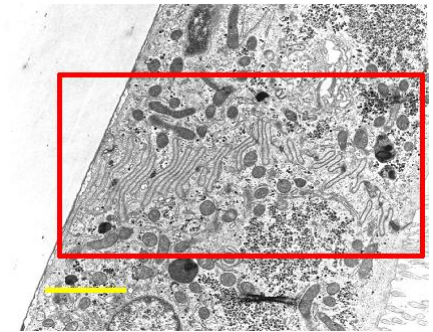


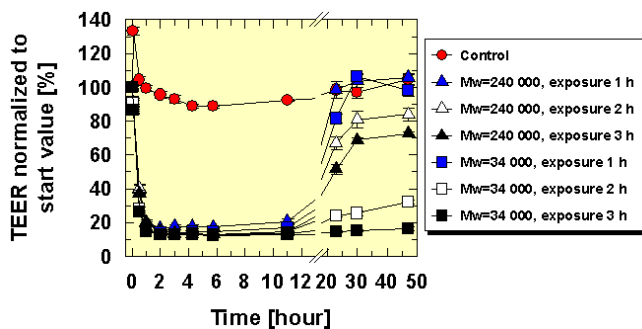
Nasal drug delivery with PROTASAN™ ultrapure chitosan salts

The development of new trans-epithelial drug delivery routes may increase the availability of many drugs. Drugs applied in this manner avoid hepatic first-pass metabolism and enzymatic degradation in the gastrointestinal tract. Permeability of a drug across an epithelial membrane is a fundamental step in trans-epithelial drug delivery. The presence of tight junctions between neighboring epithelial cells prevents the free diffusion of molecules across the epithelium by the paracellular route.

The nasal route of administration has advantages that allow the development of non-parental delivery systems for challenging drugs. Due to the ease of delivery, there is a high level of patient compliance compared to injectable systems. For many lipophilic drugs, the kinetics and even the extent of drug absorption following intranasal delivery are similar to that achieved by intravenous injection. As a consequence, nasal drug administration has application in the management of CNS disorders, acute post-operative pain and nausea. Studies have demonstrated that the cationic bioadhesive polymer chitosan can have a dramatic effect in increasing the transport of polar drugs across epithelial surfaces.



Electron micrograph of two Caco-2 cells. Right: apical side with microvilli, left: baso-lateral side. Tight junction between cells is within the marked area. Yellow bar = 2 μ m.



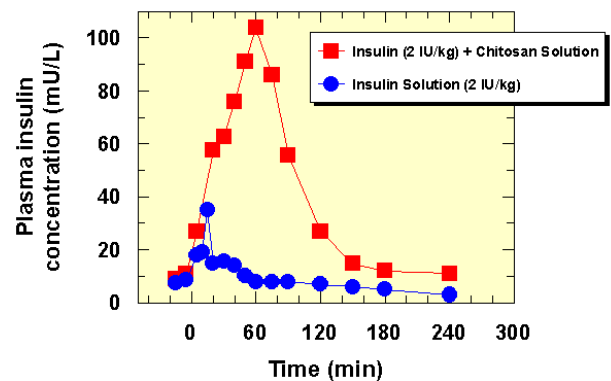
Effect of chitosan chloride (PROTASAN™, DA = 84%, 0.5% (w/v)) with high and low molecular weights on Trans-Epithelial Electrical Resistance (TEER) of Caco-2 cell monolayers after different exposure times. Each data point represents the mean of 3 replicate samples.

Solution formulations based on chitosan salts having a molecular weight of greater than 100 kD and with a defined degree of deacetylation, have found utility in improving the bioavailability of nasally administered polypeptides such as insulin, calcitonin, LHRH analogues, parathyroid hormone, growth hormone as well as non-peptide polar compounds useful in the treatment of pain (morphine). Dramatic effects that can be achieved using simple solution formulations prepared from chitosan have been demonstrated in animal models (right figure) [2] and in man. Nasal administration of chitosan appears to be a safe alternative to conventional permeability enhancers [3].

References: [1] Holme, H.K., Hagen, A., Dornish, M., Influence of chitosans on permeability of human intestinal epithelial (Caco-2) cells: The effect of molecular weight, degree of deacetylation and exposure time. *Advan. Chitin Sci.*, **4**, 259-265 (2000); [2] Dornish, M., Skaugrud, Ø., Illum, L., Davis, S.S., Nasal drug delivery with PROTASAN™. *Advan. Chitin Sci.*, **2**, 694-697 (1997); [3] Dornish, M., Hagen, A., Hansson, E., Pecheur, C., Verdier, F., Skaugrud, Ø., Safety of PROTASAN™: Ultrapure chitosan salts for biomedical and pharmaceutical use. *Advan. Chitin Sci.*, **2**, 664-670 (1997).

Chitosan is believed to exert its effect by two mechanisms. The cationic polymer can bind to negative sialic residues in the mucus lining the nasal epithelial cells thereby slowing clearance of the formulation from the nasal cavity. Chitosan also has a direct but transient effect on tight junctions between epithelial cells. The tight junctions open transiently to allow an increased paracellular transport of drug molecules. Mechanistic studies have been conducted using confluent cell monolayers as well as in animal models.

Data (left figure) demonstrate that the exposure time and molecular weight are important parameters for chitosan-induced effects on cellular tight junctions (measured as a reduction in trans-epithelial electrical resistance, TEER). Reversibility, *i.e.* re-establishment of tight junctions, was best for formulations containing a high molecular weight chitosan [1].



Nasal delivery of insulin to sheep – effect of chitosan glutamate (PROTASAN™) solution (0.5%) on insulin uptake.

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Regulatory Status

PROTASAN™ chitosan chloride meets the standards set forth in the European Pharmacopoeia (EP 1774). PROTASAN™ chitosan products satisfy ASTM F 2103 for use in tissue engineered medical products (TEMPS). PROTASAN™ chitosan products are manufactured in compliance with current Good Manufacturing Practice and described in a DMF submitted to the US FDA.

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