DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(5), 769-777 (1990)

USE OF POWDERED SOLUTIONS TO IMPROVE THE DISSOLUTION RATE OF POLYTHIAZIDE TABLETS

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ABSTRACT

Solutions of polythiazide in polyethylene glycol 400 were admixed with microcrystalline cellulose (RC-591) and silica. The resulting free-flowing powder was incorporated into tablet formulations by direct compression.

The dissolution rates of polythiazide from these tablets were significantly more rapid than from commercially available tablets. The stability of these tablets at 40°C. and high humidity was studied. The powdered solution formulas were also compared with a polythiazide dispersion in polyethylene glycol 6000 which exhibited an equally superior dissolution profile.

INTRODUCTION

A long standing problem confronting the pharmaceutical industry continues to be the poor dissolution rates of poorly soluble drugs.

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Dissolution rates have been improved through the use of water-soluble salts[1], polymorphic forms[2], molecular complexes[3], micronization[4], eutectics and solid solutions[5].

The formation of solid dispersions or coprecipitates of hydrophobic drugs with various water-soluble, pharmacologically inert carriers can increase their in vitro dissolution rates significantly[6]. Among the materials which have been tried as carriers, polyethylene glycol and polyvinylpyrrolidone are the most prominant.

Solvent-deposition systems have been described and characterized by Monkhouse and Lach[7,8]. They introduced the term "minuscular form" to describe the physical state of a drug that had undergone micronization of a molecular nature when it was dispersed on the extensive surface of a microparticulate adsorbent.

Due to their large surface area, high porosity and unique adsorption properties, inert silicas such as the Syloids (W.R. Grace & Co.) have been successfully used as dispersion systems to increase the dissolution rate of sparingly soluble drugs[9].

Powdered solution technology is a recent development which differs from solvent-deposition[10]. A powdered solution is characterized as a true solution of a sparingly soluble drug in a high-boiling, water-miscible, non-toxic solvent, such as, polyethylene glycol 400. The solution is carried on the extensive surface provided by an inert carrier such as silica. In such a system the drug is in a molecular state of subdivision. By use of such systems Liao and Jarowski[10] were able to bypass the dissolution step by the preparation of powdered solutions of various corticoids.

In the present study a powdered solution formula of polythiazide was prepared and its dissolution rate

was compared with commercially available Renese tablets (Pfizer & Co., Inc.). In addition the dissolution rate of polythiazide from a solid dispersion in polyethylene glycol 6000 was also determined for comparative purposes.

EXPERIMENTAL

Materials

The following materials were used: polythiazide, USP, micropulverized, Renese Tablets, 4 mg, amorphous silica (Syloid 244-FP), microcrystalline cellulose (Avicel pH 101 and RC 591-FMC Corp.), polyethylene glycols 400 and 6000 and ethanol.

Equipment

The following equipment was used: Thermolyne Maxi Mix TM; spectrophotometer, Perkin-Elmer, Hitachi 200; Carver hydraulic press; Acrodisc, 0.2 micron porosity, Pfizer hardness tester; and the USP XXI dissolution test assembly.

Spectrophotometric Absorption and Calibration Curves

A solution of polythiazide (60mg/ml) in polyethylene glycol 400 was prepared. After filtration through a 0.45 micron filter paper, aliquots were diluted with gastric fluid for the development of absorption spectrum and calibration curves. There was no appreciable absorption by the solvent at the wavelength of maximum absorption for polythiazide (270 nm). Calibration curves of polythiazide in simulated gastric fluid and alcohol obeyed Beer's Law.

Preparation of a Powdered Solution of Polythiazide

An accurately measured volume of polythiazide solution in PEG 400 (60 mg/ml) was triturated with different proportions of amorphous silica (1:2.4, 1:3 and 1:3.6) using a glass mortar and pestle. The powder mass was passed through a 40-mesh screen to prepare granules and to ensure homogeneity. To these screened

granules a calculated quantity of microcrystalline cellulose was added and the mixture was triturated further to absorb any remaining excess polythiazide solution. The resulting free-flowing powder was again passed through a 40-mesh screen to break up any lumps. This screened material was tested for content uniformity using ethanol as the extracting solvent.

In an alternative method, a solution of polythiazide in PEG 400 was first triturated with microcrystalline cellulose. Subsequently this mud-like mass was converted into a free-flowing powder by trituration with the silica.

Preparation of a Solid Dispersion of Polythiazide

The procedure followed was based on Chiou and Riegelman's work[11]. A 5% active level was selected for the preparation of the solid dispersion using PEG 6000 as the carrier. An accurately weighed quantity of PEG 6000 was placed in a suitable beaker and melted by direct heating on a conventional hot plate. To the melt a calculated quantity of polythiazide was added with constant stirring. The melted dispersion was allowed to solidify and the solid mass was pulverized in a mortar. The pulverized material was passed through a 40-mesh sieve, admixed with a blend of silica and microcrystalline cellulose (1:1), and then compressed into tablets.

Preparation of Tablets

Tablets were made by compressing the powder blends at 178 kg/square cm in a Carver press, keeping the compression time constant (15 sec). Tablet hardness was measured with a Pfizer hardness tester.

Dissolution Studies

Dissolution rates were determined by the USP XXI paddle method (Method-2) in 400 ml of simulated gastric fluid (without pepsin) which was maintained at 37 +/- 0.5°C. in a constant temperature bath prior to addition

of the tablet. The dissolution medium was stirred at a speed of 50 rpm. Aliquots of the dissolution medium were withdrawn periodically and passed through a 0.22 micron filter. The filtrates were assayed spectrophotometrically at 270 nm. An equal amount of dissolution medium was added to the dissolution flask to replace the volume of sample withdrawn for assay. Cumulative corrections were made for the previously withdrawn aliquots when calculating the total amount of drug that had dissolved.

Stability Studies

The effect of aging at 42% and 74.7% relative humidity and 40°C. temperature were studied. The freshly prepared tablets containing the powdered solution of polythiazide and Renese tablets were weighed and placed in 30 ml amber glass bottles. The uncapped bottles were placed in desiccators held at constant humidity. The desiccators were placed in a 40°C. oven. The absorption of moisture was verified periodically by weighing the tablets. Tablet hardness and dissolution profiles were also determined periodically.

RESULTS AND DISCUSSION

The solubility of polythiazide in simulated gastric fluid was found to be 20 mg/100 ml at 37°C. As a consequence sink conditions would not be surpassed if 4 mg of drug were to be placed into 400 ml of simulated gastric fluid. The USP XXI dissolution procedure for polythiazide tablets was modified to enable direct spectrophotometric analysis. Withdrawn samples were analyzed within 30 minutes. A concentration of 60 mg/ml of polythiazide in PEG 400 was selected for the production of the tablets. Higher concentrations would have favored precipitation of polythiazide due to localized dilution with simulated gastric juice.

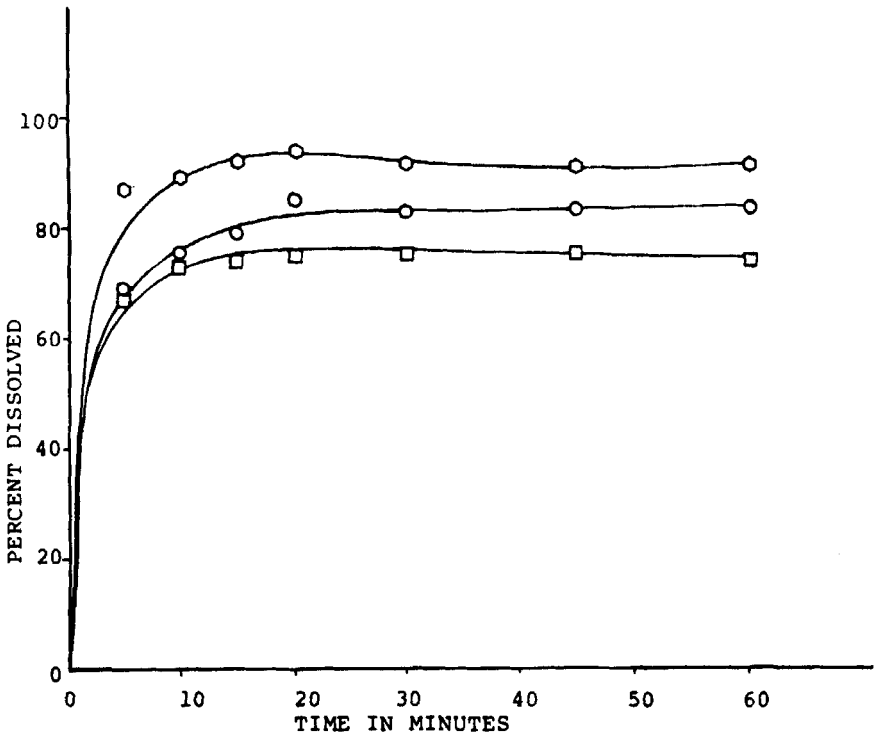

FIGURE 1.

Dissolution rate of polythiazide tablets in simulated gastric fluid (without pepsin) containing different ratios of polythiazide solution in PEG-400:amorphous silica:microcrystalline cellulose (RC-591). Paddle speed was 50 rpm. Key: ○ 1:3:3; ○ 1:2.4:3.6; and □ 1:3.6:2.4.

An earlier study had shown that the higher the proportion of amorphous silica to drug solution the slower the release rate. With different proportions of amorphous silica and microcrystalline cellulose (RC-591) no such correlation was observed. The most rapid release of polythiazide was exhibited by tablets in which the drug solution:silica:microcrystalline cellulose was in the ratio of 1:3:3 (Figure 1). Almost 90% of the polythiazide had dissolved within 5 minutes. Tablets in which the ratios were 1:2.4:3.6 or 1:3.6:2.4

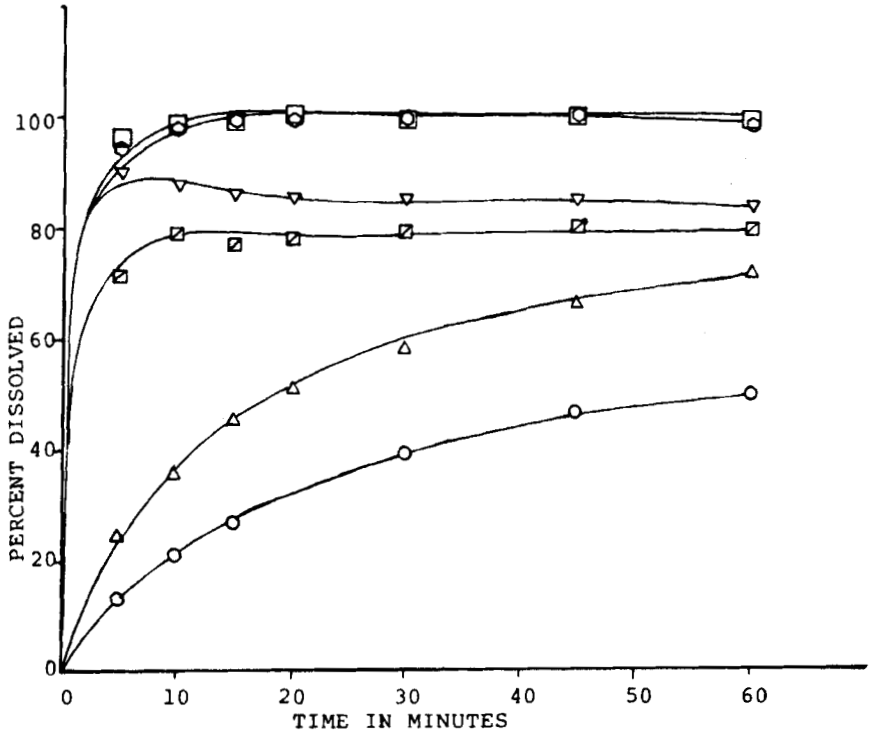

FIGURE 2.

Dissolution rate of polythiazide tablets in gastric fluid, simulated. Key:□, PEG-6000 tablets;▽, PEG-6000 granules;○, alternate procedure tablets containing Avicel RC-591;▨, regular procedure tablets (RC-591); ▲, Renese tablets;●regular procedure tablets (pH-101).

for the same components exhibited slower release rates. Thus, only 70% of the polythiazide had dissolved within 5 minutes.

The release of polythiazide from tablets containing the pH 101 grade of microcrystalline cellulose was very slow. After 5 minutes approximately 10% of the drug had dissolved in the medium (Figure 2). After 60 minutes only 50% had dissolved. Commercially available Renese tablets met the USP XXI requirement for dissolution rate. The official compendium states that at least 50% of the labeled amount of polythiazide must be

in solution within 90 minutes in 1% hydrochloric acid. Only 20 minutes was required for the lot tested to meet this requirement. However after 60 minutes less than 80% had dissolved.

As anticipated the tablets containing powdered solutions or PEG-6000 solid dispersions of polythiazide exhibited much faster rates of dissolution. For example, tablets containing a powdered solution of drug which were prepared by the alternate procedure were completely dissolved within 10 minutes. A similar rapid rate of dissolution was observed for the tablets containing the solid dispersion of drug in PEG-6000. Based on the in vitro dissolution rates the latter tablets would be expected to be more efficiently absorbed after oral administration.

Tablets which had been stored at 40°C. under controlled humidity conditions increased in weight. Such a result was anticipated since the tablet excipients in the formulations are hydroscopic. However despite the moisture pickup an insignificant change in tablet hardness was observed.

If more concentrated solutions of polythiazide in PEG-400 were to be used such moisture pickup might lead to drug precipitation within the silica pores. Such precipitation could result in entrapped drug particles and a retardation of the dissolution rate. However with the 60 mg/ml concentration of polythiazide in PEG-400 no diminutions in dissolution rates were observed for tablets exposed to 42% or 74.7% relative humidity after 6 and 12 weeks.

CONCLUSIONS

1. The dissolution rate of sparingly soluble, hydrophobic drugs can be markedly improved by the incorporation of powdered solutions into tablets.

2. Besides the proportion of drug solution:silica:microcrystalline cellulose (RC-591), other factors such as mixing time and order of excipient addition, affect the release rate.
3. Tablets exposed 40°C. and high relative humidity showed no significant change in physical properties and dissolution rates.
4. A solid dispersion of polythiazide in PEG-6000 yielded tablets with drug release rates equal to those for the powdered solution form.

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