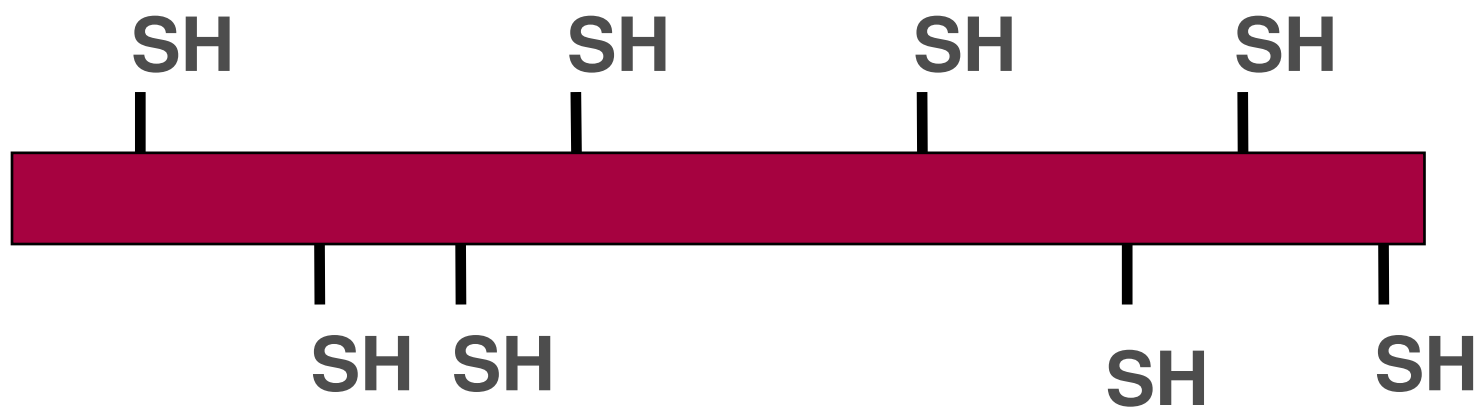




Thiolated Polymers as Potential Novel systems for Oral Delivery of Peptides and Proteins

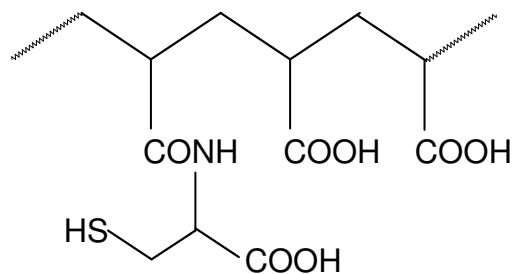
Krum Kafedjiiski, A. Bernkop-Schnürch, University of Innsbruck

Thiolated Polymers / Thiomers

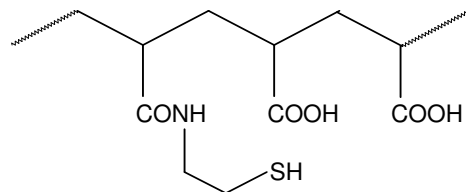


Background

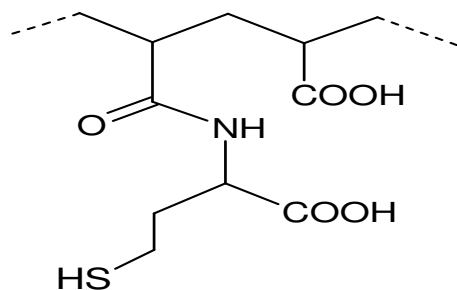
Chemical Structure of Anionic Thiomers



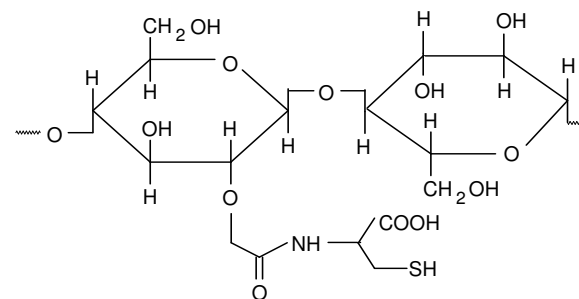
Polycarbophil-cysteine



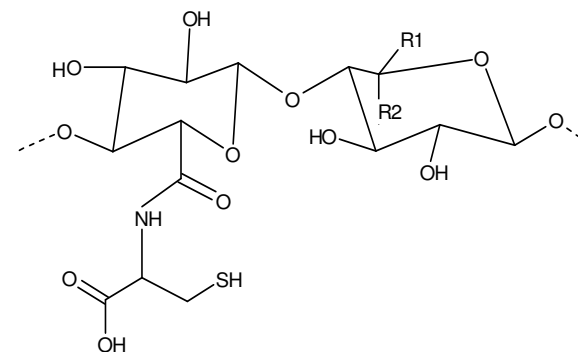
Polycarbophil-cysteamine



Poly(acrylic acid)-homocysteine



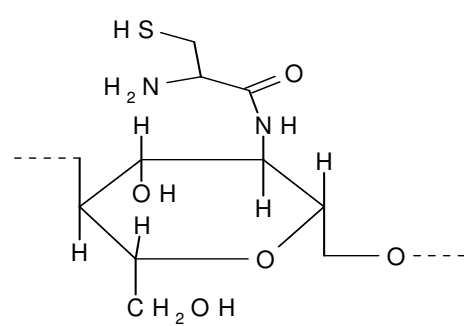
Carboxymethylcellulose-cysteine



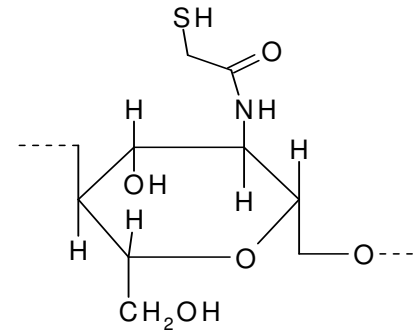
Alginate-cysteine (R₁=H, R₂=COOH or R₁=COOH, R₂=H)

Background

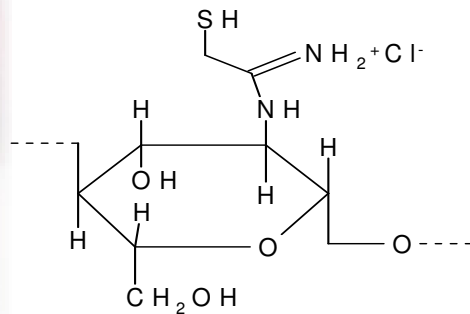
Chemical Structure of Cationic Thiomers



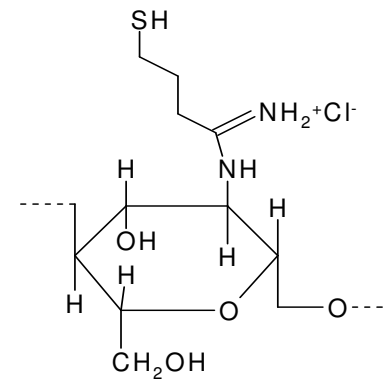
Chitosan-cysteine



Chitosan-thioglycolic acid



Chitosan-thioethylamidine



Chitosan-4-thio-butylamidine

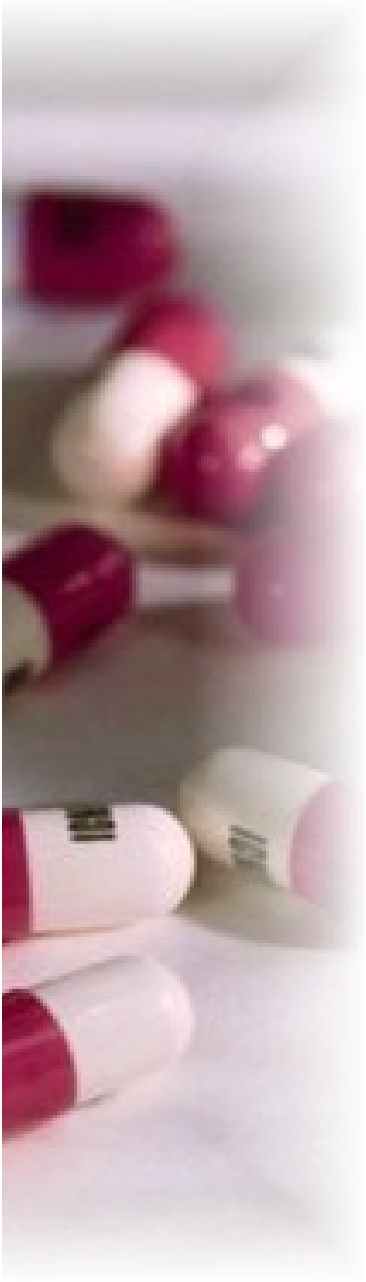
Background



Advantages of Thiomers

- Improved mucoadhesive properties
- Improved cohesive properties
- Inhibitory effect towards proteases
- Controlled drug release
- Permeation enhancing effect

Background



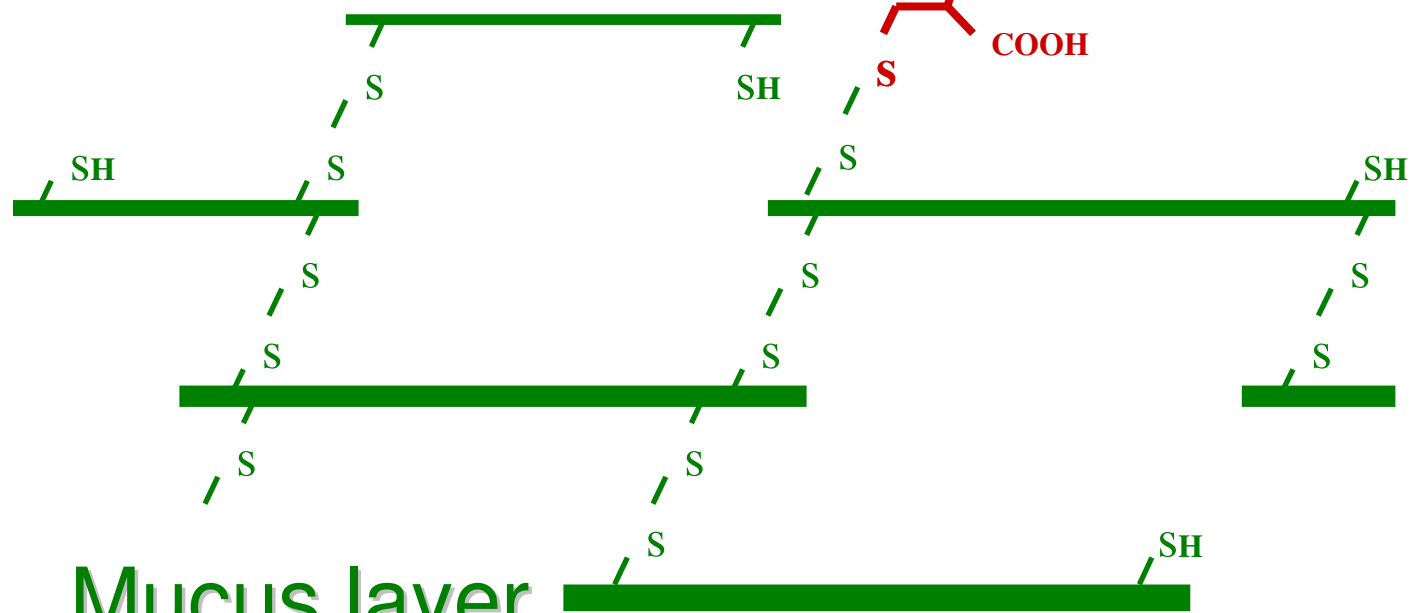
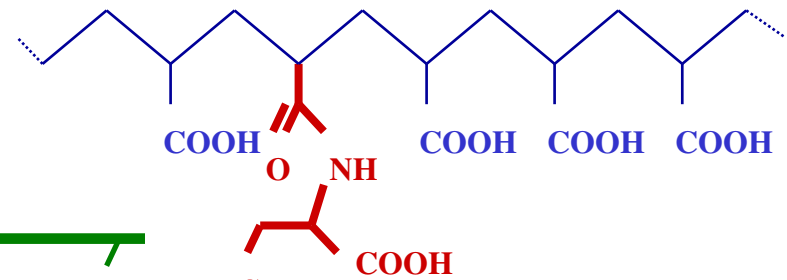
Advantages of Thiomers

- Improved mucoadhesive properties
- Improved cohesive properties
- Inhibitory effect towards proteases
- Controlled drug release
- Permeation enhancing effect

Background

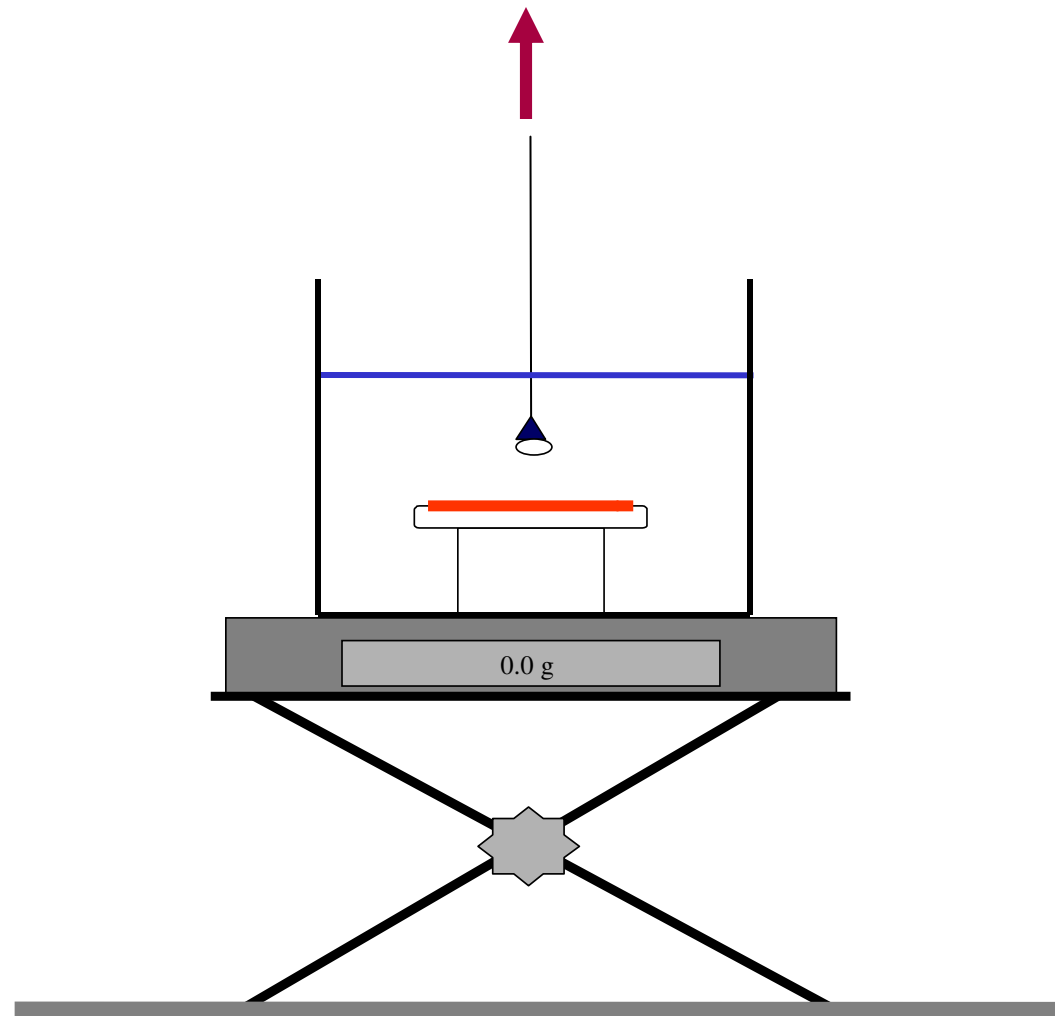
The idea behind

Polymer

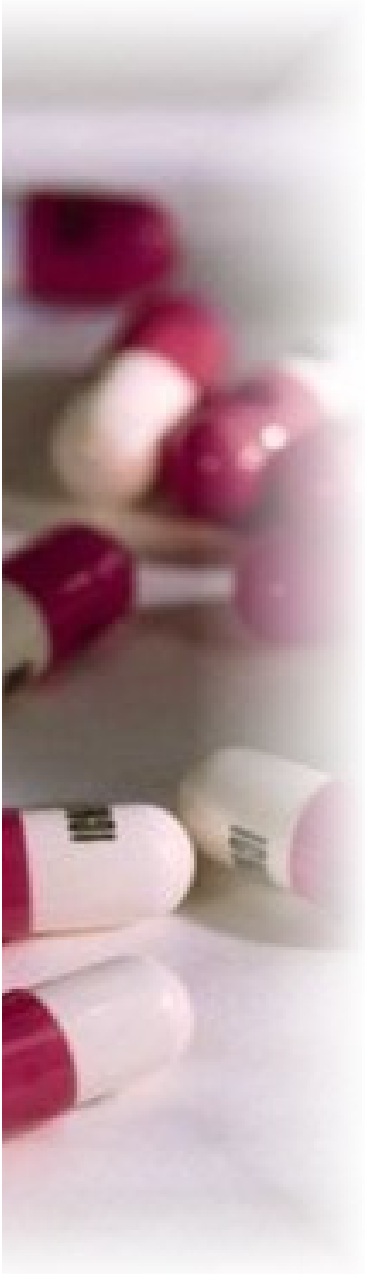


Mucoadhesion

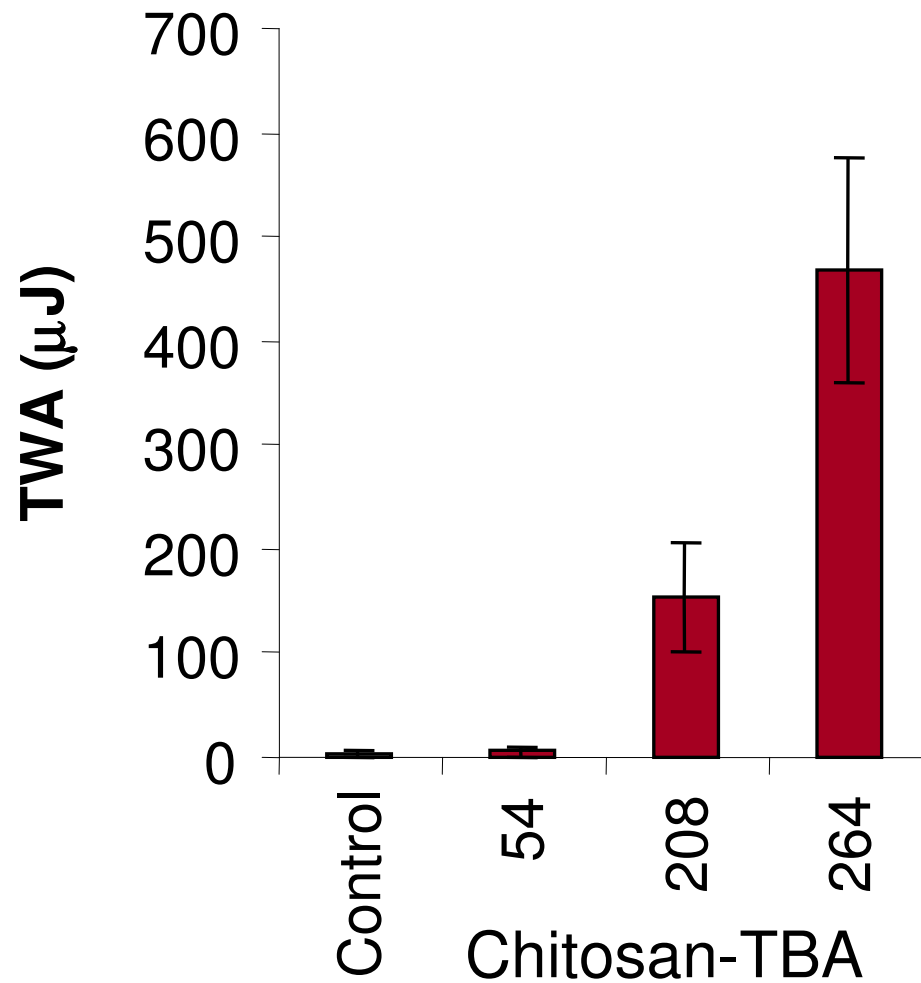
Tensile Studies



Mucoadhesion



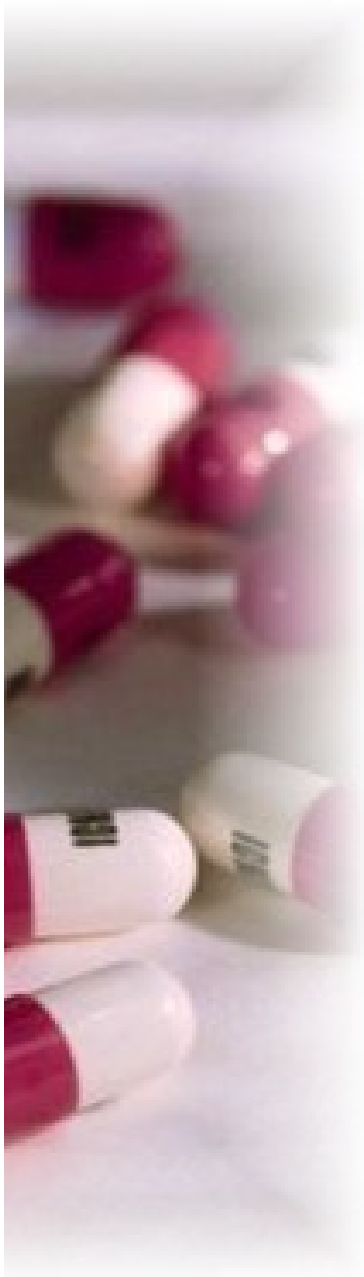
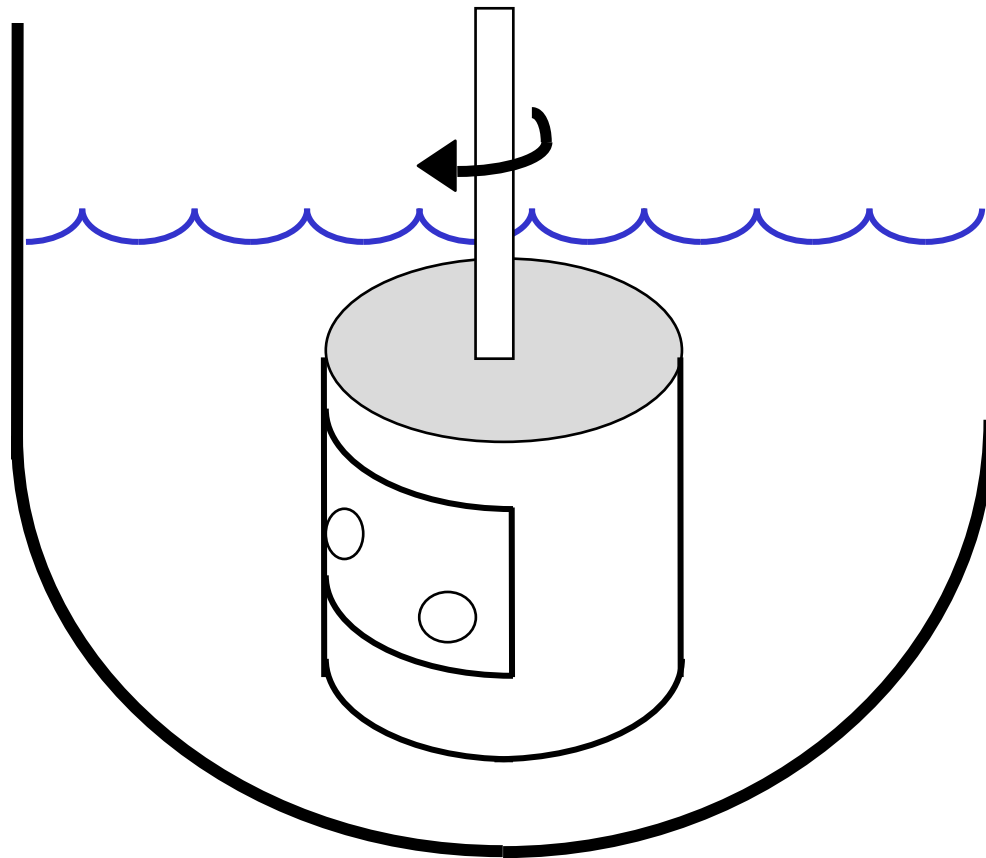
Mucoadhesive Properties



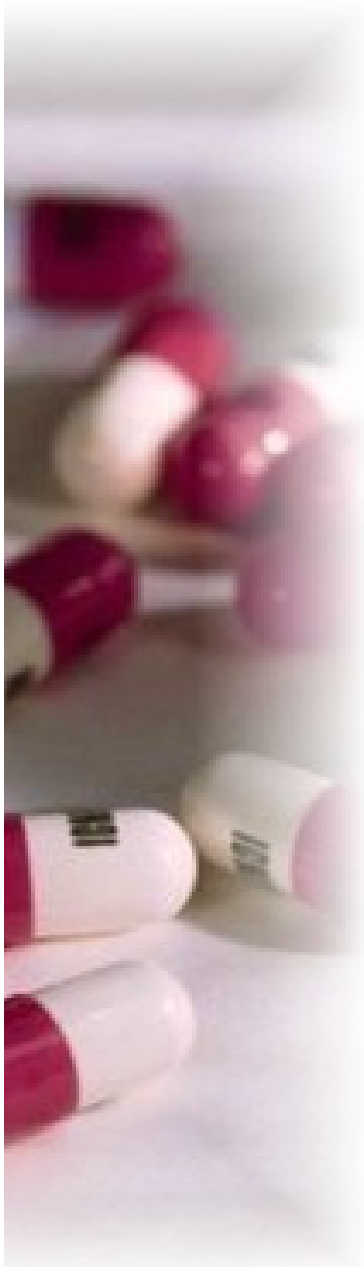
M. Roldo et al. *Eur. J. Pharm. Biopharm.* **57** (2004) 115- 121.

Mucoadhesion

Rotating Cylinder



Mucoadhesion

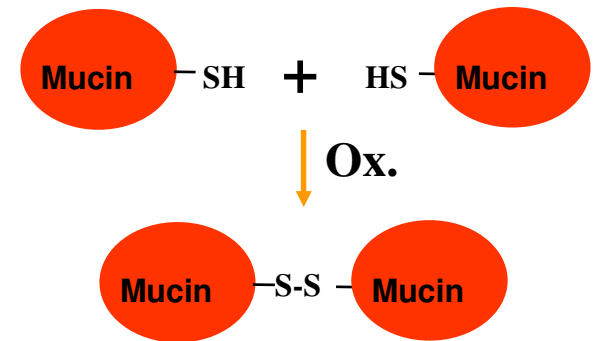
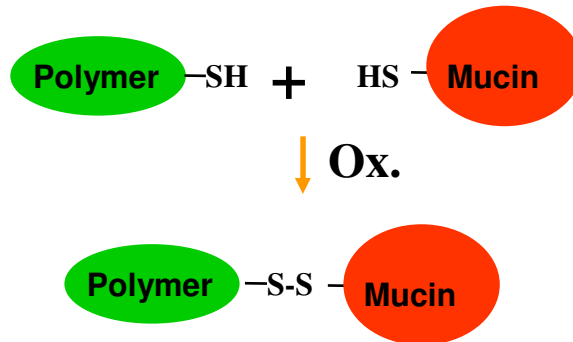
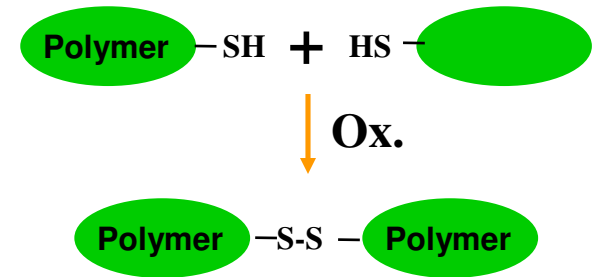
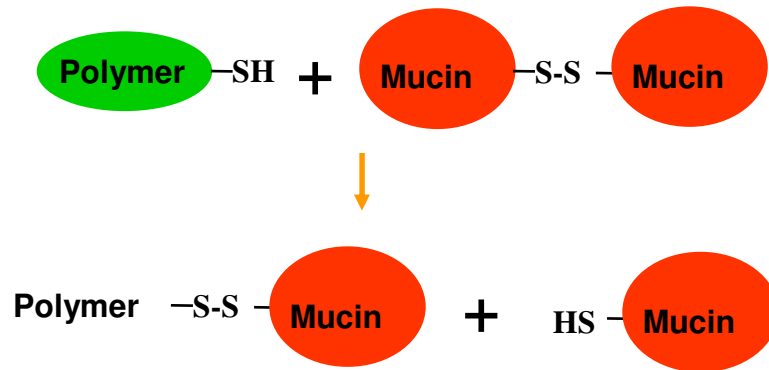


| Polymer | Degree of modification ($\mu\text{mol/g}$) | Adhesion time (h) | Improvement ratio |
|---|--|-------------------|-------------------|
| Chitosan-4-thiobutylamidine | 682 | >160 | >94 |
| Poly(acrylic acid)-cysteine | 695 | 22 | 13 |
| Chitosan-thioethylamidine | 140 | 24 | 8.9 |
| Chitosan-thioglycolic acid | 27 | 4 | 5 |
| Polycarbophil-cysteine | 12 | >10 | 2.1 |
| Sodium Carboxymethyl cellulose-cysteine | 22 | 3 | 1.2 |

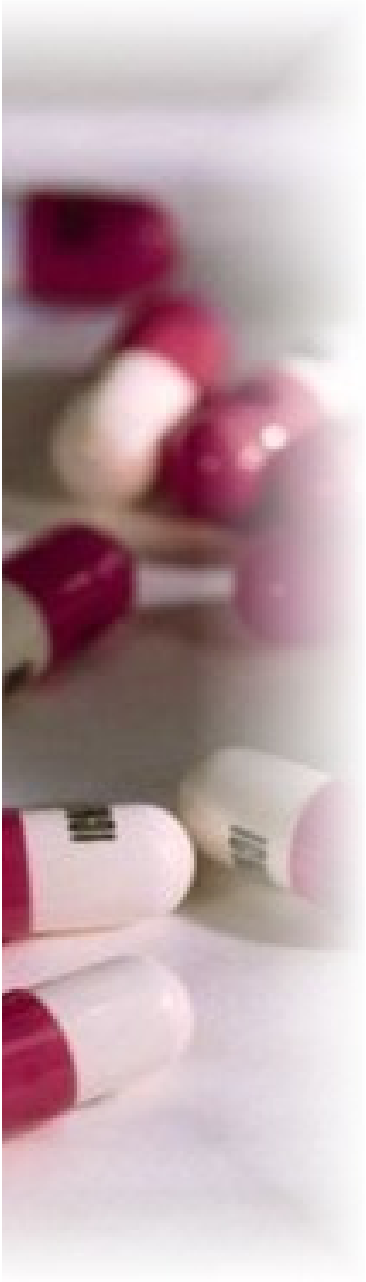
Table. Comparison of the mucoadhesive properties of various polymeric excipients. Mucoadhesion studies were performed via rotating cylinder method; Improvement ratio = adhesion time of thiomers/adhesion time of corresponding unmodified polymer.

Mucoadhesion

Oxidation and/or Thiol/Disulfide Exchange Reactions



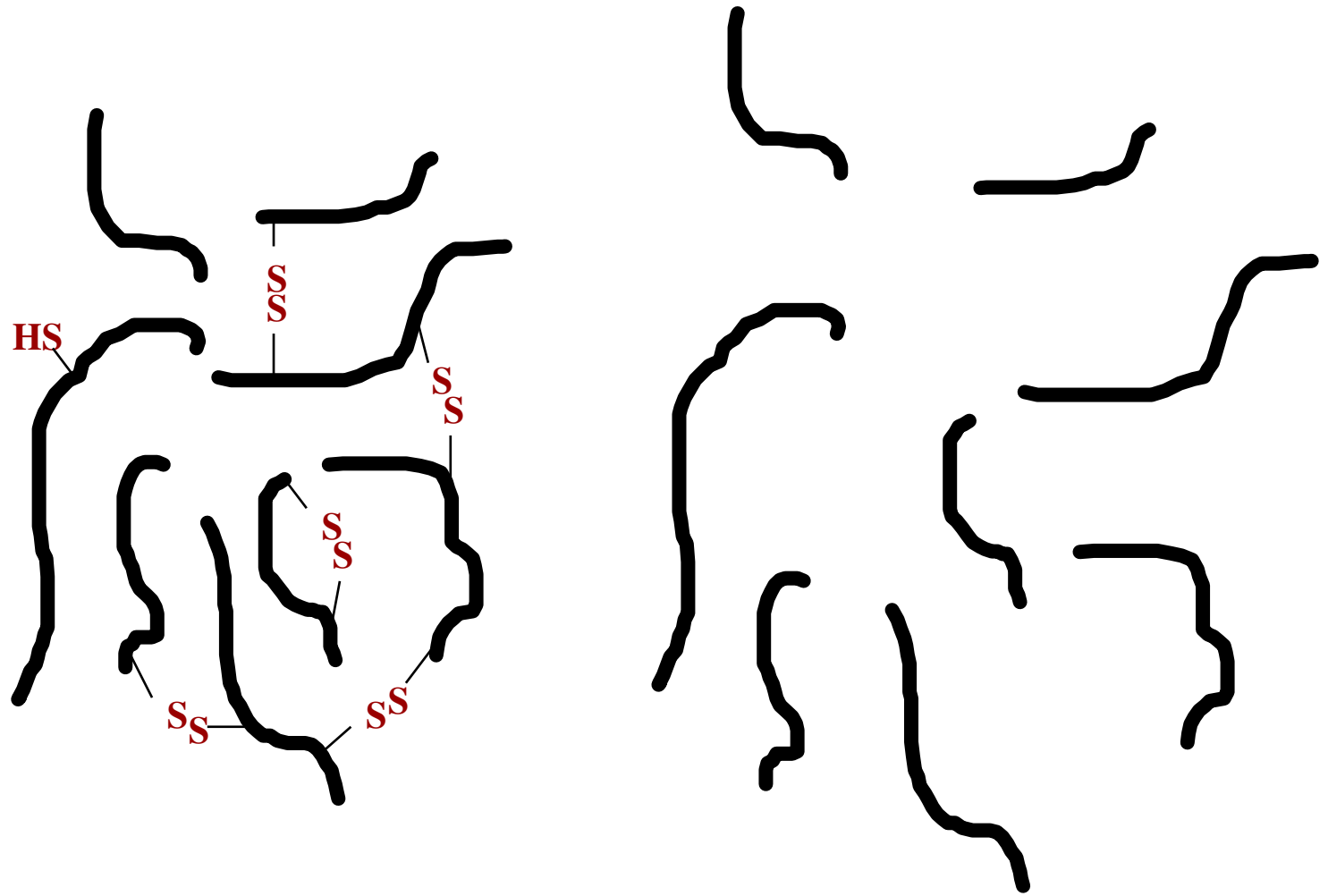
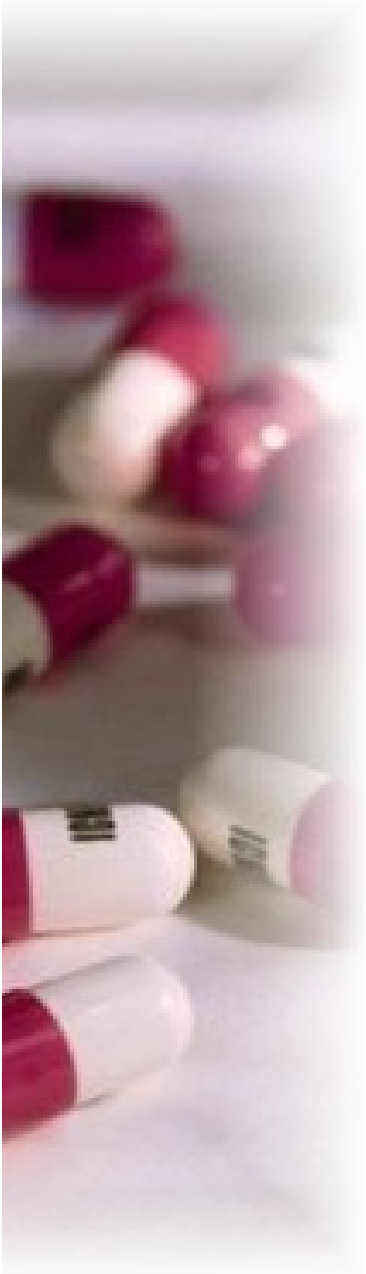
Orientating Studies



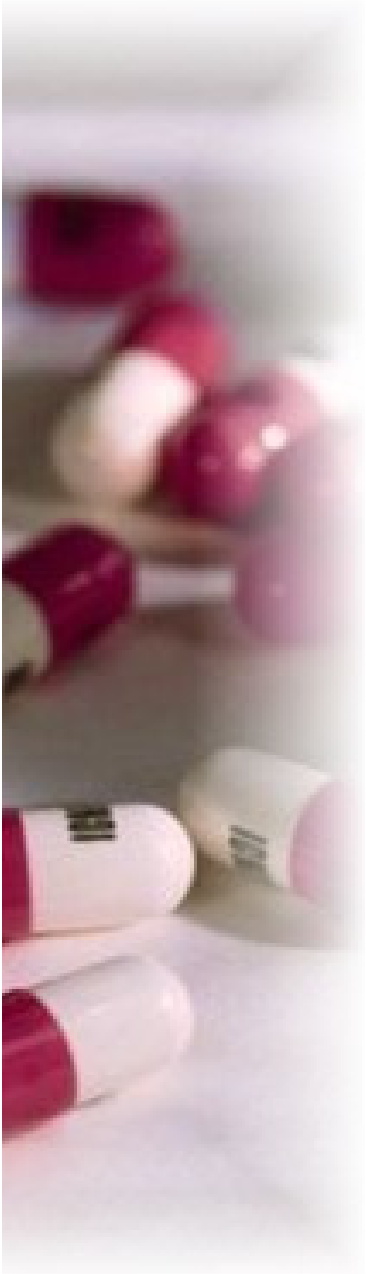
Advantages of Thiomers

- Improved mucoadhesive properties
- Improved cohesive properties
- Inhibitory effect towards proteases
- Controlled drug release
- Permeation enhancing effect

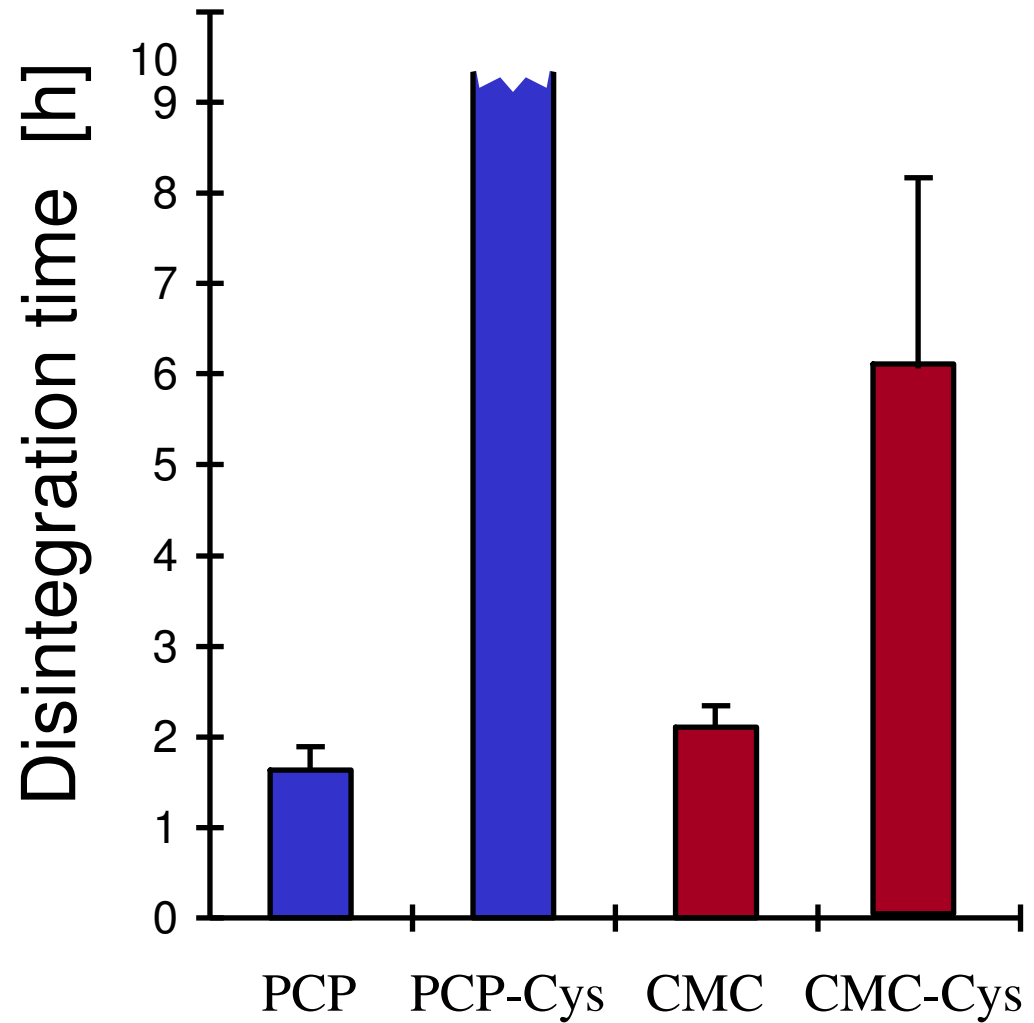
Background



Cohesion

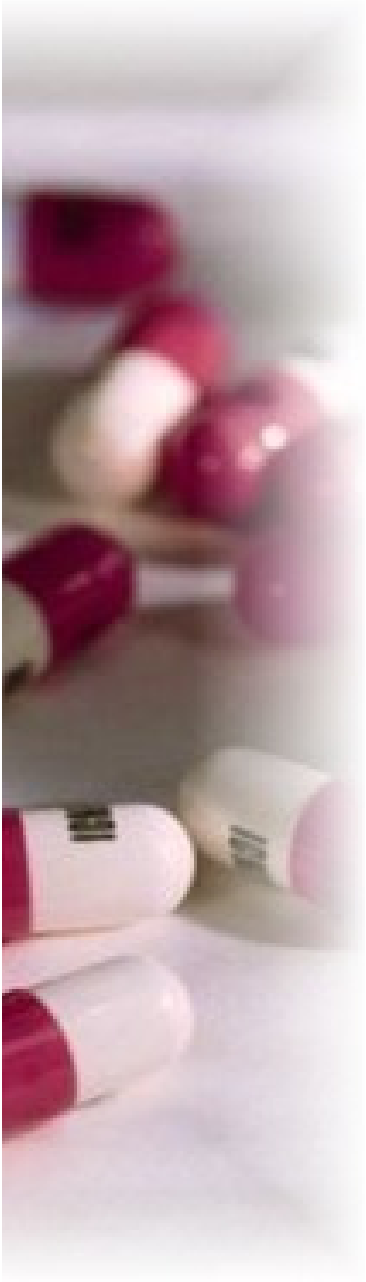


Disintegration Studies



Bernkop-Schnürch, A. et al. (2000) *J. Control. Release*, **66**, 39-48.

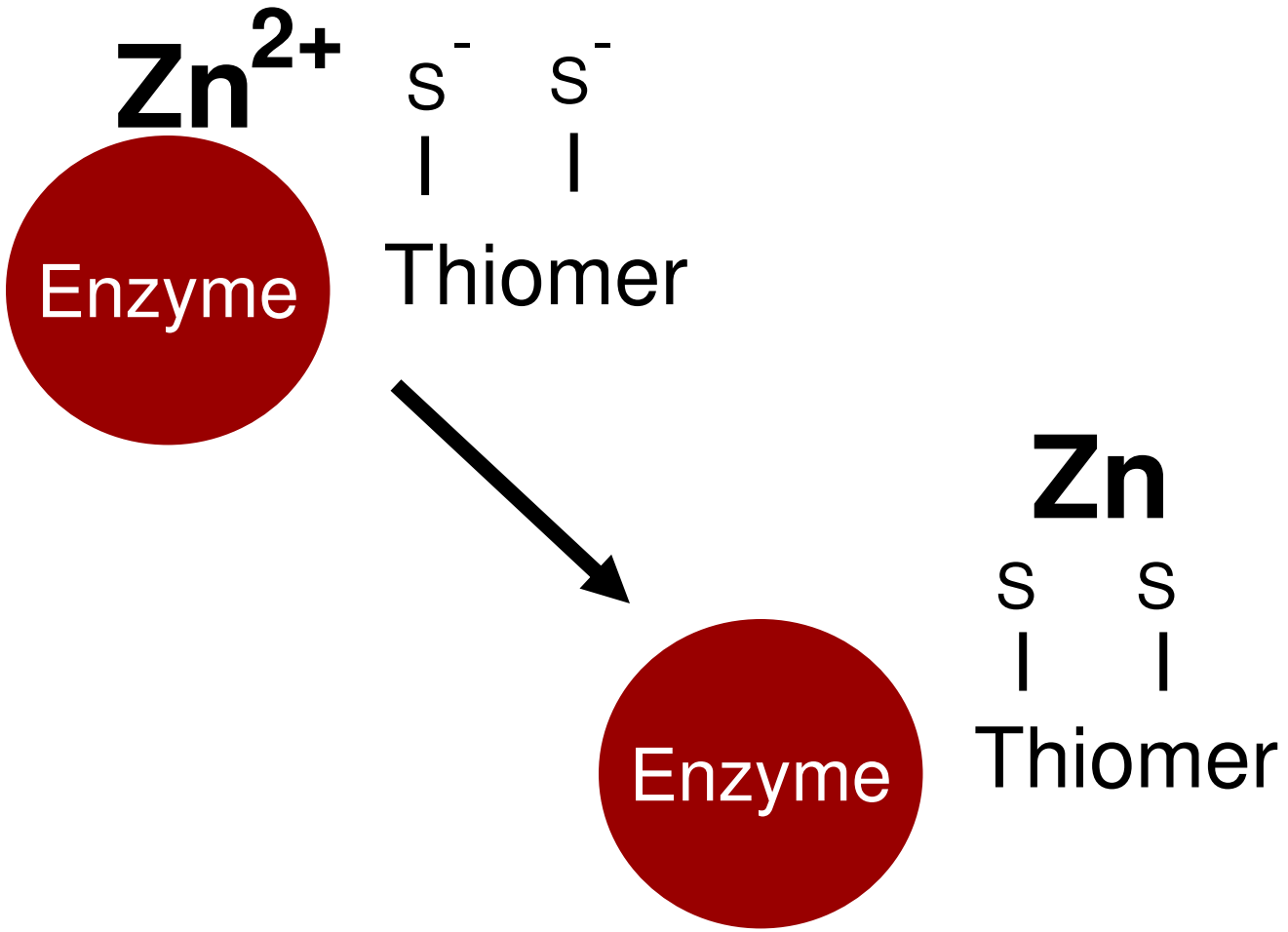
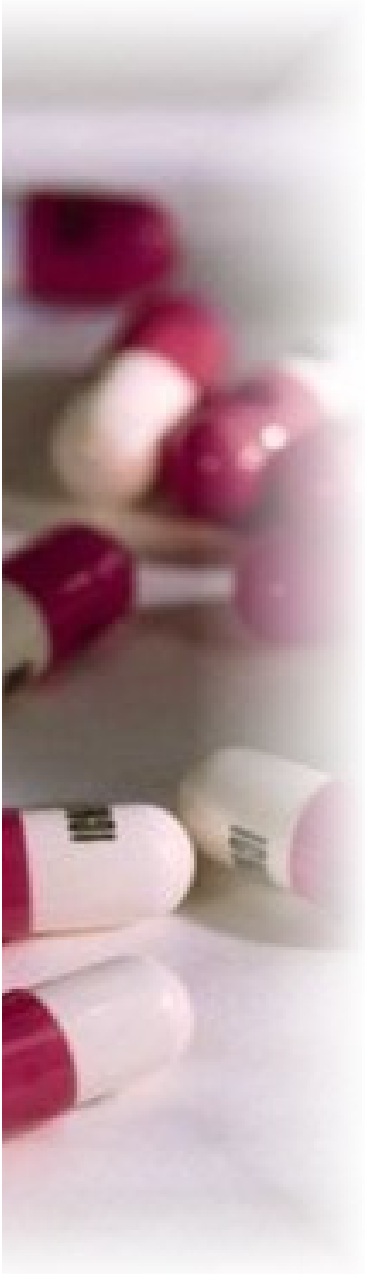
Cohesion



Advantages of Thiomers

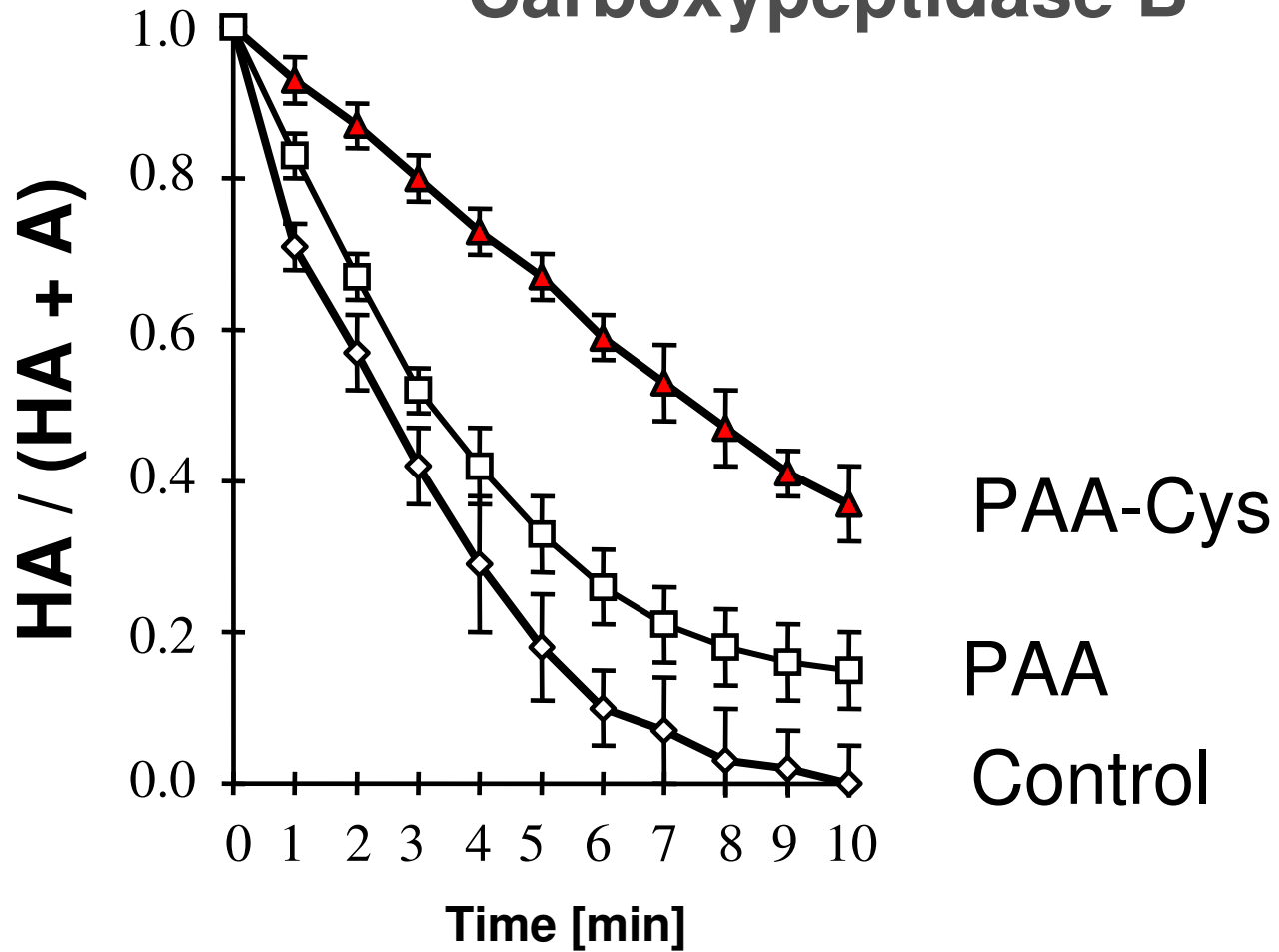
- Improved mucoadhesive properties
- Improved cohesive properties
- Inhibitory effect towards proteases
- Controlled drug release
- Permeation enhancing effect

Background



Enzyme Inhibition

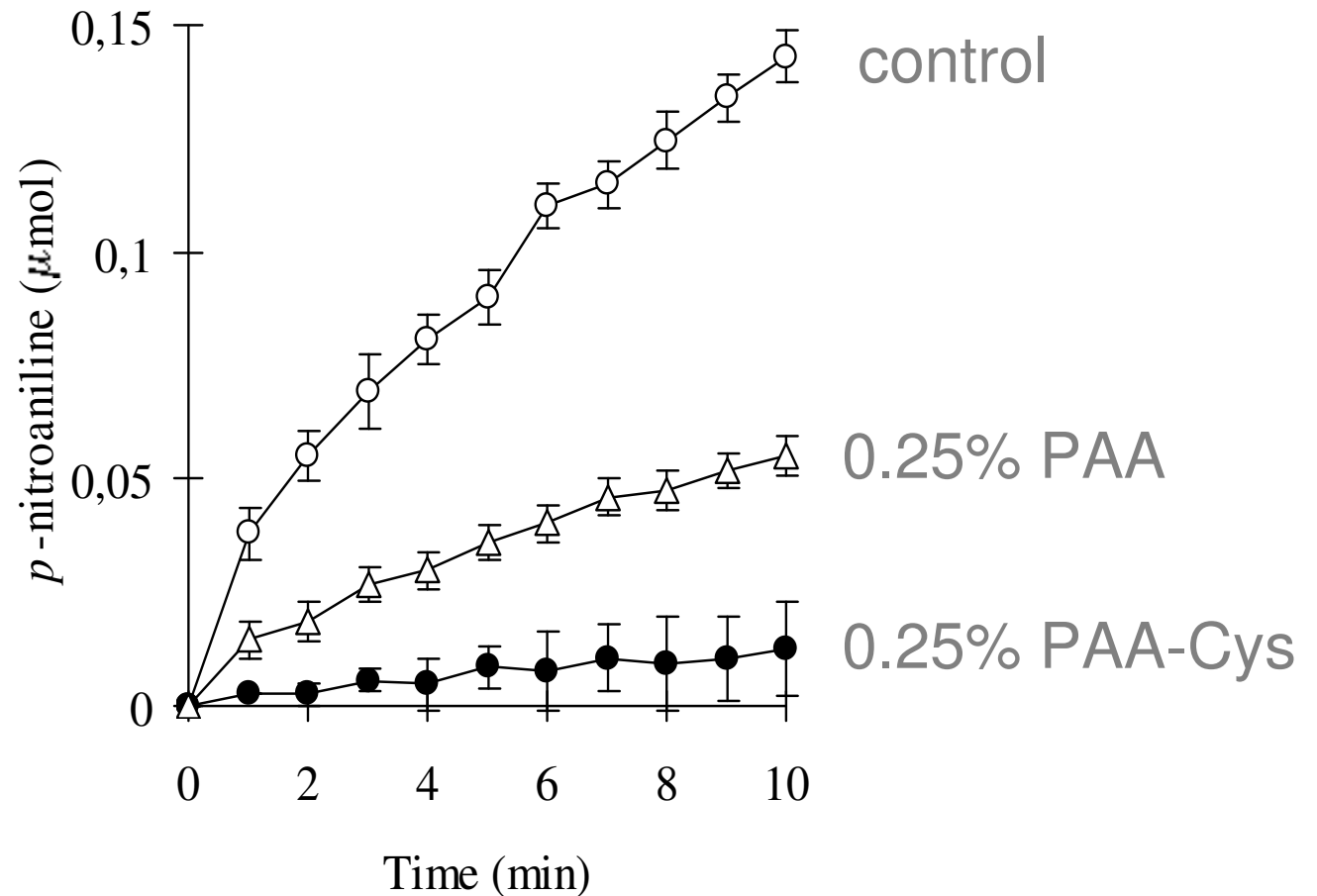
Inhibitory Effect towards Carboxypeptidase B



Bernkop-Schnürch, A. and Thaler, S. (2000). *J. Pharm. Sci.*, **89**, 901-909.

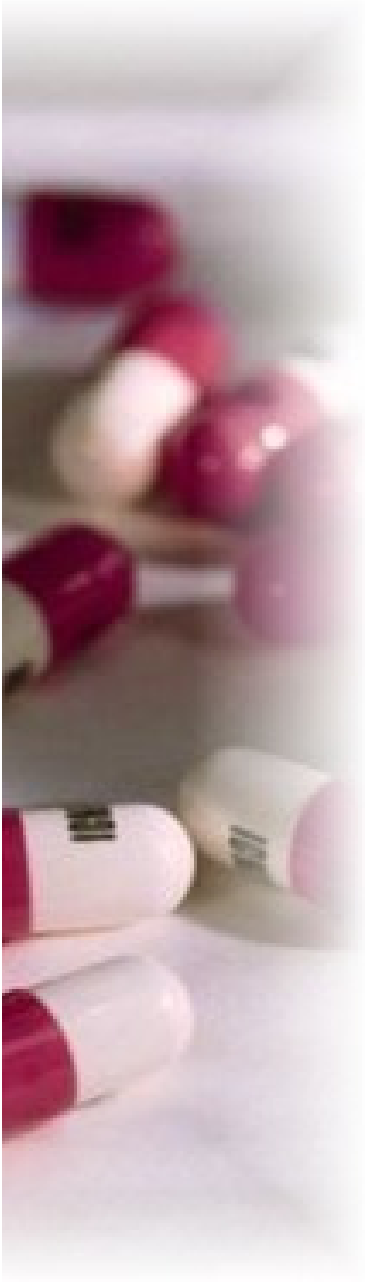
Enzyme Inhibition

Inhibitory Effect towards Aminopeptidase N



Bernkop-Schnürch et al. (2001) *J. Pharm. Sci.*, 90, 1907-1914.

Enzyme Inhibition

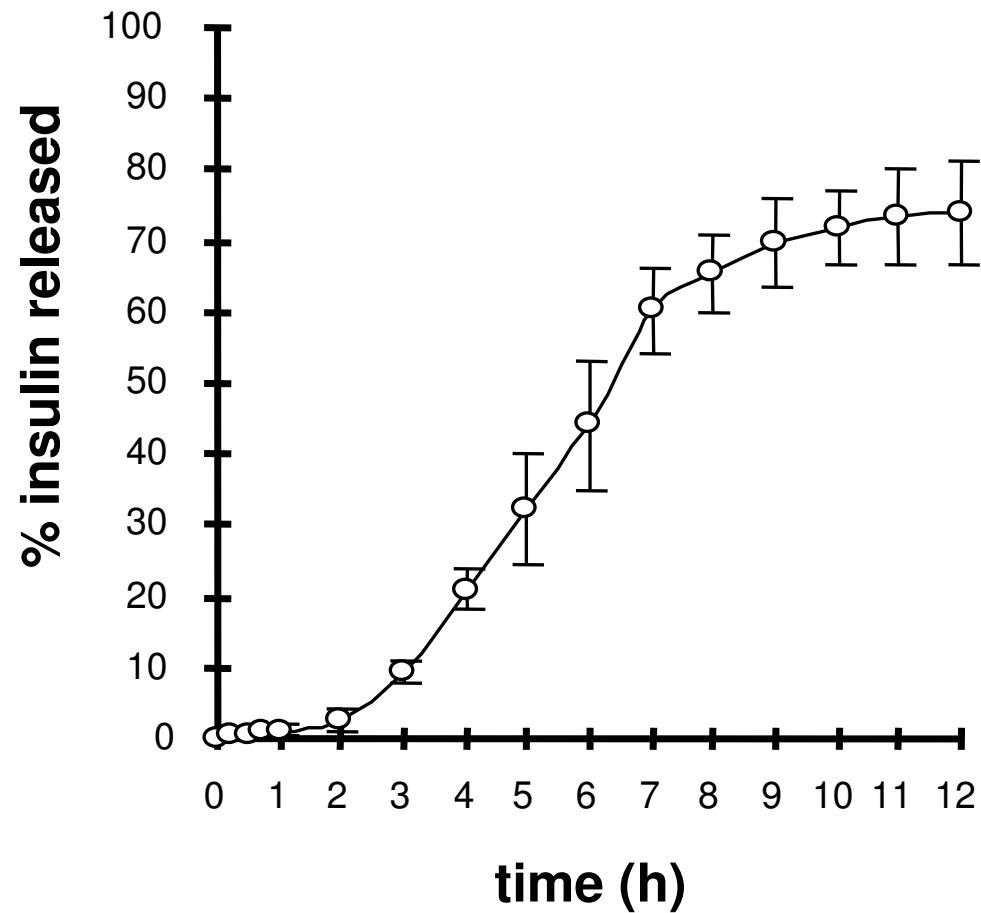


Advantages of Thiomers

- Improved mucoadhesive properties
- Improved cohesive properties
- Inhibitory effect towards proteases
- **Controlled drug release**
- Permeation enhancing effect

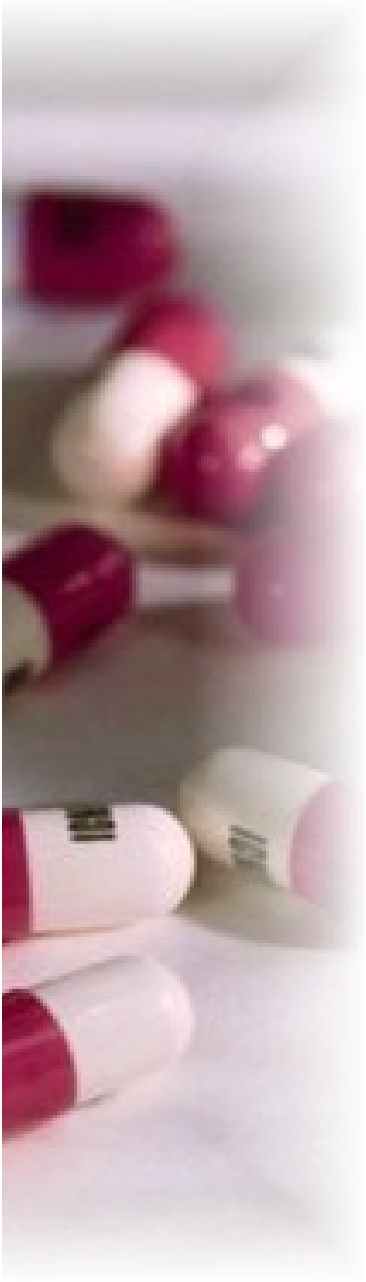
Background

Controlled Drug Release



Marschütz, et al. *Pharm. Res.* **17** (2000) 1468-1474.

Controlled Release

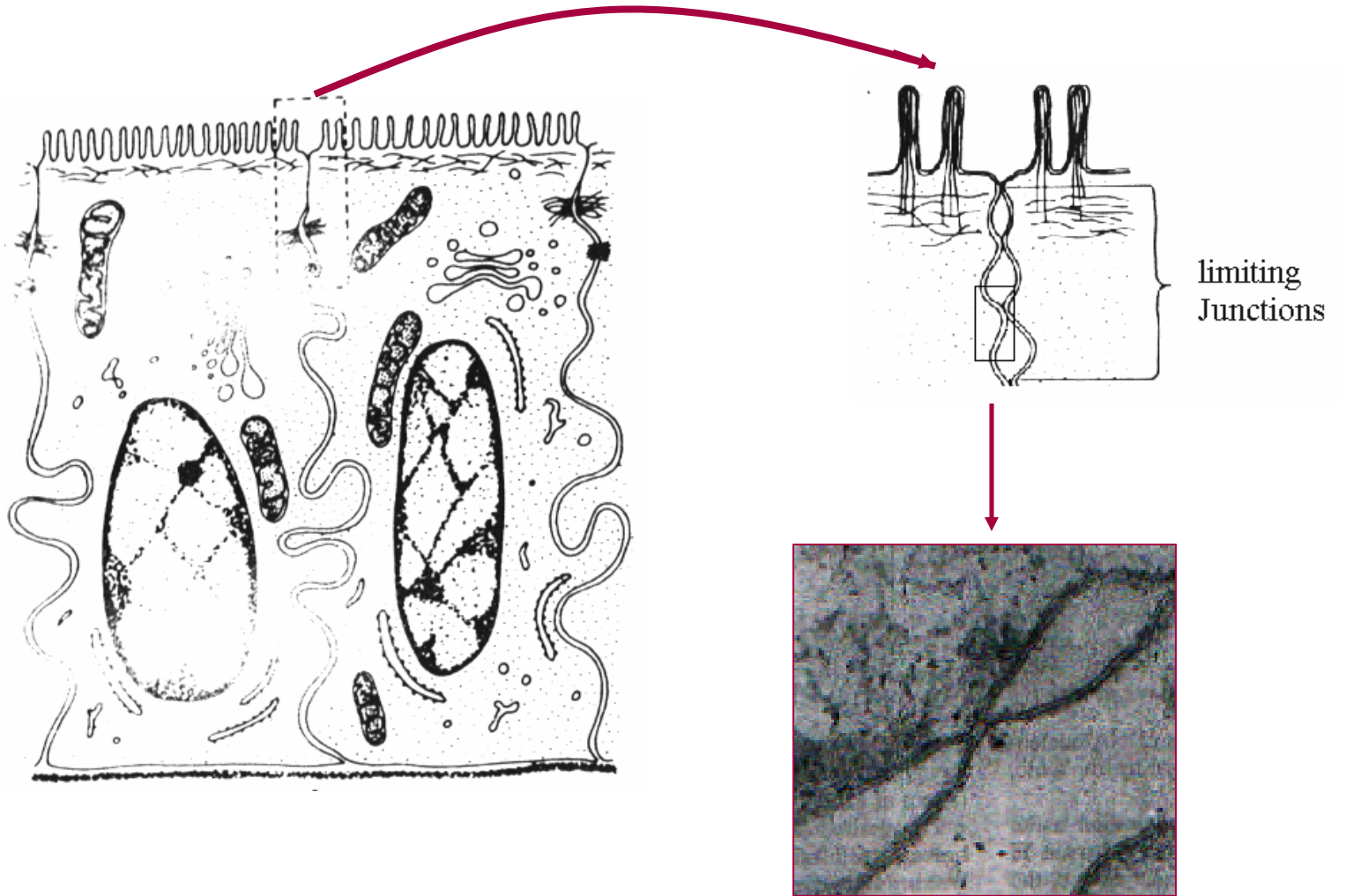


Advantages of Thiomers

- Improved mucoadhesive properties
- Improved cohesive properties
- Inhibitory effect towards proteases
- Controlled drug release
- Permeation enhancing effect

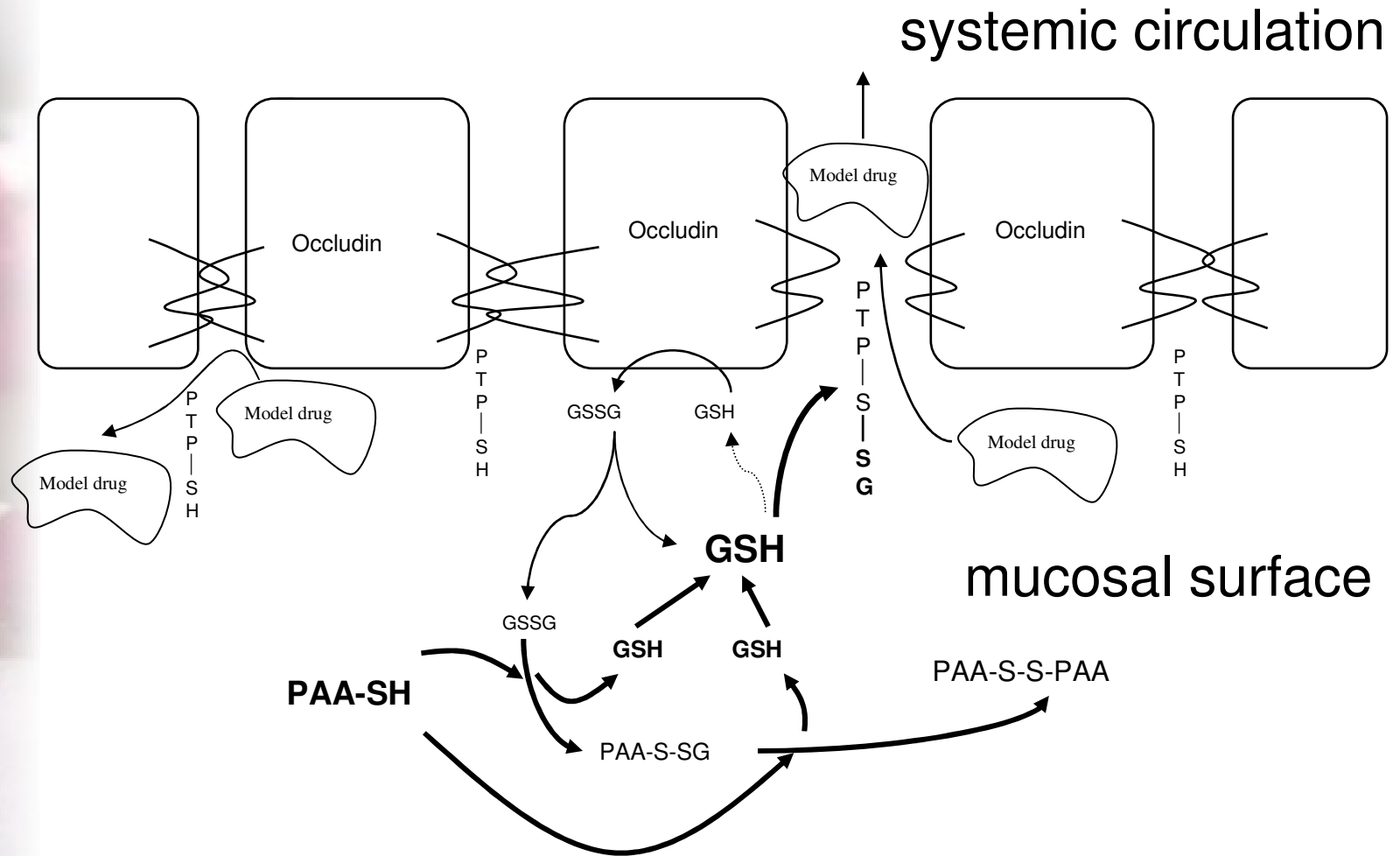
Background

Thight Junctions



Permeation Enhancement

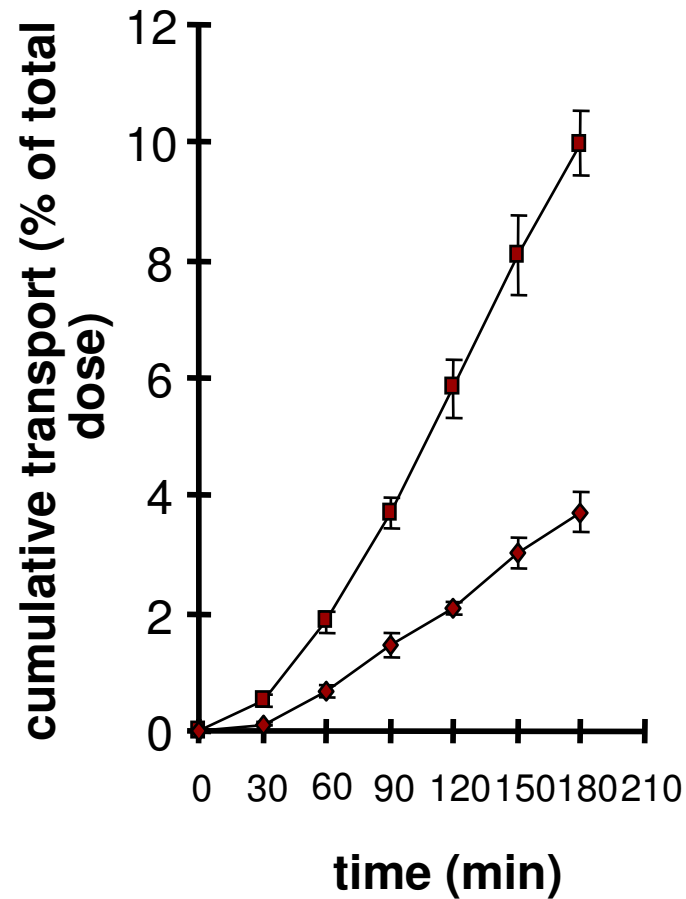
Responsible Mechanism:



Clausen, A.E., et al. (2002). *Pharm. Res.*, **19**, 602-608.

Permeation Enhancement

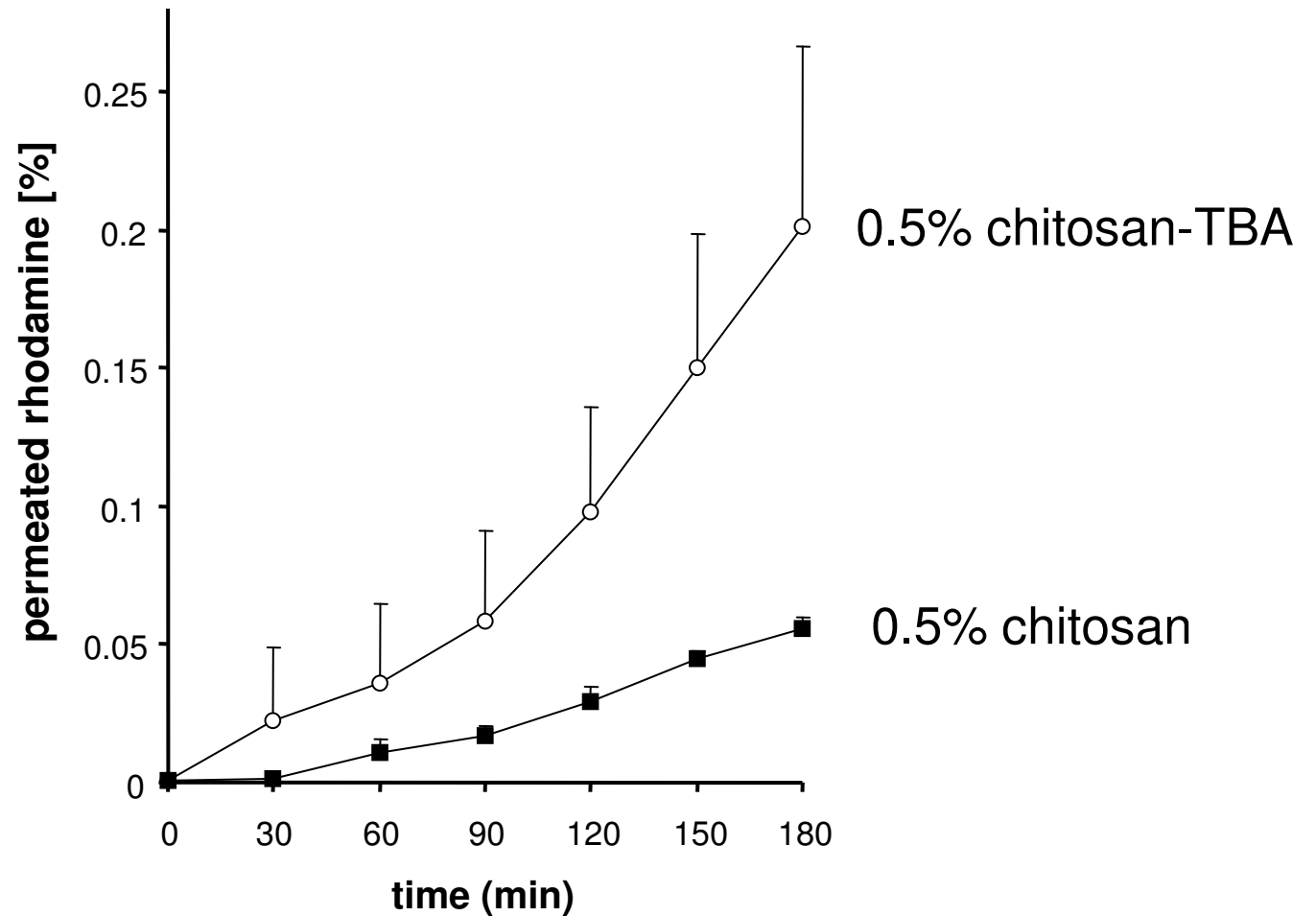
Na-Fluorescein



Clausen et al. *Pharm. Res.*, **19** (2002) 602-608.

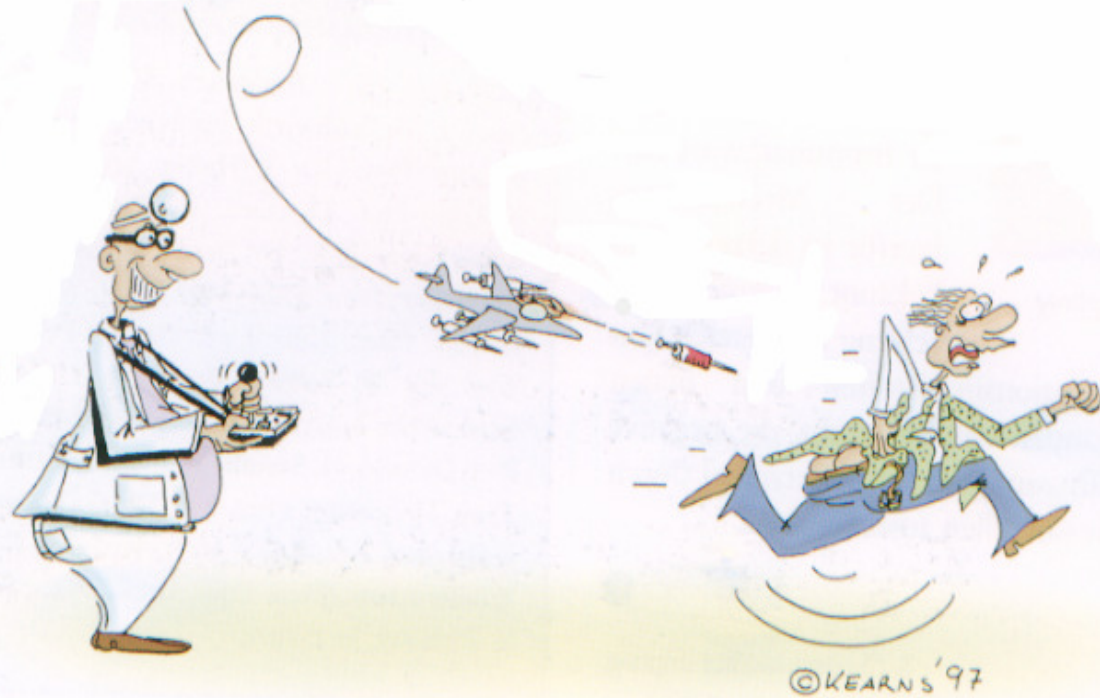
Permeation Enhancement

Permeation Enhancing Properties

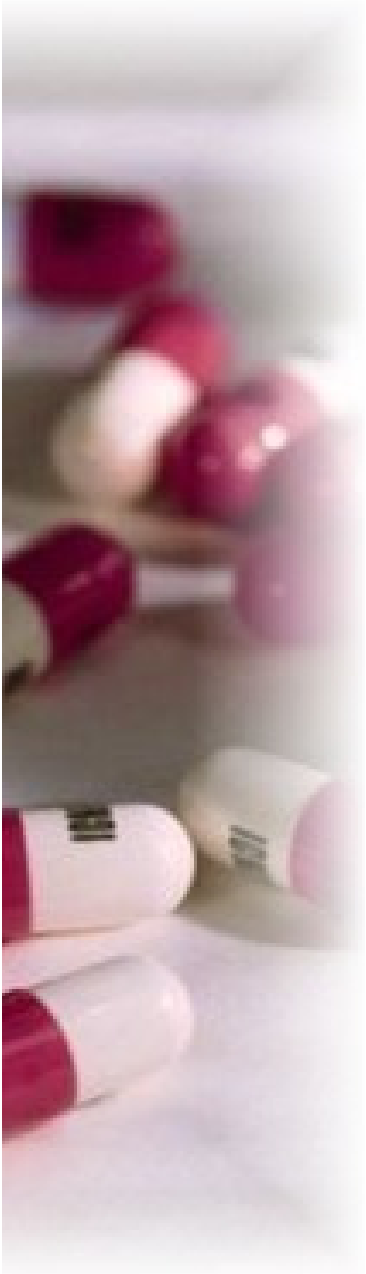


Permeation Enhancement

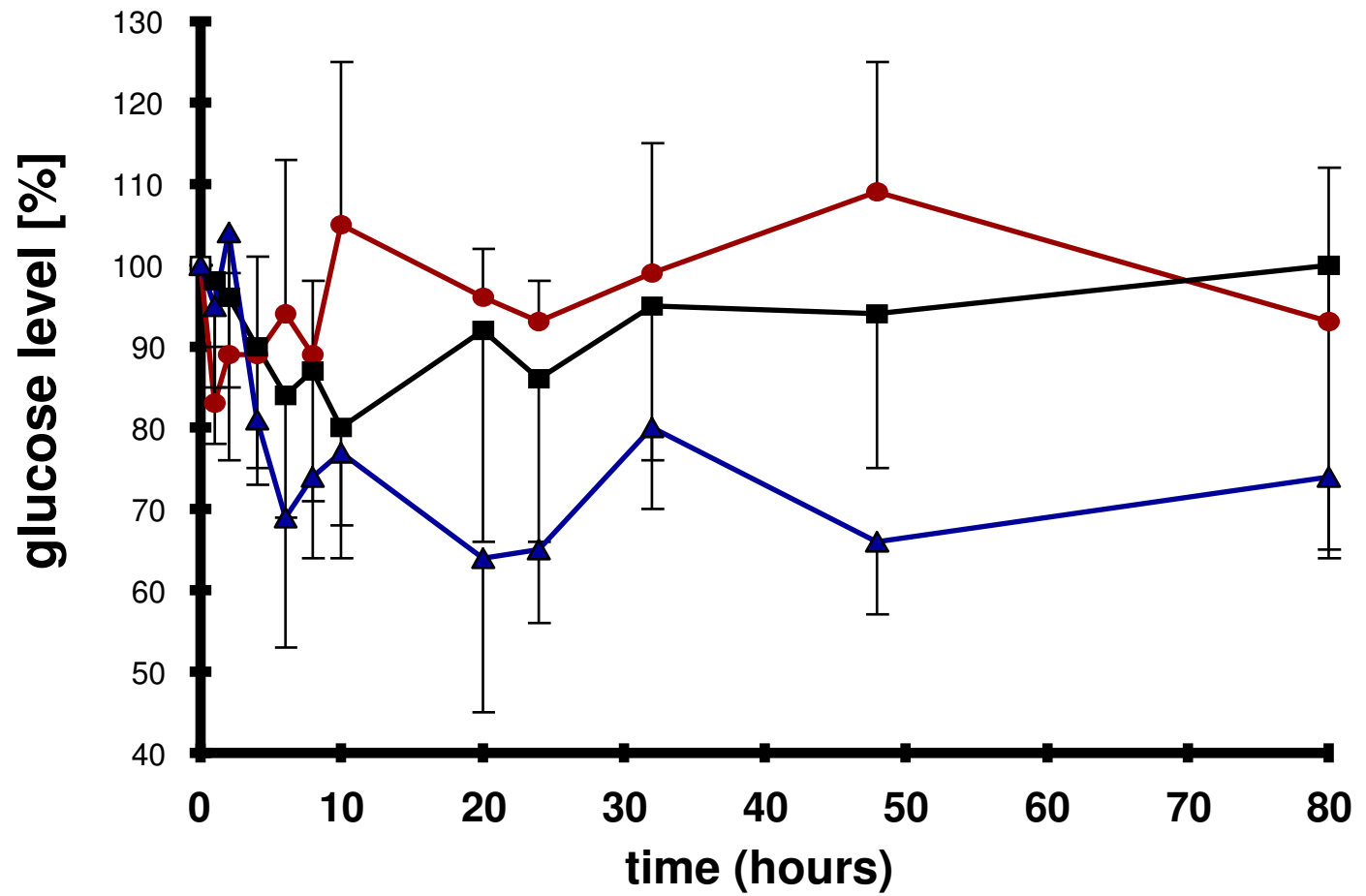
In vivo ...



‘Proof of concept‘



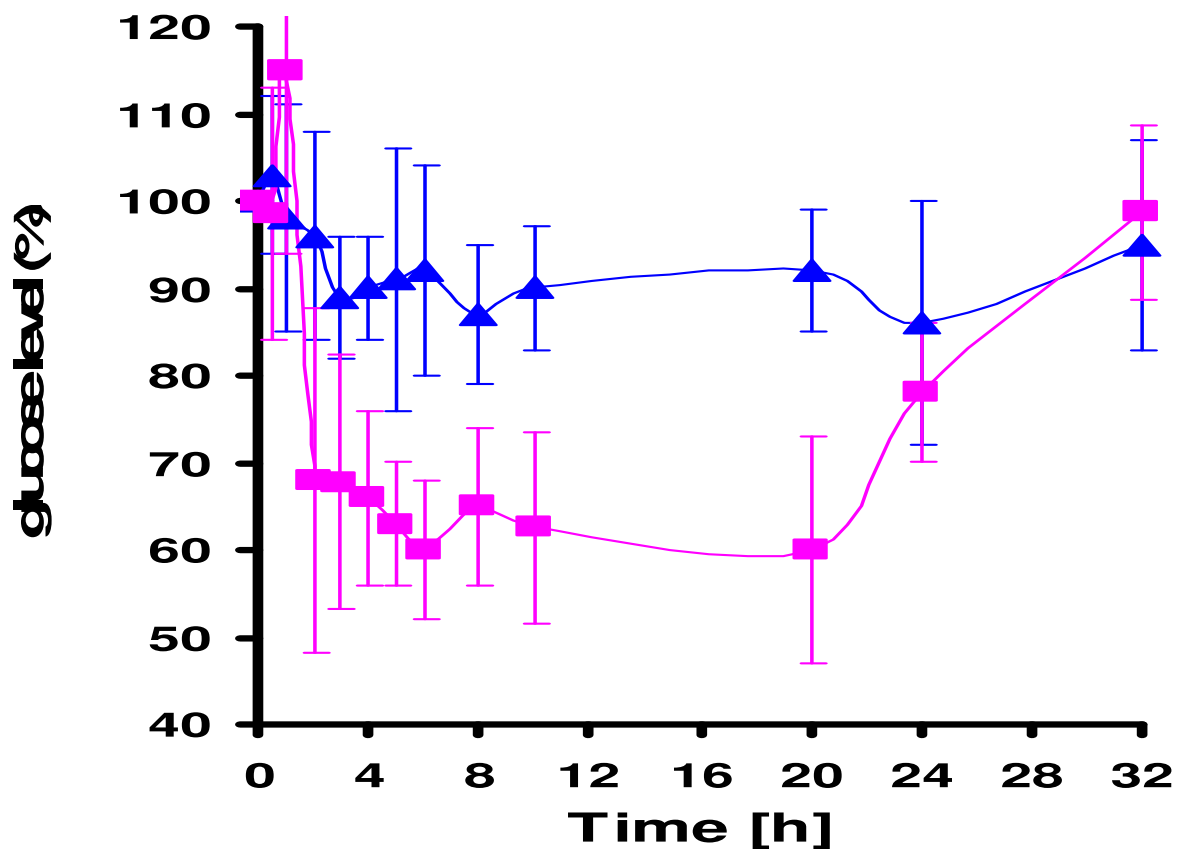
Oral Insulin



Marschütz, et al. *Pharm. Res*, 17 (2000) 1468-1474.

Proof of Concept

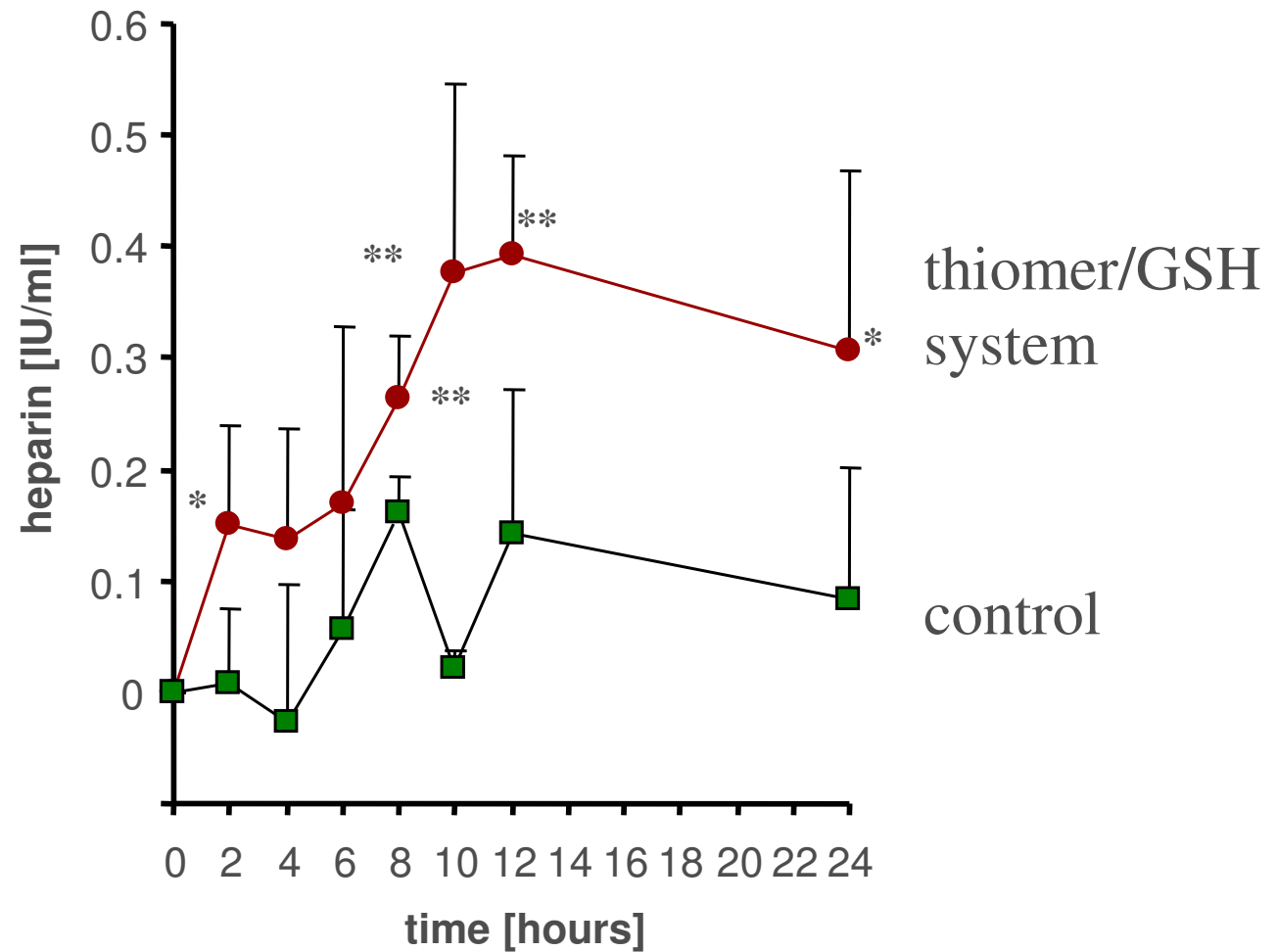
Oral administration of a thiomers formulation containing insulin-1PEG750



Caliceti et al. *Eur. J. Pharm. Sci.* **22** (2004) 315- 323

Proof of Concept

Oral Heparin



Kast et al. *Pharm. Res.* **20** (2003) 931- 936

Proof of Concept

Conclusions

By the covalent immobilization of thiol groups to well-established polymeric excipients features such as **mucoadhesive, cohesive, controlled drug release** and **permeation enhancing properties** can be strongly improved.

The efficacy of these novel polymers could be verified for numerous drugs on various mucosal membranes in various species.

Conclusion

