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Effects of baffle configuration and tank size on spherical agglomerates of dimethyl fumarate in a common stirred tank

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ABSTRACT

To pave the way for technology transfer and scale up of the spherical agglomeration (SA) process for dimethyl fumarate, effects of the US, European and Kawashima type baffles and 0.5, 2.0 and 10 L-sized common stirred tank were studied. It was found that the particle size distribution varied significantly. However, the size-related properties such as dissolution profile and flowability of agglomerates from the same size cut after sieving could remain unchanged. The interior structure-related properties such as particle density and mechanical property of agglomerates upon baffle change and scale up from the same size cut were decayed and the agglomerates could become denser and stronger by prolonged maturation time. To maintain the same size distribution, agglomerates from any batch could have been separated and classified by sieving and then blended back together artificially by the desired weight% of each cut.

1. Introduction

About 80% of all marketed drug products and more than 95% of the top selling drugs are solid oral dosage forms, which are convenient for transportation, packaging, storage, and highly acceptable to patients (Byn et al., 2005). To increase the dissolution rate and reach sufficient bioavailability of poorly water-soluble drugs, small micron-sized active pharmaceutical ingredient (API) crystals are often produced by crystallization and precipitation. However, the poor flow and mechanical properties of those fine crystals can make the downstream processing and dosage control difficult (Lee and Webb, 2003). The desired physical and mechanical properties for filtering, drying and handling, the decent flowability and packability for mixing, filling and tableting, and the uniform bulk density for predictable compressibility and dissolution, can often be obtained by agglomeration where the small crystals are assembled to larger agglomerates (Osborne et al., 1990).

The conventional ways for agglomeration are by mixer granulation and fluidized-bed granulation (Faure et al., 2001), but granulation step is time-consuming and adds additional costs to the manufacturing (Lee et al., 2010a, 2010b). A better alternative is to produce the round agglomerates directly by spherical crystallization in a common stirred tank at the crystallization step. If that worked out, granulation could be avoided, and direct tableting would become economically feasible. Consequently, less equipment and space, lower labor costs, less processing steps and lower energy consumption would be required (Lee et al., 2010a, 2010b). Spherical crystallization (Kovačič et al., 2012) can be categorized by four different ways: (1) spherical agglomeration (SA), (2) quasi emulsion solvent diffusion (QESD), (3) ammonia diffusion system (ADS), and (4) neutralization.

SA is important and popular (Kovačič et al., 2012) because of its simplicity. However, it may not be applicable for complex problems. Normally, in the SA method, an antisolvent is firstly added to the nearly saturated solution of API in a good solvent for precipitating the drug crystals immediately. Under agitation, a third solvent called the bridging liquid (or the wetting agent) is fed, which is immiscible with the poor solvent and preferentially wet the precipitated crystals. As a result of the interfacial tension and capillary force, the bridging liquid acts to adhere the crystals to one another and turns them into agglomerates of larger sizes. For the ease of studying the influence of operating parameters for SA, ball-milled and sieved crystals were used to fix and standardize the size of the crystalline building blocks of SA at the starting point. The bridging liquid was fed directly to the crystal suspension made of a poor solvent. Therefore, only two solvents were used instead of three (Chow and Leung, 1996). If water is being used as one of the solvents, it will be possible to reduce the production cost for many systems.

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In general, solvents and solvent composition (Osborne et al., 1990; Gordon and Chowhan, 1990), temperature (Osborne et al., 1990), amount of bridging liquid (Blandin et al., 2003; Amaro-González and Biscans, 2002), feeding rate of bridging liquid (Kawashima et al., 1982), feeding rate of suspension (Kawashima et al., 1982), initial particle size (Kawashima et al., 1981a), solid loading (Blandin et al., 2000), stirring rate (Maghsoodi, 2011) and maturation time (Blandin et al., 2000; Thati and Rasmuson, 2012) are the many important operating parameters which influence the success of spherical crystallization. These parameters affect not only the productivity but also the particle size distribution (Subero-Couroyera et al., 2006), morphology (Amaro-González and Biscans, 2002; Thati and Rasmuson, 2012), strength (Blandin et al., 2000) and dissolution rate (Maghsoodi, 2011; Varshosaz et al., 2011) of the agglomerates.

The effects of above operating parameters had been explored earlier by using different materials as model compounds. For instances, (1) the increase in the amount of bridging liquid would increase the agglomerate size (Blandin et al., 2003). Adding too much bridging liquid would make the agglomerates soft and pasty (Amaro-González and Biscans, 2002), (2) at high feeding rate of bridging liquid, the product particle size became larger, whereas at high feeding rate of suspension, the product agglomerate size became lower (Kawashima et al., 1982), (3) the agglomerate size increased as either the initial particle size decreased (Kawashima et al., 1981a) or the solid loading increased (Blandin et al., 2000), (4) a higher stirring speed also led to faster particle dissolution rate which might be related to particle size reduction of the agglomerates (Maghsoodi, 2011), (5) with increasing the stirring speed and the amount of bridging liquid, the particle size distribution tended to shift toward the larger particle size range (Subero-Couroyera et al., 2006), (6) the choice of the bridging liquid had an influence on the rate of agglomeration and the strength of the agglomerates (Kawashima et al., 1981b), (7) as the maturation time increased, the particle size increased. The particles became more spherical with higher strength (Thati and Rasmuson, 2012), (8) various solvent compositions would influence the particle size distribution, morphology and mechanical strength differently (Amaro-González and Biscans, 2002; Thati and Rasmuson, 2012), and (9) lower temperature led to larger and stronger agglomerates (Thati and Rasmuson, 2012).

To scale up the process for SA properly, special attention must also be paid to the effects of baffle configuration and tank size. However, systematic studies of those parameters are rare. For instances, (1) the agitator torque was found to be a function of the speed of the agitator and the number of baffles in the system (Kawashima and Capes, 1974), (2) the agglomeration rate constant was seen to increase exponentially with the shear force applied to the system as measured by the agitator torque, the total number of agglomerates per unit volume of suspension (i.e., population density) increased as the mean agglomerate size decreased (Kawashima and Capes, 1974), and (3) spherical crystallization was carried out in 2.5 L-sized (Blandin et al., 2005), 30 L-sized (Kawashima et al., 1994), and 100 L-sized (Bos and Zuiderweg, 1987) stirred vessels separately in several unrelated studies where no scale up guidelines were provided at all.

Therefore, the aim of this paper is to study the effects of baffle configuration and tank size on the relatively simple SA method systematically in addition to two other operating parameters: (1) the amount of bridging liquid added (BSR: bridging liquid volume to solid ratio), and (2) the maturation time.

A newly approved re-positioned drug in the year of 2013 for treating relapsing forms of multiple sclerosis, dimethyl fumarate (Jarvis, 2014), was chosen as our model API because it is commercially available, inexpensive and its poor solvent is water. Toluene was selected as the bridging liquid for the SA method because of its immiscibility with water (0.50 mg of toluene/mL of water at 20 °C) (Murov, 1997) and the relatively good solubility of dimethyl fumarate in toluene. The micromeritic properties of the commercial dimethyl fumarate, and the ball-milled and sieved dimethyl fumarate feed standardized for all trials were shown in Figs. S1 and S2, respectively. The loading of dimethyl fumarate solids in the aqueous suspension was kept at 0.025 g/mL. The chemical identity, polymorphism, morphology, size distribution, mechanical strength, flowability and dissolution rate of all agglomerates were characterized and checked.

2. Materials and methods

2.1. Chemicals and solvents

Dimethyl fumarate ($C_6H_8O_4$, 99% purity, MW 144.13, mp 102–105 °C, true density 1.37 g/cm^3, Lot 10183993), white crystalline platelets were purchased from Alfa Aesar (Ward Hill, MA, USA) (Fig. S1(a)). Toluene ($C_6H_5CH_3$, ACS grade, 99.5% purity, MW 92.14 bp, 111 °C, Lot ETA140403) was received from Echo Chemical (Miaoli, Taiwan). Reversible osmosis (RO) water was clarified by a water purification system (model Milli-RO Plus) bought from Millipore (Billerica, MA). Potassium phosphate buffer concentrate pH 6.8 (pH 6.78–6.82, Lot BCBN3286V) was purchased from Fluka (Ireland).

2.2. Experimental methods

2.2.1. Ball milling

100 g of commercial platelet-shaped dimethyl fumarate powders were ball-milled (MUBM-236-RTD, Shin Kwang Machinery, Taiwan, ROC) to produce the standardized dimethyl fumarate as starting materials. The volume of the ball jar was 1.5 L, and the mass ratio of ceramic-ball-to-powder was fixed to 6:1. The ball milling process was taken with a rotation speed of 500 rpm for 5 h, and the ball-milled powders are characterized in Fig. S2.

2.2.2. Spherical agglomeration

2.2.2.1. Apparatus. The temperature for all experiments was kept at 25 °C. Cylindrical glass vessels of three different sizes of 0.5, 2 and 10 L equipped with four vertical baffles of either European,

Table 1
Cylindrical tank sizes and vertical baffle configurations.

Tank size (L)	Tank diameter, T (cm)	Impeller diameter, D (cm)	Baffle type	Baffle width, B (cm)	Stirring rate, n (rpm)
0.5	8	3.6	US	0.7	600
			European	0.9	
			Kawashima	1.1	
2	13	5	Kawashima	1.6	450
10	20	7	Kawashima	2.5	350