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Research Paper

Effect of polymer species and concentration on the production of mefenamic acid nanoparticles by media milling

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ABSTRACT

The effect of four structurally different polymer species (hydroxypropylcellulose, polyvinylpyrrolidone, vinylpyrrolidone-vinyl acetate copolymer and polyvinyl alcohol) on the production of mefenamic acid nanoparticles during media milling has been studied. It was found that product particle sizes are strongly determined by the type of polymeric stabiliser as well as by its concentration at constant process conditions. With respect to small product particle sizes an optimum excipient concentration was identified and adjusted for colloidal stability of the drug nanosuspensions. Furthermore, it was found that overdosing of excipients must be omitted to suppress ripening due to enhanced solubilisation phenomena. Hence, the smallest product particle sizes were obtained using a polymeric stabiliser which exhibits a high affinity to the model drug compound and a low solubilisation capacity. Affinities of each polymer species to mefenamic acid and corresponding surface concentrations were determined using straightforward and simple viscosity measurements of the supernatant. A relationship between polymer affinity, solubilisation capacity and limiting product particle size has been observed, which supports the hypothesis that final product particle sizes are rather determined by the solid–liquid equilibrium than by pure mechanical fracture.

1. Introduction

Many new drug entities exhibit a strong hydrophobic or lipophilic character causing an extremely low aqueous solubility, which is often related to a poor oral bioavailability [1]. According to the Noyes–Whitney/Nernst–Brunner equation, the dissolution rate of a solid active pharmaceutical ingredient (API) is proportional to the specific surface area available for dissolution [2]. Therefore, an increase in specific surface area, e.g. due to size reduction, leads to an increase in dissolution rate of the solid and consequently to an improved oral bioavailability [3,4].

Top-down methods such as wet grinding allow the scalable production of nanoparticulate products at high solid content in a well-reproducible fashion [5–9]. In recent years, several top-down processes such as nanomilling and high pressure homogenisation have been applied for the production of nanosized APIs, which have been successfully transferred into commercial oral administrative drug products (e.g. Rapamune® (Pfizer (Wyeth)), Emend® (Merck) or TriCor® Lyphantyl® (Fournier Pharma, Abbott Laboratories)) [10,11].

By collisions between grinding beads and feed particles the kinetic energy of the grinding beads is transferred to the feed particles resulting in internal stress and strain fields. If the elastically stored energy in the product particles is sufficiently high to induce crack opening particle fracture occurs [12,13]. In combination with mechanically-induced fracture events, often neglected effects of mechanochemical activation may also control product properties (e.g. size and shape). Several mechanochemical phenomena such as enhanced dissolution and ripening, radical formation and phase transformations have been observed [14–20].

Along with the already mentioned advantages of organic nanoparticles, complex stability issues against agglomeration and ripening have to be addressed and solved in any sustainable formulation strategy [21,22]. Nanosized organic particles in polar solvents are typically unstable and tend to particle agglomeration. Therefore, efficient stabilisation is crucial [23,24]. Particle size and dissolution behaviour are known to be sensitive to type and concentration of the applied stabilising agents [25]. Stabilisers either can act as entropic barriers (steric stabilisation), may induce electrostatic repulsion between the dispersed particles (electrostatic stabilisation) or both mechanisms can occur in parallel (electrosteric stabilisation). Up to now, the selection of an appropriate formulation for the production of pharmaceutical nanosuspensions is rather empirical [26,27], even though several attempts were

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made to identify and correlate physicochemical key properties of drug particles and stabilisers [28–30]. In case of a broad particle size distribution and enhanced solubility of the API in the formulation, Ostwald ripening can also affect the stability of nanosuspensions [31–34].

Objective of the current study was to investigate the influence of key formulation variables on product properties of the API mefenamic acid during media milling. In particular, the impact of polymer species and concentration was studied. Mefenamic acid was wet ground in the presence of four structurally different polymeric stabilisers (hydroxypropylcellulose, polyvinylpyrrolidone, vinylpyrrolidone-vinyl acetate copolymer and polyvinyl alcohol), which are frequently used in the pharmaceutical industry in formulating poorly water soluble actives. It is shown that the final product particle size at constant process conditions is a function of the applied polymer species and concentration. A correlation between limiting product particle size and initial solubility of mefenamic acid in the pure stabiliser solution was found. A straightforward and rather simple method based on viscosity measurements is proposed to evaluate affinities and surface concentrations, respectively, of adsorbed polymer species to mefenamic acid drug particles.

2. Materials and methods

2.1. Materials

Mefenamic acid (MA) was purchased from TCI EUROPE N.V. (Belgium). Scanning electron microscopy images (see Section 2.2.6) of as received MA agglomerates and the corresponding particle size distribution as determined by static light scattering (see Section 2.2.2) are shown in Figs. 1 and 2, respectively. The feed material consists of primary particles around 2 µm (x_{Feret} = 2.2 ± 0.9 µm) as determined by image analysis, see Fig. 1B. Hydroxypropylcellulose (SSL grade (HPC-SSL)), polyvinylpyrrolidone K-30 (Kollidon® 30 (PVP K-30)), vinylpyrrolidone-vinyl acetate copolymer (Kollidon® VA 64 (KVA 64)) and polyvinyl alcohol (98–99% hydrolysed (PVA)) were used as stabilising agents (see Fig. 3 for chemical structures of the monomer units). HPC-SSL and KVA 64 were kindly gifted from Nisso Chemicals Europe GmbH (Germany) and BASF SE (Germany), respectively. PVP K-30 and PVA were purchased from BASF SE (Germany) and Sigma–Aldrich (Germany), respectively. Throughout the study, deionised water was used as solvent. All chemicals were used as received.

2.2. Methods

2.2.1. Media milling

Prior to the grinding experiments, the polymeric stabilising agents were added under stirring to deionised water. Then, MA drug feed particles were dispersed in the stabiliser solution and kept under further mechanical agitation for 30 min to ensure complete wetting. Media milling experiments were performed using the laboratory-scale batch stirred media mill PE075 (Netzsch-Feinmahltechnik GmbH, Germany) and yttrium-stabilised zirconium oxide grinding beads (YTZ®, ρ_{GM} = 6050 kg/m^3, Tosho Inc., Japan) with a nominal diameter d_{GM} of 0.5 mm. The stirrer tip speed v_{tip} has been set to 5.0 m/s. The temperature in the grinding chamber has been adjusted using the thermostat FPW80-SL (Julabo GmbH, Germany) to a mean temperature of (293 ± 1.5) K. A mass fraction of 3.0% w/v of MA has been used throughout all grinding experiments. The batch size of MA raw suspension for each milling experiment was 120 g. In the following, the amount of excipient will be given as mass fraction relative to the amount of MA. The stirred media mill was stopped for sampling at certain time intervals and samples were taken from the middle of the grinding chamber for size analysis (see Section 2.2.2).

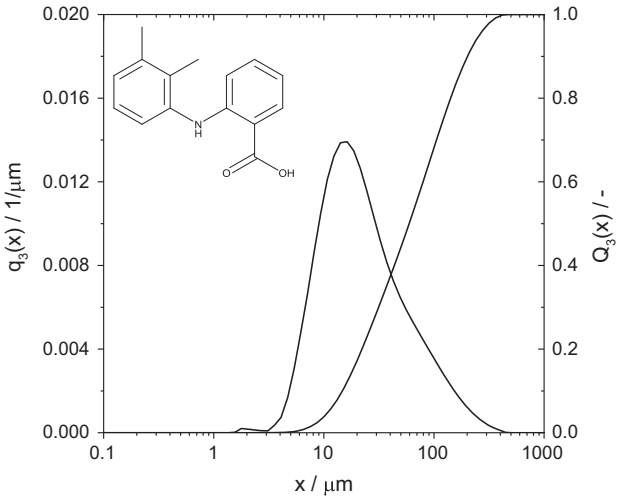

Fig. 2. Mass density distribution q_3, mass cumulative distribution Q_3 of MA feed material as determined by static light scattering and molecular structure of MA.

2.2.2. Particle size analysis

Particle size distributions were determined either by dynamic light scattering (DLS) using the ultrafine particle analyser UPA 150 (Microtrac Inc., USA) or by static light scattering (SLS) using the Mastersizer 2000 (Malvern Instruments Ltd., United Kingdom). To avoid multiple scattering and dissolution effects during size analysis, all sample suspensions were appropriately diluted using a saturated MA solution. In the following, the volume median diameter $x_{50,3}$ was used as representative value. The average values and standard deviations calculated from three single measurements are reported.

2.2.3. Solubility measurements

To determine the (apparent) saturation concentration of MA in aqueous solution in the presence of abovementioned polymer species, blank polymer solutions were prepared by dissolving each

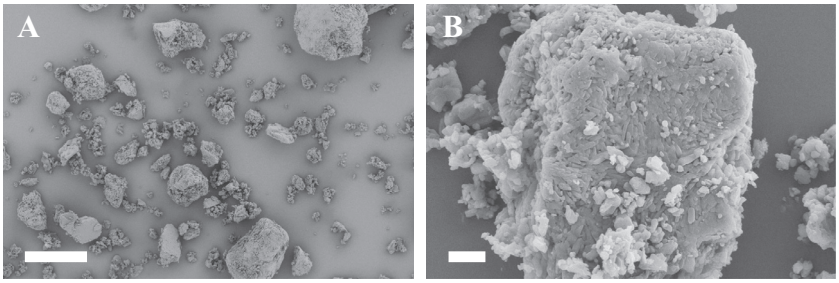

Fig. 1. SEM images of MA feed material. Scale bars correspond to 100 µm (A) and 10 µm (B), respectively.