Binder distribution onto binary mixtures of glass spheres*

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Glass spheres (0·8 and 0·4 cm diam.) in differing weight ratios were treated in a rotating pan with four pharmaceutical binder fluids. Binder uptake for a sphere of 1 g was greater onto the smaller spheres irrespective of binder or wt ratio used. There were differences in uniformity of uptake, the solution binders (PVP and gelatin) being more evenly distributed than the mucilaginous binders (starch and methylcellulose). Binder distribution on the basis of unit surface area showed less obvious differences between the sphere sizes. Possible consequences of such binder distribution through powder aggregates are discussed.

Variations in dissolution rate of active materials from tablets have been related to formulation and processing factors (Wagner, 1969; Wurster, 1972). Even within a single batch, where gross formulation differences can be discounted, wide variations in release have been reported (Hossie, McGilveray & others, 1973). This suggests non-uniformity of processing.

When tablets disintegrate, the resulting aggregates or particles available for drug release will be those of the powder mix, if further aggregation or fracture has not occurred during compression. Ideally, the aggregates will contain uniformly distributed binder, but there is evidence from model systems of mono-sized spheres that the wetting of particles by binder fluid is not always uniform (Butensky & Hyman, 1971). It is difficult to relate these findings to the multicomponent systems usually encountered in pharmaceutical granulation. Distribution of binder fluid over particle surfaces is envisaged as occurring during wet granulation with agglomeration affecting this distribution and producing variations in binder content. Drug release may be governed by the thickness of the reconstituted binder layer (Chalmers & Elworthy, 1976), so variations of binder uptake by individual particles may be a prime cause of granule size effects and inter-tablet variations.

We report on the distribution of commonly used pharmaceutical binders over the surface of glass spheres in binary size mixtures, to simulate inert, non-porous particles of uniform size, shape, surface and density as the first stage of an investigation into the potential role of binder distribution in inter-tablet variations.

MATERIALS AND METHODS

Materials

Glass spheres (Hopkin & Williams Ltd.) of 0·8 and 0·4 cm diameter (designated 'L' for large and 'S' for small) were hand sorted to eliminate those of obvious shape deviation before washing in boiling water, 0·1 M hydrochloric acid and boiling water. They were dried in a hot air oven at 50–60° and stored for 24 h over dried silica gel before binder application.

The binders used were polyvinylpyrrolidone (PVP, K29–32, GAF(U.K.) Ltd.) and gelatin B.P. (Macarthys Ltd.) as 5% w/w solutions and potato starch B.P. (BDH Ltd.) and methylcellulose, low substitution (BDH Ltd.) as 2% w/w mucilages. Erythrosine (Hopkin & Williams Ltd.) as soluble tracer, was dissolved in the freshly distilled water used in the preparation of the binder fluids.

Binder distribution

Equal total weights (approx. 40 g) of spheres in L : S weight ratio 1 : 1, 5 : 1 and 10 : 1 were placed in a cylindrical pan (120 mm internal diameter) inserted into a reducing holder clipped to the rim of an 18 inch rotating coating pan. The spheres were warmed with hot air before and immediately after binder fluid (approx. 3 g) was applied by spraying using a laboratory spray gun (Shandon Scientific Co. Ltd.) or by pouring. Fluid addition was repeated until the binder uptake was visually uniform (approx. 30 g). The coated spheres were terminally dried at 50–60° for 30 min in a hot air oven (Mitchell Driers Ltd.) before overnight storage over dried silica gel.

The large sphere size and low binder fluid viscosity were chosen and binder addition and drying regulated to reduce aggregation tendency to a minimum. Sphere weight ratio simulated drug

excipient ratios. The method of binder addition was designed to facilitate uniform coating, thus where viscosity permitted (PVP and gelatin) the binder fluid was preferentially sprayed on. This method was not feasible with the mucilaginous starch and methyl cellulose where simple pouring was employed, care being taken to avoid direct application to the pan walls. For the solution binders (PVP and gelatin) similar results were obtained using either method. Excessive rotation of the dried spheres was avoided to reduce frictional loss from the surface.

Binder uptake

(i) *By weight difference.* From each pan charge, 10 individual large coated spheres and 10 pairs of small spheres were weighed to 5 decimal places before removal of the binder by immersion in 25 ml distilled water. The sphere was then rinsed with water (2–3 ml) and dried at 50–60° for 30 min, stored overnight over dried silica gel and re-weighed.

(ii) *By tracer uptake.* The absorbance of the washing water (above) was read at 524 nm on a spectrophotometer using 1 cm cells against the relevant blank. Erythrosine content was calculated from a standard Beer graph.

RESULTS AND DISCUSSION

Distribution per sphere unit weight

In the measurement of binder, weights of individual spheres were taken in preference to mean weight since the weight variation of the beads was greater than the adhering binder weight. The results in Table 1 (Binder columns—weight) show that small spheres received a heavier coating of binder than large spheres. Mean weight uptake values for the solution binders (PVP and gelatin) were more uniform than those for the mucilaginous binders (starch and methyl cellulose), this being clearly visible on examination. Uniformity of binder deposition on the sphere surface is presented in terms of the coefficient of variation (c.v.) in Table 1 (Binder columns—c.v.), the more uniform distribution of PVP and gelatin being reflected in the generally lower c.v. values for these binders than those for starch and methyl cellulose.

For large spheres treated with PVP, the c.v. increases slightly with increasing weight ratio (10:1 >5:1 >1:1), while for the smaller spheres a more definite reverse trend is evident (1:1 >5:1 > 10:1). Similar trends were not evident for the other binders with the possible exception of starch where, for the large spheres, the c.v. for the 1:1 weight

Table 1. *Distribution of binder and tracer on glass spheres on equal weight basis.*

Sphere			Binder wt*	Tracer wt*	Uptake g⁻¹ sphere wt			
					Binder wt		Tracer wt	
Wt ratio (L:S)	Size	wt* (g)	(g × 10^{-3})	(g × 10^{-5})	(g × 10^{-3})	c.v. (%)	(g × 10^{-5})	c.v. (%)
	PVP							
1:1	L	0·712	5·1	3·7	7·2	11·3	5·0	9·9
	S	0·215	2·2	1·6	10·0	26·3	7·5	11·5
5:1	L	0·708	3·7	2·7	5·2	15·4	3·8	9·4
	S	0·216	2·0	1·6	9·3	21·5	7·4	12·3
10:1	L	0·710	4·1	2·6	5·8	17·5	3·7	19·0
	S	0·218	1·9	1·6	8·8	11·4	7·1	9·9
	Gelatin							
1:1	L	0·715	2·3	2·0	3·2	12·5	2·9	15·1
	S	0·228	1·4	1·4	6·1	16·1	6·1	11·4
5:1	L	0·708	2·2	2·0	3·1	13·8	2·9	5·8
	S	0·233	1·5	1·3	6·4	12·2	5·4	9·2
10:1	L	0·702	2·2	2·0	3·1	11·8	2·9	10·3
	S	0·211	1·3	1·3	6·2	21·9	6·1	8·1
	Starch							
1:1	L	0·703	1·2	1·7	1·7	17·0	2·4	14·7
	S	0·198	1·0	1·3	5·0	51·8	6·5	20·4
5:1	L	0·693	1·8	3·1	2·6	47·4	4·4	18·2
	S	0·210	1·7	2·3	8·0	53·6	11·3	19·9
10:1	L	0·705	1·4	1·6	2·0	40·4	2·3	14·1
	S	0·233	1·0	1·4	4·1	26·4	5·8	14·4
	Methyl-cellulose							
1:1	L	0·707	1·5	3·5	2·1	59·9	5·0	64·3
	S	0·230	0·6	1·2	2·6	55·5	5·3	36·4
5:1	L	0·701	1·0	1·9	1·5	68·5	2·7	30·1
	S	0·206	1·0	1·7	5·5	55·0	8·4	51·1
10:1	L	0·715	1·0	2·5	1·4	59·5	3·5	46·4
	S	0·181	0·4	0·6	1·9	46·4	3·5	30·0

* Each weight is mean of 10 individual determinations using single large sphere and paired small spheres.

ratio was less than for the other ratios and, for the small spheres, the c.v. for the 10:1 ratio was less than for the others. These results suggest that uniformity of binder uptake by weight onto sphere surfaces is dependent on the nature of the binder and, to a lesser degree, on the weight ratio of the binary mixture.

The erythrosine tracer shows a similar pattern of uptake (Table 1, Tracer columns—weight) to that obtained from direct determination of binder weight, i.e., that the smaller spheres retained a heavier layer of binder fluid, irrespective of the weight ratio processed. The extent of uniformity of tracer distribution, as reflected in c.v. values (Table 1, Tracer columns—c.v.), shows no trend related to weight ratio. Non-uniform uptake is only clearly evident for methyl cellulose. In starch, the c.v. values for tracer are lower than for binder weight (Table 1), thus, for the same spheres, more uniform distribution was obtained for the truly soluble tracer than for the relatively insoluble binder. Chaudry & King (1972) related the chromatographic behaviour of warfarin sodium through excipients to migratory inhomogeneity produced during drying. Excipients with low affinity for the water-soluble drug permitted migration. By analogy,

since potato starch shows little affinity for erythrosine (Zografi & Mattocks, 1963), a microchromatographic system may exist on the surface of the spheres permitting migration of the tracer, reflecting in differing uniformity compared with the simultaneously applied binder.

Distribution per mean sphere unit surface area

While uniformity of a powder system is assessed on a weight basis for quality control purposes, surface area is more relevant to release. Binder distribution based on spheres of 1 cm² surface area was thus derived from the original binder uptake data in Table 1, using mean diameters of 0·81 and 0·41 cm (Table 2—Binder columns—weight). On this basis,

Table 2. *Distribution of binder and tracer on glass spheres of 1 cm² surface area*.

	Binder				Tracer			
	L		S		L		S	
Sphere wt ratio (L:S)	wt (g × 10⁻⁵)	c.v. (%)	wt (g × 10⁻⁵)	c.v. (%)	wt (g × 10⁻⁵)	c.v. (%)	wt (g × 10⁻⁵)	c.v. (%)
PVP								
1:1	2·5	11·8	2·1	36·6	1·8	10·2	1·6	21·6
5:1	1·8	15·4	1·9	19·1	1·3	11·2	1·6	3·4
10:1	2·0	17·1	1·8	11·7	1·3	17·9	1·6	10·8
Gelatin								
1:1	1·1	13·0	1·4	21·4	1·0	13·9	1·4	15·3
5:1	1·1	13·4	1·5	6·6	1·0	6·7	1·2	13·5
10:1	1·1	12·2	1·3	16·3	1·0	10·9	1·3	11·8
Starch								
1:1	0·6	19·6	0·9	52·0	0·9	15·9	1·2	17·6
5:1	0·9	48·7	1·5	42·1	1·5	20·5	2·3	11·9
10:1	0·7	40·4	0·9	30·4	0·8	16·0	1·3	19·7
Methyl-cellulose								
1:1	0·7	60·9	0·6	63·7	1·7	65·3	1·2	38·2
5:1	0·5	70·1	1·1	48·8	0·9	29·6	1·7	52·6
10:1	0·5	57·5	0·3	52·5	1·2	46·1	0·6	26·2

* Each value derived from 10 individual determinations.

higher uptake by the smaller spheres is much less obvious or even absent in the case of PVP and methylcellulose. Uniformity of uptake, as might be expected from such derived data, was similarly greater for the solution binders (PVP and gelatin). Uptake of tracer (Table 2—Tracer columns—weight) supported the pattern previously established on a weight basis, namely that the smaller spheres received a heavier coating, with the major exception of methylcellulose.

Treatment of monosized spheres (Butensky & Hyman, 1971) showed that small particles required more granulation liquid than larger particles for production of aggregates of equivalent size. In the binary size mixtures treated in this investigation,

smaller spheres, as individual particles, showed greater binder uptake per unit weight, an effect much less obvious on the basis of unit surface area. Aggregation would then produce aggregates of higher binder content. The results for monosized spheres and those for binary mixtures presented here are thus compatible. Non-uniformity of wetting, also reported for monosized spheres by Butensky & Hyman (1971) as a reason for "fines", is reflected in the c.v. figures reported here for the binary systems. Lack of conformity in the c.v. figures for starch binder and tracer is suggested here as being the result of surface migration depending on the affinity of the binder for the water soluble component.

Extrapolation of such results to powder systems must be made with caution. Finer powders do, however, require more granulating liquid to produce granules of similar characteristics (Hunter & Ganderton, 1972) which is in agreement with our findings.

In powder granulation, spontaneously-formed aggregates will exist in the dry mix so that individual particles may have reduced opportunity of being uniformly wetted by binder fluid. When fluid is added, aggregation will certainly occur, producing an initially overwetted stage before moisture is distributed by mixing to an equilibrium granular state (Carstensen, Lai & others, 1976). Complications may arise by smaller particles wholly or partially dissolving in the fluid, thus producing particle surface changes. Achievement of such an equilibrium granular state requires time for moisture distribution, whereas in the present investigation conditions were adjusted to promote distribution over the individual sphere surface. It is probable, therefore, that binder distribution after overwetting will never achieve the uniformity per unit weight or surface area achieved with the model system examined.

Massing time, and thus binder distribution, affects dissolution (Zoglio, Huber & others, 1976). Thus, while uniform binder distribution, at least theoretically, is a desirable objective, the higher uptake onto smaller particles, as reported here, may produce an undesirable reduction in release rate (Chalmers & Elworthy, 1976). The fact that agglomeration occurs to reduce uniformity of distribution may be a desirable compensating effect as already suggested by these authors. Uniform binder distribution, while promoting more uniform inter-tablet release, may have the effect of reducing the mean rate of release of the batch. The proposed

equilibrium granular state (Carstensen & others 1976) must thus be sought to achieve acceptable inter-tablet variation without undue prejudice to the mean release rate.

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