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RESEARCH PAPER

Enhancement of Dissolution of Ethopropazine Using Solid Dispersions Prepared with Phospholipid and/or Polyethylene Glycol

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ABSTRACT

*The purpose of this study was to improve the dissolution properties of a poorly water soluble and bioavailable drug, ethopropazine HCl (ET), by incorporating the drug in three different types of solid dispersion systems. Solid dispersions of ET were prepared using 1:1 (w/w) ratios of (1) phospholipid (1,2 dimyristoyl-*sn*-glycero-phosphocholine) (DMPC), (2) polyethylene glycol 8000 (PEG8000), and (3) a novel combination of both DMPC and PEG8000. Using the solvent method of preparation, ET and DMPC and/or PEG were dissolved in chloroform, and solvent subsequently was evaporated using nitrogen gas. The resulting solid dispersion(s) was passed through a 60-mesh sieve. Characterization of ET/DMPC solid dispersion was performed by differential scanning calorimetry (DSC) and X-ray diffractometry studies. Dissolution studies conducted in phosphate buffered saline (PBS) (pH 7.4, 37°C ± 0.5°C) using the USP type II (paddle) dissolution apparatus showed significant increases in the dissolution rate of ET with all the solid dispersions in this study. Specifically, within the first 5 min (D5), solid dispersions containing ET/DMPC (1:1) showed an eightfold increase in dissolution; in combination with DMPC and PEG8000 (1:1), there was an approximately sixfold increase; and a fourfold increase was observed with PEG8000 (1:1). Complete dissolution of all solid dispersions occurred within 60 min (D60) of the run. Storage of the ET/DMPC sample for over 4.5 months revealed a decrease in the dissolution rate when compared to freshly prepared sample. Overall, it was concluded that the dissolution rate of ET*

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significantly improved when dispersed in all the selected carrier systems. However, the solid dispersion of ET/DMPC was observed to be superior to the other combinations used.

Key Words: *Dissolution; Combination; Ethopropazine; Phosphoplipids; Polyethylene Glycol; Solid Dispersions.*

INTRODUCTION

Solid dispersions (SDs) of drugs that are poorly water soluble with pharmacologically inert water-soluble carriers can be used as a means of increasing the dissolution rate of drugs (1,2). This approach has the potential to improve the bioavailability of the drug significantly when absorption is limited by solubility. Some proposed mechanisms of action of solid dispersion formulations include the solubilizing effect of the carrier; decreased agglomeration and aggregation of drug particles; particle size reduction to molecular size, yielding a solid-state solution within the carrier; and increased drug solubility via complex formation or solubilization and improved wetting (3–5).

Solid dispersions of drugs in water-soluble carriers such as urea, cyclodextrins (CDs), and various polyethylene glycols (PEGs) are known to increase the dissolution rate (6–8). The rate and extent of dissolution of the active ingredient from any dosage form often determines the rate and extent of absorption of the drug (9). In the case of a drug that is poorly water soluble, dissolution maybe the rate-limiting step in the process of drug absorption. Drugs with poor water solubility have been shown to be unpredictably and slowly absorbed compared with drugs of higher solubility (10).

The purpose of this study was to use solid dispersions, prepared by the solvent evaporation method, to improve the dissolution rate of ethopropazine HCl (ET), a drug that is poorly water soluble. ET is a phenothiazine compound used for its anticholinergic properties in the treatment of Parkinson's disease. It is available as a white or off-white crystalline powder that melts at about 210°C with decomposition. ET is only slightly soluble in water, but is soluble in alcohol and chloroform (11,12). A recent study indicated extremely poor bioavailability of ET in rats after oral administration (<5%) (11). It was postulated that, since the drug is only slightly soluble in water, the dissolution process could be the rate-limiting step in the absorption of the drug, thus resulting in poor bioavailability.

In the present study, two different compounds were chosen as carriers to prepare solid dispersion (SD) systems with ET: (1) phospholipid (1,2 dimyristoyl-*sn*-glycero-phosphocholine) (DMPC) and (2) polyethylene glycol 8000 (PEG8000). A third carrier system was prepared by blending a novel combination of both the DMPC and PEG8000. All solid dispersion systems were prepared in a 1:1 ratio. Subsequent to preparation of three solid dispersion systems, studies were initiated to evaluate in vitro dissolution kinetics and assessment of stability of the solid dispersions over a 4.5-month storage period at room temperature (25°C). Further characterization of a drug/carrier combination was conducted using differential scanning calorimetry (DSC) and X-ray diffractometry.

EXPERIMENTAL

Materials

Ethopropazine HCl was purchased from Sigma Chemical Company (St. Louis, MO). Phospholipid DMPC and PEG8000 were purchased from Northern Lipids (Vancouver, BC) and City Chemical Corporation (New York, NY), respectively. Chloroform (high-performance liquid chromatography [HPLC] grade), buffer salts, and hydrochloric acid were purchased from Fisher Scientific Company (Pittsburgh, PA). Nitrogen gas was supplied by Praxair Incorporated (Pomona, CA).

Methods

Composition of Solid Dispersions

Single-component solid dispersions contained 1 part by weight of either the phospholipid DMPC or PEG8000 and 1 part of active drug, ET. Multicomponent solid dispersions contained 1 part by weight of a DMPC and PEG8000 (1:1 by weight) mixture and 1 part of ET.

Preparation of Solid Dispersions by the Solvent Evaporation Method

Accurately weighed amounts of ET HCl and carrier(s) were dissolved in minimum quantities of chloroform. With continuous stirring, the sample was dried for 6 h

under the influence of N_2 gas. After drying, the solid dispersion containing the drug and carrier was sieved through a 60-mesh sieve and stored in a desiccator at room temperature and protected from light.

Dissolution Kinetics

The dissolution studies were conducted in phosphate buffered saline (PBS; pH 7.4) dissolution medium using the USP type II (paddle) dissolution apparatus. The dissolution medium was maintained at a temperature of 37°C ± 0.5°C and stirred at 50 rpm by an adjustable, constant-speed motor. A weighed amount of sample (amount of solid dispersion representing 30 mg drug) was introduced into the dissolution flask containing a measured amount of the PBS dissolution medium (300 ml). The lower volume (300 ml) of the dissolution fluid was determined to be adequate for reproducibility and sensitivity of the assay. At predetermined intervals, samples were withdrawn from the flask, filtered, and immediately analyzed in a UV/Vis spectrophotometer at 250 nm for the release of ET. All studies were performed in triplicate.

Thermal Analyses

A differential scanning calorimeter was used to obtain thermograms of solid dispersions of ET HCl. A cell base was used with samples weighing about 7.1 mg with a heating rate of 20°C per min from 0°C to 120°C. Peak transition temperature and the heat of melting were determined by means of an analyzer (Thermal Analyst 2000, TA Instruments, New Castle, DE). Indium was used as a reference. The peak transition temperatures and heat of fusion of the pure components and solid dispersions were compared.

X-Ray Diffraction Analysis

X-ray diffraction patterns of powdered samples of solid dispersions were obtained with a Siemens Nicolet I2 diffractometer using CuK_α radiation. Diffractographs were analyzed for the presence of peaks and peak intensities.

Stability Studies

Samples of solid dispersions prepared with DMPC as the carrier were stored in glass vials for a period of up to 4.5 months at room temperature (25°C). At the end of the storage period, these samples were subjected to dissolution by the procedure described above.

RESULTS AND DISCUSSION

Dissolution Kinetics

As expected, the dissolution rate of pure ET was extremely poor, with only about 80% of drug released during the first 120 min of the dissolution run. As stated, this observation might be attributed to poor wettability and particle agglomeration during the run. When incorporated into solid dispersions, the dissolution rate of ET from all preparations was significantly higher than that of pure ET (Fig. 1). The most rapid dissolution was observed with the ET:DMPC solid dispersion in comparison with the other two systems.

With respect to the time taken to dissolve each preparation, the phospholipid containing solid dispersions showed an eightfold increase in dissolution rate, whereas the novel combination mixture showed a more intermediate release profile, with an approximately sixfold increase in dissolution rate. With the PEG8000 solid dispersion, a fourfold increase was observed, compared to the dissolution rate of drug alone, within the first 5 min (D5) of the run. The fastest dissolution from phospholipid DMPC dispersions might be attributed to the solubilizing effects of DMPC on the active drug. It is speculated that DMPC favors the entrapment of poorly soluble compounds in the phospholipid bilayer, which cause the ethopropazine

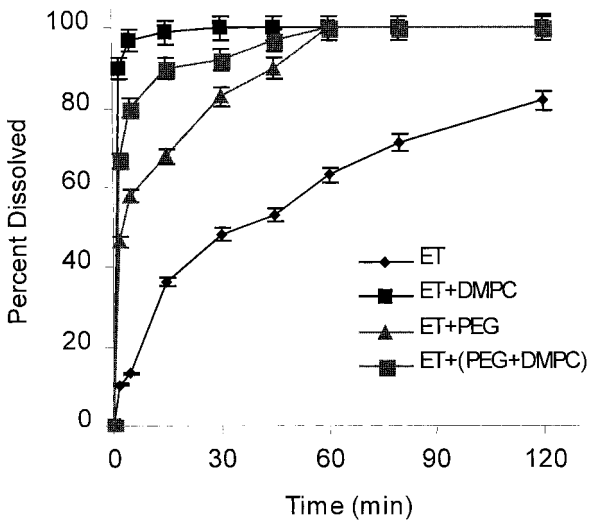

Figure 1. Dissolution of ET and solid dispersions in PBS medium (pH 7.4, 37°C ± 0.5°C).

drug to solubilize. Based on the above results, the dissolution of ET:DMPC solid dispersion was considered to be optimum and was subjected to further characterization using DSC and X-ray diffraction.

Overall, the increase in dissolution rates of drug with different carriers and their combinations may be due to lower contact angle, improved wetting, surfactant effect deaggregation, and therefore increased surface area. Another probable theory concerns an increasingly effective solubilization process by the carriers in the microenvironment (diffusion layer) immediately surrounding the drug particles. In summary, the order of solubilization effectiveness can be characterized as DMPC > (DMPC + PEG8000) > PEG8000.

Thermal Analyses

Thermograms for ET, DMPC, and the SD are shown in Fig. 2. The DSC curves for each component have a single endothermal peak for the melting of ET (228.2°C) and DMPC (65.12°C). The SD showed two endothermal peaks between 50°C and 205°C, demonstrating a marked shift in the endothermal peaks from the original endothermal peaks of DMPC and the ET. Also, a considerable decrease in peak height of the thermograms was noted. The endothermal peaks of the SD indicate the possibility of formation of crystals of the solid dispersion; however, the marked decrease in height of the peaks and the significant shifts in endothermal temperatures suggest the presence of a significant proportion of the SD in amorphous form. These observations were confirmed in the X-ray diffraction studies.

X-Ray Diffraction Studies

Figure 3 shows the X-ray diffraction peaks for ET, DMPC, and the SD. Major diffraction peaks for ET were observed at 12° and 26° 2θ, whereas for the DMPC alone, the peak was observed at 7° 2θ. The SD showed no X-ray diffraction peak formation at 7°, 12°, or 26° 2θ, which indicated that the DMPC has a masking effect over the drug ET and is present in amorphous form. However, a new X-ray diffraction peak for the SD was observed at 15° 2θ, which suggests the possibility of formation of small amounts of crystals in the SD.

Stability Studies

A 4.5-month stability test was conducted by which phospholipids containing solid dispersions were stored at room temperature (25°C) in a desiccator. At the end of the storage period, the dissolution rates of the aged samples were compared with that of freshly prepared phospholipid solid dispersions.

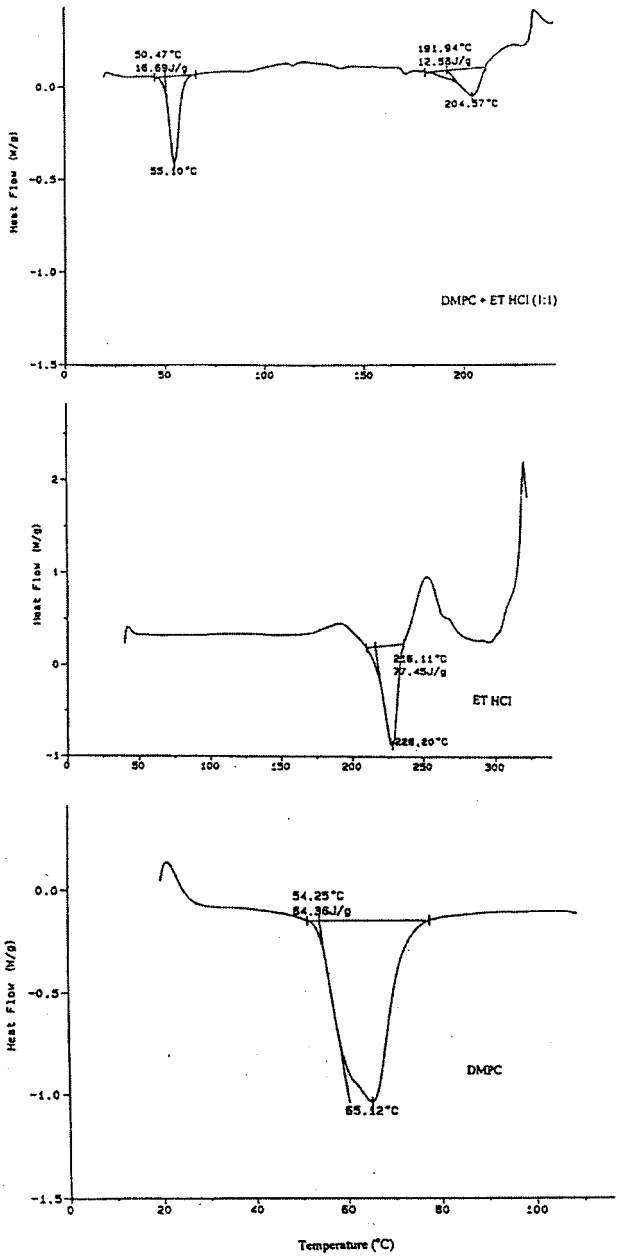

Figure 2. DSC thermograms of the pure drug ET, carrier DMPC, and solid dispersion of ET plus DMPC (1:1).

As shown in Fig. 4, approximately 50% of the aged SD dissolved 4 min into the run, compared to fresh SD, which dissolved in approximately 2 min. A 100% dissolution of the aged sample occurred in approximately 43

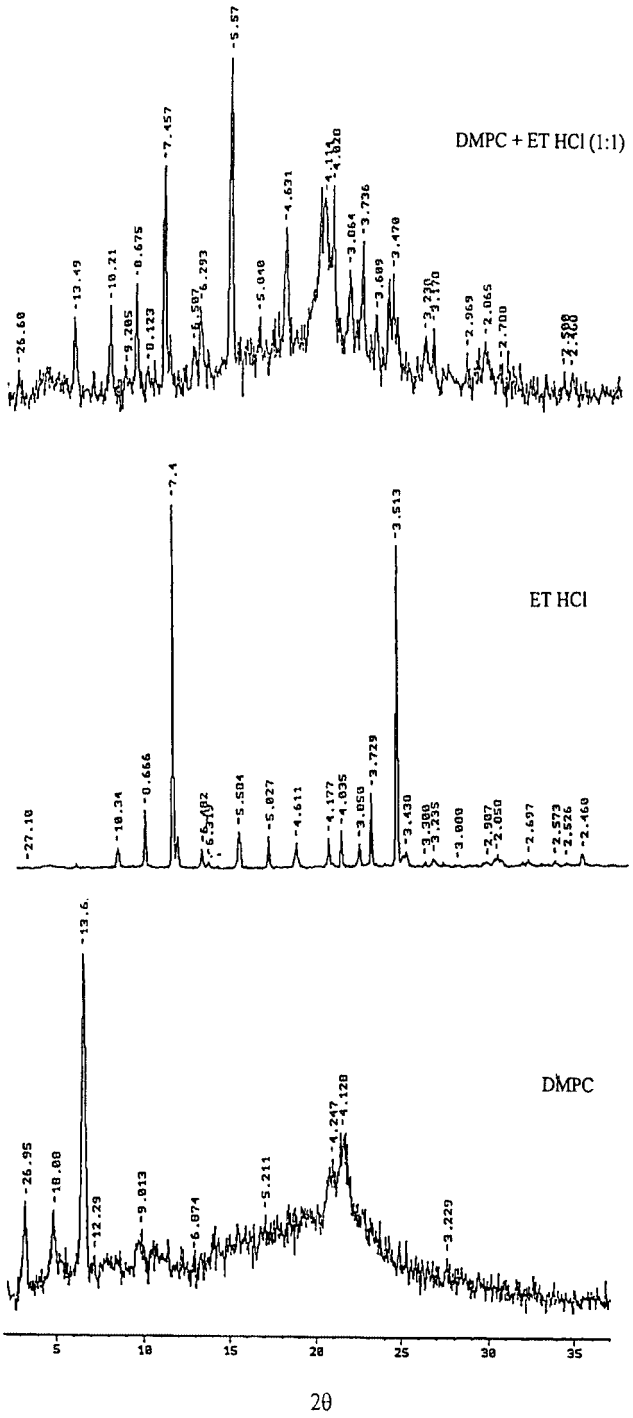

Figure 3. X-ray diffraction spectra of pure drug ET, carrier DMPC, and solid dispersion of ET plus DMPC (1:1).

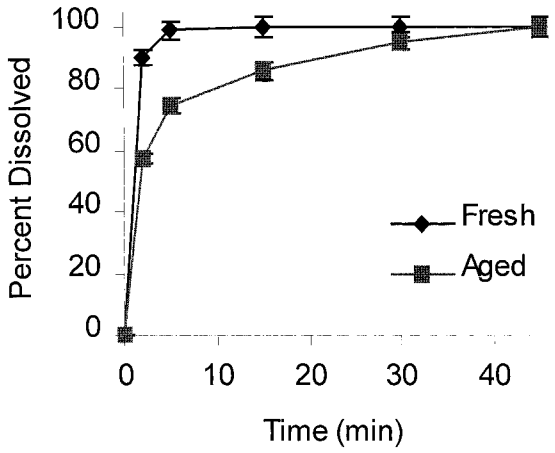

Figure 4. Comparison of dissolution behavior of freshly prepared and aged (4.5 months in storage at 25°C) phospholipid solid dispersion samples in PBS medium (pH 7.4, 37°C ± 0.5°C).

min, whereas the fresh SD sample dissolved within 5 min, demonstrating a significant increase in dissolution times for the aged sample. This discrepancy in dissolution rates for the last half of the aged SD might be attributed to the possible formation of a crystalline mass on storage that results in a decrease in dissolution rates. As reported earlier, X-ray diffraction data showed the emergence of a new peak that may be linked to the formation of a small amount of crystals in the solid dispersion.

CONCLUSIONS

Solid dispersions of phospholipid (DMPC) were superior in dissolving ET compared to solid dispersions with PEG8000 alone or in combination with DMPC. The results obtained from the effect of DMPC and that demonstrated by the novel combination of DMPC and PEG8000 (1:1) mixture could be considered for application to other low-water-soluble and bioavailable drugs. X-ray diffraction and DSC studies determined that there was significant loss of crystallinity and formation of a solid-state solution within the solid dispersion. Storing of SD samples over prolonged periods of time showed a decrease in dissolution rates.

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