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The Influence of Molecular Parameters of Chitosan on Pulmonary Absorption of Insulin Loaded Chitosan Nanoparticles

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SUMMARY*. The absorption enhancing effects of chitosan nanoparticles with various molecular parameters on the pulmonary absorption of peptide and protein drugs were studied in rats, and the pulmonary membranes damage caused by chitosan nanoparticles was also evaluated. Insulin was chosen as model for peptide and protein drugs. The drug loaded chitosan nanoparticles were obtained by ionotropic gelation, the nanoparticle characteristics and release behavior was also evaluated. The results showed that chitosan nanoparticles with various molecular parameters significantly improved the pulmonary absorption of insulin compared with the control. The absorption enhancement ratio of chitosan nanoparticles ($CS_{168\text{-}b}$-NP, $CS_{108\text{-}b}$-NP, $CS_{35\text{-}c}$-NP $CS_{35\text{-}b}$-NP $CS_{35\text{-}a}$-NP) was 3.0, 2.7, 2.3, 2.4, and 2.0, respectively. The rank order of the effect on the absorption enhancement ratios was molecular weight (M_W) (168 > 108 > 35 kDa) and degree of deacetylation (DD) (90% > 95% > 80%), respectively. These findings suggest that chitosan nanoparticles with small size and marked positive charge are useful carriers for improving the pulmonary absorption of peptide and protein drugs due to their prolonged the retention in lung tissue and penetration into the mucus layer, and the absorption-enhancing effect of chitosan nanoparticles is affected by the degree of deacetylation of chitosan and independent of the initial molecular weight. In the toxicity studies of chitosan nanoparticles, we found no significant increase in the release of total protein and activity of lactate dehydrogenase (LDH) from the pulmonary tissue in BALF in the presence of chitosan nanoparticles, indicating that chitosan nanoparticles (M_Ws from 35 to 168 kDa) was safe carriers for improving the pulmonary absorption of peptide and protein drugs. In conclusion, $CS_{168\text{-}b}$-NPs with ideal M_W and DD are suitable as a carrier for the pulmonary delivery of peptide and protein drugs, which can effectively improve the pulmonary absorption of insulin without significant membrane damage to the lung tissues.

KEY WORDS: Chitosan, Insulin, Nanoparticles, Pulmonary absorption.

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