University of Szeged

Faculty of Pharmacy

Department of Pharmaceutical Technology

Summary of the PhD thesis

DEVELOPMENT OF CO-SPRAY-DRIED CARRIER-BASED MICROCOMPOSITES FOR LOCAL PULMONARY APPLICATION OF MELOXICAM

Anita Pomázi

Pharmacist

Supervisors:

Prof. Dr. Habil. Piroska Szabó-Révész DSc

and

Dr. Rita Ambrus PhD

SZEGED

2013

University of Szeged

Graduate School of Pharmaceutical Sciences

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

Department of Pharmaceutical Technology

Supervisors: Dr. habil Piroska Szabó-Révész, DSc and

Rita Ambrus, PhD

Anita Pomázi

DEVELOPMENT OF CO-SPRAY-DRIED CARRIER-BASED MICROCOMPOSITES FOR LOCAL PULMONARY APPLICATION OF MELOXICAM

Final Exam Committee

Head

Prof. Dr. István Erős, University of Szeged, Department of Pharmaceutical Technology

Members

Dr. Miklós Vecsernyés, University of Debrecen, Department. of Pharmaceutical Technology

Dr. Róbert Gáspár, University of Szeged, Department of Pharmacodynamics and Biopharmacy

Reviewer commitee

Head

Prof. Dr. Ferenc Fülöp, University of Szeged, Department of Pharmaceutical Chemistry

Reviewers

Dr. Ildikó Bácskay, University of Debrecen, Department of Pharmaceutical Technology

Dr. György Stampf, Semmelweis University, Department of Pharmaceutics

SZEGED

2013

1 INTRODUCTION

During recent decades, the lungs have been studied as a promising route for the administration of drugs for both local treatment and systemic therapy (Clarke et al., 1984, Charokopos et al., 2009). The efficiency of treatment is related to the possibility that a substantial amount of API (Activa Pharmaceutical Ingredient) reaches the proximal airways, where it can exert its therapeutic action. This amount depends on the physiology of breathing and mucociliary clearance; the inhaler applied, and the effectiveness of the composition characteristics, such as the aerodynamic properties. As the physiological condition of the lungs varies individually, scientific studies are required to standardize the delivery systems and products (Hinds et al., 1999, Hickey et al., 2006).

Formulation of the product to be administered by the *inhalation route* is generally complicated, because it involves an active, well-defined product, and a special device. It is possible to say that the effectiveness of inhalation therapy, especially for a drug powder formulation, is dependent on factors that are related to the patient, the device and the characteristics of the formulation (Courrier et al., 2002, Chiara et al., 2008). Among pulmonary preparations, dry powder inhalers (DPIs) can ensure stability, a high payload and patient convenience (Clarke et al., 1984). The most important parameters of powder for inhalation are the particle size, particle size distribution, morphology, crystallinity of the drug and dissolution rate (Buckton 1997, Hickey et al., 2006). The DPI quality is assessed by the determination of aerodynamic properties (Wong et al., 2010) such as the aerodynamic particle size distribution, mass median aerodynamic diameter (MMAD) and fine particle fraction (FPF) (Ph. Eur. 7.2. 2012).

The particle engineering, the type of excipients and the technological processes are very important to development of DPI products. Lactose with special habit and its binary physical mixtures (API+lactose) are generally used to produce the powder form for inhalation. In this relation, novel approach is the use of D-mannitol (M) as a carrier in interactive physical mixture (Kaialy et al. 2013). M is a highly water-soluble compound with low toxicity, low hygroscopicity, gives an obvious sweet aftertaste. Another new approach is the use of M combination with co-spray-drying technique which results co-spray-dried carrier –based microcomposites.

2 AIMS

The primary aim of this study was to establish the literature background of research and development work on DPIs. We set out to study the key factors of drugs intended for use in powder form for pulmonary delivery. Another objective was to develop a carrier-based, crystalline co-spray-dried DPI product containing the low-solubility meloxicam (MX). MX can be useful for the mono- and combination treatment of cancer, pulmonary fibrosis, inflammation and pain. The pulmonary application of MX is a novelty for local anti-inflammatory treatment because it does not exhibit aspirin-like hypersensitivity reactivity and may therefore be safely applied in therapy. The main steps in our experiments were the following:

i. the identification of important factors in the preformulation for spray-drying, preparation and characterization of mannitol (M)-based co-spray-dried samples containing MX;
ii. determination of the cytotoxicity of samples by using Calu-3 cells to screen the safe MX concentration for pulmonary delivery, in order to acquire information on the availability in pulmonary formulations;
iii. study of different adjuvants (polymer and amino acid) to optimize the pulmonary formulation properties and thereby increase the respirable fraction of co-spray-dried samples, investigation of the structure of microcomposites and aerodynamic assessment of co-spray-dried powders;
iv. investigation of the accelerated stability of M-based co-spray-dried products containing MX, and the influence of the relative humidity (RH) and temperature on the physicochemical properties and aerolization parameters of the microcomposites during storage.

A new tendency in the development of DPIs is the design of carrier-based microcomposites with a particle size of 3-5 μm as pulmonary drug delivery systems involving different carriers and adjuvants. The additives are applied in small amounts in the microcomposites in order to promote physicochemical stability, wettability, dispersibility and aerodynamic properties.

3 MATERIALS AND METHODS

3.1 Materials

MX, a DPI-active pharmaceutical ingredient, was obtained from EGIS Ltd. (Hungary), β-D-M, a hydrophilic carrier, was obtained from Hungaropharma (Hungary). M is highly water-soluble compound with low toxicity, low hygroscopicity and significant stability by the DPI formulation. The polymer additives, polyvinylpyrrolidone K-25 (PVP), a stabilizing agent, and polyvinyl alcohol 3-88 (PVA), a microfine coating material, were purchased from BASF (Germany) and from ISP Customer Service GmBH (Germany), respectively. Tween 80 (TWEEN), a wetting agent, (BASF, Germany) was of pharmaceutical grade. Amino acids such as L-leucine (LEU) (Applichem, Germany) can be co-spray-dried with certain active compounds to modify drug aerolization behaviour.

3.2 Methods

3.2.1 Formulation of co-spray-dried products containing MX

The compositions of samples are presented in Table 1. The mass of each sample was 100 g and Fig. 1. shows the process of formulation of the samples. The preparation parameters and the components of the samples were optimized during the process.

Table 1: Compositions of the products.

Product	MX (g)	M (g)	PVP (g)	PVA (g)	TWEEN (g)	LEU (g)
MX-M	5	5	-	-	-	-
MX-M-PVP	5	5	0.025	-	-	-
MX-M-PVP-LEU	5	5	0.025	-	-	0.2
MX-M-TWEEN	5	5	-	-	0.05	-
MX-M-TWEEN-LEU	5	5	-	-	0.05	0.2
MX-M-PVA	5	5	-	0.1	-	-
MX-M-PVA-LEU	5	5	-	0.1	-	0.2

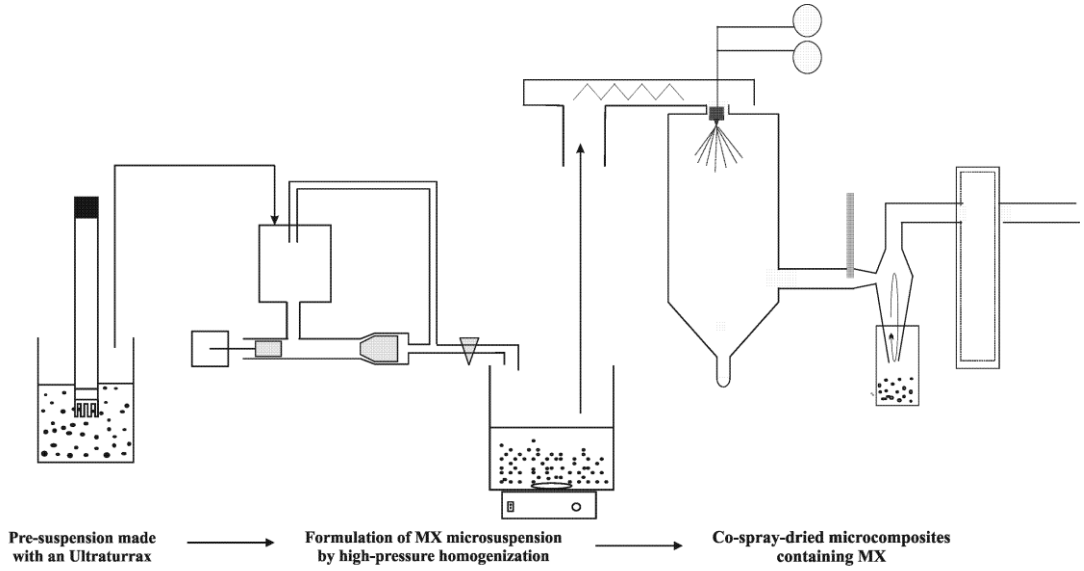

FIGURE 1: Preparation of co-spray-dried microcomposites.

Each pre-suspension was prepared from MX and M, together with TWEEN, PVP or PVA, and with LEU, and made up to 100 g with water, using an Ultraturrax operated at 24 000 rpm for 10 min. The particle size of the MX in the pre-suspension was decreased by cavitation with a high-pressure homogenizator (Avestin Emulsiflex C3, Canada) at 1500 bar for 10 cycles. The process resulted in a microsuspension of MX which contained M, PVP or PVA and LEU in dissolved form. During the co-spray-drying, the final, solid products were obtained, comprising microcomposites containing MX crystals in micronized form.

On the basis of preformulation studies the composition and the process parameters have been modified. The amount of additives was reduced and microfine coating material (PVA) and dispersity enhancer (LEU) were applied.

3.2.2 Cytotoxicity testing

The Calu-3 cell line was obtained from the American Type Culture Collection (ATCC, USA). The MTT method was used to determine the cytotoxicity of the different formulations. The absorbance was measured at 570 nm with a FLUOstar OPTIMA microplate reader (BMG LABTECH, Offenburg Germany). Absorbance values were corrected for the background absorbance, measured at 690 nm.

3.2.3 Particle size measurement

The particle size distribution was measured by laser diffraction (Mastersizer S, Malvern Instruments Ltd., Worcestershire, UK) with the following parameters: 300RF lens;

small volume dispersion unit (1000 rpm); true density of MX = 1.565 g cm^{-3} (AccuPyc 1330, Micromeritics, Norcross, USA). The particle size distribution of the microcomposites from the dry dispersion unit was also estimated by laser diffraction (Malvern Mastersizer Scirocco 2000, Malvern Instruments Ltd., Worcestershire, UK. The particle size distribution was characterized by the D(0.1), D(0.5) and D(0.9) values and the Span values were calculated.

3.2.4 Scanning electron microscopy (SEM)

The morphology of the particles was examined by SEM (Hitachi S4700, Hitachi Scientific Ltd., Tokyo, Japan). A sputter coating apparatus (Bio-Rad SC 502, VG Microtech, Uckfield, UK) was applied to induce electric conductivity on the surface of the samples. The air pressure was 1.3-13.0 mPa.

3.2.5 Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra were recorded with a Bio-Rad Digilab Division FTS- 65A/896 FTIR spectrometer (Bio-Rad Digilab Division FTS-65A/869, Philadelphia, USA) between 4000 and 400 cm^{-1}, at an optical resolution of 4 cm^{-1}. The sample, with an MX content of 0.5 mg, was mixed with 150 mg of dry KBr in an agate mortar, and the mixture was then compressed into a disc at 10 tons. Each disc was scanned 64 times at a resolution of 2 cm^{-1} over the wavenumber region 4000-400 cm^{-1}.

3.2.6 Contact angle

The OCA Contact Angle System (Dataphysics OCA 20, Dataphysics Inc., GmbH, Germany) was used for studies of the wettability of the carrier systems, and products containing MX. 0.15 g of powder was compressed under a pressure of 1 ton by a Specac hydraulic press (Specac Inc., USA).

3.2.7 Water content determination by thermogravimetry (TGA)

Residual water content was analysed by TG-DTA with a Mettler Toledo TG 821^e thermal analysis system with the STAR^e thermal analysis program V9.1 (Mettler Inc., Schwerzenbach, Switzerland) under a constant flow of dry nitrogen gas flow of 100 ml min^{-1}.

3.2.8 *In vitro release*- Modified paddle method

The paddle method with the USP dissolution apparatus (USP dissolution apparatus, type II Pharma Test, Heinburg, Germany) was used to examine MX and the products. The medium was 100 ml of phosphate buffer of pH 7.4 ± 0.1 (temperature: 37 ± 1 °C). The basket

was rotated at 100 rpm and sampling was performed up to 120 min. The MX contents of the samples were determined by spectrophotometry (ATI-UNICAM UV/VIS Spectrophotometer, Cambridge, UK) at 362 nm.

3.2.9 Statistical analysis of MX dissolution profile

The percentage dissolution efficiency (%DE) for each sample was calculated as the percentage ratio of the area under the dissolution curve up to time *t* to that of the area of the rectangle described by 100% dissolution at the same time as follows:

$$\%DE = \left(\frac{\int_0^t y \times dt}{y_{100} \times t} \right) \times 100 \quad (1)$$

The mean dissolution time (MDT) was calculated via the following expression:

$$MDT = \frac{\sum_{i-1}^{n} t_{mid} \Delta M}{\sum_{i-1}^{n} \Delta M} \quad (2)$$

where i is the dissolution sample number, n is the number of dissolution times, t_{mid} is the time at the midpoint between times t_i and t_{i-1}, and ΔM is the amount of MX dissolved (mg) between times t_i and t_{i-1}.

3.2.10 In vitro assessment of lung deposition

The Next Generation Impactor (NGI) was applied in the case of the optimization study, and the Andersen Cascade Impactor (ACI) (Copley Scientific Ltd., Nottingham, UK) for stability testing. The products were filled into hard gelatine capsules (size 3). The inhaler device applied was a plastic RS01 (Plastiape, Italy). Seven stages were coated with a 1% w/v Span 85-cyclohexane mixture to control particle rebound. All samples were quantified by UV/Vis spectrophotometry at 362 nm.

3.2.11 Stability testing

Stability tests were carried out as recommended by the international guidelines specified in ICH (International Conference on Harmonization) Q1A (R2) - Stability Testing of new Drug Substances and Products. Accelerated testing was performed at 40 ± 2 ºC with 75 ± 5% RH. Under both conditions, samples were stored in hard gelatine capsules (size 3) (Capsugel, Belgium) in open containers; the duration of storage was 6 months. Sampling was carried out after 0 and 10 days, and 1, 2, 3 and 6 months.

3.2.12 Statistical analysis

All measurements were carried out in triplicate and values are reported as means ± SD unless otherwise noted. Statistical calculations were performed with the software Statistical for Windows. To identify statistically significant differences, one-way ANOVA with t-test analysis was performed. Probability values of $p < 0.05$ were considered significant.

4 Results

4.1 Preformulation studies of M-based co-spray-dried samples

The dissolution curves present the dissolution profiles of MX, MX spd and the co-spray-dried systems (Fig. 2). It was found that the microparticles containing MX showed favourable dissolution properties at physiological conditions. The products containing the carrier as M and adjuvants (PVP, TWEEN) gave close to 100% release in the first 5 min. The dissolution in the first 5 min was ~30 times higher than that for MX.

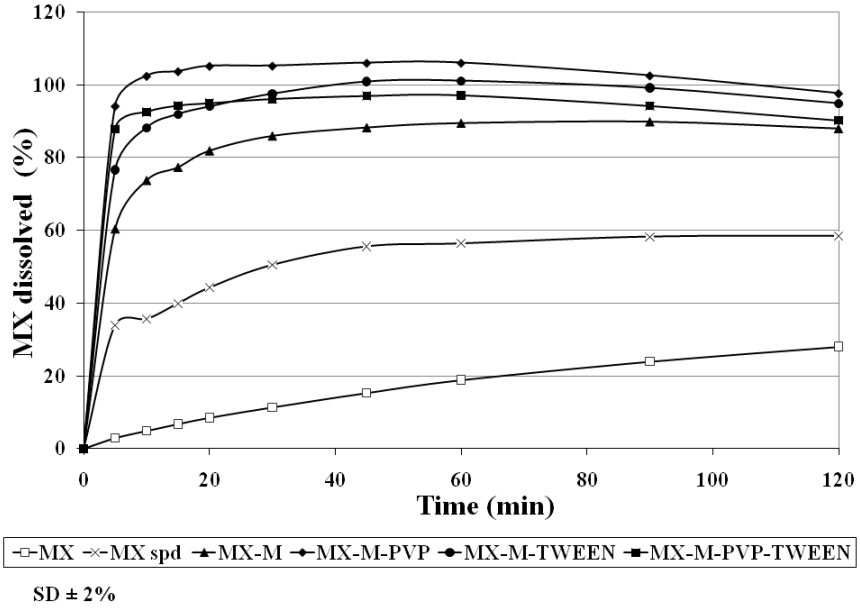

FIGURE 2: Extent of dissolution of MX from co-spray-died samples in phosphate buffer

Determination of cytotoxicity of spray-dried MX and microcomposites

Cytotoxicity testing is required for the novel inhalation delivery systems. Ten different concentrations of products between 0.01 and 50 mg ml^{-1} were applied, i.e. 0.005-25 mg ml^{-1} MX content. It was found that, up to a concentration of 0.1 mg ml^{-1} all of the products are safely applicable in the lung (Fig. 3). Between 1 and 10 mg ml^{-1}, only the MX-M-PVP-TWEEN products resulted in more than 80% cell viability.

The cytotoxicity tests indicated that, in the case of MX-M-PVP-TWEEN, the dose can be increased up to 10 mg ml^{-1}, including a maximum of 5 mg ml^{-1} MX, and the applicable amount of this drug can therefore be increased 300-fold through use of our formulation.

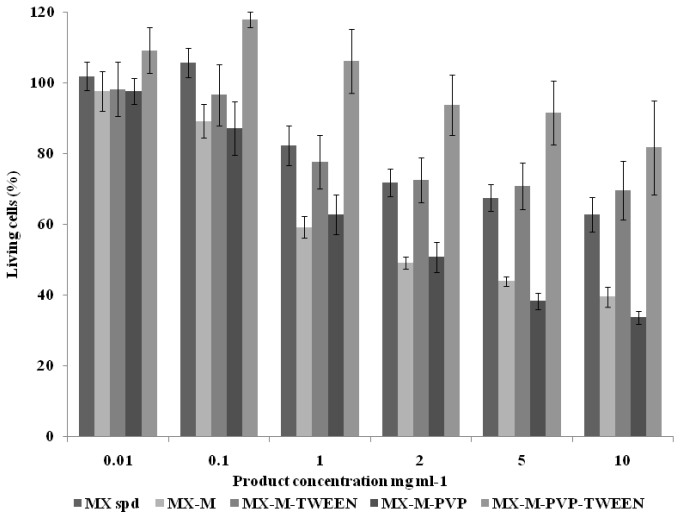

FIGURE 3: Cytotoxicity of MX spd and products containing MX.

4.2 Optimization of the specific product parameters and applied additives for the aerodynamic assessment of MX

Size analysis of the co-spray-dried samples revealed that the particle size was typical of micronized powders (< 10 µm), which is optimal for pulmonary delivery (Table 2). The distribution became homodisperse when LEU was applied.

Table 2: Particle size distributions of dried powders.

Product	D(0.1) (µm)	D(0.5) (µm)	D(0.9) µm)
raw MX	8.56	30.85	63.71
raw M	5.32	36.37	65.45
MX-M	1.38	3.09	243.68
MX-M-PVP	1.65	3.29	6.19
MX-M-PVP-LEU	1.53	3.05	5.68
MX-M-TWEEN	2.48	5.09	10.52
MX-M-TWEEN-LEU	2.08	4.16	8.88
MX-M-PVA	1.57	3.11	5.81

The crystal morphology is a critical parameter for DPI development, because the particle shape affects the aerodynamic behaviour and thus lung deposition. The particles

produced with the polymers (PVP and PVA) (*C* and *E*) appeared to be spheroidal without aggregation, and this could be a beneficial feature in the inhalatory application of these powders (Fig. 4). The spherical and regular forms met the requirements for formulation for DPIs (MX-M, MX-M-PVA, MX-M-PVP and formulations with LEU).

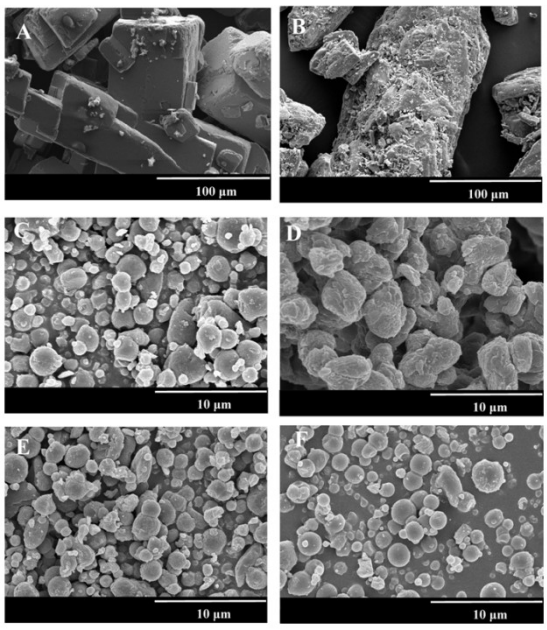

FIGURE 4: SEM images of MX (*A*) and M (*B*) before spray-drying, MX-M-PVP (*C*), MX-M-TWEEN (*D*), MX-M-PVA (*E*), and a control sample of MX after co-micronization with M in a ratio of 1:1 (*F*).

It was found that the amounts of drug deposited on the throat, on stages 1–7 and on the filter, expressed as percentages of the total amount of powder recovered (Fig. 5 and 6) PVP or PVA formulated with LEU reduced the impact of MX in the throat (< 20%) and increased its deposition in the lowest stages.

With the exception of the samples containing TWEEN, all of the products exhibited favourable aerosolization characteristics, these powder particles impacting on stages 2-5. The aerodynamic properties of MX-M-PVP and MX-M-PVA were further improved ($p < 0.05$) when LEU was introduced into the formulation. The FPFs were increased, in both cases to more than 53%. The use of LEU as excipient proved effective in reducing the cohesion between the particles and improving the powder dispersion delivered from the DPI.

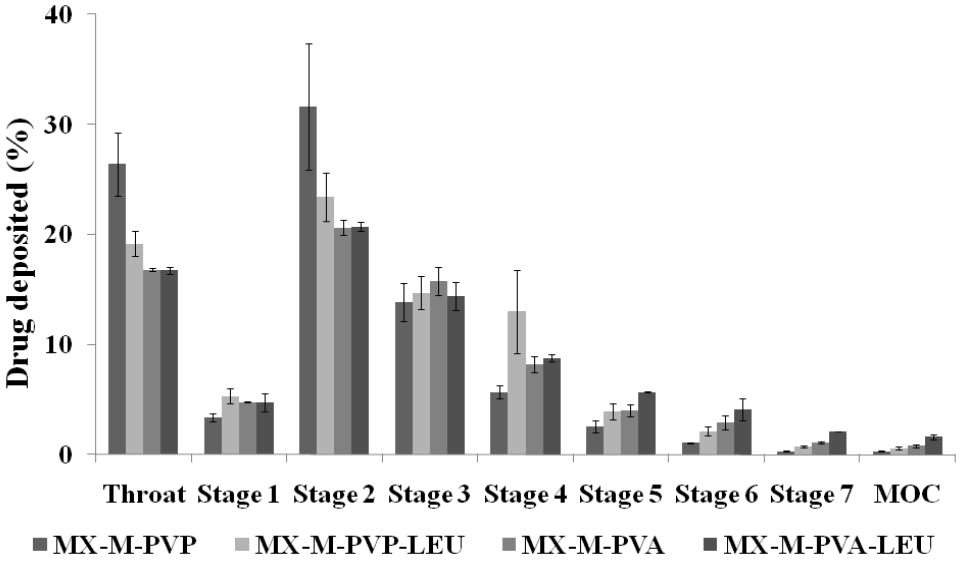

FIGURE 5: Drug deposition profiles of co-spray-dried microcomposites in the NGI at 60 l min^{-1} via the RS01 (n = 3).

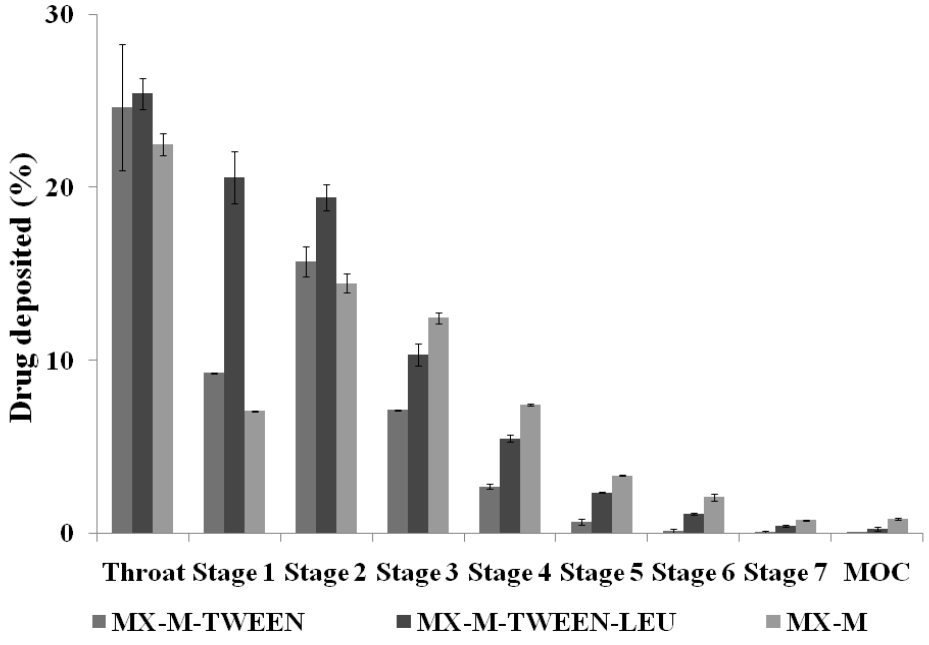

FIGURE 6: Drug deposition profiles of co-spray-dried microcomposites in the NGI at 60 l min^{-1} via the RS01 (n = 3).

4.3 Physicochemical stability testing and influence of humidity and temperature on aerodynamic properties

Accelerated testing was performed at 40 ± 2 ºC with 75 ± 5% RH. Samples were stored in hard gelatine capsules (size 3) (Capsugel, Belgium) in open containers; the duration of storage was 6 months. Sampling was carried out after 0 and 10 days, and 1, 2, 3 and 6 months.

The spectra revealed no difference in the positions of the absorption bands, especially with respect to OH, =O and NH, thereby providing evidence of the absence of H-bonding interactions in the solid state between the polymer and MX. In MX-M-PVP-LEU, the interactions are reduced during storage, as indicated by the decreases in the associated O-H bonds and H-bonding in the interval 3500-3100 cm^{-1} (Fig. 7, 8). The H-bonding did not change during storage in the case of MX-M-PVA-LEU.

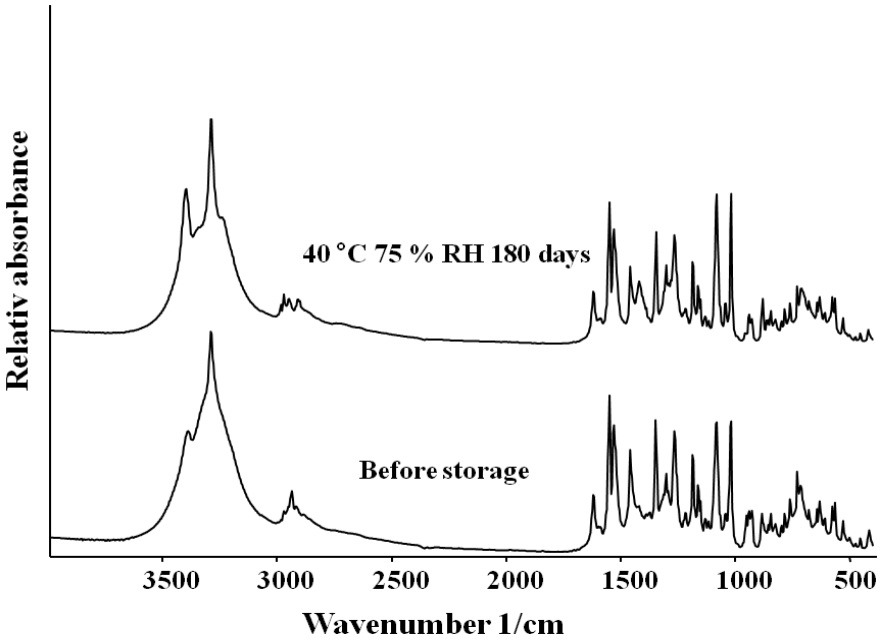

FIGURE 7: FT-IR analysis of MX-M-PVP-LEU before and after storage. The characteristic range is 3500-3100 cm^{-1}.

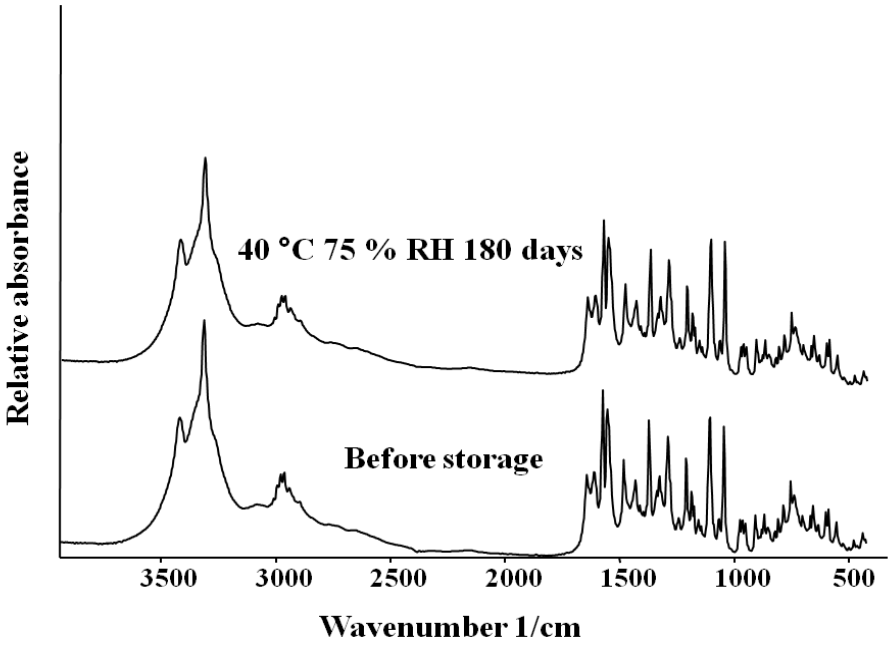

FIGURE 8: FT-IR analysis of MX-M-PVA-LEU before and after storage. The characteristic range is 3500-3100 cm^{-1}.

During stability testing, it can be concluded that PVP or PVA formulated with LEU increased the impact of MX in the device and throat and reduced its deposition in the lowest stages under both conditions. MX-M-PVA-LEU exhibited favourable aerosolization characteristics, these powder particles impacting at a higher rate on stages 2-5, and the changes in deposition in the throat and the device after storage were not pronounced.

Table 3: Deposition of co-spray-dried microcomposites in the cascade impactor at 60 l min^{-1} via RS01 (n = 3).

Product	FPD (mg)	FPF (%)	MMAD (μm)
MX-M-PVP-LEU before storage	0.60 ± 0.07	53.05 ± 1.13	3.52 ± 0.13
MX-M-PVP-LEU after storage	0.24 ± 0.02	41.16 ± 2.81	3.91 ± 0.45
MX-M-PVA-LEU before storage	0.64 ± 0.05	57.50 ± 1.0	3.04 ± 0.17
MX-M-PVA-LEU after storage	0.54 ± 0.03	52.5 ± 2.2	3.39 ± 0.11

After storage, the FPFs of the samples were reduced because of the fine particle aggregation (Table 3). This is connected with the increased capillary interaction and/or moisture adsorption of PVP at higher RH (75%). The FPF of the PVA-containing samples

(MX-M-PVA-LEU) was relatively high before storage (57.50 ± 1.0%) and after storage at 40 ºC and 75% RH was 52.5 ± 2.2%. The MMAD and FPF of the PVA embedded formulations did not change significantly during storage. PVP and PVA, as polymer agents, exhibited an aggregation-inhibitory effect and ensured the distribution of the individual particles. Such particles underwent disaggregation in the air flow of the device and their FPFs were improved.

5 Summary

The primary aim of this study was to carry out research relating to the development of DPI products. We studied the key features of powders for drugs intended for use in pulmonary delivery. Another objective was to develop a carrier-based, crystalline co-spray-dried DPI product containing low-soluble MX. Various approaches to carrier-based formulations were investigated in order to enhance the delivery of MX.

i. The particle size and morphology of the MX and its composites were investigated via the additives and the process parameters. Instead of the classical approach based on micronization to prepare drug particles followed by blending with a carrier, co-spray-drying of the MX/M/additives was performed in an one-step process. Our results point to an alternative methodology with which to achieve the rapid release of poorly-soluble drugs.

ii. Preliminary cell toxicity studies have shown that the use of additives at the given concentrations has no effect on the viability of Calu-3 cells over a 24 h period. The minimum level of cell viability was higher and non-significantly different from that exhibited with MX alone (~ 70%).

iii. The product parameters were optimized with PVA, PVP, TWEEN and LEU as additives in order to improve the drug deposition in the lung. The mean particle size in the M-based systems was in the required range (3-5 μm). We found that the polymers (PVA and PVP) modified the surface of the MX co-sprayed with M and exerted a satisfactory aggregation-inhibitory effect, thereby furnishing individual particles. The presence of LEU further improved the respirable fraction of MX, and resulted in optimum deposition in the *in vitro* assessment. The FPFs of the microparticles containing the polymers were increased, in some cases to more than 53%. Overall, this study has demonstrated that the addition of LEU in the MX-M co-spray-dried systems (MX-M-PVA-LEU and MX-M-PVP-LEU) produced co-spray-dried inhalation powders containing composite particles applicable for bronchial deposition.

iv. The accelerated stability testing of M-based co-spray-dried MX-containing DPI systems was performed in order to determine the influence of the RH and temperature on the physicochemical properties and aerolisation parameters. We found that, MX-M-PVA-LEU was stable in the accelerated stability studies; only minor changes were observed in the physicochemical properties and aerodynamic performance.

6 Practical aspects

This study has demonstrated the ability of micronization of API and spray-drying techniques to produce microcomposites containing crystalline MX and with particle dimensions suitable for pulmonary administration (< 5 μm). The pulmonary application of MX is a novelty for local anti-inflammatory treatment; at present, MX-containing DPI products are not marketed for pulmonary therapy.

- *Innovative technology:* co-spray-drying of MX from an aqueous microsuspension was used to prepare the novelty-type of microcomposites. The final crystalline microcomposites is prepared in an one-step process, which additionally ensures the respirable particle size range (3-5 μm), the spherical form and crystallinity property of the product.
- *Innovative product:* The formulated microcomposite is new tendency in pulmonary drug delivery. The hydrophilic carrier (M) and additives (PVP, PVA, LEU) are located on the surface of the API with a hydrophobic character therefore the microcomposites result in the rapid drug release. M was primarily chosen as a carrier in this study because its particle size can be readily controlled by spray-drying and the spray-dried powder is crystalline and physically stable. The sample containing PVA proved to be stable in accelerated stability studies, and is an innovative product which may be considered suitable for scaled-up processes and pulmonary application.

The innovative technology and product appear to be of great potential in pulmonary drug delivery systems.

PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

1. **Pomázi** A., Ambrus R., Sipos P., Kása P., Szabó-Révész P.
   Formulation of Meloxicam microparticles for dry powder inhalation
   Pharmaceutical Journal of Slovenia 59 (2008) 119-121.
   IF:-

2. **Pomázi Anita,** Szabóné Révész Piroska, Ambrus Rita
   Pulmonális gyógyszerbevitel, DPI készítmények formulálásának szempontjai
   Gyógyszerészet 53 (2009) 397-404.
   IF.: -

3. Ambrus R., **Pomázi A.**, Réti-Nagy K., Fenyvesi F., Vecsernyés M., Szabó-Révész P.
   Cytotoxicity testing of carrier-based microcomposites for DPI application
   Pharmazie 66 (2011) 549-550.
   IF.: 0.869

4. **Pomázi A.**, Ambrus R., Sipos P., Szabó-Révész P.
   Analysis of co-spray-dried meloxicam-mannitol systems containing crystalline microcomposites
   Journal of Pharmaceutical Biomedical Analysis 56 (2011) 183-190.
   IF.: 2.733

5. **Pomázi A**., Buttini F, Ambrus R., Colombo P., Révész P.
   Effect of polymers for aerolisation properties of mannitol-based microcomposites containing meloxicam
   European Polymer Journal 49 (2013) 2518-2527.
   IF: 2.739

6. **Pomázi A**, Ambrus R., Szabó-Révész P.
   Physicochemical stability and aerolization performance of mannitol-based microcomposites
   Journal of Drug Delivery Science and Technology
   accepted for publication (2014)
   IF: 1,088

OTHER PUBLICATIONS

1. Ambrus R., **Pomázi A.**, Aigner Z., Kocbek P., Kristl J. Szabóné Révész P.
   Nanotechnológia, nanokristályok a gyógyszerformulálásban
   Gyógyszerészet 52 (2008) 259-264
   IF.:-

2. **Pomázi A**., Ambrus R., Sipos P., Otomo N., Szabó-Révész P.
   Effect of a sucrose ester on co-micronized mannitol-based drug formulation
   European Journal of Pharmaceutical Sciences 38 (1) (2009) Suppl. 73-74
   IF.: -

3. Ambrus R., **Pomázi A**., Szabóné-Révész P.
   A nanotechnológia mint új irányvonal a hatóanyagkristályok formulálásában
   Magyar Kémiai Folyóirat 3 (2010) 96-100
   IF.: -

4. Ambrus R., **Pomázi A**., Kristl J., Kocbeck P., Szabó-Révész P.
   Effect of high-pressure homogenization on the formulation of micro- and nanocrystals containing poorly watersoluble meloxicam
   Scientia Pharmaceutica 2010. 78: 571 doi:10.3797/scipharm.cespt.8.LNM03
   IF.: -

PRESENTATIONS RELATED TO THE SUBJECT OF THE THESIS

Oral presentations

Pomázi Anita
Mikrorészecskék előállítása és vizsgálata porinhalációs készítmények formulálása céljából I.
Szent-Györgyi Albert Szakkollégium Konferencia
Budapest, 2008. március.

Pomázi Anita
Lokális hatású porinhalációs rendszerek fejlesztése és gyógyszerforma vizsgálata
X. Clauder Ottó emlékverseny
Budapest, 2011. október.

Pomázi A., Ambrus R., Révész P.
Meloxicam tartalmú porinhalációs rendszerek fejlesztése és stabilitásának vizsgálata
Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium '12
Debrecen, 2012. szeptember 13-14.

Pomázi A., Ambrus R., Révész P.
Meloxicam-tartalmú porinhalációs készítmény stabilitásának vizsgálata
XVII. Gyógyszertechnológiai és IX. Gyógyszer az ezredfordulón konferencia
Siófok, 2012. szeptember 27-29.

Poster presentations

A. Pomázi, R. Ambrus, P. Sipos, P. Kása, P. Szabó-Révész
Formulation of Meloxicam microparticles for dry powder inhalation
7th Central European Symposium on Pharmaceutical Technology & Biodelivery Systems
Ljubljana, Slovenia, September 2008.

A. Pomázi., F. Buttini., R. Ambrus., P. Colombo., P. Szabó-Révész
Development of dry powder formulations of meloxicam for pulmonary therapy
8th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology
Istanbul, 2012. March 19-22.

A. Pomázi., F. Buttini., R. Ambrus., P. Colombo., P. Szabó-Révész
Effect of polymers for aerolisation properties of mannitol-based microcomposites containing meloxicam
Advanced Macromolecular Systems Across the Length Scales Symposium
Siófok, 2012. június 3-6.

Financial support

This research was supported by the **European Union** and the **State of Hungary, co-financed by the European Social Fund** in the framework of TÁMOP 4.2.4. A/2-11-1-2012-0001 'National Excellence Program'.