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Description of the kinetics of the deagglomeration of drug particle agglomerates during powder mixing

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Abstract

A first-order kinetic equation was used to describe the deagglomeration of agglomerates of microfine furosemide particles, ranging in size from 250 μm to 1000 μm, when mixed with mono-dispersed sodium chloride particles with a mean size of 325 μm in either a V-blender or Turbula mixer rotated at different speeds. An increase in mixing time caused an initial rapid decrease in agglomerate size but eventually agglomerate breakdown acquired a self-preserving form. For example, the rate constant decreased from $k = 0.358$ min^{-1} to $k = 0.034$ min^{-1} when mixtures containing agglomerates with a mean size of 250 μm was mixed in a Turbula mixer at 90 rpm. This suggested that during an initial fast, random mixing process, agglomerates were broken down into single particles and smaller agglomerates by a ball mill effect produced by the sodium chloride particles. During this process smaller agglomerates, mean size below 28 μm, adhered to the sodium chloride particles to produce an ordered mixture. Single particles and even smaller agglomerates were removed from these agglomerates by a combination of abrasion and a process of erosion caused by the mixing process. The relative dominance of the two breakdown mechanisms, and the overall rate and intensity of the total breakdown process, depended on the type of mixer and mixer speed used, and the initial size of the agglomerates. © 1997 Elsevier Science B.V.

Keywords: Kinetics; Deagglomeration; Particle agglomerates; Powder mixing

1. Introduction

Although the spontaneous agglomeration of fine drug powder particles leads to a series of undesirable phenomena, evaluation of dosage forms do not yield quantitative information on the effects of agglomeration on dosage form performance (Staniforth, 1988). Therefore, reliable models are needed for improved understanding of the effect that agglomeration has on pharmaceutical processes such as powder mixing (Staniforth, 1987).

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The theory of powder mixing takes account of random and ordered (interactive, adhesive) mixing (Sunada et al., 1984). Random mixing requires little or no surface effects, cohesion or interparticulate interaction. As the particle size of a powder decreases cohesive properties and other surface phenomena develop and this will tend to order, rather than randomise the mixing process. During ordered mixing, the fine particles of the cohesive powder are deagglomerated and distributed over the surface of carrier particles (Hersey, 1975). In reality when mixing small, cohesive particles with large carrier particles it is therefore difficult to distinguish between the two mixing processes and to determine the relative contribution of each towards the deagglomeration process. The examination of the actual rates of breakage might provide a useful clue to the contribution of the mixing process to the deagglomeration process.

Austin et al. (1989) describes agglomerate breakdown as the sum of two basic mechanisms of size reduction. The first is the fracture of large agglomerates by impact between the agglomerates and the large, dense carrier particles or between the agglomerates and the walls of the mixing vessel. On the other hand size reduction also occurs through abrasion resulting from the rubbing of agglomerates against carrier particles and against the walls of the mixing vessel. Abrasion and erosion also occur when small agglomerates, formed by the first two processes and attached to the carrier particle surface, are broken down by the ordered mixing process (Cartillier and Moës, 1989).

In this study, a first-order breakdown model was used to describe the kinetics of deagglomeration, observed in an actual system comprised of large free-flowing agglomerates mixed with large mono-dispersed carrier particles. These simulations were carried out to explain the deagglomeration process when agglomerates of fine furosemide particles were subjected to powder mixing.

1.1. Theoretical considerations

The first-order disintegration model has been applied to mixing models, yet specific correlation of the model to the mechanism of agglomerate breakdown via powder mixing is rare. Applying the concept of first-order breakdown as representing the deagglomeration process during powder mixing, makes it possible to distinguish between the two breakdown mechanisms caused by random (fracture) and ordered (abrasion) mixing. However, the contribution of both mixing phenomena to the breakdown of agglomerates cannot be separated by simple examination of the kinetics of the total mixing process.

Austin (1971) showed that when breakage occurs in an efficient manner it can be assumed that the breakage of powdered material follows the first-order law

$$\mathrm{d}x/\mathrm{d}t = k(A - x) \tag{1}$$

where x is the particle size of material at time t, A is the original agglomerate size and k is the specific rate of breakage, with units of fraction per time unit. When using the concept of first-order breakage rates as representing normal deagglomeration, the initial size of the powder agglomerates, A, and the size of the individual particles, $x\alpha$, must be known. In the derivations used, x represents the particle size of furosemide at time t after the onset of mixing. It is obvious that x decreases as mixing proceeds. The difference in size at time t is therefore $(A - x)$. A plot of $\mathrm{Ln}(A - x)$ against t shows the progress of the deagglomeration process. For a first-order process x approaches $x\alpha$ asymptotically. The slope of the tangent to the progress curve of $\mathrm{Ln}(A - x)$ against t, represents the rate of change, k, of A against t and its dimension is time^{-1} (min^{-1}).

2. Materials and methods

2.1. Materials

Furosemide powder, generously supplied by Lennon Pty. Ltd., South Africa (batch number L125221) was screened through a series of sieves and the agglomerates in the sieve fractions 200–250 μm, 500–600 μm and above 1000 μm were used to prepare ordered mixtures. The sieve fraction between 300–350 μm of sodium chloride supplied by BDH Chemicals was used to prepare the mixtures. All other chemicals and solvents were of analytical grade and water of quality sufficient for liquid chromatography, was used.

2.2. Preparation of mixtures

Each mixture consisted of 500 mg agglomerates and 100 g sodium chloride particles (0.5% w/w). Mixtures were prepared either in a V-blender or a Turbula mixer rotated at 30, 60 or 90 rpm for increasing times up to 100 min. For each mixer, mixture speed, mixing time and agglomerate size five mixtures were prepared. The mixing vessels had approximately the same volumes (± 200 cm^3). After mixing, mixtures were transferred to 200 cm^3 wide mouth amber glass bottles and left for 24 h to reach equilibrium.

2.3. Particle size analysis

The particle size of the furosemide present in each of three of the mixtures were determined by adding first 500 cm^3 of a suspending liquid to the amber glass bottles, placing the bottles in a mechanical shaker and rotating them at 25 rpm for 2 min. The sodium chloride particles dissolved in the suspending liquid, leaving behind a fine suspension of furosemide particles (De Villiers et al., 1993). The particle size distribution of these suspended particles was then measured. The suspending liquid used, comprised of a saturated aqueous solution of furosemide containing 0.011 gdm^{-3} polyoxyethylene sorbitan monooleate.

The mean volume particle size distribution of the suspended furosemide particles was measured with a Galai-Cis-1 particle size analyser using the particles in liquid method (Galai, Israel). Results presented, are the mean of five samples taken from each mixture. The mean volume particle size of the individual furosemide particles was measured using a particle in air technique applying a dry powder disperser (Sympatec, Germany).

2.4. Removing agglomerated material

The two remaining mixtures were screened using a 300-μm sieve. The mixture content was transferred on top of the sieve and the sieve was mechanically vibrated, at a very low frequency. The sodium chloride particles remaining on top of the screen, were dissolved in 500 cm^3 of the suspending liquid and the particle size of the furosemide was then measured. The amount of furosemide removed from the mixtures and adhering to the walls of the mixing vessel was determined with a spectrophotometer by measuring the UV absorbance of methanol solutions at the wavelength of maximum absorption, i.e. 271 nm.

2.5. Calculations and statistical interpretations

Data obtained from the particle size analysis instruments were used to construct mean percentage volume particle size distributions as a function of mixing time. The volume or mass bias mean was used because it is the most useful way of representing particle diameters of milled or micronised powders. These powders have log-normal particle distributions that can be described by the geometric median or mean diameter plus geometric standard deviation. Mean volume particle sizes were compared statistically according to the Newman-Keuls test (CSS: Statistica, Statsoft). A 95% confidence level ($p \leq 0.05$) was considered satisfactory for indicating significant differences between mean measured particle sizes. Analysis of variance calculations were performed separately on rate constants, k, at all mixer, mixer speed, and mixing time combinations.

3. Results

A first-order kinetic equation, Eq. (1), was used to describe the deagglomeration of the agglomerated, microfine furosemide particles during powder mixing. First order deagglomeration data calculated from the change in agglomerate size as a function of mixing time for the unscreened

Table 1
First order deagglomeration data of unscreened mixtures containing agglomerates

Mixer type	Mixer speed (rpm)	Agglomerate size (μm)	Rate constant (min^{-1})	Y-intercept (μm)	Time (min)	Regression coefficient
V-Mixer	30	251 ± 4.5	0.085	243 ± 2.5	93 ± 0.9	0.990
	60		0.137	235 ± 2.1	68 ± 1.2	0.996
	90		0.241	243 ± 8.2	51 ± 1.9	0.987
Turbula	30	250 ± 6.1	0.165	239 ± 3.5	61 ± 1.2	0.992
	60		0.299	267 ± 6.2	47 ± 1.1	0.976
	90		0.358	236 ± 4.8	43 ± 0.6	0.994
Turbula	30	549 ± 9.9	0.131	555 ± 6.4	76 ± 1.6	0.994
	60		0.187	547 ± 1.3	62 ± 0.7	0.996
	90		0.308	602 ± 29.6	49 ± 1.5	0.985
Turbula	30	1062 ± 33.0	0.106	1081 ± 16.7	94 ± 1.4	0.997
	60		0.179	1133 ± 28.2	67 ± 1.4	0.989
	90		0.217	1124 ± 14.0	60 ± 0.5	0.977

[a] Results are based on the decrease in agglomerate size with increasing mixing time.

mixtures containing agglomerates, are listed in Table 1. This mixing process represented a combination of both random and ordered mixing. Similar results for the deagglomeration of small agglomerates attached to carrier particles during ordered mixing (change in agglomerate size of screened mixtures as a function of mixing time), are listed in Table 2.

Using these rate constants, breakdown of furosemide agglomerates in a V-blender was examined and compared with breakdown in a Turbula mixer, Fig. 1. These graphs show the effects of mixer speed and initial agglomerate size upon the rate of agglomerate breakdown as a function of mixing time. Effect of initial agglomerate size on the deagglomeration process is shown in Fig. 2. In the graphs the lines represent the best fit, according to the proposed model, and the markers the mean measured values. The lines represents a combination of the first order results for both deagglomeration processes (Tables 1 and 2. The time to which the random deagglomeration (mixing) process applied and the maximum size of agglomerates that were attached to the carrier particles, are listed in Tables 1 and 2, respectively. These two values indicated the change from a random to a ordered mixing process.

4. Discussion

The mean volume particles size of the furosemide powder was 2.5 μm which caused agglomeration of the powder. Correlation between experimental and calculated first-order kinetic parameters (Figs. 1 and 2) showed that the breakdown of these agglomerates was caused by a combination of random and ordered mixing. With an increase in mixing time, the agglomerate size spectra eventually acquired a self-preserving form indicating that an ordered mixture was produced. For example, when furosemide agglomerates with a mean size of 250 μm was mixed in a Turbula mixer at 90 rpm the rate constant, k, decreased from 0.358 to 0.034 min^{-1}. Similar results for all the mixtures are listed in Tables 1 and 2. The deagglomeration rate during random deagglomeration was significantly faster than that found during ordered mixing. For this mixture, the change from a combined random/ordered deagglomeration process to deagglomeration through ordered mixing occurred at 43 ± 0.6 min and the maximum size of the agglomerates that was attached to the carrier particles was 28 ± 2.0 μm.

For all the mixtures studied, this change in the rate of breakage could be described by the parameters listed in Tables 1 and 2. Before this change in the rate of breakage the deagglomera-

Table 2
First order deagglomeration data of screened mixtures containing no loose agglomerates

Mixer type	Mixer speed (rpm)	Agglomerate size (μm)	Rate constant (min^{-1})	*Y*-intercept (μm)	Regression coefficient
V-Mixer	30	251 ± 4.5	0.036	45 ± 3.1	0.983
	60		0.031	35 ± 1.6	0.984
	90		0.028	22 ± 1.7	0.985
Turbula	30	250 ± 6.1	0.032	24 ± 2.0	0.996
	60		0.037	29 ± 2.9	0.997
	90		0.032	28 ± 2.0	0.998
Turbula	30	549 ± 9.9	0.027	22 ± 1.0	0.995
	60		0.030	27 ± 0.9	0.993
	90		0.031	26 ± 4.5	0.998
Turbula	30	1062 ± 33.0	0.030	26 ± 2.3	0.986
	60		0.033	26 ± 3.3	0.992
	90		0.028	23 ± 1.7	0.996

[a] Results were based on the decrease in agglomerate size with increasing mixing time.

tion rate constants were larger than 0.1 min^{-1}, depending on the mixer type, mixer speed and initial agglomerate size used to prepare the mixture. Afterwards the deagglomeration rate decreased to below 0.05 min^{-1} and was not affected by a change in mixer type, mixer speed or an increase in initial agglomerate size. Initial agglomerate breakdown was faster in a Turbula mixer and an increase in mixer speed of both mixers led to an increase in deagglomeration rate (Table 1). This suggested that during an initial fast, random mixing process agglomerates were broken down into single particles and smaller agglomerates by a ball mill effect, produced by the large sodium chloride particles.

During the ordered mixing process single particles and even smaller agglomerates were removed

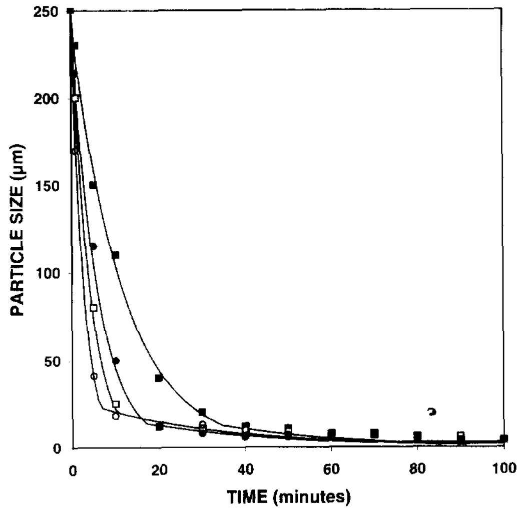

Fig. 1. Mean volume furosemide agglomerate size as a function of mixing time after mixing in a Turbula mixer rotated at (■) 30 rpm and (□) 90 rpm, and in a Turbula mixer rotated at (●) 30 rpm and (○) 90 rpm. The lines represent the best fit, according to the proposed model, and markers mean measured values.

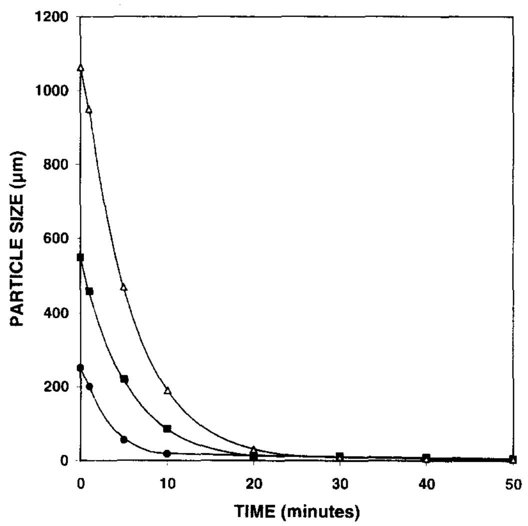

Fig. 2. Effect of initial agglomerate size on deagglomeration in a Turbula mixer rotated at 60 rpm: (●) 250 μm, (■) 550 μm, and (Δ) 1010 μm. The lines represent the best fit, according to the proposed model, and markers mean measured values.

from small agglomerates attached to the sodium chloride particles by abrasion and a process of erosion described by the results listed in Table 2. The test of rates of breakage showed that the specific rates of breakage actually slow down as particles adhere to the sodium chloride particles to produce interactive mixtures. Intercept values of the kinetic curves, listed in Table 2, provided a consistent and uniform basis for determining the maximum size of agglomerates, mean size 28 μm adhering to the sodium chloride particles. There were no significant differences in the rates of agglomerate breakdown (Table 2), and the process was not influenced by changes in mixer type, mixer speed and initial agglomerate size.

In conclusion, results obtained during this study showed correlation between calculated and experimental deagglomeration, suggesting that during mixing smaller agglomerates and aggregates were quickly formed at the initial, fractionation stage. These aggregates were very stable and were dispersed throughout the mixture on the surface of the carrier particles, where single particles were removed by slow erosion and abrasion when an ordered mixture was produced. Deagglomeration during ordered mixing, under the conditions studied, did not disperse furosemide agglomerates and did not depend on the mixer type, mixer speed and initial agglomerate size that was used. However, the overall deagglomeration process improved with increased mixer speed and was more rapid in a higher shear Turbula mixer. This was only established when an appropriate first order model was used to describe the deagglomeration process. This led to an improved theoretical description and experimental evaluation of the relationship between deagglomeration rate constants and mixing process variables. It also enabled a quantitative description of deagglomeration and provided information on the specific disintegration rate function.

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