Impact of digestion on the transport of macromolecule loaded nanoemulsion through intestine epithelium

The oral route, being the most convenient route for patients, has been extensively explored for the delivery of large molecular weight hydrophilic drugs. Oral delivery of macromolecules such as peptides and proteins has been a challenge due to their hydrophilicity, large molecular size, and susceptibility to enzymatic degradation. Lipid-based drug delivery systems have shown tremendous potential in enhancing the oral bioavailability of macromolecules by protecting the macromolecules from enzymatic degradation and enhancing the permeability through intestinal epithelium. Amongst lipid-based drug delivery systems, self-emulsified nanoemulsion (SEN) offers long-term stability and ease of preparation. SEN are isotropic mixtures of lipid and surfactant, which when diluted in water form oil-in-water nanoemulsion spontaneously. One of the mechanisms proposed to enhance the oral bioavailability of macromolecules by SEN is the absorption of intact macromolecule loaded lipid nano-droplets through the intestinal epithelium.

The lipid nano-droplets can be absorbed intact due to their small droplet size and lipid nature. However, the in-vivo oral bioavailability of macromolecules loaded SEN is less when compared to in-vitro transport of macromolecules loaded SEN through intestinal epithelium. The less enhancement effect in-vivo than in-vitro could be due to the digestion of lipid nano-droplets, which cause the release of macromolecules from the lipid nano-droplets before absorption. This release of the macromolecules from the lipid nano-droplets into the external aqueous phase may limit the membrane permeation of macromolecules and would also cause extensive degradation of macromolecules due to the harsh environment of the intestine lumen.

The objective of our research was to study the impact of digestion of macromolecule loaded SEN on the transport of macromolecules through in-vitro MDCK epithelial cell monolayer and ex-vivo rat intestines. Dextran 10 kDa was used as a model macromolecule. Dextran loaded SEN was prepared by formation of a dextran-phospholipid solid dispersion loaded in the lipid phase of SEN. In-vitro digestion model was used to mimic in-vivo intestine lumen. Dextran loaded SEN was characterized by evaluating the droplet size and encapsulation efficiency of dextran loaded SEN before and after in-vitro digestion. There was an increase in leakage of dextran from the lipid nano-droplets to the external aqueous phase after the digestion of dextran loaded SEN. A significant increase in the droplet size of dextran loaded SEN was observed after in-vitro digestion. The transport of dextran loaded SEN was compared with digested dextran loaded SEN. Digestion of dextran loaded SEN reduced the transport 3.5 times through in-vitro MDCK cell monolayer and 1.3 – 2.0 times through ex-vivo rat intestines due to the destruction of lipid nano-droplets and release of dextran to the external aqueous phase of SEN. The transport of lipid nano-droplets through intestinal epithelium can be further explored as one of the potential mechanisms for non-invasive delivery of macromolecules.

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