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.

RANDY P. JUHL▲
SEYMOUR M. BLAUG
College of Pharmacy
University of Iowa
Iowa City, IA 52240

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▲ To whom inquiries should be directed.

[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.