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# Effects of polymers on the crystallinity of nanonized meloxicam during a co-grinding process

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ABSTRACT

Particle size reduction to the submicron region in a grinding process demands a high energy input. This grinding energy requirement can be reduced by means of a suitable additive, e.g. polymer, and performing a co-grinding process. Although these excipients promote attainment of the nanoparticle size range, they can also decrease the crystallinity of the active pharmaceutical ingredient. Different types of polymers have different abilities to amorphize the active material. To demonstrate the amorphization effects of different polymers, meloxicam (MX) as a model drug was subjected to co-grinding in the presence of one or other of four different polymers (PEG 6000, PEG 20,000, PVP C30 and PVP K25) and the products were investigated by XRPD, FT-IR and SEM. Although the PEG materials slightly melted and covered the MX particles during the grinding, they did not cause any changes in crystallinity. The PVP polymers softened and covered the MX particles, but drastically reduced the crystallinity of the drug. FT-IR revealed a weak secondary bonding between MX and the PVP polymer chain.

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## 1. Introduction

Grinding is a technique that is widely used to decrease the particle size of a solid material down to the nanorange, with the purpose of enhancing the solubility, the dissolution rate and the oral absorption of poorly water-soluble compounds [1,2]. To achieve the expected nano-sized particles, a high energy input is needed, which can be provided by various equipment, such as a ball-mill, cryo-mill, jet-mill, and colloidal mill. A common problem with these methods is the high energy requirement: the smaller the particles produced, the higher the energy needed. This energy requirement can be decreased by adding a suitable excipient and performing a co-grinding procedure [3,4]. An appropriate additive also helps to prevent the aggregation of nanoparticles, lubricates the system, and increases the water solubility of the active pharmaceutical ingredient (API). Pharmaceutical excipients include several materials which meet the requirements, but most of them are polymers. The most widely used as grinding materials are polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP).

The various PEGs are used in the pharmaceutical industry as binders, carriers, lubricants, etc., thanks to their advantageous properties: PEGs are completely biocompatible, they can exhibit a combination of hydrophilic and lipophilic properties and they are commercially available in various molecular weights. As semi-crystalline materials, they have melting points in the range from 3 to 68 °C, depending on the molecular weight [5,6]. Their importance in pharmaceutical research is increasing, in consequence of their ability to enhance the dissolution rate of numerous poorly water-soluble drugs [7,8].

PVP is also produced in various molecular weights and particle sizes. These materials are mostly used as binders,

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matrix polymers, desintegrant, crystallization inhibitors and stabilizers. In the literature PVP has often been used as an additive during co-grinding, serving as a carrier or to prevent aggregation [9,10]. It has also been demonstrated that it can decrease the crystallinity of API during methods providing high energy [11–13].

We earlier verified that PEG and PVP can be applied as suitable additives to decrease the energy requirements of grinding, to help reduce the particle size to the nanorange, to prevent the aggregation of nanoparticles and to increase solubility [14]. In that study, the API was ground in the presence of two types of PVPs and PEGs. All four additives helped to reduce the mean particle size to the nanorange. It was shown that the polymers exerted different influences on the crystallinity of the API, and the dissolution rate of the nano-sized API was also improved to different extents.

The aim of our present research work was to investigate the effects of different polymers on the crystallinity of a model material during co-grinding. MX was selected as model API, and the polymers were two types of PVP and two types of PEG. We set out to quantify the decrease in crystallinity in time and to detect any bonding formed between the MX and the polymers.

MX is a non-steroidal anti-inflammatory drug that is main by applied in therapy as an anti-inflammatory and strong analgetic agent [15]. MX is practically insoluble in water while it displays a relatively high permeability through cell membranes. It was chosen as model compound because it is capable of hydrogen-bond to other materials.

## 2. Materials and methods

### 2.1. Materials

Pure crystalline MX (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-benzothiazine-3-carboxamide-1,1-dioxide) was purchased from EGIS Ltd. (Budapest, Hungary). The polymer additives that were used as grinding excipients were PVP K25 with a molecular weight of 34,000 and PVP C30 with a molecular weight 58,000) from BASF (Ludwigshafen, Germany), and PEG with molecular weights of 6000 and 20,000 from Sigma–Aldrich Chemie GmbH, München, Germany.

### 2.2. Grinding process

Physical mixtures of MX, as active pharmaceutical ingredient, and the grinding (stabilizer) polymer (PEG 6000, PEG 20,000, PVP K25 or PVP C30) were prepared and charged into the stainless steel jar of a planetary ball mill containing 10 stainless steel balls (Retsch PM 100, Retsch GmbH & Co., Haan, Germany). The mass ratios were based on previous work [14], so as to give nanoparticles (200–600 nm). For the PVPs, the drug: excipient mass ratio was 1:1, while for the PEGs it was 1:2.

Mixtures were ground for 140 min, samples being withdrawn for investigation after 20, 40, 60, 80, 100, 120 and 140 min. During the grinding process, the temperature of the mortar was measured with an infrared thermometer right before sample withdrawal. The temperature of the mortar was not higher than 56 °C through milling.

### 2.3. X-ray powder diffraction (XRPD)

XRPD analysis was performed with a Bruker D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) system with Cu K λI radiation ($\lambda$ = 1.5406 Å). The samples were scanned at 40 kV and 40 mA from 3° to 40° 2$\theta$, at a scanning speed of 0.05°/s and a step size of 0.010°. The crystallinity of the samples made with the PVPs as amorphous materials was determined via the total area beneath the curve between 12° and 30° 2$\theta$, while the determinations of the samples made with the semicrystalline PEGs were based on the curves relating to MX alone. To avoid the problems caused by the particle size reduction and randomly oriented particles, we used an internal standard method. This technique is widely applied for quantitative XRPD. As internal standard, we mixed 20% (w/w) of pure crystalline NaCl into the binary mixtures. Before its application, the particle size of the NaCl was set into the similar range as that of the MX (2643.6 ± 2629.1 nm). After Kα2-stripping, background removal and smoothing of the areas under the peaks, the area under the peak of MX was proportioned to the area under the peak of NaCl (31–32.5° 2$\theta$). All manipulations of diffractograms were performed with DIFFRAC$^{plus}$ EVA software.

### 2.4. Fourier transform infrared (FT-IR) spectroscopy

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 $cm^{-1}$; operating conditions: Harrick's Meridian SplitPea single reflection, diamond, ATR accessory. Thermo Scientific GRAMS/AI Suite software (Thermo Fisher Sciencific Inc., Waltham, USA) was used for the spectral analysis.

For FT-IR determinations, the ATR method was chosen, because with this there is no need for sample preparation, such as particle size reduction or KBr tableting, which would expose the samples to further physical stress.

### 2.5. 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. Briefly, the samples were sputter-coated with gold–palladium under an argon atmosphere, using a gold sputter module in a high-vacuum evaporator and the samples were examined at 10 kV and 10 μA. Meloxicam particle diameter distributions were obtained by analyzing several SEM images with the ImageJ software environment.

### 2.6. Dissolution studies

The dissolution of physical mixtures and samples withdrawn after 140 min of grinding were determined

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