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The effects of polymorphism, particle size and compression pressure on the dissolution rate of phenylbutazone tablets

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The dissolution rate of phenylbutazone from tablets after disintegration has been used to determine whether the drug particles underwent crushing or bonding during compression. Two polymorphic forms of the drug were used and the predominant effect for high drug concentration (60%), during compression was dependent upon the original particle size of the drug and its polymorphic form. With a low drug concentration (10%) in the tablet, the diluent protected the drug particles from bonding together. The particle size change of the drug during compression was affected by the nature of the diluent present. Lactose had an abrasive action on Form A phenylbutazone compared with Avicel but had little effect on the more ductile Form B. When the contact time of compression was decreased from 29 to 0·26 s, the 6 μm particles of drug showed less bonding at the shorter time (faster rate of compression) but the effect observed with the larger particles was independent of the compression rate.

There is extensive literature to show that a decrease in particle size of sparingly soluble drugs results in increased dissolution rates owing to the increased surface area of the drug exposed to the solvent. However, control of particle size of the drug substance may not be sufficient to control the dissolution rate of the drug from tablets if particle bonding or crushing of the drug occurs during the tableting process.

Higuchi et al (1953), Armstrong & Griffiths (1970) and Armstrong & Haines-Nutt (1970) studied the change in the surface area of the drug powder after compression and found that as compaction pressure increased, the surface area first increased but subsequently decreased at higher pressure. These studies are of significance in tablet dissolution as an increase in surface area will increase the rate of dissolution of tablets made from sparingly soluble drugs. Smith et al (1971) interpreted these data in terms of the dependency of dissolution rate on the changes in particle size or specific surface area during tablet compression. When particle bonding is the predominant factor during compression, the dissolution rate should decrease and when particle cleavage is predominant the dissolution rate would increase. Carless & Sheak (1976) showed by Coulter Counter analysis that attrition of the coarser fraction and agglomeration of the finer fraction occurred during the compression of sulphathiazole and stated that there was a critical size where the phenomena of bonding and crushing balanced each other. Kitamori & Makino (1979) showed that comparative measurement of dissolution of disintegrated tablets with that of granules can be used to elucidate whether particle bonding or cleavage occurred within the tablet during compression.

Higuchi et al (1953) and Armstrong & Griffiths (1970) measured the change in specific surface of the compacted granules by a nitrogen adsorption method. Cid & Jaminet (1971), Khan & Rhodes (1975) and Carless & Sheak (1976) studied the change in particle size distribution after disintegration of the tablets.

In the present investigation the relative change in the particle size of the drug during the compression process was assessed by comparing the dissolution rates of the drug particles before and after compression, since a change in the particle size of the drug will be reflected by a change in the dissolution rate. In order to eliminate the effect of different disintegration times, the tablets were disintegrated under standardized conditions before the dissolution test. In addition, other factors that could influence the particle size changes were studied, including polymorphism, compression pressure, drug content and rate of compression.

MATERIALS AND METHODS

Materials

Phenylbutazone crystal Form A (m.p. 105 °C, Berk Pharmaceuticals) and Form B (m.p. 103 °C) were used. The excipients used were Avicel PH-102 (Pfizer Ltd) and Lactose E.F. Crystals (Pfizer Ltd).

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STA-Rx 1500 (Colorcon Inc.) was used as disintegrant. The nomenclature of the polymorphs was that used by Tuladhar et al (1983).

Method of preparation of Form B

Phenylbutazone crystal Form B was prepared by dissolving 5 g of commercial phenylbutazone (Form A) in 100 cm^3 of n-heptane by heating in a water bath maintained at about 90 °C. The clear solution was then poured into a hot conical flask to avoid immediate crystallization. The solution was then evaporated under vacuum until the crystals were dry.

Preparation of particle size fractions

Both Form A and Form B are brittle needle-shaped crystals and could not be easily separated into different size fractions. Different size fractions of both crystal forms were therefore prepared by grinding previously compacted discs of the crystals and separating the different size fractions by dry sieving and air classification (Alpine zig-zag classifier). The mean particle size of the drug (Faxen's diameter) was obtained by microscopy when 200 particles were sized. The mean particle size of the size fractions of each crystal form is shown in Table 1. The crystal form was unchanged after the comminution process.

Table 1. Mean particle size of the crystal forms of phenylbutazone.

Crystal Form	Mean particle size (μm)						
A		369	226	137	91	42	6
B	652	387		146			6

Wet sieving method

Particle size analysis of the phenylbutazone tablets before and after compression was carried out by a wet sieving method based on the method of Ahmed (1977). Stainless steel wire mesh was cut into circular discs 55 mm in diameter and then mounted in 105 mm diameter funnels on nylon rings to achieve a rigid structure. Sylmaster epoxy putty was used to seal the mesh in place. The aperture diameters of the sieves covered the range 49·5 to 712 μm. After sieving, the weight of drug on the sieves was determined by washing the retained particles on to filter paper of known weight and drying in a vacuum oven at 50 °C to constant weight. The weight of drug that passed through the 49·2 μm mesh was determined by filtering the suspension through a 0·45 μm membrane filter and determining the dry weight retained on the filter.

Dissolution method

The dissolution rates of the original powder mix and disintegrated tablets were measured by a modification of the U.S.P. paddle method. A paddle (6·0 × 1·7 cm) was used to agitate the dissolution medium (37 °C) at 100 rev min^{-1}. The dissolution medium was 500 cm^3 0·2 M aqueous phosphate buffer, ph 7·5. The drug concentration in the solution was measured by taking a sample of 5 cm^3 every 5 min. After filtering through a 0·45 μm membrane filter the absorbance at 264 nm was measured after suitable dilution with buffer solution.

Procedures

Avicel and lactose were used as direct compression excipients together with 10% STA-Rx as disintegrant and batches of tablets containing 10 and 60% drug were prepared in each case. Tablets were compressed without lubricant at three pressure levels 48·1, 102·9 and 157·7 MNm^{-2}. An instrumented Lehman single punch tablet machine fitted with 12·0 mm die and flat faced punches was used.

In order to eliminate the effect of different disintegration times on the dissolution rates, tablets were first disintegrated in 3 cm^3 of dissolution medium. The use of an ultrasonic bath to disintegrate the tablets was not suitable owing to heating effects and the final method adopted was to standardize the disintegration time by shaking one or two tablets with 3 cm^3 of dissolution medium at 20 °C for a fixed time before adding to the dissolution medium at time zero. With the fine particle size fraction a disintegration time of 1 h was necessary. This method was found to give good reproducibility. To measure the dissolution rate of the original powder mix, it was first mixed with 3 cm^3 of the dissolution medium for the same time as that required for the tablet to disintegrate.

Respective amounts of samples corresponding to 100 mg of the drug were used in the dissolution studies for each of the original powder mix and disintegrated tablets. Each dissolution test was repeated three times and the mean time for 80 per cent dissolution ($T_{80\%}$) was determined.

Particle size analysis of the phenylbutazone tablets before and after compression was carried out by the wet sieving method using a sample of tablets (approximately 1 g), which were disintegrated in 15 cm^3 of saturated solution of phenylbutazone in 0·2 M phosphate buffer pH 7·5. For the original powder mix 1 g of sample was used. The particles collected in each sieve were washed with saturated phenylbutazone solution. Particle size analysis of

Avicel PH-102 and STA-Rx mix (3:1) before and after compression was also carried out.

To study the effect of rate of compression, tablets of phenylbutazone Form A and Form B each containing 10% drug, 10% STA-Rx 1500 and 30% Avicel PH-102 or 30% Lactose EF crystals were compressed at contact times of 0·26 and 29 s. No lubricants were used. The different particle sizes used were 369, 137, 42 and 6 μm for Form A and 652, 387, 146 and 6 μm for Form B. An instrumented single punch tablet machine was used to compress the tablets at a contact time of 29 s, but a compaction simulator (Wellcome Foundation, Dartford, Kent) was used to compress the tablets at a contact time of 0·26 s. The compression pressure used was 104 ± 2 MNm^{-2}. The dissolution test was carried out as described previously.

RESULTS AND DISCUSSION

Effect of initial particle size of phenylbutazone

Fig. 1 shows the change in dissolution rate of disintegrated tablets of phenylbutazone Form A with particle size and compression pressure. The particle sizes used were 6, 42, 91, 137 and 369 μm. The time necessary for 80% dissolution was employed to represent each dissolution rate.

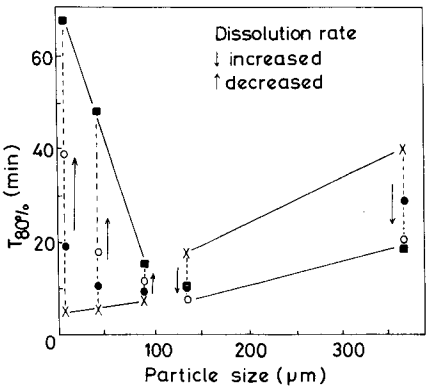

FIG. 1. Change in dissolution rate of disintegrated tablets of phenylbutazone Form A (60% drug, 30% Avicel, 10% STA-Rx) with particle size and compression pressure. X: original powder mix. ●: 48 MNm^{-2}. ○: 103 MNm^{-2}. ■: 148 MNm^{-2}.

From Fig. 1 it can be seen that with 6, 42 and 91 μm particles, an increase in compression pressure produced an increase in $T_{80\%}$. This reduced rate of dissolution suggests that these particles were bonding together during compression. However, with the 137 μm and 369 μm particles an increase in dissolution rate occurred with increase in pressure, which suggests that the predominant phenomenon in these cases was crushing of the drug particles.

The assumption that changes in the dissolution rate of the drug are related to the changes in particle size of the drug during the compression process was confirmed by particle size analysis of the disintegrated tablets of phenylbutazone by the wet sieving method (Fig. 2). The histogram was constructed from the cumulative size distribution curve. The particles analysed include drug and excipient but in a control experiment using tablets of Avicel and STA-Rx mix (3:1), the maximum particle size after disintegration did not exceed 350 μm (Fig. 3). It shows that the reduction in particle size (Fig. 2a) in the range of 350–450 μm must be due to the crushing of the phenylbutazone. In order to verify that the 350–450 μm fraction was phenylbutazone and not agglomerates of phenylbutazone with excipient, the fractions were assayed and found to contain 98% phenylbutazone. The particle size of

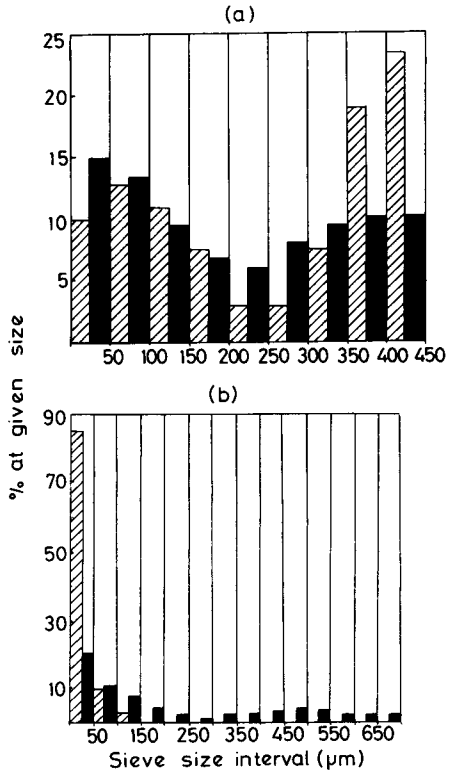

FIG. 2. Size distribution histograms (wet sieving) of disintegrated tablets of phenylbutazone Form A (60% drug, 30% Avicel, 10% STA-Rx). Cross hatched columns: Before compression. Solid columns: After compression (158 MNm^{-2}). (a) Tablets containing 369 μm particles of phenylbutazone. (b) Tablets containing 6 μm particles of phenylbutazone.

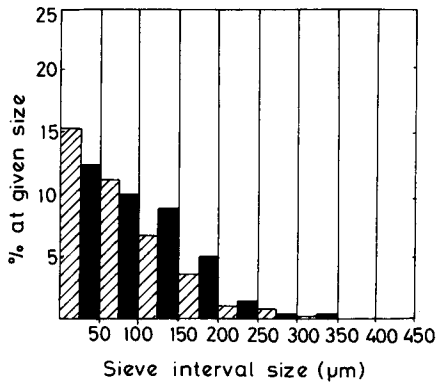

FIG. 3. Size distribution histograms (wet sieving) of Avicel PH-102 and STA-Rx 1500 mix (3:1). Cross-hatched columns, before compression. Solid columns: after compression (158 MNm^{-2}).

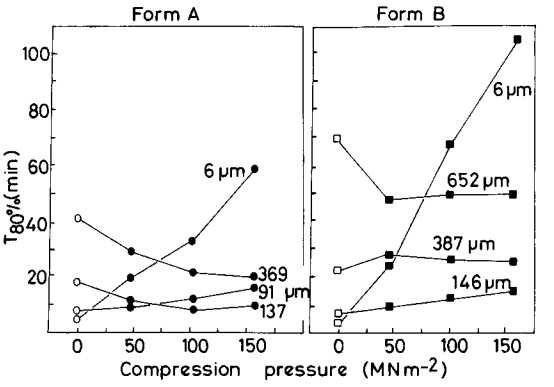

FIG. 4. Change in dissolution rate of disintegrated tablets of phenylbutazone (60% drug, 30% Avicel, 10% STA-Rx) with particle size, compression pressure and crystal form. Tablets: Form A: ●; Form B: ■; uncompressed powder mix: Form A: ○; Form B: □.

disintegrated tablets made with 6 μm particles of phenylbutazone is shown in Fig. 2b, where it is seen that there is a large reduction in small particles after compaction and a corresponding increase in larger particles. By reference to the compacted excipient tablets (Fig. 3), it is concluded that the 6 μm drug particles have undergone considerable bonding and formed larger particles. Assay of the fractions above 350 μm showed these to be 98% phenylbutazone.

Effect of crystal form

The effect of initial particle size of Forms A and B on the dissolution of the compressed tablets is shown in Fig. 4. The composition of the tablets was 60% drug, 30% Avicel, 10% STA-Rx.

The important features shown in Fig. 4 are:

(i) Form B, 6 μm particles bond to a greater extent than those of Form A under compression.
(ii) Only the largest particles of Form B studied (652 μm) showed evidence of crushing during compression.
(iii) The critical particle size where bonding and crushing balance each other is between 91 and 137 μm for Form A and between 387 and 652 μm for Form B.

The difference in the critical particle size of the two crystal forms reflects distinct differences in the physical characteristics of the two solid phases. Summers et al (1976) have shown that crystal forms of weaker bond strength undergo extensive plastic flow and bonding during compression and in effect can be considered as being more ductile or softer than the more strongly bonded forms. The difference in plasticity of Form A and Form B is shown by the study of surface hardness of the pure drug compacted at 157 MN m^{-2} using a pneumatic micro-indentation apparatus (Research Equipment Ltd., London). The study showed the Brinell hardness number of Form B (3·63 MNm^{-2}) is considerably less than that of Form A (6·67 MN m^{-2}). The low value of Form B indicates its ease of deformation or relative softness compared with Form A.

Effect of excipients

To investigate the effect of the excipients, Avicel PH-102 and Lactose EF crystals were used as diluents. Fig. 5 shows the dissolution rates of Form B from disintegrated tablets containing Avicel and lactose. There is little difference in the dissolution rates for the two formulations containing 652 and 146 μm particles. However, with the 6 μm particles mixed with Avicel, much greater bonding occurs compared with lactose as the excipient.

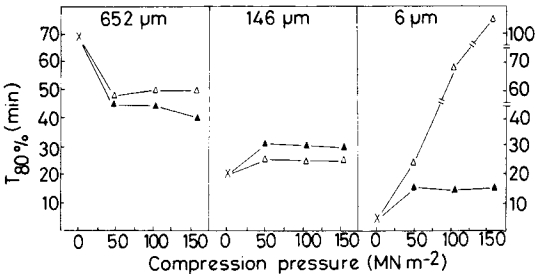

FIG. 5. Effect of excipient on dissolution of phenylbutazone tablets (Form B polymorph). X: uncompressed powder mix. △ 60% drug, 30% Avicel, 10% STA-Rx. ▲ 60% drug, 30% lactose, 10% STA-Rx.

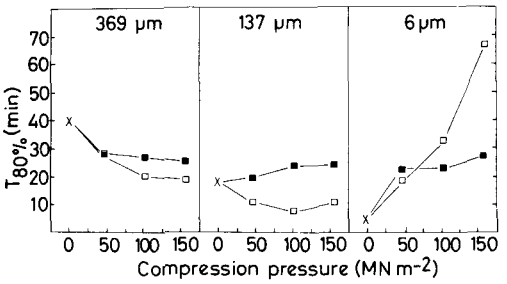

FIG. 6. Effect of excipient on dissolution of phenylbutazone tablets (Form A polymorph). X: uncompressed powder mix. □ 60% drug, 30% Avicel, 10% STA-Rx. ■ 60% drug, 30% lactose, 10% STA-Rx.

With Form A (Fig. 6) there is an interesting result with 137 μm particles of drug. When lactose was used as a diluent, the dissolution rate showed a slight decrease after compression, whereas with Avicel, an increase in dissolution rate occurred. Lactose has therefore effectively increased the critical particle size because these particles are now showing bonding rather than crushing. As these particles are now behaving like the smaller particles when Avicel was used as diluent, the effect of lactose may be to break the drug particles. This could be due to lactose grinding Form A to produce smaller particles which extensively rebond but it has little effect on Form B which undergoes extensive flow and bonding irrespective of the nature of the excipient used. To follow this point further the surface hardness of the two excipients was measured by microindentation. The test showed that lactose (Brinell hardness number 4·81 MNm^{-2}) is harder than Avicel (Brinell hardness number 2·65 MNm^{-2}) and it could have greater abrasive action on the drug than Avicel.

Effect of drug/excipient ratio

The effect of drug content (Form A) on the dissolution rate was studied by using tablets containing 10 and 60% drug. Fig. 7 compares the results for 10 and 60% drug with Avicel. The result shows a net reduction in particle size when 10% drug is used for particles in the range 369–91 μm and no apparent bonding takes place until particles of 6 μm are used. The crushing observed with the large particles could be the result of them being forced into voids between the smaller excipient particles, while the relatively constant dissolution rate with 91 and 41 μm particles could be due to protective action when a large proportion of excipient prevents drug particles bonding together. Similar results were obtained with Form B and also when lactose was used as excipient.

These results show that when the drug content in the tablet formulation is high, there will be a greater tendency for drug particles to interact with each other during the compression process and the relative hardness and size of the excipient particles and drug particles are likely to influence the degree of attrition of the drug. In the formulations of low drug content the excipient will tend to protect the drug particles from bonding with each other.

There is an additional factor that should be included when interpreting the results of 6 μm particles in the 10% mixtures, which show decreased dissolution compared with the non-compressed powder mix (Fig. 7). Owing to the high cohesion of fine particles, there is a tendency for them to agglomerate and the individual particles may not be homogeneously dispersed. Compression of these agglomerates could lead to reduction in dissolution rate. The problem of agglomerate formation when

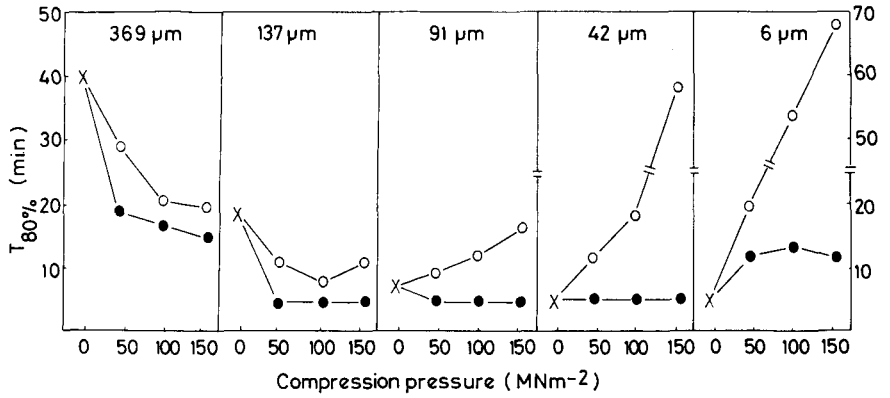

FIG. 7. Effect of drug/excipient ratio on dissolution of phenylbutazone tablets (Form A polymorph). X: uncompressed powder mix. ● 10% drug, 80% Avicel, 10% STA-Rx. ○ 60% drug, 30% Avicel, 10% STA-Rx.

micronized drugs are to be incorporated into tablets has been discussed by Orr & Sallam (1980).

Effect of rate of compression

Fig. 8 shows the dissolution rate of disintegrated tablets of Form A and Form B compressed at 0·26 and 29 s contact time. With 369 and 137 μm particles of Form A, an increase in rate of compression from 29 to 0·26 s contact time made little difference to the dissolution rate, which suggests that rate of compression has no effect on the crushing of these particles. However, with the 6 μm particles the increased rate of compression resulted in less bonding compared with the slow rate of compression. Similar results were obtained with both Avicel and lactose excipients.

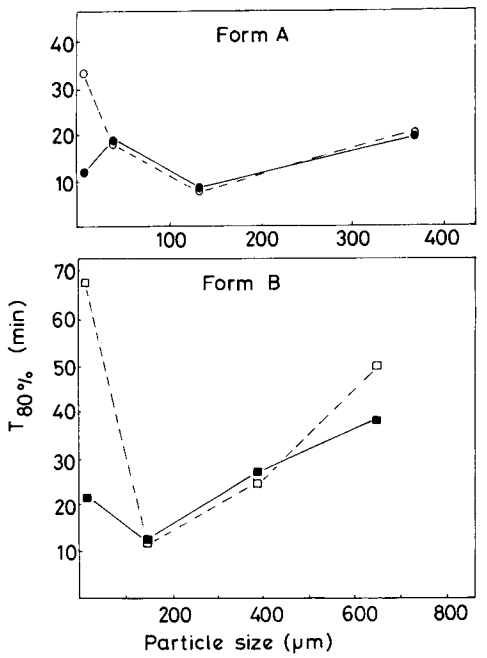

FIG. 8. Effect of rate of compression on dissolution of phenylbutazone tablets, Form A and Form B. —— 0·26 s contact time. - - - - - - 29 s contact time.

David & Augsburger (1977) and Rees & Rue (1978) have shown that the rate of compression affects the tablet strength of a plastic material to a greater extent than with the less plastic materials. Similarly in this study the dissolution rate of the more plastic crystal Form B increased by a greater extent than the less plastic crystal Form A as the contact time was reduced from 29 to 0·26 s. The increase in dissolution rate with 652 μm particles of Form B could be due to the increased rate of compression preventing bonding of particles that have been crushed.

The study shows that the effect of compression rate will be important for time-dependent materials where the degree of elastic/plastic flow will be influenced by the rate of application of stress. For instance, under high rates of compression, the elastic properties could predominate but at low rates of compression plastic flow could lead to increased bonding.

The change in particle size of the drug during the compression process may be affected by many variables other than those studied in this investigation, such as manufacturing process, i.e. wet granulation or direct compression, granulating agents, moisture content, lubricants, particle shape. Where the dissolution rate is affected by particle size, the present investigation shows that factors other than initial particle size need to be controlled in order to get a reproducible release rate of the drug. The nature and proportion of the excipients, the crystal form and the degree of compression may all influence the particle size in the final tablet and thus apparently minor changes in formulation and manufacture may have a significant influence on the efficacy of the product.

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