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Thiolated poly(aspartic acid) polymers in ophthalmic therapy

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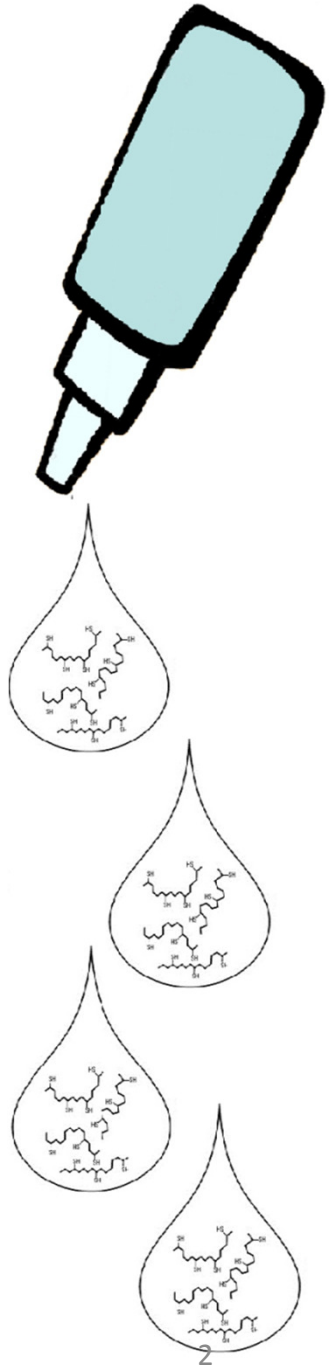
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Problems with current local ocular drug delivery systems

- Drug dilution and removal within minutes:
  - blinking,
  - baseline and reflex lachrymation

- Slow absorption of drugs:
  - anatomy,
  - physiology,
  - barrier function of the cornea

- Frequent instillations of eye drops:
  - to maintain a therapeutic drug level in the tear film or at the site of action
  - toxic side effects,
  - cellular damage at the ocular surface



VERY LOW BIOAVAILABILITY (<5%)

Ludwig, A., Adv. Drug Deliver. Rev. 2005, 57, 1595-1639

Challenges in ocular drug delivery formulation

Anatomical

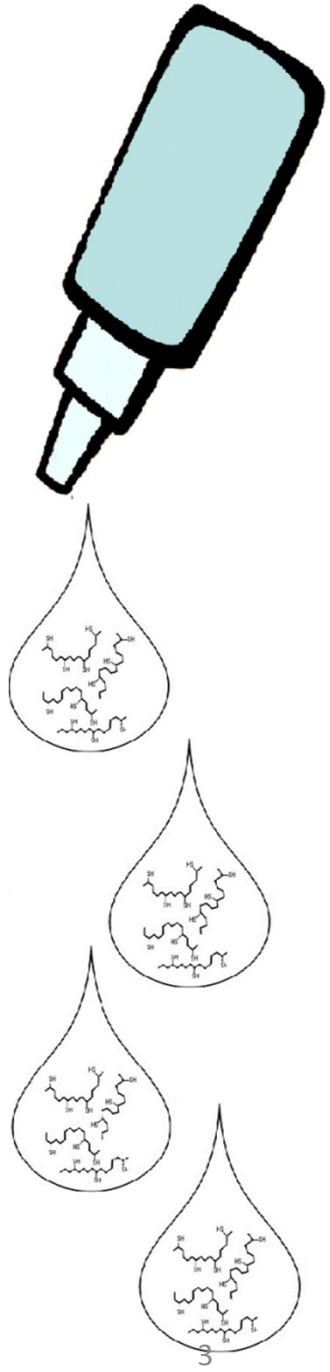
- Special anatomy
- Protective mechanisms
- Limited area for absorption

Biopharmaceutical

- Hydro - and lipophilicity
- Molecule size
- Protein bindings
- Enzymatic degradation of the drugs

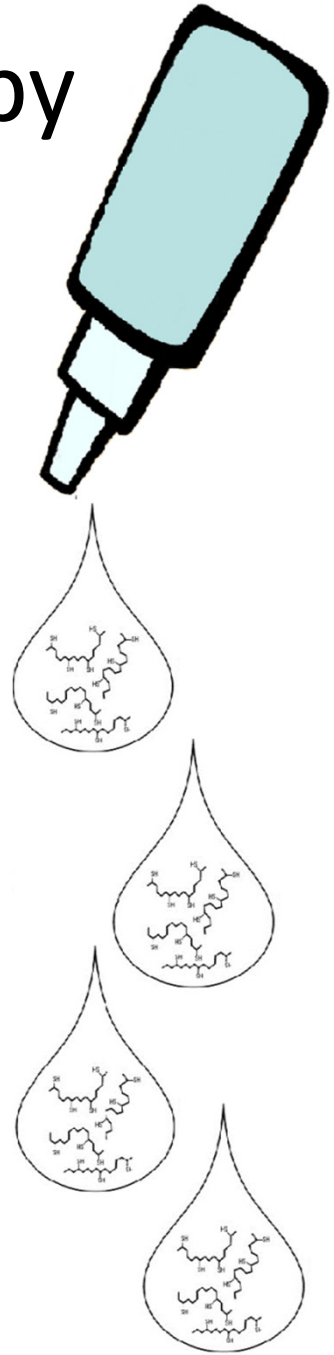
Patient

- Few applications (two or less)
- Easy handling and (self)-administration,
- No discomfort or foreign body sensation, blurring vision
- No visual disorders
- Be non-invasive
- Low price



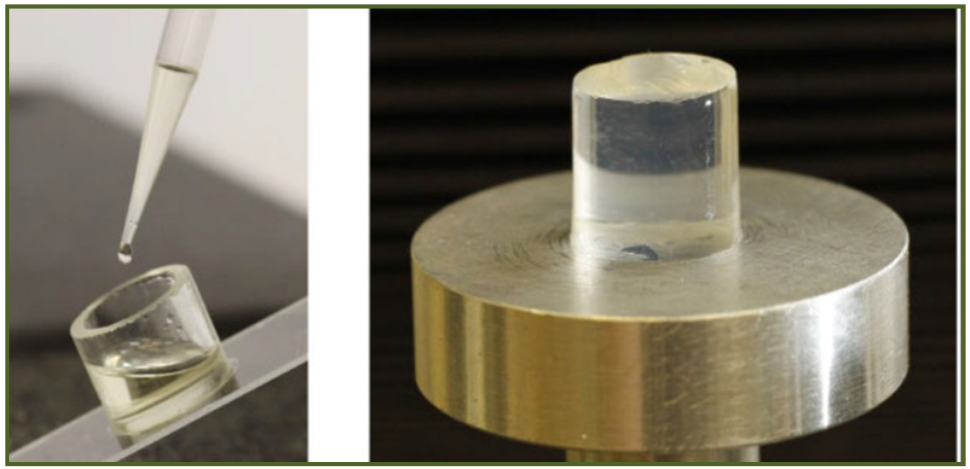
New possibility in ophthalmic therapy

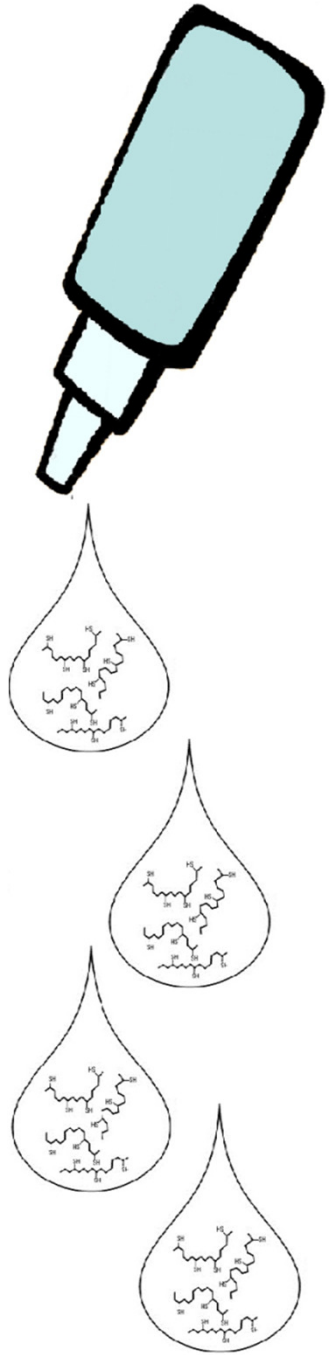
- Mucoadhesive polymers take advantage of the ocular surface mucosal layer.
- Mucoadhesion is adhesion between the drug delivery system and the mucosa.
- Physical and chemical interactions can occur during mucoadhesion.
- Methods for the investigation of mucoadhesion:
  - Rheology: determination of the changes in rheological parameters, after mixing the mucoadhesive polymer with mucin.
  - Tensile test: Adhesive strength is defined as the external force required for the separation of the two interfaces. The work of adhesion (*A*, mN mm) can be calculated as the area (AUC) under the “force versus distance” curve.



Thiolated poly(aspartic acid) polymers

- Synthetized by Soft Matters Group of Budapest University of Technology and Economics
- Thiol containing side groups bonded to poly(aspartic acid)
- Biocompatible and biodegradable polymers
- Non-toxic and do not generate immunogenicity
- Redox sensitive, *in situ* gelling
- Optically clear solution and gel

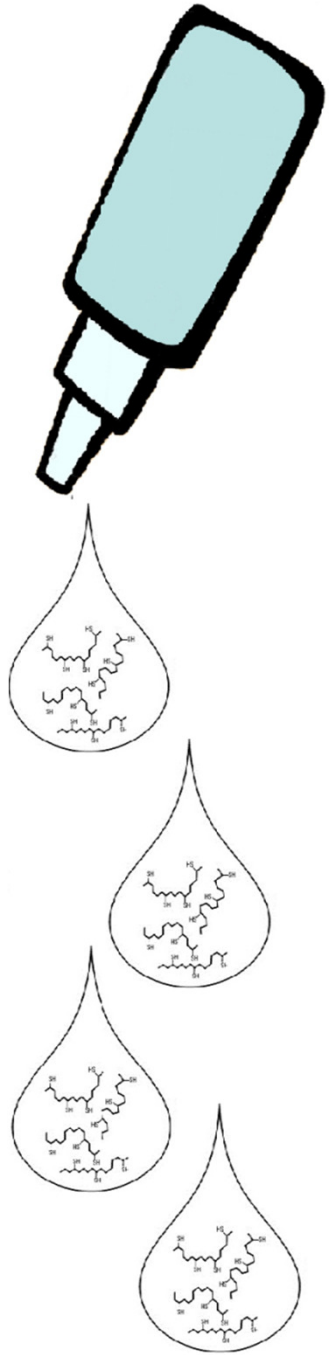




B. Gyarmati, B. Vajna, Á. Némethy, K. László, A. Szilágyi., Macromol. Biosci. 2013, 13, 633–640

Aims

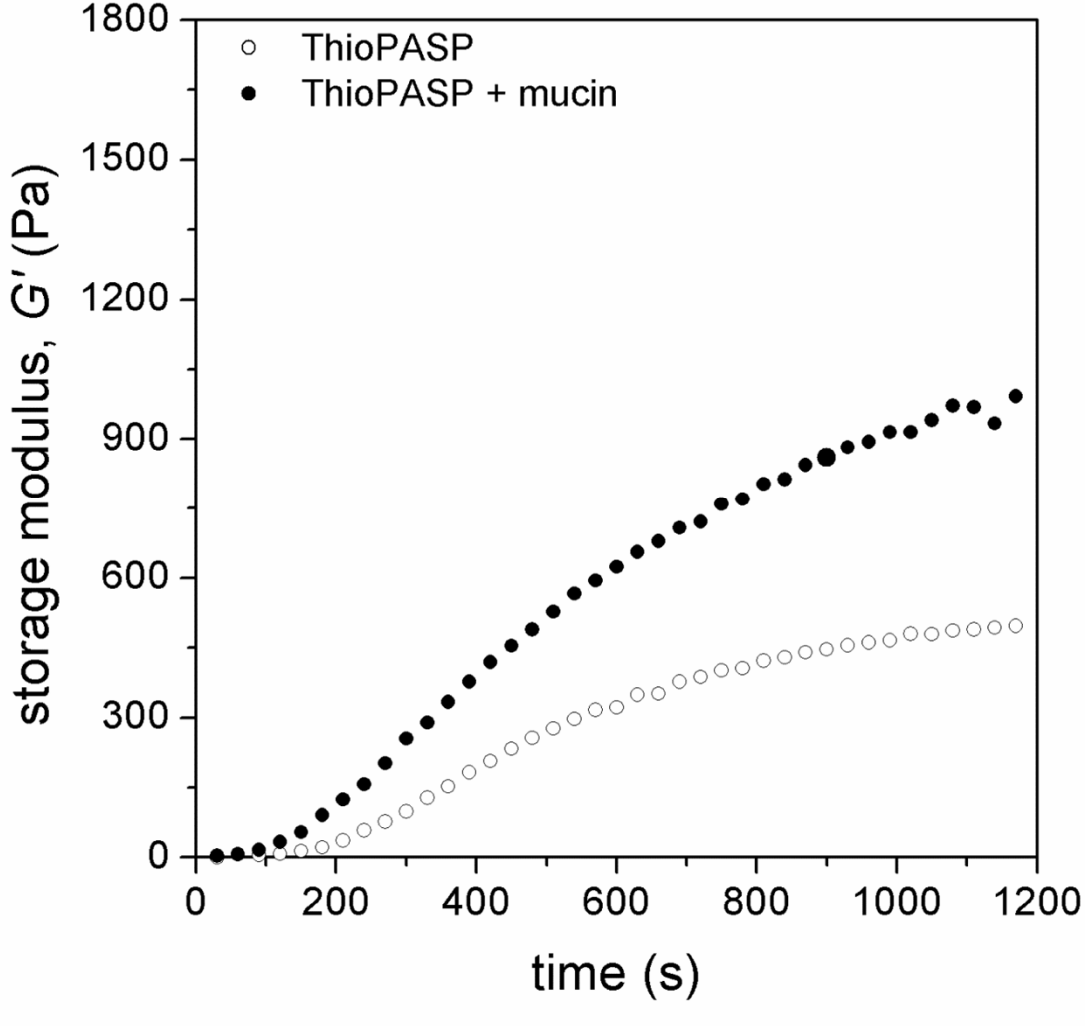
- Assign the effects of the mucin on the gelation time
- Characterize the mucoadhesion of the ThioPASP polymers
- Define the function of the thiol groups in the mucoadhesion
- Determine the drug release profile



Horvát, G., Gyarmati, B., Berkó, Sz., Szabó-Révész, P., Szilágyi, B. Á., Szilágyi, A., Soós, J., Sandri, G., Bonferoni, M.C., Rossi, S., Ferrari, F., Caramella, C., Csányi, E., Budai-Szűcs, M., Eur. J. Pharm. Sci. 67, 1-11 (2015)

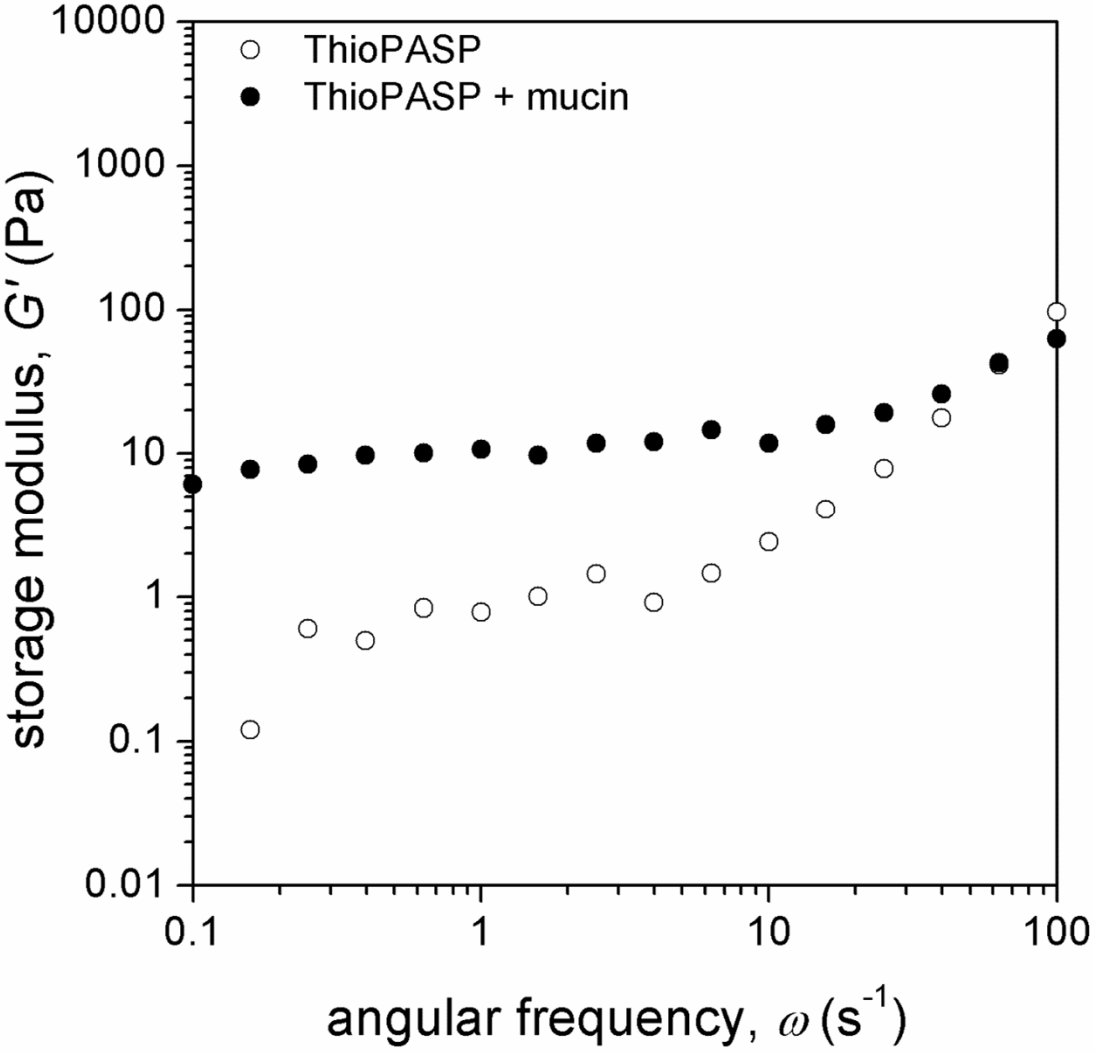
In situ gelation with and without mucin

- No gelation below 10%w/w ThioPASP
- Addition of mucin aided the gelation
- The gelation time was shorter with mucin
- The rate of gelation and final value of storage modulus increased in the presence of mucin



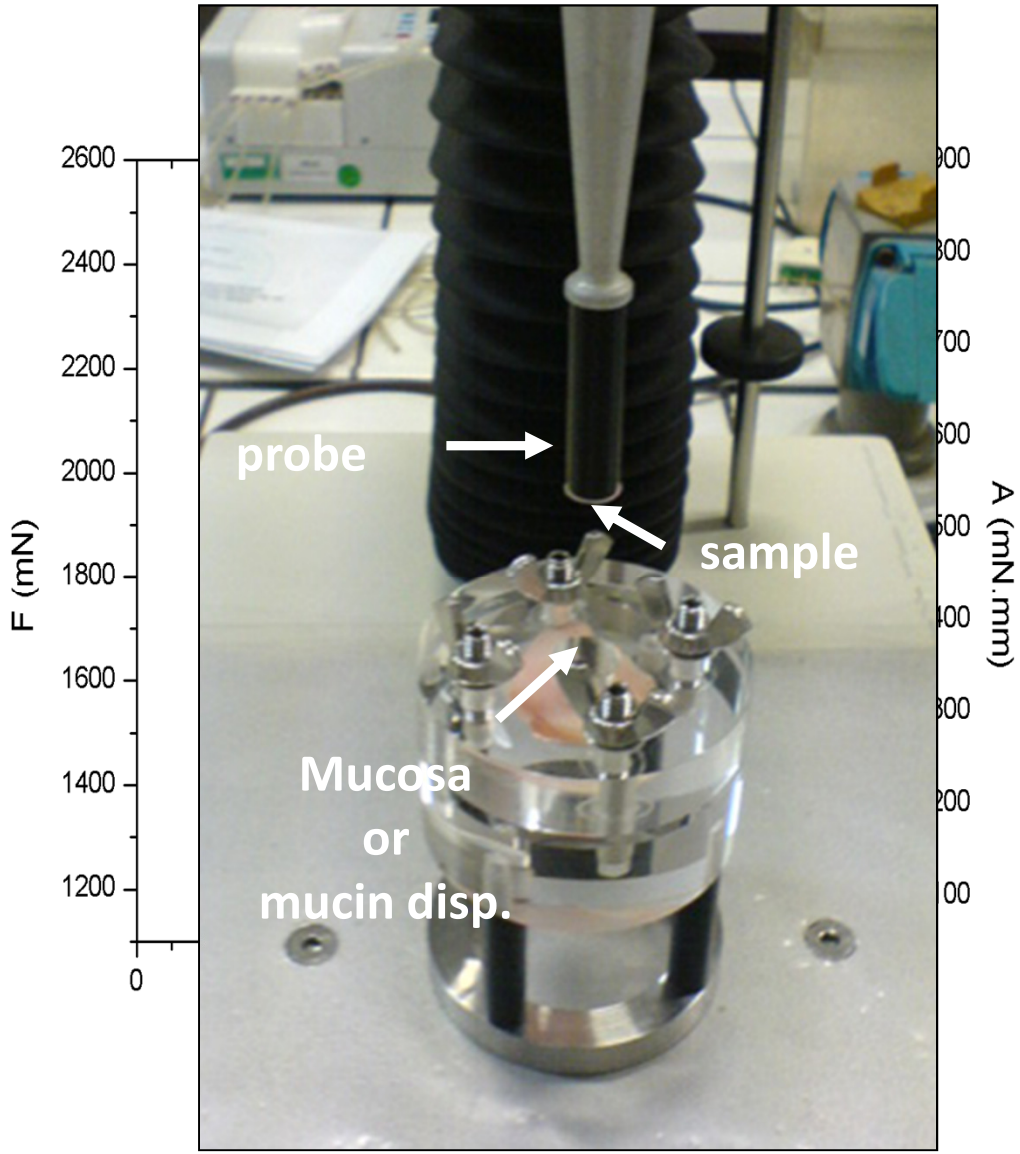
Mucoadhesion – Rheology

- Mucin augmented the elastic modulus
- Physical and chemical interactions between the polymer and the mucin
- The added mucin decreased the slope of the curves



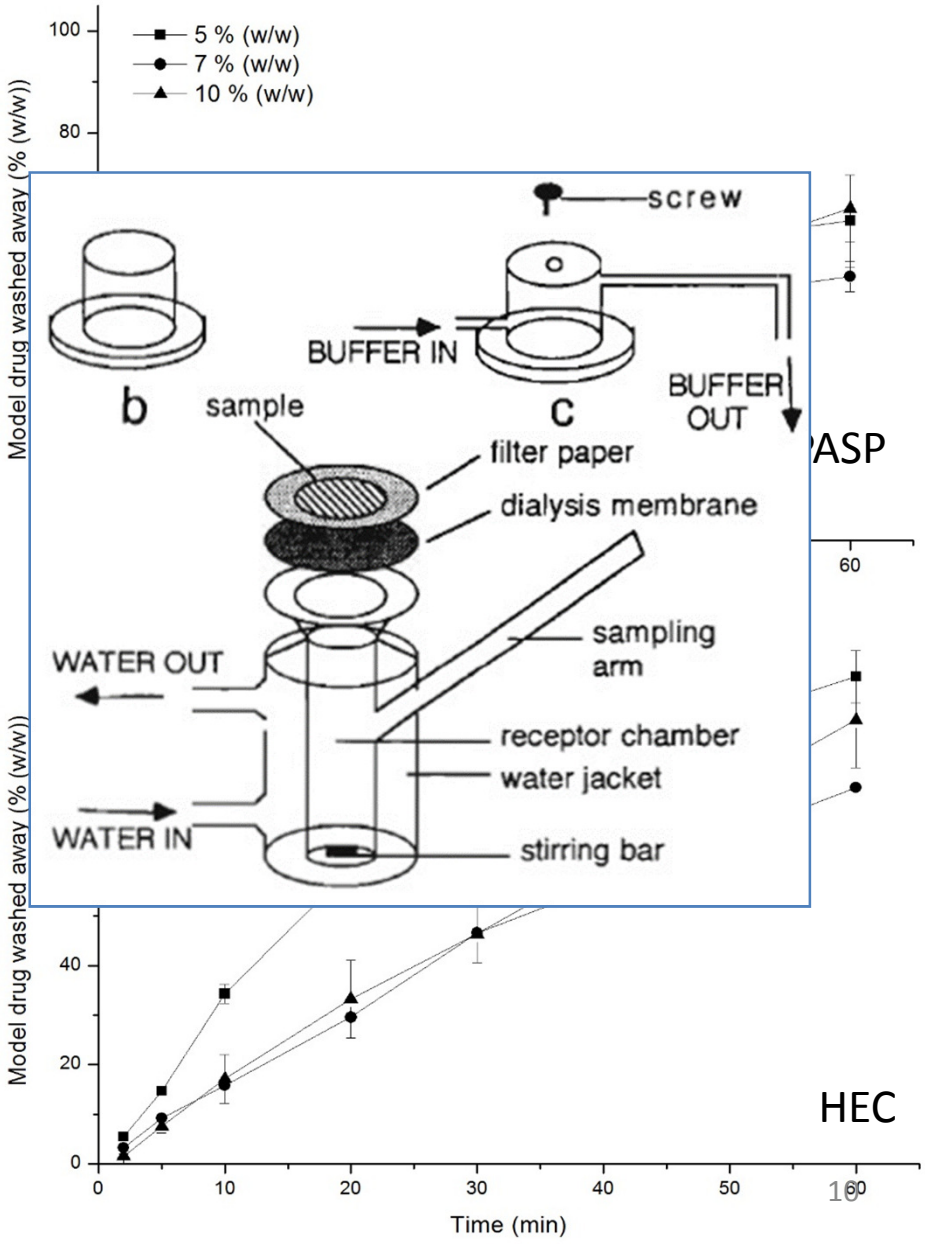
Mucoadhesion – Tensile Test

- Measurements were made both with mucin dispersion (8%) *(in vitro*) and with blank (simulated lachrymal fluid)
- *„A”* increased continuously as the concentration was elevated
- *„F”* reached a maximum at 7% w/w polymer
- The chemical bonds have a larger effect at lower polymer concentration (increasing F)
- At high polymer concentration, the potential for chemical bonds reached a maximum (the free thiol groups were saturated at the interface - plateau of F)
- *„A”* did not reach a maximum because of the increasing interpenetration. (More cross-links resulting in a gel structure, which induces increased swelling, allowing deeper and improved interpenetration)



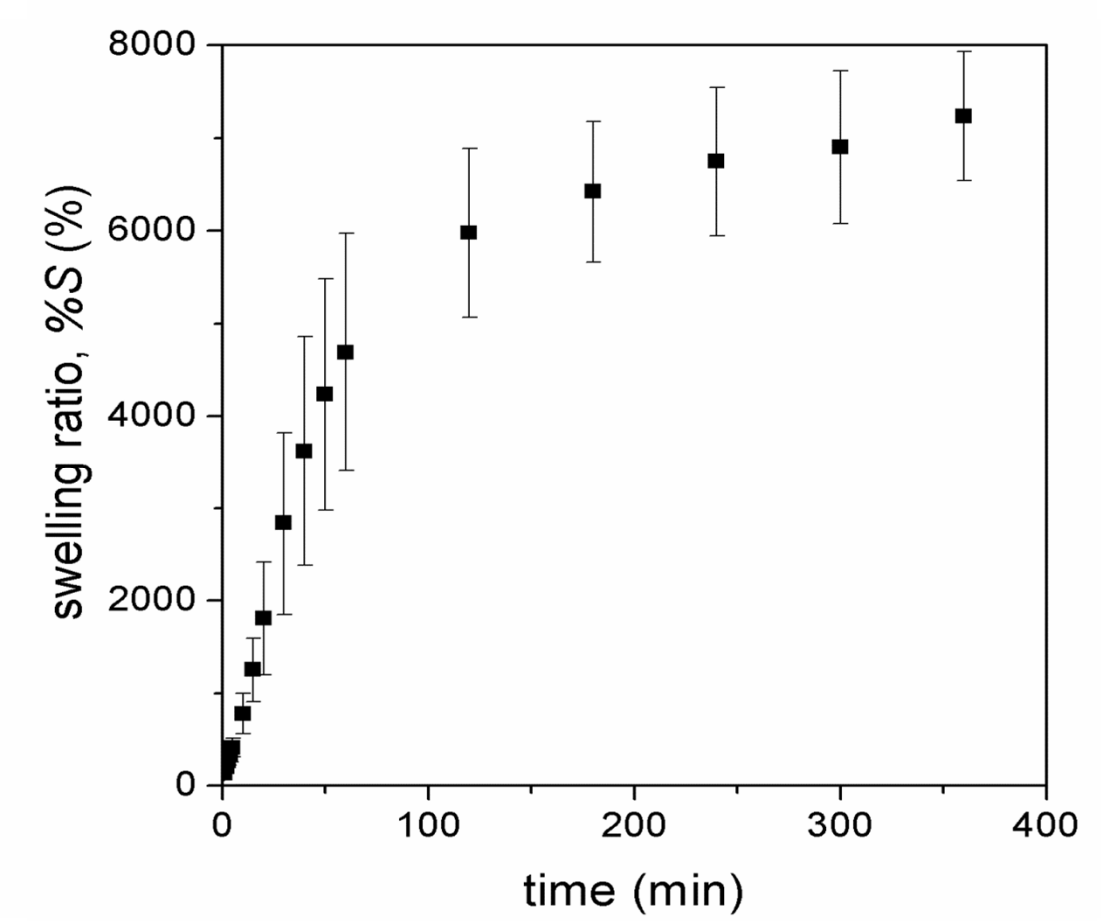
Mucoadhesion- “Wash away”

- “Wash away“ *ex vivo* measurements mimic the lachrymation of the eye, under conditions relatively close to real mucoadhesive circumstances of the eye.
- Model drug: sodium fluorescein (0.008%)
- Increase of the ThioPASP concentration was accompanied by a slight decrease in the amount of model drug being washed away.
- In the reference systems the observations were similar.
- ThioPASP formulations have a longer residence time (40-50% vs. 0-30% w/w).



Drug release kinetics I.

- Model drug: sodium diclofenac (0.01%)
- First hour: fast diffusion of the SD
- ThioPASP polymers have a high water uptake → they have a lower cross-linking density, and the SD is therefore able to diffuse through this structure more easily



Drug release kinetics II.

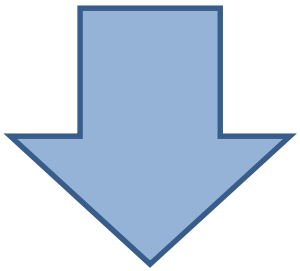
Drug release kinetics according to Korsmeyer-Peppas equation:

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t/M_∞ is the fraction of drug released, *k* is the kinetic constant and *n* is the release exponent describing the mechanism of the release

Swelling exponents (*n*): 0.874

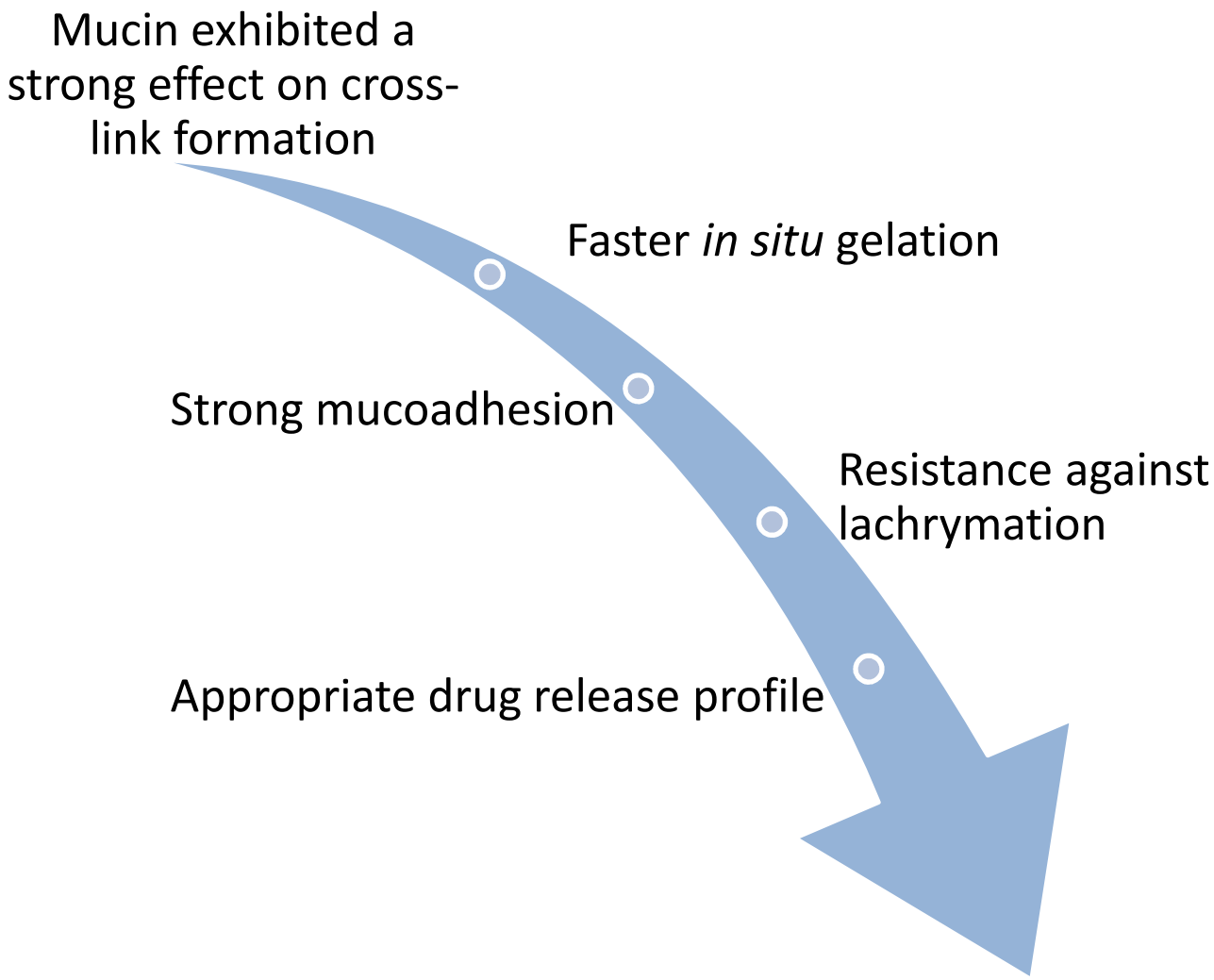
Release exponents (*n*): 0.6561



Non-Fick diffusion

0.5 < n > 1

Conclusion



ThioPASP polymers can be potential *in situ* gelling, ocular mucoadhesive drug delivery system

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  - Soft Matters Group, Budapest University of Technology and Economics
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    - *Prof.* dr. Maria Cristina Bonferoni, Ph.D.,
    - Dr. Giuseppina Sandri,Ph.D.
- Department of Pharmaceutical Technology, University of Szeged
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    - Dr. Pharm. Erzsébet Csányi, Ph.D.
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THANK YOU FOR YOUR KIND ATTENTION!



