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Comparison of static and dynamic sonication as process intensification for particle size reduction using a factorial design

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ABSTRACT

This article reports on particle engineering by a top-down method involving organic solvent-free acoustic cavitation as a wet-grinding procedure. The effects of static and dynamic sonication on particle size reduction methods were compared to each other. The most effective process parameters were determined by a factorial design plan for the particle size distribution of an important active pharmaceutical ingredient, meloxicam, as response factor after sonication. Samples sonicated with appropriate process parameters were dried and investigated. Scanning electron microscopy images showed that the sonication resulted in a rounded shape and micronized size of the particles. Differential scanning calorimetry and X-ray powder diffraction examinations revealed the crystalline structure of the produced meloxicam by both sonication methods. Fourier transform infrared spectroscopy demonstrated that no chemical degradation occurred. Static sonication is recommended primarily for particle size reduction in preclinical samples, where the amount of the drug candidate is very small (e.g. nasal formulation), while dynamic sonication may be suitable for wet-grinding of different active substances to prepare pre-suspension (e.g. micronization and nanonization).

1. Introduction

Particle design techniques are widely used for the modification of the physico-chemical and biopharmaceutical properties of Active Pharmaceutical Ingredients (APIs) [1]. Particle engineering techniques, controlling the crystal size distribution and morphology can offer improvements for the solubility, dissolution rate and permeability of poorly water-soluble drugs and can open up new, alternative administration routes, e.g. intranasally route, where the particle size (over 10 μm) is a determining factor [2–4]. Process Intensification (PI) has the goal of making substantial improvements to the efficiency of chemical processes and plants by developing innovative methods and equipment [5]. Innovative methods for these improvements can be the useage of alternative energy forms, like centrifugal fields, ultrasounds, microwaves, solar energy, electric fields, or plasmas [6]. The advantages of intensified product design processes consist of intensified process control, and/or improved product quality.

There are many different types of size reduction techniques; dry and wet grinding can be distinguished. During the wet grinding, due to the closed system the formation of dust is prevented. Less energy and time is required for grinding, the heating of the materials is reduced and after grinding the suspension can be directly used for production formulations.

Acoustic cavitation is a novel wet grinding possibility for controlling the crystal size distribution and morphology of drugs, primarily with the aim of particle size reduction [7,8]. It has the ability to erode and break down particles and increase the specific surface area of crystals [9]. It has been proven that application of ultrasound technology in the frequency range of 20–100 kHz can induce particle size reduction [10]. During the sonication process, the ultrasound waves that form in the liquid media result in alternating high-pressure and low-pressure cycles, with rates depending on the frequency. In the low-pressure cycle the high-intensity ultrasonic waves evolve small gas- or vapor-filled bubbles (cavities) in the liquid. When the bubbles reach a volume at which they can no longer absorb energy, they collapse violently during a

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high-pressure cycle. This phenomenon is called ultrasonic cavitation. The implosion of vacuum bubbles breaks down particles [11]. Ultrasonic liquid processing is described by a number of parameters (amplitude, pressure, temperature and concentrations of compounds). The effect of the process may be determined as a function of the energy (E) divided by the processed volume (V):

$$\text{effect} = f\left(\frac{E}{V}\right)$$

The energy (*E*[*Ws*]) can calculate from the power output (*P*[W]) and the duration of exposure (*t*[s]):

$$E[J] = PW] \times tS]$$

The function alters with changes in the individual parameters. Additionally, the actual power output per surface area of the sonotrode of an ultrasonic unit depends on the parameters as was written by Hielscher [12].

There are two sonication routes for wet-grinding to achieve particle size reduction. One is the static method, which means that a sample at rest is sonicated. Another possibility is the dynamic method, which allows the continuous circulation of the sample by means of a pump during the sonication. These two methods are appropriate for particle size reduction of materials with different physico-chemical properties [13]. The production of intermediates (suspension form for example for preparation of nasal spray and gel) and powder products (after drying) is carried out by applying a short-term ultrasound energy input. Application of ultrasounds can be easily scaled up, e.g. sonification is successfully applied at industrial level for the preparation of metal nanoparticles [14]. Sonochemistry involves the use of an ultrasound technique to promote chemical reactions [15]. As regards pharmaceutics, power ultrasound can be applied for emulsification and to investigate the sedimentation of emulsions and suspensions [16,17]. Supercritical, solvent diffusion [18] and melt emulsification are well-known bottom-up methods techniques in the field of sonocrystallization for solving solubility problems of drugs [19]. The disintegration of drug particles (top-down approach) has not widely investigated so far for improving properties of drugs.

Meloxicam (MEL) is a NSAID (non-steroidal anti-inflammatory drug) with anti-inflammatory, analgesic and antipyretic effects, it can be used intranasally. MEL was chosen as a model crystalline drug because of its poor aqueous solubility [20] and high melting point (270 °C) [21].

This research investigates the applicability of ultrasound technology for intensified particle size reduction and the setting of the process. Since the literature data relating to the application of ultrasound for the particle size reduction of drug materials are lacking, in this study the static and dynamic sonication methods are compared to each other (as organic solvent-free wet-grinding techniques) and their effects in reducing the particle size of MEL are investigated, using the excipient, PVP K-25, as an agglomeration inhibitor. A two-level fractional factorial design was used to determine the most effective process parameters, and the effects of ultrasound on the physico-chemical properties of MEL were studied.

2. Experimental

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 additive, PVP K-25 (polyvinylpyrrolidone), was purchased from BASF (Ludwigshafen, Germany).

2.2. Methods

2.2.1. Preparation of sonicated formulations

In our systems water was used as a liquid for the sonication studies. Meloxicam has poor aqueous solubility (4.4 μg/mL). PVP is a dispersant, it is used in the pharmaceutical industry as a synthetic polymer vehicle for dispersing and suspending drugs. The presence of weak bonding between the carboxyl group of Meloxicam and the PVP helps the molecules to separate from each other. The aggregation is prevented, therefore stability of the system could be improved. In other case, PVP can work as a wetting agent, but does not increase the solubility and dissolution of the drug significantly. In each sample, 0.5% of PVP K-25 was dissolved in an appropriate volume of water (25 and 100 mL respectively for static and dynamic sonication) at pH 5.56. Before sonication, the suspensions were stirred with a magnetic stirrer for 5 min. A high-power ultrasound device (Hielscher UP 200 S Ultrasonic processor, Germany) operating at 200 W was applied as the energy input in the sample preparation in order to achieve a particle size reduction. The working wavelength of the ultrasound used in the treatment was 6.6 cm. T. During the sonication energy is transmitted from the probe directly into the sample with high intensity and the sample is processed quickly. In the case of static sonication, samples at rest were treated (the suspensions were not circulated). In the case of dynamic sonication, the samples were circulated continuously with a peristaltic pump (Heidolph PD 5006 Pump drive) in a double-walled flow cell (Flow Cell GD14 K) during the sonication. The temperature was set with a thermostat in both cases (Julabo, Germany).

The height of the medium was 8 cm in case of the dynamic sonication and 2 cm by 25 mL and 3.5 cm by 100 mL in the case of static sonication. The wavelength of the ultrasound used in the treatment was 6.6 cm. Applying different sonotrode positions, the immersed surface area of the ultrasonic horn could be changed (Fig. 1). The surface area of the ultrasonic horn in contact with the sample was determined by the amount of the immersed area of the cylinder and of the tip surface of the probe. It was 0.15 cm^2 in case

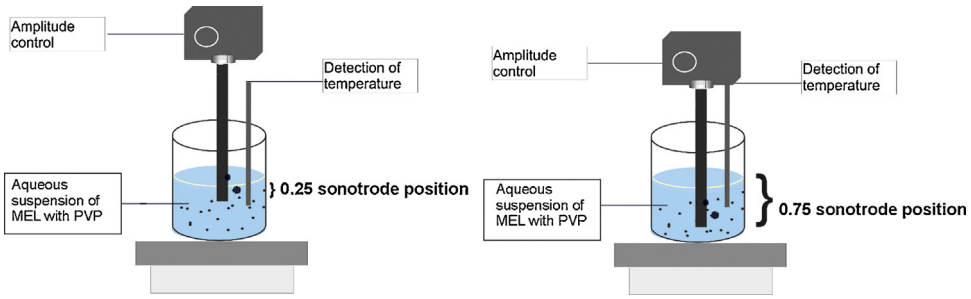

Fig. 1. Sonotrode positions in the aqueous suspension of MEL with PVP.

of the static sonication using 25 mL sample volume and at 0.25 position (means that the sonotrode was immersed to 25% of the total depth of the liquid); and 8.8 cm^2 by the position of 0.75 (the sonotrode was immersed to 75% of the total depth of the liquid). In the case of the static sonication and 100 mL sample volume, at the 0.75 position the immersed surface area was 6.77 cm^2 and at position 0.25 the immersed surface area was 1.23 cm^2. During the dynamic sonication the immersed surface area of the ultrasonic horn was constant 12 cm^2. The applied sonication parameters are given in Table 1.

Adiabatic experiments were carried out to reveal the efficiency of the transmission of the ultrasonic energy into the liquid (Fig. 2). The appropriate volume of 0.5% PVP-solution was used without the presence of meloxicam. The temperature was mesured in every 5 min, from 0 to 30 minutes under sonication processing. The temperature rise was the most notable in the case of small sample volume (25 mL). Within 5 min 90 °C could be reached using 25 mL solution. The dynamic and static methods were compared with the following parameters: 100 mL sample volume, 0.25 sonotrode position. In the case of static sonication after 10 min the temperature was higher, meaning higher energy input. In the case of the dynamic method the temperature increase was slower, due to the circulation in the vessel.

2.2.2. Preparation of solid products for physical-chemical investigations of pure MEL

Suspensions prepared with the chosen parameters were dried in order to obtain solid products for physical-chemical investigations. Samples were filtered through filter paper (MUNKTELL Filter Discs, Grade: 1290, pore size: 3–5 μm, diameter: 185 mm), the filtrate was washed with the medium of the suspension (0.5% aqueous solution of PVP K-25, pH 5.56) and the wet crystals were dried in a vacuum dryer (Binder, Germany) at 40 °C in order to obtain solid products. After drying, the percentage yield was determined and the physico-chemical properties of the products were investigated.

2.2.3. Determination of particle size distribution and specific surface area by a laser diffraction method

The volume based particle size distribution (PSD) of the raw MEL was measured by laser diffraction (Mastersizer 2000, Malvern Instruments Ltd. Worcestershire, UK) with the following parameters: 300RF lens; small volume dispersion unit (2500 rpm); refractive index for dispersed particles 1.720; refractive index for dispersion medium 1.330. Dynamic Laser Light Scattering method was used to determine the PSD. The MEL particle size was determined directly on the initial suspension in water in which PVP was dissolved. The size analysis was repeated three times. Water was used as dispersant and the obscuration was in the range 11–16% for all measurements in both cases. In all cases, the volume weighted particle size distributions, D10, D50, and D90 (where for example D50 is the maximum particle diameter below which 50% of the sample volume exists–also known as the median particle size by volume) were determined and evaluated.

Table 1
The applied sonication parameters.

	Static sonication	Dynamic sonication
Volume (mL)	25; 100	100
Position	0.25; 0.75	0.25
RPM (pump)	–	50; 100
Concentration of MEL (mg/mL)	2; 18	2; 18
Temperature (°C)	0; 36	0; 36
Amplitude (%)	30; 70	30; 70
Time (min.)	10; 30	10; 30

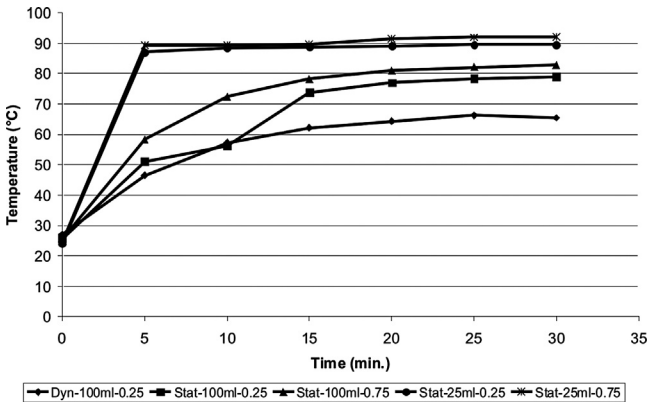

Fig. 2. Results of the adiabatic investigations for appropriate volume of 0.5% PVP solution without the presence of MEL.

The specific surface area was derived from the particle size distribution data. The assumption was made that all the particles measured were spherical.

2.2.4. Image analysis

The shape and surface characteristics of the samples were visualized by using a scanning electron microscope (Hitachi S4700, Hitachi Scientific Ltd. Tokyo, Japan). 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 15 kV and 10 μA. The air pressure was 1.3–13 MPa. In suspensions prepared with the most effective parameters PVP was washed out and the crystals were dried in order to obtain solid particles for SEM analyses.

2.2.5. Design of experiments

Six parameters were screened in the static sonication experiments, using a two-level fractional factorial design of resolution III. Here, the main effects are not confounded with each other, whereas they are confounded with two-factor interactions. This design is typically used for the rapid identification of the main effects governing the behavior of a multi-parameter system. High and low values for each parameter were set on the basis of our prior experience with similar tasks (reported in Table 1). Dynamic sonication experiments were run by screening five parameters, using the same experimental design type. High and low parameter values for the dynamic sonication experiments are presented in Table 1, as well. All the experiments were run as triplicates.

2.2.6. Further investigations of the products

2.2.6.1. X-ray powder diffraction analysis (XRPD). The physical state of the MEL in the samples was evaluated by XRPD. XRPD patterns were produced with an X-ray Diffractometer Miniflex II (Rigaku Co. Tokyo, Japan), where the tube anode was Cu with Kα = 1.5405 Å. The pattern was collected with a tube voltage of 30 kV and a tube current of 15 mA in step scan mode (4° min^{-1}). The instrument was calibrated by using Si.

2.2.6.2. Differential scanning calorimetry (DSC). DSC measurements were carried out with a Mettler Toledo DSC 821^e thermal analysis system with the STAR^e thermal analysis program V9.0 (Mettler Inc. Schwerzenbach, Switzerland). Approximately 2–5 mg of pure drug or product was examined in the temperature range between 25 °C and 300 °C. The heating rate was 5 °C min^{-1}. Argon was used as carrier gas at a flow rate of 10 Lh^{-1} during the DSC investigations.

2.2.6.3. 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 all of these investigations PVP was washed out and the crystals were dried.

3. Results and discussion

3.1. Effects of process parameters on particle size distribution

3.1.1. Static sonication

An analysis of the results measured by laser diffraction revealed that the static sonication under the various sonication parameters resulted in a roughly 25–70% decrease in average MEL particle size. The D10, D50 and D90 values are reported in Table 2.

Their relationship with the sonication variables was analyzed quantitatively on the basis of the D50 data in the main effects plots (Fig. 3.) and interaction plots (Fig. 4.). The D10 and D90 data furnished similar results. A main effect plot for a given parameter is obtained by averaging the results of each run where this parameter was set to low or to high, and connecting these averages with a line. If the studied parameters are independent, the plot gives a clear indication of the response of the system to the selected variable. The main effects plots for the MEL particle size distribution indicated that the small sample volume, the high amplitude and the long sonication time were preferred for efficient particle size reduction whereas the position of the sonotrode, the concentration of the solution and the temperature influenced the particle size less (Fig. 3.). It can be seen that small sample volume, high ultrasound amplitude and the long sonication time were preferred for efficient particle size reduction.

Interaction plots show the effects between variables, which are not necessarily 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. The interaction plots presented in Fig. 4 for D50 can be used to gain insight into the complex interactions between the sonication parameters. Longer sonication time resulted in a particle size reduction, independently of the other process parameters. The connection between the physical parameters of sonication (amplitude, position and volume) was unequivocal. The high amplitude resulted in a particle size decrease independently of the sonotrode position and sample volume. The connection between concentration, temperature and amplitude demonstrated that the particle size reduction effect of the increased amplitude occurred at low concentration and high temperature. The relationships between temperature and concentration, and temperature and volume, were unidirectional, in contrast with the temperature position relationship: increase of the temperature was useful in the lower position. At the high concentration the upper, while at the low concentration the lower position resulted in smaller particles.

To summarize the results, the appropriate parameters found for static sonication were the long time sonication (30 min), the high amplitude (70%), the small sample volume (25 mL), the high temperature (36 °C), the lower position of the sonotrode (0.75) and the low MEL concentration (2 mg/mL). In the sample at rest, the distribution of the sonication effect was inhomogeneous; the region near the sonotrode (therefore in a small volume) was the most effective. Because of the large energy input and long sonication, increased amplitude was required to achieve small particles. The larger energy investment resulted in increased cavitation activities. When the temperature was raised, the kinetic energy of the particles increased, which adverse affected the cohesive forces. When the low concentration of MEL was used, the amount of energy per particle was greater.

3.1.2. Dynamic sonication

Analysis of the produced MEL measured by laser diffraction revealed that the dynamic sonication under the various sonication parameters resulted in a roughly 15–60% decrease in the average particle size. The size distribution function is reported in Table 3.

The relationship between the sonication variables were analyzed quantitatively on the basis of the D50 data in the main effects plots (Fig. 5.) and interaction plots (Fig. 6). The D10 and D90 data furnished similar results. The main effects plots for the MEL particle size distribution indicated that the circulation of the sample at the low rpm, the high amplitude and the long sonication time resulted in the most significant particle size reduction, whereas the concentration of the suspension influenced the particle size less. The high temperature had a more significant effect on the particle size under dynamic sonication than under static sonication.

The interaction plots presented in Fig. 6. for D50 can be used to gain insight into the complex interactions between the sonication parameters. The increased amplitude and the higher temperature resulted in significant particle size reduction. The longer sonication time had no appreciable effect in the case of the low temperature and the low amplitude. The increase of the concentration had an adverse effect on the particle size at the low circulation rate.

As a conclusion, it may be stated that the most effective process parameters for dynamic sonication were the long sonication time (30 min.), the high amplitude (70%) and temperature (36 °C), the low rotation rate (50 rpm) and the low concentration of the samples (2 mg/mL). Due to the continuous circulation of the samples, the distribution of the sonication effect was homogeneous. The cavitation reduced the particle size efficiently at the low circulation rate. The sample was resident in the cavitation space for a longer period during one sonication cycle. The explanation of the effects of the other parameters is the same as in the case of the static method.

Table 2
Results of static sonication (suspension).

Volume (mL)	Position of sonotrode	Conc (mg/mL)	Temp (°C)	Amplitude (%)	Time (min)	D10 (μm)	D50 (μm)	D90 (μm)
–	–	–	–	–	–	10.82	34.03	75.81
25	0.75	2	36	70	30	1.51	10.16	19.53
100	0.75	2	0	30	30	4.81	23.07	46.88
25	0.25	2	0	70	10	2.75	18.45	42.87
100	0.25	2	36	30	10	5.92	26.52	53.39
25	0.75	18	36	30	10	3.95	19.62	41.51
100	0.75	18	0	70	10	5.19	24.16	46.98
25	0.25	18	0	30	30	3.53	17.12	29.22
100	0.25	18	36	70	30	7.19	20.83	36.62

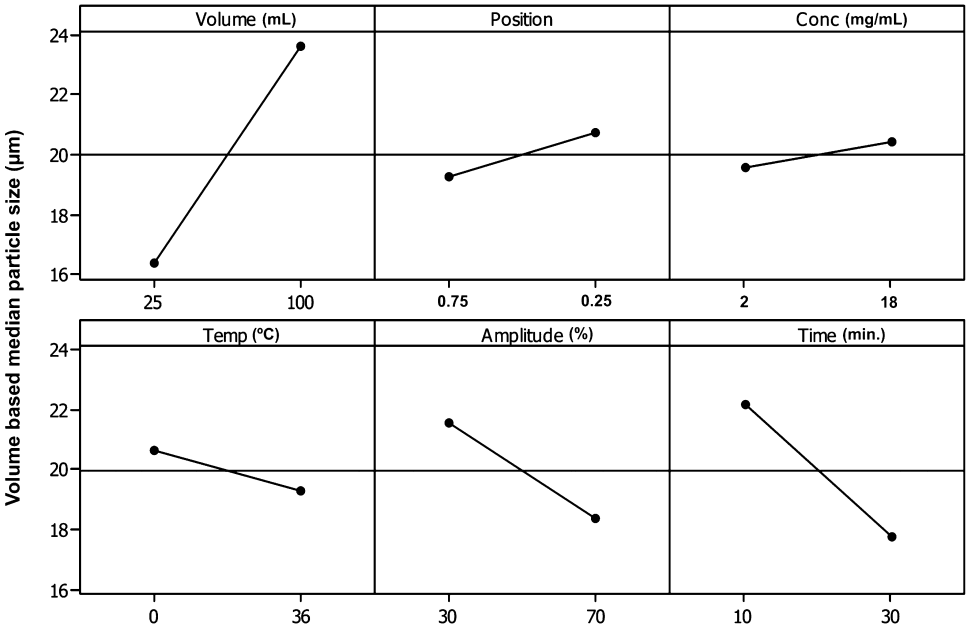

Fig. 3. The main effect plots for the case of static sonication.

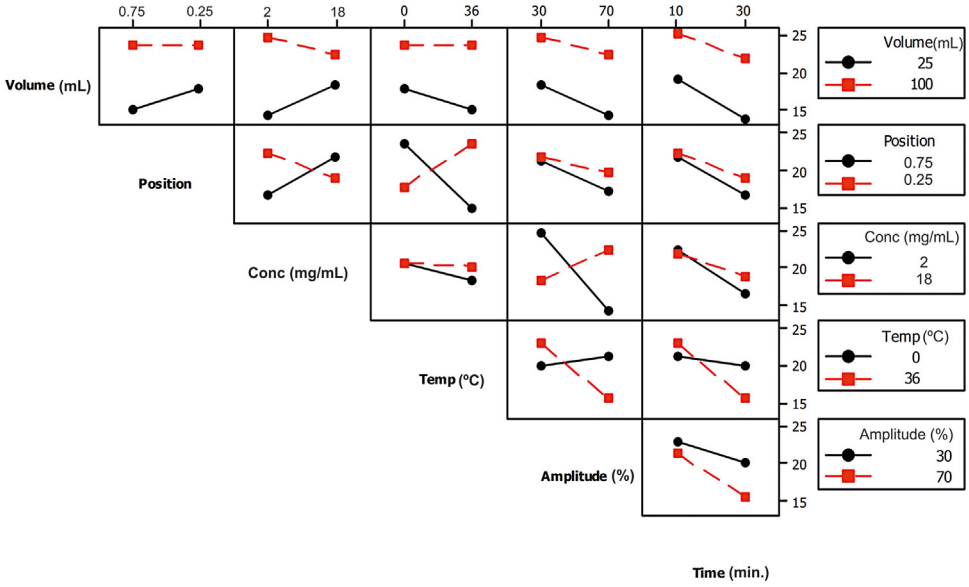

Fig. 4. Interaction plots of the main effects for the static sonication.

3.2. Particle size distribution and specific surface area

The particle size distribution of MEL (Fig. 7) was determined in the suspensions after sonications. During the dynamic sonication the sample is circulated continuously by a pump, which ensures the homogeneous sonication effect. In case of the static sonication a sample at rest is sonicated, so the cavitation effect distribution can be inhomogeneous. The raw MEL had a broad size distribution.

Table 3
Results of dynamic sonication (suspension).

Pump (rpm)	Conc (mg/mL)	Temp (°C)	Amplitude (%)	Time (min)	D10 (µm)	D50 (µm)	D90 (µm)
–	–	–	–	–	10.82	34.03	75.81
50	2	36	70	30	2.20	14.60	35.02
50	2	0	30	30	4.56	24.22	47.05
100	2	0	70	10	5.70	26.90	51.92
100	2	36	30	10	5.90	26.15	52.20
50	18	36	30	10	4.40	22.69	53.54
50	18	0	70	10	6.27	23.54	46.77
100	18	0	30	30	9.06	29.31	45.58
100	18	36	70	30	2.87	16.73	38.03

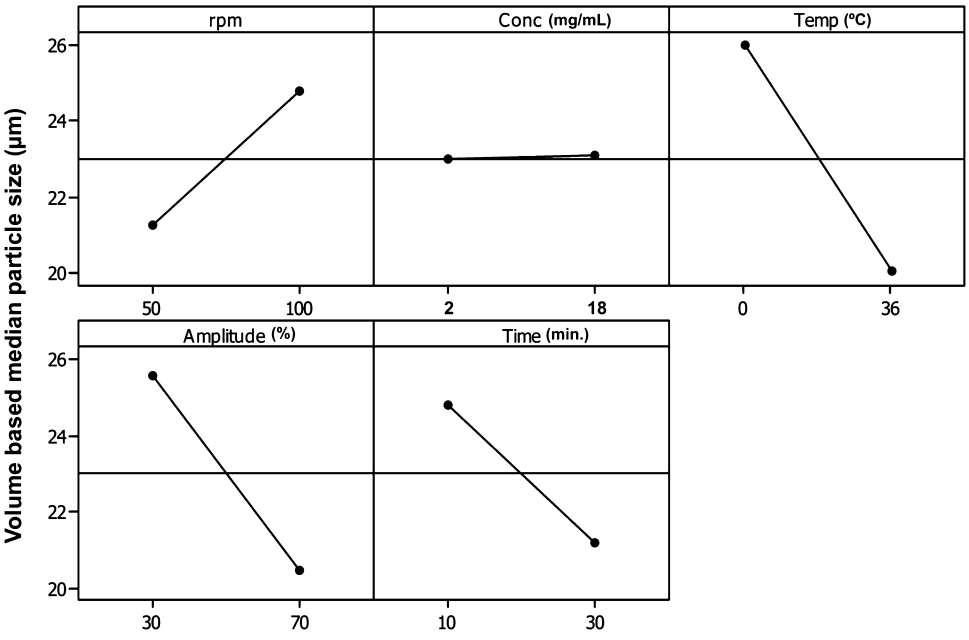

Fig. 5. The main effect plots for the case of dynamic sonication.

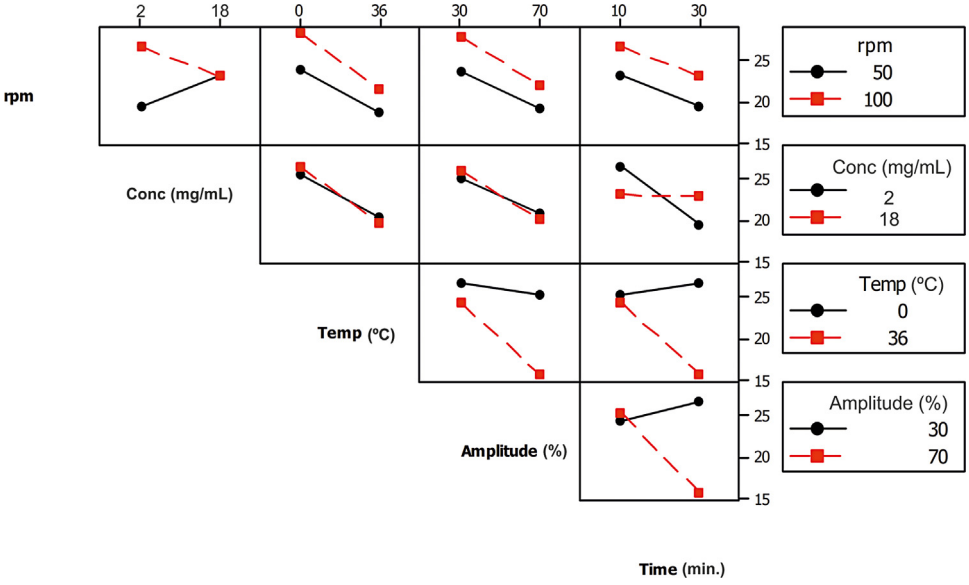

Fig. 6. Interaction plots for the dynamic sonication.

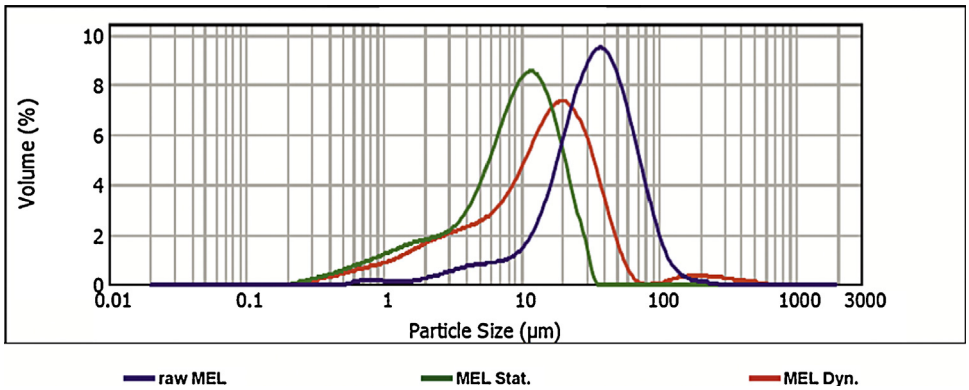

Fig. 7. Particle size distribution of raw MEL and sonicated MEL from suspensions.

Table 4
The specific surface area and size distribution of the raw MEL and the two suspensions from sonication.

	Specific surface area (m^2/g)	D10 (μm)	D50 (μm)	D90 (μm)
raw MEL	0.340	10.82	34.03	75.81
Static sonicated sample (suspension)	2.040	1.51	10.16	19.53
Dynamic sonicated sample (suspension)	1.140	2.20	14.60	35.02

The sonication methods resulted in decreased particles size. The specific surface area of the MEL increased as a consequence of acoustic cavitation in both sonication methods and for both suspensions relative to the raw MEL. The static sonication produced smaller particle sizes compared to the dynamic sonication (Table 4).

3.3. Characterization of the dried products

3.3.1. Particle shape and size

The SEM images (Fig. 8) provided an indication of the morphology of the modified particles. PVP was washed out to check how the surface and shape changed after the sonications compare with raw MEL. The crystal habit of the pure MEL has changed significantly after the procedure. The raw MEL consisted mainly of angular, prismatic crystals with a broad size distribution. The crystal lattice presumably demonstrated defects and cracks. Along them the crystals disintegrated due to the energy input of acoustic cavitation. Probably this factor is responsible for the presence of the broken pieces, which are found on the surface of the larger particles. The drying of the samples could also cause cracks and widen the PSD. The endurance during the treatment is accounted for the roundness and smooth surfaces of the crystals. The yields of the samples were 95% at 0 °C and 90% at 36 °C by both methods. The average size of the dried product was approximately 10 μm in the case of static and 15 μm in the case of dynamic sonication. Due to the high specific surface area of the dried product and since PVP is washed out, agglomeration might occur. Furthermore, aging or washing might also change the crystal size and shape.

3.3.2. X-ray diffraction

The XRPD pattern of pure MEL demonstrated its crystalline structure, as expected. The raw MEL and the sonicated dried MEL composite in both cases displayed the same X-ray diffraction patterns (see supporting information, Fig. S1.). This means that the crystalline form of the micronized MEL was not changed by the sonication and drying procedure.

3.3.3. Differential scanning calorimetry (DSC)

DSC was employed to investigate the crystallinity and the melting of MEL in the pure form and in the sonicated dried products. The DSC curve (Fig. 9) of the raw MEL revealed a sharp endothermic peak at 259.11 °C, reflecting its melting point and confirming its crystalline structure. After drying, the DSC curves exhibited the sharp endothermic peak of the MEL at 258.62 °C in the static case, and at 259.81 °C in the dynamic case, indicating that the crystallinity of the drug was retained. The value of the enthalpy and the onset-endset interval were not changed significantly for the sonicated products as compared with the values for raw MEL, and it can therefore be concluded, that the degree of crystallinity was not decreased by the treatment.

3.3.4. Chemical stability

To determine whether any decomposition occurred during the sonication process, FT-IR spectroscopy was carried out. This proved that no disintegration took place in the samples (Fig. 10). Also the contamination of solution with titanium particles by the cavitational erosion could not be detected. The applied energy did not cause chemical changes in the MEL in aqueous medium during sonication (30 min) at 36 °C. The characteristic bands of MEL were

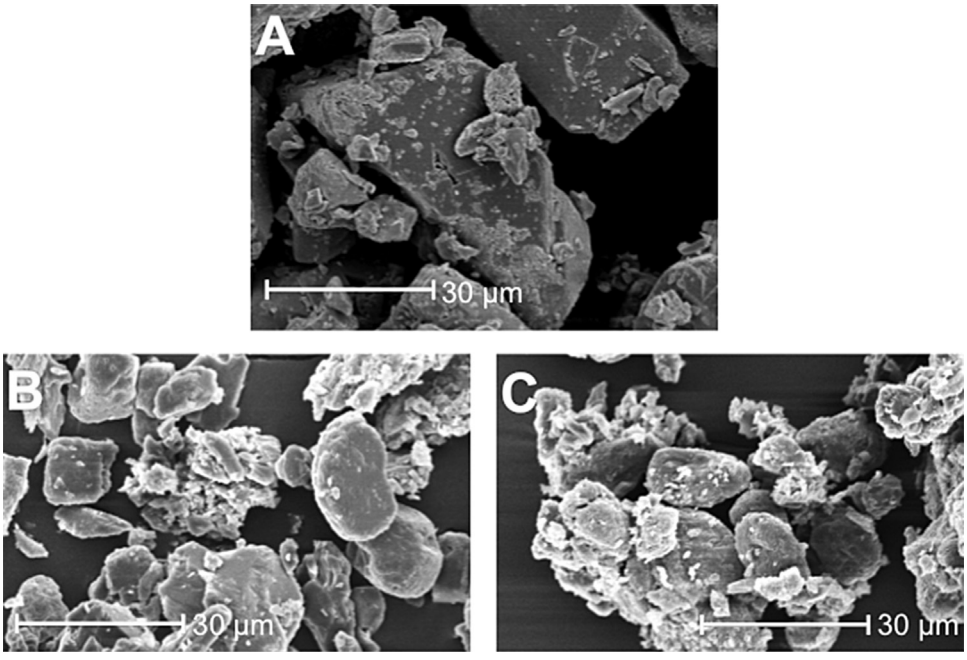

Fig. 8. SEM pictures of raw MEL (A) and the dried products after static (B) and dynamic (C) sonication after 30 min treatment (PVP was washed out).

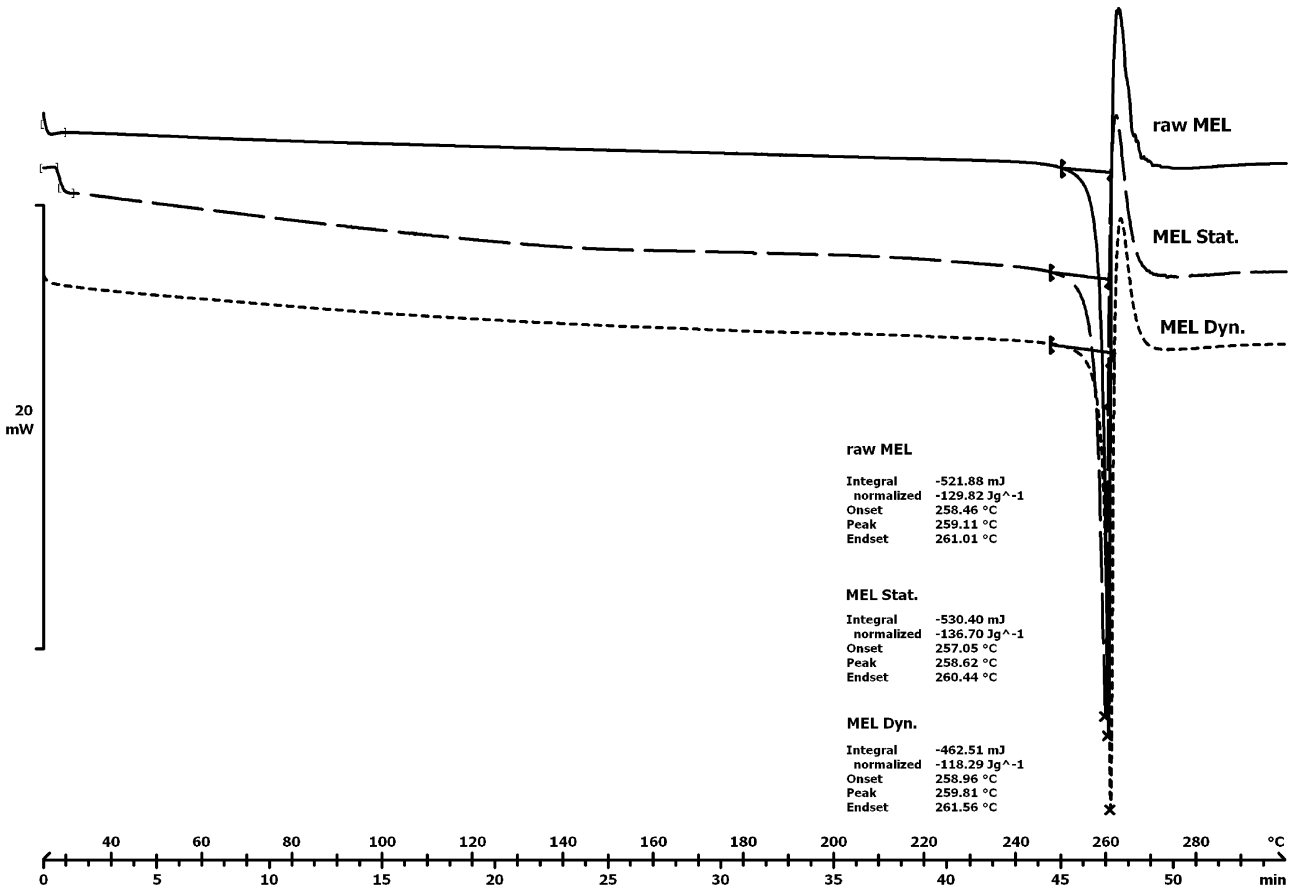

Fig. 9. DSC curves of the raw MEL and the dried sonicated products.

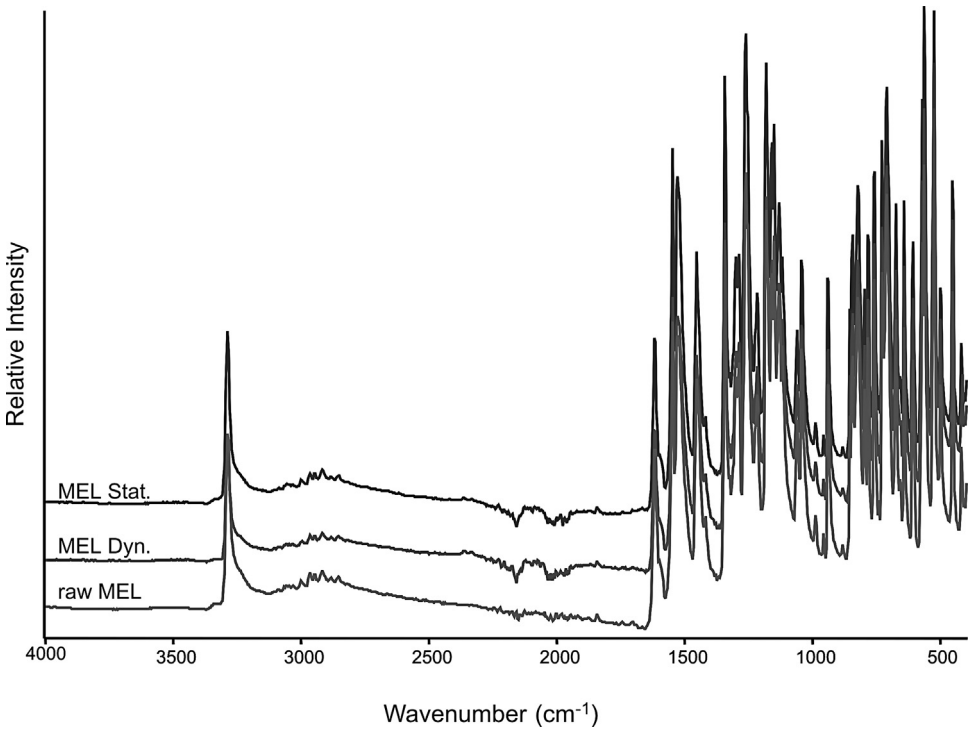

Fig. 10. FT-IR curves of raw MEL and dried sonicated products.

seen in all of the curves of the raw MEL and sonicated products, at 3289.76, 1550.04, 1530.36, 1346.73, 1265.88 and 1184.90 cm^{-1}, denoting the stretching vibration of -NH, the thiazole ring (together with that at 1184.90 cm^{-1}), the amide II band of–CO–NH–C, the asymmetric stretching vibration of the sulfone and the amide III band of–CO–NH–C, respectively.

4. Conclusions

Acoustic cavitation, as a wet-grinding procedure, can be applied to decrease the particle size and change the crystal morphology of drugs. High-intensity ultrasound equipment is easy to clean because of the few moving parts. The parameters can be set precisely and reproduced. Sonication in aqueous medium adheres to green technology: the product does not contain organic solvent residues.

This study applied a two-level factorial design plan to compare the process parameters of static and dynamic sonication methods based on their particle size reduction effects. A long sonication, a high amplitude, a high temperature and a low concentration of MEL proved to play important roles in the sonication procedures. Both of these disintegration methods with adequate process parameters involving a change in crystal habit, may decrease the particle size of MEL significantly in the presence of PVP as additive.

The investigation of the dried products showed that in both cases the crystallinity of the MEL was retained during the sonication and the process did not cause chemical degradation.

The static method is applicable for the preparation of preclinical samples with a reduced particle size of the drug candidate, for which a small sample volume is sufficient.

Dynamic sonication is suitable for preformulation of a micro-suspension, because a larger volume of sample can be used in this method. Standardization is possible, which is important for industry.

These two methods are also appropriate for particle size reduction of materials with different physico-chemical properties, applying a short-term energy input, and for the production of intermediate (in suspension form) and (after drying) dried products for additional pharmaceutical formulations.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cep.2014.10.015.

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