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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

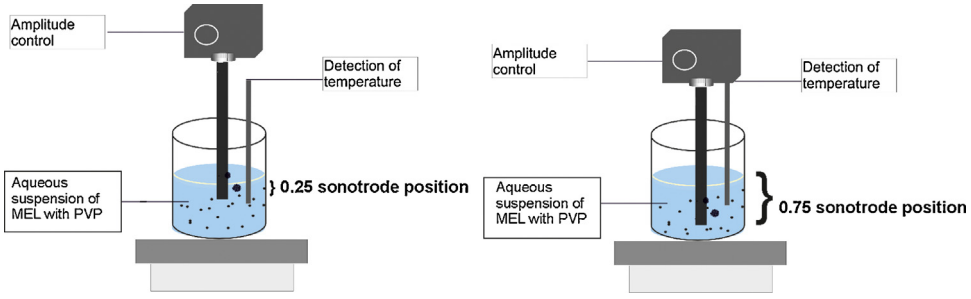

Fig. 1. Sonotrode positions in the aqueous suspension of MEL with PVP.