Solid dispersions in oncology:
a *solution* to solubility-limited oral drug absorption

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Solid dispersions in oncology:
a *solution* to solubility-limited oral drug absorption

Vaste dispersies in de oncologie:
een *oplossing* voor oplosbaarheid gelimiteerde orale geneesmiddelabsorptie
(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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This thesis is dedicated to my grandparents Teresa Szafarkiewicz-Straburzyńska and Henryk Straburzyński † whose love and dedication for pharmacy inspired me to follow their steps.

I am always doing things I can't do, that's how I get to do them.

- Pablo Picasso

CONTENTS

PREFACE

There are 33 million people living with cancer in the world and every year 14 million new cancer cases are diagnosed. Cancer is the leading cause of death worldwide, accounting yearly for 8 million deaths. The number of new cases increases drastically and is expected to be nearly doubled within two decades. There are over 100 different types of cancer, each requiring a specific treatment regimen [1,2]. Many types of cancer are treated with chemotherapy, a class of drugs that pharmacologically interferes with the life cycle of cancer cells, causing cytotoxicity and ultimately apoptosis. The first chemotherapeutic drug (oncolytic) was nitrogen mustard (in 1946), a derivative of mustard gas which was used during World War I as chemical warfare and caused leukopenia. This effect was later exploited to treat people with leukemia and other cancer types. Other oncolytics followed, such as folic acid antagonists, purine antagonists, pyrimidine antagonists, antineoplastic antibiotics, antihormones, topo-isomerase inhibitors, taxanes, vinca-alcaloids and platina compounds [3]. Most of these oncolytics are administered intravenously to ensure complete bioavailability, ensuring accurate dosing. Over the last two decades many new oncolytics were developed as formulations for oral dosing. The advantage is that oral formulations can be administered without patient hospitalization, allowing to treat cancer in a more home-based setting, which many cancer patients actually prefer. Patient-convenience is not the only reason for the intravenous-to-oral-switch; orally dosed oncolytics appear to be at least equally effective and less costly as compared to traditional intravenous chemotherapy. Another trend in oncology is "targeted chemotherapy" which refers to oncolytics that interfere with tumor-specific growth signaling pathways. The small-molecule tyrosine kinase inhibitors are such tumor-specific oncolytics and many agents belonging to this class are available in an oral formulation [4–6].

A prerequisite for orally administered oncolytics is a complete and predictable absorption process. For this, the drug must dissolve from its pharmaceutical formulation in water in the gastro-intestinal tract. The problem is that many oncolytic drugs are poorly soluble in water and consequently drugs are often inadequately absorbed, leading to incomplete and/or highly variable bioavailability. Because many oncolytic drugs have a steep dose-response curve, dissolution-limited absorption increases the chance for a negative treatment outcome such as under- or overdosing. Dissolution-limited drug absorption may be resolved by optimizing the pharmaceutical formulation. Of particular interest is the solid dispersion technique. A solid dispersion contains a drug that is finely dispersed into a hydrophilic excipient, such as a small molecule vehicle (i.e. sugar) or a biologically inactive polymer (i.e. povidone) [7]. A solid dispersion can considerably enhance drug dissolution and bioavailability: for example, the commercialized formulation of vemurafenib

(Zelboraf®) is a solid dispersion which results in a 30 times increased dissolution and a 5 times increased absorption compared to a conventional formulation [8]. There are currently nearly 30 licensed solid dispersion formulations for different health conditions, among them are 3 formulations with oncolytics, highlighting the feasibility and success of this novel formulation technique.

The goal of this thesis is to investigate pharmaceutical formulation aspects of a solid dispersion and whether it can be a useful formulation technique for the clinical development of poorly soluble drugs to be administered orally to patients with oncological conditions.

Chapter 1 of this thesis is a literature survey where pharmaceutical formulations and absorption pharmacokinetics are reviewed of oncolytics currently commercially available as an oral formulation. The literature study focuses on oral oncolytics composed in a solid dispersion formulation and discusses the principles of this formulation strategy.

Chapter 2 of this thesis illustrates the development of a solid dispersion containing elacridar hydrochloride with the purpose to resolve the drug's low aqueous solubility and to conduct proof-of-concept clinical studies. Although not having an anticancer effect itself, elacridar hydrochloride may be of relevance in oncology because it enhances the oral bioavailability of numerous oncolytics. According to animal experiments, it also enhances brain penetration of many tyrosine kinase inhibitors and is thus a promising drug to be used in the treatment of tumors in the brain. Furthermore, previous clinical trials proved that the oral bioavailability of paclitaxel and topotecan are significantly enhanced when co-administered with elacridar hydrochloride. Despite the promising clinical results, commercial development of an oral formulation was stopped and currently there is no pharmaceutical product available to conduct clinical trials. A problem of the previously used clinical tablet formulation was poor and unpredictable absorption due to the fact that elacridar hydrochloride is practically insoluble in water. To fulfil the demand to conduct more proof-of-concept clinical studies and to resolve dissolution-limited absorption we developed a novel tablet formulation containing elacridar hydrochloride as a solid dispersion.
First, an analytical method was designed for the quality control of the solid dispersion with elacridar hydrochloride. The development and validation of this analytical method is described in Chapter 2.1.

Next, the pharmaceutical development of the solid dispersion with elacridar hydrochloride is presented and discussed in Chapter 2.2. The development of a solid dispersion is more time-consuming and complex than that of a conventional pharmaceutical formulation because extensive research on excipient selection, production method and dosage form are required. To facilitate fast and efficient pharmaceutical development, we designed and followed a general systematic formulation procedure.
The pharmacokinetics of the novel solid dispersion formulation were studied in healthy human volunteers and results are described in Chapter 2.3.

Chapter 3 of this thesis discusses the optimization of two previously described solid dispersions containing docetaxel or paclitaxel as active pharmaceutical ingredients. These two formulations were freeze dried solid dispersions containing docetaxel-povidone K30-sodium dodecyl sulfate (1:9:1, w/w/w) and paclitaxel-povidone K30-sodium dodecyl sulfate (1:9:1, w/w/w), filled into gelatine capsules. These formulations were tested in phase I clinical studies, where ritonavir was co-administered as inhibitor of pre-systemic CYP3A4-mediated metabolism of docetaxel and paclitaxel. This treatment regimen resulted in relevant pharmacological exposure of docetaxel and paclitaxel with promising clinical outcome [9,10]. However, the production method for these two solid dispersions was not suitable for further clinical trials because of scalability issues: freeze drying is a slow and non-continuous process and resulted in a powder with poor flow properties, as a consequence that capsules had to be filled manually. The production method was switched to spray drying because this is a continuous process and allows better particle engineering, making it a suitable process for upscaling and improving powder mechanics [11]. The pharmaceutical development of the spray dried solid dispersion for docetaxel and paclitaxel is described in Chapter 3.1.
Finally, the drug formulations were evaluated in cancer patients and the impact of the formulation switch was evaluated with pharmacokinetic models. Chapter 3.2 describes the pharmacokinetic evaluation of the docetaxel solid dispersion and Chapter 3.3 describes the pharmacokinetic evaluation of paclitaxel solid dispersion. Finally, important findings of this thesis, conclusions and perspectives for future research are discussed.

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PART I

INTRODUCTION

INVENTORY OF ORAL ANTICANCER AGENTS: PHARMACEUTICAL FORMULATION ASPECTS WITH FOCUS ON THE SOLID DISPERSION TECHNIQUE

Emilia Sawicki
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CHAPTER 1

Cancer Treatment Reviews 2016; 50: 247 – 263

ABSTRACT

Dissolution from the pharmaceutical formulation is a prerequisite for complete and consistent absorption of any orally administered drug, including anticancer agents (oncolytics). Poor dissolution of an oncolytic can result in low oral bioavailability, high variability in blood concentrations and with that suboptimal or even failing therapy. This review discusses pharmaceutical formulation aspects and absorption pharmacokinetics of currently licensed orally administered oncolytics. In nearly half of orally dosed oncolytics poor dissolution is likely to play a major role in low and unpredictable absorption. Dissolution-limited drug absorption can be improved with a solid dispersion which is a formulation method that induces super-saturated drug dissolution and with that it enhances in-vivo absorption. This review discusses formulation principles with focus on the solid dispersion technology and how it works to enhance drug absorption. There are currently three licensed orally dosed oncolytics formulated as a solid dispersion (everolimus, vemurafenib and regorafenib) and these formulations result in remarkably improved dissolution and absorption compared to what can be achieved with conventional formulations of the respective oncolytics. Because of the successful implementation of these three solid dispersion formulations, we encourage the application of this formulation method for poorly soluble oral oncolytics.

1. INTRODUCTION

The treatment of cancer with chemotherapy is undergoing an "intravenous-to-oral" switch trend which has led to an increasing availability of oral formulations with anticancer drugs (oncolytics). The advantage is that oral formulations bypass the need for hospitalization to administer the drug, making it possible to treat cancer in a more home-based setting, which many cancer patients actually prefer [1–3]. Another advantage is that oral oncolytics make possible continuous chemotherapy schedules. An important group of oncolytics which are dosed continuously are the tyrosine kinase inhibitors which exert their antineoplastic action by interfering with tumor-specific molecular pathways, referred to as targeted chemotherapy [4]. A prerequisite for orally administered drugs, in particular for oncolytics, is a complete and consistent absorption process because these agents usually have a steep dose-response curve and a narrow therapeutic index [5]. In order to reach the systemic circulation the drug must dissolve from its pharmaceutical dosage form (capsule or tablet) in the gastro-intestinal fluid. The problem is that many drugs have a poor solubility in water which can lead to incomplete and unpredictable absorption and consequently in a negative treatment outcome such as under- or overdosing [4,6,7]. Moreover, absorption of low-solubility drugs can be significantly affected by food or drinks, e.g. by modifying the pH environment, which is obviously rather uncontrolled [8,9]. Therapeutic drug monitoring is one way to adjust the dose when inadequate in-vivo drug concentrations are achieved [5,10,11]. However, drugs with dissolution-limited absorption often result in high day-to-day variability in in-vivo drug concentrations (i.e. intra-patient variability) which is difficult to adjust to with therapeutic drug monitoring [11,12]. Besides, therapeutic drug monitoring adjusts doses retrospectively, requires extra healthcare infrastructure such as patient sampling and bioanalysis [10] and, what is more, it does not solve the problem of dissolution-limited absorption.

The core of the problem of dissolution-limited absorption might be addressed by optimization of the pharmaceutical formulation. Currently there are different formulation strategies at hand to enhance drug dissolution and a very promising one is the solid dispersion approach. There are currently 27 solid dispersion formulations commercially available (including 3 orally dosed oncolytics), with examples of achieving even a 30 times increased drug dissolution (i.e. vemurafenib solid dispersion), highlighting the feasibility and success of this formulation method [13,14].

This review discusses the basics of drug dissolution, focuses on the solid dispersion formulation technique and addresses which oral oncolytic formulations have dissolution-limited absorption pharmacokinetics and are potential candidates for a solid dispersion formulation.

2. CONVENTIONAL PHARMACEUTICAL FORMULATIONS AND THE BASICS OF DRUG DISSOLUTION

As can be seen in Figure 1, most of the commercially available oral oncolytics are physical mixture formulations (67%), followed by prodrugs (18%), lipid formulations (10%), solid dispersions (4%) and co-solvents (1%).

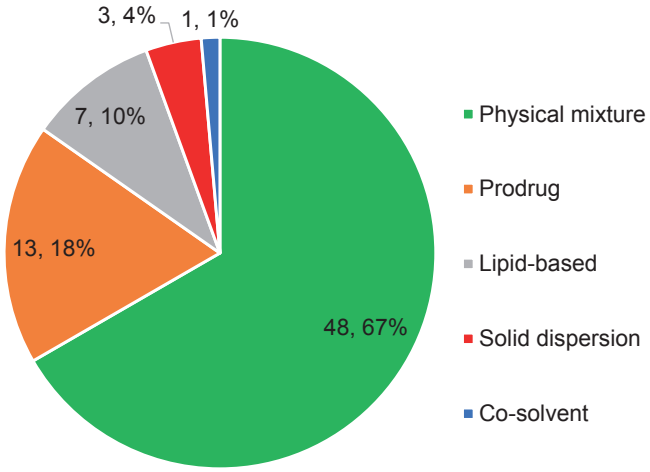


Figure 1. Number and percentage of formulation types of currently licensed orally administered oncolytics in Europe registered on 04-09-2016 (see also Table 3)

Physical mixtures contain mechanically mixed crystalline drug powder, filling powder (e.g. cellulose, lactose or starch), disintegrant (e.g. croscarmellose), glidant (e.g. silicon dioxide) and lubricant (e.g. magnesium stearate). To obtain the final dosage form, physical mixtures are pressed into tablets or filled in capsules. Physical mixtures are standard oral drug formulations because development of such a formulation is simple and inexpensive [15]. An example of a physical mixture formulation is anastrozole (Arimidex®). A schematic representation of what happens to a capsule or a tablet containing a physical powder mixture after oral intake is shown in Figure 2. The shell of the capsule dissolves in water and the powder is then wetted. In the case of tablets, penetrating water breaks down the tablet into large particles (agglomerates) and then to finer particles [16,17]. The next step is solvation and is facilitated by water molecules surrounding the drug molecule. Solvated drug molecules then diffuse into the bulk environment volume, resulting in dissolution. Only dissolved drug molecules can pass epithelial cells in the gastro-intestinal tract for absorption [18].

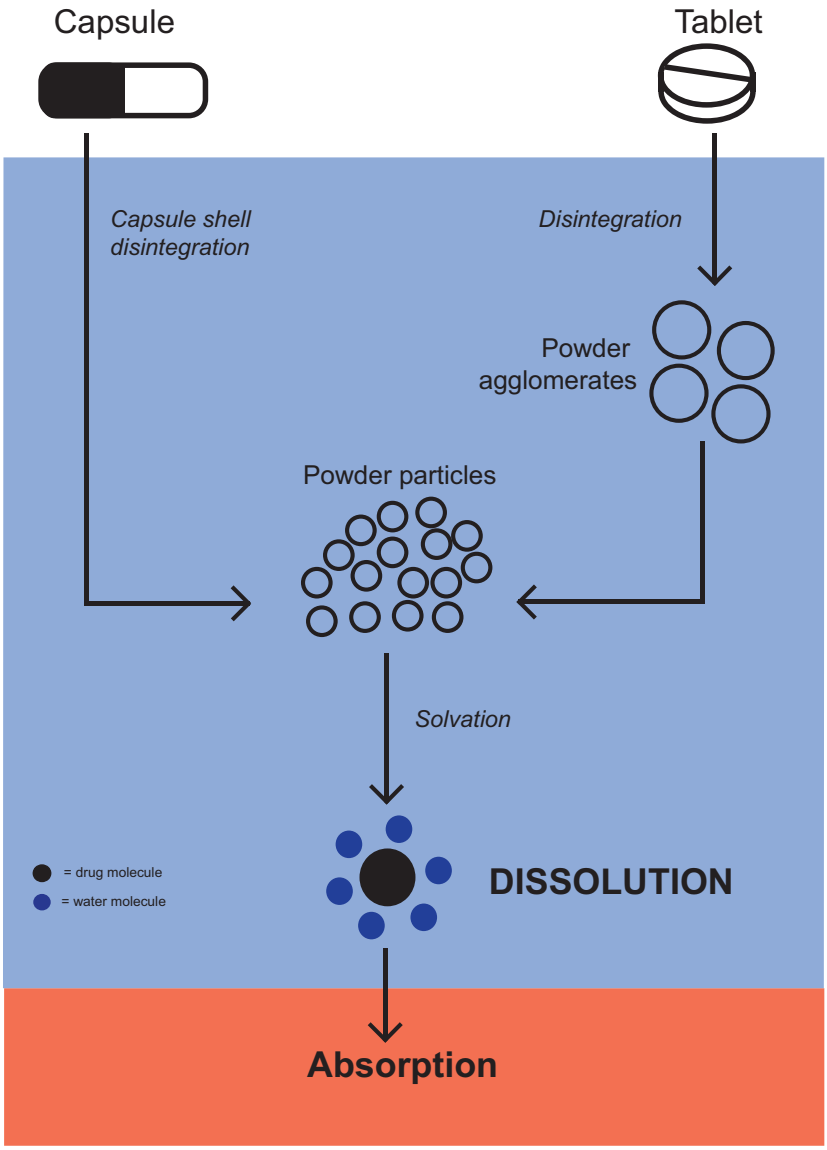


Figure 2. The pharmaceutical processes of a tablet and a capsule in the gastro-intestinal tract containing a physical powder mixture. A tablet or a capsule enters the gastro-intestinal tract and water (blue color) triggers their disintegration. Capsules contain loosely packed powder which comes in contact with water once the capsule shell is disintegrated. Tablets are first disintegrated into large powder clumps (powder agglomerates) and then to small powder particles. Finally the small powder particles disintegrate to individual molecules. Solvation occurs when water molecules surround drug molecules and this leads to drug dissolution. Only dissolved drug molecules can be absorbed into the bloodstream (red).

A prodrug formulation contains a biologically inactive compound which is converted in-vivo to the pharmacologically active drug [19], a strategy which can be used if the active drug has poor oral absorption either due to poor dissolution or due to extensive metabolism. Prodrug powders are processed into a capsule or a tablet in the same way as physical mixtures. An example of a prodrug formulation is capecitabine (Xeloda®).

In lipid-based formulations the drug is dissolved or dispersed in lipid excipients (i.e. mono, di, or triglyceride). Endogenous lipid-digesting enzymes and bile-salts transform the lipid formulation into emulsification droplets, resulting in drug dissolution. Surfactants (i.e. polyglyceride fatty esters, polyethylene glycol) can be added to speed up the emulsification process and to enhance drug dissolution, a feature which is used in a self-emulsifying drug delivery system (SEDDS). SEDDS is an isotropic mixture of lipids, surfactants and co-solvents and when agitated in water it readily forms an emulsion with droplets < 300 nm. Lipid-based formulations can be liquid, solid or semi-solid. A disadvantage is that many lipid-based formulations require careful handling and storage because they can be physically and/or chemically unstable. Lipid-based formulations (in particular SEDDS) may contain high amounts of surfactants (usually 30 – 60% of the formulation) and this can cause gastro-intestinal toxicity [20–23]. An example of a lipid-based formulation is tretinoin (Vesanoid®) and an example of a SEDDS is olaparib (Lynparza®).

A co-solvent formulation contains an organic solvent to increase drug dissolution in water (i.e. ethanol or propylene glycol). The disadvantage is that organic co-solvents can evaporate through capsule shells (even if the capsule is sealed) and this may lead to drug precipitation in the formulation. Besides, organic solvents can be toxic [15,22]. An example of a co-solvent formulation is vinorelbine (Navelbine®).

Capsules or tablets may also have a coating: an extra layer on the exterior of the capsule or tablet. Coatings can be used to protect the dosage form against light, moisture and/or mechanical stress, to make the dosage form look more attractive/recognizable or for controlled disintegration. Regarding the latter, an example is an enteric-resistant coating which has a pH-dependent solubility (no solubility in stomach pH, high solubility in the intestine), hence the dosage form does not degrade in the stomach. This can be applied to drugs with poor stability in acidic pH such as in the stomach [24].

Factors affecting drug dissolution

The process of drug dissolution is influenced by parameters that are described in the Noyes-Whitney equation [25,26]:

$$\frac{dW}{dT} = D \times A \times \frac{Cs - C}{h}$$

Where dW/dt is drug dissolution rate during a certain period of time (e.g. mg/min), D the diffusion coefficient (e.g. cm^2/min), A the surface area of the drug (e.g. cm^2), C_s the saturation solubility of the drug (e.g. mg/L), C the concentration of the drug (e.g. mg/L) and h the thickness of the diffusion layer (e.g. cm). A is related to powder particle size (smaller particles result in a larger surface area), wettability of the powder and by surfactants in gastro-intestinal fluids and bile. D describes the diffusivity of a drug and is influenced by molecule size and viscosity of gastro-intestinal fluids. Parameter h is determined by the viscosity and surfactant concentration in gastro-intestinal fluids as well as by contractile patterns in the gastro-intestinal tract [4,18]. C_s is governed by intrinsic drug molecule properties such as molecular mass, Log P, the number of hydrogen donors/acceptors and the pK_a [18,27].

Biopharmaceutics Classification System (BCS) and Biopharmaceutics Drug Disposition Classification System (BDDCS)

There are two different systems that use biopharmaceutical properties of a drug molecule to predict drug absorption [28]. The biopharmaceutical classification system (BCS) classifies drugs by solubility in water and permeability across human epithelial cells. A drug can fall in either of the four classes: high solubility-high permeability (class I), low solubility-high permeability (class II), high solubility-low permeability (class III) and low solubility-low permeability (class IV) [28–30]. A drug is considered highly permeable if >90% of the dose is absorbed by epithelial cells and soluble when the highest dose strength dissolves in 250 mL water over pH range 1.2 – 7.4 [31].

The other system, BDDCS, describes the biopharmaceutics of a drug by solubility in water and in-vivo disposition. Criteria for solubility in water are the same as used with BCS. The disposition of a drug is influenced by enzymatic, - and transporter processes, consequently BDDCS describes whether a drug undergoes first-pass metabolism and whether it is a substrate to drug efflux transporters such as ATP-binding cassette transporters (ABC) [4,32,33]. Drugs with high permeability are readily absorbed, facilitating access to metabolic enzymes and this then results in high metabolism. This makes BDDCS more representative to describe the absorption

pharmacokinetics of a drug [28,30]. BDDCS classes are: high solubility-high metabolism (class I), low solubility-high metabolism (class II), high solubility-low metabolism (class III) and low solubility-low metabolism (class IV).
Currently, 90% of orally administered drugs in clinical development are categorized as BCS/BDDCS II or IV [30] and 40% fails because of insufficient biopharmaceutical properties such as poor drug dissolution [18]. This underlines that the pharmaceutical formulation is a crucial part in drug development.

3. SOLID DISPERSIONS

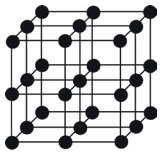
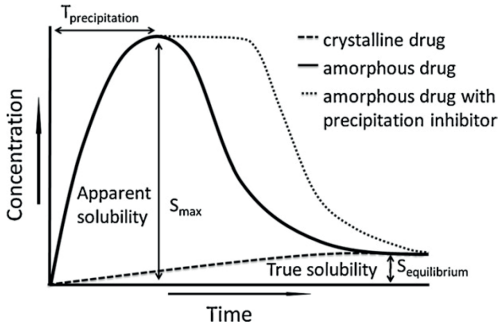
A solid dispersion consists of a drug that is dispersed in a hydrophilic excipient which can be a small molecule such as urea or sugar [34] or a biologically inactive polymer such as cellulose derivatives, polyethyleneglycols, polyvinylpyrrolidones, polyvinylalcohols, polyacrylates and sugar polyols [35–37]. A solid dispersion is not just a physical powder mixture of drug and excipient. Instead, a solid dispersion consists of powder particles in which drug and excipient are integrated and therefore appears as a one-phase powder, with considerably smaller powder particles than what can be achieved with mechanical milling processes [6,7,33,35,38–42]. The very fine dispersion of drug and excipient, decreased particle size and the hydrophilic character of the excipient result in enhanced drug dissolution [43].

Types of solid dispersions

An important feature of a solid dispersion is the physical state of the powder: it can be crystalline or amorphous [37,40,44]. The difference between crystalline powders and amorphous powders is illustrated in Table 1. Crystalline powders contain molecules that are arranged in a highly ordered way. The lattice structure in a crystal results in rigid and physically stable powder particles. Crystalline particles are relatively large and coarse (usually 50 - 1000 µm [45]). Water must first break down the lattice energy holding the crystal together in order to allow solvation and then drug dissolution. Amorphous powders are irregularly organized molecules with considerably smaller particle size, usually < 50 µm. Consequently, the particle surface area of amorphous powders is larger than that of crystalline powders. The absence of lattice energy bonds and the larger particle surface area of amorphous powders result in higher drug dissolution [46]. The disadvantage of amorphous powders, however, is that the molecular structure is physically unstable and over time crystal bonding between molecules develops, affecting the dissolution [43,46]. This makes it difficult to retain an amorphous powder. Table 1 also compares drug dissolution from a crystalline powder and an amorphous powder: the saturation

solubility from an amorphous powder is higher than from a crystalline powder and is then "super-saturated". The highest concentration in this phase is known as S_{max}. The super-saturated state is temporary because the drug precipitates back to the saturation concentration equal to that of the crystal form, $S_{equilibrium}$. The moment that precipitation starts, is the precipitation onset time, $T_{precipitation}$. The temporarily super-saturated drug solution creates a time window for enhanced in-vivo absorption. The role of the hydrophilic excipient in a solid dispersion is to support super-saturation and to inhibit precipitation [14,40,43].

Table 1. Pharmaceutical features of a crystalline powder drug particle and an amorphous drug powder particle

Feature	Crystalline	Amorphous
Schematic structure of one powder particle	 • = one drug molecule, ▬ = crystal bond	
Molecule orientation	Regular	Irregular
Particle size	Large	Small
Particle surface area	Small	Large
Stability physical structure	Strong	Weak
Dissolution	 Reprinted from Moes et al [58] with permission from Elsevier. Precipitation inhibitor is the hydrophilic excipient of a solid dispersion which supports super-saturation and increases $T_{preciptitation}$.	

S_{max}: highest apparent solubility

$T_{precipitation}$: time at which drug starts to precipitate after having reached its highest apparent solubility

$S_{equilibrium}$: intrinsic solubility of the drug

The type of the solid dispersion is determined by the physical state of drug and excipient (crystalline or amorphous). There are crystalline solid dispersions, amorphous solid dispersions and crystalline-amorphous solid dispersions and their characteristics are shown in Table 2.

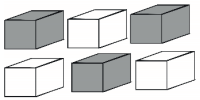
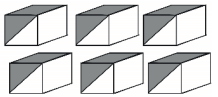
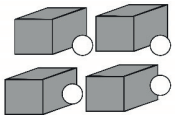
First, among crystalline solid dispersions are the *eutectic mixtures* which were actually the first known solid dispersions [40]. Eutectic solid dispersions are made by heating up a powder mixture at weight proportions at which drug and excipient melt simultaneously, followed by a cooling-down phase [34,40]. Each compound has its own specific melting temperature but when used in a particular weight proportion the mixture can melt simultaneously [40] and the temperature at which this occurs is called the eutectic temperature [34]. Because the eutectic temperature is lower than the melting temperature of the individual compounds of the mixture, the production temperature can be reduced which is particularly advantageous for thermally unstable compounds. The advantage of an eutectic mixture is that drug and excipient are more homogenously mixed than in physical mixtures and this results in higher drug dissolution [37,40].

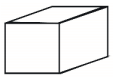
Another type of crystalline solid dispersions are *solid solutions* [34]. In solid solutions a crystalline drug is "dissolved" in a crystalline excipient which results in a single-phase powder because the lattice of the crystal consists of excipient molecules and of drug molecules. Solid solutions have smaller particles than pure crystalline drug compounds and are more homogenous than physical mixtures. This contributes to higher dissolution and absorption [40]. For example, griseofulvin-polyethylene glycol 4000 solid solution resulted in a ~2 times higher in-vivo exposure compared to crystalline griseofulvin [40].

In an *amorphous solid dispersion* (i.e. *glass solution*) the drug "dissolves" in an amorphous excipient resulting in a one-phase amorphous powder [34,40,47]. The amorphous state of the powder, homogeneously mixed at molecular level, the hydrophilic character of the excipient and the large surface area result in high dissolution and absorption enhancement [40]. For example, the antiviral drug telaprevir (Incivo®) is an amorphous solid dispersion with ~32 times increased dissolution and ~10 increased bioavailability [48]. The disadvantage of amorphous solid dispersions is that they can be unstable because amorphous materials can revert to crystalline forms [34]. Therefore, amorphous solid dispersions require more careful handling and storage than crystalline solid dispersions [47].

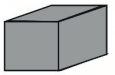
In a *glass suspension* an amorphous drug is not entirely dissolved in an amorphous excipient [40,47]. Instead the drug is dispersed as amorphous clusters or is partially amorphous-partially crystalline [40]. Glass suspensions may occur when the amount of drug in the solid dispersion is relatively large (usually at $\geq$ 35%).

Table 2. Type of solid dispersions and their pharmaceutical features, classification based on [34,37,40,44].

	CRYSTALLINE SOLID DISPERSIONS		AMORPHOUS SOLID DISPERSIONS	AMORPHOUS-CRYSTALLINE SOLID DISPERSIONS	
	Eutectic mixture	**Solid solution**	**Glass solution**	**Glass suspension**	**Amorphous precipitate**
Number of phases	2	1	1	2	2
Drug	Crystalline	Crystalline	Amorphous	Crystalline	Amorphous
Hydrophilic excipient	Crystalline	Crystalline	Amorphous	Amorphous	Crystalline
Schematic picture					



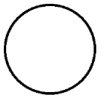
Drug crystal



excipient crystal

drug/excipient crystal

amorphous excipient



amorphous drug

Drug recrystallization is more likely to occur during storage and this makes glass suspensions less stable than glass solutions [47].
In *amorphous precipitates* the drug precipitates out as an amorphous form and is dispersed in a crystalline excipient [40,44]. The amorphous form of the drug and the hydrophilic character of the excipient contribute towards dissolution enhancement. For example, an amorphous dispersion of ritonavir in crystalline polyethyleneglycol 8000 resulted in a 3.5 - 5 times increased dissolution and a 11 - 22 times improved absorption compared to a crystalline physical mixture of ritonavir-polyethylene glycol 8000 [49,50].

Production methods

There are four production methods for solid dispersions: solvent-removing, melting, precipitation and electro-spinning [34,35,37,41,44,51–53]. In the solvent-removal method, drug and excipient are dissolved in an organic solvent and the solution is then evaporated or sublimated. A commonly used evaporation apparatus is a spray dryer and works by transforming the solution into droplets which are dried with a gas (i.e. nitrogen or air) [52]. A common sublimation apparatus is a freeze dryer which freezes the solution and then induces solvent removal by reducing the air pressure [47].
In the melting method drug and excipient are mixed and then heated until they melt. The melt mixture is then rapidly cooled and this ensures that drug and excipient stay molecularly mixed. The result is a solid mass which is then pulverized to obtain particles of a desired size [37,44]. A commonly used apparatus is a hot melt extruder [54].
In the precipitation process drug and excipient are dissolved in a solvent and then an anti-solvent is added to induce precipitation. This results in a precipitate which is further dried to remove residual solvents and finally a dry powder is obtained [13].
In electro-spinning a solution of drug and excipient is dried with electrical energy. The solution is placed in a syringe with a metal tip and pressed out with a pump. The application of high voltage between the metal tip of the syringe and metallic collecting material ejects elongated droplets from the syringe which then evaporate and the resulting product is a solid fiber [55].

Examples of commercialized solid dispersion formulations

In the field of oncology there are currently three commercialized formulations that contain a solid dispersion: vemurafenib, regorafenib and everolimus. Information sources for this paragraph are the European Public Assessment Report (EPAR), U.S. Food and Drug Administration (FDA) drug approval package and literature.

Vemurafenib (Zelboraf®, Roche)

Vemurafenib formulation was initially a physical mixture of crystalline vemurafenib in a capsule. However, the physical mixture resulted in poor bioavailability and a formulation switch to the solid dispersion technique was performed during clinical evaluation [13]. Zelboraf® is an amorphous solid dispersion of vemurafenib-hypromellose acetate succinate (30:70, w/w). The solid dispersion is prepared through precipitation in which vemurafenib and hypromellose acetate succinate are dissolved in the solvent dimethylacetamide and then the anti-solvent dilute hydrochloric acid (0.01 N) induces precipitation of vemurafenib and hypromellose acetate succinate [13]. The precipitate is vacuum-dried, compressed into tablets and film-coated. Vemurafenib dissolution from the solid dispersion is ~30 times higher than that of crystalline vemurafenib and results in approximately 5 times higher vemurafenib plasma concentrations [13] (see also Figure 3).

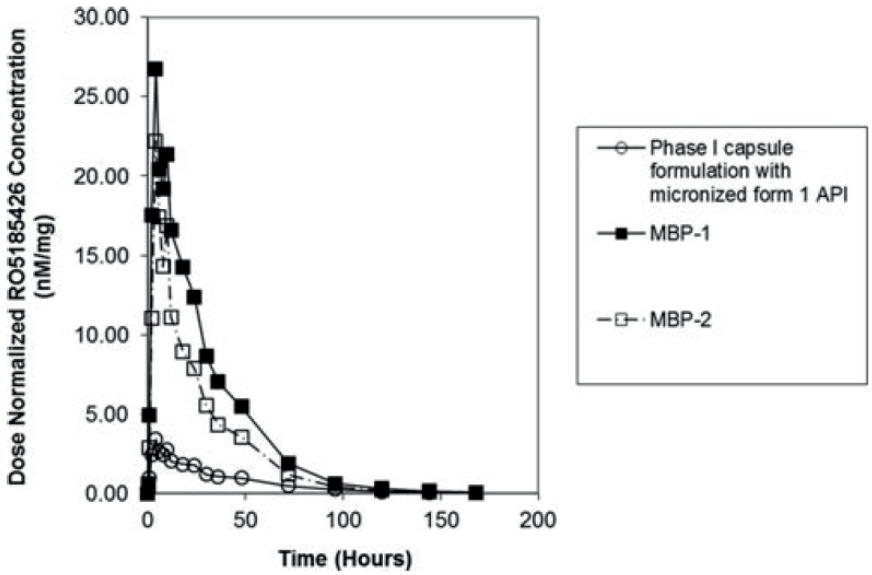


Figure 3. Example of the impact of a solid dispersion formulation on the plasma concentration-time profile of a low solubility orally administered oncolytic, in this case vemurafenib (RO5185426). MBP = microprecipitated bulk product = vemurafenib solid dispersion. MBP-1 and MBP-2 formulations contain the same vemurafenib solid dispersion but differ in the way the solid dispersion is mixed with capsule excipients: MBP-1 is dry-granulated while MBP-2 is wet-granulated. The solid dispersion formulation resulted in approximately 5 times higher vemurafenib plasma concentrations. Plasma concentrations were similar for MBP-1 and MBP-2. Further clinical development continued with MBP-1. Reprinted from Shah et al [13] with permission from Elsevier.

Regorafenib (Stivarga®, Bayer)

Regorafenib is practically insoluble in water and therefore a tablet was developed containing an amorphous solid dispersion of regorafenib-povidone K25. Regorafenib dissolution from the amorphous solid dispersion is ~4.5 times higher than from a physical mixture of regorafenib-povidone K25 [56] and the bioavailability is ~7 times higher than that of a crystalline tablet formulation.

Everolimus (Afinitor®, Votubia®, Certican®, Novartis)

Everolimus is practically insoluble in water and therefore a tablet containing a spray dried amorphous solid dispersion formulation of everolimus-hydroxypropyl methylcellulose (1:40, w/w) has been developed. The formulation also contains butylhydroxytoluene to prevent oxidation of everolimus. The dissolution from the solid dispersion is approximately 4 times higher than from crystalline powder [57]. Certican® was the first licensed formulation for prophylaxis of transplanted organ rejections and was developed in tablet strengths 0.25 mg, 0.5 mg, 0.75 mg and 1 mg. Thereafter, the oncology tablet, Afinitor®, was developed in tablet strengths 2.5 mg, 5 mg and 10 mg, the qualitative composition and drug-excipient proportions being equivalent to Certican®. Votubia® 2.5 mg, 5 mg and 10 mg tablets contain the same formulation as Afinitor® tablets but is licensed as an orphan drug for tuberous sclerosis.

4. BIOPHARMACEUTICS AND ABSORPTION PHARMACOKINETICS OF ORAL ONCOLYTICS

The absorption pharmacokinetics of commercially available oral oncolytics are shown in Table 3. Dissolution-limited absorption is defined by the BCS/BDDCS status of the drug, incomplete oral bioavailability and high variability in concentrations/exposure in blood (whole blood, plasma or serum) by criteria:

1. The drug is classified as BCS/BDDCS II or IV;
2. Oral bioavailability < 85% [28];
3. Intra-patient variability in exposure ≥ 30% [12].

In the case of unknown bioavailability and/or unknown intra-patient variability, a lack of a linear relationship between dose and concentration/exposure in blood and inter-patient variability ≥ 70% are criteria for dissolution-limited absorption. The cut-off value for inter-patient variability is based on the fact that the upper limit of the 95% confidence interval of BCS/BDDCS I/III drugs studied in this review (Table 3) is 67%.

Of the 72 studied oral oncolytics 47 are BCS/BDDCS II or IV drugs which means that 65% of oral oncolytics are poorly soluble in water. 34 out of 72 (47%) oncolytics are inadequately absorbed from the gastro-intestinal tract as a result of a poor dissolution from the pharmaceutical formulation, manifested as low bioavailability, high variability in blood concentrations and lack of a linear relationship between dose and blood concentrations. Because many oncolytics are highly potent with a steep dose-response curve, incomplete and highly variable absorption might result in treatment failure or toxicity. Improving the formulation of oral oncolytics with dissolution-limited absorption seems considerable and the solid dispersion could then be a technique of interest. Currently, only three oncolytics are commercially available as solid dispersion formulations (vemurafenib, regorafenib and everolimus) but demonstrate that drug absorption can be significantly improved, highlighting the feasibility and success of this formulation method. Therefore, we encourage research, development and widespread application of the solid dispersion technique for oral oncolytics.

Table 3. Biopharmaceutical properties and absorption pharmacokinetics of licensed oral oncolytics in Europe on 04-09-2016 (searched EudraPharm database www.eudrapharm.eu and CBG Medicine Information Bank www.cbg-meb.nl by ATC-code "L01" and administration route "oral"). Grey-shaded rows indicate drug formulations with solubility-limited absorption. L = linear, NL = not linear. QD = once daily, BID = twice daily, TID = thrice daily, QW = once a week. Q2D = once every second day, NA = not available. EPAR = European Public Assessment Report, www.ema.europa.eu. FDA = U.S. Food and Drug Administration drug approval package, www.accessdata.fda.gov/scripts/cder/drugsatfda

Drug substance	Drug product	Formulation and amount of active drug	Solubility in water (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure or blood / plasma concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose proportionality	Recommended dose	Fed or fasted	Reference
Abiraterone acetate	Zytiga®	Prodrug- Physical mixture Tablet 250 mg	0.11 (pH 1) 0.02 (pH 2) < 0.01 (pH 5)	IV	≤ 10	IaP: 71 % IerP: 33 – 141 %	250 – 1000 mg QD: L	1000 mg QD	Fasted	[59], FDA, EPAR
Afatinib dimaleate	Giotrif®	Physical mixture Tablet 20, 30, 40, 50 mg	50 (pH < 6)	I or III	NA	IaP: 33 % IerP: 57 – 105 %	10 – 100 mg: NL	40 mg QD	Fasted	FDA, EPAR
5-Amino levulinic acid hydrochloride	Gliolan®	Crystalline powder for oral solution 30 mg/mL	100 – 1000	I	100	IaP: NA IerP: 4 – 13%	0.2 – 20 mg/kg: L	20 mg/ kg before surgery	Fasted	EPAR
Anagrelide hydrochloride	Xagrid® Agrylin®	Physical mixture Capsule 0.5 mg	0.1 – 1	I or III	≥ 70	NA	0.5 – 2 mg: L	0.5 – 2.5 mg BID	Fasted or fed	[60], FDA, EPAR
Anastrozole	Arimidex®	Physical mixture Tablet 1 mg	0.5	III	NA	NA	0.1 – 60 mg: L	1 mg QD 5 years	Fasted or fed	[39,61,62], FDA
Axitinib	Inlyta®	Physical mixture Tablet 1, 3, 5, 7 mg	1.8 (pH 1) 0.3 (pH 1.7) 0.01 (pH 3) 0.0002 (pH 5 – 7.8)	II	58	IaP: 20 - 22% IerP: 80 %	1 – 20 mg BID: L	5 mg BID	Fasted or fed	FDA, EPAR
Bexarotene	Targretin®	Lipid-based Capsule 75 mg	< 0.1	II	NA	IaP: 25 – 105 % IerP: 11 – 83 %	21 – 800 mg/m^2 QD: L	300 mg/m^2 QD	Fed	[39,63–65], EPAR
Bicalutamide	Casodex®	Physical mixture Tablet 50 mg, 150 mg	0.005	II	NA	NA	10 – 30 mg QD: L 30 – 200 mg QD: NL	50 – 150 mg QD	Fasted or fed	[30,66], FDA

Table 3. (continued)

Drug substance	Drug product	Formulation and amount of active drug	Solubility in water (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure or blood / plasma concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose proportionality	Recommended dose	Fed or fasted	Reference
Bosutinib monohydrate	Bosulif®	Physical mixture Tablet 100 mg, 500 mg	11.0 (pH 1) 2.7 (pH 5.0) 0.02 (pH 6.8)	IV	34	IaP: 19 – 31 % IerP: 58 – 73 %	300 – 600 mg QD: NL	500 - 600 mg QD	Fed	[67], FDA, EPAR
Busulfan	Myleran®	Physical mixture Tablet 2 mg	0.1	II	68 - 80	IaP: 31% IerP: 24 - 46 %	NA	0.5 – 8 mg per day or 1 mg/kg 4 times a day for 4 days	NA	[30,68–75], FDA
Cabozantinib S-malate	Cometriq®	Physical mixture Capsule 20, 80 mg	< 0.1 (pH > 4)	II	NA	IaP: 25 – 34 % IerP: 37 – 61 %	100 – 175 mg QD: L 175 – 250 mg QD: NL	140 mg QD	Fasted	FDA, EPAR
Capecitabine	Xeloda®	Prodrug-Physical mixture Tablet 150, 500 mg	26	I	~100	IaP: NA IerP: 27 – 89%	251 - 1757 mg/m^2/ day in 2 doses: L	800 - 1250 mg/m^2 BID 14 days or 625 mg/m^2 BID continuously	Fed	[30,76–78], EPAR, FDA
Ceritinib	Zykadia®	Physical mixture Capsule 150 mg	12 (pH 1) 0.03 (pH 4.5) 0.01 (pH 6.8)	IV	NA	IaP: NA IerP: 74 – 93 %	50 – 750 mg: L	750 mg QD	Fasted	FDA, EPAR
Chlorambucil	Leukeran®	Physical mixture Tablet 2 mg	< 0.1	NA	> 70	IaP: NA IerP: 36 – 84%	15 – 70 mg single dose: L	4 – 15 mg QD 3 – 8 weeks	NA	[79–82], FDA
Cobimetinib hemifumarate	Cotellic®	Physical mixture Tablet 20 mg	48 (pH 2) (pH 4.5) 0.8 (pH 6.8 - 7.5)	I	46	IaP: NA IerP: 60 %	10 – 100 mg QD: L	60 mg QD 21 days	Fasted or fed	FDA, EPAR
Crizotinib	Xalkori®	Physical mixture Capsule 200, 250 mg	0.034	IV	43	IaP: NA IerP: 28 – 44 %	50 – 300 mg single dose: NL	250 mg BID	Fasted or fed	[83], FDA, EPAR

Table 3. (continued)

Drug substance	Drug product	Formulation and amount of active drug	Solubility in water (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure or blood / plasma concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose pro-portionality	Recommend-ed dose	Fed or fasted	Reference
Cyclophospha-mide monohy-drate	Cytoxan® Endoxan®	Physical mixture Tablet 50 mg	40	I	> 85	NA	NA	1 – 5 mg/ kg QD	Fasted or fed	[30,84], FDA
Dabrafenib mesilate	Tafinlar®	Physical mixture Capsule 50, 75 mg	1 – 0.1 (pH 1) < 0.1 (pH > 4) 0.007 (pH 6)	II	95%	IaP: NA IerP: 37 – 38 %	12 mg – 300 mg BID: NL	150 mg BID	Fasted	FDA, EPAR
Dasatinib mono-hydrate	Sprycel®	Physical mixture Tablet 20, 50, 70, 80, 100, 140 mg	18 (pH 2.6) 0.205 (pH 4.28) 0.008 (pH 6.0)	II	NA	IaP: 44 % IerP: 33 %	15 – 180 mg QD: L	100 – 140 mg QD	Fasted or fed	[85], FDA, EPAR
Enzalutamide	Xtandi®	Lipid-based Capsule 40 mg	0.002 (pH 1 – 7)	II	≥ 84	IaP: 59% IerP: 19 – 80 %	30 – 360 mg QD: L	160 mg QD	Fasted or fed	FDA, EPAR
Erlotinib hydro-chloride	Tarceva®	Physical mixture Tablet 25, 100, 150 mg	0.4 (pH 2) < 0.4 (pH > 2)	II	59	IaP: 16 – 38 % IerP: 60%	100 – 1000 mg single dose: NL	100 - 150 mg QD	Fasted	[86,87], FDA, EPAR
Estramustine disodium phosphate monohydrate	Estracyt® Emcyt®	Prodrug-Physical mixture Capsule 140 mg	100 - 1000	I or III	44	IaP: NA IerP: 21 %	70 – 560 mg/day: L	10 – 16 mg/ kg per day in 2 – 4 divided doses	Fasted, not with dairy products	[82,88,89], FDA
Etoposide	Vepesid®	Lipid-based Capsule 50 mg, 100 mg	< 0.1	IV	65	IaP: 23 % IerP: 35 - 58%	25 – 200 mg: L > 300 mg: NL	100 – 200 mg/m^2 QD or 200 mg/ m^2 Q2D during 5 days	Fasted	[39,82,90,91], FDA
Everolimus	Afinitor® Votubia® Certican®	Solid dispersion Tablet 0.1, 0.25, 0.5, 0.75, 1, 2.5, 5, 10 mg Dispersible tablet 2, 3, 5 mg	0.0096	IV	NA	IaP: 17 – 19 % IerP: 36 – 51 %	5 – 20 mg: L	10 mg QD	Fasted or fed	[92], FDA, EPAR

Table 3. (continued)

Drug substance	Drug product	Formulation and amount of active drug	Solubility in water (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure or blood / plasma concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose proportionality	Recommended dose	Fed or fasted	Reference
Exemestane	Aromasin®	Physical mixture Tablet 25 mg	0.086 (pH 1.5) 0.079 (pH 5.5) 0.073 (pH 7.4)	II	NA	IaP: NA IerP: 39 – 100 %	25 – 200 mg single dose: L	25 mg QD	Fed	[30], FDA
Fludarabine phosphate	Fludara®	Prodrug-Physical mixture Tablet 10 mg	1 – 10	I	~ 55	IaP: NA IerP: 32 – 56 %	50 – 90 mg/day single dose: L	40 mg/m^2 QD 5 days	Fasted or fed	[30,82,93,94], FDA
Gefitinib	Iressa®	Physical mixture Tablet 250 mg	1 (pH 1 - 4) 0.4 (pH 5) 0.01 (pH 6) < 0.01 (pH ≥ 6.8)	II	59%	IaP: 4 – 42 % IerP: 27 – 65 %	50 – 250 mg QD: L > 250 mg QD: NL	250 mg QD	Fed or fasted	[86,95], FDA, EPAR
Gimeracil	Teysuno®	Physical mixture Capsule 4.35, 5.8 mg	1 – 10	III	≥ 44	IaP: NA IerP: 12 – 33%	25 – 40 mg/m^2: L	10 mg/m^2 BID 21 days	Fasted	[96], EPAR
Hydroxycarbamide	Siklos® Hydrea®	Physical mixture Tablet 100, 1000 mg Capsule 500 mg	100 – 1000	I	~100	NA	NA	15 – 30 mg/kg QD	Fasted or lightly-fed	EPAR
Ibrutinib	Imbruvica®	Physical mixture Capsule 140 mg	2 (pH 1.2) 0.06 (pH 3) 0.003 (pH 4.5 – 8)	II	3 - 6	IaP: 27 – 43% IerP: 41 – 136%	420 – 840 mg: L	420 – 560 mg QD	Fasted or fed	FDA, EPAR
Idarubicin hydrochloride	Zavedos®	Physical mixture Capsule 5, 10, 25 mg	1	I	41	IaP: 25 % IerP: 33%	NA	15 - 30 mg/m^2 QD 3 days or 30 – 50 mg/m^2 single dose per 3 weeks	NA	[30,97,98]
Idelalisib	Zydelig®	Physical mixture Tablet 100, 150 mg	1.1 (pH 1.2) < 0.10 (pH 7.7)	II	NA	IaP: 53% IerP: NA	50 – 350 mg BID: NL	150 mg BID	Fasted or fed	FDA, EPAR

Table 3. (continued)

Drug substance	Drug product	Formulation and amount of active drug	Solubility in water (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure or blood / plasma concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose pro-portionality	Recommend-ed dose	Fed or fasted	Reference
Imatinib me-silate	Glivec® Gleevec®	Physical mixture Capsule 50 mg, 100 mg Tablet 100 mg, 400 mg	33 - 100 (pH < 5.5) 0.050 (pH 7.4)	II	98	IaP: 64 % IerP: 31 – 66 %	25 – 1000 mg QD: L	100 – 600 mg QD, 400 mg BID	Fed	[99,100], FDA, EPAR
Lapatinib ditosylate mono-hydrate	Tykerb® Tyverb®	Physical mixture Tablet 250 mg	0.007 (water) 0.001 (pH 1)	IV	< 25	IaP: 30 – 36% IerP: 45 – 99 %	500 – 1600 mg QD: NL	1000 - 1500 mg QD	Fasted	[86], FDA, EPAR
Lenalidomide	Revlimid®	Physical mixture Capsule 2.5, 5. 7.5, 10, 15, 20, 25 mg	18 (pH 1) 0.4 – 0.5 (pH > 1)	III	≥ 85	IaP: 9 – 18 % IerP: 14 – 63 %	5 – 400 mg QD: L	10 - 25 mg QD 21 days	Fasted or fed	FDA, EPAR
Lenvatinib mesilate	Levima®	Physical mixture Capsule 4, 10 mg	< 0.1 (pH 3 – 7)	II or IV	NA	IaP: NA IerP: 19 – 78%	3.2 – 32 mg QD: L	18 - 24 mg QD	Fasted or fed	[101], FDA, EPAR
Letrozole	Femara®	Physical mixture Tablet 2.5 mg	0.04	I	100	IaP: NA IerP: 30 – 60 %	0.01 – 10 mg single dose: L	2.5 mg QD	Fasted or fed	[30], FDA
Lomustine	Belustine®	Prodrug-Physical mixture Capsules 40 mg	< 0.05	II or IV	≥ 73	IaP: NA IerP: 51 – 62 %	NA	100 - 130 mg/m^2 single dose per 6 weeks	Fasted	[102–104], FDA
Melphalan	Alkeran®	Physical mixture Tablet 2 mg	< 0.1	II or IV	56 – 93	IaP: NA IerP: 47%	NA	6 – 10 mg QD 4 – 10 days, 2 mg QD	NA	[105,106], FDA
Mercaptopurine monohydrate	Puri-Nethol® Xalupurine®	Prodrug-Physical mixture Suspension 20 mg/mL Tablet 50 mg	< 0.1	II	5 – 37	IaP: 45% IerP: tabet 39 - 69% Suspension 30 - 46%	20 – 100 mg/m^2 QD: NL	25 – 75 mg/ m^2 QD	Fasted, not with dairy products	[30,107–109], FDA, EPAR

Table 3. (continued)

Drug substance	Drug product	Formulation and amount of active drug	Solubility in water (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure or blood / plasma concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose proportionality	Recommended dose	Fed or fasted	Reference
Methotrexate disodium	Methotrexate	Prodrug-Physical mixture Tablet 2.5, 5, 7.5, 10 mg	< 0.1	II or IV	18 - 42	IaP: 20% IerP: NA	13 – 76 mg/m^2: NL	15 – 40 mg/ m^2 QW or 10 – 30 mg QD 4 - 8 days	Fasted, not with dairy products	[82,110–113], FDA
Mitotane	Lysodren®	Physical mixture Tablet 500 mg	< 0.1	II or IV	35 - 40	NA	NA	2 – 6 g QD in 3 - 4 doses	Fed, high-fat meal	FDA, EPAR
Nilotinib hydrochloride monohydrate	Tasigna®	Physical mixture Capsule 150, 200 mg	1 – 10 (pH 1) 0.1 – 1 (pH 2 – 3) < 0.1 (pH ≥ 4.5)	IV	NA	IaP: 31 - 44 % IerP: 30 – 70 %	400 – 600 mg BID: NL	300 - 400 mg BID	Fasted	FDA, EPAR
Nintedanib esilate	Ofev® Vergatef®	Lipid-based Capsule 100, 150 mg	5.0 (pH ≤ 4.5) 4.3 (pH 5) < 0.1 (pH ≥ 6.0)	II or IV	5	IaP: 33% IerP: 42 %	150 – 300 mg BID: L	200 mg BID 20 days	Fed	FDA, EPAR
Olaparib	Lynparza®	Lipid-based Capsule 50 mg	0.1 (pH 1 – 6.8)	IV	NA	IaP: NA IerP: 65 – 74%	100 – 600 mg BID: NL	400 mg BID	Fasted	FDA, EPAR
Osimertinib mesylate	Tagrisso®	Physical mixture Tablet 40, 80 mg	1 – 10 (pH 1.2) 10 – 33 (pH 4.6) 0.6 (pH 7) 0.07 (pH 7.5)	III	> 80	IaP: NA IerP: 40 – 50 %	20 – 240 mg QD: L	80 mg QD	Fasted or fed	FDA, EPAR
Oteracil mono-potassium	Teysuno®	Physical mixture Capsule 11.8, 15.8 mg	1 – 10 (pH 2 – 8)	III	≥ 13	IaP: NA IerP: 38 – 62 %	25 – 40 mg/m^2: L	25 mg/m^2 BID 21 days	Fasted	[96], EPAR
Panobinostat lactate anhydrous	Farydak®	Physical mixture Capsule 10, 15, 20 mg	1.1 (pH 1 – 2) 4.8 (pH 4.5) 0.3 (pH 6.8) 0.06 (pH 7.6)	II	21	IaP: 38 – 52% IerP: 66 – 80 %	10 – 80 mg Q2D: NL	20 mg Q2D for 2 weeks	Fasted or fed	FDA, EPAR

Table 3. (continued)

Drug substance	Drug product	Formulation and amount of active drug	Solubility in water (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure or blood / plasma concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose proportionality	Recommended dose	Fed or fasted	Reference
Pazopanib hydrochloride	Votrient®	Physical mixture Tablet 200, 400 mg	1 – 10 (pH 1) < 0.1 (pH ≥ 4)	II	14 – 39	IaP: 26% IerP: 40 %	50 – 2000 mg QD: NL	800 mg QD	Fasted	[114], FDA, EPAR
Pomalidomide	Imnovid® Pomalyst®	Physical mixture Capsule 1, 2, 3, 4 mg	0.014 (pH 1.2 – 6.8)	IV	NA	IaP: 11 – 46 % IerP: 21 – 55 %	1 – 50 mg QD: NL	4 mg QD 21 days	Fasted or fed	FDA, EPAR
Ponatinib hydrochloride	Iclusig®	Physical mixture Tablet 15, 30, 45 mg	7.8 (pH 1.7) 0.0034 (pH 2.7) 0.00016 (pH 7.5)	II or IV	NA	IaP: NA IerP: 70%	15 – 60 mg: NL	45 mg QD	Fasted or fed	FDA, EPAR
Procarbazine hydrochloride	Natulan® Matulane®	Prodrug-Physical mixture Capsule 50 mg	100 – 1000	NA	≥ 70	IaP: NA IerP: 38 – 106%	NA	100 – 200 mg/m^2 per day	NA	[115–117]
Regorafenib monohydrate	Stivarga®	Solid dispersion Tablet 40 mg	0.0026 (pH 4.5 + 0.1% sodium dodecyl sulphate) < 0.1 (water)	II	NA	IaP: 32 – 64 % IerP: 43 – 182 %	60 – 160 mg single dose: L > 60 mg QD: NL	160 mg QD 21 days	Fed, low-fat meal	[56], FDA, EPAR
Ruxolitinib phosphate	Jakavi®	Physical mixture Tablet 5, 10, 15, 20 mg	> 0.5 (pH ≤ 3.3) 0.15 (pH 7.5)	I	96	IaP: NA IerP: 2 – 57%	10 – 50 mg BID: L	5 – 25 mg BID	Fasted or fed	FDA, EPAR
Sonidegib diphosphate	Odomzo®	Physical mixture Capsule 200 mg	< 0.0002 (pH > 2)	II	~5	IaP: NA IerP: 60 – 65 %	100 – 200 mg QD: L ≥ 200 mg QD: NL	200 mg QD	Fasted	FDA, EPAR
Sorafenib tosylate	Nexavar®	Physical mixture Tablet 200 mg	0.00034 (pH 1) 0.00013 (pH 4.5)	II	NA	IaP: 44 – 47% IerP: 36 – 91%	200 – 400 mg BID: L > 400 mg BID: NL	400 mg BID	Fasted or fed (low or moderate-fat meal)	FDA, EPAR

Table 3. (continued)

Drug substance	Drug product	Formulation and amount of active drug	Solubility in water (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure or blood / plasma concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose proportionality	Recommended dose	Fed or fasted	Reference
Sunitinib malate	Sutent®	Physical mixture Capsule 12.5, 25, 37.5, 50 mg	25 (pH 1.2 – 6.8) < 0.1 (pH > 6.8)	IV	NA	IaP: 29 – 52 % IerP: 25 – 60 %	25 – 100 mg QD: L	50 mg QD 28 days or 37.5 mg QD	Fasted or fed	FDA, EPAR
Tamoxifen citrate	Nolvadex®	Prodrug-Physical mixture Tablet 10, 20, 30, 40 mg	0.5 (water) 0.2 (pH 1.7)	II	100	IaP: 12 – 15 % IerP: 51 – 69 %	NA	20 mg QD – 20 mg BID	Fasted or fed	[39,118,119], FDA
Tegafur	Teysuno®	Prodrug-Physical mixture Capsule 15, 20 mg	NA	I	> 83	IaP: NA IerP: 45 %	25 – 50 mg/m^2 QD: L	25 mg/m^2 BID 21 days	Fasted	[96], EPAR
Temozolomide	Temodal® Temodar® Temomedac®	Prodrug-Physical mixture Capsule 5, 20, 100, 140, 180, 250 mg	2 – 4 (water)	I or II	100	IaP: NA IerP: 4 – 56 %	100 – 250 mg/m^2 QD: L	75 mg/m^2 QD 42 days, 150 – 200 mg/m^2 QD 5 days	Fasted	FDA, EPAR
Thalidomide	Thalidomide®	Physical mixture Capsule 50 mg	0.05	II or IV	NA	IaP: NA IerP: 17 – 53%	50 – 400 mg single dose: NL	100 – 400 mg QHS 42 days	Fasted or fed	[30], FDA, EPAR
Thioguanine	Tabloid® Lanvis®	Prodrug-Physical mixture Tablet 40 mg	< 0.1	II or IV	14 – 46	Iap: NA IerP: 83 %	NA	60 - 200 mg/m^2 QD	NA	[116,120], FDA
Tipiracil hydrochloride	Lonsurf®	Physical mixture Tablet 6.14, 8.19 mg	120 (pH 1.2 – 7.5)	III	< 50	IaP: 29 – 36% IerP: 54 – 59 %	6.14 – 14.3 mg/m^2: L	14.3 mg/m^2 BID 5 days	Fed	FDA, EPAR
Topotecan hydrochloride	Hycamtin®	Lipid-based Capsule 0.25, 1 mg	42 - 70 (pH 1 - 3) 5 (pH 4.5) 0.3 (pH 6.8)	III	32	IaP: 28% IerP: 22%	1.2 – 2.7 mg/m^2 QD: L	2.3 mg/m^2 QD 5 days	Fasted or fed	[121], FDA, EPAR
Toremifene citrate	Fareston®	Physical mixture Tablet 60 mg	0.63 (water) 0.38 (pH 1.7)	I	100	IaP: NA IerP: 32 – 46%	10 – 400 mg QD: L	60 mg QD	Fasted or fed	[30,122,123], FDA, EPAR

Table 3. (continued)

Drug substance	Drug product	Formulation and amount of active drug	Solubility in water (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure or blood / plasma concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose pro-portionality	Recommend-ed dose	Fed or fasted	Reference
Trametinib di-methyl sulfoxide	Mekinist®	Physical mixture Tablet 0.5, 2 mg	0.0003 (pH 1.2 - 8)	IV	72	IaP: NA IerP: 28 – 36%	0.125 – 4 mg QD: L	2 mg QD	Fasted	[124], FDA, EPAR
Tretinoin	Vesanoid®	Lipid-based Capsule 10 mg	< 0.1	II	50	IaP: NA IerP: 20 – 155 %	25 – 45 mg/m^2 per day: NL	22.5 mg/m^2 BID 90 days	Fed	[30,125]
Trifluridine	Lonsurf®	Prodrug-Physical mixture Tablet 15, 20 mg	60 (pH 1.2 – 7.5)	III	NA	IaP: 16 – 25% IerP: 61 – 64 %	15 – 35 mg/m^2: NL	35 mg/m^2 BID 5 days	Fed	FDA, EPAR
Vandetanib	Caprelsa®	Physical mixture Tablet 100, 300 mg	0.35 (pH 6.8) 0.008 (water)	II	NA	IaP: 10 – 20 % IerP: 60 %	50 – 300 mg QD: L	300 mg QD	Fasted or fed	FDA, EPAR
Vemurafenib	Zelboraf®	Solid dispersion Tablet 240 mg	< 0.00026 (pH 1 – 4.5) 0.0005 (pH 6.8) 0.0009 (pH 7.5)	IV	NA	IaP: 28% IerP: 45%	240 – 960 mg BID: L	960 mg BID	Fed	[126], FDA, EPAR
Vinorelbine ditartrate	Navelbine®	Co-solvent Capsule 20, 30 mg	0.115 (water) > 1000 (pH 3.5)	IV	36	IaP: 19 % IerP: 20 %	60 – 100 mg/m^2 QW: L	60 – 80 mg/m^2 QW	Fed	[39,127–129], FDA
Vismodegib	Erivedge®	Physical mixture Capsule 150 mg	1 (pH 1) 0.0001 (pH 7)	II	7 – 32	IaP: 27 – 42 % IerP: 40 %	150 – 540 mg QD: NL	150 mg QD	Fasted or fed	FDA, EPAR

5. CONCLUSIONS

A crucial characteristic for complete and predictable absorption of an orally administered oncolytic is that the drug dissolves in gastro-intestinal fluids. The problem is that many orally administered oncolytics are poorly soluble in water. In half of the currently licensed arsenal of oral oncolytics poor drug dissolution is likely to play a major role in poor absorption pharmacokinetics such as incomplete bioavailability, high intra-patient variability in blood concentrations and lack of linear relationship between dose and blood concentrations. Dissolution-limited absorption might be resolved with the solid dispersion technology because this formulation method can induce super-saturated drug dissolution and with that enhanced absorption. There are three licensed oral oncolytics with a solid dispersion formulation: vemurafenib, regorafenib and everolimus and they result in a significantly increased dissolution and enhanced absorption relative to their corresponding crystalline physical mixture formulations. We believe that the solid dispersion can be feasible and successful for improving dissolution-limited absorption of poorly soluble drugs and encourage the application of this formulation method in the pharmaceutical development of oral oncolytics.

Conflict of interest: B. Nuijen, J.H. Beijnen and J.H.M. Schellens have a patent in oral taxane formulations. J.H. Beijnen and J.H.M. Schellens are employees and stockholders of Modra Pharmaceuticals BV, a spin-off company developing oral taxanes formulated as a solid dispersion.

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PART II

DEVELOPMENT OF SOLID DISPERSION TABLETS CONTAINING ELACRIDAR HYDROCHLORIDE

VALIDATION OF A LIQUID CHROMATOGRAPHIC METHOD FOR THE PHARMACEUTICAL QUALITY CONTROL OF PRODUCTS CONTAINING ELACRIDAR

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CHAPTER 2.1

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ABSTRACT

Many anticancer drugs have an impaired bioavailability and poor brain penetration because they are substrates to drug efflux pumps such as P-glycoprotein and Breast Cancer Resistance Protein. Elacridar is a strong inhibitor of these two drug efflux pumps and therefore has great potential to improve oral absorption and brain penetration of many anticancer drugs. Currently, a clinical formulation of elacridar is unavailable and therefore the pharmaceutical development of a drug product is highly warranted. This also necessitates the availability of an analytical method for its quality control. A reverse-phase high-performance liquid chromatographic method with ultraviolet detection was developed for the pharmaceutical quality control of products containing elacridar as the active pharmaceutical ingredient. The analytical method was validated for linearity, accuracy, precision, selectivity, carry-over, stability stock and reference solutions, stability in the final extract, stability-indicating capability and impurity testing. We found that elacridar is unstable in aqueous solutions that are exposed to light because a hydroxylation product of elacridar is formed. Therefore, sample solutions with elacridar must be protected from light.

1. INTRODUCTION

One of the important reasons for chemotherapy failure is caused by the fact that many anticancer agents cannot reach tumor cells in sufficient quantities. This is often the result of drug-efflux pumps Permeability Glycoprotein (PgP) and breast cancer resistance protein (BCRP) which are present in the gastro-intestinal tract, at the blood-brain barrier and in tumor cells [1–4]. A drug that is a substrate for PgP and/or BCRP cannot enter the cell and therefore cannot be absorbed into the central systemic circulation, brain and tumor. Examples of anticancer drugs that are substrates of PgP/BCRP are topotecan, paclitaxel, docetaxel, erlotinib, pazopanib, imatinib and nilotinib [5,6].

Elacridar or N-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl) phenyl)-5-methoxy-9-oxo-9,10-dihydroacridine-4-carboxamide (GF120918) is an inhibitor of PgP and BCRP [7] and, as confirmed in several clinical trials, it can increase the oral bioavailability of orally administered anticancer drugs such as paclitaxel and topotecan [8–12]. Furthermore, in pre-clinical research elacridar inhibited PgP at the blood-brain barrier and consequently increased the penetration of various anticancer agents in the brain [13–21]. More clinical trials are warranted to study the boosting effect of elacridar but cannot be performed because currently there is no clinical formulation available. Therefore, we developed a tablet formulation containing 23.5 mg of elacridar as the active pharmaceutical ingredient (API). The formulation is to be used in proof-of-concept clinical studies that study the boosting effect of elacridar on various anticancer agents. An amorphous solid dispersion was made to improve the poor solubility in water [12]. In an amorphous solid dispersion the drug is molecularly dispersed into a hydrophilic amorphous polymer [22] and the presence of a hydrophilic polymer and amorphous drug particles result in improved drug solubility [23]. This new formulation also necessitated the availability of a validated analytical method for its quality control. There are currently no quality control monographs about elacridar published in the European Pharmacopoeia, United States Pharmacopoeia or Japanese Pharmacopoeia nor are there validated analytical methods for pharmaceutical quality control published in scientific literature. In this paper we describe the development and validation of a reverse-phase-high-performance liquid chromatography – ultra violet detection (HPLC-UV) method for the pharmaceutical quality control of a drug powder, an amorphous solid dispersion and a tablet formulation containing elacridar as the API.

2. MATERIALS AND METHODS

2.1 Chemicals

5-Methoxy-9-oxo-9,10-dihydroacridine-4-carboxylic acid (5-MODICA) and 4-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolinyl)ethyl]aniline (4-DTHIA) were purchased from AvaChem Scientific (San Antonio, TX, USA). Dimethyl sulfoxide (DMSO), acetonitrile, potassium dihydrogen phosphate and sodium dodecyl sulphate (SDS) were purchased from Merck (Darmstadt, Germany). The preparation of Simulated Intestinal Fluid without pancreatic enzymes (SIFsp, pH 6.8) was according to [24]. Distilled water was from B. Braun (Melsungen, Germany). Povidone K30 was from BasF Chemtrade (Ludwigshafen, Germany). Granulated lactose monohydrate SuperTab® 30GR was from DFE Pharma (Goch, Germany). Colloidal silicon dioxide and magnesium stearate were from Fagron (Capelle a/d Ijssel, The Netherlands). Croscarmellose sodium was from FMC (Philadelphia, USA).

2.2 Drug powder and formulated products

The drug powder was elacridar hydrochloride (> 99% purity) and was synthesized according to the procedure as described in [25]. A summary of this synthesis is displayed in Figure 1.

The entire production process was compliant with Good Manufacturing Practices. The intermediate product was an amorphous solid dispersion. For this, a solution of elacridar hydrochloride-povidone K30-SDS (12.5:75:12.5, w/w/w) in DMSO was prepared to a total excipient concentration of 80 mg/mL. The solution was transferred to stainless steel boxes (Gastronorm 1/9, The Netherlands). DMSO was removed by lyophilization and this was performed according to a process earlier used by den Brok et al [26] in a Lyovac GT4 (GEA Lyophil, Hürth, Germany). The intermediate product was a yellow powder stored in a glass bottle with an airtight polypropylene screw cap in the dark at 2 – 8 °C in a desiccator.
The final drug product was a tablet with 23.5 mg elacridar (corresponding to 25 mg elacridar hydrochloride). For this, a powder mixture of intermediate product-granulated lactose monohydrate-croscarmellose sodium-anhydrous colloidal silicon dioxide-magnesium stearate (30:63:5:1:1, w/w/w/w/w) was weighed in a 2 L stainless steel box and mixed in a Turbula Mixer T10B (Willy A. Bachofen, Muttenz, Switzerland) for 30 minutes. The powder mixture was then pressed on an eccentric tablet press (Korsch, EK0, Berlin, Germany) and tablets were sealed in aluminum blisters and stored at – 20 °C in the dark until analysis.

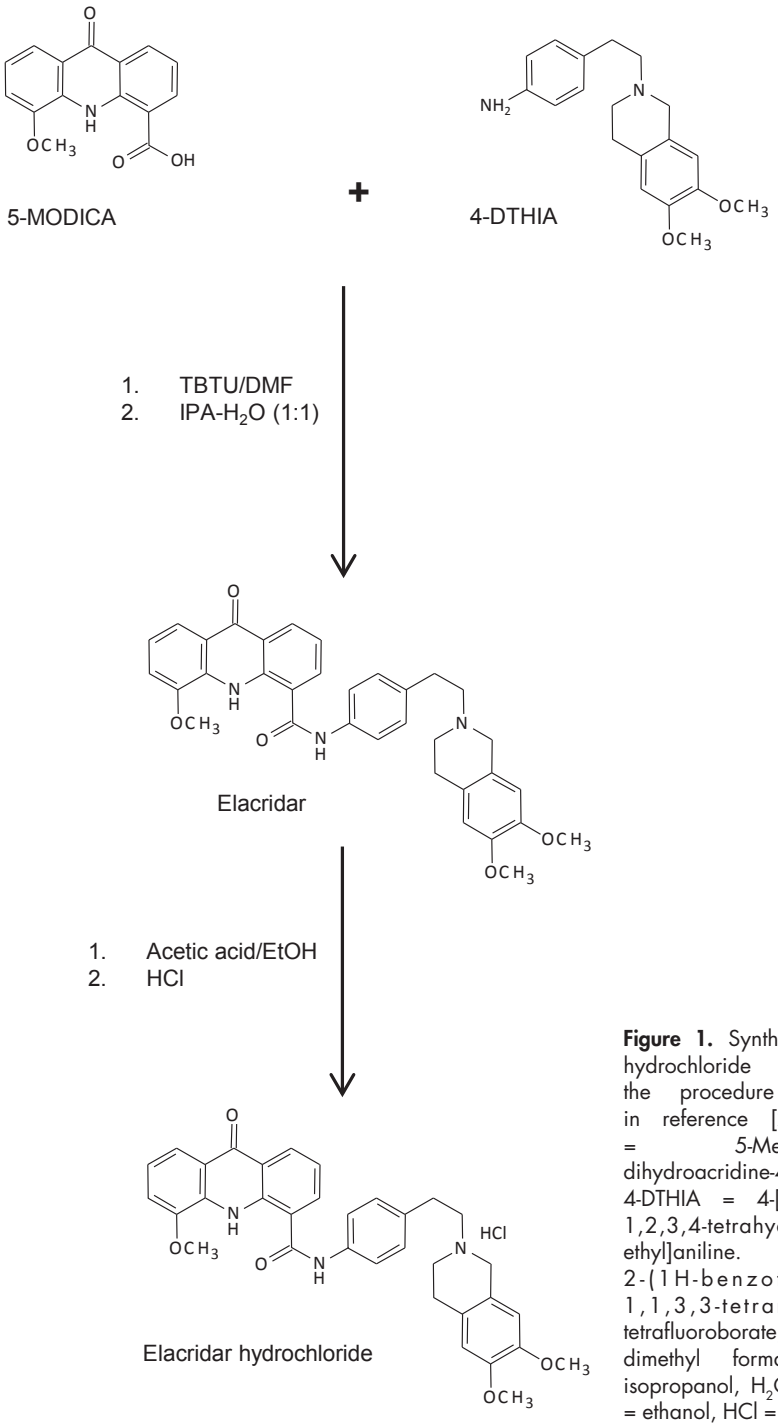

Figure 1. Synthesis of elacridar hydrochloride according to the procedure as described in reference [25]. 5-MODICA = 5-Methoxy-9-oxo-9,10-dihydroacridine-4-carboxylic acid, 4-DTHIA = 4-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolinyl) ethyl]aniline. TBTU = 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, DMF = N,N-dimethyl formamide, IPA = isopropanol, H_2O = water, EtOH = ethanol, HCl = hydrochloric acid

2.3 Sample preparation

Stock solutions contained 188 µg/mL elacridar (200 µg/mL elacridar hydrochloride) in DMSO and were stored in polypropylene tubes in the dark at – 20 °C.
Calibration standards (CAL, 1 – 20 µg/mL elacridar hydrochloride) were prepared on the day of analysis from a stock solution and diluted to the desired concentration in SIFsp-DMSO (33:67, v/v). Quality control standards (QC, 1 – 20 µg/mL elacridar hydrochloride) were diluted to the desired concentration in SIFsp-DMSO (33:67, v/v) from a separately prepared stock solution.
For the preparation of reference solutions (10 µg/mL elacridar hydrochloride), two separately prepared stock solutions were diluted in water-DMSO (20:80, v/v). Reference solutions were freshly prepared for every analytical batch.
For the quality control of drug powder and intermediate product, an amount equivalent 23.5 mg elacridar (25 mg elacridar hydrochloride) was dissolved in 50 mL DMSO by using a shaker. 0.200 mL of this solution was added to 7.800 mL of DMSO in a polypropylene tube. A volume of 2.000 mL water was added and homogenized.
For the quality control of the final drug product, tablets in blister package (stored at – 20 °C) were placed in the dark for 1.5 hours in a desiccator to prevent the adsorption of water when the tablets reach ambient temperature. Subsequently the tablet was pulverized with a mortar and pestle and dissolved in 50 mL DMSO. The solution was centrifuged at 3000 rpm for 15 minutes and 0.200 mL of the supernatant was added to 7.800 mL of DMSO. Then 2.000 mL of water was added to the polypropylene tube and the solution was homogenized.
Aqueous samples were protected from light by transferring them to amber-colored autosampler vials immediately after preparation and by storing vials at 2 – 8 °C until and during analysis. Samples were analyzed directly after preparation.

2.4 Instruments

The HPLC-UV system consisted of an 1100 Series binary HPLC pump Model G1312A, 1100 series G1367A autosampler and 1100 series G1314A UV detector (Agilent Technologies, Santa Clara, CA, USA). The column was a Waters Symmetry end-capped C-18 deactivated silica column (150 x 4,6 mm ID, particle size 3,5 µm). The eluent was an isocratic mixture of ammonium acetate (pH 5.0, 120 mM):acetonitrile (52.5:47.5, v/v) at a flow of 0.5 mL/minute and ambient column temperature. Quantification was executed at 259 nm. The runtime was 10 minutes, sample injection volume was 10 µL and the autosampler temperature was 5 ± 1 °C.

2.5 Method validation

Validation of the HPLC-UV method was based on the procedure as published by the ICH guideline on validation of analytical procedures [27]. Pre-defined acceptance criteria are shown in Table 1.

Linearity

CALs were prepared according to paragraph 2.3, analyzed in duplicate and in three different analytical batches. Least-squares linear regression was applied on the concentration versus peak area plot and the correlation coefficient (R) was calculated. Deviations from linear fit were established by comparing the back-calculated concentrations with the nominal concentrations of the calibration standards.

Accuracy

QC samples were analyzed in five-fold and analyzed on two different occasions. For each batch freshly prepared QCs and CALs were used. Concentrations in the QC samples were calculated by least-squares linear regression. The bias was calculated by dividing the difference between the measured concentration and the nominal concentration by the nominal concentration. Intra-run accuracy was obtained by calculating the average bias of five analyzed QCs per analytical batch per concentration level. Inter-run accuracy was obtained by calculating the average bias of all analyzed QCs on the two different analysis occasions per concentration level.

Precision

QC samples that were used to assess the accuracy, were also used to determine the intra-run precision (repeatability [27]) and inter-run precision (intermediate precision [27]). For intra-run precision the relative standard deviation (RSD) of the measured concentration of each QC per analytical batch per concentration level was calculated. For inter-run precision the RSD of the measured concentration of QCs of the two different analytical batches per concentration level was calculated.

Selectivity

Three "blank tablets" were used which contained all ingredients of the final drug product except the drug powder. Each blank tablet was processed as described in paragraph 2.3 and analyzed immediately after preparation.

Carry-over

After analysis of the upper limit of quantification (calibration standard containing 16.7 µg/mL) blank matrix samples (SIFsp:DMSO, 33:67 v/v) were analyzed. The procedure was repeated twice and performed on two different analysis days.

Stability of stock and reference solutions

Stock solutions were analyzed after 11 months and 21 months of storage at – 20 °C and after 24 hours at room temperature in indoor natural daylight. Stock solutions were prepared according to paragraph 2.3 and analyzed in five-fold. The concentration was measured using a reference solution prepared from a fresh stock solution. Reference solutions were stored for 4 days in the dark at 2 – 8 °C and quantified using freshly prepared reference solutions. The bias was calculated by the same formula as described in "accuracy" (paragraph 2.5).

Stability in the final extract

Calibration standards were analyzed at t = 0 and after 7 days of storage in the dark at 2 – 8 °C and quantified by least-squares linear regression using freshly prepared CALs. The bias and RSD were calculated by the same formula as described in "accuracy" (paragraph 2.5).

Stability-indicating capability

Reference solutions were prepared according to paragraph 2.3 and exposed to various stress factors: 1 M sodium hydroxide, 1 M hydrochloric acid or 25% hydrogen peroxide. Duplicate samples of each type of stress factor were prepared and one sample was stored in the dark and the other sample was stored for 24 hours in indoor natural daylight. Samples were processed and analyzed immediately after preparation and after 24 hours.

Impurity test

5-MODICA (10 µg/mL in water-DMSO (20:80, v/v)) and 4-DTHIA (10 µg/mL in water-DMSO (20:80, v/v)) were used to assess the ability of the analytical method to separate impurities related to the drug powder. Samples were measured on an HPLC system coupled to a photo diode array detector (Ultimate 3000 Series, Thermo Scientific, Waltham, MA, USA). Eluent, column, flow rate and injection volume were equal to that described in paragraph 2.4. Ultra-violet and visible light (UV-VIS) spectra were recorded from 200 nm to 800 nm.

2.6 Application of the HPLC-UV method

The HPLC-UV method was used to assess the content, purity and dissolution of the drug powder, intermediate product and final drug product. To determine content and purity samples were prepared according to paragraph 2.3 and were quantified using reference solutions.

Dissolution was tested in a European Pharmacopoeia dissolution tester (Erweka, Heusenstamm, Germany) with a type II paddle at 100 rpm [28]. SIFsp (pH 6.8, 37 °C) [24] was the dissolution medium. The final drug product was placed in a vessel with 500 mL SIFsp. Duration of the dissolution test was 4 h and samples were taken at 0, 15, 30, 45, 60, 90, 120, 180 and 240 min. One mL of each sample was directly filtrated through a 0.45 µm PVDF filter (Darmstadt, Germany) and diluted with 2 mL DMSO. CALs and QCs were freshly prepared according to paragraph 2.3. Samples were processed immediately after collection, protected from light by transferring them to amber-colored autosampler vials and stored at 2 – 8 °C until and during analysis.

2.7 Characterization of the degradation product

Two reference solutions were prepared according "sample preparation". One reference solution was stored for 4 days in indoor natural daylight at 15 – 25 °C and the other reference solution was stored for 4 days in the dark at 15 – 25 °C. Samples were analyzed on an HPLC system coupled to a LTQ XL Iontrap (Thermo Scientific, Waltham, MA, USA) operating in the negative ionization mode. The eluent was ammonium acetate (pH 5.0, 20 mM)-acetonitrile (65:35, v/v) and the flow was 0.5 mL/minute. The column was a Waters Symmetry C-18 (150 mm x 4,6 mm ID, particle size of 3,5 µm) at ambient temperature. Samples were stored in a dark autosampler at 5 ± 1 °C. Ten µL of sample solution was injected and the run time was 45 minutes.

3. RESULTS AND DISCUSSION

3.1 Liquid chromatography method development

The literature currently describes at least five HPLC methods for elacridar quantification [18,29–32]. One of them used an HPLC-UV method with isocratic eluent ammonium acetate (pH 5.0, 200 mM)-acetonitrile-methanol (57.2:35:7.8, v/v/v) and a retention time of 11 minutes [31]. The concentration of ammonium acetate was lowered to 120 mM and acetonitrile was used as modifier to improve

Table 1. Validation of the HPLC-UV method (concentrations expressed as elacridar hydrochloride)

Validation parameter	Conditions	Matrix	N	Nominal concentration (µg/mL)	Measured concentration (µg/mL)	Pre-defined criteria	Result
Linearity	Inter-run	SIFsp-DMSO (33:67, v/v)	36	1.00 – 20.09	1.01 – 20.27	$R \geq 0.995$	R: 1.000
			6			Dev ≤ ± 4%	1.00%
			6	1.00	1.01	Dev ≤ ± 4%	0.00%
			6	3.35	3.35	Dev ≤ ± 3%	-1.55%
			6	8.37	8.24	Dev ≤ ± 3%	-0.90%
			6	13.39	13.27	Dev ≤ ± 3%	0.24%
			6	16.74	16.78	Dev ≤ ± 3%	0.90%
				20.09	20.27		
Accuracy	Inter-run	SIFsp-DMSO (33:67, v/v)	10	1.00	1.00	Bias ≤ ± 4%	0.00%
			10	3.33	3.38	Bias ≤ ± 4%	1.50%
			10	8.33	8.27	Bias ≤ ± 3%	-0.72%
			10	16.66	16.60	Bias ≤ ± 3%	-0.36%
			10	19.99	20.25	Bias ≤ ± 3%	1.30%
Precision	Inter-run	SIFsp-DMSO (33:67, v/v)	10	1.00	1.00	RSD ≤ ± 4%	1.45%
			10	3.33	3.38	RSD ≤ ± 4%	1.94%
			10	8.33	8.27	RSD ≤ ± 3%	0.26%
			10	16.66	16.60	RSD ≤ ± 3%	0.28%
			10	19.99	20.25	RSD ≤ ± 3%	0.51%
Selectivity	Blank tablet*	Water-DMSO (20:80, v/v)	3	-	-	No peaks at t_r elacridar	No peak detected
Carry-over	CAL 16.74 µg/mL, then followed by matrix solution	SIFsp-DMSO (33:67, v/v)	4	-	-	≤ 20% of the lower limit of quantification	No peak detected
Stability stock solution	- 20 °C dark	DMSO					
	11 months		5	201.78	199.58	Bias ≤ ± 3%	-1.09%
	21 months		5	200.40	197.66	Bias ≤ ± 3%	-1.37%
	15-25 °C indoor natural daylight 24 h	DMSO	5	201.78	203.84	Bias ≤ ± 3%	1.02%
Stability reference solution	4 days 2 – 8 °C dark	Water-DMSO (20:80, v/v)	5	10.09	10.11	Bias ≤ ± 3%	0.20%
Stability final extract	7 days 2 – 8 °C dark	SIFsp-DMSO (33:67, v/v)	2	1.00	1.03	Bias ≤ ± 4%	3.00%
			2	3.35	3.41	Bias ≤ ± 4%	1.79%
			2	8.37	8.25	Bias ≤ ± 3%	-1.43%
			2	13.39	13.12	Bias ≤ ± 3%	-2.02%
			2	16.74	16.83	Bias ≤ ± 3%	0.54%
			2	20.09	20.65	Bias ≤ ± 3%	2.79%

* Blank tablet contains the same ingredients and in the same proportions as in an elacridar solid dispersion tablet except elacridar hydrochloride.
RSD = relative standard deviation, Dev = deviation from linear fit

the peak shape. Using this eluent the retention time was around 7 minutes and the total run time was 10 minutes.
The original HPLC-UV method detected at 227 nm because in this method a wavelength was required that could also detect two other analytes (paclitaxel and docetaxel) [31]. For the development of an HPLC-UV for elacridar quality control the detection wavelength was changed to 259 nm because the signal-to-noise ratio of elacridar was approximately 34 times higher than at 227 nm.

3.2 Method validation

The results for linearity, accuracy, precision, selectivity, carry-over, stock and reference solution stability and stability in the final extract are shown in Table 1. Linearity, inter-run accuracy and inter-run precision complied with the criteria. Intra-run accuracy/precision criteria were the same as inter-run accuracy/precision and were also fulfilled. No other components of the final drug product eluted at the retention time of elacridar and there was no carry-over. Stock solutions were stable at – 20 °C for at least 21 months and for 24 hours at room temperature in light, reference solutions could be stored in the dark at 2 – 8 °C for at least 4 days and final extracts were stable for at least 7 days at 2 – 8 °C in the dark.

The stability-indicating capability of the analytical method was studied by exposing reference solutions to light, sodium hydroxide, hydrogen peroxide or hydrochloric acid. Figure 2A shows a chromatogram of a reference solution that was stored for 24 hours in the dark or in indoor natural daylight. In reference solutions that were stored in the light two peaks were detected after the dead-time: one peak corresponded to elacridar and the other peak eluted approximately after 6 minutes. The sum of the peak area at 6 minutes and elacridar peak area equaled the area of an elacridar peak from a freshly prepared reference solution (Figure 2 A). According to Figure 3, the degradation product developed predominantly in neutral solutions and in solutions exposed to sodium hydroxide and was less prominent in solutions that were exposed to hydrogen peroxide or hydrochloric acid. This suggested that the unknown peak was a light-induced degradation product of elacridar. The UV-VIS absorption spectra of elacridar and the degradation product are shown in Figure 2B and 2C respectively. The degradation product contained an extra absorption maximum at 312 nm, indicating that the chromophore of elacridar was altered. The degradation product was also detected in formulation sample solutions with water-DMSO and SIFsp-DMSO that were stored for 24 hours in the light.

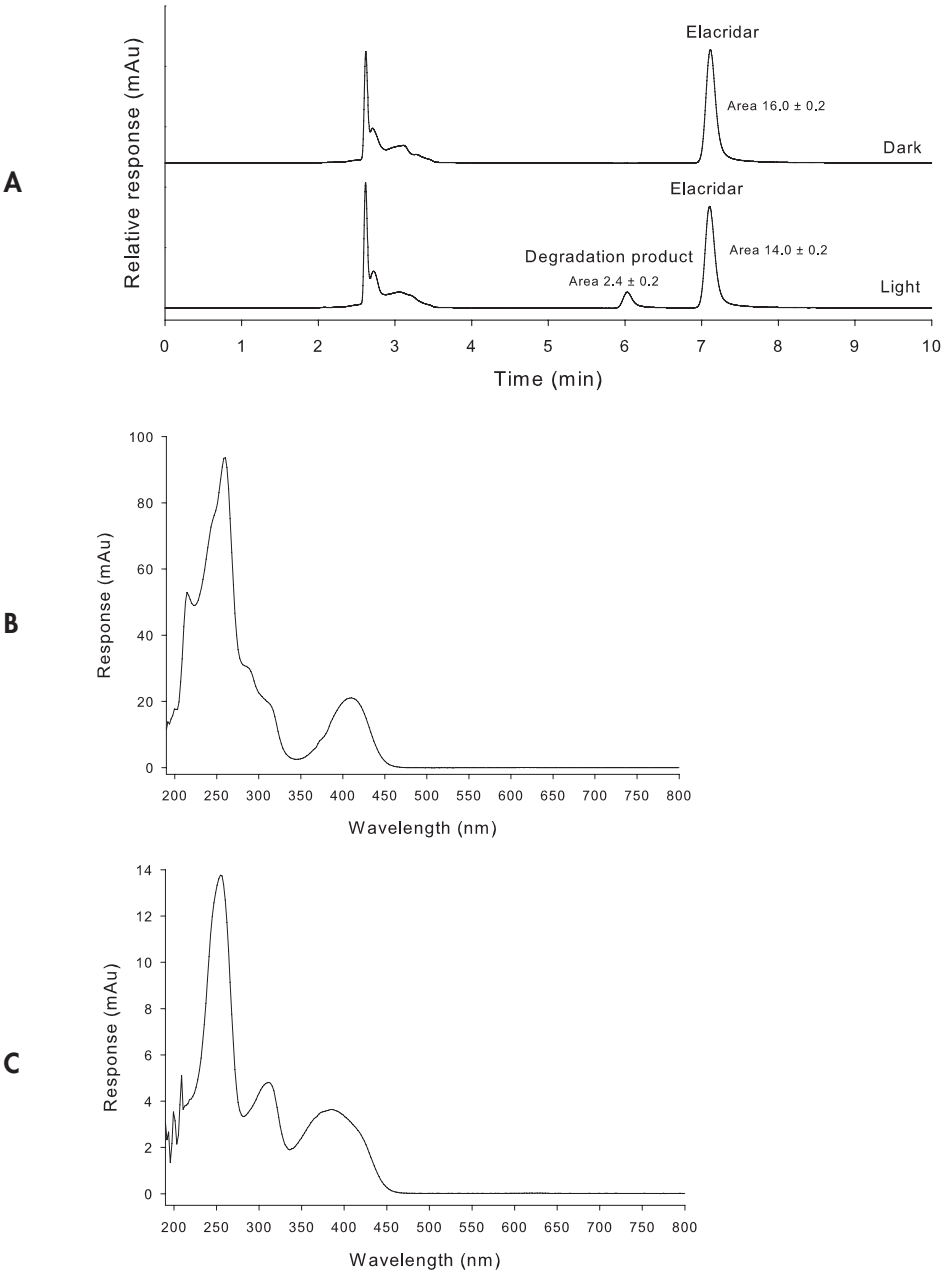

Figure 2. HPLC-UV chromatogram of a reference solution (10 µg/mL elacridar hydrochloride in water-DMSO (20:80, v/v)) that was stored for 24 hours either in the dark or in indoor natural daylight **(A)** and UV-VIS absorption spectrum of elacridar **(B)** and the degradation product **(C)**.

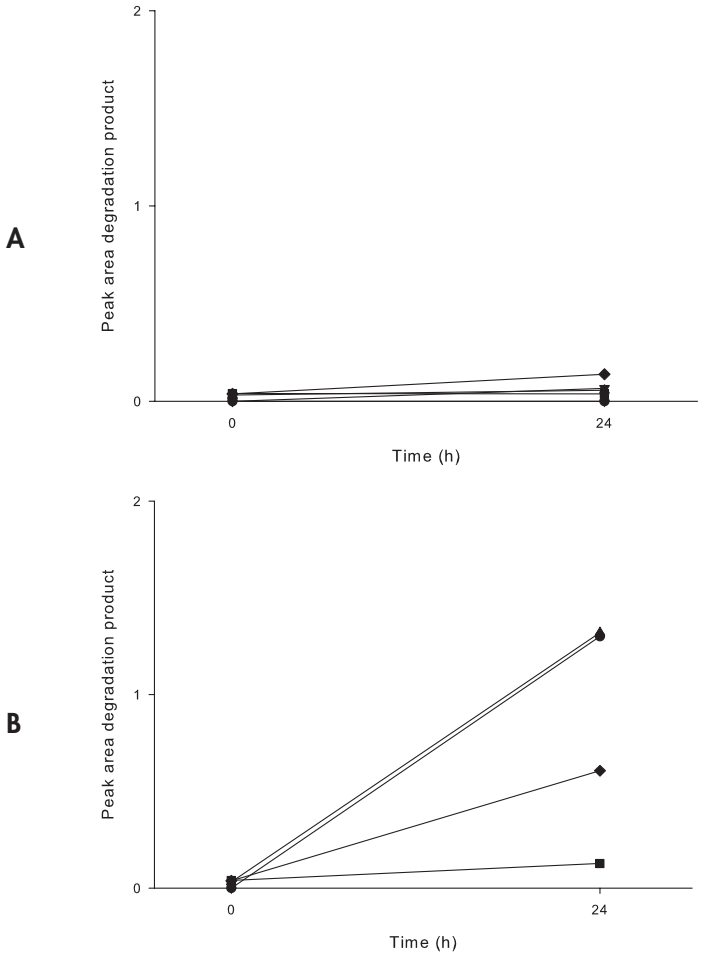

Figure 3. The peak area of degradation product (retention time 6 minutes) when 10 µg/mL elacridar hydrochloride in water-DMSO (20:80, v/v) reference solution is exposed to ● water, ■ 1 M hydrochloric acid, ♦ 25% hydrogen peroxide or ▲ 1 M sodium hydroxide and stored for 24 hours at room temperature in the dark **(A)** or in indoor natural daylight **(B)**.

For the impurity test two elacridar-related impurities (5-MODICA and 4-DTHIA) were analyzed and their chromatograms are shown in Figure 4A and 4B respectively. 5-MODICA and 4-DTHIA did not elute at the retention time of elacridar and therefore the analytical method passed the impurity test.

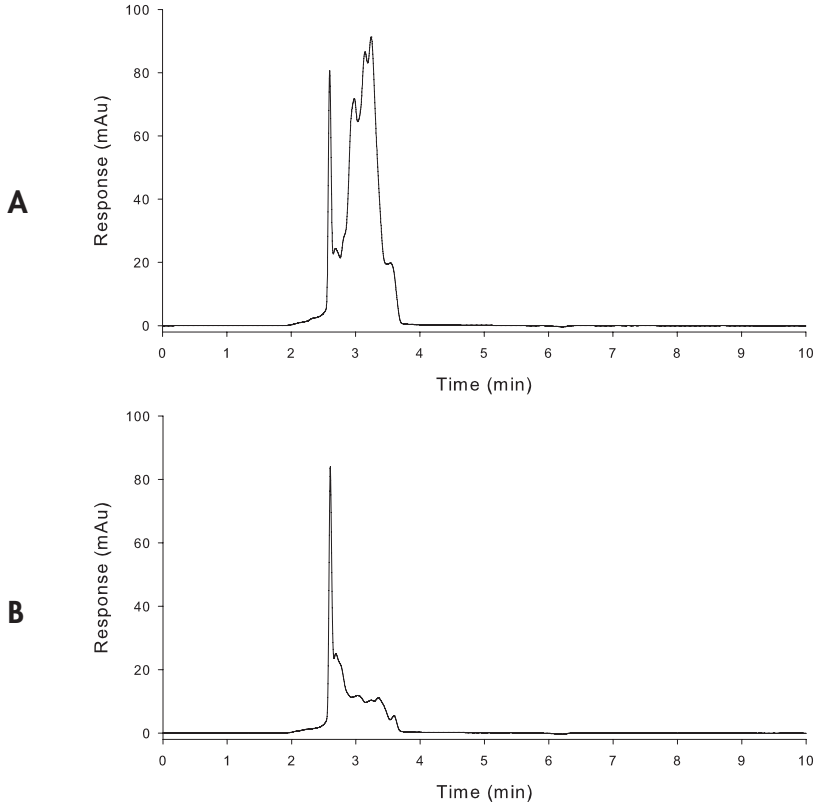

Figure 4. HPLC-UV chromatograms showing that a solution of 10 µg/mL 5-Methoxy-9-oxo-9,10-dihydroacridine-4-carboxylic acid (5-MODICA) **(A)** or 10 µg/mL 4-[2-(3,4-Dihydro-6,7-dimethoxy-2(1H)-isoquinolinyl)ethyl]benzenamine (4-DTHIA) **(B)** did not elute at the retention time of elacridar because they eluted at the dead-time (around 3 minutes).

3.3 Application of the HPLC-UV method

The HPLC-UV method was successfully validated in order to analyze the purity, content and dissolution of the drug powder, intermediate product and final drug product. As an example, the content in a batch final drug product was 99.5 ± 2.0 % and the purity was 100.0 ± 0.0 % after one week of storage at – 20 °C.

An example of the dissolution profile of the final drug product and a crystalline physical mixture (elacridar hydrochloride-PVPK30-SDS (1:6:1 w/w/w)) are shown in Figure 5. The low dissolution of crystalline physical mixture was caused by the low solubility of crystalline elacridar in water as previously reported [18]. The solid dispersion tablet significantly increased the dissolution of elacridar, however after 60 minutes the concentration decreased due to recrystallization.

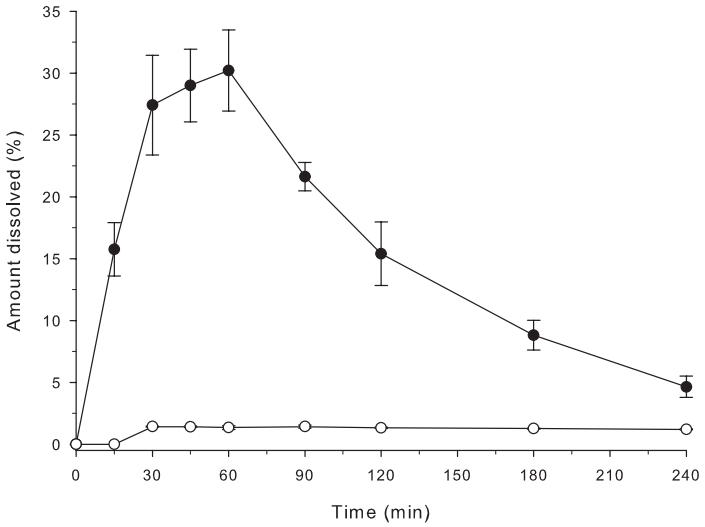

Figure 5. Dissolution from the final drug product (solid dispersion tablets, ●, n = 6) and a physical mixture of crystalline elacridar hydrochloride-PVPK30-SDS (1:6:1, w/w/w, ○, n = 3) in 500 mL SIFsp in the European Pharmacopoeia type II paddle dissolution tester and quantified with the validated HPLC-UV method.

3.4 Characterization of the unknown degradation product

To characterize the degradation product MS and MS^2 spectra were obtained. The eluent of the validated HPLC-UV method was not MS-compliant because it contained an ammonium acetate concentration that induced ion suppression. Therefore, the ammonium acetate concentration in the eluent was lowered to 20 mM. Additionally, the acetonitrile content in the eluent was lowered to 35% to improve the separation between elacridar and the degradation product. Figure 6 shows the HPLC-MS chromatograms of a reference solution that was stored for 4 days in the dark (Figure 6A) or 4 days in indoor natural daylight (Figure 6B). Elacridar (parent ion m/z 562) eluted at 31 minutes, was detected in both samples; however the peak height was decreased in the solution that was stored in indoor natural daylight. The degradation product (parent ion m/z 578) eluted at 27 minutes and was only detected in the reference solution that was stored in indoor natural daylight. The 16 amu mass increase in the degradation product suggested hydroxylation of elacridar.

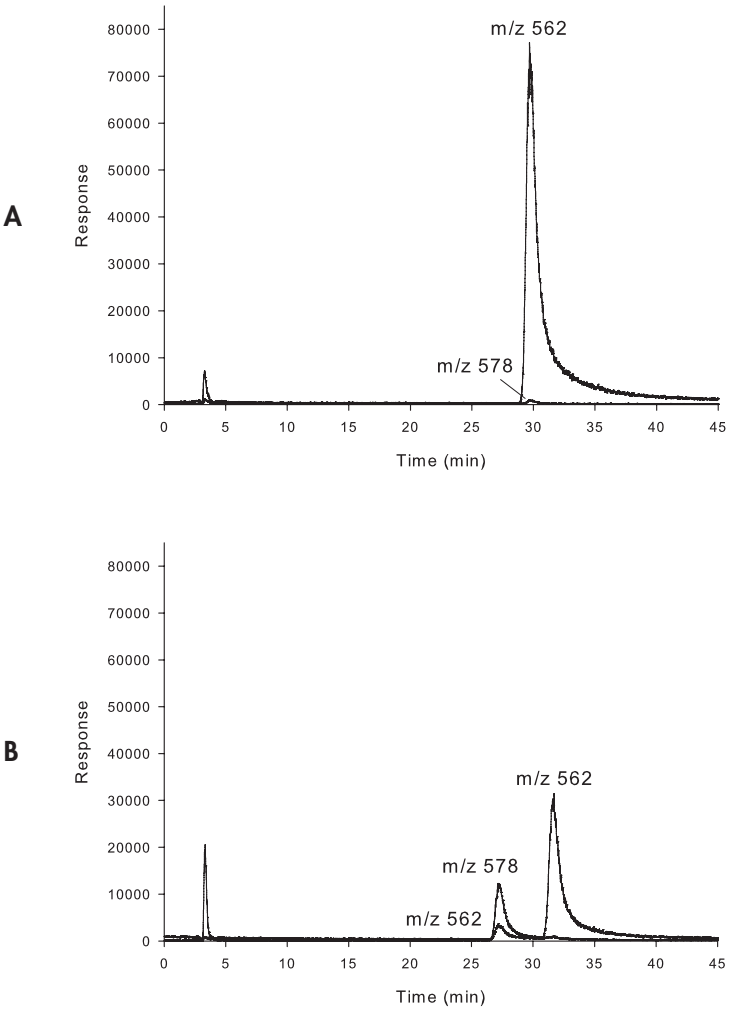

Figure 6. HPLC-MS chromatograms of a reference solution stored at room temperature for 4 days in the dark **(A)** or in indoor natural daylight **(B)**. Two traces were monitored: m/z 562 (elacridar) and m/z 578 (degradation product).

The MS and MS^2 of elacridar are shown in Figure 7A and they confirmed the identity of elacridar. The MS and MS^2 spectra of the degradation product are shown in Figure 7B. Only product ions in the 5-methoxy-9-oxo-9,10-dihydroacridine-4-carboxyl-ethylbenzenamine moiety were detected and in this part of the molecule no fragments with an increase of 16 amu were found. This indicates that the hydroxyl group was probably bound to the dimethoxyisoquinyl moiety of the molecule.

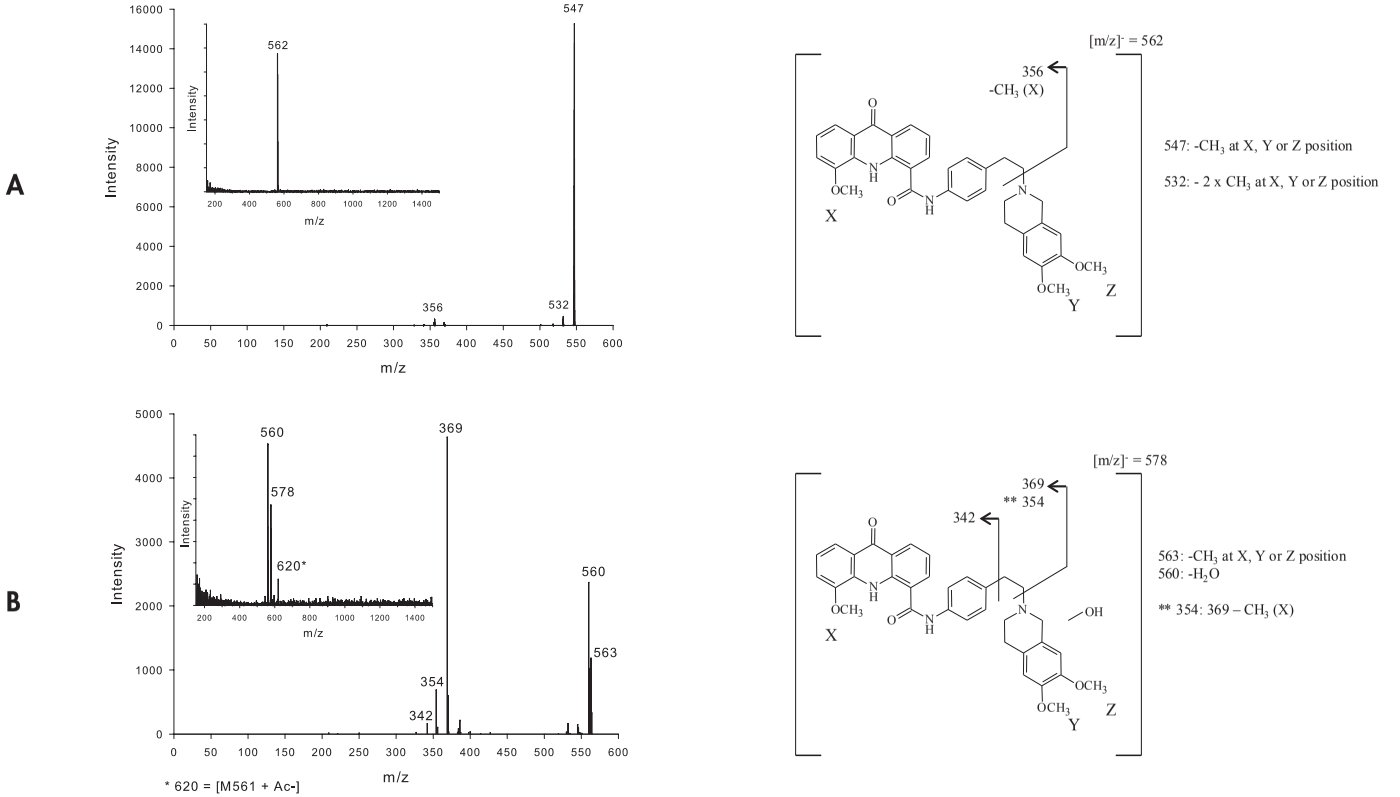

Figure 7. MS (subgraph) and MS^2 spectra of elacridar (parent ion m/z 562) from a reference solution (10 µg/mL elacridar hydrochloride water-DMSO (20:80, v/v)) stored for 4 days in the dark at room temperature (retention time 31 minutes) **(A)** and MS (subgraph) and MS^2 spectra of the degradation product (parent ion m/z 578) from a reference solution (10 µg/mL elacridar hydrochloride water-DMSO (20:80, v/v)) that was exposed for 4 days to indoor natural daylight at room temperature (retention time 27 minutes) **(B)**. X, Y and Z indicate the location of $-CH_3$ groups in the molecule.

In the HPLC-MS chromatogram of the solution that was stored in light an ion of mass m/z 562 was detected at 27 minutes (Figure 6 B) and at 31 minutes (elacridar). Although the mass of this ion was equal to the parent ion of elacridar this ion was not associated with elacridar. An isotope of ion m/z 560 which was formed after in-source fragmentation of m/z 578 (loss of water) explains the chromatographic peak detected at m/z 562 at the retention time of the degradation product. This effect could not be avoided by changing in-source ionization settings or by switching to positive ionization mode. The loss of a water molecule due to in-source fragmentation is common and was previously reported by us for ecteinascidin-743 which was a compound where an hydroxyl group coupled to a carbon atom next to an aliphatic amine group was lost in electrospray mode [33]. A similar structure is present in the degradation product.
To conclude, the fact that the degradation product elutes before elacridar, that it is 16 amu heavier than elacridar and that it only occurrs in samples that are stored in indoor natural daylight confirms that it is caused by light-induced hydroxylation of elacridar. The proposed structure of the degradation product is hydroxylated elacridar and its chemical structure is presented in Figure 7B.

4. CONCLUSION

An HPLC-UV method was developed and validated for the pharmaceutical quality control of a drug powder, an amorphous solid dispersion and a tablet formulation with elacridar as the API. The HPLC-UV method can be used to analyze the content, purity and dissolution. Light induces elacridar hydroxylation in aqueous samples and therefore light protection is required.

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PHARMACEUTICAL DEVELOPMENT OF AN AMORPHOUS SOLID DISPERSION FORMULATION OF ELACRIDAR HYDROCHLORIDE FOR PROOF-OF-CONCEPT CLINICAL STUDIES

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CHAPTER 2.2

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ABSTRACT

A novel tablet formulation containing an amorphous solid dispersion (ASD) of elacridar hydrochloride was developed with the purpose to resolve the drug's low solubility in water and to conduct proof-of-concept clinical studies. Elacridar is highly demanded for proof-of-concept clinical trials that study the drug's suitability to boost brain penetration and bioavailability of numerous anticancer agents. Previously, clinical trials with elacridar were performed with a tablet containing elacridar hydrochloride. However, this tablet formulation resulted in poor and unpredictable absorption which was caused by the low aqueous solubility of elacridar hydrochloride. 24 different ASDs were produced and dissolution was compared to crystalline elacridar hydrochloride and a crystalline physical mixture. The formulation with highest dissolution was characterized for amorphicity. Subsequently, a tablet was developed and monitored for chemical/physical stability for 12 months at +15-25 °C, +2-8 °C and -20 °C. The ASD powder was composed of freeze dried elacridar hydrochloride-povidone K30-sodium dodecyl sulfate (1:6:1, w/w/w), appeared fully amorphous and resulted in complete dissolution whereas crystalline elacridar hydrochloride resulted in only 1% dissolution. The ASD tablets contained 25 mg elacridar hydrochloride and were stable for at least 12 months at – 20 °C. The ASD tablet was considered feasible for proof-of-concept clinical studies and is now used as such.

1. INTRODUCTION

Elacridar (GF120918, GG918) is an inhibitor of Permeability glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP); drug-efflux pumps that are expressed on cell membranes in the gastro-intestinal tract, blood-brain barrier, stem cells and cancer cells [1,2]. By blocking P-gp and BCRP the absorption of drugs that are substrates to these drug-efflux pumps can be enhanced. There is a high demand for proof-of-concept clinical trials to evaluate in cancer patients the role of elacridar as an absorption enhancer, e.g. for the treatment of brain tumors, because according to pre-clinical studies elacridar considerably enhances brain penetration of various anticancer drugs [3–11]. Previous clinical trials demonstrated that elacridar was an effective absorption enhancer for paclitaxel and topotecan when elacridar plasma concentrations of at least 200 ng/mL were achieved. The formulation used for previous clinical trials was a tablet formulation containing elacridar hydrochloride and was administered to cancer patients at oral doses of 100 – 1000 mg [12–14]. A problem of the previously used tablet formulation was poor and unpredictable absorption caused by the low solubility of elacridar hydrochloride and therefore the minimum effective elacridar plasma concentration of 200 ng/mL was often not achieved in patients [14,15]. To answer the request to conduct proof-of-concept clinical studies, we developed a novel oral tablet formulation of elacridar hydrochloride and the trial for which this formulation was used is registered in the EudraCT database (registration number 2013-001131-47) and recently published [16]. To resolve the drug's low solubility in water and to ensure of achieving the minimum effective elacridar plasma concentration (200 ng/mL) we made an amorphous solid dispersion (ASD).

An ASD is a molecular dispersion of a drug and a biologically inactive hydrophilic amorphous excipient. The amorphous state of the powder, homogeneously mixed up to molecular level, the hydrophilic nature of the excipient and the large particle surface area are mechanisms that induce super-saturated drug dissolution, allowing a time window for increased absorption [17–19]. A common dissolution profile of an ASD is shown in Figure 1. The super-saturation effect is temporary because drug recrystallization eventually takes over, inducing precipitation back to the intrinsic solubility of the crystalline drug [20]. The super-saturated state should be as high and as long as possible (the "parachute" effect) and this can be done by careful selection of the amount and type of excipients. Currently there are at least 27 commercialized ASD oral drug formulations, highlighting the successful usability of this formulation method [20]. For example, the oral bioavailability of vemurafenib ASD and regorafenib ASD was increased 4 and 7 times respectively compared to crystalline physical mixtures [21,22].

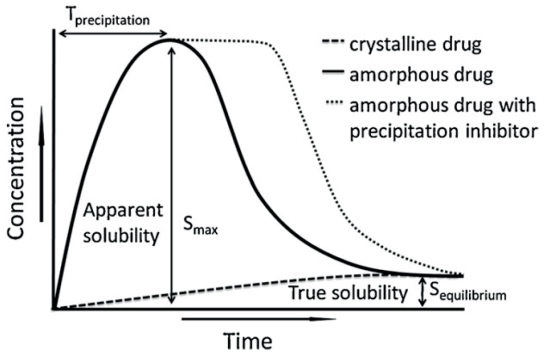


Figure 1. Example dissolution curve of an amorphous solid dispersion, reproduced from Moes et al [32] with kind permission from Elsevier.

The pharmaceutical development of an ASD, however, is more time-consuming and complex than that of a conventional pharmaceutical formulation (crystalline physical mixture) because an extensive research on excipient selection, production method and dosage form is required. To facilitate fast and efficient pharmaceutical development, we followed a general systematic formulation procedure for the development of an ASD with elacridar hydrochloride (see Figure 2).

2. MATERIALS AND METHODS

Materials

The drug, elacridar hydrochloride, was synthesized according to a procedure as earlier described [23]. Polyvinylpyrrolidone Vinylacetate 64 co-polymer (PVPVA64) and Soluplus® were kind gifts from BASF Chemtrade (Ludwigshafen, Germany). The following chemicals were purchased: povidone K30 (PVPK30) from BASF Chemtrade (Ludwigshafen, Germany), sodium dodecyl sulfate (SDS), dimethyl sulfoxide (DMSO), dichloromethane, methanol, tert-butanol and potassium dihydrogen phosphate from Merck (Darmstadt, Germany), lactose monohydrate SuperTab® 30GR from DFE Pharma (Goch, Germany), colloidal silicon dioxide and magnesium stearate from Fagron (Capelle a/d Ijssel, The Netherlands), croscarmellose sodium from Caldic (Rotterdam, The Netherlands), demineralized water from B. Braun (Melsungen, Germany), aluminum blister units with polyvinylchloride sealing from Feton (Brussels, Belgium) and hard gelatin capsules size 0 from Capsugel (Morristown, USA). Simulated Intestinal Fluid without pancreatic enzymes (SIFsp, pH 6.80) was prepared as in USP-NF [24].

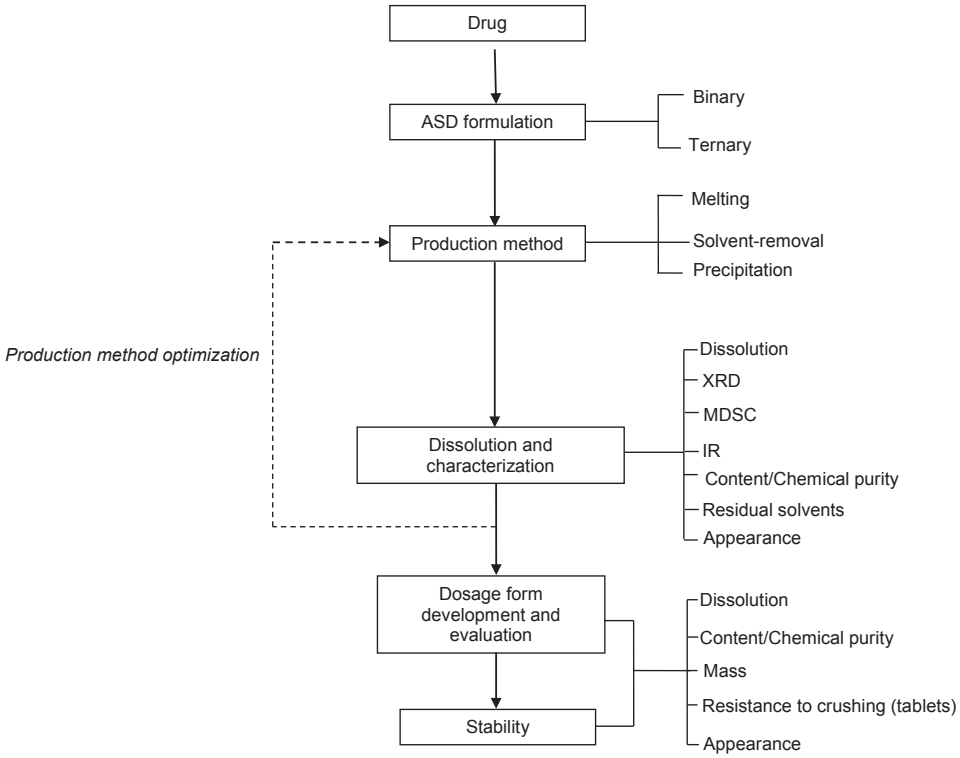


Figure 2. Formulation procedure for the elacridar hydrochloride ASD.

Methods

Thermogravimetric Analysis (TGA)

Approximately 10 mg elacridar hydrochloride was weighed on a platinum pan, placed in nitrogen gas and heated from 25 °C to 400 °C at a heating rate of 2 °C/ minute. Analysis was performed on a TGA Q50 V6.7 instrument (TA Instruments, New Castle, DE, USA).

Freeze Drying

Drug powder, polymers and SDS were dissolved in DMSO. Solutions were transferred to open stainless steel containers (Gastronorm 1/9) and dried in a Lyovac GT4 freeze dryer (GEA Lyophil, Hürth, Germany) by using a program earlier developed by us [25]. The powder was collected in an amber-colored glass container and airtight- sealed with a polypropylene screw cap and stored at +2 – 8 °C.

Spray Drying

A Büchi spray drying system consisted of the B-290 spray dryer and B-295 Inert Loop (Flawil, Switzerland) in closed mode and nitrogen as the drying gas. Drug powder, PVPK30 and SDS were dissolved in dichloromethane to an elacridar hydrochloride concentration of 1.3 mg/mL. The inlet temperature was 55 °C, outlet temperature was 44 – 22 °C, nozzle tip/cap diameter 0.7/1.50 mm, aspirator 90%, pressure of drying gas 35 mm and feed rate of solution 24 mL/min. The powder was stored at +2 – 8 °C.

Powder Mixing and Tablet Compaction

Powders were mixed in a Turbula mixer T10B (Muttenz, Switzerland) and pressed on an eccentric press EK0 (Korsch AG, Berlin, Germany). Tablets were stored in aluminum blisters with polyvinylchloride sealing at – 20 °C. To minimize hygroscopicity tablets were kept in sealed blisters and warmed up to ambient temperature in a desiccator before the seal was broken.

X Ray Diffraction (XRD)

X-ray powder diffraction measurements were done 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 30 mA and a tension of 40 kV. The scanning range was 10 – 45° 2θ with a step size of 0.020° and a scanning speed of 0.002° per second.

Modulated Differential Scanning Calorimetry (MDSC)

Reversing heat flow was measured by 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 in airtight-sealed T_{zero} aluminum pans (TA instruments, New Castle, DE, USA) were placed in the auto sampler. Each sample was equilibrated at - 20.00 °C for 5 minutes, after which the sample was heated to 60.00 °C at a speed of 2.00 °C/min. Modulation was performed every 60 seconds at ± 1.00 °C.

Residual DMSO

Residual DMSO was determined by gas chromatography. The stationary phase was an Alltech RTX-1301 column of cyanopropylphenyl-dimethylpolysiloxane (6:94,

w/w) with dimensions 30 m length x 0.53 mm internal diameter and a pore size of 3.0 µm. The liner was made of glass wool with an internal diameter of 4.0 mm. The carrier gas was helium. The column flow was 2.6 mL/minute. The inlet the temperature was 230 °C, the pressure was 0.15 bar, split ratio was 5.0, split flow was 20 mL/minute and the total flow was ± 25 mL/minute. Samples were injected by split injection (1 µL was injected into the system). The flame ionization detector set at 250 °C with a hydrogen gas flow of 40 mL/minute, oxygen gas flow of 250 mL/minute and make-up nitrogen gas flow of 40 mL/minute. The oven temperature was 55 °C, initialization time was 4 minutes, the heating rate was 40 °C/minute and the final temperature was 200 °C. Total run time was 12 minutes. Powder samples of approximately 50 mg were dissolved in 5 mL methanol-tert-butanol (90:10, v/v). Tert-butanol was the internal standard. DMSO calibration standards and DMSO quality control standards were prepared on the day of analysis from two DMSO stock solutions (stored at – 20 °C).

Residual Water

Residual water was measured by a Karl Fischer titration method by using a Metrohm 758 KFD Titrino (Herisau, Switserland). An amount of 50 mg powder was dissolved in 5 mL preconditioned methanol. The titrant was standardized with 30 mg of demineralized water.

Content and Chemical Purity

Drug powder, ASD powders and tablets were analyzed and quantified with a validated HPLC-UV method previously described by us [26]. The HPLC system was an 1100 series and consisted of a binary pump (G1312A), autosampler G1367A and a UV dectector G1314A (Agilent Technologies, Santa Clara, CA, USA).

Dissolution

A small-scale dissolution test was used to screen formulations for their solubility-enhancing effect. For this, an amount equivalent to 10 mg elacridar hydrochloride was placed in 100 mL SIFsp (37 ± 1 °C) and homogenized at 500 rpm with a magnetic stirrer. One mL was filtrated through a 0.45 µm PVDF filter and immediately diluted with 2 mL DMSO. The duration of the test was 4 hours. Samples were analyzed at 409 nm on a spectrophotometer (Shimadzu, Kyoto, Japan). Quantification was done by preparing calibration standards 1 to 100 µg/mL in SIFsp-DMSO (33:67, v/v). To study the dissolution of ASD tablets, an USP type II paddle dissolution tester was used according to a method described previously by us [26]. In brief, the

dissolution medium was 500 mL of SIFsp (37 °C) homogenized at 100 rpm. One mL sample was filtrated through a 0.45 µm PVDF filter and immediately diluted with 2 mL DMSO and quantified by the validated HPLC-UV method [26].

Stability Study

Tablets were stored in aluminum blisters with polyvinylchloride sealing at room temperature (+15 – 25 °C/60% RH), refrigerator (+2 – 8 °C) or freezer (- 20 °C) and were analyzed after 0, 3, 6, 9 and 12 months for content, chemical purity, dissolution, appearance, mass and resistance to crushing. The dissolution difference factor (f_1) and similarity factor (f_2) were calculated up to 60 minutes according to formulae previously described [27].

3. RESULTS AND DISCUSSION

Step 1: ASD Formulation

A vinyl polymer (PVP), a vinyl co-polymer (PVPVA) and a co-polymer (Soluplus®) were selected as candidate hydrophilic carrier excipients. These polymers have a pH-independent solubility and are therefore suitable for dissolution enhancement over the entire gastro-intestinal tract.

PVPK30 and PVPVA64 (vinylpyrrolidone-vinylacetate 60-40% co-polymer) are frequently used excipients for ASD formulations with T_g > 100 °C and have good solubility in many organic solvents [20,28]. Soluplus® is a co-polymer with polyethyleneglycol as the hydrophilic backbone and a polyvinylcaprolactam and polyvinylacetate as hydrophobic side chain. Soluplus® is a relatively new excipient but many papers already report promising results regarding super-saturation [29–31]. Another frequently used formulation is a ternary ASD which contains a surfactant as extra excipient (e.g. SDS) and this can increase super-saturation due to its powder-wetting properties and precipitation-inhibition [28,32].

Step 2: Production Method

There are three widely used production methods for ASDs: melting, precipitation and solvent-removing [18]. Melting is feasible for drugs and excipients that do not decompose during the melting process. However, many drugs have a high melting temperature (> 200 °C), often accompanied by decomposition [33,34]. The application of the precipitation method is limited to polymers with a pH-dependent aqueous solubility (such as hydroxypropylmethylcellulose acetate-succinate), the disadvantage being that drug release is not possible in the entire gastro-intestinal

tract. In the solvent-removal method, drug and excipient are dissolved in an organic solvent which is then evaporated (e.g. spray drying) or sublimated (e.g. freeze drying). Elacridar hydrochloride has a high melting point (280 °C, internal data) with decomposition at 200 °C (see Figure 3), thus melting was not the preferred production method.

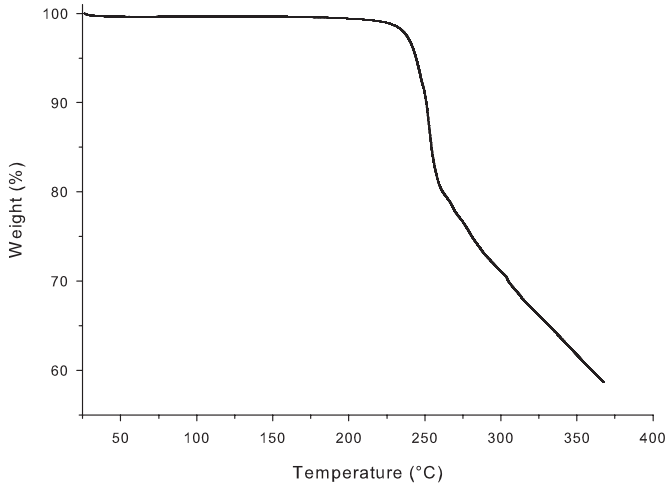


Figure 3. Thermogravimetric analysis of elacridar hydrochloride.

The precipitation method was also unsuitable because this method is restricted to polymeric excipients with a pH-dependent solubility and this does not ensure dissolution over the entire pH range in the gastro-intestinal tract. Solvent-removal was a suitable production method because elacridar hydrochloride has good solubility in DMSO, a solvent that was previously successfully removed by a freeze drying method [25]. Therefore, the pre-existing freeze drying program was used to produce formulations described in step 1. The preparation method and the composition of the formulations is shown in Table 1. Formulations A – X and Formulation Z were freeze dried in a stainless steel container (36 mL solution per container).

Step 3: Dissolution and Characterization

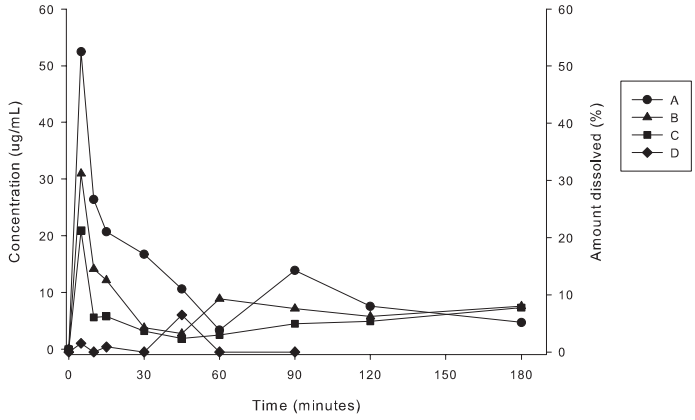
Dissolution

The dissolution of elacridar hydrochloride from freeze dried ASDs was compared to crystalline elacridar hydrochloride and freeze dried elacridar hydrochloride. The results are shown in Figure 4 (a) – (f).

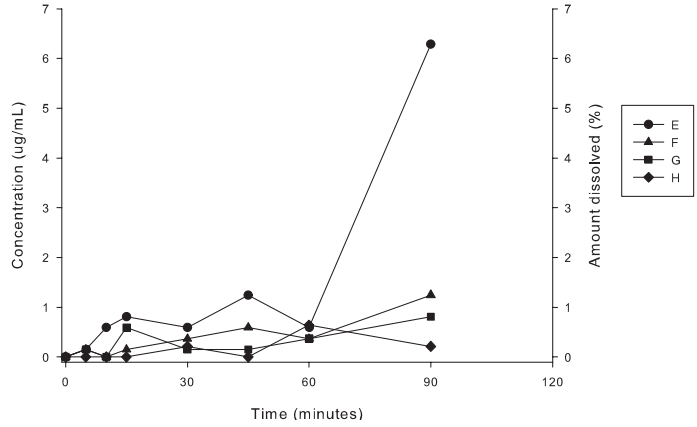
Dissolution from binary ASDs is shown in Figure 4 (a), (b) and (c). For ASDs with PVPK30 (Figure 4 (a), formulations A - D), increasing the excipient content resulted in higher dissolution, which demonstrates the importance of PVPK30 in dissolution enhancement. The highest dissolution was 52% (formulation A). However, formulations A – D already precipitated after 5 minutes. Binary ASDs with PVPVA64 (Figure 4 (b), formulations E – H) resulted in poor dissolution (< 10%) and this can be explained by the fact that PVPVA64 is less hydrophilic than PVPK30 [35]. Binary ASDs with Soluplus® (Figure 4 (c), formulations I – L) resulted in moderate dissolution and among them formulation I resulted in the highest dissolution (53%). The dissolution after 4 hours was still higher than that of crystalline elacridar hydrochloride (Figure 4 (d), Formulation Y). It is likely that long dissolution enhancement was caused by micellar formation with Soluplus®. This effect was previously also observed by Lim et al who developed a docetaxel-Soluplus® ASD [36].
Figures 4 (d) – (f) show dissolution from ternary ASDs. Formulations with PVPK30-SDS (Figure 4 (d), formulations M – P) resulted in a higher dissolution and slower precipitation compared to binary ASDs with PVPK30 (Figure 4 (a), formulations A – D). This shows that SDS plays an important role in super-saturation and in reducing precipitation. Formulation O resulted in complete dissolution (> 90%). Formulations M and N resulted in similar super-saturation but in faster precipitation than formulation O, despite the fact that these two formulations contained higher amounts of PVPK30. When placed in the dissolution medium, formulations M and N appeared as larger powder agglomerates than formulation O, therefore the disintegration process of these ASDs could be less homogeneous, affecting the dissolution. Ternary ASDs with PVPVA64-SDS (Figure 4 (e), formulations Q – T) resulted in poor dissolution (< 10%) which was related to the less hydrophilic nature of PVPVA64 [35]. ASDs with Soluplus®-SDS (Figure 4 (f), formulations U – X) resulted in good dissolution (40 – 90%) and no precipitation, again suggesting micelle formation. Increasing the amount of Soluplus® resulted in higher dissolution, showing the importance of Soluplus® in the dissolution process of elacridar hydrochloride. It is likely that SDS made finer micelles, with that less agglomeration, explaining the higher dissolution than from binary ASDs with Soluplus®.

The dissolution of crystalline elacridar hydrochloride (Figure 4 (d), formulation Y) and freeze dried elacridar hydrochloride (Figure 4 (f), formulation Z) was 1% and only 1 µg/mL, showing the drug belongs to the category "practically insoluble in water" [24].

a


Concentration (ug/mL)
Amount dissolved (%)
Time (minutes)
A
B
C
D

b


Concentration (ug/mL)
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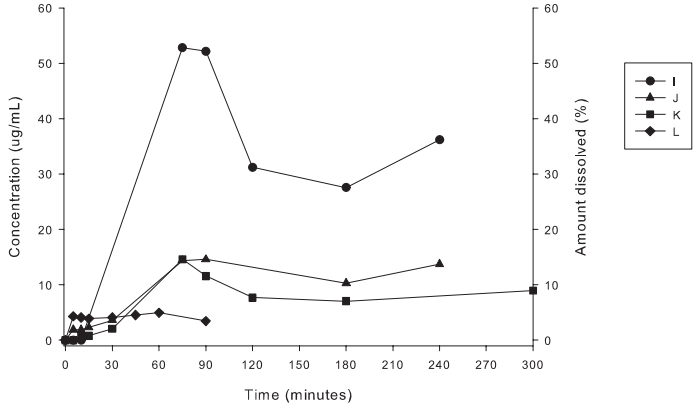
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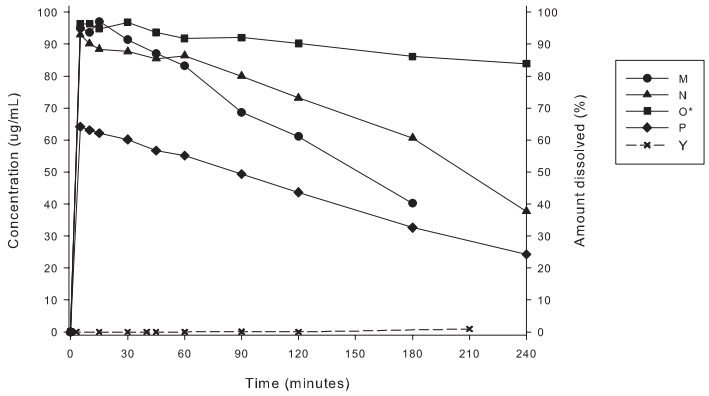
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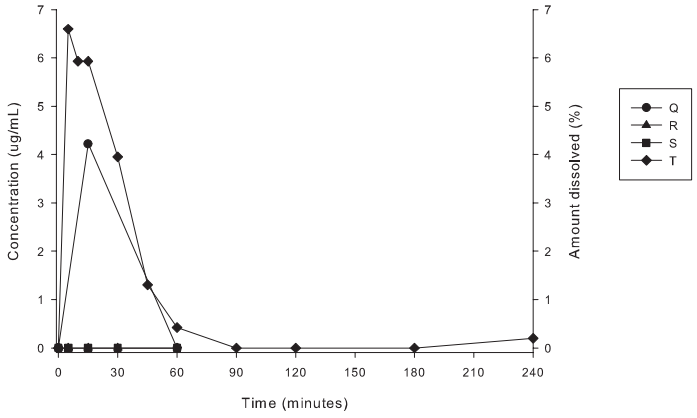
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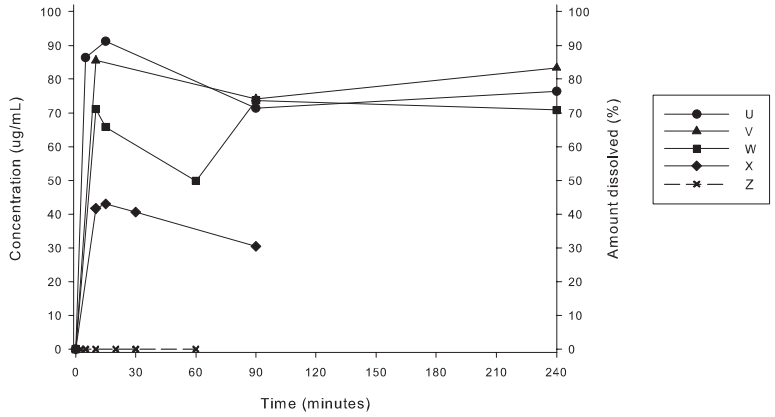
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Figure 4. Dissolution screening of freeze dried ASDs (formulations A – X, Table 1) in comparison to crystalline elacridar hydrochloride and freeze dried elacridar hydrochloride (formulations Y and Z respectively, Table 1). Each line represents one formulation (n = 1). Each figure has two Y-axes and one x-axis. The left y-axis displays the absolute concentration of elacridar hydrochloride in µg/mL and the title of this axis is shortened to "concentration (µg/mL)". The right y-axis shows the concentration of elacridar hydrochloride relative in percent to the theoretical maximum concentration of 100 µg/mL and is shortened to "amount dissolved (%)". The x-axis shows the time (x-axis) of the dissolution experiment. Binary ASDs with PVPK30, PVPVA64 or Soluplus are shown in Figures 4 (a), (b), (c) respectively. Ternary ASDs with PVPK30-SDS, PVPVA64-SDS or Soluplus-SDS are shown in Figures 4 (d), (e), (f) respectively. * = formulation chosen for further development. See previous two pages.

Formulation O was selected for further development because with this formulation highest dissolution enhancement was achieved (90 times higher than dissolution from crystalline elacridar hydrochloride). Another advantage of formulation O is that the polymeric carrier (PVPK30) is a generally regarded safe excipient, and it is already widely used in pharmaceutical and commercial development of ASDs [20].

Characterization

The physical characterization of formulation O (further referred to as ASD) is shown in Figure 5 and Figure 6. The ASD appeared as a yellow dry powder (Figure 5). The XRD examination is shown in Figure 6 (a). The absence of diffraction peaks in the spectrum of the ASD confirmed the amorphous state. Freeze dried elacridar hydrochloride was not amorphous, although the number and intensity of diffraction peaks were less compared to unprocessed elacridar hydrochloride. Amorphous elacridar hydrochloride is physically unstable because of strong crystal bonding between drug molecules, a common feature of drugs with a high melting temperature [37]. Therefore, elacridar hydrochloride requires a polymeric excipient to remain amorphous. Regarding IR (Figure 6 (b)), elacridar hydrochloride contained a sharp peak at 1660 cm^{-1} which corresponded to carbonyl (C=O), C=N and/or aromatic rings (depicted in Figure 6 (b) with a grey rectangle). In the case of PVPK30 the large and broad peak at 1660 cm^{-1} was caused by the carbonyl group. Peak 1660 cm^{-1} in physical mixtures appeared sharp, but was blunt in the ASD and this suggests the establishment of extra dispersion, polar or hydrogen bond interactions between elacridar hydrochloride and PVPK30. In the MDSC of the ASD (Figure 6 (c)) a T_g was detected (29.6 °C). Higher temperatures for MDSC were not studied because elacridar hydrochloride decomposes at 200 °C (see Figure 3) which disrupts heat flow signals. Therefore, MDSC could not be used to identify crystallinity of elacridar hydrochloride. Instead, MDSC was only used to study thermal events occurring in the ASD around ambient conditions.

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

				Freeze drying settings					
Code	**Formulation type**	**Excipients**	**Drug-excipients weight ratio**	**Elacridar hydrochloride (mg/mL)**	**PVPK30 (mg/mL)**	**PVPVA64 (mg/mL)**	**Soluplus (mg/mL)**	**SDS (mg/mL)**	**Total drug + excipients (mg/mL)**
A	Binary ASD	PVPK30	1:12	10	120	-	-	-	130
B	Binary ASD	PVPK30	1:9	10	90	-	-	-	100
C	Binary ASD	PVPK30	1:6	10	60	-	-	-	70
D	Binary ASD	PVPK30	1:3	10	30	-	-	-	40
E	Binary ASD	PVPVA64	1:12	10	-	120	-	-	130
F	Binary ASD	PVPVA64	1:9	10	-	90	-	-	100
G	Binary ASD	PVPVA64	1:6	10	-	60	-	-	70
H	Binary ASD	PVPVA64	1:3	10	-	30	-	-	40
I	Binary ASD	SOLUPLUS	1:12	10	-	-	120	-	130
J	Binary ASD	SOLUPLUS	1:9	10	-	-	90	-	100
K	Binary ASD	SOLUPLUS	1:6	10	-	-	60	-	70
L	Binary ASD	SOLUPLUS	1:3	10	-	-	30	-	40
M	Ternary ASD	PVPK30, SDS	1:12:1	10	120	-	-	10	140
N	Ternary ASD	PVPK30, SDS	1:9:1	10	90	-	-	10	110
O	Ternary ASD	PVPK30, SDS	1:6:1	10	60	-	-	10	80
P	Ternary ASD	PVPK30, SDS	1:3:1	10	30	-	-	10	50
Q	Ternary ASD	PVPVA64, SDS	1:12:1	10	-	120	-	10	140
R	Ternary ASD	PVPVA64, SDS	1:9:1	10	-	90	-	10	110
S	Ternary ASD	PVPVA64, SDS	1:6:1	10	-	60	-	10	80
T	Ternary ASD	PVPVA64, SDS	1:3:1	10	-	30	-	10	50
U	Ternary ASD	SOLUPLUS, SDS	1:12:1	10	-	-	120	10	140
V	Ternary ASD	SOLUPLUS, SDS	1:9:1	10	-	-	90	10	110
W	Ternary ASD	SOLUPLUS, SDS	1:6:1	10	-	-	60	10	80
X	Ternary ASD	SOLUPLUS, SDS	1:3:1	10	-	-	30	10	50
Y	Crystalline API	-	-	-	-	-	-	-	-
Z	Freeze dried API	-	-	10	-	-	-	-	-
PM1	Physical mixture crystalline API	PVPK30, SDS	1:6:1	-	-	-	-	-	-
PM2	Physical mixture freeze dried API	PVPK30, SDS	1:6:1	10	-	-	-	-	-

ASD: amorphous solid dispersion, PVPK30: povidone K30, PVPVA64: polyvinylpyrrolidone vinylacetate 60/40, SDS: sodium dodecyl sulfate, API: active pharmaceutical ingredient (in this case elacridar hydrochloride), PM: physical mixture

The chemical purity and content of elacridar hydrochloride were 100% and 88.1 ± 0.5 % (110.2 ± 0.6 mg/g) respectively. Residual DMSO was 9.1 ± 0.3 % and residual water was 4.2 ± 0.1 % (Table 3) despite the fact that no water was used during the production method. This was caused by residual DMSO which is hygroscopic [25].

DMSO is a solvent with low toxic potential (Class 3), and amounts higher than 50 mg / 0.5% w/w may be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice [38]. To administer a dose equivalent to 1000 mg elacridar requires 9.1 g ASD powder which contains 826 mg DMSO. This is far below the $LD_{50,oral}$ of DMSO (14.5 g/kg). DMSO is considerably less toxic compared to other solvents commonly used in pharmaceutical productions (for example ethanol, also a Class 3 solvent with $LD_{50,oral}$ of 7.1 g/kg). In fact, DMSO is used parentally to patients receiving autologous bone marrow transplantation up to 50 mL (~ 55 gram) DMSO per dose [25]. Therefore, the residual DMSO content in the ASD powder can be considered non-toxic in this context.

To conclude, a freeze dried ASD powder containing elacridar hydrochloride-PVPK30-SDS (1:6:1, w/w/w) was developed, was fully amorphous and had a 90 times increased dissolution compared to physical mixtures of crystalline elacridar hydrochloride.

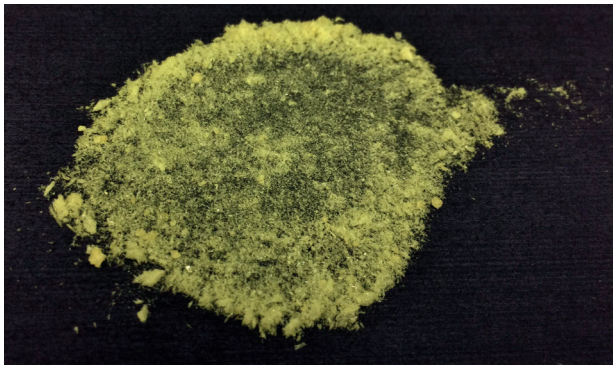

Figure 5. Photographic image of freeze dried ASD powder containing elacridar hydrochloride-PVPK30-SDS 1:6:1 (w/w/w).

Production Method Optimization

The residual solvent content in the ASD was a limitation because DMSO and water worked as plasticizers and this explained the T_g around room temperature. We investigated whether lowering the concentration resulted in less residual DMSO/

water and a higher T_g. Results are shown in Table 2. Decreasing the freeze drying concentration did not lower the total residual solvent content. In formulations 40 mg/mL and 20 mg/mL residual DMSO decreased but residual water increased and all formulations had a T_g close to room temperature. The inability to decrease total residual solvents by decreasing freeze drying concentration might have been caused by the fact that the freeze drying solution was still too viscous, even at the lowest studied concentration, and that this induced sublimation resistance [39].

Table 2. Optimization of the freeze drying process in order to reduce residual DMSO and residual water and to increase T_g by modifying the total excipient concentration in the freeze drying solution in DMSO (elacridar hydrochloride-PVPK30-SDS 1:6:1, w/w/w)

Total excipient concentration (mg/mL)	Elacridar hydrochloride concentration (mg/mL)	Content of active ingredient (%)[1]	Chemical purity (%)[1]	Residual DMSO (%, w/w)[1]	Residual Water (%, w/w)[1]	Total residual solvents (%)[1]	T_g (°C)[2]
80	10.0	90.2 ± 0.8	100.0	8.5 ± 0.4	3.5 ± 0.3	12.0 ± 0.4	34.5
60	7.5	89.7 ± 0.4	100.0	8.6 ± 0.1	4.0 ± 0.2	12.6 ± 0.2	31.6
40	5.0	91.0 ± 0.4	100.0	6.0 ± 0.2	4.7 ± 0.2	10.7 ± 0.2	33.9
20	2.5	90.5 ± 0.5	100.0	6.0 ± 0.2	6.6 ± 0.1	12.6 ± 0.2	29.8

[1]n = 3, [2]n = 1

Then, an attempt was made to develop a spray drying method. DMSO, however, was unsuitable because of its high boiling temperature (~190 °C) and could not be dried. Elacridar hydrochloride was practically insoluble in methanol, ethanol, acetone, isopropanol, ethylacetate and very slightly soluble in dichloromethane. Spray dried ASD containing elacridar hydrochloride-PVPK30-SDS (1:6:1, w/w/w) from dichloromethane was not fully amorphous and resulted in only 53% dissolution and precipitated already after 10 minutes. This shows that dissolution enhancement from spray dried ASD was considerably worse than that of freeze dried ASD. Besides, spray drying was unpractical because 10 times more solvent was required to produce the same amount of ASD as with freeze drying. Dichloromethane is a far more toxic solvent than DMSO (dichloromethane belongs to Class 2, not more than 6.0 mg/day and < 600 ppm/day and $LD_{50,oral}$ is 1.6 g/kg) [38].

To conclude, modifying the production process did not result in improved pharmaceutical features of the ASD, thus the freeze drying method was retained at a total solid concentration of 80 mg/mL (elacridar hydrochloride 10 mg/mL). Because the ASD was hygroscopic with a low T_g it required storage in an environment where further water adsorption was minimized in order to avoid further decrease of the T_g. Therefore, the powder was stored in airtight-sealed primary package material in a desiccator.

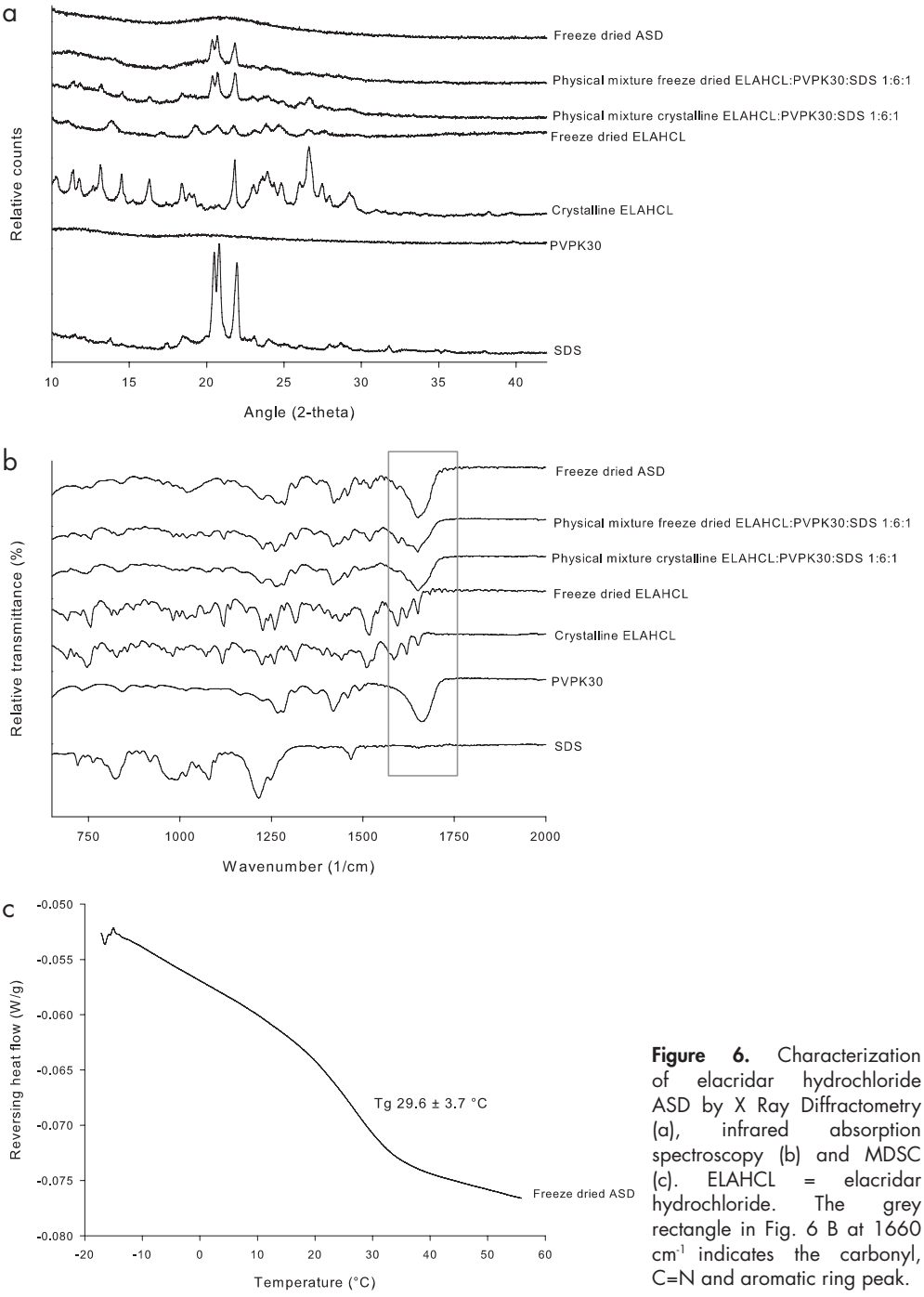

Figure 6. Characterization of elacridar hydrochloride ASD by X Ray Diffractometry (a), infrared absorption spectroscopy (b) and MDSC (c). ELAHCL = elacridar hydrochloride. The grey rectangle in Fig. 6 B at 1660 cm^{-1} indicates the carbonyl, C=N and aromatic ring peak.

Evaluation

Results of six batches freeze dried ASD are shown in Table 3. The average content was 91.0 ± 2.6 % (113.7 ± 3.2 mg/g elacridar hydrochloride), the average chemical purity was 100.0 ± 0.0 %, the average residual DMSO content was 8.6 ± 0.4 %, the average residual water content was 3.8 ± 0.5 %, all were amorphous and the average T_g was 29.6 ± 3.7 °C. These results were similar to the results discussed in Step 3 paragraph Characterization, so the production method was reproducible. The average yield efficiency was 101.4 ± 1.7 %. Yield efficiency exceeded 100% because of residual DMSO/water. The average absolute yield was 32.6 ± 0.5 g. Knowing that the average content in the ASD is 113.7 mg/g (Table 3) means that one batch of 32.6 g contains 3706.2 mg elacridar hydrochloride. Therefore, one batch supplies 3 doses of 1000 mg elacridar as hydrochloride salt. For a proof-of-concept study involving single dose administration of 1000 mg to 6 – 12 volunteers, it means that 2 – 4 production batches are required.

Table 3. Quality control results of six batches freeze dried ASD containing elacridar hydrochloride-PVPK30-SDS (1:6:1, w/w/w)

Batch	Content (%)[1]	Content (mg/g)[1]	Chemical purity (%)[1]	Residual DMSO (%, w/w)[1]	Residual water (%, w/w)[1]	Amorphous (XRD)[2]	T_g (°C)[2]	Absolute yield (g)[2]	Yield efficiency (%)[2]
1	88.1 ± 0.5	110.2 ± 0.6	100.0	9.1 ± 0.3	4.2 ± 0.1	Yes	25.9	33.1	103.1
2	89.2 ± 0.3	111.5 ± 0.4	100.0	7.9 ± 0.2	4.6 ± 0.1	Yes	33.3	32.9	102.8
3	88.9 ± 0.3	111.2 ± 0.4	100.0	8.6 ± 0.3	4.0 ± 0.1	Yes	29.7	31.6	98.4
4	93.8 ± 0.5	117.2 ± 0.6	100.0	8.3 ± 0.1	3.5 ± 0.0	Yes	ND	32.4	100.7
5	93.9 ± 0.4	117.4 ± 0.5	100.0	8.6 ± 0.3	3.4 ± 0.1	Yes	ND	32.6	101.4
6	91.9 ± 2.8	114.9 ± 3.5	100.0	8.8 ± 0.2	3.3 ± 0.1	Yes	ND	32.9	102.2

ND: not determined, [1]n = 3, [2]n = 1

Step 4: Dosage Form Development and Evaluation

The 90 times increased dissolution from ASD compared to crystalline elacridar hydrochloride implied the ASD might considerably increase the oral bioavailability. Based on this, the target dose strength of the final drug product was 10 – 100 mg. The ASD powder was highly porous and therefore it was not possible to fill one capsule with ASD powder equivalent to 25 mg elacridar hydrochloride. Compaction of ASD powder resulted in vitreous tablets, thus a diluent was required. By diluting the ASD powder with lactose (≥ 60%) it was possible to make tablets of 25 mg elacridar hydrochloride with a resistance to crushing 60 – 150 N, a mass ~750 mg and dimensions of 16 x 8.5 x 6.9 mm (length, width and thickness respectively). The tablet formulation contained granulated lactose-ASD-croscarmellose-colloidal silicon

dioxide-magnesium stearate (63:30:5:1:1, w/w/w/w/w). Tablets with higher doses with this powder mixture were not considered because they were unacceptably large. Figure 7 shows that the dissolution from the crystalline physical mixture (PM1) was 1% and the dissolution of a physical mixture formulation containing freeze dried elacridar hydrochloride (PM2) was 2%. The dissolution from the ASD tablet was ~70 %. These results show ASD tablets considerably increase the dissolution of elacridar hydrochloride.

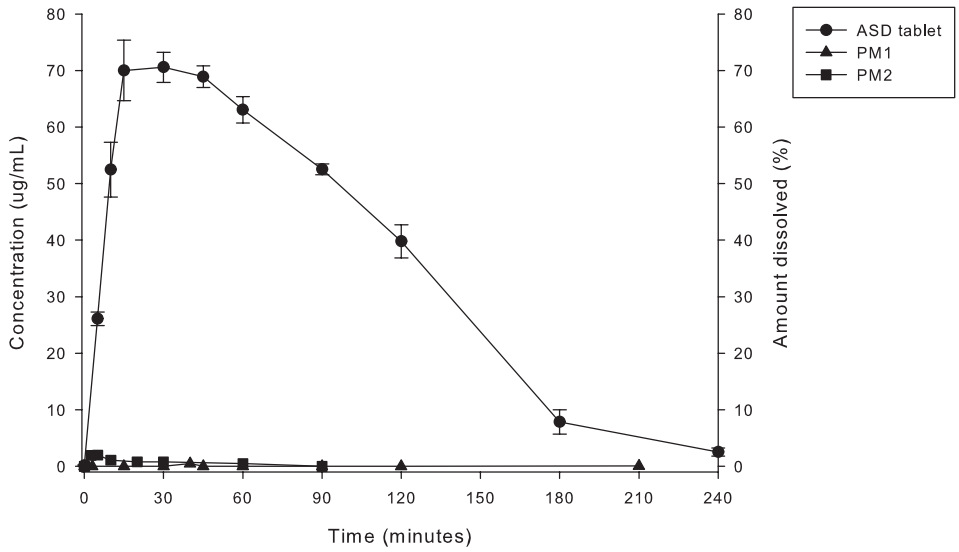

Figure 7. The dissolution of ASD tablets compared to physical mixture formulations (PM1 and PM2, Table 1).

Dissolution of ASD tablets immediately after production in the USP type II dissolution tester was 23.6 ± 3.0 % (see Figure 8 (a) – (c), ●●●). The dissolution from crystalline physical mixture (formulation PM1) was 1.4 ± 0.1% and the dissolution of pure drug powder was 0% (data not shown). The ASD tablet thus resulted in significantly enhanced dissolution compared to a crystalline physical mixture which means the ASD tablet is feasible for dissolution enhancement and provides a time window for increased in-vivo absorption.

Step 5: Stability

The critical quality attributes (CQAs) for the chemical stability were drug content 90 – 110% relative to label claim and the chemical purity ≥ 98 %. CQAs for the physical stability of ASD tablets during storage were appearance, mass increase <

3%, resistance to crushing 60 – 150 N, and dissolution similarity relative to tablets at 0 months expressed as f_1 < 15% and f_2 > 50% [27].
Results regarding the appearance, mass increase, resistance to crushing, content and dissolution similarity (f_1 and f_2) are shown in Table 4. The dissolution profile of ASD tablets stored for one year at +15 – 25 °C/60% RH, +2 – 8 °C or -20 °C are shown in Figures 8 (a), (b) and (c) respectively. The content and chemical purity were compliant with CQAs at all storage conditions during the entire study period, thus the ASD tablets containing elacridar hydrochloride were chemically stable.

Table 4. The stability of ASD tablets containing 25 mg elacridar hydrochloride

Time (months)	Storage condition	Appearance	Mass increase (%)	Resistance to crushing (N)	Content relative to label claim (%)	Difference factor (f_1)	Similarity factor (f_2)
0	- 20 °C	Intact	-	101 ± 19	99.2 ± 0.4	-	-
3	+15 – 25 °C/60%RH	Elastic	+5.6	487 ± 1	98.8 ± 7.1	85	38
3	+2 – 8 °C	Elastic	+5.1	487 ± 1	101.9 ± 5.0	14	77
6	+2 – 8 °C	Elastic	+8.4	487 ± 1	98.6 ± 4.7	63	44
3	- 20 °C	Intact	+0.9	109 ± 29	99.4 ± 4.1	10	79
6	- 20 °C	Intact	+1.4	117 ± 25	99.4 ± 4.4	8	85
9	- 20 °C	Intact	+2.6	89 ± 11	100.3 ± 0.9	12	76
12	- 20 °C	Intact	+2.5	110 ± 41	101.2 ± 5.5	13	75

Tablets stored at +15 – 25 °C/60% RH or +2 – 8 °C appeared elastic, were not resistant to crushing, their mass was considerably increased with a reduced dissolution. Tablets stored for 12 months at – 20 °C appeared intact, resistant to crushing, mass increase < 3% and equivalent dissolution. The poor stability at +2 – 8 °C and +15 – 25 °C/60% RH was a consequence of the T_g of the ASD (29.6 °C). T_g was close to these two storage conditions and therefore kinetic energy in the ASD was sufficient to induce glass transition from the hard ("intact") state into the rubbery ("elastic") state. The consequence of this was that tablets did not crush anymore, instead they were distorted ("chewing gum-like") during the tensile strength measurement. The mass increase at +15 – 25 °C/60% RH and +2 – 8 °C was caused by moist adsorption. Tablets stored at – 20 °C remained intact during storage and were crushed with the tensile strength tester at similar forces as tablets initially after production (Table 4). This is because ASD tablets at – 20 °C did not have sufficient kinetic energy to undergo glass transition and therefore remained intact. Also, at – 20 °C there was considerably less moist adsorption and therefore tablet mass did not increase significantly.

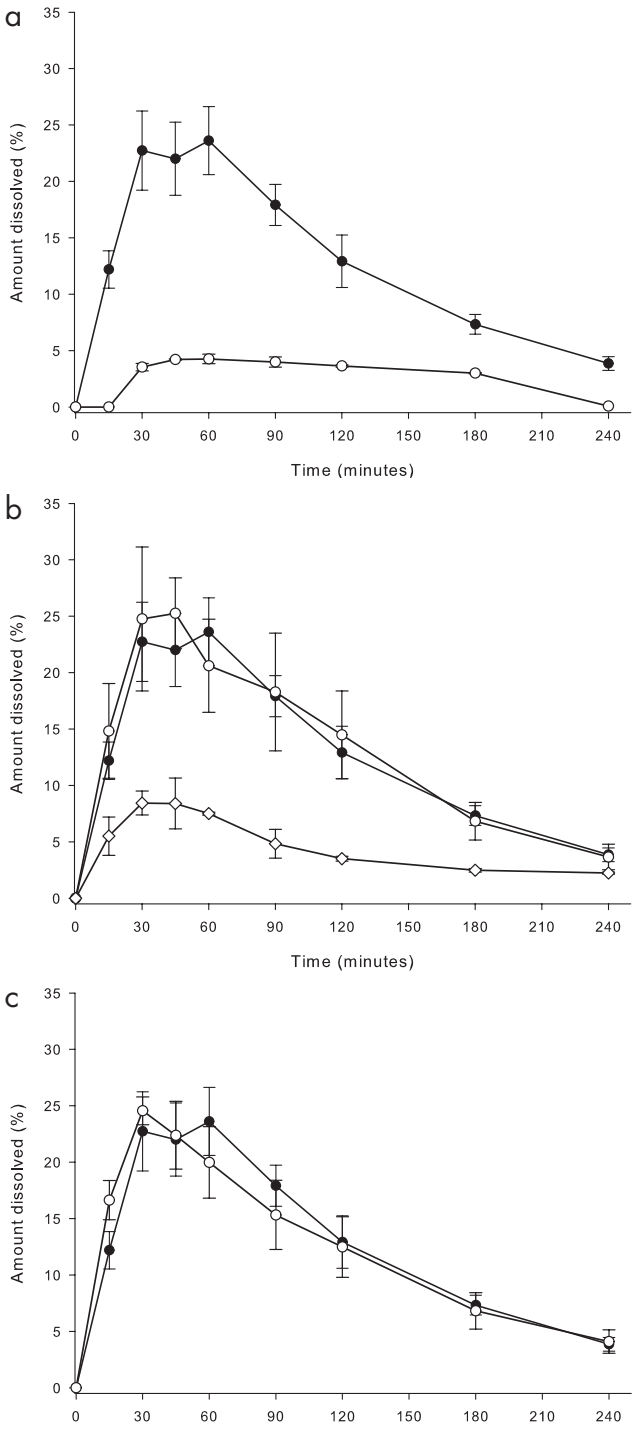

Figure 8. Dissolution in the USP type II paddle apparatus of two batches ASD tablets stored at (a) 15 – 25 °C 60% RH immediately after production (●●●) and after 3 months (○○○). (b) 2 – 8 °C dark immediately after production (●●●), after 3 months (○○○) and after 6 months (◊◊◊) (c) – 20 °C immediately after production (●●●) and after 12 months (○○○).

To conclude, ASD tablets were physically stable for at least 12 months when stored at – 20 °C. For proof-of-concept studies involving a single dose administration this was considered manageable as according to our knowledge there is currently no other GMP-compliant formulation with elacridar available. For clinical applications with daily oral dosing further research for a new formulation is required.

4. CONCLUSION

This paper discussed the pharmaceutical development of an ASD tablet containing 25 mg elacridar hydrochloride for proof-of-concept clinical trials involving a single dose administration up to 1000 mg. The dissolution from 24 different ASDs (produced by freeze drying) was compared to that of crystalline elacridar hydrochloride. Freeze dried ASD containing elacridar hydrochloride-PVPK30-SDS (1:6:1, w/w/w) resulted in a 90 times increased dissolution and was fully amorphous. Subsequently, tablets with the ASD were developed and resulted in a considerably increased dissolution compared to a crystalline physical powder mixture. Content, chemical purity and dissolution were stable for at least 12 months when stored at – 20 °C. This makes the ASD tablet feasible for proof-of-concept clinical trials and tablets were handled according to conclusions of this paper (EudraCT, registration number 2013-001131-47).

Disclosure of interest statement: The authors report no conflicts of interest.

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CLINICAL PHARMACOKINETICS OF AN AMORPHOUS SOLID DISPERSION TABLET OF ELACRIDAR

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CHAPTER 2.3

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ABSTRACT

Elacridar is an inhibitor of the Permeability Glycoprotein (P-gp) and the Breast Cancer Resistance Protein (BCRP) and is a promising absorption enhancer of drugs that are substrates of these drug-efflux transporters. However, elacridar is practically insoluble in water, resulting in low bioavailability which currently limits its clinical application. We evaluated the *in vitro* dissolution and clinical pharmacokinetics of a novel amorphous solid dispersion (ASD) tablet containing elacridar. The dissolution from ASD tablets was compared to that from a crystalline powder mixture in a USP type II dissolution apparatus. The pharmacokinetics of the ASD tablet were evaluated in an exploratory clinical study at oral doses of 25 mg, 250 mg or 1000 mg in 12 healthy volunteers. A target C_{max} was set at $\geq$ 200 ng/mL based on previous clinical data. The *in vitro* dissolution from the ASD tablet was 16.9 ± 3.7 times higher compared to that from a crystalline powder mixture. C_{max} and $AUC_{0-\infty}$ increased linearly with dose over the explored range. The target C_{max} of $\geq$ 200 ng/mL was achieved at the 1000 mg dose level. At this dose the C_{max} and $AUC_{0-\infty}$ were 326 ± 67 ng/mL and 13.4 ± 8.6 · 10^3 ng·h/mL respectively. In summary, the ASD tablet was well tolerated, resulted in relevant pharmacokinetic exposure and can be used for proof-of-concept clinical studies.

1. INTRODUCTION

Permeability Glycoprotein (P-gp; ABCB1) and the Breast Cancer Resistance Protein (BCRP; ABCG2) are two membrane-associated drug-efflux transporters that are expressed on epithelial cells lining the gastro-intestinal tract, in the endothelial cells that form the blood brain barrier, in stem cells and in cancer cells [1]. Consequently, they limit the oral bioavailability, reduce uptake in the central nervous system (CNS) of various drugs and may cause multidrug resistance of tumor cells [2]. Elacridar is a third generation inhibitor of P-gp developed in the 1990s for treatment of multidrug resistant cancers [3]. Later, it was also found to be an inhibitor of BCRP [4]. Clinical trials with transporter inhibitors to reverse multidrug resistance of tumors have been unsuccessful, but it was demonstrated that elacridar was an effective absorption enhancer of paclitaxel and topotecan at C_{max} values of $\geq$ 200 ng/mL [5–7]. Based on preclinical work it is also expected that elacridar may enhance drug delivery of substrate drugs to the CNS, which might increase the efficacy of treating brain tumors [2]. Further commercial development of elacridar was abandoned, possibly due to its challenging pharmaceutical properties. Elacridar is practically insoluble in water ($12.3 \cdot 10^{-5}$ mg/mL) [8] and appears to have a poor membrane permeability [9], suggesting it is a class IV drug according to the Biopharmaceutics Classification System (BCS) [10]. Moreover, the conventional tablet (containing elacridar hydrochloride) demonstrated poor and unpredictable oral absorption [6,11,12]. Currently no formulation is available for clinical trials. Although two new formulations are in preclinical development, according to our knowledge these have not yet been evaluated in humans [8,9].

Several formulation strategies can improve solubility-limited absorption, one of them being an amorphous solid dispersion (ASD) [13,14]. Here, the drug is dispersed in a biologically inactive hydrophilic amorphous polymer. When administered, this creates a temporarily supersaturated state with a high degree of solubilization, generating a time window for increased absorption [15,16].

ASDs have been developed for many poorly soluble drugs [17] and over 20 are already commercially available [18], underlining the feasibility and success of this approach. Because of this, we developed an ASD tablet formulation containing 25 mg elacridar hydrochloride (23.5 mg elacridar).

In this study we first evaluated the *in vitro* dissolution characteristics from the ASD tablet and based on the promising results we conducted a pharmacokinetic study in healthy volunteers.

2. MATERIALS AND METHODS

Chemicals and materials

Elacridar hydrochloride was synthesized according to previously reported procedures [19]. Povidone K30 (PVPK30) was purchased from BASF Chemtrade (Ludwigshafen, Germany); sodium dodecyl sulfate (SDS) from Merck (Darmstadt, Germany); dimethyl sulfoxide (DMSO) from VWR (Amsterdam, The Netherlands); lactose monohydrate SuperTab® 30GR from DFE Pharma (Goch, Germany); anhydrous colloidal silicon dioxide and magnesium stearate from Fagron (Capelle a/d Ijssel, The Netherlands); croscarmellose sodium from FMC (Philadelphia, USA); demineralized water from B. Braun (Melsungen, Germany). Simulated Intestinal Fluid without pancreatic enzymes (SIFsp, pH 6.8) was prepared as described in USP-NF [20]. Stainless steel boxes were from Gastronorm (The Netherlands).

Preparation of elacridar ASD tablets

Elacridar hydrochloride, PVPK30 and SDS were dissolved in DMSO (1:6:1, w/w/w) to yield an elacridar hydrochloride concentration of 10 mg/ml. The solution was dried by lyophilization in a Lyovac GT4 (GEA Lyophil, Hürth, Germany) by a method described previously [21]. This yielded the ASD powder which was immediately grinded and stored in dark airtight glass containers in a desiccator at 2 – 8 °C.
The ASD powder, lactose monohydrate, croscarmellose sodium, anhydrous colloidal silicon dioxide and magnesium stearate (30:63:5:1:1, w/w/w/w/w) were weighted in a hermetically sealed 2 L stainless steel vessel and mixed in a Turbula T10B mixer (Willy A. Bachofen AG Maschinenfabrik, Muttenz, Switzerland). Tablets were pressed on an eccentric tablet press (Korsch, EK10, Berlin, Germany). Each ASD tablet contained 25 mg elacridar hydrochloride (23.5 mg elacridar). Tablets were stored in aluminum blisters with polyvinylchloride sealing at – 20 °C. The production process and storage were performed according to Good Manufacturing Practices (GMP) and batch size was 200 – 300 tablets.

In vitro dissolution

Dissolution was studied by using a type II paddle dissolution apparatus as described in the European Pharmacopoeia [22] at rotation speed of 100 rpm. One tablet was placed in 500 mL SIFsp at 37 °C. Samples of 1 mL were taken through a 0.45 µm PVDF filter, diluted with 2 mL DMSO and measured on a previously described validated HPLC-UV system [23].

Clinical study

The pharmacokinetics of ASD formulation were assessed in healthy volunteers in a dose-escalation design, with 3 subjects per dose level. The aim was to achieve a target C_{max} of $\geq$ 200 ng/mL. The first dose level was 25 mg and each next level was based on the mean C_{max} of the previous dose level. A maximum dose was set at 1000 mg as previous clinical data indicated this is safe and well tolerated [*5–7*]. The dose level that reached the target C_{max} was expanded to a total of 6 volunteers. All subjects were instructed to fast 2 hours before and 2 hours after ingestion of the tablets. This study was approved by the Medical Ethics Committee of MC Slotervaart (Amsterdam, The Netherlands) and all volunteers provided written informed consent before enrolment. This trial was registered in the European Clinical Trial Database (EudraCT, registration number 2013-001131-*47*).

Pharmacokinetics

Blood samples (3 mL) were taken at t = 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 and 48 hours after administration of the formulation. These were centrifuged at 1500 rpm for 10 minutes and the plasma was stored at - 20°C. Elacridar concentrations were measured using a validated LC-MS/MS method as previously described [24]. Non-compartmental analysis of data was performed in R version 3.0.0, calculated parameters were C_{max}, T_{max}, $AUC_{0\text{-}48h}$ and $AUC_{0\text{-}\infty}$. These parameters were compared to values of previous clinical studies with the same once daily oral dose. To assess dose linearity and proportionality, individual observations of C_{max} and $AUC_{0\text{-}\infty}$ were plotted versus dose and a one-way ANOVA was executed on the dose normalized values of C_{max} and $AUC_{0\text{-}\infty}$ at each dose level.

3. RESULTS

In vitro dissolution

Figure 1 shows the dissolution from a crystalline physical mixture compared to the ASD tablets (98.8 ± 0.8 % content and 99.7 ± 0.5 % purity). The physical mixture resulted in 1.4 ± 0.1 % dissolution, whereas the dissolution from ASD tablets reached 23.7 ± 3.7 %, with a maximum at 30 to 60 minutes. The dissolution from ASD tablets was 16.9 ± 3.7 times higher than from a physical mixture.

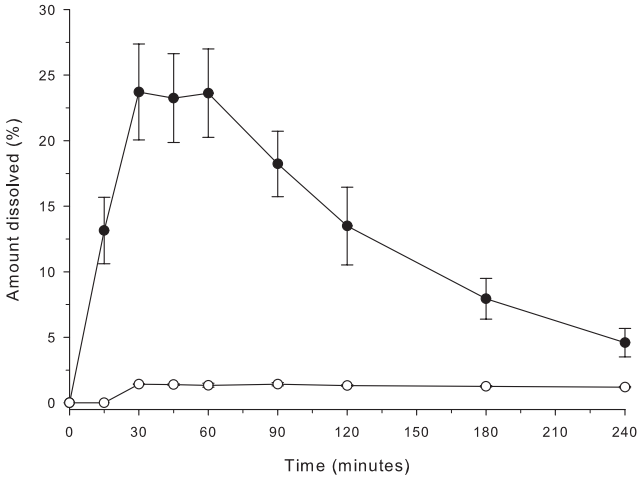

Figure 1. In vitro dissolution as mean ± standard deviation of the amount dissolved from the ASD tablets (3 batches, 6 tablets per batch, ●●●) and from a physical mixture of crystalline elacridar hydrochloride:PVPK30:crystalline SDS (1:6:1, w/w/w) (n = 3, ○○○) measured in a European Pharmacopoeia dissolution apparatus type II paddle 100 rpm 37 °C.

Clinical study

Thirteen healthy volunteers provided written informed consent. One volunteer withdrew from the trial due to problems with venous access, before taking the study medication. Of the remaining twelve volunteers 10 were female and 2 were male with a mean (± SD) age of 42 (± 9) years.

The ASD tablets were well tolerated. Adverse events were observed only at the 1000 mg dose level (nausea, dyspepsia and flatulence), they were limited to the day of ingestion and none of them exceeded grade 1 (CTC-AE v4.03).

Pharmacokinetics

Calculated pharmacokinetic parameters for each dose level are shown in Table 1. The dose levels were 25 mg, 250 mg and 1000 mg (corresponding to 23.5 mg, 235 mg and 940 mg elacridar). Plasma concentration time curves of each dose are presented in Figure 2. The 25 mg dose was taken by 3 volunteers and resulted in a C_{max} of 12.6 ± 6.52 ng/mL which was considerably below the target C_{max}. We therefore increased the dose 10-fold to 250 mg in the next 3 volunteers. Here, the C_{max} was 97.0 ± 32.1 ng/mL. The third dose level of 1000 mg (taken by 3 volunteers) resulted in a C_{max} of 350 ± 65.2 ng/mL. This level was expanded with 3 extra volunteers and the overall C_{max} was 326.0 ± 67.4 ng/mL.

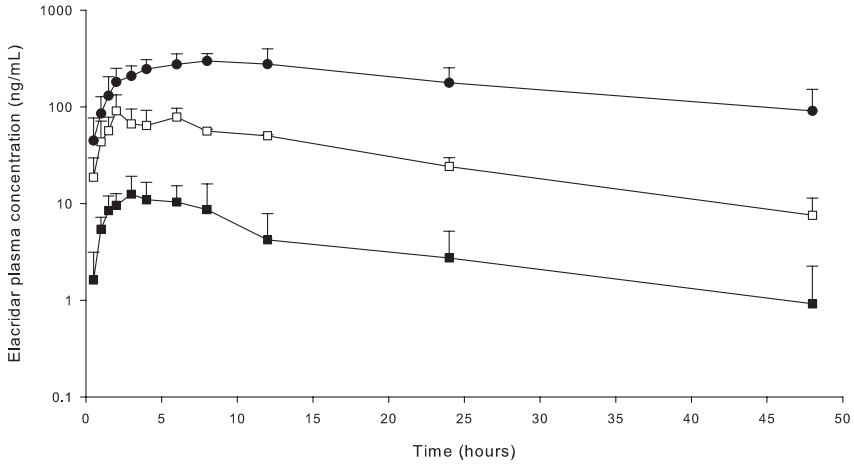

Figure 2. Elacridar plasma concentrations + standard deviation plotted on a semi-log scale for the 25 mg (n = 3, ■■■), 250 mg (n=3, □□□) and 1000 mg (n=6, ●●●) mg dose levels in the healthy volunteers.

Table 1. Pharmacokinetic parameters calculated from each dose level of elacridar

Dose	C_{max} ± SD ng/ml (CV %)	AUC $0_{0-\infty}$ ± SD ng·h/ml ·10^3 (CV %)	T_{max} ± SD h (CV %)	$AUC_{0-\infty}$/Dose ratio ± SD	C_{max} /Dose ratio ± SD
25 mg (n = 3)	12.6 ± 6.52 (52 %)	0.205 ± 0.172 (84 %)	2.7 ± 0.58 (22 %)	8.21 ± 6.87	0.504 ± 0.261
250 mg (n = 3)	97.0 ± 32.1 (33 %)	1.70 ± 0.401 (24 %)	3.3 ± 2.3 (70 %)	6.82 ± 1.60	0.388 ± 0.128
1000 mg (n = 6)	326.0 ± 67.4 (21 %)	13.4 ± 8.64 (65 %)	9.0 ± 3.5 (39 %)	13.4 ± 8.64	0.326 ±0.0674

$AUC_{0-\infty}$: Area under the curve (extrapolated to infinity)

C_{max}: Maximum concentration

CV: Coefficient of variation

SD: Standard deviation

T_{max}: Time to maximum plasma concentration

Figures 3 a and b show individual observations of C_{max} and $AUC_{0-\infty}$ as a function of dose. C_{max} and $AUC_{0-\infty}$ both increased linearly. Dose normalized values of C_{max} and $AUC_{0-\infty}$ (Table 1) did not deviate significantly from dose proportionality over the tested dose range (p = 0.277 and 0.399 respectively, ANOVA), though the C_{max}/ dose ratio seemed to decline at higher doses. Table 2 compares the pharmacokinetic results of this study with earlier clinical trials with once daily orally administered elacridar.

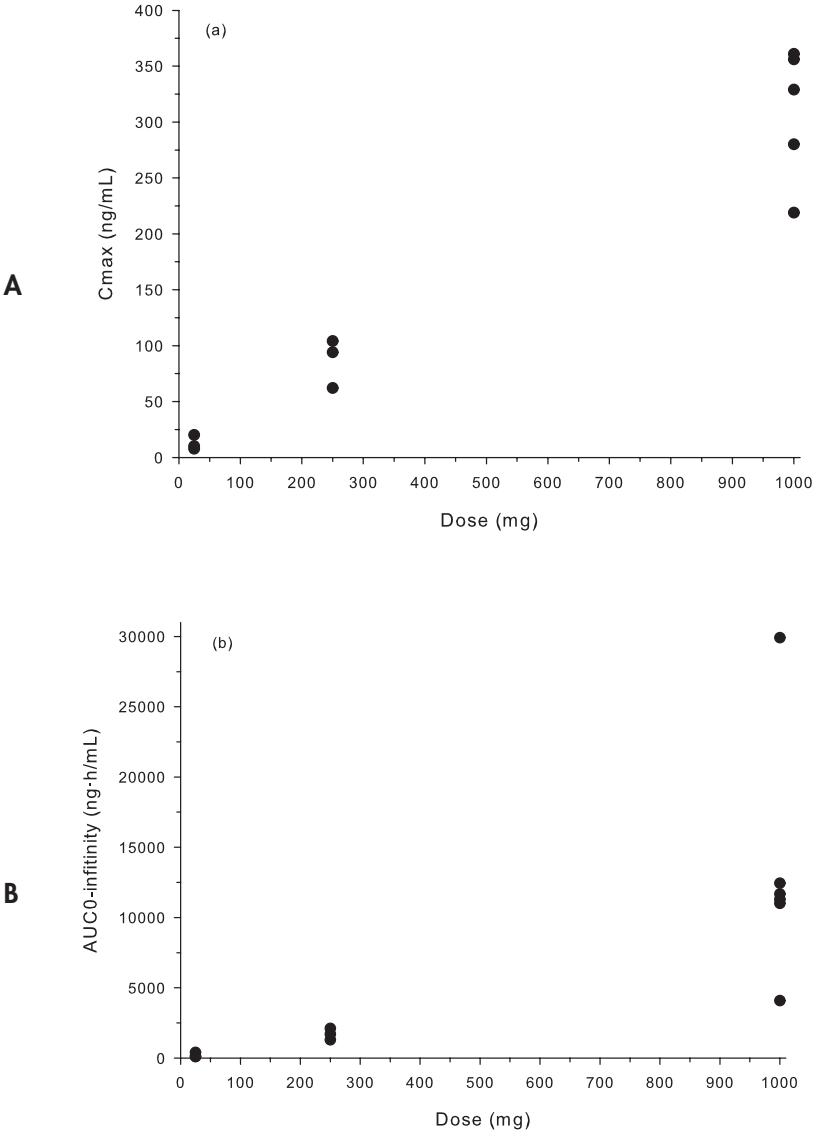

Figure 3. The relation of elacridar dose on the C_{max} **(a)** and $AUC_{0-\infty}$ **(b)** of ASD tablets administered to healthy volunteers at three different doses (25 mg n = 3, 250 mg n = 3 and 1000 mg, n = 6).

Table 2. Pharmacokinetic parameters of the current study compared with previous clinical trials

Dose (mg)	N	C_{max} ± SD, (range) or (CV %) ng/mL	AUC_{0-t} ± SD, (range) or (CV %) $\cdot 10^3$ ng·h/mL	T_{max} ± SD, (range) or (CV %)	Formulation	Reference
1000	6	326 ± 67.4 (21%)	0-24 h: 5.58 ± 1.71 (31%) 0-48 h: 8.80 ± 3.03 (34%)	9.0 ± 3.5 (39%)	ASD tablet	This study
1000	4	140 (114 – 171) NA	2.11 (1.77 – 2.51)[a] (11%)	6.0 (6.0 – 8.2)	GSK tablet	[6]
1000	4	185 (138 – 248) NA	2.63 (1.66 – 4.17)[a] (32%)	6.0 (3.0 – 9.1)	GSK tablet	[6]
1000	8	157 ± 93 (59%)	2.41 ± 1.11[a] (46%)	3.6 ± 3.4 (94%)	GSK tablet	[7]
1000	8	242 ± 122 (50%)	4.25 ± 2.04[a] (48%)	4.6 ± 2.2 (48%)	GSK tablet	[7]
1000	6	434 ± 267 (62%)	9.43 ± 5.43[b] (58%)	7.7 ± 2.5 (32%)	GSK tablet	[5]

SD = standard deviation, CV = variation coefficient, NA = not available
a AUC_{0-24h}
b AUC_{0-48h}

4. DISCUSSION

Inhibition of P-gp and BCRP by elacridar could be a valuable tool to improve drug delivery to the CNS and increase oral bioavailability of drugs which are substrates of these transporters. However, elacridar's low aqueous solubility currently limits its clinical application. The aim of this study was to assess whether the ASD tablet increases the dissolution and whether this formulation results in relevant pharmacokinetic exposure in healthy volunteers.

In vitro, the ASD formulation resulted in considerably higher dissolution (16.9 ± 3.7 fold) compared to that from a crystalline physical mixture (Figure 1). This indicated that the ASD could be a suitable approach to enhance the absorption of elacridar and supported investigation of its pharmacokinetics in a clinical trial.

In healthy volunteers, the targeted C_{max} of ≥ 200 ng/mL was achieved at a dose of 1000 mg, without grade > 1 toxicity. In fact, C_{max} and AUC at this dose were higher than values reported in most earlier clinical studies with elacridar (Table 2) [6,7] and similar to one study where elacridar was administered orally together with a paclitaxel formulation that contained polyethoxylated castor oil (Cremophor®) [5]. In contrast to previous trials, the ASD tablets showed a linear dose-dependent increase in C_{max} and $AUC_{0-\infty}$ (Figure 3). The previously used clinical formulation displayed

no clear relationship between dose, C_{max} and AUC [6]. That study only found an approximate threefold increase in C_{max} and AUC over a dose range of 100-1000 mg. Furthermore, variability of in C_{max} and exposure seemed lower in the current than in previous trials (Table 2). These observations indicate that the ASD formulation strategy resulted in more reliable absorption pharmacokinetics of elacridar.
In this study the high number of tablets at the 1000 mg dose was considered manageable as only a single administration was required and no alternative GMP-compliant formulation of elacridar was available. Nonetheless this is a limitation of the current formulation and will restrict its use to small proof-of-concept studies. For clinical applications involving daily oral administration further research into a new formulation will be needed.

The ASD formulation reached the prespecified target C_{max} of $\geq$ 200 ng/mL in healthy volunteers, however the increase in absorption did not approach the 17-fold increase as seen in the *in vitro* dissolution experiment. This could have several reasons:
Supersaturated solutions of BCS II/IV substances can be unstable *in vivo* and can recrystallize earlier than *in vitro*, thereby limiting absorption [25]. It has been proposed that with increasing degree of supersaturation the risk of *in vivo* fast nucleation and recrystallization also increases [26,27]. As the ASD tablet showed a rapid and a very high degree of supersaturation (Figure 1), the resulting system might have been particularly unstable *in vivo*, leading to recrystallization before the solubilized drug could be absorbed, causing suboptimal absorption.
The lower than expected absorption could also be due to limited membrane permeability. Though this seems unlikely based on the high log P (5.55) of elacridar [28], in an *in vitro* assay the membrane permeability was similar to that of the leakage marker inulin [9]. This could indicate that strategies aiming to improve the dissolution (such as ASDs and other supersaturating formulations) of elacridar may be insufficient to increase absorption and that future formulation efforts should also focus on increasing permeability.

5. CONCLUSION

The ASD tablet considerably improved dissolution *in vitro*. In healthy volunteers, the target C_{max} of 200 ng/mL was reached and C_{max} and $AUC_{0-\infty}$ increased linearly with dose. In summary, the ASD tablet was well tolerated, resulted in relevant pharmacokinetic exposure and can be used for proof-of-concept clinical studies.

Compliance with ethical standards. The experiments comply with the current laws of the country in which they were performed.
All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all human volunteers for being included in the study.

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Conflict of interest disclosure. Olaf van Tellingen is co-inventor of a patent application (Bunt and Van Tellingen, 2014; US 20140235631A1) dealing with development of an improved oral formulation for elacridar. All other authors declare they have no conflict of interest.

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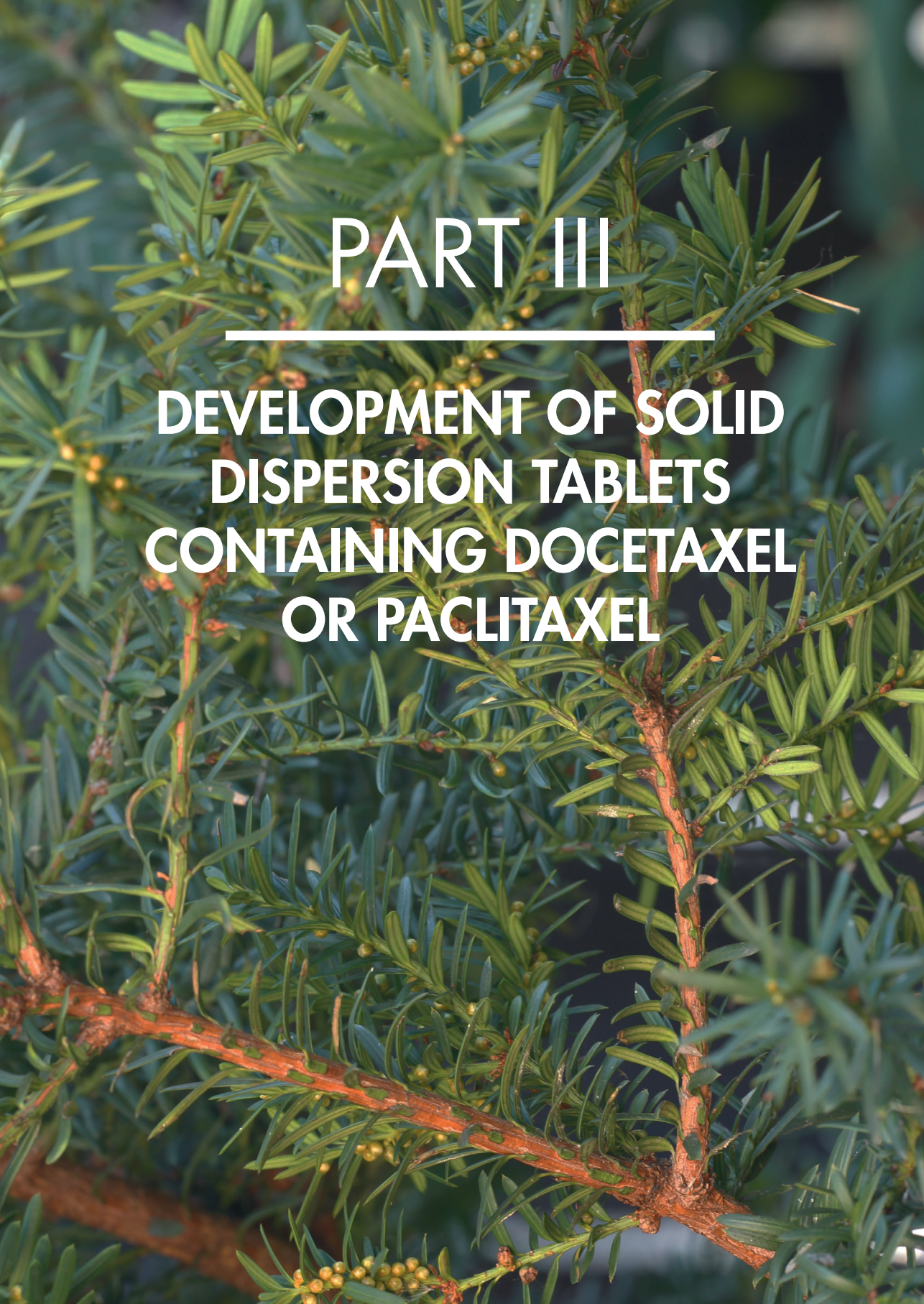

PART III

DEVELOPMENT OF SOLID DISPERSION TABLETS CONTAINING DOCETAXEL OR PACLITAXEL

PHARMACEUTICAL DEVELOPMENT OF AN ORAL TABLET FORMULATION CONTAINING A SPRAY DRIED AMORPHOUS SOLID DISPERSION OF DOCETAXEL OR PACLITAXEL

Emilia Sawicki
Jos H. Beijnen
Jan H.M. Schellens
Bastiaan Nuijen

CHAPTER 3.1

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ABSTRACT

Previously, it was shown in Phase I clinical trials that solubility-limited oral absorption of docetaxel and paclitaxel can be drastically improved with a freeze dried solid dispersion (fdSD). These formulations, however, are unfavorable for further clinical research because of limitations in amorphicity of SD and scalability of the production process. To resolve this, a spray drying method for an SD (spSD) containing docetaxel or paclitaxel and subsequently drug products were developed. Highest saturation solubility (S_{max}), precipitation onset time (T_{precip}), amorphicity, purity, residual solvents, yield/efficiency and powder flow of spSDs were studied. Drug products were monitored for purity/content and dissolution during 24 months at +15 – 25 °C. Docetaxel spSD S_{max} was equal to that of fdSD but T_{precip} was 3 times longer. Paclitaxel spSD S_{max} was 30% increased but T_{precip} was equal to fdSD. spSDs were fully amorphous, >99% pure, <5% residual solvents, mean batch yield was 100 gram and 84%. spSDs had poor flow characteristics, which could not be resolved by changing settings, but by using 75% lactose as diluent. The drug product was a tablet with docetaxel or paclitaxel spSD and was stable for at least 24 months. Spray drying is feasible for the production of SD of docetaxel or paclitaxel for upcoming clinical trials.

1. INTRODUCTION

Docetaxel and paclitaxel are effective anticancer drugs and are administered as dose-intensive treatments that often result in toxicities such as myelosuppression [1,2]. Weekly administration of low-dose docetaxel or paclitaxel causes considerably less acute toxicity while efficacy is similar to dose-intensive schedules [2,3]. On the other hand, weekly intravenous administration is patient-inconvenient and expensive because it requires hospitalization [1]. An oral formulation allows home-based drug intake and this might result in more patient-convenient and affordable metronomic chemotherapy schedules of docetaxel and paclitaxel.

However, docetaxel and paclitaxel have a low oral bioavailability (< 10%) which is caused by CYP3A4-mediated presystemic metabolism, P-glycoprotein drug efflux pumps and poor drug dissolution [1,4–8]. The dissolution of docetaxel and paclitaxel is pH-independent because the drugs are not ionizable in the physiological pH range [9,10]. The bioavailability of these two drugs can be boosted by co-administration of a strong CYP3A4 inhibitor such as ritonavir [11–13]. Poor drug dissolution can be improved by the pharmaceutical formulation such as a solid dispersion (SD) [14,15]. Previously, we described the development of a docetaxel SD (ModraDoc) and a paclitaxel SD (ModraPac) which contained povidone K30 (PVPK30) and sodium dodecyl sulfate (SDS). The excipients for the SD formulations were selected from an extensive formulation screening experiment that compared drug dissolution from 8 different excipients at drug proportions 4.8 – 71.4% with the dissolution of crystalline drugs. The formulation of active drug-PVPK30-SDS (1:9:1, w/w/w) resulted in the highest super-saturation: ~40 times higher for docetaxel and ~100 times higher for paclitaxel compared to the dissolution of crystalline drugs. In these SD formulations PVPK30 inhibited precipitation of the active drugs, while SDS worked as a wetting agent, facilitating a homogeneous and fast drug dissolution. Consequently, docetaxel SD and paclitaxel SD resulted in relevant in-vivo exposure in cancer patients and were well tolerated [4,13]. These SDs were made by freeze drying from a tert-butanol-water solution which was subsequently mixed with lactose and colloidal silicon dioxide and filled into hard gelatin capsules [4,13]. This production method, however, has two major issues. First, freeze dried SD (fdSD) containing docetaxel or paclitaxel are only partially amorphous because SDS recrystallizes during freeze drying from the tert-butanol-water mixture and this process continues upon storage [16]. This can affect drug dissolution and stability of the drug product. Second, freeze drying is a non-continuous, slow production process which causes scalability issues at development stages beyond Phase I clinical studies. Therefore, it was investigated if the production processes of the

docetaxel SD and paclitaxel SD can be improved in these respects. Examples of alternative production methods are melt extrusion, electrospinning and spray drying. Melt extrusion was not preferred due the high melting temperature of docetaxel and paclitaxel (232 °C and 213 °C respectively) and decomposition beyond 180 °C [17]. Electrospinning facilitates solvent evaporation through electric energy and with that enabling SD production at ambient room temperature and ambient air pressure. Many amorphous SD formulations with excellent dissolution enhancement have already been produced through electrospinning [18,19]. However, industrial application of electrospinning is currently limited due to poor reproducibility and low production efficiency [20] and the resulting SDs fibers require grinding/slicing before they can be further processed. Spray drying is a fast and continuous process, allows good particle engineering and the obtained SD powder is ready to use for further processing to the pharmaceutical dosage form [21]. There are already several commercialized amorphous SD drug formulations prepared by spray drying, for example everolimus (Certican®), etravirine (Intelence®) and telaprevir (Incivek®) [22], proving the feasibility of spray drying. Other researchers also used spray drying to develop solid self-emulsifying drug delivery systems and solid dispersions of docetaxel and paclitaxel and this resulted in amorphous formulations with significantly increased dissolution and absorption compared to corresponding crystalline drugs [9,23–25]. Disadvantages of these formulations are high amounts of surfactants such as polyoxyethylated castor oil and polysorbate, which cause gastro-intestinal toxicity and the fact that these formulations are not evaluated clinically. The SDs of docetaxel and paclitaxel that were developed by Moes et al contain generally-regarded safe excipients, low amount of surfactant, are free of polyoxyethylated castor oil and polysorbate and clinical trials already confirmed these drug formulations are well tolerated by cancer patients [13,26].
This article discusses the pharmaceutical development and validation of a spray drying method for the production of docetaxel/paclitaxel spray dried SD containing active drug-PVPK30-SDS (1:9:1, w/w/w) (spSD) and subsequently the development of a drug product suitable for further clinical trials.

2. MATERIALS AND METHODS

2.1 Materials

Docetaxel anhydrate was manufactured at Jiangsu Hengrui Medicines (Jiangsu, China). Paclitaxel was manufactured at Indena (Milano, Italy). Polyvinyl pyrrolidone K30 (povidone K30, PVPK30) was purchased from BASF (Ludwigshafen, Germany).

Sodium dodecyl sulfate (SDS), absolute ethanol, tert-butanol, potassium dihydrogen phosphate, methanol, acetonitrile and Millex HV polyvindylidene fluoride filter units 0.45 µm were purchased from Merck (Darmstadt, Germany). Simulated Intestinal Fluid without pancreatinic enzymes pH 6.8 (SIFsp) was prepared according to the USP-NF [27]. Distilled water was bought from B. Braun (Melsungen, Gemany). Granulated lactose monohydrate (SuperTab® 30GR) was from DFE Pharma (Goch, Germany). Croscarmellose sodium was purchased from FMC (Philadelphia, USA). Anhydrous colloidal silicon dioxide, magnesium stearate and lactose monohydrate 200 M were bought from Fagron (Cappelle a/d Ijssel, The Netherlands). Hard gelatin capsule shells size 0 were bought from Capsugel (Morristown, USA). All chemicals were GMP compliant.

2.2 Methods

Spray drying

A GMP-compliant B-290 Mini Spray Dryer was used together with a B-90 aspirator, a B-296 dehumidifier and a B-295 inert loop (Büchi, Flawil, Switzerland) in closed mode in the order: B290-B90-B296-B295 and nitrogen as drying gas. spSDs were stored at 2 – 8 °C in the dark in dark airtight glass jars.

Freeze drying

Freeze drying was performed using a Lyovac GT4 GEA (Lyophil GmbH, Hürth, Germany) according to the procedure previously described by Moes et al [4,13]. The product was grinded and stored in dark airtight glass jars at 2 – 8 °C.

Tapped density / powder flow measurements

A volumetric cylinder was filled with 25 mL of powder and was tapped 2000 times with a European Pharmacopoeia-compliant tapped density tester model 190CE5 (Erweka, Heusenstamm, Germany). Carr's compressibility index of each powder mixture was calculated [27]:

$$C = 100\ x\ (\frac{\rho tapped - \rho bulk}{\rho tapped})$$

Where C = Carr's compressibility index (%), ρ_{bulk} = bulk density (mg/mL) and ρ_{tapped} = tapped density (mg/mL). C ≤ 25.0 % indicated acceptable flow properties.

Powder mixing and tablet production

spSDs were processed within one month after production. Powders were mixed in a Turbula mixer T10B (Muttenz, Switzerland) and pressed on a GMP-compliant rotary tableting machine model JC-RT-16H (Jenn Chiang Machinery, Taiwan) with one oval punch set at a rotation speed of 10 - 16 rpm. Tablet mass and resistance to crushing were monitored on an analytical scale (Mettler Toledo PM480, Columbus, OH, USA) and a Tablet Hardness apparatus type 08FA (Erweka, Heusenstam, Germany) respectively.

X-ray powder diffraction (XRD)

Samples of approximately 0.5 mm thick were placed in a metal sample holder, placed in an X'pert pro diffractometer equipped with an X-celerator (PANanalytical, Almelo, The Netherlands), scanned at 30 mA and 40 kV from 10-45° 2θ, step size of 0.020° and scan speed of 0.002°/second.

Modulated Differential Scanning Calorimetry (MDSC)

Samples of approximately 10 mg were weighed into T_{zero} aluminum pans (TA instruments, New Castle, DE, USA), non-hermetically closed and placed in the Q2000 differential scanning calorimeter (TA Instruments, New Castle, DE, USA). Temperature scale and heat flow were calibrated with indium. 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. Data were analyzed with Trios software version 3.5.3696 (TA Instruments, New Castle, DE, USA)

Fourier Transform Infrared spectroscopy (FT-IR)

FT-IR were recorded from 650 – 3300 cm^{-1} with a resolution of 4 cm^{-1} on a FT-IR 8400S spectrometer equipped with a golden gate (Shimadzu, Kyoto, Japan). The average of 3 spectra, consisting of 16 scans each, is reported.

Laser diffraction analysis (LDA)

Particle size and particle size distribution of powders were recorded in duplicate on a HELOS H1988 laser diffraction analyzer (Sympatec, Clasuthal-Zellerfeld, Germany) at a pressure of 3 bar and a 100 mm (R3) lens.

Scanning electron microscopy (SEM)

Samples were placed on conducting double sided adhesive tape on an aluminum sample holder and imaged through back scattering electrons in a Phenom Pure SEM (Eindhoven, the Netherlands) at an acceleration voltage of 5.0 kV.

Residual water

Residual water was measured by Karl Fischer Titration on a Metrohm 758 KFD Titrino (Herisau, Switzerland) with standardized distilled water as titrant. Powders were measured in triplicate and 10 - 50 mg powder per sample was dissolved in 5 mL preconditioned methanol.

Residual tert-butanol and residual ethanol

Residual tert-butanol and ethanol were determined by gas chromatography (GC) as described earlier [28]. Fifty mg per sample was dissolved in 5 mL DMSO in triplicate.

Content, purity and identity

An amount 10 mg active drug were dissolved in 100 mL eluent (ammonium acetate (pH 5, 20 mM)-methanol-acetonitrile, 5:1:4, v/v/v) and 20 µL was injected into a reverse-phase HPLC-UV method described earlier [4,13,29].

Solubility and dissolution

The solubility was tested by adding powder equivalent to 6 mg docetaxel to 25 mL distilled water (37 °C, 720 rpm). A sample of 250 µL from t = 0 – 60 minutes was taken and each sample was filtrated with a 0.45 µm PVDF filter, diluted with 250 µl methanol-acetonitrile (1:4, v/v) and analyzed by the HPLC-UV system as described above. For paclitaxel solubility, powder equivalent to 3 mg active was added and the rest of the settings were identical as in the docetaxel solubility experiment.
Dissolution was tested in a USP type II dissolution tester [27]. One capsule or tablet was placed in 500 mL SIFsp (37 °C) with paddle speed at 100 rpm. One mL sample was directly filtrated and diluted with 1 mL methanol-acetonitrile (1:4, v/v) and analyzed by the HPLC-UV system as described above.

Stability studies

Docetaxel-containing drug products were stored in transparent polyvinylchloride blister units. The blisters were stored in polypropylene airtight 1000 mL jars at +15

– 25 °C in the dark. Paclitaxel-containing drug products were stored in airtight polypropylene 30 mL jars at +15 – 25 °C in the dark. Content, purity, mass and resistance to crushing were analyzed after 0, 6, 12, 18 and 24 months. Resistance to crushing was tested on a European Pharmacopoeia-compliant Erweka TBH20 tablet hardness tester (Erweka, Heussenstamm, Germany).

3. RESULTS AND DISCUSSION

3.1 Spray dried solid dispersions (intermediate product)

Spray drying method development

First, a solvent was selected to dissolve docetaxel, paclitaxel, PVPK30 and SDS. Ethanol was the preferred solvent because this solvent resulted in highest docetaxel/paclitaxel solubility compared to other commonly used spray drying solvents [21,30,31]. Ethanol-water (75:25, v/v) was chosen because this co-solvent resulted in an optimal docetaxel, paclitaxel, PVPK30 and SDS solubility.

The selected inlet temperature was 100 ± 1 °C because this temperature is well above the boiling temperature of the co-solvent (~83 °C). Higher inlet temperatures were not considered because the glass transition temperature (T_g) of a prototype spSD containing docetaxel was ~150 °C [16] and as a rule-of-thumb the difference between T_g and operation temperature should preferably >50 °C [32]. The outlet temperature was 65 ± 5 °C.

Variations in the total solute concentration in the spray drying solution were made because concentrated solutions could result in a higher powder density and with that a better powder flow [21]. Solutions of PVPK30-SDS (9:1, w/w) ("blank spSD") ranging from 62.5 to 175 mg/mL were spray dried from ethanol-water (75:25, v/v), inlet-outlet temperature 100-65 °C, gas flow rate 35 mm arbitrary units and nozzle tip/cap diameter of 0.7/1.50 mm. As docetaxel and paclitaxel are cytotoxic, expensive and constitute for only 9.1% of the powder it was considered acceptable to conduct these experiments without active. Approximately 40 gram powder was obtained per sample. The particle size increased with increasing solute concentration with a median particle size of 4.8 vs 7.7 µm for 62.5 mg/mL vs 175 mg/mL, respectively (Figure 1). Higher concentrations than 175 mg/mL were too viscous and could not be spray dried. Figure 1 also shows that Carr's compressibility index only slightly decreased for the 175 mg/mL solute concentration, but was still >25%, indicative for poor powder flow. From this, it was concluded that the powder flow could not be significantly improved by modifying the spray drying concentration.

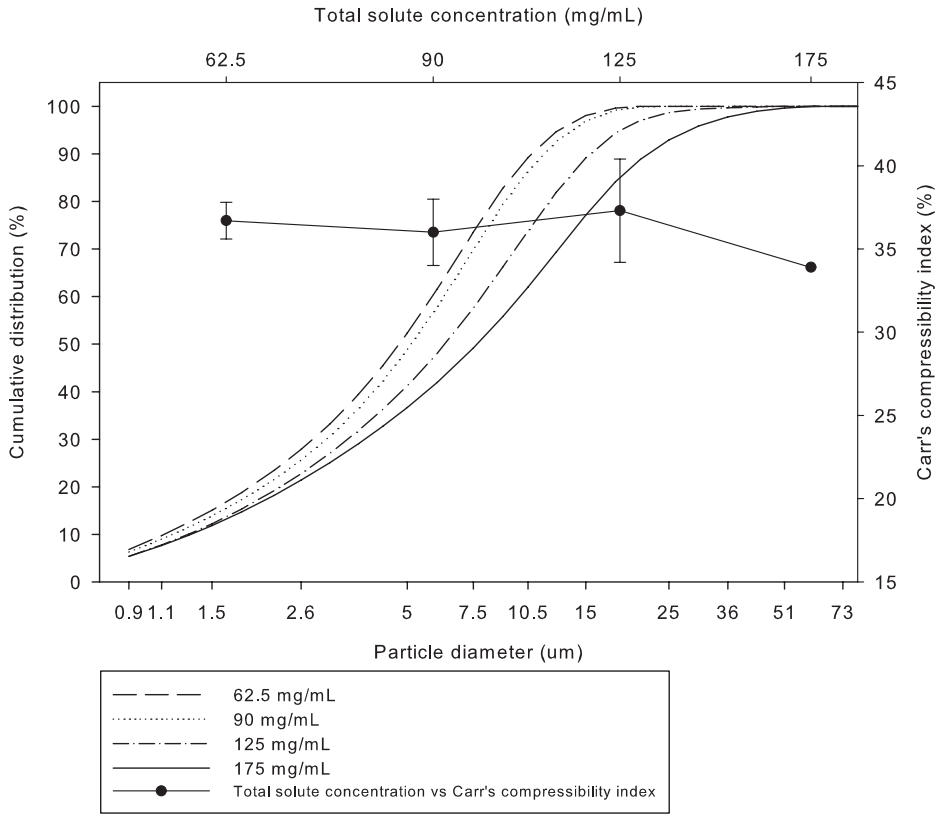
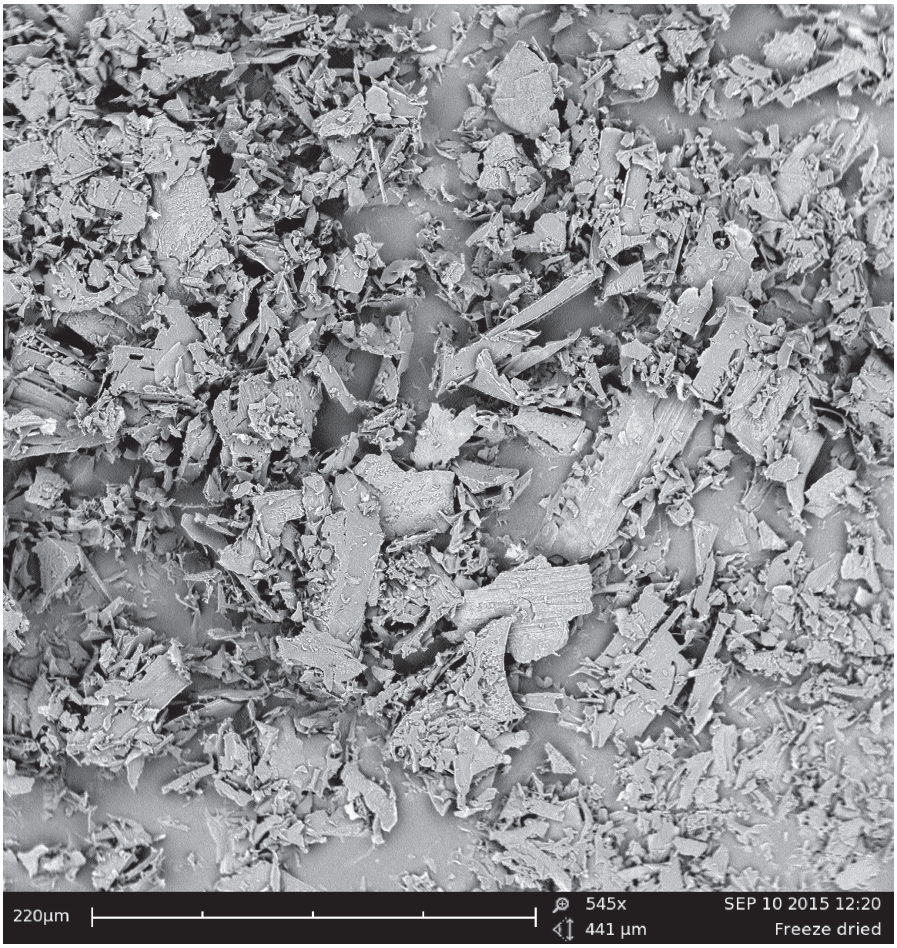


Figure 1. The influence of total solute concentration on the cumulative distribution of particle size of spray dried SD as measured by LDA (left y-axis and down x-axis, 62.5 mg/mL dashed line, 90 mg/mL dotted line, 125 mg/mL dashed-dotted line, 175 mg/mL continuous line) and Carr's compressibility index (right y-axis and upper x-axis, continuous line with black dots and error bars). Fixed parameters: solvent ethanol-water (75:25, v/v), drying gas temperature (100 ± 1 °C), outlet temperature (65 ± 5 °C), nozzle 0.7/1.5 mm, and aspirator flow 100/85%. Variable parameter: total solute concentration (62.5 – 175 mg/mL).

Next, the influence of nozzle orifice outlet diameter on powder flow properties was studied as it governs droplet size and hence influences powder particle size [21]. Blank SD was made from a total solid concentration of 175 mg/mL according to the settings described above except that the nozzle was replaced by a cap/tip of 2.0/2.8 mm diameter respectively. The powder flow was 32.0 ± 2.0 %, the yield was 72% and production time was 75 minutes for 40 gram. The increased nozzle diameter resulted in a lower drying capacity and therefore the solution feed rate had to be adjusted to 4.2 mL/minute. These modifications did not improve powder

Figure 2. Scanning electron microscopy image of fdSD **(A)** and spSD **(B)**.

A



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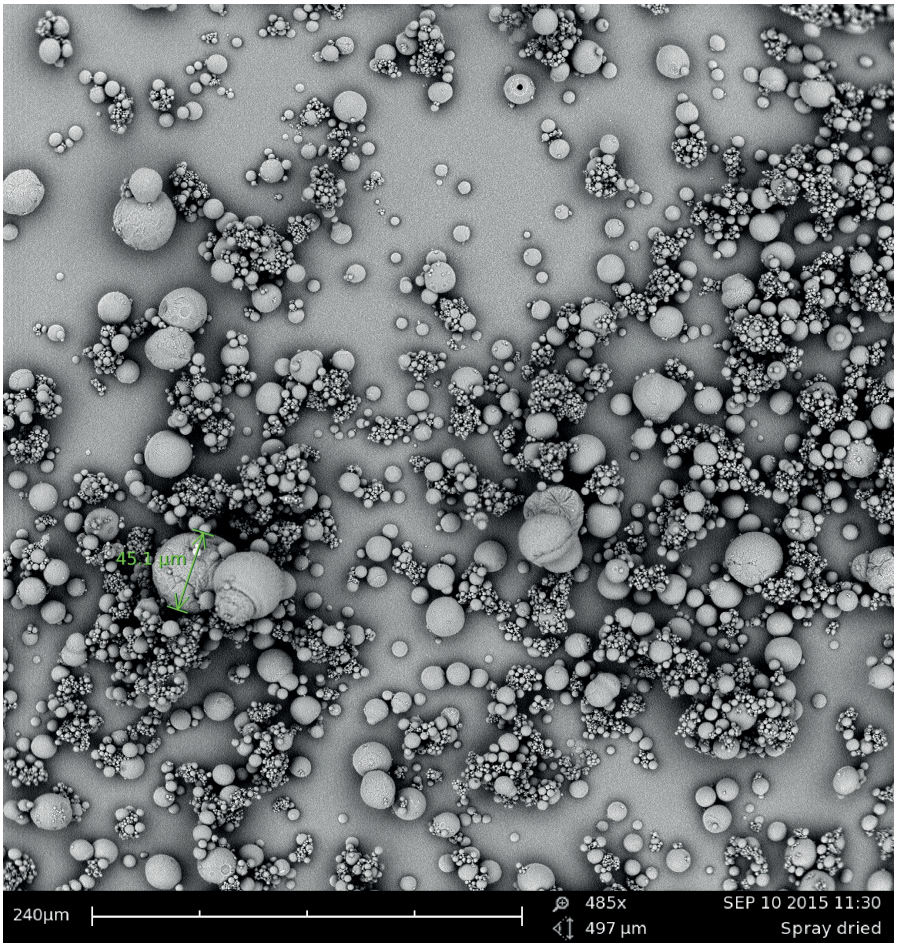

flow while yield and production time decreased. Therefore, a nozzle with cap/tip of 0.7/1.50 mm was preferred.
Then, variations in the nitrogen gas flow rate were made because a lower gas flow results in larger droplets and with that larger powder particles [21]. A flow of 20 mm instead of 35 mm resulted in 25.9 ± 0.1 % compressibility index and a yield of 73%. The decreased gas flow resulted in poorer drying capacity and required an adjustment in the solution feed rate to 3 mL/minute to produce acceptably dry particles. These settings considerably slowed down the spray drying process: 103 minutes for 40 g. Because of the decreased yield and decreased speed of the production process these settings were not preferred.
The final spray drying settings for the production method were: total solute concentration 175 mg/mL in ethanol-water (75:25, v/v), nozzle 0.7/1.5 mm, inlet temperature 100 °C, 35 mm gas pressure units and solution feed rate of 12 mL/minute. Yield was 80% and the production time was 24 minutes for 40 gram. Figure 2 A shows that fdSD consisted of irregularly shaped particles of different sizes while spSD (Figure 2 B) contained spherically-shaped, intact particles. These results were in line with LDA analysis data (Figure 1).

Physical characterization

A solution of docetaxel-PVPK30-SDS (1:9:1, w/w/w) and paclitaxel-PVPK30-SDS (1:9:1, w/w/w) were spray dried according to the final settings and compared to fdSD docetaxel-PVPK30-SDS (1:9:1, w/w/w) and fdSD paclitaxel-PVPK30-SDS (1:9:1, w/w/w) by XRD, FT-IR and MDSC (Figure 3 A - C respectively). spSD appeared fully amorphous while crystallinity diffraction at 2θ 20.5° and 22° was recorded in fdSD. Crystallinity was caused by SDS because a physical mixture of amorphous active-PVPK30-SDS also diffracted at these angles and in these formulations SDS was the only crystalline component [4]. FT-IR spectra of fdSD and spSD were nearly identical except that the CH_2 stretch peaks of SDS at 2850 and 2925 cm^{-1} [33] in fdSD had a similar shape to a physical mixture of amorphous active-PVPK30-SDS. This confirmed that not all SDS was amorphous in fdSDs. T_g of spSD was 140 °C and no melting occurred, proving its amorphous state. By contrast, fdSD had a T_m of 120 °C which was caused by SDS because the T_m of SDS was around 120 °C [10]. The MDSC of blank spSD was the same as that of spSD with active with a T_g of 140 °C, indicating that omission of the active had negligible influence on the T_g.

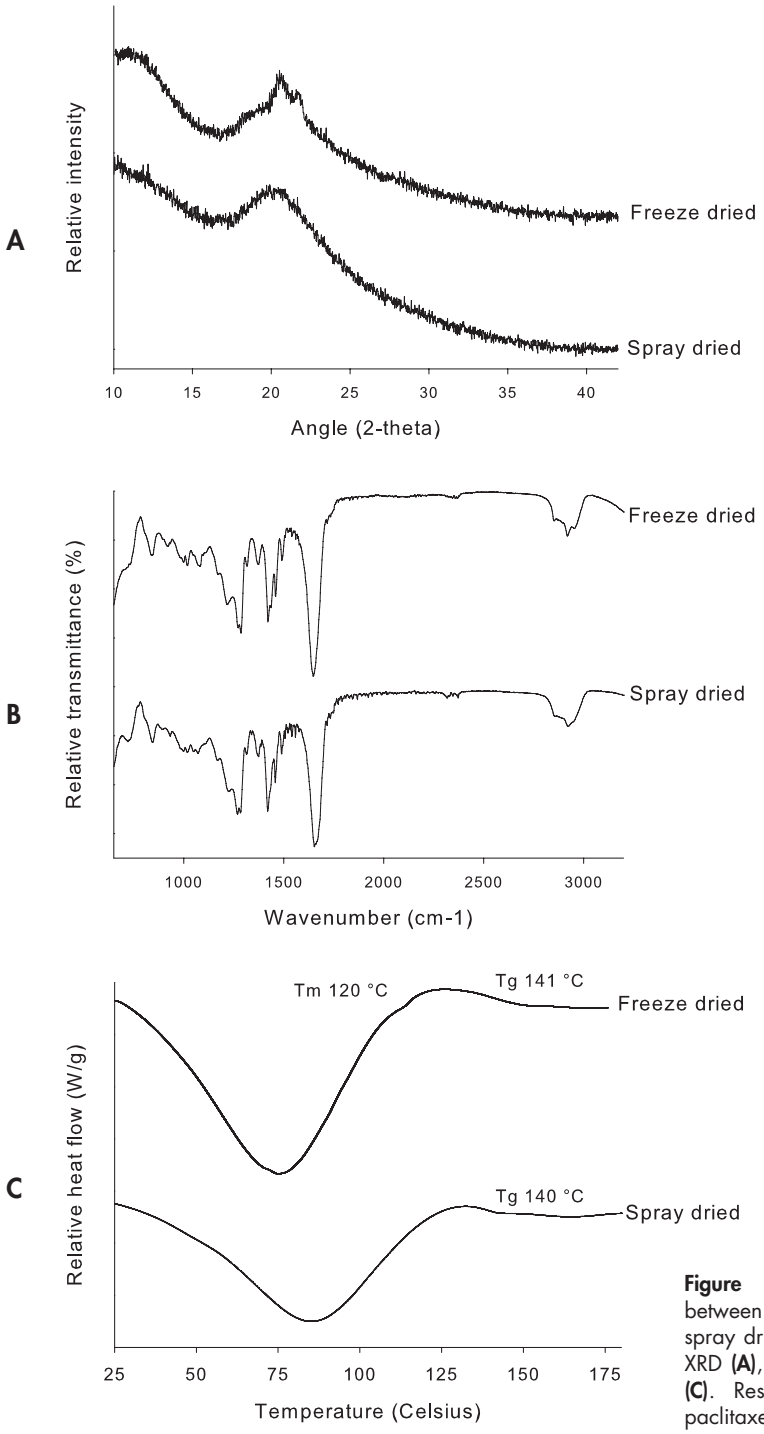

Figure 3. Comparison between freeze dried and spray dried docetaxel SD by XRD **(A)**, FT-IR **(B)** and MDSC **(C)**. Results also apply to paclitaxel SD.

Docetaxel solubility comparison from spSD and fdSD is shown in Figure 4 A. The apparent maximum solubility in the supersaturated state (S_{max}) was nearly complete for both fdSD and spSD (220 µg/mL) but the time to precipitation (T_{precip}) was 3 times longer in spSD. This can be explained by the fact that SDS is molecularly dispersed in spSD whereas in fdSD it is not. The increased T_{precip} may theoretically result in an increased absorption window in-vivo.
Paclitaxel solubility from spSD and fdSD is shown in Figure 4 B and it can be seen that S_{max} increased from 71 µg/mL (fdSD) to 92 µg/mL (spSD), proving that the wetting effect of SDS is more efficient when it is molecularly dispersed as in the case of spSD. T_{precip} in spSD was similar to fdSD which was different than the observation made for docetaxel spSD. This is because paclitaxel precipitation is more difficult to inhibit due to paclitaxel's lower intrinsic solubility compared to that of docetaxel (0.8 µg/mL versus 6 µg/mL) [4,13].

Validation and routine manufacture

Next, it was investigated if spSD can be produced in a continuous manner. For this, clogging of the outlet filter was found critical: the spray drying process was kept stable by inserting a clean outlet filter when the filter bag was full (indicated by -20 mbar pressure drop relative to starting pressure). This filter switch delayed the production process with approximately one hour in order to stabilize the system. Up to this point, this resulted in a batch size of at least 85 gram.
For validation, 3 docetaxel batches and 2 paclitaxel batches were manufactured. Results are shown in Table 1. On average 100.5 ± 6.2 grams was obtained per batch at an efficiency of 83.7 ± 1.2 % and a production time of 68 ± 3 minutes. The average yield using the freeze drying production method was 40 gram (efficiency 100%) for which 3 processing days were required. Content was 95 – 105% and purity was >99% proving that no chemical degradation occurred. Residual water and residual ethanol were on average 2.7 % and 1.7 % respectively. Carr's compressibility index was comparable to blank spSD. On the basis of these results, it was concluded that the production process was reproducible and robust for both docetaxel and paclitaxel spSD and therefore considered as validated.
Subsequently, 10 batches of spSD were routinely manufactured and results were comparable to validation batches (Table 1). Spray drying was about 10 times faster than the previously used freeze drying method. Besides, spSD had 2.3 times less residual solvents than fdSD: 4.3 ± 0.2 % vs 9.8 ± 0.2 % respectively. From the data it can be concluded that spray drying is a fast, robust and reproducible method for docetaxel/paclitaxel spSD.

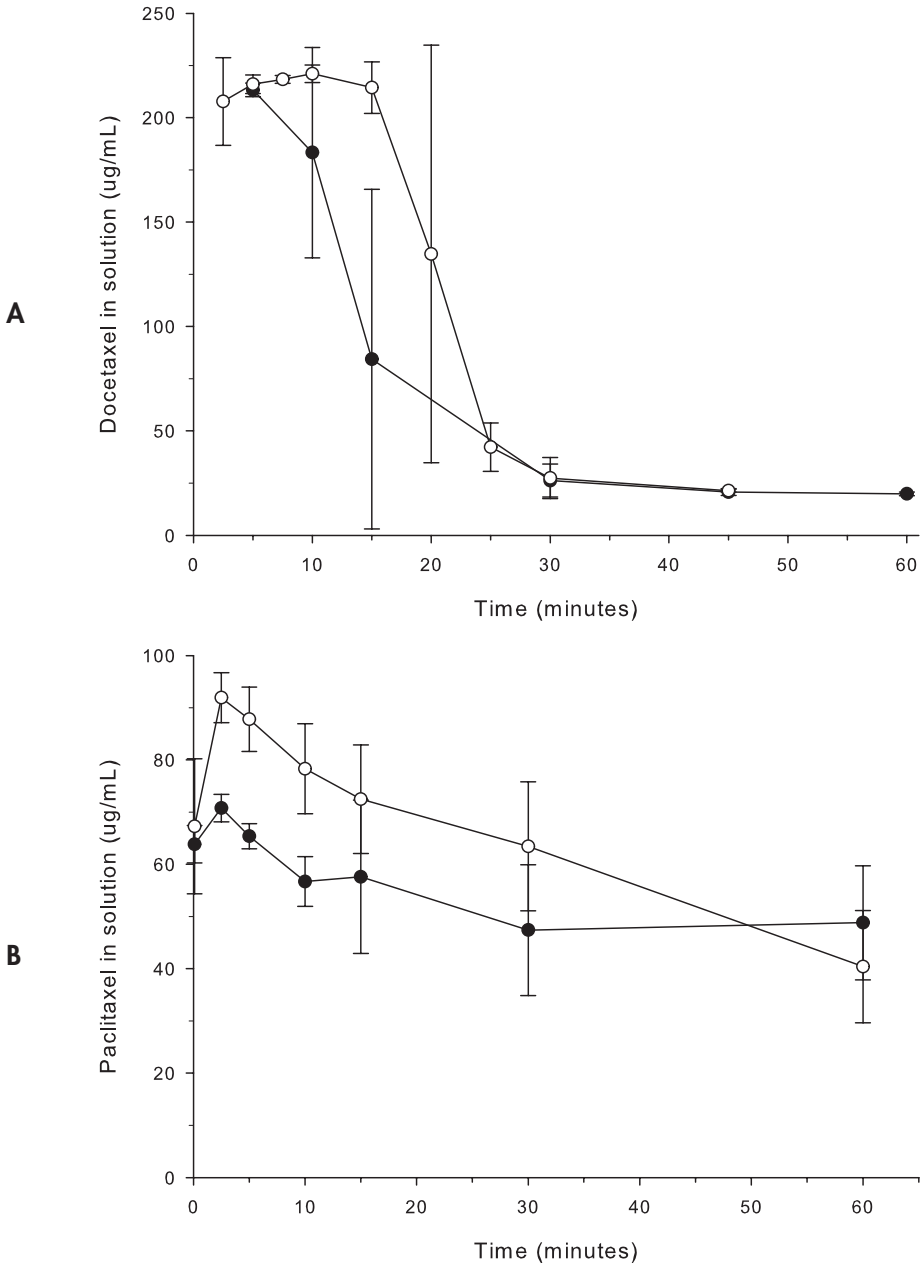

Figure 4. The solubility of docetaxel **(A)** and paclitaxel **(B)** from fdSD (●●●) and spSD (○○○) when an amount equivalent to 6 mg docetaxel (n = 4) **(A)** or 3 mg paclitaxel (n = 3) **(B)** was added to 25 mL water 37 °C stirred 720 rpm.

Table 1. Validation of the spray drying method for docetaxel spSD and paclitaxel spSD.

Batch	Validation (V) or Routine (R)	Active	Batch size (g)	Yield (%)	Production time (minutes)	Content ± stdev (%)	Residual water ± stdev (%)	Residual ethanol ± stdev (%)	Carr's compressibility index ± stdev (%)
1	V	DOC	95.3	82.5	67	97.2 ± 0.8	2.3 ± 0.2	1.8 ± 0.0	30.7 ± 2.3
2	V	DOC	96.3	83.3	66	99.1 ± 1.2	2.1 ± 0.1	1.8 ± 0.0	34.7 ± 2.3
3	V	DOC	96.7	83.6	66	101.1 ± 0.6	2.3 ± 0.1	2.0 ± 0.0	34.6 ± 2.3
4	V	PAC	108.5	85.7	70	103.2 ± 0.3	3.7 ± 0.3	1.3 ± 0.0	NM
5	V	PAC	105.9	83.6	72	103.6 ± 0.4	3.2 ± 0.1	1.4 ± 0.0	NM
6	R	DOC	87.1	83.1	60	102.2 ± 0.4	2.2 ± 0.2	1.5 ± 0.0	NM
7	R	DOC	87.4	83.0	60	103.1 ± 1.0	2.0 ± 0.1	1.5 ± 0.0	NM
8	R	DOC	87.8	83.6	60	104.2 ± 0.3	2.0 ± 0.1	1.6 ± 0.0	NM
9	R	DOC	97.6	84.5	65	100.8 ± 1.2	2.2 ± 0.0	2.0 ± 0.0	NM
10	R	DOC	106.1	83.8	72	101.2 ± 0.2	3.5 ± 0.1	1.6 ± 0.0	NM
11	R	DOC	108.0	85.3	71	100.4 ± 0.1	3.3 ± 0.2	1.4 ± 0.0	NM
12	R	DOC	107.8	85.1	71	101.0 ± 0.4	3.3 ± 0.2	1.4 ± 0.0	NM
13	R	PAC	118.6	84.6	79	101.4 ± 0.5	2.5 ± 0.1	1.5 ± 0.0	NM
14	R	PAC	119.6	85.2	78	101.4 ± 0.1	2.4 ± 0.2	1.7 ± 0.0	NM
15	R	PAC	118.2	84.3	79	102.3 ± 0.2	2.4 ± 0.1	1.6 ± 0.0	NM

stdev: standard deviation

V: validation batch

R: routine batch

DOC: active compound is docetaxel

PAC: active compound is paclitaxel

NM: not measured

Stability

The long-term stability of fdSDs was previously described [17]. This study showed that the amorphicity of active drugs is highly stable: both docetaxel and paclitaxel remain amorphous when stored for 2.5 years at 15 – 25 °C / 60% RH (measured by MDSC, XRD and IR). The stability of the SDs, however, can be affected by water adsorption to PVPK30 which disrupts dispersion-, polar-, and hydrogen bonding between PVPK30-SDS and active drug-SDS. The resulting SDS recrystallization reflected in reduced drug dissolution rate but not in the extent of drug dissolution. Water-induced SDS recrystallization can be prevented by appropriate primary packaging material. This observed stability profile can be extrapolated to spSDs, having the same composition as fdSD and with the note that spSDs start off with a significantly lower residual water content. A three-month stability study of spSDs, spanning the practical time-period of further processing of spSDs into the final product, indeed showed no changes in amorphicity, T_g, content, purity and residual water as compared to spSDs immediately after production.

3.2 Drug products

Development, validation and routine manufacture

As powder flow of spSD could not be significantly improved by modifying spray drying process parameters, flow was improved by using granulated lactose as a diluent. A powder mixture of 80% diluent and 20% spSD resulted in acceptable powder flow (Carr's compressibility index ≤ 25%). In order to limit the size of the final dosage form, it was decided to switch from a capsule to a tablet. The final powder mixture contained the docetaxel spSD or paclitaxel spSD, granulated lactose (diluent/filler), croscarmellose (disintegrant), colloidal silicon dioxide (glidant), magnesium stearate at 20:75:3:1:1, w/w/w/w/w. Tablets were oval-shaped, inscripted with MD10 (in case of docetaxel as active) or MP10 (in case of paclitaxel as active) and the length, width and thickness of each tablet were 16.00 mm x 8.50 mm x 5.35 mm respectively.

Validation was done with powder mixture containing blank spSD, docetaxel spSD and paclitaxel spSD and results are shown in Table 2. Tablets were free from cracks, capping and lamination, mass variation ≤ 1.5%, resistance to crushing 127 ± 10 N and production time 135 ± 11 minutes. Content in tablets with active was 95 – 105% and purity >99%. On the basis of the validation batches it was concluded that the production process is robust, reproducible and feasible. Subsequently, 4 batches were routinely produced and their results were similar to validation results (Table 2). Batch sizes of 700 – 3000 tablets per day were produced and all batches

Table 2. Validation and routine quality control of the tablet formulation containing an amount of spSD equivalent to 10 mg active.

Batch	Validation (V) or routine (R)	Active	Batch size (No. of tablets)	Average tablet weight ± stdev (mg)	Tablet weight variation (%)	Resistance to crushing ± stdev (N)	Production time (minutes)	Content label claim ± stdev (%)	Purity (%)
1	V	NONE	1800	587.4 ± 8.9	1.5	115 ± 10	135	NA	NA
2	V	DOC	1539	564.0 ± 8.2	1.5	135 ± 21	146	98.4 ± 3.4	99.6
3	V	PAC	1586	555.7 ± 3.6	0.7	130 ± 7	125	102.6 ± 2.0	100.0
4	R	DOC	739	556.5 ± 7.9	1.4	120 ± 17	70	102.0 ± 0.6	99.7
5	R	DOC	1578	544.6 ± 3.2	0.6	107 ± 5	125	97.7 ± 2.0	99.9
6	R	DOC	2683	555.3 ± 5.2	0.9	118 ± 12	240	98.6 ± 0.7	100.0
7	R	PAC	2913	550.7 ± 3.5	0.6	115 ± 7	168	102.6 ± 2.0	100.0

NONE: no active, blank spSD used

DOC: docetaxel as active

PAC: paclitaxel as active

complied with uniformity of content, mass variation ≤ 1.5%, resistance to crushing and were intact. This shows that the production process for the final drug product is suitable for clinical application.

The dissolution from drug products with fdSD (capsule formulation) and spSD (tablet formulation) is shown in Figures 5 A and B respectively. Both formulations resulted in ~90% drug dissolution but the dissolution rate from the capsule formulation was higher. This was caused by faster disintegration of capsules compared to that of tablets. Translated to the in-vivo situation the tablet formulation might result in a slower absorption rate.

Stability

The content and purity of docetaxel after 24 months of storage at +15 – 25 °C was compliant for both capsule- and tablet formulations: 95 – 105 % (content) and >99% (purity). The physical stability was studied with dissolution, drug product mass and resistance to crushing (tablets only). Dissolution from the capsule formulation containing fdSD was equal to that from a freshly prepared batch up to 12 months of storage at +15 – 25 °C. After 24 months of storage dissolution rate decreased, as can be seen in Figure 5 A. Additionally, after 24 months of storage the powder inside the capsule appeared wet and the mass increased 5%, indicating water adsorption during storage. An increased residual water content resulted in SDS recrystallization and this explains the delayed dissolution [17]. Delayed dissolution is disadvantageous because it might increase in-vivo variability in absorption leading to more variable plasma concentrations. The dissolution of tablet formulation did not change after 24 months of storage (Figure 5 B), tablets were resistant to crushing (155 ± 15 N) and appeared intact which means tablets did not vitrify. Tablet mass increased by 2% which means that less water adsorbed and that SDS recrystallization during storage did not occur. Similar stability results were obtained with capsule formulation and tablet formulation containing paclitaxel as the active. To conclude, the tablet formulation is more robust and stable and is therefore preferable to be used in further clinical trials.

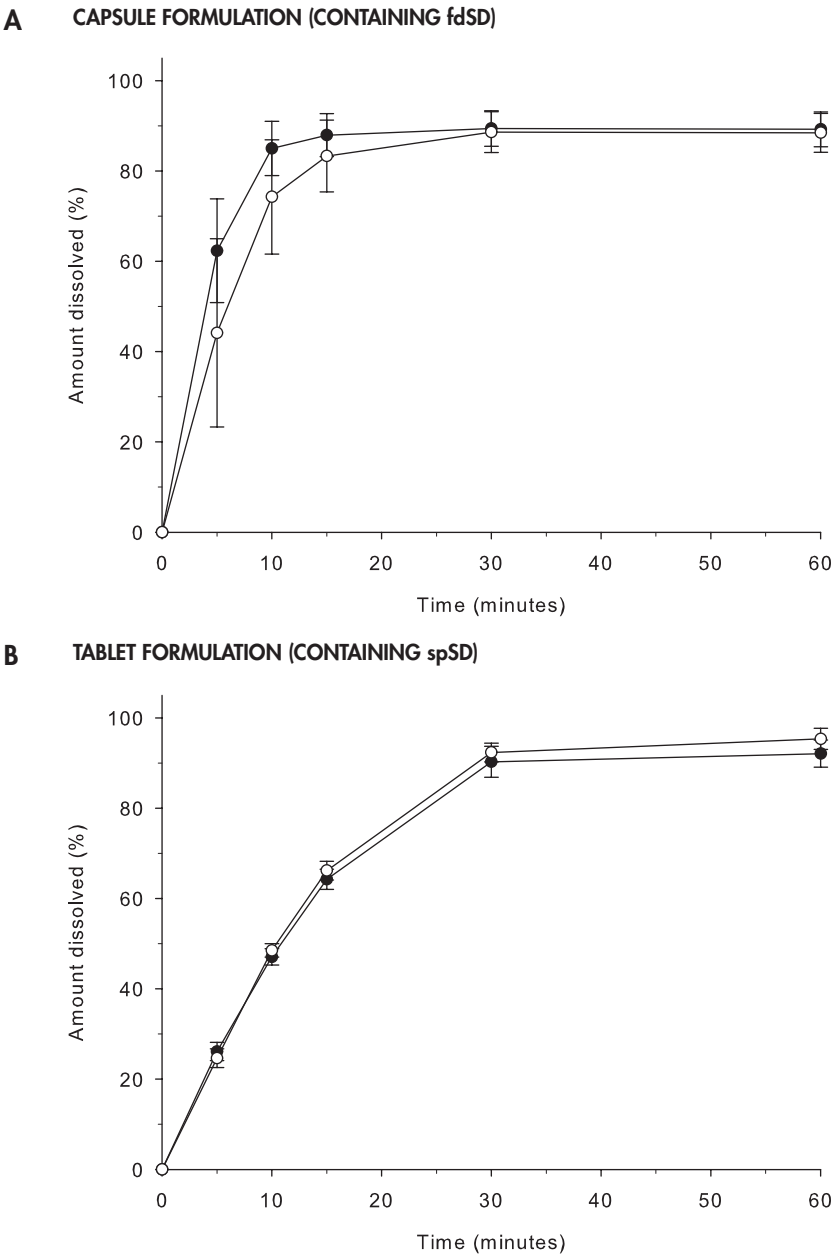

Figure 5. The dissolution of docetaxel from capsules with fdSD (capsule formulation) immediately after production (●●●, n = 24) and after 24 months storage at +15 – 25 °C (○○○, n = 19) **(A)**, and the dissolution of docetaxel from tablets with spSD (tablet formulation) immediately after production (●●●, n = 24) and after 24 months of storage at +15 – 25 C (○○○, n = 9) **(B)**. Results apply also to the capsule formulation and tablet formulation with paclitaxel as active compound.

4. CONCLUSION

This paper describes the pharmaceutical development of a spray drying method for the production of a SD containing either docetaxel or paclitaxel. Docetaxel spSD results in longer supersaturation compared to fdSD. Paclitaxel spSD results in a higher saturation concentration than fdSD. The increased solubility effect is caused by the fact that spSD is fully amorphous whereas fdSD is only partially amorphous due to recrystallization of SDS. Another advantage of spray drying is that the method is fast, efficient, robust and industrially applicable which makes it suitable for forthcoming clinical trials. The drug product is a tablet formulation which contains either docetaxel spSD or paclitaxel spSD equivalent to 10 mg active. Dissolution is complete but dissolution rate is lower compared to the capsule formulation and this is caused by longer disintegration of the tablet. Dissolution from the tablet formulation is stable for at least 2 years at room temperature whereas the capsule formulation has a decreased dissolution rate after 2 years of storage. This makes the tablet formulation preferable for further clinical trials.

Conflict of interest. Bastiaan Nuijen, Jos Beijnen and Jan Schellens are patent-holders of oral taxane formulations. Jos Beijnen and Jan Schellens are employees and share-holders of Modra Pharmaceuticals, a spin-off company developing an oral formulation of taxanes.

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A POPULATION PHARMACOKINETIC MODEL OF ORAL DOCETAXEL CO-ADMINISTERED WITH RITONAVIR TO SUPPORT EARLY CLINICAL DEVELOPMENT

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CHAPTER 3.2

Submitted

ABSTRACT

Oral administration of docetaxel is an attractive alternative for the conventional intravenous (IV) administration. The low bioavailability of docetaxel, however, hinders the application of oral docetaxel in the clinic. Previously, we have developed oral docetaxel formulations in solid dispersion formulations–ModraDoc001 capsule and ModraDoc006 tablet. These formulations were tested in phase I studies with co-administration of ritonavir in order to boost docetaxel bioavailability. The aims of the current study were to develop a population pharmacokinetic (PK) model for docetaxel and ritonavir based on the phase I studies and to support drug development of this combination treatment. In three clinical studies, we collected PK data in 161 patients who received IV docetaxel and different oral docetaxel formulations (drinking solution, ModraDoc001, and ModraDoc006) co-administered with ritonavir. A PK model was firstly developed for ritonavir. Subsequently, a semi-physiological model including gut, liver, central and peripheral tissue compartments was developed for docetaxel, which incorporated the inhibition of docetaxel metabolism by ritonavir. The uninhibited intrinsic clearance of docetaxel was estimated based on data on IV docetaxel as 1,980 L/h (relative standard error 11%). ModraDoc formulations were superior to the drinking solution of docetaxel with much lower inter-patient and intra-patient variability in important PK parameters. Ritonavir co-administration extensively inhibited the hepatic metabolism of docetaxel to 8%, which resulted in up to 13-fold higher docetaxel plasma concentrations compared to oral docetaxel administered without ritonavir. A semi-physiological PK model for docetaxel and ritonavir was successfully developed. This PK model was used to support early clinical development.

1. INTRODUCTION

Docetaxel is a widely used anticancer agent acting by inhibition of mitosis. It is approved for the treatment of breast cancer, prostate cancer, non-small cell lung cancer, head and neck cancer and gastric cancer. Docetaxel is most commonly administered as a 3-weekly 1-hour intravenous (IV) infusion, although it has been shown that once-weekly administration is associated with comparable efficacy whilst incidence of neutropenia is reduced [1,2]. A weekly schedule is infrequently used, however, most likely due to inconvenience for the patient associated with weekly clinic visits. An oral formulation of docetaxel could allow patients to receive docetaxel at home, thereby, reducing the burden for patients and costs. In addition, oral administration could avoid the regularly observed infusion reactions, induced by the formulation additives polysorbate 80 and ethanol [3].

A major limitation of oral administration of docetaxel is its low bioavailability. Docetaxel is transported by the P-glycoprotein (PgP) efflux transporter and metabolized by Cytochrome P450 3A4 (CYP3A4) in the gut and liver [4]. Previously, we have shown in a proof-of-concept study that co-administration of the CYP3A4 inhibitor ritonavir results in a strong boost of the bioavailability of docetaxel [5]. In this study, the IV docetaxel formulation was ingested orally as a drinking solution. Further, a solid dispersion capsule formulation, ModraDoc001, was developed and clinically evaluated with different dose levels of ritonavir [6]. Subsequently, a further improved solid dispersion tablet formulation, ModraDoc006, was developed and evaluated similarly [7,8].

Modelling and simulation can be used to support clinical development [9]. Previously, we described how modelling and simulation was used to bridge oral docetaxel exposure of the preclinical and the clinical setting [10], and to quantitatively study the effect of inhibition of CYP3A4 on docetaxel pharmacokinetics (PK) after oral administration of the IV formulation (drinking solution) [11]. These models, however, did not include the PK of the dedicated oral formulations (ModraDoc001 and ModraDoc006) that were developed thereafter, and also did not include PK data of ritonavir, which was not yet available at that time. Therefore, an integrated docetaxel-ritonavir model is needed to compare different dosing regimens of docetaxel and between different oral docetaxel formulations in order to support decision making in the clinical development.

The objectives of the current analysis were to update a previously developed integrated semi-physiological PK model for docetaxel [11] with data from the novel formulations and by including ritonavir PK data. Subsequently, the model was used to support clinical development of the combination of oral docetaxel and ritonavir.

2. METHODS

Clinical studies

All available PK data from the evaluation of the different formulations of docetaxel (the IV formulation administered intravenously and orally, and the oral solid dispersion formulations ModraDoc001 and ModraDoc006) were included. An overview of the different clinical studies is provided in Table 1. In the following sections, the studies are further summarized.

Study 1

Study 1 was a proof-of-concept study evaluating ritonavir as a booster of oral docetaxel. Docetaxel was administered intravenously at a dose of 100 mg/m^2, or as a drinking solution at a single dose of 10 mg or 100 mg in combination with ritonavir soft gel capsules (Norvir®, Abbott, Illinois, USA) at a dose of 100 mg. For a detailed description this study we refer to Oostendorp et al [5].

Study 2

Study 2 was a phase I dose-escalation study of orally administered docetaxel in combination with ritonavir in a weekly once-daily schedule. Patients received the approved IV formulation and/or three different oral docetaxel formulations: the orally administered IV formulation (drinking solution), the ModraDoc001 capsule formulation, and the ModraDoc006 tablet formulation. Initially, the soft gel capsule formulation (Norvir®, Abbott, Illinois, USA) of ritonavir was used. However, during execution of the study, the manufacturer switched to a tablet formulation. Docetaxel was administered at doses of 20–80 mg. Ritonavir was administered as 100 mg or 200 mg dose. For a more detailed description of these studies we refer to Moes et al [6], Koolen et al [12] and Marchetti et al [13].

Study 3a

Study 3a was a phase I dose-escalation study in which a weekly twice-daily dose of docetaxel formulated as ModraDoc001 capsules or ModraDoc006 tablets, together with ritonavir, was given at t = 0 and t = 7 hours. The total daily dose of docetaxel was between 40–80 mg and ritonavir 200 mg. For a detailed description of study 3a we refer to Stuurman et al [14].

Study 3b

Study 3b was a cross-over study aiming at comparing the exposure of different ModraDoc formulations simultaneously administered with ritonavir. As from this study only the development of ModraDoc001 was carried forward, only PK data from this formulation were included in the current analysis. Docetaxel was administered at 40 mg. Ritonavir was administered at 100 mg or 200 mg. A detailed description of study 3b we refer to Moes et al [*7*].

Table 1. Overview of included clinical studies.

	Study 1 [5]	**Study 2** [6,12,13]	**Study 3a** [14]	**Study 3b** [7]
Number of patients				
Total	37	89	29	6
Intravenous administration docetaxel	32	19	–	–
Oral docetaxel formulation of ModraDoc001 capsule	–	68	17	6
Oral docetaxel formulation of ModraDoc006 tablet	–	10	12	–
Oral docetaxel formulation of drinking solution	25	11	–	–
Docetaxel				
Oral dose levels (mg/day)	10, 100	20, 30, 40, 60, 80	40, 50, 60, 80	40
Intravenous dose levels	100 mg/m^2	20 mg	–	–
Dosing time (hours)	t=0, t=1	t=0	t=0, 7	t=0
Formulation	Intravenous Drinking solution	Intravenous Drinking solution ModraDoc001 ModraDoc006	ModraDoc001 ModraDoc006	ModraDoc001
PK data	Yes	Yes	Yes	Yes
Ritonavir				
Dose (mg/day)	0, 100	0, 100, 200	200	100, 200
Dosing time (hours)	t=0	t=0	t=0, 7	t =0
Ritonavir formulation	Capsules	Capsules Tablets	Tablets	Tablets
PK data	No	Yes	Yes	Yes

Model development

Structural model development

The PK model for the co-administration of ritonavir and oral docetaxel was sequentially developed [15].

In the first step a PK model for ritonavir was developed. Potential auto-inhibition of metabolism of previous dosing was implemented by introducing an empirical parameter describing the relative bioavailability of the second dose versus the first dose ($F_{2nd/1st,rtv}$) [16]. Similarly, the effect of the formulation switch from capsule to tablet was accounted for by introducing a parameter describing the relative bioavailability of the tablet formulation versus the capsule formulation ($F_{tablet/capsule}$).

In the second step, a model for docetaxel including the effects of ritonavir on docetaxel PK was developed. Individual parameter estimates of ritonavir were generated from the ritonavir PK model and used as an input for docetaxel model development [15]. Previously, we established a simplified semi-mechanistic PK model for docetaxel solely based on PK data of IV formulation and drinking solution [11]. We updated this model and used the well-stirred assumptions for hepatic clearance [17] as the starting point for further development. A semi-physiological approach was explored, which included separate compartments for the gut, liver, central, and peripheral compartments. Besides, the inhibitory effect of ritonavir on gut wall metabolism and hepatic metabolism of docetaxel were studied, respectively.

Statistical model development

Inclusion of between-subject variability (BSV) and within-subject variability (WSV) was guided by the change of objective function value (OFV, minus twice the log likelihood), standard errors and clinical relevance. WSV was divided in within-day and between-day variability, respectively. BSV and WSV were modelled according to Eq. 1.

$$P_i = P \cdot \exp(\eta_{i,BSV} + \eta_{i,WSV}) \qquad \text{(Eq. 1)}$$

Where P_i represents the individual parameter estimate for individual *i*, *P* represents the typical population parameter estimate and η_i either BSV or WSV effect distributed following $N(0, \omega^2)$.

Residual errors were described by proportional error models for both ritonavir and docetaxel, respectively (Eq. 2).

$$C_{obs,ij} = C_{pred,ij} \cdot (1 + \varepsilon_{p,ij}) \qquad \text{(Eq. 2)}$$

Where $C_{obs,ij}$ or $C_{pred,ij}$ represents, for the i^{th} subject and the j^{th} measurement, the observation or prediction. Proportional error $\varepsilon_{p,ij}$ was assumed distributed following $N(0, \sigma^2)$.

Comparison of the characteristics of different docetaxel oral formulations

Parameters of the PK model on absorption processes and bioavailability for different docetaxel formulations were separately estimated and compared. Furthermore, it was investigated if there were differences in the BSV and WSV of different formulations, and in the PK between once-daily and twice-daily administrations. In addition, potential saturated absorption was explored for oral docetaxel.

Model evaluation

Model evaluation was performed throughout model building by consideration of parameter precision, plausibility of parameter estimates, goodness-of-fit (GOF) diagnostics, inspection of the correlation matrix, drop of OFV with significance level of $p < 0.01$ (degree of freedom (df) = 1, dOFV > 6.63; df = 2, dOFV > 9.21) for hierarchical models, and also visual predictive checks (VPC) (n = 1000).

Simulations

Simulation studies were performed for the ModraDoc006 tablet formulation and ritonavir tablet combination, since these formulations will be used in further clinical development. In all simulations, a dose of 100 mg ritonavir was administered simultaneously with docetaxel.

The PK profiles of IV docetaxel in approved dosing schedules was compared to the different oral formulations. The docetaxel plasma concentration levels were simulated for oral docetaxel co-administered with ritonavir under the following dosing regimens of docetaxel: 40 mg, 60 mg, and 80 mg once-daily; 20 mg twice-daily (20/20 mg), 30 mg followed by 20 mg (30/20 mg), and 30 mg twice-daily (30/30 mg). For IV docetaxel, simulations were performed based on the three dosing regimens used in clinic: 3-weekly 75 mg/m^2 with 1-hour infusion; 3-weekly 100 mg/m^2 with 1-hour infusion; and weekly 35 mg/m^2 with 0.5-hour infusion (Body surface area at 1.8 m^2). The area under concentration-time curve for consecutive 96 hours after administration (AUC_{96hrs}) was used to compare between once-daily and twice-daily doses. Meanwhile, the effect of the inhibition of ritonavir on the metabolism of docetaxel was assessed. The area under concentration-time curve for consecutive 3 weeks after administration (AUC_{3wks}) was used to compare the PK profiles between IV and oral docetaxel at different dose regimens.

Software

All model estimations were performed using NONMEM (version 7.3.0) [18] together with a gfortran compiler, using first-order conditional estimation with interaction. Piraña was used as graphical interface [19], and R (version 3.0.3) was used for pre-processing of the data, plotting and model simulation [20]. In addition, the NONMEM toolkit psn [21], and the R-package Xpose [22] and deSolve [23] were used.

3. RESULTS

Model development

The schematic structure of the final model is presented in Figure 1. The parameter estimates of the final model for ritonavir and docetaxel are listed in Table 2 and Table 3, respectively.

Ritonavir pharmacokinetic model

A two-compartment model with a first-order elimination process best fitted the ritonavir plasma concentrations. The absorption of ritonavir was modelled by the Inverse Gaussian density (IG)-input function [24]. The second administration of ritonavir (approximately 7 hours after the first administration) showed 2.1-fold (relative standard error (RSE) 6%) higher relative bioavailability than that of the first administration. Switching of formulation from capsule to tablet resulted in an increment in relative bioavailability of 18% (RSE 14%).

Docetaxel pharmacokinetic model

The final PK model of oral docetaxel was a multi-compartmental model in which docetaxel after administration passed through one transit compartment to the liver compartment. Subsequently, docetaxel is metabolized by CYP3A4 in the liver or distributes between central and liver compartments. Finally, docetaxel can further distribute between central and peripheral compartment(s). Two peripheral compartments best described the PK of docetaxel IV formulation, while one peripheral compartment suited the best for oral formulations (see Figure 1).

The influence of each oral formulation of docetaxel without ritonavir co-administration on the overall gut bioavailability (F_G) was separately estimated as $F_{formulation}$. The inhibitory effect of ritonavir on gut wall metabolism resulting in an increased F_G was characterized by an empirical effect ($F_{ritonavir}$) defined as the ratio of bioavailability

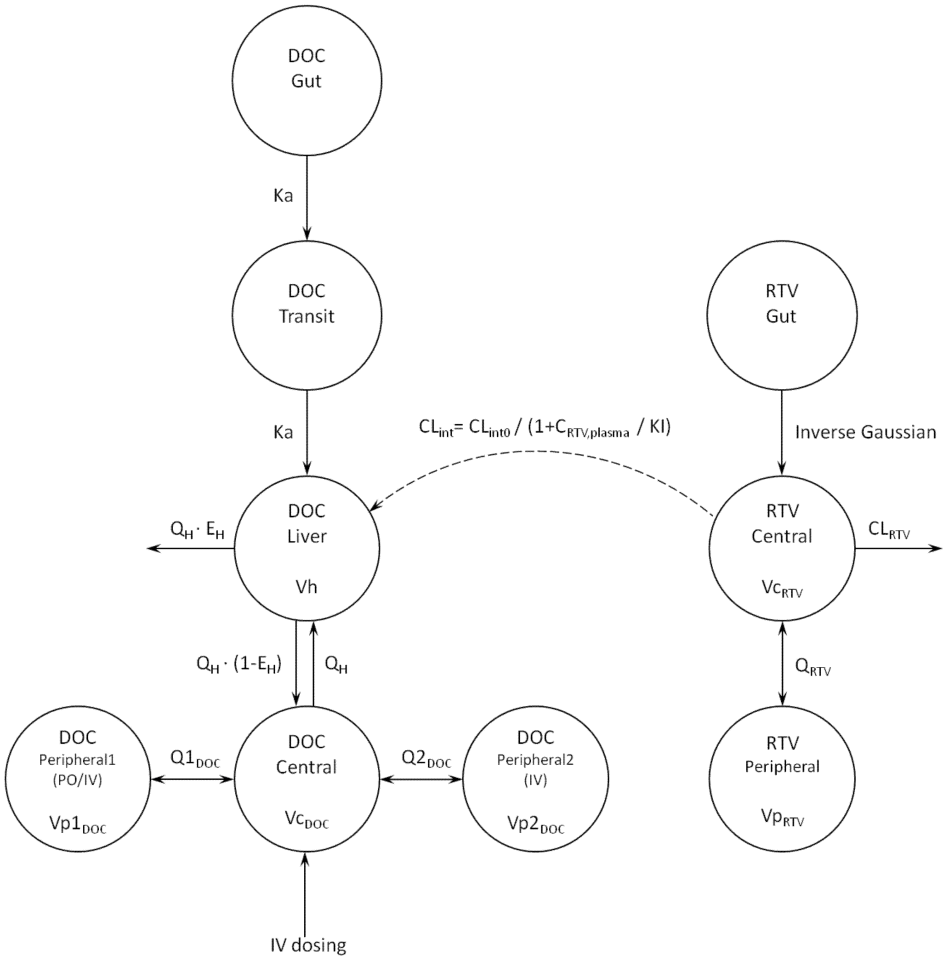

Figure 1. Schematic representation of the integrated pharmacokinetic model for docetaxel and ritonavir. CL, clearance; CL_{int}, intrinsic clearance of docetaxel; CL_{int0}, uninhibited intrinsic clearance of docetaxel; C_{RTV}, plasma, ritonavir plasma concentration; DOC, docetaxel; E_H, hepatic extraction ratio; K_a, first-order absorption rate constant; IV, intravenous; KI, inhibition constant of ritonavir on docetaxel metabolism; PO, oral; Q, inter-compartment distribution; Q_H, hepatic blood flow; RTV, ritonavir; V_c, central volume of distribution; V_h, hepatic volume of distribution; V_p, peripheral volume of distribution. Intravenous docetaxel distributes to docetaxel peripheral compartment 1 & 2; oral docetaxel only distributes to docetaxel peripheral compartment 1.

in combination with ritonavir versus without co-administration of ritonavir. Besides, time-dependent accumulation of this inhibitory effect was considered on F_G of the second dose relative to the first dose ($F_{2nd/1st,\ doc}$).

Therefore, the F_G of docetaxel was defined according to the following equation (Eq. 3):

$$F_G = F_{formulation} \cdot F_{ritonavir} \cdot F_{2nd/1st,doc} \quad \text{(Eq. 3)}$$

Docetaxel hepatic intrinsic clearance (CL_{int}) was determined as a function of the uninhibited intrinsic clearance (CL_{int0}) and the ritonavir plasma concentration ($C_{RTV,plasma}$) (Eq. 4) in which KI is the inhibition constant of CYP3A4 by ritonavir.
Based on well-stirred assumptions, docetaxel extraction ratio (E_H) and hepatic bioavailability (F_H) were defined as follows (Eq. 5, 6):

$$CL_{\text{int}}(t) = CL_{\text{int}\,0}(t) / (1 + \mathrm{C}_{\text{RTV, plasma}}(t) / KI) \quad \text{(Eq. 4)}$$

$$E_H(t) = \frac{CL_{\text{int}}(t) \cdot fu}{Q_H + CL_{\text{int}}(t) \cdot fu} \quad \text{(Eq. 5)}$$

$$F_H(t) = 1 - E_H(t) \quad \text{(Eq. 6)}$$

Here, hepatic blood flow Q_H was fixed at a value of 80 L·h^{-1} [25]. As only total concentrations of docetaxel (e.g. free and protein bound) were available, we assumed literature-reported estimates for the fractions of unbound docetaxel (*fu*) of 4.6% [26]. The volume of the liver compartment (*Vh*) was assumed as 1 L which is close to the empirically determined value [27].
Table 3 shows the parameter estimates of the model for IV and oral docetaxel. Based on the PK data of IV docetaxel, the CL_{int0} was estimated at 1,980 L/h (RSE 11%). For oral docetaxel formulations, the second co-administration in twice-daily dosing showed an increase of 14% (RSE 7%) in F_G compared to the first. Co-administration of ritonavir resulted in 3.5-fold (RSE 30%) higher F_G than oral docetaxel without ritonavir. The KI was estimated at 179 ng/mL (RSE 48%).
In addition, attempts have been carried out to describe a potential mechanism-based inhibitory effect of ritonavir on CYP3A4 instead of the competitive inhibitory effect described in Eq. 4. This was explored by an enzyme turn-over model with ritonavir inactivating CYP3A4 or accelerating the degradation rate of CYP3A4. However, these approaches failed to achieve model minimization or resulted in unreasonable parameter estimates.

Table 2. Parameter estimates of ritonavir in the final pharmacokinetic model.

Parameters	Units	Estimate	RSE (%)	Shrinkage (%)
Population parameter–ritonavir				
Mean absorption time (MAT)	h	8.07	7	–
Variability of absorption time (CV)	%	120	4	–
Clearance (CL_{RTV})	L/h	8.03	10	–
Volume of distribution of central compartment (Vc_{RTV})	L	21.1	17	–
Inter-compartment clearance (Q_{RTV})	L/h	4.35	15	–
Volume of distribution of peripheral compartment (Vp_{RTV})	L	20.6	13	–
Relative bioavailability of the second dose to the first dose ($F_{2nd/1st,rtv}$)	–	2.06	6	–
Relative bioavailability of tablet to capsule ($F_{tablet/capsule}$)	–	1.18	14	–
Between-subject variability				
Variability of mean absorption time (CV)	CV%	13.1	24	44
Clearance (CL_{RTV})	CV%	41.6	19	30
Volume of distribution of central compartment (Vc_{RTV})	CV%	102.5	10	18
Relative bioavailability (F)	CV%	55.7	14	20
Relative bioavailability of the second dose relative to the first ($F_{2nd/1st}$)	CV%	23.0	36	62
Relative bioavailability of tablet to capsule ($F_{tablet/capsule}$)	CV%	32.4	63	68
Within-subject variability				
Mean absorption time (MAT)	CV%	32.2	8	–
Variability of mean absorption time (CV)	CV%	20.3	13	–
Residual unexplained variability				
Proportional residual error	CV%	34.6	3	13

CV%, coefficient of variation; RSE, relative standard error; RTV, ritonavir

Comparison of the characteristics of different docetaxel oral formulations

The effects of the different formulations on the PK of docetaxel were estimated on absorption rate constant (k_a) and F_G. Fastest absorption was observed for the drinking solution, followed by ModraDoc001 capsule and ModraDoc006 tablet (k_a: 2.6 h^{-1} (RSE 17%), 1.4 h^{-1} (RSE 7%), and 1.3 h^{-1} (RSE 11%), respectively). The drinking solution also showed the highest $F_{formulation}$ (0.27, RSE 25%) compared to ModraDoc006 (0.19, RSE 25%) and ModraDoc001 (0.17, RSE 23%).

An effect of the formulation was also found on variability. The drinking solution, compared to ModraDoc formulations, showed much higher BSV (k_a: 81.6% (RSE 18%) vs. 39.9% (RSE 16%); F_G: 75.8% (RSE 14%) vs. 35.2% (RSE 15%)) and higher between-day WSV ((k_a: 53.1% (RSE 13%) vs. 43.7% (RSE 13%); F_G: 40.0% (RSE 21%) vs. 30.9% (RSE 9%)) (Table 3). The between-day and within-day WSV on F_G for ModraDoc formulations was 30.9% (RSE 9%) and 21.0% (RSE 21%), respectively.

Table 3. Parameter estimates of docetaxel in the final pharmacokinetic model

Formulations of docetaxel		**Oral formulations**			**Intravenous formulation**		
Parameters	**Units**	**Estimate**	**RSE (%)**	**Shrink -age (%)**	**Estimate**	**RSE (%)**	**Shrink -age (%)**
Population parameter–docetaxel							
First-order absorption rate constant (k_a)–ModraDoc001 capsule	h^{-1}	1.4	7	–	–	–	–
First-order absorption rate constant (k_a)–ModraDoc006 tablet	h^{-1}	1.3	11	–	–	–	–
First-order absorption rate constant (k_a)–Drinking solution	h^{-1}	2.6	17	–	–	–	–
Uninhibited intrinsic clearance (CL_{int0})	L/h	1980 FIX*	–	–	1980	11	–
Inhibition constant (KI)	ng/mL	179	48	–	210	20	–
Volume of distribution of central compartment (Vc_{DOC})	L	113	13	–	5.38	10	–
Inter-compartment clearance 1 ($Q1_{DOC}$)	L/h	29.6	7	–	15.4	5	–
Volume of distribution of peripheral compartment 1 ($Vp1_{DOC}$)	L	583	7	–	400	5	–
Inter-compartment clearance 2 ($Q2_{DOC}$)	L/h	–	–	–	5.56	6	–
Volume of distribution of peripheral compartment 2 ($Vp2_{DOC}$)	L	–	–	–	7.68	4	–
Gut bioavailability in combination with ritonavir relative to without ($F_{ritonavir}$)	–	3.49	30	–	–	–	–
Gut bioavailability of the second dose relative to the first dose ($F_{2nd/1st,\ doc}$)	–	1.14	7	–	–	–	–
Gut bioavailability of ModraDoc001 without ritonavir co-administration ($F_{formulation,ModraDoc001}$)	–	0.17	23	–	–	–	–
Gut bioavailability of ModraDoc006 without ritonavir co-administration ($F_{formulation,ModraDoc006}$)	–	0.19	25	–	–	–	–
Gut bioavailability of drinking solution without ritonavir co-administration ($F_{formulation,drinking\ solution}$)	–	0.27	25	–	–	–	–
Between-subject variability							
Absorption rate constant (k_a)–ModraDoc001 & ModraDoc006	CV%	39.9	16	41	–	–	–

Table 3. (continued)

Formulations of docetaxel		Oral formulations			Intravenous formulation		
Parameters	**Units**	**Estimate**	**RSE (%)**	**Shrink -age (%)**	**Estimate**	**RSE (%)**	**Shrink -age (%)**
Population parameter–docetaxel							
Absorption rate constant (k_a)–Drinking solution	CV%	81.6	18	60	–	–	–
Uninhibited intrinsic clearance (CL_{int0})	CV%	43.1	16	26	60	10	3
Volume of distribution of central compartment (Vc_{DOC})	CV%	45.7	17	23	82.2	6	7
Gut bioavailability (F_G)–ModraDoc001 & ModraDoc006	CV%	35.2	15	37	–	–	–
Gut bioavailability (F_G)–Drinking solution	CV%	75.8	14	56	–	–	–
Within-subject variability							
Between-day variability on absorption rate constant (k_a) –ModraDoc001 & ModraDoc006	CV%	43.7	13	–	–	–	–
Between-day variability on absorption rate constant (k_a) –Drinking solution	CV%	53.1	13	–	–	–	–
Within-day variability on absorption rate constant (k_a) –ModraDoc001 & ModraDoc006	CV%	51.2	16	–	–	–	–
Between-day variability on gut bioavailability (F_G) –ModraDoc001 & ModraDoc006	CV%	30.9	9	–	–	–	–
Between-day variability on gut bioavailability (F_G) –Drinking solution	CV%	40.0	21	–	–	–	–
Within-day variability on gut bioavailability (F_G) –ModraDoc001 & ModraDoc006	CV%	21.0	21	–	–	–	–
Residual unexplained variability							
Proportional residual error	CV%	37.1	2	8	26.5	6	7

CV%, coefficient of variation; DOC, docetaxel; RSE, relative standard error
* Estimated by intravenous docetaxel and fixed in the model estimation of oral docetaxel

As shown in Figure 4, F_G proved to be independent from dosing frequency (once-daily dosing and twice-daily dosing, left panel) and absolute docetaxel dose administered (right panel).

Model evaluation

The parameter estimates of the final model had adequate precision. Figure 2 and Figure 3 show graphical model evaluations, which indicate adequate description of the data.

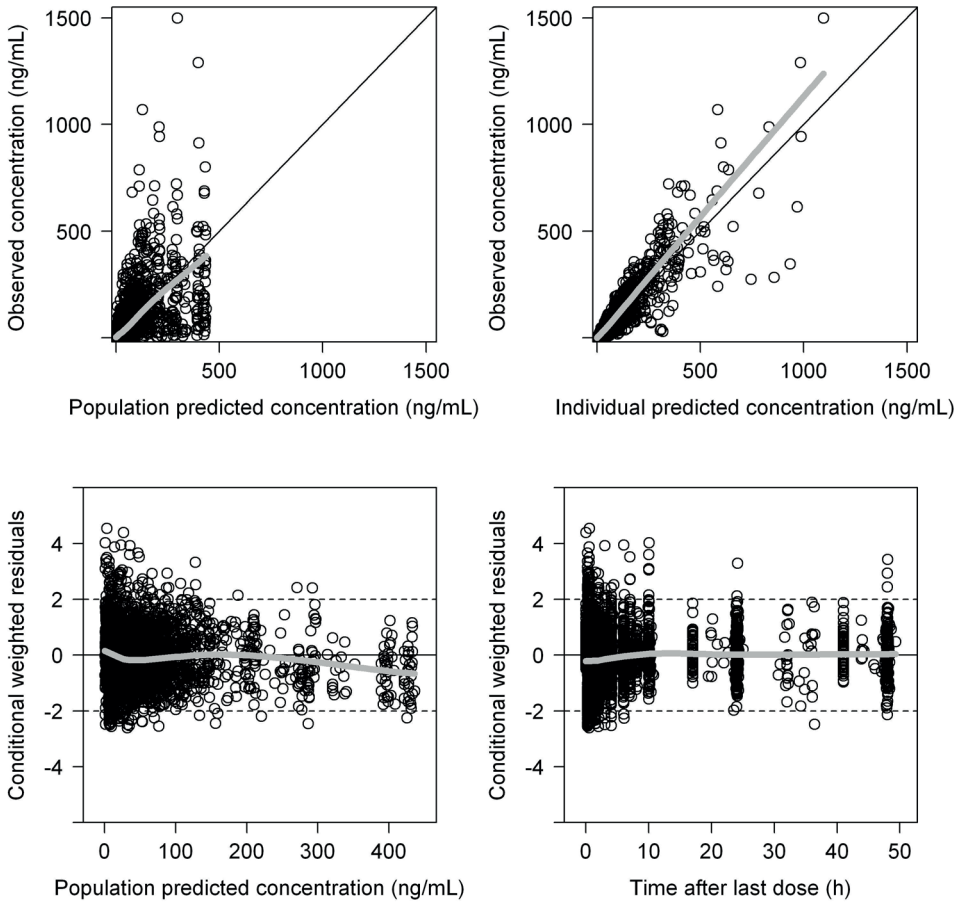

Figure 2. Goodness-of-fit plots of pharmacokinetic modelling for oral formulations of docetaxel. The plots include observed versus population predicted concentration, observed versus individual model predicted concentration, conditional weighted residuals (CWRES) versus population predicted concentration, and CWRES versus time.

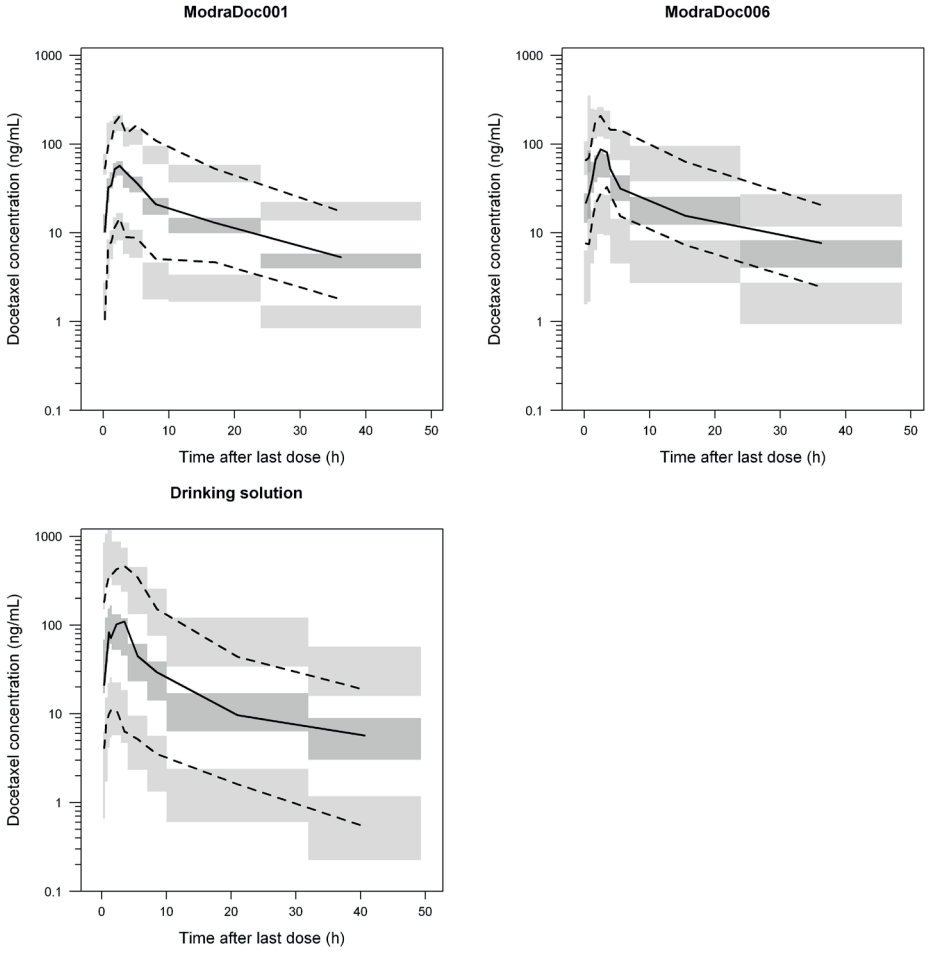

Figure 3. Visual predictive checks for docetaxel, stratified by different oral formulations (n = 1,000). Solid lines and dark grey areas represent the median observed values and simulated 95% confidence intervals (CIs). Dashed lines and light grey areas represent the 10% and 90% percentiles of the observed values and 95% CIs of the simulated percentiles.

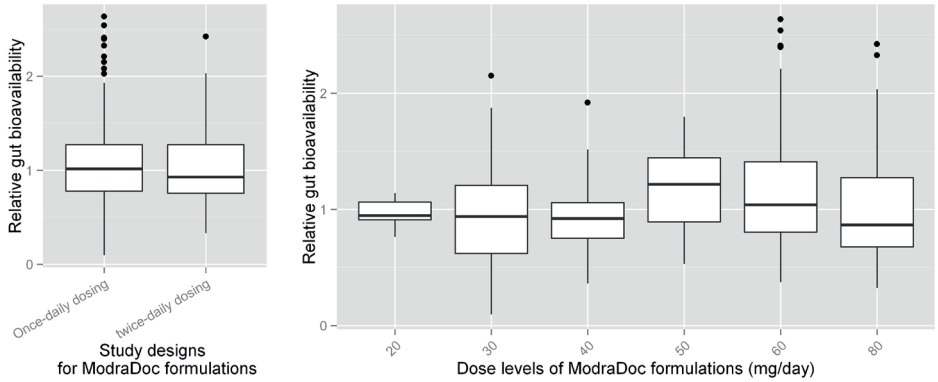

Figure 4. Comparison the effect of study designs of docetaxel on relative gut bioavailability. The left panel shows the comparison between two study designs: once-daily dosing or twice-daily dosing; the right panel shows the comparison between different daily dose levels.

Simulations

Figure 5 shows the comparison of plasma concentration levels of oral docetaxel administered as a single dose and two doses (t = 0 and t = 7 hours) without or with ritonavir co-administration over a time span of 96 hours. The corresponding changes of docetaxel CL_{int} in ritonavir co-administration are also shown. For the docetaxel dosing regimen of once-daily 60 mg, the AUC_{96hrs} with ritonavir was 9-fold higher than docetaxel monotherapy (1,088 μg·h/L vs. 125 μg·h/L); for the dosing regimen of twice-daily 30/20 mg, co-administration of ritonavir showed 13-fold higher AUC_{96hrs} (1,329 μg·h/L vs.104 μg·h/L). A single dose of 100 mg ritonavir maximally inhibited docetaxel CL_{int} to 17.4% of CL_{int0} at 3.4 hours after co-administration; twice-daily 100 mg ritonavir further inhibited the CL_{int} to 7.8% of CL_{int0} at 10.2 hours. Docetaxel CL_{int} recovered to its CL_{int0} after around three days. The AUC_{96hrs} of twice-daily 30/20 mg of docetaxel was higher than once-daily 60 mg dose.

Figure 6 shows the comparison of plasma concentration levels between ModraDoc006-ritonavir co-administration and IV docetaxel. For once-daily dosing of oral docetaxel, the median AUC_{3wks} of 60 mg docetaxel fell within the range of AUC_{3wks} of the three regularly used dosing regimens for IV docetaxel. As for the twice-daily dosing, 30/30 mg docetaxel was above the range of AUC_{3wks} of IV docetaxel, while 20/20 and 30/20 mg docetaxel regimens are within this range.

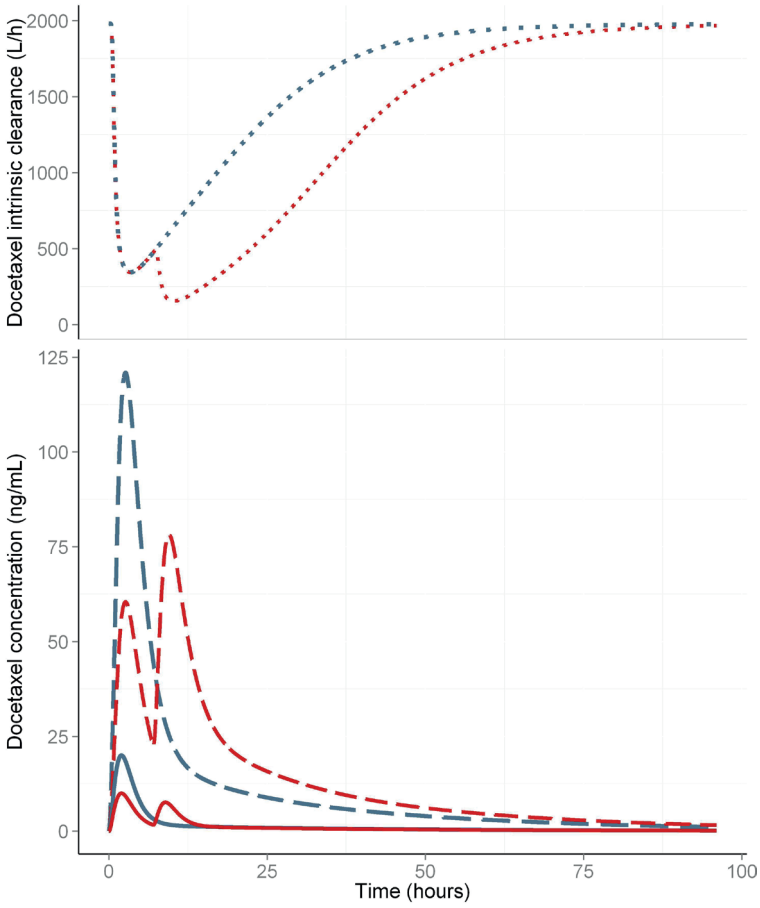

Figure 5. Simulation of population plasma concentration with corresponding intrinsic clearance of docetaxel at clinically relevant once-daily or twice-daily dosing regimens. The upper panel shows the change of docetaxel intrinsic clearance under ritonavir co-administration (dotted lines); the lower panel shows docetaxel plasma concentration without (solid lines) or with (dashed lines) ritonavir co-administration. The dosing regimens simulated in this figure are: once-daily 60 mg of docetaxel and twice-daily 30 mg followed by 20 mg of docetaxel; 100 mg of ritonavir at each intake in the co-administration.

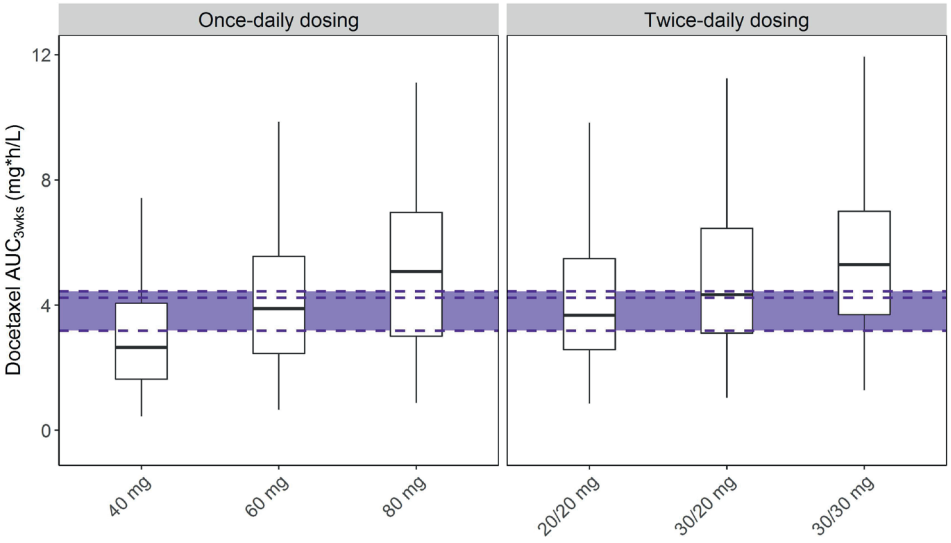

Figure 6. Comparison of docetaxel plasma concentration between ModraDoc006 and intravenous docetaxel. The boxplot shows the median and inter-quartile range of simulated 3-week-time area under concentration-time curve (AUC_{3wks}) for different dosing regimens of ModraDoc006 co-administered with ritonavir. The left panel shows once-daily dosing and the right panel twice-daily dosing. Three dashed lines from bottom to top represent the simulated AUC_{3wks} of intravenous docetaxel at dosing regimens of 3-weekly 75 mg/m^2, 3-weekly 100 mg/m^2, and weekly 35 mg/m^2, successively. The shaded area covers the range of simulated AUC_{3wks} of different dosing regimens of intravenous docetaxel.

4. DISCUSSION

In the current study we developed an integrated semi-physiological PK model for ritonavir and docetaxel. Compared to the previously described PK model of oral docetaxel [11], the current model was considerably improved by incorporation of novel data. Firstly, data on newly developed docetaxel oral formulations–ModraDoc001 capsule [6] and ModraDoc006 tablet [8] was included enabling further characterization of the absorption dynamics of oral docetaxel. Secondly, the inclusion of the data on ritonavir concentration allowed further quantification of the complex relationship between ritonavir and docetaxel PK. Thirdly, a wider dose range of docetaxel enabled further exploration of the linearity of PK. In addition, by inclusion of the free-fraction of unbound docetaxel in the well-stirred liver model, the parameters were more realistically estimated than by total docetaxel concentration.

However, there are still some limitations of the current model. For instance, ritonavir plasma concentration was used to account for the inhibitory effect instead of ritonavir

liver concentration. This may influence on the estimation of the parameter KI (inhibition constant). Also, the model failed to incorporate the mechanism-based inhibitory effect of ritonavir on CYP3A4 which could be more scientifically reasonable [28,29] than the competitive effect described in our final model. This could be mainly due to the scarce PK information available after 24 hours after administration that would have supported the kinetic change of CYP3A4 activity. Finally, other clearance routes than the liver were not considered for docetaxel. However, even with these potential limitations, the current model sufficiently describes the observation of ritonavir and docetaxel in different formulations. It was capable of supporting clinical development of docetaxel-ritonavir co-administration.

The PK characteristics of the different docetaxel formulations were quantified. The drinking solution of docetaxel was not suitable for clinical use due to its unpleasant taste [5]. Besides, albeit that the F_G of the drinking solution was higher than the solid formulations, much higher BSV and WSV were observed (Table 3). The k_a of the two solid formulations was comparable. The F_G of ModraDoc006, however, was 13% higher than ModraDoc001. This difference is explained by the physical characteristics of these two formulations. The solid dispersion of ModraDoc001 was prepared by freeze drying, which did not result in a fully amorphous state in contrast to the spray dried formulation in ModraDoc006 [8]. The WSV on F_G for ModraDoc formulations were relatively low (Table 3).

The inhibitory effect of ritonavir resulted in significantly increased docetaxel plasma exposure when co-administered, especially for the twice-daily dosing regimen (Figure 5). In the twice-daily dosing regimens an additional boost of ritonavir on the second dose was observed leading to a higher exposure of this regimen with the same docetaxel dose as compared to the once-daily dosing regimen.

Co-administration of the ModraDoc formulations with ritonavir at the recommended dose reached similar docetaxel exposure (AUC_{3wks}) as compared to IV docetaxel (Figure 6). By means of comparison, 60 mg of oral docetaxel in the once-daily dosing regimen and the regimens of 20/20 mg and 30/20 mg in the twice-daily dosing could result in clinically relevant plasma levels of docetaxel in patients.

The modelling and simulation supported the drug development in multiple aspects. The population approach enabled the comparison of the bioavailability between once-daily and twice-daily regimens and across the wide dose range of ModraDoc formulations (Figure 4). The characteristics of different formulations in absorption profiles were able to be compared (Table 3). It also separately quantified the BSV and WSV of different formulations based on the whole population. In addition, it helped us to understand better the inhibitory effect of ritonavir on the metabolism of docetaxel over time (Figure 5). The magnitude of differences on the AUCs between

oral docetaxel with and without ritonavir co-administration can be calculated from the model. In addition, the AUCs calculated from the PK model would not be biased by the limited people numbers at each dose as in clinical trials. The comparison of simulated AUCs between IV and oral docetaxel informed to suggest the clinical relevance of the plasma concentrations of different oral doses.

5. CONCLUSION

The current analysis succeeded in developing an integrated semi-physiological PK model for docetaxel and ritonavir based on phase I studies for oral docetaxel co-administered with ritonavir. Compared to the drinking solution, oral ModraDoc formulations had much lower variability in plasma concentrations between and within patients. Co-administration of ritonavir resulted in dramatically increased plasma concentrations of the oral formulations of ModraDoc, which confirmed the feasibility and necessity of co-administration in the clinic.

Conflict of interests. Bastiaan Nuijen, Jos Beijnen and Jan Schellens are inventors and hold a patent on oral ModraDoc formulations. Jos Beijnen and Jan Schellens are employees and shareholders in Modra Pharmaceuticals, a spinout company developing oral taxane formulations.

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SEMI-PHYSIOLOGICAL PHARMACOKINETIC MODEL OF DIFFERENT ORAL FORMULATIONS OF PACLITAXEL CO-ADMINISTERED WITH RITONAVIR

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CHAPTER 3.3

Submitted

ABSTRACT

Paclitaxel has a low oral bioavailability. However, when applied as a solid dispersion formulation and co-administered with ritonavir, relevant systemic exposure can be achieved. The current study aimed at characterizing the pharmacokinetics (PK) of paclitaxel and ritonavir in two clinical studies. In total 49 patients were included in the current study. The three paclitaxel oral formulations used in the current study were a drinking solution of paclitaxel, a solid dispersion capsule formulation and a solid dispersion tablet formulation. The final PK model of ritonavir was a two-compartment model with first-order elimination. Sequentially, a semi-physiological model consisting of gut, liver, central and peripheral compartments was built for paclitaxel. Absorption of paclitaxel was described with a Weibull distribution model. Paclitaxel liver metabolism was inhibited by ritonavir proportionally to ritonavir plasma concentrations. The apparent uninhibited intrinsic clearance of oral paclitaxel formulation was estimated as 163 L/h (relative standard error (RSE) 14%). The relative gut bioavailability of the paclitaxel drinking solution and the solid dispersion tablet formulation was 2.4-fold (RSE 28%) and 2.0-fold (RSE 18%) higher than the solid dispersion capsule formulation, respectively. In a 3-week period, the areas under the concentration-time curve of paclitaxel were in the similar range between intravenous and oral formulations. In conclusion, the complex pharmacokinetics of oral paclitaxel in combination with ritonavir were adequately described by the developed model.

1. INTRODUCTION

Intravenous (IV) paclitaxel is widely-used for the treatment of various malignancies, such as breast cancer, pancreatic cancer, non-small-cell lung cancer, and ovarian cancer [1]. Intravenous administration in the regular schedules results in toxicity such as neutropenia, thrombocytopenia, anemia, neurotoxicity, and myalgia [1]. An alternative dosing regimen is low-dose metronomic (LDM) chemotherapy–to frequently administer a cytotoxic drug at a relatively low dose. There is evidence that LDM chemotherapy of paclitaxel possesses anticancer activity by inhibiting angiogenesis with limited side effects [2–4]. For intravenous paclitaxel it has been demonstrated that the time during which paclitaxel plasma concentration exceeds 0.05 μmol/L ($T_{C>0.05}$) or 0.1 μmol/L ($T_{C>0.1}$) is predictive for efficacy and toxicity [5–7]. Clinical outcome improved and toxicity increased with the increment of length of $T_{C>0.1}$ or $T_{C>0.05}$. Target level of $T_{C>0.1} \geq 15$ hours [8] or $T_{C>0.05}$ 26–31 hours [9] have been suggested.

Metronomic chemotherapy with IV paclitaxel is not feasible because it will require daily administration. Furthermore, the paclitaxel IV formulation contains polyoxyethylated castor oil (Cremophor EL (CrEL)) and this excipient can induce hypersensitivity reactions and neuropathy [10]. An oral paclitaxel formulation is desired for LDM chemotherapy with paclitaxel.

Oral paclitaxel has, however, a low bioavailability. One reason is its poor solubility in water [11]. To solve this problem, a capsule with a paclitaxel solid dispersion through freeze drying has been developed and named ModraPac capsule (paclitaxel 10 mg) [12]. To scale up production, a tablet formulation using a spray dried powder was subsequently developed, named ModraPac tablet (paclitaxel 10 mg) [13].

Another reason for the low bioavailability of oral paclitaxel is its affinity for the P-glycoprotein (PgP) efflux transporter, and the metabolism by Cytochrome P450 3A4 (CYP3A4) and CYP2C8 [14]. Co-administration of a potent CYP3A4 inhibitor, such as ritonavir, can be used to boost the oral bioavailability [15]. In a previous study, we have shown the feasibility of boosting plasma concentration of oral docetaxel by ritonavir co-administration [16]. The co-administration of ritonavir also managed to bring systemic exposure of oral paclitaxel to clinically relevant concentrations in a proof-of-concept study [17]. This has been demonstrated both for the drinking solution (oral intake of the IV formulation of paclitaxel) and the novel paclitaxel solid dispersion ModraPac capsule [17]. Currently, a phase I dose-escalation study of LDM ModraPac capsules and tablets with co-administration of ritonavir is performed [18,19].

The aim of this study was to develop a semi-mechanistic model that describes the complex population pharmacokinetics of orally administered paclitaxel and ritonavir. Additionally, the absorption characteristics of the different paclitaxel formulation studies were quantified.

2. MATERIALS AND METHODS

Preparation method of drinking solution of paclitaxel, ModraPac capsules and ModraPac tablets

The commercially available IV formulation of paclitaxel (6 mg/mL in ethanol, water and CrEL) was used as a drinking solution.
The production of ModraPac capsules was previously described by Moes et al [12]. Briefly, ModraPac capsules consist of a freeze dried solid dispersion of 10 mg paclitaxel combined with povidone K30 and sodium dodecyl sulfate (SDS) in a weight ratio of (1:9:1, w/w/w).
The solid dispersion in the ModraPac tablets contain the same excipients in the same ratio as the ModraPac capsules. The solid dispersion was prepared using spray drying and subsequently tablets were manufactured by addition of lactose monohydrate (SuperTab®, 75% of tablet weight), croscarmellose sodium (3% of tablet weight), anhydrous colloidal silicon dioxide (1% of tablet weight) and magnesium stearate (1% of tablet weight) [13].

Pharmacokinetic data

The PK data was collected from two studies [17–19]. A summary is shown in Table 1. Study 1 was a proof-of-concept study in which the paclitaxel drinking solution was co-administered with ritonavir [17]. The drinking solution of paclitaxel was administered as a single 100 mg dose to 17 patients, with 100 mg or 200 mg ritonavir co-administered 30 minutes prior to paclitaxel. Subsequently, the ModraPac capsule formulation was tested in a cross-over design in four patients.
Study 2 was a phase I dose-escalation LDM study of oral paclitaxel in combination with ritonavir [18,19]. ModraPac capsules or ModraPac tablets were given to patients twice daily with ritonavir (Norvir®; Abbott, Illinois, USA) with a 7-hour interval. The daily doses studied for ModraPac capsule formulation included 5, 10, 15, 20, 30, 40 mg; and for the ModraPac tablet formulation 40, 50 and 60 mg. Ritonavir was administered at a daily dose of 200 mg in all dose-levels.

Table 1. Characteristics of data involved in the current study.

	Study 1		Study 2
Number of patients			
Total	17	4	28
Drinking solution of paclitaxel	17	4	–
ModraPac capsule	–	4	21
ModraPac tablet	–	–	7
Paclitaxel			
Dose (mg/day)–Drinking solution	100	30	–
Dose (mg/day)–ModraPac capsule	–	30	5, 10, 15, 20, 30, 40
Dose (mg/day)–ModraPac tablet	–	–	40, 50, 60
Dosing time (hours)	0.5	0.5	0, 7
PK sampling time (hours)	1, 1.5, 2, 2.5, 3.5, 4.5, 6.5, 8.5, 10.5, 24.5		1, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 8.5, 9, 9.5, 10, 11, 13, 24
Ritonavir			
Dose (mg/day)	100, 200	100	200
Dosing time (hours)	0	0	0, 7
PK sampling time (hours)	1, 1.5, 2.5, 4.5, 8.5, 10.5, 24.5	–	1, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 8.5, 9, 9.5, 10, 11, 13, 24

Structural model development

A PK model for the co-administration of ritonavir and oral paclitaxel was developed in a sequential manner [20]. First a model for ritonavir PK was established. Subsequently, the individual PK parameters of ritonavir were used in the development of paclitaxel PK model.

Various numbers of compartments were explored and different absorption models were screened for both ritonavir and paclitaxel. To account for established auto-inhibition of ritonavir metabolism [21], time-dependent accumulation of ritonavir from a previous dose was included. For this, an empirical parameter which is the bioavailability of the second dose relative to the first dose ($F_{2nd/1st}$) was included. For paclitaxel, the liver clearance was modelled using a well-stirred assumption [22]. The inhibitory effect of ritonavir on the liver clearance of paclitaxel was explored with a linear or E_{max} model. Paclitaxel formulation effect was examined on relative gut bioavailability (rF_G).

Statistical model development

Between-subject variability (BSV) and between-occasion variability (BOV) was modelled using exponential distribution according to Eq. 1.

$$P_i = P \cdot \exp(\eta_{i,BSV} + \eta_{i,BOV}) \quad \text{(Eq. 1)}$$

Where P_i represents the individual parameter estimate for individual *i*, *P* represents the typical population parameter estimate and η_i either BSV or BOV effect distributed following $N\ (0, \omega^2)$.

Residual errors were described by proportional error models for both ritonavir and paclitaxel, respectively (Eq. 2).

$$C_{obs,ij} = C_{pred,ij} \cdot (1 + \varepsilon_{p,ij}) \quad \text{(Eq. 2)}$$

Where $C_{obs,ij}$ or $C_{pred,ij}$ represents, for the *i*th subject and the *j*th measurement, the observation or prediction. Proportional error $\varepsilon_{p,ij}$ was assumed distributed following $N\ (0, \sigma^2)$.

Model evaluation

Acceptable models were required to achieve successful minimization and covariance step. Different models were evaluated based on the stability, plausibility and precision of parameter estimates, goodness-of-fit (GOF) plots, and drop of objective function value (OFV) with significance level of $p < 0.01$ (degree of freedom (df) = 1, dOFV > 6.63; df = 2, dOFV > 9.21) for hierarchical models. In addition, due to a wide range in dose-levels for which PK data is available, prediction-corrected visual predictive check (VPC) was performed (n = 1,000).

Simulations

Simulations were used to compare the characteristics of PK between two oral solid formulations of paclitaxel, ModraPac capsule and tablet, with the dosing regimen of paclitaxel (twice-daily 20 mg) co-administered with ritonavir (twice-daily 100 mg) with a 7-hour dose interval.

In addition, PK comparison between IV and oral paclitaxel was performed. Simulation of IV formulation was based on parameter estimates of the paclitaxel model presented by Joerger et al [9]. A 3-week dosing schedule at 175 mg/m^2 (BSA = 1.8 m^2) with 3-hour infusion [9], or weekly dosing schedule at 80 mg/m^2 (BSA

= 1.8 m^2) with 1-hour infusion [23,24] was simulated. PK of the ModraPac tablet formulation was simulated continuously for 3 weeks under the same dosing regimen as applied in aforementioned simulation for ModraPac formulations.

Software

NONMEM (version 7.3.0, ICON Development Solutions, Ellicott City, MD, USA) was used for the model estimation [25]. First-order conditional estimation with interaction was applied as estimation method. Piraña was used as graphical interface [26], and R (version 3.0.3) was used for pre-processing of the data, plotting and model simulation [27]. In addition, the NONMEM toolkit psn [28], and the R-package Xpose [29] and deSolve [30] were used.

3. RESULTS

Model development

The final model structure is shown in Figure 1. The parameter estimates for the PK model of ritonavir and paclitaxel are listed in Table 2 and Table 3, respectively.

Ritonavir pharmacokinetic model

Ritonavir plasma concentrations were best described by a two-compartment model with first-order elimination and first-order inter-compartment distribution. The absorption was modelled by the Inverse Gaussian density (IG)-input function [31]. The mean absorption time was 3.0 hours (relative standard error (RSE) 3%) with variability of 42.8% (RSE 10%). The bioavailability of the second dose (approximately 7 h after the first dose) was estimated to be 2.1-fold (RSE 8%) higher than that of the first dose.

Oral paclitaxel pharmacokinetic model

The systemic paclitaxel PK model consisted of gut, liver, central and peripheral compartments. Clearance and first-pass effect were described by the well-stirred liver model. In this, the inhibitory effect of ritonavir on paclitaxel metabolism could only be described by a linear relationship (Eq. 3).

$$CL_{\text{int}}(t) = CL_{\text{int}\,0}(t) \cdot (1 - C_{\text{RTV,plasma}}(t) \cdot 1/KI) \qquad \text{(Eq. 3)}$$

In which CL_{int} represents intrinsic clearance of paclitaxel, CL_{int0} represents uninhibited intrinsic clearance of paclitaxel, and $1/KI$ represents an inhibition factor for CYP3A4 linearly associated with ritonavir plasma concentration.

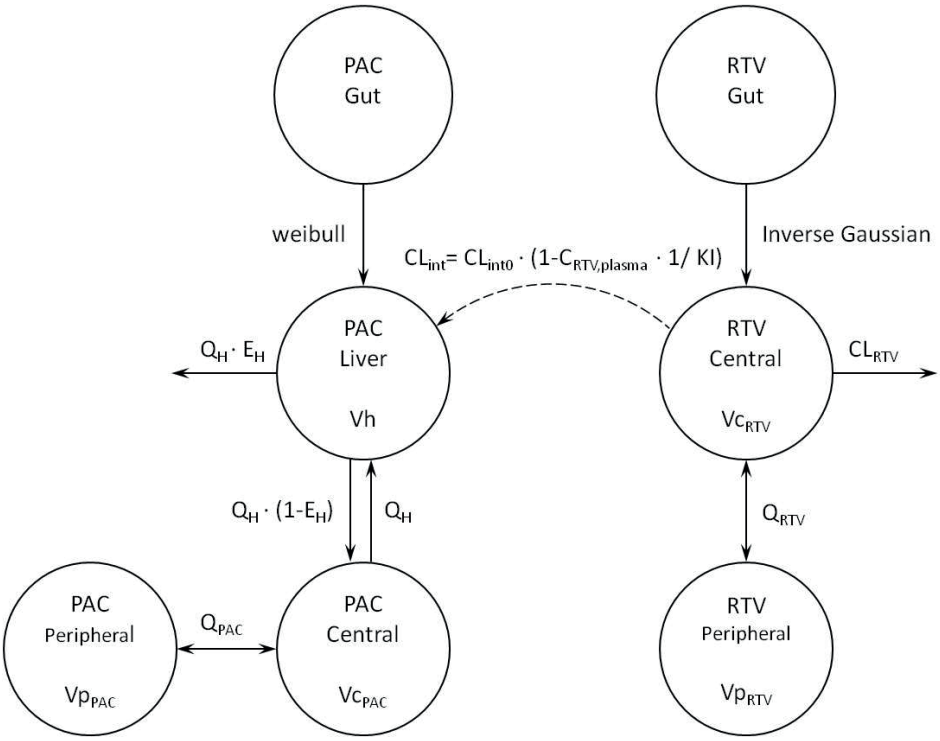

Figure 1. Schematic structure of pharmacokinetic model of co-administration of oral paclitaxel and ritonavir in human. CL, clearance; CL_{int}, intrinsic clearance of paclitaxel; CL_{int0}, uninhibited intrinsic clearance of paclitaxel; $C_{RTV,plasma}$, ritonavir plasma concentration; E_H, hepatic extraction ratio; KI, inhibition factor of ritonavir on paclitaxel metabolism; PAC, paclitaxel; Q, inter-compartment distribution; Q_H, hepatic blood flow; RTV, ritonavir; Vc, central volume of distribution; Vh, hepatic volume of distribution; Vp, peripheral volume of distribution.

Paclitaxel extraction ratio (E_H) and hepatic bioavailability (F_H) were defined in Eq. 4 and Eq. 5.

$$E_H(t) = \frac{CL_{\text{int}}(t)}{Q_H + CL_{\text{int}}(t)} \quad \text{(Eq. 4)}$$

$$F_H(t) = 1 - E_H(t) \quad \text{(Eq. 5)}$$

Here, hepatic blood flow Q_H was fixed at a value of 80 L·h^{-1} [32].

Table 2. Parameter estimates of ritonavir in the final pharmacokinetic model.

Parameters	Units	Estimate	RSE (%)	Shrinkage (%)
Population parameter–ritonavir				
Mean absorption time (MAT)	h	3.0	3	–
Variability of absorption time (CV)	%	42.8	10	–
Clearance (CL_{RTV})	L/h	8.7	22	–
Volume of distribution of central compartment (Vc_{RTV})	L	37.2	1	–
Inter-compartment clearance (Qi_{RTV})	L/h	19.0	16	–
Volume of distribution of peripheral compartment (Vp_{RTV})	L	28.2	18	–
Relative bioavailability of the second dose to first dose ($F_{2nd/1st}$)	–	2.1	8	–
Between-subject variability				
Variability of mean absorption time (CV)	CV%	24.2	29	43
Clearance (CL_{RTV})	CV%	72.9	21	9
Volume of distribution of central compartment (Vc_{RTV})	CV%	60.3	29	2
Volume of distribution of peripheral compartment (Vp_{RTV})	CV%	69.5	28	13
Relative bioavailability of the second dose to first dose ($F_{2nd/1st}$)	CV%	19.7	49	50
Between-occasion variability				
Between-day variability on mean absorption time (MAT)	CV%	57.4	49	–
Within-day variability on mean absorption time (MAT)	CV%	55.9	15	–
Between-day variability on variability of mean absorption time (CV)	CV%	50.2	34	–
Within-day variability on variability of mean absorption time (CV)	CV%	43.5	19	–
Residual unexplained variability				
Proportional residual error	CV%	18.4	2	16

CV%, coefficient of variation; RSE, relative standard error; RTV, ritonavir

Paclitaxel is firstly absorbed from the gut to the liver compartment by a Weibull distribution model (Eq. 6, 7). Subsequently, it is metabolized by CYP3A4 in the liver, or it distributes to the central PK sampling compartment (Eq. 8, 9). Finally, there is distribution between central and peripheral compartments (Eq. 9, 10).

$$W1 = (\mathrm{BETA/ALPHA}) \cdot (\mathrm{T/ALPHA})^{(\mathrm{BETA\text{-}1})} \cdot \exp(-(\mathrm{T/ALPHA})^{\mathrm{BETA}}) \quad \text{(Eq. 6)}$$

$$\frac{dA_{gut}}{dt} = -W1 \cdot A_{gut} \quad \text{(Eq. 7)}$$

$$\frac{dA_{liver}}{dt} = W1 \cdot A_{gut} \quad - Q_H \cdot E_H / Vh \cdot A_{liver} - Q_H \cdot (1 - E_H) / Vh \cdot A_{liver} \quad + Q_H / Vc \cdot A_{central}$$

(Eq. 8)

$$\frac{dA_{central}}{dt} = Q_H \cdot (1 - E_H) / Vh \cdot A_{liver} \quad - Q_H / Vc \cdot A_{central} \quad + Q / Vp \cdot A_{peripheral} \quad - Q / Vc \cdot A_{central}$$

(Eq. 9)

$$\frac{dA_{peripheral}}{dt} = Q / Vc \cdot A_{central} \quad - Q / Vp \cdot A_{peripheral} \quad \text{(Eq. 10)}$$

In which *A* represents the amount of drug in certain compartment, ALPHA is the shape parameter, BETA is the scale parameter, ALPHA and BETA define the Weibull distribution *W*1, *Q* represents inter-compartment distribution, T represents the time after each dose, *Vc* and *Vp* represent the central and peripheral volume of distribution. Finally, *Vh* represents liver volume, which was fixed to 1 L, close to empirically determined values [33].

In Table 3, it is shown that the CL_{int0} was estimated at 163 L/h (RSE 14%) with the ritonavir inhibitory effect factor–KI estimated as 6,150 ng/mL (RSE 49%). The relative gut bioavailability–rF_G of ModraPac tablet formulation and drinking solution of paclitaxel was estimated respectively 2.0-fold and 2.4-fold higher compared to that of the ModraPac capsule formulation. In addition, between-subject variability on rF_G of the drinking solution of paclitaxel was 50.7%. The between-day variability and within-day variability on rF_G for oral paclitaxel formulations were estimated as 41.2% and 42.7%, respectively.

Table 3. Parameter estimates of paclitaxel in the final pharmacokinetic model.

Parameters	Units	Estimate	RSE (%)	Shrink-age (%)
Population parameter–paclitaxel				
Shape parameter in Weibull distribution (ALPHA)	–	1.8	9	–
Scale parameter in Weibull distribution (BETA)	–	2.7	24	–
Uninhibited intrinsic clearance (CL_{int0})	L/h	163	14	–
Inhibition factor (KI)	ng/mL	6,150	49	–
Volume of distribution of central compartment (Vc_{PAC})	L	177	9	–
Inter-compartment clearance (Qi_{PAC})	L/h	46.7	7	–
Volume of distribution of peripheral compartment (Vp_{PAC})	L	449	9	–
Relative gut bioavailability (rF_G) of ModraPac capsule	–	1 FIX	–	–
Relative gut bioavailability (rF_G) of ModraPac tablet	–	2.0	18	–
Relative gut bioavailability (rF_G) of paclitaxel drinking solution	–	2.4	28	–
Between-subject variability				
Shape parameter in Weibull distribution (ALPHA)	CV%	38.7	18	7
Uninhibited intrinsic clearance (CL_{int0})	CV%	42.9	25	23
Volume of distribution of central compartment (Vc_{PAC})	CV%	53.2	23	13
Relative gut bioavailability (rF_G) of paclitaxel drinking solution	CV%	50.7	40	52
Between-occasion variability				
Between-day variability on relative gut bioavailability (rF_G) –ModraPac capsule & paclitaxel drinking solution	CV%	41.2	37	–
Within-day variability on relative gut bioavailability (rF_G) –ModraPac capsule & ModraPac tablet	CV%	42.7	33	–
Residual unexplained variability				
Proportional residual error	CV%	29.5	17	10

CV%, coefficient of variation; PAC, paclitaxel; RSE, relative standard error

Model evaluation

GOF plots (Figure 2) and prediction-corrected VPC (Figure 3) demonstrated that the developed final model adequately described the paclitaxel PK observation. There was no obvious bias of the model differentiated by study designs.

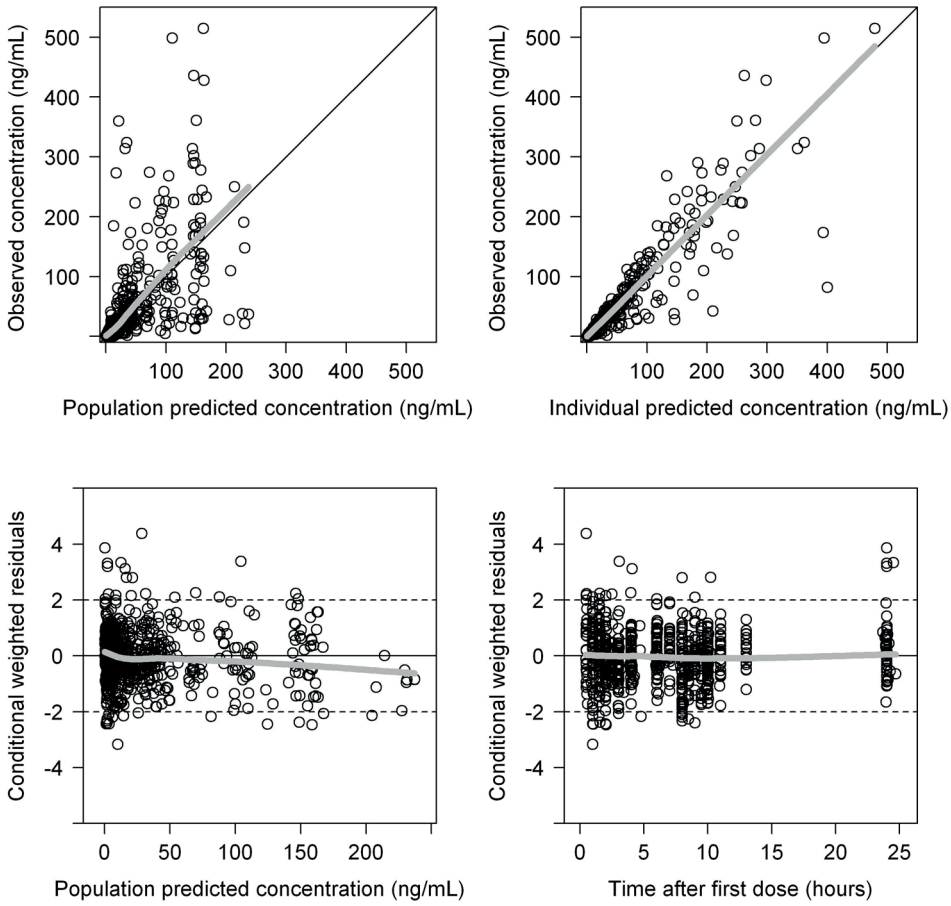

Figure 2. Goodness-of-fit plots of paclitaxel. The plots include observed versus population predicted concentration, observed versus individual model predicted concentration, conditional weighted residuals (CWRES) versus population predicted concentration, and CWRES versus time.

Simulations

The simulation of paclitaxel plasma concentration-time curves given as oral ModraPac capsule or ModraPac tablet formulation (twice-daily 20 mg) co-administered with ritonavir (twice-daily 100 mg) is shown in Figure 4. The time at maximum concentration level (T_{max}) in each dose interval was 2.2 hours after administration. The area under the concentration-time curve (AUC) of ModraPac capsule and ModraPac tablet was 135 µg/L· h and 275 µg/L·h, respectively.

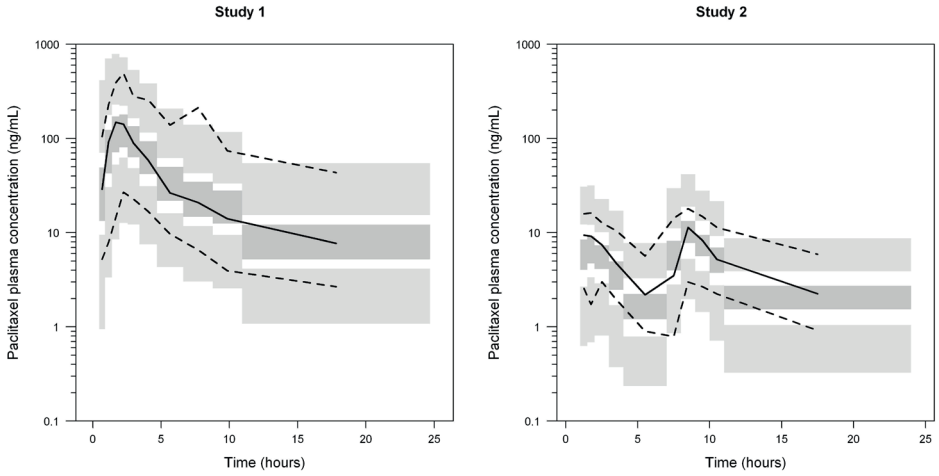

Figure 3. Prediction-corrected visual predictive check of paclitaxel plasma concentration for oral paclitaxel formulations stratified by 2 clinical studies (n = 1,000). Solid lines and dark grey areas represent the median observed values and simulated 95% confidence intervals (CIs). Dashed lines and light grey areas represent the 10% and 90% percentiles of the observed values and 95% CIs of the simulated percentiles.

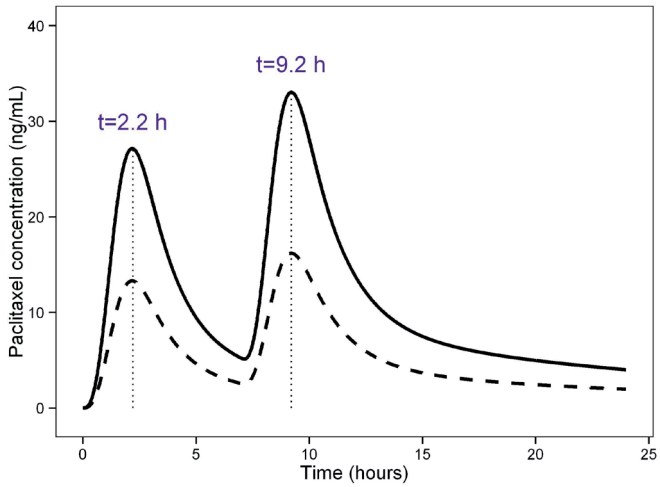

Figure 4. Comparison of pharmacokinetics between ModraPac capsule and tablet with the dosing regimen of paclitaxel (twice-daily 20 mg) co-administered with ritonavir (twice-daily 100 mg) with dosing at 0 and 7 hours. The dashed line represents the simulated paclitaxel plasma concentration of ModraPac capsule; the solid line represents the simulated paclitaxel plasma concentration of ModraPac tablet; the dotted lines show the times at peak concentration level of each dose interval.

Another simulation was performed and compared the IV formulation of paclitaxel and ModraPac tablet (Figure 5). The maximum concentration (C_{max}) of IV formulation with 3-weekly infusion was 3,973 ng/mL, C_{max} of IV formulation with weekly infusion was 3,156 ng/mL, and the steady state C_{max} of ModraPac tablet formulation was 65 ng/mL. The AUC of IV formulation with 3-weekly infusion or weekly infusion and ModraPac tablet in a 3-week period was 13,616 μg/L·h, 14,578 μg/L·h, and 13,055 μg/L·h, respectively. The $T_{C>0.05}$ for IV formulation with 3-weekly infusion or weekly infusion was 29.0 hours or 30.8 hours. As for the ModraPac tablet formulation, the sum of $T_{C>0.05}$ in 3-week period was calculated as a total of 83.4 hours.

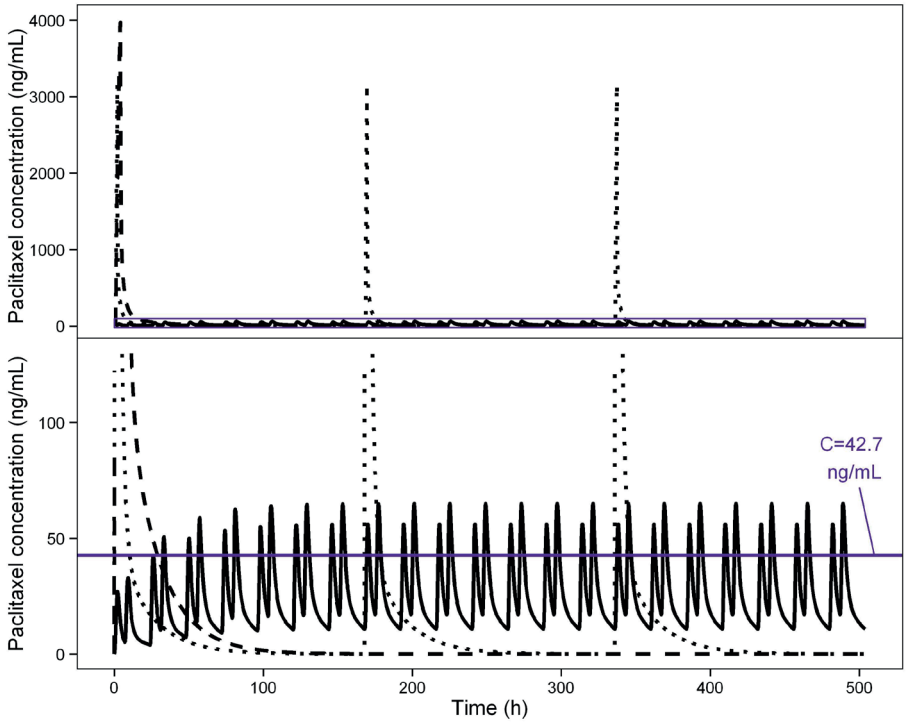

Figure 5. Comparison of pharmacokinetics between intravenous formulation of paclitaxel and co-administration of ModraPac tablet formulation with ritonavir for a 3-week schedule. There are three simulated concentration-time curves in the figure. The dashed curve represents the paclitaxel plasma concentration of intravenous formulation given 3-weekly 175 mg/m^2 (BSA = 1.8 m^2) infusion for 3 hours; the dotted curve represents the paclitaxel plasma concentration of intravenous formulation given weekly 80 mg/m^2 (BSA = 1.8 m^2) infusion for 1 hour; the solid curve represents the paclitaxel plasma concentration of ModraPac tablet formulation (twice-daily 20 mg) co-administered with ritonavir (twice-daily 100 mg). The upper panel shows the complete scope of the concentration-time curves. The lower panel is the zoomed rectangular area in the upper panel. There is a line indicating the paclitaxel plasma concentration at 42.7 ng/mL (0.05 μmol/L).

4. DISCUSSION

In the current work we established a semi-physiological PK model for three oral paclitaxel formulations co-administered with ritonavir. The model included a central and a peripheral compartment to fit the systemic paclitaxel concentration. The Weibull distribution model described the variable absorption profile of oral paclitaxel best. This variable absorption profile is the result of the complex absorption of paclitaxel with strong influence of factors such as variability in paclitaxel dissolution and precipitation, the influence of PgP-mediated drug transport, and the influence of ritonavir co-administration. Previously, a PK model was established for another oral paclitaxel formulation–DHP107 [34] where a similar systemic model structure was used. The absorption profile of DHP107 was depicted by a sequential zero-order and Weibull type absorption processes, similarly to the current model. Modelling of PK interaction of paclitaxel with the CYP3A4 inhibitor was for the first time explored in the current work. The inhibitory effect of ritonavir was included in the semi-mechanistic well-stirred liver model by a linear inhibitory relationship (Eq. 1). There has been a report on PK modelling of interaction between IV paclitaxel and a PgP modulator–zosuquidar [35] in which the inhibitory effect of the PgP modulator was explored more empirically.

Comparison between the three oral paclitaxel formulations was based on parameter estimates of gut bioavailability. The drinking solution of paclitaxel showed the highest gut bioavailability. However, the drinking solution is not suitable for the use in clinic, because of its unpleasant taste, limited physical stability, high content of ethanol and limited dosing accuracy. ModraPac tablets presented doubled gut bioavailability compared to ModraPac capsules. This difference may be the result of the switch in the preparation procedure from freeze drying used in ModraPac capsules to spray drying used in ModraPac tablets. Based on a previous study, the solid dispersion after freeze drying was not as amorphous as after spray drying [13]. Therefore, a higher maximum solubility in dissolution process could be achieved with the spray dried solid dispersion as with the freeze dried solid dispersion. In addition, the time until precipitation may be prolonged with the spray dried solid dispersion since also SDS, included as a precipitation inhibitor in the formulation, is more homogenously dispersed. There was relatively high between-occasion variability on gut bioavailability for oral paclitaxel formulations (Table 3). This may be explained by the critical pharmaceutical characteristics such as dissolution and subsequent precipitation.

The comparison between IV and oral paclitaxel illustrated that oral paclitaxel reaches systemic concentrations in the range of the conventional IV administration.

However, this interpretation should be done with caution, because the IV formulation of paclitaxel contains CrEL, which forms micelles in the central circulation. As a consequence, paclitaxel can be trapped in these micelles which results in limited distribution after IV administration as compared to oral administration [36]. Based on the current simulation set-up, the AUC of the oral formulation was in the similar range as IV formulation, yet with much lowered C_{max}. There was a longer cumulative $T_{c>0.05}$ for ModraPac tablet formulation compared to the IV formulation (83.4 hours vs. 29.0 or 30.8 hours). Furthermore, it was reported that the unbound paclitaxel concentration may be 2.6-fold higher after administration of a CrEL-free formulation than a formulation which contains CrEL [37].

5. CONCLUSION

The complex pharmacokinetics of oral paclitaxel in combination with ritonavir were adequately described with the developed semi-physiological model. Characteristics of three oral paclitaxel formulations were successfully explored. The drinking solution of paclitaxel showed the highest gut bioavailability but was unfavorable for patients. The ModraPac tablet showed similar gut bioavailability as that of drinking solution. Simulations suggested that daily dosing of oral paclitaxel results in a comparable drug exposure to the standard IV paclitaxel regimens.

Conflict of interest. Bastiaan Nuijen and Jos Beijnen are inventors and hold a patent on oral ModraPac formulations. Jos Beijnen is an employee and shareholder in Modra Pharmaceuticals, a spinout company developing oral taxane formulations.

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SUMMARY
CONCLUSIONS
PERSPECTIVES

SUMMARY

Dissolution in water is a crucial step for oral drug absorption because only dissolved drug molecules in the gastro-intestinal tract are absorbed [1]. The problem is that many orally administered drugs are poorly soluble in water and in fact 46% of orally dosed oncolytics has dissolution-limited absorption. The consequences are incomplete bioavailability, high variability in blood concentrations and a lack of a linear relationship between dose and concentrations in blood, resulting in under- or overdosing. Of particular interest for resolving dissolution-limited drug absorption is the solid dispersion formulation technique. In a solid dispersion the drug is finely dispersed in a hydrophilic excipient and appears as a single-phase powder [2–4]. The hydrophilic character of the excipient, decreased particle size and close integration of drug-excipient considerably increase drug dissolution and in-vivo absorption [5]. For example, a commercially available solid dispersion is telaprevir (Incivo®) which increases dissolution 32 times and absorption 10 times compared to crystalline telaprevir [6]. There are currently nearly 30 commercially available solid dispersions, 3 of them are orally dosed oncolytics, highlighting the feasibility and success of this formulation technique [7].
The goal of this thesis is to investigate pharmaceutical formulation aspects of a solid dispersion and whether it can be a useful formulation technique for the clinical development of poorly soluble drugs to be administered orally to patients with oncological conditions.

In Chapter 1 an inventory is made of pharmaceutical formulations of orally administered oncolytics and the principles of the solid dispersion formulation technique is discussed [8]. Over the last two decades many new oncolytics were launched as oral formulations. Oral formulations can be taken by the patient without hospitalization, which can limit hospital expenses and is more patient-convenient [9,10]. There are currently 72 oncolytics licensed as oral formulations in Europe and among this arsenal is the group of the small-molecule tyrosine kinase inhibitors. These oncolytics target tumor-specific growth signaling pathways of cancer cells, resulting in targeted or “personalized” chemotherapy. Looking closer at the formulation composition, most of orally dosed oncolytics are conventional mechanical mixtures of crystalline drug powder and excipient powder (crystalline physical mixtures). Crystalline physical mixtures are widely used because the formulation method is simple and inexpensive. However, given the fact that half of the currently licensed oncolytics are practically insoluble in water and poorly absorbed, suggests a crystalline physical mixture formulations might often result in suboptimal dissolution.

This is where the solid dispersion formulation technique comes into picture. There are various types of solid dispersions and they can be categorized by the physical state [4]. Of particular interest is the amorphous solid dispersion (ASD) in which the drug is molecularly dispersed in an amorphous hydrophilic excipient [11]. The absence of crystals makes an ASD very powerful in increasing drug dissolution [4]. There are 3 orally dosed oncolytics that are commercially available as an ASD: vemurafenib (Zelboraf®), regorafenib (Stivarga®) and everolimus (Afinitor®, Votubia®). For example, vemurafenib from the ASD formulation results in a 30 times increased dissolution and a 5 times increased bioavailability compared to a crystalline physical mixture formulation [12]. Given the feasibility and success of ASD formulations, we plea for the application of this formulation technique for drugs in oncology.

In Chapter 2 we discuss the development of an ASD containing elacridar hydrochloride for the purpose to conduct proof-of-concept clinical studies with this drug. Although elacridar hydrochloride itself is not an oncolytic, it is an intensively studied drug in oncology because of its boosting effect on the oral bioavailability and brain penetration of many oncolytics. The boost is the consequence of inhibiting drug-efflux pumps P-glycoprotein (PgP) and Breast Cancer Resistance Protein (BCRP) which are expressed in cells in the gastrointestinal tract, blood-brain barrier, stem cells and cancer cells and are responsible for limited oral bioavailability, reduced drug uptake in the central nervous system and multidrug resistance of tumor cells [13–16]. In fact, several phase I clinical trials already confirmed that co-administration of elacridar hydrochloride with oncolytics that are substrates to PgP/BCRP results in increased oral bioavailability (for example, paclitaxel and topotecan) [17–19]. Despite promising clinical results, further commercial development of elacridar hydrochloride was stopped and currently there is no formulation available for clinical trials. To facilitate the possibility of conducting proof-of-concept clinical trials with elacridar hydrochloride we developed a novel oral formulation. The pharmaceutical development of elacridar hydrochloride is not straightforward because the drug is practically insoluble in water and the previously used clinical formulation resulted in poor and unpredictable absorption [18,20,21]. To resolve dissolution-limited absorption of elacridar hydrochloride, the solid dispersion technique is implemented, hence the novel tablet contains an ASD of the drug.
Chapter 2.1 describes the development and validation of a reversed phase liquid chromatographic method for the quality control of pharmaceutical formulations containing elacridar hydrochloride [22]. The analytical method is developed because no quality control monographs about elacridar hydrochloride are published

in pharmacopoeias, neither are there validated analytical methods for quality control purposes published in the scientific literature. The analytical method is able to quantify the dissolution of elacridar hydrochloride from crystalline products and from ASD formulations.
Chapter 2.2 is about the pharmaceutical development of a novel tablet formulation containing an ASD of elacridar hydrochloride with the purpose to resolve the drug's low solubility in water and to conduct proof-of-concept clinical studies [23]. A systematic development procedure is designed and followed to facilitate fast and efficient choice for ASD design, production method, dissolution and characterization, dosage form and stability. 24 different ASDs are freeze dried and their dissolution is compared to that from crystalline drug and a crystalline physical mixture with excipients. The best performing formulation in this study is elacridar hydrochloride-povidone K30-sodium dodecyl sulfate (1:6:1, w/w/w) which is fully amorphous and has a complete dissolution whereas dissolution from a crystalline formulation is 1%. Subsequently, a tablet containing the ASD equivalent to 25 mg elacridar hydrochloride is developed and content, purity and dissolution are stable for at least 12 months when stored at – 20 °C. This makes the ASD tablet feasible for proof-of-concept clinical trials.
Chapter 2.3 discusses the pharmacokinetic results of a clinical trial where ASD tablets are administered to healthy human volunteers [24]. The ASD tablets result in plasma concentrations and exposure similar to values previously seen in clinical trials with elacridar hydrochloride [17–19]. The dose is linearly related to plasma concentration and plasma exposure. The tablets are well tolerated. Altogether, the ASD tablets containing elacridar hydrochloride are considered suitable to conduct proof-of-concept clinical studies.

Chapter 3 of this thesis is about optimization of a pre-existing production method for ASDs containing either docetaxel or paclitaxel. These two ASDs were developed previously as capsules containing a freeze dried ASD with docetaxel or paclitaxel respectively as active-povidone K30-sodium dodecyl sulfate (1:9:1, w/w/w) and named "ModraDoc001" (active = docetaxel) and "ModraPac001" (active = paclitaxel). These two ASDs were tested in phase I clinical trials where patients took ModraDoc001 or ModraPac001 together with the CYP3A4-inhibitor ritonavir. This treatment combination resulted in relevant pharmacological exposure of docetaxel and paclitaxel with promising clinical outcome [25,26]. However, the production method is unsuitable for further clinical studies because of scalability issues: freeze drying is a slow non-continuous production process that results in ASD with poor powder flow, consequently the capsulation process requires manual operation.

Spray drying, on the other hand, is a fast and continuous process, allows better particle engineering, which makes it a preferable production method for ModraDoc and ModraPac.

Chapter 3.1 describes the pharmaceutical development of a uniform spray drying process for ModraDoc and ModraPac [27]. Spray drying is a fast, continuous and robust production process. Furthermore, spray dried ASDs are entirely amorphous whereas freeze dried equivalents are only partially amorphous, caused by sodium dodecyl sulfate recrystallization during freezing of the solvent. Spray drying results in fully amorphous ASDs because of rapid evaporation of the solvent. Consequently, spray dried ASDs have a significantly increased supersaturation effect compared to freeze dried equivalents. The final drug product is a tablet containing spray dried ModraDoc or ModraPac equivalent to 10 mg active (docetaxel: ModraDoc006 10 mg tablets, paclitaxel: ModraPac005 10 mg tablets). Dissolution, content and purity of the tablet formulations are stable for at least 2 years at room temperature. To conclude, a clinically feasible tablet is developed and is implemented in further clinical trials.

Clinical evaluation of ModraDoc is discussed in Chapter 3.2. In this work, a model is developed to study the pharmacokinetics of orally dosed ritonavir with oral docetaxel formulations: drinking solution, capsules with freeze dried ASD (ModraDoc001) and tablets with spray dried ASD (ModraDoc006). Docetaxel absorption from tablets with spray dried ModraDoc is 13% higher than from capsules with freeze dried ModraDoc. Interpatient and intrapatient variability is 20 - 30% and this is considerably lower than corresponding variability values of orally administered docetaxel drinking solution (40%). A once-weekly-once-daily dose (QW) of 60 mg docetaxel and 100 mg ritonavir or a once-weekly-twice-daily (BIDW) dose of 20 mg docetaxel (2 x 20 mg) and 100 mg ritonavir (2 x 100 mg) result in pharmacologically relevant plasma concentrations and are tolerable. To conclude, the oral tablet formulation containing spray dried ModraDoc are suitable for forthcoming clinical trials.

A similar path is followed to evaluate tablets with spray dried ModraPac and results are discussed in Chapter 3.3. According to the ritonavir-paclitaxel pharmacokinetic model, paclitaxel absorption from the spray dried ASD is twice as high as from the freeze dried ASD. This is caused by the fact that spray dried ASD is entirely amorphous and that paclitaxel dissolution from spray dried ASD is higher than from the freeze dried ASD. Clinically relevant plasma concentrations are achieved with a twice-daily schedule of 2 x 20 mg paclitaxel and 2 x 100 mg ritonavir but with a considerably lower peak plasma concentration as with intravenous schedules. The time of plasma concentration beyond the paclitaxel efficacy threshold value

is 3 times longer with the tablet formulation than with intravenous schedules. This suggests that oral administration of paclitaxel can be more effective and less toxic than intravenous administration and confirms the usefulness of ModraPac tablets for further clinical studies.

CONCLUSIONS AND PERSPECTIVES

Despite that solid dispersions are a useful and feasible formulation technique for poorly soluble drugs, there are still only few oral drug products of oncolytics developed as such (everolimus, vemurafenib and regorafenib). The majority of licensed orally dosed oncolytics are crystalline physical mixtures. Although crystalline physical mixtures are simple and inexpensive to produce, practice has learnt that they are often not sufficient for the dissolution of drugs with poor aqueous solubility (Chapter 1). This can result in low and highly variable absorption which can complicate the drug development process [28]. We believe that the pharmaceutical formulation requires more attention during drug development and that the solid dispersion technique should be more often implemented, given the fact that the majority of orally dosed oncolytics are poorly soluble.

Traditionally, it is believed that intravenously administered oncolytics are preferable over oral administration in order to avoid the complex absorption process, often affected by poor dissolution. The research work in this thesis shows that this statement is not always true; poorly soluble oncolytics formulated as a solid dispersion can result in relevant in-vivo absorption and in tolerable treatment regimens. For example, oral administration of a tablet containing paclitaxel ASD (ModraPac) at a daily dose of 40 mg paclitaxel co-administered with 200 mg ritonavir results in similar exposure as the intravenous dosing schedule of paclitaxel. Furthermore, a 3 times longer paclitaxel threshold pharmacological concentration is achieved with ModraPac tablet, suggesting that the oral schedule with this formulation can be more efficient than the conventional intravenous regimen. Besides, paclitaxel peak plasma concentrations after oral administration are considerably lower than intravenously administered paclitaxel, avoiding toxic plasma concentrations and with that the oral dosing schedule of ModraPac seems to be more tolerable (Chapter 3.3).

Oral ASD formulations of oncolytics may also be safer and more patient-convenient than their intravenous equivalents. For example, the intravenous formulations of docetaxel and paclitaxel contain toxic co-solvents (polyethoxylated castor oil, polysorbate and ethanol). The oral ASD formulations of these drugs developed by us (ModraDoc and ModraPac), are free from these toxic excipients and when co-administered with ritonavir similar in-vivo exposure can be achieved as with

intravenous regimens. This provides evidence that oral administration of docetaxel and paclitaxel as ASD formulations can be clinically feasible, patient-convenient, more tolerable and safer than intravenous regimens of corresponding drugs (Chapter 3.2 and 3.3). Further clinical studies with ModraDoc and ModraPac will prove if this therapy schedule is effective and tolerable.
The fact that dozens of oral ASD formulations are commercially available and that hundreds are under development shows that this formulation technique is widely and successfully applied in the pharmaceutical field [7]. Drug dissolution can be enhanced considerably, bioavailability can be significantly increased (i.e. vemurafenib ASD and regorafenib ASD) and clinically relevant in-vivo exposure can be achieved in man. What is more, the absorption from ASD seems more predictable than from conventional formulations. For example, the ASD tablet containing elacridar hydrochloride results in a linear relationship between dose and plasma concentrations whereas absorption from the earlier used clinical tablet formulation is highly variable and not linearly related to dose (Chapter 2.3).

The dissolution test is an important parameter to predict the in-vivo performance of an ASD because the higher the dissolution the higher is in-vivo absorption. However, the relationship between in-vitro dissolution and in-vivo absorption is not always straightforward because dissolution tests can oversimplify the dissolution pattern of a drug in-vivo, in particular of supersaturated drug formulations such as ASDs. Commonly used pharmacopoeia dissolution testers are designed for sink conditions (target concentration at least 3 times lower than the saturation concentration) which makes it difficult to predict the in-vivo performance of an ASD [29,30]. For example, the dissolution of elacridar hydrochloride from the ASD tablet is 17 times increased, but in-vivo absorption is not increased in the order of this dissolution enhancement (Chapter 2.3). The gastro-intestinal tract contains considerably less water, variable amounts of water and can have irregular motion patterns [29]. Such factors can affect the dissolution of a poorly soluble drug such as elacridar hydrochloride. The target supersaturation concentration is also an important factor in the dissolution experiment. Supersaturated solutions are thermodynamically unstable and tend to revert to the thermodynamically favored state which induces precipitation. The higher the degree of supersaturation, the higher the chance of fast precipitation. This shows that the target supersaturation concentration of a solid dispersion should be carefully chosen [30].
To establish a better in vitro-in vivo correlation during development of an ASD we propose to use a more bio-relevant dissolution experimental setup rather than "traditional" pharmacopoeia dissolution testers. An example is the dissolution-

transfer model in which the drug formulation first enters a donor phase mimicking the stomach, then the medium is the pumped to the acceptor phase simulating the intestine. The advantage of this system is that it resembles more closely the gastro-intestinal tract and therefore it can study more closely the relationship between biopharmaceutics and drug dissolution/precipitation [28].

A critical feature of a solid dispersion is the physical stability during storage. Solid dispersions, in particular ASDs, are physically less stable than crystalline physical mixtures because ASDs are powders with high free energy that tend to revert to the low energy form (crystalline powders). ASDs have a glass transition temperature and when this temperature approaches the storage temperature, the formulation can undergo glass transition from the hard "intact" state to the rubbery "elastic" state, and this affects drug dissolution. Stringent storage conditions may be necessary to ensure a physically stable ASD (i.e. storage in the freezer, air-tight sealed packages, low-humidity environment, extra instructions for medical staff and patients). By adhering to above-mentioned handling conditions, ASDs can often be sufficiently stable. For example, ASD tablets containing elacridar hydrochloride undergo glass transition to the rubbery "elastic" state already after 3 months of storage at room temperature or refrigerator and this reduces dissolution. The dissolution and physical integrity are intact for at least one year when tablets are stored in the freezer (Chapter 2.2). An important factor determining the physical stability of an ASD is residual water and other residual solvents that are used during manufacturing. Water is often an unavoidable component because ASD excipients are hygroscopic due to their hydrophilic nature (i.e. povidone). Residual water can be minimized by using solvent-free production methods (i.e. melting method) or by using a fast-drying solvent-removal method (i.e. spray drying). The use of the melting method is not always possible because drugs may have a high melting temperature accompanied with degradation (i.e. elacridar hydrochloride and docetaxel). Regarding fast-drying solvent-removal method, our own formulation work demonstrates that spray dried ASD containing docetaxel or paclitaxel have 2 times less residual solvents than freeze dried equivalents and spray dried products have a longer shelf-life (Chapter 3.1). However, some drug substances are not soluble in organic solvents which excludes the use of drying methods such as spray drying (i.e. elacridar hydrochloride, Chapter 2.2).
Melting, solvent-removal, and precipitation are widely used production methods for ASDs and multiple formulations produced through these methods are currently commercially available (Chapter 1). Upcoming novel production methods such as supercritical fluid precipitation, spray-freeze drying and electrospinning are also capable of producing ASDs with excellent dissolution enhancement. However,

the disadvantage of these novel production methods is currently little experience in pharmaceutical industry, expensive, complex production process and lack of GMP-compliant apparatuses and expertise [31–33]. Nevertheless, novel production methods should be considered if conventional production methods are unfavorable. There is no uniform first-choice manufacturing method for solid dispersions and the choice is rather governed by the physical and chemical properties of the drug substance and excipients.

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NEDERLANDSTALIGE SAMENVATTING

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Dissolutie in water is een essentiële stap voor de orale absorptie van een geneesmiddel, omdat alleen de opgeloste fractie geabsorbeerd kan worden [1]. Het probleem is dat veel (circa 46%) oraal toegediende geneesmiddelen slecht oplosbaar zijn in water, resultered in een onvolledige biologische beschikbaarheid, hoge variabiliteit in bloedconcentraties en het ontbreken van een lineair verband tussen de dosis en de concentratie van het geneesmiddel in het bloed. De gevolgen hiervan kunnen onder- of overdosering van het geneesmiddel zijn. Dissolutie-beperkende orale absorptie kan verholpen worden met de formuleringtechnologie *vaste dispersie*. In een vaste dispersie is het geneesmiddel fijn gedispergeerd in een hydrofiele hulpstof waardoor het mengsel oogt als een eenfasige poeder met zeer kleine poederdeeltjes en heeft het poeder een groot poederdeeltjesoppervlakte [2–4]. Het hydrofiele karakter van de hulpstof, de grote deeltjesoppervlakte en de fijne dispersie van geneesmiddel in de hulpstof zorgen ervoor dat de dissolutie toeneemt en als gevolg daarvan een hogere in-vivo absorptie wordt bereikt [5]. Een voorbeeld van een geneesmiddel, welke in de handel verkrijgbaar is als een vaste dispersie, is telaprevir (Incivo®). De dissolutie en orale absorptie van de telaprevir vaste dispersie is respectievelijk 32 keer en 10 keer hoger dan dat van kristallijn telaprevir [6]. Er zijn momenteel bijna 30 geneesmiddelformuleringen commercieel beschikbaar als een vaste dispersie. Wat betreft oraal toegediende oncolytica, er zijn drie formuleringen beschikbaar als een vaste dispersie formulering. Dit geeft aan dat de vaste dispersie een haalbare en succesvolle formuleringstechniek kan zijn [7].
In dit proefschrift worden farmaceutische aspecten van een vaste dispersie onderzocht. Daarnaast wordt bediscussierd of de vaste dispersie een geschikte formuleringstechniek is voor geneesmiddelen met een slechte oplosbaarheid in water, welke toegepast worden in klinisch onderzoek bij patiënten met oncologische aandoeningen.

In hoofdstuk 1 worden farmaceutische aspecten van orale formuleringen met een oncolyticum besproken en wordt het principe van een vaste dispersie uitgelegd [8]. In de afgelopen twee decennia zijn veel nieuwe oncolytica op de markt gebracht als een orale formulering. Het voordeel van een orale formulering is dat de patiënt het geneesmiddel zelfstandig kan innemen zonder tussenkomst van een ziekenhuisopname, waardoor de behandeling patiënt-vriendelijker is en tot minder hospitalisatiekosten leidt [9,10]. Er zijn momenteel 72 oncolytica geregistreerd in Europa als een orale formulering en onder dit arsenaal valt ook de groep van de

laagmoleculaire signaaltransductieremmers, met name de tyrosine kinase remmers. Deze groep oncolytica blokkeert tumor-specficieke groeisignaalroutes in kankercellen, hetgeen ook wel "personalized" chemotherapie genoemd wordt. De meeste orale formulerigen van oncolytica zijn capsules of tabletten met een conventioneel mechanisch gemengd kristallijn poedermengsel van het geneesmiddel en hulpstoffen (kristallijne fysische mengsels). Kristallijne fysische mengsels worden veel toegepast omdat de formuleringsmethode eenvoudig en goedkoop is. Echter, 46% van de geregistreerde orale oncolytica leidt tot inadequate absorptie als gevolg van slechte oplosbaarheid in water. Dit suggereert dat kristallijne fysische mengsels vaak kunnen resulteren in een suboptimaal dissolutieprofiel van het geneesmiddel. Dit is waar de vaste dispersie formuleringstechniek in beeld komt. Er zijn verschillende soorten vaste dispersies en classificatie kan gebeuren op basis van de fysische toestand van de vaste dispersie [4]. Een belangrijk type is de amorfe vaste dispersie (AVD), waarin het geneesmiddel moleculair gedispergeerd is in een amorfe hydrofiele hulpstof [11]. In een AVD zijn geen kristallen aanwezig, waardoor de dissolutie aanzienlijk toeneemt [4]. Er zijn drie orale oncolytica beschikbaar als een AVD: vemurafenib (Zelboraf®), regorafenib (Stivarga®) en everolimus (Afinitor®, Votubia®). Als voorbeeld, vemurafenib AVD leidt tot een 30 keer verhoogde dissolutie en een 5 keer verhoogde biologische beschikbaarheid ten opzichte van een fysisch kristallijn mengsel [12]. Gezien de haalbaarheid en het succes van AVD formuleringen pleiten wij voor een bredere toepassing van vaste dispersies voor slecht wateroplosbare geneesmiddelen welke ingezet worden tegen de behandeling van kanker.

Hoofdstuk 2 omvat de ontwikkeling van een AVD met elacridar hydrochloride, met als doel om dit geneesmiddel toe te passen in "proof-of-concept" klinische studies. Hoewel elacridar hydrochloride zelf geen oncolyticum is, wordt deze substantie uitgebreid bestudeerd in de oncologie vanwege dat het de biologische beschikbaarheid en hersenpenetratie van vele oncolytica kan verhogen. Dit effect is het gevolg van remming van P-glycoproteïne (PgP) en Breast Cancer Resistance Protein (BCRP); twee efflux-pompen welke zich bevinden op cellen in het maagdarmkanaal, de bloed-hersen barrière en op stamcellen en kankercellen. Geneesmiddelen welke substraten zijn voor PgP en BCRP kunnen hierdoor een lage biologische beschikbaarheid en lage penetratie in het centrale zenuwstelsel hebben en tumorcellen kunnen resistent worden tegen deze geneesmiddelen. Een PgP/BCRP remmer, zoals elacridar hydrochloride, kan deze werking teniet doen [13–16]. Uit verschillende fase I klinische studies is gebleken dat de orale biologische beschikbaarheid van oncolytica, welke substraten zijn voor PgP/BCRP (bijvoorbeeld paclitaxel en topotecan), toeneemt bij co-medicatie met elacridar hydrochloride [17–

19]. Ondanks deze veelbelovende resultaten werd de commerciële ontwikkeling van elacridar hydrochloride niet voortgezet, waardoor er geen formulering beschikbaar is voor verdere klinische studies. Om het uitvoeren van proof-of-concept klinische studies met elacridar hydrochloride mogelijk te maken, is er een nieuwe orale formulering ontwikkeld. De farmaceutische formulering van elacridar hydrochloride is echter niet eenvoudig, omdat de substantie praktisch onoplosbaar is in water. De formulering, welke gebruikt werd in eerdere klinische studies, resulteerde in incomplete en onvoorspelbare orale absorptie [18,20,21]. Om het dissolutie-beperkende absorptieprofiel van elacridar hydrochloride te verbeteren, is de nieuwe formulering ontwikkeld als een AVD.

Hoofdstuk 2.1 beschrijft de ontwikkeling en validatie van een hogedruk vloeistofchromatografische analysemethode voor de kwaliteitscontrole van farmaceutische formuleringen welke elacridar hydrochloride bevatten [22]. De analytische methode is ontwikkeld, omdat er geen monografiën van elacridar hydrochloride zijn opgenomen in de farmacopee en geen gevalideerde analytische methodes voor kwaliteitscontrole zijn gepubliceerd in de wetenschappelijke literatuur. Met de analytische methode beschreven in hoofdstuk 2.1 kan de dissolutie van elacridar hydrochloride uit een kristallijn fysisch mengsel of uit een AVD formulering gekwantificeerd worden.

Hoofdstuk 2.2 gaat over de farmaceutische ontwikkeling van een nieuwe tablet formulering welke een AVD van elacridar hydrochloride bevat, met als doel om de lage oplosbaarheid te verhogen en om proof-of-concept klinische studies te faciliteren [23]. Een systematische procedure voor de farmaceutische ontwikkeling van een AVD is gevolgd, waardoor een snel en efficiënt formuleringsproces plaats kan vinden wat betreft van de keuze van de hulpstoffen, de productiemethode, dissolutie en analyse, de toedieningsvorm en de stabiliteit daarvan. 24 verschillende AVD formuleringen zijn gevriesdroogd en de dissolutie is vergeleken ten opzichte van kristallijn elacridar hydrochloride en kristallijne fysische mengsels. Formulering elacridar hydrochloride-povidon K30-natriumlaurylsulfaat (1:6:1, w/w/w) is volledig amorf en leidt tot een complete dissolutie, terwijl de dissolutie uit een kristallijne formulering slechts 1% is. Vervolgens is een AVD tablet ontwikkeld welke 25 mg elacridar hydrochloride bevat. Het gehalte, zuiverheid en dissolutie is ten minste 12 maanden stabiel bij bewaring bij – 20 °C. Dit is haalbaar voor het uitvoeren van proof-of-concept klinische studies.

Hoofdstuk 2.3 bechrijft de farmacokinetische resultaten van een klinische studie waarbij de 25 mg elacridar hydrochloride AVD tabletten toegediend zijn aan gezonde vrijwilligers [24]. De AVD tabletten resulteren in plasmaconcentraties en blootstelling welke vergelijkbaar zijn aan wat eerdere klinische studies met elacridar

hydrochloride rapporteerden [17–19]. Er is sprake van een lineair verband tussen de dosis en de in-vivo plasmaconcentraties en blootstelling. De tabletten worden goed verdragen door de deelnemers aan de studie. De AVD tabletten met elacridar hydrochloride zijn derhalve geschikt om gebruikt te worden bij andere proof-of-concept klinische studies.

In hoofdstuk 3 van dit proefschrift wordt de optimalisatie besproken van een reeds bestaande productiemethode voor een AVD, welke ofwel docetaxel of paclitaxel als actief bestanddeel bevat. Beide AVD's waren eerder ontwikkeld als capsules, welke een gevriesdroogde AVD van docetaxel of paclitaxel bevat met als samenstelling actieve stof-povidon K30-natriumlaurylsulfaat (1:9:1, w/w/w) en met de naam "ModraDoc001" (actief bestanddeel: docetaxel) en "ModraPac001" (actief bestanddeel: paclitaxel). Deze twee AVD's zijn getest in fase I klinische studies waarbij patiënten ModraDoc of ModraPac innemen samen met de CYP3A4-remmer ritonavir. Deze behandeling resulteert in relevante farmacologische blootstelling van docetaxel en paclitaxel met veelbelovend klinisch effect [25,26]. De productiemethode is echter niet geschikt voor verdere klinische studies vanwege problemen met opschaalbaarheid: vriesdrogen is een langzaam en niet-continu productieproces en resulteert in een slechtstromend poeder, waardoor het vullen van de capsules handmatig moet gebeuren. Sproeidrogen daarentegen is een continu en snel productieproces en loont zich beter voor het controleren van poedereigenschappen. Hierdoor is sproeidrogen een gunstigere methode voor de productie van ModraDoc en ModraPac.
Hoofdstuk 3.1 beschrijft de farmaceutische ontwikkeling van een uniform sproeidroogproces voor ModraDoc en ModraPac [27]. Sproeidrogen is een snel, continu en robuust productieproces. Bovendien is gesproeidroogd ModraDoc en ModraPac volledig amorf terwijl de gevriesdroogde equivalenten slechts partieel amorf zijn. Dit komt doordat natriumlaurylsulfaat tijdens de vriesfase van het vriesdroogproces uitkristalliseert, terwijl gesproeidroogde AVD's volledig amorf blijven door snelle verdamping van het oplosmiddel tijdens het sproeidrogen. Gesproeidroogde AVD's resulteren hierdoor in een hogere dissolutie ten opzichte van de gevriesdroogde equivalenten. Het eindproduct is een tablet, welke gesproeidroogd ModraDoc of gesproeidroogd ModraPac bevat, equivalent aan 10 mg actieve stof (docetaxel: ModraDoc006 10 mg tabletten, paclitaxel: ModraPac005 10 mg tabletten). De dissolutie, het gehalte en de zuiverheid van de tablet formuleringen zijn ten minste 2 jaar stabiel bij kamertemperatuur. Concluderend, de tablet met gesproeidroogd ModraDoc en de tablet met gesproeidroogd ModraPac zijn geschikt voor toepassing bij verdere klinische studies.

De klinische evaluatie van ModraDoc wordt in hoofdstuk 3.2 besproken. Een semi-fysiologisch model is ontwikkeld om de farmacokinetiek te beschrijven van oraal ritonavir in combinatie met orale docetaxel formuleringen: drinkoplossing, capsules met gevriesdroogd AVD (ModraDoc001) en tabletten met gesproeidroogd AVD (ModraDoc006). De absorptie van docetaxel uit de tabletten met gesproeidroogd ModraDoc is 13% hoger dan die van capsules met gevriesdroogd ModraDoc. Interpatiënt en intrapatiënt variabiliteit zijn 20 – 30 % en dit is aanzienlijk lager dan dat van de orale drinkoplossing (40%). Wekelijks 60 mg docetaxel en 100 mg ritonavir in één gift of wekelijks 40 mg docetaxel en 200 mg ritonavir in twee giften (2 x 20 mg docetaxel en 2 x 100 mg ritonavir respectievelijk) resulteren in farmacologisch relevante plasmaconcentraties en de behandeling wordt goed verdragen. De orale tablet met gesproeidroogd ModraDoc is geschikt voor verdere klinische studies.
Een vergelijkbare route wordt gevolgd om tabletten met gesproeidroogd ModraPac klinisch te evalueren en resultaten worden in hoofdstuk 3.3 besproken. Volgens het ritonavir-paclitaxel semi-fysiologisch model is de absorptie van paclitaxel uit gesproeidroogd AVD tweemaal hoger dan uit het gevriesdroogde AVD. Dit wordt veroorzaakt doordat gesproeidroogd AVD volledig amorf is en dat de dissolutie uit gesproeidroogd AVD hoger is dan uit gevriesdroogd AVD. Een twee maal daagse dosering van 20 mg paclitaxel (2 x 20 mg) en 100 mg ritonavir (2 x 100 mg) leiden tot klinisch relevante plasmaconcentraties en met aanzienlijk lagere piekplasmaconcentraties dan met het intraveneus schema. De tijdsduur boven de drempelwaarde van de effectieve paclitaxel plasmaconcentratie is met de tablet 3 keer langer dan met het intraveneuze toedieningschema. Dit suggereert dat orale toediening van paclitaxel effectiever is en minder toxisch is dan de intraveneuze toediening. De ModraPac tabletten zijn geschikt voor verdere implentatie in klinische studies.

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DANKWOORD
AFFILIATIONS
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LIST OF PUBLICATIONS

Publications related to this thesis

Sawicki E, Hillebrand MJ, Rosing H, Schellens JHM, Nuijen B, Beijnen JH. Validation of a liquid chromatographic method for the pharmaceutical quality control of products containing elacridar. J Pharm Anal 2016;6(4):268–75.

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Sawicki E, Schellens JHM, Beijnen JH, Nuijen B. Pharmaceutical development of an amorphous solid dispersion formulation of elacridar hydrochloride for proof-of-concept clinical studies. Drug Dev Ind Pharm 2017; Epub ahead of print.

Publications not related to this thesis

Sawicki E, Stewart K, Wong S, Leung L, Paul E, George J, Medication use for chronic health conditions by pregnant women attending an Australian maternity hospital, Aust N Z J Obstet Gynaecol 2011;51(4):333-338.

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CURRICULUM VITAE

Emilia Sawicki was born on 20th of January 1986 in Amsterdam, The Netherlands. Having parents of Polish origin, she was raised bilingually (Polish-Dutch). She obtained her Gymnasium diploma in 2004 at high school OSG De Meergronden in Almere, The Netherlands. She studied pharmacy at Utrecht University, The Netherlands. She obtained the degree Bachelor of Pharmacy in 2007 and the degree Master of Pharmacy (PharmD) in 2011. Her bachelor thesis was a study of tropical infectious diseases transmitted by insects, under the supervision of internist-infectiologist C.A.J.J. Jaspers from the Central Military Hospital in Utrecht. The bachelor thesis was awarded in 2008 with a trophy called "Went-prize" from the Department of Pharmaceutical Sciences at Utrecht University. Her master thesis was a research project about medication use for chronic health conditions during pregnancy, with a focus on asthma medicines, performed at the Royal Women's Hospital in Melbourne, Australia and supervised by Dr. J. George (Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Australia) and S. Wong (Director of Pharmacy at The Royal Women's Hospital, Melbourne, Australia). The research resulted in two international publications.

In addition to the standard courses of the pharmacy curriculum at Utrecht University, she participated in two Student Exchange Programs (SEP) organized by the International Pharmaceutical Students' Federation. The first SEP was in 2007 during which she worked for 5 months at a community pharmacy in India, where she participated in national health projects, such as improving the pharmacotherapy of tuberculosis and writing a course book for pharmacy assistants. Furthermore, she performed a literature study about traditional Indian medicines. The second SEP was in 2008 in Taiwan, where she stayed for 2 months during which she studied traditional Chinese medicine and focused on the preparation of herbal medicines.

Her PhD research started in 2011 in the hospital pharmacy of Slotervaart Hospital / Antoni van Leeuwenhoek Hospital / The Netherlands Cancer Institute. Under the supervision of Prof. Dr. J.H. Beijnen, Prof. Dr. J.H.M. Schellens en Dr. B. Nuijen she developed novel oral pharmaceutical formulations containing solid dispersions, and these formulations have been used by cancer patients. The results of this research are described in this thesis and have so far resulted in five international publications.

Emilia Sawicki currently works as a production pharmacist for Modra Pharmaceuticals, a small spin-off company which develops novel oral formulations of anticancer drugs that are currently only available in intravenous forms. She is in charge of the production of these oral formulations for clinical trials.