Thiomers – Potent Auxiliary Agents in Intraoral Drug Delivery

Intraoral drug delivery

The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and pre-systemic elimination in the gastrointestinal tract and first-pass metabolism in the liver are avoided. In case of systemic drug delivery via the buccal mucosa, however, numerous cell layers have to be permeated by the drug in order to reach first blood vessels being located in the lamina propria (Fig. 1).

For intraoral drug delivery thiomers offer the advantage of high mucoadhesive, in situ gelling, controlled release, enzyme inhibitory and permeation enhancing properties leading to a strongly improved therapeutic potential of numerous 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 as illustrated in Fig. 2. The bridging structure most commonly utilized in biological systems - namely the disulfide bond - is 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].

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.

Technology Snapshot:

Strongly prolonged intraoral residence time

Sustained drug release

Permeation enhancing properties

In situ gelling properties

Worldwide patent protection

Controlled drug release

Due to a sustained drug release, a prolonged therapeutic level can be guaranteed in the oral cavity. Consequently the frequency of dosing can be reduced contributing to an improved compliance. The release of drugs out of thiomer 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. The release behaviour of a model drug (PACAP) out of a buccal delivery system comprising a thiomer is provided in Fig. 3 [6].

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 drugs such as therapeutic peptides are degraded on the buccal mucosa by membrane bound enzymes strongly reducing their systemic bioavailability [7]. Because of their capability to bind Zn^{2+} ions via thiol groups, thiomers are potent inhibitors of most membrane bound zinc-dependent enzymes. Due to this enzyme

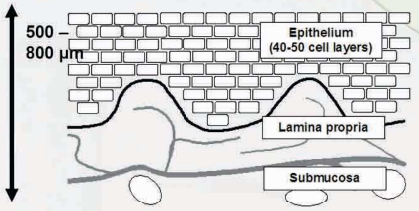

Fig. 1. *Schematic presentation of the buccal mucosa.*

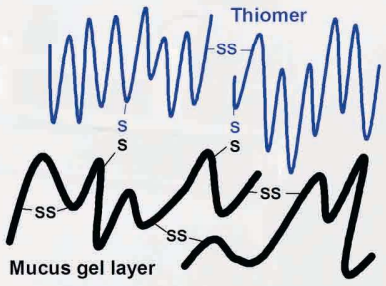

Fig. 2. *Formation of disulfide bonds between thiomers and the mucus gel layer.*

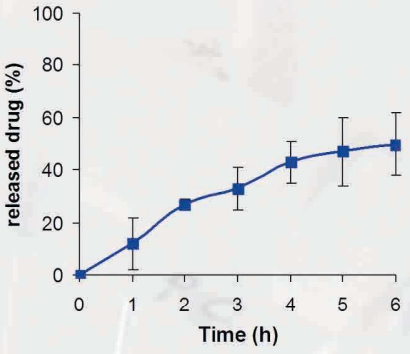

Fig. 3. *Release of a peptide drug (PACAP) out of a buccal patch comprising a thiomer. Adapted from Langoth et al. [6].*

inhibitory effect, thiomers can significantly improve the bioavailability of intraorally administered drugs. Results of enzyme inhibition studies on the buccal mucosa are illustrated in Fig. 4 [8].

Permeation enhancement

Thiolated polymers have been demonstrated to show a strong permeation enhancing effect for the uptake of drugs from mucosal membranes. 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 [9]. 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. 5 the improved buccal absorption of a peptide drug (PACAP) in the presence of 1% thiomer is illustrated [10]. Furthermore, the improvement in systemic uptake of the same drug from the buccal mucosa was demonstrated in vivo in pigs. Results of this study are illustrated in Fig. 6. PACAP being incorporated in state-of-the-art formulations was not taken up at all in the systemic circulation.

Thiomer formulations can be intraorally administered in form of:

- liquids
- gels
- tablets
- patches

Once applied they remain on the buccal mucosa for numerous hours guaranteeing a controlled drug release over the intended period.

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 buccal mucosa. Hence systemic toxic side effects can be excluded. Various biological safety reports are available. Furthermore, 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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For more information

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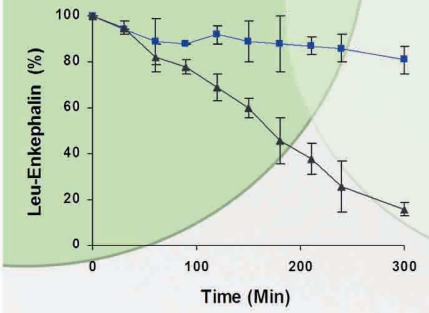

Fig. 4. *Time-course of the percentage remaining of leu-enkephalin on intact buccal mucosa during incubation with 50 mM phosphate buffer pH 6.8 containing 2% NaCl without polymer (▲) and with 0.25% (w/v) thiomer (■). Adapted from Langoth et al. [8].*

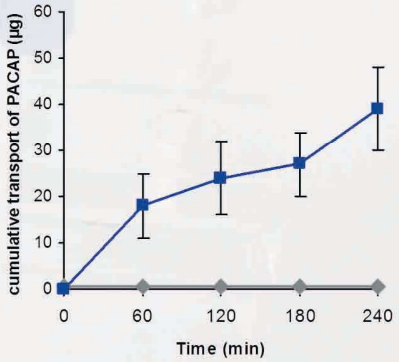

Fig. 5. *Uptake of a therapeutic peptide (PACAP) from porcine buccal mucosa (♦) and the improved uptake due to the addition of 1% thiomer (■). Adapted from Langoth et al. [10].*

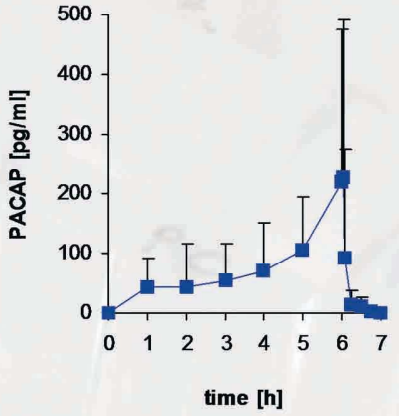

Fig. 6. *Concentration of PACAP in plasma obtained after buccal administration of the drug incorporated in a thiomer matrix. Adapted from Langoth et al. [11].*