Influence of Dispersion Method on Dissolution Rate of Digoxin–Lactose and Hydrocortisone–Lactose Triturations I

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Abstract ☐ Spreading of digoxin or hydrocortisone over a lactose surface by frictional pressure produced 1:20 triturations with significantly enhanced dissolution rates in simulated gastric fluid. Triturations prepared by simple blending or solvent deposition exhibited slower dissolution rates. These observations may help explain the variations in dissolution rate observed in manufactured tablet and capsule dosage forms of these two drugs.

Keyphrases ☐ Digoxin–lactose triturations—effect of simple blending, solvent deposition, and spreading by frictional pressure on dissolution rates ☐ Hydrocortisone–lactose triturations—effect of simple blending, solvent deposition, and spreading by frictional pressure on dissolution rates ☐ Triturations, digoxin–lactose and hydrocortisone–lactose—effect of simple blending, solvent deposition, and spreading by frictional pressure on dissolution rates ☐ Dissolution rates, digoxin–lactose and hydrocortisone–lactose triturations—effect of simple blending, solvent deposition, and spreading by frictional pressure

Recent publications pointed out the wide variation in digoxin absorption from tablets produced by various manufacturers (1–3). Furthermore, significant variations in blood levels were noted between batches made by the same manufacturer (1). Studies of

and reproducible dissolution rates of these steroidal drugs from their triturations is desirable. The use of such triturations in the manufacture of tablets and capsules should result in more rapid and reproducible rates of dissolution. These, in turn, definitely should help to correct the blood level variations currently encountered.

This report describes the dissolution of digoxin and hydrocortisone from lactose triturations prepared by the following methods: (a) simple blending, (b) solvent deposition, and (c) frictional pressure. The third method was included because steroidal compounds might be spreadable on the diluent surface by frictional force.

EXPERIMENTAL

Materials—The following were obtained from commercial sources: digoxin USP[1]; lactose USP[2]; sodium chloride USP[3]; hydrochloric acid, reagent grade[4]; alcohol USP[5]; and hydrocortisone USP[6].

Equipment—The following pieces of equipment were used: a constant-temperature water bath[7], a double-beam spectrophotometer[8], and a disintegration–dissolution apparatus (USP).

Table I—Dissolution Rates of Digoxin–Lactose (Three Batches) and Hydrocortisone–Lactose (Two Batches) in Simulated Gastric Fluid at 37°

| | Percentage Dissolved | | | | | | | |
| | Simple Blend | | Simple Blend of Ground Drug | | Solvent-Deposited Drug | | Frictionally Deposited Drug | |
Minutes	Digoxin	Hydro-cortisone	Digoxin	Hydro-cortisone	Digoxin	Hydro-cortisone	Digoxin	Hydro-cortisone
15	30.3 ± 0.4	57.0 ± 0.8	47.7 ± 0.3	54.0 ± 1.1	61.0 ± 0.4	73.2 ± 0.5	74.3 ± 0.3	94.8 ± 0.3
30	41.4 ± 6.6	65.0 ± 3.1	52.4 ± 1.2	63.6 ± 1.4	66.2 ± 7.6	77.2 ± 6.6	83.0 ± 4.4	96.3 ± 2.2
45	41.8 ± 1.0	81.0 ± 2.3	53.6 ± 1.7	72.4 ± 2.4	67.9 ± 2.1	81.1 ± 2.1	86.0 ± 3.1	96.8 ± 1.7
60	53.3 ± 5.5	84.9 ± 4.6	61.1 ± 5.8	79.2 ± 4.1	75.0 ± 3.9	84.8 ± 2.6	91.7 ± 3.5	98.6 ± 2.2
75	—	86.2 ± 3.1	—	83.3 ± 2.6	—	84.6 ± 0.8	—	98.8 ± 1.7
90	60.1 ± 4.0	87.4 ± 2.8	67.3 ± 3.8	86.0 ± 3.5	80.8 ± 4.4	85.9 ± 5.1	96.9 ± 4.5	99.2 ± 2.4
120	65.4 ± 5.2	—	72.3 ± 3.9	—	84.7 ± 6.8	—	99.4 ± 5.2	—

the blood levels of digoxin (3) and urine recovery (4) showed that the absorption efficiency from tablets was only 75% that of the drug in solution. The hydrophobicity and low aqueous solubility of digoxin account to a significant degree for these variations.

Similar problems are encountered with tablets of hydrocortisone. The biological availability of hydrocortisone from tablet dosage forms is an ongoing problem for the Food and Drug Administration (5, 6).

In the manufacture of tablet and capsule dosage forms of potent drugs such as digoxin and hydrocortisone, triturations are commonly employed. Such triturations are usually prepared by simple blending or solvent deposition. A method for ensuring rapid

Preparation of Drug-Lactose Triturations—The digoxin and hydrocortisone powders were passed through a 325-mesh screen. Microscopic examination revealed that the major portion of the powdered digoxin was in the 5–40-μm range. The major portion of the hydrocortisone powder was in the 15–30-μm range. In both powders, aggregation of fine particles was noted.

The drug–lactose triturations were prepared in a weight ratio of 1:20. Manual bottle tumbling for 15 min was conducted in preparing the *simple blend*. Mechanical shaking of the lactose dilu-

ent through a series of sieves ranging from 40 to 400 mesh established its average diameter to be 132 μm (7).

The *solvent-deposited* samples were prepared by dissolving the drug in a sufficient quantity of either 80% ethanol (digoxin) or absolute ethanol (hydrocortisone) and uniformly wetting the lactose with the solution. After drying at 32°, the sample was passed through a 60-mesh screen with the aid of a spatula.

By the conventional geometric build-up procedure, the powdered drugs were energetically hand triturated with powdered lactose. It was reasoned that the application of such frictional force would uniformly spread the drug on the lactose surface. The average diameter of the drug-lactose blends prepared with a mortar and pestle was approximately 66 μm. It was difficult to differentiate the drug from the diluent under microscopic examination. Interestingly, the absence of fine particle aggregates was noted.

A fourth drug-lactose trituration was prepared by pestle grinding the finely powdered drugs alone. After passage through a 325-mesh screen, the powders were examined microscopically. Insignificant size reduction was achieved by pestle grinding these fine powders. As before, fine particle aggregates were observed. The sieved powders were geometrically diluted with powdered lactose without additional frictional pressure. The intent in this instance was to expose the drugs to a similar pestle grinding action but not to spread them onto the lactose surface with frictional force.

Dissolution Studies—A modification of the procedure of Monkhouse and Lach (8) was used to determine the dissolution rates of the various powder blends. Two hundred milliliters of simulated gastric fluid without pepsin (USP XVIII) was added to a 400-ml beaker and permitted to equilibrate at 37 ± 0.5° in a constant-temperature bath. The dissolution medium was stirred at 60 rpm using the basket recommended for the USP dissolution test. The basket was vertically centered to a depth of 2.54 cm (1 in.) from the bottom of the beaker. At zero time, the drug-trituration (digoxin-lactose, 84 mg, or hydrocortisone-lactose, 210 mg) was spread over the surface of the dissolution medium and the apparatus was set in motion. Five-milliliter samples of solution were periodically withdrawn through a sintered-glass filter of medium porosity immersed at all times in the dissolution medium. The withdrawn aliquot was then passed through a filter[9] (0.45 μm), and the drug concentrations were measured spectrophotometrically using simulated gastric fluid as the blank. Five milliliters of simulated gastric fluid was added to the dissolution medium to replace the volume of sample withdrawn for assay.

Spectrophotometric Absorption and Calibration Curves for Digoxin and Hydrocortisone in Simulated Gastric Fluid— Twenty milligrams of digoxin was dissolved in 10 ml of hot 80% ethanol. Sufficient simulated gastric fluid was added to make 1 liter. This solution was used to determine absorption spectral and calibration curves. The concentrations of digoxin in the dissolution study obeyed Beer's law at 224 nm. Incorporation of a 20-fold excess of lactose did not alter the absorbance values for digoxin.

Fifty milligrams of hydrocortisone was dissolved in 20 ml of ethanol, and sufficient simulated gastric fluid was added to make 1 liter. This solution was used to determine the absorption spectral curve and to establish 248 nm as the wavelength for the calibration curve. Again the concentrations of hydrocortisone in the dissolution study obeyed Beer's law, and the incorporation of a 20-fold excess of lactose did not alter the absorbance values.

RESULTS AND DISCUSSION

The dissolution rates of the various triturations are shown in

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[9] Millipore.

Table I. The superiority of the frictionally prepared digoxin-lactose trituration is clearly evident. Thus, 91.7 ± 3.5% of the digoxin had dissolved within 60 min. The remaining digoxin blends did not attain 90% dissolution up to 120 min. Similarly, the frictionally prepared hydrocortisone-lactose trituration showed the fastest dissolution rate. At the end of 15 min, 94.8 ± 0.3% of the hydrocortisone had dissolved. The remaining hydrocortisone-lactose blends did not attain 90% dissolution up to 90 min.

The failure of the solvent-deposited triturations to match or exceed the dissolution rate of the frictionally applied drug-lactose blends was surprising. Deposition of the drug in a molecular state of subdivision on a 20-fold excess of powdered lactose would be expected to be a highly efficient method of increasing the total surface of the drug. Monkhouse and Lach (8) achieved enhanced dissolution of aspirin solvent deposited on 10% starch plus 10% lactose. Adverse adsorption effects can be ruled out as an explanation since lactose is soluble in simulated gastric fluid. A likely explanation for the observed results is inefficient solvent evaporation. Solvent migration during the drying step could account for a smaller total drug surface as compared to that obtained by the frictional method. Sodium warfarin was shown (9) to migrate during the drying step after wet granulation with lactose.

The frictional method of preparing triturations of steroidal, sparingly soluble drugs is worthy of further study. The reported observations can help to explain the batch-to-batch variations in dissolution rate encountered in the manufacture of capsules and tablets. Frictional forces are applied to varying degrees in the manufacture of such dosage forms. Procedures such as milling, blending, slugging, granulating, and tableting do impart frictional force on the drug and the excipients. The intensity and length of time for each operation will vary. In light of the reported results, it is not surprising that such procedural variations could account for the dissolution rate variations encountered.

Developmental experimental studies are underway in this laboratory to establish efficient mechanical methods for the manufacture of triturations, capsules, and tablets possessing reproducible physical properties.

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