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## Enhancement of drug bioavailability of quaternized chitosan by dual synergistic mechanism through transcellular and paracellular transport in the intestinal cell monolayer using Caco-2 cell model

Development of poorly soluble and unstable peptide drugs using drug delivery system has been introduced to improve drug bioavailability via oral administration. Among the novel oral drug carriers interested in nanotechnology, chitosan Quat-188, is the modified chitosan with quaternization process to improve solubility without any effect on the mucoadhesive property of core chitosan. In our previous study, chitosan Quat-188 showed well biocompatibility on human intestine in the nontoxic dose without significant effect on intestinal proliferation and differentiation [1]. However, the drug absorption enhancement of chitosan Quat-188 on human intestine remained to be unknown. Therefore, aim of this study was to further examine the potential effects of chitosan Quat-188 on improvement of drug bioavailability through transcellular and paracellular pathway in intestinal cells by using Caco-2 cells as an in vitro model.

In transcellular pathway focusing on P-glycoprotein (P-gp), the bidirectional transport and intracellular accumulation in Caco-2 cells were measured by radiolabeled digoxin (Digoxin[H3]) and calcein AM uptake, respectively. The results indicated that chitosan Quat-188 was able to inhibit the P-gp function by decreasing the efflux of P-gp substrate (Digoxin[H3]) and increasing the intracellular accumulation of calcein. In addition, in paracellular pathway, trans-epithelial electrical resistance (TEER), transport of FITC labeled dextran (FD4) and immunofluorescence of tight junction protein were investigated. Our results demonstrated that chitosan Quat-188 enhanced the paracellular permeability by decreasing the TEER value and increasing the FD4 transport in a dose-manner response. Moreover, chitosan Quat-188 acts as the reversible opener of tight junction protein since the removal of chitosan Quat-188 could attenuate the TEER value and reverse the structure of tight junction protein.

Taken together, these findings indicated that chitosan Quat-188 has the dual synergistic effects to enhance drug bioavailability on both transcellular and paracellular transport by decreasing the drug efflux via impairing the P-gp function and by increasing drug absorption via reversible opening the tight junction protein. Our results suggested the usefulness of chitosan quat-188 as the safely and controllably drug carrier in development of the oral drug delivery system.

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