Batch Production of Pharmaceutical Granulations in a Fluidized Bed II: Effects of Various Binders and Their Concentrations on Granulations and Compressed Tablets

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Abstract □ A study was made of the effects of various binders and binder concentrations on the physical properties of fluidized bed granulations. The binders investigated included gelatin USP, acacia USP, povidone NF, and hydroxypropyl cellulose. In general, increasing the binder formula weight had the following effects upon the final granulation: (*a*) increased average granule size, (*b*) decreased granule friability, (*c*) increased interparticulate porosity, and (*d*) decreased granule flowability. Due to slower solvent evaporation rates, viscous binder solutions reduce the bulkiness of fluidized bed granulations through their enhanced ability to penetrate and wet the fluidized solids. Correlations, similar to those observed with conventional granulations, exist between the physical properties of the fluidized bed granulations and their compressed tablets.

Keyphrases □ Granulation, fluidized bed—effects of binder and binder concentration on granule and tablet physical properties □ Fluidized bed granulation—effects of binder and binder concentration on granule and tablet physical properties □ Binders—effect on granule and tablet physical properties, fluidized bed granulation

New technology in the development of pharmaceutical granulations has evolved in the last decade. Rotary vacuum dryers have been modified to permit powder blending and granulating in a one-stage granulation operation, and uniform mixing of low potency tablet formulations has been demonstrated (1, 2). A spray-drying technique has been used to produce tablet granulations (3). When a slurry of tablet filler, disintegrating agent, binder, and vehicle is spray dried, a narrow range, uniform distribution of free-flowing granules results. The instantaneous drying, associated with spray drying, eliminates any migration of a colorant in the process, making the method particularly useful for colored granulations. Standard coating pans have been used to form granules (4–6). The powdered materials in the rotating pan are sprayed intermittently with a granulating solution until uniform granules are formed. The granulation is dried either in the pan by blowing heated air over the tumbling granulation or after its removal from the pan by other drying processes. With respect to ingredient distribution, this method was shown to be effective for both high and low potency medications.

Granulation of a powder in a fluidized bed for tableting purposes was first introduced by Wurster (7, 8). Thirty- and forty-mesh solid particles, suspended in a fluidized bed, were coated with a granulating solution. Because Wurster found that humidity in the column during the addition of the granulating solution affected the granulated product, humidity was controlled by regulating the inlet air temperature. At low humidity conditions, many fine particles were formed, presumably by attrition of the solids and a spray drying of the granulating solution. At the same time, when conditions in the column became too moist, aggregation of the solid particles occurred.

Theory, design, and operation of equipment for the continuous production of tablet granulations in a fluidized bed were presented by Scott *et al.* (9) and Rankell *et al.* (10), who converted a fluid bed dryer for the continuous production of tablet granulations. They provided for the continuous addition of powder and granulating solution with the simultaneous removal of the dried, granulated product. Their presentations discussed, in detail, the material and energy balances and the rates of heat and mass transfer in the granulator.

The purposes of the present investigation were to determine the effects of various binders and their concentrations on the physical properties of fluidized bed granulations and to seek relationships among the physical properties of the various granulations and their compressed tablets.

Table I—Formulations

Ingredients	Formula Weight, %
Lactose USP	84.50–87.50
Starch USP	10.0
Magnesium stearate USP	0.5
Dry binder	2.0–5.0
Distilled water	—

EXPERIMENTAL

Materials—The materials used in this study were: lactose USP (hydrous powder), starch USP, magnesium stearate USP, gelatin USP, hydroxypropyl cellulose[1], povidone NF[2], acacia powder USP, and benzene[3].

Procedure—The operation of the fluid bed spray granulator[4], with respect to granulation and drying processes, was discussed previously (11), so these procedures will be reviewed only briefly. Granulation was accomplished in an inlet air temperature of 50°. The binder solution was introduced by means of a binary nozzle

[1] Klucel-EF, Hercules Inc., Wilmington, Del.
[2] Plasdone-K 29-32, General Aniline and Film Corp., New York, N. Y.
[3] Thiophene-free, certified ACS, Fisher Scientific Co., Fair Lawn, N. J.
[4] Model WSG-15, Fa. W. Glatt, Haltingen, West Germany.

Table II—Physical Properties of Fluidized Bed Granulations Prepared Using Povidone NF as a Binder

Physical Properties	Formula Weight of Binder (% w/w)				
	2.00	2.75	3.50	4.25	5.00
Average granule size, μ	200	211	223	250	276
Friability, %[a]	—	—	13.8	13.6	11.3
Bulk density, g./ml.	0.48	0.47	0.45	0.44	0.44
Granule density, g./ml.	1.501	1.486	1.484	1.481	1.481
Porosity, %	68.02	68.37	69.68	70.29	70.29
Flow rate, g./min.	258.6	200.7	182.0	172.4	165.8

[a] Insufficient 50-mesh granules were present in granulations manufactured from 2.00 and 2.75% binder concentrations to determine granule friability.

and metering pump calibrated to deliver 100 g. water/min. regardless of the solids content of the solution. An air pressure of 1.5 kg./sq. cm. was applied to the nozzle, which was situated at a height of 72.4 cm. (28.5 in.) above the distribution grid. All granulations were dried to an exhaust dry bulb temperature of 49° after elevating the temperature of the inlet air to 65° for the drying cycle. The air volume was maintained at 350 cu. ft./min. throughout the granulating and drying cycles. All formulations, outlined in Table I, were granulated in 10-kg. batches. To maintain a constant batch size and to minimize effects on the physical properties of the final granulations, the concentration of lactose was altered slightly to compensate for the amount of dry binder in each batch.

Preparation of Binder Solutions—Binder selections were based upon their ability to granulate effectively from aqueous solutions at low formula concentrations. With the exception of hydroxypropyl cellulose, binder solutions were prepared by dissolving various preselected quantities of solid binder in 2 kg. of distilled water. Because the viscosity of hydroxypropyl cellulose solutions increases rapidly with increased concentrations, it was necessary to dilute these binder solutions with an additional 1 kg. of water to facilitate their addition through the binary nozzle and into the fluidized solids.

Gelatin solution was prepared by first thoroughly hydrating the gelatin powder in cold water for 10 min. The slurry, contained in a double boiler, was then gradually heated with constant stirring to 80°, the temperature at which the gelatin binder solution was used. Acacia and povidone solutions were made by slowly incorporating the dry powders in distilled water with constant stirring. Hydroxypropyl cellulose solution was made by adding the dry powder to three times its weight of hot distilled water (60°). This slurry was agitated for 10 min. before the addition of the remainder of the water. The solution was allowed to cool, with stirring, to room temperature before use.

Physical Properties of Granulations—Methods employed in determining the physical properties of the fluidized bed granulations were discussed previously (11).

Physical Properties of Tablets—All granulations were tableted on a rotary tablet press[5] fitted with 0.95-cm. (0.375-in.) standard concave punches. The lower punch was set to a constant filling depth of 10 mm. The press speed was maintained at 750 tablets/min., with the compaction force set at its maximum of 8000 lb./in.^{2}. All granulations were compressed to a tablet hardness of 7 ± 1 Strong Cobb units.

Granulations were tableted the day following their manufacture. This delay was necessary to assure dissipation of any static charge accumulated by the granulation in its production. Sufficient granulation was poured through a 12-mesh screen to fill the 600-in.^{3} hopper on the tablet press. The screening procedure removed any lumps of granulation which might interrupt granule flow through the feed frame during tableting. In no instance did this size granule (>1680 μ) exceed 0.1% of the total granulation. Approximately 10,000 tablets were compressed, with the first and last 1000 tablets discarded.

For determining tablet disintegration times, the USP tablet disintegration apparatus[6] and procedures for uncoated tablets were used, except for the elimination of the plastic disks (12, 13). Reported tablet disintegration times are averages of 18 tablets. Tablet hardness was determined using a tablet hardness tester with a pressure attachment[7]. Pressure was maintained at 60 lb./in.^{2} by means of compressed nitrogen gas. Tablet hardness values depicted in the tables are averages of 10 tablets. Twenty tablets from each batch granulation were dusted and individually weighed to the nearest 0.1 mg. The average tablet weight, standard deviation, and coefficient of variation were calculated. Tablet thickness measurements were made to the nearest 0.0003 cm. (0.0001 in.). Reported thickness values are averages of 10 tablets.

RESULTS AND DISCUSSION

A previous paper (11) discussed the effects of process variables on the physical properties of batch granulations manufactured in a fluid bed spray granulator. With these influences established, the present investigation is concerned with the effects of various concentrations of a number of aqueous binder solutions on the physical properties of the final granulations and the tablets compressed from these fluidized bed granulations.

By using the standard formulation and four tablet binders, the effects of the binder formula concentration on the physical properties of the fluidized bed granulations were determined. A single set of operational variables, such as the air temperature and velocity, and the rate of binder addition, was selected and maintained for all batch granulations. Selections were made such that

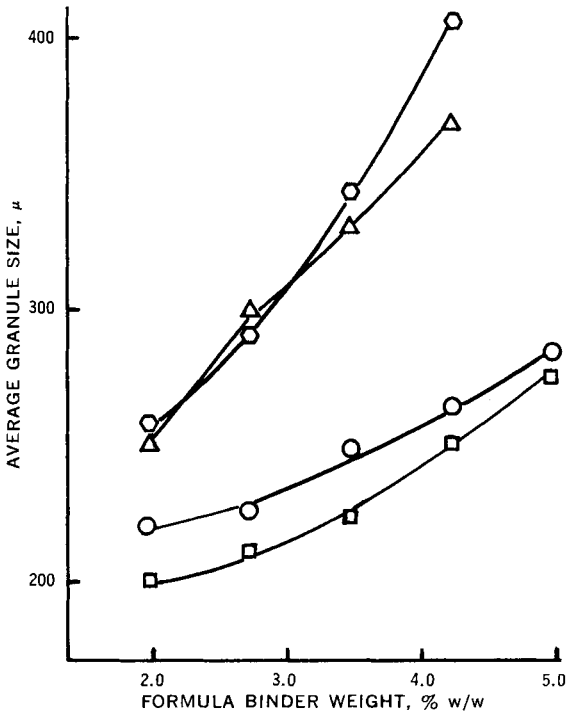

Figure 1—*Plot of the average granule size with respect to various binders and formula binder weights. Key: ○, hydroxypropyl cellulose; ○, acacia; △, gelatin; and □, povidone.*

[5] Colton model 216, Cherry-Burrell Corp., Chicago, Ill.
[6] H. J. Goepfert, Newark, N. J.
[7] Power model B, Strong Cobb Arner Inc., Cleveland, Ohio.

Table III—Physical Properties of Fluidized Bed Granulations Prepared Using Hydroxypropyl Cellulose as a Binder

Physical Properties	Formula Weight of Binder (% w/w)			
	2.00	2.75	3.50	4.25
Average granule size, μ	257	291	343	406
Friability, %	12.2	10.0	6.2	3.3
Bulk density, g./ml.	0.44	0.43	0.43	0.46
Granule density, g./ml.	1.502	1.499	1.492	1.483
Porosity, %	70.71	71.32	71.18	68.98
Flow rate, g./min.	167.4	151.9	135.8	130.4

Table IV—Physical Properties of Fluidized Bed Granulations Prepared Using Gelatin USP as a Binder

Physical Properties	Formula Weight of Binder (% w/w)			
	2.00	2.75	3.50	4.25
Average granule size, μ	249	299	328	367
Friability, %	11.8	11.3	10.2	8.2
Bulk density, g./ml.	0.43	0.39	0.36	0.34
Granule density, g./ml.	1.502	1.492	1.487	1.479
Porosity, %	71.37	74.29	75.79	77.01
Flow rate, g./min.	168.8	127.5	105.9	93.5

suitable granulations were formed with all concentrations of the individual binders. The average granule sizes and other physical properties for the individual binders and their concentrations are neither maximum nor minimum values. As demonstrated previously (11), the extent of granule formation is dependent upon a number of variable processes in the operation of the fluid bed granulator. Although this study gives some indication of the binder's effectiveness in fluidized bed granulating, it would be unjust to rate the effectivenesses of the four binders as granulating agents on the basis of these results alone.

The physical properties of the granulations prepared from the four binders are outlined in Tables II–V. The effects of binder concentration on the granule properties were similar for all binders investigated. Therefore, a general discussion of the tabular data follows.

All binders were more effective in granule formation as their concentration in the formulation was increased. In fluidized bed granulating, the greater binder effectiveness with higher concentrations was probably a result of a corresponding increase in the binder's adhesiveness. Figure 1 depicts the relationship between the formula binder weight and the average granule size. In addition to enlarging the average granule size, an increase in the formula binder weight increased its binding capabilities and yielded less friable granulations. Figure 2 shows the association between the formula binder weight and the friability of the granulated product.

Theoretically, the porosity of a granulation should increase with a larger average granule size. However, the exact bulk density, used in porosity calculations, of a granulation composed of many fines is often difficult to determine, because bridging by the fine particles in the measuring vessel tends to decrease its value. Granulations with wide size distributions also present problems in bulk density determinations, because the fine component may fill the interparticulate spaces of the larger granules unequally and interfere with density measurements. Neither of these influences seriously affected density determinations of granulations manufactured with the various concentrations of binder solutions, because the fine component of the granulations steadily decreased with increasing binder concentration. An increase in the average granule size at higher binder levels yielded a lower bulk density granulation. The decline in granule density with increasing granule size resulted from the larger volume of intraparticulate voids associated with the larger granules.

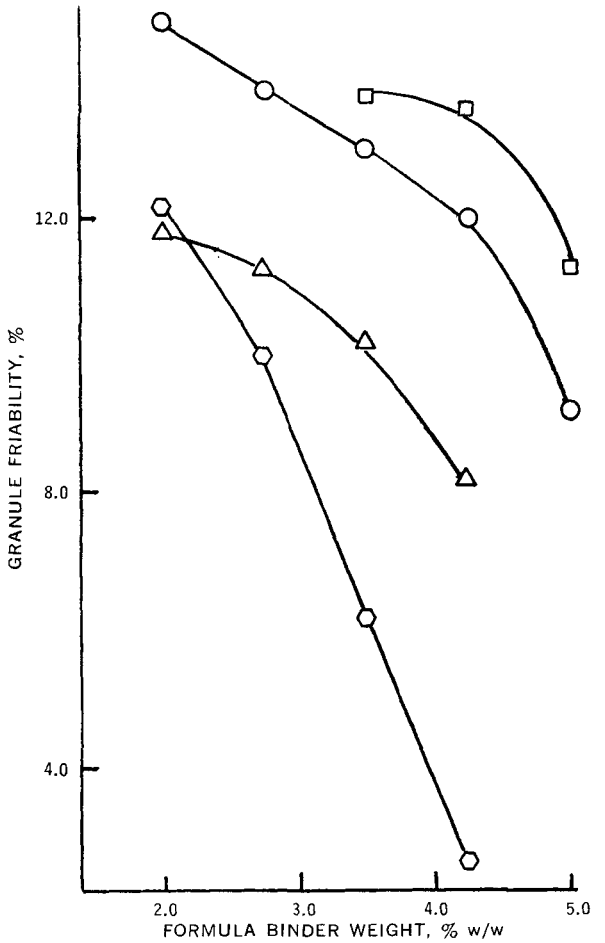

Figure 2—*Plot of the granule friability with respect to various binders and formula binder weights. Key:* ○, *hydroxypropyl cellulose;* ○, *acacia;* △, *gelatin; and* □, *povidone.*

The unusual bulk density observations with the hydroxypropyl cellulose binder were not totally unexpected. The large increases in viscosity at higher concentrations of this binder solution probably resulted in larger atomized droplets which decreased the rate of evaporation of the binder's solvent by the fluidizing medium. Therefore, there was greater penetration and wetting of the powder bed by the binder solution as its viscosity increased. This enhanced wetting ability of the binder solution increased the bulk density of the granulation to such an extent that the typical decrease in bulk density associated with increasing average granule size was overshadowed.

Table V—Physical Properties of Fluidized Bed Granulations Prepared Using Acacia USP as a Binder

Physical Properties	Formula Weight of Binder (% w/w)				
	2.00	2.75	3.50	4.25	5.00
Average granule size, μ	219	225	248	263	283
Friability, %	14.9	13.9	13.0	12.0	9.2
Bulk density, g./ml.	0.53	0.50	0.48	0.45	0.45
Granule density, g./ml.	1.523	1.511	1.506	1.505	1.500
Porosity, %	65.20	66.91	68.13	70.10	70.00
Flow rate, g./min.	257.5	233.5	193.3	169.3	162.6

Table VI—Physical Properties of Tablets Compressed from Fluidized Bed Granulations Prepared Using Povidone NF as a Binder

Physical Properties	Formula Weight of Binder (% w/w)				
	2.00	2.75	3.50	4.25	5.00
Weight, mg.	401.1	394.4	376.2	367.3	354.8
Standard deviation, mg.	2.73	2.06	2.72	4.81	3.04
Coefficient of variation, %	0.68	0.52	0.72	1.31	0.86
Hardness, Strong Cobb units	7.1	7.5	6.8	6.8	7.5
Disintegration time, min.	1.82	2.25	2.60	2.78	2.95
Thickness, cm. (in.)	0.54 (0.2138)	0.53 (0.2076)	0.52 (0.2035)	0.51 (0.2002)	0.50 (0.1973)

Table VII—Physical Properties of Tablets Compressed from Fluidized Bed Granulations Prepared Using Hydroxypropyl Cellulose as a Binder

Physical Properties	Formula Weight of Binder (% w/w)			
	2.00	2.75	3.50	4.25
Weight, mg.	349.0	334.2	323.2	325.5
Standard deviation, mg.	1.94	3.41	2.74	1.88
Coefficient of variation, %	0.56	1.02	0.85	0.58
Hardness, Strong Cobb units	7.4	7.2	7.5	7.5
Disintegration time, min.	3.07	4.38	7.35	11.75
Thickness, cm. (in.)	0.48 (0.1877)	0.47 (0.1838)	0.45 (0.1790)	0.46 (0.1802)

Crosly (14) stated that the principal factors affecting the flowability of particulate solids are size, shape, size distribution, density, porosity, and surface characteristics. Each individual factor must be considered when evaluating the flow rate of a granulation, because one factor may counteract the effect of another. All granulations showed a decrease in flow rate with increasing levels of solid binder in the formulation. An investigation of the individual physical properties of each granulation contributes support to the observed reduction in flow rate with increasing binder concentration. The increased porosity associated with the larger average granule size signifies more volume per unit weight of granulation. Since the flow rate is expressed in weight of granule flow per unit time, the flow rate is inversely related to the porosity of the granulation. One exception was observed with the highest concentration of the hydroxypropyl cellulose binder. As noted previously, with this viscous solution a reduction in porosity is encountered with increasing average granule size. Consequently, an increase in flow rate might be expected. The failure to show an increase in flow rate here is attributed to the less than ideal ratio (5:1) of the funnel orifice diameter to the largest granule fraction in this granulation. Zenz and Othmer (15) reported that for uninterrupted flow, the internal diameter of the funnel orifice should exceed 5–7 times the diameter of the largest granules.

The ultimate evaluation of a tablet granulation lies in its tableting characteristics. Therefore, tablets were compressed from granulations of the various concentrations of binder solutions; their physical properties are reported in Tables VI–IX. Correlations between granule and tablet properties were sought as the tablets were evaluated for weight, weight variation, disintegration, thickness, and general appearance. While the primary purpose of the tableting data in the present study is not to seek new relationships between the physical properties of the granulations and tablets, since these were reported elsewhere (16), it is the authors' intent to demonstrate that the physical characteristics and relationships between these fluidized bed granulations and compressed tablets do correspond to those resulting from the conventional granulation methods. To eliminate variables in tablet properties due to tablet press controls, the die fill depth, press speed, and compaction force were held constant for all batches. In addition, tablets were compressed to constant hardness for all granulations through adjustment of the lower pressure roll on the tablet press. Through maintenance of these press variables, the physical properties of each batch of tablets became solely dependent upon the individual properties of the granulations from which they were compressed.

The average tablet weight and thickness are directly dependent upon the die fill weight, which relates primarily to a combination

Table VIII—Physical Properties of Tablets Compressed from Fluidized Bed Granulations Prepared Using Gelatin USP as a Binder

Physical Properties	Formula Weight of Binder (% w/w)			
	2.00	2.75	3.50	4.25
Weight, mg.	346.5	310.8	284.7	272.1
Standard deviation, mg.	5.16	4.76	4.25	4.33
Coefficient of variation, %	1.49	1.53	1.49	1.59
Hardness, Strong Cobb units	7.2	7.6	7.2	6.6
Disintegration time, min.	2.47	2.87	3.30	3.74
Thickness, cm. (in.)	0.48 (0.1895)	0.44 (0.1747)	0.42 (0.1639)	0.40 (0.1578)

Table IX—Physical Properties of Tablets Compressed from Fluidized Bed Granulations Prepared Using Acacia USP as a Binder

Physical Properties	Formula Weight of Binder (% w/w)				
	2.00	2.75	3.50	4.25	5.00
Weight, mg.	445.5	409.7	394.1	365.0	362.5
Standard deviation, mg.	2.75	3.44	3.12	3.50	2.64
Coefficient of variation, %	0.62	0.84	0.79	0.96	0.72
Hardness, Strong Cobb units	7.1	7.2	6.8	7.1	7.7
Disintegration time, min.	2.33	3.15	3.89	4.58	5.81
Thickness, cm. (in.)	0.58 (0.2296)	0.54 (0.2115)	0.53 (0.2067)	0.49 (0.1939)	0.48 (0.1928)

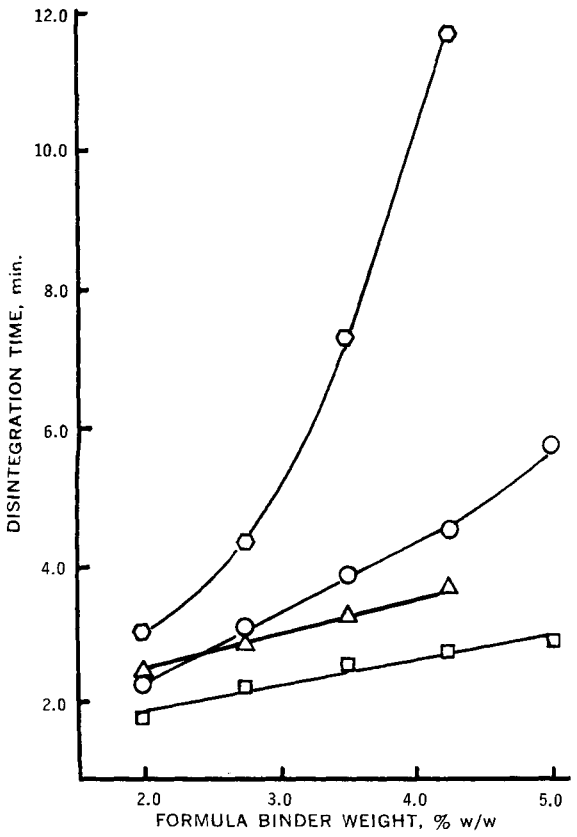

Figure 3—*Plot of the tablet disintegration time with respect to various binders and formula binder weights. Key: ○, hydroxypropyl cellulose; ○, acacia; △, gelatin; and □, povidone.*

of the granulation's porosity and flow properties. An increase in the intergranular porosity, related to the increasing average size and bulkiness of the granulation, resulted in a lower weight per unit volume die fill and, thus, a lighter tablet was compressed. As expected, a decrease in the flow rate, associated with the larger, less dense granulations manufactured at higher binder concentrations, contributed to the lighter tablets as well. One exception was noted with the granulation prepared from 4.25% w/w hydroxypropyl cellulose. Due to the enhanced wetting ability of this viscous binder solution, the resulting decrease in granule porosity offset the decreased flow rate, and a slight increase in the tablet weight was observed. This observation suggests that in tableting fluidized bed granulations, porosity may be more influential than the granulation's flow rate and this, in turn, complements the high fluidity of these granulations.

The coefficient of variation for tablets, a measure of the tablet weight variation, was correlated with granule flowability (17). A high coefficient of variation indicates a poorly flowing granulation, while low values signify highly reproducible flow rates. The lack of any correlation between the granulation's flow rate and coefficient of variation for tablets prepared from any individual binder in this investigation suggests that within individual binders the tablet weight variation is influenced less by flow rate than by other granule properties, such as porosity. In addition, observed collectively, a review of the tablet coefficient of variation data from granulations prepared from the four binders reveals that gelatin yielded the least uniform tablets. The tablet coefficient of variation values from granulations manufactured from acacia, povidone, and hydroxypropyl cellulose binders were equally small in comparison to values for gelatin. These results correlate well with the porosity values of the granulations manufactured with the various binders, because granulations prepared with gelatin were significantly more porous than those manufactured from the other binder solutions. High intergranular porosity is an indication of granule surface irregularities, which would account for greater variations in die cavity fill weights. These results imply that with a highly fluid granulation, such as those manufactured in a fluidized bed, granulations of low interparticulate porosity are more uniformly compressed with respect to tablet weight variation. Since porosity is easily controlled in the manufacture of fluidized bed granulations by the degree of powder wetting, this is a decided advantage of this granulation method.

A relationship between the formula binder weight and the tablet disintegration time is depicted in Fig. 3. Since all granulations were composed of an equal quantity of disintegrating agent and all tablets were compressed to constant hardness, these effects on tablet disintegration were eliminated. The increased disintegration times for tablets can, therefore, be related to the increased binding capacities of these granulating agents at higher concentrations in the formulations. These findings supplement the previously observed decrease in granule friability at higher binder concentrations.

SUMMARY

The physical properties of fluidized bed granulations are strongly influenced by the binder and the binder concentration. An increase in the binder concentration increases the binder adhesiveness, yielding less friable granulations with granules of a greater average size. The greater porosity and reduced flow rates of granulations produced at higher binder concentrations are associated with the increase in their average size. Due to slower solvent evaporation rates, viscous binder solutions reduce the bulkiness of fluidized bed granulations through their enhanced ability to penetrate and wet the fluidized solids. Correlations, similar to those observed with conventional granulations, exist between the physical properties of fluidized bed granulations and the tablets compressed from them.

While the physical properties of a granulation or tablet can be readily established by various direct measurements, the general appearance of the granulated product or compressed tablet is less easily defined. From the experience gained so far with the fluid bed granulator and from the flawless appearance and characteristics of all tablets compressed using fluidized bed granulations, a recommendation can be made strongly in support of this granulation method.

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