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Department of Pharmaceutical Technology

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PREPARATION AND INVESTIGATION OF POLYMETHACRYLATE-BASED MATRIX SYSTEMS

by

Anita Korbely

Pharmacist

Supervisor:

Prof. Dr. Klára Pintye-Hódi

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University of Szeged
Graduate School of Pharmaceutical Sciences

Educational Program: Pharmaceutical Technology
Head: Prof. Dr. Piroska Szabó-Révész

Department of Pharmaceutical Technology
Supervisor: **Prof. Dr. Klára Pintye-Hódi**

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1 INTRODUCTION

The development of novel drug delivery systems is one of the major focuses of formulation scientists since these systems offer several benefits compared to the conventional dosage forms. The time and site-dependent release provides a more targeted, patient and disease-centric therapeutic approach. On the other hand, it makes the researchers and formulators face a challenging situation. Nowadays the trends show that the pharmaceutical industry orients the development into the direction of individual drugs. The "one-size-fits-all" approach of ordinary drug therapy seems to decline as newer and newer chemical and biological entities reach the market. This provides several significant benefits that are capable to overwhelm the individual physiological and pathophysiological differences between patients. However, there is still a need for production of medicines that are available for a larger population, relatively cost-effective, and simultaneously meet the requirements of safety and efficacy. Controlled release is one of the most important innovative areas in pharmaceutics. These delivery systems are frequently applied for the incorporation of commercialised drugs. This strategy can extend the lifespan of patented drugs as part of the life cycle management, thus preserving the market shares from generic drug makers. Nevertheless, these novel drug delivery systems contribute to an improved patient compliance and to the reduction of material costs.

2 OBJECTIVES

Polymethacrylate-based polymers are frequently used excipients in pharmaceutical formulations. A wide range of polymers are available for tailor-made controlled release formulations. The present work focused on the preparation and investigation of solid matrix systems that contained polymers ensuring pH or time-dependent drug release.

In the first section, a gastric soluble cationic methacrylate copolymer was studied that was applied in an antacid formulation with pH-dependent drug release. In this case not only the optimization of the tablet composition but also the optimization of the processability was investigated. Therefore, the work was divided into two parts. In the first part the tablet composition was optimized through investigation of several tablet compositions. The composition that provided pH-dependent disintegration and appropriate tablet characteristics was selected for further processing. Since the powder blends prepared in the first step

exhibited poor flow properties, wet and hot melt granulation were employed to improve flow in the second part.

The second section describes the dissolution kinetics of an anti-inflammatory API from a pH-independent modified release system. Matrix systems were manufactured with different pharmaceutical processes and it was investigated how the method of production influences the dissolution properties. Mathematical modelling of the dissolution kinetics was also assessed.

3 SECTION I

A pH-dependent matrix system was developed via optimization of composition and processability. Five different compositions of tablets were studied and the one that was found eligible for further development was selected for processing by granulation.

Materials

Aluminium hydroxide (AH) was selected as active pharmaceutical ingredient (API) that reacts with gastric acid and the formed gel coats the mucosal layer of the stomach. Aluminium hydroxide does not absorb from the gastrointestinal tract and has the potential to change the pH in the stomach and it has an impact on the absorption of other drugs due to its complex forming ability.

Magnesium trisilicate (MT) was also incorporated into the formulations as API. This inorganic compound also has an antacid effect. Magnesium trisilicate is frequently combined with aluminium hydroxide due to the compensation of side effects.

Sodium bicarbonate (SB) was used as a disintegrant that facilitates the disintegration of a tablet. Sodium bicarbonate reacts with gastric acid while carbon dioxide develops that contributes to the disintegration of the tablet. Due to the antacid effect of sodium bicarbonate, it can also be considered as an API in the present formulation.

Eudragit® E PO (EE) is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate. It is soluble in gastric fluid up to pH 5, thus programmed drug release can be ensured. Frequently used as a coating agent due to its film forming capability and as a binder in tablets prepared by direct compression in 10% to 50% concentration.

Polyethylene glycol (PEG) 2000 is a water soluble polymer that can be used as a binder during melt granulation due to its low melting point (45-50°C).

Part 1

The experiments were performed with seven different compositions that always comprised a constant ratio of AH and MT while the ratio of excipients altered; the decreasing amount of EE was accompanied by the weight increase of SB. The extremities were represented by two compositions: the one that was composed exclusively of the APIs, the other one contained the largest amount of SB and the least proportion of EE. Both compositions were not suitable for tableting due to capping.

a) Evaluation of powder mixtures

Powder flow

The evaluation of powder characteristics prior to tableting has a specific importance since it provides deeper insight into powder behaviour during compression. Provided that a powder or blend has poor flow properties that can lead to fluctuations in the tablet weight and, thus it can jeopardize the content uniformity. Independently of the composition, the manufactured powder blends exhibited poor flow properties that were supported by the necessity of stirring during the flow test and high values of Carr's index (above 20%).

Water uptake

The water uptake kinetics may influence the application of pharmaceutical formulations and further processing. Therefore, both baseline materials and powder blends were tested for wettability including the determination of Enslin number (water uptake of 1 g powder in mL).

Out of the tested materials, AH had the highest water sorption capacity due to being a gel forming agent. Partially this characteristic is utilized during pharmaceutical application. The wettability of EE is negligible, SB proved low water sorption, as well. Regarding the powder mixtures, an increasing proportion of EE in the blend resulted in lower water absorption that is in good agreement with the properties of the matrix forming polymer. The wettability improved whilst the amount of EE decreased or the ratio of SB increased that had a better wetting property compared to the matrix former.

pH-changing potency

Considering the efficacy of the preparation, it is useful to study the ability how the powder mixtures can influence the pH of different solutions. The produced blends were

placed into glass beakers containing test liquids with different pH (1.2±0.1; 2.0±0.1; 2.5±0.1; and 3.0±0.1). After 20 min of constant stirring, the change in pH was checked.

The powder blends due to their antacid effect caused applicable change in the pH. The change was slightly higher for the blends that contained higher proportion of SB. The pH-changing tendency of mixtures was more pronounced in solutions with higher pH.

b) Evaluation of matrix tablets

Matrix tablets were produced by direct compression using an eccentric tablet machine. Three different compression forces were applied (5±2 kN, 15±2 kN, and 25±2 kN).

Geometry and mechanical properties of matrix tablets

The geometry of tablets including thickness and diameter was determined. Applying higher compression force or increasing the amount of SB, the thickness of tablets decreased. The latter phenomena can be partially explained by the increased loose density.

Mechanical strength was quantified by hardness and friability. The tablets with higher SB content exhibited increased friability. Using higher compression force, friability lessened independently of the composition. Nonetheless, friability values remained below 1% (threshold value for acceptance in Ph. Eur.) in each case.

Disintegration study

Disintegration study was carried out in four test liquids with different pH: 1.2; 2.0; 2.5; 3.0. Since the applied APIs changed the pH of the disintegration test liquid, the medium was replaced every 20 min to ensure the constant pH.

The elevation in the pH of the disintegration medium resulted in elongated disintegration times. Application of higher compression force contributed to longer disintegration. Increase in the proportion of SB unexpectedly decelerated the disintegration of the tablets. Supposing, the APIs developed a thin alkaline fluid layer around the tablet cores that restricted the further erosion of the matrix. Nevertheless, tablets that contained the highest amount of SB and were manufactured at the lowest compression force (5 kN) proved different disintegration properties, deviating from the observed tendency at each pH.

c) Summary

Application of EE pH-dependent matrix former ensured suitable disintegration of antacid tablets in solutions with different pH. Above pH 2, the liberation of the APIs markedly decreased. At pH 3.0, the disintegration time elongated to a significant extent that ensures that the antacid tablet does not release further API which is unnecessary at this pH.

Part 2

The powder blends discussed in Part 1 were not suitable for direct compression due to poor flow properties. Consequently, size-enlargement process was applied to improve compaction characteristics and simultaneously maintain the pH-dependent disintegration profile of the tablets. The tablet composition that exhibited appropriate, pH dependent disintegration was selected for processing.

a) Preliminary data generation

Prior to optimization of the process of granulation, preliminary data were collected about the effect of different granulation techniques on the powder flow, wetting characteristics, and disintegration of matrix tablets.

Wet and hot melt granulation

Ethanol and purified water were applied as solvents to manufacture granules by wet granulation. EE dissolves in ethanol but it is practically insoluble in water. The process of granulation was carried out in a high-shear mixer.

Hot melt granules were prepared in a laboratory scale high-shear mixer equipped with a jacketed vessel. The temperature was raised up to 70°C that was above the glass transition temperature of EE (~48°C).

Thermoanalytical study

Albeit the applied APIs and matrix forming polymer are thermally stable, SB may undergo thermal decomposition. Differential Scanning Calorimetry (DSC) was employed to detect thermal changes. SB developed the first peak indicating thermal degradation at ~90°C. At the temperature of the granulation process (~70°C) thermal phenomenon was not observed.

Evaluation of granules

The granules produced by wet granulation had remarkably good flow properties independently of the applied solvent, i.e. significant improvement has been achieved with wet granulation compared to the properties of the baseline blend. The wetting properties of the granulated products also changed; each processing method markedly increased the water uptake.

Disintegration study

Besides the improvement of compressibility, the major aim of the processing was to maintain the pH-dependent disintegration of the compressed tablets. Performing the study in four test liquids with different pH, the tablets compressed from wet granulated samples disintegrated in 1 to 4 min and the disintegration time did not correlate with the pH. Contrarily hot melt granulated samples exhibited appropriate disintegration times: the disintegration times extended alongside increasing pH.

Summary

Wet granulation technique was a suitable method to improve the flow properties of the blend, although this procedure caused unfavourable change in the disintegration profile of the matrix tablets, consequently the pH-dependent API release ceased. Hot melt granulation did not improve the processability considerably, albeit the matrix tablets composed of hot melt granules partially preserved the pH-dependent disintegration profile.

b) Optimization of hot melt granulation

Optimization of preparation of hot melt granules was initiated in order to customize the pH-dependent disintegration of matrix tablets and to achieve good flow of intermediate granules. Blend composition was supplemented by a hydrophilic melting binder, PEG 2000. Increasing amount of PEG 2000 was incorporated into the formulations. The extremities contained only one of the polymers, whether EE or PEG 2000.

Evaluation of granules

Increasing the amount of PEG 2000 contributed to the development of improved flow properties. Heating of the blend without PEG 2000 did not lead to relevant alteration in flowability and compressibility, however the water uptake significantly ($p < 0.05$) increased.

Properties of polymers prevailed in the granules, consequently the water uptake decreased. Evaluation of sample without EE revealed deterioration in each examined parameter.

Evaluation of tablets

Tablets were compressed using the above-described granules at 15±2 kN compression force. PEG 2000 increased the mechanical strength of the tablets provided EE was also present. Tablets prepared in the absence of matrix former displayed poor mechanical strength and the samples broke apart during the friability test.

Disintegration of tablets verified a pH-dependent disintegration. Application of PEG 2000 extended the disintegration time. The most pronounced delay in disintegration time was assessed in tablets that contained the highest amount of PEG 2000. Those compositions exhibited the most favourable properties that contained both PEG 2000 and EE. Thus, Differential Scanning Calorimetry and solid-state NMR spectroscopy were performed to confirm a possible physico-chemical interaction between PEG 2000 and EE.

Thermoanalytical study

The findings of Differential Scanning Calorimetry pointed to the fact that chemical interaction occurred between the matrix former and hydrophilic binder. The interaction induced process seemed not to be completed at the temperature of granulation. The completion of the phenomenon could occur above 80°C; nonetheless, the risk of decomposition of sodium bicarbonate would significantly increase at this temperature. The sample that exhibited the most favourable measures exhibited a uniform peak on the DSC curve at the temperature of the granulation.

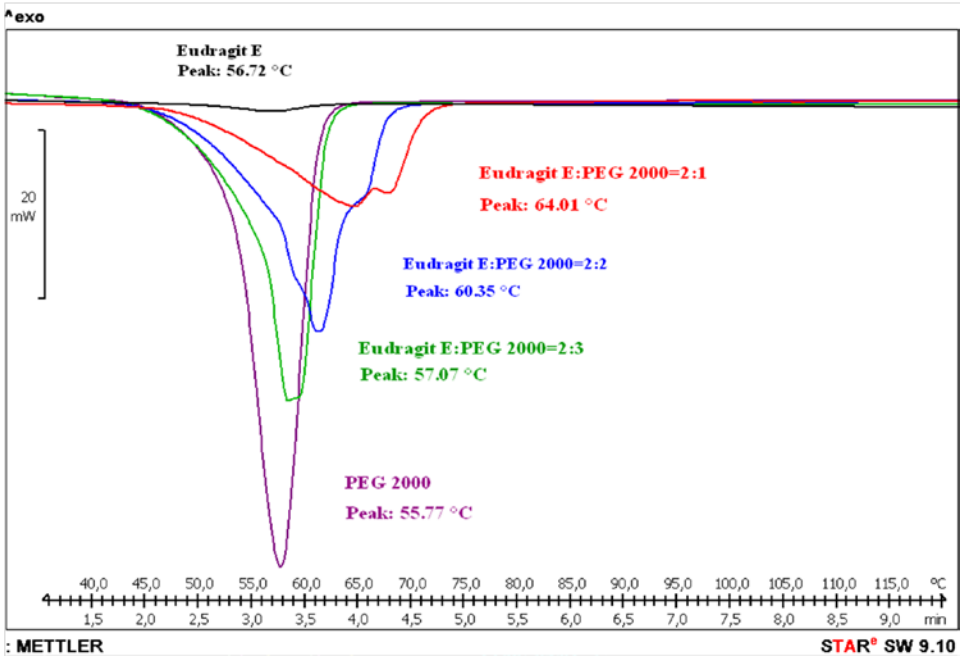

Fig. 1 DSC curves of polymers and polymer mixtures

Solid-state NMR spectroscopy

Solid-state NMR (Nuclear Magnetic Resonance) spectroscopy was carried out in order to reveal the structural changes of polymers. During the investigation, 2D ^{1}H-^{1}H and ^{1}H-^{13}C correlation measurements were performed that did not reveal considerable mixing of PEG 2000 and EE. However, the 1D ^{13}C MAS (magic angle spinning) measurements proved that the granulation process slightly altered the structure of the polymers compared to the pure baseline materials. Crystalline PEG 2000 was not detected in the granules, albeit its structure altered in the intermediates. The results of the solid-state NMR study reflected that the mixing of polymers occurred on the surface. The differences of the spectra of granules and pure polymers may explain the beneficial mechanical and disintegration properties of tablets prepared from hot melt granules.

c) Summary

Utilization of PEG 2000 enabled the formulation of suitable pharmaceutical intermediates by hot melt granulation. Nevertheless, the tablets made of hot melt granules retained the ability of the pH dependent disintegration. In so far the disintegration time at pH 3 exceeded the time that is necessary for the emptying of the stomach.

4 SECTION II

In this section the study of matrix systems containing 5-aminosalicylic acid is described. The formulations contained time-dependent polymethacrylate polymers as matrix formers with low and high permeability. Other excipients were omitted to gain a clear picture about the effect of different pharmaceutical processing methods on drug release.

Materials

5-aminosalicylic acid (5-ASA) was selected as a model drug that is a locally acting anti-inflammatory agent and it is commonly used in the first-line treatment of mild-to-moderate ulcerative colitis. Orally administered 5-ASA absorbs rapidly and almost completely from the small intestine. Since the absorption inclines to the development of side effects, colon delivery is recommended to decrease the probability of systemic events.

Eudragit® RS (E RS) and Eudragit® RL (E RL) polymethacrylate copolymers were applied as matrix formers. Chemically E RS and E RL are copolymers of ethyl acrylate, methyl methacrylate, and a low content of methacrylic acid ester with quaternary ammonium groups. The salts of the ammonium groups make the polymers permeable. These polymers are water insoluble; nevertheless, a pH-independent swelling of the matrices may occur. E RL aids a higher drug release rate compared to E RS since E RL has higher permeability than E RS. The methacrylate copolymers were used in forms of dry powder and aqueous dispersion.

a) Preparation of matrix tablets

Matrix tablets were prepared with four different processing methods: direct compression (DC), compression of the wet granulated API with polymer(s) in the external phase (G5ASA), compression of the wet granulated API and polymer(s) in the internal phase (G), and wet granulation of the API with aqueous dispersion(s) of the polymer(s) (GD). Five tablet compositions were investigated per preparation method. The compositions differed from each other in their permeability. Flat-shaped tablets were compressed with a hydraulic press. Direct compression intended to serve the basis of comparison for the other processing techniques.

b) Characterization of matrix systems

Contact angle measurement

The determination of contact angles and indirectly of surface free energy permits a deeper insight into how the materials behave during wetting. Evaluation of this property is crucial considering the fact that the extent of wetting of a solid surface influences the dissolution – wetting of the system is a prerequisite for dissolution. Contact angle measurements were performed using polar (purified water) and apolar (diiodomethane) probe liquids. Surface free energy and spreading coefficient were calculated.

The study revealed that 5-ASA had a polar characteristic and the presence of highly water-insoluble polymers in the same proportion did not decrease the polarity significantly – as it could be estimated from the equal ratio of API and excipients. The calculated spreading coefficient indicated that the polymers spread on the surface of 5-ASA; nonetheless, the fine polymer particles did not evenly cover the API crystals which exhibited large surface area. Therefore, the fine polymer particles could not significantly reduce the polarity of the API.

Evaluation of water uptake

The water was absorbed by the wet granulated samples (wet granulation with water; G) more rapidly than by the samples prepared with aqueous polymer dispersions (GD). The wetting rate was steadier in the case of the wet granulated samples, while the more compact structure of the granules produced with the aqueous dispersions allowed a slower and staggered water uptake due to the prevailing hydrophobic features. In the case of wet granulated samples that were prepared with aqueous polymer dispersions, the water uptake capacity correlated with the dissolution rate.

Dissolution study and release modelling

Investigation of the dissolution of a drug from a delivery system is required by the Pharmacopoeias and represents a critical step considering regulatory approval and proof of effectiveness. Dissolution tests were carried out in phosphate buffer solution of pH 6.8, 8 hr long. Subsequently, mathematical models were used to describe the dissolution profiles of 5-ASA from the matrices.

Matrices that were prepared by direct compression (DC) and had higher permeability exhibited faster dissolution and higher release rate. Contrarily, systems with low permeability

proved incomplete, thus extended drug release during the studied interval. The granulation of the API itself (G5ASA) did not triggered significant alteration in the release profile compared to the samples manufactured by direct compression. Both formulation methods (DC and G5ASA) verified that the release from matrices with low permeability, including the composition that involved both type of polymers in the same proportion, followed the Korsmeyer-Peppas model. Matrix systems with high permeability were characterized by the Hopfenberg model.

Wet granulation (G) resulted in substantial and unforeseen change. In general, each formulation exhibited accelerated drug liberation; however, the matrices with the lowest permeability sustained the release profile described by the Korsmeyer-Peppas model. Concurrently, the application of matrix forming polymers with high permeability provided a sudden, burst-like drug release making the formulations unsuitable for extended release. Consequently, these systems could not be fitted with any mathematical model.

The fourth processing method (GD) operated with aqueous polymer dispersions that acted as matrix former and binder in the agglomerates. Each formulation displayed delay in the drug release rate compared to the samples prepared by direct compression. Approximately 50% decrease was observed in the final percentage of the dissolved API. The change in the release profile was also confirmed by the mathematical modelling: each composition followed the release kinetics determined by the Korsmeyer-Peppas model.

Morphological analysis

The scanning electron microscope pictures revealed that the polymers formed an amorphous network. On wet granulation with the polymer dispersions, uncovered crystal particles of 5-ASA spread over the granules due to the fact that a small amount of polymer was present in the form of a thin film layer. However, there were 5-ASA crystals which were not covered by the polymer because of the relatively large amount of the API. The aqueous dispersion formed a film in the granules, providing them with a compact inner texture and a consequently prolonged drug release. In contrast, the process described above could not occur, or only partially in the solid polymers where there were insufficient time and moisture for the complete solvation of the polymeric chains, and the linkages could not form to retain the 5-ASA molecules and protect them, despite the higher amount of polymers.

Fig. 2 Morphology of granules prepared by wet granulation with water

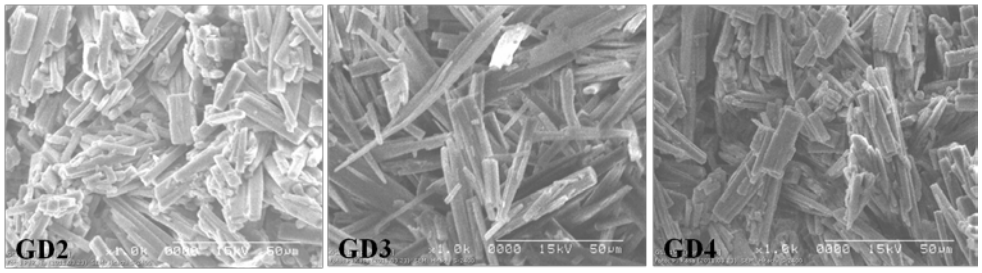

Fig. 3 Morphology of granules prepared by wet granulation with polymer dispersions

c) Summary

The investigation of release rate from polymethacrylate-based insoluble matrix systems demonstrated that the applied polymer itself does not guarantee a tailored drug release, the possible processing methods should also be considered during the design of a specific formulation. Consequently a wet granulation technique which involve only the granulation of the active compound and application of matrix forming polymers as an external phase during tableting may result in highly similar profile than that, that the directly compressed tablets provide. Nonetheless, a wet granulation affecting both the active ingredient and polymer excipients may increase the dissolution rate and accelerate the dissolution process. Contrary to this effect, utilization of the matrix formers in aqueous dispersions, simultaneously functioning as binders of granules, can lead to prolonged release; therefore, if a more retarded drug release is required, this kind of process can promote a long-lasting drug dissolution effect. Remarkably the matrix systems with low permeability released the API according to the Korsmeyer-Peppas model, i.e. diffusion was the determinant mechanism during dissolution. While the Hopfenberg model was applicable to the higher water-permeable matrices due to the more pronounced surface erosion. Nonetheless, samples of GD followed the Korsmeyer-Peppas model independently of permeability.

5 FINAL CONCLUSIONS, NOVELTY, PRACTICAL USEFULNESS

The applicability of polymethacrylate-based copolymers was investigated in orally administered, solid matrix systems in order to deliver locally acting drugs into the gastrointestinal system. Antacid matrix tablets were manufactured with an acid-soluble, pH-dependent matrix forming polymer that has mainly been used and investigated as film coating. The second system intended to serve the basis of time-controlled colon delivery. The main purpose of the study was to determine the dissolution/disintegration behaviour of matrix systems based on polymethacrylate copolymers, commonly called Eudragit® polymers. Furthermore, granulation methods and their effects were investigated as possible processing techniques aiming the improvement of processability of baseline powder blends.

Summarizing the novelty and usefulness can be stated:

- A stimulus-controlled matrix type tablet was formulated with an antacid effect. It may provide the benefit over the commercial formulations that the disintegration, and thus the liberation of active ingredients only occurs in the case of a low pH of the stomach. Elevation of the pH gradually decelerates the disintegration, therefore minimizing the possible side effects due to unnecessary drug release.
- Application of pH-independent swellable polymers in temporal control of drug release was studied in the second section. The results are useful in the design and formulation of time-dependent colon delivery systems that require high drug loading and processing of the baseline materials due to poor compressibility.

Both studies dealt with different granulation techniques that are commonly used in the pharmaceutical industry, albeit they have a significant effect on the properties of the product, these consequences have been less scrutinized. The present study had the goal to provide scientists with fundamental information about the possible behavioural alterations of polymethacrylate polymers during processing.

PUBLICATIONS RELATED TO THE THESIS

I J. Bajdik, **A. Korbely**, K. Pintye-Hódi:
Formulation of intelligent tablets with an antacid effect
Pharmaceutical Development and Technology, 14(5), 471–475, 2009 IF:0.895

II J. Bajdik, **A. Korbely**, K. Pintye-Hódi:
Evaluation of phenomena occurring during the preparation of matrix granules by the hot melt technique
Journal of Thermal Analysis and Calorimetry, 104, 241–247, 2011 IF:1.604

III **A. Korbely**, A. Kelemen, P. Kása Jr., K. Pintye-Hódi:
Effects of processing on the release profiles of matrix systems containing 5-aminosalicylic acid
AAPS PharmSciTech, 13(4), 1341–1347, 2012 IF:1.432

PRESENTATIONS RELATED TO THE THESIS

I **A. Korbely:** Formulation and investigation of matrix tablets with an antacid effect
Conference of Student Research Program (TDK), Szeged, Hungary, 2008

II J. Bajdik, **A. Korbely**, K. Pintye-Hódi: Formulation of matrix tablets with an antacid effect
6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Barcelona, Spain, 2008

III **A. Korbely:** Preparation of antacid tablets by compression of granules
Conference of Student Research Program (TDK), Szeged, Hungary, 2009

IV **A. Korbely:** Preparation and investigation of intelligent matrix tablets with an antacid effect

Hungarian Science Festival, Szeged, Hungary, 2009

V **A. Korbely,** J. Bajdik, K. Pintye-Hódi: Formulation of intelligent tablets with an antacid effect

14th National Pharmaceutical Congress (CPhH), Budapest, Hungary, 2009

VI **A. Korbely,** K. Pintye-Hódi: Role of the surface free energy in the preparation of granules and in the selection of a suitable device

8th Central European Symposium on Pharmaceutical Technology, Graz, Austria, 2010

VII **A. Korbely,** K. Pintye-Hódi: Influence of matrix forming polymers on the properties of granules with mesalazine

16th National Pharmaceutical Technology Conference and 8th „Medicine on the turn of the millennium" Postgraduate Conference, Siófok, Hungary, 2010

VIII **A. Korbely,** É. Bölcskei, K. Pintye-Hódi: Preparation of matrix systems with time-controlled release

Oral Controlled Release Dosage Forms with Eudragit® (Workshop), Budapest, Hungary, 2011

IX **A. Korbely:** Preparation of matrix systems for colonic drug delivery

10th "Ottó Clauder" Memorial Competition, Budapest, Hungary, 2011