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Breakage, temperature dependency and contamination of Lactose during ball milling in ethanol

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ABSTRACT

Wet stirred media milling is an established method for the production of drug nanoparticles which are increasing the bioavailability of poorly water-soluble active pharmaceutical ingredients (APIs). While the processability of various organic materials has been proved in aqueous suspensions, this work focuses on the milling of the organic substance Lactose in ethanol. The aim of this study was the comparison of these results with the former studies in stirred media mills with organic materials in water as well as the analysation of recrystallization processes induced by increasing suspension temperature. Regarding the milling performance different grinding media materials as well as sizes, stirrer tip speeds and the solids contents of the suspension were varied. Furthermore the amount of generated product contamination was measured and a correlation to the process parameters and the used grinding beads was analysed. A convincing valuation of the milling results is only possible if there are no agglomeration effects in the suspensions. Therefore, at the beginning a stabiliser screening with different ionic and non-ionic additives was performed in a planetary ball mill. This showed an effect of the process temperature on the recrystallization behaviour of the particles and, thus, the final product fineness and particle shapes what was furthermore confirmed by milling the Lactose under controlled conditions in a stirred media mill.

1. Introduction

It is presumed that up to 90% of the newly found active pharmaceutical ingredients (APIs) generated through drug discovery programs are poorly soluble in water [1]. The formulation of these APIs becomes even more challenging if these APIs are behaving like "brick dust" and are additionally poorly soluble in organic fluids. These characteristics often result in an erratic absorption profile and variable bioavailability affected by the limited dissolution-rate and the ingestion of food [2]. In the past years different strategies have been developed in order to increase the bioavailability of these APIs. One strategy focuses on the reduction of the drug particle sizes (top-down technique) by wet milling in stirred media mills. Based on the equation of Noyes–Whitney, describing the direct proportionality of the dissolution rate to the particle surface area (proportional to square of the particle size), this technique can provide a higher bioavailability of micronized or nanonized APIs [3].

In order to receive stable drug nano- or sub-micron suspensions, former studies found the necessity of an adequate formulation to prevent ground particles from agglomeration [4]. Investigations concerning sufficient particle stabilization against agglomeration for various poorly water-soluble drugs showed that the particles are most efficiently stabilized by steric stabilization systems [5]. Furthermore, an improvement of the product and stabilizing quality has been shown by a combination of surfactants with non-ionic polymers. In this case the surfactants ensure a better wetting of the particles, thereby fostering polymer attachment onto the particle surface [4,6,7]. While agglomeration processes are expected to result from insufficient particle stabilization, ripening effects during the milling process could also be observed [7,8]. Different theories have been developed in order to explain those phenomena, but the origin of the growth is not fully understood yet. One explanation could be the amorphization of the particle surface by mechanical activation, leading to the dissolution of the substance and recrystallization onto other particles [9,10]. In addition, Ostwald ripening should also be taken into consideration

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due to the temperature profiles during particle stressing which leads to high local temperatures [7]. Nonetheless, these theories result in the same effects and are accordingly virtually not distinguishable.

The contamination of the suspension by inorganic wear from the grinding media and milling chamber is a major drawback to the production of drug nanoparticles by wet media milling [11]. Wear reduction strategies are on the one hand, the use of special wear resistant ceramics in the high-energy zones of the mill. On the other hand, the operating parameters are influencing the amount of contamination during the wet milling process as well. Former investigations concerning the amount of wear showed a higher impact of the stirrer tip speed on the product contamination than the grinding medium size [12]. Moreover Breitung-Faes and Kwade [13] found that for the milling of inorganic particles the product contamination is lowest while the mill is operated within its optimised process parameters.

The increasing numbers of newly discovered APIs, which are poorly soluble in water and in various organic solvents, enable a wider choice of fluids for particle dissolving and wet milling. Considering the further processing of the ground suspension and its transfer into an oral solid dosage form, a following drying step of the API suspension, for example with a spray dryer, is essential [2]. Thereby the ethanol-based suspensions can change the framework conditions for the downstream-processing compared to aqueous suspensions. It is assumed that the change of the suspension fluid from water to ethanol could result in a decrease in the particle drying temperature due to its lower boiling point. Considering the thermosensitivity of several APIs, ethanol-based suspensions could reduce the degree of degradation of the API during the drying process. Based on the lower polarity of ethanol compared to water, it is assumed that a different stabilization behaviour of the particles in ethanol is achieved. In addition, the influences on the milling behaviour should be further investigated.

This study focuses on the particle stabilization against agglomeration and the milling behaviour of the organic model compound Lactose monohydrate in the fluid ethanol. A stabilizer screening in a planetary ball mill with different ionic and non-ionic additives is conducted to evaluate their influence on the resulting particle sizes and morphologies. Additionally the recrystallization behaviour of Lactose was further investigated in a planetary ball mill and stirred media mill. With a sufficiently formulated suspension the grinding behaviour is further investigated in a stirred media mill. Thereby, not only different grinding media materials and sizes were taken into consideration but also various solids contents and stirrer tip speeds. Considering product contamination, gravimetric measurements are performed in order to identify the process parameters producing the lowest inorganic wear for a given target particle size.

2. Materials and methods

2.1. Materials

α-Lactose Monohydrate (Carl Roth) with a particle size of x_{50} = 38 µm was used as a poorly ethanol-soluble organic model compound in this study. For the stabilizer screening different polymers and surfactants were used. In Table 1 the used additives are listed naming the used abbreviations and suppliers. Tw80 and DBYK142 were kind gifts from the suppliers. All milling experiments were performed in denatured ethanol (95 vol.%, VWR International).

The milling experiments were conducted with yttrium stabilized zirconium oxide (ZrO_2) and aluminium oxide (Al_2O_3) grinding media. Two different sizes of zirconium oxide media, $d_{GM,50}$ = 325 µm (Sigmund Lindner) and $d_{GM,50}$ = 475 µm (Tosoh Corporation), with a spherical shape and a density of $\rho_{GM,ZrO2}$ = 6067 kg m^{-3} were used. The aluminium oxide grinding media purchased from Saint Gobain with $d_{GM,50}$ = 320 µm and $\rho_{GM,Al2O3}$ = 3910 kg m^{-3} were irregularly shaped.

Table 1
Additives used fort the stabilizer screening.

Additive	Abbreviation	Supplier
2-[2-(2-Methoxyethoxy)ethoxy]acetic acid	TODS	Sigma Aldrich
Benzalkoniumchlorid	BAC	Sigma Aldrich
Cetyltrimethyl-ammonium-bromide	CTAB	Carl Roth
DISPERBYK-142	DBYK142	BYK
Hydroxypropyl cellulose	HPC	Sigma Aldrich
Polyoxyethylene sorbitan monooleate	Tw80	Croda
Polysodium 4-styrenesulfonate	PSS	Sigma Aldrich
Polyvinyl alcohol	PVA	Sigma Aldrich
Polyvinylpyrrolidone	PVP	Sigma Aldrich
Sodium lauryl sulphate	SDS	Sigma Aldrich

2.2. Methods

2.2.1. Stabilizer screening

The stabilizer screening was performed in a planetary ball mill (PM400, Retsch) in modified 1 ml zirconium oxide grinding chambers [14]. These grinding chambers enable stabiliser screenings suitable for small amounts of product with twelve formulations at the same time. These screening experiments were run with zirconium oxide grinding media $d_{GM,50}$ = 475 µm at a sun wheel speed v_{sun} = 400 rpm for 4 h. The solids content of the suspensions was set at c_m = 0.05 and the filling ratio of the grinding media at φ_{GM} = 0.5. For the screening experiments a concentration of the polymers and surfactants under investigation of $c_{m,Add}$ = 0.4 referring to the mass of the particles was chosen.

The influence of the temperature on the recrystallization of the Lactose particles was investigated in the Emax (Retsch). This ball mill can be tempered during the milling process and is operated in batch mode. Stainless steel grinding chambers with a volume of 125 ml were used with zirconium oxide grinding media $d_{GM,50}$ = 475 µm at a filling ratio φ_{GM} = 0.3. The mill was operated at v = 1000 rpm for t = 90 min.

The solubility of Lactose in ethanol or stabilizer solutions at different temperatures was measured using a gravimetric method. Therefore, a supersaturated Lactose solution was prepared, left to solve for 24 h at the investigated temperature and filtered through a syringe filter (mesh width 0.22 µm). The ethanol was evaporated from the solution and the remained mass of Lactose was weighted.

2.2.2. Screening of process parameter

The process parameter screening was performed in the stirred media mill MiniCer (Netzsch Feinmahltechnik GmbH) with a grinding chamber volume of 140 ml. The mill was operated in circuit mode while the separation of the grinding media was realised with a sieve (mesh width 100 µm) located in the centre of the chamber. The grinding chamber as well as the storage vessel were equipped with a double wall and cooled during the whole milling process with a standard water temperature T_{cool} = 10 °C. The grinding media filling ratio was set to φ_{GM} = 0.8 while the grinding media material and sizes as well as the stirred tip speed and the solids content were varied.

2.2.3. Particle size analysis and morphology

The particle size of the ground Lactose was analysed with dynamic light scattering (NANOPHOX, Sympatec). All samples were diluted with a saturated Lactose solution in ethanol. The viscosities of the suspensions were analysed with the Searl measuring system of Bohlin Gemini (Rotonelic Driver). The C14 cylinder with