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DISSOLUTION RATE A MEASUREMENT OF THE DEAGGREGATION OF FUROSEMIDE AGGLOMERATES DURING AN INTERACTIVE MIXING PROCESS

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ABSTRACT

Agglomerates of drug particles must be broken down and single particles attached to the carrier to ensure a completely random interactive mixture. Here it was found that the dissolution rates of samples from interactive mixtures compared to suspended furosemide was an indication of the deaggregation of furosemide agglomerates during an interactive mixing process. Deaggregation depended on the forces generated during mixing and was quicker when a high density carrier such as sodium chloride was used.

INTRODUCTION

The rate of interactive mixing depends on the number of fine particles remaining to be adhered on the larger carrier particles[1]. If the fine drug particles consist of agglomerates it must be deaggregated and attached to the carrier surface as single particles or small aggregates[2]. Deaggregation depends on the forces generated during mixing and the characteristics of the carrier[3].

In an interactive mixture a large contact surface area of drug is exposed to the dissolution medium and it may be used to increase the dissolution rate of poorly wettable fine-particulate, agglomerating drugs[2]. If small aggregates however adhere to the carrier the mean size of the attached particles increases causing a decrease in the surface area theoretically available for dissolution. Therefore the dissolution rate of drug particles in an interactive mixture compared to single particles would be an indication of the deaggregation of agglomerated particles.

The effect of mixing time and carrier density on the rate by which furosemide agglomerates were deaggregated during interactive mixing

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was investigated. The dissolution rates of samples from mixtures and suspended furosemide particles were compared to determine if single particles or small aggregates adhered to the carrier surface. Scanning electronmicroscopy was used to confirm these results.

MATERIAL AND METHODS

Mixing Components

Furosemide agglomerates from the sieve fraction between 500-700µm were mixed with either 210-250 µm sodium chloride or Avicel pH102 particles. Sodium chloride represents a high density (2.16 g/cm^3) and Avicel a low density (1.54 g/cm^3) carrier.

Mixing

One mixture consisting of 50 ml carrier and 0.5 % (w/v) furosemide was mixed for each mixing time (4, 8, 16, 32, 64, 128 and 256 minutes) in a Turbula mixer at 90 rpm. The mixtures were left for 24h to reach equilibrium, screened using the sieves that formed the size borders of the carrier fraction and then capsulated, in total, in no. 2 size hard gelatin capsules. The amount of furosemide removed by sieving from each mixture was determined with a spectrophotometric method.

The Furosemide Content of the Capsules

The furosemide content of twenty capsules from each mixture was determined by dissolving the content of a capsule in 100 ml 0.1 M sodium hydroxide, filtering the solution and measuring the uv absorbance at 271 nm. The variation caused by the analytical procedure was taken as the variation in content of samples from furosemide suspended in 0.1 M HCl. The mean content, as a percentage of the theoretical amount in each capsule, was calculated and the coefficient of variation in the content minus the coefficient of variation because of the analytical procedure taken as the homogeneity of a mixture (CV).

Dissolution

The dissolution test according to the USP XXI, paddle method, rotational speed 150 rpm and dissolution medium 500 ml Acetate buffer pH 4.6 at 37°C was used[4]. The dissolution rates of three samples (capsules) from the mixtures and suspended furosemide were determined. Suspended furosemide represents individual particles similar to totally deaggregated furosemide particles. After 1, 2, 4, 8, 16, 32 and 64 minutes 10 ml samples were taken from the dissolution medium and replaced with buffer at 37°C. After 64 minutes the dissolution flask was removed, placed in an ultrasonic bath for 15 min, a sample taken and the total amount of furosemide present determined. The concentration of furosemide in each sample was determined by measuring the uv absorbance at 271 nm.

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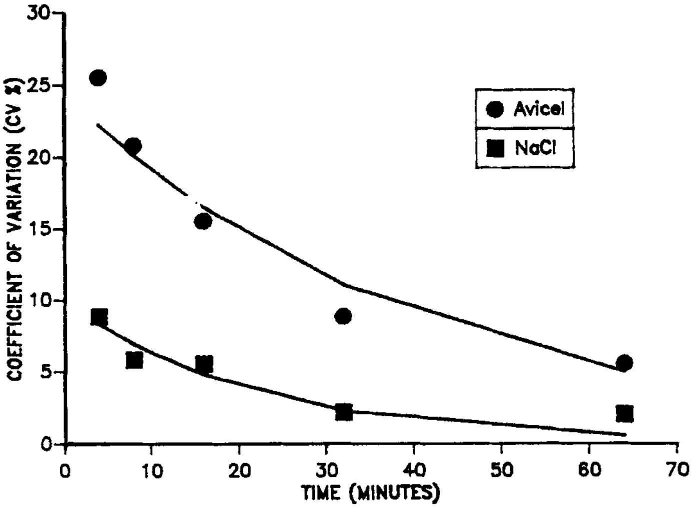

FIGURE 1

The content uniformity (CV) of the mixtures against time. The symbols represent the measured values and the lines the first order fit.

Calculations and Statistical interpretation

The coefficients of variation (CV) were compared using the F-test. A 95% confidence level, $p \leq 0.05$, was considered satisfactory for indicating significant differences between the CV values. To obtain a single factor to compare the dissolution profiles, the area under each curve (AUC) was calculated[4]. The mean AUC's for each mixture, AUC(m), and suspended furosemide, AUC(s), were compared for significant differences at a 95% confidence level, using Dunnett's test for the comparison with a single control group (BMDP7D, BMDP Statistical Software, University of California).

Electronmicroscopy

Electronmicrographs of the carrier mixed with and without furosemide were taken with a Phillips Stereoscan 250 electronmicroscope. The samples were sputter coated with a 12-15 nm layer of a gold palladium mixture.

RESULTS AND DISCUSSION

The CV's of the mixtures showed a first order decline, average r = 0.973, before it stayed constant after mixing for 32 and 64 minutes for

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TABLE 1

Percentage furosemide removed from the mixtures.

Mixing Time (min)	Sodium Chloride	Avicel
4	25.24	58.42
8	16.52	49.24
16	8.36	50.36
32	-	38.81
64	-	2.98

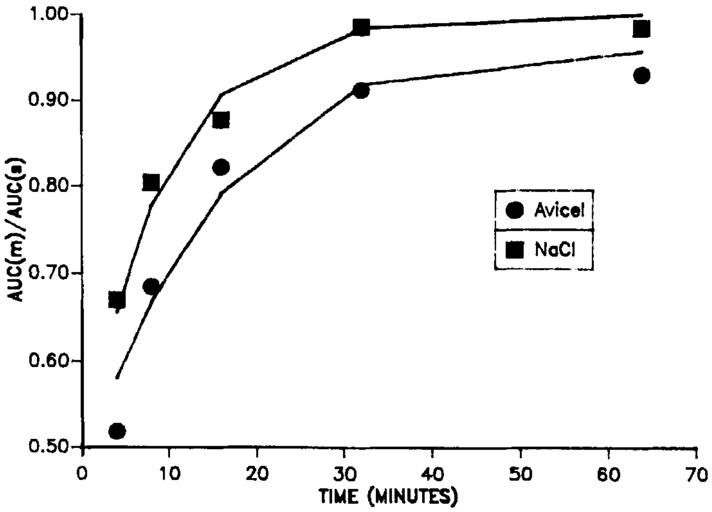

FIGURE 2

The effect of increasing mixing time on the ratio AUC(m)/AUC(s) for the different mixtures. The symbols represent the calculated values and the lines the first order fit.

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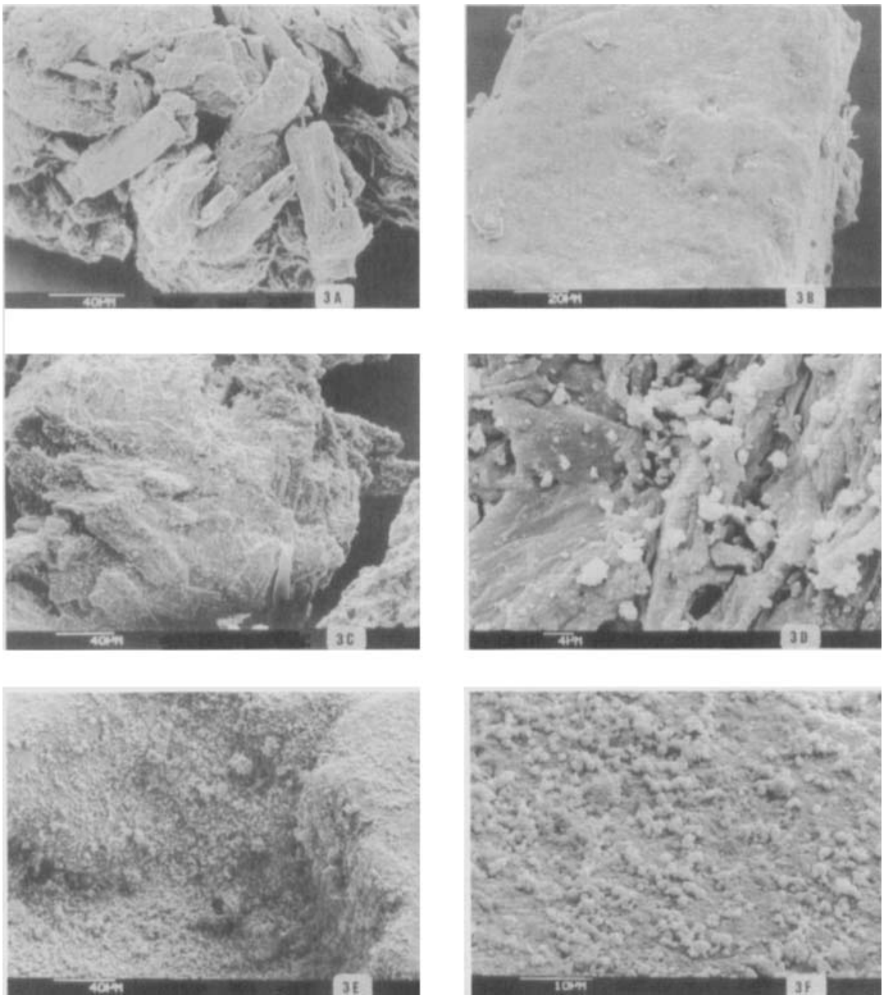

FIGURE 3

Electronmicrographs of the surfaces of A) an Avicel and B) a sodium chloride particle mixed without and C)-D) an Avicel particle, 400× and 2000× enlarged, mixed for 64 minutes and E)-F) a sodium chloride particle, 400× and 1800× enlarged, mixed for 32 minutes with furosemide.

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sodium chloride and Avicel respectively (figure 1). From 64 minutes the CV's weren't significantly different for the respective carriers.

The mixtures were screened to ensure that no more furosemide agglomerates bigger or smaller than the carrier particles were present. In table 1 the amount of furosemide removed as a percentage of the amount put into the mixture are given. After mixing for 16 and 64 minutes no more furosemide were removed from the sodium chloride and Avicel mixtures respectively.

Figure 2 represents the relation between the AUC of the mixtures, AUC(m), and suspended furosemide, AUC(s), against time. The ratios showed a first order increase, average r = 0.987, before it stayed constant after mixing for 32 and 64 minutes for sodium chloride and Avicel respectively. Except for the sodium chloride mixtures mixed for 128 and 256 minutes the AUC(m) values were significantly smaller than the AUC(s) value. The AUC(m) values of the Avicel mixtures were significantly smaller than the sodium chloride mixtures.

Figure 3 are electronmicrographs of carrier particles from the mixtures. Although the mixtures were screened there were free furosemide agglomerates present in the mixtures mixed for shorter than 16 minutes, explaining the big difference between the dissolution rates of the mixtures and single furosemide particles. The carrier surfaces of the Avicel mixtures mixed for longer than 64 (figure 4 C-D) and sodium chloride mixtures for 32 minutes (figure 4 E-F) were covered with small furosemide particles and aggregates. The particles and aggregates seemed to adhere in clefts and crevices in the carrier surface. In these mixtures no free furosemide agglomerates could be detected with the electronmicroscope.

CONCLUSIONS

The dissolution rates of the mixtures increased with increasing mixing time, showing that the furosemide agglomerates were deaggregated during mixing, increasing the surface area of drug available for dissolution. This showed that the dissolution rate was an indication of the deaggregation of furosemide agglomerates during an interactive mixing process. In mixtures with dissolution rates equal to suspended furosemide the agglomerates were totally deaggregated. The ratio AUC(m)/AUC(s) showed a first order increase that coincided with the first order decline in the coefficient of variation in the content therefore deaggregation followed first order kinetics.

During deaggregation the agglomerates were broken down into smaller agglomerates not attached to the carrier and single particles or small aggregates adhering to the carrier. Deaggregation was quicker when a high density carrier, such as sodium chloride, was used. Only mixtures containing this carrier and mixed for longer than two hours

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produced dissolution rates equal to suspended (single) furosemide particles.

The lower dissolution rates of the optimally mixed Avicel mixtures could have been caused by small furosemide aggregates attached in clefts and crevices in the macroporous carrier surface, effectively removed from abrasion during mixing. The shear forces generated by this particles could possible not have been enough to totally deaggregate the furosemide agglomerates, leaving small agglomerates, equal in size to the carrier, in the mixture.

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