Drug Development and Industrial Pharmacy, 2009; 35(12): 1487–1495

informa
healthcare

ORIGINAL ARTICLE

Shear-induced APAP de-agglomeration

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Abstract

Context: Active pharmaceutical ingredient agglomerates can generate many solid product regulatory compliance issues. *Objective*: To study the effects of shear rate, strain, type of excipient, and grade of acetaminophen (APAP) on the process of APAP de-agglomeration. *Materials and Methods*: A shear-controlled environment is used to expose six different blends that consist of one of three APAP grades and one of two possible types of excipient to 10 different combinations of shear rate and strain. APAP agglomerates are sifted and weighed. *Results*: Finer APAP grades lead to blends with more APAP agglomerates and type of excipient only affects the de-agglomeration process for the finest APAP grade. De-agglomeration proceeds mainly as a function of strain with a minor contribution toward further de-agglomeration when larger shear rates are used. *Discussion*: When mechanical stress (which us proportional to shear rate) overcomes interparticle forces, de-agglomeration occurs. Higher shear rates (and stress) contribute slightly to further APAP de-agglomeration. Extended exposure to stress (strain) reduces the size and the number of agglomerates. Blends with finer APAP present more agglomerates, particularly after low strain exposure. *Conclusions*: This article presents a useful method for formulation and process development. Exposing blends to higher shear rates and especially to strain mitigates APAP agglomeration in blends. Finer APAP presents more agglomerates and the type of excipient used affects the degree of APAP agglomeration.

Key words: *Agglomerates; content uniformity; homogeneity; mixing; shear*

Introduction

Agglomerates—groups of particles bound by surface forces, and particularly those constituted by drug particles—are the cause of several problems for dry solid pharmaceutical formulations[1]. For example, they increase the variability in blend and tablet active pharmaceutical ingredient (API) concentration[2,3], and they sometimes generate inadmissibly super potent tablets[4,5]. In addition, agglomerates may dissolve more slowly than dispersed particles[6,7], reducing the bioavailability of the drug. In fact, dissolution rates can sometimes be used to determine the degree of agglomeration of low solubility drugs in blends[8]. Agglomeration is particularly a challenge for the preparation of low-dose direct compression formulations.

Agglomeration is influenced by several particle properties and by environmental and processing conditions. De-agglomeration of cohesive granular materials, however, is achieved when shear stresses overcome interparticle forces. The processing variables in blending units are shear rate, which determines shear stress, and strain, which is proportional to the duration of exposure to shear rate. Shear rate in blenders is typically nonuniform and unknown. Therefore, studies performed in blenders can hardly offer any information about the correlation between these variables and the degree of API de-agglomeration.

This article has two main aims. The first aim is to use a new shear-controlled environment that allows us to study this correlation. Particle properties such as size, surface area, asperity, and tribo-charging tendency, both for the API and excipients, also affect API de-agglomeration. The second aim of this article is to study the effect of different excipients and different acetaminophen (APAP) grades on APAP de-agglomeration.

De-agglomeration studies are needed for several reasons. Shear rate in blenders is affected by several

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(Received 12 Dec 2008; accepted 6 May 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.3109/03639040903025863

operating and configuration parameters; however, these dependences are poorly understood. Therefore, most published studies correlate API homogeneity and de-agglomeration with variables associated to the type of blender (tumbling or ribbon) such as blender scale[9], fill level, drug load[10], use of intensifier bars in the tumbling blenders, design of the ribbon blade[11], speed of rotation of the body[12] or the ribbon blade[11], and with mixing time[1,13]. In general, API de-agglomeration is typically the limiting step for the API mixing rate[14,15], and longer mixing times (i.e., larger strain) contribute to more extensive de-agglomeration[8]. Most times, a tumbling blender does not provide the shear rates necessary to achieve API de-agglomeration, therefore blenders with an intensifier bar or even mills are often used[16]. These studies provide valuable insight about the operation of a particular equipment but little information about the effects of more fundamental variables (shear rate and strain) on API de-agglomeration and homogeneity. This article provides an alternative analysis of the de-agglomeration phenomenon as a function of fundamental variables such as shear rate and strain, instead of blender operating parameters, internal configuration, and mixing time. A controlled shear environment that uniformly exposes the blend to specific shear conditions is used. This environment has been already used to study the effect of shear rate and strain on formulation properties such as flow, density, and also tablet hardness[17]. This type of information will render our understanding of manufacturing equipment more complete and will also help us to develop and implement adequate online and off-line analytical technologies[18]. The intensity of shear rate in a process is an important issue because very high shear rates can lead to product with poor homogeneity and dissolution properties. For example, drug micronization (i.e., mill) is sometimes performed to modify the particle size distribution. However, the outcome may be particles with a tendency to form agglomerates because of acquired electric charge and increased importance of surface forces (i.e., Van der Waals) that hinders the intended enhancement in drug homogeneity and solubility[19,20].

The other aspect that determines the existence of agglomerates is particle physical properties. Particle size is very important because as particle size decreases, particle surface area and all the effects of interparticle forces that are a function of size (i.e., Van der Waals) increase[21,22]. Consequently, the behavior of small particles becomes dominated by surface forces and by neighboring particles rather than by the gravitational force. Electrical forces (i.e., dipoles, net charge) can be instrumental in particle agglomeration because they are several orders of magnitude larger than other surface forces (i.e., Van der Waals)[23–25]. Surface characteristics also affect particle cohesion[26] and API de-agglomeration[27]. Smooth particles can develop large contact areas and therefore large interacting forces. In such cases, glidants – particles generally much smaller than most pharmaceutical excipients – can be added to the formulation to reduce cohesion. Glidants attach to the surface of large particles, increasing the distance between them and decreasing the influence of surface forces[28,29]. In this article, we studied how APAP particle size and more importantly how the type of excipient, which is the major component in the blend and is responsible for shear stress transmission, affect APAP de-agglomeration.

The Materials and Methods section describes the controlled shear environment and its operation, the blend preparation procedure, and the sifting technique used to separate and quantify agglomerates. The Results section discusses the effects of excipient formulation, API grade, shear rates, and strain on API de-agglomeration. The Conclusion section summarizes the results and provides guidelines to apply this technique to practical situations.

Materials and Methods

Formulations

The six blend formulations used throughout all experiments reported here are a mix of either lactose (Fast flo lactose, ~100 μm, spherical particles; Foremost Farms, Newark, NJ, USA) or cellulose (microcrystalline cellulose, Avicel PH 102, ~90 μm, needle-like particles; FMC, Rothschild, WI, USA) and any of three grades of APAP (fine, semifine, and micronized, Mallinckrodt, St. Louis, MO, USA). Figure 1 shows the particle size distributions for APAP. The formulations contain either 300 g of lactose and 15 g of APAP or 230 g of cellulose and 15 g of APAP. The difference in excipient mass is because of their different densities and the requirement that to impart similar strain to the blends, the area of contact

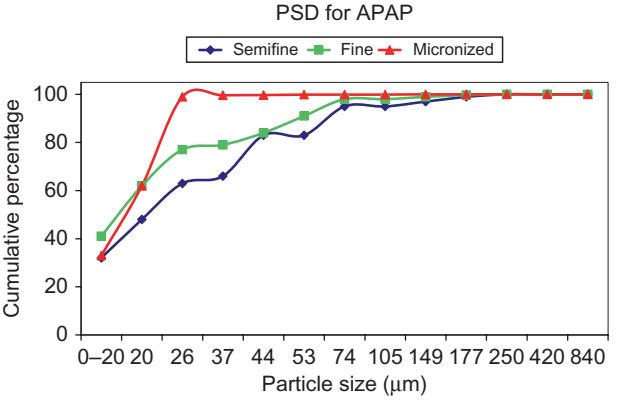

Figure 1. Particle size distributions for the three types of APAP.

between the walls of the instrument and the blend must be the same. Therefore, the controlled shear environment must have the same fill level in all experiments. The API mass was kept constant to be able to facilitate analysis in terms of the absolute mass in the agglomerated form and also in the terms of the API percentage in agglomerated form.

Controlled shear environment: modified Couette system

The geometry of the controlled shear environment is based on an annular Couette rheometer typically used for measuring viscosity of liquids. The device consists of two concentric aluminum cylinders, 4.3-in. long (11 cm), with a gap of 0.75 in. (1.9 cm) that allows a powder volume of approximately 0.6 L. The internal cylinder (Figure 2a) has a diameter of 6.5 in (16.51 cm). The internal cylinder can rotate at any speed in the range of 1–245 rpm whereas the external cylinder is stationary. Both cylinders are made of aluminum, and they are supplemented with equally spaced interlocking pins that create a nearly homogeneous shear field in the flow region (Figure 2a and b). The controlled shear environment has a lid and a seal.

Procedure to prepare formulations under controlled shear conditions

The first step in the de-agglomeration experiments consists of preparing a pre-blend with all the ingredients.

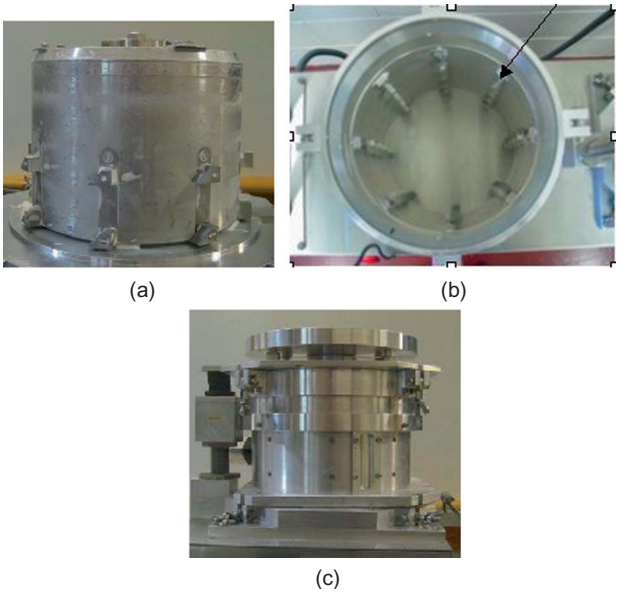

Figure 2. Couette shear-controlled shear environment. (a) Internal cylinder with pins. (b) External cylinder with pins. (c) Gap between cylinders.

The practice of using a pre-blend is adopted because the controlled shear environment is not a good mixer along the axis of rotation. Dispersion is the main axial macro-mixing mechanism in the device, convection along the axis of rotation is very slow. When the controlled shear environment is loaded with the excipients and the APAP in a stratified manner, it takes a long time to achieve APAP homogeneity throughout the controlled shear environment. APAP particles can form agglomerates again, if they are in contact with like particles. Thus, a pre-blend is prepared in a small V-blender (Figure 3). To minimize uncontrolled exposure to shear, the mixing time is short (50 revolutions), the rotational speed of the blender is moderate (10 rpm), the blender scale is small (4 qt), and the loading pattern for API and excipients is top-bottom.

The controlled shear environment is loaded to full capacity (~0.6 L) with pre-blend and one of the shear conditions indicated in Table 1 is applied. Table 1 displays the shear rates in rows (with the corresponding rotational speeds of the cylinder in rpm), the strain in columns (in dimensionless shear units and the equivalent number of revolutions) and a sparse diagonal design (marked with 'X') that allows examining the effect of shear rate for similar amounts of strain, and the effect of strain at a constant shear rate. In the experiments

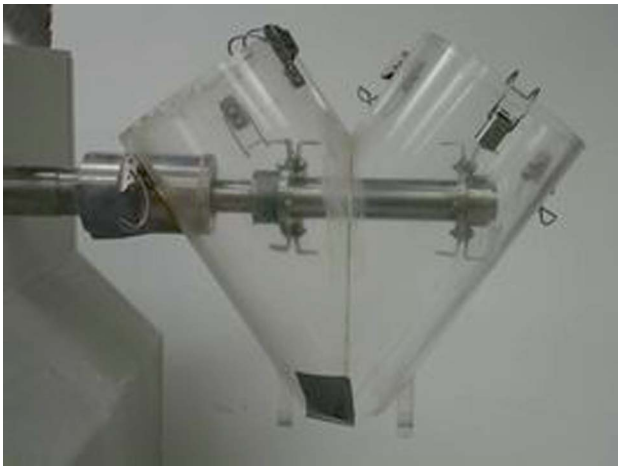

Figure 3. V-blender.

Table 1. Grid showing the shear environments under which the experiments were performed.

	10 revs (267)	80 revs (2136)	320 revs (8544)	2000 revs (53,400)
2 rpm (0.9 s^{-1})	**X**	**X**		
40 rpm (17.8 s^{-1})	**X**	**X**	**X**	
160 rpm (71.2 s^{-1})		**X**	**X**	**X**
245 rpm (109 s^{-1})			**X**	**X**

reported here, strain varies over two orders of magnitude from ~270 to ~53,000, while shear rate varies from 0.9 s^{-} (at 2 rpm) to 109 s^{-1} (at 245 rpm). This range comprises typical values for most industrial units, including tumblers with and without intensifier bars and 'high shear' mixer granulators.

Separation of agglomerates: sieving

The method to separate and characterize agglomerates followed in this study consists of sifting the entire blend[30] using the following sequence of sieves (classified according to their mesh and opening diameters): 10 (2 mm), 12 (1.85 mm), 14 (1.55 mm), 18 (1.2 mm), 20 (0.925 mm), and 40 (0.6375 mm). The mass of agglomerates retained in each sieve is weighed and then the total proportion of agglomerated APAP is calculated. The blends used here flow easily through the sieves without having to use vibration. For these blends to flow through a mesh finer than 40, the trays must be subject to vibration, and this energy input can destroy some agglomerates. Therefore, the current procedure does not analyze smaller agglomerates that pass through the sieves with the excipients.

Design of experiments and statistical analysis

The values of shear rate and strain analyzed here correspond to those found in the majority of industrial equipment and they form an incomplete factorial model (Table 1). The factorial experiment consists of 10 'shear treatments', which are tested for six different formulations, generating 60 experimental conditions. Each condition is tested twice, starting from the pre-blend preparation. The experiments are performed randomly, which means the conditions are not tested in any predetermined order, and the repetitions are not performed in a sequence. This number of measurements (120 values) gives enough degrees of freedom to analyze the effects of shear rate (df = 3), strain (df = 3), APAP grade (df = 2), type of excipient (df = 1), and also all the possible interactions between processing variables and type of excipient and APAP as well as the interaction between type of excipient and APAP.

The statistical analysis is performed with the Minitab software, using a General Linear Model (GLM), which takes into account the imbalance in the data sheet generated by the fact that not all the combinations of revolutions and rpm are studied.

Results

Table 2 compiles the agglomerate mass fraction for all the combinations of shear treatment, APAP grade, and type of excipient examined (120 values). The GLM test for these data sets (Table 3) shows that, for a significant P-level of 0.05, shear rate (P = 0.004), strain (P = 0), APAP grade (P = 0), and type of excipient (P = 0.021) affect APAP de-agglomeration. Additionally, there is a significant interaction between strain and APAP grade (P = 0.014). Figure 4 shows the effect of the levels of each of these variables on APAP de-agglomeration. The plot in the upper left corner shows that larger shear rates (or rpm) lead to more extensive de-agglomeration. The plot in the upper right corner shows that strain (or number of revolutions for this cell) has a major effect on APAP de-agglomeration. The plot in the lower left corner shows that coarser (semifine APAP) presents less agglomeration. Finally, the plot of the lower right corner shows that Avicel leads to more de-agglomeration than lactose. In subsequent sections, the effects of API grade, type of excipient, shear rate, and strain on the APAP de-agglomeration are analyzed in more detail. Figure 5 analyzes the interaction between APAP grade and strain or number of revolutions. Such interaction is evident especially between the two finest APAP grades: fine and micronized.

Table 2. Percentage of APAP agglomerated in the experimental conditions tested.

Excipient	Avicel 102	Lactose	Avicel 102	Lactose	Avicel 102	Lactose
APAP	Micronized	Micronized	Fine	Fine	Semifine	Semifine
2 rpm – 10 revs	0.264, 0.288	0.369, 0.322	0.328, 0.298	0.356, 0.239	0.211, 0.247	0.201, 0.215
40 rpm – 10 revs	0.282, 0.267	0.398, 0.277	0.325, 0.345	0.326, 0.361	0.168, 0.201	0.276, 0.201
2 rpm – 80 revs	0.113, 0.139	0.178, 0.141	0.109, 0.163	0.111, 0.160	0.051, 0.059	0.081, 0.115
40 rpm – 80 revs	0.169, 0.195	0.139, 0.101	0.083, 0.115	0.164, 0.182	0.115, 0.065	0.071, 0.061
160 rpm – 80 revs	0.101, 0.178	0.148, 0.125	0.071, 0.093	0.092, 0.080	0.037, 0.057	0.051, 0.015
40 rpm – 320 revs	0.037, 0.115	0.135, 0.085	0.033, 0.032	0.147, 0.049	0.025, 0.045	0.011, 0.014
160 rpm – 320 revs	0.034, 0.005	0.035, 0.076	0.043, 0.038	0.060, 0.051	0.011, 0.011	0.001, 0.043
245 rpm – 320 revs	0.038, 0.016	0.120, 0.051	0.033, 0.036	0.069, 0.049	0.018, 0.021	0.001, 0.036
160 rpm – 2000 revs	0.013, 0.004	0.010, 0.009	0.045, 0.040	0.004, 0.031	0.004, 0.008	0.010, 0.002
245 rpm – 2000 revs	0.027, 0.005	0.045, 0.004	0.017, 0.030	0.003, 0.026	0.025, 0.003	0.023, 0.001

Table 3. Results of a three-factor ANOVA analysis on APAP de-agglomeration.

Source	*DF*	Seq. SS	Adi. SS	Adi. MS	*F*	*P*
RPM	3	0.568293	0.013161	0.004387	4.81	0.004
Revolutions	3	0.514552	0.514552	0.171517	187.89	0.000
APAP grade	2	0.076688	0.069749	0.034874	38.20	0.000
Excipient	1	0.005441	0.005054	0.005054	5.54	0.021
RPM*APAP	6	0.015676	0.001459	0.000243	0.27	0.951
RPM*Excip	3	0.001695	0.000511	0.000170	0.19	0.905
Rev*APAP	6	0.015658	0.015658	0.002610	2.86	0.014
Rev*Excip	3	0.003395	0.003395	0.001132	1.24	0.300
APAP*Excip	2	0.002329	0.002329	0.001165	1.28	0.284
Error	90	0.082158	0.082158	0.000913		
Total	119	1.285884				

Effect of type of excipient on APAP de-agglomeration

The effect of type of excipient on APAP de-agglomeration is graphically analyzed for each of the three grades of APAP. Figures 6–8 plot the APAP mass fraction in the form of agglomerates for micronized, fine, and semifine APAP versus the number of revolutions (strain) of the internal cylinder of the controlled shear environment. The different patterns for curves in each of these figures correspond to different speeds of rotation (shear rate) of the cylinder, whereas the curves for the experiments performed in lactose have circles and the curves for the experiments performed in Avicel 102 have triangles. The first letter in the notation to identify the curves indicates the grade of APAP; the second letter indicates the type of excipient, followed by the speed of the internal cylinder of the controlled shear

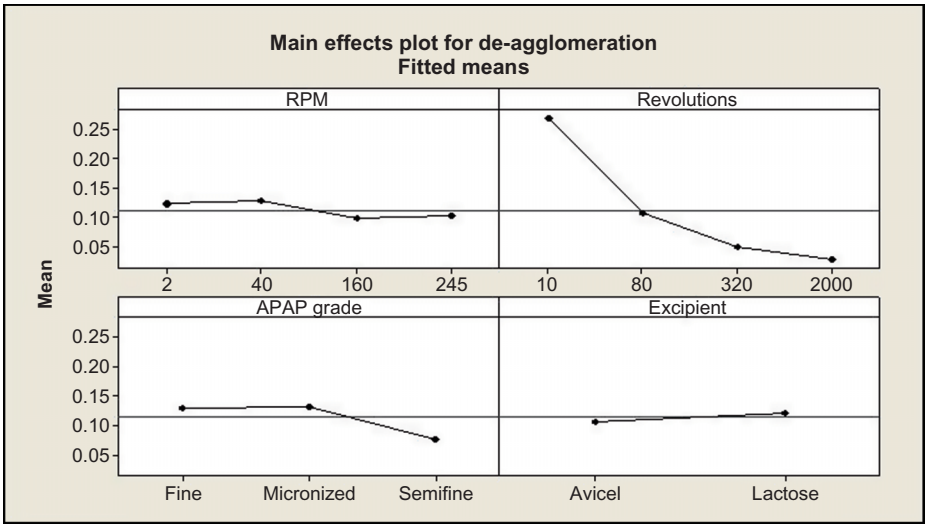

Figure 4. Effect of the four variables studied on APAP de-agglomeration.

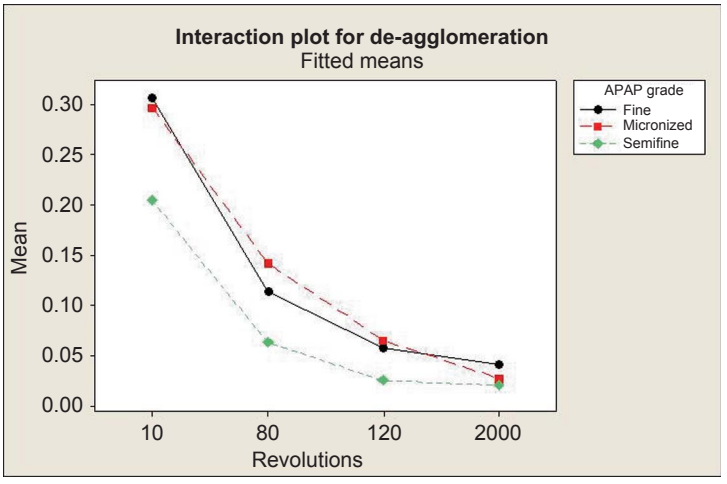

Figure 5. Interaction between APAP grade and strain (or revolutions of the cylinder).

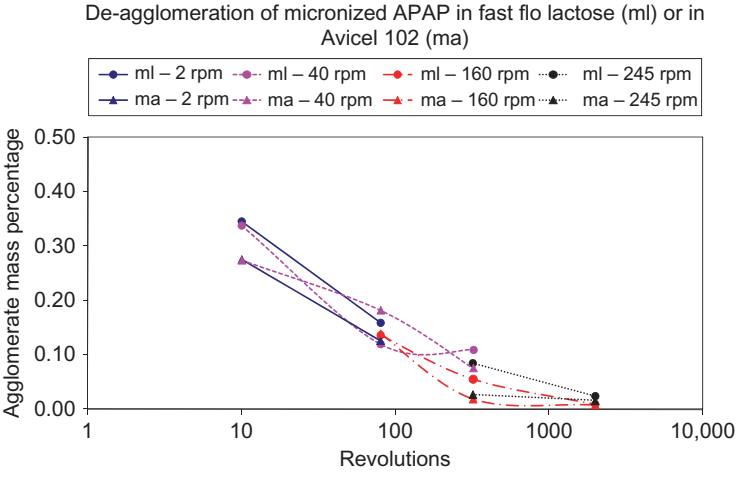

Figure 6. Micronized APAP de-agglomeration in lactose (ml) and in Avicel 102 (ma).

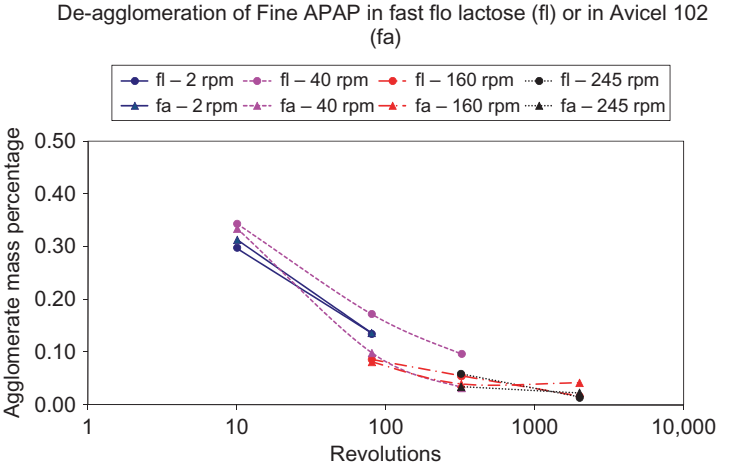

Figure 7. Fine APAP de-agglomeration in lactose (ml) and in Avicel 102 (ma).

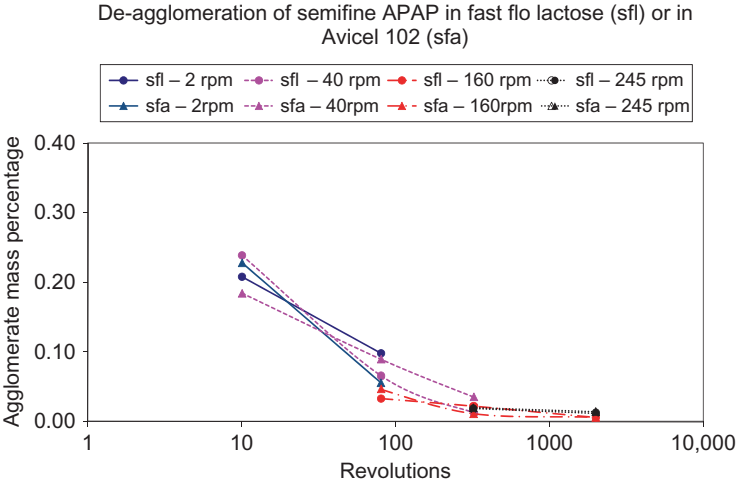

Figure 8. Semifine APAP de-agglomeration in lactose (ml) and in Avicel 102 (ma).

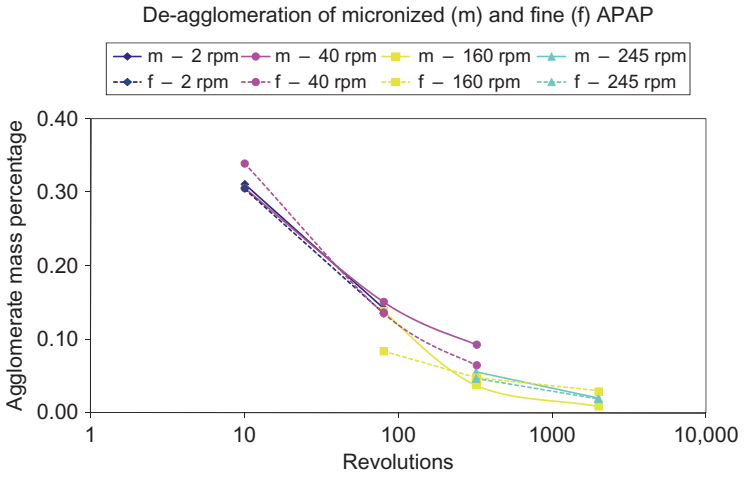

Figure 9. De-agglomeration of micronized (m) and fine (f) APAP (the two finest grades).

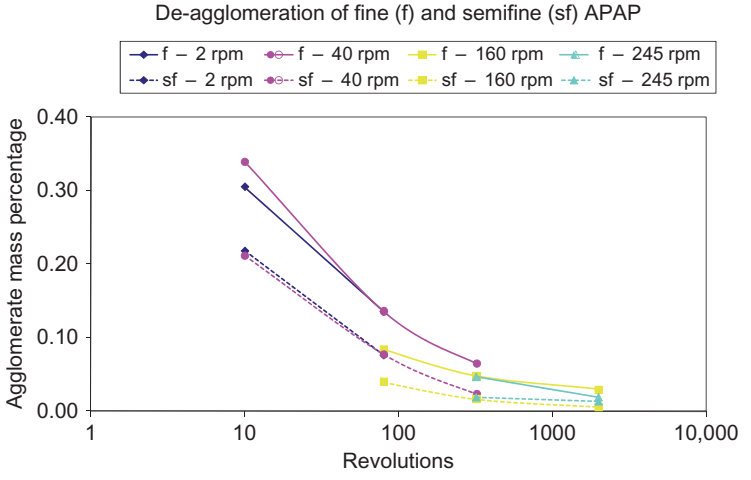

Figure 10. De-agglomeration of fine (f) and semifine (sf) APAP.

environment. For example, the curve 'ml – 2 rpm' is for a blend of micronized (m) APAP in lactose (l) and the controlled shear environment operating at 2 rpm. Figure 6 compares the de-agglomeration data, in lactose and in Avicel 102, for micronized APAP. Figures 7 and 8 do the same for fine and semifine APAP. The effect of type of excipient is not so evident in the figures because the curves have similar values, although the curves for Avicel are generally lower. However, the statistical analysis establishes that the differences are relevant and Avicel slightly enhances APAP de-agglomeration.

Effect of APAP grade on APAP de-agglomeration

The effect of APAP grade is illustrated in Figures 9 and 10. These figures present the drug mass fraction in the form of agglomerates versus the number of revolutions of the internal cylinder of the shear controlled shear environment (strain) and the different markers on the curves correspond to different speeds of rotation of the cylinder (shear rate). Figure 9 compares the de-agglomeration of micronized (full lines) and fine APAP (broken lines), which are the two finest APAP grades, and shows that they proceed in a similar manner. Figure 10 compares the APAP de-agglomeration for fine (full lines) and semifine APAP (broken lines), the latter is the coarsest APAP grade. The curves for these two grades are visually and statistically different, especially at low strain values (below 80 revolutions)[1]. Semifine APAP, which is the coarser grade, presents a smaller number of agglomerates.

[1]Since excipient plays a minor role in the de-agglomeration of semifine and fine APAP, the values in the curves for each shear treatment (Figures 9 and 10) are a contribution of the agglomerate fraction values whether they are mixed with lactose or with Avicel. The excipient plays a role in the de-agglomeration of micronized APAP; however, the agglomerate fraction values were combined to facilitate the comparison among APAP grades.

The results show that the de-agglomeration process is very different for fine and semifine APAP grade. On the other hand, this process is very similar for micronized and fine APAP grades, where APAP grade has a smaller effect on de-agglomeration.

Effect of shear rate and strain

The curves in Figures 6–10 suggest that APAP de-agglomeration occurs mainly as a function of strain (revolutions of the cylinder) while it is difficult to assess the effect of shear rate. The mass of API agglomerates strongly decreases with the number of revolutions of the controlled shear environment, whereas the mass values obtained using different shear rates (or speeds of rotation of the cell) and same number of revolutions seem similar.

Conclusions

The first aim of this article was to study the effects of shear rate and strain on APAP de-agglomeration. The statistical and graphical results show that APAP de-agglomeration is influenced by strain and to a lesser extent by shear rate. Larger shear rates and mainly larger exposure to strain enhance the APAP de-agglomeration process. The technique presented in this article can be used when developing formulations and units and blending protocols that minimize API agglomeration.

The second aim of this article was to study the effect of particle properties, in this case determined by APAP grade and type of excipient, on APAP de-agglomeration. The statistical and graphical results show that APAP de-agglomeration is influenced by APAP grade to a less extent by type of excipient. The coarsest APAP ('semifine') presents fewer agglomerates than the other two finer grades, and the larger the exposure to strain (more revolutions of the cell), the smaller number of agglomerates present in the blends. The type of excipient affects APAP de-agglomeration marginally. However, the selection of excipients was based on the fact that both flow very well and facilitate the agglomerate separation in sieves. In fact, these excipients are not very different in terms of average particle size. Intuition indicates that the effect of type of excipient on de-agglomeration would be larger when their differences are more remarkable.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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