



Preparation of stable colloidal suspensions of superdisintegrants via wet stirred media milling



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ABSTRACT

Superdisintegrants are cross-linked polymers that can be used as dispersants for fast release of drug nanoparticles from nanocomposite microparticles during *in vitro* and *in vivo* dissolution. Currently available superdisintegrant particles have average sizes of approximately 5–130 μm , which are too big for drug nanocomposite applications. Hence, production of stable superdisintegrant suspensions with less than 5 μm particles is desirable. Here, we explore the preparation of colloidal suspensions of anionic and non-ionic superdisintegrants using a wet stirred media mill and assess their physical stability. Sodium starch glycolate (SSG) and croscopovidone (CP) were selected as representative anionic and nonionic superdisintegrants, and hydroxypropyl cellulose (HPC) and sodium dodecyl sulfate (SDS) were used as a steric stabilizer and a wetting agent/stabilizer, respectively. Particle sizing, scanning electron microscopy, and zeta potential measurements were used to characterize the suspensions. Colloidal superdisintegrant suspensions were prepared reproducibly. The extensive particle breakage was attributed to the swelling-induced softening in water. SSG suspensions were stable even in the absence of stabilizers, whereas CP suspensions required HPC–SDS for minimizing particle aggregation. These findings were explained by the higher absolute (negative) zeta potential of the suspensions of the anionic superdisintegrant (SSG) as compared with those of the nonionic superdisintegrant (CP).

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1. Introduction

Superdisintegrants are water-insoluble, swellable, cross-linked polymers that have found common use in tablet formulations for reduction of disintegration time (Augsburger, Brzeczko, Shah, & Hahm, 2007; Omidian & Park, 2008). Sodium starch glycolate (SSG), croscarmellose sodium (CCS), and croscopovidone (CP) are commonly used superdisintegrants for pharmaceutical applications (Quadir & Kolter, 2006). Bilgili, Bhakay, Azad, and Dave (2013) have recently proposed that milled superdisintegrant particles with sizes smaller than 5 μm can serve as a novel class of dispersants when incorporated into drug-carrying nanocomposite microparticles. Such nanocomposite particles can significantly improve the dissolution rate and bioavailability of poorly water-soluble drugs by enabling fast redispersion of drug nanoparticles during *in vitro* and *in vivo* dissolution (Bhakay, Azad, Dave, & Bilgili, 2012; Bilgili et al., 2013). It is important to note that currently available superdisintegrant grades have particles of average sizes in the range of approximately 5–130 μm , which are apparently too big for the above-mentioned

nanocomposite microparticle applications. The finest grades of CP and SSG available in the market have average particle sizes of 5.4 and 41 μm , respectively (Quadir & Kolter, 2006), and the smallest median size of CCS is reported to be about 5 μm (Zhang, 2011). Hence, production of superdisintegrant particles with sizes smaller than 5 μm in a reproducible and scalable process is highly desirable.

In general, either dry milling or wet milling may be used to produce fine superdisintegrant particles. In pharmaceutical literature, scant information is available for the dry milling of superdisintegrants. Thibert and Hancock (2001) milled SSG, CCS, and CP with a ball mill and an automatic pestle-mortar. According to their study, extensive size reduction of superdisintegrants did not take place: the median size of CP particles was reduced from 80 to 45 μm and that of SSG particles was reduced from 41 to 20 μm . This finding suggests that producing very fine superdisintegrant particles by dry milling is a challenging task, which could be due to the cross-linked polymeric nature of the superdisintegrants. Moreover, significant frictional heat generation, poor heat transfer, and high stress intensities in some dry milling equipment can lead to locally high temperatures and mechano-chemical reactions, which in turn cause degradation of the thermoplastic polymers (Liang, Hu, Zhu, & Yu, 2002) and the cross-linked polymers (Bilgili, Arastoopour, Bernstein, & Hamey, 2008). Some of these issues can be

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circumvented by using liquid nitrogen during milling (Barbosa, Stranz, Katzenberg, & Köster, 2009; Burford & Pittolo, 1982); however, the use of liquid nitrogen makes the dry milling more expensive and less attractive (Makarov & Drozdovski, 1991).

Due to the aforementioned issues associated with dry milling, wet milling is preferred for the production of superdisintegrant particles of sizes less than 5 μm . In general, wet milling is more effective at reducing the particle size of a large variety of materials to submicron scale than dry milling (Lowrison, 1974). It is easier to disperse colloidal particles or ultra-fine particles in the milling medium with some dissolved stabilizers, i.e., polymers and/or surfactants, which are used to impart physical stability to the milled suspensions (Klimpel, 1999). Wet milling in stirred media mills allows the production of ultrafine particles down to the nanometer scale: 10–100 nm (e.g. Bilgili, Hamey, & Scarlett, 2006; Stenger, Mende, Schwedes, & Peukert, 2005). Most importantly, as wet media milling has already been widely used in the production of colloidal drug particles (less than 1000 nm) in pharmaceutical industry (Bruno et al., 1996; Lee, 2003; Merisko-Liversidge, Liversidge, & Cooper, 2003), it is natural to use the same technology for the milling of superdisintegrants. To the best of the authors' knowledge, no systematic study is available in literature for the production of less than 5 μm superdisintegrant particles by wet stirred media milling (Bhakay et al., 2012; Bilgili et al., 2013).

Drug-carrying nanocomposite particles with wet-milled superdisintegrants can be produced by three different methods (Bhakay et al., 2012; Bilgili et al., 2013). In the first method, a milled superdisintegrant suspension is dried first and the dried particles are dispersed in a drug nanosuspension, followed by the drying of the final suspension. In a second method, the milled superdisintegrant suspension is directly mixed with a drug nanosuspension, and then the final suspension is dried. In a third method, the superdisintegrant and drug particles are wet-milled together and the resultant suspension is dried. In most drug nanocomposite applications, the drying operations are usually carried out shortly after the wet milling (see e.g. Bhakay, Dave, & Bilgili, 2013). The milled superdisintegrant suspensions, especially in the first two methods, should remain physically stable before the drying is performed (typically over a period of few days); hence, a 3-day storage is deemed suitable for physical stability testing here.

In this study, we explore the preparation of colloidal superdisintegrant particles in a stable aqueous suspension, which is intended as precursor material for the production of drug nanocomposite microparticles, via wet stirred media milling. The potential impact of the electrical charge of the superdisintegrants on the physical stability of the suspensions was investigated by considering an anionic superdisintegrant (sodium starch glycolate, SSG) and a nonionic superdisintegrant (crospovidone, CP). They were milled in the presence/absence of two stabilizers dissolved in water: a non-ionic biopolymer (hydroxypropyl cellulose, HPC) and an anionic surfactant (sodium dodecyl sulfate, SDS). Particle sizing, scanning electron microscopy, and zeta potential measurements were used to characterize the milled suspensions. The physical stability and aging of the suspensions were studied via zeta potential and particle size measurements after milling and 3 days of storage.

2. Materials and methods

2.1. Materials

The superdisintegrants, CP (polyplasdone XL-10) and SSG (primojel), were donated by ISP (Wayne, NJ, USA) and DMV-Fonterra Excipients LLC (Princeton, NJ, USA), respectively. The cellulosic biopolymer, HPC (SL grade with viscosity 3.0–5.9 cps), was

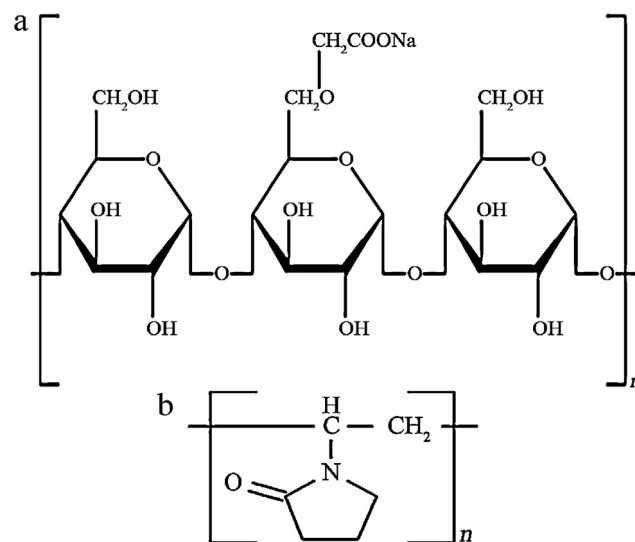


Fig. 1. Chemical structure of (a) SSG and (b) CP.

donated by Nisso America Inc. (New York, NY, USA), while the anionic surfactant, SDS, was purchased from Sigma Aldrich (99% ACS reagent, St. Louis, MO, USA).

Table 1 presents the physical properties of the two superdisintegrants (Quadir & Kolter, 2006; Shah & Augsburger, 2001, 2002). Both superdisintegrants are water-insoluble and swell in water. SSG is a sodium salt of a carboxymethyl ether of starch (Fig. 1(a)). The carboxymethyl group induces hydrophilicity while cross-linking minimizes solubility in water. On the other hand, CP is a synthetic, cross-linked homopolymer of N-vinyl-2-pyrrolidone (Fig. 1(b)). The branched (popcorn) polymerization of the vinylpyrrolidone yields crospovidone. The cross-linking is of both chemical and physical nature, which is mainly associated with the entanglement of the polymer chains (Quadir & Kolter, 2006). SSG is anionic due to the presence of the negatively charged functional group CH_2COO^- , whereas CP is nonionic (neutral). SSG particles are nonporous with shapes ranging from oval to rounded (Fig. 2(a)), whereas CP particles consist of agglomerates of smaller particles that are fused together and have a spongy, porous appearance (Fig. 2(b)).

2.2. Methods

2.2.1. Milling equipment

The mill used in this study was a MicroCer wet stirred media mill manufactured by Netzsch Premier Technologies, LLC. (Exton, PA, USA). The mill was equipped with a 500 mL holding/stirring tank along with a variable speed paddle mixer (Fig. 3). The milling chamber is lined with zirconium and has an effective volume of 80 mL. It was loaded with 55 mL (bulk volume) milling media, i.e., Yttrium-stabilized zirconia beads, with a nominal size of 400 μm . The d_{10} , d_{50} , and d_{90} values were 369, 430, and 502 μm , respectively (see Section 2.2.4 for particle sizing), where d_{10} is the 10% passing size, d_{50} is the median or 50% passing size, and d_{90} is the 90% passing size of the cumulative passing volume distribution. Inside the milling chamber, a zirconium oxide rotor stirs the suspension consisting of the superdisintegrant particles to be ground and the media. A peristaltic pump circulates the suspension from the holding tank through the milling chamber and back to the holding tank continuously (recirculation mode). A 200 μm screen prevents the beads from leaving the milling chamber while the suspension passes through the screen. A chiller (M1-25A-11HFx,

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