Ph.D. Thesis

FORMULATION AND INVESTIGATION OF ERODING HYDROPHILIC MATRIX SYSTEMS

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1. **INTRODUCTION**

Efforts to innovate existing medication include the development of medicines with higher selectivity of action, less toxicity and side-effects, higher stability, a more favorable pharmacokinetic profile and improved patient compliance. At the administration of solid dosage forms, the active pharmaceutical ingredients (APIs) have to bind their own receptors in an optimal concentration to affect the body. It is influenced by liberation, absorption and elimination, but it can be modified with special pharmaceutical technological methods.

Modern pharmaceutical technology concentrates on new dosage forms which are targeted to the exact site at the appropriate time, with maximum efficiency and with reduced side effects. These dosage forms can be found for example in the European Pharmacopoeia and United States Pharmacopeia; and they are named as systems with sustained release, delayed release or pulsatile release. In these systems the dissolution of the APIs are accurately controlled by special composition and/or by special manufacturing process.

The properties of additives and APIs applied in pharmaceutical experiments rarely make possible the direct processibility, therefore we should use some intermediate steps, such as granulation, in the development of complete dosage forms.

2. **AIMS**

The aim of this study was the formulation and investigation of solid, erodible, hydrophilic matrix systems. These matrix systems were planned to be applied via different administration routes, thus different model APIs were chosen for the formulation. One of the systems was planned to be administered intravaginally to restore normal vaginal pH. The intended system would have sustained release and effect locally in the vagina, and could be used in the treatment of gynecological conditions caused by changed pH, e.g. irritation. The other drug delivery system was a gastroretentive matrix system that might be therapeutically effective in Wilson’s disease. It would also have sustained release and float in the stomach for hours. The hydrophilic matrix former was different types of HPMC in both drug delivery systems, thus the mechanism of disintegration and the API’s dissolution through the gel layer were the same, however some major characteristics, such as swelling and viscosity differed between the types.

In the selection of additives, bioadhesive (mucoadhesive) and bioerodible properties of the materials were taken into consideration; thus the solid dosage form would not irritate the mucus membrane in the vagina and the stomach; and on the other hand, mucoadhesiveness
would make possible the attachment of the tablet to the vaginal wall and the wall of the stomach, and the control of the API’s liberation.

A strong acid and a metal ion having a net positive charge of +2, usually being in interaction with the majority of polymers were applied in the delivery systems as APIs, thus the curiosity of this work was the investigation of APIs’ effect on the properties of polymer matrices influencing the APIs’ release.

As two different drug delivery systems were formulated and investigated, they are described and discussed separately. First, the vaginal system, after that, the gastroretentive delivery system is to be detailed.

3. SECTION I.

In this study, the sequence that is usually applied in pharmaceutical research was followed. On the ground of that, the experiments can be divided into two parts. First, the properties of the starting materials were studied; then matrices without the API were prepared; and finally the complete system with lactic acid were produced and examined.

Applied materials

Lactic acid (LA) was applied as a model API having pH-decreasing effect. LA, also called milk acid is very important in the vagina’s self-defense cycle. It is prepared by the fermentation of carbohydrates with microorganisms whose growth is in turn also facilitated by LA. LA creates an acidic environment to guard the vagina from an overgrowth of harmful bacteria which leads to different infections. Because of the favorable effects of LA, its incorporation into a solid dosage form can be very beneficial. Different acidic liquids may be applied as well, but a large amount of such liquid can cause the washing-out of the Lactobacillus flora, their effects are not long-lasting, and their application is inconvenient. A small amount of liquid can be formulated into tablets.

Hydroxypropyl methylcellulose (HPMC) was used as a matrix forming agent. Microcrystalline cellulose (MCC) was applied as a filler/binder. The fibres of this filler/binder agent were used to bind the liquid (they acted as a carrier). α-Lactose monohydrate was used as a filler. Solid vaginal products often contain lactose as filler, since this is a natural substrate for the vaginal microflora.
Part I.

The aim of this part was to determine the main factors which can influence the preparation of hydrophilic matrices and to choose the best parameters for the production of granules. As the API was liquid, granulation was the chosen method of production, and from the different granulating methods, high shear granulation was applied.

a) Preparation of the carrier system

The ratio of the filler components was 1:1 in all samples. HPMC was applied in 0, 10, 20, 30, 40, 50 and 100%.

Enslin number is a simple semi-quantitative measure of water uptake of powders. The higher the concentration of HPMC, the lower the Enslin number of the samples was. The curves became linear at approximately 40% HPMC content and it means that the binder did not induce a significant change in the wetting properties of the powders. It can be seen that not only the quantity of water, but also the speed of this process was the lowest for HPMC. This is demonstrated by the gel forming property of this material and the barrier function of this gel layer.

Matrix compacts were produced from powder mixtures with a Korsch EK0 instrumented eccentric tablet machine. The erosion of these tablets was evaluated with the disintegration tester and method specified in the Pharmacopoeia. The change in erosion time was very relevant while the concentration of the matrix former was increasing. The values for the samples containing at least 40% of HPMC did not differ significantly from that for pure HPMC.

A connection was detected between erosion times of the samples and Enslin numbers. The samples containing 30% of HPMC were the most optimal; therefore they were used in the subsequent part of our study.

b) Determination of the optimum quantity of granulating fluid

The chosen powder mixture was granulated with different quantities of water in a high-shear granulator. The quantities of liquid to 100 g powder mixture were 20 g, 25 g, 27.5 g, 30 g, 35 g and 40 g.

Sizes and size distributions of the samples were evaluated with an analytical sieve series. Mean particle size (D50) was determined with the sieving system software. In case of samples prepared with 35 g water to 100 g powder, the amount of powder fraction was small and
particle size was not too high either, so in the following experiments this amount of water was applied.

c) Optimization of the granulating process

In this part of the study, the quantities of the powder mixture and the liquid remained the same but the technical parameters (speed of chopper, speed of impeller, dosing speed, kneading time) were changed. A $2^4$ full factorial design was utilized to choose the relevant factors. After the determination of the response surface, fitting was very good ($R^2 = 0.9829$) for D50 value, but there was no significant factor. The largest effect was observed for dosing speed.

The high-speed moving of the parts of a small-scale high-shear granulator – impeller and chopper – can cause a relevant increase in the temperature of the powder/granules. Its importance is emphasized by the temperature-sensitive nature of the solubility of the components. Both the rate of dissolution and the quantity of materials dissolved can depend on temperature. The temperature increase during the granulation process also exhibited a great variance (4.8–18.6 °C). The fitting of the response surface for the temperature elevation resulted in a model with $R^2 = 0.982$ and two significant factors ($p<0.05$). Increase of the impeller speed significantly enhanced temperature elevation, and it was also increased by reduction of the dosing speed.

The understanding of formation of individual bridges is critical for optimization of the granulation process. In addition, it is well-known that an amorphous form can change during storage and can indicate stability problems. On the basis of that, these phenomena were investigated in details.

**Differential scanning calorimetry** (DSC) examinations, **thermomechanical analysis** (TMA) and **X-ray diffraction** (XRD) tests were performed.

**Conclusion**

Not only the particle size of the granules, but also the temperature of the powder mixture changed considerably during granulation at different operational parameters. The temperature increase was an indirect factor which can influence the dissolution of the powder mixture during granulation. At higher temperatures, a higher proportion of lactose and less HPMC are dissolved. The significant factors causing temperature increase were the impeller speed and the dosing speed. Alteration of the batch size can induce a relevant change in the temperature increase.
The crystalline behavior of lactose disappeared in films containing lactose and HPMC, as confirmed by DSC and XRD measurements. TMA indicated that an increase of the proportion of lactose in the film decreased the $T_g$ of the film. This can be ascribed to the interaction of the components. At a lactose:HPMC ratio of 3:5, a second glass transition appeared. It points to the formation of a separate amorphous phase of lactose. Its crystallinity was changed during the storage.

In addition, it may be stated that evaluation of the temperature increase during granulation is necessary, since the small-scale granulation procedure can induce a dramatic change in this parameter. This should be kept in mind before prediction of the parameters applied for the granulation scale-up. Direct study of the composition of every individual binder bridge formed from soluble materials in the granules is impossible, but their indirect evaluation can be useful. These data provide additional information towards an understanding of granule formation in a small-scale high-shear granulator.

Finally, it can be concluded that testing of the wetting properties is necessary for the determination of the best composition and the conditions for the preparation of a matrix system. The effect of operational factors can be predicted from the results of such preformulation studies.

**Part II.**

*Preparation of matrix granules and tablets containing lactic acid*

The aim of this part was to study the applicability of the prepared solid matrix system for the formulation of long-acting tablets containing LA. Different aqueous solutions of LA were used as granulating liquids. The effect of LA concentration on the pH-decreasing effect of the tablets was also evaluated.

Granules were prepared in ProCepT granulator. In accordance with our previous results, the quantity of liquid was 35 g to 100 g of powder mixture. The composition of granulating fluid was changed. The operational parameters were as follows: impeller speed: 500 rpm, chopper speed: 3500 rpm, liquid dosing speed: 15 mL/min, kneading time: 4 min.

**Sizes and size distributions** of the granules were assessed, which were similar for all the samples. The presence of LA in the granulating fluid did not alter the particle size distribution of the products.

**Friability** was applied to determine the mechanical properties of the granules. A special friability test was used which was developed in the Department of Pharmaceutical Technology. The mechanical properties of the products were not changed relevantly either,
the friability was <5% in every case and no clear tendency could be observed.

Tablets were prepared with a hydraulic press. The in vitro dissolution test was also a special one because the quantity of vaginal fluid is so low that the prescribed test for conventional oral tablets in the Ph. Eur. would not have given accurate information. Each of the samples exhibited very similar behavior in the dissolution medium. Swelling of the tablets and erosion of the samples could be detected in the liquid. The shape constantly changed during the test, the main alteration could be seen after 4 h (Figure 1).

![Figure 1. Change in tablets during dissolution test (A – starting tablet, B – after 4 h, C – after 8 h)](image)

**Discussion**

It can be established that all of the formulated matrix systems have a pH-decreasing effect throughout 8 h. It is well known that the dissolution of an API from a hydrophilic matrix is controlled by erosion and diffusion. In this case, the liberation of API is also controlled by the detachment from the carrier MCC.

The rate-limiting process of dissolution in the starting period (0-4 h) was mainly erosion of the system and the quicker liberation of API from the carrier. In the second stage (5-8 h), after sphere formation, erosion of this surface was slower. Thus, the importance of the slower phenomena (diffusion and the slower detachment of LA) was higher in this case.

**Summary**

On the basis of this study the following can be concluded:

- There is a correlation between the wetting properties of powder mixtures and the erosion of inert comprimates.
Factors which increase wetting time are relevant for temperature elevation during the formulation of this system. The effect of operational factors can be predicted from the results of such preformulation studies.

The composition applied was appropriate for the incorporation of LA. It can be processed into the granulating fluid (up to concentration of 15%). The presence of LA in the granulating fluid altered significantly neither the particle size distribution, nor the mechanical properties of the granules. The shape of the tablets constantly changed during the dissolution, the main alteration could be seen after 4 h. Erosion and change in shape were very similar for each of the samples.

The pH-decreasing effect of the tablets was influenced by the concentration of LA applied in the granulating fluid. Erosion is the main parameter responsible for the liberation of LA from this system in the first part of dissolution. This phenomenon increased the possibility of detachment of LA from the insoluble carrier. When the concentration of LA reached a given level, the more readily liberating sites were saturated. In the second stage of dissolution the relevance of erosion was lower and the slower process became more important.

Finally, it can be stated that a controlled release intravaginal matrix tablet can be formulated from the matrix former HPMC and the carrier MCC to ensure a long-acting preparation containing LA. In addition, there was no sign of matrix destruction caused by the LA as a strong acid.

4. SECTION II

In this part of the work, compatibility of the materials was investigated from a technological point of view through the effect of them on the properties of the dosage form. The aim was the evaluation of the phenomena influencing the functioning and properties of the matrix system and the release of the API in case of a nonionic polymer reacting with an inorganic salt.

Materials

Zinc acetate dihydrate (Zn(Ac)$_2$) was used as model API. It has a wide range of medical and dietary applications, as an oral daily supplement, this metal ion is used for the treatment of Wilson’s disease. The primary site of absorption of exogenous zinc in the human is in the proximal small bowel. Zinc has shown clinical efficacy at doses of 50 mg three times daily.
The elimination half-life of zinc in healthy subjects is in the range 0.9-1.2 hours, which necessitates several applications a day. Patients’ compliance and tolerance could be increased with long-acting sustained and controlled release preparations as the daily intake could be decreased and they make a constant blood level of the APIs possible.

Forms of hydroxypropyl methylcellulose (HPMC) with different viscosities were used as matrix former agents. The notations were as follows: 100 SR – LV, 4000 SR – MV and 100,000 SR – HV. Sodium bicarbonate was applied as gas-forming agent. Lactose monohydrate was used as a substituent of the API at a certain part of the study.

The amount of API was calculated on the basis of the zinc requirement, which is equivalent to 500 mg of Zn(Ac)\textsubscript{2} a day. Compositions were given for tablets with 1.0 g in mass. Tablets were prepared with a hydraulic press. In the second part of the work, powder mixtures containing lactose monohydrate as the substituent of Zn(Ac)\textsubscript{2} were prepared; the ratio of the components was not changed.

**a) Water uptake properties**

For an understanding of the effects of the individual components on the water uptake of the system, the starting components and the binary and ternary powder mixtures were tested. The water uptakes of the different forms of HPMC were prolonged: for the LV and MV samples, there was no significant difference between the values, whereas the quantity of water was higher for the HV sample. Their wetting was not finished by the end of the test. This was caused by the restriction of the gel layer of the swelling polymer. The process was very short (10 s) in the case of NaHCO\textsubscript{3}; and the API took up the maximum quantity of water in the first 6 min. The theoretical Enslin numbers were calculated from the Enslin numbers of each component in the ratio of their presence in the powder mixtures. Relative deviations from the calculated values were also determined.

First, the water uptakes of the ternary powder mixtures were determined. The quantity of water taken up increased with increasing amount of NaHCO\textsubscript{3} in all cases. This change was unexpected as the HPMC content decreased with increasing amount of NaHCO\textsubscript{3}. It would appear obvious that NaHCO\textsubscript{3} formed bubbles, which weakened the gel layer formed and the powder mixtures, so that they could hydrate more quickly. Hydration on the surface was definitely quick, it could be detected visually, but penetration of water through this gel layer was delayed. Powder mixtures with 10% NaHCO\textsubscript{3} could not take up the calculated amount of water, in contrast, all of the other powders took up much more water than expected (almost
double the calculated value). This indicates that some interaction happened when the powder mixture came into contact with water.

When there was no NaHCO$_3$ in the powder mixtures, a lower quantity of water was taken up, confirming that NaHCO$_3$ is required to change the structures of the powder mixtures and the gel layer of the polymer, enhancing the water uptake. Zn(Ac)$_2$ itself slowed down the water uptake and reduced the amount of water taken up.

For the binary powder mixtures containing only the additives, lower amounts of water were taken up as compared with the calculated values, clearly demonstrating that the API was also indispensable for the unpredicted wetting.

The properties of powder mixtures without HPMC were also studied. These two components together (Zn(Ac)$_2$ and NaHCO$_3$) were able to take up more water than expected. At 20 and 25% NaHCO$_3$ contents, the amounts of water taken up were more than double. It may be assumed that factors other than the loosing effect of the bubbles formed contribute to the properties of the systems as in case of these powder mixtures there was no matrix-former in the compositions, thus there was not gellified layer which could be loosened by NaHCO$_3$. This interaction was also observed for the ternary powder mixtures, where higher amounts of water were taken up.

b) **Disintegration studies**

The disintegration of tablets was evaluated with the official disintegration tester and method detailed in the Pharmacopoeia. For LV, the time needed for disintegration of the tablets with the highest HPMC content was approximately 10 min, which was slightly more than for the other compositions. Thus, there was no prolonging effect in these tablets. At higher viscosities, unexpected behavior of the tablets was experienced. For these tablets, the disintegration time did not decrease with increasing amount of NaHCO$_3$ as expected, but continuously increased, so that there was a prolonged effect. The presumed interaction appeared to be proven, as the composition and consequently the properties of the powder mixtures changed on contact with water.

To confirm this, other tests were performed. The duration of disintegration of the polymers, the binary powder mixtures containing Zn(Ac)$_2$ and the different forms of HPMC, and the binary powder mixtures containing NaHCO$_3$ and the different forms of HPMC were also measured, and any of them disintegrated during 8 h. Hence, it can be stated that the presence of NaHCO$_3$ and the API is necessary for the detected disintegration time.
In the following step, the API, which is a necessary component of the interaction, was substituted with lactose monohydrate. A decrease in the erosion time of the tablets was detected with increasing content of NaHCO₃. In accordance with expectations, the binding effect of the smaller amount of polymer was insufficient to counteract the disintegration effect of the gas-forming component.

Interactions between drugs and HPMC that negatively impact polymer hydration are relatively rare. The combination of Zn(Ac)₂ and NaHCO₃ is supposed to act enhancing hydration and swelling of HPMC, thereby accelerating gel layer formation. This blocks solvent to percolate to the interior of the tablet, leading to delayed disintegration.

c) Buoyancy

The floating lag times – the duration of the period between the placing of the tablet in the medium and the tablet floating – and durations of tablet floating were determined by visual observation. On the basis of these studies, it can be stated that only HV samples might be appropriate for the formulation of a floating drug delivery system. Thus, only HV tablets were investigated further in this study. The samples with 10 or 15% NaHCO₃ content were not appropriate for the formulation of a floating system, whereas the samples with 20 or 25% gas-forming agent floated for a minimum of 4 h (Figure 2).

![Figure 2. Flotation of matrix tablets (0-4 min)](image)

d) Dissolution study

The rates of in vitro release of Zn(Ac)₂ from the matrix tablets were determined in gastric acid (pH=1.2) by the paddle method (Ph. Eur.). Recent methodology as described in Ph. Eur. states: “For the paddle apparatus, place the preparation at the bottom of the vessel before starting rotation of the blade; dosage forms that would otherwise float are kept horizontal at the bottom of the vessel using a suitable device, such as a wire or glass helix”. On the basis of
that, dissolution tests were carried out under sink conditions. Zn contents were measured by X-ray fluorescence analysis.

It was obvious, that the bulk of the API dissolved in the initial period of time after coming into contact with the gastric acid, while the dissolution of the remaining part was slow and continuous. The initial fast dissolution of the API may be explained by the fact that the hydration, swelling and erosion – or we can say disintegration – of the floating tablet was very intensive in the first minutes of its reaction with gastric acid. Formulation of air bubbles loosened the structure of the developing matrix, the evolving gas permeated through the gel layer leaving gas bubbles or pores which could have increased the rate of release of the API from the matrix. After 10-15 min, the outer layer of the tablet reached its optimal hydration state, most of the gas bubbles were entrapped in the gel layer, which could have slowed down the dissolution. Thus in this part, diffusion became the rate-limiting step.

It is important to emphasize that conditions of the dissolution study were relevantly different from the conditions present in the stomach. In the in vitro dissolution studies, the dosage form was not able to float – it was the requirement of the Pharmacopoeia, however in the stomach the dosage form would probably float on the surface of the gastric fluid.

Conclusions
On the basis of this study the following can be concluded:

- On the basis of the preformulation studies, it can be stated that polymers with low viscosity grades did not prove to be appropriate for the formulation of a controlled release preparation in this system.

- Alteration of the ratio of the excipients resulted in an unpredicted significant influence on the properties of the dosage form. The interaction between Zn(Ac)$_2$ and NaHCO$_3$ caused a relevant modification in the water uptake of the powder mixture and in the disintegration of the tablets. Independent tests revealed an interaction between these two components when they came into contact with water, so that prediction of the properties of the dosage form from the parameters of the starting components was impossible.

- The combination of Zn(Ac)$_2$ and NaHCO$_3$ at certain ratios acts to enhance hydration and swelling of HPMC, thereby accelerating gel layer formation. This blocks solvent to percolate to the interior of the tablet, leading to delayed disintegration. Therefore, this phenomenon was applied to develop a prolonged effect.

Finally, it can be stated that appropriate systems with prolonged disintegration times, appropriate buoyancy and controlled release can be formulated from Zn(Ac)$_2$ by using
NaHCO₃ as gas-forming agent and HV HPMC as a matrix and gel-forming component. The phenomena experienced during the investigations occurred only in the ternary systems, so prediction of them from the properties of the binary systems was impossible. Therefore, in case of such systems, compatibility studies are recommended to be carried out in complex systems.

5. **FINAL CONCLUSION, NOVELTY, PRACTICAL USEFULNESS**

To achieve an optimal drug release, solid hydrophilic matrices applied via two different administration routes were studied in details. The main aims of the study were the formulation and detailed investigation of eroding hydrophilic matrix systems applying HPMC as matrix forming agent. Additionally, investigation of the effect of the aggressive APIs from the technological point of view was the goal of the study as well; therefore, their effect on the drug release from the matrix systems has been studied in details.

Novelty and practical usefulness of the systems formulated:

- As an alternative for vaginal washing solutions controlling the vaginal pH, a solid vaginal hydrophilic drug delivery system containing a fluid API, a mucoadhesive and bioerodible matrix former and a filler familiar with the vaginal flora was successfully formulated, and it has showed controlled release during 8 h.

- Formulation of a gastroretentive drug delivery system as an alternative for patients suffering from Wilson’s disease has been prepared. The results may be useful in the development of a sustained release dosage form containing Zn(Ac)₂ with a prolonged gastric residence time for the treatment of Wilson’s disease.

- The combination of Zn(Ac)₂ and NaHCO₃ at certain ratios acts to enhance hydration and swelling of HPMC, thereby accelerating gel layer formation. This blocks solvent to percolate to the interior of the tablet, leading to delayed disintegration. Therefore, this phenomenon was applied to develop a prolonged effect.

In case of both systems, some kind of unexpected phenomena occurred. These are good examples of significant changes occurring during the formulation of new sensitive delivery systems. It can be stated that different types of HPMC can be utilized for the formulation of hydrophilic matrix systems with different administration routes but very well structured preformulation studies must be performed. These tests should not be only chemical evaluations, but others considering technological aspects as well.
PUBLICATIONS RELATED TO THE THESIS

   *IF*=0.989

   *IF*=2.629

3. G. Baki, J. Bajdik: Vaginal dosage forms
   *Gyógyszerészet (Journal of the Hungarian Society for Pharmaceutical Sciences – MGYT), 2008/9., 521-528*

4. G. Baki, J. Bajdik, A. Kelemen, K. Pintye-Hódi: Formulation of a solid intravaginal matrix system to prolong the pH-decreasing effect of lactic acid
   *J. Drug Del. Sci. Tech. 19, 133-137, 2009*  
   *IF*=0.440

   *IF*=2.453

PRESENTATIONS RELATED TO THE THESIS

1. G. Baki: Formulation and investigation of eroding vaginal matrix systems
   *Conference of Student Research Program (TDK), Szeged, Hungary, 2007*

   *2nd BBBB Conference on Pharmaceutical Sciences, Tallinn-Tartu, Estonia, 2007*

   *MGYT Symposium on Pharmaceutical Research, Szeged, Hungary, 2007*
4. **G. Baki:** Formulation of an eroding hydrophilic matrix system  
   *Hungarian Science Festival, Szeged, Hungary, 2008*

5. **G. Baki:** Formulation and investigation of vaginal matrix tablets  
   *9th “Ottó Clauder” Memorial Competition, Budapest, Hungary, 2009*

6. **G. Baki,** J. Bajdik, K. Pintye-Hódi: Formulation and investigation of a gastroretentive matrix system  
   *16th National Pharmaceutical Technology Conference and 8th „Medicine on the turn of the millennium” Postgraduate Conference, Siófok, Hungary, 2010*

   *7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Malta, Valetta, 2010*

**OTHER PUBLICATIONS**

   *Gyógyszerészet (Journal of the Hungarian Society for Pharmaceutical Sciences), 2009/2., 131-135*

2. **G. Baki,** J. Bajdik: The main technological aspects of pediatric formulations, Part II: Pharmaceutical dosage forms and excipients used for the formulation  
   *Gyógyszerészet (Journal of the Hungarian Society for Pharmaceutical Sciences), 2009/3., 195-202*

3. **G. Baki,** J. Bajdik: The main technological aspects of geriatric formulations  
   *Gyógyszerészet (Journal of the Hungarian Society for Pharmaceutical Sciences), 2009/11., 645-651*

4. **G. Baki,** J. Bajdik, D. Djuric, K. Knop, P. Kleinebudde, K. Pintye-Hódi: Role of surface free energy and spreading coefficient in the formulation of active agent-layered pellets  
   *Eur. J. Pharm. Biopharm. 74, 324-331, 2010*  
   *IF=3.344*
OTHER PRESENTATIONS

1. **G. Baki, J. Bajdik, D. Djuric, K. Knop, P. Kleinebudde, K. Pintye-Hódi:** Effects of the properties of the core on the parameters of active agent layered products
   
   *6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Barcelona, Spain, 2008*

2. **G. Baki, J. Bajdik, Djuric D., K. Knop, P. Kleinebudde, K. Pintye-Hódi:** Evaluation of the effectiveness of layering on pellet cores with different composition
   
   *7th „Medicine on the turn of the millennium” Postgraduate Conference, Sopron, Hungary, 2008*

3. **G. Baki, J. Bajdik, Djuric D., K. Knop, P. Kleinebudde, K. Pintye-Hódi:** Evaluation of the effectiveness of layering on pellet cores with different composition
   
   *14th National Pharmaceutical Congress (CPhH), Budapest, Hungary, 2009*

OTHER

1. **G. Baki:** Formulation and investigation of a long-acting vaginal matrix system
   
   *Szeged Talent Program award work, 2007*

2. **G. Baki:** Formulation and investigation of eroding hydrophilic matrix tablets
   
   *Regional Committee in Szeged of the Hungarian Academy of Sciences award work, 2008*