Tablet Granulations Composed of Spherical-Shaped Particles

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Abstract □ A novel pelletizing process, spheronization, was used to prepare spherical particles for use in tablet compression. Dibasic calcium phosphate, acetaminophen, magnesium hydroxide, and sulfadiazine granulations were prepared and compressed into acceptable tablets. Tests showed that the spheronizing process resulted in an improved granulation flow rate and narrow particle-size distribution as compared to a conventionally processed wet granulation. Granulation reproducibility and change of size distribution with processing time were also studied. Tablets were compressed from all granulations, and hardness and disintegration times were determined.

Keyphrases □ Spheronization—preparation of spherical particles for tablet compression, compared to conventional wet granulation method □ Granulation—effect of spheronization on flow rate and particle-size distribution, compared to conventional wet method □ Tablet granulations—spheronization method compared to conventional wet granulation, hardness, disintegration times

Spherical particles formed using pelletizing equipment[1], described by Conine and Hadley (1) and Reynolds (2), afford several possible advantages over conventional wet granulations. This process of spheronizing, they reported, should result in faster drying times, shorter and less complex processing, minimal dust and cross-contamination, and optimal flow rate.

In the early stages of investigating the properties of these spherical particles, it was observed that spheres could be prepared using only 10–20% inactive ingredients. Obviously, this process might present advantages in preparing granulations for large dose medications.

This report compares data obtained from a wet granulation of a common tablet diluent, dibasic calcium phosphate, by conventional and pelletizing techniques. In addition, three different granulations consisting of 80% active ingredient and 20% binder were prepared and evaluated. Tablets were compressed from both conventional and pelletized granulations and compared with respect to hardness and disintegration properties.

Previous work (3, 4) showed microcrystalline cellulose to be an acceptable binder for the wet granulation process. Tablets compressed from granules containing microcrystalline cellulose binder exhibit acceptable disintegration characteristics without addition of a disintegrating agent. Microcrystalline cellulose as a dry binder for tablets was investigated in detail by Fox *et al.* (4) and Shangraw *et al.* (5).

[1] Extruder type EXDS-60 and Marumerizer type Q-230, available from Elanco Products Co., a division of Eli Lilly and Co., Indianapolis, Ind.

EXPERIMENTAL

Materials—Microcrystalline cellulose[2], dibasic calcium phosphate[3], magnesium hydroxide NF[3], sulfadiazine USP[4], acetaminophen NF[5], acetaminophen NF micropowder[6], and magnesium stearate USP[7] were used.

Manufacturing and Testing Procedures—The binder (microcrystalline cellulose) and active ingredient (or placebo diluent) were combined in a blender[8]. Purified water was added until the material was sufficiently wetted. The amount used was held constant for each particular formulation.

For the conventionally processed wet granulations, the wet mass, 500–600 ml. of water/kg. of dry granulation, was passed through an 8-mesh screen, spread on trays, and dried overnight at 40°. The dried granulations were forced through a 12-mesh screen and, in the case of sulfadiazine only, lubricated with 1% magnesium stearate. Approximately 500 tablets of each were compressed on the single-punch tablet press[9] using 0.8-cm. (0.33-in.) standard concave punches.

The granulations to be pelletized were blended, wetted with purified water (400–500 ml./kg. of dry ingredients), passed through the extruder equipped with either 0.5- or 1.0-mm. screens, and transferred to the Marumerizer for 60 sec. The resulting spheres were dried (lubricated in the case of sulfadiazine only) and compressed into tablets as already described.

Tests performed on the dried, unlubricated granulations included the following: flow rate, using 500 g. of granulation allowed to pass through the standard funnel described in Table I; sieve analysis utilizing a sieve shaker[10], number six setting, for 5 min. with a 200-g. sample size; and final moisture content, determined on a moisture determination balance[11] (5.5-w. lamp setting for 15 min. with standard 10-g. sample). All tests were performed in triplicate and showed reasonable reproducibility.

Hardness and disintegration time of the resulting tablets were determined; the reported values represent an average of tests on three and six tablets, respectively.

RESULTS AND DISCUSSION

Spherical particles and tablets from pelletized material were successfully prepared containing 80% dibasic calcium phosphate, magnesium hydroxide, sulfadiazine, or acetaminophen. All of the granulations were also prepared by the conventional wet granulation process, and a comparison of the results showed that pelletizing increased flow rate from 38 to 102% and provided a narrower particle-size distribution and much less fines. Up to 80% of a pelletized granulation may be contained in one sieve fraction (Table I).

Since 1.0-mm. screens were used in the extruder, it would be expected that, with the pelletized granulations, the 16–20-mesh

[2] Avicel RC-581, FMC Corp., Marcus Hook, Pa.
[3] Mallinckrodt Chemical Works, Jersey City, N. J.
[4] American Cyanamid Co., Pearl River, N. Y.
[5] Amend Drug and Chemical Co., New York, N. Y.
[6] S. B. Penick and Co., New York, N. Y.
[7] Ruger Chemical Co., Irvington, N. Y.
[8] Erweka KU1, Chemical and Pharmaceutical Industry Co., Inc., New York, N. Y.
[9] Stokes model E.
[10] Cenco-Meinzer, Central Scientific Co., Chicago, Ill.
[11] Model 6010, Ohaus Scale Corp., Union, N. J.

Table I—Properties of Granulations and Tablets Prepared by Conventional (CWG) *versus* Pelletizing (P) Wet Granulation Techniques[a]

Test	Dibasic Calcium Phosphate CWG	Dibasic Calcium Phosphate P	Magnesium Hydroxide CWG	Magnesium Hydroxide P	Sulfadiazine[b] CWG	Sulfadiazine[b] P	Acetaminophen CWG	Acetaminophen P
Sieve analysis, % w/w[c]								
8 mesh	0.0	6.0	0.0	0.0	0.0	0.2	0.0	0.4
8–16 mesh	37.5	35.1	30.8	0.1	21.6	2.2	23.7	0.5
16–20 mesh	19.7	46.1	22.3	38.9	23.7	76.3	29.0	15.7
20–40 mesh	19.0	12.0	30.3	60.4	24.6	21.1	23.9	81.6
40–80 mesh	10.0	0.1	12.7	0.5	14.8	0.3	12.9	1.7
80–100 mesh	1.6	0.0	0.6	0.0	2.8	0.0	1.6	0.0
>100 mesh	12.2	0.7	3.3	0.0	12.6	0.0	8.9	0.0
Flow rate[d], g./sec.	14.3	24.5	13.4	19.7	8.2	16.6	13.1	18.1
Tablet hardness, kg.[e]	7.8	7.0	9.5	5.0	9.0	3.5	7.0	5.5
Disintegration time, min.[f]	1.0	1.0	0.8	0.3	3.5	6.5	1.3	12.5

[a] Process conditions for all runs: extruder speed, 50 r.p.m.; Marumerizer speed, 1000 r.p.m.; residence time of segments for spheronizing, 60 sec.; final water content, 1–1.5%; binder, 20% Avicel RC 581; and extruder screen, 1.0 mm. [b] 1% magnesium stearate USP. [c] U. S. Standard sieves, rated 2.38 mm. (8), 1.19 mm. (16), 0.84 mm. (20), 0.42 mm. (40), 0.177 mm. (80), and 0.149 mm. (100), respectively. [d] Grams of granulation per second flowing through 1.27-cm. (0.5-in.) diameter orifice of a conical funnel. (A flow rate of 10.0 g./sec. was considered the minimum acceptable rate.) [e] Stokes hardness tester. [f] USP Vanderkamp apparatus.

Table II—Reproducibility of Granulations and Tablets Prepared by Conventional (CWG) *versus* Pelletizing (P) Wet Granulation Techniques[a]

Test	Dibasic Calcium Phosphate CWG	Dibasic Calcium Phosphate CWG	Dibasic Calcium Phosphate P	Dibasic Calcium Phosphate P	Magnesium Hydroxide CWG	Magnesium Hydroxide CWG	Magnesium Hydroxide P	Magnesium Hydroxide P
Sieve analysis, % w/w[b]								
8 mesh	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
8–16 mesh	41.5	37.5	3.0	3.8	26.5	30.8	0.3	0.1
16–20 mesh	18.4	19.7	79.6	77.0	22.9	22.3	24.7	38.9
20–40 mesh	19.7	19.0	17.3	19.2	31.6	30.3	72.8	60.4
40–80 mesh	10.7	10.0	0.0	0.1	12.7	12.7	2.1	0.5
80–100 mesh	1.4	1.6	0.0	0.0	1.0	0.6	0.1	0.0
>100 mesh	8.3	12.2	0.0	0.0	5.3	3.3	0.0	0.0
Flow rate[c], g./sec.	16.1	14.3	22.1	25.5	12.5	13.4	20.8	19.7
Tablet hardness, kg.[d]	7.8	7.8	7.8	7.0	10.5	9.5	5.0	5.0
Disintegration time, min.[e]	1.0	1.0	0.5	1.0	0.5	0.8	0.3	0.3

[a] Process conditions for all runs: binder, 20% Avicel RC 581; extruder speed, 50 r.p.m.; Marumerizer speed, 1000 r.p.m.; residence time of segments for spheronizing, 60 sec.; final water content, 1–1.5%; and extruder screen, 1.0 mm. [b] U. S. Standard sieves, rated 2.38 mm. (8), 1.19 mm. (16), 0.84 mm. (20), 0.42 mm. (40), 0.177 mm. (80), and 0.149 mm. (100), respectively. [c] Grams of granulation per second flowing through a 1.27-cm. (0.5-in.) diameter orifice of a conical stainless steel funnel. (A rate of 10.0 g./sec. was considered the minimum acceptable value.) [d] Stokes hardness tester. [e] USP Vanderkamp apparatus.

fraction would contain the largest percentage of particles. This was true for the dibasic calcium phosphate and sulfadiazine pelletized granulations, whereas the magnesium hydroxide and acetaminophen pelletized granulations had the largest percentage of particles on the next smaller size sieve fraction, which is somewhat smaller than the screen size used in the extruder.

Table II shows the reproducible size distribution and minimal amount of fines that may be expected from replicate pelletizing experiments. These preliminary trials indicate that this technique may provide an efficient, rapid process for preparing tablet granulations of large dose medicinals, which frequently require special processing and compacting equipment to provide acceptable tablets. The spheronizing step also gives evidence of affording a more convenient way of lubricating the granulation because lubricant may be added into the Marumerizer immediately after formation of the spheres. Pelletizing of materials may also provide an advantage in reduced drying time requirements. The materials used in this study were dried to a water content of 1.0–1.5% in 6–7 hr. of heating at an oven temperature of 40°, compared to 18 hr. for conventional wet granulation. In addition, the cake formed is easily broken without use of granulating equipment.

Table III—Change of Size Distribution with Residence Time in the Marumerizer, Percent by Weight[a]

Sieve Fraction[b]	1 Minute	2 Minutes	5 Minutes
12–16	0.08	0.09	0.17
16–20	0.08	0.18	0.42
20–30	1.43	1.40	1.60
30–40	27.37	36.39	50.97
40–60	67.58	59.02	43.79
60–80	2.84	2.26	2.00
80–100	0.30	0.40	0.70
>100	0.30	0.26	0.25
Flow rate, g./sec.	23.3	23.3	23.3

[a] Process conditions: acetaminophen micropowder, 80%; Avicel RC-581, 20%; final moisture content, 1.5%; extruder screen, 0.5 mm.; extruder speed, 50 r.p.m.; and Marumerizer speed, 1200 r.p.m. [b] U. S. Standard sieves.

The Marumerizer utilizes screens with openings varying from 0.5 to 3.0 mm. While little data have been accumulated using the largest size, all results seem to indicate that pelletized granulations can be prepared in which 95% or more of the particles, by weight, occur in two consecutive sieve fractions. Table III shows the effect of residence time in the Marumerizer on size distribution. These sizes appear to be characteristic for a particular screen size over a wide variety of conditions and for a variety of active ingredients.

These preliminary studies will be expanded to determine the process variables that are significant in forming pelletized spheres suitable for tableting, capsule filling, or coating and to propose control tests that are meaningful in relation to providing products with desirable drug availability.

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Circuit for Simulation of Multiple-Dosing Kinetics

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Abstract □ An electronic circuit is described which simulates the theoretical curves associated with multiple-dosing kinetics. The output is an analog voltage which generates plasma concentration *versus* time curves consistent with the assumptions in a one-compartment open model with rapid intravenous injection. Potentiometer settings offer wide variations in dosing schedules, distribution volumes, and elimination rate constants. Also, once steady-state levels are achieved, a second circuit can be used to produce sudden changes in the elimination rate constant. Both circuits use commercially available electronic components and have been used in student lecture/demonstrations to display multiple-dosing kinetics graphically.

Keyphrases □ Multiple-dosing kinetics—simulation, electrical circuits □ Electrical circuits—simulation of multiple-dosing kinetics □ Simulation of multiple-dosing kinetics—electrical circuits

An understanding of drug accumulation through repeated administration is an important aspect in the teaching of pharmacology. Concepts such as dosing interval, volume of distribution, and half-life can be made more meaningful if time–concentration curves are generated to illustrate significant points. Both analog and digital computers can simulate models of multiple-dosing kinetics (1–3). Likewise, hydrolic analogies have been employed in discussions of one- and two-compartment systems (4, 5). These models, however, are often expensive or inconvenient to use during a lecture/demonstration. The purpose of this report is to present a simple and inexpensive electrical circuit which can be used to simulate the theoretical curves associated with multiple-dosing kinetics. The device can be used in both the training of research scientists and the teaching of medical students.

DISCUSSION

The model discussed in this paper is an analog device which was constructed from standard electronic components to simulate the theoretical plasma concentration *versus* time curves associated with repetitive dosing. This simple analog consists of two independent circuits. The first, or multiple-dosing circuit, generates an output voltage proportional to the time-varying drug concentration. The time–concentration curves are consistent with the multiple-dosing conditions set on four potentiometers representing dosing interval, volume of distribution, dose magnitude, and elimination half-life. Plasma concentration falls exponentially between individual administrations, with drug accumulation from sequential administrations following equations given by Goldstein *et al.* (6) and Wagner (7).

A second, or level-change circuit, employs a level controller to alter automatically the elimination half-life when a certain preset voltage, *i.e.*, drug concentration, is reached. The multiple-dosing circuit functions independently of the level-change circuit.

The multiple-dosing circuit is shown in Fig. 1. The circuitry consists of an oscillator to control pulse rate, a monostable multivibrator to regulate pulse duration, and a constant-current source to charge rapidly capacitor C of the RC network. These active components control drug injection parameters, while the RC network is analogous to the "patient." A ±5-v. power supply[1] drives all of the circuitry with the exception of the battery supply[2] to the operational amplifier in the constant-current circuit.

The first component, a unijunction oscillator, produces a pulse train output. Each pulse is analogous to a single dose. The pulse frequency is variable, with a rate determined by potentiometer R_1 in the oscillator circuit. In the parameters of pharmacokinetics, altering R_1 would be analogous to varying the dosing interval. The output pulse rate can be accurately monitored by an oscilloscope as indicated in Fig. 1 and is variable from 3 to 60 pulses/sec.

The oscillator output drives a monostable multivibrator[3]. The multivibrator provides a pulse at the oscillator rate but with a duration that is a function of potentiometer R_2. Altering R_2 is equivalent to changing the volume of distribution on a multiple-dosing time–concentration curve. The exact electrical analogy of varying the volume of distribution consists of a change in capacitor C, *i.e.*, a change in the distribution volume of the patient. This, however, is technically difficult to accomplish without also changing the time constant of the RC network and, consequently, the drug half-life. To simplify the circuitry in this particular model, pulse duration is used as the electrical parameter corresponding to distribution volume. For pragmatic reasons the volume of drug distribution is controlled by the electronic circuit involved with drug injection rather than the circuit components of the patient.

The multivibrator is coupled to a constant-current source by a photoisolator[4]. A constant-current circuit is employed to accomplish rapid buildup of charge across the passive RC network, thereby adequately describing instantaneous drug absorption. Constant current is achieved by using an operational amplifier[5]. The output

[1] 2.6.100, Semiconductor Circuits, Inc.
[2] TRII5R-6.75 V, Mallory, Inc.
[3] 9601, Fairchild, Inc.
[4] MCT2, Monsanto Corp.
[5] UC-4250C, Solitron Devices, Inc.