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Non-Invasive Oligonucleotide Delivery System Based on a Thiolated Polymer: Development and *In Vitro* Evaluation

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It was the purpose of this study to develop an oral oligonucleotide delivery system based on thiolated polymer/ reduced glutathione (GSH) system providing protective effect towards nucleases, permeation enhancement and controlled drug release. Polycarbophil-cysteine conjugate (PCP-Cys) was synthesized by the covalent attachment of cysteine to polycarbophil via amide bond formation. Incubation of 30-mer phosphorothioate oligonucleotide with DNase I and freshly collected intestinal fluid were performed in order to evaluate the protective effect of the polymer. Based on PCP-Cys conjugate together with GSH, permeation studies were performed on Caco-2 monolayer cell culture and on freshly excised intestinal rat mucosa in Ussing chambers. Additional drug release studies of tablets containing PCP–Cys, reduced GSH, and the oligonucleotide were performed in 100 mM phosphate buffer pH 6.8.
PCP-Cys displayed 223±13.8 µmol thiol groups per gram polymer. After 4 h the unprotected ODNs, which were incubated with DNase I and intestinal fluid, were significantly degraded by 61 % and 80 %, respectively. In contrast, less than 41 % (in DNase I) and 60 % (in intestinal fluid) of the ODNs were degraded in the presence of 0.02 % (m/v) of PCP-Cys. Permeation studies demonstrated due to the addition of PCP-Cys/GSH an 8-fold and 10-fold increase in the apparent permeability coefficient (P_{app}) on Caco-2 monolayer and on intestinal rat mucosa in comparison to the buffer only, respectively. Tablets containing PCP–Cys, GSH, and oligonucleotide showed a sustained drug release over 2 h. According to these results the PCP-Cys/GSH system might be a promising tool for the oral administration of oligonucleotide.
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