

# Thiomers – Potent Auxiliary Agents in Nasal Drug Delivery

# ThioMatrix

## Nasal drug delivery

Nasal drug administration has been proposed as the likely most feasible alternative to parenteral injections. Furthermore, the nasal mucosa offers direct access to the compartment of the central nervous system via the olfactory route [1]. A number of limitations such as mucociliary clearance and limited drug absorption, however, represent a great challenge for the development of potent nasal drug delivery systems. Formulations providing a prolonged residence time in the nasal cavity—as illustrated in Fig. 1—and permeation enhancing properties turned out to be most promising within recent years. Thiomers offer the advantage of high mucoadhesive, controlled release and permeation enhancing properties leading to a strongly improved therapeutic potential of numerous nasally administered drugs.

## Mucoadhesion

In contrast to 'conventional' polymers, whose mucoadhesive properties are exclusively based on non-covalent bonds, thiolated polymers or designated thiomers are capable of forming covalent bonds with cysteine-rich subdomains of the mucus gel layer. The bridging structure most commonly utilized in biological systems—namely the disulfide bond—is thereby used. Due to the immobilization of thiol groups the mucoadhesive properties of chitosan and poly(acrylic acid), for instance, are improved at least 140-fold [2] and 20-fold [3], respectively. Thiomers are therefore by far the most mucoadhesive polymers to our notice [4]. The mucoadhesive properties of drug delivery systems based on thiomers were also demonstrated in human volunteers [e.g. 5].

## Controlled drug release

Due to a sustained drug release, a prolonged therapeutic level can be guaranteed. Consequently the frequency of dosing can be reduced contributing to an improved compliance. The release of drugs out of polymeric carrier systems can be controlled

**Technology Snapshot:**  
Strongly prolonged nasal residence time  
Permeation enhancing properties  
Sustained drug release  
Worldwide patent protection

rolled by a simple diffusion process and/or ionic interactions.

Hence, a controlled drug release for a prolonged period of time can be guaranteed. This controlled drug release has also been demonstrated by studies in human volunteers [5].

## Permeation enhancement

In case of systemic drug delivery via the nasal mucosa a permeation enhancing effect of the delivery system is often advantageous. Thiolated polymers have been demonstrated to show a strong permeation enhancing effect for the uptake of drugs from the nasal mucosa [6]. In comparison to most low molecular weight permeation enhancers, thiolated polymers offer the advantage of not being absorbed from the mucosal membrane. Hence, their permeation enhancing effect can be maintained for a comparatively longer period of time and systemic toxic side effects of the auxiliary agent can be excluded. The mechanism being responsible for the permeation enhancing effect of thiomers has been discovered within the last years showing a reversible opening of tight junctions and the role of glutathione as permeation mediator [7]. As this permeation enhancing mechanism differs from most conventionally used permeation enhancers such as fatty acids, the effect can be even further improved by the combination of both types of permeation enhancing systems. In Fig. 2 the improved nasal absorption of a peptide drug (Leu-enkephalin) in the presence of 0.5% thiomers is illustrated [8].

Furthermore, the improvement in systemic uptake of insulin and human growth hormone (hGH) from the nasal mucosa was demonstrated in vivo [9, 10]. Results of these studies are illustrated in Fig. 3 and 4. More recent studies showed that by making use of thiomers-microparticles an even higher nasal bioavailability for hGH in the range of 8% can be gained [11].

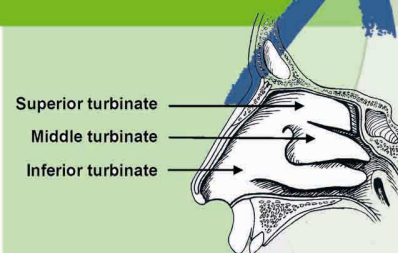


Fig. 1. Anatomy of the nasal cavity.

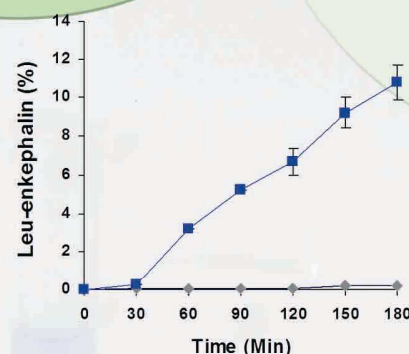


Fig. 2. Transport of Leu-enkephalin across freshly excised bovine nasal mucosa in buffer solution (♦) and in the presence of 0.5% thiomers (■). Adapted from Bernkop-Schnürch et al. [8].

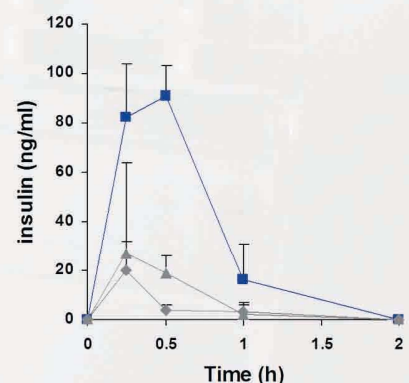


Fig. 3. Concentration-time profiles of insulin in rat plasma obtained after nasal application of thiolated chitosan-insulin microparticles (■), of chitosan-insulin microparticles (▲) and of mannitol-insulin microparticles (◆), respectively. Adapted from Krauland et al. [9].

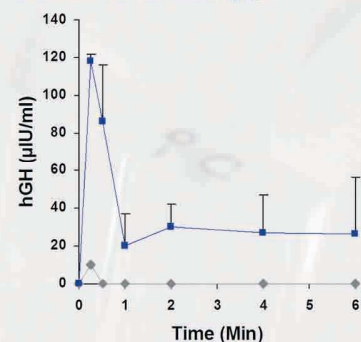


Fig. 4. Because of its comparatively high molecular mass (22 kDa), hGH is not absorbed from the nasal cavity in significant quantities (♦). Utilizing a thiomers as auxiliary agent, however, an absolute nasal bioavailability of 2.6% was reached (■). Adapted from Leitner et al. [10].

Thiomers are among the most potent polymeric efflux pump inhibitors currently available. They show, for instance, a 2.7-fold higher effect *in vivo* than PEGs and PEG derivatives such as Pluronic P85 [12].

In comparison to most other efflux pump inhibitors thiomers offer the advantage of

- not being absorbed from the nasal mucosa due to their high molecular mass
- 100% reversible inhibition of efflux pumps

### In situ gelation

Various polymers are capable of prolonging the residence time of drug delivery systems by their *in situ* gelling properties. In comparison to so far used *in situ* gelling polymers, thiolated polymers are capable of providing a comparatively more pronounced increase in viscosity after application, as an extensive crosslinking process by the formation of disulfide bonds between the polymer chains takes place. For instance, in case of thiolated chitosan a more than 1000-fold increase in viscosity by the formation of disulfide bonds within the polymeric network based on a simple oxidation process was shown [2]. Being applied in liquid form, they become viscous gels on the nasal mucosa, which avoids an unintended elimination and outflow of the semisolid delivery system. ThioMer formulations can be nasally administered in form of:

- liquids
- gels
- aerosols

For liquid suspensions and aerosol formulations thioMer micro- and nanoparticles can be utilized. Particles can be stabilized via disulfide bonds still exhibiting sufficient free thiol groups on their surface as illustrated in Fig. 5 [13]. Even for thioMer-nanoparticles size distribution is in a narrow range as illustrated in Fig. 6.

### Scaled-up production / GMP material

The production capacity for certain thiomers is already in the range of several 100 kg per year and can be further 10- up to 100-fold scaled-up within a year on demand. Moreover for certain thiomers GMP material is available.

### Safety and clinical trials

Due to their high molecular mass thiomers are not absorbed from the nasal mucosa. Hence systemic toxic side effects can be excluded. Ciliary beat frequency (CBF) studies with human nasal epithelial cells demonstrated that the impact of polymeric excipients such as poly(acrylic acid) (PAA) on CBF is not at all altered due to thiolation. In Fig. 7 an example is given. Various thiomers have already been tested in human volunteers showing neither damage nor any irritation to mucosal membranes as sensitive as the ocular surface [5].

### Partnering opportunity

The thioMer-technology is worldwide protected by various patents. ThioMatrix offers the thioMer-technology for licensing to third parties on a product-by-product basis.

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### For more information

For further details please contact:  
Prof. Dr. Andreas Bernkop-Schnürch,  
CSO ThioMatrix, Trientlgasse 65,  
6020 Innsbruck, Austria;  
phone: 0043 650 753 62 70;  
e-mail: a.bernkop@thiomatrix.com

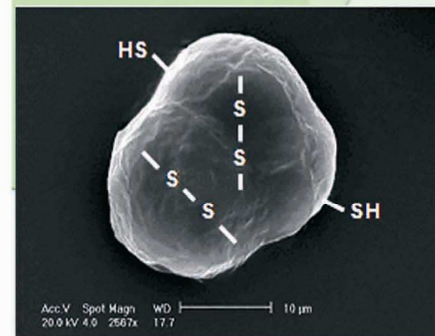


Fig. 5. Schematic presentation of thioMer microparticles.

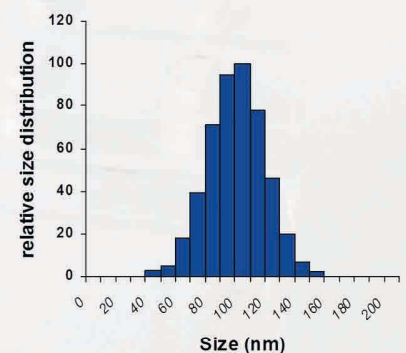


Fig. 6. Size distribution of thioMer nanoparticles.

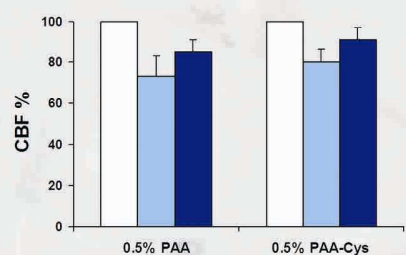


Fig. 7. Ciliary beat frequency (CBF) studies with poly(acrylic acid) (PAA) and thiolated poly(acrylic acid) (PAA-Cys); white bars: buffer only control; blue bars: 0.5% tested polymer; dark blue bar: recovery after having removed the polymer.