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Compactibility of granules prepared by a novel method of granulation and their dissolution

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Increasing particle size during prolonged grinding by a ballmill has been used as a novel means of producing a pharmaceutical granulation. The compactibility properties of granules of sodium chloride and of paracetamol produced by this method have been elucidated and compared with those produced by conventional granulation techniques. Force-displacement diagrams and double compactions were used to measure the net energy input on tableting. When compared with conventional granulation methods, the agglomerative phase of comminution (APOC) method produced mechanically stronger tablets with a higher dissolution rate than those compacted from granules made by a conventional wet granulation method irrespective of the compaction energy used. Tablet tensile strength is related to the elasticity and yield strength of the substance used. It is suggested that binderless tablets may be prepared using this method, thus simplifying tablet formulation and enhancing stability. A possible mechanism for the increased dissolution rate is the increased internal surface area of the granules produced by the prolonged grinding method.

To achieve a high degree of homogeneity in the mixing of granules, the particle size of the ingredients has to be reduced and this causes poor particulate flow which, in turn, affects the content uniformity of the final dosage form (tablets and capsules). Poorly water-soluble materials must similarly be size-reduced to offer a greater surface area available for subsequent dissolution, thus enhancing bioavailability. A particle size enlargement process (granulation) subsequent to mixing, improves flow, can prevent segregation, facilitate compactibility and dispersibility and prevent contamination associated with air-borne particles.

Moist granulation methods are widely employed, but are labour intensive and require high outlay in equipment (Seager 1977). The liquid component present may cause crystal bridge formation and lower the activity of micronized drugs (Pietsch 1970), or may act as a vehicle for chemical reactions through hydrolysis and microbial growth. Subsequent drying is costly, may decompose thermally labile substances, and affect content uniformity through solute migration (Travers 1975).

After the prolonged grinding of various substances (Owe Berg & Avis 1970; Beke 1973; Dialer & Kuessner 1973; Roth 1977) and pharmaceuticals (Kaneniwa & Watari 1977), agglomeration was shown to occur spontaneously. Ho & Hersey (1979) have demonstrated that this agglomerative phase of comminution can be used to produce pharmaceutical granules.

It is well known that stronger tablets will be formed from larger interparticulate surfaces (Sixsmith 1977). Plastic deformation is mainly responsible for this bond formation. Gregory (1962) pointed out that deformation behaviour of material varies with particle size. Granules formed by this 'prolonged grinding method', which involves particle size changes, could confer some distinct advantages on the resulting tablet properties. The present investigation is aimed at comparing the compactibility of granules formed by the agglomerative phase of comminution and with those formed by conventional granulation methods and the effects on dissolution since Ho (1979) has found that granules prepared by agglomeration have a higher dissolution rate than those produced by wet granulation or slugging.

Since tablets make up a large proportion of solid dosage forms, compactibility offers a practical means of evaluating granule properties.

Compacting parameters

Compaction has been monitored by applied, reactionary forces, punch force ratio (Rees 1979), pressure cycle and residual die wall pressures (Carless & Leigh 1974). Compaction forces in a reciprocating tablet machine are determined by the distance the upper punch travels. Because of irregularities of shape, larger granules will pack more closely than smaller ones. Thus whilst the machine may be opera-

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ted at identical settings, the size and packing of the granules will influence the energies used, although the maximum applied pressure may be unchanged. Compaction energy is thus a more logical parameter for use in the comparison of granulates that may pack differently, since they have been prepared by different methods.

Energy in compaction is consumed (Polderman & De Blaey 1971; Juslin & Jarvinen 1974) by: (i) particle rearrangement; (ii) interparticle friction; (iii) particle-die wall friction; (iv) elastic deformation; (v) plastic deformation; (vi) bond formation.

(i) and (ii) are negligible, so the applied force is largely used to overcome (iii), (iv), (v) and (vi). In this derivation (v) and (vi) cannot be distinguished.

In the following derivation the subscript 1 and 2 refer to the first and second compaction, respectively. Other notations are as follows.

Fa, Fb	applied force on upper punch and experienced on lower punch
ds	infinitely small displacement of the upper punch relative to the lower punch
F	frictional force
Dm, Ds	position of upper punch where force applied is maximum and minimum
We	energy of elastic deformation
Wpl	energy of plastic deformation and for bond formation
UPW	upper punch work
LPW	lower punch work

So in the first compression, applied energy (iii) + (iv) + (v) + (vi), that is,

$$\int_{Ds_1}^{Dm_1} Fa\ ds = \int_{Ds_1}^{Dm_1} Fds + We + Wpl \quad .. \quad (1)$$

Rearranging equation 1

$$\therefore \int_{Ds_1}^{Dm_1} (Fa - F)\ ds = We + Wpl$$

$$\therefore \int_{Ds_1}^{Dm_1} Fb\ ds = We + Wpl$$

$$\therefore \quad LPW_1 = We + Wpl \quad .. \quad .. \quad .. \quad (2)$$

A second compression is performed on the tablet without allowing it to be ejected. Since the force applied is the same, material that is deformed plastically will not deform again. Thus, in the second compression, work consumed is We. Following the same derivation as in equation (1) to (2), equation (3) can be derived.

$$LPW_2 = We \quad .. \quad .. \quad .. \quad .. \quad .. \quad (3)$$

Subtracting equation (3) from (2)

$$\therefore \quad Wpl = LPW_1 - LPW_2 \quad .. \quad .. \quad .. \quad (4)$$

In Fig. 1a,b typical first and recompression traces are shown. A is the point when the upper punch is at maximum descent. On raising the upper punch, a

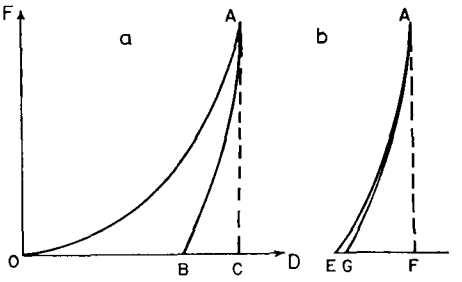

FIG. 1. Force-displacement diagrams for compaction and recompaction. Ordinate: force. Abscissa: displacement of upper punch relative to lower punch. *1st compaction.* A corresponds to maximum force registered on the upper punch. B corresponds to the point where temporary contact between upper punch surface and the compact is lost. C corresponds to maximum displacement of the upper punch. *Recompaction.* E corresponds to point where compaction force begins to register on the upper punch. F corresponds to maximum displacement of upper punch. G corresponds to point where contact between upper punch surface and the compact is just lost.

temporary contact is still maintained until B is reached. So area AOC LPW_1. Area ABC is part of the elastic energy recovered, whereas Area AEF LPW_2 (De Blaey & Polderman 1970; De Blaey et al 1971a, b).

Tensile strength

Mechanical strength of tablets can be described by crushing strength (F), hardness, tensile strength (σx) (Newton et al 1971), and tensile work of failure (Wf) (Rees et al 1977). In this investigation, σx is chosen as it is simple to measure and has a narrow scatter of results.

$$\sigma x = \frac{2F}{\pi Dt} \quad (5)$$

where D, t are tablet diameter and thickness respectively.

Tensile failure occurs on diametral crushing of tablets when they split into two identical halves.

MATERIALS AND METHODS

All materials were of pharmacopoeial quality.

(i) Sodium chloride was chosen to study the effect of

granulation on tablet strength using slugging, moist granulation and grinding (agglomerative phase of comminution APOC) methods.

(ii) Paracetamol is difficult to compact and tablets often fail by capping (Doelker & Shotton 1977). It was the purpose here to show the commercial advantage of this new APOC granulation process on compaction.

(iii) A formulated paracetamol mixture with the following formula, granulated by wet and APOC granulation, was used: paracetamol 200, polyvinylpyrrolidone 7·2, starch 24, lactose 7·6 g.

Granules were prepared by the three methods below. In each case, the 500–710 μm size fraction of granules was selected for compaction. For each granulation, 0·5% magnesium stearate was added before tableting.

Wet granulation

The ingredients (300 g for both sodium chloride, and for paracetamol mixture) were mixed in a glass jar (11 cm diam. and 25·3 cm height) rotating at 76 rev min, for 10 min. A baffle inside the jar broke up any lumps. Purified water (20 ml for sodium chloride and 30 ml for the paracetamol mixture) was added and the jar was rotated for another 15 min until a moist, but not wet, mass was formed. Size reduction was achieved by passing this mass through a 1490 μm sieve in a Jackson-Crocket No. 6 Granulator. The granules were then dried in a Glatt fluidized dryer at 30 °C for 1 h with ventilation flap at setting 3. The granules obtained were sized through a stack of test sieves.

Slugging (granulation by precompression)

Slugs were formed using a Comprex II heavy duty tableting machine with a 20 mm plain punch. Slugging was carried out on sodium chloride only as paracetamol tended to cap.

APOC granulation

Agglomeration was carried out in a ball mill rotated at 62·3% of critical speed. The end points were selected arbitrarily. Subsequent granulation and sieving were performed as described under wet granulation.

Table 1. Comparison of yield strength by Heckel plot.

	Yield strength (1/K) in MPa	
Size	Paracetamol	NaCl (Hersey et al 1973)
500–710 μm	148·4	55·6
410–500 μm	102·8	—
250–410 μm	152·7	67·7
180–250 μm	135·4	53·4

The compaction equipment used was modified from that used by De Blaey et al (1971a). Tableting was performed using a reciprocating tablet machine, instrumented with strain gauges (SR-4 type B) and an inductive displacement transducer (Phillips, PR 9314/10). The electrical signal output was fed into an XY double beam Cathode Ray Oscilloscope (Tektronix 502A) with an accessory camera to photograph the CRO trace if required. Calibration curves for strain displacement were linear in the range used for these studies.

Conditioning of tablet machine

To condition the tablet machine, it was hand-turned for 10 cycles and the first few tablets were rejected. The die wall and upper and lower punch surfaces were lubricated with 1% of magnesium stearate in acetone. 15 s was allowed for the acetone to evaporate before hand filling the die by pouring a known weight (500 mg of paracetamol or paracetamol mixture, or 700 mg of sodium chloride) of granules at an angle of approximately 45°. The time of powder and upper punch contact was limited to not more than 5 s. To prevent premature tablet ejection, the fly-wheel was turned in the opposite direction to effect the second compression. The die was brushed clean before a further compaction. Photographs were taken for the lower punch force-displacement curve and the first and second compression.

Five tablets were compressed doubly and eight singly. Only the singly compacted tablets were used for tensile strength measurement. Altogether no more than 8 nor less than 5 force settings were used for each granulation.

Diametral crushing was performed on tablets stored for 24 h to allow for elastic recovery.

Dissolution study

The dissolution study was carried out in a modified U.S.P. rotating basket assembly. Paracetamol tablets were introduced into the basket, rotated at 160 ± 5 rev min^{-1} by a constant drive mechanism (Hansen Research Corp, Model 53). 900 ml of 0·005% polysorbate 80 in purified water was used as the dissolution medium, maintained at 25 ± 0·5 °C. The solution was pumped continuously through a 1 cm pathlength flow-through cell in a Perkin Elmer UV-Vis spectrophotometer, model 402 and returned to the dissolution cell. A Watson Marlow HR flow inducer was used for pumping the medium at a rate of 71 cm^3 min^{-1}. Analysis of paracetamol was

carried out by continuously monitoring the solution at a wavelength of 296 nm, where a linear absorption concentration relationship had been demonstrated. Excipients did not interfere with paracetamol at the wavelength used. Five tablets prepared at each level of net energy input were used to obtain a mean value of dissolution rate. The tablets were tested after not less than one day nor more than seven days storage to allow for any time dependent relaxation effects to occur.

RESULTS AND DISCUSSION

Figs 2 and 3 show tensile strength data for sodium chloride and paracetamol tablets. Fell & Newton (1971) reported that the tensile strength of tablets

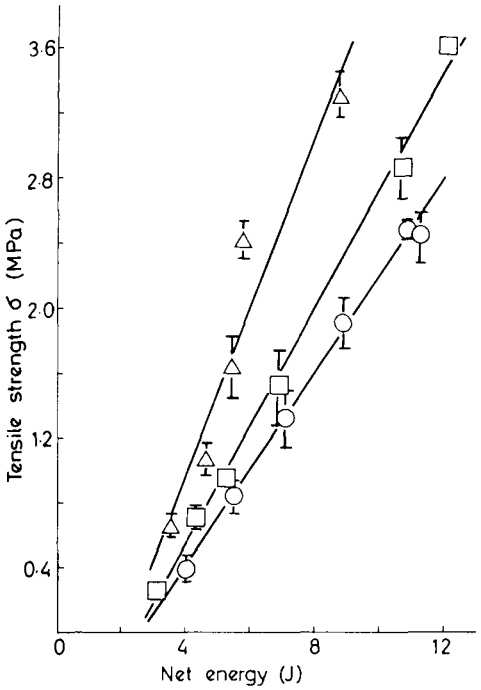

FIG. 2. Tablet strength of sodium chloride tablets using different granulation methods. Each point is an average of 5 experimental results. The vertical error bar is one standard deviation. △ APOC granulation for 4 h. □ Slugging. ○ Wet granulation.

depends on particle size and amount of work done during the compaction. In this investigation, particle size was fixed so that variation in tablet properties was due to different granulation methods. Good linear relationships between tensile strength and net energy input were found for all granules. It can be seen that for tablets of the same materials, those prepared from the APOC method always gave higher tensile strength, suggesting better energy utilization.

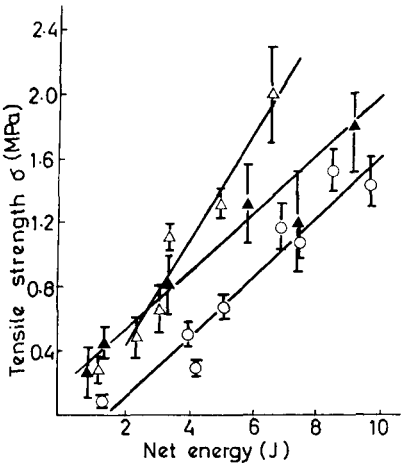

FIG. 3. Tablet strength of paracetamol tablets using different granulation methods. Each point is an average of 5 experimental results. The vertical error bar is one standard deviation. ○ Wet granulation of formulated paracetamol. ▲ APOC for 35 h on pure paracetamol. △ APOC for 35 h on formulated paracetamol.

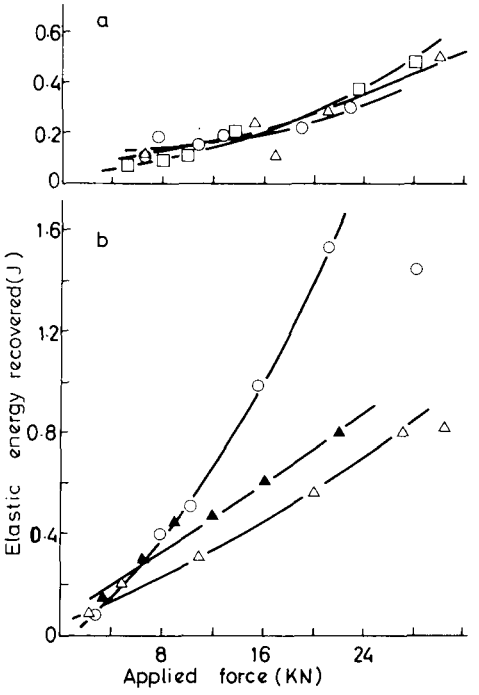

FIG. 4. Elastic energy versus applied force plot for (a) sodium chloride (b) paracetamol. Ordinate: elastic energy recovered (J). Abscissa: applied force (KN). y-axis for sodium chloride: ○ Wet granulation. □ Slugging. △ APOC for 4 h. For paracetamol: ○ Wet granulation of formulated paracetamol. ▲ APOC for 35 h on pure paracetamol. △ APOC for 35 h on formulated paracetamol.

To further investigate the cause of the strength of the compacts, elastic energy (LPW_2) was plotted against applied force for different sodium chloride granules (Fig. 4). As expected, elastic energy increases with applied force, although no significant difference was found between sodium chloride granulations.

With paracetamol, granules produced by wet granulation method had higher elastic energy and lower strength than those produced by APOC (Fig. 4). This trend was realized when comparing

Paracetamol always had a higher yield value and consequently was more elastic (Healey et al 1974; Aulton 1977).

Dissolution profiles were generated by plotting time for 66·7% of material dissolution (T66·7%) versus amounts of net energy input (see Fig. 6). Tablets made from granules produced by the APOC method always dissolved faster and were not as affected by net compaction energy, when compared with those prepared by the moist granulation method.

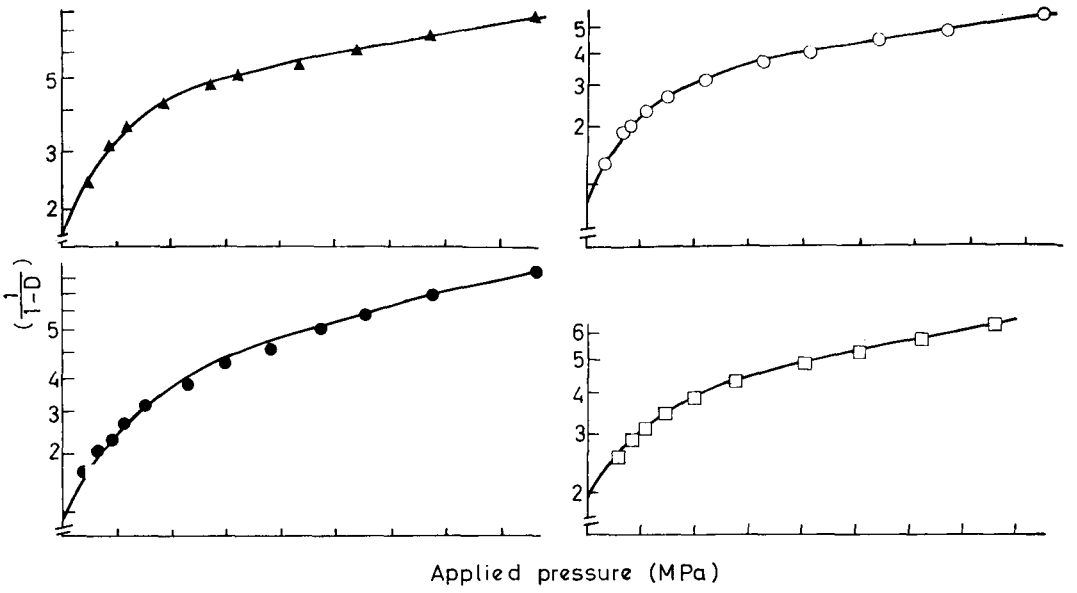

FIG. 5. Heckel plot for paracetamol. Ordinate: 1/1-D. Abscissa: applied pressure (MPa). ⬚ Particle size 180–250 μm. ○ Particle size 250–410 μm. ● Particle size 410–500 μm. ▲ Particle size 500–710 μm.

sodium chloride and paracetamol plots. All paracetamol tablets made by different granulation methods had higher elastic energy and lower strength than the corresponding sodium chloride tablets. This indicates that elastic energy is one of the factors governing mechanical strength of the compact.

From the Heckel plot on different size of paracetamol (Fig. 5) the yield strength, k, can be obtained from

$$\ln\left(\frac{1}{1-D}\right) = \frac{1}{K}P + A \quad .. \quad .. \quad .. \quad (6)$$

where D is the relative density, P is the applied pressure and A is a function depending on original compact volume.

Dissolution rate of an active ingredient in the tablet is influenced by (i) nature and proportion of other excipients (Johnsgard & Wahlgren 1971); (ii) method of incorporating active ingredient (Shotton & Leonard 1972); (iii) tableting force or energy (Khan & Rhodes 1972), and (iv) granule size compacted.

The two types of paracetamol granules were of identical formulation and size. By plotting the dissolution rate parameter against net energy input, any changes in these profiles reflect the effect of the granulation method.

When the dissolution data were plotted according to Wagner's plot (1969), equation (7), biphasic profiles were obtained in 'APOC-granulated' tablets made at the highest compaction pressure (Fig. 7)

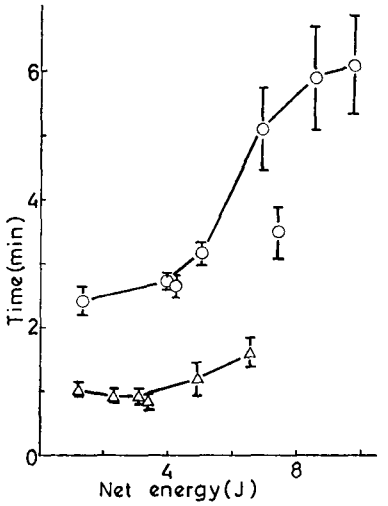

FIG. 6. Dissolution (T66·7%) of paracetamol tablets prepared at different energy levels. ○ Paracetamol tablets prepared by wet granulation method. △ Paracetamol tablets prepared by APOC method. Each point is the average of five determinations. The error bar represents one standard deviation. Ordinate: T 66·7%.

and in all 'wet-granulated' tablets, except those made at the lowest pressure.

$$\log(\%\text{ of material undissolved}) = A - \frac{kt}{2{\cdot}303} \quad (7)$$

where A and K are constant.

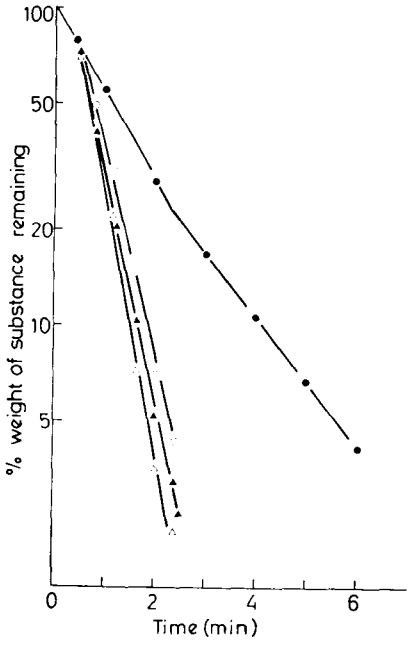

FIG. 7. Wagner's Plot for APOC—granulated paracetamol tablet dissolution. ● 6·45 J. ○ 4·95 J. ▲ 3·38 J. △ 3·12 J. Tablets were compacted with different net energy input.

The point of inflexion was shown to correlate with disintegration time (Kitazawa et al 1977; Pilpel et al 1978). Fig. 8 shows the higher the compaction energy, the longer the disintegration time. This indicates that water penetration may be the rate determining step in disintegration. Increase in compaction pressure will deform the excipient particles, occluding the pores that are required for solvent penetration. On the other hand, if disruptive force was the main determinate, increase in compaction pressure will decrease disintegration time. In 'APOC-granulated' tablets and 'wet-granulated' tablets compacted at lower energy, disintegration was achieved within the

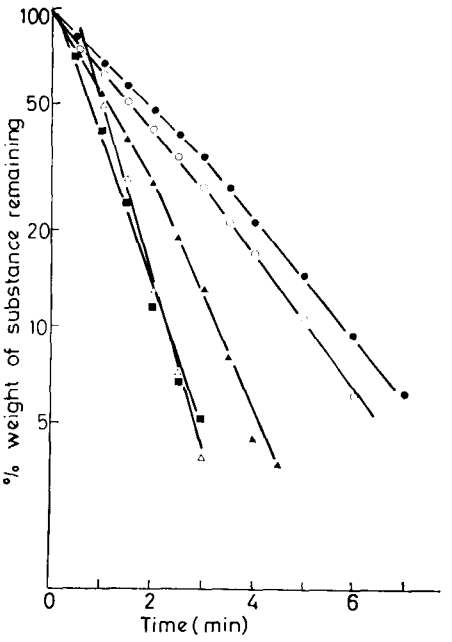

FIG. 8. Wagner's Plot for wet granulated paracetamol tablet dissolution. ● 9·66 J. ▲ 7·41 J. ○ 6·87 J. △ 4·20 J. ■ 1·33 J. Tablets were compacted with different net energy input.

first minute and was not apparent from the graphs (Figs 7, 8). 'Wet-granulated' tablets made from lower compaction pressure are more porous. The fact that their dissolution profiles are similar to those of 'APOC-granulated' tablets made at high pressures indicates 'APOC-granulated' tablets may have a more porous structure. They provide a large internal surface area of dissolution, resulting in a higher dissolution rate. The porous nature of the granules and resultant tableting was also implied from findings on intragranular pore size measurement (Ho & Hersey 1979) and granule compactibility. However, other mechanisms such as increased swelling

capacity of disintegrant after milling (Ingram & Lowenthal 1968) should not be ignored.

In this investigation, APOC granulation was shown to produce mechanically stronger tablets than by conventional wet granulation or by slugging of both plastically or elastically deforming substances. Hence, the use of a binder can be eliminated, thus reducing the chance of interactions between formulation components and enhancing tablet stability.

The reason why APOC provides strong granules is not established. Grinding apparently does not change material deformation behaviour. Partial bonding may be provided by the agglomeration and by the fine particles, carried over from the initial comminution, acting as an 'adhesive' between larger granules.

It can be envisaged that tablets made without binders could dissolve even faster (Van Outdshoorn et al 1971).

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