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Drug distribution during massing and its effect on dose uniformity in granules

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Summary

Drug distribution during the initial stages of wet massing in a wet granulation process has been studied as a function of the relative solubility of the drug and the composition of the binder. The results of this initial wet massing process have been correlated with the drug distribution/granule size profile of the granulations.

Introduction

In a wet granulation process, a binder solution is initially added to a drug/diluent mix. The site of addition of the binder results in a locally overwetted region (Carstensen et al., 1976). The massing action subsequently distributes the binder to other areas of the mass until an equilibrium granular state has been achieved. Variation in granule size has been reported to be a consequence of variation in binder uptake by the material being granulated (Dingwall and Ismail, 1977). The largest granules have been shown to be formed from the wettest region of the mass (Opankule and Spring, 1976). Thus the initial overwetted region of the mass will give rise to the majority of the largest granules.

If one considers a mix containing a drug and diluent, both of which are to some extent water-soluble, on addition of the water, some dissolution of both the drug and diluent will take place in the overwetted region. The binder which is then distributed to the rest of the mass, is no longer water but a solution of the drug and diluent.

When the ratio of the drug to diluent in solution is higher than in the dry mix,

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there will be a net loss of drug from the overwetted region together with a corresponding net gain in other areas of the mass.

Occasionally in granulation, the solvent system may be presaturated with the drug before massing takes place. It is thought to ensure a more uniform distribution of a low dose drug throughout the batch of granules. The addition of such a binder will inhibit drug dissolution from the overwetted region. Initially this region will have a high drug content. As the binder is distributed the drug concentration will fall. However, even at the end of massing, the drug concentration will still be highest in those overwetted regions which produce the majority of the largest granules.

This paper studies the effect of the binder solution composition, with respect to the drug, on the distribution of that drug throughout the wet mass and relates these effects to the distribution of low dose drugs in the respective size ranges of granules in the batch.

Materials and methods

Borax, sodium salicylate and sulphadimidine were used as low dose drugs. Lactose was used as a diluent. All materials were of B.P. quality. Their particle sizes as measured by a Fischer sub-sieve are given in Table 1.

Solubilities

The solubility of borax, sodium salicylate and sulphadimidine were determined by preparation of saturated solutions both in water and in saturated lactose solutions at 20°C. The relative solubility of the drug and diluent in the binder was determined according to the following equation:

$$R_s = \frac{C_a}{C_a + C_b} \times 100$$

where R_s is the relative solubility of the drug (at 20°C) expressed as a percentage of total dissolved material, and C_a and C_b are the respective concentrations (w/v) of the drug and diluent in solution. The results are shown in Table 2.

TABLE 1

PARTICLE SIZE ANALYSIS OF MATERIALS USED IN STUDY

Material	Particle size (μm)
Borax	10.0
Sodium salicylate	8.7
Sulphadimidine	8.6
Lactose	13.5

TABLE 2

SOLUBILITIES AND RELATIVE SOLUBILITIES OF DRUGS USED IN THE STUDY (at 20°C)

Drug	Solubility	% Relative solubility
Borax	1 : 10 (co-saturated)	46.1
Sodium salicylate	1 : 1	23.1
Sulphadimidine	1 : 1897	0.3

Preparation of the granules

The batch size was held constant at 0.5 kg, throughout the study. The overall drug concentration was also held constant at 2%. The binders were: water; a solution of sodium salicylate in water; a solution of sodium salicylate in saturated lactose solution; a saturated solution of lactose; a saturated solution of borax; a solution co-saturated with borax and lactose (all at 20°C). When solutions other than water were used as the binder, the composition of the dry mix was adjusted to maintain an overall concentration of 2%. The binder volume was 14% (v/w) for all granulations except that of sulphadimidine/lactose when a binder volume of 20% was found to be necessary.

The dry mixing and massing procedures were as described previously (Ojile et al., 1980). Drying was carried out in a hot air oven maintained at 48°C. In all cases the granules were dried to a constant weight. The granules were then dry screened through a sieve of 1200 μm aperture size.

The granules so produced were sieved into 7 fractions as retained by sieve apertures of 1000, 710, 500, 355, 259, 180 and particles less than 180 μm, respectively. Granule size distribution of each granulation was determined. The drug concentration in each granule size fraction was determined by assaying 10 samples of each granule size fraction.

Analysis of drug concentration in agglomerates

Agglomerates in this context refer to those portions of the mass overwetted by initial contact with the binder during massing. Large agglomerates formed in these regions are subsequently broken down as massing proceeds. At 1-min intervals after the addition of the binder, the mixer was stopped and samples of the agglomerates removed by gently sieving small portions of the mass with a coarse sieve of aperture size 6500 μm. The agglomerates were dried to constant weight and assayed for their drug concentration. A total massing time of 5 min was used.

Results and Discussion

The change in drug concentration in the agglomerates as a function of massing time is shown in Fig. 1 for systems massed with water. Both the borax and the sodium salicylate granulations showed a steady fall in drug concentration with

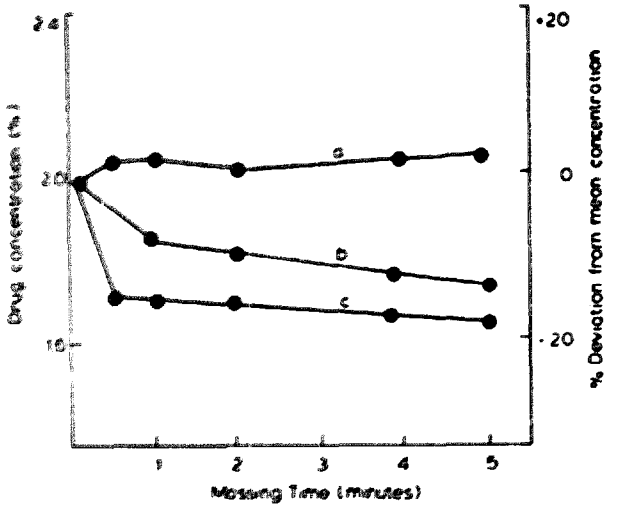

Fig. 1. The changes in drug concentration of agglomerates with time (water as binder): (a) sulphadimidine: lactose; (b) borax : lactose; and (c) sodium salicylate : lactose.

massing time. This fall was greatest in the sodium salicylate granulation. The sulphadimidine granulation only gave a small rise in drug concentration with massing time.

In the case of both the sodium salicylate and the borax, the ratio of drug to diluent in the binder solution is considerably higher than in the dry mix, i.e. they have high relative solubility values. This is shown in Table 2.

The highest relative solubility was found with the sodium salicylate granulation. Thus the highest net loss of drug from the overwetted region during massing was found with this drug. Since sulphadimidine had a relative solubility of less than one, the net loss from the overwetted region was not of the drug but of the diluent. This gave rise to the slight increase in sulphadimidine concentration shown in Fig. 1.

A different pattern of results was found when the binder was first presaturated with the drug. This is shown for the sodium salicylate granulation in Fig. 2. In this case, the initially overwetted region contained a marked excess of the drug. This excess was steadily reduced as the massing process distributed the drug from the overwetted region to the rest of the mass. Even after 5 min massing the concentration of sodium salicylate did not fall significantly below the overall mean concentration. A similar situation was found when the binder was saturated with both sodium salicylate and lactose.

The equivalent results for the borax granulation are shown in Fig. 3. Borax represented a slightly different set of physical/chemical parameters in as much as borax and lactose mutually increase each other's solubility, (Ojile et al., 1980). If the binder is saturated with borax alone it will cease to be saturated as lactose is dissolved during massing. Accordingly the saturated solution of borax behaved similarly to the dry mix. A comparable result was obtained when the binder was presaturated with lactose only, (Fig. 3).

However, a markedly different result was observed when a co-saturated solution

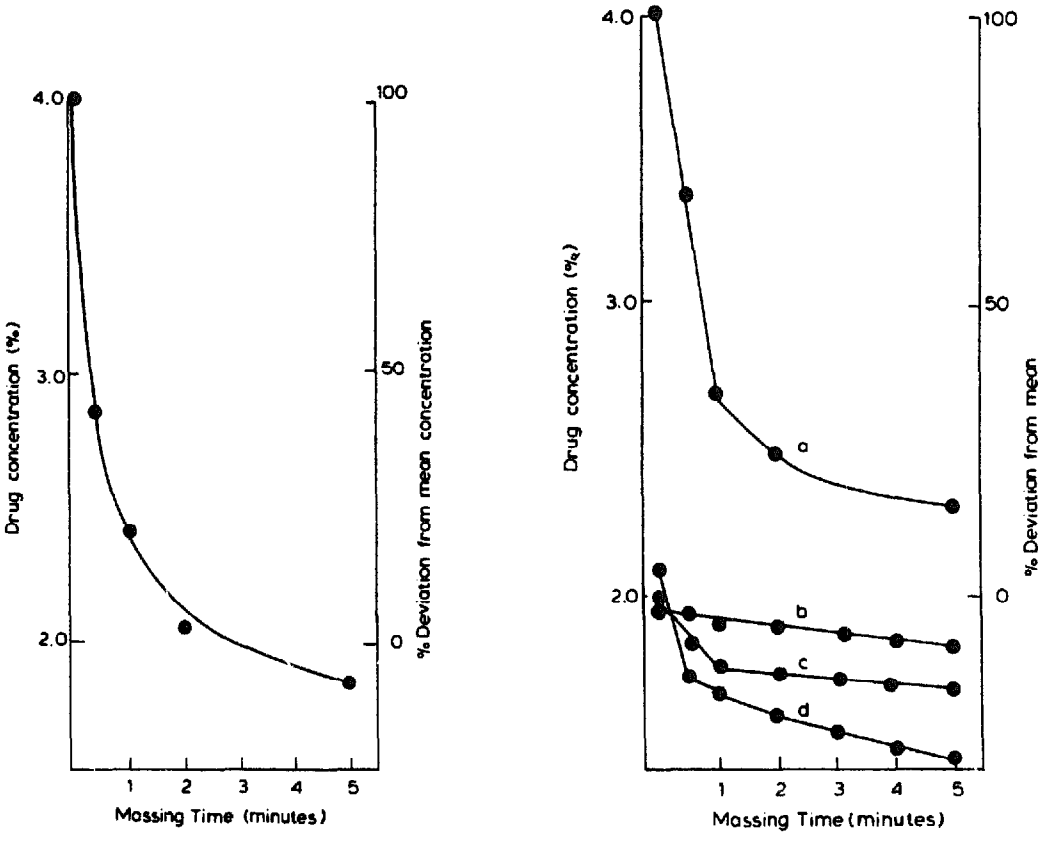

Fig. 2. The effect of presaturation of the binder on the change in drug concentration of agglomerates with time.

Fig. 3. The effect of binder composition on the change in concentration of agglomerates with massing time: (a) co-saturated borax/lactose binder; (b) saturated lactose binder; (c) water binder; and (d) saturated borax binder.

of borax and lactose was used as the binder. Here a result similar to the saturated sodium salicylate solution, shown in Fig. 2, was found. Therefore a similar rationale can be applied. It is interesting to note that even after 5 min massing the borax concentration was still around 20% higher than the overall concentration of the mix. It was observed that after the addition of this co-saturated binder solution, it did not wet the dry mix very readily. It is, therefore, possible that for this system an equilibrium granular state cannot be reached, due to this lack of wettability. A similar situation for an erythrosine/lactose system, using a starch binder, has been reported by Tiamraj (1979).

Fig. 4 shows the results when the drug concentration of unagglomerated material, in the vicinity of the agglomerates was determined as a function of massing time. The increase in drug concentration was consistent with the concept of drug removal from the overwetted region to the rest of the mass. The subsequent fall in the curve may be attributed to a further distribution of drug to other areas of the mass as an equilibrium situation was approached.

Fig. 4.

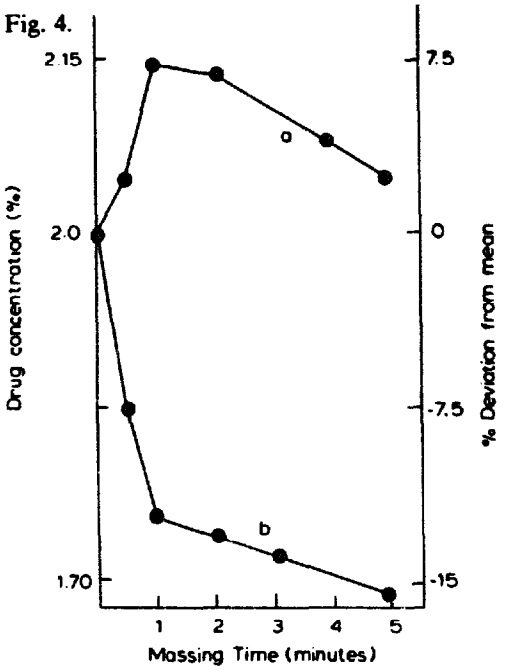

Fig. 5.

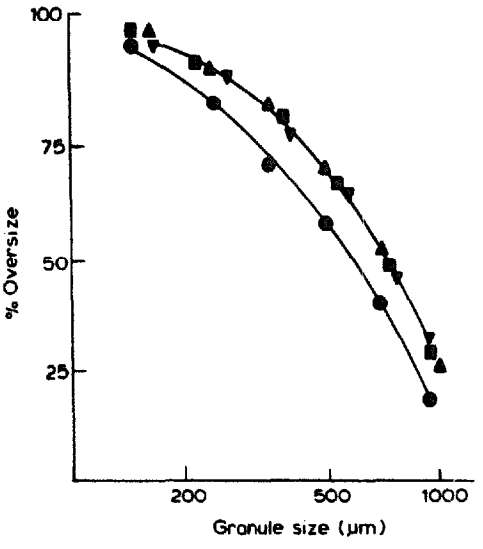

Fig. 4. The change in drug concentration with massing time of different sections of the mass: (a) unagglomerated material; and (b) agglomerates.

Fig. 5. The effect of binder composition on the granule size distribution of a 2% borax/lactose granulation. ●, co-saturated borax/lactose binder; ■, saturated lactose binder; ▲, water binder; ▼, saturated borax binder.

The very low aqueous solubility of the sulphadimidine made it unrealistic to attempt to presaturate the binder with this drug. The effect of binder composition on the granule size distribution of the borax granulations is shown in Fig. 5 and of the sodium salicylate granulation in Fig. 6.

Only the co-saturated solution of borax and lactose had any significant effect on the granule size distribution. In this case there was a lower percentage of large granules together with a higher percentage of fines. This was consistent with the poor wettability of this binder. These results showed that provided the binder adequately wets the mass, presaturation of any excipients of drugs in a binder solution has very little effect on the size distribution of the granules produced.

The variation in drug concentration with granule size for the various granulations is shown in Fig. 7, 8 and 9.

In Fig. 7 there was a marked difference between the granulation using the co-saturated borax/lactose solution as binder and the other granulations. The granulation using this co-saturated binder showed a steady decrease in drug concentration with decrease in the granule size. The other 3 granulations showed a peak concentration in the intermediate-sized granules.These differences may be directly attributed to the differences in the concentrations in the agglomerates during wet massing. Since the overwetted region gives rise to the majority of the largest granules it is to be expected that a fall in concentration of the agglomerates, below the overall

Fig. 6.

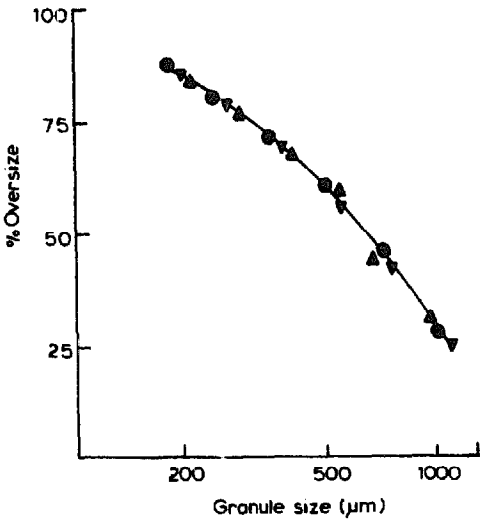

Fig. 7.

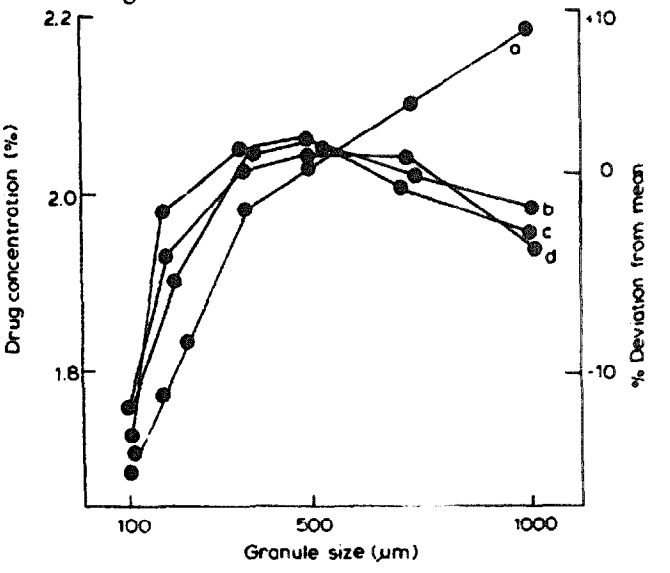

Fig. 6. The effect of binder composition on the granule size distribution of a 2% sodium salicylate granulation. ▲, water binder; ▼, saturated sodium salicylate binder; ●, co-saturated sodium salicylate/lactose binder.

Fig. 7. The effect of binder composition on the drug concentration–granule size profile of a 2% borax granulation: (a) co-saturated borax/lactose binder; (b) saturated borax binder; (c) saturated lactose binder; (d) water binder.

Fig. 8.

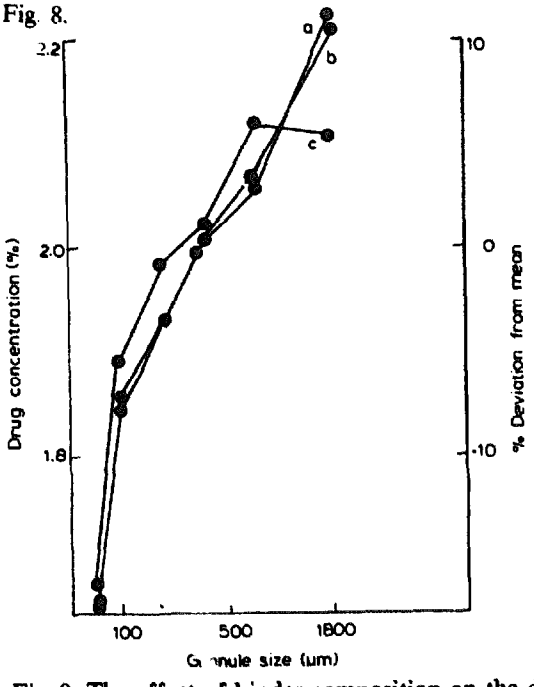

Fig. 9.

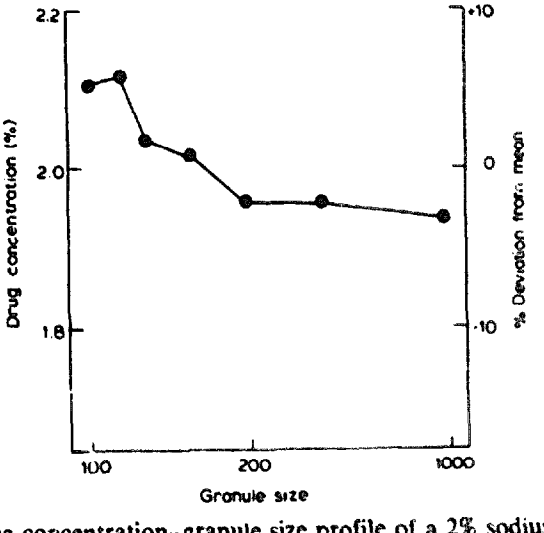

Fig. 8. The effect of binder composition on the drug concentration–granule size profile of a 2% sodium salicylate granulation: (a) saturated sodium salicylate binder; (b) co-saturated sodium salicylate/lactose binder; (c) water binder.

Fig. 9. The drug concentration–granule size profile of a 2% sulphadimidine granulation.

average concentration would give rise to a relative deficiency of drug in the largest granules. This is shown in Fig. 7. The fact that the extent of deviation was less than may be expected from the agglomerate study, is readily attributed to the fact that the larger granules contained disproportionately larger amounts of binder, (Dingwall and Ismail, 1977), which would tend to minimize the deficiency.

Similarly the higher concentrations of borax in the large granules found with the co-saturated binder, amy be directly related to the concentration of the agglomerates during massing (Fig. 3).

In all cases the fines were depleted of borax. The fines in a granulation can arise in two main ways. They may arise from the original fine powder which has failed to become incorporated into the wet mass to form granules. They may also be formed by abrasion of the granules, mainly during the dry screening process.

Since the relative solubility of borax is high the concentration of borax in any ungranulated fines will be considerably lower than the initial overall concentration.

If one supposes that all the borax and lactose capable of going into solution does, there will be an initial powder mix of 10 g of borax and 490 g of lactose. After dissolution during massing, 3 g of borax and 467 g of lactose will remain undissolved, i.e. a borax concentration of 0.64%.

While this is a gross simplification of the conditions occurring during wet granulation, it does provide a good explanation for the low borax concentration in the fines. In addition, as the binder becomes co-saturated with borax and lactose, it becomes less effective in wetting the solid materials and thus less likely to incorporate any remaining fine powder into the wet mass.

The concentration of borax will, on the other hand, be enhanced by abrasion of a borax-rich crust during dry screening of the granules. This borax-rich crust is formed by solute migration during drying (Ojile et al., 1980).

The above hypothesis was further supported by the increase in concentration of sulphadimidine in the fines as shown in Fig. 9. Since the relative solubility of sulphadimidine was less than one, an increase in sulphadimidine concentration in the fines was expected.

The sodium salicylate results, Fig. 8, also support the above hypothesis. The low concentration of sodium salicylate in the fines, regardless of the binder solution, was consistent with its high relative solubility. In addition the granulations carried out using a presaturated binder also showed a steady decrease in drug concentration with decrease in granule size. When water only was used as the binder, the characteristic peak in drug concentration at intermediate granule sizes was again found although it was not as marked as in the borax granulations.

Conclusions

In the initial stages of wet massing overwetted regions of the mass were found. These overwetted regions have a significantly different drug concentration from the rest of the mass in granulations where the relative solubility of the drug was greater than one. The variation of drug concentration is different-sized granules could be directly related to the differences found in the overwetted regions during massing.

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