The Measurement of Mixture Homogeneity and Dissolution to Predict the Degree of Drug Agglomerate Breakdown Achieved Through Powder Mixing

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Interactive mixing of agglomerates of small, cohesive particles with coarse carrier particles facilitate the deaggregation of agglomerates. In this study dispersion of agglomerates of microfine furosemide particles by such a mixing process was followed by measuring changes in the content uniformity and area under the dissolution curve. Interactive mixtures between agglomerates of different sized furosemide particles and coarse sodium chloride particles were prepared using different mixers, mixing times and mixer speeds. The dissolution rate of the drug from and content uniformity of the mixtures were measured, and degrees of dispersion were calculated. These degrees of dispersion were compared to the dispersion values obtained from the decrease in agglomerate size after mixing. An increase in mixing time led to an increase in dispersion. An initial fast deagglomeration, indicated by an increase in dissolution, increase in content uniformity and a decrease in particle size, was followed by substantially slower deaggregation of remaining agglomerates and smaller aggregates. For all mixtures studied the degree of dispersion estimated from dissolution measurements, when compared to equivalent content uniformity measurements, agreed closely with the degree of dispersion as indicated by the decrease in particle size. The use of the area under the dissolution curve to predict agglomerate breakdown proved useful and may find application in situations where it is impossible to follow directly deagglomeration through particle size measurements.

KEY WORDS: homogeneity; dissolution; interactive mixtures; agglomerate dispersion.

INTRODUCTION

The association of small particles into clusters or agglomerates is a significant factor in many facets of particle processing. Agglomeration occurs as an accompaniment, often unwanted, of particulate processing operations such as fine grinding, mixing, blending, transport and flow (1). When the particle size of a drug decreases the cohesiveness of the powder increases, thereby affecting the dispersion of drugs in liquids, granulation, fluidisation and mixing operations (2). Numerous methods are available for dispersing powder agglomerates. A number of mills (3) and ultrasonic forces are sometimes employed to disperse agglomerates in liquids (4). Improving the wettability of a drug leads to a decrease in the agglomeration of the drug particles in contact with a liquid (5).

Mixing a cohesive powder with excipients can also facilitate the deaggregation of powder agglomerates. For instance coarse, equally sized and weighted particles are mixed rapidly with agglomerates of small cohesive particles by an interactive mixing process (6). Interactive mixing breaks the cohesive forces between fine particles and creates strong adhesion forces between adhering and carrier particles (7). The mixing process breaks down the agglomerates and deaggregated particles are dispersed over the carrier surface. Successful dispersion of drug powder agglomerates often leads to better performance of a solid dosage form because of an increase in dissolution rate and subsequent bioavailability (8).

A number of methods may be used to measure the degree of dispersion achieved by a dispersion process. The most accurate assessment of dispersion is to measure the decrease in agglomerate particle size after dispersion (9). However, it is not always possible to measure the particle size and it would be useful if dispersion could be measured indirectly from measurements such as dissolution behaviour and mixture homogeneity.

Degree of Dispersion Measured by Following the Decrease in Particle Size

During interactive mixing the particle size of furosemide decreases from that of agglomerates (P_a) to single particles (P_p) distributed randomly throughout the mixture. The difference between P_a and P_p measures the degree of dispersion (D_p) achieved by mixing according to the following relationship

$$Dp = \frac{(Pa - P)}{(Pa - Pp)} \quad (1)$$

where P is the particle size of furosemide in a particular mixture. For complete dispersion $D_p = 1$ and for no breakdown of agglomerates $D_p = 0$.

Degree of Dispersion Measured from Mixture Homogeneity

Egermann (10) concluded, based on an equation developed by Johnson (11), that the highest attainable degree of interactive mixing conforms to the quality of a non-interactive random mixture and is given by the following equation

$$CV = 100\sqrt{\left(\frac{m}{G}\right)} \quad (2)$$

where CV is the coefficient of variation of the drug content expressed as a percentage of the mean weight, G, of drug per sample and m the mean weight of a single particle of the cohesive ingredient. For the same material an increase in particle size would lead to an increase in m. Therefore particle size also determines CV.

During interactive mixing the homogeneity increases

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from that of a theoretical free flowing random mixture between agglomerates and carrier particles (CV_a) to a completely random interactive mixture (CV_p) where single particles adhere randomly to the carrier surface. The increase in mixing homogeneity indicated by the difference between CV_a and CV_p measures the possible dispersion achieved by the interactive mixing process. Thus the difference between CV_a and the coefficient of variation determined for a mixture, CV, indicates the degree of dispersion (D_m) achieved through mixing by the following relationship

$$Dm = \frac{(CVa - CV)}{(CVa - CVp)} \quad (3)$$

For a completely random free flowing mixture of agglomerates with carrier particles $D_m = 0$ and for a completely random interactive mixture $D_m = 1$. $D_m < 0$ applies when the equilibrium situation is not a random mixture. When $D_m < 0$ large CV values are measured because the particles are not randomly distributed throughout the mixture. D_m values smaller than zero therefore depends on the degree of mixing, randomisation, and not on the degree of dispersion.

Degree of Dispersion Measured from Dissolution Rate

The dissolution rate of a powder depends on the particle size of the dissolving particles. Interactive mixing increases the dissolution of sparingly soluble drug particles because a large surface area is exposed to the dissolution medium (8). De Villiers and Van der Watt (12) used the area under the dissolution curve (A) to describe the dissolution process because it indicates the rate and amount dissolved during dissolution. Differences in the dissolution rates of agglomerates (A_a) and completely dispersed suspended particles (A_p) are an indication of the degree of dispersion because if CV values are substituted with A values equation 1 becomes

$$Dd = \frac{(Aa - A)}{(Aa - Ap)} \quad (4)$$

For a free flowing random mixture between agglomerates and carrier particles dissolution is equal to that of particles equal in size to the agglomerates ($D_d = 0$). In a completely random interactive mixture single particles are distributed throughout the mixture and dissolution is equal to that of single particles ($D_d = 1$).

In this study the degree of agglomerate dispersion achieved through interactive mixing was measured from the content uniformity and dissolution rate of drug from mixtures prepared by mixing agglomerates of different sized furosemide particles with coarse sodium chloride particles. The objective was to determine the effect that changes in mixing conditions and drug particle size had on the degree of mixing and the dissolution of drug from mixtures. Results were used to describe the process whereby agglomerates are dispersed through mixing and to employ mixture homogeneity and dissolution data to measure the degree of dispersion. The use of mixture homogeneity and dissolution rate represents a novel approach for describing the dispersion of drug agglomerates through interactive mixing.

MATERIALS AND METHODS

Materials

Mixtures consisted of a carrier material, sodium chloride particles 300–350 μm (BDH Chemicals Pty. Ltd., Poole, England) and furosemide agglomerates (supplied by Fine Chemicals, batch number CSR 60099, South Africa). Three different sized furosemide powders, prepared by recrystallisation of the supplied powder, were used. All reagents were of analytical grade and water fit for HPLC was used.

Particle Size Analysis

The mean volume particle size of agglomerates was measured in suspension with a Galai-Cis-1 particle size analyser (Galai, Israel) and that of the dry powders with a Sympatec Helos particle size analyser combined with a Rodos dry disperser (Sympatec, Germany) (9). Measured agglomerate sizes were confirmed by scanning electron microscope studies of the powders prior to particle size analysis (9). The particle size of furosemide present in the mixtures was measured by randomly taking five one gram samples from each mixture and suspending it in 50 cm^3 of a saturated furosemide solution containing 0.011 gdm^{-3} polyoxyethylene sorbitan monooleate as a wetting agent. The sodium chloride carrier particles dissolved while the furosemide particles were suspended in the solution (9). The particle size in suspensions was measured with a Galai-Cis-1 particle size analyser.

Preparation of Mixtures

Mixtures weighing 50 g and containing 0.5% w/w furosemide were mixed in a Turbula mixer (model T2C, WA Bachofen-AG, Switzerland) at 90, 60 or 30 rpm and in a V-mixer and cylindrical drum mixer at 60 rpm. The volumes of the mixing vessels used were the same. After mixing, the mixtures were left for 24 hours to reach equilibrium, then divided into 50 samples, each weighing one gram. Mixtures were studied under a scanning electron microscope to follow the mixing process (12). Throughout mixing experiments were duplicated.

Content Uniformity and Dissolution of Furosemide from Mixtures

The drug content of 40 and dissolution of drug from 5 samples taken randomly from each mixtures, was determined. The dissolution was measured in 500 ml Acetate buffer pH 4.6 kept at 37°C using the USP XX11 dissolution apparatus rotated at 150 rpm (12). Samples were taken from the dissolution medium at 2 minute intervals up to 40 minutes. From the UV-absorbency at 271 nm the amount of drug in solution was determined. The data were used to calculate coefficients of variation (CV) and to construct dissolution curves from which the area under the dissolution curves (A) were calculated.

Calculations and Statistical Assessments

Mean CV and A values were compared with control groups, the content uniformity and dissolution of suspended

particles, for significant differences at a 95% confidence level using Dunnett's test for the comparison with a single control group. Calculations were done with a BMDP7D program (BMDP Statistical Software, University of California).

RESULTS AND DISCUSSION

The mean volume particle size of agglomerates and single particles of the furosemide powders used to prepare interactive mixtures are listed in table I. The finest particles, with a mean size of 2.54 μm, were extremely cohesive with a large difference in size between the agglomerates, 107.16 μm, and single particles. An increase in mean volume particle size led to a decrease in agglomeration because the mean size of a powder composed of particles with a mean size of 18.95 μm was only 27.13 μm before dispersion. The particle size before and after dispersion was used to calculate theoretical minimum and maximum dispersion (D_m) values. Under ideal mixing conditions theoretical coefficients of variation, calculated using equation 2 and listed in table I, of a completely random mixture between agglomerates and carrier particles (CV_a) and an interactive mixture containing single furosemide particles (CV_p) were respectively taken as the minimum and maximum degree of mixing possible.

In figure 1 typical dissolution profiles obtained for agglomerates, single dispersed particles and samples taken from interactive mixtures are shown. There was a significant difference between the dissolution profiles of dispersed particles and agglomerates. This difference was also reflected in a difference in the area under the dissolution profiles (A). The area under the dissolution curve (A) of agglomerates and dispersed particles was respectively taken as the minimum and maximum dissolution rate possible. A suspension of single particles was obtained by subjecting the suspended agglomerates to low frequency ultrasonic sound waves for 15 minutes (9). These values are listed in table I.

To obtain the optimum mixing conditions required to disperse agglomerates present in the powders and to determine the effect of changes in mixing conditions on the deagglomeration process, powder mixtures were prepared using different tumbling mixers at different speeds. For each mixing time, mixer and mixer speed combination the content uniformity (CV), dissolution rate (A) and decrease in particle size (P) were measured. Respective degrees of dispersion were calculated using equation 1, 3 and 4 and compared to the optimum theoretical values listed in table 1. In Figure 2, 3 and 4 the degrees of dispersion measured from the decrease in particle size (D_p), increase in mixture homogeneity

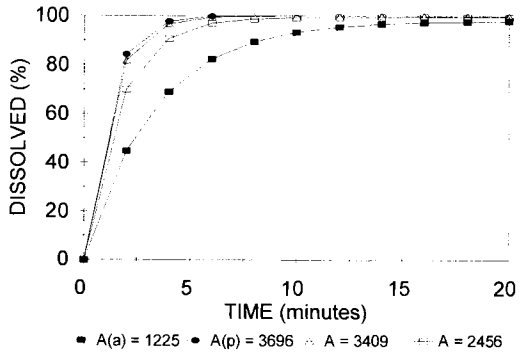

Figure 1: Dissolution profiles of suspensions of microfine furosemide powders (■) agglomerates (●) single particles and the powder mixed in a Turbula mixer at 90 rpm for (△) 5400 and (□) 480 rotations.

(D_m) and increase in area under the dissolution curve (D_d) as a function of mixing time is shown. These mixtures were prepared with the furosemide powder with a mean individual particle size of 2.54 μm. The smallest mean particle size (P = 8.72 μm), highest degree of mixing (CV = 0.57%) and fastest dissolution (A = 3486) was achieved after mixing the furosemide agglomerates in the high shear Turbula mixer at 90 rpm for 5400 rotations. Any further increase in the number of rotations did not lead to an increase in the degree of dispersion.

Results illustrated in figure 2 to 4 show that the degree of dispersion of furosemide agglomerates increased with an increase in the number of mixer rotations. An initial fast deagglomeration, indicated by an increase in dissolution, increase in content uniformity and a decrease in particle size, were followed by substantially slower deaggregation of remaining agglomerates and smaller aggregates. For all mixer and mixer speed combinations the degree of dispersion measured by following the decrease in particle size (D_p, figure 2) were not significantly different from that measured by the increase in dissolution rate (D_d, figure 4). The degree of dispersion measured by the increase in homogeneity of the mixtures (D_m, figure 3) was consistently lower than measured by dissolution and particle size changes. This difference was the result of incomplete mixing ($D_m < 0$) because homogeneity not only depended on size reduction of agglomerates but also on the distribution of drug particles throughout the mixture. When $D_m < 0$, figure 3, furosemide particles were not randomly distributed throughout the mixture.

Mixture homogeneity could therefore only accurately describe the degree of dispersion if mixing started with a

Table I. Area Under the Dissolution Curve (A) of Agglomerates and Single Particles, and Theoretical Coefficients of Variation (CV) for Random and Interactive Mixtures Prepared with Different Sized Furosemide Powders

Particle size (μm)		Mixture homogeneity (%)		Dissolution suspension	
Agglomerates (Pa)	Single particles (Pp)	Random free flowing (CVa)	Interactive (CVp)	Agglomerates (Aa)	Single particles (Ap)
107.16	2.54	5.94	0.07	1225	3696
37.75	9.61	1.77	0.82	2131	3194
27.13	18.95	1.35	1.07	2431	2635

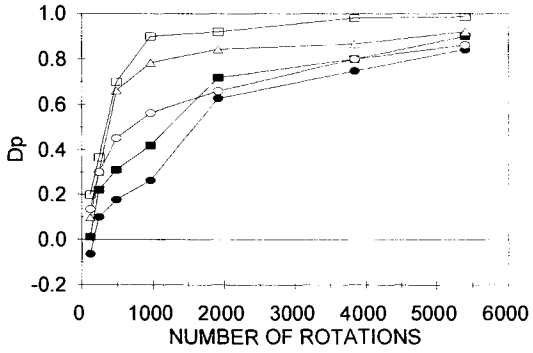

Figure 2: Degree of dispersion (D_p) measured by following the decrease in particle size as a function of the number of rotations for mixtures mixed in a Turbula mixer at 90 rpm (□), 60 rpm (△) and 30 rpm (○) and a V-mixer (■) and cylindrical drum mixer at 60 rpm (●).

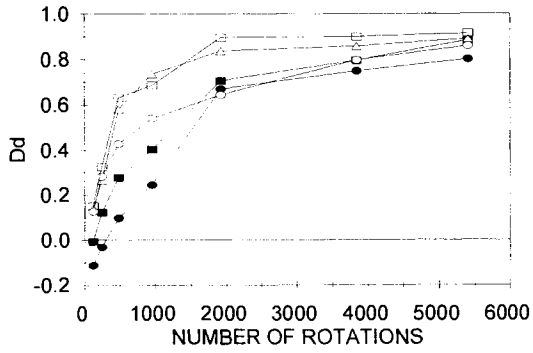

Figure 4: Degree of dispersion (D_d) measured by following the increase in dissolution rate as a function of the number of rotations for mixtures mixed in a Turbula mixer at 90 rpm (□), 60 rpm (△) and 30 rpm (O) and a V-mixer (■) and cylindrical drum mixer at 60 rpm (●).

random mixture between agglomerates and carrier particles. Only then an increase in mixture homogeneity would be the result of a decrease in agglomerate size. In reality mixing started with a non-random mixture and mixing led to an increase in the degree mixing (CV) and degree of dispersion (D_m). It was difficult to distinguish between these two processes, making it impossible to determine the effect deagglomeration had on mixture homogeneity. The best method to describe the degree of dispersion achieved by interactive mixing was by measuring the difference in particle size before and after mixing. Overall D_p values showed agglomerates were broken down in all the mixtures studied. When compared to maximum theoretical D_p values, measured D_p values indicated none of the mixtures were completely random interactive mixtures in which single particles were dispersed over the surface of the carrier particles.

In table II the changes in particle size, mixture homogeneity, dissolution and calculated degrees of dispersion are listed for mixtures prepared with different sized furosemide particles. Mixtures were mixed in a Turbula mixer at 60 rpm and rotated for 5400 rotations. D_m values were again significantly smaller than corresponding D_p and D_d values. An increase in particle size from 2.54 μm to 18.95 μm led to an increase in the mixing rate. D_m increased from 0.795 to 0.885. Because larger particles were less cohesive, mixing led primarily to an increase in the random distribution of particles not a reduction in agglomerate size. There was no significant difference in the D_p values of mixtures prepared with the three powders and the D_d values of mixtures prepared with the two larger sized powders. The D_d value for the mixture prepared with the 2.54 μm sized powder was significantly smaller because these particles were extremely cohesive and were never completely dispersed.

For all the mixtures studied the degree of dispersion estimated from dissolution measurements, when compared to equivalent content uniformity measurements, agreed closely with the degree of dispersion as indicated by a decrease in particle size. Compared to D_m values, dissolution was more effective at describing deagglomeration because it depended on the size of the dissolving particles not their distribution throughout the mixture. D_d values showed the dissolution of drug was fastest from mixtures with a high degree of mixing in which agglomerates were completely dispersed and the maximum drug surface was exposed to the dissolution medium. When larger furosemide particles were used to prepare mixtures it was easier to correlate an increase in homogeneity with an increase in the degree of dispersion. Mixing did not need to disperse agglomerates in larger sized powders, making it easier to increase the random distribution of furosemide throughout the mixture.

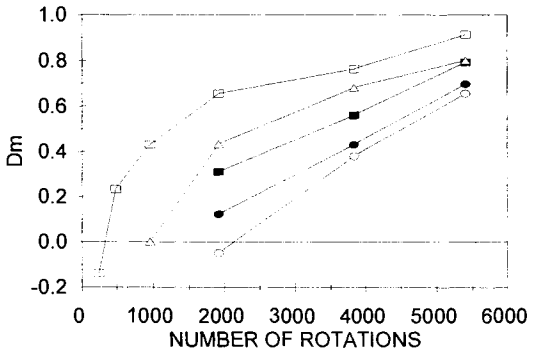

Figure 3: Degree of dispersion (D_m) measured by following the increase in homogeneity as a function of the number of rotations for mixtures mixed in a Turbula mixer at 90 rpm (□), 60 rpm (△) and 30 rpm (O) and a V-mixer (■) and cylindrical drum mixer at 60 rpm (●).

Table II. Mean Particle Size (P), Coefficients of Variation (CV), Dissolution Rate (A) and Corresponding Degrees of Dispersion Obtained after Mixing Different Sized Furosemide Particles with Sodium Chloride Carrier Particles in a Turbula Mixer at 60 rpm for 5400 Rotations

Particle size powder	Particle size after mixing P		Homogeneity CV		Dissolution rate A	
(μm)	(μm)	(D_p)	(%)	(D_m)	A	(D_d)
2.54	9.32	0.935	1.27	0.795	3409	0.884
9.62	11.16	0.945	1.01	0.802	3100	0.912
18.95	19.06	0.986	1.10	0.885	2624	0.945

Degrees of dispersion obtained from mixtures prepared with different mixers, rotated at different speeds and mixed for increased times showed the measurement of mixture homogeneity and dissolution, when compared to the decrease in particle size after mixing, predicted the degree of agglomerate dispersion achieved through powder mixing. Especially the use of the area under the dissolution curve to predict agglomerate breakdown may prove useful in situations where it is impossible to follow deagglomeration through particle size measurements.

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