Available online at www.sciencedirect.com
ScienceDirect
ELSEVIER
European Journal of Pharmaceutics and Biopharmaceutics 64 (2006) 193–199
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Agglomeration tendency in dry pharmaceutical granular systems

Emilie DesRosiers Lachiver [a,c], Nicolas Abatzoglou [a,*], Louis Cartilier [b], Jean-Sébastien Simard [c]

[a] *Department of Chemical Engineering, Université de Sherbrooke, Sherbrooke, Que., Canada*
[b] *Faculty of Pharmacy, Université de Montréal, Montréal, Que., Canada*
[c] *Product and Process Development, Technology, Wyeth Canada Inc., Montréal, Que., Canada*

Received 24 January 2006; accepted in revised form 26 April 2006
Available online 10 May 2006

Abstract

The agglomeration tendency of dry pharmaceutical mixtures containing various concentrations of Xylitab®100 (Xylitol), calcium carbonate precipitated (CCP) and magnesium stearate (MgSt) was evaluated statistically as a function of mixing time. A Ro-Tap tester was employed to mix the three pharmaceutical components, and the agglomerates formed were measured with respect to their weight and size. An experimental design was devised and applied to structure and then statistically analyze the results.

Xylitab was found not to be influential in the formation of agglomerates, but aided in deagglomeration when mixed with other components. CCP and MgSt formed agglomerates over time and showed positive interactions favouring agglomeration. The agglomerates started to fracture when they reached a critical size, at which stage the particles' attraction forces (cohesion forces) were weaker than both gravity and inertia.

It has been shown and quantitatively demonstrated that the mixing time and ingredient concentrations of a three-component pharmaceutical mixture can affect agglomeration tendency.

Keywords: Agglomeration; Powder; Granular systems; Mixing; Flow; Lubricant

1. Introduction

The mixing of dry pharmaceutical solids is a crucial step in the manufacture of solid dosage forms. Two major problems are often encountered in powder-mixing operations, i.e., segregation and agglomeration, which lead to content homogeneity problems [1–3]. These phenomena depend on the physico-chemical characteristics of the raw material(s), namely, particle size, shape, surface nature, humidity and conductivity [4]. The extent of such phenomena relies on interactions between the raw materials involved and is driven mainly by capillary, electrostatic and van der Waals forces [5–7]. The presence of agglomerates may also negatively influence the desired dissolution properties of the drug dosage form, especially in the case of poorly soluble drug components [8]. Before undertaking a theoretical analysis of these interactions, which is part of our larger research work, a statistical analysis was performed to assess the influence of mixing time and ingredient concentration on agglomeration tendency.

1.1. Theoretical considerations

Particle agglomeration, in a dry pharmaceutical granular system, occurs when attractive interparticle bonding forces are sufficiently powerful between individ-

* Corresponding author. Department of Chemical Engineering, Faculty of Engineering, Université de Sherbrooke, 2500 Boulevard Université, Sherbrooke, Que., Canada J1K 2R1. Tel.: +1 819 821 7904; fax: +1 819 821 7955.
E-mail address: Nicolas.Abatzoglou@USherbrooke.ca (N. Abatzoglou).

0939-6411/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2006.04.005

ual particles to regroup them. Fine cohesive particles adhere to each other under the influence of electrostatic forces [9,10], van der Waals [3] or a liquid bridge, to form agglomerates that are responsible for their asymmetric distribution in the mixture [11,12]. Mixing time, mixing speed, mixer type and filling level can also affect agglomeration tendency [13,14].

Dry powder agglomeration mechanisms for multicomponent mixtures are not well understood, and only a few studies describing this phenomenon have appeared in the literature so far. Orr and Sallam [11] have suggested that when a V-blender is rotated, powders succumb to compaction forces, thus allowing the formation of agglomerated "chunks" of powders. These "chunks" are broken down into smaller units by the blender's mixing mechanism, the stress of the free powder mass, and collisions between them and the equipment walls. This transforms the chunks into "balls" of higher density. Free balls are found on the surface of the powder mass, rolling along the slope while simultaneously increasing in size. The phenomenon of powder accumulation on the surface of the ball is similar to that of creating a snowball by rolling it down a snow-covered hill. Kaye [12] has stated that the more the powder is tumbled around with a stearate, the larger are the spontaneously formed agglomerates.

The need to understand the behaviour of these process systems is growing because of the high pressure exerted by industry to maximize productivity and optimize product quality at low cost, while adhering to tight production deadlines. To improve knowledge in this field, researchers are now looking at new experimental techniques to investigate, model and simulate these phenomena more efficiently [15]. Factorial design enables studies of the effect(s) of different operational parameters and their interactions as well as the effects of mixture component concentrations on the process response, with a minimum of trials and a maximum of precision. Once statistical or purely mathematical models are built, they are linked with the physical reality of the studied process behaviour for validation purposes [16].

Scientists are starting to use this approach to study powder behaviour. Harnby et al. [3] developed a generalized model to predict the mixture quality of cohesive systems that took into account the relative bonding strengths between coarse/fine particles and fine/fine particles to express the degree of agglomeration of a two-component mixture of spheres. Deiva Venkatesh et al. [17] designed a preliminary model to predict the agglomeration and deagglomeration behaviour of powders under vibration conditions. They simulated the formation and destruction of interparticle bonds of 3 mm diameter particles during collisions. In the present study, a further step is taken to explore, as quantitatively as possible, the agglomeration tendency of three individual components and their various blends as a function of weight and size increase with time.

2. Materials and methods

2.1. Materials

The three pharmaceutical excipients chosen for this study are currently used in multivitamin and multimineral formulations:

Calcium Carbonate Precipitated USP (Bihoku Funka Kogyo Co., Ltd., Niimi, Okayama, Japan) (mean particle size 2.6 μm), a diluent employed in solid dosage forms;
Xylitab®100 (Xylitol, Danisco Sweeteners Ltd., Thomson, IL, USA) (mean particle size 200 μm), a sweetening and diluent agent in chewable tablets;
Magnesium Stearate NF/BP/EP (Crompton Corporation, Memphis, TN, USA) (99.99 through 325 mesh (44 μm)), a lubricant widely deployed in oral solid dosage forms.

2.2. Method

The blends were prepared according to a Crossed D-Optimal Mixture Design of experiment generated by Design-Expert® software, version 6.0.9 (Stat-Ease® Inc., Minneapolis, MN, USA). The Test Design plans are shown in Tables 1 and 2 [18]. The raw materials were screened through a 16-mesh sieve into a pan which was shaken for 0.17, 2.5, 5, 7.5, or 10 min in a Ro-Tap RX-29 Model tester (W.S. Tyler, Mentor, OH, USA). When the Ro-Tap operates, particles roll on the pan surface and collide with each other and with the pan walls, simulating their behaviour during blending. When shaking is completed according to the needs of the statistical design, the pan content is unloaded in piled screens of

Table 1
Factorial design plan for the average weight (%) of agglomerates formed in the blend

Points #	Concentration (%v/v)			Weight (%)				
	Xylitab	CCP	MgSt	Time (min)				
				0.17	2.50	5.00	7.50	10.00
1	0.00	0.00	1.00	30.73	55.75	67.04	67.28	65.64
2	0.00	0.00	1.00	31.38	63.14	74.41	76.19	74.80
3	0.00	0.50	0.50	23.54	34.48	54.02	89.50	37.58
4	0.00	1.00	0.00	23.79	25.85	39.64	36.39	62.84
5	0.00	1.00	0.00	23.79	30.05	39.20	82.03	95.16
6	0.17	0.67	0.17	9.00	14.70	10.34	18.10	16.83
7	0.33	0.33	0.33	10.33	8.53	8.26	8.68	8.64
8	0.67	0.17	0.17	6.92	7.90	7.64	8.03	8.00
9	0.17	0.17	0.67	26.08	32.35	25.39	35.89	31.71
10	0.50	0.00	0.50	11.96	11.43	10.43	12.61	14.71
11	1.00	0.00	0.00	6.37	5.16	5.14	5.44	5.70
12	1.00	0.00	0.00	7.79	6.42	5.89	5.88	6.36
13	0.50	0.50	0.00	14.79	12.39	16.40	17.84	15.79
14	0.50	0.50	0.00	16.01	13.76	14.61	14.99	14.34