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BATCH VARIATION OF MAGNESIUM STEARATE AND ITS EFFECT ON THE DISSOLUTION RATE OF SALICYLIC ACID FROM SOLID DOSAGE FORMS.

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ABSTRACT

The effects of different batches of magnesium stearate on the release of salicylic acid from capsules and from a compacted formulation have been investigated. The results indicate that retardation of salicylic acid release becomes independent of the particle size of magnesium stearate when the blending of the two substances prior to encapsulation or compaction is prolonged for a sufficient time.

Variation in the release rates observed after prolonged blending times have been shown to exhibit a rank order correlation with the different hydrophobicities of the batches of magnesium stearate as indicated by the results of contact angle measurements on drops of dissolution medium on compacts of this lubricant.

Determination of the surface tension of an aqueous extract of each batch of lubricant has indicated that water-soluble, surface-active impurities may be responsible for this apparent variation in the degree of hydrophobicity and hence for the change in the release rate of salicylic acid from solid dosage forms when they are manufactured with different batches of magnesium stearate.

INTRODUCTION

Magnesium stearate is frequently used as a boundary lubricant in both tablet and capsule formulations in order to reduce friction between the tablet and die wall surfaces during compression and ejection[1] or between the powder plug and dosator nozzle surfaces during capsule manufacture[2]. The term 'lubricant' can also be used to describe a material with glidant or anti-adherent properties and magnesium stearate has been shown, under certain conditions, to exhibit both of these characteristics[3,4].

It is well documented that the hydrophobic nature of magnesium stearate will cause an increase in disintegration time of both tablets and capsules[5] and will also inhibit dissolution of active agent from these dosage forms[6]. Much work has been concerned with elucidation of the effects of different concentrations of magnesium stearate on the uptake of dissolution medium into a solid dosage form and the subsequent release of drugs from these products[7,8,9,10]. Bolhuis et al.[11] have also shown that as the time taken for the blending of lubricant with granules is increased, so the dissolution rate of a drug from the subsequently compressed tablets falls.

However, personal communications from industrial pharmacists have indicated that samples of magnesium stearate from different batches produce these effects on dissolution rate to different and unpredictable degrees even when using standard blending times and methods at constant concentrations.

These observations are perhaps not surprising as some workers have shown that batch variation with respect to both chemical and physical properties does exist. For example Pilpel[12] has shown that magnesium stearate is not a pure compound. The stearic acid from which it is manufactured invariably contains about 10% of other long chain fatty acids in particular palmitate, myristate, oleate and linoleate. Butcher and Jones[13] have demonstrated marked physical dissimilarities between batches of magnesium stearate and Hanssen et al.[14] have shown that batch variation can affect the compression behaviour of certain pharmaceutical bulk solids. Muller[15] has correlated the efficiency of magnesium stearate as a lubricant with its moisture content and demonstrated further[16] that different crystalline forms of the lubricant, produced by varying the method of manufacture, are responsible for the different hydrates and hence the lubricating efficiency. The purpose of this investigation was, therefore, to ascertain on a laboratory scale whether variations in dissolution rate of a standard formulation occurred with different batches of magnesium stearate as lubricant and to determine possible causes.

MATERIALS

Salicylic Acid B.P. (powdered), batch number 7E 5243, was obtained from Evans Medical Ltd., Speke, Liverpool. Samples were passed in a standard manner through a 180 µm sieve before use.

Eight batches of magnesium stearate were obtained in commercial quantities of not less than 15 kg from six suppliers within the U.K. Samples from each batch were taken from a point approximately 150 mm below the surface and in the centre of each container using a powder sampler. These samples were sieved as above and stored at a relative humidity of 52% at 25°C before use.

Lactose Ph.Eur., batch number 32, and Maize Starch Ph.Eur., batch number 27, were obtained from Charnwood Pharmaceuticals Ltd., Leicester.

Hard gelatin capsules were supplied by Parke Davis & Co., Hounslow, London.

METHODS

Particle Size Determination of Magnesium Stearate

The mass median diameter for each batch of lubricant was calculated from results obtained using a Coulter Counter, Model A equipped with a 140 µm aperture tube. The magnesium stearate was dispersed in isotonic saline containing 0.004% sodium lauryl sulphate. Samples were sonified immediately prior to counting and the results are shown in Table 2.

Dissolution of Salicylic Acid from Granules Lubricated with Magnesium Stearate

Using a standard wet granulation technique, 2 kg of granules were prepared according to the following formulation:

Salicylic Acid	800 g
Lactose	920 g
Maize Starch	240 g
Maize Starch as a 10% paste	400 g

After sieving, followed by drying overnight at 45°C, the granules were resieved and the 710-1000 μm fraction retained for use. Using a sample divider, 8 x 100 g quantities were collected and each blended with a 1 g sample from one of the batches of magnesium stearate using a small Y-cone blender at 50 rpm.

The choice of blending time was primarily based on the results of the following work. Bolhuis et al.[11] demonstrated that as mixing time between drug and lubricant progrssed, the magnesium stearate was sheared onto the drug particles forming a hydrophobic sheath which resisted penetration of dissolution fluid. This, therefore, reduced dissolution rate. Gunning and Stead[17] showed that during the blending of a 100 kg batch of granules with magnesium stearate for a typical time of 20 minutes, the degree of shearing of the lubricant onto the granule surface, as determined by dissolution rate measurements, could only be equalled on the laboratory scale after a mixing time of approximately 5 hours.

Presumably, once the hydrophobic sheath has been fully formed, any further mixing would not cause any further reduction in dissolution rate, in which case small variations in mixing time may not be significant when this stage is reached. A preliminary investigation into this possible effect was considered expedient at this stage using two of the batches of magnesium stearate having differing degrees of subdivision.

Two samples of lubricant designated batch numbers 4 and 5 and having mass median diameters of 13 and 7 µm respectively were each blended with the standard granule formulation as described above. Samples were taken at 5, 30, 60, 120, 240, 300 and 360 minute intervals during the process. From each of these samples, 200 mg aliquots were packed by hand into size 1 hard gelatin capsules and the dissolution rates determined using a method based on that described in the British Pharmacopoeia 1980[18] using a basket speed of 100 rpm and 900 cm^3 of hydrochloric acid (0.1 mole/dm^3) as the dissolution medium. The times for 50% dissolution ($t_{50\%}$) were determined and the mean values are shown in Table 1.

This initial experiment demonstrated that after 5 hours of blending no significant difference in dissolution rates between the two batches lubricated with coarse and finely divided material was apparent. In addition, any further blending in excess of approximately 4 hours did not significantly alter the dissolution rates. On the basis of these results and those of Gunning and Stead[17] a blending time of 5 hours was chosen for subsequent experiments. Each dissolution rate determination was carried out five times and the mean results are shown graphically in Figure 1a.

Dissolution of Salicylic Acid from Compacts of Salicylic Acid and Magnesium Stearate

In order to exaggerate the differences between batches of lubricant as demonstrated above and hence produce a more significant rank order for effect on dissolution rate, a 50:50 mix of salicylic acid/magnesium stearate from each batch was blended as before for 5 hours. Samples of 200 mg from each mix were compressed into compacts of diameter 10 mm and thickness 1.45 mm using a hydraulic press to 214 MPa at constant rate. Each dissolution rate determination was carried out three times and the mean results shown graphically in Figure 1b.

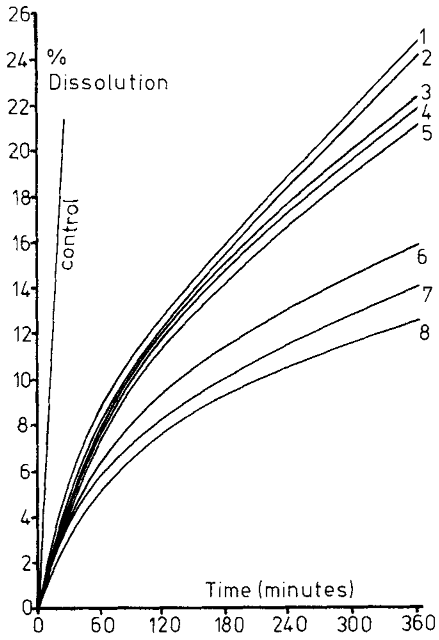

FIGURE 1a

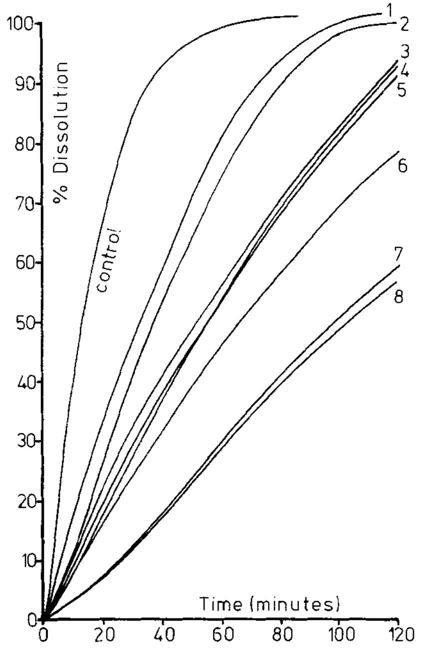

FIGURE 1b

Dissolution of Salicylic Acid against Time from (a) Granules lubricated with Magnesium Stearate and Packed into Hard Gelatin Capsules and (b) 200 mg Compacts of Salicylic Acid and Magnesium Stearate. The Numbers 1 to 8 Indicate the Batch Numbers of the Lubricant used for Each Formulation.

Determination of Contact Angles of Hydrochloric Acid (0.1 mole/dm^3) on Compacts of Magnesium Stearate

Each compact was manufactured by compressing 2 g of the lubricant to a diameter of 25.4 mm and approximate thickness 4.1 mm using a hard chrome faced punch and die assembly.

Compression was carried out at a constant rate to 33MPa. All compacts were stored at 100% relative humidity at 23°C prior to use. After much preliminary work it was decided that the most appropriate method for contact angle measurement was that based on the method of Kossen and Heertjes[19] as modified for pharmaceuticals by Lerk et al.[20]. The contact angles, as recorded in Table 2, were calculated from the maximum height at equilibrium of a drop of hydrochloric acid on the surface of the compact by means of the equation:

$$\text{Cos } \theta = -1\sqrt{(2 - Bh^2)\,\frac{2}{3(1 - \varepsilon)}}$$

Where θ is the contact angle,

h is the height of the drop of the liquid

ε is the porosity of the compact and

$$B = \frac{\rho_L g}{2\gamma_{LV}}$$

Where ρ_L is the density of the liquid

g is the acceleration due to gravity and

γ_{LV} is the liquid/vapour interfacial tension

The apparatus consisted of a modified bench scale humidity cabinet, the interior of which was painted matt black to reduce unwanted reflections. Two optical glass windows allowed the compact and droplet inside to be illuminated by an external mono-chromatic light source of 490 nm and a travelling microscope (ex Precision Tool and Instrument Co. Ltd.) to be used to monitor droplet height. The hydrochloric acid was introduced to the surface of the compact via silicone tubing and a hypodermic needle and transferred from an external source using a peristaltic

TABLE 1

Time of Blending (minutes)	$t_{50\%}$(minutes)	
	Batch 4	Batch 5
0	13.5	13.5
5	18.5	22.5
30	23.5	36.1
60	30.6	45.1
120	41.5	50.1
240	53	54.5
300	54	55
360	54	55

Effect of Blending Time on the Dissolution of Salicylic Acid from Granules using Two Batches of Magnesium Stearate of Different Particle Size.

pump. The interior of the cabinet was maintained at a relative humidity of 100% and a temperature of 23°C.

At six-second intervals 0.008 cm^3 of the acid were dropped onto the surface of the horizontal compact. When ten consecutive drops did not cause any further increase in height this maximum value was recorded. It was noticed, however, on continual monitoring, that the droplet height then fell steadily over a period ranging from 20 minutes to about 3 hours in the saturated atmosphere to a new equilibrium value, the values of which are recorded in Table 2.

The method used to determine particle density was based on B.S. 3482 using specific gravity bottles. The disperison medium used was absolute spectroscopic ethanol, the density of which was taken as 0.78506 g/cm^3 [21]. The ethanol was added under reduced pressure to ensure complete wetting. Five values were obtained for each batch of lubricant using a different specific gravity bottle each time. The porosity of the compacts was calculated using the mean of each set of results.

TABLE 2

Batch Number of Magnesium Stearate	Mass Median Diameter (μm)	Mean Contact Angle (Θ^o) at Equilibrium	Surface Tension of Water Soluble Extract (mN/m)
1	30	94.12	57.5
2	27	95.77	60.6
3	12	99.34	67.0
4	13	99.62	67.6
5	7	97.84	68.0
6	16	101.90	69.4
7	15	101.40	70.0
8	12	102.53	71.5

The surface tension of the hydrochloric acid was taken as 72.0 mN/m, this being the mean of 10 values as recorded using a torsion balance (ex White Industries Ltd.) at a temperature of 23°C.

Determination of the Surface Tension of Water Soluble Extractives of Magnesium Stearate

A 5 g sample was taken from each batch of lubricant and placed with 100 cm^3 of double distilled water in a 200 cm^3 capacity stoppered flask. Each container was mechanically shaken for six hours and then allowed to stand for a further eighteen hours. The suspension was then filtered through a Millipore filter of pore size 0.45 μm. After standing undisturbed for thirty minutes the surface tension of the filtrate was determined using a torsion balance at 23°C. Each value as recorded in Table 2 is the mean of ten determinations. This procedure was repeated for a 100 cm^3 sample of double-distilled water, but omitting the magnesium stearate. A value of 72.3 mN/m was recorded for the surface tension of this control.

RESULTS AND DISCUSSION

The results as shown above provide an indication of the effect of degree of subdivision of magnesium stearate and time of blending on the dissolution rate from a capsule formulation. They suggest that on this particular scale, blending time is not of critical importance after prolonged mixing. At this stage presumably most of the lubricant has been sheared onto the surface of the granules and there is, therefore, no further significant decrease in dissolution rate.

A further possibility indicated by these results is that the particle size of the lubricant is only of significance after short mixing times. A large total surface area of lubricant should impede penetration of dissolution medium to a greater extent than would a batch of material not so finely subdivided. Presumably the mechanism for this is similar to that outlined by Finholt et al.[22] who demonstrated a decrease in dissolution rate for a hydrophobic drug as particle size was reduced. He suggested that this was possibly due to air adsorption at the solid/liquid interface impeding the wetting process. After prolonged mixing, and possibly even after a high intensity/short mixing process, once the hydrophobic sheath has been formed it may be that the original physical form is lost and therefore differences in particle size of lubricant, as determined before use, become insignificant.

Comparison of the results given in Figures 1a and 1b shows a rank order of 1 to 8 for the effect of different batches of magnesium stearate on dissolution rate. The degree of significance for the results shown in Figure 1a can be summarised as 1:2>3:4:5>6>7:8 where the symbol > between batch numbers indicates a significant difference between those batches at $p < 0.05$. The results shown in Figure 1b were produced solely for verification of those above. They also showed a significant difference between batches 7 and 8 but only at $p < 0.10$. It must be realised, of course, that the compact formulation, while producing valid results, would rarely be used practically. The apparent lack of significance between the results for batches 1 and 2 is perhaps not surprising as they were both obtained from the same supplier, though from different batches. By the same token, however, batches 3 and 8 were also from one supplier. Table 2 shows the values of mass median diameter for each batch of magnesium stearate and demonstrates that particle size of lubricant cannot be related to effect on dissolution rates from both the granule and compact formulations thus confirming the results shown in Table 1. It is of interest to note, however, that the two batches of magnesium stearate which were shown to

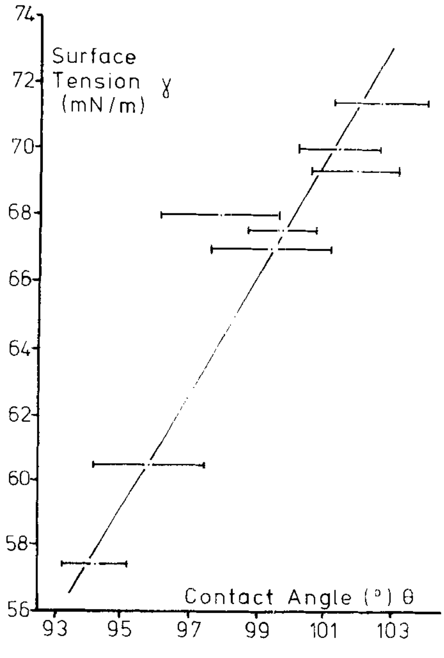

FIGURE 2

Relationship between Surface Tension of a Water Soluble Extract of Each Lubricant and Contact Angle of a Drop of Liquid on the Lubricant Compact Surface.

retard dissolution the least, exhibited by far the largest particle sizes. Obviously further work is required in this field to ascertain the ease or otherwise of shearing of lubricant onto host particles and its inter-batch variation.

Having demonstrated a significant variation between different batches of magnesium stearate with respect to their effect on dissolution rate, not obviously related to particle size, it seemed a logical step to investigate the wettability of each batch. Although contact angle measurement is perhaps a technique with which it is often difficult to obtain reproducible results, the same rank order, within experimental error, was obtained for increasing value of equilibrium contact angle as was found for reduction in dissolution rate. This indicated that differences in the ability of the dissolution medium to wet the hydrophobic lubricant might affect dissolution rate.

Although the maximum drop height indicated a contact angle of about 124° which was similar to values obtained by other workers[20], this value fell steadily over a period varying from 20 minutes to about 3 hours to reach an equilibrium value. It may be, therefore, that water-soluble surface-active impurities in the magnesium stearate were leaching out into the droplet to cause this fall. Surface tensions of aqueous extracts of each batch of lubricant confirmed this suspicion. These values are shown in Table 2 and their effect on contact angle is graphically presented in Figure 2. As expected from the Young-Dupre equation[23] a linear relationship was obtained.

A linear relationship was not obtained between surface tension and dissolution time as shown in Figures 3a and b. This is perhaps surprising as Finholt et al.[24] have shown a linear correlation between surface tension of dissolution fluid and rate of dissolution of the drug. Work on this aspect is continuing. It is apparent, however, that different batches of magnesium stearate can contain varying amounts of water-soluble surface-active materials which may affect dissolution of a drug from a solid dosage form.

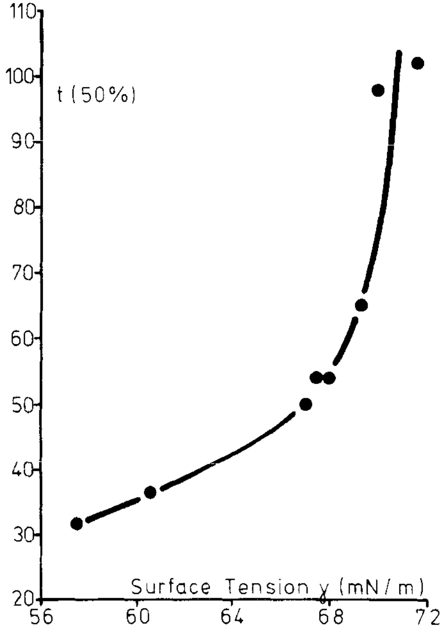

FIGURE 3a

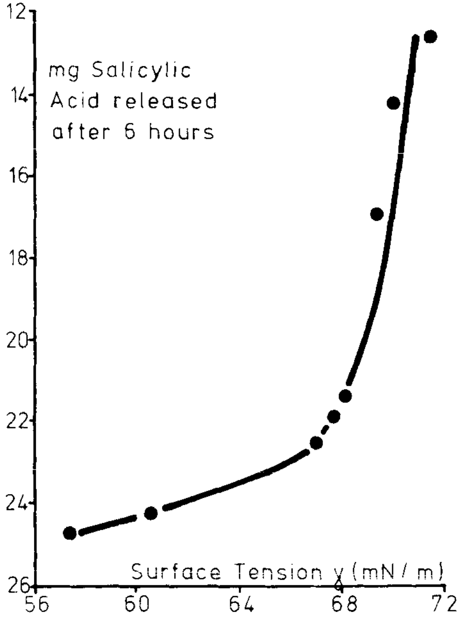

FIGURE 3b

Relationship Between Surface Tension of the Aqueous Extract of the Lubricant and (a) the Time for 50% Dissolution of Salicylic Acid from the Granule Formulation and (b) the Amount of Salicylic Acid Released from Each Compact after 6 Hours. The ordinate Axis of this Graph is plotted in a Reverse Manner to show the Similarity Between the Graphs.

CONCLUSION

This work has provided further evidence towards a growing awareness that improving the purity of a pharmaceutical excipient although reducing batch-to-batch variability, may not always produce a better material for its intended purpose.

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