spot on the developed chromatogram was determined by the dropwise addition of hexane to each spot and reexamination of the chromatogram under UV light. The areas apparently not influenced by the hexane were then treated with benzene. The areas containing the more polar substances had either little or no apparent solubility in benzene. Most impurities in the reaction products of both I and II were removed by washing the reaction residues with hexane. The washed residues, representing nearly pure I and II, were recrystallized from mixtures of benzene and hexane until a chromatogram indicated a pure substance.

Antibacterial and Antifungal Testing—Both I and II were tested for antifungal activity against *M. audouini*[5] and *T. mentagrophytes*[5] in Sabouraud liquid medium by the serial dilution method (13). Griseofulvin, used as the control agent, prevented growth of the microsporum at 1.25 μg/ml, as indicated by the absence of turbidity in the culture. Griseofulvin prevented growth of the trichophyton at 2.5 μg/ml. Neither thiosulfonate showed antifungal activity at the highest concentration tested, 125 μg/ml.

The antibacterial activity was tested by the serial dilution method using a culture of *S. aureus* (subcultured from FDA 209) in nutrient broth[6] (14). Streptomycin, used as the control agent, prevented growth of the *S. aureus* at 5 μg/ml but not at 2.5 μg/ml.

Compound I prevented growth of the *S. aureus* at 16 μg/ml but not at 8 μg/ml, while II prevented growth at 62.5 μg/ml but not at 31.3 μg/ml.

DISCUSSION

Compound I was first prepared by reacting methanesulfonyl chloride with a solution of commercial potassium sulfide to form potassium methanethiosulfonate. After combining the product of this reaction with 1,4-dibromobutane and purifying the products as described, 150 mg (representing a 2% yield) of a white crystalline compound was obtained. IR, NMR, and mass spectra were obtained for this material, Compound I.

The small yield of I obtained by this procedure was probably due to the fact that much of the commercial potassium sulfide is actually sulfurated potash, a mixture of potassium sulfides. Knowledge of the properties of I obtained from this initial preparation facilitated the separation of I in a much better yield from the reaction mixture as described. Previous attempts to synthesize I using commercial sodium sulfide had proven unsuccessful.

[5] University of Nebraska Hospital isolate No. 1.
[6] Bacto.

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Effect of Compression Force and Corn Starch on Tablet Disintegration Time

PHILIP M. HILL

Abstract □ An unusual occurrence of decreasing tablet disintegration time with increasing tablet hardness was explored. Tablets were made with varying ratios of starch disintegrant to starch paste and compressed with eight different forces. This unusual disintegration pattern is modified by changes in the starch ratios. The reason for this phenomenon is ascribed to grain swelling as the mechanism by which starch acts as a disintegrant.

Keyphrases □ Tablets—disintegration time, hardness, effect of various ratios of starch disintegrant to starch paste and various compression forces □ Disintegration time, tablet—effect of various ratios of starch disintegrant to starch paste and various compression forces □ Hardness, tablet—effect of various ratios of starch disintegrant to starch paste and various compression forces □ Dosage forms—tablets, disintegration time, hardness, effect of various ratios of starch disintegrant to starch paste and various compression forces □ Starch—effect of various ratios of disintegrant to paste on tablet disintegration time and hardness

Most articles dealing with tablet compressing report that increased compression forces result in tablets with longer disintegration times. Lowenthal (1) cited 31 references supporting this conclusion in a review of tablet disintegration. This cause–effect relationship is logical and not surprising. Higher compression forces

Table I—Formula Variations

Component, mg/Tablet	Formula A	B	C	D	E	F
Lactose	172	177	181	172	172	172
Corn starch (disintegrant)	9.4	4.7	0	9.4	4.7	0
Corn starch (paste)	5.2	5.2	5.2	5.2	9.9	14.6
Talcum powder	6.8	6.8	6.8	6.8	6.8	6.8
Magnesium stearate	1.95	1.95	1.95	1.95	1.95	1.95

Table II—Water Penetration Rate (Time in Seconds for Penetration of 10 μl) of Tablets Compressed at Various Forces

Formula	Compression Force, tons 1.0	1.3	1.7	2.0	2.3	2.7	3.0	3.3
A	9.4	10.3	13.5	15.5	18.1	20.9	26.1	31.1
B	16.9	19.0	20.5	21.1	23.5	30.7	34.0	45.7
C	34.6	63.1	266.0	—	—	—	—	>15 min
D	14.1	16.3	16.5	18.4	24.1	25.0	29.3	33.5
E	14.0	15.8	16.2	18.4	22.5	29.1	40.7	45.9
F	18.4	24.9	25.5	35.2	30.5	46.1	75.1	93.7

result in less porous tablets with the particles more strongly bonded together, as reflected by increasing tablet hardness values. Comparatively few investigators (2, 3) reported the opposite effect of faster tablet disintegration times with increasing compression forces.

The study of starch as a tablet disintegrant has not been neglected by pharmaceutical scientists (4–9). Two major theories as to how starch performs as a tablet disintegrant were proposed. One is that the starch grains form channels or pores that act to draw water into the tablet by capillarity or wicking (10). Disintegration or erosion occurs when the water dissolves the soluble components in the tablet. The other theory is that the starch grains swell upon contact with water and cause the tablet to disintegrate by physically rupturing the particle-to-particle bonds (2).

As compression force increases, a tablet becomes more dense and consequently less porous. Particle-to-particle bonds also usually become stronger. The reduced porosity, *i.e.*, smaller pore diameter, results in a longer penetrating time for water into the tablet (3, 11, 12). If wicking is the primary mode of action, disintegration time should increase with increased compression force. If grain swelling is the mechanism by which starch acts as a disintegrant, a decreasing tablet porosity should result in faster disintegration times because the starch grains can exert a force on the surrounding particles more effectively. A lightly compressed tablet has larger intergranular spaces, and the starch grains can swell considerably before they begin to exert a disruptive pressure (2).

The purpose of this paper is to present data on studies of tablet disintegration times *versus* compression force, showing that tablet disintegration times can become faster when compression force is increased. It is proposed that this occurrence indicates that the starch grain swelling mechanism of tablet disintegration is in force.

EXPERIMENTAL

A lactose–starch paste formula (Table I) was used to make the granulations. The portion of starch added to the granulations as a dry powder is referred to as disintegrant starch. The lactose and dry starch were mixed in a planetary action mixer. The starch for paste was cooked in five parts of water by weight and added to the lactose–starch blend. This was mixed to form granules and then passed through a 6-mesh screen and dried at 50°. The dried granules were sized to 16 mesh and then blended with the talcum powder and magnesium stearate. To control process variables, the starch paste was cooked to the same temperature (72 ± 1°) in each experiment.

The granulations were compressed with special semistandard, concave, 0.714-cm square punches on an instrumented rotary tablet machine[1] at eight different forces, starting at 900 kg and increasing in approximately 300-kg increments. Mean tablet thickness varied between 3.29 mm at the lowest compression force and 2.99 mm at the highest force. In Formulas A, B, and C (Table I), the total amount of starch (dry mix plus paste) per tablet decreased as the disintegrant starch was decreased. In Formulas D, E, and F, the total amount of starch in the tablet was kept constant by increasing the amount in the paste as the disintegrant starch was decreased.

Tablet disintegration times were measured in the USP tablet disintegration apparatus in 37 ± 1° water. Disintegration testing was performed without disks to avoid obscuring the differences in times between tablets compressed at the various forces. When disks are used, the disintegration time always shows an increasing trend starting from the lowest compressing force in all experiments. The mechanical action exerted by the disks apparently aids the disintegrating tablet to break up into smaller pieces which are even more susceptible to breakage by mechanical force. Use of disks thus seems to result in disintegration times that reflect the mechanical strength of the tablets, as do hardness values.

Tablet hardness values were obtained on an air-operated hardness tester[2]. The water penetration rate was measured by observing the disappearance of a 10-μl drop of water into the tablet under a low power microscope. The end-point was determined by extinction of reflected light. The values shown in Table II are the averages of three determinations.

RESULTS

Disintegration times are shown by a bar chart (Fig. 1) and are the averages of six tablets. The corresponding tablet hardness values at each compression force are shown by the curves on the same chart and are the averages of 10 tablets. Tablets compressed at the lower forces had longer disintegration times (A, B, and D, Fig. 1), except for those formulations containing no disintegrant starch (C and F, Fig. 1).

Formula E contained an increased quantity of starch paste and did not clearly show the longer disintegration times at lower pressures. In the A, B, and C series, disintegrant starch was reduced in B and absent in C. The disintegration profile in C differed completely from

[1] Stokes model B-2.
[2] Modified Strong-Cobb.

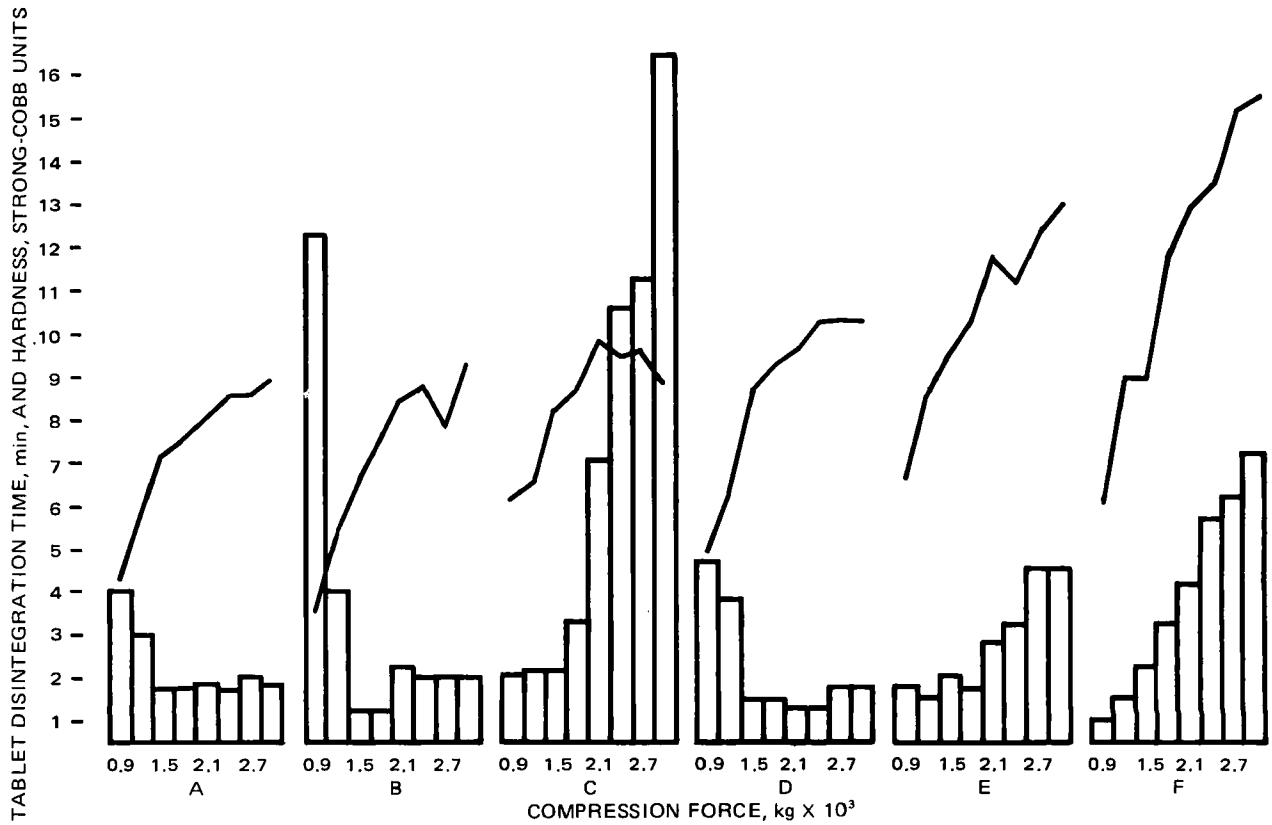

Figure 1—*Tablet disintegration times at various compression forces. Bars show disintegration time; lines show tablet hardness.*

that of A and B, illustrating the effect exerted by starch. With no disintegrant starch in C, the disintegration times at the higher compression forces were much longer than in A or B. The disintegrant starch in A and B was shown to be more effective at the higher compression forces, despite increased tablet hardness.

In D, E, and F, where the total amount of starch per tablet was kept constant, the disintegration profiles differed from those of A, B, and C. In this case, the tablet with reduced disintegrant starch (E) had a disintegration profile similar to that of tablets without disintegrant starch (C and F). The extra binder activity of the increased paste starch in E, as reflected in higher tablet hardness values, may counter the grain swelling of the disintegrant starch.

DISCUSSION

The water penetration rate values in Table II show that paste starch by itself is not as effective as disintegrant starch (uncooked starch) in providing water absorbency to a tablet (compare Formula C with A or B in Table II). However, of the two formulas containing paste starch only, the one with the greater quantity had better water absorbency (compare Formula F with C, Table II). This improved absorbency of F probably accounts for its generally faster disintegration time as compared to C (Fig. 1).

The varying disintegration times of tablets compressed at the same compression forces is related to the presence or absence of disintegrant starch in the tablet as well as to the ratio of disintegrant starch to paste starch. When disintegrant starch was present in a quantity approximately equal to or greater than the quantity of paste starch, disintegration time was shorter at the higher compression forces. When disintegrant starch was absent or was greatly exceeded in quantity by paste starch, tablet disintegration times at the higher compression forces were longer. This effect was very striking in the A, B, and C series, where the paste starch quantity was kept constant.

If it is accepted that the longer disintegration times at the low compression forces are typical of the starch grain swelling mechanism of disintegration, then it might be expected that tablets without disintegrant starch will disintegrate by a different mechanism and show a different disintegration time–compression force profile. With Formulas C and F, tablet disintegration time followed the more generally expected pattern of increasing time with increasing compression force. Here the mechanism might be postulated to be water penetration by capillary movement and disintegration by dissolution of particle bonds. The disintegration time–compression force profile shows a positive correlation with the water penetration time *versus* compression force data for these trials and suggests that tablet porosity is controlling disintegration time.

This finding is in contrast to that for Formulas A, B, and D, where the disintegration time–compression force profile does not correlate positively with water penetration times. The water penetration data show that water readily entered the tablets compressed at the lowest forces. The fact that the tablets did not disintegrate as quickly as those compressed at higher forces supports the starch grain swelling theory, and this theory would explain why the water penetration rates do not correlate with disintegration times in A, B, and D.

Tablets without a disintegrant have a shorter disintegration time at the lowest compression forces than do the tablets containing a disintegrant. The starch seems to inhibit disintegration at low compression forces. This result could be explained by theorizing that the expanded starch granules occlude some of the relatively larger channels of the softer tablets, resulting in nonuniform water penetration and breakup of the tablet.

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Quantitative Determination of Morphine in Paregoric USP by High-Pressure Liquid Chromatography

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Abstract □ The quantitative determination of morphine in paregoric by reversed-phase high-pressure liquid chromatography is described. The method is simple, accurate, and fast compared to the USP method. Benzoic acid in paregoric also can be determined quantitatively with the same column. The method was applied to two commercial samples with excellent results.

Keyphrases □ Morphine—high-pressure liquid chromatographic analysis in commercial samples of paregoric □ High-pressure liquid chromatography—analysis, morphine in commercial samples of paregoric □ Paregoric—high-pressure liquid chromatographic analysis of morphine and benzoic acid, commercial samples □ Analgesic agents—morphine, high-pressure liquid chromatographic analysis in commercial samples of paregoric

The USP method (1) for the quantitative determination of morphine in paregoric is tedious and time consuming. No other easy method is available for determining morphine in paregoric USP. The purpose of these investigations was to develop a simple, accurate, and fast method for the analysis of morphine using high-pressure liquid chromatography (HPLC). A method for the quantitative determination of benzoic acid in paregoric using the same column also is described.

EXPERIMENTAL

Apparatus—A high-pressure liquid chromatograph[1] capable of operating at an inlet pressure up to 6000 psig was used.

Column—The column[2] (30 cm long and 4 mm i.d.) was purchased and used as received. It consisted of a monomolecular layer of octadecyltrichlorosilane permanently bonded to silica *via* silicon–carbon bonds.

Recorder—The recorder[3] was equipped with an integrator.

Chromatographic Conditions—The chromatographic solvents were: (*a*) 0.1 *M* KH_2PO_4 buffer solution in 7% (v/v) methanol in water for morphine and (*b*) 0.1 *M* KH_2PO_4 buffer solution in 10% (v/v) methanol in water for benzoic acid. The temperature was ambient. The flow rate was 1.8 ml/min (inlet pressure approximately 1000 psig) for morphine or 3 ml/min (inlet pressure approximately 2100 psig) for benzoic acid. The absorbance unit full scale was 0.16, and the chart speed was 30.5 cm (12 in.)/hr.

Chemicals and Reagents—All chemicals and reagents were USP, NF, or ACS grade. Morphine sulfate[4] USP and all other reagents were used without further purification.

Solutions—*Benzoic Acid Standard Solution*—Weigh 100.32 mg of benzoic acid, dissolve in 15.0 ml of approximately 0.1 *N* NaOH solution, and dilute to volume (100.0 ml) with water.

Morphine Standard Solution—Weigh 53.3 mg of morphine sulfate (equivalent to 40.0 mg of anhydrous morphine) and dissolve in enough water, containing 8.0 ml of approximately 0.1 *N* H_2SO_4, to bring to 250.0 ml.

Standard Mixture Similar to Paregoric—Dissolve 53.3 mg of morphine sulfate in 4–5 ml of water; dissolve 0.38 ml of anise oil, 0.38 g of benzoic acid, 0.38 g of camphor, and 3.8 ml of glycerin in 48 ml of alcohol. Mix the aqueous and alcoholic solutions and dilute to volume (100.0 ml) with water.

Assay Procedure for Morphine in Standard Mixture and Paregoric—Transfer 10.0 ml of the standard mixture or paregoric to a 150-ml beaker and add 2.0 ml of ~0.1 *N* H_2SO_4 and 20 ml of water. Boil on a hot plate until the volume is approximately 8 ml, cool, and dilute to volume (25.0 ml) with water. Filter if necessary and inject 40.0 μl, using the described chromatographic conditions.

The detector response to the standard mixture and one commercial sample is presented in Fig. 1. Since preliminary investigations indicated that concentration (4–8 μg) was directly related to the peak area,

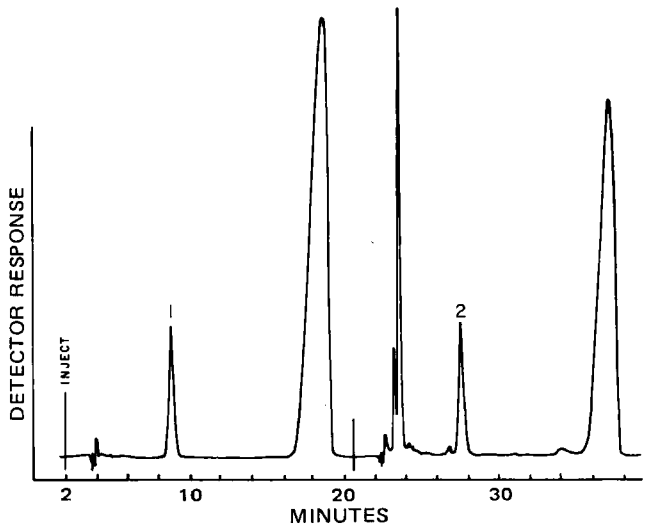

Figure 1—*HPLC analysis of morphine in paregoric USP (for chromatographic conditions, see text). Key: 1, standard mixture; and 2, paregoric sample.*

[1] Waters ALC 202 equipped with U6K Universal liquid chromatograph injector and UV detector (254 nm), Waters Associates, Milford, Mass.
[2] μBondapak/C_{18}, Waters Associates, Milford, Mass.
[3] Omniscribe model 5213-12, Houston Instruments, Austin, Tex.
[4] Merck & Co.