

**University of Szeged**  
**Department of Pharmaceutical Technology**

**Formulation and Investigation of Gel-Emulsions Containing  
Polymeric Emulsifiers**

Summary of PhD Thesis

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# 1 INTRODUCTION

An emulsion is a heterogeneous preparation composed of two immiscible liquid (by convention described as oil and water), one of which is dispersed as fine droplets uniformly throughout the other. Emulsions have been used for centuries in various domains in the pharmaceutical, cosmetic, food, paint and road industry.

Manufacturers of pharmaceutical and cosmetic products have recently shown increasing preference for multifunctional products in which different active agents can be incorporated, and for controlled drug delivery systems which decrease the usage frequency (hence increase patient compliance) and can decrease side effects or toxicity due to a lower active agent content. Emulsions are able to ensure these terms.

In pharmacy and medicine they are formulated for virtually all the major routes of administration: dermatological, oral and parenteral. Although emulsions have several advantages over other dosage forms (often improve bioavailability and/or reduce side effect) they are not used as extensively as other dosage forms (mainly oral and parenteral) because of emulsion instability, which results in unpredictable drug release profiles and possibly toxicity. Therefore one of the most important tasks is to ensure the kinetic stability of these systems. In addition to stability, other requirements also have to be satisfied by emulsions used in cosmetic and pharmaceutical industries, e.g. appropriate consistence and safety of ingredients. Gel-emulsions, besides microemulsion gels and creams, belong to coherent emulsions. Possibilities to form a gel-emulsion are the following:

- gel formation of the water phase by hydrophilic or hydrophobic polymers such as polysaccharides, carrageenan, gelatine acrylic acids or wax;
- in situ gelation of the polymer at the interface or in the continuous phase during/after the emulsification procedure or after the application;
- using polymeric emulsifiers.

Polymeric emulsifiers are one of the most effective stabilizers as manifested by lower usage concentration. Three different types of polymeric emulsifiers can be found in the literature: i) linear block, ii) graft and iii) star copolymers. In this work formulation and investigation of gel-emulsion containing polymeric emulsifiers is presented.

## **2 AIMS**

The aims of my research were the follows:

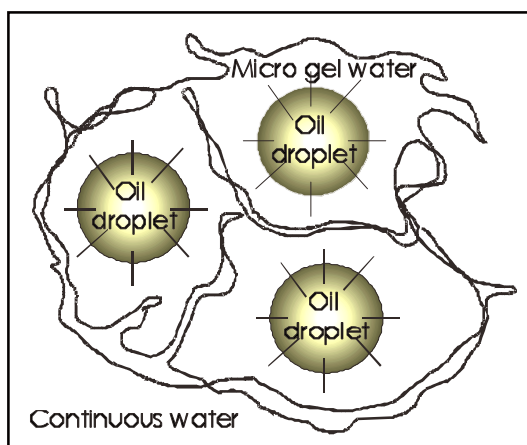
- 1) To get to know the properties of the polymeric emulsifier (surface activity, wetting, swelling).
- 2) To determine the effect of the pH on the gels prepared with polymeric emulsifier and their oil loading capacity.
- 3) On the basis of the preformulation studies to define the formulation environment of the emulsions containing polymeric emulsifier.
- 4) To investigate the structure and properties (rheological behaviour, droplet size distribution, bounding of the water, gel structure) of emulsions and gels by: i) direct methods: image analyser, confocal laser scanning microscopy; and ii) indirect methods: rheology, thermogravimetry.
- 5) To study the stability of the emulsions using the methods mentioned above during 3-month storage (on 25°C).
- 6) To allocate the possible application fields of these systems by examining: bioadhesive behaviour and drug release profile using lipophilic and hydrophilic model drugs.
- 7) To determine the relationship between the formulation and the structure, the formulation and the stability, the formulation and the applicability.

## **2 MATERIALS AND METHODS**

### **2.1 Materials**

#### **Polymeric emulsifiers: Pemulen TR1 and TR2**

Pemulen TR1 and Pemulen TR2 (PTR1 and PTR2) are cross-linked block copolymers of poly(acrylic acid) and hydrophobic long-chain methacrylates. Traditional ionic or non-ionic surfactants stabilize oil-in-water emulsions principally by adsorbing and forming lamellar liquid crystalline layers at the emulsion interface requiring usage levels of 3-7% of surfactant. Contrarily, emulsions created with very low levels of Pemulens are highly stable, because the hydrophobic portion of the polymer anchors in the oil phase while oil droplets are protected and held in place as a result of the viscous aqueous gel formed by the lipophilic part of the molecule around each oil droplet (Fig.1).



*Fig.1 Structure of an emulsion containing Pemulens*

### **Other components**

- Oil phase: Miglyol 812 (Fractioned coconut oil, Triglycerida saturata media, Ph.Hg.VII.)
- Coemulsifier: Synperonic PE/L 31; 61; 62; 101 (Uniqema, UK) (ethylene oxide-propylene oxide block copolymer) (S31; S61; S62; S101)
- Neutralizing agent: Trolamine (Ph.Hg.VII.)
- Hydrophilic model drug: Metronidazole (Ph.Hg.VII.)
- Lipophilic model drug: Lidocaine (Ph.Hg.VII.)

## **2.2 Methods**

### **Emulsions preparation**

The Pemulens were added to purified water containing trolamine. After 24 hours the oil was added to this gel while the sample was stirred with mixer (MLW ER-10, 800 rpm) for 20 minutes. In the samples containing coemulsifiers, the mixture of the coemulsifier and oil was added to the water phase.

### **Measurement of the surface tension**

The measurement of the surface activity was carried out with Krüss tensiometer. The air-liquid surface tension was detected.

### **Contact angle measurements**

Dataphysics OCA20 was used to determine the wetting especially the contact angle between the polymer probes and the water, and between them and the oil. The contact angle was calculated from the Leplace-Young equation.

### **Measurement of the Enslin number**

The measurements were performed with Enslin instrument. The polymer was laid onto the filter paper of the instrument. The swelling was followed for 10 min, and the loaded water was determined.

### **Droplet size analysis**

The particle size and the particle size distribution were measured with the Leica Q500MC image analyser system. 500 droplets were analysed in each emulsion.

### **Thermogravimetric investigation**

The measurements were carried out with a MOM Derivatograph-C (MOM GmbH, Hungary) instrument. Samples were weighed (40-50 mg) in platinum pans (No.4). The reference was a pan containing aluminium oxide. The samples were heated from 25 to 200 °C at 5 °C min<sup>-1</sup> or at 10 °C min<sup>-1</sup>. TG (weight loss % vs. temperature), DTG (derivative TG) and DTA curves were plotted.

### **Rheological investigation**

HAAKE RheoStress 1 Rheometer (HAAKE GmbH., Germany) with cone and plate geometry was used to study the rheological profile of the samples. The flow curve and the viscosity curve of the samples were determined by rotation tests controlled shear rate. The storage ( $G'$ ), the loss ( $G''$ ) moduli and loss tangent ( $\tan\delta = G''/G'$ ) were examined as function of frequency.

### **Tensile test**

The mucoadhesive properties of the gel-emulsions were investigated by TA-XT2 Plus Texture Analyser (Stable Micro Systems, Enco, Italy). The detachment force was determined and the adhesive work was calculated from the area under the force-distance curve.

### **Confocal laser scanning microscopy**

The visualization of the gel structure and the bioadhesive bond between the emulsion and the mucin was carried out with Confocal Microscope System Leica TCS SP2 (Leica Microsystems Heidelberg GmbH., Germany) interfaced with a Leica DMIRBE inverted microscope. The gel structure was dyed with rhodamine B, and the bioadhesive bonds were formed with mucin from porcine submaxillary glands.

## **Drug release test**

In vitro drug release tests were carried out with Hanson SR8-Plus™ Dissolution Test Station (Hanson Research Corporation, USA) using special ointments cells. The quantitative determination of the drugs was performed by UV-VIS spectrophotometer (Unicam Helios- $\alpha$ , Spectronic Unicam, UK).

## **3 RESULTS AND DISCUSSION**

### **3.1 Preformulation studies**

In the course of the preformulation studies, it was established that the wetting of these polymeric emulsifiers is very weak with purified water, but better with Miglyol. There is no remarkable alteration between the values of different polymerization-degree polymers.

The swelling of the polymers takes long time, the amount of the water taken up is quite low (low Enslin number). These two properties have to be considered for the preparation of the gels or emulsions. This is the cause why the samples had been stored for 24h before the emulsification procedure.

In the course of the surface tension measurements Pemulens like other polymeric emulsifiers showed low surface activity, which suggests that the presence of a coemulsifier is also required to facilitate the emulsification procedure.

When the pH was changed at low polymer content, constant value was detected; contrarily, at high (1.00% w/w) concentration the pH affected the viscosity especially at PTR2

Adding Miglyol to the gel drop wise, the maximum oil concentration was determined. The two different polymerization-degree polymers showed alteration . The gels containing the lower polymerization-degree polymer could take up more oil than the higher one, which can be explained by flexibility at the interface.

### **Rheological Investigation**

Few pieces of information can be found in the literature about the Pemulen's rheological characteristics. An increase in viscosity was described with the polymeric emulsifier and the concentration and the emulsions showed thixotropy or antithixotropy. In my studies initial viscosity ( $\eta_0$ ), and the damping factor ( $\tan\delta$ ) were used to characterize the rheological properties of the gels and emulsions.

Initial viscosity was determined by the power law model:

$$\eta = \eta_0 D^n \quad (1)$$

where  $\eta$  is the viscosity,  $\eta_0$  is the initial viscosity,  $D$  is the shear rate and  $n$  is the power (shear thinning) index. (In the further results viscosity means the initial viscosity.)

For the viscoelastic characterization of the emulsions  $\tan\delta$  (loss tangent or damping factor),  $G'$  (storage modulus) and  $G''$  loss modulus were used.

$$\tan\delta = G''/G' \quad (2)$$

Where  $G'$  is the storage modulus,  $G''$  is the loss modulus. The smaller  $\tan\delta$  (or the greater  $G'$ ) is, the stronger the interaction is in the gel structure.

By correlating the viscosity values of the emulsions to one of the simple gels it can be concluded that there is not a pregnant difference between the gels and emulsions with the same polymer content for PTR1 samples (Fig.2A). Contrarily, for PTR2 ones the inner phase increased the viscosity.

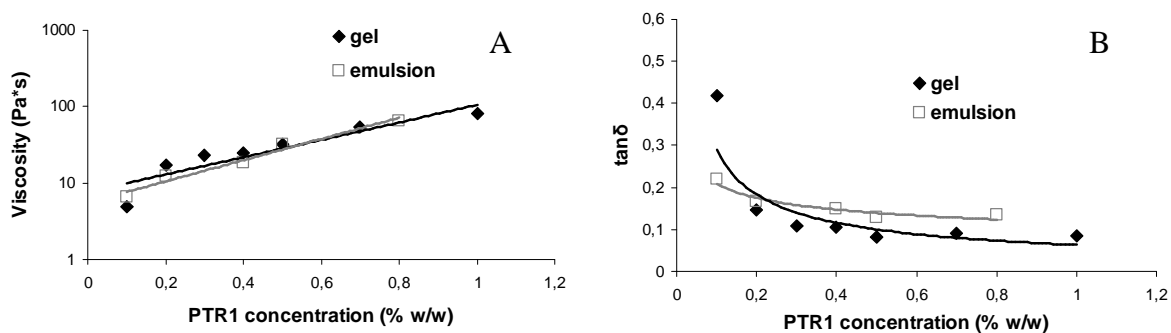


Fig.2 Viscosity (A) and damping factor (B) as function of the polymeric emulsifier concentration (emulsions oil concentration is 20%)

In the course of the oscillation measurement at low polymer content the emulsions showed higher elasticity, while at high concentration the gels did (Fig.2B). It can be supposed that the presence of the inner phase improves the formation of the gel structure and therefore the elasticity at low concentration, but (relatively) decreases that at a high one.

Raising the amount of the oil increased the viscosity in case of the both of the polymers. In turn damping factor showed an increase with the oil concentration in the PTR2 samples, while an decrease in the PTR1 samples, which indicates that the increase of the volume fraction depresses the elasticity in these sample types.

When coemulsifiers were used the viscosity usually increased with the cosurfactant concentration, while the damping factor decreased. This tendency was most remarkable in the case of S101 where those values changed extremely at high (1.00%) concentration (Fig.3).

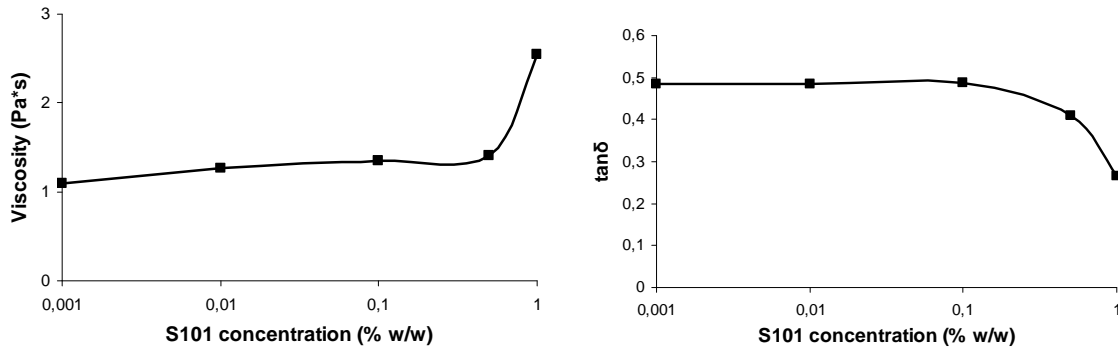


Fig.3 Variation of the viscosity and the damping factor in function of the S101 concentration (PTR2 0.10%, oil 20%)

### Thermogravimetric investigations

My basic assumption was that the polymer, due to its surfactant nature, migrates toward the interface; consequently its concentration will decrease in regions far from the oil droplets. If this concentration difference is considerable, two aqueous phases are obtained, which can be separated well on the thermograms. The first one is the bound water in the micro gel, and the second one is relatively free water. In the case of a low polymer content two peaks can be separated well on the dTG curve, one peak corresponds to free water at about 100-110°C, the other to micro gel (bound) water at about 140-150 °C. When the quantity of the polymer is increased (over 0.40% w/w) the two peaks disappear, and only one peak can be observed (Fig.4).

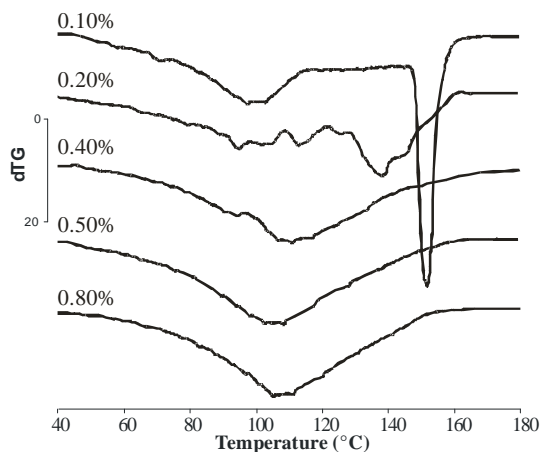


Fig.4 DTG curves at different PTR2 concentration (oil 20%)

If a coemulsifier is also used, changes in the microstructure can be assumed. The coemulsifier with its smaller molecules is also oriented on the interface; therefore in a higher concentration it can displace the polymeric emulsifier with greater molecules. As a result, the micro gel around the droplet will disappear.

The relationship between microstructure (which was influenced by the added coemulsifier) and rheology is illustrated well by Figure 5, showing the relationship between the quantity of

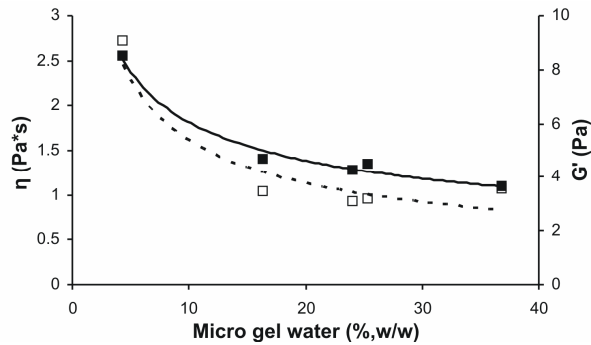


micro gel water and the rheological constants (viscosity, storage modulus), which can be described with a power function:

$$\eta = 4.45c^{-0.39} \quad (R^2 = 0.980) \quad (3)$$

$$G' = 17.24c^{-0.51} \quad (R^2 = 0.851) \quad (4)$$

where  $\eta$  is the viscosity,  $G'$  is the storage modulus and  $c$  is the water content in the micro gel.



*Fig.5 Correlation between the micro gel water and the viscosity/ storage modulus of the emulsions containing PTR1 and S101 at constant water oil ratio (PTR1 0.10%, oil 20%)*

## Microscopical investigations

### Droplet size analysis

The average droplet size of the emulsions exponentially decreased with the emulsifier content as it was expected. By increasing the oil concentration, maximum points were on the curves. At both polymeric emulsifiers a maximum average droplet size was shown at 30% w/w oil content. Above this value the droplet size started decreasing. This phenomenon can be explained with the better stability of the emulsion at about the same concentration of the two phases. With the use of coemulsifier the changes of the droplet size are not definite. At low coemulsifier content the droplet size oscillated. The interface may still be changing in this range; it is not a good ratio of the two emulsifiers to form a stable interface. Contrarily, at a high coemulsifier concentration a new interface could have been built up and formed a stable structure. The combination of the Pemulens and S101 was shown as the best one.

### Confocal laser scanning microscopy

In this study the location of the polymer was detected by this method. With the use of rhodamine B, which can be considered as a tertiary amine, hydrogen bonding or electrostatic interaction may form between the carboxyl groups of the polyacryl-acid and the fluorophore, so the dye concentration will be higher where the polymer concentration is higher. Fig.6 shows the difference between the dye distributions of the different types of fluorophores.

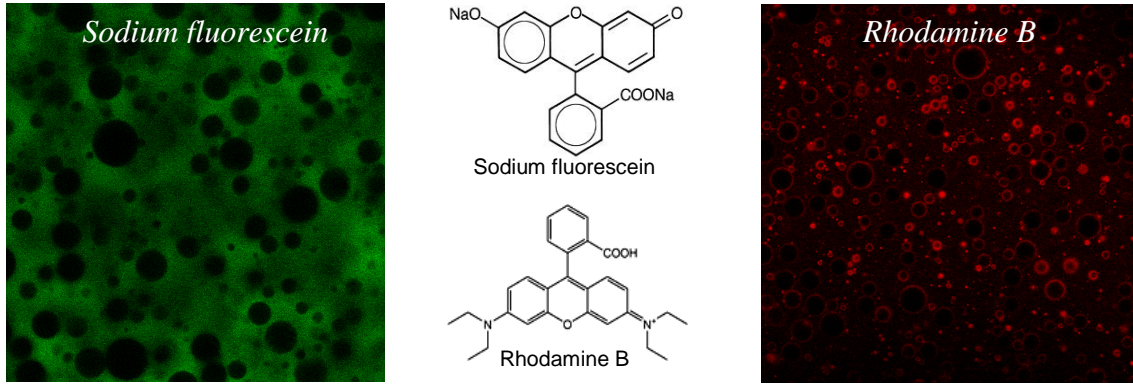


Fig.6 Difference of the dye distribution of the sodium fluorescein and rhodamine B

### 3.3 Stability

In the case of the gel structure investigation the evaporation rate and the amount of the bound water were followed during a 3-month storage time.

It was established that the evaporation rate ( $v$ ) decreased during the storage time, which can be described with a semi-empirical equation:

$$v = A_0 t^k \quad (5)$$

where  $A_0$  is the evaporation rate at  $t=0$ ,  $t$  is the storage time and  $k$  is the velocity constant.

Besides the hydration state of the emulsions, other changes occurred in the micro gel structure. In the case of PTR1 the amount of the micro gel water decreased, while it increased in the case of PTR2.

In this work microscopical droplet size analysis and rheological methods were used for predicting the emulsion stability and the parameters were followed during 3-month storage time.

If flocculation occurs on storage (without Ostwald ripening and/or coalescence) the value of the initial viscosity ( $\eta_0$ ) and the yield value ( $\sigma_0$ ) will increase. In my study  $\eta_0$  was calculated from the power law as it had been described previously and  $\sigma_0$  was calculated from the flow curve model on the basis of the Herschel-Bulkley equation:

$$\sigma = \sigma_0 + kD^n \quad (6)$$

where  $k$  is the flow coefficient and  $n$  is the Herschel-Bulkley index.

The cohesive energy ( $E_c$ ) is also used to measure the extent and strength of the flocculated structure:

$$E_c = \frac{1}{2} G' \gamma_{cr}^2 \quad (7)$$

where  $G'$  storage modulus and  $\gamma_{cr}$  is the critical strain value which is the minimum strain over which the structure breaks down. The higher  $E_c$  is, the more flocculated the structure is. In this type of gel emulsions flocculation is the most expected process during storage.

The viscosity and yield value usually changed parallel in the course of the rheological tests (Fig.7) but in the case of emulsions with very low polymer content the change of these parameters was different, which may suggest that special flocs formed or coalescence and/or Ostwald ripening occurred in the emulsions (Fig.8). However, in the case of a gel-emulsion it is not possible to separate the gel structure changes and the emulsion breakdown processes from each other, so the increase in the viscosity and yield value may have happened because of one or both of them.

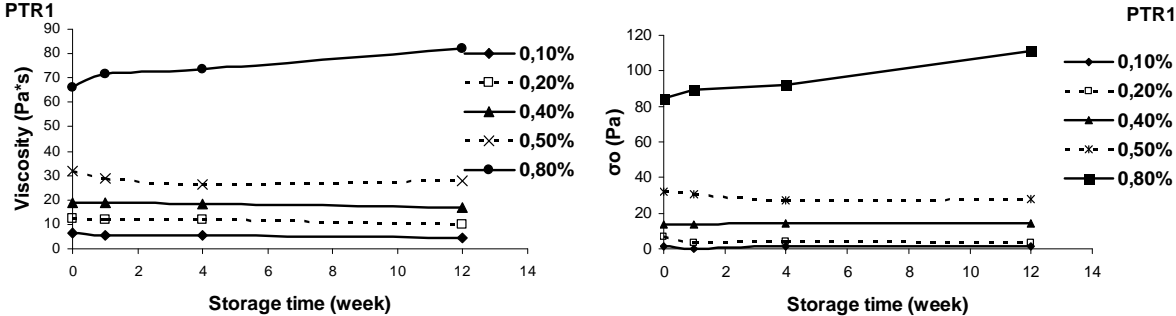


Fig.7 Changing of the viscosity and the yield value during the storage time at different polymer concentration (oil 20%)

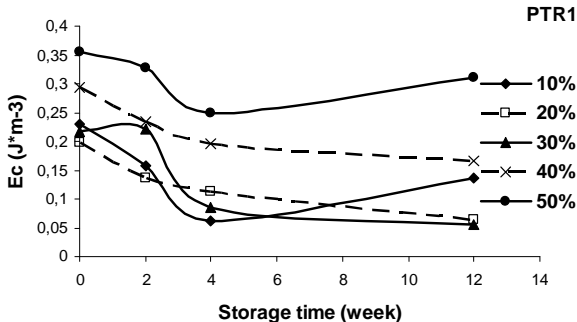


Fig.8 Changing of the cohesive energy during the storage time at different oil concentration (PTR1 0.10%)

In the course of the image analysis there were no remarkable changes in the average droplet size of the emulsions during storage. It means that coalescence has not occurred during that time (Fig.9).

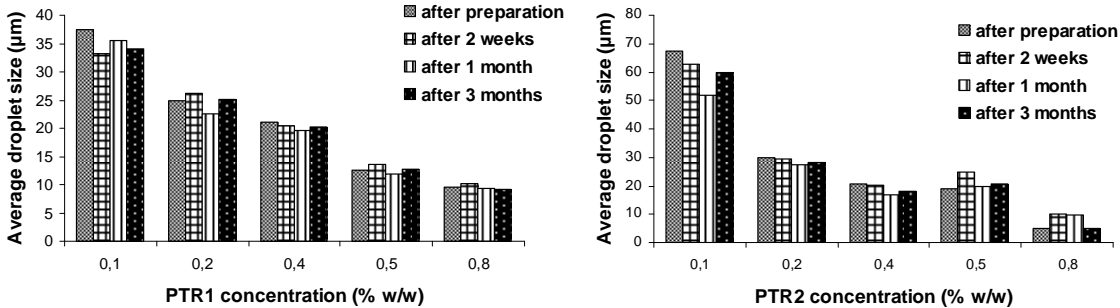


Fig.9 Changing of the average droplet size during the storage time at different polymer concentration

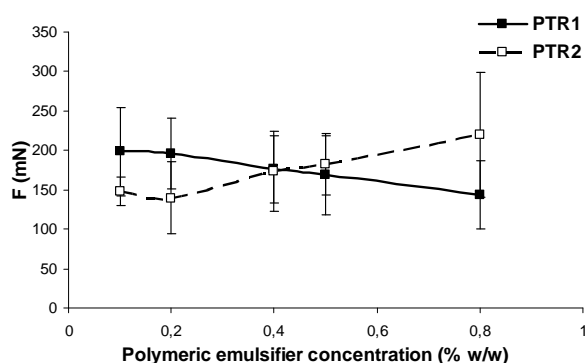
### 3.4 Applicability

#### Bioadhesion

The bioadhesive behaviour of the emulsions was different depending on the different polymerization-degree polymers used in the preparation. When increasing the polymer concentration at low values, there were changes neither in detachment force nor in adhesive work. Above 0.2% w/w both detachment force and adhesive work decreased with the amount of the polymer in the case of the higher polymerization-degree polymer and increased in the case of the lower polymerization-degree polymer (Fig.10).

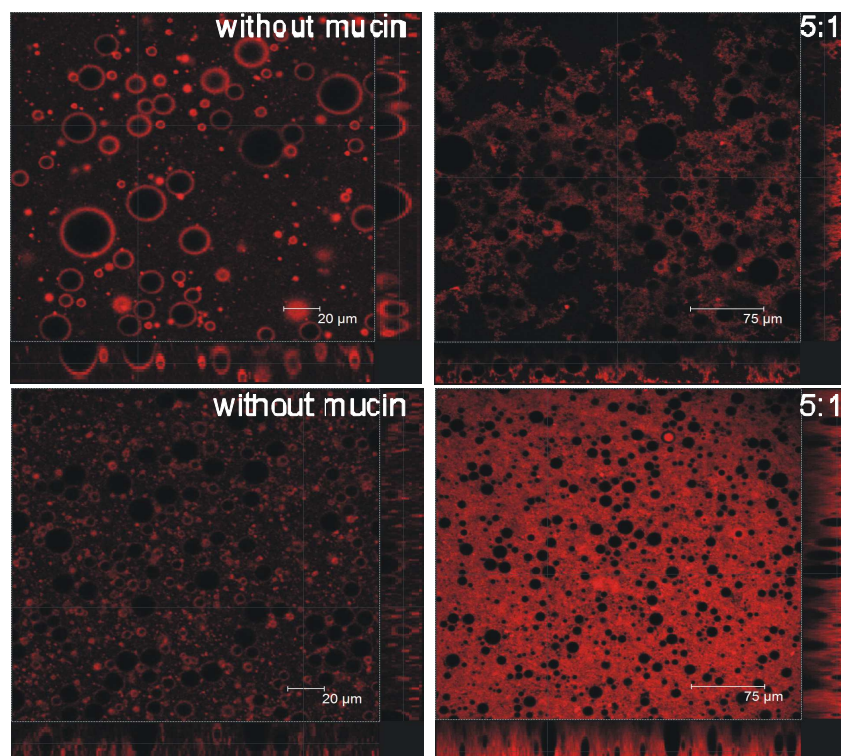
No significant change was observed in detachment force when increasing the oil concentration. There was a slight decrease in both detachment force and adhesive work between the simple gel and emulsion, which suggests that the added oil reduced the bioadhesivity of the samples.

When a coemulsifier was used, a decrease in detachment force and adhesive work was observed, which is more expressed at a high S101 concentration.



*Fig. 10 Effect of the emulsifier concentration on the detachment force (oil 20%)*

At low polymer concentration, due to the interaction between mucin and poly(acrylic-acid), polymer agglomeration can be observed in the pictures. In addition, oil droplets were retained in them. It can be assumed that mucin formed bioadhesive bonds with the micro gel around the droplets and not with a network. In the course of the tensile test measurements the samples in this range did not show changes in the bioadhesive behaviour. At high polymer content (above 0.2 % w/w) no agglomeration can be seen, so interaction arose with the total polymer network (Fig.11)



*Fig.11 CLSM images of the simple emulsion and 5:1 emulsion-8.0% w/w mucin solution mixture at low (first row) and high (second row) polymeric emulsifier concentration*

### **Drug release**

No considerable difference could be observed using water soluble Metronidazole. When the components such as polymer, oil or coemulsifier concentration of the emulsions were changed, no difference was found in the dissolution profile. Only a few alterations can be seen between the simple gels and the gel emulsions. Emulsion structure lowers the dissolution rate in the first hours. The micro gel structure may have slowed the drug release.

When a Lidocaine base was dissolved in the oil phase, the components of the emulsion affected drug release. With the increase of the polymer concentration it can be observed that the rate of drug release and the amount of the released drug increased, while with the increase of oil concentration the lidocaine release decreased (Fig.12). These phenomena can be explained by i) structure of the interfacial layer; ii) changes of interface area and iii) concentration gradient between the oil and the water phases.

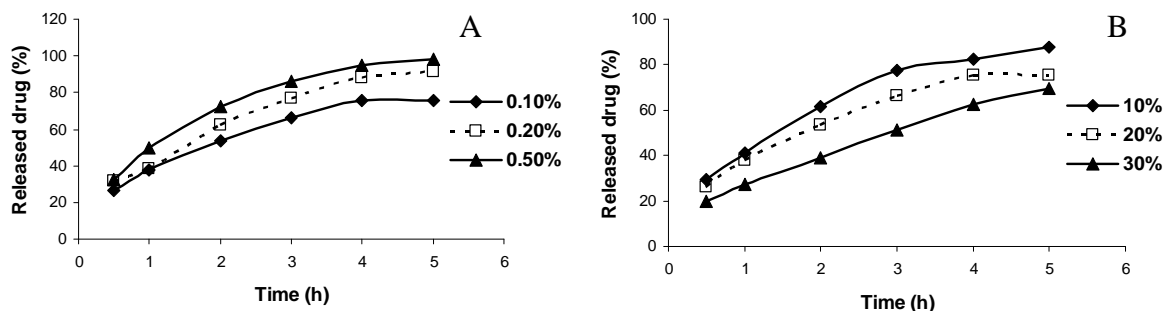


Fig.12 Effect of the polymer (A) and the oil(B) concentration on the lidocaine release

When a coemulsifier is used, a minimum release rate can be observed at 0.10 % coemulsifier concentration (Fig.13). It suggests that the change of the interfacial layer has an important role in this phenomenon. 1:1 can be the best combination rate of the two emulsifiers at which the distribution of the Lidocaine between the two phases is the slowest.

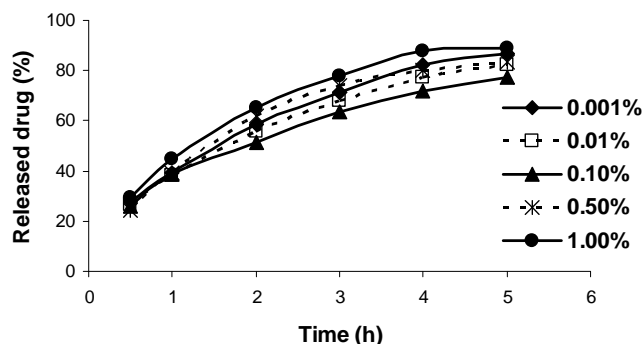


Fig.13 Effect of the coemulsifier concentration on the lidocaine release (PTR1 0.10%, oil 20%)

#### 4 SUMMARY

The aim of this research work was to identify and clarify the formation, structure and stability of gel-emulsions. As a summary of my experimental work, the following conclusions can be made:

- The wetting and the swelling of these polymeric emulsifiers is a prolonged procedure, and Pemulens show low surface activity.
- Gel-emulsions have viscoelastic properties, the polymer, the oil and the coemulsifier concentration have an influence on the rheological properties.
- Gel emulsions containing Pemulens form a special (micro gel) structure which can be identify by thermogravimetric investigations and by confocal laser scanning microscopy.
- The stability of the emulsions can be divided into two groups: change of i) macrostructure, and ii) microstructure. The macrostructure (the droplet size) can be considered quite stable while the microstructure (the solvation of the polymer chain, the evaporation rate, the

amount of the micro gel water, the rheological properties) changed continuously during the storage.

- The oil added to the emulsion slightly modified their rheological and bioadhesive behaviour. With increasing polymer concentration, the two different polymerization-degree polymers showed different results. The added coemulsifier modified the structure of the emulsions, which influenced the bioadhesive characteristics.
- Comparing the thermogravimetric end bioadhesive measurements, it can be concluded that i) the emulsion containing mainly micro gel around the droplets shows a more remarkable bioadhesive force than the sample with a coherent polymer network; ii) there is no difference between the bioadhesivity of the samples where the coherent gel structure had not built up.
- Drug release from the gel emulsions is influenced by the special gel structure in addition to the well known factors (e.g. viscosity, droplet size, water-oil ratio etc...). This phenomenon could be observed in the case of a lipophilic drug (Lidocaine base), but could not in the case of a hydrophilic drug (Metronidazole).

In conclusion, gel emulsions can be used well as bioadhesive topical dosage forms. Their structure is influenced by different factors. As it was presented in this study, the gel structure can modify the bioadhesive behaviour and the drug release profile of the systems. It suggests that a structure analysis is needed to predict the properties and hence the applicability.

## 5 ANNEX

### Articles related to the Ph.D. Thesis

- I. **Szűcs Mária**, Budai Szabolcs, Erős István, Gel-emulsion systems I: Physical-chemical characterisation, *Acta Pharmaceutica Hungarica* 78 (2008) 11-21 **IF: -**
- II. Budai Szabolcs, **Szűcs Mária**, Erős István, Gel-emulsion systems II: Stability, *Acta Pharmaceutica Hungarica* 78 (2008) 23-30 **IF: -**
- III. **Mária Szűcs**, Giuseppina Sandri, M. Cristina Bonferoni, Carla M. Caramella, Patrizia Vaghi, Piroska Szabó-Révész, István Erős, Mucoadhesive behaviour of emulsion containing polymeric emulsifier, *European Journal of Pharmaceutical Science* 34 (2008) 226-235 **IF: 3.127**
- IV. **Mária Szűcs**, Patrizia Vaghi, Giuseppina Sandri, M. Cristina Bonferoni, Carla M. Caramella, Piroska Szabó-Révész, István Erős: Thermoanalytical and microscopical investigation of the microstructure of emulsions containing polymeric emulsifier, *Journal of Thermal Analysis and Calorimetry* 94 (2008) 271-274 **IF: 1.483**

### Other publication

- I. Péter Sipos, **Mária Szűcs**, András Szabó, István Erős, Piroska Szabó-Révész, An assessment of the interaction between diclofenac sodium and ammonio methacrylate copolymer using thermal analysis and Raman spectroscopy, *Journal of Pharmaceutical and Biomedical Analysis* 46 (2008) 288-294 **IF: 2.761**

### Abstracts

- I. **Szűcs Mária**: Polimer emulgensekkel stabilizált emulziók, Ph.D. *Tudományos Nap, Szegedi Akadémiai Bizottság Székháza, 2006. május 3.*
- II. István Erős, **Mária Szűcs**, Szabolcs Budai, Erzsébet Csányi, Zsolt Makai, Péter Sipos, András Fehér and Piroska Szabó-Révész: Physico-chemical investigation of acrylate based polymeric emulsifiers, *5th World Meeting on Pharmaceutics Biopharmaceutics and Pharmaceutical Technology, Geneva, Switzerland, 27<sup>th</sup> to 30<sup>th</sup> March 2006*
- III. **Szűcs Mária**, Révész Piroska, Erős István: Polimer emulgensek fizikai-kémiai vizsgálata, *Congressus Pharmaceuticus Hungaricus XIII, Budapest, 2006. május 25-27.*



- IV. Szűcs Mária, Révész Piroska, Erős István:** Polimer emulgenst tartalmazó emulziók szerkezetvizsgálata, *Gyógyszerkutatási Szimpózium, Debrecen, 2006. november 24-25.*
- V. Szűcs Mária:** Polimer emulgensek bioadhéziója, *Magyar Tudomány Ünnepe, Szegedi Akadémiai Bizottság Székháza, 2007. november 6.*
- VI. Erős István, Szűcs Mária:** Gél-emulziók tervezése és vizsgálata, *Kozmetikai Szimpózium 2007, Budapest, 2007. november 8.*
- VII. Szűcs Mária, Giuseppina Sandri, Carla Caramella, Szabóné Révész Piroska, Erős István:** Polimer emulgenseket tartalmazó rendszerek bioadhezív tulajdonságainak jellemzése, *Gyógyszerkutatási Szimpózium, Szeged, 2007. november 9-10.*
- VIII. Mária Szűcs, Giuseppina Sandri, M. Cristina Bonferoni, Carla M. Caramella, Patrizia Vaghi, Piroska Szabó-Révész, István Erős,** Bioadhesive study of gel-emulsions: effect of the components and the microstructure, *6<sup>th</sup> World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Barcelona, Spain, 7<sup>th</sup> to 10<sup>th</sup> April 2008*