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Note

Influence of agglomeration of cohesive particles on the dissolution behaviour of furosemide powder

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Abstract

The objective of this particular study was to describe a method whereby the dissolution rate of a powder may be calculated from its mean weighted particle size distribution. This method was used to determine the effect of particle size, powder agglomeration and methods used to disperse powder agglomerates on dissolution behaviour. In particular, the dissolution rates of agglomerates and dispersed particles of furosemide powders with different particle size distributions were studied. Provided the particle size distribution of the particles, or agglomerates, in the dissolution medium was known, simulated dissolution profiles agreed with measured dissolution profiles. Results showed that microfine furosemide powder with a mean volume particle size of 3 μm was agglomerated to such an extent that the dissolution of this powder was never equal to that of single particles. Even strong, forceful methods such as interactive mixing and sonication in a surfactant solution did not completely disperse this powder.

Keywords: Powder dissolution; Microfine; Cohesive particles; Furosemide

The most important feature determining the bulk properties of a powder are the characteristics of the single particles it is composed of. Most powders are made up of three types of particle assemblies: primary particles, aggregates of primary particles and larger loose agglomerates of primary particles or aggregates (Allen, 1990). Agglomeration depends on the size of the individual particles. Fine particles are more cohesive than coarse particles, which are mainly influenced by gravitational forces (Hartley et al., 1985).

The property of particles to form agglomerates is very important during the dissolution of a poorly water-soluble drug because when particles form coherent masses in the dissolution medium, the surface area available for dissolution is reduced (De Villiers et al., 1993). Agglomeration in the dissolution medium may be overcome by the addition of a surface active agent below the critical micelle concentration to improve the wettability of suspended particles (Finholt and Solvang, 1968). Several physical methods including sonication of powder agglomerates in dispersing liquids or vortexing suspended particles with glass pearls before dissolution testing are also used to disperse agglomerates (Lötter et al., 1983). Dry powder

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agglomerates are also broken down through powder mixing by a process called interactive mixing (Hersey, 1975).

The objectives of this particular study were to describe a method whereby the dissolution rate of a powder may be calculated from its mean weighted particle size distribution and to compare measured dissolution results with calculated dissolution profiles to determine the effect of particle size and agglomeration on dissolution results. In particular, the dissolution rate of agglomerated furosemide powders dispersed through sonication in a surfactant solution and interactive mixing were studied.

An equation developed by Dressman and Fleisher (1986) and utilised and improved by Hintz and Johnson (1989) and Lu et al. (1993) was used to simulate the dissolution of the polydispersed powders under non-sink conditions

$$-\mathrm{d}w/\mathrm{d}t = [(3DW_0^{1/3}W_s^{2/3})/(\rho h r_0)](C_s - (W_t/V)) \quad (1)$$

where W_0 is the initial weight of drug, r_o the initial radius of the particles, ρ the density, D the diffusion coefficient, h the diffusion layer thickness, C_s the solubility and t time. A computer program using the Runge–Kutta numerical algorithm with an interval of 1 min was used to calculate the amount dissolved as a function of time. After each minute the total amount of drug in solution (W_s) was calculated. From this and the initial weight of drug the percentage dissolved was calculated as a function of time.

The micronised furosemide powder used was supplied by Fine Chemicals, South Africa. Larger particles were prepared by milling large particles, recrystallised from saturated ethanol solutions of the drug, with a Retz high speed mill (Haan, Germany). X-ray powder diffraction analysis showed the recrystallised material to be the same as the starting material. All solvents and chemicals were analytical grade and water fit for chromatography was used.

Particle size distributions were measured with a Sympatec Helos laser diffraction particle sizer for measuring particles in suspension or dry powders (Sympatec, Germany). For dry powder analysis the instrument was combined with a Rodos dry particle disperser. For the particles in liquid measurements, powder samples were suspended in a 0.011 g dm^{-3} polyoxyethylene sorbitan monooleate (Tween 80, Fluka, Switzerland) solution saturated with furosemide and filtered through a 0.25 μm microporous filter (De Villiers, 1995). To ensure optimum dispersion of agglomerates prior to particle sizing, powders suspended in the dispersing solution were placed in a low frequency ultrasonic bath for 15 min (De Villiers et al., 1993). The mean size of agglomerates was measured without dispersion.

In order to simulate dissolution profiles from particle size data the Stokes–Einstein equation was used to calculate the diffusion coefficient of furosemide ($D = 2.86 \times 10^{-4}$ $cm^2\ min^{-1}$). The diffusion layer thickness, h, was taken to be equal to the particle radius up to 30 μm, above which it was assumed to be constant at 30 μm (Hintz and Johnson, 1989). The solubility of furosemide (C_s) was calculated from the intrinsic dissolution rate obtained in an acetate buffer pH 4.6 and was found to be 2.26×10^{-4} g cm^{-3} (Singh et al., 1968).

The dissolution rate in an acetate buffer pH 4.6 (1:1 solution of 0.2 mol dm^{-3} sodium acetate and 0.2 mol dm^{-3} glacial acetic acid) was measured in a rotating bottle apparatus (Hanson, 1982). The rotating action of the bottles ensures that particles are submersed during dissolution testing. The volume of dissolution medium was 100 ml and the bottles were rotated at 10 rotations per minute. Ten milligram powder samples, representing 44% of the solubility of furosemide in the dissolution medium, or samples from mixtures and suspensions equivalent to 10 mg powder, were placed in a bottle. At predetermined times bottles were removed, samples taken suitably diluted with 0.1 M sodium hydroxide solution and from the UV absorbance at 271 nm the amount dissolved was calculated. The percentage dissolved as a function of time was then used to construct dissolution profiles. Each point on these graphs represents an average of at least five experiments.

The mean volume particle sizes of the three micronised furosemide powders measured before and after dispersion are listed in Table 1. All the powders showed a significant decrease in particle

Table 1
Mean volume particles size, before and after dispersion, of different sized microfine furosemide powders

Powder	Agglomerates		Dispersed particles	
	Size (μm)	Method	Size (μm)	Method
A	108	Helos	3	Rodos
B	38	Helos	10	Rodos
C	27	Helos	19	Rodos

size after dispersion. Powder C, with a mean volume particle size of 19 μm, showed the least tendency towards agglomeration because there was a small difference in the mean size measured before and after dispersion. The particle size distributions measured after dispersion (Fig. 1) were unimodal, normal distributions indicating that agglomerates were completely dispersed by the dry powder disperser attached to the particle size analysis instrument.

Dissolution results confirmed the presence of agglomerates because the dissolution of the powders before dispersion (Fig. 2) was significantly slower than that of powders dispersed by ultrasonication in an surfactant solution before dissolution testing (Fig. 3). Correlation between simulated and measured dissolution profiles of agglomerated material (Fig. 2) indicated that agglomerates were compacted to such an extent that the dissolution medium could not penetrate it and

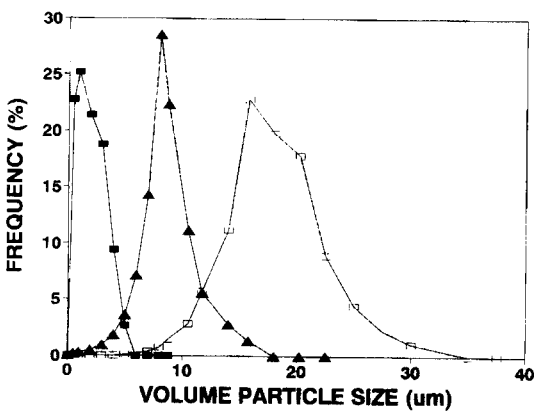

Fig. 1. Relative percentage frequency particle size distributions of different sized furosemide particles measured after dispersion: (■) powder A; (Δ) powder B and (□) powder C.

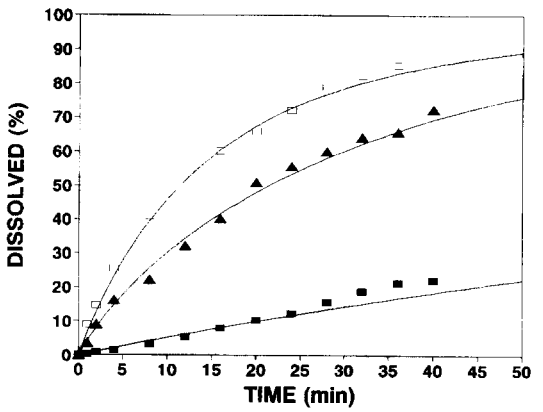

Fig. 2. Dissolution of different sized furosemide particles before dispersion: (■) powder A; (Δ) powder B and (□) powder C. Markers represent the mean measured values and lines the best fit according to Eq. (1).

the dissolution of these agglomerates was therefore equal to that of single particles equivalent in size. It also confirmed that particle size analysis did indeed distinguish between agglomerates and single particles. Dissolution profiles were simulated using Eq. (1) and the results are shown as solid lines in Figs. 2–4.

After dispersion of powders B and C (Table 1) by ultrasonication in a surfactant solution, dissolution profiles (Fig. 3) agreed with that simulated from the mean individual particle size distribu-

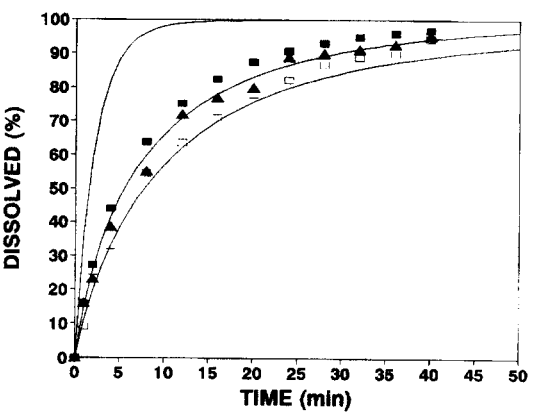

Fig. 3. Dissolution of different sized furosemide particles after dispersion: (■) powder A; (Δ) powder B and (□) powder C. Markers represent the mean measured values and lines the best fit according to Eq. (1).

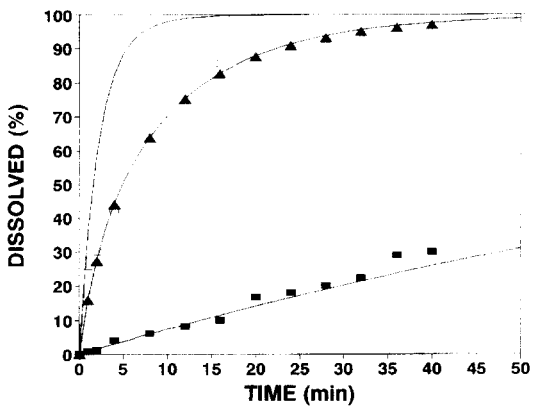

Fig. 4. Dissolution profiles of agglomerates of microfine furosemide particles (■) and the powder dispersed by ultrasonication (□) and interactive mixing (Δ). The solid bold line represents the simulated dissolution of completely dispersed particles with a mean size of 3 μm.

tions measured after complete dispersion with a dry powder disperser. Therefore, ultrasonication in a surfactant solution completely dispersed powders B and C. The validity of the simulations was estimated by calculating the ratio of the weight of drug dissolved measured experimentally W_{te} to that simulated W_{ts}, i.e. $W_{te}/W_{ts} = R$, as a function of time and comparing variances statistically using the F-test. Throughout, the simulated values were a little higher in the initial stage and a little lower in the middle stage of the dissolution, than those measured (Figs. 2 and 3). These results agreed with that obtained by Dressman and Fleisher (1986).

Dispersion of the powder with the smallest mean individual particle size, powder A, by ultrasonication in a surfactant solution did not produce a dissolution rate (Fig. 3) equal to the

Fig. 5. Electron micrograph of microfine furosemide particles mixed with coarse sodium chloride particles by an interactive mixing process.

theoretical dissolution. Even after interactive mixing (Fig. 4) the mean volume particle size of this powder only decreased to 8 μm. The interactive mixtures, containing 0.5% w/w furosemide, were prepared by mixing 0.25 g furosemide with 50 g sodium chloride particles, with a mean size of 350 μm, in a Turbula mixer (W.A. Bachofen, Switzerland) for 64 min at 90 rotations per minute (De Villiers and Van der Watt, 1990). The size of the furosemide particles present in mixtures was measured using a method described De Villiers et al. (1993). Aggregates of small particles still present in the mixture (Fig. 5) may explain the difference between the simulated and measured dissolution rates. However, simulated dissolution profiles of furosemide particles equal in size to that measured after mixing, 8 μm, did agree with measured dissolution profiles (Fig. 4).

Results showed that changes in size distribution of cohesive furosemide particles during a dispersion process, for instance interactive mixing, may be monitored by measuring the dissolution rate provided the particle size distribution of the dissolving particles or agglomerates was known. Using well defined fine, particulate material measured dissolution profiles corresponded well with results simulated from particle size distributions. It was also shown that very fine furosemide particles with a mean volume size of 3 μm were agglomerated to such an extent that the dissolution of this powder was never equal to that of single particles. Even a strong forceful dispersion method, such as interactive mixing, did not disperse agglomerates to single particles. Dispersion, however, depended on particle size and larger particles, mean size 10–20 μm, were less cohesive and easier to disperse.

In summary, to ensure optimal dissolution and subsequent bioavailability of a poorly soluble drug such as furosemide it is important to completely disperse agglomerated, cohesive powders during incorporation into a solid dosage form. To ascertain if this was indeed achieved during formulation is not always possible. The excellent agreement between measured and dissolution profiles simulated from particle size data found during this study could ease problems associated with the evaluation of dispersion processes because correlation between measured and simulated dissolution profiles was found to be an indication of the degree of dispersion.

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