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Research paper

Agglomeration tendency in dry pharmaceutical granular systems

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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.
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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-

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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

Table 2
Factorial design plan for average agglomerates size (μm) formed in the blend

Points #	Concentration (%v/v)			Size (μm)				
	Xylitab	CCP	MgSt	Time (min)				
				0.17	2.50	5.00	7.50	10.00
1	0.00	0.00	1.00	829.96	809.61	810.60	811.50	844.34
2	0.00	0.00	1.00	849.34	809.95	807.95	814.30	805.09
3	0.00	0.50	0.50	862.70	1,234.63	2,165.48	4,198.74	3,912.61
4	0.00	1.00	0.00	797.39	1,041.47	1,263.53	1,386.35	3,848.88
5	0.00	1.00	0.00	797.39	995.09	1,189.22	2,491.68	3,972.69
6	0.17	0.67	0.17	833.86	882.90	1,019.59	1,323.23	1,353.71
7	0.33	0.33	0.33	837.37	828.53	813.79	821.95	829.71
8	0.67	0.17	0.17	824.83	828.53	813.79	821.95	1,189.22
9	0.17	0.17	0.67	810.91	885.08	971.08	1,030.96	2,491.68
10	0.50	0.00	0.50	807.48	812.60	852.84	861.86	870.70
11	1.00	0.00	0.00	799.01	811.10	828.29	822.70	826.75
12	1.00	0.00	0.00	810.30	821.00	818.98	822.44	831.97
13	0.50	0.50	0.00	802.16	866.89	853.32	879.67	869.30
14	0.50	0.50	0.00	799.12	821.41	855.74	868.93	849.31

different opening sizes, i.e., 6 (3360 μm), 8 (2380 μm), 10 (2000 μm), 12 (1680 μm), 14 (1410 μm), 16 (1190 μm), 18 (1000 μm), 20 (840 μm) and 30 (590 μm) mesh, to gently separate and distribute the particles and agglomerates according to their size. The agglomerates retained at the surface of the screens are weighed. Their weight fraction (%) formed during the Ro-Tap operation is calculated by the sum of the agglomerates retained on all screens divided by the initial powder weight multiplied by 100. The average mean size (x) of weight distribution (F) is calculated from the cumulative area under the curve of a plot of F versus x by the trapezoid method [18]. The weight fraction (%) of the agglomerated particles serves as the response in the weight model, and the mean size (μm) of the agglomerates is taken as the response in the size model. The concentrations of the raw materials in the mixture tested are in %v/v. Volume concentrations are converted to mass units, using the bulk density [19] of each material. The total volume of each mixture is 62.5 mL.

3. Results

The aim of this work was to develop models that could predict the size and weight of agglomerate formation of a three-component mixture as a function of time and mixture component concentrations. These models will be helpful in predicting agglomeration tendency and extend to pharmaceutical formulations. The authors chose the phenomenological approach to model agglomeration tendency because at this stage of the work it was impossible to account for all parameters affecting agglomeration and to derive a more stochastic model. The statistical models are presented in this section and Section 4, with model terms analyzed individually to validate the statistical model with the observed physical behaviour.

3.1. Modeling to predict agglomerates weight

Various models and transforms can be applied to the data to fit them to a model. According to the mixture process crossed model of Stat-Ease, linear order for the process parameter and quadratic order for the mixture order correlated best with the experimental data. Table 3 reports the analysis of variance (ANOVA) results for the weight model, and in the following lines, the data and model equation are discussed. An example of MgSt agglomerates formed during mixing is shown in Fig. 1.

The F value is a test used to compare term variance with residual (error) variance. If the two variances are similar, their ratio will be close to 1, and it is less likely that the term has a significant effect on the response. Prob > F represents the probability of seeing the observed F value if there is no factor effect. In other words, if the Prob > F value is very small (less than 0.05), then the terms in the model have a significant effect on the response.

Table 3
Analysis of variance (ANOVA) for the weight (%) model

Source	Sum of squares	df	Mean square	F value	Prob > F
Model	10,986.16	8	1,373.27	19.61	<0.0001
Linear mixture	7,067.87	2	3,533.94	50.47	<0.0001
AB	358.53	1	358.53	5.12	**0.0349**
AC	1,023.96	1	1,023.96	14.62	**0.0011**
BC	429.90	1	429.90	6.14	**0.0223**
BD	586.79	1	586.79	8.38	**0.0090**
CD	1,324.74	1	1,324.74	18.92	**0.0003**
BCD	283.69	1	283.69	4.05	**0.0578**
Residual	1,400.34	20	70.02		
Lack of fit	1,357.95	17	79.88	5.65	0.0894
Pure error	42.38	3	14.13		
Total correlation	12,386.50	28			

A, Xylitab; B, CCP; C, MgSt; D, time (min).
Bold characters are used for the statistically significant terms.

Fig. 1. Example of MgSt agglomerates (mean size 0.8 mm).

Table 3 presents the ANOVA results modeling as a function of agglomerates weight. The model F value of 19.61 implies that the model is significant and there is only a 0.01% chance that such a F value could occur due to noise. The linear mixture components AB, AC, BC, BD and CD are significant model terms because they are characterized by their Prob > F values of less than 0.05. BCD interaction is also considered significant on the basis of process knowledge and since the Prob > F value is close to 0.05.

Lack of fit (LOF) evaluates the variation of data around the fitted model. If the model does not fit the data well, this parameter will be significant. A LOF value of 5.65 implies that the LOF is not significant relative to the net error, and that there is only a 8.94% chance that such a LOF could occur due to noise.

Table 4 presents a summary of relevant statistics for the model. Predicted (Pred) R-squared is a measure of variation in new data given by the model and predicts how well the model can predict the response. Furthermore, it can explain 74% of variability in the new model. Adjusted (Adj) R-squared is a measure of variation around the mean given by the model, adjusted for the number of terms in the model. Adj R-squared and Pred R-squared should be as high as possible and within approximately 0.20 of each other to be in reasonable agreement. Adequate (Adeq) Precision is a signal-to-noise ratio that compares the range of predicted values at design points to the average prediction error. Ratios greater than 4 indicate adequate model discrimination.

The model Pred R-squared value 0.72 is in reasonable agreement with the Adj R-squared value of 0.84. The model Adeq Precision ratio of 14.8 is higher than 4, indicating an adequate signal-to-noise ratio. The predicting weight model is presented in the following equation:

$$\begin{aligned}\text{Weight } (\%) = {} & 6.89 * \text{A} + 25.52 * \text{B} \\ & + 37.23 * \text{C} - 47.78 * \text{AB} \\ & - 78.12 * \text{AC} + 1.50 * \text{BC} \\ & + 3.05 * \text{BD} + 3.46 * \text{CD} \\ & - 10.51 * \text{BCD}, \end{aligned} \quad (1)$$

where A = % Xylitab, B = % CCP, C = % MgSt, and D = time in min.

Table 4
Summary of relevant statistics for the model

R-squared	0.89
Adj R-squared	0.84
Pred R-squared	0.72
Adeq Precision	14.81

3.2. Modeling to predict agglomerates size

Several models and transforms were applied to the data obtained to fit them in a model similar to the one expressing agglomerates weight with initial concentration and time.

Even if ANOVA of the Design of Experiments allowed us to identify that the linear parameter and some of the double and triple interactions were significant, no appropriate fitting was effective in expressing agglomerates size behaviour.

This means that so far, no model was found to predict well the combined effect of time and concentration on agglomerates size. In the case of pure MgSt and Xylitab, there was evidence that the agglomerates reached maximum size rapidly (plateau) while CCP agglomerates size increased over time.

4. Discussion

4.1. Individual component analysis

Each component was tested separately to evaluate the pure component's tendency to form agglomerates. Figs. 2–4 show agglomerates formation in terms of weight (%) as a function of time for Xylitab, CCP and MgSt. Figs. 5–7 illustrate agglomerates formation in terms of size (μm) as a function of time for Xylitab, CCP and MgSt.

According to Figs. 2 and 5 and visual observations, Xylitab did not form a significant amount of agglomerates, even when treated in accordance with the protocol presented in Section 2, for 10 min. This was probably due to its large particle size (mean 200 μm) and its ionic properties [20–22].

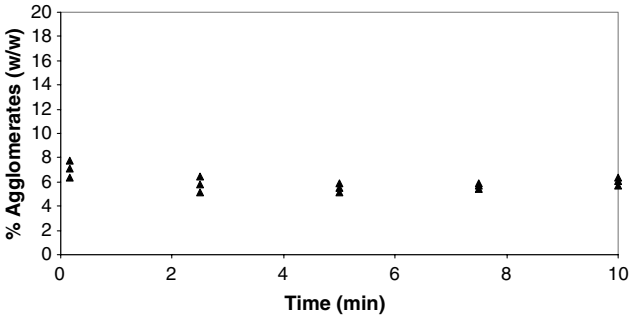

Fig. 2. Xylitab agglomerates weight as a function of time.

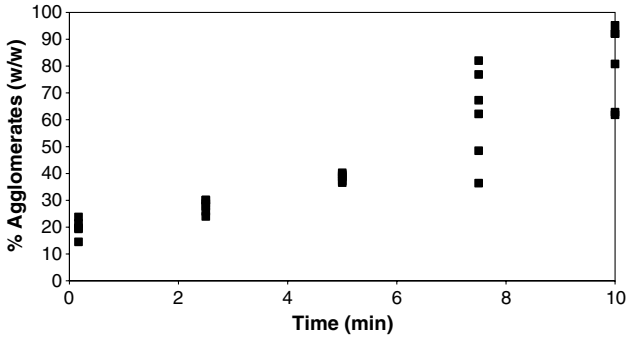

Fig. 3. CCP agglomerates weight as a function of time.

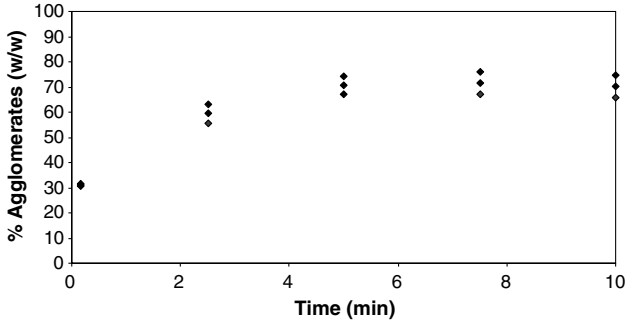

Fig. 4. MgSt agglomerates weight as a function of time.

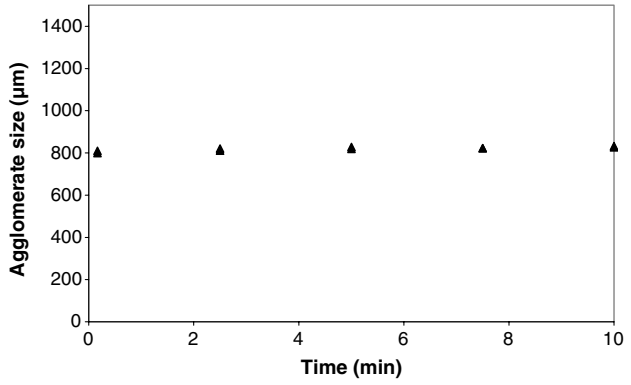

Fig. 5. Xylitab agglomerates size as a function of time.

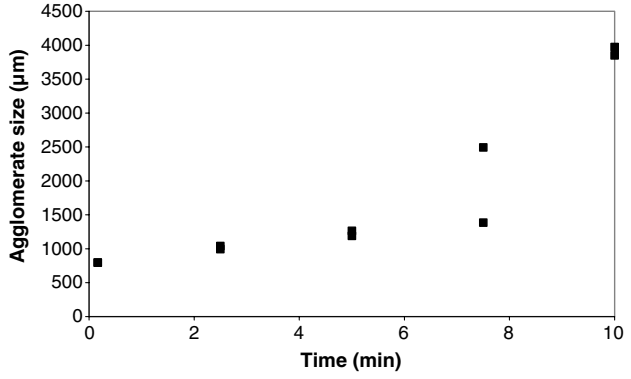

Fig. 6. CCP agglomerates size as a function of time.

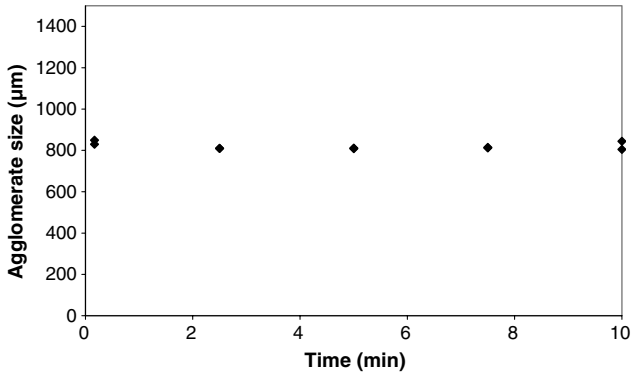

Fig. 7. MgSt agglomerates size as a function of time.

On the other hand, CCP particles were attracted to each other and increasingly spherical agglomerates were formed over time (Figs. 3 and 6). It was also visually observed that all CCP particles agglomerated over time until no loose particles were left in the pan. During the process, agglomerates broke off, thus freeing single particles; these in turn stuck to other agglomerates to form larger ones. After reaching a critical size, the size of the agglomerates tended to stabilize. A plausible explanation is that, at the critical size, attraction forces at the surface of the agglomerates and within them were not enough to hold new particles at their surface. This led to dynamic equilibrium, during which the amount of particles leaving the surface of the agglomerates equalled that of particles adhering to it.

Regarding MgSt, its particles formed small agglomerates (Fig. 4), and their number increased with time (Fig. 7). The agglomerates formed were spherical and had an average diameter of 0.8 mm. The majority of MgSt particles formed uniform agglomerates, but a significant amount (around 30%) of loose particles adhered irreversibly to the pan walls.

4.2. Physical analysis of the weight model

Two general observations were made during the experiments: (1) the greater the amount of Xylitab added to the mixture, the lower the number of agglomerates formed; and (2) pure CCP and MgSt formed spherical agglomerates.

The model is presented in Eq. (1), and the response surface is shown in Fig. 8. Only statistically significant terms were included in the model, and they were expressed in actual (%v/v) values. Terms 1, 2 and 3 represented the initial concentration of each component in the pan, multiplied by their respective coefficient. As demonstrated with the individual models, CCP and MgSt favoured agglomeration phenomena while Xylitab did not. Each term is individually analyzed in the following section.

AB and AC are significant terms that affect the amount of agglomerates formed in the mixture, and their negative signs mean that these products proportionally favour

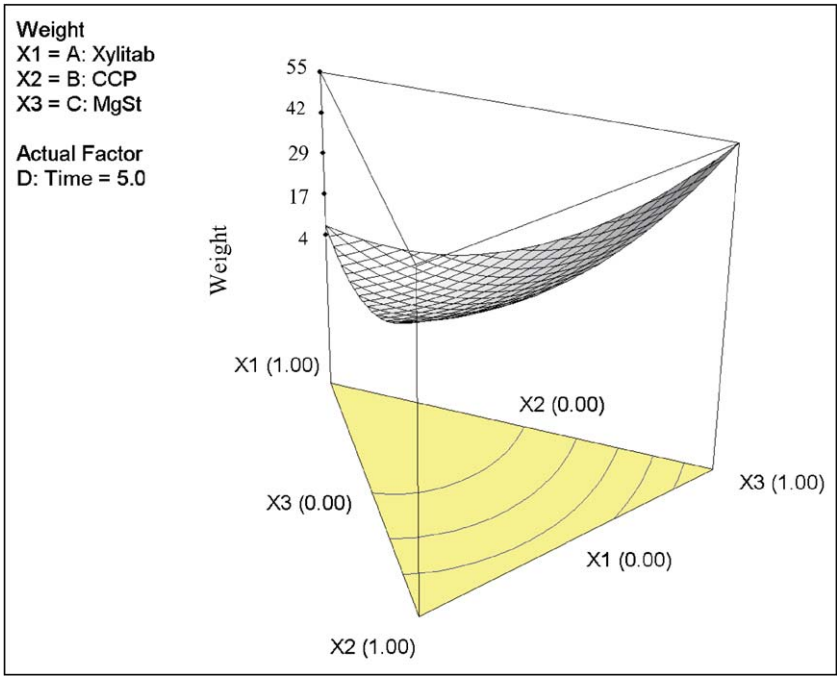

Fig. 8. Response surface for agglomerate weight (%).

deagglomeration mechanisms. The model indicates that Xylitab favours deagglomeration phenomena and that all terms involving Xylitab are negative, except the first, which represents the presence of the individual ingredient in the mix.

Therefore, when mixed with other components, the deagglomeration effect of Xylitab was greater than the agglomeration effect favoured by either CCP or MgSt, resulting in a reduction of the final amount of agglomerates in the mix. Xylitab had a larger particle size and was suspected to act as "grinding media in a ball mill", destroying the agglomerates as they formed during mixing. It is also used as a diluent in pharmaceutical formulations [19] because it has no agglomeration tendency. Cartilier and Moës [2] and Villiers [21] have observed that an increase in excipient particle size facilitates the destruction of cohesive particle agglomerates because of its ball milling effect.

The terms BD and CD are significant, positive and represent the interaction of CCP and MgSt, respectively, over time. As demonstrated with the individual models, CCP and MgSt favour the extent of agglomeration over time; their small particle size as well as their polarity and electrostatic forces favoured cohesion between particles and, therefore, agglomeration tendency. If the electrostatic charges between these particles and the other substances are opposite, they exert a negative effect on agglomeration, and if they are of the same sign (both negative or positive) they exert a positive effect on agglomeration [23]. The interaction between CCP and MgSt is also significant and contributes to increased agglomeration. This is indicated by the term BC, which is positive.

By examining double interactions, it is noted that the term AD, representing the interaction between Xylitab and time, does not appear in the model equation. The interaction is absent because it is not significant according to the statistical analysis. This is expected because individual models demonstrate that Xylitab does not form agglomerates over time.

The term BCD represents the interaction of CCP and MgSt with time. The negative sign means that this interaction favours deagglomeration phenomena. It was visually observed during the experiments that agglomerates reached a critical size where equilibrium occurred between breakdown and size increase of the agglomerates. The forces attracting particles at the surfaces of the agglomerates were offset by other forces (inertial and gravitational) upon increased particle diameter, reaching a point where they became too weak to retain new particles or groups of particles at the surfaces of the agglomerates, in comparison to other active forces. At this point, the agglomerates broke down and equilibrium seemed to be established, where the rates of agglomeration and deagglomeration were dynamically balanced.

4.3. Physical analysis of the size model

The following trend can be observed from the data presented in Table 2:

1. All trials performed with an initial concentration of more than 33% Xylitab (points #7, 8 and 10 to 14) showed rapid agglomeration growth at a size of less than 0.9 mm diameter. After that, the size of the agglomerates

obtained was stable for 10 min. Under these initial conditions, Xylitab seemed to control agglomeration growth and stabilization.

2. The same pattern was observed with MgSt when the initial concentration of this component was 100% (points #1 and 2). However, in this case, the mean size of the MgSt agglomerates stayed about the same over time, but their number increased. Also, for the same agglomerate size, about 6% of Xylitab agglomerated, whereas not less than 70% of MgSt did.
3. The presence of CCP became predominant on agglomeration size growth when the Xylitab concentration was not more than 0.17% (points #3 to 6 and 9).

5. Conclusion

It has been demonstrated quantitatively that time and ingredient concentrations of the three-component dry pharmaceutical mixture can affect agglomeration tendency. A statistical model has been presented to express agglomeration weight as a function of initial concentrations and time. General rules of thumb have been found to explain agglomeration size variation with time for the different concentrations tested.

Xylitab alone did not form a significant amount of agglomerates, but when mixed with other components, it favoured deagglomeration when agglomerates were formed. MgSt alone formed small agglomerates of uniform size that did not increase with time while their number did. CCP alone formed agglomerates with increasing size as a function of mixing time. MgSt and CCP presented a positive interaction and favoured agglomeration tendency and growth with mixing time.

Agglomeration size and weight growth were stabilized when a critical size was reached where agglomerates started to break up because the attracting forces became equal to or eventually weaker than gravitational and inertial forces acting on them.

This work has shown the importance of these ingredients at different concentrations with time, which are beyond the real concentrations used in pharmaceutical formulations (especially MgSt and CCP). Nevertheless, the conclusions are very helpful in understanding the general behaviour of these components during a mixing process. Additional work with other ingredients is necessary for comprehensive knowledge of the mixing process and its modeling.

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