Aerodynamic and structural evaluation of microcomposites containing meloxicam potassium

R. Ambrus, A.Chvatal, A. Pomazi, P. Szabó-Révész*

Department of Pharmaceutical Technology, University of Szeged, Szeged, Hungary

***e-mail: arita@pharm.u-szeged.hu**

Introduction, aim

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

A new possibility in drug formulation is applying Meloxicam in a salt form (Meloxicam Potassium (MXP)) to develop DPI. Using its salt form could be a novel application, trough alternative routes, because it has never used before in the drug therapy.

Our aims were therefore to apply aqueous solution of MXP containing additives in different concentrations (using one-step green technology), which help to improve the aerodynamic properties of the product.

Experimental methods

◆**Materials**

Meloxicam Potassium (MXP) purchased from EGIS Ltd., Budapest, Hungary, PVA 3-88 from ISP Customer Service GmbH, Cologne, Germany, Leucin (LEU) from Hungaropharma, Budapest, Hungary.

◆**Preparation of products**

The heated solutions containing MXP,LEU and/or PVA, were spray-dried with a Büchi Mini Dryer B-191 (Fig. 1).

◆**Particle characterization**

The particle size distribution of the microcomposites was also estimated by laser diffraction (Malvern Mastersizer Scirocco 2000, Malvern Instruments Ltd., Worcestershire, UK). The morphology of the microcomposites was examined by SEM (Hitachi S4700, Hitachi Scientific Ltd., Tokyo, Japan).

Andersen Cascade Impactor (ACI) (Copley Scientific Ltd., Nottingham, UK) is used for measuring the mass distribution of pharmaceutical aerosols via the aerodynamic diameter using 60Lmin^{-1} flow rate. The products were filled into hard gelatine capsules (size 3). The inhaler device applied was a plastic RS01 (Plastiape, Italy).

◆**Structural investigations**

XRPD was carried out in order to determine the crystalline form and crystallinity of the produced materials. Samples were measured with a Bruker D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany). Thermoanalitical measurements were also applied (Mettler Toledo, Stare program W9, Mettler Inc. Swerzenbach Switzerland)

Results

◆**Particle characterization**

The particle sizes of the samples satisfied the pharmacopoeial requirements, the average size was between 2.5-4.5 μm. Moreover, the particle size distribution of MXP and many products was heterodispers only MXPspd, MXP-PVA0.1 and MXP-LEU2-PVA0.1 resulted homogenous distribution (Fig. 2-3 and Table 1). The crystal morphology is a critical parameter for DPI development, because the particle shape affects the aerodynamic behaviour and thus lung deposition. The effect of spray-drying procedure on the morphology of particles was determinative. The nearly spherical form of the microcomposites could be advantageous for suitable pulmonary depositions.

Fig. 4 and Table 2 show the amounts of drug deposited on the throat, on stages 7 and on the filter of ACI, expressed as percentages of the total amount of powder recovered. All of the products exhibited favourable aerolisation characteristics, these powder particles impacting on stages 2-5. Bigger concentration of PVA without LEU resulted only poor aerodynamic character, because of the sticky of the particles. But PVA in small concentration shown an excellent result. The MMAD values were around 3 μm, and 46-66 % FPF could be acceptable for pulmonary application and presented better result compare with the marketed DPI products.

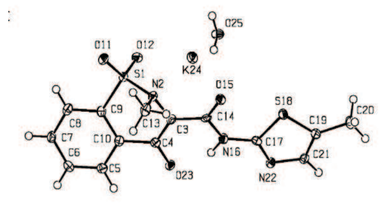
◆**Structural investigations**

Evaluation of the structural analysis using DSC and XRPD, we can conclude that the raw MXP is crystalline and additives are semi-crystalline materials. The crystalline form of MXP turned to amorphous character in the presence of PVA (crystallization inhibitor effect). When LEU was applied the characteristic peaks of MXP on the XRPD patterns and its melting on the DSC curves were detected(Figs. 5-7).

The goal of our study was to find the optimized co-spray drying parameters, sample compositions for the preparation of DPI form of a novel MXP salt monohydrate. The MXP-PVA0.1 and MXP-LEU2-PVA0.1 could be an innovative products which may be considered suitable for scaled-up processes and pulmonary application. It is a novel possibility in anti-inflammatory treatment and for the mono- and combination therapy of cancer, pulmonary fibrosis and pain.

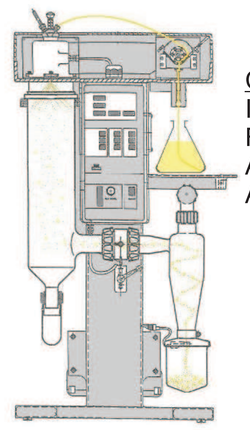
"This project was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (2014-2017)."

Figure 1. Compositions and preparation procedure



Meloxicam-Potassium(MXP)
Structure: $C_{14}H_{13}KN_3O_5S_2$
M_w: 407.5
Egis Company, Budapest
Pattent: WO2006064298A1
water solubility: 13.1 ± 0,015 mg/mL

Samples	MXP	PVA	LEU
MXP_{SPD}	1	-	-
MXP-LEU1	1	-	1
MXP-LEU2	1	-	2
MXP-PVA0.1	1	0.1	-
MXP-PVA0.25	1	0.25	-
MXP-LEU1-PVA0.25	1	0.25	1
MXP-LEU2-PVA0.1	1	0.1	2



Co-spray-drying procedure:
Inlet temperature: 140 °C
Feed rate: 005 %
Aspirator air: 600 L/min
Aspirator rate: 75 %

Figure 2. Particle size distribution

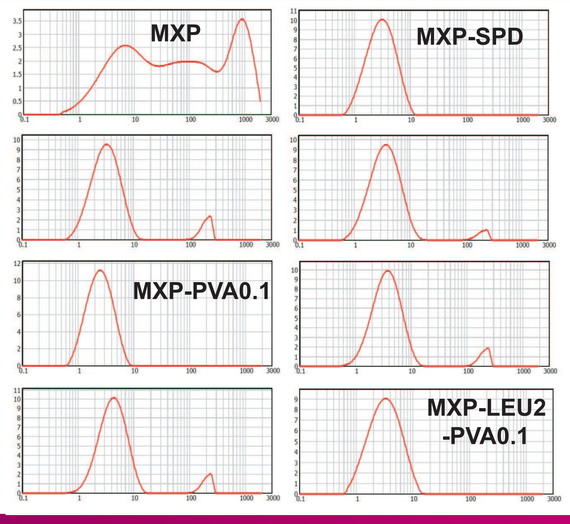


Figure 3. Morphology of the products

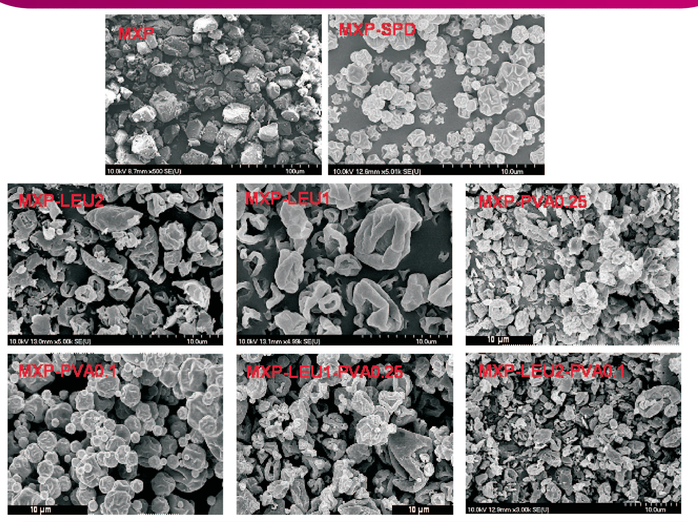


Table 1. Particle size analyses

Samples	D(0.1) [μm]	D(0.5) [μm]	D(0.9) [μm]
MXP	3.35	58.43	993.75
MXP_{SPD}	1.40	3.01	6.16
$MXP\text{-}LEU_1$	1.53	3.39	8.80
$MXP\text{-}LEU_2$	1.16	3.66	8.34
$MXP\text{-}PVA_{0.1}$	1.24	2.44	4.69
$MXP\text{-}PVA_{0.25}$	1.75	3.83	9.03
$MXP\text{-}LEU_1\text{-}PVA_{0.25}$	2.07	4.42	10.24
$MXP\text{-}LEU_2\text{-}PVA_{0.1}$	1.38	3.21	7.12

Table 2. Aerodynamic properties

Samples	MMAD (μm)	FPF (%)
MXP	12.11	10.50
MXP_{SPD}	3.18	55.97
$MXP\text{-}LEU_1$	3.91	49.10
$MXP\text{-}LEU_2$	3.67	54.78
$MXP\text{-}PVA_{0.1}$	3.04	66.32
$MXP\text{-}PVA_{0.25}$	7.23	21.53
$MXP\text{-}LEU_1\text{-}PVA_{0.25}$	3.05	46.63
$MXP\text{-}LEU_2\text{-}PVA_{0.1}$	2.83	57.58

FPD: Fine Particle Dose
FPF: Fine Particle Fraction
MMAD: Median Mass Aerodynamic Diameter

Figure 4. Aerodynamic-pattern by Cascade impactor

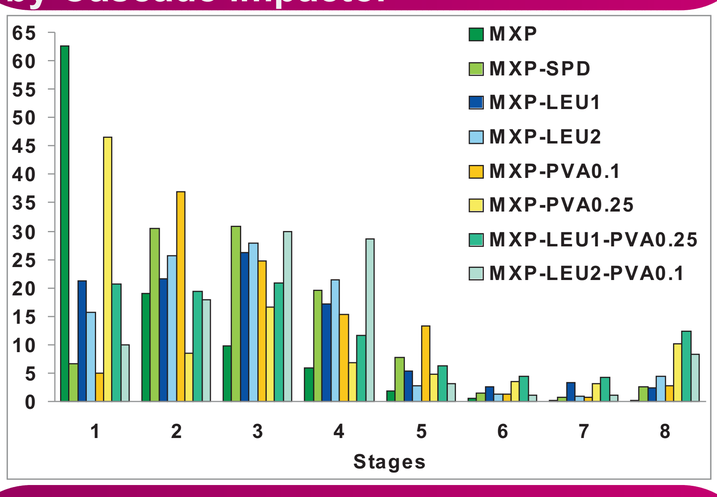


Figure 5. Structure of the raw samples

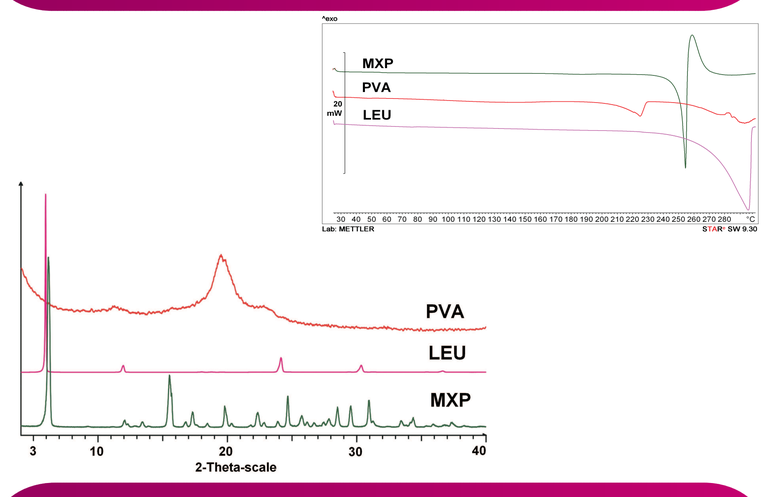


Figure 6. DSC curves of the samples

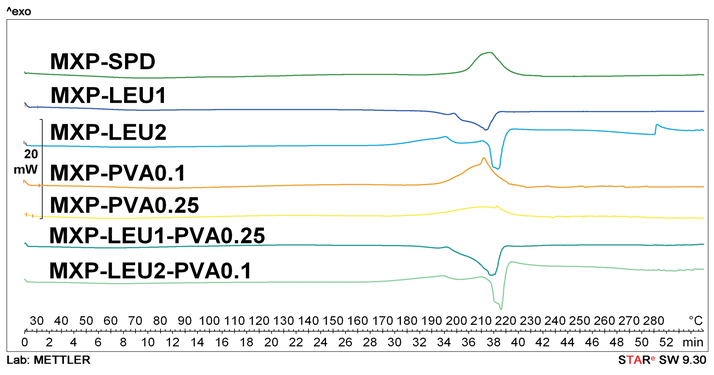


Figure 7. XRPD patterns of the samples