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Impact of stressing conditions and polymer–surfactant interactions on product characteristics of organic nanoparticles produced by media milling

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ABSTRACT

Stirred media milling as a feasible method to produce organic nanoparticles was studied for the polycyclic aromatic hydrocarbon pyrene in aqueous environment using vinylpyrrolidone-vinyl acetate copolymer (KVA 64) and sodium dodecyl sulphate (SDS) as well as hydroxypropylcellulose (HPC-SSL) as stabilising agents during batch and continuous processing. The influence of stressing conditions described by means of stress energy, stress number as well as mass-specific energy input on product particle sizes is presented. Grinding kinetics observed for batch and continuous operation are comparable under similar stressing and formulation conditions. Furthermore, it was found that the use of small grinding media, i.e. stress conditions where low stress energies and high stress numbers apply, are advantageous with respect to fast kinetics and minimum energy consumption. Moreover, the relationship between product characteristics and formulation parameters, i.e. type and concentration of stabilising agents are thoroughly investigated. Complex formation of KVA 64 and SDS has been proven by means of tensiometry and fluorescence spectroscopy. It is demonstrated that solubilisation of pyrene occurs in the system and that product characteristics are not only determined by pure breakage events or colloidal stability issues but also by dissolution and ripening phenomena: Minimum product particle sizes at similar stressing conditions are observed under conditions where solubilisation and ripening are less pronounced, whereas larger product particles are observed in systems with high solubilisation capacities.

1. Introduction

The demand of organic submicron particles in different branches of industry increased significantly in recent years. Especially in the life science sector the need of organic nanoparticles is enormous. The reduction of particle size down to the submicron range provides many advantages, which are known to positively affect key product characteristics such as dissolution rate and bioavailability [1–3].

Stirred media milling is an established and frequently used top-down approach, which allows the scalable production of crystalline organic nanosuspensions in a well-reproducible manner [4,5]. During collisions of grinding beads with feed particles the kinetic energy of the milling beads is transferred into internal stress and strain in the product particles and, hence, product formation occurs by fracture [6,7]. The effect of material properties on fracture of organic crystals was discussed by Meier et al. [8].

Particularly in the submicron range, product properties are strongly influenced by particle–particle interactions [9], i.e. the grinding success is dependent on colloidal stability. By decreasing the particle size, the specific surface area increases and so the Gibbs free energy in the system. Since nanosuspensions are thermodynamically unstable colloidal systems, suitable steric, electrosteric or electrostatic stabilisers have to be selected to inhibit particle agglomeration [10,11].

Furthermore, a broad particle size distribution and high solubility of the processed compound in the formulation may induce Ostwald ripening resulting in further suspension instabilities [11–13]. Thus, besides breakage and de-agglomeration phenomena, enhanced dissolution and ripening phenomena as a result of mechanical activation have been reported to affect product particle sizes during media milling [14–19].

Several systematic screening attempts are listed in the literature to correlate suspension stability and physicochemical properties of organic compounds and stabilisers [20–22]. Surface energies of drug and

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stabiliser as well as the hydrophobicity of the drug were found to be two decisive factors for suspension stability. However, the selection of suitable formulation parameters is up to now rather empirical due to a lack of fundamental understanding of the underlying interaction mechanisms. It is generally suggested that formulations containing both, a neutral polymer and an anionic surfactant, provide the best performance with respect to limiting product particle size and suspension stability.

In this study the stirred media milling process of the polycyclic aromatic hydrocarbon pyrene was investigated. Influences of stressing and formulation conditions on product characteristics at constant process temperature have been studied. It was found that grinding kinetics and the energetic efficiency of the milling process are strongly influenced by the chosen process parameters: Applying low stress energies and high stress numbers is advantageous with respect to process kinetics and minimum energy consumption. Moreover, it was found that the apparent low solubility of pyrene is significantly affected by polymer–surfactant interactions in the formulation, which was proven by means of surface tension measurements, fluorescence and UV–Vis spectroscopy. A correlation of initial solubility of pyrene in the applied formulations and final product particle sizes at comparable stressing conditions during media milling was found. It could be shown that product particle sizes are not only determined by pure mechanical energy input and size reduction but also by dissolution and ripening phenomena: Smallest product particles were obtained when applying formulations with low solubilisation capacities.

2. Materials and methods

2.1. Materials

Pyrene feed material (purity ≥95%, $x_{10,3} = 13.2$ μm, $x_{50,3} = 51.2$ μm, $x_{90,3} = 112.1$ μm as determined by static light scattering (see Section 2.2.2)) was purchased from Sigma Aldrich (Germany). Key physicochemical characteristics of the model compound are provided in Table 1. Scanning electron microscopy images (see Section 2.2.6) of irregular shaped pyrene feed crystals are shown in Fig. 1. Sodium dodecyl sulphate (SDS) was purchased from Merck KGaA (Germany). Hydroxypropylcellulose (SSL grade, HPC-SSL) and vinylpyrrolidone-vinyl acetate copolymer (Kollidon® VA 64 fine (KVA 64)) were kindly gifted from Nisso Chemicals Europe GmbH (Germany) and BASF SE (Germany), respectively. Chemical structures of pyrene and the applied stabilising agents are given in Fig. 2. Deionised water was used as solvent throughout the study. All chemicals were used as received without further purification.

2.2. Methods

2.2.1. Media milling

Media milling experiments were performed in batch as well as in recirculation mode. Grinding experiments in batch mode were carried out using a vertical lab-scale stirred media mill PE075 (Netzsch-Feinmahltechnik GmbH, Germany) in the speed range of 850–2000 rpm corresponding to stirrer tip speeds in the range of 2.9–6.4 m/s. The mill was equipped with an Al_2O_3 three-disc-stirrer and a double-walled grinding chamber lined with zirconium oxide of 0.6 L volume. The process temperature inside the milling chamber has been set to (293.0 ± 1.5) K using a thermostat unistat 905w (Peter Huber Kältemaschinenbau GmbH, Germany). For quantification of the consumed mass-specific grinding energy the mill was equipped with a torque metre installed at the shaft (DR3000, Lorenz® Messtechnik GmbH, Germany). Milling experiments in recirculation mode were performed using a horizontal laboratory bead mill PML 2 (Buehler Holding AG, Switzerland). The mill was equipped with a double walled SiSiC grinding chamber of 0.9 L volume and a disc stirrer with five polyurethane discs. Temperature control was realised by cooling water flow. Milling was performed at (293.0 ± 2.0) K at a constant volume flow of the product suspension (20 L/h). The energy input was measured by recording the electrical power consumption. All grinding experiments were carried out with wear resistant yttrium-stabilised zirconium oxide beads (YTZ®, ρ_{GM} of 6050 kg/m^3, Tosoh Inc. (Japan) and Sigmund Lindner GmbH (Germany)) of different sizes ($d_{GM} = 0.1$–2.0 mm). Aqueous suspensions with mass concentrations of 5.0 wt.% of pyrene were processed throughout this study. Mass concentrations of all excipients are given as relative concentrations with respect to the amount of pyrene. Samples for size analysis during batch milling were taken from the middle of the grinding chamber after stopping the PE075 stirred media mill at certain time intervals. Regarding the experiments with the horizontal stirred media mill PML 2, all samples were taken from the stirred storage vessel.

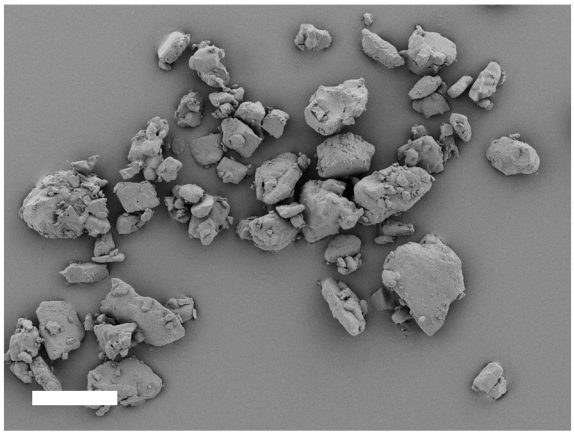

Fig. 1. SEM micrograph of pyrene feed crystals. Scale bar corresponds to 100 μm.

Table 1
Key physicochemical properties of pyrene.

Solubility in H_2O (298.2 K)[a] μg/mL	Molecular weight[b] g/mol	Density ρ[b] (298.2 K) g/cm^3	Melting point[b] K	Log (octane–water partition coefficient) $logP_{ow}$[c]
0.14 ± 0.01	202.25	1.27	423.8	5.18

[a] [23]
[b] [24]
[c] [25]

2.2.2. Particle size analysis

Size analysis of pyrene feed material was performed by static light scattering (SLS) using the Mastersizer 2000 (Malvern Instruments Ltd., Malvern, UK). Particle size distributions of milled pyrene suspensions were measured by dynamic light scattering (DLS) using a Honeywell Ultrafine Particle Analyser 150 (UPA, Microtrac Inc., USA) or Nanophox (Sympathec GmbH, Germany) at (293.0 ± 0.5) K. Prior to size analysis all sample suspensions were properly diluted with a saturated pyrene solution to avoid dissolution effects and multiple scattering during size analysis. The measured particle size distributions are depicted as mass density (q_3) and mass cumulative (Q_3) distributions. Average values and the standard deviations obtained from three single measurements are reported in the following.

2.2.3. Surface tension measurements

Surface tensions were determined by the pendant drop method using a drop shape analyser DSA100 (Krüss GmbH, Germany) at (293.0 ± 1.0) K. Drop profiles were fitted using the Young-Laplace equation to extract the surface tension. Hereafter, average values and calculated standard deviations obtained from ten individual drops are reported.