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Summary of the Ph.D. thesis

Mucoadhesive polymers in ophthalmic therapy

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MUCOADHESIVE POLYMERS IN OPHTHALMIC THERAPY

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1. INTRODUCTION

With the aging of the population, the need for the treatment of ocular diseases and disorders has become more important than ever. Increasingly high incidences of age-related macular degeneration, glaucoma, diabetic retinopathy and ocular inflammatory diseases demand better, more effective and innovative treatments. If we are to maintain the quality of life for this aging population, the preservation of vision is critical.

Unfortunately, the ophthalmic formulations on the market suffer from poor bioavailability (< 2%) and it would be useful to design a new formulation which is able to prolong the residence time and reduce the administration frequency. Since topical ocular delivery treatments are considered to be the safest, least invasive and most self-administrable, their development is highly sought.

The formulation of ocular drug delivery systems poses many challenges, but also offers many opportunities to overcome the inadequacies of the current formulations. The corneal epithelium has a complex hydro- and lipophilic character that limits drug absorption, and the eye has many protective mechanisms, including blinking, tear turnover and reflex lacrimation. There is therefore a need for the frequent instillation of eye drops, which is accompanied by discomfort and a decrease in patient compliance, especially in the long term.

One way to overcome the natural anatomical barriers of the eyes is to take advantage of the mucosal layer and to formulate a drug delivery system with mucoadhesive properties. Polymer matrices which exhibit strong mucoadhesion are promising platforms in ocular drug delivery from the aspect of improved bioavailability.

In my Ph.D. work, first (hyaluronic acid (HA) derivatives) and second generation (thiolated polymers) mucoadhesive polymers were characterized as potential ocular drug delivery systems. I carried out gel characterization (rheology) and determinations of mucoadhesion and drug release. Thiolated polymers, as new potential excipients in ophthalmic therapy, were characterized in a wide range.

2. EXPERIMENTAL AIMS

In ophthalmic drug delivery systems, the polymers applied play an important role in the increase of the bioavailability. The use of mucoadhesive polymers can increase the residence time on the ocular surface or in the cul-de-sac. For this reason, it is very important to determine the mucoadhesive properties of the polymers. Since these polymers are planned to be used in ophthalmic therapy, the matrix also has to be characterized with regard to its potential for drug release.

In my Ph.D. work, I characterized hyaluronic acid derivatives as first generation and thiolated poly(aspartic acid) (ThioPASP) polymers as second generation mucoadhesive polymers, as potential vehicles for ocular drug delivery systems.

The aims of my experimental work can be summarized as follows (Fig. 1):

- Comparisons of a nanosized cross-linked sodium salt (CLNaHA), a linear sodium salt (NaHA) and a linear zinc salt of hyaluronic acid (ZnHA):
 - investigation of their biocompatibility,
 - rheological characterization of the matrix of the HA derivatives,
 - mucoadhesion determination:
 - *in vitro* (rheology and tensile test) measurements,
 - *ex vivo* (tensile test) measurements,
 - drug release profile determination.
- Characterization of ThioPASP as a potential new type of excipient in ophthalmic therapy:
 - preformulation measurements from the aspect of ophthalmic drug delivery system formulation,
 - investigation of biocompatibility,
 - polymer matrix characterization:
 - swelling capability,
 - rheological properties,
 - determination of mucoadhesion:
 - *in vitro* (rheology and tensile test) measurements,
 - *ex vivo* (tensile and 'wash away' test) measurements,
 - drug release profile determination,

- determination of the effects of the stabilizing agents (dithiothreitol, glutathione and acetylcysteine stabilization) on the properties of the ThioPASP polymers:
 - determination of mucoadhesion (rheology and tensile test),
 - drug release profile determination.

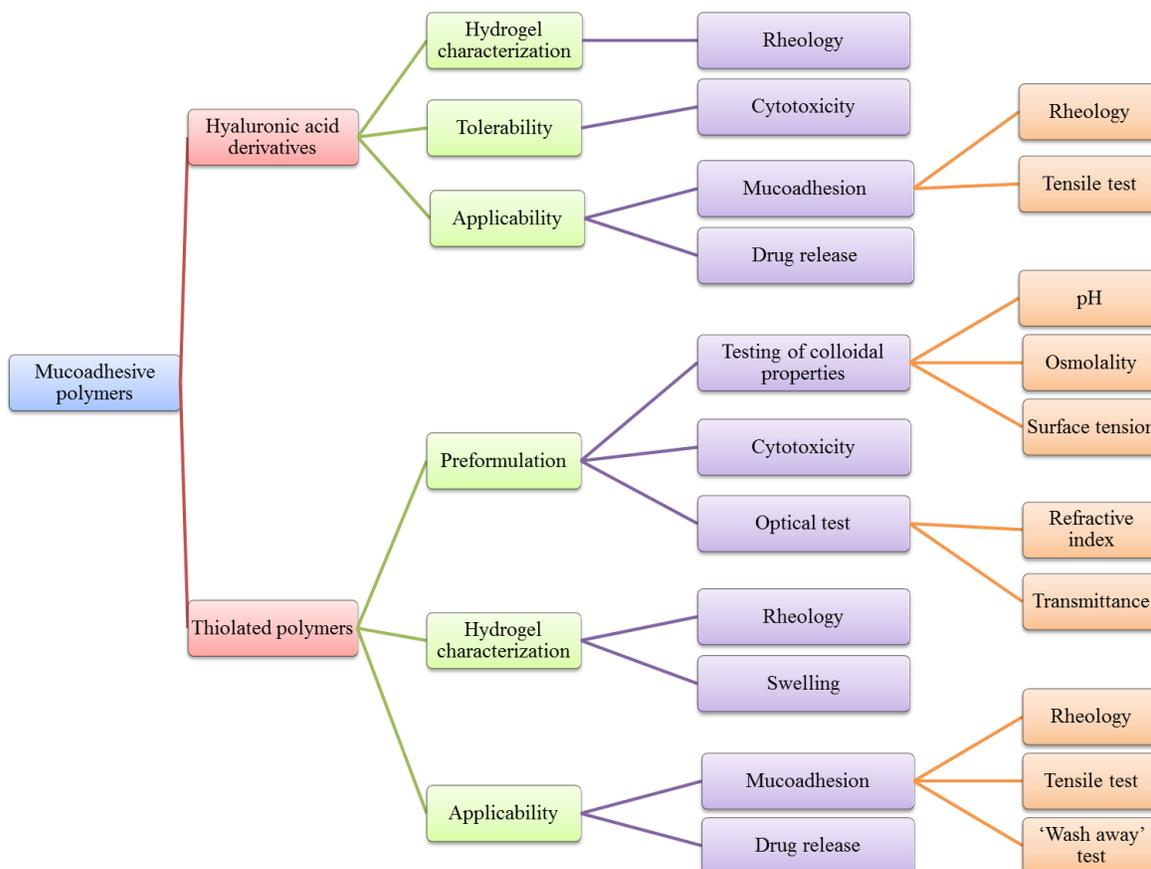


Fig. 1. Measurements performed with first and second generation mucoadhesive polymers

3. MATERIALS AND METHODS

3.1. Materials

3.1.1. Hyaluronic acid derivatives

NaHA (Mw: 4350 kDa) and ZnHA (Mw: 498 kDa) were purchased from Richter Gedeon Ltd. (Budapest, Hungary), and CLNaHA was prepared by BBS Biochemicals LLC (Debrecen, Hungary).

Gels of CLNaHA, NaHA and ZnHA were prepared in concentrations of 0.5, 1 and 2% w/w.

3.1.2. Thiolated poly(aspartic acid) polymers

In our work, thiol-containing side-groups were bonded to poly(aspartic acid) (PASP). PASP polymers were synthesized by the Soft Matters Group at Budapest University of Technology and Economics.

The following reducing agents were used as antioxidants during the synthesis: dithiotreitol (Merck), glutathione (Merck) and N-acetylcysteine (Reanal Hungary).

1 M NaBrO₃ solution was used as a model oxidant.

3.2. Methods

3.2.1. Preformulation measurements

Osmolality (*osmometer – Knauer Semi-micro Osmometer, Germany*), surface tension (*OCA Contact Angle System, Dataphysics OCA 20, Dataphysics Inc., GmbH, Germany, pendant drop method*), refractive index (*Abbe refractometer*), pH (*pH-meter, Testo 206-pH2, UK*) and transmittance (*UV-spectrophotometer (Unicam Helios α Thermospectronic UV-spectrophotometer v4.55, UK, wavelength range 200-600 nm)*) were measured in aqueous solutions of ThioPASP at five concentrations (1, 3, 5, 7 and 10% w/w).

3.2.2. Cytotoxicity

For the cytotoxicity measurements, MTT tests were performed on the rabbit corneal epithelial (RCE) cell line by a method described previously. CLNaHA, NaHA and ZnHA formulations of 4% w/w were used in 20-fold dilution. ThioPASP solutions were measured in concentrations of 5, 7 and 10% w/w. All samples were brought into contact with cells for 3 h.

3.2.3. Rheology

The rheological properties were studied with a Physica MCR101 rheometer (Anton Paar, Austria). The tests were performed by a method described previously.

All measurements (HA derivatives and ThioPASP) were performed with and without mucin (final mucin concentration in the mixtures was 5% w/w). The gelation time (ThioPASP) and the viscoelastic character (frequency sweep tests, CLNaHA, NaHA, ZnHA and ThioPASP) were made over the angular frequency range from 0.1 to 100 s⁻¹, whereby storage modulus (G'), loss modulus (G'') and complex viscosity (η^*) were determined.

3.2.4. Swelling

The water absorption capacity of the ThioPASP gels was determined gravimetrically by a method described previously. 20% w/w mixtures of ThioPASP with oxidant (1 M NaBrO₃, 20% w/w) were measured.

3.2.5. Tensile test

Tensile tests were performed with a TA-XT Plus (Texture analyser (ENCO, Spinea,I)) instrument equipped with a 1 kg load cell and a cylinder probe with a diameter of 1 cm. Samples were placed in contact with mucin dispersion (*in vitro*), simulated lacrimal fluid (blank) or excised porcine conjunctiva (*ex vivo*). The measurements were performed by a method described previously.

3.2.5.1. Tensile test data analysis

In the tensile test, the normalized mucoadhesion parameters ($\Delta AUC/AUC$) were calculated as followed:

$$\frac{\Delta AUC}{AUC} = \frac{AUC_m - AUC_b}{AUC_b} \quad (1)$$

where AUC_m is the work of adhesion in presence of mucin and AUC_b is the work of adhesion of blank measurements (with simulated lacrimal fluid).

3.2.6. 'Wash away' measurement

To perform the 'wash away' measurements, modified Franz diffusion cell was used. The measurements were performed by a method described previously. *Ex vivo* tests were made on excised porcine conjunctiva placed on the acceptor chamber and simulated lacrimal fluid was streamed through the donor chamber. 5, 7 or 10% w/w ThioPASP gels were used, with sodium fluorescein (0.008% w/w) as the measured marker. HEC gels under the same experimental conditions were used as reference.

3.2.7. Drug release

The drug release profile of SD was determined with a vertical Franz diffusion cell system (Hanson Microette Plus TM). 1% w/w formulations of CLNaHA, NaHA or ZnHA and 7 and

10% w/w ThioPASP gel concentrations were prepared. All samples contained 0.1% w/w SD. The measurements were performed by a method described previously.

3.2.8. Statistical analysis

The results were evaluated and analysed statistically with GraphPad Prism version 5 software. Two-way ANOVA analysis was applied with Bonferroni post-tests. The values are expressed as means \pm standard deviation (SD). A level of $p \leq 0.05$ was taken as significant, $p \leq 0.01$ as very significant, and $p \leq 0.001$ as highly significant.

4. RESULTS AND DISCUSSION

4.1. First generation mucoadhesive polymers

4.1.1. Preformulation

Figure 2 illustrates the results of the biocompatibility determination of CLNaHA, NaHA and ZnHA on RCE cells by the MTT test. As control, HBSS was used.

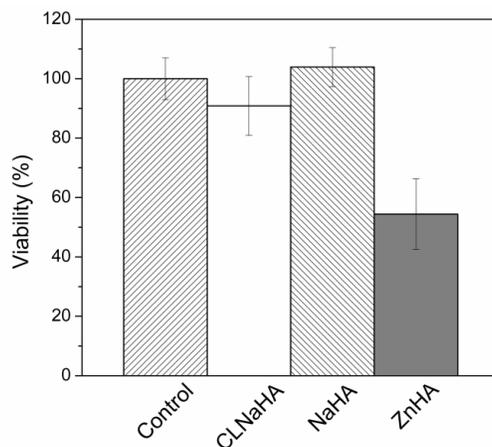


Fig.2. Biocompatibility of CLNaHA, NaHA and ZnHA

Our results demonstrate that CLNaHA and NaHA are biocompatible. Although ZnHA exhibits lower biocompatibility in the RCE cell line, under *in vivo* conditions it may have better biocompatibility thanks to the *in vivo* homeostatic mechanisms.

4.1.2. Gel characterization

The viscoelastic characters of CLNaHA, NaHA and ZnHA were determined by frequency sweep testing in the frequency range 0.1 to 100 Hz.

CLNaHA and NaHA displayed viscoelastic behaviour, acting as viscous solutions in the lower frequency range, and demonstrating elastic properties at higher frequency. The cross-over point for NaHA was seen at lower frequency than that for CLNaHA, from which it can be concluded that CLNaHA shows less elastic behaviour. In contrast with CLNaHA and NaHA, ZnHA behaves as a viscous fluid; G'' predominates over G' , and no cross-over point can be detected.

4.1.3. Mucoadhesion

In vitro and *ex vivo* tensile test measurements were performed of CLNaHA, NaHA and ZnHA. Gels were placed in contact with mucin and excised porcine conjunctiva (Fig. 3). The *ex vivo* measurements related to conditions closer to the real mucoadhesive circumstances of the eye.

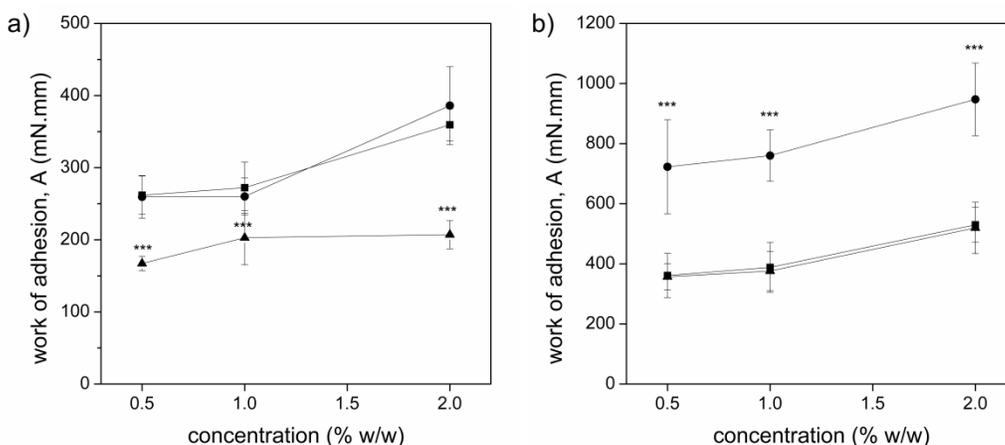


Fig. 3. Work of adhesion of (●) CLNaHA, (■) NaHA and (▲) ZnHA as a function of the concentration of the polymer a) *in vitro* (mucin) and b) *ex vivo* (porcine conjunctiva) (***: $p \leq 0.001$, highly significant compared with CLNaHA)

In case of *in vitro* test the values of work of adhesion increased with increase of the polymer concentration thanks to the physical mechanisms between the polymer and the mucin. The values of work of adhesion were at least twice as high in the *ex vivo* measurements as those measured with mucin in the case of the *in vitro* measurements. This is beneficial for ophthalmic therapy, because it can be predicted that the mucoadhesion of the gels will be higher on the surface of the eye. The nanosized structure of CLNaHA leads to easier and deeper interpenetration and more facile chemical bond formation with the mucus layer of the eye, resulting a significantly higher

work of adhesion values than those of the other two derivatives. The pronounced mucoadhesive behaviour of CLNaHA at 0.5% w/w was also seen in the *ex vivo* measurements, proving the possibility of prolonging the residence time on the eye surface even at low CLNaHA concentration.

4.1.4. Drug release

The drug release from CLNaHA, NaHA and ZnHA at 1% w/w polymer concentration containing 0.1% w/w SD was measured with a vertical Franz diffusion cell. Figure 4 shows the amount of drug released (% w/w) during the examination time (h).

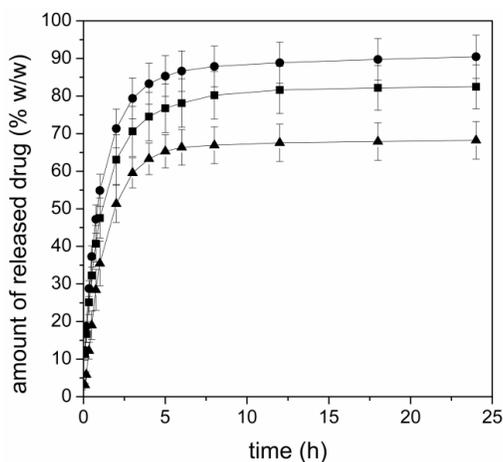


Fig. 4. Release of SD from (●) CLNaHA, (■) NaHA and (▲) ZnHA

In the first hour of measurements, a rapid diffusion of SD was observed from all three formulations, but their release profiles then diverged. There was no significant difference between CLNaHA and NaHA in the first hour, but CLNaHA later released a higher amount of SD as compared with NaHA. This can be explained by the easier diffusion of SD from the CLNaHA gels, due to the smaller particle size and lower viscosity. ZnHA released a significantly lower amount of SD, even in the first hour, possibly because interactions may occur between SD and ZnHA. This needs to be investigated, but did not constitute part of the present research work.

4.2. Second generation mucoadhesive polymers

4.2.1. Preformulation

The osmolality, surface tension, refractive index, transmittance and pH measurement results indicate that ThioPASP may be a very promising eye drop formulation. Thanks to its inert

properties, ThioPASP solution does not affect the tear stability, and the ophthalmic requirements can be achieved through the addition of necessary excipients such as the isotonicizing and surface tension-modifying agents.

Cytotoxicity measurements were performed with the MTT assay on the RCE cell line. Only the viable cells are able to reduce the dye MTT to formazan. Figure 5 shows the viability of cells after contact with ThioPASP solution samples relative to control cells.

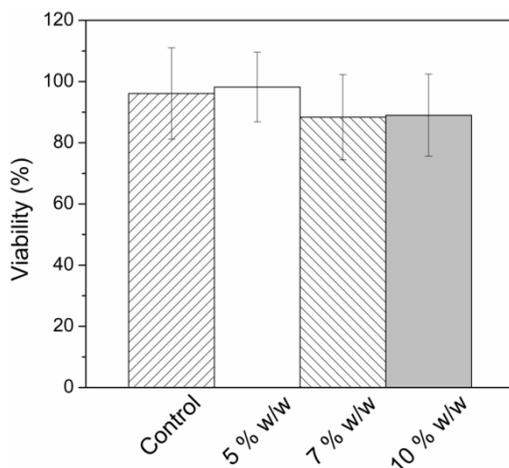


Fig. 5. Cell viability after contact with ThioPASP solutions

The results demonstrate that ThioPASP solution is biocompatible, because the cell viability was >90% after a contact time of 3 h in all cases. This is an extremely important finding, especially because RCE cells are very sensitive, so that it can be predicted that ThioPASP solution will highly probably not have a toxic effect on the eye.

4.2.2. Gel characterization

The swelling of the hydrogels was characterized by a gravimetric method. During the 6-h measurements, the swollen polymer discs maintained their coherent structure and shape, because of the formation of disulfide linkages between the polymer chains. The swelling ability of the hydrogel was large because of the lower cross-linking density resulting from the weaker elastic interactions inside the polymer network. This led to a marked water uptake of the formulation. ThioPASP was able to swell to 6000-7000% of the volume of its dry mass.

The gelation process and the gel structure were characterized by means of rheology. The effects of the polymer concentration (7 or 10% w/w) were studied (Fig. 6).

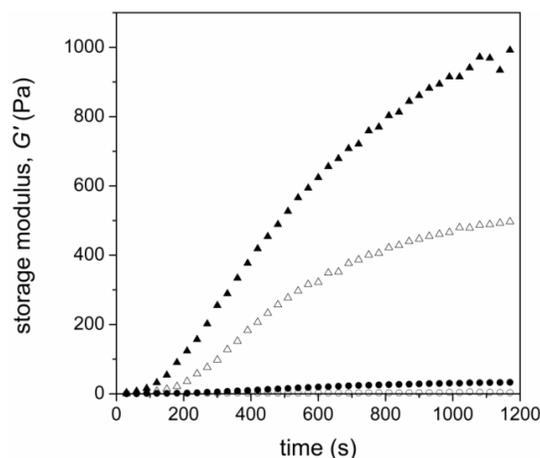


Fig. 6. Evolution of storage modulus (G') as a function of time at (●) 7% w/w and (▲) 10% w/w polymer concentrations with (solid symbols) or without (open symbols) mucin

At polymer concentrations lower than 7% w/w, the changes of the polymer concentration did not affect the gelation, G' did not change significantly and the precursor solutions remained in the liquid state even after the addition of oxidant (G' was similar in order of magnitude to G''). At polymer concentration of 7% w/w, a gel structure formed (G' was more than an order of magnitude higher than G''). The gel obtained at 10% w/w ThioPASP displayed the strongest gel structure, indicating that the elevation of the polymer concentration enhanced the cross-linking density by increasing the concentration of disulfide linkages.

Measurements were performed also after the addition of mucin to the ThioPASP gels. In the cases of 7 or 10% w/w polymer, the gelation time was shorter (Fig. 6.). The addition of mucin aided the gelation and in each case the gelation time was shorter in the presence of mucin. The rate of gelation and the final value of G' were higher in the presence of mucin.

4.2.3. Mucoadhesion

Tensile test measurements were made with 3, 5, 7 and 10% w/w polymer (a) *in vitro* with mucin dispersion and (b) *ex vivo* with excised porcine conjunctiva (Fig. 7).

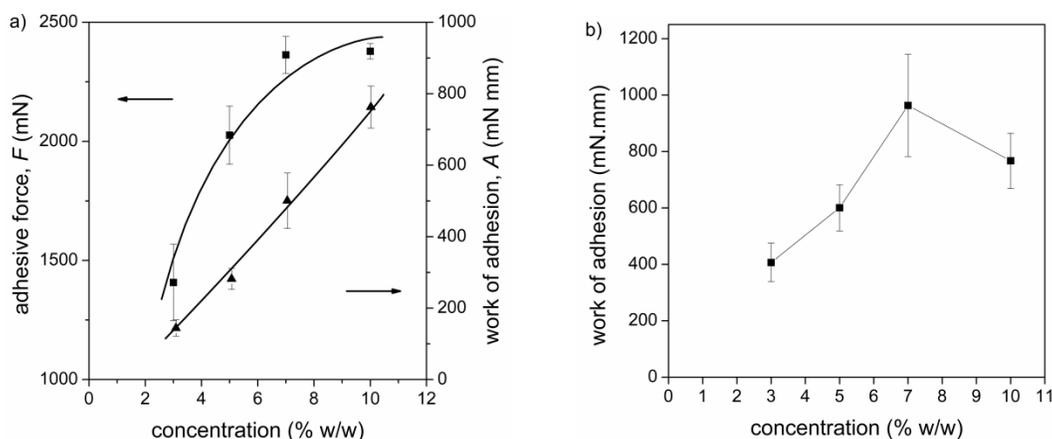


Fig. 7. (a) (■) Adhesive force (F) and (▲) work of adhesion (A) as functions of polymer concentration *in vitro* and (b) work of adhesion (A) as functions of polymer concentration *ex vivo*

Fig. 7a reveals that work of adhesion increased continuously as the concentration was elevated, while the adhesive force (F , mN) reached a maximum at 7% w/w polymer. In our work the chemical bonds probably have a larger effect at lower polymer concentration, and it is likely that covalent bonds and secondary bonds were formed with the mucin glycoproteins. Thus, adhesive force increased continuously with increasing polymer concentration. At high polymer concentration, the potential for chemical bonds reached a maximum because the free thiol groups were saturated at the interface. Accordingly, a plateau was observed in the adhesive force vs. concentration curve. Work of adhesion did not reach a maximum, but increased continuously, because interpenetration prevails in the process of mucoadhesion rather than chemical bonding at higher polymer concentrations. In our case, the ThioPASP gel at higher concentration has more thiol groups and more cross-links, resulting in a gel structure, which induces increased swelling, allowing deeper and improved interpenetration.

In *ex vivo* tensile test measurements, work of adhesion increased continuously as the polymer concentration was elevated up to 7% w/w. At high concentration (10% w/w), the ThioPASP polymer is not able to interpenetrate into the mucous layer of the porcine conjunctiva, probably because a highly cross-linked structure, which is less flexible is formed at this concentration.

‘Wash away’ *ex vivo* measurements mimic the lacrimation of the eye, under conditions relatively close to real mucoadhesive circumstances of the eye. The amount of sodium fluorescein washed away from the porcine conjunctiva can indicate the amount of the dosage form remaining on the surface. Comparison of the ThioPASP systems with the HEC gels

indicated that the ThioPASP formulations have a longer residence time, because 40% w/w of the model drug remained on the conjunctiva, in contrast with 10-30% w/w for the reference systems.

4.2.4. Drug release

Drug release measurements were performed with a vertical Franz diffusion cell system with gels containing 10% w/w polymer and 0.1% w/w SD. Figure 8 shows the amount of drug released (% w/w) during time.

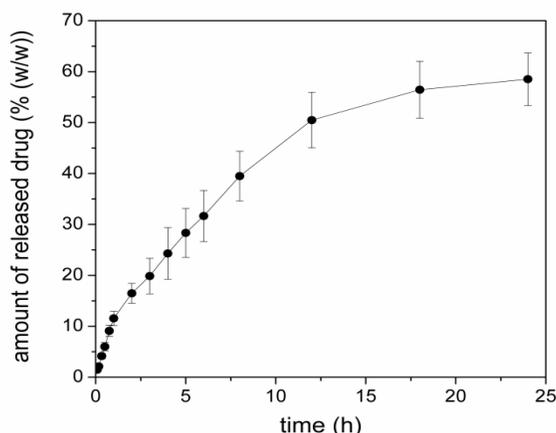


Fig. 8. Release of model drug, SD from ThioPASP gel

In the first hour, the diffusion of the SD was fast, and this was followed by a sustained release. The drug release results correspond with the swelling measurement results. The formulation has a higher water uptake, suggesting a lower cross-linking density, and the SD is therefore able to diffuse through this structure more easily.

4.2.5. Effect of the polymer stabilization

4.2.5.1. Mucoadhesion

The calculated normalized mucoadhesion parameters in the case of the tensile test are depicted in Figure 9. Dithiothreitol (*DTT*), glutathione (*GSH*) and acetylcysteine (*ACC*) stabilized ThioPASP polymers were characterized.

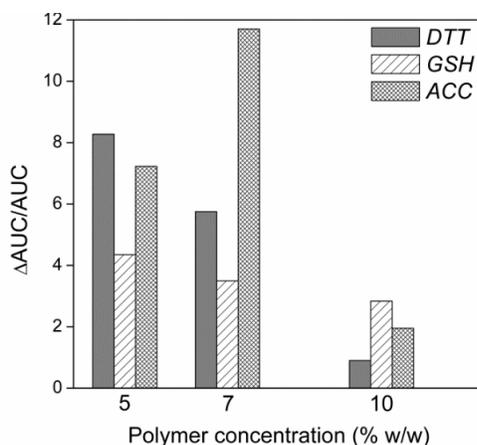


Fig. 9. The calculated normalized mucoadhesion parameters of work of adhesion in tensile test measurement

In the case of dithiothreitol stabilized formulations mucoadhesion was observed, which decreased as the concentration was elevated. These calculations predict that dithiothreitol as stabilizing agent prefers polymer–polymer interactions, but even in this case it can provide a limited mucoadhesion on the interface.

The *GSH*, as a glutathione stabilized sample at low polymer concentration was mucoadhesive, but with increase of the polymer concentration its mucoadhesivity decreased. As compared with the dithiothreitol stabilized samples, the tensile tests indicated a weak mucoadhesive property, which can be explained by its weak cohesivity (the gels fell apart during the experiments) and resistance against the tensile strength.

Up to 7% w/w polymer concentration, the acetylcysteine stabilized formulation (*ACC*) showed marked mucoadhesivity relative to the other two formulation types. At 7% w/w, a gel structure was formed which can provide optimum mucoadhesion.

4.2.5.2. Drug release

The SD release from the *DTT*, *GSH* and *ACC* gels (at the optimum, 7% w/w polymer concentration) was determined with the vertical Franz diffusion cell system during 24 h (Fig. 10).

The results revealed that the *GSH* gels released the highest amount of SD (~80% w/w) during 24 h, while there was no significant difference between the lower amounts of SD released by *DTT* and *ACC*. *GSH* has the fastest release thanks to the disrupted structure, which cannot be predicted and planned in advance. Even if *DTT* and *ACC* release lower amounts of SD, their

release profile can be designed thanks to their stable structure. The *in vitro* results indicate that the formulations can provide 24 h continuous release.

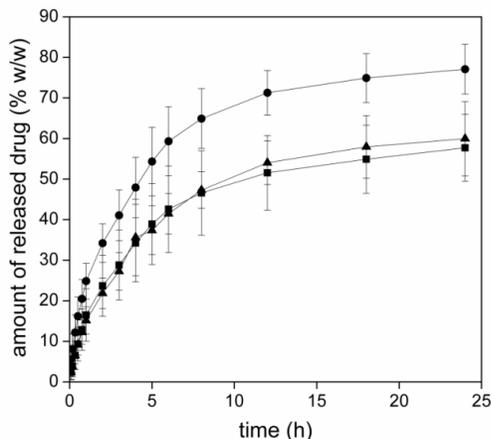


Fig. 10. Release of SD from ThioPASP gels at 7% w/w polymer concentration: (■) G1; (●) G2; (▲) G3

5. SUMMARY

The aim of my research work was to characterize hyaluronic acid (HA) derivatives as first generation and thiolated poly(aspartic acid) (ThioPASP) polymers as second generation mucoadhesive polymers as potential ocular drug delivery system vehicles. The generally poor bioavailability of ophthalmic formulations can be improved by new formulations with a prolonged residence time.

Comparative studies of HA derivatives from the aspects of mucoadhesion and drug release have not been reported previously. Likewise, a cross-linked sodium salt of HA (CLNaHA) has not been used before as a potential ocular drug delivery system vehicle.

ThioPASP polymers as a new type of mucoadhesive polymers were studied first in a wide range from the aspects of ophthalmic preformulation (osmolality, surface tension, refractive index, transmittance and cytotoxicity) and formulation (hydrogel characterization, mucoadhesion and drug release).

The results of the measurements with the HA derivatives and the ThioPASP polymers led to the following conclusions:

- Both the HA derivatives and the ThioPASP polymers are biocompatible, as proved by the MTT test on RCE cell line.

- Their good mucoadhesive property was verified *in vitro* (rheological and tensile tests) and *ex vivo* (tensile tests). In the *ex vivo* tensile tests, higher values of adhesive work were measured, predicting a better *in vivo* mucoadhesion. Thanks to this property, the residence time on the eye can be prolonged.
- Both HA derivatives and ThioPASP polymers exhibit a fast initial release of sodium diclofenac, followed by a sustained release up to 24 h. This is beneficial in ophthalmic therapy because the therapeutic effect can be achieved at the beginning of the application, which is followed by a sustaining dosage.
- The use of HA derivatives gives an opportunity to find the optimum salt and structure for the required therapy.
- Although ZnHA displayed lower biocompatibility and mucoadhesion, its bactericidal and fungicidal properties can give an opportunity to decrease or eliminate the amount of preservatives from the formulation (such preservatives can cause cellular damage during long-term ophthalmic therapy).
- Of the HA derivatives tested, CLNaHA had the optimum structure for mucoadhesion and drug release. These results justify the use of CLNaHA in ophthalmic therapy in the future.
- *In situ* gelling can be achieved through the use of ThioPASP polymers. This property is very beneficial in ocular therapy because such polymers can be used as eye drops and will gellify *in situ*.
- ThioPASP polymers are inert excipients, which simplifies the formulation of ocular drug delivery system.
- ThioPASP polymers are also resistant against lacrimation and blinking, as proved by the “wash away” and rheological tests. These properties also play an important role in prolongation of the residence time on the ocular surface.
- The ThioPASP polymer stabilized with acetylcysteine exhibited the best mucoadhesive and drug release properties.

All of the results of the measurements performed excellently illustrated the potential of the application of the HA derivatives and the ThioPASP polymer as mucoadhesive ocular drug delivery system vehicles, with the beneficial property of reducing the necessary frequency of use.

PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

- 1. Gabriella Horvát**, Benjámín Gyarmati, Szilvia Berkó, Piroska Szabó-Révész, Barnabás Áron Szilágyi, András Szilágyi, Judit Soós, Giuseppina Sandri, Maria Cristina Bonferoni, Silvia Rossi, Franca Ferrari, Carla Caramella, Erzsébet Csányi, Mária Budai-Szűcs
Thiolated poly(aspartic acid) as potential *in situ* gelling, ocular mucoadhesive drug delivery system
Eur. J. Pharm. Sci. 67, 1-11, 2015
IF: 3.350
- 2. Gabriella Horvát**, Szilvia Berkó, Erzsébet Csányi, Piroska Szabó-Révész, Judit Soós, Andrea Facskó, Mónika Maroda, Michela Mori, Giuseppina Sandri, Maria Cristina Bonferoni, Carla Caramella, Mária Budai-Szűcs
Comparative study of nanosized cross-linked sodium-, linear sodium- and zinc-hyaluronate as potential ocular mucoadhesive drug delivery systems
Int. J. Pharm. 494, 321-328, 2015
IF: 3.650
- 3. Mária Budai-Szűcs**, **Gabriella Horvát**, Benjámín Gyarmati, Barnabás Áron Szilágyi, András Szilágyi, Tímea Csihi, Szilvia Berkó, Piroska Szabó-Révész, Michela Mori, Giuseppina Sandri, Maria Cristina Bonferoni, Carla Caramella, Erzsébet Csányi
In vitro testing of thiolated poly(aspartic acid) from ophthalmic formulation aspects
Drug Dev. Ind. Pharm., DOI: 10.3109/03639045.2015.1118497
IF: 2.101

PRESENTATIONS RELATED TO THE SUBJECT OF THE THESIS

Oral presentations

1. Mária Budai-Szűcs, Benjámín Gyarmati, **Gabriella Horvát**, Szilvia Berkó, Piroska Szabó-Révész, Barnabás Szilágyi, Giuseppina Sandri, Maria C. Bonferoni, Carla Caramella, András Szilágyi, Erzsébet Csányi

In situ gelling mucoadhesive drug delivery system for ophthalmic use

2nd International Conference on Bio-based Polymers and Composites, Visegrád, Hungary, 24th to 28th August 2014.
2. Benjámín Gyarmati, **Gabriella Horvát**, Mária Budai-Szűcs, Szilvia Berkó, Barnabás Szilágyi, Erzsébet Csányi, András Szilágyi

Mucoadhesive thiolated poly(aspartic acid)

Polymer Network Groups Meeting and Gel Symposium, Tokyo, Japan, 10th to 14th November 2014.
3. **Gabriella Horvát**, Benjámín Gyarmati, Szilvia Berkó, Piroska Szabó-Révész, Barnabás Áron Szilágyi, András Szilágyi, Judit Soós, Giuseppina Sandri, Maria Cristina Bonferoni, Carla Caramella, Erzsébet Csányi, Mária Budai-Szűcs

Thiolated poly(aspartic acid) polymers in ophthalmic therapy

5th International Conference and Exhibition on Pharmaceuticals & Novel Drug Delivery Systems, Dubai, UAE, 16th to 18th March 2015.
4. Benjámín Gyarmati, Barnabás Szilágyi, **Gabriella Horvát**, Mária Budai-Szűcs, Erzsébet Csányi, András Szilágyi

In situ gelling poly(aspartic acid)s for pharmaceutical applications

16. Österreichische Chemietage 2015, Joint Meeting of the Italian and Austrian Chemical Societies, Innsbruck, Austria, 21st to 24th September 2015.
5. **Horvát Gabriella**, Csányi Erzsébet, Budai-Szűcs Mária

Szemészeti terápia során alkalmazható első és második generációs mukoadhezív polimerek

Gyógyszertechológiai és Ipari Gyógyszerészeti Konferencia, Siófok, Magyarország, 2015. Október 15-17.

Poster presentations

- 1. Horvát Gabriella**, Gyarmati Benjámín, Szilágyi Barnabás, Budai-Szűcs Mária, Berkó Szilvia, Révész Piroska, Csányi Erzsébet, Szilágyi András
Új típusú aminosav alapú polimerek in situ gélesedő szemészeti rendszerekben
Congressus Pharmaceuticus Hungaricus XV. Budapest, Hungary, 2014. április 10-12.
- Mária Budai-Szűcs, **Gabriella Horvát**, Mónika Maroda, Piroska Szabó-Révész, Erzsébet Csányi, Szilvia Berkó
Cross-linked and linear hyaluronic acid in focal drug delivery
International Conference on Bio-Friendly Polymers and Polymer Additives, Budapest, Hungary, 19th to 21st March 2014.
- Gabriella Horvát**, Szilvia Berkó, Piroska Szabó-Révész, Erzsébet Csányi, Mónika Maroda, Giuseppina Sandri, Maria Cristina Bonferoni, Carla Caramella, Mária Budai-Szűcs
Hyaluronan and its salts as mucoadhesive ocular drug delivery systems
2nd International Conference on Bio-based Polymers and Composites, Visegrád, Hungary, 24th to 28th August 2014.
- Gabriella Horvát**, Benjámín Gyarmati, Barnabás Szilágyi, Tímea Csihi, Giuseppina Sandri, Maria Cristina Bonferoni, Carla Caramella, András Szilágyi, Erzsébet Csányi, Mária Budai-Szűcs
Mucoadhesion of thiolated poly(aspartic acid) polymers for ophthalmic use
1st European Conference on Pharmaceutics – Drug Delivery, Reims, France, 13th to 14th April 2015.
- Barnabás Áron Szilágyi, Benjámín Gyarmati, **Gabriella Horvát**, Mária Budai-Szűcs, Erzsébet Csányi, András Szilágyi
Thiolated poly(aspartic acid): an in situ gelling mucoadhesive polymer
16. Österreichische Chemietage 2015, Joint Meeting of the Italian and Austrian Chemical Societies, Innsbruck, Austria, 21st to 24th September 2015.