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PREPARATION AND IN VITRO DISSOLUTION PROFILES OF TOLAZAMIDE-POLYETHYLENE GLYCOL SOLID DISPERSIONS

G. V. Betageri[1] and S. R. Dipali

Department of Pharmacal Sciences, School of Pharmacy, Auburn University, Auburn, AL 36849-5503

ABSTRACT

The objective of this study is to prepare solid dispersions of tolazamide (TLZ) using polyethylene glycol (PEG) and measure the dissolution of TLZ. PEG 8000 was used as carrier to prepare solid dispersions by melt and solvent methods. Dissolution studies indicated a remarkable increase in the rate of dissolution of TLZ when dispersed in PEG as well as with physical mixture of TLZ and PEG. The rate of dissolution of TLZ was faster with solid dispersions containing TLZ:PEG (1:5) and (1:10) compared to physical mixtures and pure TLZ. The effect of buffer on dissolution was studied. In general the dissolution of TLZ was less in phosphate buffered saline (PBS, pH 7.4) compared to Tris buffer. However, there was no significant difference in the extent of dissolution of TLZ from solid dispersions and physical mixture compared to pure TLZ. Solid dispersions prepared by solvent method showed faster dissolution rates compared to melt method. These results suggest that the rate of dissolution can be increased by improving the wetting property of tolazamide.

INTRODUCTION

Tolazamide (TLZ) is an oral hypoglycemic drug of the sulfonylurea class. It is a white to off-white crystalline powder that is odorless and very slightly soluble in water. It is used as an adjunct to diet for the management of non insulin-dependent diabetes mellitus in patients where hyperglycemia cannot be controlled by diet alone (1). Tolazamide is slowly but well absorbed from the gastrointestinal tract following oral administration. After oral administration the plasma levels reach a peak in 4-8 hr and the plasma half-life is about 7 hr (2).

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[1]To whom all correspondence should be directed

Solid dispersion technique was proposed by Sekiguchi and Obi (3) to improve the solubility and bioavailability of poorly water drugs. Solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs (4-12).

This study was designed to prepare solid dispersions of TLZ using polyethylene glycol (PEG) 8000 in order to enhance the aqueous solubility. High molecular weight PEG was chosen because of high water solubility, low melting point (< 65° C) and also a solid dosage form can be prepared.

MATERIALS AND METHODS

Materials

Tolazamide was a gift from Upjohn Laboratories (Kalamazoo, MI), PEG 8000 was a gift from Union Carbide Corporation (Danbury, CT). Chloroform (HPLC grade), dibasic sodium phosphate, monobasic sodium phosphate, sodium chloride (anhydrous), cyclohexanol (reagent grade), methanol (HPLC grade) were purchased from Fisher Scientific Company (Fairlawn, NJ). Glass triple distilled water was used in the preparation of all aqueous solutions. All other chemicals and solvents were reagent grade.

Methods

Composition of Solid Dispersions

Single component solid dispersions and physical mixture contained either 5 or 10 parts by weight of PEG 8000 and 1 part of TLZ.

Preparation of Solid Dispersions

The Fusion (Melt) Method : Accurately weighed amount of carrier was placed in an aluminium pan on a hot plate and melted, with constant stirring, at a temperature of about 120° C. To the melted PEG the drug was added and the melt was cooled at room temperature. The dispersions were stored in a desiccator. The solid dispersions were passed through # 40 sieve and collected on sieve # 60 and used for dissolution study.

The Solvent Method : Accurately weighed amount of TLZ and carrier were dissolved in minimum quantities of chloroform in a round bottom flask. The solvent was removed using a rotary evaporator. The resultant solid dispersions were transferred to an aluminium pan and allowed to dry at room temperature and stored in a desiccator and were passed through # 40 sieve and collected on sieve # 60 just before the dissolution study.

Preparation of Physical Mixture

The PEG 8000 was passed through sieve # 40 and collected on sieve # 60 and mixed with TLZ just before the dissolution study.

Dissolution Study

The dissolution studies were conducted in a USP Standard Dissolution Apparatus. The dissolution medium was maintained at 37±0.5° C and stirred at 100 rpm by means of an adjustable constant speed motor. Dispersion containing 20 mg of TLZ was introduced into the flask and recorded the time (time 0). Five ml samples were withdrawn at different time intervals, filtered through 0.22 μ filter and same volume of fresh dissolution medium, maintained at 37±0.5° C, was added to the flask to maintain constant volume. The samples were immediately assayed using UV spectrophotometer (Beckman DU-65). Dissolution studies for each formulation were performed in triplicates.

Statistical Analysis

A cumulative correction factor was applied to compensate for the previously withdrawn samples in the dissolution studies. The following equation was used (13):

$$C_n = C_{nobs} + (5/450)\, C_n\text{-}1$$

where C_{nobs} = observed concentration of the n^{th} sample.
C_n-1 = concentration of n-1 sample.
C_n = corrected concentration of the n^{th} sample.

One way analysis of variance and Student-T test were used to determine the presence of any significant differences ($p < 0.05$) among the test groups.

RESULTS AND DISCUSSION

The rate of dissolution of TLZ was significantly higher with physical mixtures and solid dispersions of TLZ with PEG as shown Figures 1 and 2. Higher dissolution with physical mixture indicates that PEG do indeed exert solubilizing properties. Similar results have been reported for etopside and carbamazepine (11,14). The method of preparation of solid dispersions had no significant effect on the rate of dissolution of TLZ. The time required to dissolve 90% of TLZ from solid dispersions and pure TLZ is shown in Figure 3. Solid dispersion containing 10 parts of PEG 8000 and 1 part of TLZ needed 5 minutes for solid dispersions prepared by melt method and 3 minutes for solid dispersions prepared by solvent method to dissolve 90% of drug whereas it was 10 and 15 minutes for solid dispersion containing 5 parts of PEG and 1 part of TLZ prepared by melt and solvent method respectively and 45 minutes for pure TLZ. The physical mixtures needed 15 and 17 minutes to dissolve 90% of TLZ for 1:5 and 1:10 drug to PEG ratios respectively.

The effect of buffer solution on dissolution of TLZ is shown in Figure 4. The rate of dissolution was higher when it was measured using Tris buffer compared to phosphate buffered saline. USP requirement for dissolution of TLZ (70% in 30 minutes) was achieved with solid dispersions containing either 5 or 10 parts of PEG and 1 part of drug in both PBS and Tris buffer. However, in case of pure TLZ it was achieved only in Tris buffer.

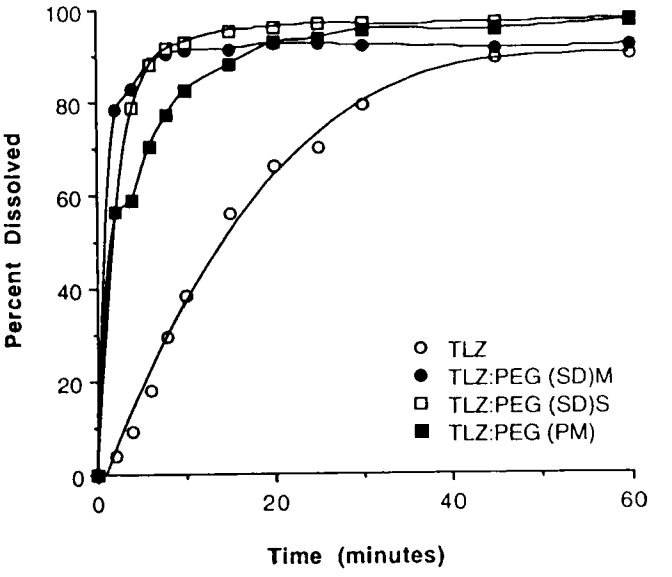

FIGURE 1

Dissolution profiles of pure tolazamide (TLZ) and from TLZ:PEG 8000 (1:5) solid dispersions prepared by melt and solvent methods and physical mixtures at 37° C in Tris buffer (pH 7.6).

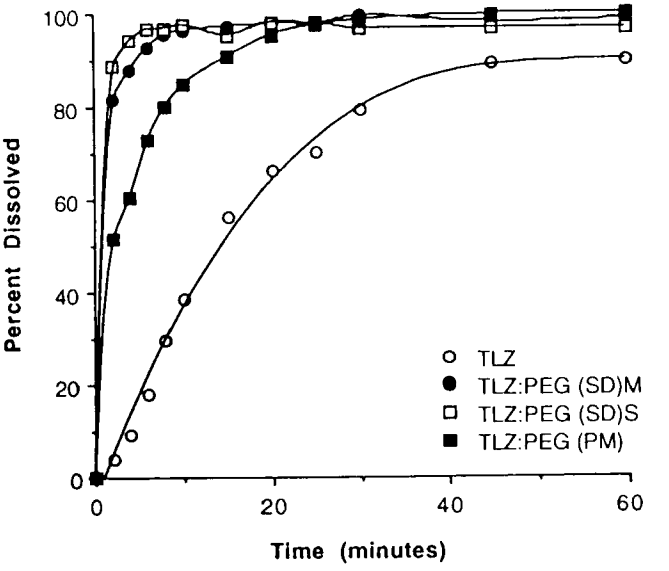

FIGURE 2

Dissolution profiles of pure tolazamide (TLZ) and from TLZ:PEG 8000 (1:10) solid dispersions prepared by melt and solvent methods and physical mixtures at 37° C in Tris buffer (pH 7.6).

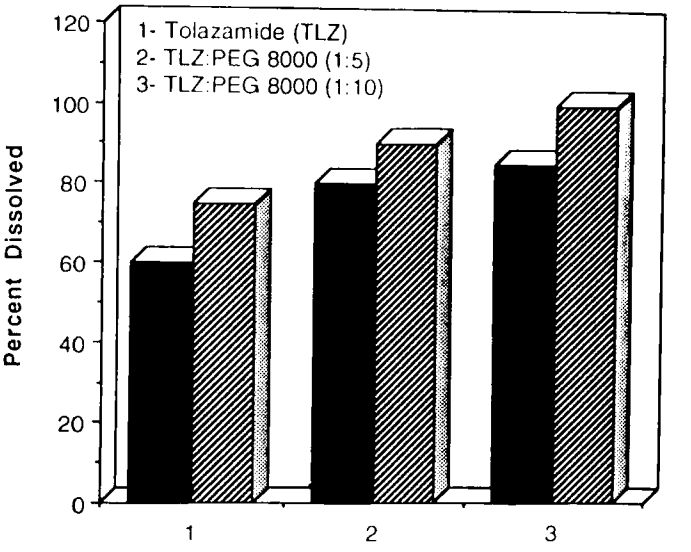

FIGURE 3

Dissolution of Tolazamide in phosphate buffered saline (▩) and Tris (▨) buffer after 30 minutes at 37° C.

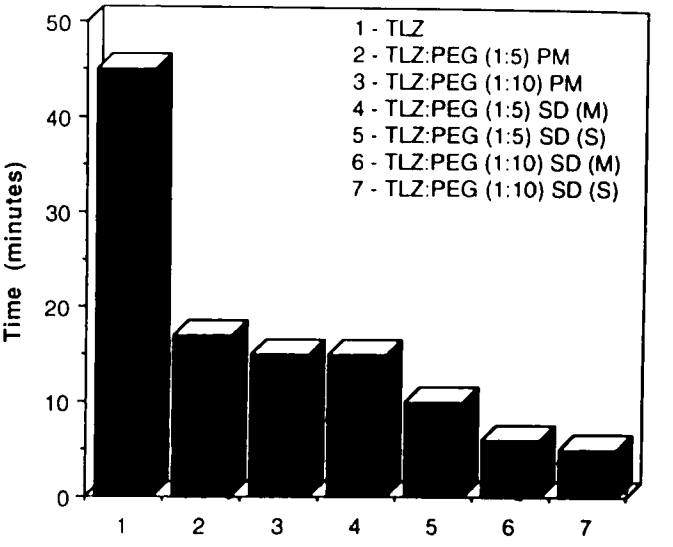

FIGURE 4

Time required to dissolve 90% of tolazamide from physical mixtures and solid dispersions in Tris buffer (pH 7.6) at 37° C.

The rate of dissolution of TLZ was significantly increased when incorporated in PEG 8000 either as physical mixture or in molecular dispersion. The rate of dissolution of TLZ increased with an increase in the proportion of PEG in physical mixture as well as solid dispersion. This could be due to the breaking of water structure by the carrier and creating favorable environment for solubilization of TLZ (15). The dissolution medium has an effect on the rate of dissolution of TLZ. However, there was no difference in the extent of dissolution of TLZ. The rate of dissolution can be increased by improving the wetting property of tolazamide either by physical mixture or by preparing solid dispersions using PEG 8000 as carrier.

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