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PHYSICAL PROPERTIES OF GRANULES CONTAINING POLYSORBATE 80

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ABSTRACT

The friability and crushing load of granules containing polysorbate 80 were determined. It was found that while polysorbate 80 decreased granule hardness, as indicated by the load required to crush it, friability values increased to a maximum then decreasing at higher polysorbate 80 concentration. Thus the use of granule friability to measure granule strength may be erroneous unless good correlation between granule friability and direct crushing weight was obtained.

Direct measurement of granule strength tends to vary with granule shape and size giving a rather wide scatter of results. For overcoming this difficulty, tablet triturates could be prepared and the crushing strength determined. The crushing strength of the tablet triturates was found to be similar to that of granules but with a smaller scatter and more easily handled.

Studies of other physical properties of the granules containing polysorbate 80 were also made. Small amounts of the nonionic surfactant (0.002 - 0.2%) generally improved granule fluidity as characterised by the orifice flow velocity and the angle of repose of the granules.

INTRODUCTION

Characterisation of physical properties of granules is useful for evaluating the suitability of the granules for tabletting. Among the various properties, the abrasion resistance, granule strength and flow properties are important to ensure the integrity of the granules during processing and the smooth flow of granules during tabletting.

Direct measurement of granule strength using various methods had been carried out (1-5). These methods range from simple crushing of the granules with a spatula (2) to more complex instrumented method (4). The results obtained based on the crushing loads generally have a rather wide scatter and this could be attributed to the differences in size and shape of individual granules.

Faced with this and the tedium of using the direct measurement of individual granule strength by the crushing load methods requiring large sample size, several investigators had proposed using granule friability as an index for evaluating granule strength or hardness (6-10). Only Hunter (8) showed the correlation between directly measured crushing strength and the granule friability obtained. Others had assumed this correlation.

The determination of granule friability or abrasion resistance had evolved from shaking or tumbling of the granules in a closed container to the use of attrition or milling agents within the container. Friability after undergoing abrasion was first analysed using a single sieve. Later multiple sieves analysis was employed.

This paper reports the investigations into the effect of a nonionic surfactant, polysorbate 80 on the friability of sulphanilamide granules containing starch and varying amounts of polysorbate 80 and compares the granule friability findings with direct crushing strength. Other physical tests for assessing granules were also done.

EXPERIMENTAL

Materials - Sulphanilamide (A/S Syntetic, Denmark) and starch (Corn Brand, Holland) were used. Polysorbate 80 (Tween 80, Honeywill-Atlas Ltd., Division of ICI, England) was of commercial grade.

Preparation of Granules

The granules were prepared by moistening with water a well mixed sulphanilamide and starch mass and granulating through sieve 1.0 mm then dried for 4 hours at 60°C. The dried material was regranulated through the same sieve and the granules retained by sieve 420 um were used. For crushing strength measurements, the granules retained by sieve 710 um were used. Where polysorbate 80 was used, the surfactant was incorporated with a fixed volume of granulating fluid, water.

Preparation of Tablet Triturates

Tablet triturates were prepared using some of the moistened material used for preparing granules to fill the tablet moulds. The moulded mass was removed from the mould then dried for 4 hours at 60°C. The tablet triturates have a mean diameter of 5.8 mm.

Characterisation of Granules

(a) Sieve analysis. Sieve analysis was carried out using a nest of Endecotts test sieves (.710, .600, .425, .355, .250, .150, .106 mm) on an Inclyno test sieve shaker (Pascall Engineering Ltd., England) and vibrated for 2.5 minutes. The fraction retained on each sieve and the base receiver was weighed. A short sieve shaker vibration time was chosen to avoid sieve shaker-induced fragmentation of the very friable granule batches.

(b) Granule friability. A Roche friabilator (Erweka, Type TA3-R) was used. 10 g of granules were tumbled for 4 minutes with and without attrition agents. The attrition agents were added with the granules in the friabilator. The attrition agents used were twenty-five plastic beads (diameter 5.9 mm weighing 110 mg), small steel balls (3.96 mm, 254 mg) or large steel balls (6.35 mm, 1.042 g). The granule friability was determined by sieve analysis.

(c) Repose angle. The angle of repose was obtained by the method of fixed funnel and free standing cone as described by Train (11). The repose angle was an average of five readings.

(d) Orifice flow. Orifice flow time was obtained using the granulate flow tester (Erweka, Type GDT-E). 50 ml of granules was weighed and used. The readings were triplicated and averaged. From the average flow time, the granule flow velocity was calculated by dividing the weight of granules used with the orifice flow time.

(e) Bulk density. The bulk density of the granules was determined using a 50 ml specific density flask. The granules were poured in a steady stream into the flask till overflowing. The flask was then tapped gently, levelled and weighed.

Bulk density was taken as the quotient of the weight of granules and the flask volume. The determinations were duplicated.

Determination of CrushingLoad

Crushing load was obtained by placing the granule or tablet triturate on the end of a rod, held vertically, and crushing it using an incremental load of water introduced into a light container placed over the granule or tablet triturate. The weight of container and water required to crush the granule or tablet triturate was taken as the crushing load. For granules, the average crushing load derived from twenty-five 0.71-1 mm size fraction granules was used. For tablet triturates, the mean of ten crushing load determinations was used.

RESULTS AND DISCUSSION

Sulphanilamide granule formulations containing varying concentrations of polysorbate 80, a nonionic surfactant were prepared according to the formula in Table 1.

TABLE 1. Formula of Granulations

Batch	B1	B2	B3	B4	B5
Excipient			Proportion		
Sulphanilamide	100	100	100	100	100
Starch	10	10	10	10	10
Polysorbate 80	0	0.002	0.02	0.2	2

The particle size distribution of the various granulations was analysed and plotted as cumulative % oversize against log sieve aperture size (Fig. 1). Except for the formulation B3 containing 0.02% polysorbate 80, the particle size distributions of B1, B2, B4 and B5 did not differ very much. B3 appeared to be in a lower size range indicating a more severe fragmentation during regranulation and possibly during sieve analysis. These granules are also likely to be more friable.

The results of the sieve analysis of the granules after abrasion in a

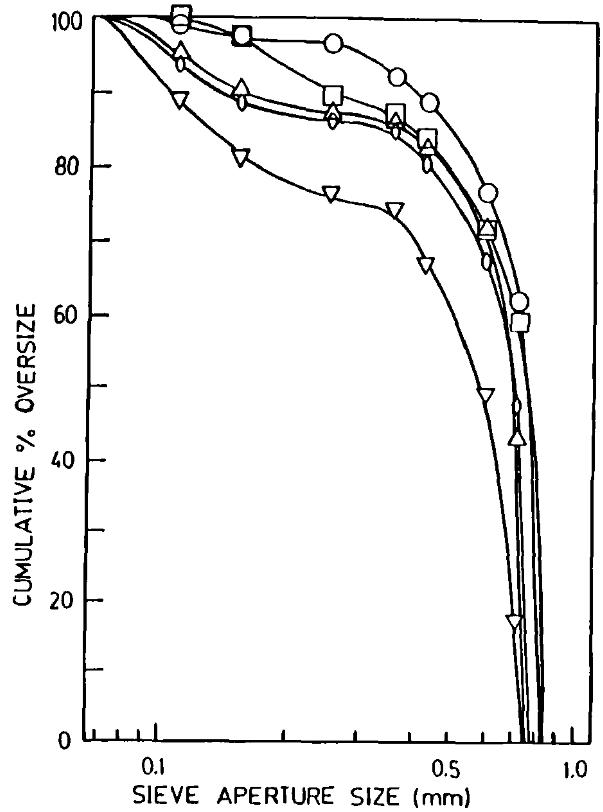

FIGURE 1

The cumulative weight percent oversize graphs for sulphanilamide granules used. Key: ○, B1; △, B2; ▽, B3; (), B4; □, B5.

friabilator with and without plastic beads is shown in Fig. 2. It was noted that the friability test carried with and without beads as attrition agents showed identical pattern of results although the results differed quantitatively. Inclusion of the beads appeared only to help reduce friability testing time.

Using the friability index suggested by Rubinstein and Musikabhumma (9), a minimun value was noted at around 0.02% polysorbate 80 (Fig. 3). The friability index is the quotient, expressed as percentage, of the mass median diameter after friability test and that before the test. Although the friability index provided a method to compare friability, it does not adequately examine the friability of the whole granule size distribution. Wells and Walker (10) used the log-probit

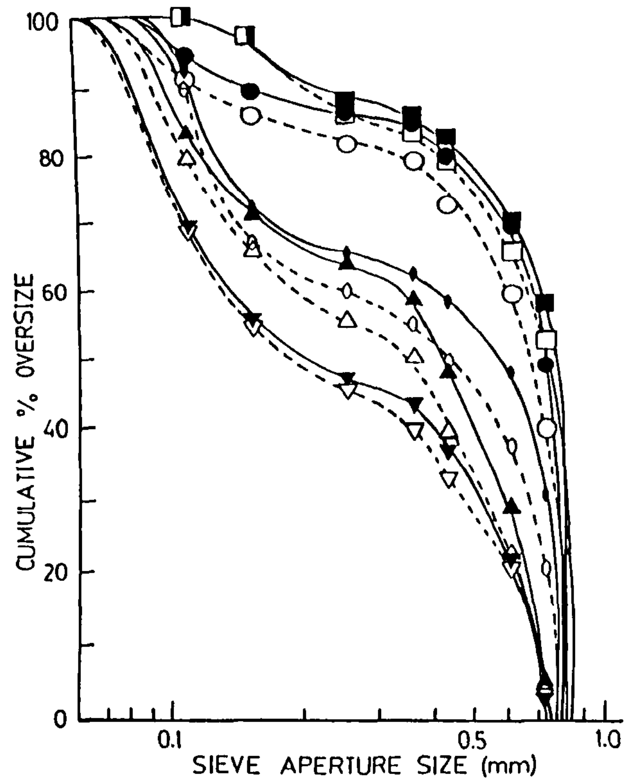

FIGURE 2

The cumulative weight percent oversize graphs for granules after friability test with (open symbols) and without (closed symbols) plastic beads.

Key: ○ ●, B1; △ ▲, B2; ▽ ▼, B3; () ●, B4; □ ■, B5.

analysis in an attempt to involve the total size distribution but the analysis requires rather idealised granule distribution for linear fitting.

A simple alternative to evaluate the degree of granule friability before and after friability test is by calculating the difference between the cumulative percent oversize before and after the friability test at a particular sieve aperture size and express this as a percentage of the cumulative percent oversize before the test. This percentage, denoted as the percent fragmentation, plotted against the sieve aperture size can give a better account of the overall granule friability (Fig. 4). The general inclination of the plot would indicate the

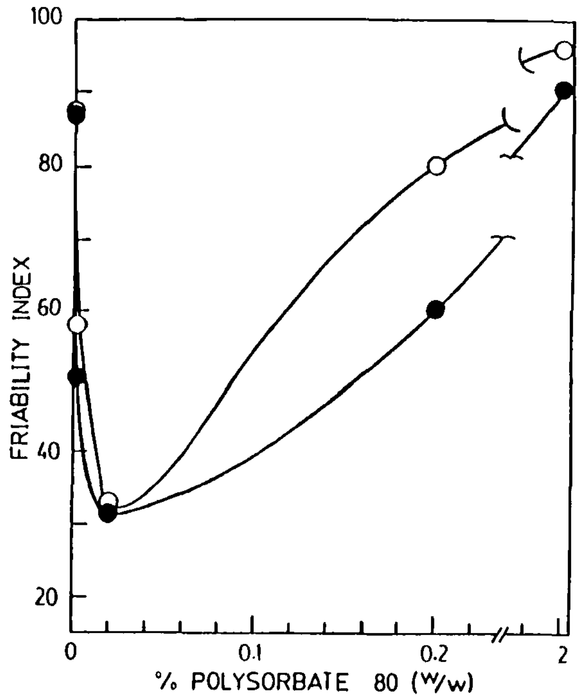

FIGURE 3

Friability index of granules containing varying concentrations of polysorbate 80. Key: Friability test with beads, ●; without beads, ○.

degree of granule fragmentation. It is interesting to note that although B3 containing 0.02% polysorbate 80 was found to be the most friable by the friability index (Fig. 3), the extent of fragmentation of the larger granules of B3 appeared to be less than that of B2 (Fig. 4). However, the relative degree of fragmentation into finer powders was greater with B3 as the percent size change was greater on the smaller sieve aperture size.

Although the granules of B5 was found least friable (Fig. 3 and 4), it was noted that the granules with high surfactant content were rather soft by touch. Furthermore tablets prepared from such granules were very soft. It was imperative that the tensile strength of the granules be determined directly. The determination of crushing load of the granules was first done but several difficulties were encountered. The crushing load values of granules had a large

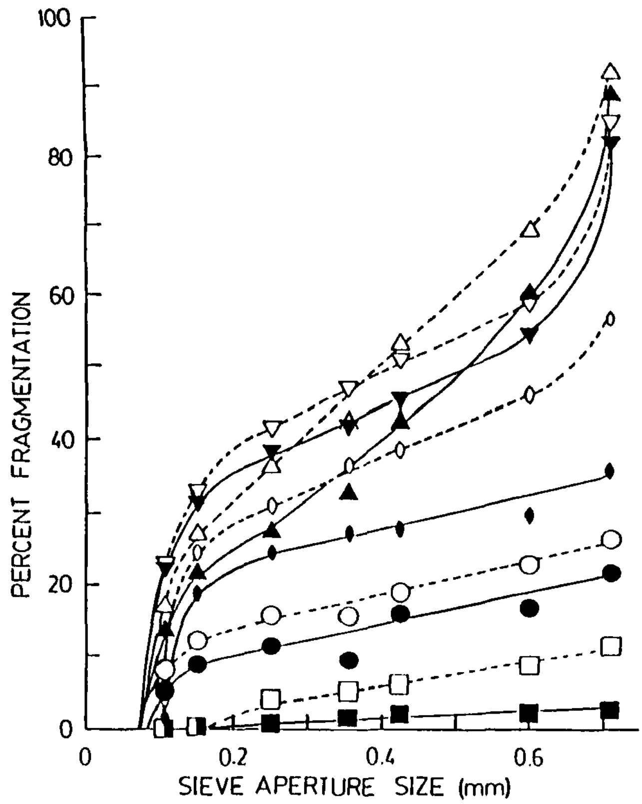

FIGURE 4

Plot of percentage fragmentation against sieve aperture size after friability test with (open symbols) and without (closed symbols) plastic beads.

Key: ○ ●, B1; △ ▲, B2; ▽ ▼, B3; ⬯ ⬮, B4; □ ■, B5.

scatter and depended on the granule size. Owing to the smallness of the granules, the point of granule crushing may sometimes be difficult to determine. For some soft granules, the granule may sag slowly under the stress of a load rather than instant crushing.

It was found that the crushing load of tablet triturates reflect closely to that of the granules but were devoid of much of the difficulties associated with the determination of the crushing load of granules. Comparison of the crushing loads of granules and tablet triturates are shown in Table 2. From Table 3 it can be seen increased surfactant content in tablet triturates reduced tablet strength

TABLE 2

Comparison of the Mean Crushing Load of Granules and Tablet Triturates

	Crushing Load (g)	S.E.[a]	No.[b]	Ratio[c] (B1/B5)
Granules (0.71-1.0 mm Fraction)				
i) B1	15.88	0.38	25	3.46
ii) B5	4.59	0.32	25	
Tablet Triturates				
i) B1	301.47	0.23	10	3.52
ii) B5	85.75	0.18	10	

[a]Standard error = standard deviation/mean;

[b]Number of determinations;

[c]Ratio of the mean crushing loads.

TABLE 3

Mean Weights and Crushing Loads of Tablet Triturates

Batch	Polysorbate 80 Content (%, w/w)	Tablet Weight[a] (mg) ± S.D.[c]	Crushing Load[b] (g) ± S.D.[c]
B1	0	73.1 ± 4.8	301.47 ± 68.92
B2	0.002	73.2 ± 4.2	286.16 ± 75.93
B3	0.02	70.8 ± 3.3	107.25 ± 18.59
B4	0.2	75.8 ± 2.7	103.69 ± 15.36
B5	2	82.3 ± 2.7	85.75 ± 15.04

[a]Mean weight of 10 tablet triturates;

[b]Mean crushing load of 10 determinations;

[c]Standard deviation.

as measured by the crushing load. The reduction was more marked at low surfactant concentrations. Granule strength can also be expected to be likewise. These findings showed a marked contrast between granule strength and granule friability. While B5 granules are the least friable (Fig. 3), they have been shown to be the softest. It is imperative that the use of granule friability to evaluate granule strength warrant further investigation. As such, unless the two parameters are correlated, care should be exercised when extrapolating granule friability to granule strength.

The mean weight of tablet triturates increased with the surfactant content with the exception of B3 (Table 3). The B3 tablets were found to be most friable by touch and having rounded edges indicating some degree of fragmentation after preparation. This had contributed to its lower mean weight.

Attempts were made to increase the severity of the friability test by using steel balls, diameters 3.96 and 6.35 mm, as attrition agents. Using B1 and B5 granules, it was found that in all cases, B1 granules were more friable (Fig. 5) although B5 granules were much softer (Table 2). It is apparent that granules with high polysorbate 80 content have a significant degree of plasticity. It is also interesting to note in Fig. 5 that for all the plots of percent fragmentation against sieve aperture size of the same granulation, the lines converge to a point on the x-axis. The value of this point for B1 is about 57 microns and for B5, 98 microns. These values can represent the size of the smallest particles present. The larger value obtained for B5 could be due to the stickiness of the very fine particles of B5 tending to aggregate forming larger particles.

Studies of other physical parameters of the sulphanilamide granules containing varying concentration of polysorbate 80 were also done. The bulk density, angle of repose and orifice flow velocity of the formulations were determined (Fig. 6). Lubricative properties of nonionic surfactants on sulphanilamide granules containing starch had been investigated (11-12). Duchene et al., (12) found that the nonionic surfactants including polysorbate 80 generally improved granule flow velocity. The angle of repose was however generally higher than that of similar granules without surfactant. The surfactant concentration used was 4%. Bulk densities were generally reduced in the presence of 1% and 4% nonionic surfactants.

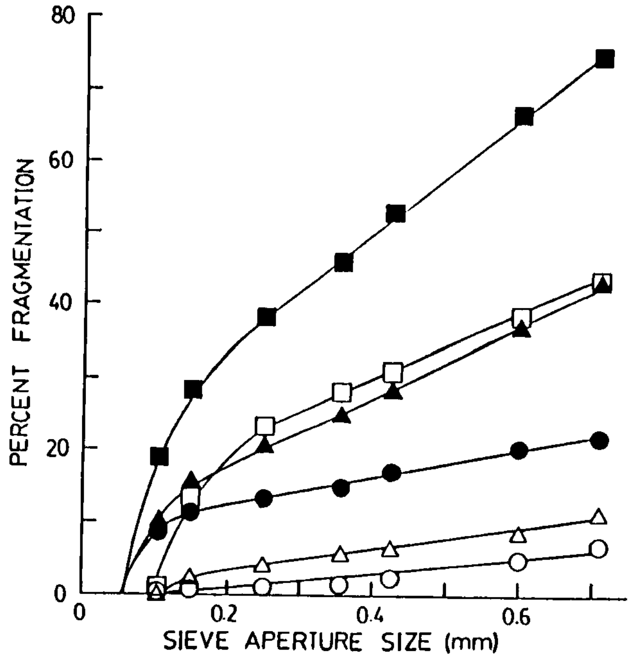

FIGURE 5

Effect of using steel balls as attrition agents in granule friability testing. Key: Open symbols = B5 granules; closed symbols = B1 granules. ○ ●, no attrition agent; △ ▲, small steel balls (3.96 mm); □ ■, large steel balls (6.35 mm). Sieve analysis time = 5 min.

In this study, increasing polysorbate 80 content in the granules increased the bulk density of the granules. The bulk density increase levelled off with higher surfactant content. Since the granules, except B3, had essentially similar size distribution, the increased bulk density of the granules can only be attributed to the denser packing of the granules. Denser material packing in tablet triturates containing surfactant could also account for the increased mean tablet weight with the surfactant content (Table 3)

The presence of surfactant in the moistening liquid during wet granulation had helped to lubricate the wet massing and screening processes allowing greater slippage of particles and thus forming denser granules by enabling tight packing. However at very low polysorbate 80 concentration (0.002%; Fig. 6), bulk density showed a decrease. It is likely that with low polysorbate 80 content, the

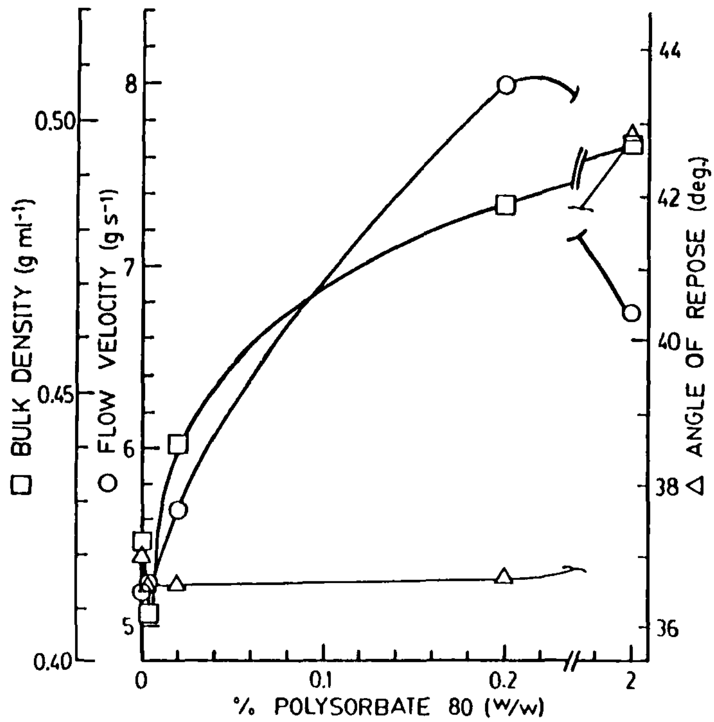

FIGURE 6

Some physical properties of granules containing varying concentrations of polysorbate 80.

surfactant was inadequate to promote significantly particle slippage during the wet massing process but had eased screening, producing granules with lower bulk density.

The angle of repose is commonly used as a parameter for evaluating interparticulate forces of powders and granules. Large angle of repose angle often indicate significant cohesive and frictional forces. Fig. 6 showed the effect of varying concentration of polysorbate 80 on the angle of repose of sulphanilamide granules. The plot of the angle of repose against surfactant concentration produced a minimum at low polysorbate 80 concentrations. High (2%) polysorbate 80 content in the granules appeared to impart a degree of tackiness to the granules producing a large angle of repose.

From the orifice flow velocity of the various formulations, the inclusion of polysorbate 80 improved flow (Fig. 6). An optimum concentration around 0.2% polysorbate 80 was obtained. Reduced flow velocity with high polysorbate 80 was probably due to the increased tackiness of the granules as shown by its large angle of repose.

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