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The role of disintegrants in hard-gelatin capsules

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Experiments were designed to investigate the efficacy of various disintegrants on hydrochlorothiazide dissolution from soluble (lactose) and insoluble (dicalcium phosphate) fillers at various lubricant concentrations and compression forces. Capsule fill weights as well as slug hardness appeared to be influenced by the addition of disintegrants. Disintegration times were not always in rank order agreement with dissolution data. Analysis of the dissolution data by 3-way analysis of variance revealed that all the main factors (disintegrant, compression force, lubricant and/or diluent) and their interactions were significant. The presence of interactions limits the conclusions to be drawn; however, an assessment of the averaged effect of each factor separately revealed several important relationships. A compression force effect was evident in most cases at the lower disintegrant concentration, and lower lubricant concentrations or a more soluble filler appeared to require lesser amounts of disintegrant. The magnitude and order of effectiveness of the disintegrants were altered when the filler system was changed from lactose to dicalcium phosphate.

Only as recently as the current revision have the USP XX/NF XV included an official disintegration test procedure for capsules. It is not surprising, therefore, that a review of the literature reveals a paucity of information in this area.

Even though investigators often have pointed out the importance of the rate of deaggregation of the powder mass before dissolution (Aguiar et al 1968; Newton & Razzo 1977), few reports can be found dealing with the role of disintegrating agents in capsule formulations. Earlier studies (Shah & Moore 1970; Goodhart et al 1973; Samyn & Jung 1970) often produced mixed results and usually involved formulations or filling methods which are unrealistic in terms of modern, high-speed capsule manufacture. In a more recent study (Botzolakis et al 1982), in which many of the new "super" disintegrants were compared with starch in capsules filled on an automatic capsule filling machine, it was found that in-vitro drug release was improved by as much as ten-fold.

Formulation and process variables play a determining role in drug release from capsules and its availability for absorption. The solubility of the major component (drug or filler) affects the rate and mechanism of drug release (Newton & Razzo 1974), whereas lubricants introduce hydrophobicity (Samyn & Jung 1970; Goodhart et al 1973) and/or slug softening (Mehta & Augsburger 1981a) which affect disintegration and dissolution. With fully automatic capsule filling machines in which capsule contents are actually compressed (often to form tablet-like slugs), machine variables like compression force and its effect on slug hardness may also affect disintegration and dissolution (Mehta & Augsburger 1981b). Consequently, any evaluation of the efficacy of disintegrants in capsule formulations should take into account the interaction of formulation and process variables.

This study was designed to more thoroughly compare and evaluate the most effective among the disintegrants investigated in the preliminary work (Botzolakis et al 1982). Included in this investigation is a consideration of the role of the lubricant, diluent, compression force and any significant interactions among these factors.

MATERIALS AND METHODS

Materials and formulations

All materials were used as received from the suppliers except for the lubricant which was sieved through an 80 mesh screen to facilitate blending. Hydrochlorothiazide (Merck, Sharp and Dohme, West Point, PA), U.S.P., was used to represent a low dose drug having limited solubility and magnesium stearate (Amend Drug and Chemical Co., Irvington, NJ), was used as the lubricant. Unmilled dicalcium phosphate dihydrate (Stauffer Chemical

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Co., Industrial Chemical Div., Westport, CT), USP, and anhydrous lactose (Sheffield Products, Memphis, TN), USP, were utilized as insoluble and soluble fillers, respectively. The representative disintegrating agents included croscarmelose type A (Ac-Di-Sol, FMC, Food and Pharmaceutical Products, Philadelphia, PA) croscarmelose type B (CLD-2, Buckeye Cellulose Corp., Memphis, TN) and sodium carboxymethyl starch (Primojel, Generichem Corp., Little Falls, NJ). The general formulation used was: Hydrochlorothiazide 4%, magnesium stearate 0.5, 1 or 2%, disintegrant 4 or 6%, filler qs 100%. Batches of 800 g were prepared by adding the excipients to the diluent, hand mixing in a plastic bag and finally blending the mixture for 15 min in a two-quart twin-shell blender (Patterson-Kelly Co., Model LB-3974, East Stroudsburg, PA).

Preparation of capsules

The powder mixtures were filled into size No. 1 hard gelatin capsules using an automatic capsule filling machine (Zanasi LZ-64, Z-Packaging, Nanuet, N.Y.) which had been instrumented to measure compression and ejection forces (Small & Augsburger 1977). The piston height was set at 18 mm and the powder bed height was set to its maximum (49·4 mm). Capsule fill weights varied according to the bulk density of the formulation. The machine was initially run until the powder bed came to equilibrium, as evidenced by the uniform compression force tracings on the recorder. Capsules were then prepared at the desired compression force by appropriate adjustment of the compression knob. Ten slugs were collected before their insertion into the bodies, and their hardness, whenever possible, was determined immediately using a previously described slug hardness tester (Mehta & Augsburger 1981a). Where intact slugs could not be collected their appearance was noted qualitatively. Approximately 100 capsules were collected from each run and stored in tightly closed bottles for further studies.

Disintegration test

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

Dissolution rate

The dissolution rate of hydrochlorothiazide from the various formulations was determined by means of USP method II. The paddles were rotated at 50 rev min^{-1} in 900 ml of dilute HCl (1:100) solution maintained at 37 ± 1 °C in a constant temperature bath. 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 Corp., Northridge, CT) coupled to a multiple flow cell dissolution spectrophotometer (Model 25-F, Beckman Instruments, Silver Spring, MD). Hydrochlorothiazide concentrations were determined at 272 nm. The mean percent dissolved in 30 min is reported.

RESULTS AND DISCUSSION

The original experimental design called for the use of magnesium stearate at 0·5 and 1% concentration for both dicalcium phosphate and lactose based capsules. However, lactose formulations with 0·5% magnesium stearate gave unacceptably high ejection forces at the range of compression forces studied. Thus for lactose formulations, magnesium stearate was used at 1 and 2%.

A separate factorial design experiment was set up for each filler. The disintegrants, each at the 4 and 6% concentration, and the control (no disintegrant) were grouped as one factor. The other factors were lubricant (at two concentrations, as indicated) and compression force (at three values: nominally 10, 20 and 30 kg). The parameters measured were weight variation, ejection force, slug hardness (or appearance) and disintegration and dissolution times. For each filler-lubricant value, the capsule fill weights were found to vary according to the type and concentration of disintegrant used. In general, these fill weight differences were seen to parallel differences in the formulation tapped bulk density.

The results for the dicalcium phosphate based capsules are reported in Table 1 and those for the lactose based capsules in Table 2. The dissolution data were analysed using separate 3-way analyses of variance for both the soluble and insoluble fillers. To determine the effect of diluent on the efficacy of the disintegrants, the data for the 1% lubricant (Table 1 and Table 2) were analysed by 3-way analysis of variance.

Dicalcium phosphate-based capsules

The capsules containing no disintegrant produced hard slugs and hardness increased greatly as compression force increased, indicating a great deal of bonding between the filler particles. However, the incorporation of disintegrants in the formulation clearly reduced the slug hardness significantly (Table 1). The most dramatic change in slug hardness

Table 1. Effect of disintegrants on selected physico-mechanical properties and hydrochlorothiazide dissolution for dicalcium phosphate based capsules.

Disintegrant Concn (% w/w)	Compression force (kg)*	Slug hardness (g) 0·5% Lubricant	Slug hardness (g) 1% Lubricant	Disintegration time (min) 0·5% Lubricant	Disintegration time (min) 1% Lubricant	% Drug dissolved in 30 min 0·5% Lubricant	% Drug dissolved in 30 min 1% Lubricant
0%	10	24·8 (1·16)	17·7 (1.48)	26 (0·97)	>60	40·7 (1·18)	9·0 (0·23)
	23	69·4 (2·29)	63·3 (2·46)	44 (0·63)	>60	30·2 (2·09)	11·1 (0·637)
	32	102 (0.860)	97·6 (1·57)	47 (0·69)	>60	28·6 (1·12)	11·2 (0·400)
4% Ac-Di-Sol	10	pieces	powder	4·6 (0·20)	5·5 (0·32)	69·8 (2·38)	47·2 (3·94)
	23	2-piece	2-piece	3·7 (0·17)	4·6 (0·19)	72·5 (1·20)	58·9 (4·07)
	32	2-piece	<3·0	3·9 (0·10)	4·8 (0·21)	68·4 (3·36)	65·1 (1·47)
6% Ac-Di-Sol	10	pieces	powder	4·1 (0·20)	5·3 (0·26)	70·0 (2·80)	60·0 (2·45)
	23	2-piece	2-piece	3·3 (0·11)	4·6 (0·20)	70·1 (1·05)	64·6 (1·59)
	32	2-piece	<3·0	4·2 (0·27)	4·7 (0·26)	67·0 (2·67)	68·3 (0·968)
4% CLD-2	10	powder	powder	5·1 (0·16)	6·6 (0·21)	67·9 (1·92)	30·5 (2·13)
	23	powder	powder	4·0 (0·10)	5·2 (0·15)	75·0 (2·76)	32·6 (1·71)
	32	powder	powder	4·5 (0·33)	4·9 (0·12)	73·0 (1·29)	38·5 (1·54)
6% CLD-2	10	powder	powder	4·7 (0·22)	5·2 (0·14)	71·8 (2·49)	60·7 (2·09)
	23	powder	powder	4·2 (0·32)	4·0 (0·10)	78·4 (2·58)	72·7 (1·91)
	32	powder	powder	3·9 (0·28)	3·9 (0·31)	77·5 (2·17)	72·2 (3·06)
4% Primojel	10	pieces	pieces	6·5 (0·43)	13 (0·79)	65·9 (1·59)	18·5 (0·849)
	23	2-piece	<3·0	6·1 (0·48)	12 (0·63)	63·6 (1·85)	19·0 (0·784)
	32	16·8 (1·23)	15·5 (1·02)	5·5 (0·37)	11 (0·38)	66·0 (2·34)	21·3 (0·914)
6% Primojel	10	pieces	pieces	4·0 (0·37)	7·6 (0·17)	69·3 (0·800)	35·7 (1·98)
	23	<3·0	2-piece	3·5 (0·28)	6·4 (0·26)	76·9 (2·25)	55·1 (2·24)
	32	16 (0·91)	10·6 (0·920)	3·4 (0·13)	6·3 (0·14)	76·6 (0·914)	98·8 (0·249)

( ) Standard error of the mean.
* × 9·81 = N (SI units).

Table 2. Effect of disintegrants on selected physico-mechanical properties and hydrochlorothiazide dissolution for anhydrous lactose based capsules.

Disintegrant concn (% w/w)	Compression force (kg)*	Slug hardness (g) 1% Lubricant	Slug hardness (g) 2% Lubricant	Disintegration time (min) 1% Lubricant	Disintegration time (min) 2% Lubricant	% Drug dissolved in 30 min 1% Lubricant	% Drug dissolved in 30 min 2% Lubricant
0%	10	6·2 (0·21)	19·6 (1·32)	6·3 (0·21)	11 (0·70)	56·8 (1·60)	32·4 (0·747)
	23	23·8 (1·77)	32·2 (1·34)	5·5 (0·19)	10 (0·16)	59·0 (2·73)	40·2 (1·53)
	32	†	50·9 (2·18)	5·5 (0·19)	8·6 (0·23)	60·3 (0·727)	48·8 (1·58)
4% Ac-Di-Sol	10	<3·0	<3·0	4·0 (0·12)	5·6 (0·22)	67·3 (1·11)	66·8 (1·72)
	23	8·7 (0·71)	4·7 (0·29)	3·9 (0·12)	5·1 (0·11)	66·4 (1·17)	67·4 (2·81)
	32	9·0 (0·51)	6·9 (0·35)	3·8 (0·16)	5·1 (0·10)	66·6 (1·46)	69·5 (2·15)
6% Ac-Di-Sol	10	<3·0	2-piece	3·5 (0·17)	5·0 (0·12)	68·1 (1·07)	72·2 (1·44)
	23	3·3 (0·24)	<3·0	3·4 (0·15)	5·0 (0·19)	68·7 (1·31)	71·7 (0·290)
	32	5·0 (0·45)	4·1 (0·33)	3·2 (0·12)	5·1 (0·16)	66·6 (2·40)	75·7 (1·35)
4% CLD-2	10	powder	pieces	3·8 (0·10)	4·0 (0·10)	79·5 (1·13)	70·0 (2·07)
	23	2-piece	2-piece	3·1 (0·10)	4·3 (0·11)	77·0 (1·59)	69·3 (1·14)
	32	<3·0	<3·0	3·0 (0·10)	4·1 (0·11)	72·2 (1·38)	68·4 (1·79)
6% CLD-2	10	powder	pieces	3·0 (0·10)	4·8 (0·31)	70·1 (1·16)	75·8 (2·05)
	23	pieces	pieces	2·9 (0·10)	4·9 (0·16)	74·0 (1·00)	76·1 (0·837)
	32	2-piece	2-piece	3·0 (0·10)	4·7 (0·11)	82·2 (2·69)	78·2 (1·12)
4% Primojel	10	pieces	pieces	4·2 (0·20)	5·8 (0·33)	66·2 (1·28)	67·0 (1·48)
	23	2-piece	2-piece	4·5 (0·38)	5·8 (0·23)	65·6 (2·34)	68·2 (1·43)
	32	5·5 (0·46)	3·4 (0·39)	4·2 (0·14)	5·8 (0·10)	66·3 (0·584)	68·0 (1·26)
6% Primojel	10	powder	pieces	4·5 (0·11)	5·8 (0·21)	67·6 (1·56)	65·3 (2·17)
	23	2-piece	2-piece	3·9 (0·13)	5·7 (0·13)	67·5 (1·69)	68·8 (1·63)
	32	3·4 (0·39)	3·0 (0·36)	4·3 (0·20)	5·5 (0·20)	72·9 (1·08)	70·4 (0·947)

* × 9·41 = N (SI units).
† Slugs could not be collected.
( ) Standard error of the mean.

occurred with the CLD-2 formulation for which only loose powder fills was obtained at any compression force. In any particular case, the slug hardness generally could be ranked in decreasing order as: control > Primojel > Ac-Di-Sol > CLD-2. An increase in magnesium stearate concentration had little or no effect on the slug hardness in any of the formulations.

Disintegration times did not always show good rank-order agreement with the dissolution data. This was especially apparent among the compacts which disintegrated in less than 5 min. However, it should be pointed out that the determination of the end point is difficult when disintegration is so rapid. Although this test appeared unable to differentiate between formulations that disintegrated rapidly, low disintegration times, in general, indicated fast dissolution rates.

The results of the 3-way analysis of variance are given in Table 3. The complexity of the effects is evident. An important feature of the results is the significant effect of the disintegrant ($P < 0{\cdot}01$). The lubricant concentration and compression force effects are found also to be significant ($P < 0{\cdot}01$). However, the presence of first and second order interactions indicates that the effects produced by each additive are dependent on the presence and values of the other two.

Table 3. Results of the analysis of variance for the effect of various factors on the percent hydrochlorothiazide released in 30 min for dicalcium phosphate based capsules.

Source	SS	Df	MS	F-Ratio
DS	70583	6	11764	477·011*
LC	26241	1	26241	1064·07*
CF	2877·5	2	1438·7	58·339*
DS × LC	13563	6	2260·5	91·660*
LC × CF	2741·4	2	1370·7	55·581*
DS × CF	6331·1	12	527·59	21·393*
DS × LC × CF	3730·3	12	310·86	12·605*
Error	5178·9	210	24·661	

* Significant at $P < 0.01$.
DS: Disintegrant.
LC: Lubricant conc.
CF: Compression force.

Despite the presence of interactions, an assessment of the magnitude of the effect of each factor can be made by averaging the results for a given value of a factor, irrespective of the other factors. For example, the effect of 4% Ac-Di-Sol is obtained by averaging the results of all the experiments containing 4% Ac-Di-Sol. When treated in this way the results for the values of each factor may be seen as depicted in Fig. 1. By using Tukey's simple comparison test it was possible to compare the effectiveness of the three disintegrants. It was found ($P < 0{\cdot}05$) at the 6% addition that there was no difference in the effect produced by either Ac-Di-Sol or Primojel, CLD-2 being the most effective. However, at 4% Ac-Di-Sol was significantly more effective than the other two in enhancing the percent dissolved in 30 min.

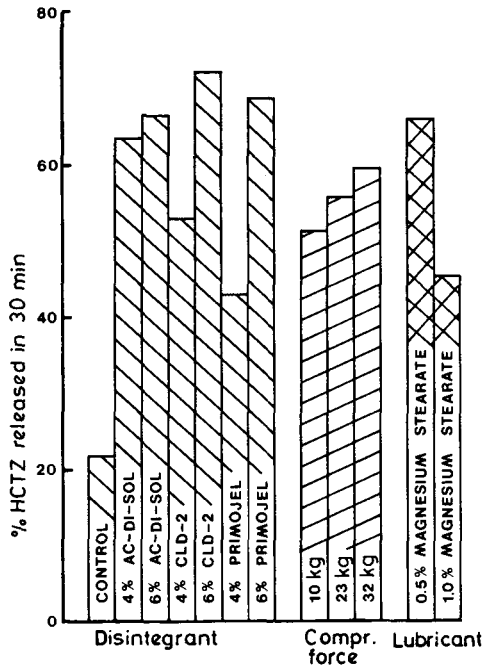

FIG. 1. The averaged effect of disintegrant, compression force and lubricant on the release of hydrochlorothiazide from dicalcium phosphate based capsules.

The expected effect of the lubricant was observed; that is, increasing magnesium stearate concentration decreases dissolution rates. The results also show that the higher the compression force, the faster the drug release. This effect comes as no surprise. The hardness data indicate that the powder mass is compacted to very soft tablet-like slugs which suggests high compact porosity (compared to compressed tablets). At low compression forces, some of the swelling of the disintegrants may be expected to be accommodated within the void spaces. As the compression force increases, the porosity of the system may be expected to decrease and, as the disintegrant particles swell, they will exert a more powerful disruptive action. Kahn & Rhodes (1975) reported a similar phenomenon with starch and

cation exchange resins as disintegrants in dicalcium phosphate tablets. Similar observations with tablets have also been reported by other researchers (Lowenthal & Burruss 1971).

It is not always possible to predict from a knowledge of the values of the individual factors how combination of these factors will influence drug release. This is illustrated in Figs 2 and 3 where the effect of compression force on drug release is shown for each value of the various disintegrants at two values of magnesium stearate. If there were no interactions, each curve for the various disintegrants and the control would have the same general shape, and these would be repeated at each lubricant concentration.

It is evident from Figs 2 and 3, that the differences between the various types and concentrations of disintegrants are minimized when low lubricant values are present in the formulation. Poor wetting of the powder mass at higher lubricant values appears to be an important factor and disintegrants help overcome this to varying degrees. Fig. 3 shows that Ac-Di-Sol is much more effective than CLD-2 or Primojel at 4%. At 6% these differences are diminished, with Primojel showing a significant compression force effect. A possible explanation is that 4% of CLD-2 or Primojel is insufficient to break

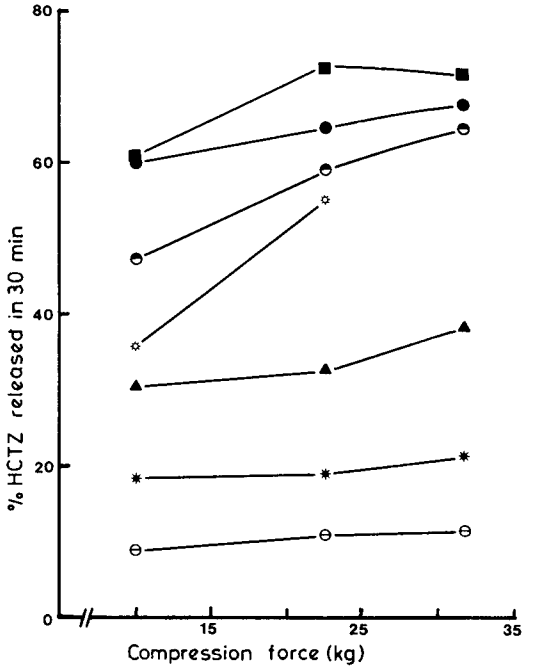

FIG. 3. Effect of compression force on hydrochlorothiazide dissolution from dicalcium phosphate based capsules containing 1% magnesium stearate. See Fig. 2.

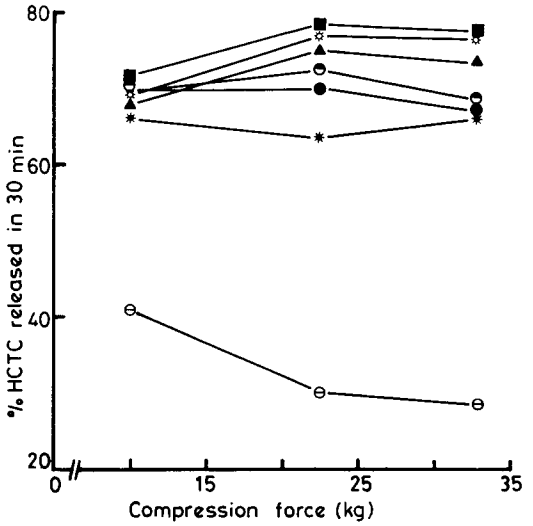

FIG. 2. Effect of compression force on hydrochlorothiazide dissolution from dicalcium phosphate based capsules containing 0·5% magnesium stearate. Ac-Di-Sol: 4% ◓, 6% ●, CLD-2: 4% ▲, 6% ■, Primojel 4% ★, 6% ☆, Control: ⊖.

the structure of the compact rapidly. One consequence of prolonged disintegration which could adversely affect drug dissolution is an increase in the viscosity of the powder mass. We therefore compared a low viscosity grade of modified starch, Primojel LV, in the same formulation as the regular grade of the same disintegrant (Fig. 4). As can be seen, at all compression forces Primojel LV improved dissolution by about 20 to 30% over the regular grade of this material. Although these data would appear to support this hypothesis, it should be pointed out that disintegration times also improved by approximately the same margin. This suggests that factors other than strictly a viscosity effect may be involved.

As previously pointed out, the averaged, overall effect of increasing the compression force was improved dissolution. This was particularly evident among individual disintegrants at the higher lubricant value (Fig. 3). However, in certain cases at the lower lubricant value, 0.5% magnesium stearate in this instance (Fig. 2), the disintegrants apparently reach a maximal effectiveness at low pressures and further increases in compression force resulted in little or no improvement in dissolution. In other cases dissolution rate was actually retarded.

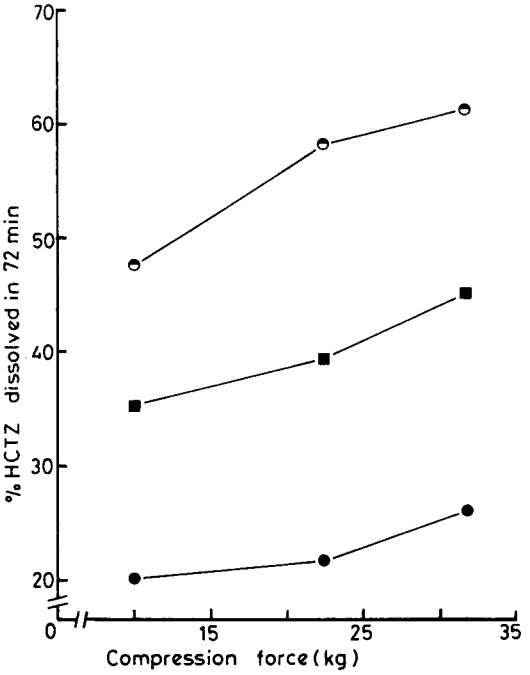

FIG. 4. Effect of compression force on hydrochlorothiazide dissolution from dicalcium phosphate based capsules containing two grades of Primojel and 1% magnesium stearate. 4% Primojel LV: ⊖, 4% Primojel: ■, Control: ●.

Anhydrous lactose-based capsules

As noted previously, 1% and 2% magnesium stearate had to be used in the anhydrous lactose formulations because of high ejection forces at lower lubricant concentrations. The use of even these strengths of magnesium stearate yielded relatively high ejection forces at higher compression forces. Slugs of measurable hardness were found at all compression forces (Table 2). The hardness data indicate that the control formulation with the higher lubricant concentration produced harder slugs than those with the lower lubricant concentration, at any compression force. This apparent discrepancy could be due to the fact that at 1% magnesium stearate, the ejection forces were very high and some damage to the slugs occurs upon ejection.

The addition of disintegrants to the formulation decreased slug hardness in all cases (Table 2). However, it was noted that CLD-2, when used in lactose capsules, produced harder compacts than those produced with dicalcium phosphate. The discrepancies noted between disintegration times and dissolution data for dicalcium phosphate based capsules were also evident with the lactose formulations. However, low disintegration times, again, usually indicated rapid drug dissolution.

Table 3 summarizes the results of the 3-way analysis of variance for the dicalcium phosphate based capsules and Table 4 for the lactose capsules. As can be seen, again, the main factors were all significant at $P < 0{\cdot}01$. The possible interactions were also significant except for that between lubricant and compression force. To assess the magnitude of each factor, the results were again averaged for each value of a factor, irrespective of the other factors, as described previously. The results are shown in Fig. 5. The disintegrants produce a significant effect on drug release at all concentrations used. From the data in Figs 1 and 5, it can be seen that the degree of improvement over the control for the soluble filler is far less than that observed for the insoluble filler. However, the lactose control exhibited more rapid drug dissolution than did the dicalcium phosphate control. Soluble fillers tend to dissolve rather than disintegrate; nevertheless, the disintegrants will help by improving wetting and capillary action. In the case of dicalcium phosphate, liquid penetration together with deaggregation are likely to be the determining factors of the rate of drug dissolution.

Table 4. Results of the analysis of variance for the effect of various factors on the percent hydrochlorothiazide released in 30 min for anhydrous lactose based capsules.

Source	SS	Df	MS	F-Ratio
LC	379·14	1	379·14	24·817*
DS	155536	6	2589·4	169·49*
CF	373·50	2	186·75	12·224*
LC × DS	3334·4	6	555·73	36·376*
DS × CF	880·57	12	73·381	4·803*
LC × CF	70·294	2	35·147	2·301
LC × DS × CF	508·80	12	42·400	2·775*
Error	3208·3	210	15·277	

* Significant at $P < 0{\cdot}01$.
LC: Lubricant concn.
DS: Disintegrant.
CF: Compression force.

With the use of Tukey's test on the averaged data, it was found ($P < 0{\cdot}05$) that 6% CLD-2 was more effective than the other two disintegrants, with 4% CLD-2 producing the same effect as 6% Ac-Di-Sol or Primojel. However, averaged over all conditions, all disintegrants provided between 65 and 75% drug dissolution after 30 min.

The effect of compression force and lubricant also can be seen in Fig. 5. This effect also is less marked with the soluble filler than with the insoluble filler. It is apparent from Table 2 that the differences between disintegrants are greatly diminished in this

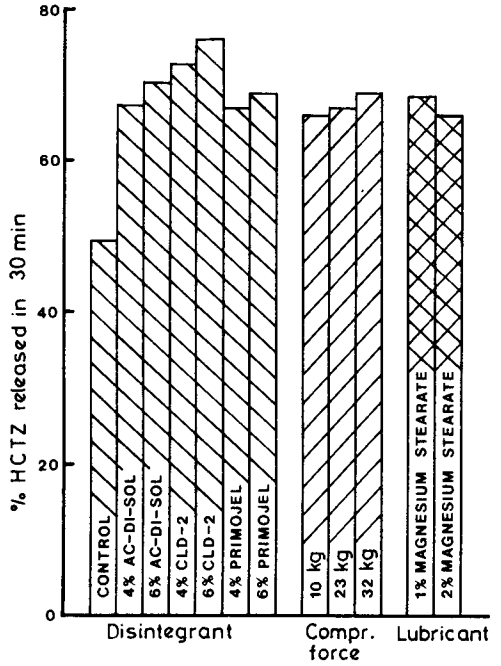

FIG. 5. The averaged effect of disintegrant, compression force and lubricant on the release of hydrochlorothiazide from anhydrous lactose based capsules.

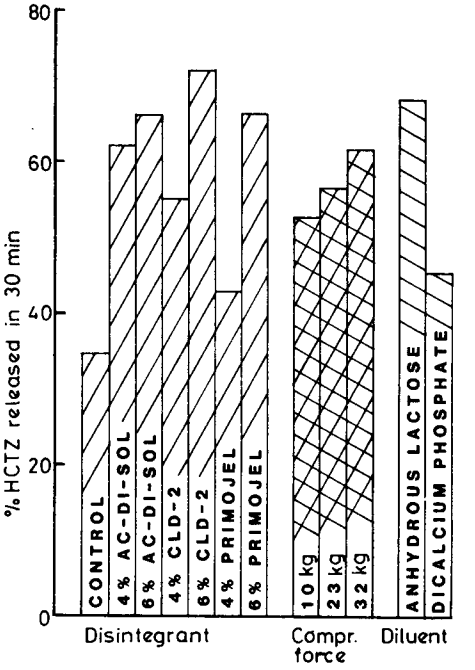

FIG. 6. The averaged effect of disintegrant, compression force and diluent on the release of hydrochlorothiazide.

comparatively fast releasing lactose formulation. The most dramatic improvement over the control was observed with the more slowly dissolving formulation containing 2% magnesium stearate.

Effect of type of diluent on drug release

The analysis of variance in Table 5, shows that the type of diluent will have a significant effect on drug release. This phenomenon was not unexpected but it

Table 5. Results of the analysis of variance for the effect of various factors on the percent hydrochlorothiazide released in 30 min for either anhydrous lactose or dicalcium phosphate based capsules.

Source	SS	Df	MS	F-Ratio
CF	3375·9	2	1688·0	87·010*
DS	40495·0	6	6749·2	347·90*
DL	34277·0	1	34277·0	1766·86*
DS × CF	5550·7	12	462·56	23·844*
CF × DL	2242.4	2	1121.2	57.795*
DS × DL	23977·0	6	3996·1	205·99*
CF × DS × DL	4148·1	12	345·68	17·819*
Error	4073·9	210	19·40	

* Significant at $P < 0{\cdot}01$.
DS: Disintegrant.
DL: Diluent.
CF: Compression force.

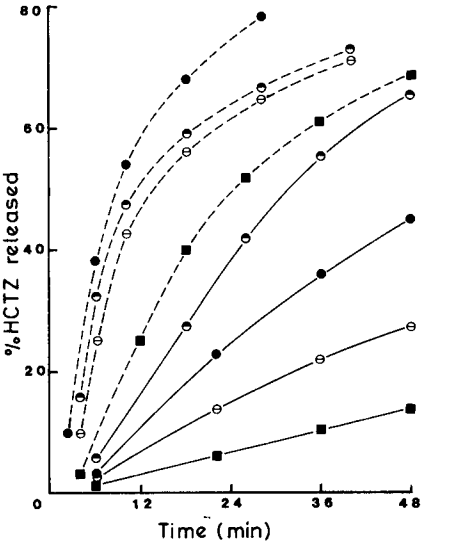

FIG. 7. Effect of 4% disintegrant on hydrochlorothiazide dissolution from anhydrous lactose (----) or dicalcium phosphate (——) based capsules containing 1% magnesium stearate (compression force = 10 kg). Ac-Di-Sol: ◓, CLD-2: ●, Primojel: ⊖, Control: ■.

was interesting that there were significant interactions between the type of diluent, disintegrant and compression force. The averaged effect of each value of a factor is shown in Fig. 6. Comparison of the various disintegrants by Tukey's test showed that all comparisons were significant except for 6% Ac-Di-Sol versus 6% Primojel.

The complete dissolution profiles of lactose and dicalcium phosphate capsules containing 4% of the various disintegrants are compared in Fig. 7. This figure clearly demonstrates that the degree of improvement over the controls is greater with dicalcium phosphate than with lactose. It is also interesting to observe that in changing from a soluble filler to one which is less soluble, the order of effectiveness of the various disintegrants also changes. This observation suggests that certain disintegrant properties are more important for one type of filler than the other. When the disintegrants are included in the formulations at higher levels (Fig. 8) these differences are diminished, especially those for Ac-Di-Sol and CLD-2. In all cases, Primojel was the least effective of the three. Ac-Di-Sol and CLD-2 are fibrous and it is possible that their wicking action is greater than that of Primojel.

Disintegrants have been demonstrated to enhance drug dissolution from capsules filled on an automatic filling machine in which the powder mixture is compressed. Compression force, lubricant concentration and filler type were found to influence the effectiveness of the disintegrants and should be considered in designing a successful capsule formulation.

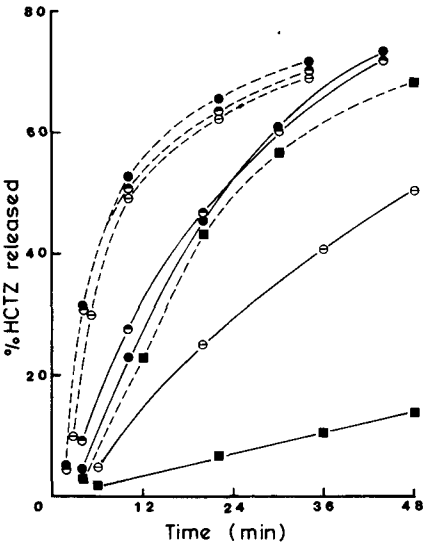

FIG. 8. Effect of 6% disintegrant on hydrochlorothiazide dissolution from anhydrous lactose (----) or dicalcium phosphate (——) based capsules containing 1% magnesium stearate (compression force = 10 kg). See Fig. 7.

Note:

It is the author's understanding that the only grade of Primojel currently available in the market is the low viscosity grade previously designated as Primojel LV.

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