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In vitro and *in vivo* investigations on the binary meloxicam-mannitol system

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The objective of the study in rats was to investigate the anti-inflammatory effects of pure meloxicam (ME) with different particle sizes and of physical mixtures of the binary ME-mannitol system. The level of local inflammation was significantly decreased when the amount of mannitol was the highest and the particle size of ME was the lowest as well as the components had the interparticulate interaction. The same results were achieved in *in vitro* experiments.

Various methods are used to increase the rate of dissolution of water-insoluble drug materials (Leuner and Dressman 2000), e.g. the use of a carrier (solid dispersion), complexation (the use of cyclodextrins) or salt formation (Han and Choi 2007). In some cases, preparation of a simple physical mixture (PM) with a water-soluble carrier can improve the dissolution of the drug material. Through the establishment of an ideal ratio for the binary system and an appropriate particle size for a drug material, use of a physical mixture can be as effective as any other method, involving, for example, an eutectic mixture or complexation.

Meloxicam (ME), a nonsteroidal anti-inflammatory drug (NSAID), which selectively inhibits COX2 rather than COX1 (Altnöz et al. 2002), belongs to class II of the Biopharmaceutical Classification System (BCS) with low aqueous solubility and high permeability (Lipka and Amidon 1999).

ME1 with a bigger particle size and ME400 which was made by the milling of ME1 with a ball mill (PM200 Retsch GmbH & Co. KG. Germany) were used. Beta-D-mannitol was used as a carrier (Reisi Nassab et al. 2006) which is a highly water-soluble sugar alcohol with low hygroscopicity, suitable even for diabetic patients (Zajc et al. 2005; Arias et al. 1995).

PMs of ME1 and ME400 with mannitol were prepared with a Turbula mixer. After mixing, an appropriate amount of mixture was placed in a gelatin capsule.

The results of *in vitro* experiments are shown in the Table.

After the successful *in vitro* experiments, the anti-inflammatory effects of the pure MEs and PMs were investigated on rats. This study was approved by the Committee on Animal Research, University of Szeged, Hungary (IV/4316-7/2002).

Table: *In vitro* and *in vivo* results on MEs, mannitol and their PMs

Samples	*In vitro* (90 min) dissolved amount (%) (SD±)	Anti-inflammatory effect (%)
ME1	33.11 (0.61)	45.94
ME400	39.07 (0.60)	47.43
PM1 3 : 7	38.30 (2.22)	58.21
PM400 3 : 7	83.00 (0.92)	58.71
PM1 1 : 10	34.40 (2.48)	53.57
PM400 1 : 10	99.60 (1.52)	71.48
Mannitol	100 (−)	3.82
Empty capsule	0 (−)	0

The differences in the extent of edema formation due to the various pretreatments were expressed as percentages of the control value. The results are shown in the Table in comparison with the *in vitro* results and in the Figure for the *in vivo* investigations.

The particle size of the pure MEs (ME1 and ME400) did neither influence either the dissolved drug amount (*in vitro*) nor the anti-inflammatory effect. On decrease of the particle size, the dissolution rate for ME400 increased, but a smaller particle size was not sufficient to achieve a dissolution rate of 40% in 90 min and the anti-inflammatory effect of 50%. Further decrease of the particle size of the ME resulted in agglomeration of the small particles.

It was demonstrated earlier (Reisi Nassab et al. 2007) that 3 factors affect the dissolution of the drug material in binary ME-mannitol system:

- The ME particle size with given specific surface,
- The amount of carrier (mannitol) with enough specific surface for ME particles,
- The interaction (adhesion) between the ME and mannitol particles.

Each factor is important in increasing the rate of dissolution of ME and all three must act together. However, with the ideal particle size of the drug (ME400) and the ideal ratio of ME400 and mannitol (1 : 10), total dissolution of drug was achieved (99.60 % within 90 min). In this interactive mixture, the mannitol functioned as a core covered with a monolayer of ME particles. This was confirmed in *in vivo* experiments. PM400 1 : 10 was exhibited the best (71.48%) anti-inflammatory effect. Statistically, a positive correlation was found between the *in vitro* and *in vivo* data ($P < 0.05$, $R^2 = 0.937$).

The results confirmed the applicability of the interactive binary physical mixture for increase of dissolution and better bioavailability of water-insoluble drugs.

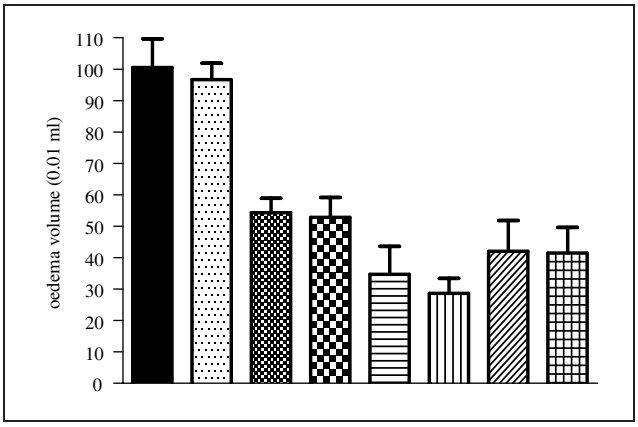

Fig.: Anti-inflammatory effects of ME1, ME400, mannitol and different PMs of meloxicams and mannitol on rats
Control (0.5% of carrageenan, s.pl.), Mannitol (30.0 mg/kg, p.o.), Meloxicam1 (3.0 mg/kg, p.o.), Meloxicam400 (3.0 mg/kg, p.o.), Meloxicam1 + mannitol 1 : 10 (3.0 mg/kg + 30.0 mg/kg, p.o.), Meloxicam400 + mannitol 1 : 10 (3.0 mg/kg + 30.0 mg/kg, p.o.), Meloxicam1 + mannitol 3 : 7 (3.0 mg/kg + 7.0 mg/kg, p.o.), Meloxicam400 + mannitol 3 : 7 (3.0 mg/kg + 7.0 mg/kg, p.o.)

Experimental

1. Material

ME sample (**ME1**) was supplied by EGIS Ltd, (Budapest, Hungary). ME1 (d 90% = 206.2 μm, specific surface = 0.07 m^2/g) and ME400 (d 90% = 131.1 μm, specific surface = 1.37 m^2/g), Mannitol (d 90% = 239.5 μm, specific surface = 0.23 m^2/g) from Hungaropharma Ltd. (Budapest, Hungary).

2. Preparation of binary systems

PMs of ME1 and ME400 with mannitol (PM1 and PM400) in (drug : carrier) ratios of 3 : 7 and 1 : 10 were obtained by mixing the individual components for 10 min in a Turbula mixer (Turbula WAB, Systems Schatz, Basel, Switzerland) at 50 rpm. The products of PM binary systems were filled into hard gelatine capsules (No 2). Each one of capsules contented 15 mg of ME.

3. In vitro experiment

Dissolution tests were performed with a Pharmatest equipment (Hainburg, Germany), at a paddle speed of 100 rpm. 900 ml of artificial enteric juice pH 7.5 (± 0.1), Ph.Eur. 5, at 37 °C (± 0.5 °C) was used. The ME contents of the samples were measured spectrophotometrically at 362 nm (Helios α Spectronic, Unicam, Cambridge, UK). The dissolution experiments were conducted in triplicate.

4. In vivo experiments

48 rats (male, SPRD, 200–220 g) were divided into 8 groups. Appropriate amounts, (determined in pilot experiments) of pure ME1, ME400 and PMs were filled into special capsules. These capsules were then administered into the stomach of the rats by using a Capsules-kit (CapsuGel, Greenwood. USA), which is specific for preclinical studies. A local inflammatory response was elicited by the injection of 0.1 ml of carrageenan (Viscarin, Marine Colloids Inc, Springfield, USA) into the left hind paw. The contralateral foot was injected subcutaneously with isotonic saline (control). Edema (caused by Viscarin) was measured with a plethysmometer (7140, Hugo Sachs Electronic GmbH, Germany) 5 h after the injection of carrageenan.

5. Statistical methods

Two-way ANOVA was performed to analyse the effect of ME and mannitol treatments, Bonferroni and Dunnett tests were applied in the *Post-hoc* analysis.

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