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A microhydrodynamic rationale for selection of bead size in preparation of drug nanosuspensions via wet stirred media milling

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ABSTRACT

Although wet stirred media milling has proven to be a robust process for producing nanoparticle suspensions of poorly water-soluble drugs and thereby enhancing their bioavailability, selection of bead size has been largely empirical, lacking fundamental rationale. This study aims to establish such rationale by investigating the impact of bead size at various stirrer speeds on the drug breakage kinetics via a microhydrodynamic model. To this end, stable suspensions of griseofulvin, a model BCS Class II drug, were prepared using hydroxypropyl cellulose and sodium dodecyl sulfate. The suspensions were milled at four different stirrer speeds (1000–4000 rpm) using various sizes (50–1500 μm) of zirconia beads. Laser diffraction, SEM, and XRPD were used for characterization. Our results suggest that there is an optimal bead size that achieves fastest breakage at each stirrer speed and that it shifts to a smaller size at higher speed. Calculated microhydrodynamic parameters reveal two counteracting effects of bead size: more bead–bead collisions with less energy/force upon a decrease in bead size. The optimal bead size exhibits a negative power-law correlation with either specific energy consumption or the microhydrodynamic parameters. Overall, this study rationalizes the use of smaller beads for more energetic wet media milling.

1. Introduction

An increasing number of newly developed molecules exhibit poor water solubility and hence poor bioavailability (Merisko-Liversidge and Liversidge, 2011). One of the approaches for enhancing the bioavailability of these drugs, in particular the Biopharmaceutical Classification System (BCS) Class II drugs, is size reduction of drug particles to nanoscale, which increases the surface area and dissolution rate. Owing to their larger surface area and higher curvature, nanoparticles exhibit higher saturation solubility and dissolve faster than micron-sized particles (Hall, 2010; Noyes and Whitney, 1897). In pharmaceutics literature, particles of sizes up to 1 μm have been regarded as "nanoparticles". While preparation of sub–100 nm drug particles is highly desirable because of their increased surface area and potentially higher solubility as compared with 100–1000 nm drug particles, it is very challenging to prepare such small drug nanoparticles (refer to Li et al., 2015, 2016a). Hence, nanoparticles with a median/mean size between 100 nm and 500 nm have been commonly prepared with the objective of enhancing the bioavailability of BCS Class II drugs (Kumar et al., 2014; Nash et al., 2002).

Among various methods used for the production of drug nanoparticles, wet stirred media milling (WSMM) has been popular and applied to a multitude of poorly water-soluble drugs (Li et al., 2016a). Several marketed products such as Rapamune® (Pfizer (Wyeth), New York City, NY, USA), Emend® (Merck, Kenilworth, NJ, USA), Tricor® (AbbVie, North Chicago, IL, USA), Megace® ES (PAR Pharmaceuticals, Woodcliff Lake, NJ, USA), and Invega® SustennaTM (Janssen, Beerse, Belgium) made use of wet media milling. In this method, micron-sized drug particles in an aqueous solution of stabilizers, usually polymers and/or surfactants, pass through a milling chamber, while the milling media (beads) are retained inside the milling chamber by a screen. High speed rotation of the mill stirrer induces turbulent motion in the suspension, which leads to frequent bead–bead collisions (Eskin et al., 2005b). The particles captured by the colliding beads are subjected to stress and broken down to smaller particles, eventually forming nanoparticles. Stabilizers are usually added to prevent the aggregation of the milled drug particles and inhibit ripening during milling and storage (Kesisoglou et al., 2007; Li et al., 2016a; Verma et al., 2011). Depending on the route of administration intended, milled drug suspensions, shortly

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Nomenclature

Symbols

a	Average frequency of drug particle compressions, Hz
c	Fractional volumetric concentration of the beads
d	Particle diameter (size), m
E	Cumulative energy consumption by the slurry, J
E^*	Specific energy consumption per unit mass of drug suspension, J/kg
F	Milling intensity factor, $m^{0.6}/s^{2.6}$
F_b^n	Average maximum normal force during collision of two identical elastic beads, N
k	Restitution coefficient for bead–bead collisions
K	Coefficient obtained from an empirical correlation
m_{sus}	Total mass of drug suspension, kg
p	Probability for a single drug particle to be caught between the beads
P	Power applied by the mill stirrer (rotor), W
P_w	Stirrer power per unit volume, W/m^3
Q	Volumetric flow rate of the drug suspension, m^3/s
R	Radius, m
R_{diss}	Dissipation (effective drag) coefficient of the bead
R_{diss0}	Dissipation coefficient when relative motion of the bead–liquid is absent
t	Milling time, s
t_{d50}	Milling time required to attain a median drug particle size d_{50} of 0.5 μm, s
t_{d90}	Milling time required to attain a 90% passing size d_{90} of 1 μm, s
u	Stirrer tip speed, m/s
u_b	Average bead oscillation velocity, m/s
V_m	Volume of the milling chamber, m^3
Y	Young modulus, Pa
Y^*	Reduced elastic modulus for the bead–drug contact, Pa

Greek letters

α	Radius of the contact circle formed at the contact of two beads, m
ε	Volumetric fraction of drug particles in the drug suspension
ε_{coll}	Energy dissipation rate due to partially inelastic bead–bead collisions, W/m^3
ε_{ht}	Power spent on shear of equivalent liquid of the slurry at the same shear rate but calculated (measured) as if no beads were present in the flow, W/m^3
ε_m	Non-dimensional bead–bead gap thickness at which the lubrication force stops increasing and becomes a constant
ε_{tot}	Total energy dissipation rate, W/m^3
ε_{visc}	Energy dissipation rate due to both the liquid–beads viscous friction and lubrication, W/m^3
η	Poisson's ratio
λ	Material-dependent factor, $kg/m^{1.6}\,s^{0.4}$
μ_L	Apparent shear viscosity of the equivalent fluid, Pa s
ν	Frequency of single-bead oscillations, Hz
Π	Energy dissipation rate attributed to the deformation of drug particles per unit volume, W/m^3
θ	Granular temperature, m^2/s^2
ρ	Density, kg/m^3
σ_b^{max}	Maximum bead contact pressure at the center of the contact circle, Pa
σ_y	Contact pressure in a drug particle when the fully plastic condition is obtained, Pa
τ_p	Characteristic time constant of the milling process, s
ω	Stirrer (rotational) speed, rpm

Indices

b	Beads
L	Equivalent liquid (milled drug suspension)
p	Drug particle
y	Yield
T	Total
50, 90	50% passing size and 90% passing size of the cumulative PSD

nanosuspensions, can be dried and formulated into traditional solid dosage forms which exhibit fast drug dissolution and enhanced bioavailability (see the review by Chin et al., 2014).

WSMM process is considered time-consuming, costly, and energy-intensive (Kawatra, 2006; Li et al., 2016a), which limits its potential use as a platform technology in pharmaceutical industry for bioavailability enhancement of BCS Class II drugs. Process parameters such as stirrer speed, bead loading, and suspension flow rate can significantly affect the breakage kinetics and milling time required for desired product fineness (Afolabi et al., 2014; Ghosh et al., 2012). In addition, proper selection of bead size along with processing conditions can reduce the energy consumption, cycle time, and operational costs for a desired drug particle size (Kawatra, 2006; Li et al., 2015). Although WSMM process design and optimization entails a good understanding of the breakage kinetics and its controlling process parameters, a great majority of the wet media milling studies have focused on the formulation–physical stability of drug suspensions (Merisko-Liversidge and Liversidge, 2011; Merisko-Liversidge et al., 2003; Wang et al., 2013). Few investigations (Ghosh et al., 2012, 2013; Peltonen and Hirvonen, 2010; Singare et al., 2010; Singh et al., 2011) have made use of experimentation and/or statistically-motivated design of experiment tools for studying the impact of milling process parameters. However, these studies have not used first-principle-based modeling approaches.

Although selection of bead size is of utmost importance in wet media milling (Li et al., 2016a), this has been largely performed as an empirical exercise throughout the literature, based on trial-and-error, which is usually costly and labor/material intensive. A cursory review of recent literature, which is not intended to be comprehensive, on bead sizes used in pharmaceutical wet media milling is presented in Table 1. For each study in Table 1, the optimal bead size, among several bead sizes used, was selected here based on the smallest final particle size after the same duration of milling (fastest overall breakage). While shorter milling has potentially other benefits such as lower risk of degradation, lower total energy consumption besides reduced cycle time and operational costs, these additional performance metrics were not considered in the analysis. Table 1 illustrates that zirconium dioxide (zirconia) beads with wide range of sizes (e.g., 50–15,000 μm) have been used for the production of drug nanoparticles. Besides zirconia beads, beads made up of cross-linked polystyrene with various sizes were also used in wet media milling (Bhakay et al., 2011; Deng et al., 2008; Juhnke et al., 2010). The investigations cited above and in Table 1 were mostly empirical, providing little to no first-principle mechanistic understanding of the impact of bead size. Moreover, they did not provide any *fundamental rationale* behind the selection of specific bead sizes. Another important consideration is that wet media mills of different energetic levels (specific energy consumption), ranging from low/medium-energy mills such as ball mills including planetary or centrifugal ball mills to high-energy mills such as WSMM, oscillating bead mill, etc. were used from small-scale to