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Solubility and bioavailability improvement of pazopanib hydrochloride

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ABSTRACT

The anti-cancer drug pazopanib hydrochloride (PZH) has a very low aqueous solubility and a variable oral bioavailability. A new pharmaceutical formulation with an improved solubility may enhance the bioavailability and reduce the variability. A broad selection of polymer excipients was tested for their compatibility and solubilizing properties by conventional microscopic, thermal and spectrometric techniques. A wet milling and mixing technique was used to produce homogenous powder mixtures. The dissolution properties of the formulation were tested by a pH-switch dissolution model. The final formulation was tested *in vivo* in cancer patient following a dose escalation design. Of the tested mixture formulations, the one containing the co-block polymer Soluplus® in a 8:1 ratio with PZH performed best in terms of *in vitro* dissolution properties. The *in vivo* results indicated that 300 mg of the developed formulation yields similar exposure and a lower variability (379 µg/mL*h (36.7% CV)) than previously reported values for the standard PZH formulation (Votrient®) at the approved dose of 800 mg. Furthermore, the expected plasma-$C_{through}$ levels (27.2 µg/mL) exceeds the defined therapeutic efficacy threshold of 20 µg/mL.

1. Introduction

Pazopanib Fig. 1 is a multiple kinase inhibitor that is currently trademarked as Votrient®. It is indicated for the treatment of advanced renal cell carcinoma and advanced soft tissue sarcoma (European Medicines Agency (EMA), 2011; US Food and Drug administration (FDA), 2012). The recommended dose is 800 mg once daily taken without food.

Pazopanib hydrochloride (PZH) was found to exhibit a low aqueous solubility (US Food and Drug administration (FDA), 2009a). The intestinal permeability of PZH is considered to be high (Australian Therapeutic Goods Administration, 2010). Therefore, the drug is classified as a class II compound in the biopharmaceutics classification system (BCS). This implies that its absorption and bioavailability is primarily hindered by solubility.

The commercial formulation of PZH consists of a physical mixture of microcrystalline cellulose, povidone K30, magnesium stearate and sodium starch glycolate in the form of an immediate release tablet. The oral bioavailability of 800 mg of the commercial formulation was found to have a median of 21% (Deng et al., 2013). Pazopanib exhibits a relatively large inter-patient variability in both exposure and plasma concentrations (Hurwitz et al., 2009). The intra-patient variability in these pharmacokinetic parameters was found to be similarly large (de Wit et al., 2015). This large variability may be related to the variable absorption process of pazopanib (Yu et al., 2017).

Since bioavailability and drug exposure are tightly linked, pharmacokinetic parameters are influenced by poor solubility and permeability. Variability in drug exposure may cause drug plasma levels to be inadequately low or toxically high (Herbrink et al., 2015). Enhancing the solubility of PZH through improvement of its formulation may increase the bioavailability and possibly reduce pharmacokinetic variability. An open-label study has been reported that compared crushed Votrient® tablets and a pazopanib suspension to regular Votrient® and that showed the interventions to significantly increase both exposure and plasma concentrations (Heath et al., 2012). Co-administration with food also increases the pazopanib exposure by twofold, further supporting the possible impact of solubility enhancement (Pick and Nystrom, 2012).

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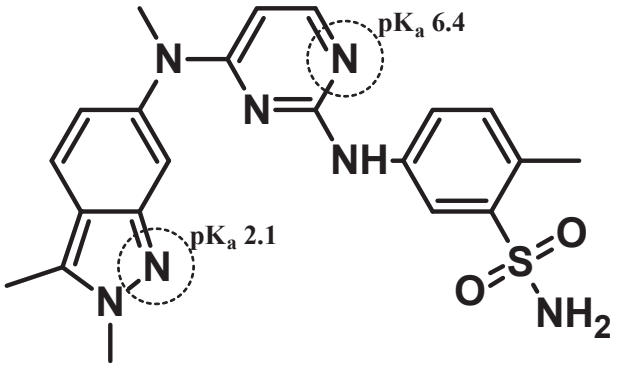

Fig. 1. Molecular structure of pazopanib with pK$_a$ values and associated nitrogen atoms.

As of yet, no clinical study has been performed with an improved-solubility solid oral formulation containing pazopanib hydrochloride, as far as we know.

Improvement of drug solubility may be achieved through the use of various techniques (Aungst, 2017; Berry and Steed, 2017; Rumondor et al., 2016). Amongst the possible methods, the preparation of tablets or capsules from physical powder mixtures with solubility-enhancing excipients is most straightforward. Excipients like these are able to undergo a physical interaction with dissolved drug molecules, thereby stabilizing the dissolved system at higher drug concentrations than would occur in an excipient-free drug solution. As the preparation of physical mixtures most often does not require relatively expensive equipment or extensive product pre-treatment steps, it can be considered as the most economical formulation approach (Li et al., 2017). Furthermore, the manufacture of powder mixtures does not involve thermal processing, as is the case with techniques such as spray-drying and hot-melt extrusion.

Self-emulsifying excipients have been shown to be effective in increasing the oral bioavailability of poorly water-soluble drugs (Mandić et al., 2017; Tran et al., 2017). These excipients can be mixed with drug substances in vastly different ways, amongst which is physical mixing. In solution, these excipients can form emulsions or micelles that incorporate the hydrophobic drug molecules and subsequently solubilize these. Recent successful examples include the solubility improvement of cinacalcet, daptomycin, aciclovir and vinpocetine (Cao et al., 2018; Djekic et al., 2017; Liu et al., 2017; Zupančič et al., 2016). The co-block polymer Soluplus® is a self-emulsifying micelle former that has been demonstrated in several studies to enhance the solubility and oral bioavailability of poorly water soluble drugs (Kang et al., 2016; Lavra et al., 2017; Lee et al., 2015). Soluplus® was also found to greatly improve the solubility and bioavailability of the small molecular kinase inhibitor nilotinib (Herbrink et al., 2017; Jesson et al., 2014).

The aim of this study was to develop such an oral solid dosage form of PZH with an increased solubility and to characterize this formulation both *in vitro* and *in vivo*. This study is first and unique in several aspects concerning the PZH and the formulation design approach. Firstly, it takes into account the excipient compatibilities of PZH. Secondly, excipient selection and formulation composition fine-tuning was performed through the utilization of model pH-switch system to account for different environments in the gastro-intestinal system. Additionally, the nature of the solubility improvement of the best-performing excipient is explored. Finally, the optimal formulation was tested *in vivo* in cancer patients.

The above constitutes an efficient and economical procedure that resulted in new data, especially for the drug PZH and the excipient Soluplus®, that may be of value to future formulation projects.

2. Materials and methods

2.1. Materials

PZH was purchased from Avachem Scientific (San Antonio, TX, USA). Kollidon 12PF, 30. VA64, 90F, polyethylene glycol (PEG) 6000 (6K) and 35,000 (35 K), Lutrol F68, and Soluplus® were kindly supplied by BASF (Ludwigshafen, Germany). Lactose monohydrate was obtained from DFE Pharma (Goch, Germany). Crystalline Cellulose PH102 and gelatine capsules size 1 were purchased from Spruyt Hillen (Ijsselstein, The Netherlands). All other reagents were purchased in analytical grade.

2.2. Fourier transform infrared spectroscopy (FT-IR)

Infrared spectra were recorded from 600 to 4000 cm^{-1} with a resolution of 2 cm^{-1} with a FT-IR 8400S Spectrophotometer equipped with a Golden Gate® (Shimadzu, 's-Hertogenbosch, The Netherlands). A total of 64 scans were averaged into one spectrum.

2.3. Thermogravimetric analysis (TGA)

TGA was performed on a Q50 thermogravimetric analyzer (TA Instruments, New Castle, DE, USA) under a nitrogen flow of 50 mL min^{-1}. The sample (approximately 10 mg) was weighed into a platinum sample pan (TA Instruments). Samples were heated in a temperature range of 25–1000 °C. Temperature calibration was carried out using a high purity magnetic reference (nickel) for Curie temperature determination. The analysis was performed in triplicate and the spectra were averaged. The data were analyzed with the Advantage software v5.5 (TA Instruments).

2.4. Differential scanning calorimetry (DSC)

DSC was carried out with a Discovery DSC (TA Instruments, New Castle, DE, USA) equipped with a refrigerating device that was suitable for direct heat capacity measurements. Temperature scale and heat flow were calibrated with indium reference discs. The sample masses of 3 mg (± 0.3 mg) were placed in Tzero aluminum pans (TA instruments). An empty pan of the same type was used as a reference. The heating rate was set at 10 °C min^{-1} in the range of 25–300 °C. Analysis of the results was carried out with Trios discovery evaluation software version v4.0.2.30774 (TA Instruments). Each analysis was done in triplicate for the different types of samples whereafter the obtained data were averaged.

2.5. Preparation of PZH formulations

Physical mixtures of PZH and polymers were prepared with mortar and pestle in the presence of methyl tert-butyl ether (MTBE, 10 mL) as a wetting agent. PZH was first deagglomerated and suspended in MTBE. Excipient was added following geometric dilution and the components were thoroughly mixed. Subsequently, the mixture was grinded in wetted condition. Batch sizes were between 900 and 9000 mg with a total mixing and grinding time of 10 min. The best performing physical mixture was filled out in cellulose capsules size 1. Content uniformity of screening powder mixtures was determined on 3 samples from each batch. Content uniformity of clinical batches was performed according to the European Pharmacopoeia 9th ed. All samples were dissolved in eluent and were subsequently analyzed using a validated stability-indicating High performance liquid chromatography (HPLC)-UV method: injection volume of 10 µL on a gemini C18 column (50 × 2.0 mm, 4.6 µm; Phenomenex, Torrance, CA, USA) at 55 °C, isocratic elution at 0.4 mL/min with 55%B (A: 10 mM NH_4OH in water; B, 1 mM NH_4OH in methanol) and UV-detection at 268 nm.

2.6. Dissolution testing

The pH-solubility profile of PZH was assessed by measuring dissolved drug in NaCl/HCl and phosphate buffers at different pH values. An excess amount of PZH was placed in a known volume of buffer and allowed to saturate for 1 h after which a sample was analyzed after filtration through an 0.20 µm filter by HPLC-UV.

A collection of different excipients were efficiently screened on their potential solubility improving properties by suspending an excess of PZH in 10% polymer solutions with a pH of 6.8 for 2 and 24 h.

The dissolution behavior of various formulations was determined with a small-scale dissolution test. Briefly, an amount of powder equivalent to 10 mg PZH was added to a 25 mL beaker containing 10 mL medium. The temperature was kept at 37 °C and the medium was stirred at 200 rpm. The commercial formulation (Votrient®) and the capsulated investigational formulations were tested in a larger dissolution volume of 200 mL. Dissolution tests were performed in single pH environment (simulated intestinal fluid without pancreatin (SIF_{sp}), pH 6.8) and a pH-switch system. In this system, the 25 mL beaker contained 10 mL of simulated gastric fluid without pepsin (SGF_{sp}), pH 1.6. The sample was kept in this environment for 30 min after which the pH and composition were changed into that of SIF_{sp} in a step-wise manner by briefly adding phosphate or carbonate buffer while monitoring the pH during the dissolution. The switch of pH and the composition adjustment was typically completed within 32 min with a total endo volume of 20.72 mL for the phosphate system and 22.10 mL for the carbonate system. Samples were taken at designated time points, filtered using a 0.20 µm filter (Millipore, Burlington, MA, USA) and diluted 2-fold with methanol. All samples were subsequently analyzed using the validated stability-indicating (HPLC)-UV method. Each dissolution experiment was carried out in triplicate.

2.7. Micelle size measurements

The presence and size of micelles formed by Soluplus® were detected and measured through dynamic light scattering (DLS) by using a Zetasizer Nano S90 particle size analyzer (Malvern Instruments, Worcestershire, UK). Samples were taken from the dissolution media at different time points for micelles, placed in polystyrene cuvettes (Malvern Instruments) and analyzed in threefold at 10 analyses per measurement.

2.8. Electron microscopy

The morphology and particle size of the bulk and physical mixture powders were studied using scanning electron microscopy (SEM). Samples were placed on conducting double sided adhesive tape and on an aluminium holder. Samples were sputter-coated with gold using a SCD 040 sputter coater (Oerlikon, Balzers, Liechtenstein). Imaging was performed through back-scattering with a Sigma Field Emission Gemini system (Zeiss, Oberkochen, Germany). Each microscopy analysis was applied on three separate samples.

The shape and size of micelles were visualized with Transmission Electron Microscopy (TEM). Samples from dissolution media were diluted 100 times and were applied on Agar1 formvar/carbon coated copper grids (van Loenen instruments, Zaandam, The Netherlands). Negative staining with 2% (w/w) phosphotungstic acid was applied with subsequent drying for 10 min prior to the microscopy. Recording was performed with a Tecnai T12 G2 Spirit Biotwin set-up (FEI company, Hillsboro, OR, USA).

2.9. X-ray powder diffraction (XRD)

X-ray diffraction of powder samples was performed with a 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. Samples were scanned at a current of 30 mA and a tension of 40 kV. The scanning range was 10–60 degrees 2-θ, with a step size of 0.020 degrees 2-θ and a scanning speed of 0.002 degrees 2-θ per second. Analyses were performed in triplicate.

2.10. Residual solvents

Residual MTBE was determined with capillary gas chromatography (GC) analysis. Samples of approximately 20 mg of powder were dissolved or suspended in 1.0 mL water and shaken for 3 h. Aliquots were subsequently filtered and transferred to autosampler vials. Analyses were performed using 6890 N GC system (Agilent, Santa Clara, CA, USA) equipped with a Flame-ionization detector (Agilent) and an RTX-1301 capillary column (3.0 µm film, 30 m x 0.53 mm; Restek Corporation, Bellefonte, PA, USA). Analyses were performed in triplicate.

2.11. Clinical study design

The clinical study was designed as an open-label, proof-of-concept study. The pharmacokinetic parameters of pazopanib after administration of formulation-filled capsules were determined in cohorts consisting of 3 patients per dose level. The capsules were administered in combination with approximately 150 mL tap water after an overnight fast. The study objective was to find the dose of the formulation that could provide similar PK parameters as 800 mg of Votrient®. The dose level of the first cohort was set on 100 mg (4 capsules of 25 mg). Doses were increased in-between cohorts with a cap at 200% of the previous dose. This continued for a maximum of 3 cohorts, after which an expansion of 3 patients at the highest dose cohort was planned for statistical purposes.

A complete physical examination along with a review of the medical history and concomitant medication was performed before inclusion. During the study, vital signs, WHO performance status, weight, hematology, blood chemistry, and adverse events were monitored. The study protocol was approved by the medical ethics committee of the Netherlands Cancer Institute; all patients had to give written informed consent prior to the start of the study. The study was registered on ClinicalTrials.gov under NCT02768441 and at EudraCT under 2016-001105-16.

2.12. Pharmacokinetics and bioanalysis

Blood samples were drawn in potassium EDTA tubes at baseline and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after pazopanib intake. Samples were immediately centrifuged at 2000*g* for 10 min at 4 °C. Plasma was stored at or below −20 °C until analysis. Pazopanib was quantified in plasma by use of HPLC with tandem mass spectrometric detection (LC-MS/MS) as described previously (Herbrink et al., 2016).

2.13. Data analysis

For all quantitative analyses, results were pooled per sample type and means and standard deviations (SD) were calculated.

Individual pharmacokinetic parameters were analyzed using descriptive pharmacokinetic methods and validated R scripts (R version 3.3.2). The areas under the plasma concentration–time curves up to 24 h ($AUC_{0\text{-}24}$) were estimated by the linear trapezoidal rule for the absorption phase and the logarithmic trapezoidal rule for the elimination phase. The observed maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}) and the time to the maximum plasma concentration (t_{max}) were reported.

Table 1
Data (mean (SD)) from the compatibility study of PZH and excipient:PZH (1:1) physical mixtures after 6 months of storage at 30 °C and 60%RH.

Powder	DSC Type	Temperature (°C)	TGA T_{onset} (°C)	FTIR Indication of chemical interaction*:	HPLC-UV Content (%)
PZH	–	–	190 (3.2)	–	–
MCC	T_g	160 (0.5)	260 (4.1)	None	99.8 (2.2)
MCC:PZH		158 (1.0)	185 (3.0)		
LM	T_m	221 (1.7)	301 (2.9)	Yes	94.7 (4.2)
LM:PZH		208 (3.1)	187 (2.4)		
SLP	T_g	69 (0.6)	248 (3.4)	None	101.2 (3.2)
SLP:PZH		70 (1.1)	192 (2.7)		
12PF	T_g	87 (0.4)	183 (5.1)	None	99.6 (0.5)
12PF:PZH		86 (0.8)	185 (1.7)		
K30	T_g	147 (0.2)	175 (2.8)	None	99.3 (1.6)
K30:PZH		147 (0.3)	177 (3.5)		
VA64	T_g	97 (0.8)	203 (4.6)	None	98.9 (4.8)
VA64:PZH		96 (0.7)	189 (2.0)		
90F	T_g	153 (0.6)	180 (3.9)	None	99.7 (1.4)
90F:PZH		151 (0.5)	182 (3.0)		
6 K	T_m	61 (2.1)	197 (2.1)	None	96.7 (5.2)
6 K:PZH		55 (2.5)	134 (4.5)		
35 K	T_m	70 (3.2)	201 (1.9)	None	94.6 (4.5)
35 K:PZH		65 (2.4)	147 (2.1)		
F68	T_m	53 (1.1)	203 (2.0)	None	100.4 (1.8)
F68:PZH		53 (2.8)	195 (2.8)		

MCC, Microcrystalline Cellulose; LM, Lactose monohydrate; SLP, Soluplus®; 12PF, Kollidon 12PF; K30, Kollidon 30; VA64, Kollidon VA64; 90F, Kollidon 90F; 6 K, PEG 6000; 35 K, PEG 35,000; F68, Lutrol 68F. *Indicated by deviation from overlap spectrum (t = 0) of more than 1%.

3. Results

3.1. Powder mixing

Dry mixing of PZH and excipients did not yield homogenous mixtures. Physical mixtures were therefore produced by wet milling and mixing. For the wetting, several organic solvents were tested for their possible undesirable ability to dissolve (> 0.5 µg/mL) one or both components of the physical mixture. Only MTBE was found to not dissolve or react with any of the components. Additionally, MTBE evaporates relatively quickly, leaving less than 100 ppm after 10 min as determined by GC analysis. Additionally, it was found that powder mixtures had appropriate uniformity of content (content > 98% and SD < 2%) after a mixing time of 10 min.

3.2. Excipient compatibility

The excipient compatibility study was carried out for 6 months at 30 °C in the dark. The results are listed in Table 1. Of the examined excipient-PZH combinations, the mixtures with lactose monohydrate showed signs of interaction in FTIR. DSC analysis showed shifts in melting temperatures for lactose monohydrate, PEG 6K and PEG 35K. Furthermore, TGA revealed a shift in degradation temperatures from 190 °C for PZH for the PEG 6K and the PEG 35K combinations. A reduced content was found by HPLC-UV (for each of the three excipients suggesting chemical reactivity. The formulation development study was continued with the excipients that displayed no interaction with PZH.

3.3. Dissolution

Fig. 2 a presents the dissolution curves of both Votrient® tablets, the pure PZH drug material and the pH solubility curve at equilibrium (2h) of PZH. The initial 30 min of the dissolution curve represents the stomach (pH 1.6) in which the percentage of dissolved PZH from Votrient® accumulates up to approximately 47%. At time points 35, 40 and 45 min a relatively small increase to 52% in the dissolved drug was observed when the pH rises from 1.6 to 3.2. From 50 min on the dissolved amount decreases to less than 0.5% when the pH is raised above 5.2 and is subsequently adjusted to 6.8. The same behavior is seen with the pure PZH of which the pH-solubility profile in a series of buffers is shown in Fig. 2b.

The excipient screening experiments were performed for both 2 and 24 h (Fig. 3a). PZH has a solubility of approximately 0.1 µg/mL in this buffer system after both periods. The tests show that the addition of Kollidon VA64, Soluplus®, Kollidon 30 and Kollidon 90F to the formulation provided the highest PZH concentrations after both 2 h and 24 h.

Several physical mixtures with different ratios between drug and excipient were produced (Table 2) and their dissolution behavior was tested using the pH-switch system. The results are shown in Fig. 3b and Table 2. After the initial solubility increase upon elevating the pH, the concentration of PZH in all of the Kollidon powder mixes collapsed to > 1% before the pH reaches 6.8. A slight concentration increase beyond the pH-switch was seen for the 1/5 Soluplus® mixture, but this collapsed around pH 6.0. The 1/10 Soluplus® mixture proved to be able to maintain the concentration of PZH. Furthermore, it increased solubility to 100% during the pH increase to 6.8. Additional physical mixtures of PZH and Soluplus® were prepared and subjected to dissolution tests to further optimize the composition between the two components. The results are presented in Fig. 4a. Increasing the amount of Soluplus® relative to PZH increased solubility up to 8 equivalent parts (Fig. 4b). This composition was chosen as the best performing formulation and was designated PZHSol001 and filled out in cellulose capsules size 1 with a potency of 25 mg per capsule.

3.4. Characterization of the final formulation

PZHSol001 shows an increase in solubility upon the transformation from SGF_{sp} to SIF_{sp}. It was observed that this increase was accompanied by the medium becoming more clear. Initially, in SGF_{sp}, the solution was opaque. Analysis of medium samples by TEM clearly showed the presence of uniformly shaped micelles at both stomach and intestinal pH values (Fig. 5).

At different time points during the dissolution in both phosphate and carbonate systems, samples were taken to measure the micelle diameters, Fig. 5a and b. In both systems, the micelle diameter initially increases upon pH increase from 91 ± 4.2 nm in SGF_{sp} to 194 ± 10 nm at pH 1.8 in the carbonate system and to 169 ± 8.2 nm at pH 2.6 in the phosphate system. In both systems, the micelle diameter decreased at higher pH values up to 6.8 to 80 ± 2.1 nm

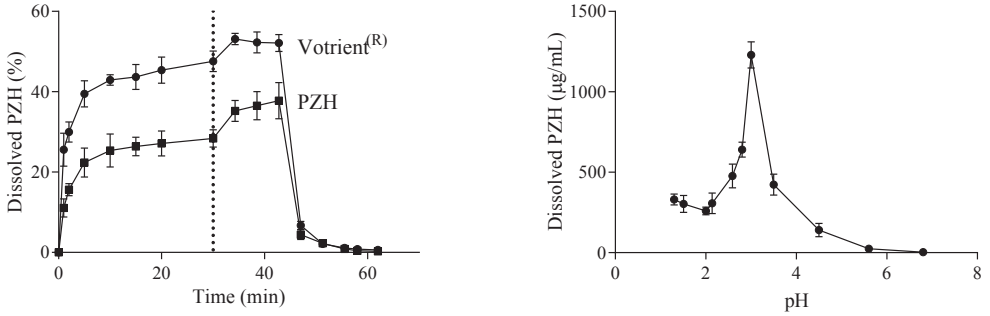

Fig. 2. A. Dissolution curves of Votrient® tablets and PZH bulk powder; B. pH-solubility curve of PZH. The dotted line indicates the start of the pH-switch.

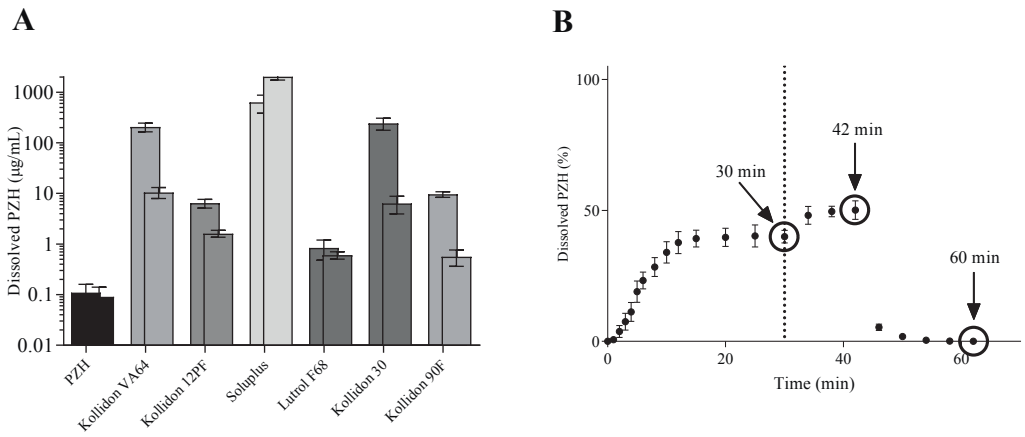

Fig. 3. A. Excipient screening results: PZH solubility after 2 (left bars) and 24 h (right bars); B. Dissolution curve of PZH:Kollidon VA64 mixture (1:1, w/w) with dissolution points referring to Table 2.

(carbonate) and 101 ± 5.0 nm (phosphate). The micelle size of Soluplus® in absence of PZH showed no significant increases in either system. Fig. 5c shows TEM micrographs of micelles from the physical mixture of PZH and Soluplus® 1:8 in SGF_{sp} and SIF_{sp}. The micrographs confirm the similarity of sizes in SGF_{sp} and SIF_{sp} and the magnitude of the micelle diameters as measured by DLS.

Fig. 6 presents the SEM micrographs of PZH and Soluplus® bulk powder and PZHSol001 powder. The images illustrate the size difference between the drug and excipient particles. Additionally, it shows that the wet mixing and milling method reduces the overall particle size of the formulation. The size of the Soluplus® particles is especially decreased, which is beneficial to the mixture homogeneity.

Both bulk powder and final product were analyzed using XRD (Fig. 6). The pattern of Soluplus® did not display characteristic 'crystal' reflections and can, therefore, be considered amorphous. The obtained pattern of PZHSol001 exhibited the same reflections as the pattern of PZH, albeit reduced in intensity due to the presence of Soluplus®.

After 12 months of storage in open containers at 20–25 °C and 60% relative humidity (RH) and after 6 months in open containers at 40 °C and 75% RH the formulation was subjected to dissolution and assay tests. In this period, no significant changes occurred in drug content and dissolution properties. The moisture content did show an increase of 2.7% (60% RH) and 4.5% (75% RH).

Table 2
Components, weight ratios, content uniformity (mean (SD)) (n = 3) and essential dissolution time points (means (SD)) (n = 3) of PZH physical mixture formulations.

Formulation	Components	Weight ratio (w/w)	Content uniformity (%)	Dissolution (%)*		
				30 min	42 min	62 min
A	PZH	–	–	28 (2.2)	38 (4.5)	0.3 (0.0)
B	PZH, Kollidon VA64	1/1	98.4 (1.2)	40 (2.4)	50 (2.0)	0.1 (0.0)
C	PZH, Kollidon VA64	1/5	99.1 (1.0)	69 (5.4)	81 (4.1)	0.1 (0.0)
D	PZH, Kollidon VA64	1/10	100.2 (0.5)	99 (3.0)	100 (4.0)	0.3 (0.1)
E	PZH, Soluplus®	1/1	99.4 (0.6)	40 (2.5)	50 (2.1)	0.1 (0.0)
F	PZH, Soluplus®	1/5	99.2 (0.8)	56 (2.7)	70 (2.6)	2.5 (0.2)
G	PZH, Soluplus®	1/10	99.5 (0.3)	83 (2.3)	98 (3.1)	100 (2.3)
H	PZH, Kollidon 30	1/1	98.7 (1.1)	40 (3.6)	49 (2.4)	0.1 (0.1)
I	PZH, Kollidon 30	1/5	98.8 (1.8)	67 (2.3)	81 (2.8)	0.2 (0.1)
J	PZH, Kollidon 30	1/10	99.2 (1.4)	97 (3.5)	100 (8.7)	0.5 (0.1)
K	PZH, Kollidon 90F	1/1	99.0 (0.4)	40 (2.1)	48 (3.2)	0.0 (0.0)
L	PZH, Kollidon 90F	1/5	99.5 (0.7)	55 (2.5)	66 (3.6)	0.0 (0.0)
M	PZH, Kollidon 90F	1/10	99.3 (0.9)	77 (5.1)	93 (1.2)	0.0 (0.0)

* Time points correspond to the dissolution time points as indicated inFig. 3.

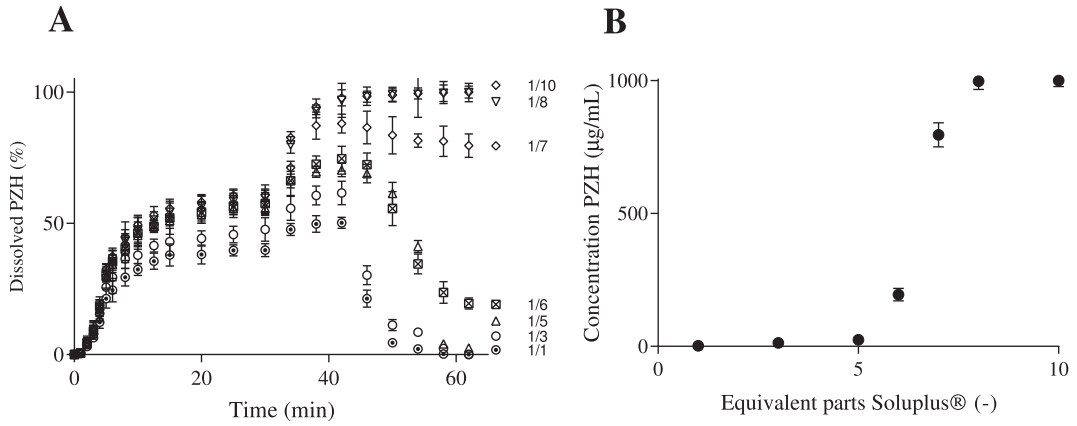

Fig. 4. A. Dissolution curves of PZH:Soluplus® with different compositions as indicated on the right. The dotted line indicates the start of the pH-switch; B. Solubility of PZH from physical mixtures with Soluplus® as a function of the equivalent parts of Soluplus® with a maximum of 1 mg/mL.

3.5. Human in vivo clinical study

Twelve evaluable patients were included in the study, relevant patient characteristics are listed in Table 3. The cohort doses were as follows: cohort 1: 100 mg (n = 3), cohort 2: 200 mg (n = 3), cohort 3: 300 mg (n = 3). Cohort 4 (n = 3) was an extension of cohort 3. All patients received PZHSol001 25 mg capsules at the designated cohort dose level. Fig. 7 shows the mean concentration–time curves of pazopanib after administration for each dose level. The relevant pharmacokinetic parameters (T_{max}, C_{max}, C_{min}, and $AUC_{0\text{-}24}$) and the variations thereof are shown in Table 4. for the cohorts of PZHSol001.

The single dose administrations of PZHSol001 were well tolerated. Adverse events that were possibly related to the administration of PZHSol001, were: bleeding gums, headache, productive cough (all CTCAE grade 1; n = 1; dose 300 mg).

4. Discussion

4.1. Powder mixing

Dry mixing of the powder components did not yield homogenous mixtures, mainly due to the electrostatic charging of PZH. The size initial difference between excipient and drug may also account for this as shown in the SEM micrographs. For this reason, the powder components were wetted prior to mixing and left to dry in a desiccator thereafter. This approach allowed for the deagglomeration of PZH particles and sharply reduced particle sizes of both PZH and the excipients, especially for Soluplus®, and offers an explanation for the more homogenous powder mixtures. Particle size may also influence mixing efficiency. The results from the content uniformity show that the mixing and grinding approach is sufficient in minimizing the effect of the particle size on the homogeneity of the powder mixtures. Additionally, this was also found to be reproducible.

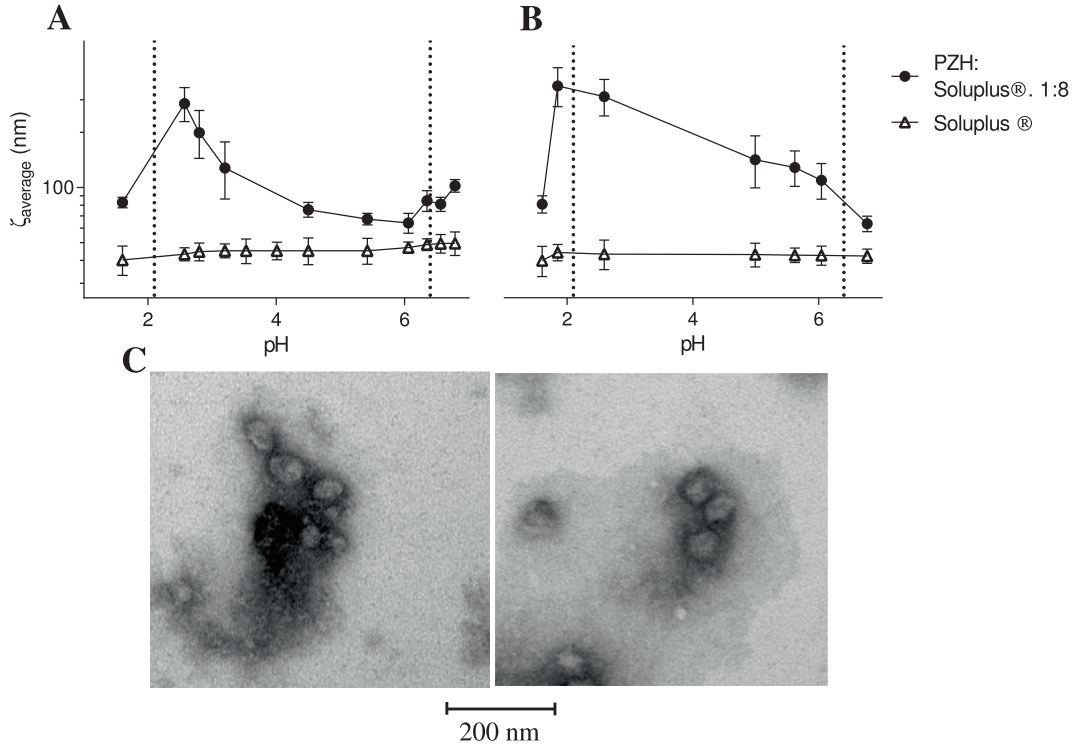

Fig. 5. Results from the micelle analyses. Mean micelle diameters as a function of the pH of the dissolution medium: A. Phosphate SIF_{sp}; B. Carbonate SIF_{sp}; C. TEM micrograph of PZH:Soluplus® micelles from a 1:8 physical mixture in SIF_{sp} (Magnification: 120000, high voltage: 100 kV), left: in SGF_{sp}, right: in phosphate SIF_{sp}.

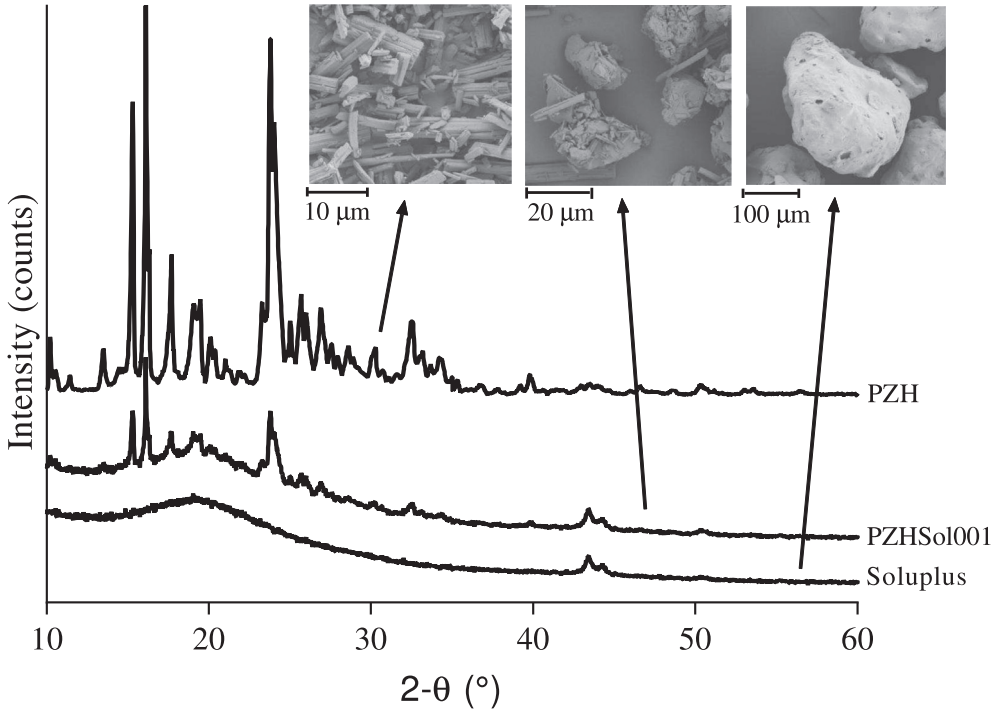

Fig. 6. XRD patterns of PZH bulk, Soluplus® bulk and PZHSol001 (physical mixture PZH:Soluplus®, 1:8). Inserts show SEM micrographs (extra high tension: 2.00 kV) of the corresponding materials (magnifications: 500×, 50× and 250× respectively).

Table 3
Patient characteristics of the clinical study per cohort.

Parameter	N		
Cohort	1	2	3 & 4
Dose	100 mg	200 mg	300 mg
Sex			
Male	1	2	5
Female	2	1	1
Age (years)			
Median	63	56	61
Range	45–73	40–60	47–74
Ethnic background			
Caucasian	3	3	4
African			2
WHO performance status			
0	2	3	6
1	1		
Pathological diagnosis			
Soft Tissue	1	2	2
Kidney	1		
Skin	1		1
Breast		1	
Gastric			2
Colorectal			1
Number of prior treatments (chemotherapy)			
0	1	1	2
1	1	1	4
2	1	1	

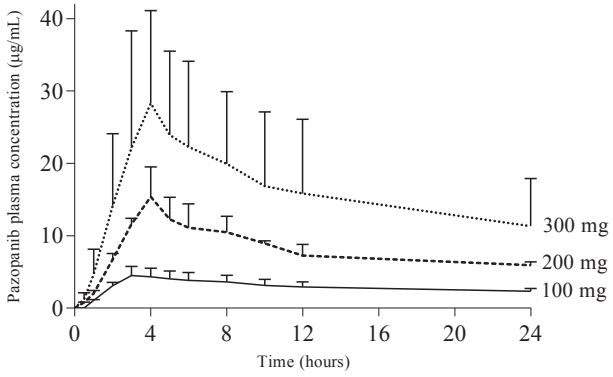

Fig. 7. Mean plasma concentration-time curves of pazopanib after oral administration of single PZHSol001 (physical mixture PZH:Soluplus®, 1:8) doses as 25 mg capsules; doses are indicated on the right, 100 mg (n = 3), 200 mg (n = 3) and 300 mg (n = 6).

4.2. Excipient compatibility

Drug-excipient interactions have been shown to negatively affect the pharmaceutical properties of drug formulations. The interaction with lactose monohydrate may be due to the secondary amine and/or sulfonamide structures of PZH undergoing the Maillard reaction (Sheth et al., 1990; Wirth et al., 1998). The mechanism behind the interaction with PEG 6 K and PEG 35 K is unknown but a similar drug-excipient interaction has been described before (Malan et al., 1997).

4.3. Dissolution

The pH-solubility profile of PZH displays an expected low solubility at higher pH levels that seems to be in line with its pK_a values of 2.1 and 6.4 (US Food and Drug administration (FDA), 2009). The maximum solubility was observed around a pH of 3 below which the solubility decreases. The cause of this may be a common ion effect with Cl- ions. These may form apolar ion-pairs with the positively charged pazopanib in solution which causes crystallization (Miyazaki et al., 1979).

As it is important to take the different regions of the gastrointestinal tract into consideration, the formulation needed to increase and maintain the solubility of PZH at both stomach and intestinal pH-values and compositions. To evaluate this during the *in vitro* testing of experimental formulations, a pH-switch was included after 30 min during

Table 4
PK parameters from the patients of the clinical study (means (CV%)) and PK parameters from the Votrient ® phase I trial (Hurwitz et al., 2009).

Dose (mg)	Parameter	PZHSol001	Votrient®
100	n	3	3
	t_{max} (h)	2.65 (23.5)	4.0*
	C_{max} (μg/mL)	4.52 (39.2)	6.5 (25.7)
	C_{min} (μg/mL)	2.31 (38.9)	2.8 (11.2)
	$AUC_{0\text{-}24}$ (μg/mL*h)	70.3 (40.3)	96.9 (17.6)
200	n	3	3
	t_{max} (h)	4.01 (0.66)	3.0*
	C_{max} (μg/mL)	15.4 (28.4)	7.5 (54.5)
	C_{min} (μg/mL)	5.9 (12.1)	2.9 (53.6)
	$AUC_{0\text{-}24}$ (μg/mL*h)	192 (18.1)	104.5 (54.6)
300	n	6	–
	t_{max} (h)	4.02 (1.11)	–
	C_{max} (μg/mL)	28.4 (33.1)	–
	C_{min} (μg/mL)	11.3 (41.2)	–
	$AUC_{0\text{-}24}$ (μg/mL*h)	379 (36.7)	–
800	n	–	10
	t_{max} (h)	–	3.5*
	C_{max} (μg/mL)	–	19.4 (1 7 6)
	C_{min} (μg/mL)	–	9.4 (2 4 0)
	$AUC_{0\text{-}24}$ (μg/mL*h)	–	275.1 (2 0 3)

* No CV values were reported.

the dissolution experiments. This was done to simulate the worst-case scenario of short residence time in a fasted stomach (Mudie et al., 2010).

The formulation components in Votrient® seem to only increase PZH solubility by a factor 1.5 at a low pH. No improvement was seen at higher pH levels The observed curves were in accordance with the pH solubility curve of PZH. The solubility increase is less substantial than is seen in the pH profile. This may be due to the dissolution phosphate buffer and the relative short after which the samples were taken from the dissolution vessel compared to the samples of the pH-profile. According to the dissolution of Votrient® and pure PZH results, the bottleneck for the dissolution of PZH lies within its poor solubility at higher pH values. Therefore, the starting point of this study was to increase the solubility of PZH at pH 6.8. To simulate a worst-case-scenario where the crystalline drug is solubilized by an excipient at a pH in which it is very poorly soluble, the initial excipient-screening was performed at SIF_{sp} with pH 6.8. The observed solubility increases in this set-up may be the result of non-complexing hydrophilic and/or hydrophobic interaction between the excipients and the drug molecules in solution (Bansal et al., 2007; Li et al., 2012). The increase in solubility by Soluplus® between 2 and 24 h can possibly be caused by the relatively high viscosity of the solution, in comparison to the other solutions. This slows the process of wetting and dissolution to continue after the initial 2 h.

The Kollidon excipients all increase the solubility of PZH in SGF_{sp}, this was not seen for any of the Soluplus® formulations. This may be due to the time effect, as was seen in Fig. 3A. The increase in PZH solubility in SGF_{sp} could only be maintained into SIF_{sp} if a 'parachute' effect of the excipients were to occur. After the initial solubility increase upon elevating the pH, the solubility of PZH in all of the Kollidon powder mixes collapsed. None of the Kollidon types were capable of providing the 'parachute' effect. This parachute effect was observed for the Soluplus® mixtures of 5 equivalent parts and up. An explanation for this observation can be found in the micelle-forming capacity of Soluplus®, which the Kollidon excipients do not have. The possible interactions between PZH and the Kollidon excipients in solution are apparently not enough to sustain the solubility of PZH when the pH of the solution increases.

From the investigation of the influence of the ratio between PZH and Soluplus® equivalent parts in the formulation (Fig. 4B), it is clear that reducing this ratio below 8 equivalent parts strongly reduces the solubility of PZH The composition 1/8 was therefore chosen as the best performing formulation. Although this makes for a bulky dosage form, possible bioavailability improvement may correct by necessitating less intake of PZH, and hence, the formulation. This phenomenon may be the results of the number of Soluplus® molecules that are needed to efficiently form micelles smaller than 200 nm with PZH. It may be that below the composition 1/8, the formation of small micelles is not possible. In such a situation the relative shortage of Soluplus® may cause bulky and unstable micelles to form along with undissolved PZH that agglomerates and precipitates over time. At or above the 1/8 composition, sufficient Soluplus® is present to adequately incorporate PZH molecules in small micelles and thus prevent precipitation.

4.4. Characterization of the final formulation

With the Soluplus® formulation, initially an opalescent solution in SGF_{sp} was observed, which is in accordance with the observations that maximally approximately 50% of PZH was dissolved. In the relatively short period of time at stomach pH, the Soluplus® does not seem to solubilize PZH to a significant extent above that of pure PZH at the studied concentrations. Thus, Soluplus® seems to be unable to overcome the common-ion effect. The formation of micelles by Soluplus® has been described in literature. As it may provide an explanation for the solubilizing effect on PZH, micelles were studies by TEM and their size was determined.

An explanation for the behavior of the PZH and Soluplus® combination may be found in the pH-solubility relationship and the pK_a values of PZH. At pH values below 2.1, the dissolved part of PZH is diprotonated and is likely not to be included in the micelles of Soluplus® because it can sustain itself in solution, this is supported by the fact that the micelle size in this region of pH is relatively small.

As the pH increases to 3.0, the solubility of unsolubilized PZH reaches a maximum. Additionally, in this pH region between 2.1 and 6.4, PZH molecules are largely monoprotonated. It may be hypothesized that the PZH molecules in such a state interact very differently with the Soluplus® micelles, as was seen with the drug nilotinib (Herbrink et al., 2017). The PZH may then partly be located in the outer, more hydrophilic ranges of the micelles as they need solubilization for the non-protonated part of the molecule which is then located in the more hydrophobic parts of the micelle. This may, in turn, change the overall size of the micelles. As the solution equilibrium of PZH molecules is directed towards the Soluplus® micelles just above pH 3.0, more 'room' is made available in the medium for undissolved PZH to dissolve. This hypothesis is supported by the fact that additional PZH dissolved above pH 3.0 and that no new precipitation of crystalline PZH is observed in this pH region.

At pH levels above 6.4, PZH is largely unprotonated. Without solubilization, the drug molecules will precipitate virtually instantly from the dissolution medium. In the presence of Soluplus® PZH is fully incorporated into the hydrophobic parts of the micelles. To test this hypothesis, spectroscopic studies (with labeled PZH) should be performed in the future to localize PZH in the micelles. Additionally, possible release and/or transfer of PZH from and between micelles should be studied in the future to offer more clarity about the nature of the solubility increase. The clinical relevance of these phenomena is still unclear as the micelles seem to minimize to their stomach size at pH > 6. Therefore, *in vivo* investigation was crucial.

The filtration prior to HPLC analysis was performed using filters with a pore size of 200 nm. The increase in micelle diameter upon a change in pH is therefore not reflected in a change in the concentration of dissolved PZH. An increase in micelle diameter may prove troublesome for the uptake *in vivo*, however. Micelles with an increased diameter may be prone to agglomerate and precipitate at a much faster rate.

This increase in micelle diameter was observed to be more profound

in the formulations with a smaller number of equivalent parts of Soluplus®. It may in part explain the observed loss of solubility at higher pH values of these formulations. To test whether the pH-dependent increase in micellar diameter was not related to the dissolution medium, a pH-switch system was designed that leads to a SIF_{sp} with a carbonate buffer. The same trend in micelle size was observed in this system as well.

The XRD experiments showed that the pattern of PZH is consistent with patent data on the anhydrous polymorph Form I (Chava et al., 2014) and that the obtained pattern of PZHSol001 exhibits the same peaks as the pattern of PZH, albeit reduced in intensity due to the presence of Soluplus®. This indicates that no solid phase transitions have occurred during the production of PZHSol001.

4.5. Human in vivo clinical study

The PK parameters of PZH after a single administration of 100 mg PZHSol001 in the first cohort were found to be similar to the reported parameters of 100 mg Votrient®. Although mean values differ between the two formulations, the CV-ranges overlap and drug absorption may, therefore, be comparable. It could be that the absolute amount of Soluplus® present from 100 mg is not sufficient to solubilize PZH in the volumes of the gastrointestinal tract. As an increased dose also increases the absolute amount of Soluplus®, the 2nd cohort dose was set at the maximum of 200 mg.

A more-than-linear increase in the PK parameters was observed for the 200 mg dose. An apparent difference is observed between the PK parameters of a single 200 mg dose of the formulations. 200 mg of PZHSol001 yields higher plasma concentrations (C_{max} and C_{min}) and exposure than a similar dose of Votrient®. A strong relationship between C_{SSmin} > 20 µg/mL and tumor shrinkage and progression-free survival has been established (Verheijen et al., 2017). Based on the results of the 200 mg cohort and an accumulation index of 2.41 (assuming a half-life of 31 h and a dosing interval of 24 h), the observed C_{min} is not sufficient for clinical application (theoretical C_{SSmin} of 14.2). Therefore, the dose for the 3rd cohort was increased to 300 mg. The PK parameters roughly doubled after the dose increase from 200 to 300 mg. Furthermore, the parameters were slightly higher than earlier data on Votrient® 800 mg. The estimated C_{SSmin} for 300 mg PZHSol001 was 27.2 µg/mL, which is well above the defined efficacy threshold.

The non-linear increase in PK parameters in relation to the dose might be caused by the concentration of Soluplus® present in the immediate vicinity of PZH in the gastrointestinal system. As was observed *in vitro*, the solubilizing effect of Soluplus® on PZH occurs in an apparent exponential fashion. Assuming that the stomach and intestinal dissolution volume *in vivo* were approximately constant in the study population, the linearly increasing concentration of Soluplus® facilitated a more-than-linear solubilizing effect. This means that although the composition of Soluplus® and PZH remained constant throughout the cohorts, the absolute amount of Soluplus® per volume may have been an important factor. This might have had a similar effect on the absorbed amount of PZH and consequently, the PK parameters. Furthermore, the formulation itself as encapsulated loose powder may have contributed to an increased absorption by increasing the overall surface area for dissolution. This was also seen in a study that compared the PK of whole Votrient® tablets to crushed tablets (Heath et al., 2012).

An additional observation was the low variability in PK parameters of PZHSol001 compared to the parameters of Votrient®, albeit that the numbers are small.

Based on these results, 300 mg PZHSol001 might be a usable alternative to 800 mg Votrient®. The large overall volume of this dose level (12 capsules, size 1) makes the administration possibly troublesome. Special attention should therefore be aimed at minimizing the formulation volume with regard to the administration burden. This could be achieved through the development of a tablet formulation for example. Furthermore, future studies also need to be directed to the scale-up and the stability of the formulation.

5. Conclusions

In this study, we proved that the solubility of PZH can be significantly improved by formulation of the drug with the excipient Soluplus®. The optimal composition that produced full solubility in SIF_{sp} was 1/8 PZH/Soluplus® (PZHSol001). In a clinical-proof-of-concept study, we demonstrated that the improved-solubility formulation PZHSol001 25 mg capsule in a dose of 300 mg produces a clinically useful pharmacokinetic profile.

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