

# Thiomers – Potent Auxiliary Agents in Oral Drug Delivery

ThioMatrix

## Oral drug delivery

Amongst the various routes of drug delivery, the oral route is perhaps the most preferred to the patient and the clinician alike. It is regarded as the safest and most convenient method of drug administration. For many existing and new drugs such as therapeutic peptides, peptidomimetics, oligonucleotides, siRNA or plasmid DNA, however, the bioavailability is below a level, which would justify an oral dosage form out of economical reasons.

## Mucoadhesion

Due to the use of mucoadhesive drug delivery systems providing an intimate contact with gastrointestinal mucosa the bioavailability of numerous drugs can be strongly improved. In Fig. 1 a comparison in the performance of a mucoadhesive versus a non-mucoadhesive particulate delivery system for riboflavin in human volunteers is provided [1]. 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 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 [2] and 20-fold [3], respectively. In Table 1 the rank order of the most mucoadhesive polymers tested via the rotating cylinder method is provided [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 [6]. Consequently the frequency of dosing can be reduced contributing to an improved compliance. The release of drugs out of

### Technology Snapshot:

Intimate contact with the GI-mucosa  
Protection towards presystemic metabolism

Permeation enhancement  
Controlled drug release  
Worldwide patent protection

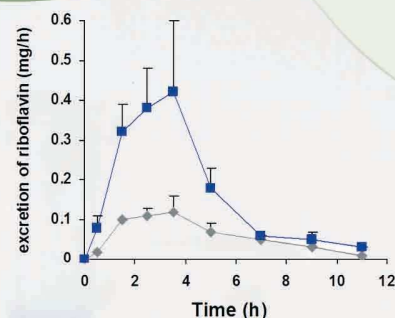
polymeric carrier systems can be controlled by a simple diffusion process and/or ionic interactions. Hence, a controlled drug release for numerous hours can be guaranteed (Fig. 3). This controlled drug release out of thiomers has also been demonstrated by studies in human volunteers.

## Permeation enhancement

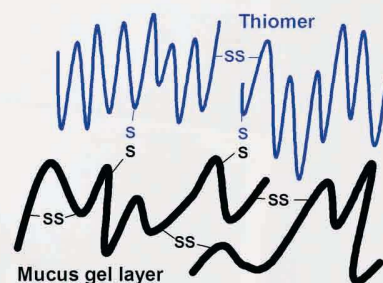
In order to improve the bioavailability of orally administered drugs permeation enhancing drug delivery systems are often essential. Thiolated polymers have been demonstrated to show a strong permeation enhancing effect for the uptake of drugs from the intestinal mucosa [7-9]. In comparison to most low 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 [10]. As this permeation enhancing mechanism differs from most

**Table 1.** Rank order of most mucoadhesive polymers. Adapted from Grabovac et al. [4]

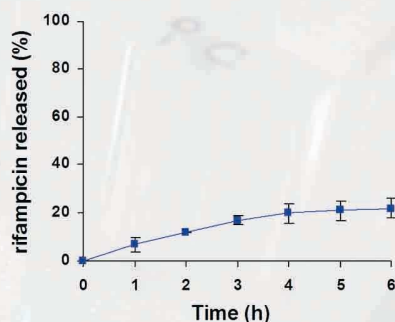
Polymer	Adhesion time in hours; means $\pm$ SD (n = 3-5)
Thiolated Chitosan	161.2 $\pm$ 7.2
Thiolated Polycarboxiphil	26.0 $\pm$ 0.9
Thiolated Poly(Acrylic Acid)	19.4 $\pm$ 0.8
Hydroxypropylcellulose	15.2 $\pm$ 0.4
Carbopol 980	12.5 $\pm$ 0.9
Carbopol 974	10.3 $\pm$ 0.9
Polycarboxiphil	10.2 $\pm$ 0.8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



**Fig. 1.** Oral bioavailability of riboflavin in human volunteers measured via the rate of urinary excretion; riboflavin was administered utilizing mucoadhesive particles (■) and non-mucoadhesive particles (◆); Adapted from Akiyama et al. [1].



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



**Fig. 3.** Release profile of rifampicin from tablets based on thiolated carboxymethylcellulose. Adapted from Bernkop-Schnürch et al. [6].

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. 4, for example, the improved absorption of low molecular weight heparin (LMWH) in the presence of a thiomers is illustrated [11].

### High efflux pump inhibitory potential

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 Fig. 5 an example for the improved oral bioavailability of an efflux pump substrate (rhodamine 123) due to the co-administration of a thiomers is shown.

### 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

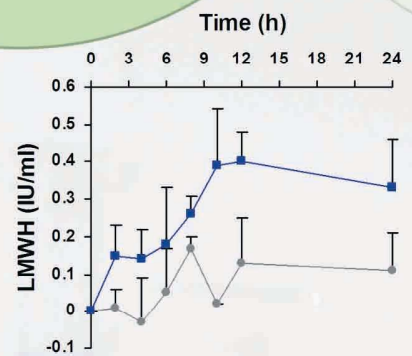
Due to their high molecular mass thiomers are not absorbed from the GI-mucosa. Hence systemic toxic side effects can be excluded. Various biological safety reports are available. Thiomers have already been tested in human volunteers showing neither damage nor any irritation to mucosal membranes as sensitive as the ocular surface [5].

### Partnering opportunity

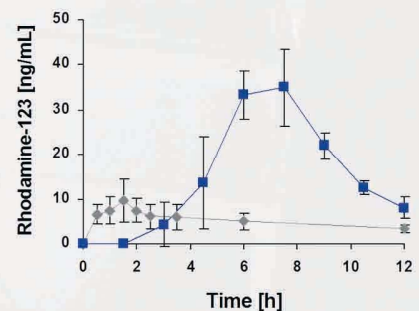
The thiomers-technology is worldwide protected by various patents. ThioMatrix offers the thiomers-technology for licensing to third parties on a product-by-product basis.

## References

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**Fig. 4.** Comparison of the concentration profiles of heparin in plasma obtained after oral administration of heparin incorporated in thiomers tablets (■) and in unmodified polymer tablets (◆) in rats. Adapted from Kast et al. [11].



**Fig. 5.** Pharmacokinetic of rhodamine 123 being administered with (■) and without (◆) a thiomers. Adapted from Föger, F. et al. [13].

## For more information

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