Disintegration Properties of Calcium Phosphate Dibasic Dihydrate Tablets

K. A. KHAN * and C. T. RHODES ‡×

Abstract □ The effect of compressional force on the disintegration time of tablets prepared from calcium phosphate dibasic dihydrate containing various tablet disintegrants was examined. The results show that effects of compressional force on disintegration time are of two types. The first type is that of insoluble disintegrants, *e.g.*, starch and a cation-exchange resin, where the disintegration time initially shows a dramatic decrease. After this decrease, a further increase in compressional force appears to have no effect on the disintegration time. The second type is that of soluble disintegrants, *e.g.*, calcium sodium alginate, sodium carboxymethylcellulose, and sodium starch glycolate, where variation in compressional force has very little effect on the disintegration time. These results are discussed in terms of the differing mechanism whereby these substances act as disintegrants.

Keyphrases □ Calcium phosphate dibasic dihydrate—disintegration time □ Disintegrants—effect of compressional force on disintegration of starch, cation-exchange resin, calcium sodium alginate, sodium carboxymethylcellulose, sodium starch glycolate

Several investigators have studied the effect of compressional force on the disintegration time of tablets. Most published reports have shown that an increase in compressional force increases the disintegration time. The disintegration time for tablets was shown (1, 2) to continue to increase as the compressional force increased, even though the compression ratio of the tablets had reached a maximum.

Similarly, a semilogarithmic relationship was found (3, 4) between the disintegration time and the compressional force for certain tablets made by static methods, despite the fact that their porosities reached constant values. A linear relationship between the compression pressure and disintegration time of tablets containing lactose and potato starch was found (5). From studies (6) of starch and aspirin tablets, a two-phase increase was reported when the results were plotted on a linear scale. When using various celluloses in different organic and inorganic bases, there was a two-stage linear increase in the logarithm of the disintegration time with increasing compression pressure (7).

It was found that although the disintegration time increases with increasing compressional force, the relationship differs with each formulation (8). An entirely different relationship was recently shown (9) for dicalcium phosphate dihydrate tablets containing a cation-exchange resin; an increase in compressional force enhanced the dissolution efficiency and reduced the disintegration time. Following this work, it was considered important to examine the effect of the presence of different disintegrants on the relationship between compressional force and disintegration time of tablets prepared from an insoluble direct-compression system, since these areas have not been investigated previously.

EXPERIMENTAL

Materials—Starch (BP grade), calcium sodium alginate[1], cation-exchange resin[2], sodium starch glycolate[3], sodium carboxymethylcellulose[4], calcium phosphate dibasic dihydrate[5] (unmilled), and magnesium stearate (BPC grade) were used.

Methods—The excipients were mixed with the lubricant and 10% (w/w) of disintegrant by quartering and shaking vigorously in a plastic bag. The lubricant used was 1% magnesium stearate, which was passed through a No. 60 hand screen before blending with the other powders. The tablets were made on an instrumented single-punch machine[6] using 1.02-cm (0.4-in.) flat punches.

The upper punch forces were measured by using Kistler load cells in a similar manner as described by Marshall (10). The particle density of the mixtures was determined using a specific gravity bottle, with benzene as the supernatant liquid. Apparent tablet densities were obtained from thickness and diameter measurements of at least 10 tablets.

Tablet porosity was calculated from particle density and apparent tablet density values. The mean hardness[7] of at least five tablets was obtained. Disintegration times were determined on a disintegration apparatus[8] using the BP method. The mean of at least five determinations was obtained.

RESULTS AND DISCUSSION

Figure 1 shows the effect of compressional force on the porosities of the calcium phosphate tablets containing different disinte-

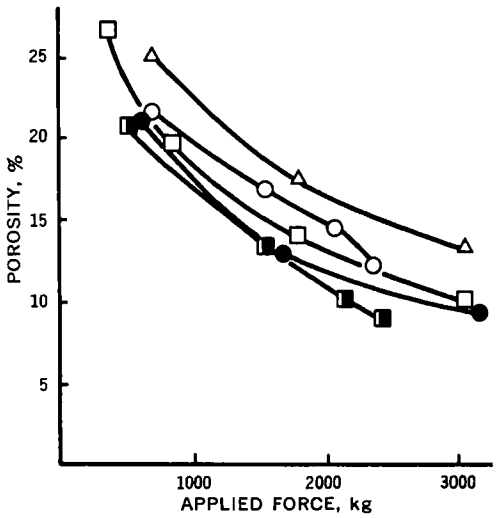

Figure 1—*Effect of applied force on the porosity of tablets prepared from calcium phosphate dibasic dihydrate containing different disintegrants. Key:* △, *cation-exchange resin;* ○, *sodium carboxymethylcellulose;* □, *sodium starch glycolate;* ●, *calcium alginate; and* ■, *starch.*

[1] Alginate F417, supplied by Alginate Industries, London, England.
[2] Amberlite 1RP88, supplied by Lemming Chemical Ltd., London, England.
[3] Primojel, supplied by Gordon Slater Ltd., Cheshire, England.
[4] Courlose P20, British Celanese Ltd., Coventry, England.
[5] Supplied by Albright and Wilson, Idbury, Worcestershire, England.
[6] Manesty type F3.
[7] Erweka hardness tester.
[8] Manesty.

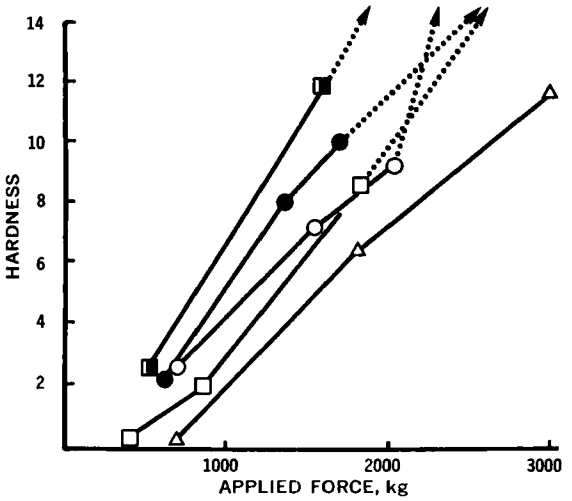

Figure 2—*Effect of applied force on the hardness of tablets prepared from calcium phosphate dibasic dihydrate containing different disintegrants. Key: △, cation-exchange resin; ○, sodium carboxymethylcellulose; □, sodium starch glycolate; ●, calcium sodium alginate; and ■, starch.*

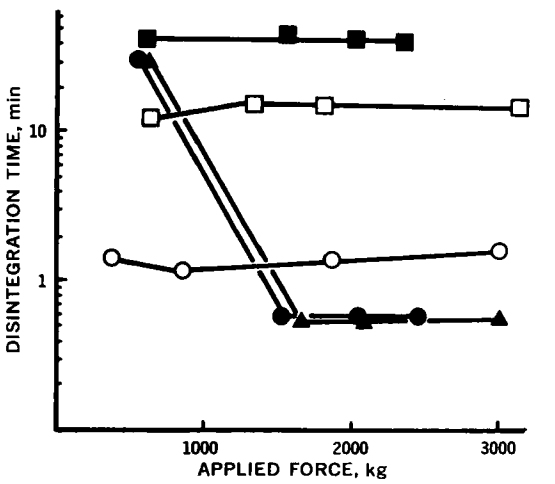

Figure 3—*Effect of applied force on the disintegration time of tablets prepared from calcium phosphate dibasic dihydrate containing different disintegrants. Key: ▲, cation-exchange resin; ■, sodium carboxymethylcellulose; ○, sodium starch glycolate; □, calcium sodium alginate; and ●, starch.*

grants. It is apparent that the porosity of all tablets decreased with increasing compressional force. The rate of decrease in porosities with increasing pressure appears to be the same with all disintegrants. The cation-exchange resin produced the most porous tablets and starch the least porous.

It is well known that starch undergoes plastic deformation under compression (11); its glidant action may have also contributed to the closer packing. The higher porosity of tablets containing the cation-exchange resin probably resulted mainly from the poor compression characteristics of this disintegrant (12). The poor adhesion between the cation-exchange resin and calcium phosphate particles is further confirmed by the effect of compressional force on tablet hardness (Fig. 2). Here again, the tablets containing cation-exchange resin were softer.

The effect of compressional force on tablet disintegration time reveals that there are two types of disintegrant behavior (Fig. 3). In the first type (starch and the cation-exchange resin), the disintegration time initially shows a dramatic decrease, after which a further increase in compressional force appears to have no effect on the disintegration time. In the second type (calcium sodium alginate, sodium carboxymethylcellulose, and sodium starch glycolate), variation of compressional force has very little effect on the disintegration time.

The literature generally reports that harder tablets take longer to disintegrate, but Fig. 3 shows that in the systems investigated the reverse appears to be the case. Although the finding of Higuchi *et al.* (4) cannot be compared with those presented in this paper because of great differences in the formulations used, there is one important similarity. These workers found an initial decrease in the disintegration time for tablets containing starch. A similar behavior was found in this study for tablets containing starch and the cation-exchange resin (Fig. 3).

This behavior might be explained by the hypothesis proposed (1) for potato starch and phenacetin tablets. As the compression force increases, the tablet porosity decreases, and the pore diameter may also decrease, as noted previously (13, 14) using tablets of aspirin and starch. At low compression forces, often as much as 20% void space exists within the tablet, and the pore diameter is large. Penetration by the disintegration fluid is, therefore, very rapid, and the disintegrant particles begin to swell and fill the void space without immediately affecting tablet disintegration.

As the compression force increases, the time taken for penetration of fluid and the swelling of disintegrant particles with subsequent tablet disintegration is increased by the reduction in pore size. There is, however, a decrease in porosity (Fig. 1), which means that the swelling particles have a more immediate effect on the tablet structure. The effectiveness of starch and the cation-exchange resin, when used at 10% concentration, perhaps counteracts the effect of reduced penetration. Thus, further increase in compressional force does not affect the disintegration time.

Other reasons for the reduction of disintegration time with increased compressional force (for tablets prepared from calcium phosphate dibasic dihydrate) have been described (9). The phenomenon of initial decrease in disintegration time with increasing compression force is more pronounced for insoluble disintegrants because the rate-determining step becomes that of water penetration with subsequent swelling of disintegrant particles.

The second group of disintegrants (sodium starch glycolate, sodium carboxymethylcellulose, and calcium sodium alginate) is somewhat soluble. The disintegration of tablets containing these disintegrants is brought about by a number of factors, including dissolution of disintegrant particles. After the penetration of water, the disintegrant particles absorb water and begin to swell and also to dissolve. All these factors are additive in their effect and counteract the effect of reduced penetration due to reduction in pore size. The result (Fig. 3) is that disintegration time is largely unaffected by the increase in compressional force.

In conclusion, it is suggested that the effect of compressional force on tablet disintegration may depend upon the disintegrant and the diluent used. Generalizations such as the harder the tablet, the slower the disintegration rate are not applicable to all systems.

This study also reveals an extremely important property of calcium phosphate dibasic dihydrate. The disintegration time of tablets prepared from this material, contrary to most published reports, does not increase with increasing compressional force.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 2, 1974, from *Beecham Pharmaceuticals Limited, Worthing, Sussex, England, and the ‡Department of Pharmaceutics, State University of New York at Buffalo, Buffalo, NY 14214

Accepted for publication July 25, 1974.

The authors thank Winthrop Laboratories, Newcastle upon Tyne, for use of the instrumented tablet machine. Thanks are due to Mr. C. G. Barlow and Dr. M. P. Short for assistance in this work.

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Improved Synthesis of 18-Hydroxydeoxycorticosterone

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Abstract □ Hypoiodite photolysis of 3β-acetoxy-5-pregnen-20β-ol gave 3β-acetoxy-5-pregnene-18,20-lactone in 46% yield. Lithium aluminum hydride reduction of the latter afforded 3β,18,20β-trihydroxy-5-pregnene (91% yield) which, on Oppenauer oxidation, was converted to 18-hydroxyprogesterone (66%). Lead tetraacetate oxidation followed by mild saponification gave 18-hydroxydeoxycorticosterone (58% yield).

Keyphrases □ 18-Hydroxydeoxycorticosterone—synthesis □ 18,-20-Oxido-20-hydroxy-4-pregnen-3-one—synthesis □ 18-Hydroxyprogesterone—synthesis

Because recent evidence suggests that 18-hydroxydeoxycorticosterone (I) may be an important causative agent in hypertension (1–6), considerable interest recently has been shown in the synthesis of this compound. Syntheses reported to date have either been overly long (7), low in yield (7, 8), or lacking in needed experimental detail (9). The details of a short, reproducible, high yield synthesis of I from 3β-acetoxy-5-pregnen-20-one (II) are now reported (Scheme I).

DISCUSSION

3β-Acetoxy-5-pregnen-20β-ol (III), prepared in 69% yield by borohydride reduction of pregnenolone acetate (II), was subjected to photolysis in the presence of lead tetraacetate and iodine (10) to afford 3β-acetoxy-5-pregnene-18,20-lactone (IV) in a yield of 46%. Lithium aluminum hydride reduced IV to 3β,18,20β-trihydroxy-5-pregnene (V) in a yield of 91%. Oppenauer oxidation converted V to 18,20-oxido-20-hydroxy-4-pregnen-3-one (VI) in 66% yield.

The latter hemiketal (VI) was oxidized by lead tetraacetate in acetic acid (9) and then hydrolyzed with dilute hydroxide to form I. Reaction for 18 hr with excess tetraacetate caused the intermediate 21-acetoxy Compound VII to cleave to form the lactone VIII. However, by limiting the reaction time to 6 hr, VI could be transformed to I in 58% yield. An attempt to improve this yield by limiting the amount of tetraacetate proved futile.

In summary, the reported procedure has permitted the reproducible preparation of I from a cheap and readily available starting material in an overall yield of 11%.

EXPERIMENTAL[1]

3β-Acetoxy-5-pregnen-20β-ol (III)—Pregnenolone acetate (20 g) in tetrahydrofuran (100 ml) was added to sodium borohydride (3 g) in water (10 ml) and stirred at room temperature for 72 hr. Acetic acid was added and then the mixture was diluted with water. The solvent was concentrated under reduced pressure.

The solid was filtered, dried, and then chromatographed on a column of 200 g of acidic alumina. Elution with benzene–ethyl acetate (100:20) afforded III in a yield of 14 g (69%); mp 167° [lit. (11) mp 165°]; IR ($CHCl_3$): ν 3610 and 1720 cm^{-1}; NMR: δ 0.78 (s, C-18 H), 1.04 (s, C-19 H), 2.03 [s, $O(O{=})CCH_3$], and 5.39 (d, $J \approx 4$ Hz, C-5 H).

3β-Acetoxy-5-pregnene-18,20-lactone (IV)—To a stirred suspension of lead tetraacetate (15 g) and calcium carbonate (5 g) in cyclohexane (500 ml) at 80° were added iodine (4 g) and III (5 g). The stirred mixture was refluxed and irradiated with a 250-w tungsten lamp for 150 min and then was cooled and filtered. The filter cake was washed with cyclohexane, and the filtrate was washed with aqueous sodium thiosulfate (5%) and water. After pyridine (1.25 ml) was added, the filtrate was concentrated under reduced pressure.

The residue was dissolved in acetone (100 ml), and silver chromate (2.5 g) was added. The mixture was cooled to 0°, and 5.7 ml of a solution prepared by dissolving chromium trioxide (13.3 g) in sulfuric acid (11.5 ml) and diluting to 50 ml with water was added slowly. After 60 min a solution of sodium acetate (60 g) in water (100 ml) was added. The mixture was extracted two times with benzene.

The organic layer was washed (water), dried (magnesium sulfate), and concentrated under reduced pressure. Crystallization from benzene–ether gave IV in a yield of 2.4 g (46%), mp 208–210°; IR ($CHCl_3$): ν 1745 and 1720 cm^{-1}; NMR: δ 1.13 (s, C-19 H), 2.02 [s, $O(O{=})CCH_3$], and 5.40 (s, C-5 H).

Anal.—Calc. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.23; H, 8.66.

3β,18,20β-Trihydroxy-5-pregnene (V)—A mixture of IV (1 g) and lithium aluminum hydride (1 g) in tetrahydrofuran (60 ml)

[1] Melting points were determined in an open capillary tube on a Mel-temp apparatus and are uncorrected. IR spectra were recorded on a Beckman IR-8. NMR spectra were determined on a Varian A-60 spectrometer in deuterochloroform solution and are reported in parts per million downfield from a tetramethylsilane internal standard. Elemental analyses were determined by Atlantic Microlab, Inc.