls within the 0.80 to 1.25 bioequivalence interval; [c]n=6; [d]Total n=12 of which n=10 ritonavir 100 mg capsules and n=2 ritonavir 100 mg tablets

Safety evaluation

Oral docetaxel was overall well tolerated. The most common adverse event which are possibly, probably or definitely related to the study drug, were nausea (78%), diarrhea (78%) and fatigue (67%), the majority being grade 1-2. Two patients experienced a drug-related grade 3 toxicity. In both patients the adverse event was fatigue which occurred after completion of the pharmacokinetic part of the study, i.e. during treatment with 80 mg of docetaxel and 100 mg of ritonavir. One of the patients experiencing grade 3 fatigue had already experienced grade 1 fatigue before start of the study.

Discussion

To obtain information about the in vivo release rates of docetaxel and ritonavir all formulations were subjected to an in vitro dissolution test. The in vitro dissolution test revealed clear differences between the capsule and tablet formulations (Figure1). The tablet formulations exhibited a gradual release rate of the active substance, which is a typical release profile for eroding tablets. In contrast, the capsule formulations initially had a very limited dissolution rate followed by a burst release of the active substance upon penetration of the capsule shell. During the burst release approximately 60% of the

active substance was released within 5 minutes. The difference in capsule shell material is probably responsible for the difference in in vitro release rates of docetaxel and ritonavir from the ModraDoc001 10 mg capsule and the ritonavir 100 mg capsule (Figure 1).
More importantly, the in vitro release rates of docetaxel from the ModraDoc001 10 mg capsule and the ModraDoc003 10 mg tablet were higher compared to the in vitro release rates of ritonavir from the ritonavir 100 mg capsule and the ritonavir 100 mg tablet (Figure 1). This could indicate that in vivo docetaxel is released prior to ritonavir, which could lead to precipitation or degradation of docetaxel [8, 11, 12] resulting in a lower amount of docetaxel absorbed. In contrast, the ModraDoc004 10/50 mg tablet released docetaxel and ritonavir in vitro simultaneously (Figure 1); this is an indication that the ModraDoc004 10/50 mg tablet will release docetaxel and ritonavir in vivo at the same time as well.
Because the ritonavir 100 mg capsule ran out of stock before all patients had completed the pharmacokinetic part of the study, we were forced to use the ritonavir 100 mg tablet in combination with the ModraDoc001 10 mg capsule for patient 8 and 9. Unfortunately, use of the ritonavir 100 mg tablet under fasting conditions could significantly increase the $AUC_{0\text{-}inf}$ (>40%) and C_{max} (>65%) of ritonavir compared to the use of ritonavir 100 mg capsule [22]. However, patient 8 and 9 did receive the ritonavir 100 mg capsule in combination with the ModraDoc003 10 mg tablet. This enabled us to assess the impact of changing the ritonavir formulation on the individual pharmacokinetic parameters of ritonavir. Because for both patients there were no significant differences in the $AUC_{0\text{-}inf}$ and C_{max} of ritonavir between both ritonavir formulations, we included the results of the ritonavir 100 mg tablet and the ModraDoc001 10 mg capsule in the pharmacokinetic and statistical analysis.
For all formulations, the values of the pharmacokinetic parameters of docetaxel (Figure 2a and Table 2) were comparable to the values established in the Phase I dose escalation study [10]. The exposures to ritonavir ($AUC_{0\text{-}inf}$) after administration of the ritonavir 100 mg capsule (Figure 2b and Table 2) were higher and more variable than the exposure to ritonavir reported in the Summary of Product Characteristics (SPC) of NORVIR [15]. The differences between the values reported in the SPC and our values could very well be due to the low number of patients in our study. Because ritonavir is primarily responsible for the oral bioavailability of docetaxel [7, 23] the high variability in the C_{max} and $AUC_{0\text{-}inf}$ of docetaxel can to a large part be attributed to the high variability of the

pharmacokinetic parameters of ritonavir (Table 2).

By calculating the exposure ratio of docetaxel and ritonavir the variability in the exposure to the boosted drug caused by the variability of the booster drug is removed. The ModraDoc001 10 mg capsule had a mean docetaxel/ritonavir exposure ratio of 0.028 ± 0.0074 (27%), the ModraDoc003 10 mg tablet had a mean docetaxel/ritonavir exposure ratio of 0.031 ± 0.0089 (29%), and the ModraDoc004 10/50 mg tablet had a mean docetaxel/ritonavir exposure ratio of 0.034 ± 0.0061 (18%). For all formulations the variability in the exposure ratio is considerably lower than the variability in the exposures to docetaxel. This result strengthens the hypothesis that most of the exposure variability of docetaxel is caused by ritonavir. Furthermore, the tendency towards a higher and less variable docetaxel/ritonavir exposure ratio for the ModraDoc004 10/50 mg tablet might indicate that the FDC tablet is the most effective formulation.

Although not significant, the exposures to docetaxel and ritonavir were higher after administration of the ModraDoc004 10/50 mg tablet compared to the other two treatment regimens (Figure 2 and Table 2). This difference was primarily caused by patient no. 2 who had a remarkably high exposure to docetaxel ($AUC_{0\text{-}inf}$ 2881 ng · h/mL) and ritonavir ($AUC_{0\text{-}inf}$ 94165 ng · h/mL) compared to the other patients. These high exposures coincided with the occurrence of pneumonia in patient no. 2 and the subsequent treatment with amoxicillin and clavulanic acid. It is not likely that amoxicillin or clavulanic acid caused the increased exposure, because there are no indications that these drugs act on the CYP3A4 enzyme system or on P-glycoprotein pumps [24, 25]. However, there is strong evidence that patients with an acute inflammatory reaction have reduced expression of the CYP3A4 enzyme system [26, 27]. Moreover, the average exposure to ritonavir in patient no. 2 was considerable higher compared to the average exposure to ritonavir in the other: 72390 ± 21913 ng · h/mL vs. 23692 ± 8189 ng · h/mL. Furthermore, excluding patient no. 2 from the dataset would lower the mean exposure and inter-patient variability of docetaxel and ritonavir and would decrease the differences in exposure between the formulations. In addition to this, without patient no. 2 the exposures to ritonavir for both the ritonavir 100 mg capsule and the ModraDoc004 10/50 mg tablet would be in line with the exposure to ritonavir reported in the SPC of NORVIR [15]. In conclusion, most likely the occurrence of pneumonia in patient no. 2 led to a decreased activity of the patients CYP3A4 enzyme system which caused a decreased clearance of ritonavir and finally resulted in an increased exposure to ritonavir and docetaxel.

As this study was not designed to assess the bioequivalence of the docetaxel and ritonavir formulations it was expected that the low number of patients would cause the 90% confidence intervals to be outside the bioequivalence limits (Table 3). The higher point estimates for the C_{max} and $AUC_{0\text{-}inf}$ of ritonavir of the ModraDoc004 10/50 mg tablet are probably a combined effect of the solid dispersion formulation and administration of the formulations under fasting conditions. Bioequivalence studies between solid dispersion and liquid filled capsule formulations of ritonavir (NORVIR and KALETRA) have shown an increased exposure to ritonavir after administration of solid dispersion formulations, especially under fasting conditions [22, 28]. The higher point estimates for the C_{max} and $AUC_{0\text{-}inf}$ of docetaxel of the ModraDoc004 10/50 mg tablet might be the result of the higher exposure to ritonavir and the simultaneous release of docetaxel and ritonavir throughout the gastrointestinal tract. Excluding patient no. 2 from the bioequivalence calculations decreased the differences between the docetaxel and ritonavir formulations, although the point estimate for the $AUC_{0\text{-}Inf}$ of docetaxel of the ModraDoc004 10/50 mg tablet remained 19% higher compared to the ModraDoc001 10 mg capsule and the ModraDoc003 10 mg tablet.

Conclusions

In this study we have shown that the single drug formulations of docetaxel, the ModraDoc003 10 mg tablet and the ModraDoc001 10 mg capsule, gave a comparable exposure to docetaxel after oral administration in combination with ritonavir. Furthermore we have shown that the FDC tablet of docetaxel and ritonavir, the ModraDoc004 10/50 mg tablet, gave exposures to docetaxel and ritonavir comparable to single drug formulations. In addition to this, we found a tendency towards a higher and less variable docetaxel/ritonavir exposure ratio for the FDC tablet; this is probably the result of a simultaneous release of docetaxel and ritonavir in the gastrointestinal tract. We have now presented three promising oral formulations of docetaxel to be further investigated in clinical phase I, II and III trials.

References

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Chapter 8

Summary, Conclusions and Perspectives

Summary and Conclusions

Despite the development and approval of new anticancer agents, taxanes remain at the cornerstone of adjuvant and metastatic chemotherapy against solid tumors. Because of their anti-mitotic mechanism of action it is believed that chronic treatments regimens could result in increased efficacy of taxanes. However, to make patient convenient chronic treatment regimens possible new oral formulations of the most widely used taxanes paclitaxel and docetaxel are warranted.

Our group started pre-clinical studies to unravel the mechanism behind the low bioavailability of paclitaxel some 25 years ago and showed that the P-glycoprotein (PgP) plays a pivotal role [1, 2]. These promising pre-clinical results led to phase I clinical trials in which the exposure of orally administered paclitaxel and docetaxel was increased by concomitant administration of the PgP-inhibitor cyclosporin A [3-5]. Over the years a number of oral paclitaxel formulations in combination with cyclosporin A were tested [6-8]. However, clinical development of these formulations was put on hold due to the unfavorable safety profile and the impractical formulation of cyclosporin A.

More recently we showed that the exposure to orally administered docetaxel could be increased by concomitant administration of ritonavir as well [9]. Although the bioavailability of paclitaxel was thought to be mainly inhibited by PgP efflux pumps, we showed that paclitaxel could also be boosted by ritonavir [10, 11]. Boosting of paclitaxel and docetaxel with ritonavir instead of cyclosporin A is preferred because ritonavir is effective in relatively low doses of 100 to 200 mg, it is supplied in a practical formulation, and it has proven to be a safe pharmacokinetic booster for various anti-retroviral drugs [10].

With a suitable pharmacokinetic booster at hand the only remaining hurdle for physicians to start developing oral taxane treatment regimens was the availability of clinically feasible oral formulations of docetaxel and paclitaxel which could replace the unpractical and inconvenient IV premix solution.

The aim of this thesis was to develop oral dosage forms of docetaxel and paclitaxel with increased solubilities and dissolution rates in-vitro. The increased solubility and dissolution rate in vitro should result in an improved pharmaceutical availability of docetaxel and paclitaxel in the gastrointestinal tract. In combination with ritonavir, this should lead to clinically relevant exposures to docetaxel and paclitaxel.

Our review of pre-clinical and clinical oral formulations of docetaxel and paclitaxel

showed that a wide variety of formulation strategies have been applied to improve the low oral bioavailability of docetaxel and paclitaxel (Chapter 2). However, to date most of the formulations have only been tested in the lab or in pre-clinical studies. A few formulations have reached the clinic but development was halted because of the safety profile of the pharmacokinetic booster cyclosporin A [6-8].

Currently, one oral formulation of docetaxel and three oral formulations of paclitaxel are in active clinical development. The first two formulations are described in this thesis and make use of the Modulated Drug Absorption (Modra) concept by combining oral solid dispersion formulations of docetaxel (ModraDoc) and paclitaxel (ModraPac) with the pharmacokinetic booster ritonavir. The third formulation, currently under phase II clinical investigation, is a combination of paclitaxel and the novel PgP-inhibitor HM30181 (Oraxol) [12-14]. Unfortunately the composition of this formulation nor pharmacokinetic data is publicly available. The fourth oral formulation, currently in phase III testing, is the lipid based paclitaxel formulation DHP107 [15-17]. DHP107 is developed without a PK booster, however the oral bioavailability of paclitaxel seems to be lower than the ritonavir boosted ModraPac formulation (Chapter 2).

Although a typical solid oral dosage such as a capsule or tablet is easy to use and patient convenient , the very low solubilities of docetaxel and paclitaxel [18, 19] posed a major pharmaceutical development challenge. It was expected that the low solubility would inevitably lead to low dissolution rates from typical solid oral formulations which would negatively affect their oral bioavailability. We therefore chose to combine our successful boosting strategy [10, 20] with a solid dispersion formulation of docetaxel or paclitaxel.

A solid dispersion formulation consists of a crystalline or amorphous drug that is molecularly dispersed in a hydrophilic matrix or carrier [21-23]. The large surface area of the drug particles, the intimate 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 [24].

We showed that freeze-drying of crystalline docetaxel dissolved in a water/tert-butyl alcohol (TBA) mixture resulted in amorphous docetaxel (Chapter 3). When amorphous docetaxel was combined with polyvinylpyrrolidone (PVP)-K30 and sodium lauryl sulphate (SLS) in a physical mixture the dissolution rate was significantly improved. An even higher apparent solubility and dissolution rate was reached when docetaxel,

PVP-K30, and SLS were freeze-dried simultaneously to form a solid solid dispersion (ModraDoc001 SD powder). Using X-ray powder diffraction (XRD) and modulated differential scanning calorimetry (mDSC) we showed that docetaxel and PVP-K30 were amorphous in the freeze-dried solid dispersion. SLS however, remained at least partially crystalline. Furthermore, we showed that SLS was essential for improving the dissolution rate of ModraDoc001 SD powder encapsulated in hard gelatin capsules (ModraDoc001 15 mg capsules).

In a subsequent phase I clinical trial, with ritonavir as pharmacokinetic booster, we found no significant differences between the pharmacokinetic parameters of docetaxel after administration of the docetaxel premix solution or the ModraDoc001 15 mg capsule. Even more, there was a trend towards a lower variability in exposure to docetaxel after oral administration of the ModraDoc001 15 mg capsule (513 ± 219 vs. 790 ± 669 ng·h/mL). This low inter-individual variability of docetaxel exposure (44%), the dosing accuracy, and the absence of ethanol and polysorbate were considered major advantages of ModraDoc001 15 mg capsules over the docetaxel premix solution. Based on these results it was decided to test the ModraDoc001 formulation in a phase I dose escalation study of oral docetaxel. We further improved the encapsulation properties of the ModraDoc001 SD powder by adding lactose monohydrate and colloidal silica; in addition the amount of docetaxel per capsule was reduced to 10 mg (ModraDoc001 10 mg capsule) to facilitate the incremental dosing in the dose escalation study. Stability tests performed on the ModraDoc001 10 mg capsule showed that docetaxel was chemically and physically stable during 2 years of storage at 2-8°C and at 25°C / 60% RH.

Following the success of the ModraDoc001 SD formulation of docetaxel we started the development of an oral formulation with paclitaxel (Chapter 4). Hanssen solubility parameters suggested that paclitaxel might be able to form an even beter solid dispersion with PVP-K30 and SLS compared to docetaxel. After we confirmed that paclitaxel could be rendered amorphous by freeze drying, we showed with dissolution screening experiments that the optimal solid dispersion for paclitaxel indeed contained 1/11 w/w paclitaxel, 9/11 w/w PVP-K30 and 1/11 w/w SLS (ModraPac001 SD powder). Further analysis of the solid dispersion formulation by XRD, Fourier transform infrared (FT-IR) spectroscopy, and mDSC confirmed the amorphous nature of paclitaxel, and the fine dispersion of paclitaxel in the matrix of PVP-K30 and SLS. The ModraPac001 SD powder was mixed with lactose and colloidal silica and encapsulated in hard gelatin

capsules (ModraPac001 10 mg capsule).

To test the clinical significance of the improved apparent solubility and dissolution rate of paclitaxel, the pharmacokinetic parameters of paclitaxel were compared between the ModraPac001 10 mg capsule and the paclitaxel premix solution in four patients with advanced cancer. There were no significant differences in the pharmacokinetic parameters of paclitaxel between the two formulations, and oral administration of ModraPac001 resulted in clinically relevant systemic exposure to paclitaxel [25, 26]. Because of the comparable pharmacokinetic parameters and the favorable pharmaceutical characteristics, such as the neutral taste, dosing accuracy, and the two-year ambient shelf life, the ModraPac001 10 mg capsule was selected for a phase I study into oral low dose metronomic treatment with paclitaxel.

In Chapter 3 and 4 we showed that the improved dissolution rate of the amorphous solid dispersions (ModraDoc001 and ModraPac001) was due to the higher apparent solubility of the amorphous active ingredient, the increased surface area of the finely dispersed active ingredient, and an improved wetting of the active ingredient by the hydrophilic carrier PVP-K30 and the surfactant SLS [27, 28]. Hence to ensure a reproducible pharmaceutical availability of the active ingredient it is of prime importance that these characteristics are maintained throughout the pharmaceutical shelf life.

Solid dispersion excipients are vital to maintain the amorphous state of the active ingredient upon storage and after dissolution [22, 29, 30]. The selection process of the excipients should therefore take into account physical and chemical stability, and initial and long term dissolution performance. In principle, crystallization of amorphous substances occurs above the glass transition temperature (Tg). However, molecular mobility already occurs above the Kauzmann temperature, which is 50 °C below the Tg [31]. In addition to this, the Tg can be substantially lowered by the plasticizing effect of water.

Another threat to the stability of amorphous solid dispersion is phase separation of the amorphous solid dispersion components. Phase separation is induced by the absorption of water and decreases the interaction between the hydrophobic drug and the hydrophilic solid dispersion excipients. The decreased interaction could lead to decreased dissolution performance especially if phase separation results in crystallization of the amorphous active ingredient [24, 32]. In conclusion, the two most important factors which influence the physical and chemical stability of amorphous solid dispersion formulations are

humidity and temperature.

As the standard tests and specification used during the preliminary stability testing of ModraDoc001 and ModraPac001 10 mg capsules were not expected to detect these subtle changes we decided to analyze the stability samples using XRD, mDSC, FT-IR and dissolution screening experiments (Chapter 5). We showed that upon stability the amount of water in the ModraDoc001 and ModraPac001 SD powder increased from 6.3% w/w to 27% w/w (dried weight). This facilitated the total removal of TBA (3.4% w/w to 0.12% w/w dried weight) and induced phase separation of SLS. Despite these changes both docetaxel and paclitaxel remained amorphous and no chemical degradation was observed. Furthermore, it was hypothesized that phase separation of SLS made way for stronger interactions between docetaxel and PVP-K30 which led to an increased time to precipitation. Nevertheless, phase separation of SLS did lead to a decreased wetting of the PVP based solid dispersion which resulted in a significant change in the dissolution profile after more than 52 weeks of storage at 25 °C /60% RH.

In Chapter 3 and 4 we showed that clinically relevant exposures to docetaxel and paclitaxel could be reached by combining the pharmacokinetic booster ritonavir with the solid dispersion formulations of docetaxel and paclitaxel [27, 33]. Although the ModraDoc001 and ModraPac001 capsules proved to be suitable for phase I clinical testing their labor intensive and low capacity manufacturing method was not considered suitable to support future phase II and III clinical trials. Hence, a new manufacturing method suitable for large scale manufacturing was warranted for the SD powders.

For large scale manufacturing of the SD powder spray drying was chosen over freeze-drying because it is a well-established and industrially scalable method. Furthermore, it can be used in continuous processing, and it is a cheap, fast, and one step process. Moreover, spray drying allows for control of the size, density and morphology of the particles which aids downstream processing of the SD powder into tablets [34, 35].

Special formulations such as micellar solutions (docetaxel premix solution) and solid dispersions (ModraDoc001 10 mg capsule) can increase the pharmaceutical availability of docetaxel. However, over time these formulations cannot prevent docetaxel precipitation or degradation in the gastrointestinal tract [27, 36, 37]. It is therefore essential that the pharmacokinetic booster ritonavir is present to promote rapid absorption of the dissolved docetaxel before the onset of degradation or precipitation [20]. Given the available docetaxel and ritonavir formulations we were not fully able to fulfill this

prerequisite. After oral administration of the premix micellar solution, docetaxel will be immediately available for absorption while the hard capsule shell of the ritonavir formulation will first have to be penetrated before ritonavir can be released. Indeed, administration of the ritonavir formulation 60 minutes prior to administration of the docetaxel micellar solution showed a tendency towards a higher exposure to docetaxel compared to simultaneous administration of both formulations [20]. Moreover, both theory and practice show that the timing and site of the ritonavir release relative to the docetaxel release influence the absorption of docetaxel. Consequently, docetaxel and ritonavir have to be released at the same time at the same site to achieve optimal pharmacokinetic boosting of docetaxel.

A fixed-dose combination (FDC) tablet of docetaxel and ritonavir has potentially several advantages over single agent formulations. First of all, patient convenience and compliance is likely to improve due to the reduced number of dosage units and the simplified dosing schedule [38]. Secondly, the FDC tablet eliminates the possibility that docetaxel is administered without its pharmacokinetic booster ritonavir. Finally, simultaneous release of docetaxel and ritonavir could probably increase the exposure to docetaxel and decrease its variability. In conclusion, we decided to develop a fixed-dose combination formulation of docetaxel and its pharmacokinetic booster ritonavir to further improve patient convenience.

Because of its low solubility and permeability ritonavir is classified as a class IV drug according to the biopharmaceutical classification system [39, 40]. Hence, like docetaxel it also needed a special formulation to improve its pharmaceutical and biological availability. Inclusion of ritonavir into the SD matrix of PVP-K30 and docetaxel was chosen to be the best way forward. However, inclusion of both ritonavir and docetaxel in the SD powder and FDC tablet may not negatively influence their release rates and oral bioavailability. Moreover, it was essential that spray drying produced SD powder that was chemically and physically comparable to the previously developed freeze-dried product.

In Chapter 6 we show with XRD, mDSC, and FT-IR analysis that the spray dried SD powders of docetaxel and ritonavir are fully amorphous and suggested a molecular distribution of docetaxel and ritonavir in the PVP-K30/SLS matrix. In contrast to the freeze-dried SD powders SLS was amorphous and/or molecularly dispersed over docetaxel, ritonavir, and PVP-K30 in the spray dried SD powder. This was a clear

indication that this might result in increased and simultaneous dissolution rates in-vivo and in-vitro. It was concluded that spray drying produced comparable or better SD powder than freeze-drying. It was advised to further optimize the spray drying process to reduce the residual solvents and, more importantly, to optimize the powder flow characteristics to enable automated compaction of spray dried SD tablets of docetaxel and ritonavir.

Release rates of docetaxel and ritonavir from single agent tablets and FDC tablets were comparable and depended on the release of PVP-K30. The simultaneous release rate of docetaxel and ritonavir from the FDC tablets was considered a major advantage for clinical applications and was hypothesized to increase the in-vivo exposure to docetaxel. Based on the results of the spray drying experiments it was decided to compare the ModraDoc001 10 mg capsule to the new spray dried tablet formulations in a phase I clinical study. By then, parallel clinical studies with the ModraDoc001 10 mg capsule had shown that CYP3A4 inhibition in the liver and gut wall is primarily responsible for the increase in docetaxel exposure and that. 200 mg ritonavir leads to a higher exposure to docetaxel compared to 100 mg of ritonavir [41]. At the same time, the preliminary conclusion of the ongoing dose escalation study was that 60 mg of docetaxel and 200 mg of ritonavir was a safe dose. Therefore, the dosing level for the crossover study was defined at 40 mg docetaxel and 200 mg ritonavir. To match the amount of docetaxel in the existing formulation of docetaxel it was decided to prepare a single agent tablet containing 10 mg of docetaxel (ModraDoc003 10 mg tablet) and a FDC tablet containing 10 mg of docetaxel and 50 mg of ritonavir (ModraDoc004 10/50 mg tablet).

The stability of the new formulations was evaluated using the methods described in Chapter 5. Although water absorption by the spray dried SD powders during storage caused no crystallization of docetaxel or ritonavir it did induce phase separation of SLS which led to a decreased in-vitro dissolution performance. ModraDoc003 10 mg tablets were considered stable at ambient conditions for at least 52 weeks while the ModraDoc004 10/50 mg tablets were considered stable at ambient conditions for at least 25 weeks.

The phase I cross over study described in Chapter 7 concluded that the single agent formulations of docetaxel, the ModraDoc003 10 mg tablet and the ModraDoc001 10 mg capsule, gave a comparable exposure to docetaxel after oral administration in combination with ritonavir. Furthermore, we showed that the FDC tablet of docetaxel

and ritonavir, the ModraDoc004 10/50 mg tablet, gave exposures to docetaxel and ritonavir comparable to single agent formulations. In addition to this, a tendency towards a higher and less variable docetaxel/ritonavir exposure ratio found for the FDC tablet,was hypothesized to be the result of a simultaneous release of docetaxel and ritonavir in the gastrointestinal tract.

In conclusion we developed oral solid dispersion formulations of docetaxel, paclitaxel, and docetaxel/ritonavir using freeze-drying and spray drying as preparation methods. Analysis of the solid dispersion formulations by XRD, mDSC, FT-IR, and dissolution testing showed a good stability profile which could be further improved by limiting the absorption of water. The solid dispersion formulations increased the solubilities and dissolution rates of the active ingredients which resulted in clinically relevant exposures to docetaxel and paclitaxel. To date (July 2013), the ModraDoc001 10 mg capsules have been used by 97 patients in ongoing phase I clinical studies [42, 43] while the ModraPac001 capsules were administered to 21 patients [44]. In general, the capsules were well tolerated and were considered easy to use. Moreover, based on the studies described in this thesis it can be concluded that we developed clinically feasible oral formulations of paclitaxel, docetaxel and docetaxel/ritonavir which made way for development of oral chronic anticancer treatment with taxanes.

Perspectives

The studies described in this thesis prove that oral administration of docetaxel and paclitaxel is feasible by combining the pharmacokinetic booster ritonavir with oral solid dispersion formulations.

It would be of interest to elucidate the molecular interactions between the solid dispersion components and the effect of the preparation methods on these molecular interaction. Especially the difference in the molecular structure of SLS after freeze-drying or spray drying is of interest because of the observed phase separation of SLS during stability. Dynamic vapor sorption (DVS) studies on solid dispersions with various weight ratios could measure the degree of hydrophobization which could give more insight in the molecular interactions between the active ingredients and PVP-K30 [45–47].

Given the importance of the amorphous nature of the solid dispersion and the inability of

FT-IR to readily detect changes it is advised to make XRD and/or mDSC analysis part of the release and stability testing. Hence, a standard test procedure and specifications should be developed for these techniques.

The clinical relevance of changes upon storage or batch-to-batch differences in in-vitro dissolution profiles should be tested to be able to set proper release and stability specifications. Additional pre-clinical tests with physical mixtures and stress tested solid dispersion formulations in combination with optimization of the in-vitro dissolution method could be used to establish in-vivo – in-vitro correlation (IVIVC) for the solid dispersion formulations of docetaxel and paclitaxel. Once established IVIVC could aid in assessing the stability of the solid dispersion formulations and provide performance boundaries for future formulations [48].

It is advised to select air tight packaging materials and provide individual packaging of the solid dispersion formulations to prevent water mediated phase separation of SLS and a decreased dissolution performance. This should increase the pharmaceutical shelf life and consequently the applicability in outpatient treatment. It could also be considered to apply protective coatings, although care should be taken not to influence release characteristics.

Although we showed that the solid dispersion formulation was improved by spray drying we were initially only able to produce spray dried solid dispersion tablets by manual compaction due to the poor powder characteristics. We recently improved the powder flow properties by adding large amounts of filler (80% w/w), which enabled large scale automated manufacturing of docetaxel and paclitaxel tablets. However, optimization of the spray dried product is still warranted [49]. Even more because the large amount of filler excludes the manufacturing of higher strengths and FDC tablets. If this cannot be achieved using spray drying, other manufacturing methods such as hot melt extrusion (HME) could be considered [50]. In this perspective, HME is also attractive from a stability perspective as it is a solvent-free manufacturing method.

In line with the FDC tablet of docetaxel and ritonavir it would be beneficial to develop an FDC of paclitaxel and ritonavir. Hanssen solubility parameters and preliminary experiments already indicated that paclitaxel and ritonavir could form a fully amorphous solid dispersion.

The results of the ongoing dose escalation studies with oral docetaxel and oral paclitaxel should define preferred daily and weekly dosing of docetaxel, paclitaxel and ritonavir.

Based on the established dose suitable strengths should be selected for both the single agent and FDC tablets. From a manufacturing point of view the number of tablet strengths should be kept at a minimum and would preferably be made from a single SD powder strength. However, from a patient and clinician of view the amount of tablets to be taken per dose should be as low as possible, the tablet size should be acceptable to prevent swallowing problems, and the tablet strength combination would allow for common dose reductions of 25% and 50%. Once the final formulations have been made a crossover study should be conducted to determine the bioequivalence between the new and old formulations.

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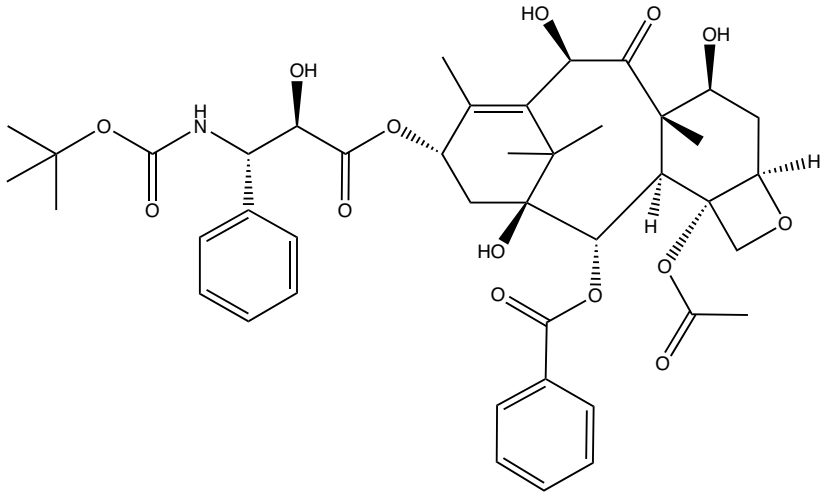
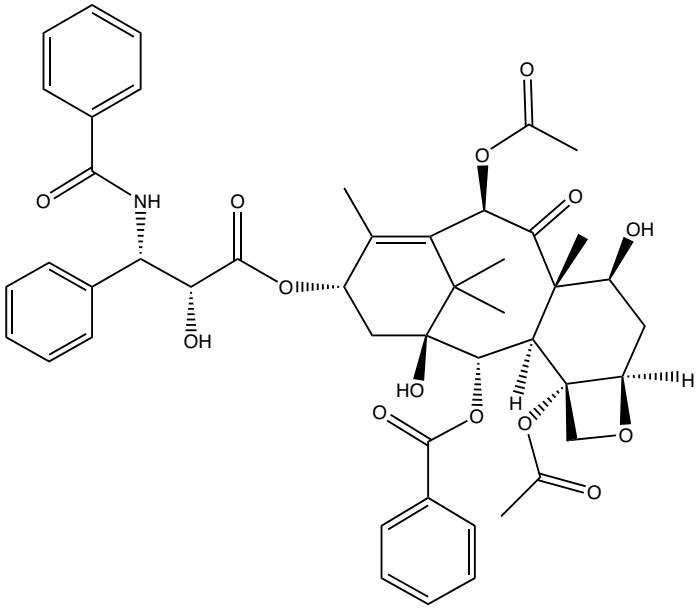
Chemical Structures



Docetaxel



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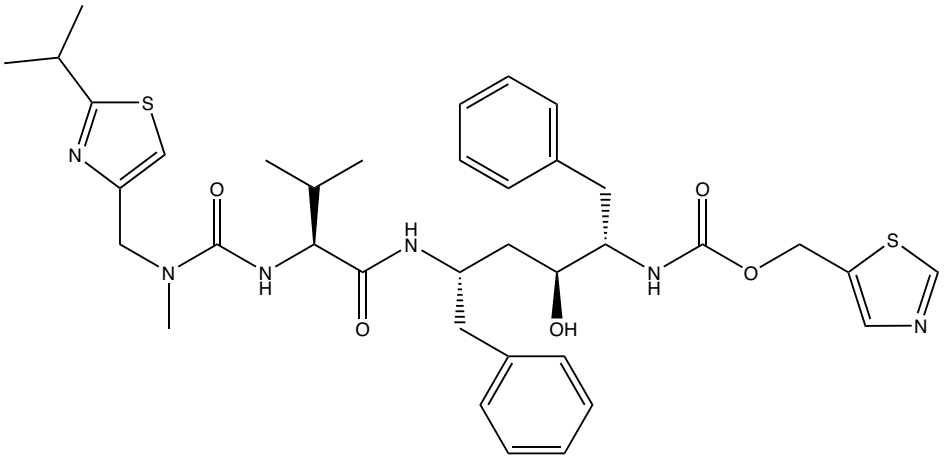

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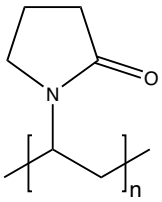
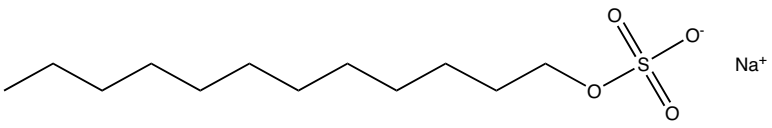


Polyvinylpyrrolidone



Sodium lauryl sulfate

Samenvatting en Conclusies

Ondanks de introductie van nieuwe antikanker middelen blijven de taxanen een essentieel onderdeel van (adjuvante) chemotherapie tegen solide tumoren. Vanwege hun antimitotische werking is de verwachting dat chronische toediening de werkzaamheid van taxanen zou kunnen verbeteren. Om patiëntvriendelijke chronische toediening mogelijk te maken zijn er wel nieuwe orale formuleringen van de meest gebruikte taxanen, docetaxel en paclitaxel, nodig.

Ongeveer 25 jaar geleden startte ons onderzoek naar de oorzaak van de lage orale biologische beschikbaarheid van paclitaxel. Met preklinische onderzoek toonden we aan dat het P-glycoproteïne (PgP) hierbij een belangrijke rol speelt [1, 2]. Deze veelbelovende preklinische resultaten leidden tot fase I klinisch onderzoek waarin we de blootstelling aan oraal toegediend paclitaxel en docetaxel verhoogden door gelijktijdige toediening van de PgP-remmer cyclosporine A [3-5]. Hierna zijn verscheidene orale formuleringen van paclitaxel getest in combinatie met cyclosporine A [6-8]. De verdere klinische ontwikkeling van deze formuleringen werd echter stopgezet vanwege het nadelige veiligheidsprofiel en de onpraktische formulering van cyclosporine A.

Enkele jaren geleden lieten we zien dat de blootstelling aan oraal toegediend docetaxel ook verhoogd kon worden door gelijktijdige toediening van ritonavir [9]. Hoewel tot dan toe werd aangenomen dat de biologische beschikbaarheid van paclitaxel voornamelijk werd gereduceerd door de PgP efflux pompen, bleek dat de blootstelling aan paclitaxel ook verhoogd kon worden door ritonavir [10, 11]. Het vergroten van de blootstelling aan paclitaxel en docetaxel door gebruik van ritonavir in plaats van cyclosporine A heeft de voorkeur omdat: ritonavir effectief is bij relatief lage doses (100 tot 200 mg), ritonavir beschikbaar is in een praktische orale formulering, en omdat ritonavir al lange tijd veilig gebruikt wordt als booster van meerdere antiretrovirale geneesmiddelen [10]. Met selectie van een geschikte farmacokinetische (PK) booster voor beide taxanen was de laatste barrière die medici weerhield van het ontwikkeling van orale therapieën het gebrek aan patiëntvriendelijke orale formuleringen van docetaxel en paclitaxel.

Het doel van het promotieonderzoek beschreven in dit proefschrift was de ontwikkeling van orale toedieningsvormen van docetaxel en paclitaxel met een hogere in-vitro oplosbaarheid en dissolutiesnelheid. De hogere in-vitro oplosbaarheid en dissolutiesnelheid zouden moeten leiden tot een verhoogde farmaceutische

beschikbaarheid in het maagdarmkanaal. In combinatie met ritonavir zou de hogere farmaceutische beschikbaarheid moeten leiden tot klinisch relevante spiegels van docetaxel en paclitaxel.

Ons overzicht van de (pre)klinische orale formuleringen van docetaxel en paclitaxel laat zien dat er vele formuleringsstrategieën zijn toegepast om de orale biologische beschikbaarheid van taxanen te verhogen (Hoofdstuk 2). Tot op heden zijn de meeste formuleringen echter alleen in-vitro of in preklinische studies getest. Enkele formuleringen zijn getest in patiënten maar de verdere ontwikkeling daarvan is gestopt vanwege het nadelige veiligheidsprofiel van cyclosporine A [6-8]. Op dit moment worden voor zover wij konden nagaan één formulering van docetaxel en drie formuleringen van paclitaxel onderzocht in de kliniek. De formulering van docetaxel en een van de formuleringen van paclitaxel zijn beschreven in dit proefschrift en maken gebruik van het Modulated Drug Absorption (Modra) concept. Zij combineren een orale solid dispersion formulering van docetaxel (ModraDoc) en paclitaxel (ModraPac) met de PK-booster ritonavir. De twee paclitaxel formulering wordt onderzocht in een fase II klinische studie en is een combinatie van paclitaxel en de nieuwe PgP-remmer HM30181 (Oraxol) [12-14]. Helaas is er nog niet gepubliceerd over de samenstelling van deze formulering of haar farmacokinetische eigenschappen. De derde orale paclitaxel formulering wordt in een fase III klinische studie getest. Het is een op vetten gebaseerde formulering genaamd DHP107 [15-17]. De onderzoekers claimen dat bij DHP107 het gebruik van een PK booster niet noodzakelijk is. In vergelijking met toediening van de ModraPac capsules en ritonavir lijkt de orale biologische beschikbaarheid van paclitaxel wel lager na toediening van DHP107 (Hoofdstuk 2).

Hoewel capsules en tabletten makkelijk zijn in te nemen en patiëntvriendelijk zijn zorgt de lage oplosbaarheid van docetaxel en paclitaxel [18, 19] ervoor dat de farmaceutische ontwikkeling van de standaard orale toedieningsvormen lastig is. De lage oplosbaarheid zou namelijk vrijwel zeker leiden tot lage dissolutiesnelheden wat de orale biologische beschikbaarheid negatief zou beïnvloeden. Vandaar dat we onze succesvolle PK-boosting strategie [10, 20] besloten te combineren met een solid dispersion van docetaxel en paclitaxel.

Een solid dispersion (SD) bestaat uit een kristallijne of amorfe actieve stof die moleculair is verdeeld over een hydrofiele matrix [21-23]. Het grote oppervlak van de actieve stof, de nabijheid van de zeer goed oplosbare matrix en de hogere schijnbare oplosbaarheid van

de amorfe toestand zijn verantwoordelijk voor de hoge dissolutiesnelheid van actieve stoffen in SD's. SD's zijn inmiddels succesvol toegepast bij verscheidene slecht oplosbare geneesmiddelen [24].

In hoofdstuk 3 laten we zien dat vriesdrogen van kristallijn docetaxel opgelost in water/tert-butanol mengsels resulteerde in amorf docetaxel. Wanneer amorf docetaxel fysisch werd gemengd met polyvinylpyrrollidone (PVP)-K30 en natrium lauryl sulfate (SLS) verbeterde de dissolutiesnelheid significant. De schijnbare oplosbaarheid en dissolutiesnelheid werd nog verder verhoogd door docetaxel, PVP-K30 en SLS vanuit één oplossing te vriesdrogen en een SD te vormen (ModraDoc001 SD powder). Met behulp van röntgen poederdiffractie (XRD) en *modulated differential scanning calorimetry* (mDSC) toonden we aan dat docetaxel en PVP-K30 als amorfe stoffen aanwezig waren in de SD. Dit in tegenstelling tot SLS dat in ieder geval gedeeltelijk als kristallijne stof aanwezig was. Daarnaast lieten we zien dat SLS essentieel was voor het verhogen van de dissolutiesnelheid van docetaxel in gecapsuleerd ModraDoc001 SD poeder (ModraDoc001 15 mg capsules). In de eerste klinische fase I studie met de ModraDoc001 15 mg capsule en ritonavir als PK-booster vonden we geen significante verschillen tussen de PK- parameters van docetaxel na toediening van de docetaxel premix oplossing of de ModraDoc001 15 mg capsule. Bovendien zagen we een tendens naar een lagere variabiliteit in de blootstelling aan docetaxel na orale toediening van de ModraDoc001 15 mg capsule (513 ± 219 vs. 790 ± 669 ng·h/mL). De lage interindividuele variabiliteit in blootstelling aan docetaxel (44%), de nauwkeurigheid van doseren en de afwezigheid van ethanol en polysorbaat waren de voordelen van de ModraDoc001 15 mg capsules ten opzichte van de docetaxel premix oplossing.

Op basis van deze resultaten werd besloten de ModraDoc001 formulering te gebruiken in een fase I dosis escalatie studie van oraal docetaxel. Om de capsuleerbaarheid van het ModraDoc001 SD poeder te verbeteren voegden we lactose monohydraat en colloidaal silica toe. Tegelijkertijd verlaagden we de hoeveelheid docetaxel per capsule tot 10 mg (ModraDoc001 10 mg capsule), omdat deze dosering beter aansloot bij de dosis escalatie stappen van de studie.

Stabiliteitsstudies die werden uitgevoerd bij 2-8°C en bij 25°C / 60% relatieve luchtvochtigheid (RH) toonden aan dat docetaxel gedurende 2 jaar chemisch en fysisch stabiel was in de ModraDoc001 10 mg capsule.

Vanwege het succes van de ModraDoc001 10 mg capsules begonnen we met de

ontwikkeling van een orale formulering van paclitaxel (Hoofdstuk 4). Op basis van Hanssen oplosbaarheidsparameters werd geconcludeerd dat paclitaxel wellicht zelfs een betere SD kon vormen met PVP-K30 en SLS dan docetaxel. Nadat was vastgesteld dat paclitaxel amorf gemaakt kon worden met vriesdrogen lieten we met dissolutie screening experimenten zien dat de optimale SD van paclitaxel bestond uit 1/11 w/w paclitaxel, 9/11 w/w PVP-K30 en 1/11 w/w SLS (ModraPac001 SD powder). Nadere analyses van de SD met XRD, Fourier transformatie infrarood (FT-IR) spectroscopie en mDSC bevestigden de amorfe toestand van paclitaxel en de fijne verdeling van paclitaxel over de matrix van PVP-K30 en SLS. Het ModraPac001 SD poeder werd vervolgens gemengd met lactose monohydraat en colloidal silica en ten slotte gecapsuleerd in harde gelatine capsules (ModraPac001 10 mg capsule). Om de klinische relevantie van de hoge schijnbare oplosbaarheid en de verhoogde dissolutiesnelheid van paclitaxel te testen werden de PK-parameters van paclitaxel vergeleken na toediening van de ModraPac001 10 mg capsule en de paclitaxel premix oplossing. We vonden geen significante verschillen in de PK-parameters van paclitaxel na orale toediening van de twee formuleringen. Bovendien resulteerde orale toediening van ModraPac001 in klinisch relevante systemische blootstelling aan paclitaxel (25, 26). Vanwege de vergelijkbare PK-parameters en de gunstiger farmaceutische eigenschappen, zoals de neutrale smaak, de nauwkeurigheid van doseren, en de twee-jarige stabiliteit bij kamertemperatuur, werd de ModraPac001 10 mg capsule geselecteerd voor gebruik in onze fase I studie naar het effect van regelmatige laag gedoseerde orale toediening van paclitaxel (metronome therapie).

In hoofdstuk 3 en 4 lieten we zien dat de verhoogde dissolutiesnelheid van de amorfe SD's (ModraDoc001 en ModraPac001) werd veroorzaakt door de hogere schijnbare oplosbaarheid van de amorfe actieve stof, het toegenomen oppervlak van de fijn verdeelde actieve stof en een verbeterde bevochtiging van de actieve stof door de hydrofiele matrix van PVP-K30 en SLS [27, 28]. Om een reproduceerbare farmaceutische beschikbaarheid van de actieve stoffen te garanderen is het dus zeer belangrijk dat deze eigenschappen niet veranderen tijdens opslag.

De hulpstoffen in SD's zijn zeer belangrijk bij het in stand houden van de amorfe toestand van de actieve stof tijdens opslag en na dissolutie in het maagdarmkanaal [22, 29, 30]. Bij de selectie van hulpstoffen moet daarom rekening gehouden worden met de fysische en chemische stabiliteit in vaste toestand, maar ook met de mogelijke veranderingen in

dissolutie-eigenschappen.

Kristallisatie van amorfe stoffen vindt in principe plaats boven de glastransitie temperatuur (Tg). Er is echter aangetoond dat de moleculaire bewegingen die noodzakelijk zijn voor kristallisatie al plaats vinden vanaf temperaturen 50 °C onder de Tg: de Kauzmann temperatuur [31]. Bovendien kan de Tg sterk verlaagd worden door de absorptie van water dat een weekmakend effect heeft.

Een andere bedreiging voor de stabiliteit van amorfe SD's is fasescheiding van de stoffen. Fasescheiding vermindert de interactie tussen de hydrofobe actieve stof en de hydrofiele hulpstoffen in de SD en kan veroorzaakt worden door absorptie van water. De verminderde interactie met de actieve stof zou kunnen leiden tot een lagere dissolutiesnelheid, zeker wanneer fasescheiding leidt tot kristallisatie van de amorfe actieve stof [24, 32]. Kortom, de relatieve luchtvochtigheid en de temperatuur zijn de twee belangrijkste factoren die de fysische en chemische stabiliteit van amorfe SD's beïnvloeden.

Omdat de testen die gebruikt werden tijdens de initiële stabiliteitsstudies van ModraDoc001 en ModraPac001 formuleringen deze kleine verandering waarschijnlijk niet zouden detecteren besloten we XRD, mDSC, FT-IR en dissolutiescreening experimenten te gebruiken bij de nieuwe stabiliteitsonderzoeken beschreven in hoofdstuk 5. We toonden aan dat tijdens opslag de hoeveelheid water in ModraDoc001 SD poeder toenam van 6.3% w/w tot 27% w/w (droog gewicht). De absorptie van water leidde tot de vrijwel volledige verwijdering van TBA (van 3.4% w/w tot 0.12% w/w) en veroorzaakte fasescheiding van SLS. Desondanks bleven docetaxel en paclitaxel amorf en werd geen chemische degradatie waargenomen tijdens opslag. De fase scheiding van SLS leidde mogelijk tot een sterkere interactie tussen docetaxel en PVP-K30 wat zou kunnen verklaren waarom docetaxel langer in oplossing bleef. In ieder geval was de fasescheiding van SLS de oorzaak van de slechtere bevochtiging van de gecapsuleerde SD. Na meer dan 52 weken bij 25 °C / 60% RH te zijn opgeslagen leidde de fasescheiding van SLS tot een significante daling van de dissolutiesnelheid.

In hoofdstuk 3 en 4 toonden we ook aan dat klinisch relevante spiegels van docetaxel en paclitaxel bereikt konden worden door de PK-booster ritonavir te combineren met SD's van docetaxel en paclitaxel [27, 33]. Hoewel de ModraDoc001 en ModraPac001 capsules geschikt waren voor fase I klinisch onderzoek werd de arbeidsintensieve bereiding van de capsules niet geschikt geacht om toekomstige fase II en III klinische studies te voorzien van capsules. Vandaar dat het noodzakelijk was een productie methode te

ontwikkelen die wel geschikt was voor grootschalige bereiding van de SD's.
Voor grootschalige bereiding van de SD's kozen we voor sproeidrogen in plaats van vriesdrogen, omdat sproeidrogen een breed geaccepteerde en op industriële schaal toepasbare methode is, het gebruikt kan worden bij continue processen en het een goedkoop, snel één-staps-proces is. Bovendien is het bij sproeidrogen mogelijk om de grootte, dichtheid en morfologie van de deeltjes te controleren wat het verwerken van SD's in tabletten makkelijker maakt [34, 35].
Speciale formuleringen zoals oplossingen van micellen (docetaxel premix oplossing) en SD's (ModraDoc001 10 mg capsule) kunnen de farmaceutische beschikbaarheid van docetaxel verhogen. Deze formuleringen kunnen uiteindelijk de precipitatie of de degradatie van docetaxel in het maag-darmkanaal niet voorkomen [27, 36, 37]. Daarom is het essentieel dat de PK booster ritonavir aanwezig is in het maagdarmkanaal om de absorptie te bevorderen voordat docetaxel kan precipiteren of degraderen [20]. Met de op dat moment beschikbare docetaxel en ritonavir formuleringen waren we niet in staat om deze voorwaarde volledig te vervullen. Na orale toediening van de docetaxel premix oplossing komt docetaxel vrijwel onmiddellijk beschikbaar terwijl de harde capsule van de ritonavir formulering eerst doorbroken moet worden voordat ritonavir beschikbaar komt. Een studie waarin gelijktijdige toediening van docetaxel en ritonavir werd vergeleken met toediening van ritonavir 60 minuten eerder dan de docetaxel premix oplossing liet inderdaad een tendens zien tot een hogere blootstelling wanneer ritonavir eerder dan docetaxel werd toegediend [20]. Op basis van theorie en praktijk kan geconcludeerd worden dat het tijdstip en de locatie van het beschikbaar komen van ritonavir ten opzichte van het beschikbaar komen van docetaxel invloed heeft op de blootstelling aan docetaxel. Docetaxel en ritonavir moeten gelijktijdig en op dezelfde plaats in het maag-darmkanaal beschikbaar komen om een optimale PK boosting van docetaxel te verkrijgen.
Een vaste dosis combinatie (fixed dose combination: FDC) van docetaxel en ritonavir heeft in principe meerdere voordelen ten opzichte van formuleringen met alleen docetaxel of ritonavir. Ten eerste is het waarschijnlijk dat de patiëntvriendelijkheid en therapietrouw toeneemt door het lagere aantal in te nemen doseereenheden en het simpeler doseerschema [38]. Ten tweede voorkomt de FDC dat docetaxel zal worden ingenomen zonder de PK booster ritonavir. Ten derde zou gelijktijdige afgifte van docetaxel en ritonavir de blootstelling aan docetaxel kunnen verhogen en de variabiliteit

kunnen verkleinen. Kortom, om de toepasbaarheid van orale docetaxel therapie verder te verbeteren besloten we een FDC te ontwikkelen van docetaxel en ritonavir.
Vanwege zijn lage oplosbaarheid en permeabiliteit is ook ritonavir geclassificeerd als klasse IV stof volgens het biofarmaceutische classificatie systeem (BCS) [39,40]. Net als voor docetaxel is het daarom nodig om een speciale formulering te maken om de farmaceutische en biologische beschikbaarheid te verbeteren. Het toevoegen van ritonavir aan de SD matrix van PVP-K30, docetaxel en SLS leek de meest geschikte optie. Uiteraard mocht de combinatie van ritonavir én docetaxel in een SD en in de FDC de dissolutiesnelheden en orale biologische beschikbaarheid van de afzonderlijke actieve stoffen niet negatief beïnvloeden. Bovendien moest sproeidrogen SD's produceren die zowel chemisch als fysisch vergelijkbaar waren met de eerder ontwikkelde gevriesdroogde SD.
In hoofdstuk 6 laat de analyse met XRD, mDSC en FT-IR zien dat gesproeidroogde SD's van docetaxel en ritonavir volledig amorf zijn en dat docetaxel en ritonavir mogelijk moleculair verdeeld zijn over de PVP-K30/SLS matrix. In tegenstelling tot de gevriesdroogde SD's was SLS wel amorf en/of moleculair verdeeld over docetaxel, ritonavir en PVP-K30 in de gesproeidroogde SD. Dit is een indicatie dat sproeidrogen zou kunnen leiden tot verhoogde en gelijktijdige in-vitro en in-vivo dissolutiesnelheden. De conclusie van dit onderzoek was dat gesproeidroogde SD's gelijkwaardig of beter waren dan gevriesdroogde SD's. Daarnaast adviseren we om het sproeidroogproces verder te optimaliseren om het gehalte residuale oplosmiddelen te verlagen, en belangrijker nog, om de poederstroomeigenschappen te verbeteren en op die manier volautomatisch tabletteren van gesproeidroogde SD tabletten van docetaxel en ritonavir mogelijk te maken.
De dissolutiesnelheden van docetaxel en ritonavir in enkele en vaste dosis combinatie tabletten waren vergelijkbaar en bleken gerelateerd te zijn aan de afgiftesnelheid van PVP-K30. Op basis van deze resultaten besloten wij de ModraDoc001 10 mg capsule te vergelijken met nieuwe tabletten gemaakt van gesproeidroogd SD's in klinische fase I studie. Op dat moment had een andere klinische studie met de ModraDoc001 10 capsule laten zien dat de remming van CYP3A4 door ritonavir in de darmwand en de lever primair verantwoordelijk was voor de toename van de blootstelling aan docetaxel. Bovendien leken de resultaten van deze studie te suggereren dat 200 mg in plaats van 100 mg ritonavir zou leiden tot een hogere blootstelling aan docetaxel [41]. Tegelijkertijd was uit de dosis-escalatie studie gebleken dat 60 mg docetaxel in combinatie met 200 mg ritonavir een veilige dosis was. Op basis van deze gegevens

werd voor de vergelijkingsstudie 40 mg docetaxel in combinatie met 200 mg ritonavir gekozen als dosis. Om de hoeveelheid docetaxel per formulering gelijk te laten zijn werd een docetaxel tablet van 10 mg (ModraDoc003 10 mg tablet) en een vaste combinatie tablet van 10 mg docetaxel en 50 mg ritonavir (ModraDoc004 10/50 mg tablet) gemaakt. De stabiliteit van de twee nieuwe formuleringen werd onderzocht met dezelfde methoden die beschreven zijn in hoofdstuk 5. Alhoewel de wateropname tijdens opslag van de gesproeidroogde SD's niet leidde tot kristallisatie van docetaxel of ritonavir leidde het wel tot fase scheiding van SLS wat resulteerde in een verlaagde in-vitro dissolutiesnelheid. Bij kamertemperatuur waren de ModraDoc003 10 mg tabletten minstens 52 weken stabiel terwijl de ModraDoc004 10/50 mg tabletten bij deze condities ten minste 25 weken stabiel waren.

De vergelijkingsstudie van ModraDoc001, ModraDoc003 en ModraDoc004 formuleringen is beschreven in hoofdstuk 7. Op basis van de resultaten werd geconcludeerd dat de enkele formuleringen van docetaxel, de ModraDoc003 10 mg tablet en de ModraDoc001 10 mg capsule, voor een vergelijkbare blootstelling aan docetaxel zorgden na orale toediening in combinatie met ritonavir. Verder laten we zien dat de vaste dosis combinatie tablet van docetaxel en ritonavir, de ModraDoc004 10/50 mg tablet, zorgde voor een vergelijkbare blootstelling aan docetaxel en ritonavir in vergelijking met de enkele formuleringen. Bovendien vonden we een tendens naar hogere en minder variabele verhouding tussen de blootstelling aan docetaxel en aan ritonavir voor de ModraDoc004 10/50 mg tablet. De hogere blootstellingsratio zou mogelijk het resultaat zou zijn van de gelijktijdige afgifte van docetaxel en ritonavir in het maagdarmkanaal.

Concluderend hebben wij orale solid dispersion formuleringen van docetaxel, paclitaxel, en docetaxel/ritonavir ontwikkeld met vriesdrogen en sproeidrogen als bereidingsmethode. Analyses van de SD's met XRD, mDSC, FT-IR en dissolutie testen lieten een goede stabiliteit zien die nog verder verbeterd zou kunnen worden door de opname van water door de SD's te verminderen. De solid dispersion formuleringen verbeterden de oplosbaarheid en dissolutiesnelheden van de actieve stoffen wat resulteerde in klinisch relevante blootstellingen aan docetaxel en paclitaxel. Tot op heden, juli 2013, zijn de ModraDoc001 10 mg capsules toegediend aan 97 patiënten in lopende klinische fase I onderzoeken [42, 43], terwijl de ModraPac001 capsules zijn toegediend aan 21 patiënten [44]. Over het algemeen waren de capsules makkelijk in te

nemen en goed te verdragen. Op basis van de studies beschreven in dit proefschrift kan geconcludeerd worden dat we klinisch toepasbare orale formuleringen van paclitaxel en docetaxel en docetaxel/ritonavir hebben ontwikkeld die de weg vrij maken voor de ontwikkeling van orale antikanker therapie met taxanen.

Toekomstperspectieven

De studies die in dit proefschrift beschreven staan, tonen aan dat orale toediening van docetaxel en paclitaxel mogelijk is door de farmacokinetische booster ritonavir te combineren met solid dispersion formuleringen. Het zou interessant zijn de moleculaire interacties tussen de solid dispersion componenten en de invloed van de bereidingsmethode op deze interacties verder op te helderen. Met name de verschillen in de moleculaire structuur van SLS na vriesdrogen en sproeidrogen is interessant vanwege de geobserveerde fasescheiding van SLS tijdens opslag. Analyses met dynamic vapor sorption (DVS) van SD poeders met verschillende verhoudingen van de actieve stof en hulpstoffen zouden gebruikt kunnen worden om de mate van hydrofobisering te meten; dit zou meer inzicht kunnen verschaffen in de moleculaire interactie tussen de actieve grondstoffen en PVP-K30 [45-47].

Gezien het belang van de amorfe toestand van de solid dispersion en het onvermogen van FT-IR om kristallisatie snel te meten, wordt aangeraden om XRD en/of mDSC analyse standaard te gebruiken tijdens de vrijgifte en stabiliteitstesten. Hiervoor is het wel noodzakelijk dat er specificaties en standaard test methodes worden ontwikkeld.

De klinische relevantie van de verschillen in de in-vitro dissolutieprofielen die optreden tijdens opslag en tussen verschillende charges zouden in kaart gebracht moeten worden om de juiste vrijgifte en stabiliteitsspecificaties op te stellen. Preklinische experimenten met fysische mengsels en aan extreme condities blootgestelde SD's in combinatie met het optimaliseren van de in-vitro dissolutiemethode zou gebruikt kunnen worden om in-vivo – in vitro correlaties (IVIVC) te definiëren voor SD's van docetaxel en paclitaxel. Eenmaal gedefinieerd zouden IVIVC kunnen helpen bij het inschatten van de stabiliteit van SD's en zouden doelen voor nieuwe formuleringen gesteld kunnen worden [48].

Het is aan te raden om water- en luchtdichte omverpakkingen te gebruiken en de SD tabletten individueel te verpakken om de door water veroorzaakte fase scheiding van

SLS en de daaropvolgende verlaging van de dissolutiesnelheid te voorkomen. Dit zou de houdbaarheid van de formuleringen moeten verbeteren en daarmee ook de toepasbaarheid van deze formuleringen buiten de kliniek. Een andere optie om de stabiliteit te verbeteren is het aanbrengen van een beschermende coating, alhoewel hierbij wel opgelet moet worden dat de dissolutiesnelheden niet negatief worden beïnvloed.

Hoewel we hebben laten zien dat de SD's verbeterd werd door te sproeidrogen waren we door de slechte poederstroomeigenschappen in het begin alleen in staat om handmatig tabletten te slaan. Recent hebben we de poederstroomeigenschappen verbeterd door grote hoeveelheden vulmiddel (~80% w/w) toe te voegen. Dit stelde ons in staat om op grote schaal automatisch tabletten te slaan van docetaxel en paclitaxel. Echter, een optimalisatie van het sproeidroogproces is nog steeds zeer gewenst [49], zeker omdat de grote hoeveelheid vulmiddel een probleem is. Door de grote hoeveelheid vulmiddel wordt het maken van formuleringen met hogere hoeveelheden van één of twee actieve stoffen niet makkelijk. Mocht blijken dat het sproeidroogproces niet verder geoptimaliseerd kan worden, zouden andere bereidingsmethodes, zoals *hot melt extrusion* (HME) overwogen kunnen worden [50]. Gebruik van HME zou ook voordelig kunnen zijn voor de stabiliteit omdat er tijdens de bereiding geen oplosmiddelen worden gebruikt.

Net als een FDC tablet van docetaxel én ritonavir zou het handig zijn als een dergelijke combinatie tablet van paclitaxel en ritonavir zou worden gemaakt. Hanssen oplosbaarheidsparameters en initiële experimenten lieten al zien dat paclitaxel en ritonavir waarschijnlijk een volledig amorfe SD zullen krijgen.

De resultaten van de lopende dosis escalatie studies met oraal docetaxel en oraal paclitaxel zouden gebruikt moeten worden om de dagelijkse en weekdosering van docetaxel en paciltaxel en ritonavir te selecteren.

Op basis van de gedefinïeerde dosis zou er zowel voor de standaard tablet als voor de FDC tablet een doseereenheid moeten komen. Vanuit productie gaat de voorkeur uit naar zo min mogelijk verschillende sterktes die bij voorkeur bereid zijn vanuit een SD. In het belang van de patiënt en de behandelaar zou het aantal doseereenheden per dosis beperkt moeten blijven, zou de omvang en de vorm van de tablet geen slikproblemen moeten geven en zou het eenvoudig moeten zijn om het doseerschema met 25% of 50% te verlagen. Wanneer het gehalte van de uiteindelijke doseereenheid is gekozen zal een afsluitende vergelijkingsstudie moeten worden verricht om de nieuwe en gebruikte formuleringen met elkaar te vergelijken.

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Dankwoord

Het is zo goed als af, na 4 jaar labwerk en nog 2 jaar deeltijdschrijven is het boekje klaar. Langs deze weg wil ik graag alle mensen bedanken die een bijdrage hebben geleverd aan mijn onderzoek. Tot slot wil ik ook nog enkele personen persoonlijk bedanken.

Als eerste de patiënten en hun familie voor hun bereidheid mee te werken aan het testen van de nieuwe formuleringen.

Beste Jos, Jan en Bastiaan bedankt dat jullie mij mee hebben laten werken aan dit prachtige project.

Beste Stijn dank voor de prettige samenwerking bij het begin van Modra. Beste Alwin, Rik en Jeroen dank voor jullie waardevolle bijdragen aan mijn onderzoek.

Beste Kees dank voor de vele dissolutietesten en GC-metingen. Beste Jan en Dieuwke dank voor alle waterbepalingen. Beste Dr. Fu bedankt voor je hulp en uitleg bij het verrichten van de X-ray metingen. Beste Mies dank voor het reserveren van de DSC en het mailen van de resultaten. Beste Edith, Nourredin en John, dank voor jullie assistentie bij het bereiden, etiketteren en verpakken. Beste Roel en Denise dank voor het beheer van de sleutel van de Modrakast en het verwerken van de BDV's, AV's en SOP's.

Beste Formulettes dank voor jullie introductie in de FU en het mogen testen van de filters. Beste Joost dank voor de mooie week in Kopenhagen. Beste Jelte dank voor de koffie en lunches tijdens het schrijven.

Beste Bas dank voor het inwerken op de HPLC en chromeleon. Beste Abadi en Luc dank voor jullie assistentie bij problemen.

Beste oude en nieuwe keetbewoners dank voor de mooie tijd, de OIO-weekenden, de vrijdagmiddagborrels, de uurtjes later na de promotieborrels en de zin om met mij in discussie te gaan. Beste collega's van TSA dank voor jullie blijvende belangstelling voor de voortgang van mijn proefschrift.

Beste broers en zus dank voor jullie hulp en commentaar. Beste Marjan, Arie, Roelof en Geke dank voor jullie zorg voor onze kinderen en het ter beschikking stellen van jullie huizen tijdens de vele schrijfweekenden.

Beste Casper en Carolijn bedankt voor de afleiding. Beste Josee dank voor je hulp en geduld, zonder jou was dit proefschrift er niet geweest.

Excuses en dank aan iedereen die ik vergeten ben.

Curriculum Vitae

Johannes Jan Moes werd op 8 december 1979 geboren te Nijeveen. In 1998 behaalde hij zijn VWO diploma aan de C.S.G Dingstede in Meppel. Na aanvankelijk begonnen te zijn met de studie Economie stapte hij in 2000 over naar de studie Farmacie aan de Rijksuniversiteit Groningen waar hij in december 2004 zijn bachelors diploma kreeg. Tijdens het onderzoeksjaar van de Masteropleiding heeft hij in 2005 onderzoek verricht naar het gebruik van Nabij Infrarood (NIR) als Process Analytical Technology (PAT) tijdens de productie van orale toedieningsvormen bij Solvay Pharmaceuticals in Weesp onder leiding van dr. M. Ugwoke en Prof. Dr. H.W. Frijlink. In augustus 2007 behaalde hij zijn Masters- en Apothekersdiploma (cum laude) en startte hij met zijn promotieonderzoek naar de ontwikkeling van orale toedieningsvormen van taxanen onder leiding van promotores Prof. Dr. J.H. Beijnen, Prof. dr. J.H.M. Schellens en co-promotor dr. B. Nuijen. Naast het afronden van zijn promotieonderzoek werkte hij vanaf oktober 2011 bij de Technological & Scientific Affairs afdeling van TEVA Pharmachemie in Haarlem aan de introductie en het opschalen van complexe steriele antikankerformuleringen. Vanaf september 2013 is hij werkzaam als onderzoeker bij de Pharmaceutical and Material Sciences afdeling van Janssen Pharmaceutica in Beerse (België).

Johannes Jan Moes was born in Nijeveen on December 8, 1979. He received his VWO exam at CSG Dingstede in Meppel in 1998. He initially studied Economics before he switched to Pharmacy at the University of Groningen in 2000. After receiving his Bachelor's degree in December 2004 he studied the application of Near Infared (NIR) spectroscopy as Process Analytical Technology (PAT) during manufacturing of oral solid dosage forms at Solvay Pharmaceuticals in Weesp under the supervision of Dr. M. Ugwoke and Prof. dr. H.W. Frijlink. In August 2007 he received his Master's degree and PharmD. (cum laude) and started with his PhD research into the development of oral dosage forms of taxanes under the supervision of Prof. dr. J.H. Beijnen, Prof. dr. J.H.M. Schellens and dr. B. Nuijen. Apart from finishing his PhD research he worked at the Technological and Scientific Affairs department of TEVA Pharmachemie in Haarlem on the introduction and scale-up of complex sterile anticancer formulations as of October 2011. Since September 2013 he is working as scientist in the Pharmaceutical and Material Sciences department of Janssen Pharmaceutica in Beerse (Belgium).

List of publications

Articles

Moes JJ, Stuurman FE, Hendrikx JJ, Marchetti S, Huitema ADR, Beijnen JH, et al. Pharmacokinetic evaluation of three oral formulations of docetaxel boosted with ritonavir: Two single-drug formulations vs. a fixed-dose combination tablet. Drug Deliv Transl Res. 2013; 3 (3): 243.

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Moes JJ, Koolen SLW, Huitema ADR, Schellens JHM, Beijnen JH, Nuijen B. Pharmaceutical development and preliminary clinical testing of an oral solid dispersion formulation of docetaxel (ModraDoc001). Int J Pharm. 2011; 420 (2): 244. PMID: 21907780.

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Abstracts

Marchetti S., Stuurman F. S., Koolen S. L. W., Moes J. J., Hendrikx J. J., Thijssen B., et al. Phase I study of weekly oral docetaxel (ModraDoc001) plus ritonavir in patients with advanced solid tumors. 2012. Available from: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/2550.

Koolen SLW, Moes JJ, Huitema ADR, Nuijen B, Thijssen B, Keessen M, Maas-Bakker RF, Meijerman I, Beijnen JH, Schellens JHM. Boosting of oral docetaxel (ModraDoc001) with different CYP3A4 inhibitors. Br J Clin Pharmacol. 2010; 69 (6): 711

Moes JJ, Koolen SLW, Huitema ADR, Schellens JHM, Beijnen JH, Nuijen B. Docetaxel solid dispersion ModraDoc001 results in clinically relevant systemic exposure. 36th Annual meeting of the controlled release society June 2009. Abstract no. 1318