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The effect of intra- and extragranular maize starch on the disintegration of compressed tablets

E. SHOTTON AND G. S. LEONARD*

Department of Pharmaceutics, The School of Pharmacy, University of London, Brunswick Square, London, W.C.1, U.K.

The effect of maize starch on the particle sizes recovered from sulphadiazine tablets subjected to the B.P. disintegration test has been examined. A size analysis of the resulting suspension was made using a combination of wet sieving techniques and the Coulter Counter. Intragranular starch resulted in the recovery of finer particles than when extragranular starch was used, but the disintegration time was longer with intragranular starch. The use of both intra- and extragranular starch in a tablet gave intermediate disintegration time and mean diameter.

The official disintegration test for compressed tablets in the B.P. is concerned solely with the ability of the formulation to break up in water into particles of a size which will readily pass through a 10 mesh screen. This can be a misleading criterion, especially for tablets made from drugs of low solubility when the rate of solution can be increased by using a smaller particle size. Van Ootghem, Boni & Herbots (1969) investigated the effect of some formulation factors on the particle size produced by the disintegration of aspirin tablets, although they ensured that all particles were less than 300 μm before measuring them on the Coulter Counter. Sanders (1969) described a simple test using three screens supported in a standard U.S.P. disintegration apparatus, whilst Sandell (1970) simplified this further by resting the tablet on the uppermost of three screens standing in a beaker of water. For agitation the screens were raised and lowered 1 cm every 10 s. We describe the combination of a wet sieving technique and the use of a Coulter Counter to achieve an overall size distribution of disintegrated tablets, with some results for sulphadiazine/maize starch tablets.

MATERIALS AND METHODS

Materials

The sulphadiazine, maize starch (moisture content 11% w/w) and magnesium stearate used were of B.P. quality and the sodium chloride and polyvinyl pyrrolidone (PVP) were Analar and reagent grades respectively. The sulphadiazine powder had a mean particle size of 9·7 μm (range 2 to 32 μm) as assessed with the Coulter Counter.

Methods

The experimental work is divided into three separate stages for which separate pieces of apparatus were required: (i) Disintegration time measurement; (ii) wet sieving of the particles larger than 75 μm; (iii) Coulter Counter sizing of the particles below 90 μm.

* Present address: Lilly Research Centre Ltd., Earl Wood Manor, Windlesham, Surrey, U.K.

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Disintegration Apparatus

The basic requirements for the B.P. disintegration test were used to construct an apparatus which could simultaneously test ten tablets, or batches of tablets. The operating conditions were as follows:

Rate of reciprocation of basket, 30·5 cycles min^{-1}; depth of immersion of basket, 75 mm; volume of disintegrating medium, 235 ml ($\pm$5 ml); depth of disintegrating medium, 15·5 cm ($\pm$0·35 cm); internal diameter of reservoir tube, 44 mm; operating temperature, 37° ($\pm$0·1°).

A pre-requisite of this technique is that the disintegration medium should be a saturated solution of the drug under test to prevent solution of disintegrated particles, and also be a suitable medium for use in the Coulter Counter, and so a 0·9% w/v sodium chloride solution saturated with sulphadiazine was employed.

Apparatus for wet sieving

A series of 1½ inch diameter brass sieves conforming to the British Standard Specification (B.S. 410) were nested together using polytetrafluoroethylene (PTFE) tape to form a watertight seal between each sieve. The screens were mounted in the mouth of a one litre conical flask using a PTFE gasket. The ten sieves used are listed below, the first nine conforming to the proposed International Standard.

Mesh No.	12	16	22	30	44	60	85	120	170	200
Aperture (μm)	1400	1000	710	500	355	250	180	125	90	75

Coulter Counter

The particles in the suspension which had passed through the sieves were sized by a standard Model A Coulter Counter using a 200 μm diameter orifice sampling tube and a 0·5 ml sample volume. The electrolyte solution required was as used for the initial disintegration and it was filtered before use through a millipore filter.

Granulation

Granules were prepared with a rotating screen. Erweka Granulator (Type FAG) using sufficient of a 10% w/v solution of PVP in distilled water to be equivalent to 3% w/w dry PVP in the final tablet. If intragranular disintegrant was required it was dry mixed with the sulphadiazine before the addition of the granulating solution. After drying in a hot air oven at 55° for 2 h the granules were cooled in air tight containers and the sieve fraction 1·0 to 1·2 mm. collected. Extragranular disintegrants were now added, mixing being achieved in a sealed jar placed on the drive of a roller mill. The granules contained less than 0·6% of moisture. Lubricant was deliberately omitted to avoid the opposing effects of lubricants and disintegrating agents.

Compression of granules

The tablets were prepared individually using an instrumented single punch machine (Shotton & Ganderton, 1960) and the applied and transmitted forces were monitored. The wall of the die was lightly dusted with magnesium stearate powder as a lubricant; the face of the lower punch and the whole of the upper punch being wiped clean.

Size analysis

Using the disintegration apparatus, disintegration time was determined for five tablets individually. The resultant suspension from three of these tablets was used

in the size analysis. When disintegration was complete the liquid in the reservoir tube was gently swirled to resuspend the settled particles and this suspension poured onto the sieves. Any particles remaining were carefully washed in using a low pressure stream of filtered disintegration medium from a wash bottle. At this point the nest of sieves usually contained an almost continuous column of liquid. To ensure that all particles capable of passing through each mesh did so, two techniques were employed. The first was to gently rock each sieve in the one below to force liquid and air back up through the mesh whilst maintaining a watertight seal. Where large quantities of particles lay on a sieve this was not totally successful and a forced reverse streaming process was used. The uppermost sieve was partially separated from the one below and it was tilted so that half its screening area was immersed in the liquid lying on the sieve below. Whilst the screen was being continually rotated, a wash bottle was used to pass a gentle stream of disintegration fluid back up through the exposed region of the mesh. Thus, liquid was flowing in two directions across the mesh and a reservoir of fluid remained above it. The two methods kept the particles gently swirling in suspension and those that could pass the mesh were carried by the streaming of the liquid. The total analysis was made quickly (within 3 min) and gently so that little further breakdown of the particles occurred. The sieves were then separated, inverted onto watchglasses and partially dried at 40° until the particles could be easily removed from the screen and dried for a further hour which then gave constant weight. The quantity of sodium chloride and sulphadiazine dissolved in the small volume of adherent liquid was shown to be insufficient to affect the weight of the granules. The wet particles were removed from the finer screens by distilled water, dried directly and when the weight at each size level was determined.

The volume of suspension collected in the conical flask was measured and the particles sized in the Coulter Counter using predetermined machine settings so that particles of 20 to 70 μm, in 5 μm increments (this simplified computation), and of 80 and 90 μm diameter were measured. To check that no dissolution or particle breakdown had occurred during counting, repeat counts at four separate levels were made. It was not practicable during the analysis to obtain a full Coulter Counter scan to include particles below 20 μm since this would involve at least a fourfold dilution even for poorly disintegrated tablets. To give counts below the dilutions required would introduce errors such as excessive and immeasurable particle breakdown caused by agitation during dilution, inherent errors in obtaining homogeneous samples from large volumes of suspension, and dissolution of small particles, even into a 'saturated' solution, when no excess solid is present.

Particles < 20 μm were therefore considered to be the original form of the drug.

A sample of tablets from each batch was tested for hardness using a modified form of the apparatus developed by Shotton & Ganderton (1960).

RESULTS AND DISCUSSION

To correlate the two sets of data the Coulter Counter results were converted to absolute weights. Since the total volume of suspension is known, the number of particles between any two given diameters can be calculated from the raw counts after corrections have been made for background count and coincidence at the aperture. The mean particle diameter (D_1) between any two adjacent size levels (d_1 and d_2) was calculated. To calculate the absolute weights at any given size level

two assumptions were made: (*a*) Particles were spherical; (*b*) density of particles was that of the original material. The first assumption is valid for the Coulter Counter since the principle of this instrument does not allow for significant discernment of particle shape and the results are expressed as spherical equivalents. The particles are assumed to be solid and of irregular shape surrounded by a continuum of electrolyte, and the size measured will be equivalent to the volume of solid present. One source of error in this assumption is the difference in density between disintegrant and drug in addition to any small quantities of entrapped air; these are acceptable, however, since only a maximum of 20% of the total distribution was measured by the Coulter.

The absolute weight of particles of any given size (W_1) was calculated from:

W_1 = individual particle weight (mg) × corrected no. of particles per size level × total volume of suspensions (ml) × 2

where: Individual particle weight $= \frac{D_1^3}{6} \times 3{\cdot}142 \times 1{\cdot}505^* \times 10^{-9}$ mg, and the corrected no. of particles per size level = mean raw count + coincidence correction − background count.

The number of 0·5 ml samples in the suspension is twice the total volume in ml.

The distributions by sieving and Coulter Counter were then combined to give an overall distribution and the weight moment arithmetic mean diameter for each sample was also calculated to characterize the distribution. All the calculations were made using a computer program written by one of us (G.S.L.).

Seven formulations of sulphadiazine and maize starch were investigated and the characteristics of the tablets produced are in Table 1 which shows that, as the content maize starch is increased, the disintegration time decreases with both types of formulation. The extragranular maize starch causes more rapid disintegration than the equivalent intragranular formulation because being confined to the spaces between granules it offers an easier passage for water penetration by forming a hydrophilic capillary system throughout the tablet (Fig. 1A). Most of the intragranular starch remains as discrete grains within the granules thus presenting a less easily wettable matrix, since no capillary system is present (Fig. 1B). The hardness of the tablets may also contribute to the differences in disintegration time between the two formulation types. Extra-granular starch grains reduce the effectiveness of the inter-

Table 1. *The disintegration time and mean particle size recovered after disintegration for tablets of different sulphadiazine/maize starch formulations.*

% and site of maize starch	Mean applied compression force (kg)	Mean hardness (kg)	Mean disintegration time (s)	Mean particle size recovered (μm)
2·5e	984	14·0	694	1033
5·0e	1007	12·4	163	564
10·0e	1018	11·2	67	316
2·5i	985	16·3	864	455
5·0i	1017	17·3	340	274
10·0i	1013	15·4	143	56
5i & 5e	1007	12·3	88	108

Where e = Extragranular. i = Intragranular.

* Density of sulphadiazine.

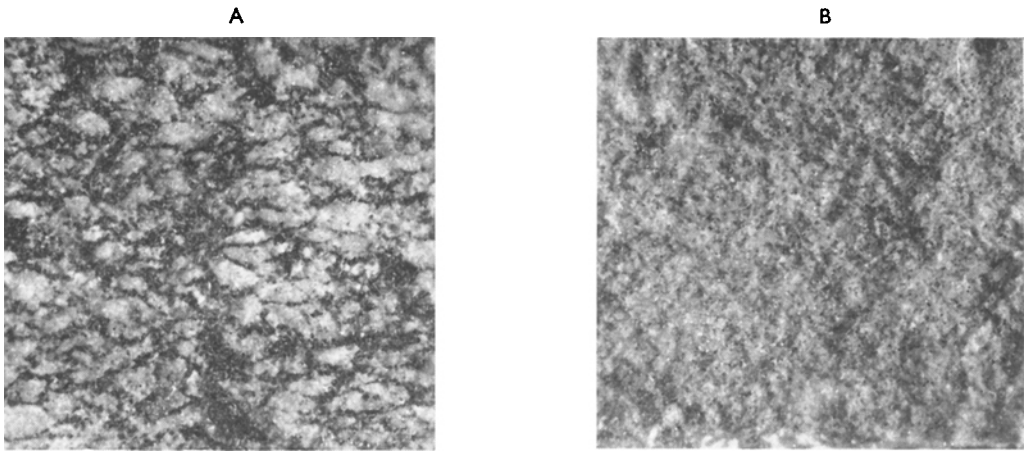

FIG. 1. The distribution of starch in a tablet. 10% maize starch; A, extragranular (granule size 710–850 μm) F_a = 1500 kg; B, intragranular (granule size 1000–1200 μm) F_a = 1800 kg.

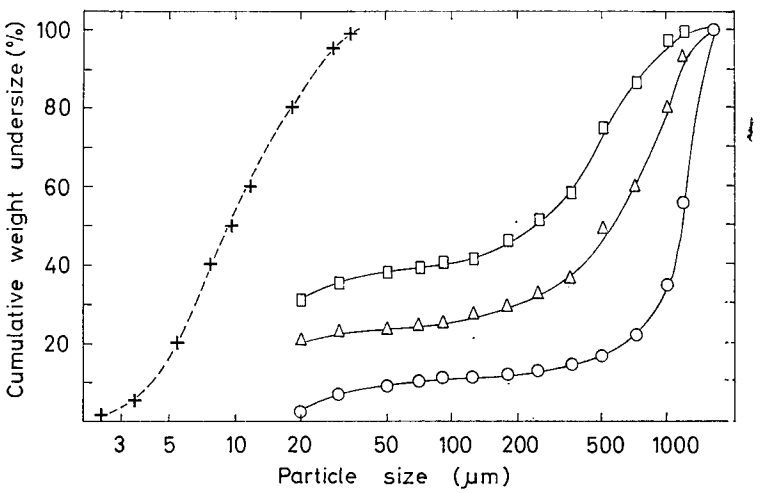

FIG. 2. A comparison between the particle size distribution of sulphadiazine powder and the distribution curves for disintegrated sulphadiazine tablets containing different quantities of extragranular maize starch. ---- Original powder. □ 10% maize starch. △ 5% maize starch. ○ 2·5% maize starch.

granular binding which occurs on compression, so a tablet that is weaker than the corresponding intragranular formulation is formed. The disintegration time for the mixed formulation lies between the results for the two separate 10% formulations and its hardness corresponds to that for 5% extragranular maize starch.

The size distributions of the disintegrated tablets are shown in Fig. 2 for extragranular and Fig. 3 for intragranular formulations. These clearly show the effect of changing the concentration of disintegrant, the curves moving towards that of the original material, also shown, as the amount of starch increases.

Extragranular maize starch causes tablet disintegration mainly into original granules with some granule breakdown, as the curves indicate by near vertical and near horizontal sections. The vertical portion becomes shorter and of a smaller particle size as the concentration of disintegrant increases showing that the granules

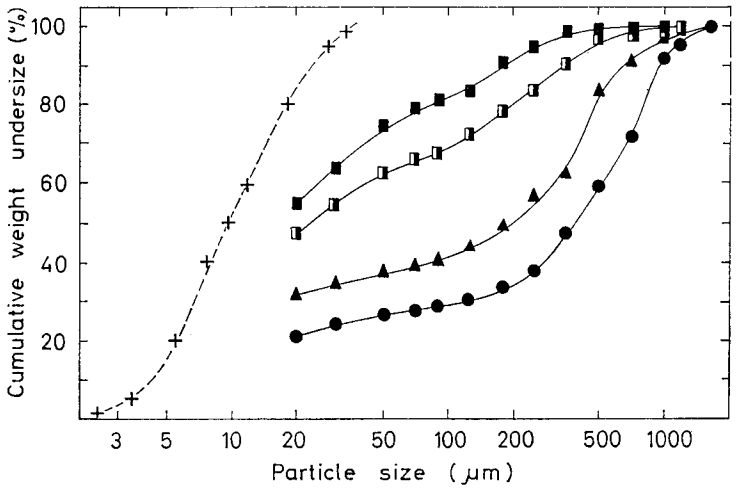

FIG. 3. A comparison between the particle size distribution of sulphadiazine powder and the distribution curves for disintegrated sulphadiazine tablets containing different quantities of intragranular maize starch and equal quantities of extra and intra-granular maize starch. ---- Original powder. ▲ 10% maize starch. ■ 5% maize starch. ● 2·5% maize starch. ◨ 5% extra and 5% intra-granular maize starch.

recovered become generally smaller. The horizontal part of the distribution indicates that the smaller particles tend mainly to be within the size range of the original powdered drug (3 to 32 μm) endorsing the finding that erosion of granules has taken place. Erosion plays an important role in the disintegration of intragranular formulations where Roland's (1967) microgranular breakdown directly to fine particles from a single core tends to predominate. Here the disintegrant is intimately mixed with the drug before granulation and so tablet breakdown follows this pattern and hence the distribution curves in Fig. 3 show a wider spread of particle size, especially with the highest concentration of maize starch. The less vertical sections indicate that fewer original granules are recovered. Included in Fig. 3 is the distribution curve for the mixed formulation containing 5% intragranular and 5% extragranular maize starch. This shows that even though the distribution recovered is not as good as that from a 10% intragranular formulation, it is still an improvement upon those using extragranular disintegrant. However, the disintegration times shown by these formulations would indicate that this is the preferred formulation, since the particle size recovered is much smaller than that from the 10% extragranular formulation which disintegrates in a similar time.

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