(10) R. Mozingo and K. Folkers, *ibid.*, chap. 8.
(11) H. W. Florey, E. Chain, N. G. Heatley, M. A. Jennings, A. G. Sanders, E. P. Abraham, and M. E. Florey, "Antibiotics," vol. II, Oxford University Press, London, England, 1949, pp. 839–870.
(12) B. B. Levine, *Arch. Biochem. Biophys.*, **93**, 50(1961).
(13) K. H. Dudley, T. C. Butler, and D. Johnson, *J. Pharmacol. Exp. Ther.*, **179**, 505(1971).
(14) J. M. Blaha, A. M. Knevel, and S. L. Hem, *J. Pharm. Sci.*, **64**, 1384(1975).
(15) P. Finholt, G. Jurgensen, and H. Kristiansen, *ibid.*, **54**, 387(1965).
(16) R. E. Lindsay and S. L. Hem, *ibid.*, **61**, 202(1972).

ACKNOWLEDGMENTS AND ADDRESSES

Received July 5, 1974, from the *Department of Industrial and Physical Pharmacy and the ‡Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, and the §School of Chemical Engineering, Purdue University, West Lafayette, IN 47907

Accepted for publication October 9, 1975.

Abstracted from a dissertation submitted by J. M. Blaha to the Graduate School, Purdue University, in partial fulfillment of the Doctor of Philosophy degree requirements.

Supported in part by a National Defense Educational Act Fellowship and an American Foundation for Pharmaceutical Education Fellowship (J. M. Blaha).

The authors are grateful to Pfizer, Inc., for generously providing penicillin G potassium.

¶Present address: Squibb Institute for Medical Research, New Brunswick, N.J.

xTo whom inquiries should be directed.

Effect of Intragranular and Extragranular Disintegrating Agents on Particle Size of Disintegrated Tablets

E. SHOTTON x and G. S. LEONARD *

Abstract □ Five materials were compared for their effectiveness as disintegrating agents: maize starch, sodium calcium alginate, alginic acid, microcrystalline cellulose, and a colloidal aluminum silicate. The effect of the proportion of the agent present and the position with respect to the granule, intra- and extragranular, was examined. The extragranular formulations disintegrated much more rapidly than the intragranular ones, but the latter gave a much finer dispersion of particles. A combination of intra- and extragranular disintegrating agents gave the best compromise; of those tested, the alginates appeared to effect the breakdown to the smallest particles when placed intragranularly. A method of assessing the effectiveness of disintegrating agents for uncoated tablets is suggested, but the resulting weight mean particle size is the more important criterion for tablets complying with a pharmacopoeial disintegration test. The porosity and crushing strength of tablets are useful as guides to disintegration only when a given formulation is used.

Keyphrases □ Disintegrating agents—intra- and extragranular, effect on particle size of disintegrated tablets □ Particle size—disintegrated tablets, effect of intra- and extragranular disintegrating agents □ Tablets—effect of intra- and extragranular disintegrating agents on particle size □ Dosage forms—tablets, effect of intra- and extragranular disintegrating agents on particle size

The disintegration test described in the British Pharmacopoeia ensures that the tablet will break down to pass a 1.70-mm sieve aperture. This size is larger than the granule size used for most tablets and has been criticized (1). A few attempts have been made to assess the particle sizes formed on disintegration.

A nest of three sieves with apertures of 0.81, 0.54, and 0.27 mm was used in the USP disintegration test apparatus instead of the tube described (2). An automated particle counter[1] was used to determine particle-size frequencies for tablets prepared from aspirin and starch mixtures (3). Sandell (4) used a method similar to that of Sanders (2), but the sieves had apertures of 0.1, 0.5, and 2.0 mm.

Previous work on the sizing of the disintegrant has been reviewed (5). To obtain rapid dissolution, disintegration should release drug as near as possible to its original particle size.

EXPERIMENTAL

Materials—Sulfadiazine BP was used as the active drug. The solubility was determined as 14.4 mg in 100 ml of water at 37°, and the density was 1.505 g/ml at 21°.

The size distribution of the sulfadiazine powder was determined using an automated particle counter[1] with 0.9% (w/v) solution of sodium chloride saturated with sulfadiazine as the electrolyte. The average mean weight diameter was approximately 9 μm (6).

The following disintegrating agents were used: maize starch BP, microcrystalline cellulose[2], sodium calcium alginate[3], alginic acid, and a synthetic colloidal aluminum silicate[4]. Povidone was used as a binder to form the granules.

Preparation—Wet granulation was accomplished by moistening sulfadiazine with a sufficient quantity of 10% povidone solution to give a final content of 3% (w/w) followed by additional distilled water. The moistened mass was pushed through a granulator[5], the granules were then dried, and a sieve fraction of 355–500-μm particles was used. Extragranular agents were added to the dried granules.

Intragranular disintegrating agents were mixed with the sulfadiazine powder before granulating with the povidone solution.

Granulation by precompression was used only for the sodium calcium alginate, since this method was recommended by the suppliers. One gram of the mixed powders was compressed in a 15.35-mm diameter die to form a weak tablet. Such tablets were then broken to form granules, and a 355–500-μm fraction was selected. Before precompression, povidone powder (3%) was incorporated in one batch of powder but not in a second batch. The tablets produced from these granules were thus comparable with the intragranular tablets containing sodium calcium alginate from the wet granulation method.

The proportions of these agents are shown in Table I.

[1] Coulter.
[2] Avicel PH.
[3] Alginate F417, Alginate Industries Ltd.
[4] Laponite CP, Laporte Industries Ltd.
[5] Erweka F.A.G.

Table I—Disintegration Times, Crushing Strengths, and Mean Particle Sizes of the Disintegrated Tablets Made with Five Disintegrating Agents

Disintegrating Agent and Siting	Percentage Disintegrant															
	2.5				5.0				10.0				20.0			
	T_d	S_m	F_c	ϵ	T_d	S_m	F_c	ϵ	T_d	S_m	F_c	ϵ	T_d	S_m	F_c	ϵ
Maize starch:																
Intragranular	2939	540	16.6	16.8	748	372	16.5	16.7	212	46	15.4	17.0	—	—	—	—
Extragranular	736	616	15.8	14.7	106	295	15.0	15.3	30	181	10.7	17.1	—	—	—	—
5% intragranular and 5% extragranular	—	—	—	—	—	—	—	—	79	84	12.8	17.7	—	—	—	—
Microcrystalline cellulose:																
Intragranular	>1 hr	—	18.2	17.1	>1 hr	—	18.4	17.1	2959	322	18.3	17.3	331	182	19.1	17.5
Extragranular	>1 hr	—	18.2	16.7	>1 hr	—	17.7	16.7	2659	425	17.4	17.3	550	428	17.2	17.9
Percent intragranular and percent extragranular		2.5i and 7.5e				5.0i and 5.0e				10.0i and 10.0e				20.0i and 10.0e		
	847	451	17.9	17.5	1952	479	17.7	17.6	184	222	16.8	17.9	98	118	16.3	17.9
Sodium calcium alginate:																
Percent disintegrant		1				2				4				8		
Intragranular SP	>1 hr	—	7.1	15.6	369	745	8.0	16.3	75	478	7.2	15.5	—	—	—	—
Intragranular S	>1 hr	—	8.4	15.1	639	806	7.8	15.3	59	500	8.2	15.1	—	—	—	—
Intragranular	1984	82	18.5	17.2	1754	37	19.7	17.1	1490	26	19.9	16.9	1258	18	19.3	17.5
Extragranular	367	514	16.9	16.3	237	390	17.4	16.1	93	292	15.0	16.4	84	267	14.9	16.8
Alginic acid:																
Intragranular	2034	406	18.6	16.7	635	215	18.3	16.9	243	127	17.6	17.2	156	48	17.2	17.4
Extragranular	2147	516	17.6	16.6	556	336	17.3	16.3	195	255	15.9	16.6	97	253	13.0	17.0
Colloidal aluminum silicate:																
Extragranular	>1 hr	—	19.2	15.9	1242	462	17.4	16.0	151	233	16.5	16.6	57	149	14.7	17.6

[a] All tablets were prepared from granules 355–500 μm in diameter and were compressed at approximately 1000 kg (F_a). Key: i = intragranular, e = extragranular, T_d = disintegration time (seconds), S_m = mean particle-size disintegrated tablet (micrometers), F_c = crushing strength (kilograms), ϵ = porosity expressed as a percent of the tablet volume, S = granulation by precompression without povidone, and SP = granulation by precompression with povidone.

Table II—Tablet Crushing Strengths for Different Maize Starch Formulations[a]

Disintegrating Agent, % and Siting	Mean Applied Compression Force, kg											
	750			1000			1500			1800		
	T_d	F_c	S_m	T_d	F_c	S_m	T_d	F_c	S_m	T_d	F_c	S_m
2.5i	268	13.1	186	2939	16.6	540	>1 hr	21.8	n.d.	>1 hr	23.4	n.d.
5.0i	146	12.6	168	748	16.5	372	>1 hr	21.2	n.d.	>1 hr	23.1	n.d.
10.0i	124	12.5	34	212	15.4	46	4530	21.6	258	>1 hr	22.5	n.d.
2.5e	125	13.2	359	736	15.8	616	>1 hr	21.5	n.d.	>1 hr	24.5	n.d.
5.0e	54	10.1	131	106	15.0	295	2182	20.4	646	>1 hr	22.7	n.d.
10.0e	32	8.2	89	30	10.7	181	79	14.0	310	147	14.9	387
5.0i and 5.0e	69	10.8	53	79	12.8	84	269	18.8	216	695	20.9	316

[a] All tablets were prepared from granules 355–500 μm in diameter. Key: e = extragranular, i = intragranular, n.d. = not done, F_c = tablet crushing strength (kilograms), T_d = disintegration time (seconds), and S_m = mean particle size of the disintegrated tablet (micrometers).

Table III—Disintegration Factors for Some Disintegrating Agents[a]

Disintegrating Agent, % and Siting		Disintegration Factor	Disintegration Time, sec	Mean Particle Size, μm
Starch	10e	161	30	181
Starch	5i and 5e	131	79	84
Alginic acid	8i	117	156	48
Colloidal aluminum silicate	8e	103	57	149
Starch	10i	89	212	46
Microcrystalline cellulose	20i and 10e	75	98	118
Sodium calcium alginate	8e	39	84	267
Sodium calcium alginate	8i	39	1258	18
Alginic acid	8e	36	97	253
Sodium calcium alginate	4e	32	93	292
Sodium calcium alginate	4iS	30	59	500
Alginic acid	4i	28	243	127
Starch	5e	28	106	295
Colloidal aluminum silicate	4e	25	151	233
Sodium calcium alginate	4iSP	24	75	478
Sodium calcium alginate	4i	23	1490	26
Microcrystalline cellulose	10i and 10e	21	184	222
Alginic acid	4e	18	195	255
Microcrystalline cellulose	20i	15	331	182
Microcrystalline cellulose	20e	4	550	322
Starch	5i	3	748	372
Microcrystalline cellulose	10i	0.9	2959	428
Microcrystalline cellulose	10e	0.8	2659	425

[a] All tablets were prepared from granules 355–500 μm and were compressed at approximately 1000 kg. Key: i = intragranular, wet granulation; e = extragranular, wet granulation; S = granulation by precompression without povidone; and SP = granulation by precompression with povidone.

Compression of the granules was carried out on a single-punch, hand-driven tablet machine with both top and bottom punches instrumented with strain gauges. The die wall and punch faces were dusted lightly with magnesium stearate as a lubricant, the excess being wiped away with a paper tissue. A total dry weight of granules of 500 ± 5 mg was hand filled into the die for each compression, and 12 tablets were prepared from each granulation. The flat-faced punches used for the final tablet were 12 mm in diameter, and the machine was driven at a rate equivalent to 20 compression cycles/min.

A series of experiments in which the applied force was kept roughly constant at 1000 kg was carried out using a sieve fraction of the granules with a diameter in the 355–500-μm range.

Tablet Crushing Strength—A diametral crushing strength tester, as described by Shotton and Ganderton (7) and modified by Leonard (8), was used to determine the force applied diametrically to break the tablets. The results given in this report are the mean figures from five tablets.

Disintegration Time—The method described in the British Pharmacopoeia was used; the five tablets were timed individually. The internal diameter of the reservoir tube was 44 mm, and the aqueous medium was 0.9% sodium chloride saturated with sulfadiazine. This medium was chosen to act as the electrolyte in the counter and to prevent dissolution of the sulfadiazine particles. A guided disk was not used.

For very slowly disintegrating tablets, the test was stopped after 1 hr.

Size Analysis of Disintegrated Tablets—The suspensions from three of the five tablets, which had intermediate disintegration times, were passed through a nest of 3.8-cm diameter sieves with the following apertures: 1400, 1000, 710, 500, 355, 250, 180, 125, 90, and 75 μm. The apparatus was described previously (6).

The liquid, with particles less than 75 μm, was collected in a flask, and the particles in a sample of 0.5 ml were sized with an automated particle counter using a 200-μm diameter sampling tube. The wide range of particle sizes imposed limitations on the orifice size of the counting tube that could be used with the counter. In addition, to count the high proportion of particles present below 20 μm would involve considerable dilution. Further stirring and dilution would break down more aggregates above 20 μm. Therefore, in each case, the particles below 20 μm were assumed to be the original sulfadiazine powder with a mean particle size of 9 μm (6). This value was used in calculating the mean size of particles obtained from the disintegrated tablet (Tables I–III) to give comparative values.

Tablet Porosity—The mass, diameter, and thickness of the tablets were measured before subjecting them to further tests, and the porosity was calculated from these values. The volume of the powder used was obtained from the mass and density of each constituent present, and the porosity was the difference between this value and the volume of the tablet. The porosity is expressed as a percentage of the tablet volume.

RESULTS

The porosity of the tablets from all wet granulation formulations was within 17 ± 1%, except for 2.5 and 5.0% extragranular starch which was between 14.5 and 15.5%. Tablets prepared from granules formed by precompression were between 15 and 16.3% porosity (Table I).

The crushing strength, the time taken for the tablets to disintegrate, and the mean particle size of the disintegrated tablets are also given in Table I for disintegrants incorporated both intra- and extragranularly. Table II gives the mean disintegration time, crushing force, and particle size for tablets containing maize starch and compressed at four pressure levels.

Examples of particle-size distributions obtained from disintegrated tablets, from which the mean size was calculated, are given in Fig. 1 for sodium calcium alginate; similar curves for maize starch and the sulfadiazine powder were published previously (6).

DISCUSSION

The disintegration of oral tablets in the GI tract is desired to facilitate the dissolution of the drug and thus its absorption. The effectiveness of a disintegrating agent could be assessed based on the time taken for the wet tablet to break up and on the size of the recovered particles. The size of the disintegrated particles should be compared with the particle size of the original powdered drug. The effect of the proportion of the disintegration agent on the disintegration time is well known, and this work examines the effect of the position, intra- and extragranular, and concentration of the agent upon the particle size of the disintegrated tablets. Previous work (6) showed the effect of 2.5, 5.0, and 10% maize starch upon the disintegration time and the recovered mean particle size of sulfadiazine tablets, and some results are included for comparison with the other disintegrating agents.

A more rapid disintegration of the tablets was found at all concentrations with extragranular agents than with intragranular agents (Fig. 2). This result may be explained by the local concentrations of these substances around the granules. Hydrophilic channels are formed which are rapidly penetrated by water, as shown by placing a drop of dilute iodine solution on the tablet (6). With tablets having intragranular agents, the particles of the agent are isolated and sur-

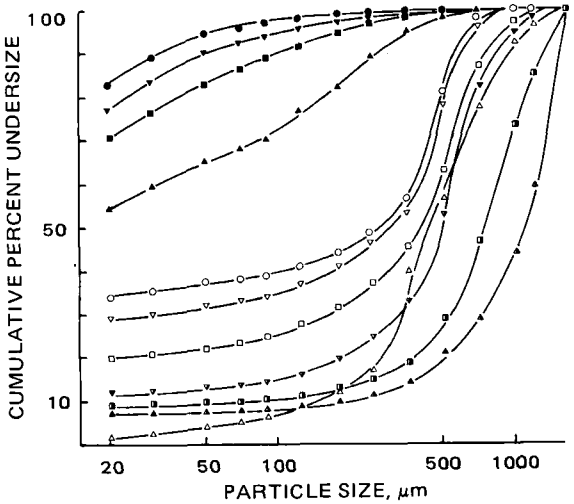

Figure 1—*Effect of formulation and granulation on the particle-size distribution of disintegrated tablets containing sodium calcium alginate. Disintegrating agent was 1% (△), 2% (□), 4% (▽), or 8% (○). Open symbols represent extracellular agents; solid symbols represent intragranular agents by wet granulation; half-open symbols represent intragranular agents by precompression. Granules were 355–500 μm, and applied compression force was 1000 kg.*

rounded by sulfadiazine particles which are not so readily wetted. Thus, although the porosities of comparable formulations are similar (Table I), the disintegration times are very different.

Similar results were obtained at the four compression forces used, as shown in Table II for maize starch as the disintegrating agent. From Fig. 2, the most effective agent would appear to be extragranular maize starch at the greater proportions, with alginic acid, colloidal aluminum silicate, and sodium calcium alginate being slightly less effective. At low concentrations, 1 and 2% sodium calcium alginate was superior to the other agents used.

The crushing force required to break the tablets was affected very little by the concentration of disintegrating agent placed intragranularly. With extragranular agents, however, weaker tablets were formed, which also contributed to the shorter disintegration time.

The disintegration patterns of the two formulation types were

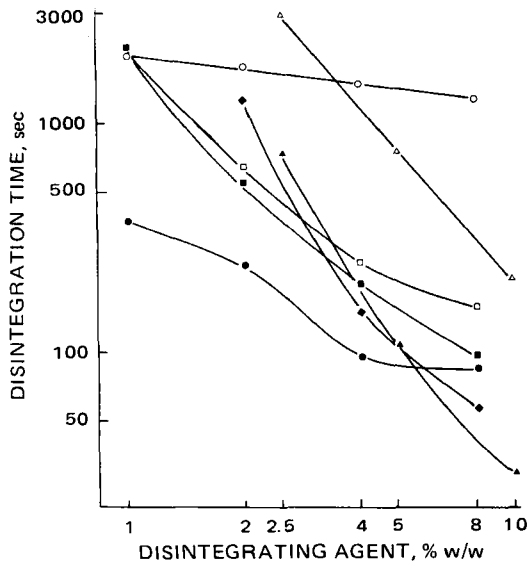

Figure 2—*Effect of concentration of disintegrating agent on tablet disintegration time. Key: ● ○, sodium calcium alginate; ■ □, alginic acid; ♦, colloidal aluminum silicate; and ▲ △, maize starch. Open symbols represent intragranular agents; solid symbols represent extragranular agents. Granules were 355–500 μm, and applied compression force was 1000 kg.*

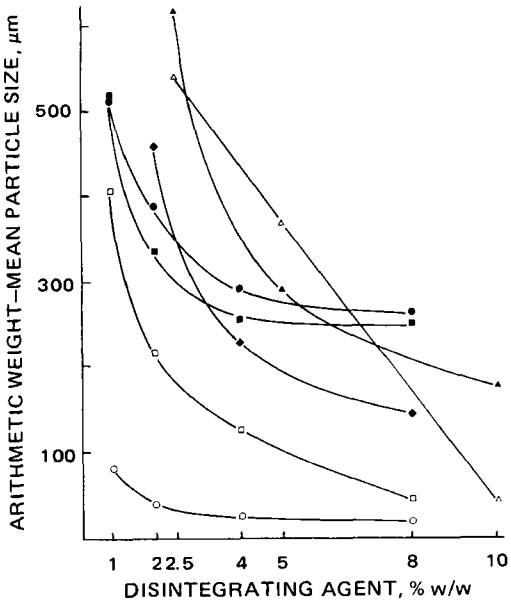

Figure 3—*Effect of concentration on the arithmetic weight-mean particle size of disintegrated tablets. Key: see Fig. 2.*

different in that the extragranular disintegrant caused the tablet to break up rapidly to aggregates, many of which corresponded in size to the original granule. In contrast, the intragranular disintegrant caused erosion of the tablet from the outside since penetration was slow, but the mean aggregate size was much smaller (Table I), with only few aggregates corresponding to the granule size.

Figure 1, concerning sodium calcium alginate, shows that a high proportion of particles and aggregates fell below 20 μm for all intragranular proportions of this agent and that very few were greater than 100 μm. With 4 and 8% of sodium calcium alginate, a mean particle size of 26 and 18 μm, respectively, was obtained so that a high proportion of the sulfadiazine must have been released as original particles. These granules had a mean particle size of about 9 μm and 80% below 20 μm (6).

The effect of the proportion of the agent upon the weight-mean particle size of the disintegrated tablet is shown in Fig. 3. The effectiveness of the intragranular agent compared with the extragranular formulation is clearly indicated. The alginic acid and sodium calcium alginate were much more effective as intragranular agents even at proportions as low as 1 and 2%.

Again, at this compression force, the weight-mean particle size of the intragranular formulations is affected by the proportion of the agent but not by the breaking strength of the tablet or the porosity, which are nearly constant. No allowance for the particle size of the disintegrating agent was made since the sodium calcium alginate, alginic acid, and colloidal aluminum silicate all swell considerably in water to form a gel. Since the maize starch size range was between 5 and 30 μm, correcting for its presence would have increased the weight-mean particle size with all proportions of starch and the comparison with the alginate would have been less favorable. Only comparative values have meaning in this context, because the results are greatly influenced by the compression force and materials being compressed.

The tablets formed from granules prepared by precompression (Table I) gave weaker tablets than those from the wet granulations. These contained intragranular sodium calcium alginate, and the porosity was only a little less than for tablets from wet granulations. Although the disintegration time was greatly reduced, the size of aggregates after disintegration of the tablet was of the same order as the original granules. It may be assumed that the second compression consolidated the granules further so that penetration of water into the granule was resisted.

Microcrystalline cellulose was not very effective, either intra- or extragranularly, and it is used principally as a direct compression diluent (Table I). Its binding properties are good.

When using a mixture of 5% intragranular and 5% extragranular maize starch, intermediate values for disintegration time and weight-mean particle size were obtained.

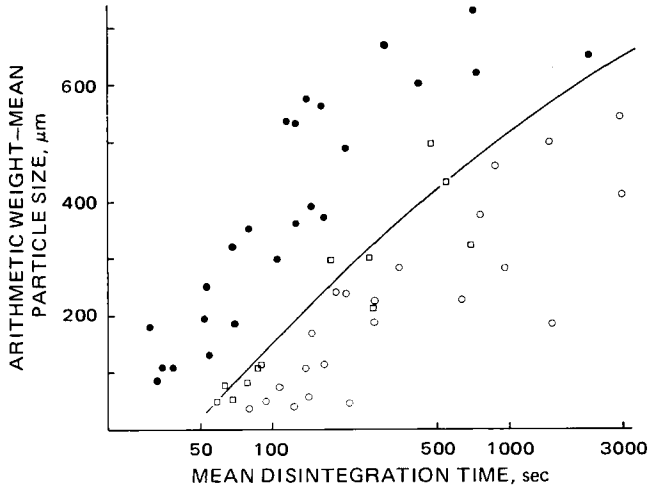

Figure 4—*Relationship between the disintegration time and the mean particle size recovered on disintegration for maize starch formulations. Key: ●, extragranular formulations; ○, intragranular formulations; and □, mixed formulations.*

When all values for mean particle size were plotted against the mean disintegration time for maize starch formulations, Fig. 4 was obtained. This figure shows that, for a given disintegration time, the intragranular agent gave a smaller particle size than the extragranular formulations; the mixed formulations were intermediate. These results do not discriminate between different concentrations of maize starch or the effect of compression pressure. Figure 5 shows a similar plot for alginic acid and sodium calcium alginate.

When comparing disintegrating agents, both the disintegration time and the mean particle size should be considered together. For uncoated tablets, a factor comparing the disintegration time with the official limit for uncoated tablets (15 min in the British Pharmacopoeia) and the particle size of the drug should be useful initially:

$$\text{disintegration factor} = \frac{15\text{ min}}{\text{actual disintegration time}} \times \frac{\text{arithmetic mean size of drug}}{\text{arithmetic mean size from tablet}} \times 100 \quad \text{(Eq. 1)}$$

The larger the factor, the more effective is the disintegrating agent. Examples of values of this factor for the materials examined are shown in Table III together with the approximate disintegration times and the mean particle sizes of disintegrated tablets. By using different ratios of intra- and extragranular agents, or different agents intra- and extragranularly, a tablet with improved properties can be formulated, particularly if sodium calcium alginate or alginic acid is incorporated intragranularly.

For drugs absorbed from the GI tract, the particle size of the disintegrated tablet and the disintegration time are both important for obtaining the desired dissolution characteristics.

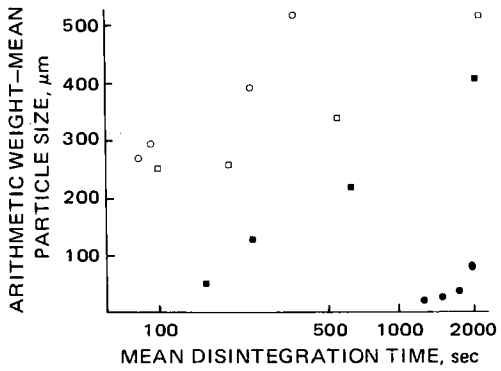

Figure 5—*Disintegration time and mean particle size recovered on disintegration for alginic acid and sodium calcium alginate formulations. Key: ■, intragranular alginic acid; ●, sodium calcium alginate; □, extragranular alginic acid; and ○, sodium calcium alginate.*

REFERENCES

(1) A. D. Nair and V. N. Bhatia, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 131(1957).

(2) J. C. Sanders, *Pharm. Weekbl.*, **104**, 485(1969).

(3) M. Van Ootghem, R. Boni, and H. Herbots, *Cesk. Farm.*, **18**, 122(1969).

(4) E. Sandell, *Acta Pharm. Suec.*, **7**, 55(1970).

(5) W. Lowenthal, *J. Pharm. Sci.*, **61**, 1695(1972).

(6) E. Shotton and G. S. Leonard, *J. Pharm. Pharmacol.*, **24**, 798(1972).

(7) E. Shotton and D. Ganderton, *ibid.*, **12**, 877(1960).

(8) G. S. Leonard, Ph.D. thesis, University of London, London, England, 1971.

ACKNOWLEDGMENTS AND ADDRESSES

Received May 23, 1975, from the *Department of Pharmaceutics, School of Pharmacy, University of London, Brunswick Square, London, WC1N 1AX, England.*

Accepted for publication October 9, 1975.

Adapted in part from a thesis submitted by G. S. Leonard to the University of London in partial fulfillment of the Doctor of Philosophy degree requirements.

The authors thank the School of Pharmacy for the financial support of G. S. Leonard which enabled this work to be undertaken.

* Present address: Smith Kline and French Ltd., Welwyn Garden City, Herts., England.

ˣ To whom inquiries should be directed.