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Effect of disintegrants on drug dissolution from capsules filled on a dosator-type automatic capsule-filling machine

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Summary

Various levels of newer disintegrants were compared against 10% starch and 0% disintegrant in dicalcium phosphate-based hard gelatin capsules filled on an instrumented Zanasi machine at a constant compression force. Hydrochlorothiazide or acetaminophen were included for drug dissolution studies. Disintegration time, ejection force and overall running characteristics were also considered. In general, the modified celluloses were most effective in enhancing drug dissolution, followed, in order, by the modified starches, corn starch, cross-linked PVP and the control (0% disintegrant). Reducing the lubricant level (magnesium stearate) or using a more soluble drug (acetaminophen) required less modified cellulose (AcDiSol) to exert a similar effect on drug dissolution. Disintegration and dissolution data correlated best with the more soluble drug.

Introduction

Disintegrating agents are routinely included in compressed tablets to promote moisture penetration and dispersion of the tablet in dissolution fluids. Although starch traditionally has been the disintegrant of choice, many newer disintegrants have been introduced in recent years which have superior swelling and moisture absorbing properties and which are effective in tablets at much lower concentrations

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(Shangraw et al., 1980, 1981). Although numerous studies have been reported detailing the influence of various additives on drug release from capsules (Whithey and Mainville, 1969; Newton et al., 1971; Newton, 1972; Newton and Razzo, 1977, Mehta and Augsburger, 1981), few studies have included disintegrants. Those studies which did report on disintegrants generally produced negative or mixed results (Shah and Moore, 1970; Samyn and Jung, 1970, Goodhart et al., 1973). A major feature of these studies is that they involved capsules filled by hand which provides little compression of the contents. Such capsules are far more porous than tablets and there is little structure for disintegrants to swell against to effect disintegration. In such cases, wettability and moisture penetration are likely more important determinants of deaggregation, and this had led to interest in the inclusion of surfactants in capsule formulations, at times with contradictory results (Newton et al., 1971; Newton and Razzo, 1977). Although the role of disintegrants in capsule formulations has never been clearly established in the literature, it appears that such agents, particularly the newer disintegrants, would be highly desirable components of formulations designed for modern automatic filling machines in which capsule contents are actually compressed. To test this hypothesis, representative disintegrants were evaluated and compared for their ability to promote disintegration and drug dissolution from capsules filled on a dosator-type automatic capsule filling machine.

Experimental

Materials and formulations

The filler was unmilled dicalcium phosphate dihydrate, NF (Ditab, Stauffer Chemicals, Westport, CT) and the lubricant was magnesium stearate, NF (Amend Drugs and Chemicals, Irvington, NJ). A glidant, hydrated sodium silicoaluminate (Zeolex 7; J.M. Huber, Edison, NJ) was incorporated to promote powder fluidity. Hydrochlorothiazide, USP (Merck, Sharp and Dhome, West Point, PA) was included as a poorly soluble drug for dissolution. For comparison, a more water-soluble drug, acetaminophen, USP (Mallinckrodt, St. Louis, MO) was included in some formulations. The newer disintegrants evaluated included two brands of cross-linked sodium carboxymethyl cellulose (AcDiSol; FMC, Philadelphia, PA; and CLD-2; Buckeye Cellulose, Memphis, TN), two brands of sodium carboxymethyl starch (Explotab; Edward Mendell, Carmel, NY; and Primojel; Generichem, Little Falls, NJ) and cross-linked polyvinylpyrrolidone (Polyplasdone-XL; GAF, New York, NY). All disintegrants were compared to corn starch (Best Foods, New York, NY). All materials were used as received except for magnesium stearate which was passed through an 80 mesh sieve prior to blending.

All formulations tested were of the following general form: hydrochlorothiazide—4% or acetaminophen—10%; magnesium stearate—0.5% or 1%; glidant—0.2%; disintegrant [1]—0, 2, 4 or 6%; filler q.s. a.d.—100%. The batch size

[1] Corn Starch was used at the 10% level.

was 600 g in all cases. Preblending of the lubricant with a small amount of filler was done in a plastic bag and the batches were blended in a 1.9 liter twin-shell blender (Patterson-Kelly, Stroudsburg, PA) for 10 min without the intensifier bar.

Capsule filling

No. 1 gelatin capsules were filled on a Zanasi LZ-64 automatic capsule-filling machine instrumented with strain gauges to permit continuous monitoring of slug compression and ejection forces (Small and Augsburger, 1977). Piston height and powder bed height were kept constant at 18 mm and 49.4 mm, respectively. The compression force was standardized at 22.6 kg for all runs. Capsules were evaluated for disintegration and drug dissolution. The net weights of 20 capsules from each batch were determined on an electronic balance (Millibalance Model 7500, Cahn Div., Ventron Instruments, Paramount, CA).

Disintegration time. Capsule disintegration times were measured in 900 ml of dilute HCl (1 : 100) at 37 ± 1°C, using the USP disintegration test for hard gelatin capsules.

Dissolution. Drug dissolution was determined by means of USP Method no. 2 at a paddle rate of 50 rpm. The capsules were prevented from floating with the aid of stainless steel spirals. The medium was 900 ml of dilute HCl (1 : 100) maintained at 37 ± 1°C. Six capsules from each batch were evaluated simultaneously using an automated dissolution apparatus consisting of a multiple drive stirrer (Model QC-72R-115B, Hanson Research, Northridge, CA) coupled to a multiple flow cell dissolution spectrophotometer (Model 25-7, Beckman Instruments, Silver Spring, MD). Hydrochlorothiazide and acetaminophen concentrations were determined at 272 nm and 243 nm, respectively. The mean time required for 60% of the drug content to dissolve ($T_{60\%}$) or the mean percent dissolved in 72 min (slow dissolvers) is reported.

Results and discussion

The level of newer disintegrants most often utilized in tablet formulations is 2% to 4% depending on the type of disintegrant and the particular formulation. These levels were initially incorporated in this series of experiments and the results are tabulated in Table 1.

It can be observed that the 2% level of the disintegrants did not appreciably increase the dissolution of hydrochlorothiazide over that of the control (0% disintegrant), even though there was an appreciable decrease in disintegration times. The official disintegration test may lack sufficient sensitivity to differentiate these batches since all slugs were observed to fragment on impact with the oscillating basket. During dissolution, there is no comparable impact and/or abrasion since slugs remain localized in the concavity of the flask under the paddle where they are subject to relatively gentle mixing currents. It also may be seen from Table 1 that the use of 4% AcDiSol dramatically enhances dissolution whereas 4% Explotab appeared ineffective. It is apparent that higher levels of these materials are required in

TABLE I

EFFECT OF CONCENTRATION AND TYPE OF DISINTEGRANT ON VARIOUS PHYSICOMECHANICAL PROPERTIES AND HYDROCHLOROTHIAZIDE DISSOLUTION FOR DICALCIUM PHOSPHATE-BASED CAPSULES (1.0% MAGNESIUM STEARATE, 0.2% ZEOLEX, COMPRESSION FORCE = 22.6 kg

Disintegrant concentration (% w/w)	Ejection force (kg)	Net weight (mg)	Disintegration time (min)	Dissolution	
				$T_{60\%}$ (min)	% Dissolved at 72 min
0% Disintegrant	1.2	525 (5.08)	> 100	–	20 (0.58)
2% AcDiSol	1.1	541 (1.02)	23 (0.71)	–	27 (1.1)
2% CLD-2	1.2	527 (2.65)	14 (0.84)	–	34 (1.2)
2% Primojel	1.6	522 (5.48)	21 (1.33)	–	26 (0.48)
2% Explotab	1.3	547 (2.02)	25 (1.75)	–	23 (0.75)
4% Explotab	1.3	530 (5.41)	15 (0.70)	–	24 (0.49)
4% AcDiSol	1.2	536 (2.88)	4.3 (0.14)	53 (2.8)	–
10% Corn starch	1.4	590 (1.02)	26 (0.33)	–	42 (2.1)
6% CLD-2	0.9	507 (2.77)	4.2 (0.12)	24 (1.7)	–
6% Explotab	1.1	542 (1.96)	8.4 (0.77)	–	47 (4.4)
6% AcDiSol	0.9	526 (1.50)	4.0 (0.14)	25 (1.9)	–
6% Primojel	1.1	547 (5.37)	6.9 (0.38)	38 (3.2)	–
6% Polyplasdone-XL	0.9	442 (1.03)	9.7 (0.76)	–	29 (1.1)

Standard error of the mean given in parentheses.

capsule formulations than those commonly used in tableting. This relative ineffectiveness of low levels of these disintegrants in capsules is probably related to the high porosity of the powder mass. Since the compression forces used in these systems are low, relative to tableting, soft tablet-like slugs are produced which in most cases broke into two-pieces upon ejection. Compared to tablets, the porosity of these compacts is high and a relatively larger proportion of the swelling of the disintegrants may be accommodated by the voids of the powder mass before disintegration occurs. Additionally, it may be necessary that sufficient concentration of the disintegrant be present in the compact to form a capillary network, if wicking is to occur.

Comparing the various disintegrants at the 6% level against 10% corn starch, it is obvious that the newer disintegrants can play a significant role in capsule formulations (Table 1), with the modified celluloses being more effective than the modified starches or cross-linked PVP. As can be seen from the complete dissolution profiles (Fig. 1) CLD-2 and AcDiSol were found to be the most effective ($T_{60\%}$ = 24 min and 25 min, respectively), followed by Primojel with $T_{60\%}$ = 38 min. Six percent Explotab and 10% corn starch appeared to be less effective with 47% and 42% of drug released in 72 min, respectively. Polyplasdone-XL did not appear to improve dissolution significantly.

It is important to note that Primojel and Explotab, which appear to be chemically similar materials, exhibited dramatically different performance when incorporated in

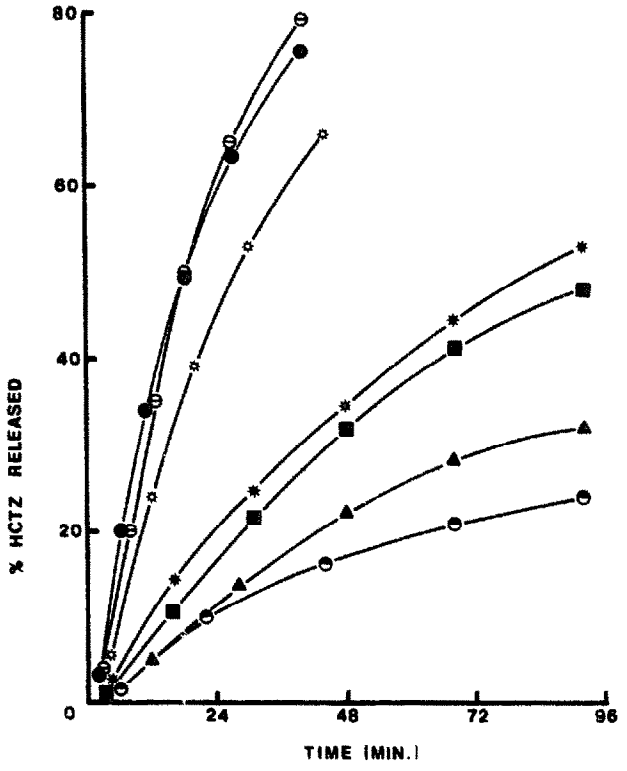

Fig. 1. Effect of disintegrants on the dissolution of hydrochlorothiazide for dicalcium phosphate-based capsules (1% magnesium stearate). Key: ⊖, 6% CLD-2; ●, 6% AcDiSol; ☆, 6% Primojel; ★, 6% Explotab; ■, 10% corn starch; ▲, 6% Polyplasdone-XL; ⊖, 0% disintegrant.

the same capsule formulation. The more rapidly dissolving formulation (containing Primojel) tended more to produce intact slugs which disintegrated slightly more rapidly. Shangraw et al. (1980) point out that different brands of modified starch could behave differently due to differences in the raw-material starch or to differences in various manufacturing steps.

Polyplasdone-XL is reported to act mainly by capillary action with a secondary swelling effect (Kornblum and Stoopak, 1973). Thus in encapsulated compacts where a relatively high degree of swelling is apparently needed this material appears to be ineffective. The modified celluloses, on the other hand, apparently owe their effectiveness to both fast wicking action through the cellulose fibers and significant fiber swelling (Shangraw et al., 1980).

Corn starch appears to improve dissolution by about two-fold. Since starch has been found to swell only minimally (Patel and Hopponen, 1966), it is likely that its activity here is attributed to other factors, such as capillarity and/or slug softening.

The relative effectiveness of AcDiSol and Explotab at 2, 4 and 6% levels on hydrochlorothiazide release is shown in Fig. 2. It is evident that AcDiSol is more effective than Explotab at all 3 levels; even 4% AcDiSol is significantly more effective than 6% Explotab.

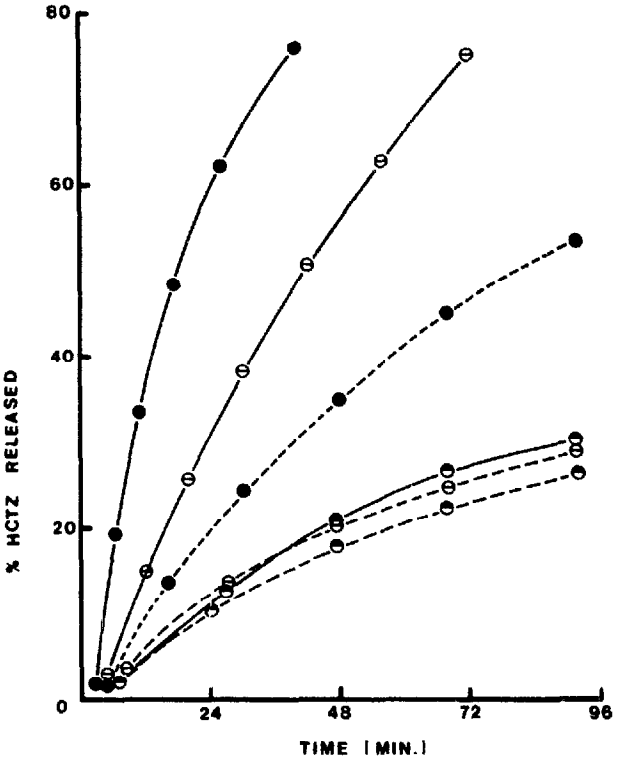

Fig. 2. Effect of AcDiSol (———) or Explotab (— — —) concentration on the dissolution of hydrochlorothiazide for dicalcium phosphate-based capsules (1% magnesium stearate). Key: Disintegrant Concentration—⊖, 2%; ⊖, 4%; ●, 6%.

All disintegrants decreased disintegration times but there was not always rank order agreement between disintegration and dissolution (Table 1). This indicates that the mechanism by which these disintegrants produce their effect is complex and factors other than swelling, such as wetting and liquid penetration may be also involved.

The running characteristics of all test formulations (approximately 200 capsule runs) appeared excellent and there was no problem with transferring of slugs to the capsules. The ejection forces were not significantly affected by the addition of disintegrants in the formulation. The net weight of the capsules varied according to the bulk density of the formulation.

It was of interest to obtain some indication of the influence of lubrication on the disintegrant effect of at least one disintegrant. The data in Table 2 were obtained by employing 0.5% magnesium stearate with various levels of AcDiSol in dicalcium phosphate-based capsules. As expected $T_{60\%}$ values for hydrochlorothiazide decreased with increasing AcDiSol concentrations. A rank order correlation was observed in this case between disintegration times and $T_{60\%}$ values, while the slug hardness of dicalcium phosphate compacts appeared to be decreased by AcDiSol. The effectiveness of various levels of AcDiSol with 0.5 or 1% magnesium stearate is shown in Fig. 3. It can be observed that 2% and 4% AcDiSol levels in the 0.5%

TABLE 2

EFFECT OF AcDiSol CONCENTRATION ON VARIOUS PHYSICOMECHANICAL PROPERTIES AND HYDROCHLOROTHIAZIDE DISSOLUTION ($T_{60\%}$) FOR DICALCIUM PHOSPHATE-BASED CAPSULES (0.5% MAGNESIUM STEARATE, 0.2% ZEOLEX, COMPRESSION FORCE = 22.6 kg

AcDiSol concentration (% w/w)	Ejection force (kg)	Net weight (mg)	Disintegration time (min)	$T_{60\%}$ (min)
0	1.0	510 (4.76)	47 (1.1)	106 (4.04)
2	1.1	550 (1.72)	5.5 (0.34)	43 (3.3)
4	1.2	518 (3.13)	4.0 (0.14)	29 (1.8)

Standard error of the mean given in parentheses.

lubricant system give similar dissolution profiles as those found with 4% and 6% AcDiSol in the 1% magnesium stearate system. It is apparent that the lubricant is an important determining factor in this formulation. Lower disintegrant concentrations are required when lower lubricant levels are used.

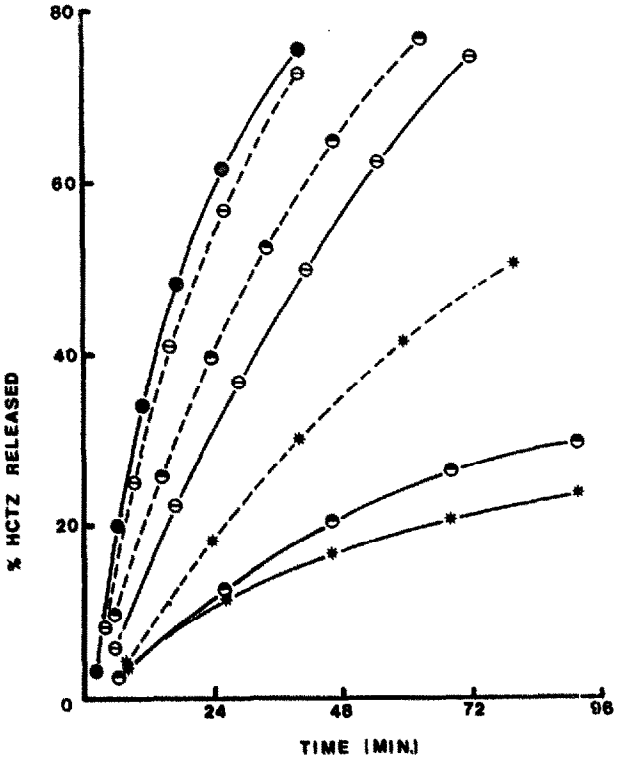

Fig. 3. Effect of AcDiSol concentration on the dissolution of hydrochlorothiazide from capsules prepared with dicalcium phosphate and 0.5% (— — —) or 1% (———) magnesium stearate. Key: ★, 0%; ⊖, 2%; ⊖, 4%; ●, 6%.

TABLE 3

EFFECT OF AcDiSol CONCENTRATION ON VARIOUS PHYSICOMECHANICAL PROPERTIES AND ACETAMINOPHEN DISSOLUTION ($T_{60\%}$) FOR DICALCIUM PHOSPHATE-BASED CAPSULES (1.0% MAGNESIUM STEARATE, 0.2% ZEOLEX, COMPRESSION FORCE = 22.6 kg)

AcDiSol concentration (% w/w)	Ejection force (kg)	Net weight (mg)	Disintegration time (min)	Dissolution	
				$T_{60\%}$ (min)	% Dissolved at 72 min
0	2.1	569 (1.23)	> 60	–	42 (0.68)
2	1.8	568 (1.43)	15 (0.38)	61 (4.4)	–
4	1.6	564 (1.71)	3.9 (0.13)	17 (0.86)	–

Standard error of the mean given in parentheses.

Since drug solubility has also been found to be a controlling factor in dissolution from capsule formulations, similar capsules were prepared with acetaminophen, a more water-soluble drug (Table 3). As would be expected with a more water-soluble drug, both disintegration times and $T_{60\%}$ values decreased with increasing AcDiSol

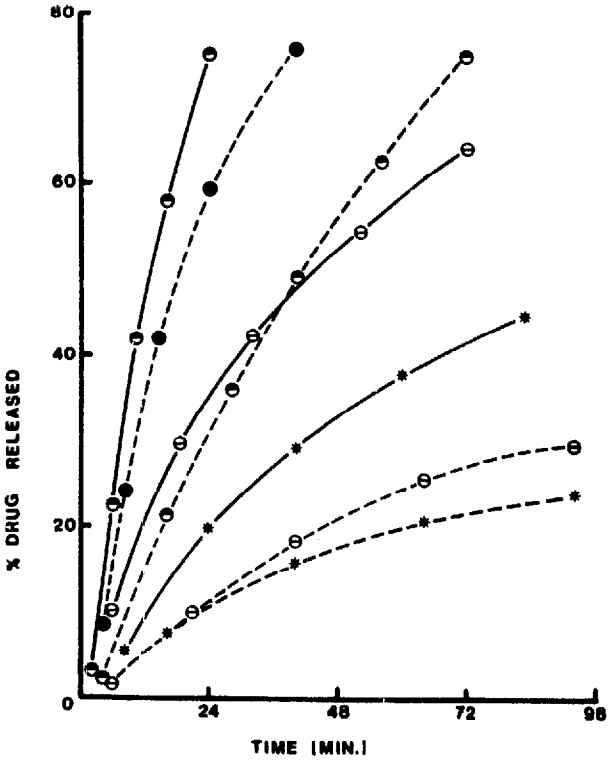

Fig. 4. Effect of AcDiSol concentration on the dissolution of hydrochlorothiazide (— — —) or acetaminophen (———) from capsules prepared with dicalcium phosphate and 1% magnesium stearate. Key: ★, 0%; ⊖, 2%; ⊜, 4%; ●, 6%.

concentration. A softening effect of the disintegrant on the slugs of dicalcium phosphate was observed; however, this did not interfere with efficient slug transfer. In comparison with the less water-soluble hydrochlorothiazide (Fig. 4), it is apparent that lower levels of AcDiSol are required to exert similar increases in dissolution rate.

Conclusion

The role of disintegrants in capsules filled on a dosator-type automatic filler was investigated. A significant improvement in drug release over the control containing no disintegrant was found. The modified celluloses were found to be most effective, followed in order by the modified starches, corn starch and cross-linked PVP.

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