Effect of Compressional Force on Tablets Containing Cellulosic Disintegrators I: Dimensionless Disintegration Values

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Abstract □ Spray-dried lactose tablets containing cellulosic disintegrators or microcrystalline cellulose were compressed at different compressional forces. USP disintegration times were measured as a function of pH and compressional force. Two dimensionless quantities were derived from the experimentally determined disintegration times, and their utility in the study of tablet formulations was demonstrated. These dimensionless quantities were used to assess the effect of compressional force and pH on distintegration behavior as well as to compare disintegrator efficiency. Two internally cross-linked sodium carboxymethylcellulose disintegrators were found to be the most efficient; their efficiency increased with increasing compressional force at all pH values.

Keyphrases □ Compressional force—effect on tablets containing cellulosic disintegrators, dimensionless disintegration values □ Disintegrators, cellulosic—effect of compressional force on tablets, dimensionless disintegration values □ Disintegration—dimensionless values, effect of compressional forces on tablets containing cellulosic disintegrators

Considerable knowledge has been accumulated in the past concerning the behavior and mechanism of action of disintegrators, particularly those belonging to the starch family (1, 2). With the introduction of several new disintegrators in recent years, interest has become focused on methods of evaluation of disintegrator function and on the elucidation of their mechanism of action (3–7). The one basic measurement generally used in evaluating disintegrators in a tablet formulation, regardless of all other aspects of the study, is the measurement of disintegration time.

It is the aim of this paper to define two dimensionless quantities which can be derived from the experimentally determined disintegration times and, furthermore, to illustrate by the use of a simple tablet formulation that their application gives access to a wealth of information concerning the performance of disintegrators under a variety of processing and testing conditions. Also, our aim is to demonstrate that information inherent, but not immediately evident, in disintegration times can be extracted by a simple and considerably underutilized technique of data analysis. Compressional force was chosen as the processing variable and pH as the testing variable to demonstrate the utility of dimensionless disintegration values. The importance of pH in the evaluation of disintegrator behavior has been demonstrated by Shangraw *et al.* (4).

EXPERIMENTAL

Materials—The tablet matrix consisted of spray-dried lactose[1] containing 0.25% magnesium stearate[2] as the lubricant. The disintegrators used were two sodium carboxymethylcellulose derivatives (croscarmellose sodium type A[3] and type B[4]) and low-substituted hydroxypropyl cellulose[5]. Microcrystalline cellulose[6] was included for comparison in an additional series of tablets. All excipients were used at a fixed concentration of 3%.

Methods—A portion of the spray-dried lactose (~90%) was mixed with the disintegrator in a laboratory-scale twin-shell blender[7] for 7 min. The remaining spray-dried lactose was mixed with the magnesium stearate, the mix passed through a 60-mesh screen, and added to the bulk material. The entire mixture was then blended for 7 min.

Tablets were compressed on an instrumented rotary tablet machine (8) tooled with 12.7-mm round flat-faced punches. The tablet weight of each formulation was 725 mg. Samples of each tablet formulation were compressed at four different compressional forces. Although the forces were not identical in each series, their values were comparable (Table I). Values for tablet hardness were determined using a Schleuniger hardness tester[8] and are reported in kiloponds (kp, 1 kilogram-force) as the average of 10 measurements.

Disintegration times were measured according to USP XX method. Besides distilled water (pH 6.0), USP simulated gastric fluid (pH 1.5) and intestinal fluid (pH 7.5) without enzymes were also used to assess the effect of pH. All measurements were carried out using 1-day-old tablets.

RESULTS AND DISCUSSION

Physical Properties and USP Disintegration Times—The compressional forces used and the resulting physical properties of the control matrix and tablets containing the disintegrators are listed in Table I. Tablet hardness showed typical compressional force-dependent behavior as expected; *i.e.*, tablet breaking strength increased with increasing compressional force within each tablet formulation. Tablets containing low-substituted hydroxypropyl cellulose or microcrystalline cellulose had breaking strengths considerably higher than the control matrix. The increase was found to be approximately the same with these two excipients.

Since spray-dried lactose is soluble in aqueous media, its behavior in the absence of disintegrators should be properly described as slow dissolution rather than disintegration. However, for sake of uniformity and for purposes of comparison, the term disintegration will be used throughout the paper to describe the behavior of the control matrix.

Disintegration times of the control tablets were found to be both compressional force and pH dependent, as indicated by the values listed in Table II. Regardless of the pH of the test fluid, disintegration times increased with increasing compressional force and at each compressional force, the shortest disintegration time was measured at pH 1.5.

Tablets containing croscarmellose sodium, type A or B, had disintegration times apparently independent of both the processing and testing variable, *i.e.*, within both series, disintegration times were approximately the same at all compressional forces and at all pH values. A somewhat similar insensitivity of disintegration times to compressional force was found by Miller *et al.* (9) when studying the behavior of acetaminophen tablets containing these disintegrators. The disintegration times of tablets containing low-substituted hydroxypropyl cellulose were relatively insensitive to pH, but varied with compressional force exhibiting a minimum at 92.9 MN/m^2 (sample 2) and then increasing with increasing compressional force. The presence of 3% microcrystalline cellulose resulted in a decrease in disintegration times for the lower compressional forces (samples 1 and 2), followed by a considerable increase at higher compressional forces (samples 3 and 4) at all pH values.

Except for the control matrix, disintegration times did not correlate with tablet hardness in any of the tablet formulations. Such a lack of correlation has been reported recently (10) for theobromine tablets containing cornstarch, microcrystalline cellulose, or crospovidone as disintegrators.

Dimensionless Disintegration Value, T_N—To facilitate comparison among

[1] Foremost Foods, agent Charles Tennant & Co. Canada Ltd., Dorval, Quebec.
[2] Witco Chemicals, Montreal, Quebec.
[3] AcDiSol; FMC Corp, Dorval, Quebec.
[4] CLD-2; Buckeye Cellulose, Memphis, Tenn.
[5] L-HPC Type LH-11; Shinetsu, agent Biddle Sawyer, New York, N.Y.
[6] Avicel PH 101; FMC Corp., Dorval, Quebec.
[7] The Patterson-Kelley Co. Inc., East Stroudsburg, Pa.
[8] Vector Corp., Marion, Iowa.

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Table I—Physical Properties of Tablets

Disintegrator	Sample No.	Average Compressional Force, MN/m^2	Average Tablet Thickness ± *SD*, mm	Average Breaking Strength ± *SD*, kp
Control	1	52.9	4.81 ± 0.02	4.1 ± 0.1
	2	86.1	4.60 ± 0.01	6.4 ± 0.2
	3	120.3	4.38 ± 0.01	9.3 ± 0.2
	4	155.9	4.24 ± 0.01	13.9 ± 0.5
Croscarmellose sodium Type A	1	64.9	4.82 ± 0.02	3.2 ± 0.2
	2	93.2	4.60 ± 0.01	5.9 ± 0.3
	3	128.8	4.40 ± 0.01	9.3 ± 0.4
	4	161.8	4.28 ± 0.01	12.7 ± 0.5
Type B	1	63.0	4.88 ± 0.02	4.5 ± 0.2
	2	90.1	4.62 ± 0.01	6.7 ± 0.3
	3	129.1	4.36 ± 0.01	11.2 ± 0.3
	4	166.2	4.23 ± 0.01	15.1 ± 0.5
Low-substituted hydroxypropyl cellulose	1	55.0	4.74 ± 0.01	5.2 ± 0.5
	2	92.0	4.45 ± 0.01	8.0 ± 0.2
	3	125.4	4.29 ± 0.01	13.0 ± 0.2
	4	167.2	4.14 ± 0.01	17.2 ± 0.9
Microcrystalline cellulose	1	61.9	4.74 ± 0.02	5.7 ± 0.3
	2	92.9	4.47 ± 0.02	9.3 ± 0.3
	3	123.8	4.29 ± 0.02	13.1 ± 0.6
	4	159.4	4.18 ± 0.02	17.5 ± 0.6

tablets of different compositions, the disintegration times were normalized to that of tablets compressed at the lowest compressional force (sample 1) in each series according to the definition given by Eq. 1A (see *APPENDIX*). Values of T_N are plotted in Fig. 1.

The use of a dimensionless quantity such as T_N allows direct comparison of trends in tablet behavior with compressional force or with any other variable affecting disintegration times, *e.g.*, concentration of disintegrator, concentration of other excipients such as materials to improve the powder flow and lubricants, and the length of time of mixing of tablet ingredients prior to compression. In such a comparison the disintegration time of the first tablet of the series (in this case the tablet compressed at the lowest compressional force) becomes unity. Values of $T_N < 1$ are indicative of a beneficial effect of the variable on disintegration, whereas values of $T_N > 1$ indicate a detrimental effect.

In addition to overall trends, small differences in disintegration properties due to the presence of different disintegrators in the tablet matrix become immediately apparent, as illustrated in Fig. 1. Admixing of croscarmellose sodium type A is shown to result in a complete insensitivity of disintegration behavior to both pH and compressional force, at least within the limits used in this study. The addition of croscarmellose sodium type B results in complete pH insensitivity and an apparent slight compressional force dependence. This behavior was found to be reproducible.

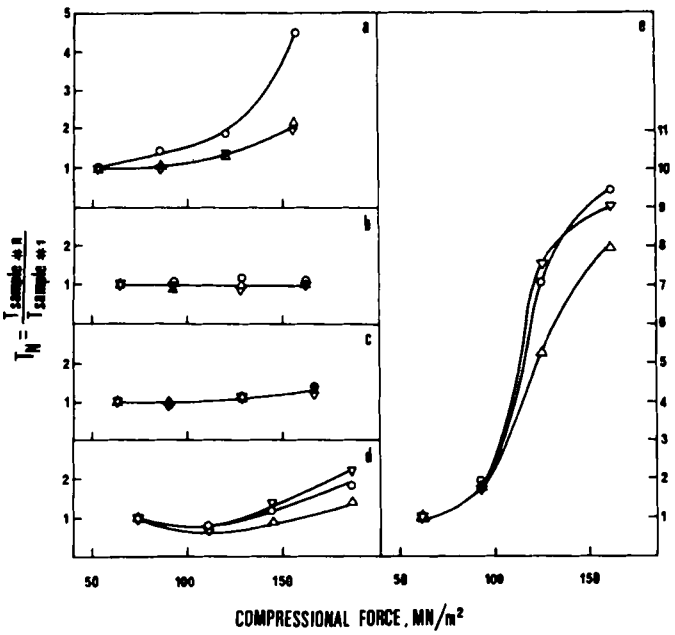

Figure 1—*Plots of the dimensionless disintegration quantity (Eq. 1A) as a function of compressional force and pH of test fluid. Values of* T_N *were calculated from the experimentally determined USP disintegration times for spray-dried lactose tablets containing (a) no disintegrant, (b) croscarmellose sodium, type A, (c) croscarmellose sodium, type B, (d) low-substituted hydroxypropyl cellulose, and (e) microcrystalline cellulose. Key: (○) pH 1.5; (△) pH 6.0; (▽) pH 7.5.*

Dimensionless Disintegration Value, T_C—A second dimensionless quantity may be derived from the experimentally determined disintegration times according to Eq. 2A (see *Appendix*). Here, the disintegration times of tablets containing a variety of disintegrators are normalized to the disintegration times of a common matrix. The quantity so obtained allows one to quantitatively assess and compare disintegrator efficiency.

Values of T_C are plotted in Fig. 2. While the previously discussed dimensionless quantity T_N allows direct comparison of the disintegration behavior of tablets of widely different disintegration times, T_C gives clear indications of disintegrator performance with respect to pH, *i.e.*, whether the tablet is effectively designed to disintegrate in a particular medium.

To illustrate this point one may compare the behavior of tablets compressed at ~90 MN/m^2 (sample 2) and containing either croscarmellose sodium (type

Table II—Disintegration Times [a] as a Function of Compressional Force and pH of Test Fluid

Disintegrator	Sample No.	Disintegration Time, s pH 1.5	pH 6.0	pH 7.5
Control	1	115	312	340
	2	168	345	370
	3	218	392	500
	4	525	680	720
Croscarmellose sodium Type A	1	90	95	115
	2	100	83	110
	3	105	88	100
	4	100	100	120
Type B	1	73	78	95
	2	70	78	90
	3	85	83	102
	4	98	98	110
Low-substituted hydroxypropyl cellulose	1	125	180	138
	2	100	145	88
	3	150	160	188
	4	225	250	283
Microcrystalline cellulose	1	64	95	105
	2	125	165	180
	3	460	500	790
	4	615	755	945

[a] The average of the longest disintegration times measured on two sets of six tablets is given.

A or B) or low-substituted hydroxypropyl cellulose. In simulated gastric fluid, the tablet containing croscarmellose sodium type A has a T_C value of 0.6; *i.e.*, due to the presence of the disintegrator, the disintegration time of the tablet is 60% of that of the control matrix in a highly acidic medium. The tablet containing croscarmellose sodium type B has a T_C value of 0.42, and that containing low-substituted hydroxypropyl cellulose has $T_C = 0.60$. Clearly, the most efficient disintegrator in this case is croscarmellose sodium type B, since its presence in the tablet formulation results in a larger reduction of disintegration time than the inclusion of either of the other two cellulosic disintegrators.

In simulated intestinal fluid, however, the behavior of all three tablet formulations is very nearly identical, as indicated by the values of T_C. For the tablet containing croscarmellose sodium type A, $T_C = 0.30$ (*i.e.*, a 70% reduction in disintegration time in a near neutral medium), and for those containing croscarmellose sodium type B or low-substituted hydroxypropyl cellulose, $T_C = 0.24$. Here, then, any of the three disintegrators would be similarly efficient.

In addition to allowing the formulator to assess disintegrator efficiency, the dimensionless disintegration quantity, T_C, has further utility. It was noted earlier that the absolute values of disintegration times were independent of compressional force when either croscarmellose sodium type A or B were used as the disintegrator. When describing the behavior of these tablet formulations in terms of T_C, the effect of compressional force becomes evident. In fact, values of T_C indicate that all tablet formulations used in this study exhibited compressional force as well as pH-dependent behavior from the point of view of disintegrator efficiency. In all tablet formulations the disintegrators were found to be the least efficient at pH 1.5, where the spray-dried lactose matrix disintegrated most readily, and were about equally efficient at pH 6.0 and 7.5, except low-substituted hydroxypropyl cellulose, which seemed to be most efficient at pH 7.5 in tablets processed at low compressional forces.

Examining the trends shown by tablets containing the sodium carboxymethylcellulose derivatives, the effect of compressional force on these two disintegrators is highlighted quite dramatically. The higher the compressional force applied to the tablets, the more efficient these two disintegrators become, *i.e.*, the reduction in disintegration times from that of control increases with increasing compressional force. This effect is most pronounced at pH 1.5, as illustrated by Fig. 2a and b. It is felt that this type of behavior is a strong indication of the importance of deformation due to compression in the mechanism of action of croscarmellose sodium.

Tablets containing microcrystalline cellulose show a biphasic trend, as already mentioned when discussing disintegration times (Table II). It is interesting to note here that in terms of disintegrator efficiency, microcrystalline cellulose (used at the unusually low concentration of 3%) did indeed act as a true disintegrator at the two lower compressional forces, where the reduction of disintegration time with respect to the control was found to be comparable with that obtained with the other disintegrators. The two samples made at higher compressional force, however, showed increased disintegration times at all pH values when compared with the appropriate controls. Here, the excipient caused retardation of disintegration rather than facilitating it. The extent to which microcrystalline cellulose facilitated or hindered disintegration is numerically expressed by values of T_C.

CONCLUSIONS

Two dimensionless quantities were defined and calculated from the experimentally determined USP disintegration times, and their use was demonstrated with a simple tablet formulation. Although the practice of using dimensionless quantities is not widespread in physical pharmacy, their utility may be considerable when comparisons must be made among systems of widely differing properties, such as those encountered during the development of pharmaceutical dosage forms.

APPENDIX—DEFINITION OF DIMENSIONLESS DISINTEGRATION VALUES

The first dimensionless quantity, T_N, facilitates comparison within a given tablet formulation and is defined as:

$$T_N = \frac{T_{\text{sample } n}}{T_{\text{sample 1}}} \qquad \text{(Eq. 1A)}$$

where $T_{\text{sample } n}$ is the disintegration time of the nth member of a series of tablets all containing the same disintegrator and compressed at different compressional forces, and $T_{\text{sample 1}}$ is the disintegration time of the tablet processed at the lowest compressional force within the series. Both disintegration times must be determined at the same pH.

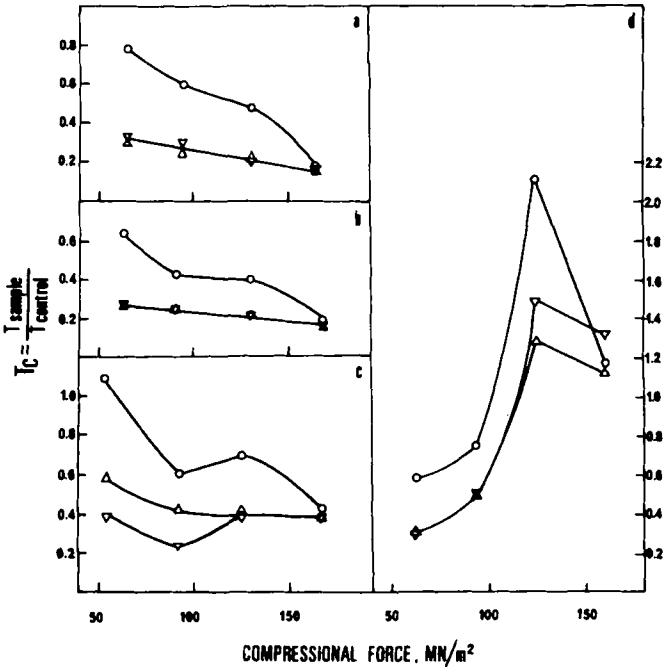

Figure 2—*Plots of the dimensionless disintegration quantity (Eq. 2A) as a function of compressional force and pH of test fluid obtained for spray-dried lactose tablets containing (a) croscarmellose sodium, type A, (b) croscarmellose sodium, type B, (c) low-substituted hydroxypropyl cellulose, and (d) microcrystalline cellulose. Key: (○) pH 1.5; (△) pH 6.0; (▽) pH 7.5.*

The second dimensionless quantity, T_C, is used to evaluate disintegrator efficiency and is given by:

$$T_C = \frac{T_{\text{sample}}}{T_{\text{control}}} \qquad \text{(Eq. 2A)}$$

where T_{sample} is the disintegration time of a tablet containing a specific disintegrator and compressed at a given compressional force, and T_{control} is the disintegration time of a tablet which contains no disintegrator and is compressed at the same compressional force. Both T_{sample} and T_{control} must be determined at the same pH.

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