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Application of Lecithin (PL90) and Poloxamer 188 in SLC Transporter-Mediated Drug Interaction Studies

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PURPOSE

Solute Carrier (SLC) transporter-mediated drug interaction studies are essential in drug development. However, poor solubility and/or non-specific binding issues of highly lipophilic compounds pose significant challenges in *in vitro* research. Pharmaceutical excipients such as lecithin (PL90) and poloxamer 188 can improve solubility and/or reduce non-specific binding of highly lipophilic compounds. This study aimed to evaluate the effects of PL90 and poloxamer 188 on SLC transporter activities and to establish a good method for assessing transporter-mediated drug interaction studies of highly lipophilic compounds.

METHOD

Human embryonic kidney 293 (HEK293) cells stably expressing OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, and mock cells were purchased from GenoMembrane (Kanagawa, Japan) and used in this study. Estradiol 17-(β-D-glucuronide) (for OATP1B1 and OATP1B3), p-aminohippuric acid (for OAT1), estrone 3-sulfate (for OAT3) and metformin (for OCT2, MATE1 and MATE2-K) were used as the probe substrates, and rifampicin (for OATP1B1 and OATP1B3), probenecid (for OAT1 and OAT3), cimetidine (for OCT2), pyrimethamine (for MATE1 and MATE2-K) were used as the reference inhibitors. HEK293 mock cells were incubated in the absence and presence of 0.5 and 1 mM PL90 or 1% and 2% (w/v) poloxamer 188 in the cytotoxicity assay. These 7 transfected HEK293 and mock cells were incubated in the absence and presence of 0.5 and 1 mM PL90 or 1% and 2% poloxamer 188 in the transporter activity assay, and the transfected HEK293 cells were incubated in the absence and presence of 0.5 mM PL90 or 1% poloxamer 188 in the inhibition assay. The transporter activities and the inhibitory potentials of its reference inhibitors in the presence and absence of the excipients were compared.

RESULTS

1. The %Released LDH (percentage of the released LDH in the transport buffer) values of HEK293 mock cells treated with 1% or 2% (w/v) poloxamer 188, 0.5 or 1 mM PL90 were 2.2, 2.4, 2.7 and 3.4 (Figure 1), respectively, suggesting no or limited cytotoxicity.
2. In the absence and presence of 1% poloxamer 188 or 0.5 mM PL90, the relative transport activities (ratio of the transporter activity in the presence the excipient to that in the absence of the excipient) of all 7 transporters were greater than 70% (Figure 2), and the IC_{50} values of the reference inhibitors for all 7 transporters did not change significantly ($p > 0.05$) (Table 1), indicating that 0.5 mM PL90 and 1% poloxamer 188 had no or limited impact on the activities of all these 7 SLC transporters.

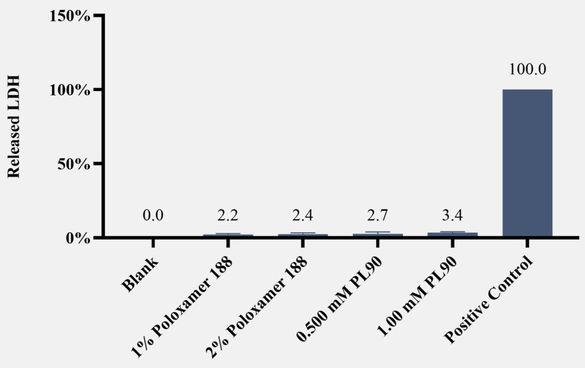

Figure 1. Cytotoxicity of HEK293-MOCK cells in the absence and presence of Poloxamer 188 (1% and 2%, w/v) or PL90 (0.5 mM and 1 mM) (Positive Control: cell lysate samples of blank wells)

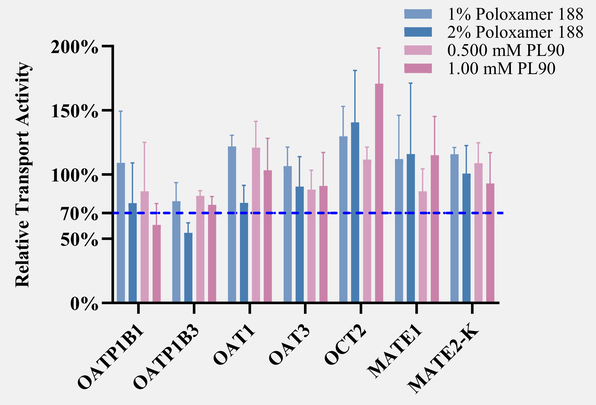

Figure 2. Comparison of the Relative transport activities of 7 SLC transporters in the absence and presence of Poloxamer 188 (1% and 2%, w/v) or PL90 (0.5 mM and 1 mM). The dotted line indicates the acceptable cut-off value of 70%.

Table 1. Effects of PL90 (0.5 mM) or Poloxamer 188 (1%, w/v) on the Inhibitory Potentials of Transporter Inhibitors

Transporter	Reference Inhibitor	IC_{50} (μM)			
		PL90 (Mean ± SD, n=3)		Poloxamer 188 (Mean ± SD, n=3)	
		-	+ 0.500 mM	-	+ 1%
OATP1B1	Rifampicin	0.707±0.252	0.986±0.158	0.450 ± 0.0692	0.564 ± 0.213
OATP1B3	Rifampicin	0.647 ± 0.315	0.534 ± 0.145	0.372 ± 0.0982	0.386 ± 0.180
OAT1	Probenecid	8.02 ± 1.35	8.53 ± 2.65	10.2 ± 2.32	10.9 ± 1.42
OAT3	Probenecid	2.41 ± 0.202	2.74 ± 0.184	2.25 ± 0.514	2.39 ± 0.547
OCT2	Cimetidine	184 ± 46.5	142 ± 41.7	123 ± 48.6	111 ± 44.9
MATE1	Pyrimethamine	0.0136 ± 0.00292	0.0308 ± 0.0148	0.0172 ± 0.0111	0.0297 ± 0.0262
MATE2-K	Pyrimethamine	0.0340 ± 0.0325	0.0330 ± 0.0333	0.0148 ± 0.000611	0.0206 ± 0.0155

CONCLUSION

PL90 at 0.5 mM and poloxamer 188 at 1% (w/v) can be applied in all these 7 SLC transporter-mediated drug interaction studies to improve solubility and reduce non-specific binding of highly lipophilic compounds.

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