

Nano-in-micro formulation for further pulmonary administration of meloxicam in lung diseases

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INTRODUCTION

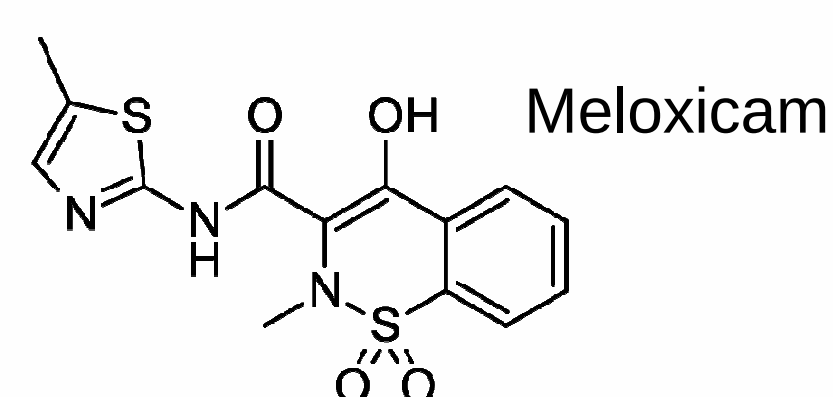
Formulation of inhalable carrier-free dry powders, consisting of nanoparticles are gaining much attention in the pharmaceutical research area. The appropriate particle engineering technique is the most important factor to get enhanced aerosolization properties and improved therapeutic effect.

AIMS

Our aim was to produce inhalable nano-structured dry powders with spray drying, containing poorly water-soluble meloxicam and special additives. We also aimed to characterize the habit, physicochemical and aerodynamic properties of the prepared samples.

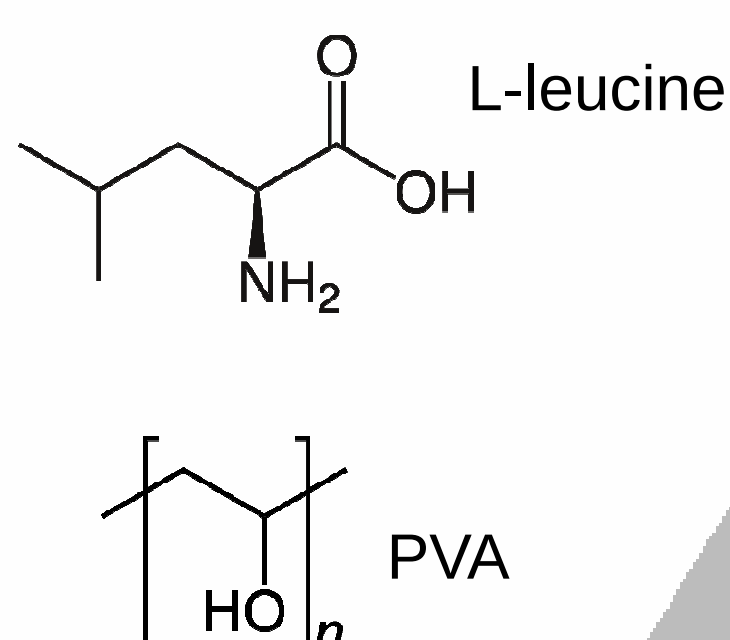
MATERIALS

Meloxicam (Egis Pharmaceuticals PLC., Hungary) (MX) was used as a model active ingredient, which is a non-steroidal anti-inflammatory agent. As additives we used polyvinyl alcohol 3-88 (PVA), (ISP Customer Service GmbH, Germany) and L-leucine (LEU), (AppliChem, Germany).



MICROMETRIC PARAMETERS

The particle size distribution and morphology were determined with laser diffraction (Malvern Mastersizer Scirocco 2000, Malvern Instruments Ltd.) and scanning electron microscopy (Hitachi S4700, Hitachi Scientific Ltd.).



Samples	D[0.5] (μm)
1. nanoMX1_LEU0	3.19
2. nanoMX1_LEU0.5	3.80
3. nanoMX1_LEU1	4.40

Table 1. Particle size

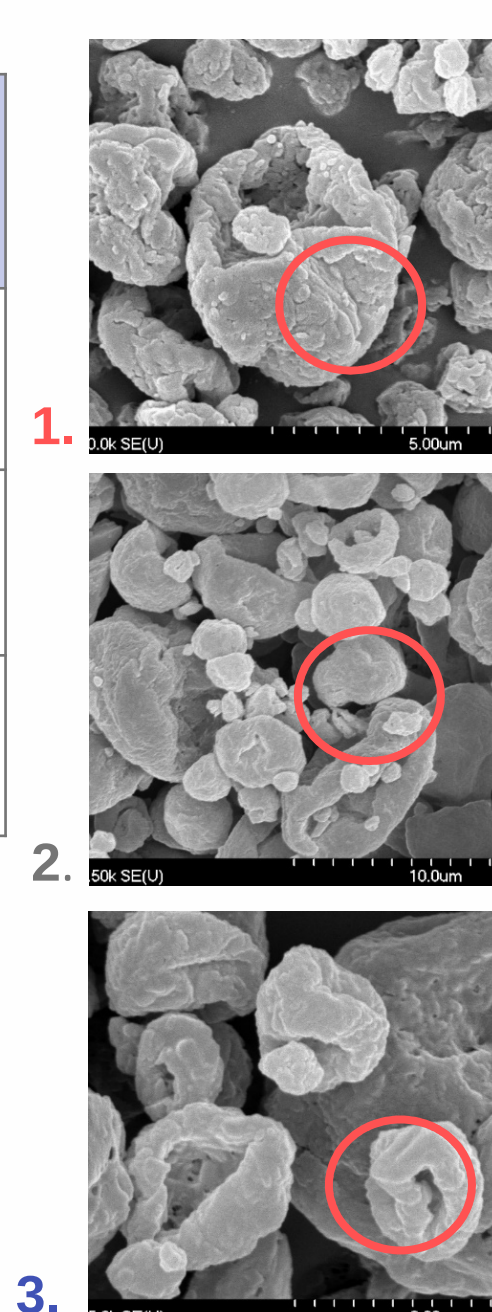


Figure 1. SEM pictures

The powder rheological properties were also measured (Ph. Eur., 2004). The surface adhesion was analyzed using contact angle system (OCA, Dataphysics Inc).

Samples	Tap density (g/cm ³)	Hausner ratio	Carr index (%)	Pol (%)	W _c (mN/m)
1. nanoMX1_LEU0	0.262	1.488	32.39	42.29	146.76
2. nanoMX1_LEU0.5	0.274	1.759	43.09	41.54	123.68
3. nanoMX1_LEU1	0.204	1.398	27.65	33.19	99.96

Table 2. Rheological and interparticle properties

We managed to prepare spherical, 3-4 μm sized microparticles with density lower than 0.3 g/cm³ built up by MX nanoparticles. (Table 1, 2 and Fig. 1)

PHYSICO-CHEMICAL PROPERTIES

Amorphization was analyzed with differential scanning calorimetry (Mettler Inc.) and X-ray powder diffraction (Bruker D8 Advance). Amorphous form of active ingredient was detected in the spray dried microcomposites (Fig. 2-3).

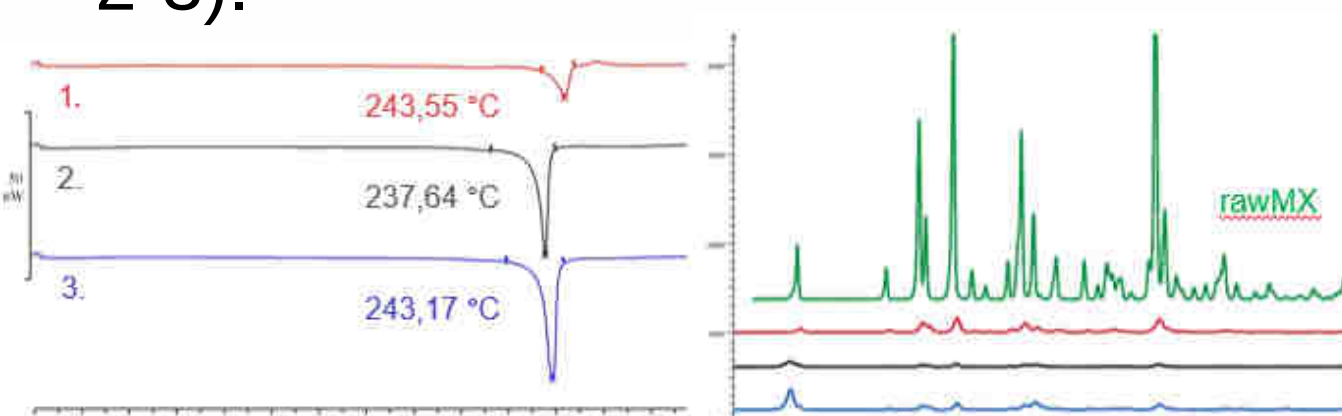


Figure 2. DSC

Figure 3. XRPD

In vitro dissolution in simulated lung media was tested. Thanks to the improved surface area and amorphization the dissolved amount of drug increased, compared to the raw MX. (Fig. 4)

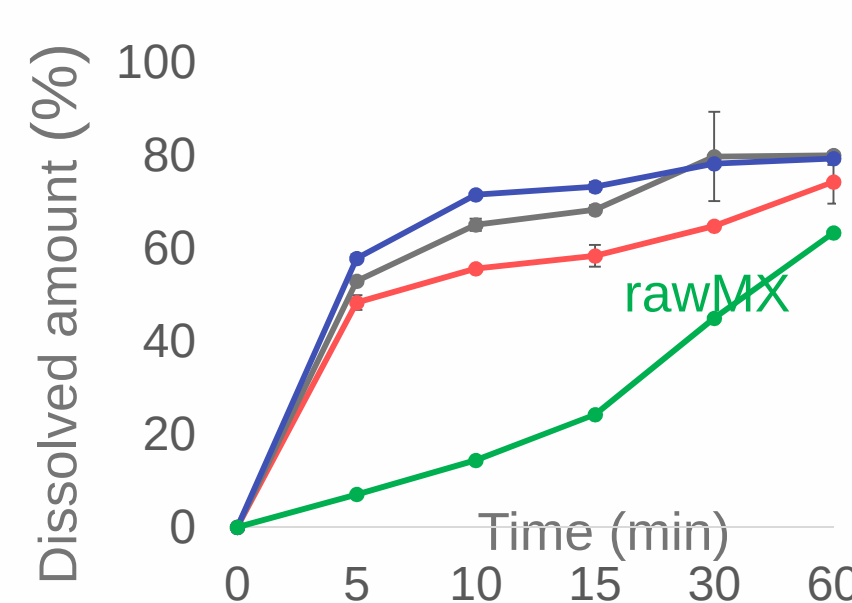


Figure 4. *In vitro* dissolution

CONCLUSION

- Preparation method combining wet milling and spray drying
- 135 nm MX nano particles
- 3-5 μm microcomposite
- Improved yield with LEU
- Amorphous active ingredient
- 0.25 g/cm³ tap density
- 2 μm MMAD
- 40-55% lung deposition

Our samples are suitable for efficient pulmonary therapy.

PREPARATION

We used a two-step preparation. First, the nano-size pre-suspension (d[0.5]=0.135 nanometer) was prepared with wet milling technology, using PVA and MX. The final microsized powders were obtained with co-spray drying of the diluted suspension and LEU.

Samples	MX (g/L)	PVA (g/L)	LEU (g/L)	Yield (%)
1. nanoMX1_LEU0	4	0.9	-	44.50
2. nanoMX1_LEU0.5	4	0.9	2	56.76
3. nanoMX1_LEU1	4	0.9	4	57.78



WET MILLING

20 g of ZrO₂ pearls, 60 min, 500 rpm, Ball Mill PM 100 MA, Retsch GmbH

SPRAY DRYING

inlet temperature: 165°C, outlet temperature: 100°C, aspirator capacity: 85%, air flow rate: 500 L/min, feed pump rate: 10%, (Büchi Mini Spray Dryer B-190)



AERODYNAMIC PROPERTIES

Aerodynamic properties (FPF-fine particle fraction, MMAD-mass medium aerodynamic diameter, ED-emitted fraction) were tested with *in vitro* assessment (Andersen cascade impactor) and *in silico* model (Stochastic Lung Model).

IN VITRO ASSESSMENT

28.3 L/min inhalation flow, 4 s inhalation time, Breezhaler® device, Size 3 gelatin capsules (Capsugel)

The *in vitro* results showed appropriate aerodynamic properties and deep lung deposition. (Table 3) The realistic *in silico* modeling gives an exact aerodynamic behaviour of the samples completing the testing with extra data. (Fig. 5)



Samples	FPF (%)	MMAD (μm)	EF (%)
1. nanoMX1_LEU0	54.62	2.21	70.92
2. nanoMX1_LEU0.5	44.13	2.33	69.44
3. nanoMX1_LEU1	39.65	2.65	71.73

Table 3. *In vitro* results

IN SILICO MODELLING

inhalation volume: 1700 mL
inhalation time: 2 s
breath-hold time: 10 s
exhalation time: 3 s

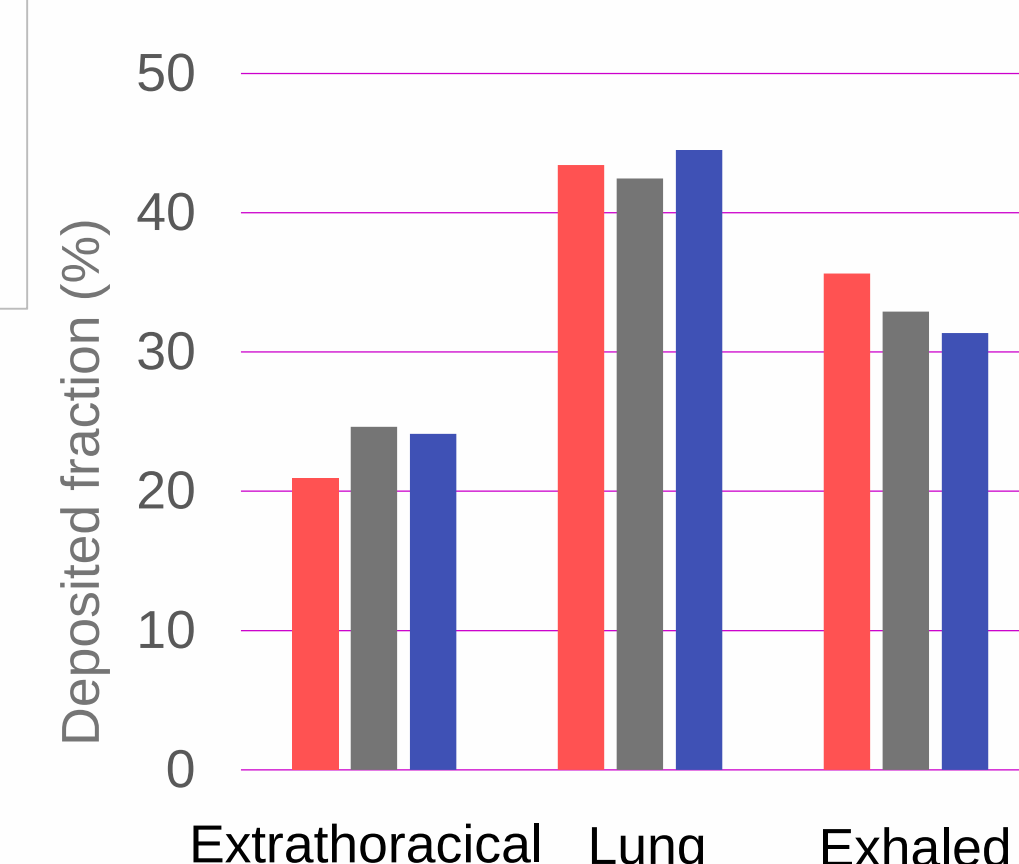
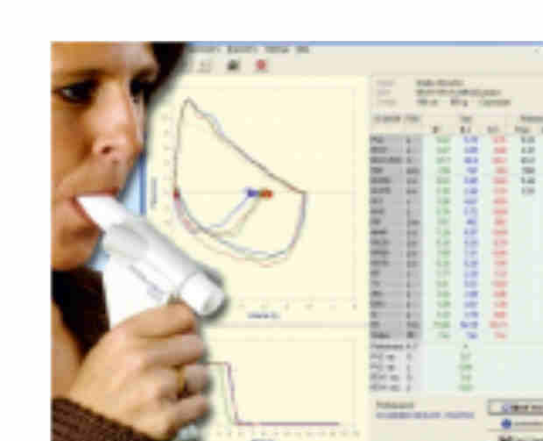


Figure 5. *In silico* deposition

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