Thiolated poly(aspartic acid) polymers in ophthalmic therapy

Gabriella Horvát¹, Benjámin Gyarmati², Barnabás Szilágyi², András Szilágyi², Szilvia Berkó¹, Erzsébet Csányi¹, Piroska Szabó-Révész¹, Giuseppina Sandri³, Maria Cristina Bonferoni³, Carla Caramella³, Mária Budai-Szűcs¹

¹ Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Szeged, Szeged, Hungary
² Soft Matters Team, Department of Physical Chemistry and Materials Science, Budapest University of Technology and Economics, Budapest, Hungary
³ Department of Drug Science, Faculty of Pharmacy, University of Pavia, Pavia, Italy

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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%)

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 \( (A, \text{ mN mm}) \) 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

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

**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%) \textit{(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:

\[ \frac{M_t}{M_\infty} = k t^n \]

where \( \frac{M_t}{M_\infty} \) 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

\[ 0.5 < n > 1 \]
Mucin exhibited a strong effect on cross-link formation.

- Faster *in situ* gelation
- Strong mucoadhesion
- Resistance against lachrymation
- Appropriate drug release profile

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