Development of dry powder carrier systems for pulmonary application

R. Ambrus, B. Szabó, P. Szabó-Révész*

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

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

Introduction, aim

The effectiveness of inhalation therapy, especially for a drug dry powder formulation (DPI), is dependent on factors that are related to the patient, the device and the characteristics of the formulation.

The engineered drug particles theirselves are typically highly cohesive and display poor aerosolization properties, necessitating the addition of a coarse carrier particle to the micronized drug.

Our aims were to develop mannitol-based carrier systems containing aqueous and ethanolic solution during co-spray-drying procedures and application of different types of additives could help the DPI formulation of also watersoluble and insoluble drug.

Experimental methods

Materials

Mannitol (M), a hydrophilic carrier, was obtained from Hungaropharma Budapest, Hungary; PVA 3-88 is ordere from ISP Customer Service GmBH, Cologne, Germany; amino acid such as L-leucine (LEU) is from Applichem, Germany. Hydroxypropyl beta cyclodextrin as complex former and permeability improving agent is from Cylolab Ltd (Budapest, Hungary).

Sample preparation

The procedure of spray-drying (spd) was from a aqueous(w) and ethanolic solution (10% of EtOH and 90 % of water (mix)) of M, LEU with/without LEU or CD or PVA using a Büchi Mini Dryer B-191. The amount of additives was determined according to our preliminary work. The amount of CD was calculated according its complex former ratio e.g. 1:1;2:1;4:1. (Fig. 1-2).

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

In our present work three suitable ways were applied to developed pulmonary drug delivery systems (PDDS) of different drugs. During spray-drying procedure aqueous and ethanolic solution of the excipients could be applied, which help to solve or disperg the drug. If the drug is very poorly soluble in water or ethanol/water mixture, the present of CD can help by formation of inclusion complex. According to the morphology, the size, size distribution and fine particle fraction (FPF) calculation of the samples, they are applicable as PDDS (Fig. 2).

Particle characterization

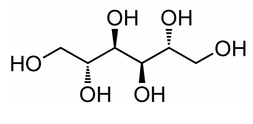
The particle sizes of the samples satisfied the pharmacopoeial requirements, the average size was between 2.5-5.5 µm and resulted homogenous distribution (Table 1). According to the aerodynamic measurements the FPF are higher compare with the maketed products.The crystal morphology is a critical parameter 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 spherical form of the microcomposites could be advantageous for suitable pulmonary depositions (Figs. 3-4).

Structural investigations

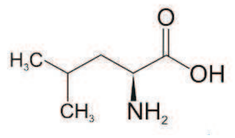
Evaluation of the structural analysis using DSC and XRPD, we can conclude that the raw M is crystalline and additives are semi-crystalline/amorphous materials. The samples are mainly crystalline, the degree of the crystallinity decreased and because of the increased concentration of CD turned to amorphous character. (Figs. 5-8).

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

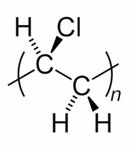
Figure 1. Materials and preparation procedure



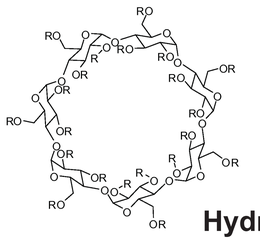
Mannitol



Leucin



PVA



Hydroxypropyl beta cyclodextrin

Sample	M	PVA	LEU	CD	solvent
M-w	5	-	-	-	water
M-mix	5	-	-	-	mix
M-PVA-w	5	0.2	-	-	water
M-PVA-mix	5	0.2	-	-	mix
M-LEU-w	5	-	0.4	-	water
M-LEU-mix	5	-	0.4	-	mix
M-LEU-$CD_{0.9}$	5	-	0.4	0.9	mix
M-LEU-$CD_{1.8}$	5	-	0.4	1.8	mix
M-LEU-$CD_{3.6}$	5	-	0.4	3.6	mix

Co-spray-drying procedure:

Inlet temperature: 140 °C
Feed rate: 75 %
Apirator air: 600 L/min
Aspirator rate: 5 %

Büchi Mini Dryer B-191

Figure 2. Development-protocol

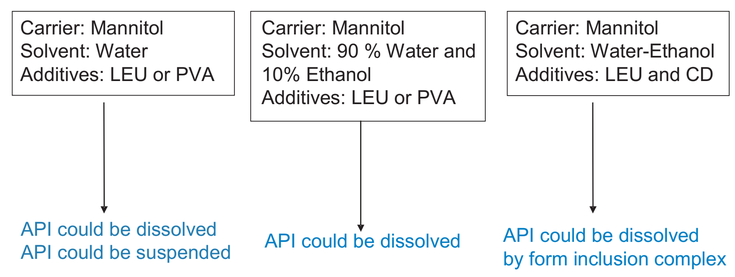


Table 1. Size and Aerodynamic properties

Sample	D 0.1 (µm)	D 0.5 (µm)	D 0.9 (µm)	FPF (%)
M-w	1.38	2.91	4.63	81.45
M-mix	1.51	2.79	4.57	70.27
M-PVA-w	2.95	6.36	10.18	25.85
M-PVA-mix	2.41	4.72	9.49	38.91
M-LEU-w	2.27	4.05	8.32	72.33
M-LEU-mix	1.38	2.83	5.57	59.51
M-LEU-$CD_{0.9}$	1.61	3.30	6.46	46.52
M-LEU-$CD_{1.8}$	2.35	5.47	10.22	40.78
M-LEU-$CD_{3.6}$	3..95	8.25	12.10	36.91

Figure 3. Morphology of the products

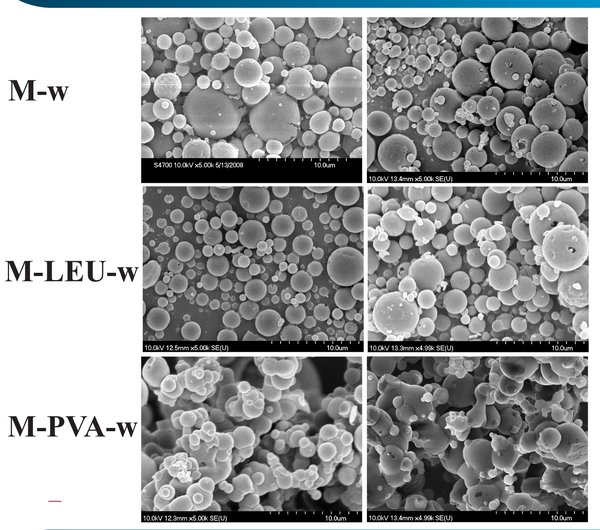


Figure 4. Morphology of the products

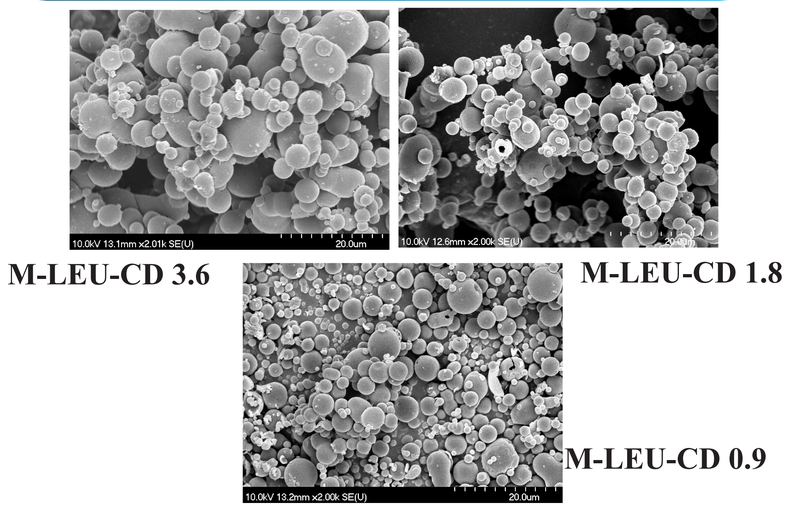


Figure 5. DSC curves of the samples containing PVA

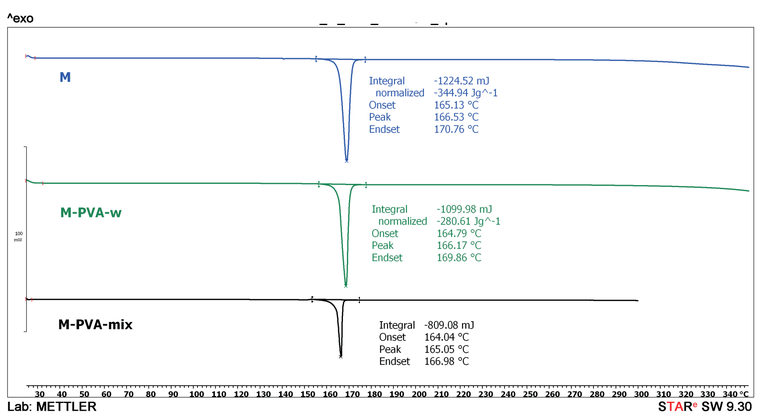


Figure 6. DSC curves of the samples containing LEU

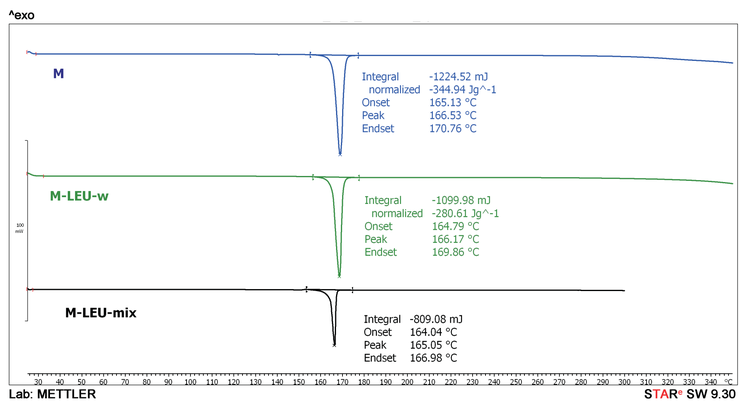


Figure 7. XRPD patterns of the samples containing mannitol

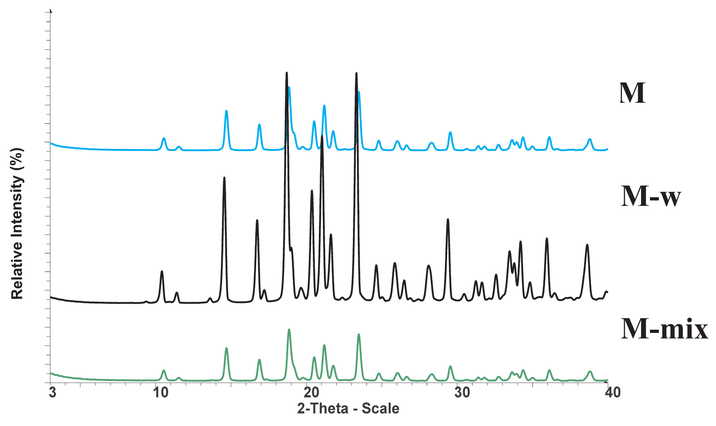


Figure 8. XRPD patterns of the samples containing cyclodextrins