International Journal of Pharmaceutics 511 (2016) 765–773

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical development of an oral tablet formulation containing a spray dried amorphous solid dispersion of docetaxel or paclitaxel

Emilia Sawicki[a,*], Jos H. Beijnen[a,b,c], Jan H.M. Schellens[b,c], Bastiaan Nuijen[a]

[a] Department of Pharmacy and Pharmacology, Antoni van Leeuwenhoek Hospital/MC Slotervaart, Amsterdam, The Netherlands
[b] Department of Clinical Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[c] Faculty of Science, Department of Pharmaceutical Sciences, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 30 May 2016
Received in revised form 7 July 2016
Accepted 28 July 2016
Available online 29 July 2016

Compounds studied in this article:
Docetaxel (PubChem CID: 148124)
Paclitaxel (PubChem CID: 4666)
Polyvinylpyrrolidone K30 (PubChem CID: 6917)
Sodium dodecyl sulphate (PubChem CID: 3423265)

Keywords:
Spray drying
Freeze drying
Lyophilization
Powder flow
Dissolution
Validation
Stability

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 g and 84%. spSDs had poor powder 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 (Engels et al., 2005; Green et al., 2005). Weekly administration of low-dose docetaxel or paclitaxel causes considerably less acute toxicity while efficacy is similar to dose-intensive schedules (Engels and Verweij, 2005; Green et al., 2005). On the other hand, weekly intravenous administration is patient-inconvenient and expensive because it requires hospitalization (Engels et al., 2005). 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 (Engels et al., 2005; Hendrikx et al., 2014; Malingré et al., 2001a, 2001b; Moes et al., 2011; Stuurman et al., 2013). The dissolution of docetaxel and paclitaxel is pH-independent because the drugs are not ionizable in the physiological pH range (Beijnen et al., 2010; Chen et al., 2011). The bioavailability of these two drugs can be boosted by co-administration of a strong CYP3A4 inhibitor such as ritonavir (Jibodh et al., 2013; Koolen et al., 2010; Moes et al., 2013c). Poor drug dissolution can be improved by the pharmaceutical formulation such as a solid dispersion (SD) (Alam et al., 2012; Vo et al., 2013). Previously, we described the development of a docetaxel SD (ModraDoc) and a paclitaxel SD (ModraPac) which contained povidone K30 (PVPK30) and sodium dodecyl sulphate

Abbreviations: SD, solid dispersion; fdSD, freeze dried solid dispersion; spSD, spray dried solid dispersion; SDS, sodium dodecyl sulphate; PVPK30, Povidone K30; S_{max}, highest saturation solubility; T_{precip}, precipitation onset time.

* Corresponding author.
E-mail address: emilia.sawicki@gmail.com (E. Sawicki).

http://dx.doi.org/10.1016/j.ijpharm.2016.07.068
0378-5173/

(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 drug. 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 (Moes et al., 2013c, 2011). 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 (Moes et al., 2013c, 2011). 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 (Moes et al., 2013a). 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 (Moes et al., 2013b). 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 (Démuth et al., 2016; Lopez et al., 2014). However, industrial application of electrospinning is currently limited due to poor reproducibility and low production efficiency (Persano et al., 2013) 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 (Paudel et al., 2013). There are already several commercialized amorphous SD drug formulations prepared by spray drying, for example everolimus (Certican®), etravirine (Intelence®) and telaprevir (Incivek®) (Démuth et al., 2015), 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 (Chen et al., 2011; Quan et al., 2013; Seo et al., 2013; Shanmugam et al., 2015). 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 (Moes et al., 2013c, 2013d).

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 sulphate (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 (USP, 2015). 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. 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.

2.3. 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 (Moes et al., 2013c, 2011). The product was grinded and stored in dark airtight glass jars at 2–8 °C.

2.4. 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 (USP, 2015):

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

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.

2.5. 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.

2.6. 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°/s.

2.7. 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 min, after which the sample was heated to 190.00 °C at a speed of 2.00 °C/min. Modulation was performed every 60 s at ±1.00 °C. Data were analyzed with Trios software version 3.5.3696 (TA Instruments, New Castle, DE, USA)

2.8. Fourier transform infrared spectroscopy (FT-IR)

FT-IR were recorded from 650 to 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.

2.9. 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.

2.10. 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.

2.11. 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.

2.12. Residual tert-butanol and residual ethanol

Residual *tert*-butanol and ethanol were determined by gas chromatography (GC) as described earlier (Van der Schoot et al., 2007). Fifty mg per sample was dissolved in 5 mL DMSO in triplicate.

2.13. 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 (Huizing et al., 1995; Moes et al., 2013c, 2011).

2.14. 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 min 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 (USP, 2015). 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.

2.15. 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)

3.1.1. 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 (EMA, 2010; Paudel et al., 2013; Singla et al., 2002). 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 (Moes et al., 2013a) and as a rule-of-thumb the difference between T_g and operation temperature should preferably >50 °C (Baird and Taylor, 2012). 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 (Paudel et al., 2013). 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 g powder was obtained per sample. The particle size increased with increasing solute concentration with a median particle size of 4.8 vs 7.7 um for 62.5 mg/mL vs 175 mg/mL, respectively (Fig. 1). Higher concentrations than 175 mg/mL were too viscous and could not be spray dried. Fig. 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.

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 (Paudel et al., 2013). Blank SD was made from a total solid concentration of 175 mg/mL according to

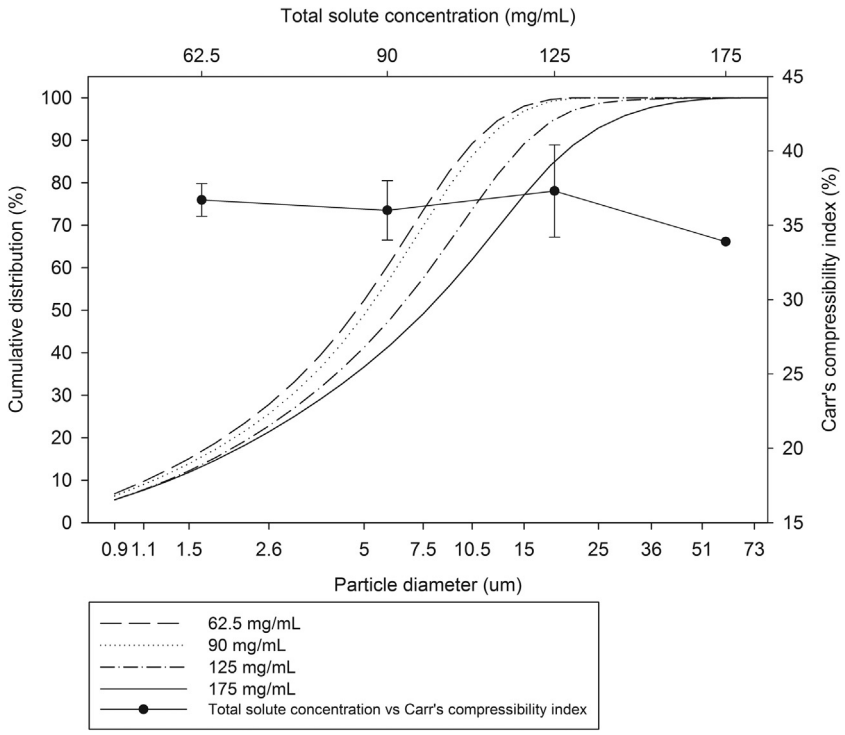

Fig. 1. The influence of total solute concentration on the cumulative distribution of particle size of spray dried SD as measured by LDA (left y-axis and down x-axis, 62.5 mg/mL dashed line, 90 mg/mL dotted line, 125 mg/mL dashed-dotted line, 175 mg/mL continuous line) and Carr's compressibility index (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).

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 min for 40 g. The increased nozzle diameter resulted in a lower drying capacity and therefore the solution feed rate had to be adjusted to 4.2 mL/min. These modifications did not improve powder 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 (Paudel et al., 2013). 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/min to produce acceptably dry particles. These settings considerably slowed down the spray drying process: 103 min 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/min. Yield was 80% and the production time was 24 min for 40 g. Fig. 2A shows that fdSD consisted of irregularly shaped particles of different sizes while spSD (Fig. 2 B) contained spherically-shaped, intact particles. These results were in line with LDA analysis data (Fig. 1).

3.1.2. 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 (Fig. 3A–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 (Moes et al., 2011). 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} (Viana et al., 2012) 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 (Beijnen et al., 2010). 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.

Docetaxel solubility comparison from spSD and fdSD is shown in Fig. 4A. 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 Fig. 4B 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

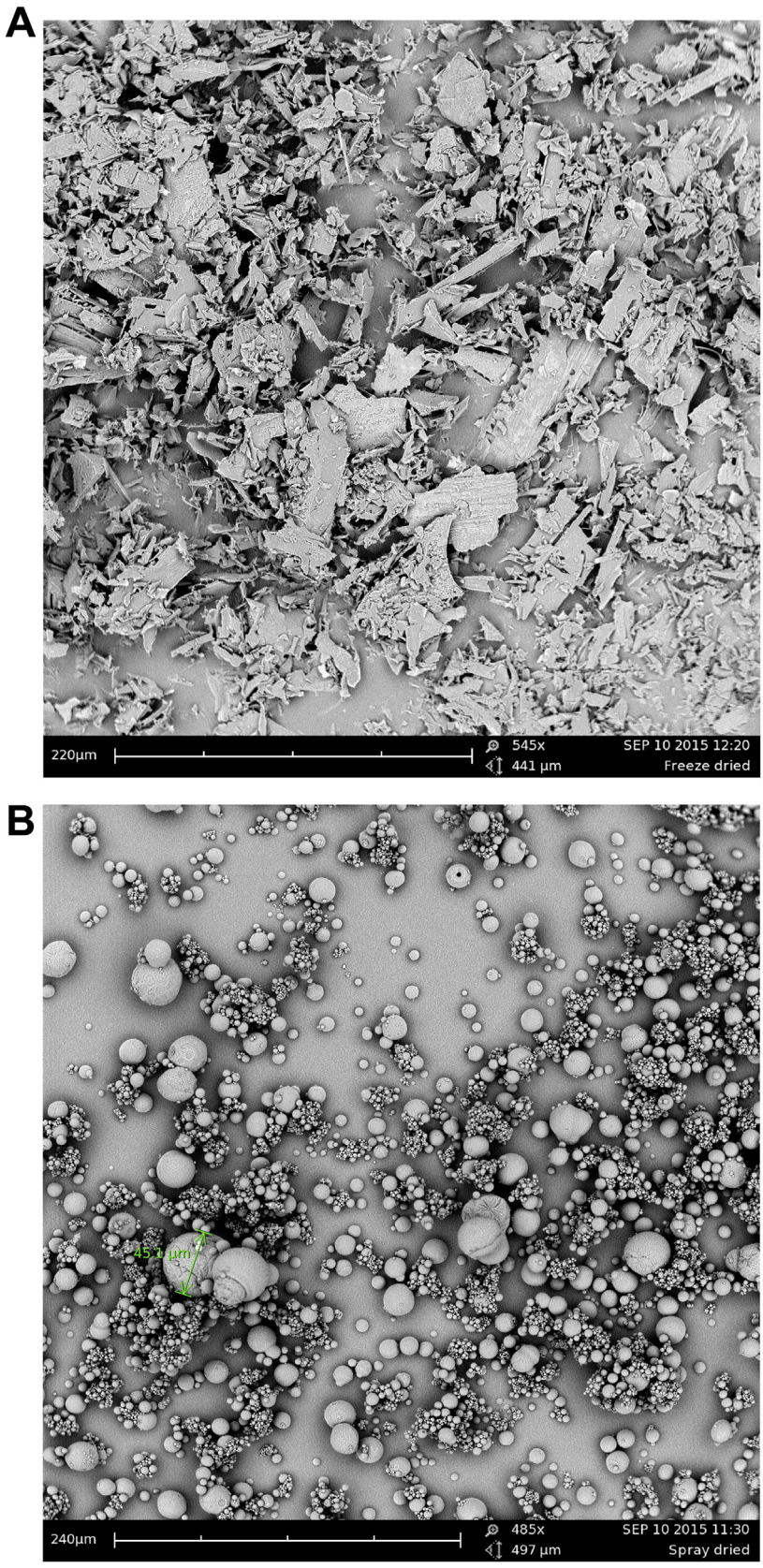

Fig. 2. Scanning electron microscopy image of (A) fdSD (B) spSD.

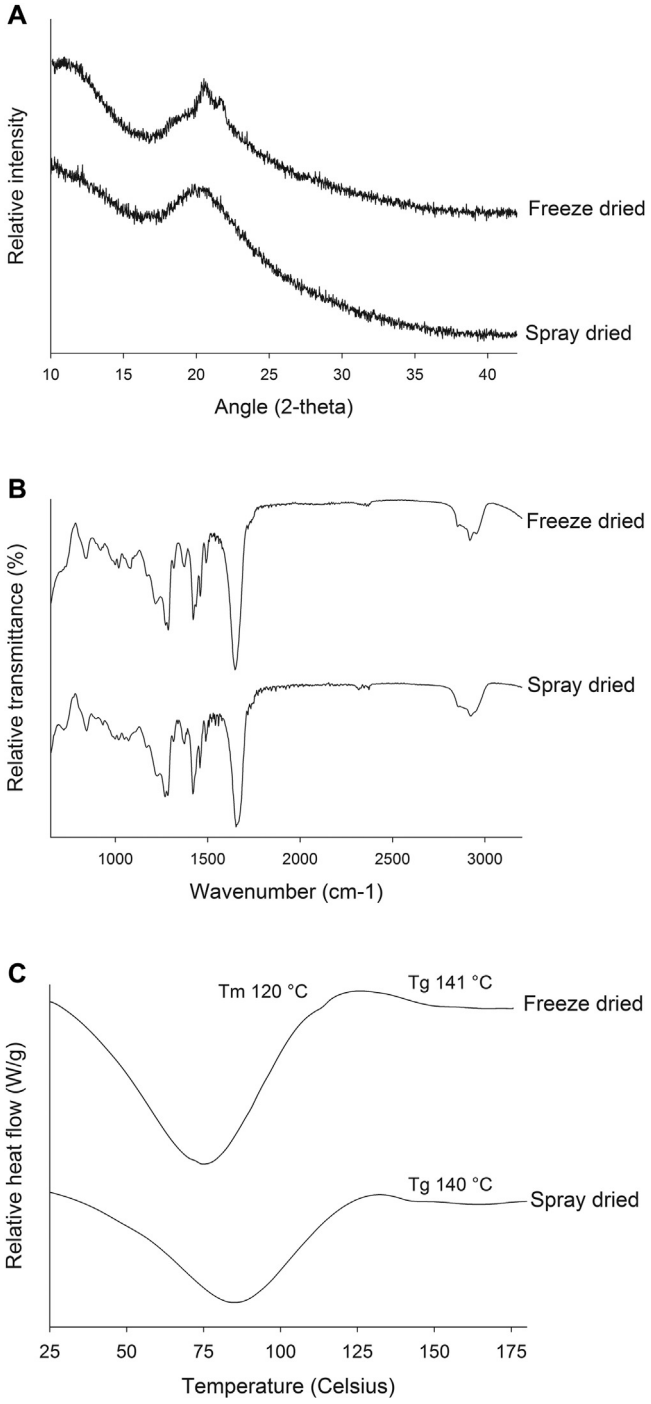

Fig. 3. Comparison between freeze dried and docetaxel spSD by XRD (A), FT-IR (B) and MDSC (C). Results also apply to paclitaxel spSD.

compared to that of docetaxel (0.8 μg/mL versus 6 μg/mL) (Moes et al., 2013c, 2011).

3.1.3. 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 g.

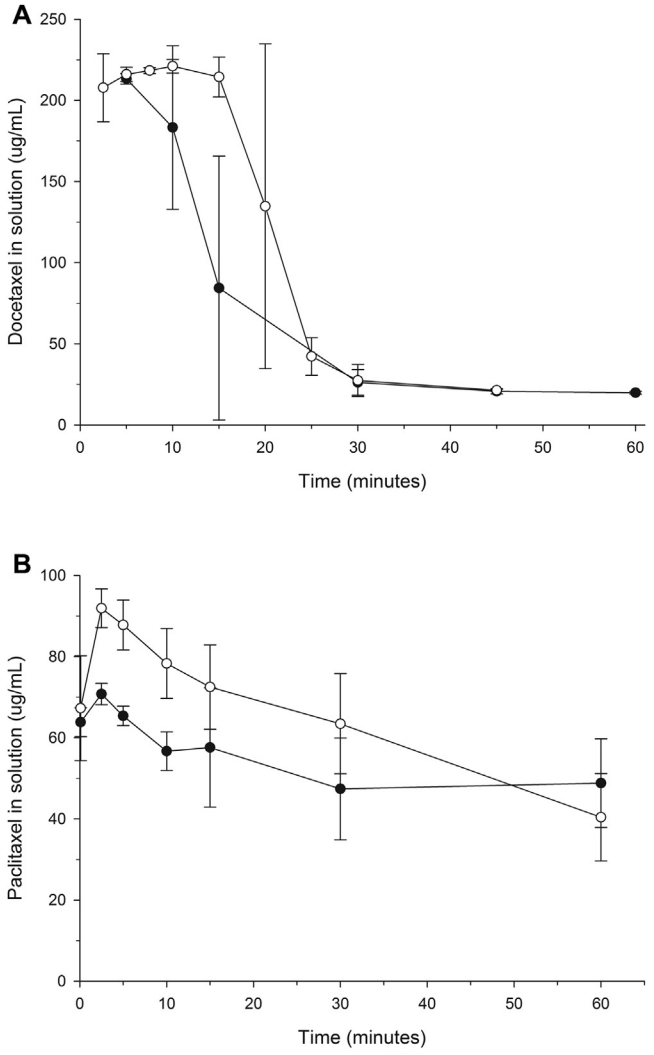

Fig. 4. The solubility of (A) docetaxel and (B) paclitaxel from fdSD (●●●) and spSD (○○○) when an amount equivalent to (A) 6 mg docetaxel (n = 4) or (B) 3 mg paclitaxel (n = 3) was added to 25 mL distilled water 37 °C stirred 720 rpm.

For validation, 3 docetaxel batches and 2 paclitaxel batches were manufactured. Results are shown in Table 1. On average 100.5 ± 6.2 g was obtained per batch at an efficiency of 83.7 ± 1.2% and a production time of 68 ± 3 min. The average yield using the freeze drying production method was 40 g (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 docetaxel/paclitaxel spSD.

3.1.4. Stability

The long-term stability of fdSDs was previously described (Moes et al., 2013b). This study showed that the amorphicity of

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.

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

3.2.1. 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) and MP10 (in case of paclitaxel as active) and the length, width and thickness of each tablet were 16.00 mm × 8.50 mm × 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 min. 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 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 Fig. 5A 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.

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.

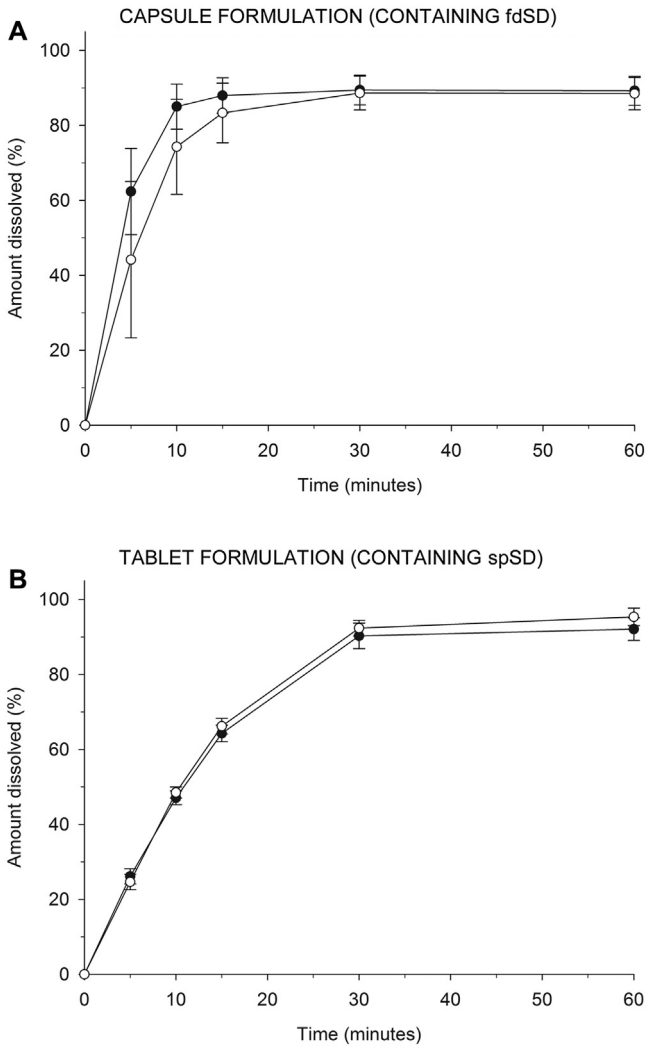

Fig. 5. A) the dissolution of docetaxel from capsules with fdSD (capsule formulation) immediately after production (●●●, n = 24) and after 24 months storage at +15–25 °C (○○○, n = 19), B) the dissolution of docetaxel from tablets with spSD (tablet formulation) immediately after production (●●●, n = 24)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

3.2.2. 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 Fig. 5A. 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 (Moes et al., 2013b). Delayed dissolution is disadvantageous because it might increase in-vivo variability in absorption leading to more variable plasma concentrations. The dissolution of the tablet formulation did not change after 24 months of storage (Fig. 5B), 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.

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.

References

Alam, M.A., Ali, R., Al-Jenoobi, F.I., Al-Mohizea, A.M., 2012. Solid dispersions: a strategy for poorly aqueous soluble drugs and technology updates. Expert Opin. Drug Deliv. 9, 1419–1440.
Baird, J.A., Taylor, L.S., 2012. Evaluation of amorphous solid dispersion properties using thermal analysis techniques. Adv. Drug Deliv. Rev. 64, 396–421.
Beijnen, J.H., Schellens, J.H.M., Moes, J.J., Nuijen, B., 2010. Compositions for the treatment of neoplastic diseases. Patent number WO2010020799.
Chen, Y., Chen, C., Zheng, J., Chen, Z., Shi, Q., Liu, H., 2011. Development of a solid supersaturatable self-emulsifying drug delivery system of docetaxel with improved dissolution and bioavailability. Biol. Pharm. Bull. 34, 278–286.
Démuth, B., Nagy, Z.K., Balogh, A., Vigh, T., Marosi, G., Verreck, G., Van Assche, I., Brewster, M.E., 2015. Downstream processing of polymer-based amorphous solid dispersions to generate tablet formulations. Int. J. Pharm. 486, 268–286.
Démuth, B., Farkas, A., Pataki, H., Balogh, A., Szabó, B., Borbás, E., Sóti, P.L., Vigh, T., Kiserdei, É., Farkas, B., Mensch, J., Verreck, G., Van Assche, I., Marosi, G., Nagy, Z. K., 2016. Detailed stability investigation of amorphous solid dispersions prepared by single-needle and high speed electrospinning. Int. J. Pharm. 498, 234–244.
EMA, 2010. Assessment Report for Docetaxel Teva, Available at www.ema.europa.eu (accessed 13.09.2015).
Engels, F.K., Verweij, J., 2005. Docetaxel administration schedule: from fever to tears? A review of randomised studies. Eur. J. Cancer 41, 1117–1126.
Engels, F.K., Sparreboom, A., Mathot, R.A.A., Verweij, J., 2005. Potential for improvement of docetaxel-based chemotherapy: a pharmacological review. Br. J. Cancer 93, 173–177.
Green, M.C., Buzdar, A.U., Smith, T., Ibrahim, N.K., Valero, V., Rosales, M.F., Cristofanilli, M., Booser, D.J., Pusztai, L., Rivera, E., Theriault, R.L., Carter, C., Frye, D., Hunt, K.K., Symmans, W.F., Strom, E.A., Sahin, A.A., Sikov, W., Hortobagyi, G. N., 2005. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. J. Clin. Oncol. 23, 5983–5992.
Hendrikx, J.J.M.A., Lagas, J.S., Wagenaar, E., Rosing, H., Schellens, J.H.M., Beijnen, J.H., Schinkel, A.H., 2014. Oral co-administration of elacridar and ritonavir enhances plasma levels of oral paclitaxel and docetaxel without affecting relative brain accumulation. Br. J. Cancer 110, 2669–2676.
Huizing, M.T., Rosing, H., Koopman, F., Keung, A.C., Pinedo, H.M., Beijnen, J.H., 1995. High-performance liquid chromatographic procedures for the quantitative determination of paclitaxel (Taxol) in human urine. J. Chromatogr. B. Biomed. Appl. 664, 373–382.

Jibodh, R.A., Lagas, J.S., Nuijen, B., Beijnen, J.H., Schellens, J.H.M., 2013. Taxanes: old drugs, new oral formulations. Eur. J. Pharmacol. 717, 40–46.
Koolen, S.L.W., Oostendorp, R.L., Beijnen, J.H., Schellens, J.H.M., Huitema, A.D.R., 2010. Population pharmacokinetics of intravenously and orally administered docetaxel with or without co-administration of ritonavir in patients with advanced cancer. Br. J. Clin. Pharmacol. 69, 465–474.
Lopez, F.L., Shearman, G.C., Gaisford, S., Williams, G.R., 2014. Amorphous formulations of indomethacin and griseofulvin prepared by electrospinning. Mol. Pharm. 11, 4327–4338.
Malingré, M.M., Beijnen, J.H., Rosing, H., Koopman, F.J., Jewell, R.C., Paul, E.M., Ten Bokkel Huinink, W.W., Schellens, J.H.M., 2001a. Co-administration of GF120918 significantly increases the systemic exposure to oral paclitaxel in cancer patients. Br. J. Cancer 84, 42–47.
Malingré, M.M., Richel, D.J., Beijnen, J.H., Rosing, H., Koopman, F.J., Ten Bokkel Huinink, W.W., Schot, M.E., Schellens, J.H.M., 2001b. Coadministration of cyclosporine strongly enhances the oral bioavailability of docetaxel. J. Clin. Oncol. 19, 1160–1166.
Moes, J.J., Koolen, S.L.W., Huitema, A.D.R., Schellens, J.H.M., Beijnen, J.H., Nuijen, B., 2011. Pharmaceutical development and preliminary clinical testing of an oral solid dispersion formulation of docetaxel (ModraDoc001). Int. J. Pharm. 420, 244–250.
Moes, J.J., Beijnen, J.H., Schellens, J.H.M., Nuijen, B., 2013a. Pharmaceutical development of spray dried oral solid dispersion tablets of docetaxel and ritonavir. Thesis: Development and Clinical Application of Oral Taxanes. J.J. Moes, Amsterdam/Goes, pp. 114–139.
Moes, J.J., Beijnen, J.H., Schellens, J.H.M., Nuijen, B., 2013b. Stability of freeze-dried amorphous solid dispersion formulations used in oral taxane chemotherapy. Thesis: Development and Clinical Application of Oral Dosage Forms of Taxanes. J.J. Moes, Amsterdam/Goes, pp. 88–111.
Moes, J.J., Koolen, S.L.W., Huitema, A.D.R., Schellens, J.H.M., Beijnen, J.H., Nuijen, B., 2013c. Development of an oral solid dispersion formulation for use in low-dose metronomic chemotherapy of paclitaxel. Eur. J. Pharm. Biopharm. 83, 87–94.
Moes, J.J., Stuurman, F.E., Hendrikx, J.J.M.A., Marchetti, S., Huitema, A.D.R., Beijnen, J. H., Schellens, J.H.M., Nuijen, B., 2013d. Pharmacokinetic evaluation of three oral formulations of docetaxel boosted with ritonavir: two single drug formulations vs a fixed-dose combination tablet. Drug Deliv. Transl. Res. 3, 243–251.
Paudel, A., Worku, Z.A., Meeus, J., Guns, S., Van den Mooter, G., 2013. Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: formulation and process considerations. Int. J. Pharm. 453, 253–284.
Persano, L., Camposeo, A., Tekmen, C., Pisignano, D., 2013. Industrial upscaling of electrospinning and applications of polymer nanofibers: a review. Macromol. Mater. Eng. 298, 504–520.
Quan, Q., Kim, D.W., Marasini, N., Kim, D.H., Kim, J.K., Kim, J.O., Yong, C.S., Choi, H.G., 2013. Physicochemical characterization and in vivo evaluation of solid self-nanoemulsifying drug delivery system for oral administration of docetaxel. J. Microencapsul. 30, 307–314.
Seo, Y.G., Kim, D.H., Ramasamy, T., Kim, J.H., Marasini, N., Oh, Y.K., Kim, D.W., Kim, J. K., Yong, C.S., Kim, J.O., Choi, H.G., 2013. Development of docetaxel-loaded solid self-nanoemulsifying drug delivery system (SNEDDS) for enhanced chemotherapeutic effect. Int. J. Pharm. 452, 412–420.
Shanmugam, S., Im, H.T., Sohn, Y.T., Kim, Y.I., Park, J.H., Park, E.S., Woo, J.S., 2015. Enhanced oral bioavailability of paclitaxel by solid dispersion granulation. Drug Dev. Ind. Pharm. 41, 1864–1876.
Singla, A.K., Garg, A., Aggarwal, D., 2002. Paclitaxel and its formulations. Int. J. Pharm. 235, 179–192.
Stuurman, F.E., Nuijen, B., Beijnen, J.H., Schellens, J.H.M., 2013. Oral anticancer drugs: mechanisms of low bioavailability and strategies for improvement. Clin. Pharmacokinet. 52, 399–414.
United States Pharmacopoeia National Formulary (2015) Online. Available at: <www.usp.org/usp-nf>.
Van der Schoot, S.C., Nuijen, B., Flesch, F.M., Gore, A., Mirejovsky, D., Lenaz, L., Beijnen, J.H., 2007. Development of a bladder instillation of the indoloquinone anticancer agent EO-9 using tert-butyl alcohol as lyophilization vehicle. AAPS PharmSciTech 8, E1–E10.
Viana, R.B., da Silva, A.B.F., Pimentel, A.S., 2012. Infrared spectroscopy of anionic, cationic, and zwitterionic surfactants. Adv. Phys. Chem. 2012, 1–14.
Vo, C.L., Park, C., Lee, B.J., 2013. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. Eur. J. Pharm. Biopharm. 85, 799–813.