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Research paper

Development of a polymeric micellar formulation for valspodar and assessment of its pharmacokinetics in rat

Ziyad Binkhathlan [a], Dalia A. Hamdy [a], Dion R. Brocks [a], Afsaneh Lavasanifar [a,b,*]

[a] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada
[b] Department of Chemical and Material Engineering, University of Alberta, Edmonton, Alberta, Canada

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ABSTRACT

The aim of this study was to assess the potential of polymeric micelles to solubilize valspodar and modify its pharmacokinetics following intravenous and oral administration in rat. Drug-loaded methoxy poly(ethylene oxide)-*b*-poly(ε-caprolactone) (PEO-*b*-PCL) micellar solutions were prepared and administered either intravenously or orally to healthy Sprague–Dawley rats. Plasma pharmacokinetic parameters of valspodar in its polymeric micellar formulation were compared to its clinical formulation, which uses Cremophor EL and ethanol as solubilizing agents. High loading level was achieved for valspodar in PEO-*b*-PCL leading to an aqueous solubility of 2.8 mg/mL. Following i.v. administration (5 mg/kg), valspodar in the PEO-*b*-PCL micelles provided significantly higher (~77%) plasma AUC compared to the Cremophor EL formulation. The PEO-*b*-PCL micelles also significantly decreased the volume of distribution (Vd_{ss}) and clearance (CL) of valspodar by nearly 49% and 34%, respectively. After oral administration (10 mg/kg), the average C_{max} were similar for both formulations and were both reached at ~2 h. The plasma unbound fraction of valspodar in the polymeric micellar formulation was significantly lower than control (8.27% versus 14.85%). Our results show that PEO-*b*-PCL micelles can efficiently solubilize valspodar and favorably modify its pharmacokinetic profile in rat after i.v. administration by decreasing the CL and Vd.

1. Introduction

Valspodar is a non-competitive inhibitor of P-glycoprotein (Pgp) developed to overcome multi-drug resistance (MDR) to various chemotherapeutic agents *in vitro* and in preclinical and clinical studies [1,2]. It is a more hydrophobic derivative of cyclosporine A (CyA) that displays no evidence of nephrotoxicity or immunosuppressive activity [3–8]. Moreover, its P-gp inhibiting activity is superior to CyA both *in vitro* and *in vivo* [3,6,9,10]. Valspodar has shown to significantly prolong the survival rates of several oncologic disease animal models [11,12]. Furthermore, the Pgp-inhibiting activity of valspodar has been demonstrated in clinical trials in combination with chemotherapeutic agents [13–16]. The major drawback in the clinical application of valdospar is its non-specific inhibitory action on cytochrome P-450 3A (CYP3A) which results in reduced elimination and enhanced accumulation and toxicity of several anticancer drugs after co-administration with valspodar in patients with cancer [10,13,14,17–19]. Moreover, the non-specific action of valspodar on P-gp expressed in normal tissues can enhance the concentration and toxicity of anticancer drugs that are P-gp substrates in those organs leading to normal tissue toxicity.

The general goal of our research is to develop a delivery system that can prevent the non-specific distribution of P-gp inhibitors to normal tissues expressing P-gp and at the same time enhance their access to tumor P-gp. In previous studies, we have been exploring the potential of methoxy poly(ethylene oxide)-*block*-poly(ε-caprolactone) (PEO-*b*-PCL) micelles as vehicles for the solubilization and controlled delivery of CyA as a model P-gp inhibitor [20,21]. The results of our previous studies showed that PEO-*b*-PCL micelles were not only able to solubilize CyA at clinically relevant concentrations, but favorably change the plasma protein binding, pharmacokinetic and biodistribution profile of CyA after a single i.v. dose to rats keeping the incorporated CyA mainly in blood circulation and away from sites of CyA toxicity, i.e., kidneys [22,23]. This has led to a reduction in the nephrotoxic side effects of CyA upon multiple dosing of its polymeric micellar formulation compared to the Cremophor EL formulation.

The main objective of current study was to investigate the capacity of PEO-*b*-PCL micellar formulations as vehicles for the solubilization of valspodar, the non-immunosuppressive and more effective derivative of CyA for P-gp inhibition. Valspodar is poorly soluble in various solvents and practically insoluble in water. Similar to CyA, the clinical formulation of valspodar (Amdray®) uses ethyl alcohol and Cremophor EL for valspodar solubilization.

* Corresponding author. Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada. Tel.: +1 780 492 2742; fax: +1 780 492 1217.
E-mail address: alavasanifar@pharmacy.ualberta.ca (A. Lavasanifar).

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However, the use of Cremophor EL has been associated with several adverse effects such as hypersensitivity reactions [24,25] and neurotoxicity [25,26]. Based on the higher hydrophobicity of valspodar, even a better solubility and stability profile for PEO-*b*-PCL micellar formulation of valspodar than what achieved for CyA was expected. In fact, in recent years, hydrophobic derivatives of paclitaxel and geldanamycin have been synthesized and shown better solubility and reduced release from PEO-*b*-PCL micellar carriers, *in vitro* [27,28], and enhanced tolerability and pharmacokinetics in rats [27,29]. In this study, the plasma protein binding and pharmacokinetics of PEO-*b*-PCL micellar formulation of valspodar in healthy rat models was studied to assess the *in vivo* stability of this formulation shedding light to its potential in reducing the non-specific distribution of valspodar when compared to the Cremophor EL formulation.

2. Materials and methods

2.1. Materials

Valspodar was a kind gift from Novartis (Basel, Switzerland). Cremophor EL was purchased from Sigma–Aldrich (St. Louis, MO, USA). Sodium chloride injection (USP) 0.9% was obtained from Hospira Healthcare Corporation (Montreal, QC, Canada). Heparin sodium for injection, 1000 IU/mL was purchased from Leo Pharma Inc. (Thornhill, ON, Canada). Potassium dihydrogen orthophosphate, dipotassium hydrogen orthophosphate, and potassium chloride were obtained from Caledon Laboratories (Georgetown, ON, Canada). Acetonitrile, ammonium hydroxide, methanol, and water were all of HPLC grade and were purchased from Caledon Laboratories (Georgetown, ON, Canada). All other chemicals were of reagent grade.

2.2. Methods

2.2.1. Preparation of valspodar-loaded PEO-b-PCL micelles

Previously reported methods [20,22] were employed for the synthesis of PEO-*b*-PCL block copolymer and the preparation of the polymeric micelles. Valspodar and polymer were dissolved in acetone with an initial concentration of 3 and 10 mg/mL, respectively, followed by drop-wise addition of acetone to distilled water in a ratio of 1:6. The hydrodynamic diameter of PEO-*b*-PCL micelles with and without valspodar was measured by dynamic light scattering (3000 HSA Zetasizer Malvern, Zeta-Plus™ zeta potential analyzer, Malvern Instrument Ltd, UK). Sucrose was added to the polymeric micellar solution to achieve a final sucrose concentration of 95.76 mg/mL to adjust the tonicity. The micellar solution was then centrifuged at 12,000 rpm for 5 min, to remove unloaded valspodar. The level of encapsulated valspodar was determined in the supernatant using HPLC after destroying the micellar structure through addition of 80 times volume of methanol. The HPLC instrument consisted of a Chem Mate pump and Basic-marathon autosampler (Spark Holland, Netherlands). An LC1 column (Supleco, Bellefonte, PA, USA) was equilibrated with a mobile phase of KH_2PO_4 (0.01 M), methanol, and acetonitrile (23:50:28) at a flow rate of 1 mL/min. The column was heated at 65 °C using an Eppendorf CH-30 column heater (Westbury, NY, USA). Valspodar concentrations were estimated by UV detection at 205 nm (Waters, model 481, Millipore Corporation, Milford, MA, USA) after injection of 100 μL samples. Valspodar loading content and encapsulation efficiency were determined using the following equations:

$$\text{Valspodar loading content } (w/w) = \frac{\text{Amount of loaded valspodar (mg)}}{\text{Amount of polymer(mg)}}$$

$$\text{Encapsulation efficiency } (\%) = \frac{\text{Amount of loaded valspodar (mg)}}{\text{Amount of valspodar added (mg)}} \times 100$$

2.2.2. Animals and pharmacokinetic study

Animal studies were conducted based on protocols approved by the University of Alberta Health Sciences Animal Policy and Welfare Committee. Male Sprague–Dawley rats (250–350 g) were housed in temperature-controlled rooms with 12 h of light per day. The animals had free access to food and water prior to experimentation. The right jugular vein of all rats was cannulated with Silastic® Laboratory Tubing (Dow Corning Corporation, Midland, MI, USA) under isoflurane anesthesia as previously described [30]. After surgery, the rats were transferred to their regular holding cages and allowed free access to water, but food was withheld overnight. The next morning, rats were transferred to metabolic cages and divided into four groups (5–8 rats/group). Valspodar, from each formulation, was administered as single dose of 5 mg/kg intravenously (i.v.) or 10 mg/kg orally.

Animals were administered valspodar either in its standard formulation (5 mg/mL, diluted in 0.9% NaCl for injection [31]) or in the micellar formulation. The i.v. dose was injected over 2 min via the jugular vein cannula, immediately followed by injection of normal saline solution. At the time of first sample withdrawal, the first 0.2 mL volume of blood was discarded. For oral dosing, the rats received the desired dose by oral gavage. For both routes of administration, food was provided to animals 4 h after the dose administration. Serial blood samples (0.15–0.25 mL) were collected at 0.08, 0.33, 0.67, 1, 2, 4, 6, 9, 12, and 24 h after i.v. dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, and 48 h after oral dose. Heparin in normal saline was used to flush the cannula after each collection of blood. Blood samples were immediately centrifuged for 3 min; plasma was separated and stored at −20 °C until analysis. The plasma concentrations of valspodar were analyzed by a liquid chromatography–mass spectrometry (LC–MS) method (as described later), and the plasma concentration versus time curve was profiled.

2.2.3. Determination of valspodar unbound fraction

For determination of valspodar plasma protein binding *in vitro*, an erythrocyte vs. buffer or plasma partitioning method was used [32,33]. This method intuitively assumes that the mechanism of drug entry into the erythrocytes is by passive diffusion.

2.2.4. Valspodar blood-to-plasma ratio

Known amounts of valspodar micellar formulation were added to heparinized tubes containing freshly obtained rat blood to provide final concentrations of 0.5 and 2.5 μg/mL. The tubes were placed in a shaking water bath at 37 °C for 1 h. At that time, the tubes were removed, and 100 μL of blood was transferred to new glass tubes ($n = 5$) containing 100 μL of water. The remaining blood was centrifuged at 2500*g* for 10 min. A volume of 100 μL of the plasma layer was transferred to new glass tubes ($n = 5$). Samples were kept frozen at −20 °C until being assayed for valspodar concentrations. The results were then compared with the ones reported earlier for the Cremophor EL formulation [33].

2.2.5. Determination of valspodar levels

The concentrations of valspodar in all samples were analyzed by a recently reported LC–MS method [34]. For quantitation in blood, plasma, and buffer samples, concentration ranges of 0.01–5 μg/mL were employed in the calibration samples. The intra- and interday variability (% coefficient of variation) ranged from 2.5% to 18.3% and 5.5% to 17.2%, respectively. The assay quantitation limit was 10 ng/mL.

2.2.6. Data and statistical analysis

Non-compartmental methods were used to calculate the pharmacokinetic parameters. The elimination rate constant (λ_z) was estimated by linear regression of the plasma concentrations in

the log-linear terminal phase and the corresponding half-life ($t_{1/2}$) was calculated by dividing 0.693 by λ_z. The $AUC_{0-\infty}$ was calculated using the combined linear-log trapezoidal method [35] from time 0 h post-dose to the time of the last measured concentration plus the quotient of the last measured concentration divided by λ_z. The concentration at time 0 h after i.v. dosing (Cp_0) was estimated by extrapolation of the log-linear regression line using the first three measured plasma concentrations to time 0. The mean residence time (MRT) was calculated by dividing area under the first moment curve ($AUMC_{0-\infty}$) by $AUC_{0-\infty}$, clearance (CL) by dividing dose by $AUC_{0-\infty}$, and volume of distribution at steady-state (Vd_{ss}) by multiplying CL by MRT. The maximum plasma concentration (C_{max}) and the time at which it occurred (t_{max}) were determined by visual examination of the data. The oral bioavailability (F) for each formulation was calculated as follows:

$$F = \frac{\text{mean AUC}_{\text{oral}}}{\text{mean AUC}_{\text{iv}}} \times \frac{\text{Dose}_{\text{iv}}}{\text{Dose}_{\text{oral}}}$$

The plasma unbound fraction (f_u) was calculated by using the equations outlined by Schuhmacher et al. [32]. The mean blood CL of valspodar was estimated by dividing the mean plasma CL by the blood-to-plasma ratio. The hepatic extraction ratio (E) was estimated, assuming negligible extrahepatic CL, by taking the quotient of i.v. blood CL divided by average hepatic blood flow of 55.2 mL/min/kg [36]. The gastrointestinal availability (f_g) in turn was calculated as the quotient F divided by $(1 - E)$, where $1 - E$ represents the hepatic availability (f_h).

All data are reported as mean ± SD, unless otherwise indicated. Differences between the means were compared by Student's unpaired t-test assuming unequal variance. The level of significance was set at $\alpha = 0.05$.

3. Results

Valspodar achieved high drug loading levels (4.16 mol/mol) and very efficient encapsulation (93.6%) in PEO-*b*-PCL micelles (Table 1). This loading was superior to what was reported for CyA encapsulation in PEO-*b*-PCL micelles using an identical method (3.42 mol/mol CyA loading content and 75.9% encapsulation efficiency) [21,23]. The average diameter of valspodar-loaded PEO-*b*-PCL micelles was 62 nm, which is smaller than the size reported for CyA-loaded micelles [21,23].

Fig. 1 shows the concentration–time profile of valspodar for both formulations in plasma following an i.v. dose of 5 mg/kg in rats. The 24-h profile for the control formulation shows a rapid decline in plasma concentration in the first two h representing a distribution phase, which was followed by an elimination phase with an average $t_{1/2}$ of approximately 13 h. On the other hand, valspodar in the micellar formulation was associated with a less steep decline in plasma concentration especially at the early time points (up to ~6 h) with a terminal phase $t_{1/2}$ of nearly 10 h. The difference in the terminal phase $t_{1/2}$ between the two formulations was not statistically significant. However, valspodar in PEO-*b*-PCL micelles yielded higher plasma concentrations when compared to the Cremophor EL formulation. Non-compartmental analysis of the plasma concentrations showed a significant change in the pharmacokinetic parameters of valspodar in polymeric micelles in comparison with the Cremophor EL formulation (Table 2). PEO-*b*-PCL micelles provided ~77% higher plasma AUC compared to the Cremophor EL formulation. The PEO-*b*-PCL micelles also significantly decreased the volume of distribution (Vd_{ss}) and clearance (CL) of valspodar by 49% and 34%, respectively. The pharmacokinetic parameters following intravenous administration of valspodar are listed in Table 2.

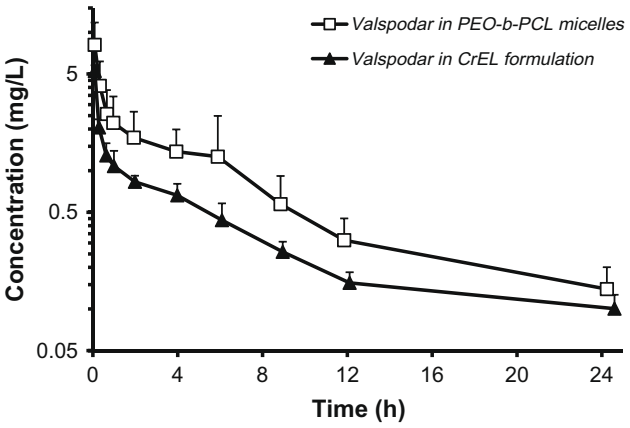

Fig. 1. Plasma concentration versus time profile in rat following a single i.v. dose (5 mg/kg) of valspodar control formulation ($n = 7$) and PEO-*b*-PCL micellar formulation ($n = 8$). Each data point presents the mean ± SD.

The concentration–time profile of valspodar in plasma following oral dose of 10 mg/kg is shown in Fig. 2. The 48-h profile shows a rapid absorption phase reaching average C_{max} of 1.17 mg/L and 1.00 mg/L for control formulation and the polymeric micellar formulation, respectively. The median t_{max} was very similar between the two formulations. Mean absolute F for the control and the polymeric micellar formulations were 42.3% and 28.9%, respectively. However, the relative F, where the AUC of the control formulation served as the reference AUC formulation, for the polymeric micellar formulation was 121%. The pharmacokinetic parameters following oral administration of valspodar are listed in Table 3.

The polymeric micellar formulation showed a significantly lower f_u for valspodar (8.3%) compared to the control formulation

Table 2
Plasma pharmacokinetic parameters (mean ± SD) of valspodar in rats following a single i.v. administration (5 valspodar mg/kg).

Parameter	Valspodar in CrEL ($n = 7$)	Valspodar in PEO-*b*-PCL micelles ($n = 8$)
AUC_{0-24h} (mg h/L)	9.10 ± 1.38	17.51 ± 8.67*
$AUC_{0-\infty}$ (mg h/L)	10.99 ± 1.62	19.43 ± 8.78*
$t_{1/2}$ (h)	12.71 ± 3.40	9.62 ± 3.41
MRT (h)	12.66 ± 3.62	9.54 ± 3.42
CL (L/kg/h)	0.462 ± 0.06	0.303 ± 0.13*
Vd_{ss} (L/kg)	5.83 ± 1.87	3.03 ± 1.78*

* Significant difference between groups.

Table 1
Characteristics of the polymeric micellar formulation of valspodar and CyA.

Drug	Block copolymer used	Initial drug concentration (mg/mL)	Average diameter[b] (nm)	Loading level ± SD (M/M)	Encapsulation Efficiency ± SD[c] (%)
Valspodar	PEO_{114}-*b*-PCL_{114}	3	62.25 ± 0.70	4.16 ± 0.21	93.61 ± 4.79
CyA[a]			89.30 ± 15.3	3.42 ± 0.32	75.90 ± 7.51

[a] Reproduced from Ref. [23].
[b] Average diameter size estimated by the dynamic light scattering (DLS) technique.
[c] Measured by HPLC. Values are recorded as mean ± SD ($n = 3$–6).

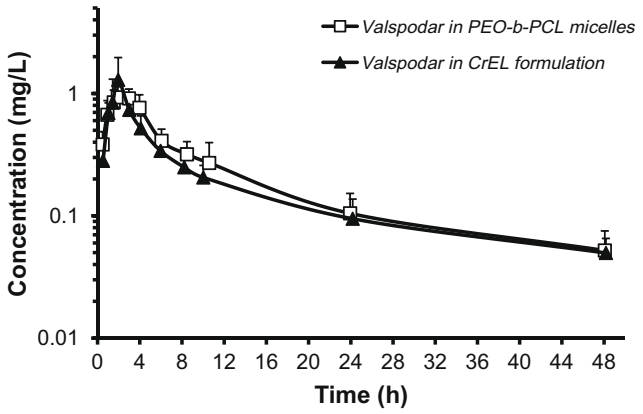

Fig. 2. Plasma concentration versus time profile in rat following a single oral dose (10 mg/kg) of valspodar control formulation ($n = 6$) and PEO-*b*-PCL micellar formulation ($n = 5$). Each data point presents the mean ± SD.

Table 3
Plasma pharmacokinetic parameters (mean ± SD) of valspodar in rats following a single oral administration (10 valspodar mg/kg).

Parameter	Valspodar in CrEL ($n = 6$)	Valspodar in PEO-*b*-PCL micelles ($n = 5$)
AUC_{0-48h} (mg h/L)	8.69 ± 1.67	9.54 ± 2.37
$AUC_{0-\infty}$ (mg h/L)	9.30 ± 1.83	11.23 ± 2.56
$t_{1/2}$ (h)	14.82 ± 5.02	16.34 ± 4.52
MRT (h)	17.80 ± 4.19	18.70 ± 4.68
CL/F (L/kg/h)	1.09 ± 0.30	0.94 ± 0.27
F	0.423	0.289
C_{max} (mg/L)	1.17 ± 0.70	1.00 ± 0.15
t_{max} (h)[a]	1.96 (1.43–1.97)	1.92 (1.55–3.85)

[a] Data were presented as median (range in parenthesis).

Table 4
Valspodar and CyA unbound fraction (f_u) in rat plasma.

Drug	Formulation	f_u (%)
Valspodar	Control (CrEL)	14.8 ± 3.0
	PEO-*b*-PCL	8.3 ± 4.1
CyA[a]	Control (CrEL)	37.4 ± 2.3
	PEO-*b*-PCL	15.1 ± 1.9

Data were represented as mean ± SD ($n = 4$).
[a] Data were reproduced from Ref. [23].

(14.8%) [33] (Table 4). However, the mean blood-to-plasma ratios of valspodar at 0.5 and 2.5 μg/mL were the same with the average values of 0.52 [33] and 0.49 for the control formulation and the polymeric micellar formulation, respectively. These values indicate minimal blood-cell partitioning for valspodar and its restriction primarily to the plasma fraction within the blood matrix.

The mean blood CL for the control and polymeric micellar formulations were 0.894 L/h/kg and 0.620 L/h/kg, respectively. By using the reported mean hepatic blood flow in rat [36] and assuming that the majority of the CL of valspodar occurs in liver, *E* was estimated to be 0.27, and f_g was found to be 0.59 for the control formulation. The corresponding values of *E* and f_g for the polymeric micellar formulation were 0.19 and 0.36, respectively.

4. Discussion

The main objective of this study was to assess the potential of polymeric micelles as alternative vehicles to Cremophor EL formulation, which could solubilize valspodar effectively and modify its pharmacokinetics. Micelles of PEO-*b*-PCL were chosen for this study since these polymeric micelles were successful carriers efficiently solubilizing CyA and changing its pharmacokinetic and biodistribution profile by reducing CyA accumulation in normal tissues (e.g. spleen and kidneys) and increasing its levels in blood by decreasing CL after a single i.v. dose.

Through a co-solvent evaporation method, identical to the one used for CyA, valspodar was encapsulated in PEO-*b*-PCL micelles effectively. A high level of drug loading was achieved (4.16 mol drug/mol polymer) leading to an aqueous solubility of nearly 2.8 mg/mL. This loading level was significantly higher than the one achieved with CyA at the optimum conditions (3.42 mol drug/mol polymer; aqueous solubility ~2.3 mg/mL) (Table 1) [21,23]. This was not surprising since valspodar is a more hydrophobic derivative of CyA, and therefore it is perhaps more compatible with the hydrophobic micellar core (PCL). Based on a better compatibility between valspodar and PCL, valspodar was expected to remain associated with the PEO-*b*-PCL micelles to a higher extent, as well.

Although the PEO-*b*-PCL micellar formulation was able to solubilize more valspodar (compared to CyA) and decrease the f_u of valspodar by ~45% compared to the control formulation, it was unexpectedly less effective in changing the pharmacokinetics of valspodar from what observed for the Cremophor EL formulation. To facilitate the comparison between valspodar and CyA data, valspodar blood AUC, CL, and Vd_{ss} were estimated from their corresponding plasma values by using the blood-to-plasma ratio data. Following a single i.v. dose of 5 mg/kg to rats, PEO-*b*-PCL polymeric micelles provided ~67% higher blood AUC compared to the Cremophor EL formulation (9.5 versus 5.7 mg h/L, respectively). The blood CL and Vd_{ss} of valspodar were 0.89 L/h/kg and 11.2 L/kg for Cremophor EL, and 0.62 L/h/kg and 6.2 L/kg for PEO-*b*-PCL micelles, respectively, representing reduction of blood CL and Vd_{ss} by 30% and 45%, respectively. However, it has previously been demonstrated that PEO-*b*-PCL micelles were able to change the pharmacokinetics of the encapsulated CyA to a higher extent showing a 90% decrease in blood CL and Vd_{ss} of polymeric micellar CyA in comparison with CyA in Cremophor EL (Sandimmune® formulation) [23]. Moreover, the blood AUC of CyA in Sandimmune® was only 12% of the AUC encompassed with the polymeric micellar formulation.

Assuming that its pathway of elimination is mostly hepatic, the hepatic extraction ratio (*E*) for valspodar was found to be nearly 30% lower in the polymeric micellar formulation compared to the Cremophor EL preparation. Since valspodar is a low *E* drug ($E < 0.3$), its clearance is expected to be proportional to the product of the intrinsic clearance of unbound drug and the f_u. Therefore, the lower *E* in the polymeric micellar formulation can be largely attributed to the lower f_u, since it is about 45% lower than the control formulation.

The potential use of polymeric micelles as oral drug delivery systems has not been widely demonstrated *in vivo*. For instance, Préat and coworkers have investigated the potential of polymeric micelles based on methoxy poly(ethylene glycol)-poly(ε-caprolactone/trimethylene carbonate) [PEG-p(CL-co-TMC)] for oral administration utilizing risperidone as a model drug [37,38]. They showed that PEG-p(CL-co-TMC) was able to form micelles and reach a bioavailability of 40%, while the absolute bioavailability of drug (risperidone) was 19% in rats. Moreover, the mechanistic studies suggest that the drug-loaded micelles were absorbed by pinocytosis, whereas the polymeric unimers diffused passively across the membrane concomitantly with micellar endocytosis [39]. Furthermore, Pierri and Avgoustakis have studied the *in vitro* degradation and drug-release properties of poly(ethylene glycol)–poly(lactide) (PEG–PLA) micelles using griseofulvin as a model drug [40]. They demonstrated that PEG–PLA micelles were stable and exhibited sustained release properties in PBS (pH = 7.4) as well as in simulated gastric (pH = 1.2) and intestinal fluids (pH = 7.5). Here, we report on the pharmacokinetics of

valspodar-loaded micelles compared to the standard Cremophor EL formulation following a single oral dose of 10 mg/kg to rats.

The median t_{max} of valspodar was similar in both formulations (~2 h). Likewise, the C_{max} did not differ significantly between the two formulations (Table 3). The absolute *F*% calculated for valspodar in the polymeric micellar formulation (28.9%) was lower than the Cremophor EL formulation (42.3%). This is clearly due to the significantly higher AUC obtained for the i.v. micellar formulation compared to the control formulation (19.4 versus 11.0 mg h/L), as the relative F% was ~120%. The f_g, however, was ~47% lower in the polymeric micellar formulation. It is possible that the lower f_g is due to a lower absorption, suggesting that the polymeric micellar formulation somehow restricts the drug to the confines of the gastrointestinal fluids. The mechanisms involved in micellar transport across intestinal mucosa are not well defined but several studies suggest that cellular uptake of intact polymeric micelles is through fluid-phase endocytosis (pinocytosis) [41–43]. In this study, however, it is not known whether the drug-loaded polymeric micelles were stable in the gastrointestinal fluids, and whether the micelles were able to pass the intestinal barrier (as intact micelles) or not. Further studies need to be performed to investigate the route and extent of polymeric micellar absorption from the gastrointestinal tract.

5. Conclusions

Overall, the polymeric micelles of PEO-*b*-PCL seem to be a good alternative to Cremophor EL, and may serve as a potential candidate for i.v. and oral drug delivery of poorly water soluble drugs. In this study, we showed that after intravenous doses, PEO-*b*-PCL micelles were able to significantly lower the clearance and volume of distribution of valspodar compared to the control formulation. The extent of these changes by PEO-*b*-PCL carriers for valspodar, however, was not as significant as the degree of change in pharmacokinetics observed with its structural analogue, CyA. Moreover, following oral administration, the AUC of valspodar in the polymeric micellar formulation was similar to the Cremophor EL formulation. However, PEO-*b*-PCL formulation did not substantially impact the AUC and other pharmacokinetic parameters when given orally. The replacement of Cremophor EL with the polymeric micellar formulation of valspodar for oral administration is not justified at this point, since both formulations have shown similar pharmacokinetics and it is known that Cremophor EL is well tolerated orally. Nevertheless, the results imply a potential for PEO-*b*-PCL micelles to possibly serve as a suitable vehicle for oral administration of hydrophobic drugs. Overall, our results show that PEO-*b*-PCL micelles can efficiently solubilize valspodar and favorably modify its pharmacokinetic profile in rat following intravenous administration.

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