Thiomers – Potent Auxiliary Agents in Non-invasive Peptide Drug Delivery

Non-invasive peptide drug delivery

Therapeutic peptides and proteins have become an important class of drugs due to advancement in molecular biology and recombinant technology. A safe, effective and patient friendly delivery of these drugs is the key to commercial success. Currently, most of therapeutic peptides and proteins are administered by the parenteral route which has numerous drawbacks. Consequently, 'injectable to non-invasive conversions' are highly on demand.

Mucoadhesion

Due to high mucoadhesive properties a presystemic metabolism of peptide drugs on the way between the delivery system and the absorption membrane—as illustrated in Fig. 1—can be excluded. 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, were improved at least 140-fold [1] and 20-fold [2], respectively. In Table 1 the rank order of the most mucoadhesive polymers tested via the rotating cylinder method is provided [3]. The mucoadhesive properties of drug delivery systems based on thiomers were also demonstrated in human volunteers [e.g. 4].

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 by a simple diffusion process and/or ionic interactions. Hence, a controlled drug release for numerous hours can be guaranteed. In Fig. 2 the release of a peptide drug (antide) out of thiomer tablets is illustrated [5]. This controlled drug release has also been demonstrated by studies in human volunteers.

Technology Snapshot:

Intimate contact with the absorption membrane

Protection towards presystemic metabolism

Permeation enhancement

Controlled drug release

Worldwide patent protection

Table 1. *Rank order of most mucoadhesive polymers. Adapted from Grabovac et al. [3]*

Polymer	Adhesion time in hours; means ± SD (n = 3–5)
Thiolated Chitosan	161.2 ± 7.2
Thiolated Polycarbophil	26.0 ± 0.9
Thiolated Poly(Acrylic Acid)	19.4 ± 0.8
Hydroxypropylcellulose	15.2 ± 0.4
Carbopol 980	12.5 ± 0.9
Carbopol 974	10.3 ± 0.9
Polycarbophil	10.2 ± 0.8
Carbopol 980	9.8 ± 0.2

Enzyme inhibition

Many non-invasively administered drugs such as therapeutic peptides or nucleic acids are degraded on the mucosa by membrane bound enzymes strongly reducing their bioavailability. In case of oral administration this 'enzymatic barrier' is even more pronounced as an additional degradation caused by luminally secreted enzymes takes place. Because of their capability to bind Zn^{2+} ions via thiol groups, thiomers are potent inhibitors of most membrane bound and secreted zinc-dependent enzymes. Due to this enzyme inhibitory effect, thiomers can significantly improve the bioavailability of non-invasively administered drugs. Results of enzyme inhibition studies on the intestinal mucosa are illustrated in Fig. 3.

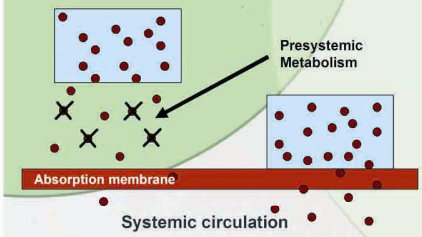

Fig. 1. *Due to high mucoadhesive properties a presystemic metabolism of peptide drugs on the way between the delivery system and the absorption membrane can be excluded.*

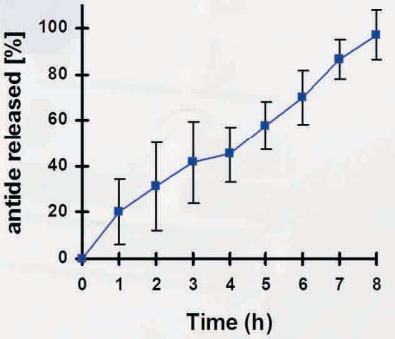

Fig. 2. *Release profile of a peptide drug (antide) from thiomer matrix tablets. Adapted from Bernkop-Schnürch et al. [5].*

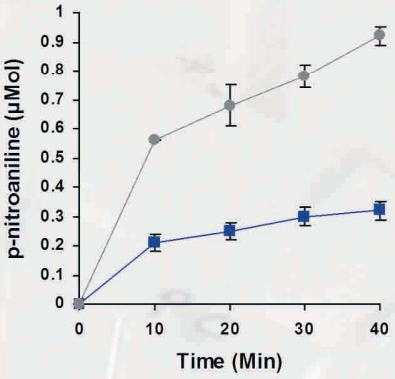

Fig. 3. *Time-course of the formation of p-nitroaniline from leu-p-nitroanilide by intact intestinal mucosa after incubation in control buffer (•) and in control buffer containing 0.25% thiomer (▪). Adapted from Bernkop-Schnürch et al. [6].*

Permeation enhancement

In order to improve the bioavailability of non-invasively administered drugs permeation enhancing delivery systems are often essential. Thiolated polymers have been demonstrated to show a strong permeation enhancing effect for the uptake of drugs from mucosal membranes such as the intestinal [7-9] and nasal mucosa [10]. In comparison to most low molecular mass 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 the 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. The permeation enhancing properties of thiomers were also demonstrated in various in vivo studies.

In Fig. 4 the improved absorption of a peptide drug from the nasal mucosa in the presence of 0.5% thiomer is illustrated. Furthermore, the improvement in systemic uptake of another peptide drug from the intestinal mucosa was demonstrated in pigs. Results of this study are illustrated in Fig. 5. In another study the blood glucose level was decreased by 40% for almost 24 hours after oral administration of PEG-ylated insulin with a thiomer formulation in diabetic mice (Fig. 6). In contrast, PEG-ylated insulin having been administered without a thiomer did not lead to any decrease in the blood glucose level [12].

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 mucosal membranes. Hence systemic toxic side effects can be excluded.

Various biological safety reports are available. Thiomers have already been tested in human volunteers showing neither damage nor any irritation of as sensitive mucosal membranes as the ocular epithelium [4].

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.

References

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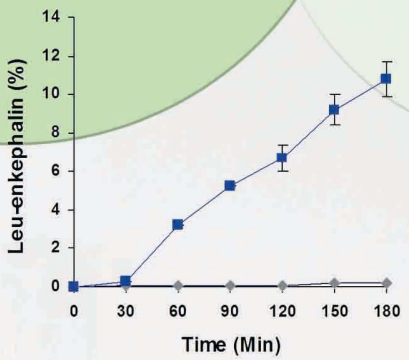

Fig. 4. *Transport of Leu-enkephalin across freshly excised bovine nasal mucosa in buffer solution (♦) and in the presence of 0.5% thiomer (■) [11].*

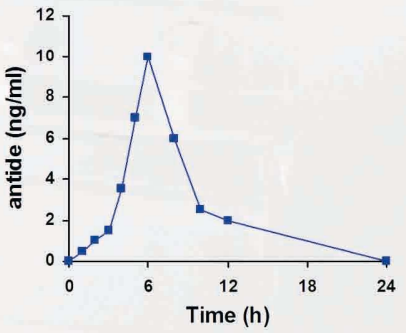

Fig. 5. *Concentration profile of an orally administered peptide drug (antide) utilizing a thiomeric carrier system in plasma of pigs. Adapted from Bernkop-Schnürch et al. [5].*

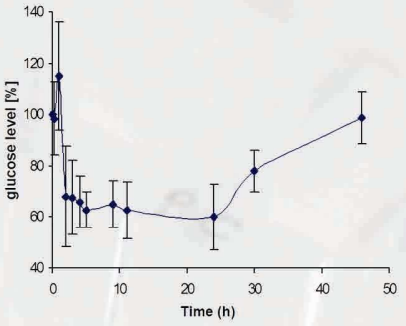

Fig. 6. *Blood glucose level of diabetic mice after oral administration of PEG-ylated insulin with a thiomer formulation. Adapted from Caliceti et al. [12].*

For more information

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