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

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PURPOSE

A83B4C63 is a novel inhibitor of polynucleotide kinase/phosphatase (PNKP), a DNA repair enzyme that plays a critical role in the repair of DNA damage causes by radiation and topoisomerase I inhibitors. Reducing PNKP activity makes cancer cells more sensitive to radiation and chemotherapy by topoisomerase I inhibitors. However, it may do the same in normal cells as well. In addition to the need for tumor targeted drug delivery, A83B4C63 is a poorly water-soluble compound. The objective of this study was to develop a nano-delivery systems for solubilization and the tumor targeted delivery of A83B4C63. Here, we evaluated the potential of polymeric micelles based on poly(ethylene oxide)-*b*-poly(e-caprolactone; PEO-PCL) and poly(ethylene oxide)-*b*-poly(a-benzyl carboxylate-e-caprolactone; PEO-PBCL) for solubilization and targeted delivery of A83B4C63.

METHOD

A83B4C63 was encapsulated in polymeric micelles using the co-solvent evaporation method.[1]Micellar size and polydispersity index (PDI) as well as drug loading (DL) and encapsulation efficiency (EE) were determined. The release of A83B4C63 from Controls (Cremophor: ethanol, PEG 400), and micellar formulations were assessed. Single 10 mg/kg i.v. doses of A83B4C63 were administered to Sprague Dawley rats (n=4/group). Serial blood samples were collected for 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

Table 1 and Figure 1 represent characterizations of micellar formulations and A83B4C63 release profiles respectively.

In vivo

Our pharmacokinetic results indicate both micellar formulations produced significantly longer MRT and $t_{1/2}$ when compared to Controls. (Table 2, Figure 2)

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

Table 1. Characteristics of A83B4C63 formulations

Polymer	Encapsulation efficiency (%)	Drug loading (%)	Micelle diameter (nm)	PDI
PEO-PBCL DP 26	57.2±17.3*	19.6±7.3	70.3±11.3	0.204±0.02
PEO-PCL DP 44	88.3±6.8	28.1±2.7	57.1±3.1	0.172±0.04

Table 2. Pharmacokinetic parameters of A83B4C63

Parameter	PEO-b-PBCL	PEO-b-PCL	Cremophor	PEG400
$C_{0\ (ng/mL)}$	1248.4±392.7	1856.2±890.2	1416.4±572.9	1360.3±504.9
$AUC_{0-\infty\ (ng*h/mL)}$	708.1±183.7	904.8±312.3	665.1±102.8	840.9±101.2
$T_{1/2\ (h)}$	6.1±3.3	13.2±3.6[a,b,c]	1.6±0.5	1.9±0.7
$CL_{\ (L/kg/h)}$	22.1±4.5	18.1±5.9	21.8±3.2	18.1±2.4
$Vd\beta_{\ (L/kg)}$	193.9±123.8	322.1±24.1[a,b]	51.5±17.4	51.6±24.3
$MRT_{\ (h)}$	7.1±3.8[a,b]	7.1±1.7[a,b]	0.9±0.4	1.8±0.3
$Vdss_{\ (L/kg)}$	157.5±97.1[a,b]	130.1±50.8	22.2±10.6	32.5±8.9

[a] significantly different from PEG 400, [b] significantly different from Cremophor, [c] significantly different from PEO-PBCL

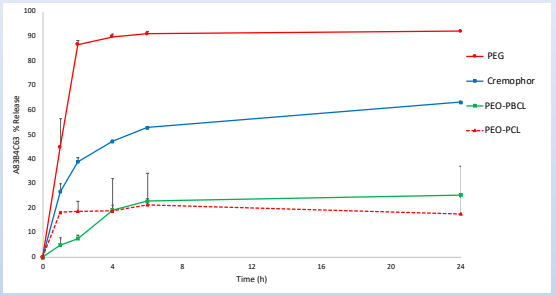

Figure 1.Release profile of A83B4C63 formulations

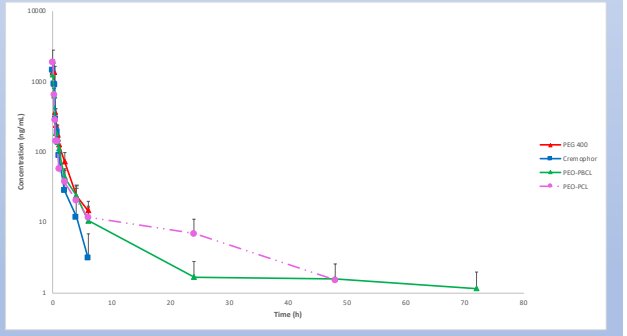

Figure 2. Mean plasma concentration-time curves of A83B4C63 formulations

CONCLUSION

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

ACKNOWLEDGEMENT This research was funded by Alberta Cancer Foundation and NanoMedicine Innovation Network (NMIN).