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Pharmacokinetics of Nano versus Conventional Formulations of A83B4C63, a Novel Inhibitor of DNA Repair in Rat

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PURPOSE

The long term objective of this study is to develop nanodelivery systems for solubilization and tumor targeted delivery of A83B4C63, a novel inhibitor of polynucleotide kinase/phosphatase (PNKP) which is involved in single and double strand DNA repair. Here, we evaluated the potential of polymeric micelles based on poly(ethylene oxide)-*b*-poly(ε-caprolactone) and poly(ethylene oxide)-*b*-poly(α-benzyl carboxylate-ε-caprolactone)(PEO-PCL and PEO-PBCL, respectively) for delivery of A83B4C63, by studying the encapsulation, *in vitro* release and pharmacokinetics of encapsulated versus free drug after i.v. administration in rats.

METHOD

PEO-*b*-PCL and PEO-*b*-PBCL copolymer were synthesized and used to form micelles encapsulating A83B4C63[1]. Micellar size and polydispersity index (PDI) as well as drug loading (DL) and encapsulation efficiency (EE) were determined. The release of A83B4C63 from Cremophor: ethanol (Control), PEG 400 (Control), PEO-*b*-PCL_{44} and PEO-*b*-$PBCL_{26}$ formulations were assessed. Single 10 mg/kg i.v. dose of A83B4C63 formulations were administered to Sprague Dawley rats (n=4/group). Serial blood samples were collected up to 72 h and plasma A83B4C63 concentrations were determined using LC/MS/MS. Pharmacokinetic parameters were calculated using a non-compartmental method.

RESULTS

In vitro

There was no differences in %EE, %DL, size and PDI of different micellar formulations. The A83B4C63 was rapidly released from Cremophor: ethanol formulation and PEG 400. In comparison, both polymeric micellar formulations showed a significant ability to retain the drug. No significant differences were observed in the release pattern between the two polymeric micellar formulations.

Table 1. Characteristics of A83B4C63 formulations

Formulation	%DL	%EE	Size (nm)	PDI	% Release (24h)
PEO-PCL	28.05±2.69	88.32±6.81	57.08±3.09	0.172±0.04	17.64±6.85
PEO-PBCL	19.56±7.25	57.18±17.28	70.28±11.25	0.204±0.02	25.31±11.80
Cremophor	-	-	-	-	63.18±0.56
PEG 400	-	-	-	-	92.17±0.41

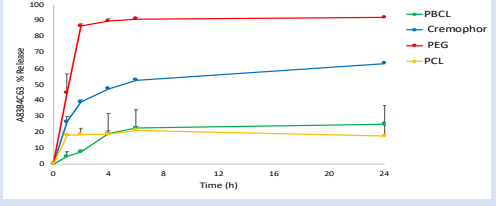

Figure 1.Release profile of A83B4C63 formulations

In vivo

Our pharmacokinetic results indicating both micellar formulations produced significantly longer MRT and $t_{1/2}$ when compared to Cremophor: ethanol and PEG formulations.

Table 2. Pharmacokinetic parameters of A83B4C63

Parameter	PEO-PBCL	PEO-PCL	Cremophor	PEG 400
AUC (ng*h/mL)	507.91±176.20	1243.46±1048.21	466.76±50.44	540.81±71.41
CL (mL/h per kg)	21.22±5.56	20.73±18.45	23.98±5.46	18.86±2.85
$T_{1/2}$ (h)	84.89±69.37	40.67±29.86	2.33±2.47	2.86±0.77
Vdβ (mL/kg)	2596.47±2585.41	716.44±531.47	86.03±91.73	76.21±14.66
MRT (h)	30.79±15.15	53.95±50.92	1.14±1.02	1.99±0.36

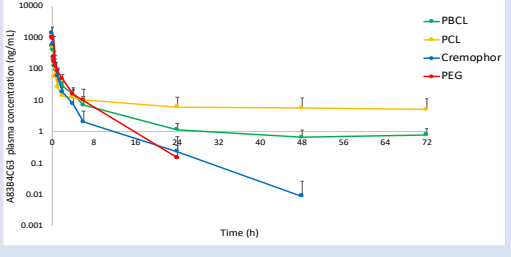

Figure 2. Concentration-time curves of A83B4C63 formulations

CONCLUSION

Our results show that both PEO-*b*-PCL and PEO-*b*-PBCL micelles can prolong biological half life and residence time of A83B4C63, when compared to its PEG 400 or Cremophor: Ethanol formulation. At the same time both polymeric micellar formulations serve as good solubilizing carriers for i.v. administration of this drug.

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REFERENCES[1] Shire Z et al. Mol Pharm. 2018 Jun 4;15(6):2316-2326