Factors Affecting Release of Medicaments from Hard Gelatin Capsules

Keyphrases ☐ Drug release from hard gelatin capsules—effect of temperature and pH ☐ Capsules, hard gelatin—effect of temperature and pH on drug release ☐ Dissolution, hard gelatin capsules—effect of temperature and pH

Sir:

In a recent communication, it was suggested that decreased absorption of encapsulated tetracycline when administered concurrently with antacids was due to the insolubility of the gelatin capsules (1). The authors investigated the dissolution of tetracycline capsules at pH 1–9 and found that the capsules disintegrated in acidic media but remained intact in basic media. Although no mention was made of temperature, the study was apparently conducted at room temperature. Because it is not unusual to administer antacids with a number of encapsulated drugs, this finding gives rise to a number of unfavorable implications.

An attempt was made to reproduce the authors' results in a similar experiment in which size 0 gelatin capsules were filled with amaranth and added to solutions whose pH ranged from 1.2 to 9.0. Prolonged release times were obtained at pH greater than 1.2. The capsules did not dissolve or disintegrate to release their contents; instead they swelled and the two halves of the capsules pulled apart.

It was decided to do more closely controlled experiments using 250-mg. chloramphenicol capsules made with a gelatin band around the center[1]. This band prevented the halves of the capsule from separating. For the drug to be released, the capsules would have to disintegrate and/or dissolve.

The capsules were added to a 600-ml. beaker containing 300 ml. of 0.05 *M* phosphate buffer at varying pH. The solutions were stirred at 60 r.p.m. with a Plexiglas paddle, 4.6 × 2.6 × 0.1 cm. The time required for the capsules to break open was recorded at 22.5 and 37.0°.

At body temperature, varying the pH (1.2–9.0) did not affect the average release time (120.7 ± 6.5 sec.) of the capsules. However, at room temperature, pH did affect the release times. The average release times at pH 1.2, 3.0, and 9.0 were 51, 38, and 320 min., respectively. At pH 5.0 and 7.0, the capsules remained intact after 24 hr.

From these data it appears that temperature is the major determinant in the disintegration and/or dissolution of gelatin capsules. The temperature of the stomach is normally about 36°. This temperature can be lowered by eating such things as ice cream, but the temperature returns to normal within 30 min. (2). It is unlikely that this variation in stomach temperature would frequently interfere with the release of encapsulated medications. Also, it is clear that raising the gastric pH does not, as the authors suggest, affect the disintegration and/or solubility of hard gelatin capsules unless accompanied by a lowering of the temperature of the stomach's contents.

(1) G. R. Elliot and M. F. Amstrong, *Clin. Pharmacol. Ther.*, **13**, 459(1972).

(2) J. G. Wagner, "Biopharmaceutics and Relevant Pharmacokinectics," Drug Intelligence Publications, Hamilton, Ill., 1971, p. 5.

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[1] Parke-Davis, Lot No. P16907A.

Batch Production of Pharmaceutical Granulations in a Fluidized Bed III: Binder Dilution Effects on Granulation

Keyphrases ☐ Granulation, fluidized bed—effects of binder dilution on granule properties ☐ Binder dilution effect—fluidized-bed granulation

Sir:

Previous reports (1, 2) were concerned with process variables in the operation of a fluid-bed spray granulator[1] and the effects of various binders and their concentrations on the physical properties of fluidized-bed granulations and tablets compressed from these granulations. The present communication describes the effects of two aqueous dilutions of various formula weights of gelatin binder on the physical properties of fluidized-bed granulations.

Successful granulation in a fluidized bed results primarily from a balance of material input and output (3, 4) which is determined by operational factors such as the rate of binder addition, fluidizing air temperature, and volume and nozzle height with respect to the fluidized solids (1). In addition, further studies showed that the quantity of binder solvent used for fluidized-bed granulating may be equally influential. Since the quantity of solvent used in preparing a binder solution may often be arbitrary, depending upon solution viscosity, binder solubility, desired granulating cycle time, *etc.*, the influence of the solvent quantity on the physical

[1] Glatt model WSG-15, Fa. W. Glatt, Haltingen, West Germany.

Table I—Physical Properties of Fluidized-Bed Granulations Prepared from Various Formula Weights and Aqueous Dilutions of Gelatin Binder[a]

Physical Properties	Formula Weight					
	2.75% w/w		3.50% w/w		4.25% w/w	
	2.0[b]	4.0[b]	2.0[b]	4.0[b]	2.0[b]	4.0[b]
Average granule size, μ	299	287	328	317	367	351
Friability, %	11.3	6.6	10.2	7.2	8.2	6.9
Bulk density, g./ml.	0.39	0.45	0.36	0.42	0.34	0.39
Granule density, g./ml.	1.492	1.480	1.487	1.472	1.479	1.471
Interparticulate porosity, %	74.3	69.6	75.8	71.5	77.0	73.5
Flow rate, g./min.	127.5	156.8	105.9	129.6	93.5	116.5

[a] For comparison purposes, results of the physical properties of granulations prepared with 2.0 kg. of distilled water as the binder dilution factor are reprinted from *Reference 2*. [b] Aqueous dilution factor in kilograms.

properties of the final granulation should be investigated. The following formulation was manufactured in 10-kg. batches in the fluid-bed granulator:

	% w/w
lactose USP	85.25–86.75
starch USP	10.00
gelatin USP	2.75–4.25
magnesium stearate USP	0.50
distilled water	—

Three formula concentrations (2.75, 3.50, and 4.25% w/w) of gelatin binder were selected, and two aqueous dilution factors (2.0 and 4.0 kg. distilled water) were utilized in preparing the binder solution at each concentration. Preparation of the binder solutions, granulation and drying procedures, and the fluid-bed spray granulator were extensively discussed previously (1, 2) along with the methods employed in determining average granule size, granule friability, loose bulk density, granule density, interparticulate porosity, and flow rate.

The effects on the granulation's physical properties of various formula weights of gelatin binder dissolved in 2.0 and 4.0 kg. of distilled water are illustrated in Table I. Since the effects of the formula binder weight, *i.e.*, 2.75–4.25% (w/w), on the physical properties of fluidized-bed granulations were discussed in a previous paper (2), only the effects of the quantity of water utilized in binder solution preparation are now interpreted. Those binder solutions prepared with 4.0 kg. of distilled water were approximately one-half the concentrations of their respective solutions made with 2.0 kg. of water. Since this dilution doubles the binder solvent employed in the granulation operation, the lack of any significant influence on the average granule size implies that water, alone, would be a poor granulating agent for these particular formulations. In fact, a slight decrease in the average granule size was noted on dilution of each of the three formula binder concentrations. Presumably, this may be attributed to a decrease in the binder solution's tackiness or adhesiveness.

The most significant changes in the physical properties affected by binder dilution were found in granule friability and bulk density. It is obvious from the data presented in Table I that the granule size was most affected by the formula binder concentration, *i.e.*, 2.75–4.25% (w/w), while granule friability was most influenced by aqueous binder dilution, *i.e.*, 2.0–4.0 kg. water. This development is significant since weak granulations may be made less friable simply by further diluting the binder solution prior to its addition in the granulating cycle. This effect of strengthening granules may be somewhat correlated with previous investigations (1), where similar results were observed by increasing the penetration and wetting of the fluidized solids by the binder solution.

Dilution of the binder solution with an additional 2.0 kg. of water (4.0-kg. total) increased the bulk density of the granulation similarly by prolonging the exposure of the fluidized solids to the binder solution. This method of increasing granule strength and density by further diluting the binder system has one noted distinction from previously reported methods (1), *i.e.*, increasing binder solution addition rate, decreasing binary nozzle atomization pressure, decreasing inlet air temperature, *etc.* These latter process changes all resulted in significant increases in the average granule size; this particle growth was not observed when granulating with the less adhesive diluted binder solutions.

The differences observed in the granule densities were small. Since granule density is a measure of the entrapped air within the interstices of the granules, it may be concluded that the intraparticulate void spaces of the granules were unaffected by binder dilution. The increased flow rates of granulations manufactured from equal but diluted formula binder concentrations are associated with the decreased porosities of these more dense granulations.

In summary, while binder dilution has insignificant effects on the average granule size and granule density of granulations manufactured in a fluid-bed spray granulator, considerable influence was observed on granule friability, bulk density, interparticulate porosity, and, thus, on flow rate.

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