095
Novel amphiphilic polyethylenimine (PEIs) for oral delivery of poorly soluble drugs

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The oral delivery of hydrophobic drugs is still a challenge as drugs that do not dissolve appreciably in the aqueous environment of the gastrointestinal tract suffer from poor bioavailability. We have previously reported that polyethylenimine (PEI) amphiphiles are able to solubilise the hydrophobic immune suppressant cyclosporine (CsA, MW¼1202 Da) (Cheng & Uchegbu 2003). CsA has an intrinsic aqueous solubility of 23 _gmL_1 and PEI amphiphiles increase the aqueous solubility 87 fold and promote the absorption of CsA via the oral route, producing similar blood levels to that obtained with the commercial microemulsion formulation Neoral (Cheng & Uchegbu 2003). The mechanism by which these oil free PEI formulations promote the oral absorption of this hydrophobic drug is currently unknown and we thus set out to examine whether the inhibition of the intestinal P-glycoprotein efflux pump or the opening of paracellular transport pathways was involved in the absorption enhancement observed with these solubilising PEI amphiphiles. Nine PEI amphiphiles were synthesised and characterised (Table 1) using techniques, previously reported (Cheng & Uchegbu 2003) and their ability to reverse the P-glycoprotein efflux pump evaluated by using a doxorubicin MTT assay on a cell line expressing the P-glycoprotein pump — the A2780 AD cell line. Doxorubicin (dox) has an IC50 in the resistant A2780 AD cell line that is 190 times that shown in the sensitive A2780 cell line, the latter of which is largely devoid of the P-glycoprotein efflux pump. Additionally the cytotoxicity of these PEI amphiphiles against Caco-2 cells was studied using the MTT assay and the effect of these amphiphiles on the transepithelial resistance of a Caco-2 cell monolayer evaluated. The high (25 kDa) and medium (10 kDa) molecular weight amphiphiles were less cytotoxic than their parent molecules (Table 1), whereas with the low molecular weight amphiphile (1.8 kDa), amphiphilicity had very little effect on cytotoxicity. These data (Table 1) indicate that increasing the number of amine groups increases the cytotoxicity of the polyamines and that amine substitution (presumably conversion to quaternary ammonium non protonable amines) reduced the cytotoxicity of the long chain polyamines. Up to a level of 2 _gmL_1 (10–13% of the Caco-2 IC50 values), none of the polymers had any effect on the integrity of the paracellular junctions in the Caco-2 cell monolayer or on the P-glycoprotein pump (Table 1). It appears that, at biocompatible concentrations, the PEI amphiphiles do not act by either a modulation of the P-glycoprotein pump or by altering the paracellular junctions.

Table 1 Polyethylenimine amphiphiles

Polymer	MW (k Da)	% Cetyl group	% Quarternary Methyl groups	Caco-2 cell IC50 ($ugmL^{-1}$)	Magnitude of change in dox IC50 in A2780 AD cell line (polymer concn= 2 $ugmL^{---1}$)
PE125	25	-	-	3.7	
Q125	25	5.0 ± 0.35 (n=2)	62.2± 2.60 (n=4)	15.2	1.1
Q225	25	5.0 ± 0.35 (n=2)	79.6 ± 2.37 (n=4)	12.7	1.7
PE110	10	-	-	4.5	
Q110	10	5.6	62.1 ± 3.0 (n=3)	21.9	1.5
Q210	10	5.6	88	24.3	0.81
PEI1.8	1.8	-	-	12.4	
C1.8	1.8	6.4	-	6.1	1.5
Q21.8	1.8	6.4	109	13.8	5.3

Cheng, W. P., Uchegbu, I. F. (2003) Proceedings of Winter Symposium & 11th International Symposium on Recent Advances in Drug Delivery Systems in Salt Lake City, Utah