The influence of binder concentration on the bond formation of pharmaceutical granules

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The formation of particle mucilage bonds with dicalcium phosphate dihydrate and starch mucilage binder reduces the B.E.T. nitrogen adsorption surface area from 1·6 to 0·96 $m^2 g^{-1}$. The maximum reduction (40%) of granule surface area at a binder concentration of 10% w/w corresponded to similar optima in friability, compressability and median granule size. Surface and pore-void structural analysis by mercury intrusion could not discriminate between pore-void sizes in the range 0·5–100 nm. Nitrogen adsorption measurements showed, however, that the microporous surface area decreased from 0·3 to 0·18 $m^2 g^{-1}$ as binder surface coverage increased over the concentration range 2 to 20% w/w starch mucilage.

In recent years the evaluation of granule characteristics, such as tapped density, flowability, compressibility and both inter- and intra-granular porosities, has been used as a means to predict the effects upon the processing properties and dissolution of pharmaceutical tablets compacted from granules. How a binder is distributed in, or adheres to, powder surfaces to form granules and the subsequent effect of binder concentration on granule size, compressibility, friability and surface topography has, however, received scant attention.

Although characterization of granules by pore or void size analysis is useful in assessing the penetration of fluids into matrices, as well as compact strength, whenever a solid is in contact with a fluid, particle surface area is of paramount importance.

Chalmers & Elworthy (1976a), examining the influence of formulation and process variables on both granules and tablet properties, measured the external surface area of batches of oxytetracyline dihydrate before granulation, with a Fisher Sub-Sieve Sizer and both optical and electron microscopy. The changes in dissolution (T 50%) and disintegration times of tablets produced from granulated drug were attributed to changes in wet mixing time rather than to changes in surface properties.

The permeametric method used to measure the external surface area may not, however, have been able to discriminate the subtle changes in the surface properties. Although, in an extension of this work (Chalmers & Elworthy 1976b), the internal surface areas of various batches of ground oxytetracyline dihydrate were measured by low temperature nitrogen adsorption, surface area was not used to characterize tablet or granule properties. In addition, pore size distributions and intragranular porosities were calculated from a high pressure mercury intrusion method (Rowe et al 1973) and correlated with the breaking load of the granules (Ganderton & Hunter 1971), but the internal surfaces of the granules and the effect of binders on these surfaces were not measured.

The present investigation evaluates the effect of binder concentration on the compressibility, friability, granule size and size distribution together with the variation of surface area measured by low temperature nitrogen adsorption of granules produced by wet mixing granulation. The binder used with the dicalcium phosphate particles was potato starch mucilages of various concentrations chosen because of its wide use pharmaceutically.

MATERIALS AND METHODS

Materials
Dicalcium phosphate dihydrate (Emcompress: Kingsley and Keith, Croydon) with a surface area, by low temperature nitrogen adsorption (British Standard 4359: Part 1, 1969), of 1·6 $m^2 g^{-1}$, and density $2·35 \times 10^3$ kg m^{-3}, by air pycnometry (Beckman Air Comparison Pycnometer, Model 980, Beckman Instruments, Glenrothes, Fife) was used. Potato starch was B.P. quality (Hopkin & Williams, Romford).

Granulation
Starch mucilages contained 2, 5, 10, 15 and 20% w/w of potato starch B.P. initially suspended in an equal weight of cold distilled water to form a slurry. Transparent mucilages were produced by the addi-

* Correspondence

tion of the appropriate slurry to the required weight of boiling water and cooling to 60 °C. The dicalcium phosphate dihydrate was dry blended for 2 min in a planetary mixer (Hobart Manufacturing Co. Ltd., London) at 89 rev ml⁻¹ to break up any aggregates. A constant weight, 300 g, of cooled freshly prepared mucilage was added to 1 kg of dicalcium phosphate dihydrate and massed at a speed of 165 rev min⁻¹ for a total of 15 min. No difference in granule size distribution or size was observed for massing times of 10 or 20 min. The wet mass was then forced through a 1·0 mm screen on an oscillating granulator. The resultant granules were dried at 45 °C overnight (16 h) in a hot air tray oven, further screened through a 1·7 mm sieve, dried for an additional 4 h and stored in glass jars at 20 °C and 35–40% R.H. The moisture content of the granules was <0·5% w/w as determined by loss of weight in a vacuum at 50 °C. The above technique was the standard granulation process used for all concentrations of prepared mucilage.

Characterization of granules (Table 1)

Granule size analysis. The size distribution of the granules was measured by sieve analysis (B.S. 410) (1962) and B.S. 1796 (1952) of 100 g granules shaken for 15 min on an Endecotts test sieve shaker (Model EFLI, Endecotts Ltd., London).

Granule density. The granule density of each batch of granules was measured with an air comparison pycnometer (Model 930, Beckman Instruments Ltd.), using air and helium.

Bulk density. A loose bulk density was measured on all granulations. 30 g of each granulate was gently and slowly poured through a short-stemmed glass funnel into a 100 ml graduated cylinder. The orifice of the funnel stem was aligned with the 100 ml graduation mark. The volume occupied by the granules was read to the nearest 0·5 ml and the bulk density calculated in g ml⁻¹. The bulk densities

recorded are the average of at least six determinations.

Tapped density. The tapped density of an unfractionated sample of granule was measured according to Neumann (1953). The graduated-cylinder was dropped 20 times, from a height of 2·54 cm onto a wooden bench and the volume recorded. The tapped density was calculated in g granules ml⁻¹ tapped granules.

Per cent compressibility. The percentage compressibility of the granules was calculated from the difference between the tapped and bulk densities divided by the tapped density and the ratio expressed as a percentage (Schwartz et al 1975).

Granule friability. Granule friability was assessed by the determination of the resistance to abrasion of the −710 to +355 μm size fraction of each granulation using a Roche friabilator (J.E.L. Ludwigshafen, Rhein, W. Germany). A 10 g sample was rotated in the friabilator at 24 rev min⁻¹ for 4 min. The resultant sample was sieved on a 250 μm Endecotts test sieve for 1 min on an Endecotts test sieve shaker. The amount retained on the 250 μm sieve was weighed and expressed as a percentage—the friability percentage—of the initial weight.

Geometric surface area. The geometric surface area of each granulation was calculated from the granule size distribution. The weight harmonic mean, $_wd_h$, of each of the sieve size classes within the distribution was evaluated. Summation of the proportion of surface area or $_wd_h$ in each of these size classes gives the geometrical surface area of the sample (B.S. 4359: Part 3 (1971)). Table 2 shows the calculation of the weight harmonic mean and geometric surface area, from the seive size distribution of dicalcium phosphate dihydrate. The surface-volume sieve shape factor, $\alpha_{sv.t.}$ used to calculate the geometric surface area of all samples, was taken as 6 which is the shape factor for a sphere.

Surface-volume diameter. The reciprocal of the weight

Table 1. Physical parameters of dicalcium phosphate dihydrate granulated with various concentrations of starch mucilage.

Muc. concn. % w/w	Median size μm	Surf. vol. dia. d_{vs} μm	Gran dens. ρ_g kg m⁻³ × 10³	Tap dens. ρ_T kg m⁻³ × 10³	Bulk dens. ρ_B kg m⁻³ × 10³	Geom. surf. area* cm² g⁻¹	B.E.T. surf. area† m² g⁻¹	Compres- sibil. %	Friabil. %	Reduct. in B.E.T. surf. area %	Median pore diam.‡ μm	Total pore vol.‡ cm³ g⁻¹
Powder	158	86	2·350	0·993	0·75	178	1·6	24·5	—	—	49·5	0·68
2	550	205	2·336	0·652	0·566	58·1	1·2	13·2	22·6	25	51·0	0·413
5	830	428	2·310	0·619	0·561	36·4	1·056	11·2	1·3	34	17·5	0·34
10	1000	451	2·290	0·606	0·566	34·9	0·96	6·6	0·49	40	15·5	0·25
15	960	320	2·26	0·896	0·811	49·8	1·03	7·5	0·61	35·6	23·7	0·389
20	930	316	2·22	0·923	0·83	51·3	1·165	9·8	0·70	27·2	23·3	0·37

* size distribution.   † Nitrogen adsorption.   ‡ From Hg intrusion.

Table 2. Geometric surface area of dicalcium phosphate from sieve analysis.

Sieve sieve range $d_1{}^1$–$d_2{}^1$	Median diam. of class d_1	Wt in class g_1	Fract. wt in class g_1/G	Prop. Surf. area in class $\dfrac{g_1}{G\,d_1}$
μm	mm	g	—	m^2/m^3
1000–710	0·855	0	0	0
710–355	0·533	0·4	0·004	7·5
355–250	0·303	1·0	0·010	33·0
250–180	0·215	39·0	0·392	1823·25
180–125	0·153	35·0	0·351	2294·0
125–75	0·10	17·2	0·173	1730·0
75–53	0·064	7·0	0·07	1093·75
		99·6 $\Sigma g = G$	1·00	6980·0 $\Sigma g_1/G d_1$ (m^{-1})

$$Sw(m^2g^{-1}) = \frac{\alpha sv.tSv(m^{-1})}{\rho\,(kg\,m^{-3})} = \frac{6\cdot0 \times 6980\cdot0}{2\cdot35 \times 10^3} =$$

17·8 m^2kg^{-1} or 178 cm^2g^{-1}

harmonic mean is equivalent numerically to the reciprocal of the surface volume diameter, d_{vs} (Herdan 1960):

$$\frac{1}{d_{vs}} = \frac{1}{wd_h} = \Sigma\frac{g_1}{G.d_1}$$

where g_1 is the weight of the particle or granule of size d_1 in a total sample weight of G.

B.E.T. (*Brunauer et al 1938*) *surface area.* The adsorption isotherms of nitrogen gas at 77K onto the surface of dicalcium phosphate dihydrate particles and granules were measured using an Orr Surface Area Pore-Volume Analyser Model 2100 (Micromeritics Instrument Corp., Coulter Electronics Ltd., Dunstable).

All samples were degassed before nitrogen adsorption measurements at room temperature (24 $\pm$ 1 °C) for 40 h and at a vacuum of less than 10^{-3} torr to remove any physically adsorbed gases. The prolonged degassing times at ambient temperature ensured that no thermal decomposition of the particles or granules occurred. The specific surface area of the powder and granules, prepared at various binder concentrations, was calculated from the monomolecular volume of nitrogen and the B.E.T. equation (B.S. 4359: Part 1 (1969)) between the range of 0·05 to 0·35 relative pressure.

Pore volume and pore size distribution. Measurements were made on unfractioned dried samples degassed at room temperature (24 $\pm$ 1 °C) for 40 h at a vacuum of less than 10^{-2} torr. Pore volume and

median pore sizes were determined by measurement of the volume of mercury penetrating the pores or voids within granules using a high pressure Micromeritics Porosimeter Model 905-1 (Coulter Electronics Ltd., Dunstable). Pressure is increased incrementally from below atmospheric (6·9 kN m^{-2}) up to approximately 50 000 p.s.i. (345 MN m^{-2}). The median pore size was calculated using the Young-Laplace equation (Adam 1956) as described by Stanley-Wood (1975) assuming a surface tension of 0·474 N m^{-1} and a contact angle of 130 ° for mercury.

Microscopic examination. The starch mucilage around the samples of powder and granules was stained with aqueous iodide solution. Photomicrographs of each sample, at 100×, 250× and 400× magnifications, were obtained using a Ultraphot II camera microscope (Carl Zeiss, Oberbocken, Württ, W. Germany) to show the degree and penetration of starch mucilage around and in the particles of dicalcium phosphate dihydrate.

RESULTS AND DISCUSSION

With a massing time of 15 min and constant weight of binder, an increase in the mean granule size and variation in the granule size distributions occurs with mucilages up to 10% w/w. With the 15 and 20% w/w starch mucilage, however, a decrease in mean granule size from the optimum granule size at 10% w/w was observed (Fig. 1).
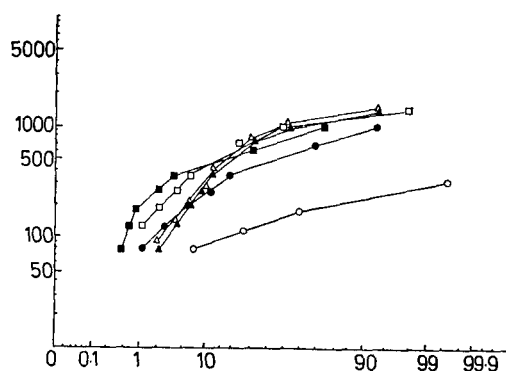

FIG. 1. Particle and granule sieve size distributions. Ordinate: Particle sieve diameter (μm). Abscissa: probability. (○) Dicalcium phosphate; (●) Dicalcium phosphate with 2% w/w starch mucilage; (■) Dicalcium phosphate with 5% w/w starch mucilage; (□) Dicalcium phosphate with 10% w/w starch mucilage; (△) Dicalcium phosphate with 15% w/w starch mucilage; (▲) Dicalcium phosphate with 20% w/w starch mucilage.

The increase in granule size may be attributable to the increase in the penetration, covering or wetting of the dicalcium phosphate particles by the mucilages (Davies & Gloor 1971). The starch mucilage, up to 10% w/w, may alternatively cause an increase in the number of bond formations until an equilibrium granular state is achieved (Carstensen et al 1976). At higher mucilage concentrations the more viscous mucilages produced pasty masses which were not easily screened. The difficulty in the production of large firm granules was due to a decrease in bond formations and resulted in the production of a large amount of fines. The production of stable particle-mucilage-particle bonds can be quantitatively described by comparison of the percentage of less than 75 μm sized granules (fines) found in the granule size distributions of the various granulated samples. The percentage of fines (<75 μm) in granules prepared from 15 and 20% w/w starch mucilages was 2 and 6% w/w respectively, whilst from 10% w/w or below it was less than 0.8% from a powder containing 7% w/w of particles <75 μm.

It can be surmised that at concentrations of 15–20% w/w starch the cohesion of the mucilage molecules to each other is such that the powder particles are not bonded to each other by a mucilage bridge while at 2% the particles are coated with only a small proportion of mucilage which bind particles together. Photomicrographs show the dicalcium phosphate particles are bonded together by the mucilage while few unbound dicalcium phosphate particles remain, the percentage of fines present in this granulation being 0.8% w/w. With 5 and 10% starch mucilage the proportion of mucilage surrounding the particles increased whilst the percentage of visible fines decreased to 0.2% w/w with both 5 and 10% w/w mucilage granulations. At the 15 and 20% starch mucilage concentrations small individual 'globules' of mucilage were visible to which dicalcium phosphate particles were attached but no particle-mucilage-particle bridges were formed. The visible fines also increased to 2 and 6% w/w respectively.

The degree of particle-mucilage bond formation could also be assessed from the change of either the geometric or B.E.T. surface area at different mucilage concentrations. Table 1 shows that there is a steady reduction in B.E.T. surface area of granules produced from the 2 to 10% w/w starch mucilages. A minimum surface area of granules was obtained with the 10% w/w starch mucilage which resulted in a 40% reduction in B.E.T. surface area from that of the initial dicalcium phosphate powder. This reduction in surface area indicated that the

binder had covered or penetrated the particles, with the formation of particle-mucilage bonds and granules of increasing size. At the same time the variation in friability (Fig. 2) indicated that the granules had an increase in strength with decrease in B.E.T. surface area which in turn could be related to an increase in bond formation. With the 15 and 20% w/w mucilages, the B.E.T. surface area increased with friability increase thus there is a correlation between bond formation, granule strength and available surface area.
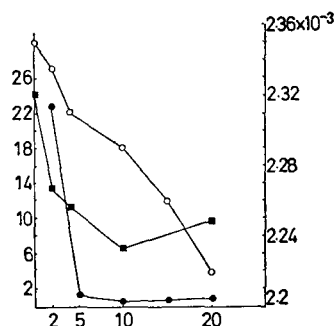

FIG. 2. Variation of density, percentage friability and compressibility with binder concentration. Left ordinate: percentage friability and compressibility (%); right ordinate: granule density (kg m^{-3}). Abscissa: binder concentration (% w/w) (●) friability; (■) compressibility; (○) density.

The reduction of the geometric surface area, which was measured at different mucilage concentrations independently from the B.E.T. surface area, also shows the same trend as the B.E.T. surface area relationship with friability (Fig. 3). Direct comparison of reduction of the geometric surface area with that
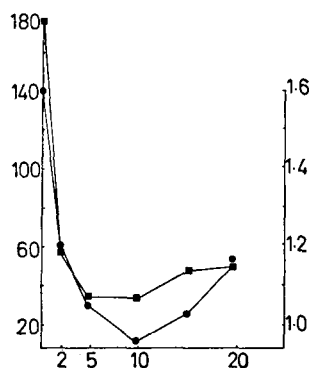

FIG. 3. Variation of surface area with binder concentration. Left ordinate: geometric surface area (cm^2 g^{-1}); right ordinate: B.E.T. surface area (m^2 g^{-1}). Abscissa: binder concentration (% w/w) (■) Geometric surface area; (●) B.E.T. surface area.

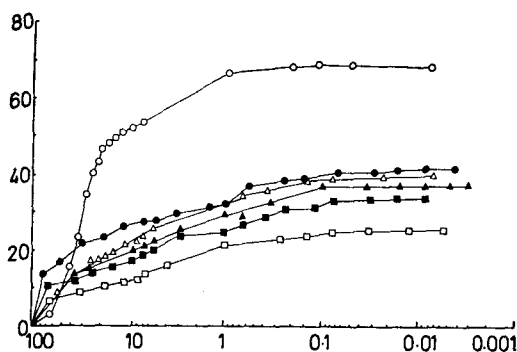FIG. 4. Pore volume distribution from high pressure mercury intrusion. Ordinate: pore volume $(cm^2 g^{-1} \times 10^2)$. Abscissa: pore radius (μm). ($\bigcirc$) Dicalcium phosphate; ($\bullet$) Dicalcium phosphate with 2% w/w starch mucilage; ($\blacksquare$) Dicalcium phosphate with 5% w/w starch mucilage; ($\square$) Dicalcium phosphate with 10% w/w starch mucilage; ($\triangle$) Dicalcium phosphate with 15% w/w starch mucilage; ($\blacktriangle$) Dicalcium phosphate with 20% w/w starch mucilage.

of the B.E.T. surface area reductions cannot, however, be made because the methods measure different parameters.

The degree to which the starch mucilage penetrates and covers dicalcium phosphate particles and forms particle-mucilage bonds can also be obtained from mercury intrusion measurement of the median pore size and pore volume of granules (Fig. 4) manufactured at different mucilage concentrations. Both the median pore size and pore volume decrease to a minimum at a binder concentration of 10% w/w (Fig. 5). Reduction of surface area, either geometrical or B.E.T., indicates the coating power of the mucilage whilst the pore volume and friability reduction indicate the formation of particle bonds. Both the B.E.T. and the geometric surface
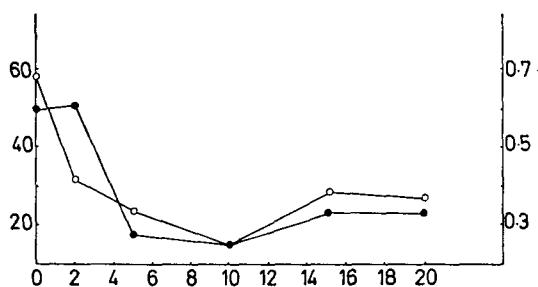
area of granules prepared from dicalcium phosphate and starch mucilage showed a rank order relationship with compressibility. The percentage compressibility showed the same binder concentration optimum, 10% w/w, as seen with friability and granule size.

Conclusions

The results from the addition of different concentrations of starch mucilage to dicalcium phosphate dihydrate indicate that the same mucilage concentration has an optimal effect on friability, compressibility, granule size, pore volume and media pore size and both geometric and B.E.T. surface area of granules. The 10% w/w optimum mucilage concentration, with a standard method of massing and granulation, can be related to the penetration or covering of the surface irregularities and bond formation of the dicalcium phosphate particles. Measurement of the surface area of granules by low temperature nitrogen adsorption, together with high pressure mercury penetration can give a deeper insight into the bonding mechanisms of pharmaceutical materials.

FIG. 5. Variation of pore volume and median pore diameter with binder concentration. Left ordinate: median pore diameter (μm), right ordinate: total pore volume $(cm^3 g^{-1})$. Abscissa: binder concentration (% w/w). ($\bullet$) Median pore diameter; ($\bigcirc$) Total pore volume.

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