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A PRELIMINARY STUDY OF THE EFFECT OF SLUG HARDNESS ON DRUG DISSOLUTION FROM HARD GELATIN CAPSULES FILLED ON AN AUTOMATIC CAPSULE-FILLING MACHINE

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SUMMARY

The effect of magnesium stearate on slug hardness and the dissolution of hydrochlorothiazide from hard gelatin capsules filled on an instrumented Zanasi automatic capsule-filling machine at constant compression force is reported. The fillers were microcrystalline cellulose and anhydrous lactose. Slug hardness was assessed by measuring the breaking load of slugs in a three-point bending test. With microcrystalline cellulose, $t_{60\%}$ first decreases to a minimum and then increases with increased lubricant levels, confirming the findings of Stewart et al. (1979). This is accompanied by a dramatic decrease in slug hardness. With lactose, $t_{60\%}$ increases with the lubricant level while slug hardness decreases slightly, although not significantly (5% level) at the levels tested. With microcrystalline cellulose, it is proposed that the increased hydrophobicity of the slug with increasing lubricant levels initially is more than offset by reduced slug hardness which probably enhances deaggregation and wetting of capsule contents.

INTRODUCTION

Excipients have often been shown to influence drug dissolution from capsule formulations (Withey and Mainville, 1969; Newton and Razzo, 1974). In a recent study, it was reported that the effect of magnesium stearate concentration on the dissolution of a model low-dose drug (riboflavin) from capsules containing various fillers was dependent in some manner on the type of filler (Stewart et al., 1979). Soluble fillers exhibited the expected prolonged dissolution times with increasing lubricant levels whereas the trends with insoluble fillers were less predictable. Certain insoluble fillers were only slightly affected by lubricant concentration whereas for others, such as microcrystalline cellulose, there appeared to be an optimum concentration of lubricant at which dissolution rate was

maximized. This latter observation is an extremely important one with regard to formulation design because it suggests the possibility that for certain formulations, reducing the hydrophobic lubricant to the lowest level at which the formulation can run will not necessarily enhance the drug dissolution rate, but may actually retard it. This study was one of very few such studies in which an attempt is made to replicate modern filling conditions, i.e. test capsules were filled by means of an isolated Zanasi dosator fitted to a moveable crosshead. It is important to note that the dosator functions much like a tablet press in that a piston first compresses a volume of powder to form a slug, which often resembles a soft tablet in firmness, and then ejects the slug into a capsule body. In view of this similarity to tableting, and since lubricants are known to soften tablets to varying degrees depending on the filler, the lubricant and lubricant concentration (Salpekar and Augsburger, 1974), we considered that a similar effect on slug hardness could help account for the results reported by Stewart et al. (1979). In a preliminary examination of this possibility, we developed a method to measure slug hardness and compared the hardness data with the rate of dissolution of hydrochlorothiazide from capsules filled on an instrumented Zanasi [1] automatic capsule-filling machine.

MATERIALS AND METHODS

Preparation of powder blends

All formulations tested were of the following general form: hydrochlorothiazide 15 g; magnesium stearate q.s.; and filler, q.s.ad. 350 g.

The magnesium stearate was of N.F. grade (Amend Drug and Chemicals, Irvington, N.J.). The fillers used were: microcrystalline cellulose, N.F. (Avicel PH 102, FMC, Food and Pharmaceutical Products, Philadelphia, Pa.) and anhydrous lactose, N.F. (Humko Sheffield, Memphis, Tenn.). Hydrochlorothiazide, U.S.P. (Merck, Sharp and Dohme, West Point, Pa.) was included as a model, low-dose, poorly soluble drug.

Preblending of the required amount of prescreened (80 mesh) lubricant with a small amount of filler was done in a plastic bag. Batches were blended in a 1.9 liter twin-shell blender (Model LB-3794, Patterson-Kelly, Inc., Stroudsburg, Pa.) for 15 min, the last two minutes with the intensifier bar running.

Capsule filling

The blends were filled into No. 1 gelatin capsules (Gelatin Pre-fit Capsules, Parke-Davis, Detroit, Mich.). Filling was carried out on an instrumented Zanasi LZ-64 automatic capsule-filling machine (Small and Augsburger, 1977) using a more sensitive piston (Small and Augsburger, 1978). The use of this machine ensures capsules are filled under actual processing conditions and permits the continuous monitoring of slug precompression, compression and ejection forces. In all cases, the powder bed height was set to its maximum of 49.4 mm. Powder blends were added to the hopper while the machine was running and with the instrumented dosator in place. At least 2 min were allowed for the powder bed and reservoir powder bed to come to equilibrium, as evidenced by the recorder trace. The compression and ejection forces were noted and the average of 10

[1] Model LZ-64, Z-Packaging, Nanuet, N.Y.

determinations is reported. Although the LZ-64 operates with two dosators, only the instrumented dosator was used. A previously described solenoid switching system (Small and Augsburger, 1977) prevented feeding of empty capsules for the missing dosator. The machine was run at the 'slow' speed position, providing 33 capsules/min (equivalent to 66 capsules/min with both dosators fitted). Fill weights varied according to the bulk density of the blends and the powder bed height and piston height settings.

A preliminary run using microcrystalline cellulose as filler was made to see if the results of Stewart et al. (1979) could be replicated in our laboratory. The magnesium stearate concentration ranged from 0.01 to 1.5%. Piston height was kept constant at 18 mm and the compression force was held at 15 kg. Samples of these capsules were evaluated for drug dissolution.

In a second experiment, the effect of lubricant concentration on both slug hardness and drug dissolution was evaluated. Two fillers were utilized: anhydrous lactose and microcrystalline cellulose. Magnesium stearate was incorporated at the levels of 0.05, 0.1, 0.2, 0.5, and 0.75%. All capsules were compressed with the same compression force of 21.7 kg. Piston height was kept constant at 15 mm for the lactose batches; however, piston heights ranging from 18 to 20 mm were required to achieve the 21.7 kg target compression force in the case of the microcrystalline cellulose batches. Reducing the piston height tends to increase the precompression force for a given powder bed height since a smaller volume is forced through a given powder depth (Small, 1980).

Dissolution

The dissolution of hydrochlorothiazide was determined by means of U.S.P. method 2 (paddle, round-bottom flask) at a paddle speed of 50 rpm. The capsules were held in stainless steel spirals to prevent their floating. The dissolution medium was 900 ml of 1 : 100 hydrochloric acid maintained at 37°C. Six randomly selected capsules of each batch were evaluated simultaneously using an automated dissolution apparatus consisting of a multiple drive stirrer (Model QC-72R-115B, Hanson Research, Northridge, Calif.) and a multi-cell dissolution spectrophotometer (Model 25-7, Beckman Instruments, Silver Spring, Md.). In this apparatus, the filtered solution from each flask is pumped through individual 1 mm pathlength flow cells mounted in the spectrophotometer and back to the respective flasks. Hydrochlorothiazide concentration was determined at 272 nm. The time required for 60% of the drug content to dissolve ($t_{60\%}$) for each of the 6 capsules from each batch was determined from computer-generated per cent dissolved–time profiles. The mean $t_{60\%}$ for each batch is reported. The solubility of hydrochlorothiazide in this medium at 37°C is 0.106% (Augsburger et al., 1980). Since the drug content of test capsules was in the range of 10–20 mg, dissolution determinations were generally made under conditions of 2% or less of saturation of the medium, well below the 10–20% maximum considered satisfactory for approximating sink conditions (Levy, 1966).

Hardness measurements

To determine the effect of the lubricant on the hardness of slugs, a hardness tester was constructed from an existing bench-type tensile strength tester (Gardiner Laboratory, Bethesda, Md.) as illustrated in Fig. 1. A cross-beam is attached at one end to the moving head. At the other end of this beam, a force transducer (G1-1.5-300, Statham Trans-

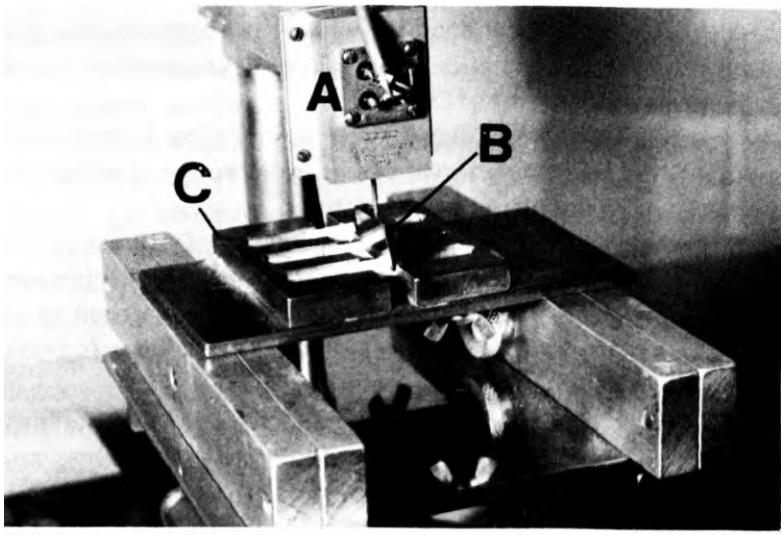

Fig. 1. View showing slug hardness tester. Key: A, force transducer; B, stainless steel blade; C, slug holder.

ducers, Hato Rey, Puerto Rico) is mounted. A blunt edge stainless steel blade is suspended from the transducer. The design is such that the blunt edge of the blade is brought down at a controlled rate (4.4×10^{-3} cm/s) against the midpoint of the slug which is suspended by supports at each end (i.e. the slugs are broken in a bending mode). The blunt edge measures 2.5×0.09 cm. The distance between the supports of the slug holder (i.e. the fulcrum) measures 0.8 cm. The bending strength of the slugs was taken as a measure of slug hardness.

The output of the transducer, after being amplified (Model 311A, Sanborn, Hewlett Packard, Palo Alto, Calif.), is recorded on a strip chart recorder (Model 7101B, Hewlett Packard, Palo Alto, Calif.). When calibrated, the set-up yielded a slope of 271 mm deflection per gram force ($r^2 = 0.9999$). The mechanics of the Zanasi permit the collection of slugs prior to their insertion into capsules, thus avoiding possible damage to the slugs from having to remove them from filled capsules. The values reported represent the means of 10 determinations.

RESULTS AND DISCUSSION

Fig. 2 summarizes the results of the initial run using microcrystalline cellulose as the filler. These results confirm the findings originally reported by Stewart et al. (1979). As the lubricant level was increased, the $t_{60\%}$ values first decreased to a minimum at about 1% magnesium stearate and then increased. Literature dealing with tableting reveals that magnesium stearate decreases tablet hardness, the effect being most marked in the case of fillers which undergo extensive plastic deformation, such as starch and starch derivatives (Salpekar and Augsburger, 1974; DeBoer et al., 1978). Since microcrystalline cellulose has been reported to exhibit a relatively high degree of plasticity (David and Augsburger, 1977), it was considered that the initial increase in dissolution with increasing lubricant

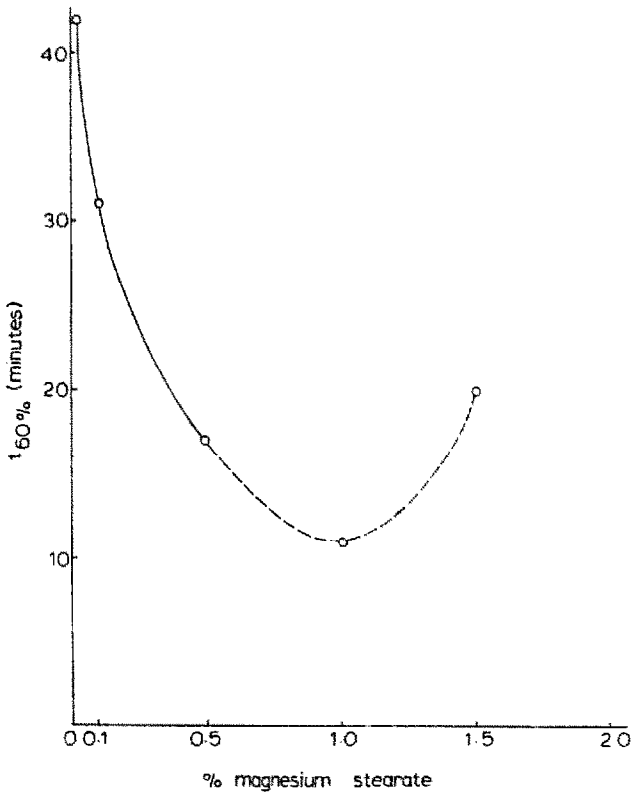

Fig. 2. Effect of magnesium stearate concentration on the time for 60% ($t_{60\%}$) of the hydrochlorothiazide content of the capsule to dissolve – microcrystalline cellulose filler; compression force 15 kg.

levels may be due to reduced slug hardness which could promote deaggregation and wetting of the capsule contents. As a preliminary test of this hypothesis, a second experiment was conducted wherein capsules formulated with microcrystalline cellulose were compared to those formulated with lactose with respect to slug hardness and hydrochlorothiazide dissolution. Both series of capsules were prepared with the same lubricant levels (0.05–0.75%) and compressed with the same compression force of 21.7 kg. Under these conditions, the microcrystalline cellulose based slugs containing 1 or 2% concentrations of magnesium stearate were too soft to evaluate in the hardness tester, although such capsules could be filled without difficulty in the Zanasi machine. Lactose was selected for comparison since it has been reported to deform primarily by brittle fracture in tableting (Cole et al., 1975). The results are summarized in Tables 1 and 2. With microcrystalline cellulose, there was a dramatic decrease in hardness from 84.0 to 1.76 g as the concentration of magnesium stearate was increased. Paralleling this decrease in hardness was a decrease in $t_{60\%}$ from 55 to 12 min. These results are further illustrated in Fig. 3. On the other hand, with the lactose capsules, the $t_{60\%}$ was found to rise from 12 to 18 min while the hardness showed little change. Although hardness with lactose did show a decreasing trend, the difference between any pair of values was found to be not significant at the 5% level. Although the increase in $t_{60\%}$ values with lactose was not great, the difference in dissolution rates between the lactose and microcrystalline cellulose capsules

TABLE 1

EFFECT OF LUBRICANT (MAGNESIUM STEARATE) CONCENTRATION ON SLUG HARDNESS AND THE TIME FOR 60% ($t_{60\%}$) OF THE HYDROCHLOROTHIAZIDE CONTENT OF THE CAPSULE TO DISSOLVE – MICROCRYSTALLINE CELLULOSE FILLER

Lubricant (% w/w)	Piston height (mm)	Net [a] weight (g)	Compression force (kg)	Ejection force (kg)	Hardness [b] (S.E.M.) (g)	$t_{60\%}$ [c] (S.E.M.) (min)
0.05	20.0	0.241	21.7	2.3	84.0 (1.70)	55 (1.22)
0.10	20.0	0.242	21.7	2.3	76.0 (1.14)	36 (0.82)
0.20	19.2	0.241	21.7	2.3	27.2 (1.52)	16 (2.04)
0.50	18.0	0.241	21.7	1.4	4.0 (0.36)	14 (1.63)
0.75	18.0	0.243	21.7	1.4	1.76 (0.06)	12 (0.98)

[a] n = 20.
[b] n = 10.
[c] n = 6.
S.E.M. = standard error of the mean.

at higher lubricant levels is further enhanced by the fact that lactose is soluble in the dissolution medium whereas microcrystalline cellulose is not. Apparently, with microcrystalline cellulose the increased hydrophobicity of the slug with increasing lubricant levels is initially more than offset by reduced slug hardness. Since increasing the magnesium stearate concentration to beyond 1% decreases the dissolution rate (Fig. 2), it appears that the hydrophobicity imparted by the lubricant eventually supercedes its softening effect on capsule contents. With lactose capsules, even though the filler is soluble, the minimal softening of capsule contents apparently is insufficient to overcome the increased hydrophobicity imparted by the lubricant. The greater softening of microcrystalline cellulose

TABLE 2

EFFECT OF LUBRICANT (MAGNESIUM STEARATE) CONCENTRATION ON SLUG HARDNESS AND THE TIME FOR 60% ($t_{60\%}$) OF THE HYDROCHLOROTHIAZIDE CONTENT OF THE CAPSULE TO DISSOLVE – ANHYDROUS LACTOSE FILLER

Lubricant (% w/w)	Piston height (mm)	Net [a] weight (g)	Compression force (kg)	Ejection force (kg)	Hardness [b] (S.E.M.) (g)	$t_{60\%}$ [c] (S.E.M.) (min)
0.05	15.0	0.351	21.7	4.1	17.6 (2.03)	12.0 (1.04)
0.10	15.0	0.360	21.7	2.7	15.2 (1.20)	12.6 (0.90)
0.20	15.0	0.365	21.7	2.3	15.4 (1.42)	12.9 (0.70)
0.50	15.0	0.366	21.7	2.0	14.2 (1.62)	13.2 (0.59)
0.75	15.0	0.366	21.7	1.8	12.8 (1.16)	18.3 (1.21)

[a] n = 20.
[b] n = 10.
[c] n = 6.
S.E.M. = standard error of the mean.

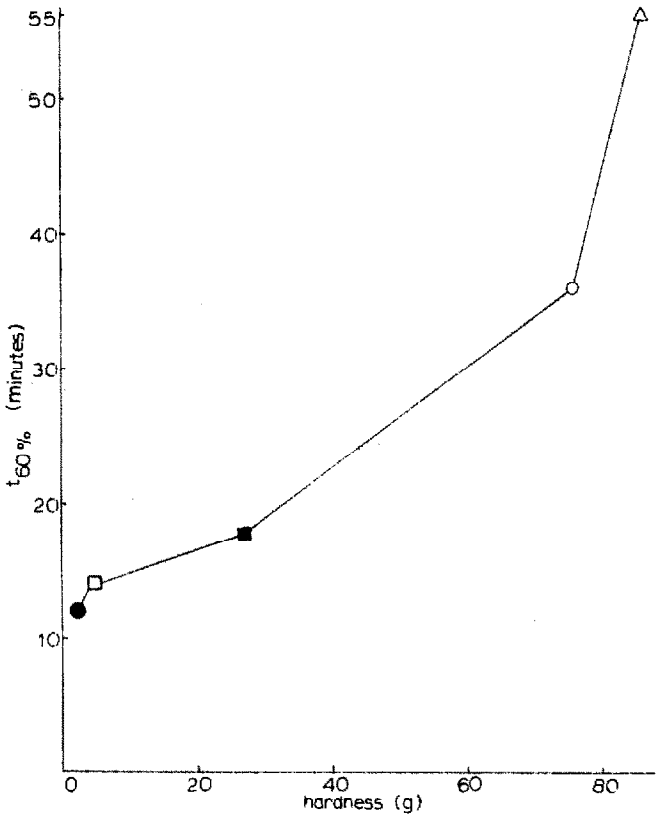

Fig. 3. Effect of magnesium stearate concentration on slug hardness and the time for 60% ($t_{60\%}$) of the hydrochlorothiazide content of the capsule to dissolve – microcrystalline cellulose filler; compression force 21.7 kg. Magnesium stearate: ●, 0.75%, □, 0.5%; ■, 0.2%; ○, 0.1%; △, 0.05%.

slugs in the presence of lubricant as compared to lactose parallels similar observations in tableting.

CONCLUSIONS

Hydrophobic lubricants such as magnesium stearate are generally required in capsule formulations, particularly when using such capsule-filling equipment as the Zanasi machine in which slugs are compressed and ejected into the capsule shells. In such cases, it is generally assumed that the lubricant concentration should be kept to the lowest level at which the formulation can be run successfully. However, with certain fillers such as microcrystalline cellulose, it may be advisable to exceed this minimum concentration to improve drug dissolution. The hardness of capsule slugs may be reduced by the amount of lubricant used which, in turn, may have a beneficial effect on drug dissolution. Slug hardness measurement is one more tool which can be utilized by product development pharmacists in the rational design of capsule formulations.

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