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Interactive mixing between agglomerated drug particles and coarse carrier particles

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Abstract

The equation of Egermann[1] was used to calculate the theoretical coefficient of variation in drug content of completely random interactive mixtures containing furosemide and sodium chloride. These coefficients of variation (CV) were compared to that obtained experimentally. Although no free furosemide agglomerates or aggregates were present in the mixtures, the experimental values were consistently higher. This could only be explained if small furosemide aggregates accumulated in clefts and crevices in the sodium chloride particle surfaces. For the system examined random interactive mixtures were produced with furosemide concentrations between 0.05 and 4 %.

Introduction

According to Egermann[1] the highest attainable degree of mixing of binary interactive mixtures containing a polydispersed cohesive ingredient and a monodispersed diluent conforms to the quality of a noninteractive random mixture and is given by equation 1.

$$Cr = 100\sqrt{m/G} \quad \text{- - - - - - - (1)}$$

Where Cr 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 particle weight of the cohesive ingredient. For a completely randomised mixture a plot of log Cr against log sample size should be linear with a slope of -0.5.

If the particles of the polydispersed ingredient are extremely cohesive the resulting agglomerates must be deagglomerated during the mixing

process. Small aggregates formed during deagglomeration can also adhere in clefts and crevices in the carrier surface where it effectively lie within the carrier projected perimeter unexposed to deagglomeration[2].

In this investigation different amounts of furosemide agglomerates were mixed with a narrow sieve fraction of sodium chloride particles. The furosemide content of samples with different sizes were measured and the carrier surfaces examined by scanning electronmicroscopy before and after mixing. This was done to determine the degree of homogeneity and deagglomeration of furosemide in the mixtures.

Materials and methods

Furosemide agglomerates from the sieve fraction between 500-700 µm were mixed with 300-350 µm sodium chloride particles. Mixtures weighing 100 g containing 0.05, 0.1, 0.5, 1, 2 and 4 % furosemide were mixed in a Turbula mixer at 90 rpm. The mixtures were mixed for 300-500 minutes. The exact mixing time was taken as the time needed so that no furosemide could be removed from the mixture when it was lightly screened using the sieves that formed the size borders of the carrier fraction.

The furosemide content of twenty 50, 100, 200 and 400 mg samples, from each mixture, were determined. The samples were dissolved in 100 ml 0.1 M sodium hydroxide, the solution filtered and the UV absorbance measured at 271 nm. The variation caused by the analytical procedure was taken as the coefficient of variation in the content of samples from furosemide suspended in 0.1 M HCl, containing amounts of furosemide equivalent to the mixtures.

The mean furosemide content, as a percentage of the theoretical amount per sample, was calculated. The coefficients of variation in the furosemide content, minus the coefficient of variation due to the analytical procedure (CV = 0.942), was taken as the degree of mixing. The coefficients of variation (CV's) were compared using the F-test. A 95 % confidence level, $p < 0.05$, was considered satisfactory for indicating significant differences between the CV's.

Electronmicrographs of unmixed furosemide particles, and sodium chloride particles 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 and palladium mixture.

Results and discussion

The average furosemide content of the mixtures was 98.91 % of the theoretical content, with a standard deviation of 3.49 %. Indicating that almost all the furosemide were attached to the carrier. The 200 mg and 400 mg samples of the 0.05 % mixture had the lowest (92.81 %) and

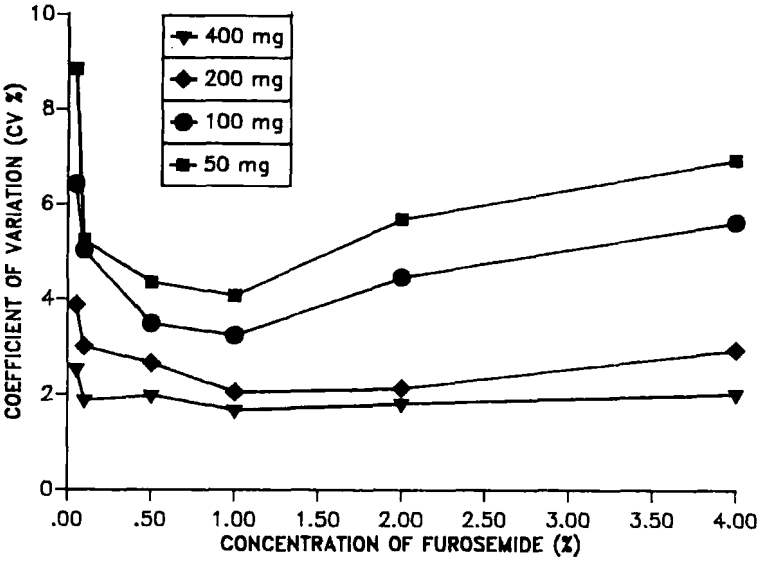


Figure 1

The coefficients of variation (CV) in furosemide content of different sample sizes minus the variation due to the analytical procedure as a function of the furosemide concentration.

Table 1

The slopes and correlation coefficients for the logarithm of sample size against the logarithm of the CV.

Furosemide Concentration (%)	Slope	Correlation Coefficient
0.05	-0.612	0.996
0.1	-0.517	0.957
0.5	-0.379	0.998
1.0	-0.453	0.968
2.0	-0.603	0.988
4.0	-0.628	0.984

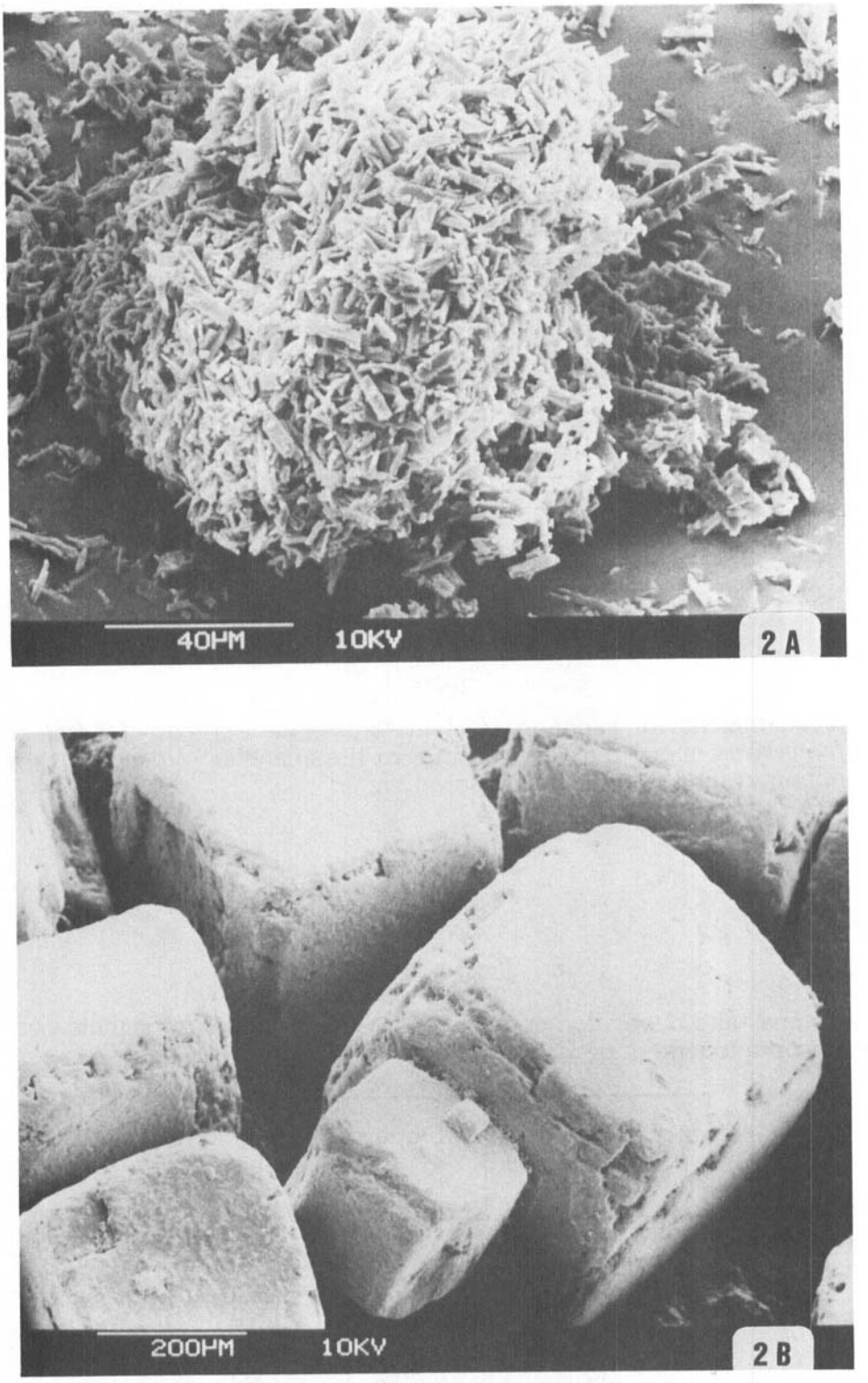
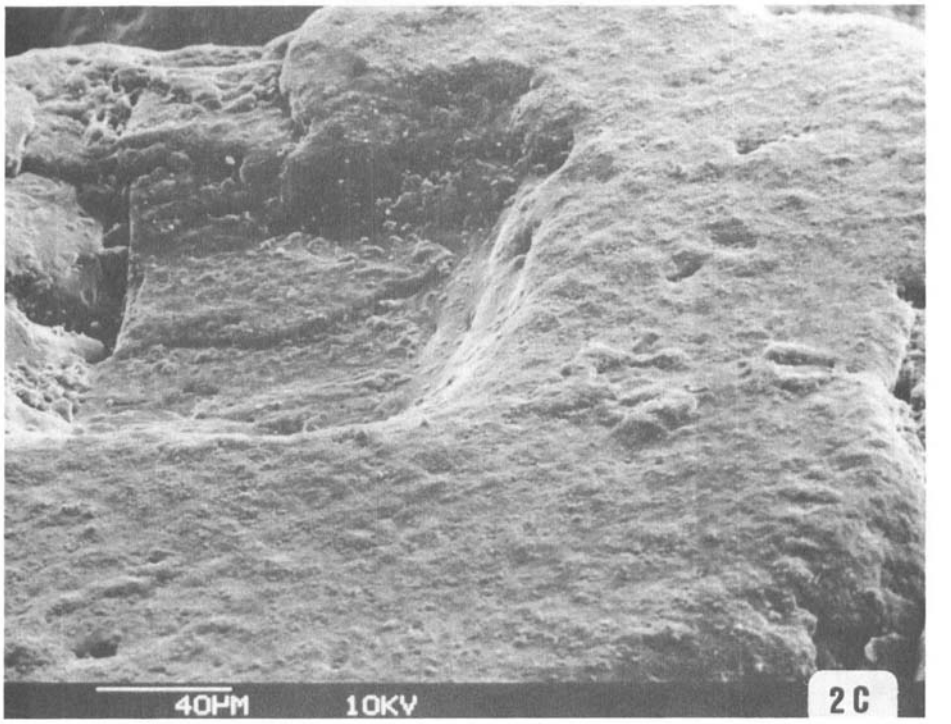


Figure 2

Scanning electronmicrographs of A) unmixed furosemide agglomerates and the surface of a sodium chloride particle mixed B) without, C) 0.05 and D) 1 % furosemide.



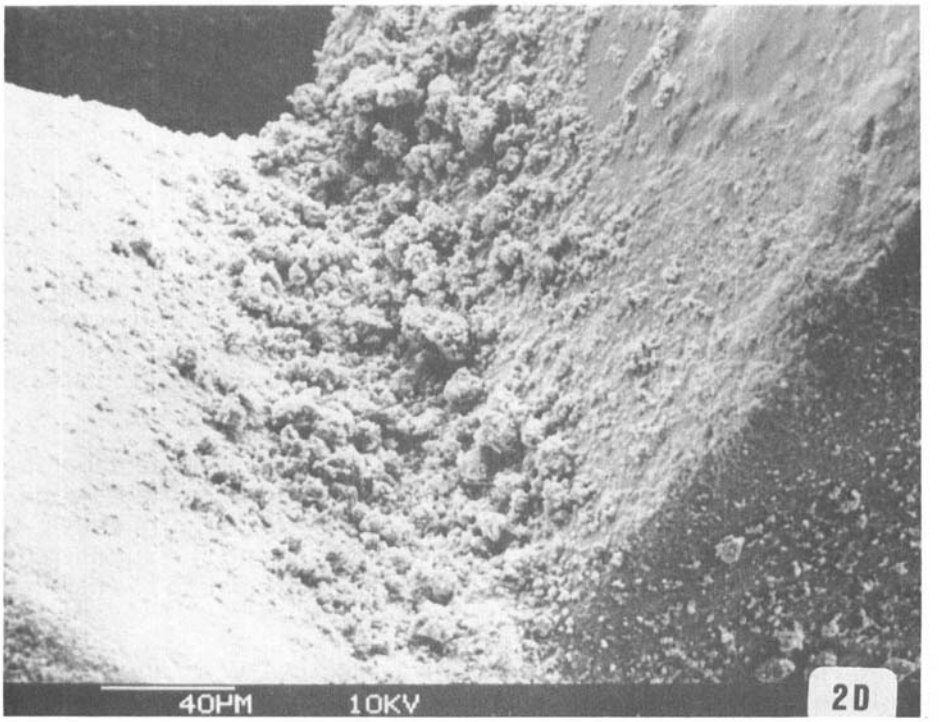


Figure 2 continued

highest (106.65 %) content respectively showing that in this mixtures only a small percentage of the carrier surface were covered with furosemide.

Statistical analysis showed that for each sample size the 0.5 and 1% mixtures had the smallest CV's (figure 1). The CV's of samples taken from these mixtures weren't significantly different.

The CV's of the different sample sizes were however considerably higher than the corresponding theoretical CV's, calculated with equation 1. These differences made it difficult to assess the homogeneity of the mixtures. For a completely randomised interactive mixture the logarithm of sample size and the logarithm of CV are linearly related with a slope of -0.5. The values for the slopes and correlation coefficients of the mixtures are given in table 1. The slopes were approximately the same as completely random interactive mixtures, while the correlation coefficients showed that log CV against log sample size were linear. The slopes of the 0.5 and 1 % mixtures were smaller than 0.5.

Figure 2 are electronmicrographs of unmixed furosemide particles, and the surface of a sodium chloride particle mixed with 0, 0.05 and 1% furosemide. The surfaces of the carrier mixed without furosemide were clean. In the 0.05 and 0.1 % mixtures the furosemide was unevenly distributed on the carrier and not easily detected. Although the smooth carrier surfaces of the other mixtures were evenly covered with furosemide, small particles and bigger aggregates seemed to accumulate in clefts and crevices in the carrier surface.

Conclusions

Although the mixtures showed higher variations in the furosemide content than theoretically completely randomised interactive mixtures, sodium chloride and furosemide produced randomised interactive mixtures for concentrations of furosemide between 0.05 and 4 %. The differences were because of small furosemide particles and aggregates adhering in clefts and crevices in the carrier surface where it effectively lie within the carrier particle projected perimeter, unexposed to abrasion during further mixing.

A low concentration of furosemide occupy a small percentage of the carrier surface explaining the higher CV, and bigger difference in homogeneity of small and big samples, taken from such mixtures. Too much furosemide produces too many aggregates and the surplus could have accumulated in bigger clefts and crevices explaining the rise in the CV.

To produce random interactive mixtures with spontaneously agglomerating, cohesive particles it would be better to use carriers with smooth surfaces, so long as the concentration of cohesive ingredient is enough to randomly cover the surface available for adhesion.

References

1. H. Egermann, J. Pharm. Sci., **74**, 999 (1985).
2. J.N. Staniforth, J. Pharm. Pharmacol., **39**, 329 (1987).