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Evaluations of the Mechanism of Disintegrant Action

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ABSTRACT

The disintegrant properties of eight tablet disintegrants (a cation exchange resin, cross-linked carboxymethyl cellulose, sodium starch glycolate, U.S.P., Crospovidone, U.S.P., corn starch, an insoluble anionic cellulose polymer, a modified food starch, and a soybean cellulose derivative) have been evaluated. Three techniques were applied to some or all of the materials. Water uptake rates and capacities were determined for all disintegrants in bulk powders. Disintegration times of tablets formulated with varying concentrations of the different disintegrants in a matrix comprising 75% unmilled dibasic calcium phosphate dihydrate and 25% anhydrous lactose were measured. For four disintegrants, a novel computer assisted cinephotomicrographic technique was applied to investigate the interaction of water with individual disintegrant particles, both in terms of swelling rate and maximum water capacity.

Comparative evaluation of tablet disintegrants and studies of the mechanism of disintegrant action have quite properly attracted the

attention of a number of pharmaceutical scientists. (1-16) However, it is clear that at present there is no concensus concerning a general theory rationalizing disintegrant action and at least five separate mechanism have been proposed (1, 2, 4).

In the present paper, the disintegrant action of eight disintegrants has been studied using three separate approaches. Firstly, the rate and capacity of the bulk powders to take up water and to swell as a result has been evaluated using an apparatus similar to that used by Nogami and coworkers (5). Secondly, the disintegration times of tablets containing varying concentrations of disintegrant and compressed using a matrix of 75% unmilled dibasic calcium phosphate dihydrate and 25% anhydrous lactose were determined in a manner similar to that described by Rudnic and his associates (6). Thirdly, the authors are able to report - apparently for the first time - the use of a new method for evaluating the rate and extent of swelling of individual units in an assembly of disintegrant particles. This method exploits a cinephotomicrographic technique in which groups of disintegrant particles are photographed under a microscope by a high speed movie camera with the resultant film being analyzed by a special computer technique which allows the size of both individual and all particles, in any given visual field, to be followed over the very short period of time which elapses during the interaction of the disintegrant particles with water. The results presented in this paper demonstrate that a combination of the three methods described above and, in particular, the computer assisted cinemicrophotographic technique allow considerable insight to be gained of the disintegration process.

THEORY

The simplest model which we may consider for disintegrant action consists of a spherical disintegrant particle, of volume V_o, embodied in an insoluble isotropic matrix of a specified standard porosity. Water reaches the particle which then swells eventually

reaching a new size, V_{max}. A number of authors have directed attention to the role of disintegrant swelling in the disintegrant sequence (3, 5, 7, 8, 15, 16). The change in volume, $V_{max} - V_o$, sets up a stress in the vicinity of the disintegrant particle which, depending on the elasticity of the matrix, will be transmitted throughout the tablet or to some extent, be accommodated locally by changes in molecular conformation of matrix or disintegrant. Measurement of transmitted pressure resulting from disintegrant action (9), although of considerable interest, has a distinct limitation that since tablet matrices differ in degree of elasticity, the pressure developed at the loci of action will differ, to varying extents for different matrices to that measured at the tablet surface. It is, of course, well established from instrumented press studies that there is a significant difference between applied and transmitted forces.(8, 13 and 14).

Although the magnitude of the force produced by disintegrants, as described for example by List and Muazzan (9), has obvious relevance to disintegrant action, the rate at which that force develops, dF/dt, is also likely to be a factor involved in governing disintegrant action. If the force builds up slowly, then the tablet matrix may be able to adjust to the stress without loss of structural integrity whereas if the force is developed very rapidly, matrix accommodation to the stress will not be possible and disintegration will occur.

It is proposed that the rate of swelling of a disintegrant is related to the rate at which disintegrant force develops

$$dF/dt = K\ dV/dt \qquad (1)$$

where dV/dt is the rate of swelling and K is a constant for any given matrix of formulation at a constant porosity value. If the porosity of the tablet is high, then dV/dt will be governed by the properties of the disintegrant such as surface area or number

of hydratable functional groups. However, if the porosity is low, then the value of dV/dt could be primarily controlled by the rate at which water can reach the disintegrant. A similar situation probably exists if tablets of high porosity are exposed to water vapor rather than liquid water (10).

The simple model discussed above clearly indicates the importance of both swelling capacity of disintegrant particles, $V_{max}-V_o$, and rate of swelling, dV/dt however, it is clear that the model must be elaborated if it is to be usefully applied to real situations. Firstly, since pharmaceutical tablets are only compressed in one dimension, it is probably unjustifiable to define the matrix as isotropic. The compaction process will result in stress in the plane of compaction. Experimental evidence supporting this view was obtained by Khan and Rhodes who determined the ratio value, R, of changes in thickness to changes in diameter of tablets, swelling under conditions of controlled relative humidity (10). In all cases, R was greater than unity. This indicates that tablets are more likely to disintegrate in the plane of compaction than the planes of non-compaction. Also, it has been shown that swelling rates, for some disintegrants at least, are dependent on the pH of the disintegrant media (3). The pH at the loci of disintegration will be controlled by the pH of the dissolution field (e.g., gastric or intestinal juice) and by any soluble acidic or basic components within the formulation (e.g., sodium carbonate). Further, not all disintegrants swell equally in all dimensions. Cross-linked carboxymethyl cellulose derivates, which are often approximately cylindrical in shape, increase in radius but show little change in length when exposed to water. This vectorial dysymmetry in swelling may perhaps be of relevance in disintegrant action, although it might reasonably be predicted that since the orientation of an assembly of disintegrant particles distributed throughout a tablet matrix is likely to be random, the disintegrant force may be non-vectorial.

EXPERIMENTAL

Tablets containing 75 percent unmilled dibasic calcium phosphate dihydrate[1] and 25 percent anhydrous lactose[2] were compressed on a single punch tablet press[3] to the same hardness as the control system previously reported (6) i.e., nine kilograms. Eight tablet disintegrants were used (an ion-exchange resin[4], cross-linked carboxymethylcellulose[5], sodium starch glycolate, U.S.P.[6], cross-linked polyvinylpolypyrrolidone[7] (Crospovidone U.S.P.), corn starch U.S.P.[8], an insoluble anionic cellulose polymer[9], a modified food starch[10] and a soybean cellulose derivative[11]) and incorporated separately into the control matrix in concentrations of 1/4, 1/2, 1 and 2 percent (w/w). Each system and the control was lubricated by incorporating magnesium stearate[12] into the system at a concentration of 1/2 percent (w/w). The magnesium stearate was passed through a 60-mesh bolting cloth prior to mixing. All ingredients were mixed together after weighing using a roller mixer for 30 minutes. All systems were compressed to hardness similar to those reported previously (10), and tablets were tested for weight, hardness (Erweka) and disintegration time (using a USP apparatus, with disks). The

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[1] Stauffer Chemical Co.

[2] Foremost Food Co.

[3] Stokes Model F Single Punch Press, Stokes-Penwalt Co.

[4] Amberlite IRP-88, Rohm and Haas Co.

[5] Ac-Di-Sol, FMC Corporation

[6] Explotab, Edward Mendell Co.

[7] Polyplasdone XL, GAF Corporation

[8] Ruger Chemical Co.

[9] CLD-2, Buckeye Corp., Memphis TN

[10] STA-Rx 1500 Starch, Stawy Starch Co.

[11] Emcosoy, Edward Mendell Co.

[12] Ruger Chemical Co.

disintegration times were ranked and correlated with the previous study (6).

Bulk and tapped density[12], particle size (as estimated by seive analysis[13]) and bulk swelling capacity of the disintegrants were determined. The apparatus used to test bulk swelling was a modification of the apparatus reported by Nogami, et al (5). This apparatus is shown in Fig. 1. A sample of 500 mg of each disintegrant was placed in the sample tube and the volume of the powder and the liquid taken up into the sample (both measured in ml.) were observed simultaneously at pre-determined time intervals. Distilled water was used as test media. The reproducibility of this method is evident in Table I.

The bulk swelling of the tablet disintegrants, V_b, was estimated as a percent of original volume using equation two:

$$V_b = ((h_t - h_o/h_o)100 \qquad (2)$$

where h_o is the original height of powder bed and h_t is the height of powder bed at time t. Water uptake was measured in milliliters.

In addition, intrinsic swelling rates of the individual particles of four disintegrants were measured. The method consisted of observing the wetting and swelling of particles through a microscope,[14] and recording the event with a movie camera[15]. The camera speed was set at either 24, 32 or 64 frames/second. The camera was calibrated by filming a stopwatch. Some frames, identified chronologically, were photo-enlarged. These photographs were then image analyzed using a computer, which was interfaced with a camera[16]. By this method, a very accurate measurement of the intrinsic

[12]Numinco Tapper Model JBL-ST-2, J. Englsmann A.-G

[13]Allen-Bradley Sonic Sifter, Allen-Bradley Co., Milwaukee, Wis.

[14]Zeiss Photomicroscope II, Carl Zeiss, Co., Switzerland

[15]Bolex, 16 mm Double Sprocket Movie Camera

[16]Imanco Quantimet 720, System 25 with Digital rx01 Drive and PDP 11/04 computer. The Macrounit used a Vivitar Zoom Lens (35-85 mm) with a Vidicon Scanner.

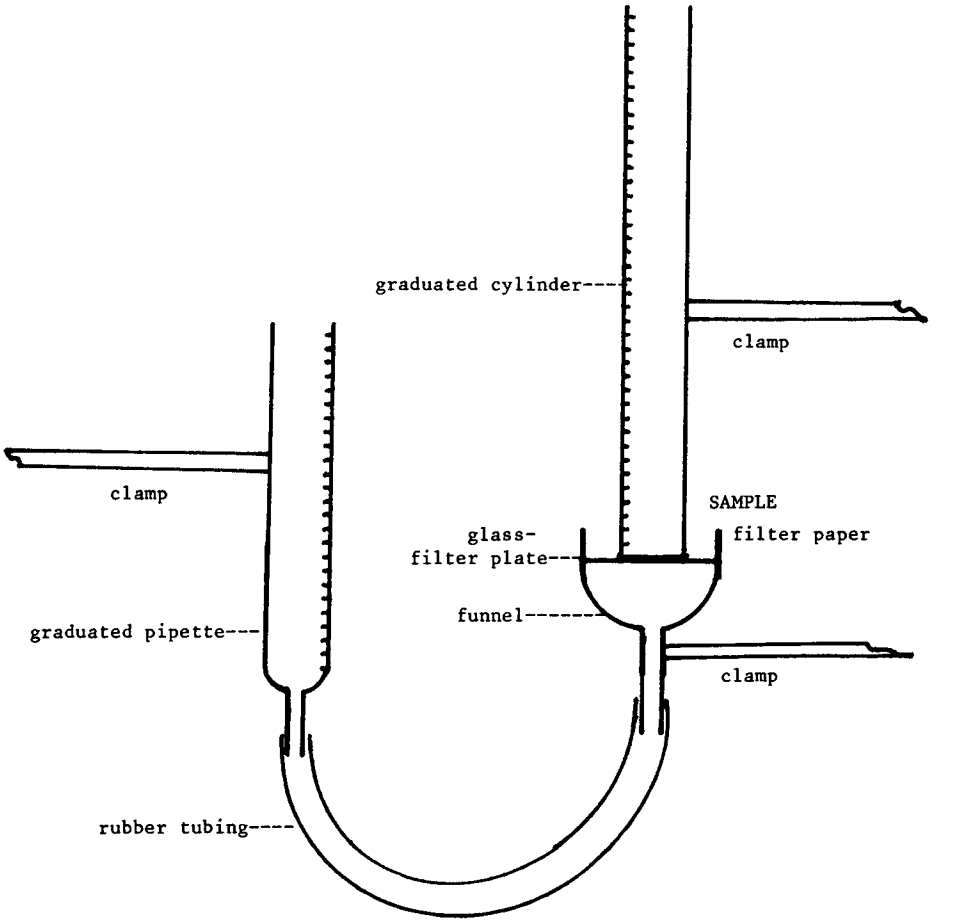

FIG. 1. Apparatus for measurement of swelling rate and water uptake.

swelling rate of a statistical number of particles was achieved. An example of this analysis for one particle is shown in Fig. 4.

The intrinsic swelling rate, dS_i/dt, was estimated using equation three:

$$dS_i/dt = ((A_t - A_o)/A_o) \times 100 \quad (3)$$

where A_o is the original area of the disintegrant particles, and A_t is the area of particles at time t.

Table I

Reproducibility of Bulk Swelling Test Data of

Sodium Starch Glycolate, U.S.P.

Time (min.)	Mean (Percent)[1]	R.S.D.[2]
0	0	0
1	141	28.0
2	257	22.6
4	378	14.5
6	462	13.3
10	641	4.6
15	745	5.4
20	862	3.8
30	1011	2.6
60	1263	2.4

1. n=6, values are mean percent increase in volume
2. Relative Standard Deviation
   i.e., (Standard Deviation/Arithmetic Mean) x 100

RESULTS AND DISCUSSION

Characterization data, bulk and tapped density and sieve analysis, for the eight disintegrants are given in Tables II and III. Tables IV to XI record the properties of tablets made containing the various disintegrants. It can be seen that, as the disintegrant concentration is increased, there is a progressive reduction in disintegration time for any given disintegrant.

Table II

Density (gm/ml) of Eight Tablet Disintegrants

Disintegrant	Bulk	Tapped*
Ion-Exchange Resin	0.48	0.62
Carboxymethyl Cellulose	0.48	0.67
Crospovidone, U.S.P.	0.24	0.29
Corn Starch, U.S.P.	0.52	0.81
Sod. Starch Glycolate,U.S.P.	0.76	0.89
Modified Food Starch	0.63	0.81
Anionic Cellulose Polymer	0.19	0.29
Soybean Cellulose Derivative	0.17	0.26

*Tapped for 1000 times on a motorized tapper.

Table III

Seive Analysis Data for Eight Tablet Disintegrants

	% smaller than (microns)					
Disintegrant	45	63	90	125	180	250
Ion-Exchange Resin	32.1	46.9	68.9	90.2	96.9	98.4
Carboxymethyl Cellulose	87.4	91.0	93.4	95.1	96.5	98.0
Crospovidone U.S.P.	5.1	10.7	26.0	47.5	69.7	82.9
Corn Starch U.S.P.	28.2	35.3	72.2	85.0	93.1	96.5
Sodium Starch Glycolate,U.S.P.	53.3	85.1	93.4	96.5	97.4	98.7
Modified Food Starch	20.3	31.5	55.7	77.4	95.1	98.6
Anionic Cellulose Polymer	45.4	70.3	90.3	96.0	98.8	98.7
Soybean Cellulose Derivative	30.4	53.1	76.3	86.8	96.6	98.7

*All samples were seived using an Allen-Bradley Sonic Sifter, for five minutes with all settings at a level of five.

Table IV

Effect of Ion Exchange Resin on Tablet Weight, Hardness and Disintegration

Tablet:	Control	% Concentration 1/4	1/2	1	2
Weight (mg)	406.5	400.6	404.2	395.5	394.1
R.S.D.[1]	0.70	0.29	0.42	0.40	0.33
Hardness (kg)	9.20	8.55	8.45	8.20	8.70
R.S.D.[2]	8.15	5.76	6.35	5.12	4.23
Disintegration time (min)	120+	9.96	4.60	2.62	0.84
Range[3]	-	8.94-10.4	4.3-5.1	1.9-2.9	0.5-1.2
R.S.D.[3]	-	10.0	7.1	18.6	10.4

1. n = 20
2. n = 20
3. n = 6

Note: R.S.D. refers to Relative Standard Deviation
i.e., (Standard Deviation/Arimetric Mean) x 100

Table V

Effect of Carboxymethyl Cellulose on Tablet Weight, Hardness and Disintegration

Tablet:	Control	% Concentration 1/4	1/2	1	2
Weight (mg)	406.5	407.1	404.1	401.9	397.4
R.S.D.[1]	0.70	0.58	0.38	0.41	0.27
Hardness (kg)	9.20	9.35	9.45	8.80	8.70
R.S.D.[2]	8.15	7.16	7.30	4.77	4.83
Disintegration time (min)	120+	4.92	2.59	1.38	0.88
Range[3]	-	4.6-5.3	2.4-2.8	1.3-1.6	0.9-0.9
R.S.D.[3]	-	6.8	7.1	10.6	5.6

1. n = 20
2. n = 20
3. n = 6

Table VI

Effect of Sod. Starch Glycolate on Tablet Weight, Hardness and Disintegration

Tablet:	Control	% Concentration 1/4	1/2	1	2
Weight (mg)	406.5	400.9	394.2	405.4	401.3
R.S.D.[1]	0.70	0.19	0.52	0.52	0.33
Hardness (kg)	9.20	9.90	9.35	9.65	8.55
R.S.D.[2]	8.15	3.94	7.17	6.94	5.15
Disintegration time (min)	120+	9.02	4.14	2.36	1.13
Range[3]	-	8.5-9.8	3.9-4.9	2.1-2.8	0.9-1.4
R.S.D.[3]	-	3.4	7.6	8.2	11.4

1. n = 20
2. n = 20
3. n = 6

Table VII

Effect of Crospovidone, U.S.P. on Tablet Weight, Hardness and Disintegration

Tablet:	Control	% Concentration 1/4	1/2	1	2
Weight (mg)	406.5	398.5	398.1	397.3	389.9
R.S.D.[1]	0.70	0.24	0.34	0.24	0.19
Hardness (kg)	9.20	8.65	9.25	7.90	8.65
R.S.D.[2]	8.15	10.67	7.78	4.94	4.74
Disintegration time (min)	120+	9.34	3.81	2.56	1.13
Range[3]	-	8.3-9.9	2.8-3.9	2.4-3.0	0.9-1.5
R.S.D.	-	4.1	8.4	9.3	13.1

1. n = 20
2. n = 20
3. n = 6

Table VIII

Effect of Corn Starch, U.S.P. on Tablet Weight, Hardness and Disintegration

		% Concentration			
Tablet:	Control	1/4	1/2	1	2
Weight (mg)	406.5	409.1	406.8	411.4	413.0
R.S.D.[1]	0.70	0.39	0.57	0.48	0.56
Hardness (kg)	9.20	8.85	8.30	8.70	8.55
R.S.D.[2]	8.15	9.24	7.20	8.87	8.38
Disintegration time (min)	120+	19.86	14.10	12.78	9.64
Range[3]	-	17.5-21.6	13.6-14.7	13.3-14.2	9.1-10.2
R.S.D.[3]		7.2	2.7	2.8	4.4

1. n = 20
2. n = 20
3. n = 6

Table IX

Effect of Anionic Cellulose Polymer on Tablet Weight, Hardness and Disintegration

		% Concentration			
Tablet:	Control	1/4	1/2	1	2
Weight (mg)	406.5	402.6	401.0	400.4	390.9
R.S.D.[1]	0.70	0.31	0.17	0.17	0.35
Hardness (kg)	9.20	9.35	9.05	9.40	9.30
R.S.D.[2]	8.15	6.47	7.62	4.15	7.20
Disintegration time (min)	120+	9.19	7.17	1.97	1.42
Range[3]	-	8.7-10.1	6.2-7.4	1.6-2.4	1.3-1.6
R.S.D.[3]	-	5.4	5.2	6.6	5.4

1. n = 20
2. n = 20
3. n = 6

Table X

Effect of Modified Food Starch on Tablet Weight, Hardness and Disintegration

		% Concentration			
Tablet:	Control	1/4	1/2	1	2
Weight (mg)	406.5	406.5	406.8	408.5	408.6
R.S.D.[1]	0.70	0.42	0.40	0.44	0.49
Hardness (kg)	9.20	8.20	8.55	9.95	7.70
R.S.D.[2]	8.15	6.60	8.38	8.30	7.89
Disintegration time (min)	120+	19.67	13.79	8.49	6.71
Range[3]	-	18.8-20.8	13.2-14.4	8.3-8.9	6.5-6.9
R.S.D.	-	6.5	2.6	4.8	2.5

1. n = 20
2. n = 20
3. n = 6

Table XI

Effect of Soybean Cellulose Derivative On Tablet Weight, Hardness and Disintegration

		% Concentration			
Tablet	Control	1/4	1/2	1	2
Weight[1] (mg) R.S.D.	406.5	403.2	401.6	400.1	398.8
Hardness (kg) R.S.D.[2]	0.70	0.41	0.32	0.34	0.31
Disintegration time (min)	120+	11.91	9.21	2.96	2.41
Range[3]	-	10.5-13.3	8.8-10.3	1.9-3.4	2.2-2.6
R.S.D.[3]	-	5.1	5.2	5.8	2.6

1. n = 20
2. n = 20
3. n = 6

Sedimentation volumes of the eight tablet disintegrants is given in Table XII. This data confirms previous published reports (3, 5) that sedimentation volume is poorly correlated with the relative activity of the disintegrant.

Bulk swelling and water uptake data are shown in Fig.'s 2 and 3. It is apparent that there is no simple relationship although it can be seen that there is general tendency for substances with high rates and extent of water uptake and swelling to give tablets with shorter disintegration times.

Fig. 4 exemplifies the type of photographic data obtained during the cinemicrophotographic studies and Fig. 5 records average disintegrant areas, as a function of time, for four disin-

Table XII

Sedimentation Volumes of Eight Tablet Disintegrants

Disintegrant	ml/gm*
Ion-Exchange Resin	6.0
Carboxymethyl Cellulose	13.0
Crospovidone, U.S.P.	8.0
Corn Starch, U.S.P.	1.8
Sodium Starch Glycolate, U.S.P.	24.4
Modified Food Starch	8.6
Anionic Cellulose Polymer	49.8
Soybean Cellulose Derivative	14.0

* note-the sediment was read in milliliters, and then adjusted for a one gram sample (a 0.5 gram sample was placed in a 50 milliliter graduated cylinder, with 25 milliliters of distilled water subsequently added.

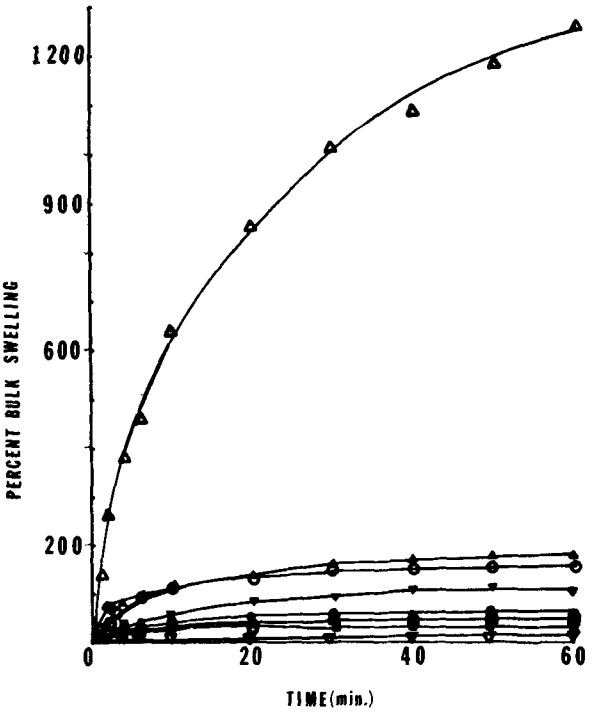

FIG. 2. Bulk swelling of eight tablet disintegrants.
- Δ Sodium Starch Glycolate, U.S.P
- ▲ Sodium Carboxymethyl Cellulose
- ▽ Corn Starch
- ▼ Crospvidone, U.S.P.
- ■ Ion Exchange Resin
- ● Modified Food Starch
- o Anionic Cellulose Polymer
- ◘ Soybean Cellulose Derivative

tegrants. The swelling rate of the individual particles exposed to a vast excess of water is extremely rapid and maximum size is reached in less than fifteen seconds. However, the rate and extent of swelling for any given type of disintegrant varies with particle size. Fig. 6 records the swelling profiles for four different particle sizes of sodium starch glycolate, U. S. P. It is most interesting to note that, despite the fact that area to volume ratios are

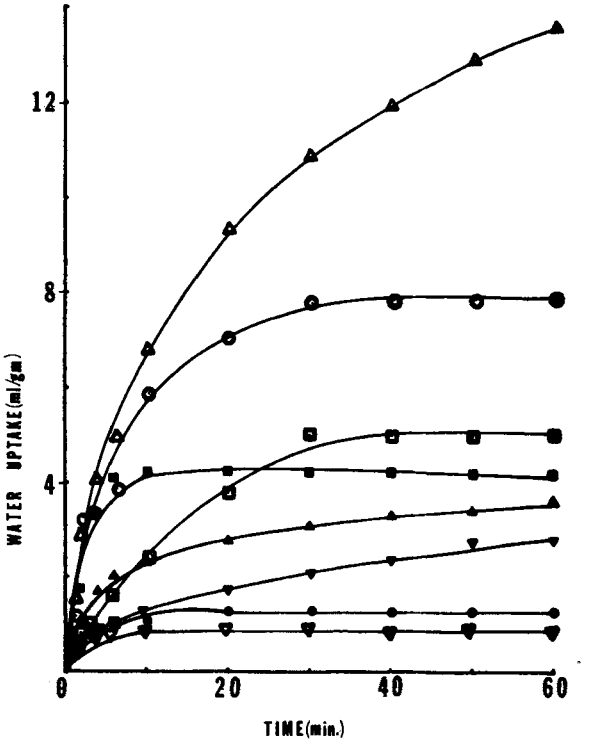

FIG. 3. Water uptake of eight tablet disintegrants.
- Δ Sodium Starch Glycolate, U.S.P.
- ▲ Sodium Carboxymethyl Cellulose
- ▽ Corn Starch
- ▼ Crospovidine, U.S.P.
- ■ Ion Exchange Resins
- o Modified Food Starch
- o Anionic Cellulose Polymer
- ◘ Soybean Cellulose Derivative

highest for the smallest particles, the large size (98 and 114 m) show substantially greater rates and extent of swelling than do the small particles (38 and 62 m). Obviously the contribution made to total disintegrant action made by the different partical size fractions depends partly on the relative number, or weight, of particles in any given fraction. The data shown in Fig.'s 7 and 8 and the

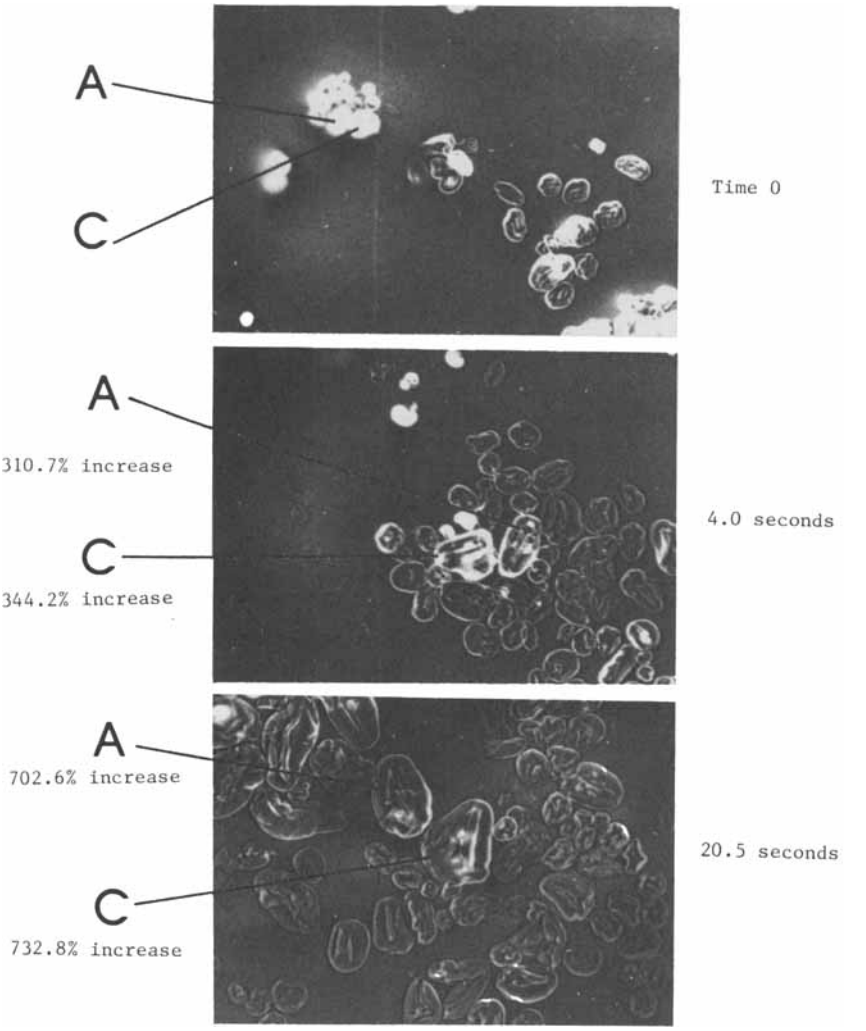

FIG. 4. Computer image analysis of two particles of sodium carboxymethyl stach in a filmed sequence.

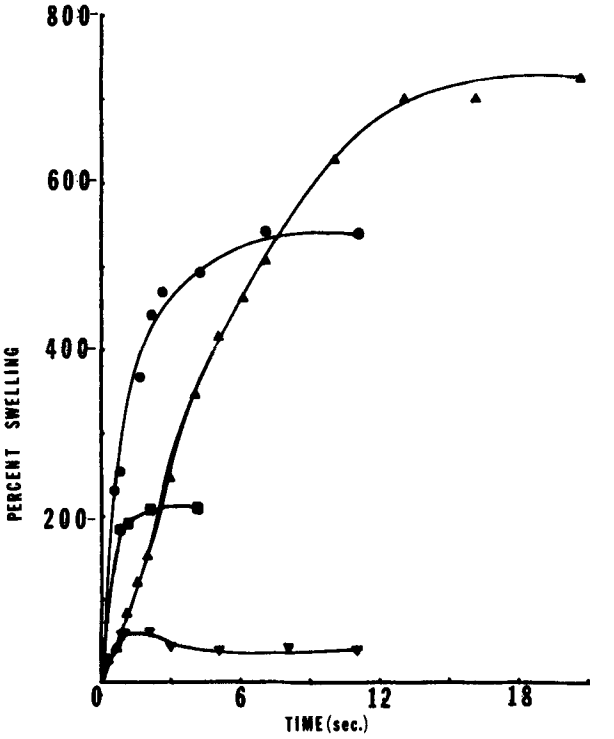

FIG. 5. Intrinsic swelling of four tablet disintegrants.
▲ Sodium Starch Glycolate, U.S.P.
▼ Crospovidone, U.S.P.
■ Sodium Carboxymethyl Cellulose
● Anionic Cellulose Polymer

particle size histograms displayed suggest that there may be advantage, for some disintegrants at least, in using materials with a greater proportion of larger particles. This hypothesis is supported by the results published by Rudnic and his associates who showed that a comparative evaluation of three different particle size grades of cross-linked polyvinylpyrrolidone demonstrated that the coarsest material had the greater disintegrant efficiency (12).

Tables XIII and XIV compare the rate and extent of bulk disintegrant swelling (as determined using the equipment shown in Fig. 1)

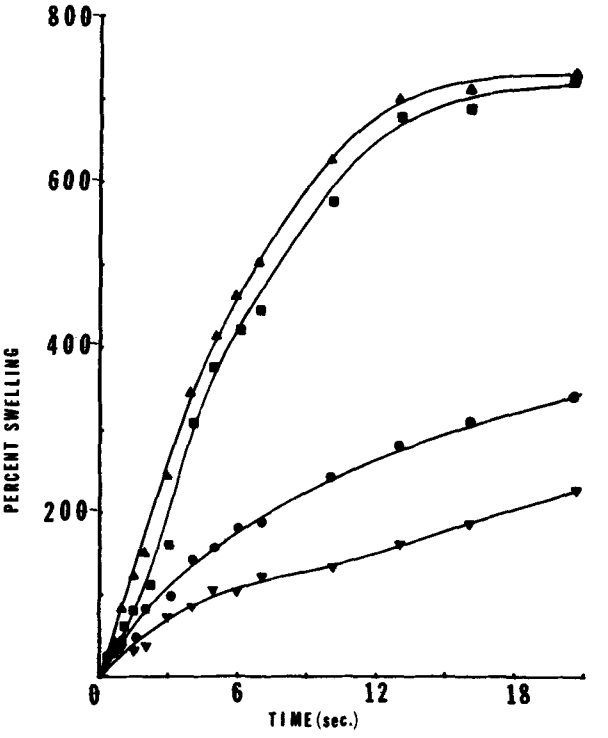

FIG. 6. Intrinsic swelling of particles of sodium starch glycolate, U.S.P..

114 mm^2* 62 mm^2

98 mm^2 38 mm^2

* note: the areas measured were areas represented on filmed sequences.

with rate and extent of intrinsic swelling. No simple correlation is apparent. It will be appreciated that since the cinephotomicrographically determined determined intrinsic swelling rates with bulk swelling rate should be squared in order to estimate a three dimensional value.)

Bulk swelling rates, although of value in evaluating disintegration efficiency, suffer from several disadvantages. Firstly, in the tablet, the disintegrant particles are almost certainly likely to be

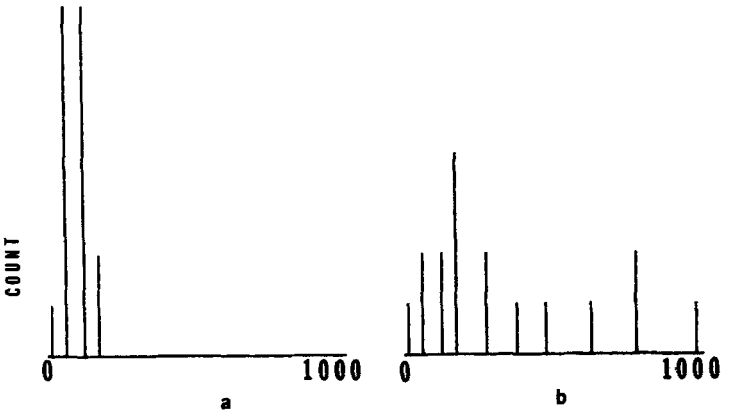

FIG. 7. Particle size histograms for sodium starch glycolate.
a) Particle size = mm^{2*} at Time 0
b) Particle size = mm^2 at 20.5 seconds
* note: the areas measured were areas represented on filmed sequences.

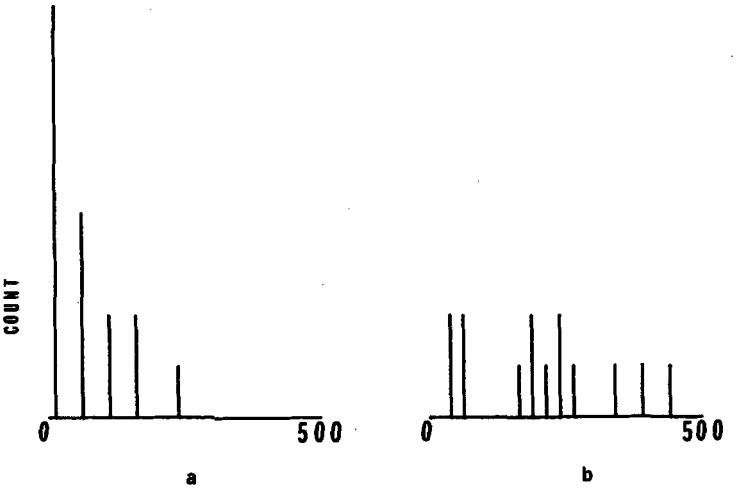

FIG. 8. Particle size histograms for sodium carboxymethyl cellulose.
a) Particle size = mm^{2*} at Time 0
b) Particle size = mm^2 at 2 seconds
* note: the areas measured were areas represented on filmed sequences.

Table XIII

Maximum Percent Swelling of Eight Tablet Disintegrants

Disintegrant	Intrinsic[1]	Bulk[2]
Sod. Starch Glycolate,U.S.P.	726.7	1260
Carboxymethyl Cellulose	541.4	165
Anionic Cellulose Polymer	208.7	176
Crospovidone, U.S.P.	39.2	112
Ion-Exchange Resin	-	36
Modified Food Starch	-	57
Soybean Cellulose Derivative	-	45
Corn Starch, U.S.P.	-	13

1. Area was measured as mm^2 on film
2. Volume was measured as ml.

Note: Both indices are presented as percent of original area or volume.

Table XIV

Maximum Rate of Selling of Eight Tablet Disintegrants

Disintegrant	Intrinsic	Bulk
Sod. Starch Glycolate,U.S.P.	98.5	140.0
Carboxymethyl	271.8	32.5
Anionic Cellulose Polymer	216.4	25.0
Crospovidone, U.S.P.	57.9	15.0
Ion-Exchange Resin	- *	17.0
Modified Food Starch	-	7.0
Soybean Cellulose Derivative	-	5.0
Corn Starch, U.S.P.	-	5.0

*Data not available, as image analysis was not possible.

isolated from one another. Secondly, the time to reach steady state is often substantially greater than tablet disintegration time. Thirdly, such factors as differences in time of exposure to water and differences in particle restraint with the bed introduce complications which may well preclude effective evaluation of disintegration mechanism.

The data presented in this paper indicates that no one method of examining disintegrants is likely to provide all the answers to questions concerning disintegrant mechanism which presently exist. A combination of several techniques as used in this paper is required. The cinophotomicrographic technique for investigating disintegrant action clearly merits further use.

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