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## **Enhancement of the dissolution of meloxicam in binary systems**

Summary of PhD thesis

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## 1. Introduction

The oral route is the one most frequently used for drug administration. Oral dosage forms are usually intended for systemic effects resulting from drug absorption through the various epithelia and mucosa of the GI tract. Compared with other routes, the oral route is the simplest, the most convenient and safest means of drug administration.

The physicochemical properties of a drug play an important role in drug absorption. Solubility is one of the physicochemical properties of the drug material. On the other hand, solid drugs need to dissolve before they can be absorbed.

The poor solubility of drug substances in water and their low dissolution rate in the aqueous gastro-intestinal fluids often lead to insufficient bioavailability and is one of the most difficult and unsolved problems in pharmaceutical technology. It is estimated that more than 35% of the known drugs and more than 25% of the newly discovered drugs face such a problem. Choosing a proper method to improve solubility remains one of the most challenging aspects in pharmaceutical technology. That is why different methods have been used to overcome this problem, e.g.: increasing the surface area of a drug, complexation, salt formation, etc. but using a water-soluble material as a carrier is one of the easiest methods.

On top of that, fast dissolution is important in the case of some diseases in which the fast effect of the drug is necessary, such as analgetics, antipyretics, etc.

Drugs are absorbed in two general ways, by passive diffusion and by specialized transport mechanisms. Lipid solubility and the degree of the ionization of the drug at the absorbing site influence the rate of diffusion. Several specialized transport mechanisms are postulated, including active and facilitated transport.

Once the drug is absorbed, it can exert a therapeutic effect either locally or at a site of action remote from that of administration.

Oral dosage forms have to go through long processes to be absorbed by the body, pharmaceutical methods can be useful in this field to increase the bioavailability of the drug.

## 2. Aim

The main aim was to improve the dissolution rate of meloxicam (ME) (a new member of NSAID) in capsule form. Meloxicam is practically insoluble in water but its permeability is high so we can classify it in class II of the Biopharmaceutical Classification System (BCS).

- First of all the influence of the particle size of pure MEs was investigated on dissolution rate. According to Noyes-Whitney, decreasing of particle size (increasing of surface area) is one of the methods to increase dissolution rate.
- In the second step the water-soluble carrier was used to improve the dissolution of ME. Binary systems (physical mixture and melted products) were made by using different amounts of mannitol as a carrier.
- DSC, X-ray diffractometry, morphological investigation and chemometric methods were used to study the crystal's structure.
- Cohesion and adhesion, as well as spreading surface were investigated in order to possibly predict dissolution rate.
- The last step was the investigation of the efficacy of ideal interactive mixtures on animals (rats).

### 3. Materials and Methods

**Meloxicam** (Ph. Br. 2001) is a pale yellow powder. It is practically insoluble in water. The molecular weight of meloxicam is 351.4 and it melts at 253-255°C. Mobic<sup>®</sup> (generic name of meloxicam) is available as a tablet for oral administration containing 7.5 mg of meloxicam, mostly used in the case of rheumatoid pain. MEs with different particle sizes were used for preparation of binary systems (Table 1).

**Mannitol** (USP, 25th) is a white odourless crystalline powder or free-flowing granules with a sweet taste. 1g is soluble in 5.5 of water. The molecular weight of mannitol (C<sub>6</sub>H<sub>14</sub>O<sub>6</sub>) is 182.17 and it melts at 166-168°C. It is used in pharmacy as an excipient and diluent for solids and liquids, in pharmaceutical and food industries as a sweetener (Table 1).

Table 1 Particle sizes and specific surface areas of the materials

| Material | d(10%) $\mu\text{m}$ | d(50%) $\mu\text{m}$ | d(90%) $\mu\text{m}$ | Specific surface area (m <sup>2</sup> /g) |
|----------|----------------------|----------------------|----------------------|---|
| ME1      | 50.50                | 106.66               | 206.20               | 0.071                                     |
| ME400    | 1.62                 | 25.74                | 131.15               | 1.370                                     |
| ME2      | 0.72                 | 2.49                 | 5.97                 | 2.514                                     |
| Mannitol | 17.61                | 86.74                | 239.45               | 0.226                                     |

#### Preparation of physical mixtures (PMs)

PMs of ME1, ME2, and ME400 with mannitol (PM1, PM2 and PM400) in (drug:carrier) ratios of 3:7 and 1:10 were obtained by mixing the individual components for 10 min in a Turbula mixer (Turbula WAB, Systems Schatz, Basel, Switzerland) at 50 rpm.

#### Preparation of melted products (MPs)

MPs of ME1 and ME2 and mannitol (ME1-MP and ME2-MP) in ratios of 3:7 (w/w) and 1:10 (w/w) were made as follows: The MEs were added to melted mannitol (170 °C) and the melts solidified at room temperature ( $20 \pm 1$  °C). The products were triturated in a mortar and were sieved. The particle size range of the products was between 100 and 250  $\mu\text{m}$ .

#### Dissolution studies

Dissolution tests were performed by using Pharmatest equipment (Hainburg, Germany) at a paddle speed of 100 rpm. 900 ml of artificial enteric juice pH 7.5 ( $\pm 0.1$ ) (Ph.Eur.4) at 37 °C ( $\pm 0.5$  °C) was used. The ME contents of the samples were measured spectrophotometrically at 362 nm (Helios  $\alpha$  Spectronic, Unicam, Cambridge, UK). The dissolution experiments were conducted in triplicate. Kinetic equations (e.g. First order, Zero order) were used to describe the rate of the dissolution.

#### Contact angle measurements

Compacts of the powders (150 mg) were made with a highly polished stainless steel punch (13 mm in diameter) in a Specac hydraulic press (Specac, England) with a 20 s dwell time at a pressure of  $4 \times 10^8$  Pa. The contact angle ( $\theta$ ) of the solids was determined by means of the sessile drop technique (OCA 20 Dataphysics Instruments GmbH, Fielderstadt, Germany), using a charging pipette (Hamilton Microliter Syringe). Photos were taken with a video camera every second up to 30 s from the coming into contact of the drop with the compact. The contact angles were calculated from the contours of the drop.  $\gamma_s$  results were calculated from the contact angles at 1 s to avoid the error arising from drop penetration. The liquids used for contact angle measurement were bidistilled water ( $\gamma^d = 50.2$  mN/m,  $\gamma^d = 21.8$  mN/m) and diiodomethane ( $\gamma^d = 0$  mN/m,  $\gamma^d = 50.8$  mN/m).

#### Calculation of surface free energy ( $\gamma_s$ )

In the method of Wu,  $\gamma_s$  is taken as the sum of depressive (d) and polar (p) components. The  $\gamma_s$  data of solid materials can be determined by means of contact angle measurements on two liquids with known polarities. They can be assessed by solving two equations with two unknowns:

$$(1 + \cos \theta) \gamma_l = \frac{4(\gamma_s^d \gamma_l^d)}{\gamma_s^d + \gamma_l^d} + \frac{4(\gamma_s^p \gamma_l^p)}{\gamma_s^p + \gamma_l^p}$$

where  $\theta$  is the contact angle,  $\gamma_s$  is the solid surface free energy and  $\gamma_l$  is the liquid surface tension. The work of cohesion ( $W_c$ ) is twice  $\gamma_s$ , since two identical surfaces interact:

$$W_c = 2\gamma_s$$

The work of adhesion ( $W_a$ ) is the energy that arises when two surfaces come into contact:

$$W_a = 4 \left[ \frac{\gamma_s^d \gamma_l^d}{\gamma_s^d + \gamma_l^d} + \frac{\gamma_s^p \gamma_l^p}{\gamma_s^p + \gamma_l^p} \right]$$

#### Differential scanning calorimetry (DSC)

Thermal analysis was carried out with a DSC821<sup>o</sup> instrument (Mettler-Toledo GmbH, Switzerland). Sixteen milligrams of sample was weighed into a non-hermetically sealed aluminium pan. The samples were heated from 25 to 300 °C at a heating rate of 5 °C/min. The instrument was calibrated by using indium. All the DSC measurements were made in argon atmosphere and the flow rate was 100 ml/min. From the DSC curves, the calorimetric enthalpy,  $\Delta H$  (integral normalized value) and the peak temperature ( $T$ ) were calculated by software (Stare version 6).

#### Powder X-ray diffractometry (XRPD)

XRPD was performed with a Philips X-ray diffractometer (PW 1050/70 PW 1710), where the tube anode was Cu with  $K\alpha = 1.54242 \text{ \AA}$ . The pattern was collected with 50 kV of tube voltage and 40 mA of tube current in step scan mode (step size 0.035, counting time 1 s/step). The instrument was calibrated by using silicium produced by Philips. The setting error to silicium ethanol was not more than 0.01/2 $\theta$ .

#### Chemometric method

The method of multivariate curve resolution with alternative least squares (MCR-ALS), as a chemometric method, can decompose the data matrix to profiles (composition profiles and pure diffractogram profiles) with the use of certain constraints. The usual assumption in multivariate resolution methods is that the experimental data follow a bilinear model similar to the Lambert–Beer law in absorption spectroscopy. In matrix form, this model can be described as

$$\mathbf{R} = \mathbf{D} \cdot \mathbf{C}^T$$

$\begin{matrix} I \times K & I \times N & N \times K \end{matrix}$

where  $\mathbf{R}$  is the response matrix (i.e. the counts in a diffractometry measurement against 2 theta from sample to sample),  $\mathbf{D}$  is the diffractogram profile matrix of the components, and  $\mathbf{C}$  is the composition profile matrix for the samples. The matrix dimensions

are indicated below the symbols of the matrices in the equations, where index  $I$  denotes the number of  $2\theta$  values,  $K$  is the number of samples, and  $N$  means the number of crystalline components of the samples (mixtures) to be analysed. Suitably chosen initial estimations of  $\mathbf{D}$  or  $\mathbf{C}$  are optimized

by solving Eq. (1) iteratively by alternating least squares optimization:

$$\begin{aligned} \mathbf{D}^* \cdot \mathbf{R}^* &= \mathbf{C}^T \\ \mathbf{R}^* \cdot (\mathbf{C}^T)^* &= \mathbf{D} \end{aligned}$$

$\begin{matrix} N \times I & I \times K & N \times K \\ I \times K & K \times N & I \times N \end{matrix}$

where the matrix  $\mathbf{R}^*$  is the reproduced data matrix obtained by principal component analysis for the selected number of components, and  $*$  means the pseudoinverse. Unfortunately, this decomposition is very often not unique because of the rotational and intensity (scaling) ambiguities. The rotational ambiguities can be moderated or even eliminated if convenient constraints can be used. Tauler and coworkers developed a Matlab code for MCR-ALS with some constraints

#### Morphological study

The binary systems were investigated with a scanning electron microscope (Hitachi 2004 S, Hitachi Scientific Instruments Ltd, Tokyo, Japan). A polaron sputter coating apparatus (Bio-Rad SC502, VG Microtech Uckfield, UK) was applied to create electric conductivity on the surface of the samples. The air pressure was 1.3-13.0 mPa.

#### In vivo study

48 rats (male, SPRD, 200-220 g) were divided into 8 groups. Appropriate amounts, (determined in pilot experiments) of pure ME1, ME400 and PMs were filled into special capsules. These capsules were then administered into the stomach of the rats by using a Capsules-kit (CapsuGel, Greenwood, USA), which is specific for preclinical studies. A local inflammatory response was elicited by the injection of 0.1 ml of Carrageenan (Viscarin, Marine Colloids Inc, Springfield, USA) into the left hind paw. The contralateral foot was injected subcutaneously with isotonic saline (control). Edema (caused by Viscarin) was measured with a plethysmometer (7140, Hugo Sachs Electronic GmbH, Germany) 5 h after the injection of Carrageenan. The differences in the extent of edema formation due to the various pretreatments were expressed as percentages of the control value. Bonferroni and Dunnett tests were applied in the *Post-hoc* analysis.

#### 4. Results and discussion

##### 1. Influence of particle size on dissolution rate

The drug profiles of pure ME1 with  $d(90\%)=206.20\mu\text{m}$  and ME2 with  $d(90\%)=5.97\mu\text{m}$  were first studied. The wettability of the particles was very low because ME is a poorly water soluble drug. Difference in release between the two drugs could be observed after 60 min. The effect of the higher specific surface area of ME2 was not manifested because of the tendency of the small ( $\sim 6\mu\text{m}$ ) crystals to agglomerate. After the dissolving of the capsule, the particles that were in a very hydrophobic form clustered in the artificial enteric juice (Fig. 1).

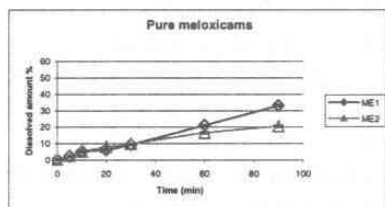


Fig. 1 Rate of dissolution of ME1 and ME2

##### Physical mixture (PM)

PMs of ME1 and ME2 with mannitol (PM1 and PM2) in (drug:carrier) ratios of 3:7 and 1:10 were obtained by mixing the individual components for 10 min in a Turbula mixer (Turbula WAB, Systems Schatz, Basel, Switzerland) at 50 rpm.

It seems in the case of PM-ME2 with ratio of 3:7, the amount of mannitol was not enough to overcome dissolution problem. In the case of ME2, on increasing of the amount of mannitol (1:10), dissolution was faster. This is connected with the specific surfaces of ME2 and mannitol. ME2 with small particles presumably adheres to the surface of mannitol. Nevertheless, it should be noted that the total amount of ME2 did not dissolve (Fig. 2).

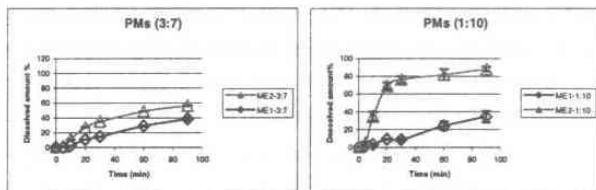


Fig. 2 Rate of dissolution of MEs from PMs in 3:7 and 1:10 ratio

#### *Melted product (MPs)*

MPs of ME1 and ME2 and mannitol (ME1-MP and ME2-MP) in ratios of 3:7 (w/w) and 1:10 (w/w) were made as follows: The MEs were added to melted mannitol (170 °C) and the melts solidified at room temperature (20±1 °C). The products were triturated in a mortar and were sieved. The particle size range of the products was between 100 and 250µm.

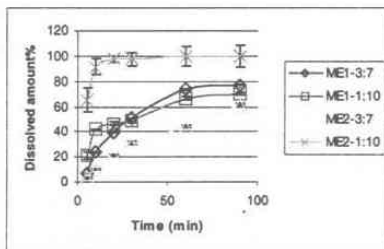


Fig. 3 Rate of dissolution of MEs from MPs in 3:7 and 1:10 ratio

For the MP-ME2 samples, we achieved perfect dissolution with a higher concentration of mannitol (10 parts). The results revealed the different effects of melt technology on the rate of dissolution of the MEs.

#### **Investigations on (ME1 and ME2)-mannitol binary systems**

- **Differential scanning calorimetry**

The DSC scans of the PMs and the MPs of ME-mannitol always included two endotherms, attributed to the separate melting processes of the two components (Fig. 4). It can be seen in the DSC curve of the PM that a proportion of the ME was dissolved in the melted mannitol (a broad, double endothermic peak), but the samples prepared by melting technology did not display the double peak because this dissolution might occur during the preparation of the samples. The peaks observed for the ME1 cases were analogous to those observed for ME2 at the corresponding ratios. A small additional peak is seen at a ratio of 1:10, but not at 3:7.



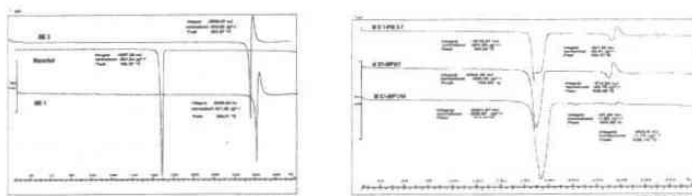


Fig. 4 DSC curves of ME1, ME2 and Mannitol and DSC curves of PMs and MPs

We wanted to confirm the findings by powder X-ray investigation of the appearance of the new endothermic peak between the melting points of mannitol and ME.

- **Powder X-ray diffractometry**

The diffractograms of the PMs showed the characteristic values of the starting materials. Those of the MPs (3:7 and 1:10) had the same characteristic values as those of the PMs. The drug was distributed in the carrier in fine crystal (suspended) form.

A proportion of ME dissolved in the melted mannitol, but it was recrystallized during cooling. The remainders of the crystals were in a suspended form in the binary system during the melting process.

- **Chemometric method**

The evaluation of the X-ray measurements with MCR confirmed the conclusions drawn from the DSC measurements: ME-MP 1:10 gave the highest amount of the new crystal phase; the new endothermic peak appeared only at the 1:10 ratio. The PMs predominantly display the characteristics of mannitol.

## 2. Optimization of particle size for physical mixtures (PMs)

Because the 100% dissolution could not be achieved by a simple physical mixture (even by increasing the amount of mannitol), we decided to find a proper particle size. That is why ME1 was milled to make a ME400.

The aim of this part is to investigate the surface properties of different physical mixtures to find a possible relation between the surface properties and the dissolution of physical mixtures.

The work of cohesion of ME samples is in every case lower than that of mannitol. This is necessary for the spreading of the ME over mannitol. The work of adhesion between mannitol and ME samples is in every case higher than the work of cohesion of the

corresponding ME samples. This is also a necessary condition for the spreading of the active agent on the surface of the excipient (Table 2).

Table 2 Surface properties data of the pure components

| Samples  | Contact angle (°) |        | Surface free energy (mN/m) | Polarity (%) | Work of cohesion (mN/m) | Work of adhesion (mN/m) |
|----------|-------------------|--------|----------------------------|--------------|-------------------------|-------------------------|
|          | Water             | SD (±) |                            |              |                         |                         |
| ME1      | 54.4              | 2.4    | 67.9                       | 27.8         | 135.8                   | 144.7                   |
| ME400    | 59.9              | 1.2    | 65.9                       | 24.4         | 131.8                   | 140.7                   |
| ME2      | 69.4              | 3.7    | 59.2                       | 19.4         | 118.3                   | 129.5                   |
| Mannitol | 24.0              | 4.5    | 80.6                       | 40.7         | 161.2                   | -                       |

The surface free energy and polarity data on the PM1s were closer to those on mannitol than to those on ME1. For the PM400s and PM2s, the coverage of mannitol by the ME results in the surface free energies approximating to those for the pure MEs (Table 3).

Table 3 Surface properties data of ME-mannitol PMs in a ratio 1:10

| Samples    | Contact angle (°) |        | Surface free energy (mN/m) | Polarity (%) |
|------------|-------------------|--------|----------------------------|--------------|
|            | Water             | SD (±) |                            |              |
| PM1-1:10   | 31.4              | 2.1    | 77.9                       | 38.4         |
| PM400-1:10 | 42.8              | 4.9    | 73.9                       | 32.9         |
| PM2-1:10   | 54.4              | 1.2    | 66.4                       | 27.8         |

Dissolution studies were done on ME400 and its binary systems, the results of this investigation were compared to the other 2 MEs and their binary systems (Fig. 5).

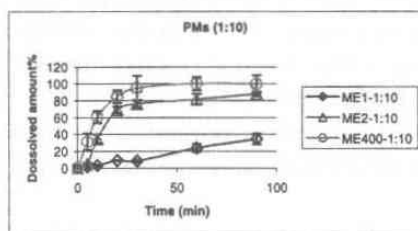


Fig. 5 Rate of dissolution of ME1, ME2 and ME400 from PMs in 1:10 ratio

Even though the particles of the milled ME1 (ME400) were not as small as those of ME2, it was able to attain a higher surface area in contact with the dissolution medium and the dissolved amount was improved to 100%.

### 3. *In vitro and in vivo investigations on the binary meloxicam-mannitol system*

After the successful *in vitro* experiments, the anti-inflammatory effects of the pure MEs and PMs were investigated on rats (Fig. 6).

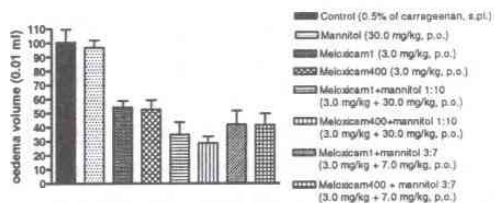


Fig. 6 Anti-inflammatory effects of ME1, ME400, mannitol and different PMs of meloxicams and mannitol on rats

It was demonstrated that 3 factors affected the dissolution of the drug material in binary ME-mannitol system:

1. The ME particle size with a given specific surface
2. The amount of carrier (mannitol) with enough specific surface for ME particles
3. The interaction (adhesion) between the ME and mannitol particles

Each factor is important in increasing the rate of dissolution of ME and all three must act together. However, with the ideal particle size of the drug (ME400) and the ideal ratio of ME400 and mannitol (1:10), the total dissolution of the drug was achieved (99.60 % within 90 min). In this interactive mixture, mannitol functioned as a core covered with a monolayer of ME particles. This was confirmed in *in vivo* experiments. PM400 1:10 exhibited the best (71.48%) anti-inflammatory effect. Statistically, a positive correlation was found between the *in vitro* and *in vivo* data ( $P < 0.05$ ,  $R^2 = 0.937$ ).

The results confirmed the applicability of the interactive binary physical mixture for the increase of dissolution and better bioavailability of water-insoluble drugs.

## 5. Summary

The anti-inflammatory drug, meloxicam (ME) has poor water solubility. The object of this project was to improve the rate of dissolution of meloxicam in capsule form.

- ME samples with different particle sizes were investigated without a carrier. A smaller (micronized) particle size did not improve the dissolution of the drug.
- Mannitol, a sugar alcohol, is a cheap and readily available excipient which was used as a carrier in different ratios, in physical mixtures and melted forms (Binary systems).
- Differential scanning calorimetry (DSC) and X-ray diffractometry were used to investigate the characteristics of meloxicam-mannitol binary systems. Multivariate curve resolution (MCR) as a chemometric method was applied to interpret the X-ray diffractograms.
- According to the results, the amount of mannitol and the particle size of ME were important factors in the rate of dissolution. For the perfect dissolution of ME, the melt technology (MP) was used which resulted in mixed crystals. This technology was made by 10 parts of mannitol and 1 part of ME2 with about 6  $\mu\text{m}$  in average particle size.
- In physical mixtures (PMs), the interactions between the particles are determined by the forces of adhesion and cohesion. The size and the specific surface area of the particles are also determinative factors in the interparticle interactions. However, with the ideal particle size ( $d_{90\%} = 131.15 \mu\text{m}$ ) of the drug (ME400) and the ideal ratio of ME and mannitol (1:10), the total dissolution of the drug was achieved. In this case, mannitol functioned as a core covered with a monolayer of ME particles.
- Contact angle, surface free energy, polarity, work of adhesion, and work of cohesion of the drug, the carrier, and their physical mixtures were calculated.
- According to the results, contact angle, surface free energy, polarity and work of adhesion can be used as critical parameters to characterize powder interactive mixtures and to determine the optimum dissolution profile.
- A study was made of the anti-inflammatory effects on rats of pure meloxicam (ME) with different particle sizes and of physical mixtures of the binary ME-mannitol system.
- The level of local inflammation was significantly decreased when the amount of mannitol was the highest and the particle size of meloxicam was  $d_{90\%} 131.15 \mu\text{m}$ . These results are the same as the ones achieved in *in vitro* experiments.

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## Publications

- I. **P. Reisi Nassab, R. Rajkó, P. Szabó-Révész**  
*Physicochemical characterization of meloxicam-mannitol binary system*  
J. Pharma. Biomed. Anal. 41 (2006) 1190-1197  
Cit = 1 (IF 2006: 2.032)
- II. **A. Szűts, O. Laczkovich, P. Reisi Nassab, Z. Aigner, P. Szabó-Révész:**  
*Applicability of sugar esters in hot-melt technology*  
Acta Pharm. Hung. 77 (2007) 97-102  
(IF: -)
- III. **P. Reisi Nassab, Zs. Túske, P. Kása Jr., A. Bashiri-Shahroodi, P. Szabó-Révész**  
*Influence of work of adhesion on dissolution rate in binary solid systems*  
J. Adhesion 83 (2007) 799 – 810  
(IF 2006: 1.046)
- IV. **A. Bashiri-Shahroodi, R. Rajkó, P. Reisi Nassab, P. Szabó-Révész**  
*Preparation of a solid dispersion by a dropping method to improve the rate of dissolution of meloxicam*  
Drug Dev. Ind. Pharm. (in press)  
(IF 2006: 0.821)
- V. **P. Reisi Nassab, G. Blazsó, T. Nyári, G. Falkay, P. Szabó-Révész**  
*In vitro and in vivo investigations on the binary meloxicam-mannitol system*  
Pharmazie (in press)  
(IF 2006: 0.606)

## Abstracts

- I. **P. Reisi Nassab, P. Szabó-Révész, A. Bashiri-Shahroodi, I. Erős**  
*Dissolution properties of meloxicam-mannitol binary system*  
6<sup>th</sup> Central European Symposium on Pharmaceutical Technology and Biotechnology.  
Siófok, Hungary. May 25-27, 2005  
Eur. J. Pharm. Sci. (2005), 25/S1, S161-162
- II. **P. Szabó-Révész, P. R. Nassab, R. Rajkó**  
*Dissolution properties of meloxicam-mannitol binary system*  
5<sup>th</sup> World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical  
Technology. Geneva, Switzerland. 27-30 March, 2006
- III. **P. Reisi Nassab, P. Szabó-Révész**  
*Effect of particle size and carrier on dissolution behaviour of meloxicam*  
European Federation for Pharmaceutical Sciences. Verona, Italy. April 26-27, 2006
- IV. **P. Reisi Nassab**  
*Physicochemical characterization of meloxicam-mannitol binary systems*  
Ph.D Tudományos nap. Szeged, Hungary. May 3, 2006
- V. **P. Reisi Nassab, P. Kása Jr, P. Szabó-Révész**  
*Effect of particle size and carrier amount on dissolution properties of meloxicam*  
Congressus Pharmaceuticus Hungaricus XIII. Budapest, Hungary. May 25-27, 2006
- VI. **P. Reisi Nassab, A. Szűts, P. Szabó-Révész**  
*Dissolution improvement of meloxicam for development of solid dosage form*  
Gyógyszerkutatási Szimpózium. Debrecen, Hungary. November 24-25, 2006