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# ROLE OF SURFACTANT ON DRUG RELEASE FROM TABLETS

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## ABSTRACT

The addition of a surfactant into a tablet formulation appears to be an attractive method to improve the drug release rate. The improved release rate is often associated with the effect of surfactant increasing the hydrophilicity of the dosage form thereby promoting drug dissolution. The findings of this investigation showed that the presence of surfactant influenced the tablet disintegration rate, producing a finer dispersion of disintegrated particles. It follows that the action of surfactant improving drug dissolution from tablets may be attributed to the action of surfactant producing fine disintegrated particles with correspondingly larger surface area for drug dissolution. It was also demonstrated that upon tablet disintegration the disintegrated particles have a tri-modal frequency distribution.

## INTRODUCTION

In the evaluation of compressed tablets, the disintegration time of tablets is the time for the complete passage of deaggregated particles through a mesh during the disintegration test, according to the official pharmacopoeia. The mesh size specified is rather large, usually about 1 mm. Fineness of the disintegrated particles is not taken into consideration. Roland [1] had demonstrated the significance of the size of the disintegrated particles on the drug release rate. It was proposed that disintegrated particles may be grouped into three main categories: marcogranular, microgranular and micronised. In the studies on deaggregation of compressed tablets, Rubinstein et al. [2-3] determined the surface area of tablets generated through the process of disintegration and showed that the surface generated correlated with the dissolution rate.

Tablet formulations containing surfactant have been reported to produce tablets with good dissolution rate [4-6]. It was however, found that disintegration time does not necessary improve in the presence of a surfactant. Tablets containing starch as a disintegrant [4] showed prolonged disintegration in the presence of a surfactant although the dissolution rate was improved. The present paper reports the findings of the study on the role of surfactant in improving tablet dissolution.

## MATERIALS AND METHODS

**Materials** - Sulfanilamide and sulfaguanidine (B.P. grade) were used without purification. The surfactant, polyoxyethylene sorbitan monooleate (polysorbate 80, Honeywill-Atlas Ltd., I.C.I., England) and starch (maize, Corn Brand, Holland) were also included in the formulations.

**Preparation of Tablets** - Granules containing the drug and 5% starch were prepared by wet massing and screening through a 1.0 mm mesh sieve, oven dried at 60°C for 6h and regranulated through the same sieve. The surfactant, when used, was incorporated with the granulating fluid, water. The granules retained on a 0.375 mm mesh sieve were compressed (Model F3, Manesty, England) into tablets containing 250 mg drug and having a porosity of 0.13 ± 0.01.

**Evaluation of Tablets** - Tablet hardness was the mean of 10 determinations using an automated hardness tester (Erweka, Model TBH). Disintegration time (Pharma Test, PTZ 3) was determined according to the BP method. The disintegration time is defined as the time for all residue (from six tablets) to pass through the screen of the disintegration baskets. A mean of three determinations was taken as the disintegration time. The dissolution test was in distilled water at 31° ± 1°C using the rotating basket apparatus (Hanson Research Corp., 72RL Easi-lift) with a basket speed of 100 rpm. Progress of the dissolution was monitored continuously using flow cells in a spectrophotometer (LKB Ultrospec, 4052 TDS) controlled via a microcomputer (Apple II with LKB dissolution software). The results from five tablets were averaged.

**Determination of Particle Size of Disintegrated Tablet** - Immediately after tablet disintegration, the size distribution of the disintegrated particles can be very large. Larger particles tend to settle very rapidly. Any attempt to resuspend these particles require significant agitation which can be severe for the freshly disintegrated particles. Thus, two methods of size analysis were employed for the sizing of the disintegrated particles: wet sieving and Coulter Counter method (Coulter Electronics, TA II). (i) Sieving Method - Immediately after disintegration (40 s or slightly more for tablets with a longer disintegration time) as described above for six weighed tablets, the disintegration medium was poured onto a sieve. The weight gained by the sieve after oven drying for half an hour at 120°C, was taken as the weight of particles retained. Sieves of 250,

TABLE 1

Effect of Polysorbate 80 on the Hardness and Disintegration Time of Sulfanilamide and Sulfaguanidine Tablet Formulations.

| Formulation | Hardness (N) | Disintegration Time (s) |
|---|---|---|
| Sulfanilamide | | |
| + 5% starch only | 14.8 ± 4.4 | 29.6 |
| + 5% starch and 0.2% P80 | 12.3 ± 2.7 | 33.6 |
| Sulfaguanidine | | |
| + 5% starch only | 27.2 ± 4.6 | 37.0 |
| + 5% starch and 0.02% P80 | 24.3 ± 3.0 | 38.3 |
| + 5% starch and 0.2% P80 | 22.0 ± 3.2 | 44.0 |

150, 105 and 75 um mesh size were used. (ii) Coulter Counter Method - Disintegrated particles not retained by 75 um mesh sieve were sized using the Coulter Counter.

## RESULTS AND DISCUSSION

The effect of polysorbate 80 on hardness and disintegration of sulfanilamide and sulfaguanidine tablets containing 5% starch are given in Table 1. Tablets containing the surfactant showed reduced hardness but had prolonged disintegration times. Polysorbate 80 had been reported previously to reduce the disintegration efficiency of starch [4].

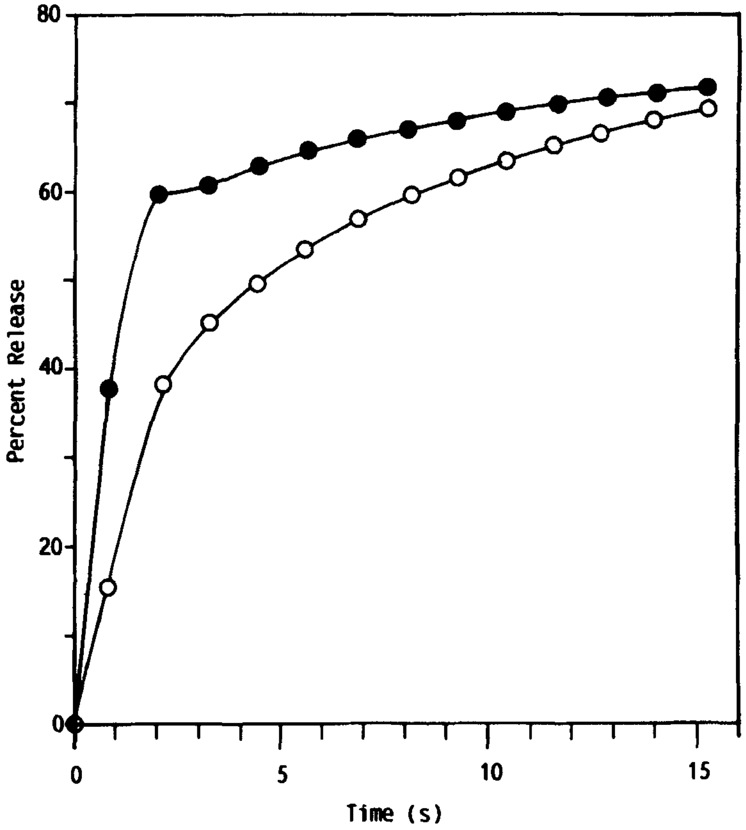

FIGURE 1
Dissolution profiles of sulfaguanidine tablets containing 5% starch (open circles) and corresponding tablets containing 0.2% polysorbate 80 (closed circles).

Despite the prolonged disintegration time of tablets containing starch and surfactant, the dissolution rates of these tablets (containing 0.2% polysorbate 80) were faster than that from similar tablets without polysorbate 80 (Fig. 1). In other investigations into the role of surfactant in tablet formulations containing disintegrants such as microcrystalline cellulose and calcium sodium alginate, the presence of surfactant was also shown to produce improved dissolution rate [4-6].

From Figure 1, it can be seen that during the first minute, the dissolution rate for tablets containing polysorbate 80 was 45.6 % $s^{-1}$ whilst that for tablets without polysorbate 80 was 18.0 % $s^{-1}$. For dissolution from drug surfaces, considered as diffusion-controlled, the Noyes-Whitney equation [7] may be written as:

$$dm/dt = k.A.(S-C) \qquad (i)$$

where m is the amount of material that has dissolved from a solid, A is the surface area, S is the saturation solubility, C is the solute concentration and k is the rate constant per unit area. The rate constant, k for a particular drug is the quotient of the diffusion coefficient, D, divided by the thickness of the diffusion layer, h. In the initial stages,

$$S >> C; (S-C) \dashrightarrow S \text{ and thus } \quad dm/dt = k.A.S \qquad (ii)$$

Applying the modified Noyes-Whitney equation (ii) to the drug dissolution from a tablet in the dissolution apparatus, the high initial dissolution rate from the tablet containing surfactant (Fig. 1) must be attributed to either the effect of surfactant on the rate constant, k, or the surfactant effecting a large increase in the available surface, A, for drug dissolution. The saturation solubility, S, is likely to be almost constant, since the usual surfactant content of a tablet, when dissolved into the dissolution media, have negligible effect on S.

From the studies of drug release [4, 8], the inclusion of surfactant in tablets and granules containing sulfanilamide and no other excipient failed to elicit any significant enhancement in drug release. Thus, it is unlikely that the surfactant improves drug release *per se* although the wetting potential of the surfactant may act to increase the 'effective surface'[9] but the influence of this effect on the overall tablet dissolution is not likely to be dominant. In fact, from the studies on drug release from granules, the addition of surfactant [8] retarded drug release. Using a rotating disk method, Itai et al. [10] also demonstrated that the presence of the surfactant, polysorbate 80 beyond the critical micelle concentration in the dissolution media decreased the dissolution rate constant of flufenamic acid.

Thus it appears that the action of surfactant in promoting drug dissolution from tablets containing the surfactant is likely to be brought about by the action of the surfactant influencing the tablet disintegration process rather than the action of surfactant improving wettability per se. The most likely parameter affecting the dissolution rate is probably the area (A) generated for drug release upon tablet disintegration.

The surface area generated by a disintegrating tablet may be equated to the degree of fragmentation. Size analysis of the tablet particles upon disintegration can reflect the extent of new surface generated. It is however, difficult to obtain the exact size distribution of the disintegrated particles due to the instability and transient nature of the intermediate particles. The particles are likely to be very fragile. For large particles, they rapidly settle and are not available for size analysis using methods such as techniques employing the transfer of particles through an aperture. Thus, a combination of two methods, wet sieving for large particles and Coulter Counter sizing for the smaller particles is more appropriate.

Particle size distribution of disintegrated particles using sieve analysis for tablets with and without polysorbate 80 showed that

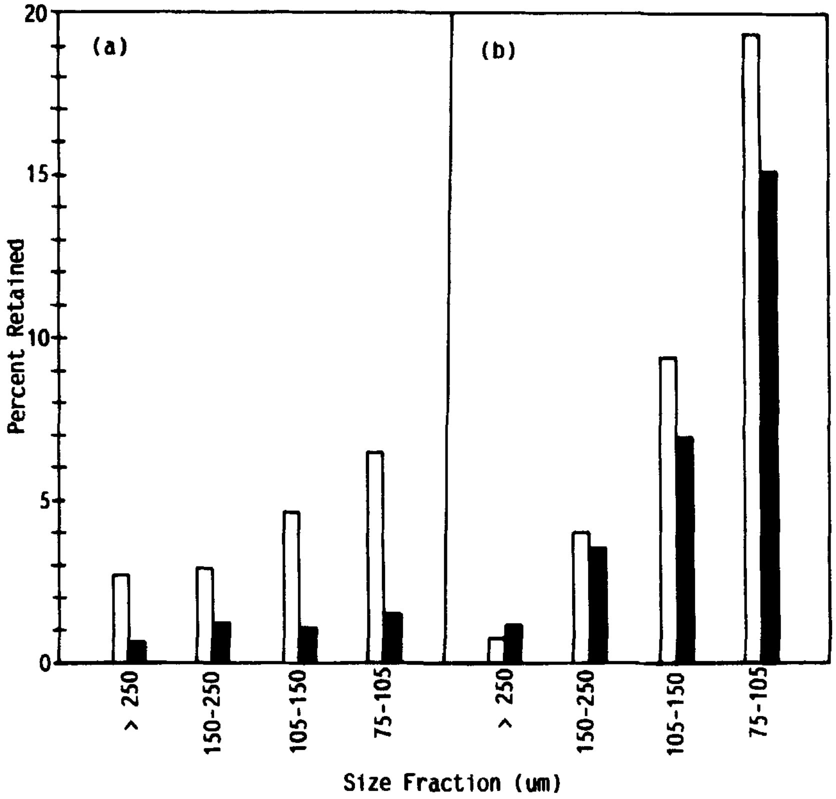

FIGURE 2
Size distributions of disintegrated particles from sulfanilamide (**a**) and sulfaguanidine (**b**) tablets without polysorbate 80 (clear) and with 0.2% polysorbate 80 (shaded) .

both sulfanilamide and sulfaguanidine tablets without polysorbate 80 produced coarser disintegrated particles than the tablets in which the surfactant had been incorporated (Fig. 2).

For a complete size distribution characterization, a composite plot of the size distributions obtained using sieve analysis for the large particles (greater than 75 microns) and the Coulter Counter for the finer particles, were obtained (Fig. 3a). It can

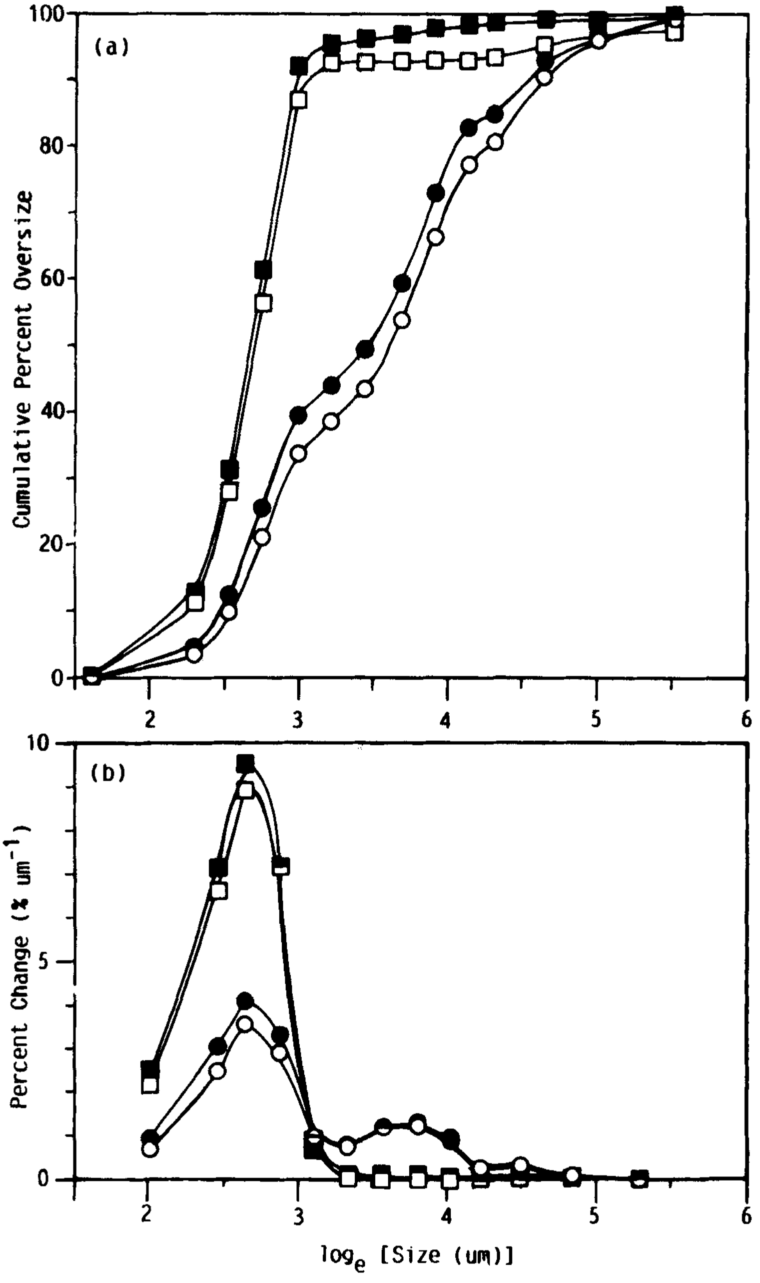

FIGURE 3
Cummulative size distributions (a) and frequency distributions (b) of disintegrated particles of sulfanilamide (squares) and sulfaguanidine (circles) without polysorbate 80 (open) and with 0.2% polysorbate 80 (closed) .

be seen that tablets containing polysorbate 80 produced a finer dispersion of disintegrated particles. If the frequency distribution of the disintegrated particles is plotted (Fig. 3b), the disintegrated particles of sulfaguanidine tablets produced a tri-modal distribution with class modes at approximately 14, 45 and 90 um, suggesting that the break-down of tablets takes the course of disintegrating first to granules then to finer aggregates and finally deaggregating to the original particulate state of the materials which have not dissolved. Since swollen starch grains have a mean size about 14 um, it is likely that the smallest particles are mainly the insoluble starch grains.

In the case of sulfanilamide tablets, only one distinct peak was obtained. The disintegration rate of the sulfanilamide tablets was extremely rapid. The disintegrated particles containing the more soluble sulfanilamide is likely to dissolve much faster. The tablets are also softer (Table 1).

The inclusion of the surfactant, polysorbate 80 in tablet formulations containing starch, had elicited faster drug dissolution rates despite the prolonged disintegration. From size analysis data of the disintegrated particles, it is evident that the ability of the surfactant to produce a finer dispersion of disintegrated particles had enabled an enhanced drug release rate. As a wetting agent, the surfactant may have a role in promoting drug release through improved wettability of the drug particles as suggested by many workers [11-12] but it had been shown that the improved wetting by surfactant does not necessary produce the expected enhancement in release [8]. Of greater importance is the size of the disintegrated particles.

The size of the disintegrated particles have a more significant influence on drug release rate from tablets. Where the excipient is able to produce finer dispersion of disintegrated particles, it follows that it would enhance drug release through the increased surface area for dissolution. Surfactant is often claimed to produce improved drug release through the well documented surfactant action of wetting, solubilization and even flocculation [13]. However, it appears from this investigation that the most likely effect of the surfactant in enhancing drug release is through the effect of the surfactant in altering the integrity of the tablet. The reduced tablet integrity can be seen by the lower hardness values obtained in the presence of surfactant (Table 1). Tablets containing surfactant are known to be softer than similar tablets without surfactant but compressed to the same pressure or porosity. As the tablets containing surfactant are softer due to reduced interparticulate bonding [14], the disintegrated particles from such tablets are likely to be of a smaller size.

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