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Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques

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Abstract

Glyburide (GLY) is an oral hypoglycemic agent that is poorly soluble in water. The present study describes the preparation of solid dispersions and lyophilization of the dispersions designed to increase the solubility. Solid dispersions of GLY were prepared using polyethylene glycol 4000 (PEG 4000), PEG 6000 and a mixture of PEG 4000 and PEG 6000 (1:1 mixture). The effect of melt and solvent methods of preparation of solid dispersion on dissolution behavior was also investigated. Dissolution studies indicated a significant increase in dissolution of GLY when dispersed in PEGs. Physical mixtures containing PEGs also showed improved dissolution of GLY as compared with that of pure drug, indicating the solubilizing effect of PEGs. Solid dispersions containing GLY/PEG 6000, 1:8, showed a 14-fold increase in dissolution after 60 min (D60) and another dispersion containing GLY/PEG 4000, 1:10, showed an 8-fold increase in the phosphate buffer system. The dispersion containing six parts of the PEG mixture (PEG 4000/PEG 6000, 1:1 mixture) showed a 12-fold increase in D60 as compared with pure drug. When multi-carrier solid dispersion containing six parts of mixture was prepared by the solvent method, the D60 value was about 2-fold that of the same dispersion prepared by the melt method. The dissolution of lyophilized solid dispersions further increased the dissolution of GLY significantly.

Keywords: Glyburide; Physical mixture; Solid dispersion; Lyophilization; Polyethylene glycol; Dissolution

1. Introduction

The rate and extent of dissolution of the active ingredient from any solid dosage form determines the rate and extent of absorption of the drug. In the case of a poorly water soluble drug, dissolution is the rate limiting step in the process of drug absorption. Poorly soluble drugs have been shown to be unpredictably and slowly absorbed as compared with drugs with higher solubility.

Several methods have been employed to improve the solubility of poorly water soluble drugs. A solid dispersion technique has been used by various researchers who have reported encourag-

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ing results with different drugs (Hajratwala, 1974; Puisieux and Henry, 1981; Vila-Jato and Alonso, 1986; Law and Chiang, 1990; Fernandez et al., 1992; Jachowicz et al., 1993; Sheu et al., 1994). The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (1961). Gibbs et al. (1976) proposed an alternative solvent technique for the preparation of solid dispersions. Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin and Wilken, 1980).

Polyethylene glycol (PEG) 4000 and PEG 6000 either individually or in combination were used as carriers in this study. Effect of drug to carrier ratios on the dissolution of glyburide was also studied. Solid dispersions were prepared by both melt and solvent methods to compare the rates of release of drug and extent of solubility.

The solid dispersion and the lyophilization techniques seem to possess great potential to significantly enhance the solubility and dissolution rate of drugs. The objective of this study was to apply these techniques to a model drug, glyburide, to achieve increased dissolution.

2. Materials and methods

2.1. Materials

Glyburide was a gift from Upjohn Laboratories (Kalamazoo, MI), PEG 4000 and PEG 6000 were obtained from City Chemical Corp., (New York, NY). 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). Absolute ethanol was obtained from Florida Distillers (FL).

2.2. Composition of solid dispersions

Single component solid dispersions contained either 4, 6, 8 or 10 parts by weight of PEG 4000 or PEG 6000 and 1 part of glyburide. Multicomponent solid dispersions contained either 4, 6, 8 or 10 parts by weight of a PEG 4000 and PEG 6000 (1:1, by weight) mixture and 1 part of glyburide. Physical mixtures containing either PEG 4000 or PEG 6000 contained equal amounts of carrier and glyburide. Table 1 lists the solid dispersion preparations used and gives their code numbers.

2.3. Preparation of solid dispersions

2.3.1. The fusion (melt) method

Accurately weighed amounts of carrier(s) were placed in an aluminium pan on a hot plate and melted, with constant stirring, at a temperature of about 120°C. An accurately weighed amount of glyburide was incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous

Table 1
Code numbers for solid dispersion preparations

Carrier	Drug/Carrier	Method	Code number
Glyburide	–	–	GLY
PEG 4000	1:4	Melt	M40-4
	1:4	Solvent	S40-4
	1:6	Melt	M40-6
	1:6	Solvent	S40-6
	1:8	Melt	M40-8
	1:8	Solvent	S40-8
	1:10	Melt	M40-10
	1:10	Solvent	S40-10
PEG 6000	1:4	Melt	M60-4
	1:4	Solvent	S60-4
	1:6	Melt	M60-6
	1:6	Solvent	S60-6
	1:8	Melt	M60-8
	1:8	Solvent	S60-8
	1:10	Melt	M60-10
	1:10	Solvent	S60-10
PEG-Mix[a]	1:4	Melt	MX-4
	1:4	Solvent	SX-4
	1:6	Melt	MX-6
	1:6	Solvent	SX-6
	1:8	Melt	MX-8
	1:8	Solvent	SX-8
	1:10	Melt	MX-10
	1:10	Solvent	SX-10

[a]PEG 4000 + PEG 6000 (1:1).

melt was obtained. The pan was then removed from the hot plate and allowed to cool at room temperature.

2.3.2. The solvent method

Accurately weighed amounts of glyburide and carrier(s) were dissolved in minimum quantities of chloroform in a round-bottom flask. The solvent was removed using a rotary evaporator. The resultant solid dispersion was transferred to an aluminium pan and allowed to dry at room temperature.

2.4. Lyophilization of solid dispersions

The selected solid dispersions were dissolved in a minimum amount of cyclohexanol. This solution was rapidly solidified by transferring small portions with a Pasteur pipette onto the inner surface of a cold Labconco (Labconco Corp., MO) flask rotating in a −50°C methanol bath. After a certain layer thickness was obtained, the Labconco flask was attached to the vacuum adapter of the lyophilizer. The solvent was sublimed under a pressure of 8–10 mmHg and condensed onto a −75°C condenser. After the solvent was completely removed, the powder residue appeared as a porous, light and fluffy mass. The lyophilized preparations were stored in a desiccator at room temperature.

2.5. 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 rev./min by means of an adjustable constant speed motor. A dispersion containing 20 mg of glyburide was introduced into the flask and the time recorded (time 0). Five-milliliter samples were withdrawn at different time intervals 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 a UV spectrophotometer (Beckman DU-65). Dissolution studies for each formulation were performed in triplicates.

2.6. Aging studies

Aging studies were performed after 12 months and 8 months, respectively, for the selected plain and corresponding lyophilized solid dispersions. The samples were stored at room temperature in the desiccator. Dissolution studies were conducted following the same procedure as described previously.

2.7. Statistical analysis

A cumulative correction factor was applied to compensate for the previously withdrawn samples in the dissolution studies. The following equation (Wurster and Taylor, 1965) was used:

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

where $C_{n\text{obs}}$ is the observed concentration of the nth sample, $C_n - 1$ is the concentration of $n-1$ sample and C_n is the corrected concentration of the nth sample.

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

3. Results and discussions

The dissolution of glyburide from physical mixtures (GLY/PEG 1:1) is shown in Fig. 1. The dissolution rate of GLY from all the physical mixtures was significantly higher than GLY alone. This demonstrates the solubilizing effects of the PEGs. The dissolution profiles of solid dispersions prepared using PEG 4000 exhibited significant increase in rate of dissolution in the phosphate buffer system (pH 7.4). Dissolution for all the dispersions were significantly greater than those for GLY alone. Rate of dissolution was higher with the dispersions prepared by the solvent method. The dispersion prepared with 10 parts of PEG 4000 had the highest dissolution at 60 min (D60) of 9.85 μg/ml, which is significantly greater than the other dispersions. M40-4 and S40-4 showed a slightly lower rate of dissolution compared with GLY alone. This may be attributed to

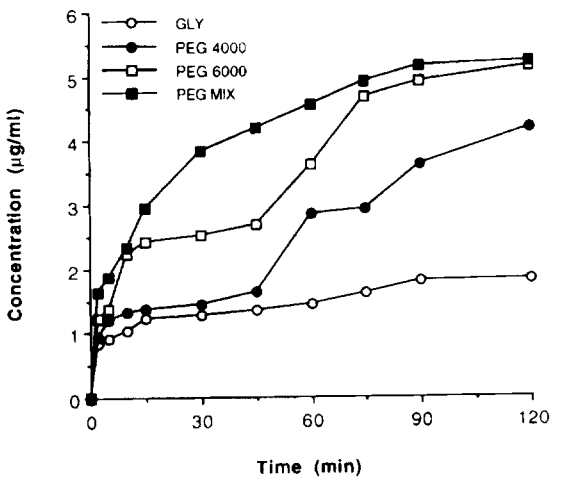

Fig. 1. Dissolution profiles of pure glyburide (GLY) and physical mixtures GLY/PEG 4000, GLY/PEG 6000; and GLY/PEG mixture (PEG 4000/PEG 6000, 1:1) at 37°C in phosphate buffer (pH 7.4).

some chemical anomalies upon formation. In both methods, the D60 values exhibited a direct proportionality with the amount of PEG contained in the solid dispersions.

The dissolution profiles of solid dispersions containing PEG 6000 show identical dissolution for dispersions containing 1 part of GLY and 4, 6, 8 and 10 parts of PEG 6000. Dispersions containing 8 parts of PEG 6000 appears to be the best preparation, showing a D30 value of 18.24 μg/ml and a D60 value of 19.6 μg/ml, which is about a 17- and 18-fold increase, respectively, compared with GLY alone.

Dissolution profiles of solid dispersions prepared using a PEG 4000 and PEG 6000 mixture (1:1) were significantly higher than that of pure GLY. The dispersion containing 1 part of GLY and 6 parts of PEG mixture has the highest D30 and D60 values. The dissolution profiles of these preparations show identical dissolution for dispersions containing 1 part of GLY and 4, 6, 8 and 10 parts of PEG mixture.

Solid dispersions prepared with 10 parts of PEG 4000, 8 parts of PEG 6000 and 6 parts of mixtures of PEG 4000 and PEG 6000 were chosen for lyophilization because these dispersions provided the best dissolution profiles. The rate and extent of dissolution increased with all the lyophilized solid dispersions. However, the extent of dissolution was maximum with the dispersions prepared using PEG 6000 and PEG mixture.

Dissolution of GLY, physical mixtures, solid dispersions and lyophilized solid dispersions at 60 min (D60) are shown in Fig. 2. All the lyophilized solid dispersions show a significant increase in D60 values compared with their respective plain solid dispersions. Lyophilized solid dispersion prepared with 6 parts of PEG mixtures showed the steepest increase, with D60 almost doubling upon lyophilization.

The non-equilibrium solubility studies with powdered materials give a good indication of the dissolution profiles of solid dispersions of different drugs. The dissolution of the drug from the solid dispersion is also affected by the method of preparation of the solid dispersion. It also depends on the proportion and properties of the polymer carrier used in the composition of solid dispersion (Corrigan, 1985).

Solid dispersions containing PEG 4000, PEG 6000 and a mixture of the two PEGs all showed higher dissolution rates compared with GLY alone. Physical mixtures also exhibited higher dissolution rates as compared with GLY alone, demonstrating the solubilizing properties of PEGs. However, dissolution rates of solid dispersions were significantly higher than their corresponding physical mixtures.

The process of lyophilization occurs in three stages: freezing, primary drying (ice sublimation) and secondary drying (water desorption) (Pikal et al., 1983). The freezing process largely determines the physical traits of the dried solid product (MacKenzie, 1976). Primary drying represents the initial onset of the drying process from the top. Secondary drying process begins when the ice has been completely removed from that area. Thus, primary and secondary drying could occur simultaneously. The resultant dry mixture is porous and fluffy and the original starting volume is maintained. This increases the surface area and hence, the surface free energy is also higher, resulting in an increase in the dissolution rate. The initial rapid dissolution of glyburide could be due to finely divided particles of glyburide in a

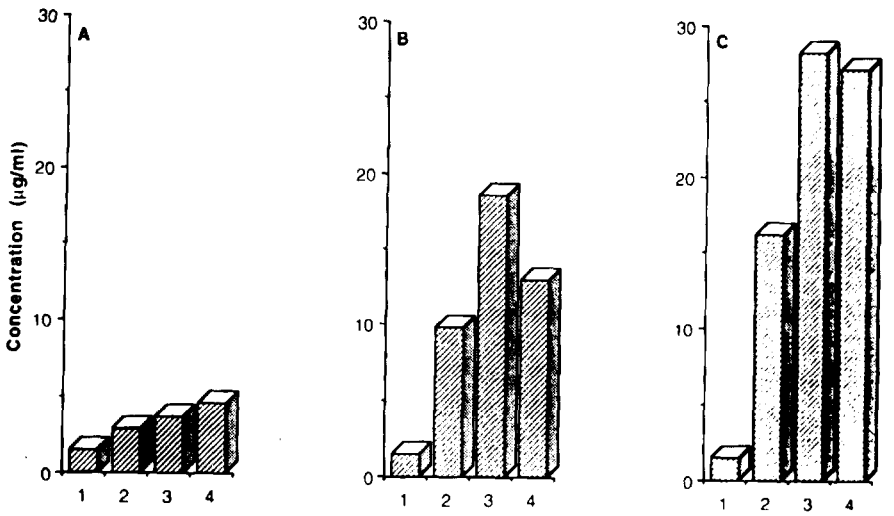

Fig. 2. Dissolution of GLY after 60 min. (A) Physical mixtures; (B) solid dispersions; (C) lyophilized solid dispersions.

lyophilized solid dispersion surrounded intimately in the matrix by the PEG particles.

The D60 values of fresh and aged dispersions are given in Table 2. The aged dispersions show slightly erratic dissolution profiles as compared with their respective fresh samples. The aged plain dispersion SX-6 shows significantly less values compared with the fresh samples. In the case of lyophilized dispersions, M40-10 exhibits a significant decrease in the rate of dissolution. The D60 values of lyophilized S60-8 and SX-6 are also significantly lower than that of the fresh sample. This may be due to agglomeration of the fine amorphous powder that could have been formed after lyophilization.

Table 2
Dissolution of glyburide after 30 min (D30) and 60 min (D60) from plain and lyophilized solid dispersions before and after aging

Solid dispersion	D30 (μg/ml)Mean ± S.D.	D60 (μg/ml)Mean ± S.D.
Plain		
M40-10 Fresh	9.12 ± 1.27	9.85 ± 0.64
M40-10 Aged	8.93 ± 1.17	9.16 ± 1.52
S60-8 Fresh	18.24 ± 1.14	19.60 ± 0.37
S60-8 Aged	15.62 ± 0.97	19.12 ± 0.28
SX-6 Fresh	10.30 ± 1.77	13.28 ± 1.54
SX-6 Aged	9.46 ± 0.21	11.63 ± 0.14
Lyophilized		
M40-10 Fresh	12.62 ± 0.93	16.23 ± 1.12
M40-10 Aged	10.45 ± 0.35	12.53 ± 1.14
S60-8 Fresh	26.26 ± 1.15	28.30 ± 1.21
S60-8 Aged	23.43 ± 2.23	25.31 ± 0.73
SX-6 Fresh	18.56 ± 0.98	27.22 ± 1.23
SX-6 Aged	18.45 ± 1.46	22.57 ± 1.45

Two theories have been proposed to explain the higher dissolution rates of solid dispersions. One theory proposes that higher energy metastable states of the components are formed as a function of the carrier system being used and the proportion of carriers present (Simonelli et al., 1969). This could explain the fact that solid dispersions exhibit higher dissolution rates than physical mixtures. The method of preparation of solid dispersions could also determine the solid phase energy states.

The second theory states that the dissolution is affected because of the formation of a solid solution of the drug. The particle size is reduced to molecular size when the carrier brings the drug into the dissolution medium. Thus, the faster dissolution rate can be explained based merely on the particle size without anything to do with energy changes. The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution.

The wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug and, hence, higher dissolution rates. The presence of carrier polymers also inhibits crystal growth of the drug which facilitates faster dissolution (Sekikawa et al., 1979).

In conclusion, physical mixtures, solid dispersions and lyophilized solid dispersions increase dissolution of glyburide. Lyophilized solid dispersions of PEGs had the maximum effect on the rate and extent of dissolution of glyburide. The results of this study clearly suggest that lyophilization of solid dispersions is ideal for poorly water soluble drugs and aging has an adverse effect on the dissolution.

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