



Study of the parameters influencing the co-grinding process for the production of meloxicam nanoparticles

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ARTICLE INFO

Article history:

Received 9 July 2010

Received in revised form 31 March 2011

Accepted 21 May 2011

Available online 1 June 2011

Keywords:

Nanoparticle

Meloxicam

Co-grinding

Scanning electron microscopy

Factorial experimental design

Nasal powder system

ABSTRACT

Co-grinding is a procedure for the preparation of nanoparticles in which the drug is ground together with one or more excipients. The grinding of meloxicam, a crystalline solid, together with amorphous polyvinylpyrrolidone (PVP) or semi-crystalline polyethylene glycol (PEG) as excipients, is expected to lead to a drastic reduction in particle size. We optimized meloxicam grinding using a three level full factorial response surface design. In the case of PVP the optimum co-grinding parameter set in our study proved to be a meloxicam to PVP-C30 ratio of 1:1, and a rotation frequency of 400 rpm. The best size reduction was achieved at a meloxicam to PEG 6000 ratio=1:2 at a rotation frequency of 400 rpm: nanoparticles averaging $d_{SEM} = 174$ nm in diameter and with a very narrow size distribution (standard deviation 35% of mean) were obtained. X-ray powder diffraction analysis indicated that the optimized products contained amorphous meloxicam nanoparticles in the PVP-C30 composition, although meloxicam nanocrystals could also be detected in the samples which contained PEG 6000. The dissolution properties were significantly increased under nasal conditions (pH 5.1, temperature 30 °C), especially in the case of the amorphous product. Such dry powder systems can offer novel opportunities in systemic nasal drug delivery.

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1. Introduction

Nanonization offers an excellent possibility to overcome mucosal barriers [1,2] and has several advantages in drug delivery [3,4]. It is believed that nanoparticles can be transported across barriers into the bloodstream without prior dissolution [5]. Nano-sized drugs with carriers can overcome the resistance offered by the physiological barriers in the body because the efficient delivery of drugs to various parts of the body is directly affected by the particle size [6].

Several techniques are available for the production of drug nanoparticles [7]. Basically, bottom-up and top-down technologies can be differentiated. The bottom-up technologies start from the molecules, which are precipitated (crystallized) in a controlled fashion to yield the desired particle size. Nowadays, bottom-up techniques are not the main choice for drug nanoparticle production due to the use of organic solvents. The top-down technologies are disintegration methods e.g. various types of milling (high-intensity ultrasonication, high-pressure homogenization, grinding or co-grinding) are more frequently used [8].

The size reduction of pharmaceutical materials is often performed by means of dry milling [9,10], but the size reduction possible by dry

milling is known to be limited to around 3 μm due to aggregation of the particles. Experiments focusing on a particle size reduction to the submicron region by co-grinding with additives have recently been attempted [11–14].

Nanonization has become a popular approach to produce particles in the size range of 200–400 nm, to improve both the dissolution rate and the solubility of the compound [15]. The latter phenomenon is due to the well-known dependency of solubility on particle size as described by the Ostwald–Freundlich equation. Breakage of micron-sized drug crystals into nanoparticles creates an increased particle surface area, which is thermodynamically unfavorable. Thus, nano-sized particles tend to agglomerate to reduce their surface area. Particle agglomeration can be prevented by steric stabilization using polymeric excipients [16].

Co-grinding is a top-down disintegration procedure for the preparation of nanoparticles by grinding of the drug together with one or more excipients [17,18]. A main advantage of co-grinding as compared to other methods is that it is a simple procedure and organic solvents are not needed for the preparation of nanoparticles; it is therefore an economically and environmentally desirable technology [19]. It is important to control the parameters (e.g. duration of grinding, the grinding rate, the material and the volume of the grinding pot, the material and the number of the grinding balls, the grinding excipients and the drug/excipient ratio) by means of a factorial experimental design [20,21].

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Meloxicam, a non-steroidal anti-inflammatory and analgesic water-insoluble drug (NSAID), is an enolic acid oxamic derivative [22,23]. The single oral dose of meloxicam is 7.5–15 mg. The favorable side-effect profile and the low quantity of a single dose make this NSAID suitable for administration via alternative pathways, e.g. intranasally. This may result in novel opportunities for the easing of pain, which affects the region of the head.

A reduction of the particle size of meloxicam into the nano-size range (100–1000 nm) is possible by crystallization methods through formulation of the drug in a nanosuspension [24]. However, co-grinding offers a simpler and environmentally friendly way of preparing meloxicam nanoparticles. Nanoparticles are a formulation principle for all poorly soluble drugs for which the dissolution velocity is the rate limiting step for absorption and thus the reason for a too low bioavailability. The increase in surface area leads to an increase in the dissolution velocity.

Water-soluble polymers have typically been used as co-grinding excipients [13,25,26]. An example is polyvinylpyrrolidone (PVP), an amorphous excipient which does not melt during the grinding process therefore it could also help particle size reduction and to prevent the agglomeration, as stabilizer agent [27–29]. On the contrary, polyethylene glycol (PEG) is a semicrystalline grinding excipient with low melting point which could melt due to friction work and as a consequence it cannot help as efficiently as PVP the size reduction.

The grinding of meloxicam, a crystalline solid, together with amorphous PVP or semicrystalline PEG as excipients is expected to lead to a drastic reduction in particle size and to possible changes in the crystallinity of meloxicam without any harmful alterations in its pharmaceutical effect. The crystalline and the amorphous form of an active agent have no difference in their effect, although the onset of action can be improved with faster dissolution rate.

Multivariate problems similar to meloxicam grinding are often optimized by using the COST (Change One Separate factor at a Time) approach: all parameters but one are fixed, and the response of the system is studied as a function of the changing variable. Each variable is scanned in this way, and the combination of their optimum values is accepted as the overall optimum. Unfortunately, this method is slow, since the number of necessary experiments increases considerably with the number of variables. Moreover, the COST approach can seldom find the true overall optimum of a system since it assumes that the effects of all variables are completely independent, whereas the response of a real system to change in any single parameter often appears as the overall effect of several parameter alterations (i.e. real-life multidimensional parameter spaces are seldom orthogonal). A good strategy for finding the overall optimum of a multivariate problem is to fit the response surface on the basis of the responses obtained from well-chosen parameter sets. Since the effect of any single variable can usually be accounted for by a second-order polynomial, it is customary to test parameters at three different levels: a high, a medium and a low setting. Such designs, called three-level full factorial designs, have been applied successfully in the past to optimize the synthesis of carbon nanotubes [20,30], the deposition of titanate nanowires on glass [31] and the wet peroxidation of aqueous phenol solution [32]. The simplest three-level full factorial design is to pick three values for one independent variable (x_1 : rotation speed), chart the three corresponding response (d : particle diameter) values in a standard two dimensional Cartesian coordinate system and fit the $d = f(x_1)$ function by a parabola. In case of two independent variables (x_1 : rotation speed and x_2 : meloxicam to excipient ratio) we need to sample $3 \times 3 = 9$ points in the x_1x_2 plane and chart the corresponding d values as elevation above the x_1x_2 plane in a three dimensional coordinate system.

The aim of our present research work was to produce meloxicam nanoparticles by co-grinding process with PVP and PEG, investigating the influence of different parameters on particle size and optimizing them by using a three-level full factorial design so that nano-sized

meloxicam particles of uniform size distribution are obtained. The optimized products were investigated from the aspects of crystallinity and extent of dissolution under *in vitro* nasal circumstances.

2. Materials and methods

2.1. Materials

Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-benzothiazine-3-carboxamide-1,1-dioxide) was obtained from EGIS Ltd. (Budapest, Hungary). The grinding additives, polyvinylpyrrolidone (PVP) K25 and C30 were purchased from BASF (Ludwigshafen, Germany). Types of PVP (K25 and C30) differ in molecular weight, viscosity and field of application. Molecular weight of PVP-K25 is about 34,000 and PVP-C30 has a higher molecular weight (about 58,000). Because their viscosity relating to molecular weight so the viscosity of PVP-C30 is higher, than for K25. In the case of PVP the letter "C" indicates applicability also for preparation of aseptic dosage forms. Polyethylene glycol (PEG) 6000 and 20,000 were from Sigma-Aldrich Chemie GmbH, Germany. The numbers of PEG (6000 and 20,000) refer to the molecular weight of the polymer.

2.2. Methods

2.2.1. Preliminary experiments

Several pharmaceutical excipients were tested, and the results of the co-grinding of meloxicam with PVP and PEG were the most promising in the aspect of particle size reduction. In these preliminary experiments some optimum parameters of the grinding (the duration of grinding, the material and the volume of the grinding pot and the material and the number of grinding balls) were also set.

2.2.2. Preparation of co-ground formulations and their physical mixtures

Binary mixtures of as-received meloxicam powder and the carriers PVP-C30, PVP-K25, PEG 6000 and PEG 20,000 were mixed and charged into the chamber of the planetary monomill (Fritsch Pulverisette 6, Fritsch GmbH, Idar-Oberstein, Germany) in various drug-carrier ratios (1:0.5, 1:1 and 1:2). The grinding was performed in an 80 cm³ silicon nitride (Si₃N₄) milling drum containing 25 silicon nitride balls 10 mm in diameter. In each experiment, 1.0 g of meloxicam was ground together with the calculated amount of polymer additive.

The milling parameters are given in Table 1 and the investigated parameters are listed in Table 2. After grinding, the samples were stored in plastic vials until use.

The physical mixtures of drug-carrier were prepared by accurately weighing the calculated amounts of meloxicam and carrier, mixing them well in a porcelain mortar and storing in plastic vials until use.

2.2.3. Determination of particle size by scanning electron microscopic image analysis

2.2.3.1. Scanning electron microscopy (SEM). Co-ground products were washed and centrifuged three times in distilled water to separate the water-soluble excipient from the water-insoluble meloxicam (the solubility of meloxicam is 4.4 ± 0.7 µg/mL [24]), so that individual meloxicam particles could be studied. The particle size and the surface

Table 1
General parameters of co-grinding, independent variables.

Material of the grinding pot	Si ₃ N ₄
Material of the grinding balls	Si ₃ N ₄
Number of the grinding balls	25
V _{grinding pot}	80 mL
D _{grinding ball}	10 mm
t _{milling}	2 h

Table 2
Compositions of different samples, parameters of optimization.

Meloxicam/excipient ratio	1:0.5, 1:1, 1:2
Excipients	PVP-C30, PVP-K25, PEG 6000, PEG 20,000
Revolutions per minute (rpm)	200, 300, 400

morphology of the meloxicam particles were visualized by SEM. Samples were fixed onto a metallic stub with double-sided conductive tape (diameter 12 mm, Oxon, Oxford Instruments, UK). Images were taken in secondary electron image mode on a Hitachi S-4700 Type II instrument at an acceleration voltage of 10 kV.

2.2.3.2. Image analysis. Meloxicam particle diameter distributions were obtained by analyzing several SEM images with the ImageJ software environment [33]. Over 150 individual particle measurements were made in at least five different images in order to determine the particle size accurately. Although less frequently used than TEM or dynamic light scattering, SEM image analysis is an established method for nanoparticle size analysis: for instance, it was applied successfully for the characterization of carbon nanotube networks [30], Zn-glycerolate microstacks [34] and co-grinding products of PVP and CaCO₃ [35].

2.2.3.3. Design of experiments. In a series of pre-screening experiments the following parameters were fixed (see Table 1): (i) the milling drum size and material, (ii) the ball size and number, and (iii) the milling duration. The remaining variables, *i.e.* the excipient type, the excipient-to-meloxicam ratio and the milling rate were the parameters featuring in the optimization. A full factorial design plan was created and carried out with the meloxicam particle size distribution defined as response factor. All calculations were performed by using Minitab 14 (Minitab Statistical Software).

2.2.4. Further investigations of the optimized products

2.2.4.1. X-ray powder diffraction analysis (XRPD). The physical state of meloxicam in the different samples was evaluated by XRPD. Diffraction patterns were analyzed with a Miniflex II X-ray Diffractometer (Rigaku Co. Tokyo, Japan), where the tube anode was Cu with $K\alpha = 1.5405 \text{ \AA}$. The pattern was collected with a tube voltage of 30 kV and a tube current of 15 mA in in-step scan mode ($4^\circ/\text{min}$). The instrument was calibrated by using Si.

2.2.4.2. Studies of the extent of dissolution under *in vitro* nasal conditions. The dissolution of different powder samples containing the same amount of drug (10 mg) was determined according to the European Pharmacopoeia (6th Edition) paddle method (Pharma test, Heinburg, Germany), which means a rotating paddle in the dissolution vessel. 50.0 mL of phosphate buffer solution (pH 5.6 ± 0.1) at $30 \pm 0.5^\circ \text{C}$ was used as a dissolution medium and the rotation speed of the paddles was 100 rpm. At predetermined times, 1 mL samples were withdrawn and immediately filtered (cut-off $0.2 \mu\text{m}$, Minisart SRP 25, Sartorius, Germany) and the amount of dissolved drug was determined spectrophotometrically ($\lambda = 364 \text{ nm}$). Withdrawn samples were replaced with 1 mL of fresh medium.

3. Results and discussion

Fig. 1 presents typical SEM images of meloxicam particles before grinding (A) and after grinding in the presence of the various excipients (B–D). The particle size was reduced by roughly one order of magnitude, regardless of the additive used. This primary effect originated from the high-energy collisions taking place in the planetary ball mill [36]. Ball milling is a process with complex mechanics, analyzed in detail by Chattopadhyay et al. [37]. On the basis of their model, it was possible to calculate the energetics of the co-grinding experiments performed. The results in Table 3 indicate

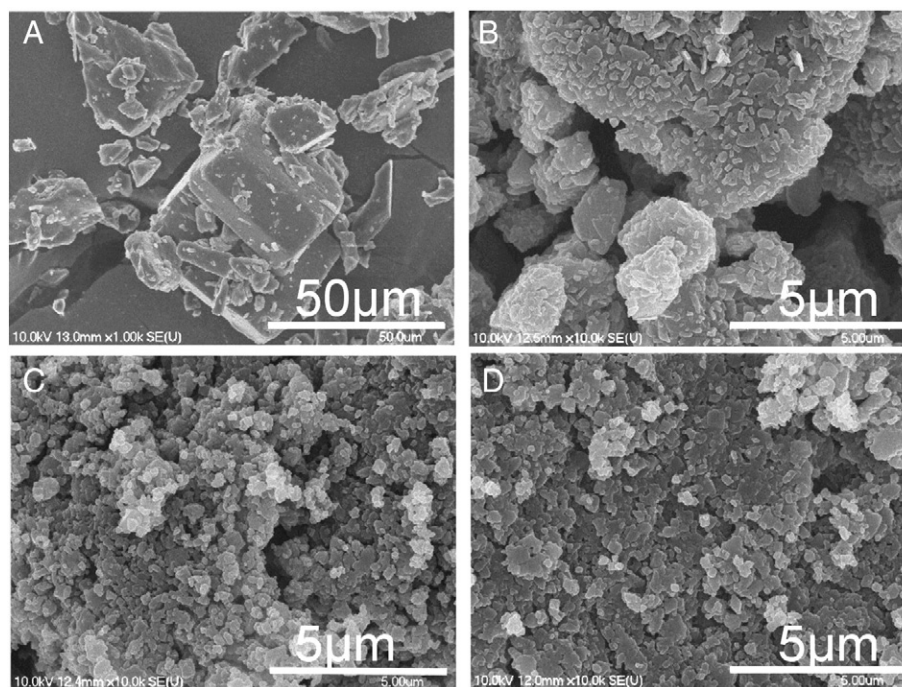


Fig. 1. Scanning electron microscopic images from meloxicam before grinding (A), after co-grinding with PVP-K25 in a ratio of 1:0.5 at 300 rpm (B), with PEG 20,000 in a ratio of 1:0.5 at 400 rpm (C), with PEG 6000 in a ratio of 1:0.5 at 400 rpm (D)/from all of the products PVP and PEG were dissolved by distilled water due to the visualization of meloxicam particles/.

Table 3
Milling energetics map of the experiments performed.

Rotation speed (rpm)	Collision frequency (s ⁻¹)	Cumulative collision energy transferred (kJ·g ⁻¹)			
		Meloxicam to additive weight ratio			
		No additive	1:0.5	1:1	1:2
200	240	8.56	5.71	4.28	2.85
300	360	28.89	19.27	14.45	9.63
400	480	68.50	45.67	34.25	22.83

that the total energy transferred to the meloxicam–excipient mixture via collisions in our system lies in the range of 2.80–68.50 kJg⁻¹.

A closer analysis of the SEM micrographs revealed that there were considerable differences in nanoparticle size distribution as a function of the excipient type used. The size distribution function is characterized by the mean particle diameter and the standard deviation of the diameter (given as a percentage of the mean and denoted as SD%). These values are reported in Table 4, and their relationship with the grinding variables is analyzed quantitatively in the main effects plots (Figs. 2 and 3) and interaction plots (Figs. 4 and 5). The main effects plot shows the average response for each value of each variable, combining the effects of the other variables as if all variables were independent. The main effects plots for the meloxicam particle diameter indicate that the tested excipients can all promote size reduction (Fig. 2). Increasing the relative amount of meloxicam in the system resulted in larger product particles, whereas increasing the milling energy (grinding rate) reduced the particle size. Since our goal was to grind meloxicam into uniformly small particles so that its administration can be controlled, it was important to study the main effects plots characterizing the broadness of the particle size distribution curve (SD%) (Fig. 3). It is evident from Fig. 3 that the excipients PVP-K25 and PEG 6000 provide significantly broader and narrower diameter distributions, respectively, than the other two tested additives. Increase of the meloxicam to additive ratio resulted in a less uniform product. On the other hand, the distribution uniformity as a function of the milling energy exhibited a minimum at 300 rpm.

Interaction plots illustrate the effects between variables, which are not independent by showing the means of the responses for each level of a factor for each level of a second factor pairwise for all factors involved in the study. Therefore, the interaction plots presented in Figs. 4 and 5 for the mean diameter and the SD%, respectively, can be used to gain insight into the complex interactions between the grinding parameters. For example: (i) all additives but PVP-C30 result in a particle diameter increase at higher milling rates, (ii) increasing the milling frequency can compensate the diameter differences introduced by changing the meloxicam to additive ratio, (iii) the use of PEG 6000 as additive results in particularly narrow size distributions, regardless of the choice of the other two parameters, etc.

We are now in a position to summarize the grinding behavior of the novel NSAID meloxicam in a high-energy ball mill with Si₃N₄ as grinding material. In the absence of any grinding additives, the final product particles are too large at low milling energy ($d_{SEM} = 364$ nm at 200 rpm) and aggregate rapidly at high energy ($d_{SEM} = 343$ nm at 400 rpm). There is an optimum at 300 rpm. However, even at this setting, the average product particle size is above $d_{SEM} = 270$ nm. It is interesting to note that, without additives, the relative broadness of the particle size distribution function was independent of the milling energy (SD~61%).

With PVP-C30, it was possible to push the average meloxicam particle size below 250 nm and the average SD below 50%. This was a significant improvement relative to the additive-free grinding result. The optimum co-grinding parameter set for PVP-C30 was a meloxicam to excipient ratio = 1:1, and a rotation frequency of 400 rpm.

Table 4
Particle diameter (d_{SEM}) of meloxicam particles in different compositions.

Excipient	Meloxicam/excipient ratio	Rotation speed (rpm)	$d_{SEM} \pm SD$ (nm)
–	1:0	–	2643.6 ± 2629.1
–	1:0	200	364.5 ± 228.1
–	1:0	300	275.0 ± 170.6
–	1:0	400	343.5 ± 205.9
PVP-C30	1:0.5	200	511 ± 333
PVP-C30	1:1	200	267 ± 158
PVP-C30	1:2	200	221.7 ± 105.4
PVP-C30	1:0.5	300	243 ± 115
PVP-C30	1:1	300	242 ± 141
PVP-C30	1:2	300	302.3 ± 115.7
PVP-C30	1:0.5	400	209.9 ± 85.3
PVP-C30	1:1	400	140.4 ± 69.2
PVP-C30	1:2	400	238.6 ± 147.9
PVP-K25	1:0.5	200	203.6 ± 190.0
PVP-K25	1:1	200	192.7 ± 74.4
PVP-K25	1:2	200	229.1 ± 203.2
PVP-K25	1:0.5	300	266.3 ± 117.0
PVP-K25	1:1	300	351.7 ± 227.7
PVP-K25	1:2	300	277.6 ± 139.9
PVP-K25	1:0.5	400	251.5 ± 362.6
PVP-K25	1:1	400	246.4 ± 108.5
PVP-K25	1:2	400	262.8 ± 124.7
PEG 6000	1:0.5	200	175.2 ± 57.4
PEG 6000	1:1	200	212.3 ± 92.0
PEG 6000	1:2	200	–
PEG 6000	1:0.5	300	165.0 ± 59.6
PEG 6000	1:1	300	204.4 ± 88.9
PEG 6000	1:2	300	358.1 ± 145.3
PEG 6000	1:0.5	400	197.3 ± 84.8
PEG 6000	1:1	400	229.5 ± 92.3
PEG 6000	1:2	400	173.8 ± 60.3
PEG 20,000	1:0.5	200	368.7 ± 238.0
PEG 20,000	1:1	200	318.8 ± 136.2
PEG 20,000	1:2	200	200.0 ± 134.6
PEG 20,000	1:0.5	300	235.5 ± 117.7
PEG 20,000	1:1	300	217.6 ± 103.7
PEG 20,000	1:2	300	–
PEG 20,000	1:0.5	400	185.1 ± 73.7
PEG 20,000	1:1	400	234.5 ± 122.9
PEG 20,000	1:2	400	333.8 ± 151.0

If the target drug administration task allows the application of PEG 6000 as additive, then it is possible to improve the co-grinding process further. The parameter setting meloxicam to PEG 6000 = 1:2 at a rotation frequency of 400 rpm yields nanoparticles averaging $d_{SEM} = 174$ nm in diameter and a very narrow size distribution, characterized by SD = 35%. This set is the overall optimum result in our study.

The most promising products of the co-grinding process were further investigated by XRPD analysis. The optimized products (Table 5, Fig. 6) differ in their crystallinity, which can be observed in the diffraction spectra (Fig. 7). The XRPD patterns of meloxicam, physical mixtures and products containing meloxicam and excipients in the optimized ratio are presented. The presence of numerous distinct peaks in the XRPD spectrum indicates that meloxicam is a crystalline material; its characteristic peaks appear at diffraction angles 2θ of 13.22, 15.06, 26.46 and 26.67°. The crystallinity of meloxicam was decreased in the co-grinding process with PVP-C30; in the other optimized product, which contains PEG 6000 the crystallinity of meloxicam did not change significantly comparing to the physical mixture. The crystalline meloxicam was altered in the co-grinding process with the amorphous excipient, PVP-C30, leading to amorphous nanoparticles. With PEG 6000 as excipient, the crystallinity of meloxicam was proved (Fig. 7), i.e. meloxicam nanocrystals were prepared.

The extent of dissolution was determined under conditions of nasal drug delivery (Fig. 8). Under *in vitro* circumstances, we attempted to mimic the physiological conditions of the human nose; the temperature of the dissolution medium was 30 °C and the

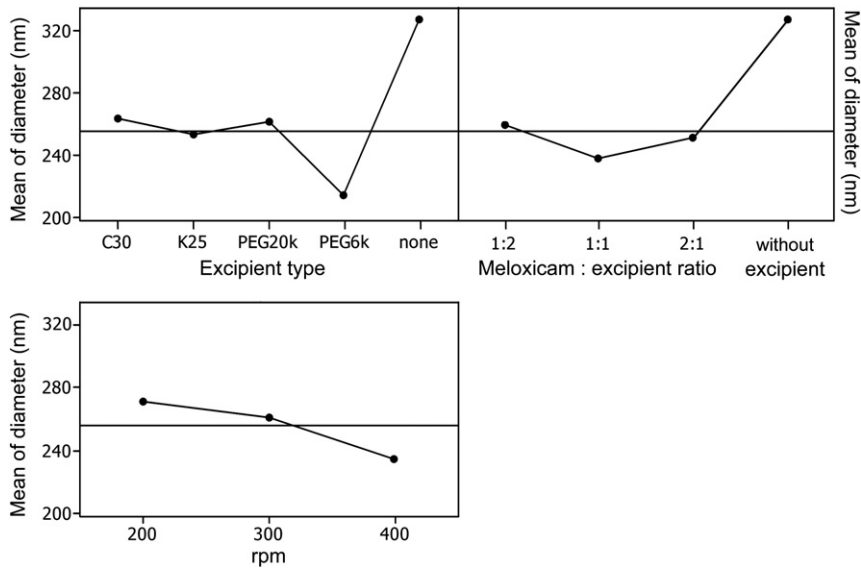


Fig. 2. Influence of different parameters (main effects plot, data means) on meloxicam crystal diameter (C30 = PVP-C30, K25 = PVP-K25, PEG20k = PEG 20,000, PEG6k = PEG 6000).

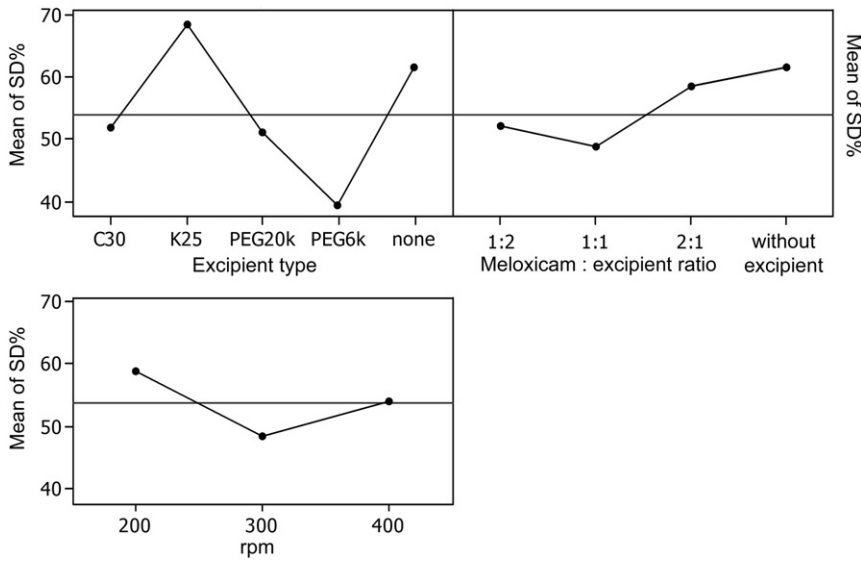


Fig. 3. Main effects plot (data means) for SD% (C30 = PVP-C30, K25 = PVP-K25, PEG20k = PEG 20,000, PEG6k = PEG 6000).

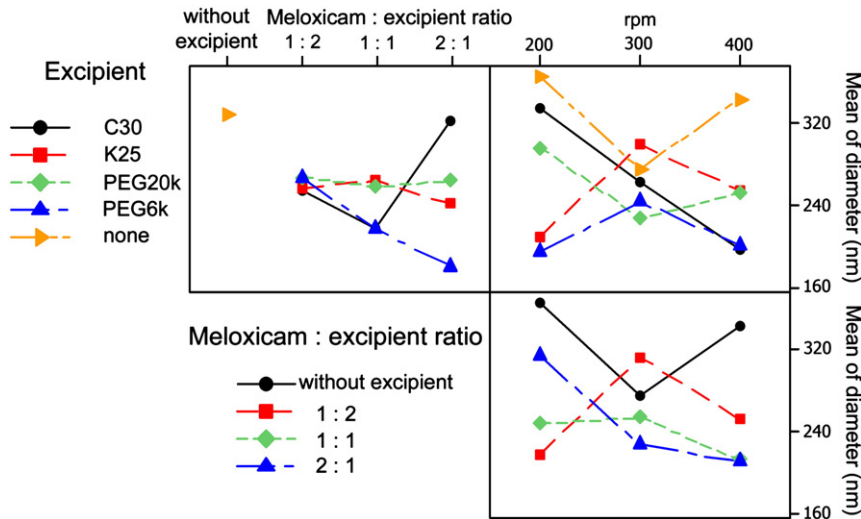


Fig. 4. Interaction plot (data means) for diameter (C30 = PVP-C30, K25 = PVP-K25, PEG20k = PEG 20,000, PEG6k = PEG 6000).

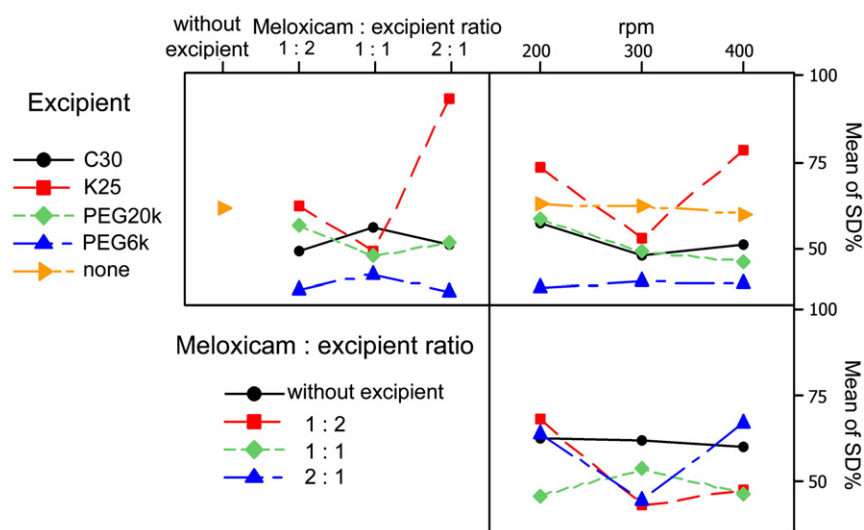


Fig. 5. Interaction plot (data means) for SD% (C30 = PVP-C30, K25 = PVP-K25, PEG20k = PEG 20,000, PEG6k = PEG 6000).

Table 5

Optimized products.

Grinding excipient of meloxicam	Drug to excipient ratio	Rotation speed (rpm)
PVP-C30	1:1	400
PEG 6000	1:2	400

pH was 5.6. These conditions alter the dissolution properties of the effective agent: lower temperature and pH decreases the extent of meloxicam dissolution, although the particle size reduction enhances the extent of dissolution. In the meloxicam PVP-C30 composition, the extent of dissolution after 60 min increased in case of the co-ground product from $4.1 \pm 0.21\%$ to $66.2 \pm 4.73\%$ relative to the physical mixture of the effective agent and the excipient. In the background of this phenomenon stands in one hand the reduction of the particle size (nanonization) and on the other hand the decrease in crystallinity of the effective agent (amorphization). Nanoparticles improve dissolution rate and bioavailability of poorly water-soluble drugs [38–41] owing to increased surface area available for dissolution as described by the Noyes–Whitney equation [42]. The co-grinding technique has already been employed for amorphization of drugs [43,44].

A two-fold enhancement of the extent of meloxicam dissolution was observed in the case of the meloxicam PEG 6000 co-ground product, in which meloxicam is in nanocrystal form. By now, main attention was focussed on size and related surface area. It was recently reported that the interfacial reaction resistance is getting the velocity determining parameter for crystals below $1 \mu\text{m}$. Design of nanocrystals

with faster interfacial reaction can further enhance the dissolution velocity [45]. In addition, nanomaterials possess improved adhesiveness to biological membranes [7]. The extent of meloxicam dissolution after 60 min in the physical mixture was $4.1 \pm 0.21\%$, while that for the optimized product was $8.3 \pm 0.08\%$. In the physical mixtures the excipient had no influence on the extent of meloxicam dissolution, contrary products, which were undergone nanonization with co-grinding process, showed significantly higher extent of dissolution.

Nanonization and amorphization of meloxicam resulted in significantly better dissolution properties in the *in vitro* dissolution studies under conditions, which mimic the physiological pH and temperature of the human nose.

Insoluble powders are likely to be effective for nasal systemic drug delivery [46]. The nasal powder formulations enhance systemic bioavailability, and are superior to liquid formulations [47,48] from the aspects of increased chemical stability of the drug, no requirement for preservatives in the formulations, and the feasibility of administering relatively large amounts of drug [49–51].

4. Conclusions

This study explored the effects of additives on the co-grinding behavior of the frequently applied NSAID meloxicam in a high-energy planetary ball mill. It was shown that both PVP and PEG as additives can act as efficient excipients in the mechanical size reduction of meloxicam particles. The influence of the grinding parameters: additive type, meloxicam to additive ratio and milling frequency on the product particle size distribution function was studied via a full

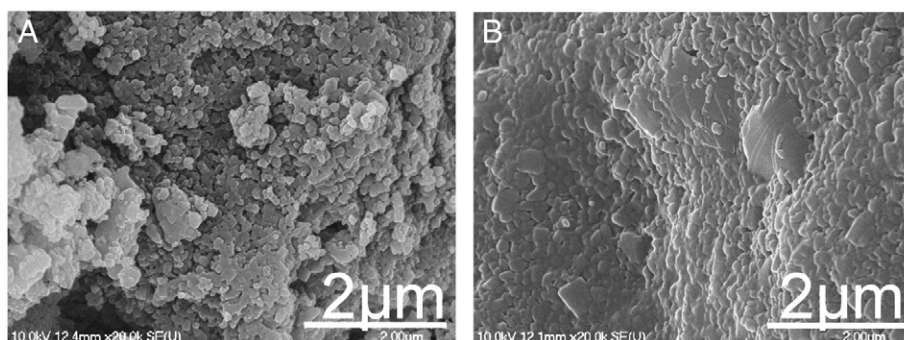


Fig. 6. Scanning electron microscopic images from the optimized products: meloxicam after co-grinding with PVP-C30 in a ratio of 1:1 at 400 rpm (A), meloxicam after co-grinding with PEG 6000 in a ratio of 1:2 at 400 rpm (B)/from all of the products PVP and PEG were dissolved with distilled water due to the visualization of meloxicam particles/.

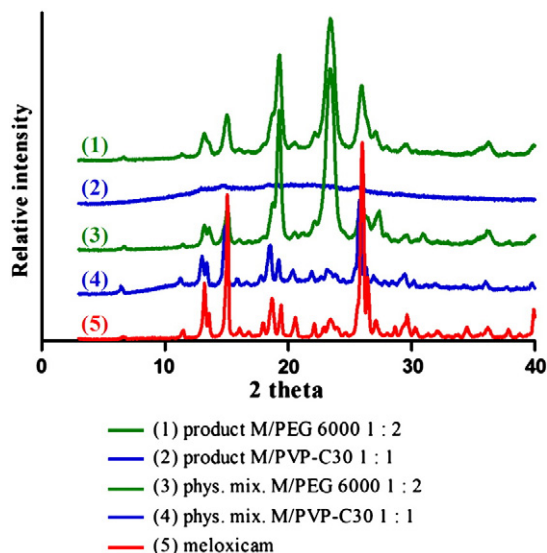


Fig. 7. X-ray powder diffraction spectra of meloxicam (5), physical mixtures (4, 3) and products of meloxicam co-grinded with PVP-C30 (2), meloxicam with PEG 6000 (1).

factorial design. Optimum grinding parameter sets for the nitrogen-containing additive PVP (meloxicam to PVP-C30 ratio = 1:1, rotation frequency 400 rpm) and for nitrogen-free PEG 6000 (meloxicam to PEG 6000 = 1:2, rotation frequency 400 rpm) were identified.

XRPD analysis indicated that the optimized products contained amorphous meloxicam nanoparticles in the PVP-C30 composition, although meloxicam nanocrystals could be detected in the samples which contained PEG 6000. The dissolution properties are also significantly increased under nasal conditions (pH 5.1, temperature 30 °C), especially in the case of the amorphous product. These dry powder systems can offer novel opportunities in systemic nasal drug delivery.

These products are suitable for further investigations in *in vitro* cell culture models, in *ex vivo* tissue models and in *in vivo* animal experiments with the aim of intranasal systemic drug delivery.

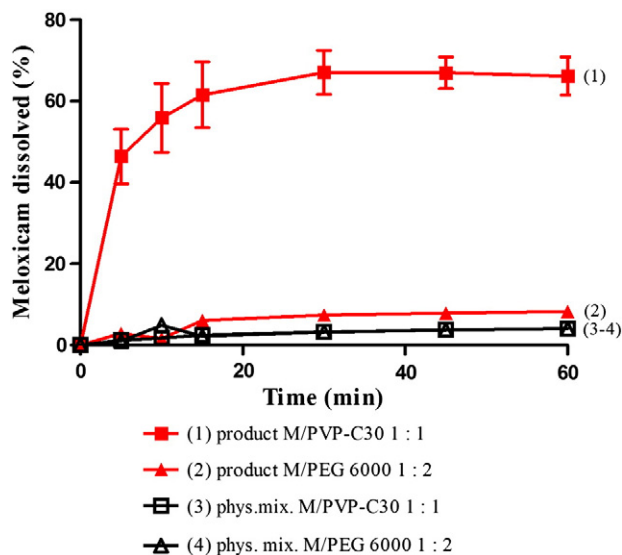


Fig. 8. The extent of meloxicam dissolution in the optimized products and in the physical mixtures, dissolution circumstances: pH 5.6 ± 0.1 , 30 ± 0.5 °C.

Acknowledgement

This work was supported by the TÁMOP research project TÁMOP-4.2.1/B-09/1/KONV-2010-0005 and the OTKA-NNF 78920 project.

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