Design and Use of a Laboratory Extruder for Pharmaceutical Granulations

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Abstract □ The purposes of this study were to design and build a laboratory extruder and to evaluate various factors relating to its use for the preparation of both wet and hot fusion granulations. The extruder used is a specially designed, single screw type, equipped with removable anvils, liquid addition ports, a heating jacket, and a thermocouple probe. A study of the extrusion of a typical antacid granulation was made. The variables studied were: *(a)* type of granulating fluid, *(b)* type of endplate, *(c)* number of mixing anvils, and *(d)* screw speed. Measurements were made on torque, powder throughput, liquid required, and whether or not a uniform consistency was obtained. Mesh sizes of both milled and unmilled granulations were measured along with bulk densities of 30–40-mesh fractions. A series of wax fusion granulations was also made with varying jacket temperatures, and drug release rates for 1 and 5 hr. were tested.

Keyphrases □ Extruder for pharmaceutical granulations—evaluation of granulating fluid, endplate, mixing anvils, screw speed □ Granulation extruder—evaluation of granulating fluid, endplate, mixing anvils, screw speed

Because of the large volume needed, conventional batch techniques of manufacture are no longer economically or practically feasible for a number of solid pharmaceutical products. Modern advances in tablet compression machinery have contributed to high production rates. Advances in the processing of pharmaceutical granulations have also been made but to a lesser extent. Use of fluid bed granulation and drying and of special mixers has become common. However, research and development groups have given relatively little attention to the continuous processing of solid dosage forms.

Several examples of continuous tableting processes were reported (1, 2) and others are certain to exist within the industry. The continuous processing of aspirin tablets was described (1), and this method includes: mixing, compaction in a Chilsonator, size reduction, conveying, and compression. A continuous method of producing antacid tablets using the extrusion method of granulation was described (2). In this process the dry ingredients are mixed in a ribbon blender and conveyed automatically to a hopper from which the material is metered into a Rietz extruder. Liquid is added to the dry material in the extruder where the granulation is mixed and blended to the proper consistency for extrusion. After extrusion, the wet granulation is dried automatically in Witte fluid bed driers and pneumatically conveyed to a hopper and mill. Following size reduction, the flavor and tablet lubricant are metered into a constant stream of dried granulation. The material is transported to a mezzanine and dumped into large overhead hoppers above tablet machines. In this last example, the continuity of the process is broken since the finished granulation is not transported automatically to the tablet machines.

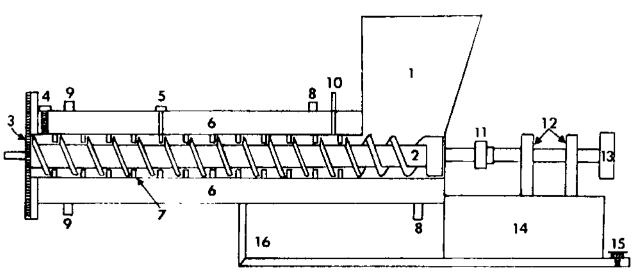

Figure 1—*Schematic diagram of laboratory extruder. Key: 1, feed hopper; 2, screw; 3, endplate; 4, pressure transducer well; 5, thermocouple well; 6, heating and cooling jacket; 7, anvils; 8, jacket inlet ports; 9, jacket outlet ports; 10, liquid feed ports; 11, screw coupling; 12, bearings; 13, drive coupling; 14, base; 15, attaching bolt; and 16, brace.*

The continuous operation of a tableting process consists of simply linking various parts of the basic procedures which have customarily been used. The most critical aspect of the continuous processing described above was the mixing extruder step. While this process was well adapted to antacid granulations made currently, it is not always possible to process other formulations by the extrusion method. Since it was desired to use extrusion processes for other products, smaller scale research and development equipment was required. However, no equipment was available on a laboratory or pilot scale that could be used for formulation or development work. Therefore, a special extruder-mixer was designed and built to serve this function.

The equipment desired was to be multipurpose, since both standard wet granulation formulations and hot fusions were to be made on a continuous basis. For wet granulations, a premixed dry powder would be fed to the extruder where liquid could be added and mixed thoroughly with the powder. A mass of the proper consistency would be extruded at the end of the mixing chamber. Wetting of the material in the extruder itself was deemed necessary so that a separate mixer need not be used prior to the extrusion step. The achievement of uniform, reproducible mixing in the extruder was an important and difficult objective. It was also envisioned that the same extruder could be used for fusion and extrusion of waxy granulations commonly used to produce timed-release tablets.

EXPERIMENTAL

Design Requirements—Considerable experience in extrusion was obtained over the years using the Rietz equipment[1]; therefore, the design of a new extruder should consider the deficiencies of existing equipment and correct them accordingly. One problem with the Rietz equipment was the cycling from an overwet to an overdry condition. This problem was caused by inadequate wetting or mix-

[1] Rietz Manufacturing Co., West Chester, PA 19380

Table I—List of Screw Configurations

Pitch, cm.	Number of Anvils	Root Diameter[a], cm.	Special Remarks
2.54 (1.0 in.)	3	1.91 (0.75 in.)	—
3.81 (1.5 in.)	3	2.54 (1.0 in.)	—
4.08 (2.0 in.)	3	2.54 (1.0 in.)	—
3.81–4.08 (1.5–2.0 in.) combination	8	2.54 (1.0 in.)	Double flight at end[b]
3.81–4.08 (1.5–2.0 in.) combination	11	2.54 (1.0 in.)	Double flight at end[b]
3.81–4.08 (1.5–2.0 in.) combination	12	2.54 (1.0 in.)	Double flight at end[b]

[a] Thickness of screw exclusive of flight portion. [b] Flight is the length of screw required for one helix.

Table II—List of Endplates

Hole Diameter, mm.	Plate Thickness, mm.	Open Area, %
1.0	3.18	—
1.2	3.18	—
1.4	3.18	—
2.0	3.18	—
4.0	1.59	63
4.2	1.59	51

Table III—Amounts of Powder and Liquid Used at Various Extrusion Conditions

Powder Delivery	
Extruder Speed, r.p.m.	g./min.
40	260
50	320
60	365

	Liquid Delivery, ml./min.			
	Water		Water, 75%–Isopropanol, 25%	
	Endplate Open Area		Endplate Open Area	
Speed, r.p.m.	51%	63%	51%	63%
Eight Interruptions				
40	55	70	80	95
50	75	85	100	110
60	85	95	125	—
12 Interruptions				
40	50	60	80	80
50	70	75	95	95
60	—	85	105	105

ing and periodic surges. The adequacy of the screw pitch and its root diameter was unknown. To make a general pharmaceutical extruder, it was believed that a longer barrel would be required and that better mixing must be obtained. With this in mind, the general requirements were provision for a long mixing chamber and an adequate impediment of material flow. A split barrel allowed easy cleaning and maintenance as well as quick interchange of screws and endplates. The extruder was jacketed, which provided a method of producing wax fusion granulations or other granulation types that require temperature control. A well and hole were made for the placement of a thermocouple for measurement of granulation temperature. The drive unit provided excess power, since it was envisioned that a larger extruder might someday be coupled to the same drive system. The instruments on the drive unit were a tachometer and a recording dynamometer for torque measurement.

Construction—With the above requirements in mind, the general design of the extruder was made and a drive unit was selected. Figure 1 illustrates the design, and Fig. 2 shows the extruder coupled to the drive unit[2]. The extruder is of the single screw type, 50.8 cm. (20 in.) long and 5.4 cm. (2.125 in.) wide. The closed section or barrel is 40.64 cm. (16 in.) long and the hopper portion is 10.16 cm. (4 in.). Two ports near the hopper end are used for addition of liquid. A spraying attachment was also made for wetting powders in the hopper. The barrel is made in two sections and is hinged along the long axis so that it may be opened readily and cleaned easily. The barrel contains two permanent steel anvils and 10 removable anvils made of an acetal resin[3]. Blank anvils can be used in any of the 10 positions, so it is possible to experiment with various anvil arrangements. Each side of the barrel is jacketed and contains two inlet and two outlet ports for the circulation of heated liquid when fusion granulations are made. The top section contains a well for a thermocouple probe. Construction is of type 304 stainless steel, except for the extruder support which is aluminum.

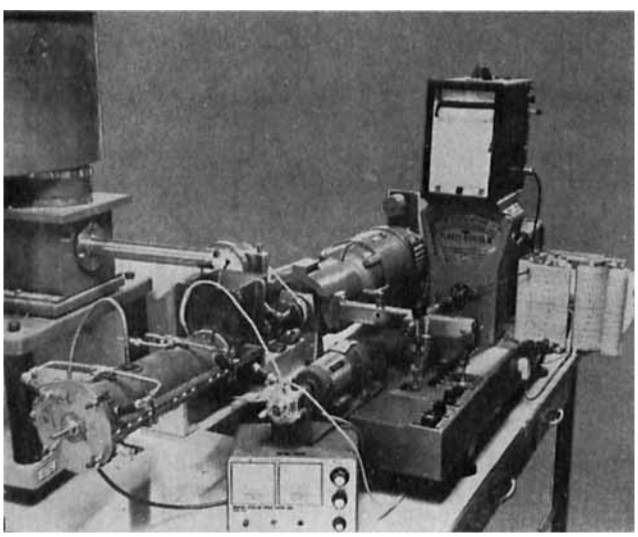

Figure 2—*Photograph of the extruder, drive unit, metering pump, and powder feeder.*

The drive unit[2] consists of a 3.4-hp. adjustable speed d.c. motor, a recording dynamometer, a tachometer, and a two-point temperature recorder. A high and low sensitivity speed adjustment permits screw revolutions per minute to be adjusted from 0 to 240, and constant speed can be maintained regardless of the torque on the screw.

Accessory Equipment—A heater-circulator[4] was used to provide heat to the extruder jacket, and a 2-cu. ft. live bin feeder[5] was used to feed powder at a fixed rate. The feeder has a variable-speed drive and tachometer so powder feed rate can be closely controlled. It is mounted on an adjustable hydraulic platform for easy height adjustment. A metering pump and controller[6] were used to feed liquids.

Startup—Initial experimentation was concerned with such factors as screw pitch, screw root diameter, number of anvils, and endplate configuration. Screw root diameter and pitches were made in a number of combinations (Table I).

A screw of 2.54-cm. pitch conveyed material too fast for good mixing and extruding. Both the 2.54- and 3.81-cm. screws gave considerable back-pressure during extrusion. A series of three screws was made; they were all alike except for the number of interruptions. These screws are the last three listed in Table I. The screws start out having a 3.81-cm. pitch, which conveys material from the hopper into the barrel. Inside the barrel, the screw pitch is 4.08 cm., which allows more slippage and mixing of material. A twin flight at the end of the screw improves the rate of output and prevents, to some degree, high back-pressures.

Endplates were made having the dimensions shown in Table II.

[2] C. W. Brabender Plasticorder model PL-V34D, C. W. Brabender Instruments, Inc., South Hackensack, NJ 07606

[3] Delrin, E. I. Dupont de Nemours & Co., Inc., Wilmington, DE 19898

[4] C. W. Brabender Instruments, Inc., South Hackensack, NJ 07606

[5] Vibra Screw Inc., Totawa, NJ 07512

[6] Model 7561, Cole-Parmer, Chicago, IL 60648

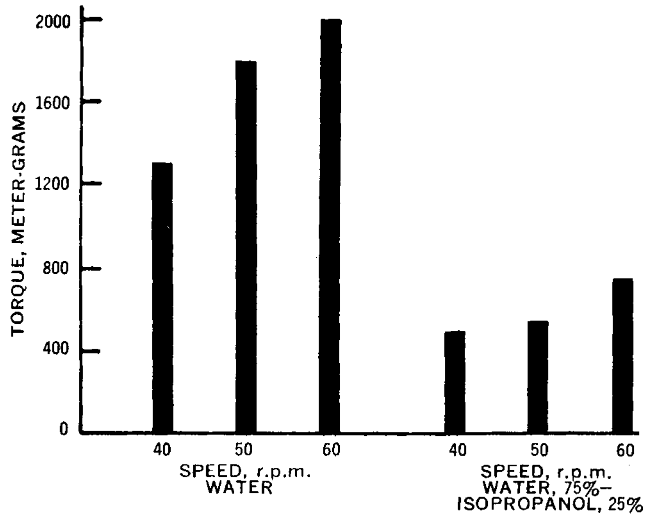

Figure 3—*Average torque values for an antacid granulation as a function of extruder factors and kind of granulating fluid.*

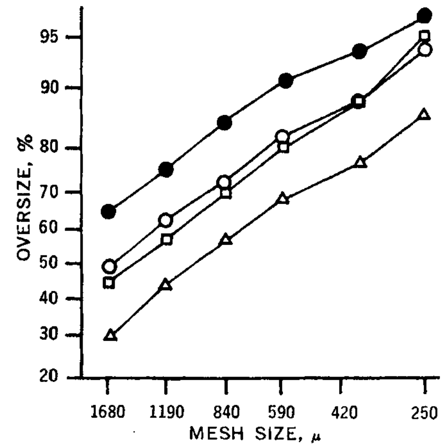

Figure 4—*Mesh sizes of dried unmilled antacid granulations. Key:* ●, *water, 12 interruptions;* ○, *water, eight interruptions;* □, *water–isopropanol (75:25), 12 interruptions; and* △, *water–isopropanol (75:25), eight interruptions.*

Endplates of 3.18-mm. thickness and hole size 2 mm. or less were satisfactory for hot fusion granulations. However, a 1.59-mm. endplate with hole sizes listed in Table II was needed for extruding the antacid granulation. Thicker plates and plates with too little open area gave too much back-pressure.

These factors were studied during various trials. Some of the initial problems were to obtain good fits of the screw in the extruder, to obtain a fixed position for the screw, and to avoid rubbing the inside of the endplate and barrel. A spray system for the addition of liquid to the powder in the hopper was unsatisfactory for granulation because of agglomeration and sticking in the hopper and on the screw. Therefore, the two barrel ports were used to add liquid for all wet granulations. Circulation of hot liquid through the extruder barrel was very good and heat exchange was excellent for wax fusion granulations.

Extrusion of Antacid Granulation—The extrusion of a typical antacid granulation was studied. The variables were: (*a*) granulating fluid, *i.e.* water alone *versus* water–isopropanol (75:25); (*b*) endplates with 4.0-mm. hole diameter and 63% open area or 4.2-mm. hole diameter and 51% open area; (*c*) number of anvils, either 8 or 12; and (*d*) screw speeds of 40, 50, and 60 r.p.m.

A powder blend was made containing two antacids and powdered sugar. The powder blend was fed to the extruder by means of the feeder[5], which had previously been calibrated in grams of antacid powder delivered per minute. Powder throughput was adjusted according to the screw speed to maintain a constant extruder hopper level. Rate of delivery was 260, 320, and 365 g./min. at 40, 50, and 60 r.p.m., respectively (Table III). Liquid feed was adjusted using the metering pump to give the most consistent granulation at each experimental condition (Table III). Granulations were tray dried at 38° to 4.8–6.3% loss on drying.

Experimental observations and measurements were: (*a*) torque produced during extrusion, (*b*) extent of cycling, (*c*) bulk density, (*d*) mesh pattern of unmilled material obtained by sieve analysis, (*e*) tablet texture, and (*f*) mesh pattern of milled and unmilled material.

Table IV—Extent of Cycling[a] with Various Extrusion Conditions

Speed, r.p.m.	Water—Endplate Open Area 51%[b]	63%[c]	Water, 75%–Isopropanol, 25%—Endplate Open Area 51%	63%
	Eight Interruptions			
40	1	1	1	3
50	1	1	2	3
60	2	2	3	—
	12 Interruptions			
40	2	2	2	3
50	3	2	2	2
60	—	1	2	3

[a] 1, least cycling; 2, moderate cycling; and 3, heavy cycling. [b] Hole diameter = 4.2 cm. [c] Hole diameter = 4.0 cm.

RESULTS AND DISCUSSION

Torque measurement is in meter-grams, a unit directly related to viscosity measurement. The torque can be recorded or read directly on a scale on the drive unit. This principle of operation is based on a weighted arm connected to the drive unit. The drive unit is mounted to swing freely as force is applied by the driving screw. The arm can be loaded with various weights, which offset the driving torque, and the torque working range during an experimental run can be measured. The practical meaning of torque is that higher readings relate to a thicker, stiffer granulation which requires more work for extrusion. A granulation that is less agglomerated and softer is extruded, giving a lower torque reading. This also relates to a softer textured granulation and tablet. A summary of the average torque reading during various runs is shown in Fig. 3. The main effect on

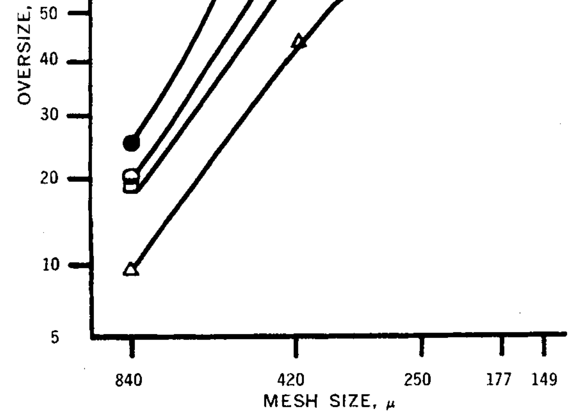

Figure 5—*Mesh sizes of dried and milled antacid granulations. Key:* ●, *water, 12 interruptions;* ○, *water, eight interruptions;* □, *water–isopropanol (75:25), 12 interruptions; and* △, *water–isopropanol (75:25), eight interruptions.*

Table V—Composition of Wax Fusion Granulation Used in Extruder Experiments

	Percent by Weight
Spray congealed fat–wax mixture (1:4)	25
Drug–diluent blend	75

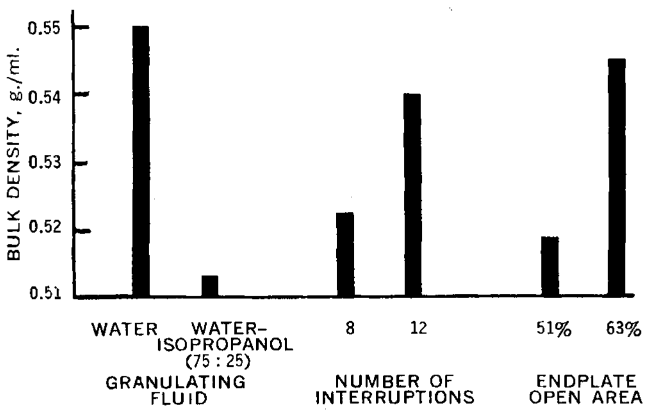

Figure 6—*Bulk densities of antacid granulations as a function of the kind of granulating fluid and various extruder factors.*

torque is the granulating fluid. In these experiments the average torque is 1360 for water and 580 for water–isopropanol. This result is not unexpected since water-isopropanol produces a lighter mass than water for this granulation. Probably less sugar is dissolved in the water–alcohol solution, thus providing less binding of ingredients. Higher speed rates also increase torque because more material is being processed in a given period of time.

Generally, more granulating fluid is used for the 63% open area endplate than the 51% open area endplate. This occurs because of less back-pressure and mixing with the 63% open area endplate compared to the plate with the lesser open area.

The property of the extrudate to change from a relatively wet condition to a relatively dry condition (referred to as cycling) was graded by observation and given ratings of 1, 2, 3. Class 1 was very little cycling, Class 2 was moderate cycling, and Class 3 was heavy cycling (Table IV). As Table IV indicates, the least cycling occurs with water as the granulating fluid, but low cycling was obtained for one condition using water–isopropanol as the granulating fluid. Speed, number of interruptions, and endplate open area are relatively insignificant factors. However, experiments using less than eight interruptions indicate that more and more cycling will occur as additional anvils are removed. A minimum number of interruptions and thus a minimum L/D ratio (extruder length to diameter ratio) are required for good extrusion.

Mesh patterns of dried unmilled granulations are shown in Fig. 4. In general, the mesh analysis is similar for all granulations[7], but water–isopropanol granulations show a significantly lower mesh size. Significant mesh size variations also occurred between the milled granulations made with water alone compared to water–isopropanol granulating fluid (Fig. 5). Fewer coarse particles and more fines are made with the water–isopropanol granulating fluid, probably due to the fact that an all aqueous granulating fluid binds particles more strongly than an alcoholic solution.

The bulk densities of 30–40-mesh granulation were measured using an automatic tapping device (600 taps). The trends shown in Fig. 6 indicate that bulk density differences exist for various extrusion conditions. The largest significant factor is the granulating fluid, closely followed by endplate open area and the number of interruptions. On the average, a more dense particle is obtained from water as opposed to water–isopropanol. Denser granulations are also obtained from more interruptions and a more open endplate area.

Tablet Texture—All the machine and formulation variables previously discussed have an effect on the ultimate texture of the tablet. The single most significant variable is the type of granulating fluid (water *versus* water–isopropanol).

Tablets made from granulations using the water–isopropanol mixture were considerably less gritty and smoother than tablets made from granulations using water alone. The addition of alcohol as a cosolvent with water reduces the solubility of sugar in that fluid as opposed to using water by itself. This reduction of sugar solubility causes less binding of the powders, thus giving a softer and less dense granulation with improved texture properties.

Based on the data collected on endplate opening, speed of extruder, number of interruptions, torque reading, densities, and mesh patterns, a general statement can be made concerning conditions that give a tablet of improved texture: A water–isopropanol granulating fluid, eight interruptions, and a 51% open area endplate tend to give granulations having lower bulk densities.

Wax Fusion Granulations—Experimental runs made during startup indicated that the extruder held promise for making fused granulations. A series of experiments was run to determine the optimum extrusion condition for meeting the release specifications of an existing formulation. To obtain a good physical mix prior to fusion and extrusion, a modification was made in the existing formula. The fat and wax ingredients were used as a fine uniform spray-congealed mixture. The formulation used is shown in Table V.

A uniform blend of the mixture was made and fed to the extruder by hand. Three extrusion runs were made under the conditions given in Table VI. Twelve anvils were used, and the throughput was 150 g./min. In general, low extrusion temperatures give slightly fused granulations whereas temperatures that are too high give an overfused and sticky extrusion. The smaller sized endplates, 2 and 1.4 mm., are preferable to the 3-mm. endplate for producing a uniform extrudate.

Table VI—Effect of Fusion Temperature on Drug Release[a]

Jacket Temperature	Material Temperature	Drug Release, %, 1 hr.	Drug Release, %, 5 hr.
70°	60°	26	81
90°	78°	26	86
95°	82°	28	90

[a] Method of Souder and Ellenbogen, *Drug Stand.*, **26**, 77(1958).

The drug release rates listed in Table VI show that about the same amount is released at the 1-hr. interval regardless of the fusion temperature. However, at the 5-hr. interval, drug release is affected by fusion temperature.

CONCLUSIONS

The design and construction of a laboratory extruder for the preparation of a wide range of tablet granulations are described. The machine conditions for successful preparation of antacid granulations and wax fusion granulations are discussed. The special features included in this extruder seem to warrant consideration of extrusion on a larger scale, using the principles developed with the laboratory model.

Future uses will include the preparation of extrusions for pelletizing using the Marumerizer. The extruder will be used in new product development, in testing of presently marketed products, and for feasibility of preparing effervescent granulations.

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[7] All granulations were milled using the Fitzmill comminuting machine, with a No. 2A round hole screen, knives forward, at medium speed. The Fitzpatrick Co., Elmhurst, IL 60126