

Characterization of gliclazide-polyethylene glycol solid dispersion and its effect on dissolution

Moreshwar Pandharinath Patil^{1*}, Naresh Janardan Gaikwad²

¹T. V. E. S's Hon'ble LMC College of Pharmacy, Faizpur,

²Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University

The present study was initiated with the objective of studying the *in vitro* dissolution behavior of gliclazide from its solid dispersion with polyethylene glycol 6000. In this work, a solid dispersion of gliclazide with polyethylene glycol was prepared by the fusion method. *In vitro* dissolution study of gliclazide, its physical mixture and solid dispersion were carried out to demonstrate the effect of PEG 6000. Analytical techniques of FT-IR spectroscopy, differential scanning calorimetry and X-ray diffractometry were used to characterize the drug in the physical mixtures and solid dispersions. The dissolution studies of solid dispersion and physical mixture showed greater improvement compared to that of the pure drug. The mechanisms for increased dissolution rate may include reduction of crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of the drug from the dispersion, dissolution of the drug in the hydrophilic carrier or conversion of drug to an amorphous state. The FT-IR spectra suggested that there was no interaction between gliclazide and PEG 6000 when prepared as a solid dispersion. DSC and XRD study indicated that the drug was converted in the amorphous form.

Uniterms: Gliclazide. Polyethylene glycol 6000. Solid dispersion. *In vitro* dissolution.

O presente trabalho foi realizado com o objetivo de estudar o comportamento *in vitro* da dissolução da gliclazida a partir da sua dispersão sólida com polietileno glicol 6000. Neste trabalho, as dispersões sólidas de gliclazida com polietileno glicol foram preparadas pelo método de fusão. Os estudos de dissolução *in vitro* da gliclazida, na mistura física e nas dispersões sólidas foram realizados para demonstrar o efeito de PEG 6000. Técnicas analíticas como espectroscopia FT-IR, calorimetria diferencial de varredura e difração de raios-X foram empregadas para caracterizar o fármaco nas misturas físicas e nas dispersões sólidas. Os estudos de dissolução demonstraram maior melhoria. Os mecanismos para aumentar a velocidade de dissolução podem incluir a redução do tamanho dos cristais, a solubilização do carreador, a ausência de agregação dos cristais do fármaco, a melhoria da molhabilidade e dispersibilidade do fármaco a partir da dispersão, a dissolução do fármaco no carreador hidrofílico ou conversão da forma cristalina do fármaco para estado amorfo. Os espectros de FT-IR sugeriram que não houve interação entre gliclazide PEG 6000 e na sua combinação. Os estudos de DSC e DRX indicaram que o fármaco foi convertido para a forma amorfa.

Unitermos: Gliclazide. Polietileno glicol 6000. Sólidos/dispersão. Dissolução *in vitro*.

INTRODUCTION

Solid dosage forms such as tablets and capsules represent the highest share in the market despite advancements in innovative dosage forms. Drug dissolution from oral solid dosage forms depend on the release of the drug from

the dosage form and subsequent solubilization of drug particles in physiological fluid. The dissolution characteristics of poorly water-soluble drugs remain a major problem for the pharmaceutical industry because dissolution is the rate-limiting process in the absorption of these drugs from solid dosage forms. Among the various approaches employed to improve the dissolution of poorly soluble drugs, solid dispersion has been proven successful. Fast or immediate drug dissolution from solid dispersions has been observed

*Correspondence: Moreshwar P. Patil. T. V. E. S's Hon'ble Loksevak Madhukarrao Chaudhari College of Pharmacy, Nehru Vidyannagar, Faizpur, Dist-Jalgaon, (M.S), India. E-mail- morupatil@gmail.com

due to increased wettability, improved dispersibility of drug particles, existence of the drug in amorphous form with improved solubility, and absence of aggregation of drug particles (Chowdary *et al.*, 1995; Kerc *et al.*, 1998).

Solid dispersion is one of the most widely-used techniques for dissolution improvement (Chiou, Riegelman, 1971). Two basic procedures used to prepare solid dispersions are the melting or fusion (Sekiguchi, Obi, 1961) and solvent evaporation techniques (Tachibana, Nakamura, 1965).

The mechanisms for increased dissolution rate may include reduction of crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier or conversion of the drug to an amorphous state (Ford, Robenstein, 1986; Craig, 2002; Liu *et al.*, 2005; Shah *et al.*, 2007).

Gliclazide, 1-(3-azabicyclo (3,3,0)oct-3yl)-3-*p*-tolylsulphonylurea is a potential oral hypoglycemic drug which is useful for the treatment of non-insulin-dependent diabetes mellitus (Palmer, Brogden, 1993; Mailhot, 1993). Due to short duration of action, it is considered suitable for diabetic patients with renal impairment and for elderly patients that have reduced renal function and are in use of sulphonylurea treatment, which may increase the risk of hypoglycemia (Tessier *et al.*, 1994). However, gliclazide has low solubility and low dissolution in gastric fluids and hence shows variation in bioavailability (Gillman *et al.*, 1990).

MATERIAL AND METHODS

Materials

Gliclazide was obtained from Indi Pharma Pvt. Ltd., Goa (India). Polyethylene glycol 6000 was purchased from Qualigens Fine Chemicals (India). Sodium hydroxide and potassium dihydrogen phosphate were purchased from Loba Chemie, Mumbai, and hydrochloric acid from Ranbaxy Fine Chemicals Ltd., New Delhi.

Methods

Physical mixtures and corresponding solid dispersion

Physical mixtures of gliclazide with three different mass ratios (1:1, 1:3 and 1:5 as PM 611, PM 613 and PM 615) of PEG 6000 were prepared in a glass mortar by light trituration for 5 minutes. Solid dispersions were prepared by the fusion method (Sekiguchi, Obi 1961). Polyethylene glycol 6000 was placed in a porcelain dish and allowed to melt by heating up to 70 °C. To the molten mass, an

appropriate amount of gliclazide was added, and the mixture stirred constantly until a homogenous dispersion was obtained. For rapid solidification, the resultant solution was cooled in an ice bath and stored in dessicator for 24 h. The solid was then scraped, pulverized and passed through a sieve. The prepared solid dispersions at different mass ratios (1:1, 1:3 and 1:5 as SD 611, SD 613 and SD 615) were then introduced into glass bottles, sealed and stored in a dessicator until further use.

In vitro dissolution study

Dissolution of drug powder, gliclazide (40 mg), its physical mixtures (in drug: PEG 6000 ratio 1:1, 1:3 and 1:5 as PM 611, PM 613 and PM 615) and solid dispersions (in drug: PEG 6000 ratio 1:1, 1:3 and 1:5 as SD 611, SD 613 and SD 615) with PEG 6000 (equivalent to 40 mg), was carried out using USP dissolution test apparatus (Type II) at a temperature of 37 ± 0.5 °C, at 100 rpm using 900 mL of dissolution medium. The dissolution study was carried out separately for two hours in 2 different dissolution mediums viz. hydrochloric acid buffer (pH 1.2, 0.2 M potassium chloride (50 mL) and 0.2 M hydrochloric acid (85 mL) and phosphate buffer (pH 7.4) (USP, 2000). Samples (5 mL) were withdrawn at predetermined time intervals (5, 10, 15, 30, 45, 60, 90 and 120 minutes), filtered through Whatman filter paper No. 41, suitably diluted and assayed for gliclazide at 226 nm. Sink conditions were maintained by replenishing the medium with equal amounts (5 mL) of dissolution medium. The percentage of gliclazide dissolved was calculated from the regression equation generated from standard data.

Characterization of gliclazide and its solid dispersions (Leuner, Dressman, 2000)

• FT-IR study

The samples, gliclazide, PEG 6000, their physical mixtures and solid dispersions were previously ground and mixed thoroughly with potassium bromide. Forty scans of each sample were obtained at a resolution of 4 cm⁻¹ from 4500 to 400 cm⁻¹ using a FT-IR spectrophotometer (8101A, Shimadzu Co., Japan).

• DSC

The DSC measurements were performed on a differential scanning calorimeter (DSC-60, Shimadzu Co., Japan) with a thermal analyzer. Accurately weighed samples (about 5–10 mg) were heated in hermetically sealed aluminum pans under a nitrogen atmosphere at a flow rate of 20 mL min⁻¹ with a scanning rate of 15 °C min⁻¹ from 60 to 250 °C. An empty aluminum pan was used as a reference.

• X-ray diffractometry

The state of gliclazide, its physical mixtures and solid dispersions was evaluated with X-ray powder diffraction. Diffraction patterns were obtained using an XPERT-PRO diffractometer (PANalytical Ltd., The Netherlands) with a radius of 240 mm. The Cu K α radiation (K α 1.54060 Å) was Ni filtered. A system of diverging and receiving slits of 1° and 0.1 mm, respectively, was used. The pattern was collected with 40 kV of tube voltage and 30 mA of tube current and scanned over the 2 θ range of 5–60°.

RESULTS AND DISCUSSION

In vitro dissolution study

Physical mixtures of drug with PEG 6000 at three different mass ratios showed 65.90%, 43.13% and 65.14% drug release, while solid dispersions showed

48.01%, 63.98% and 56.27% during the first hour of study. The percentage drug release from solid dispersions was initially slow but at the end of 120 min was 90.43%, 92.97% and 97.93%. This may be due to the formation of a drug-rich surface layer which further prevents erosion of the matrix or could be due to rapid dissolution of carrier.

Similar dissolution studies were carried out in phosphate buffer. In the first 30 min, cumulative % drug release from physical mixtures was 57.40%, 62.26% and 67.10, respectively, while solid dispersions showed 52.94%, 62.62% and 57.40%. At the end of the study, solid dispersions showed 92.40%, 94.89% and 98.00 % drug release and physical mixtures showed 84.02%, 86.37% and 89.22% drug release. The dissolution test was repeated in triplicate. Drug dissolved at specific time periods was plotted on cumulative percent release versus time (hours) curves.

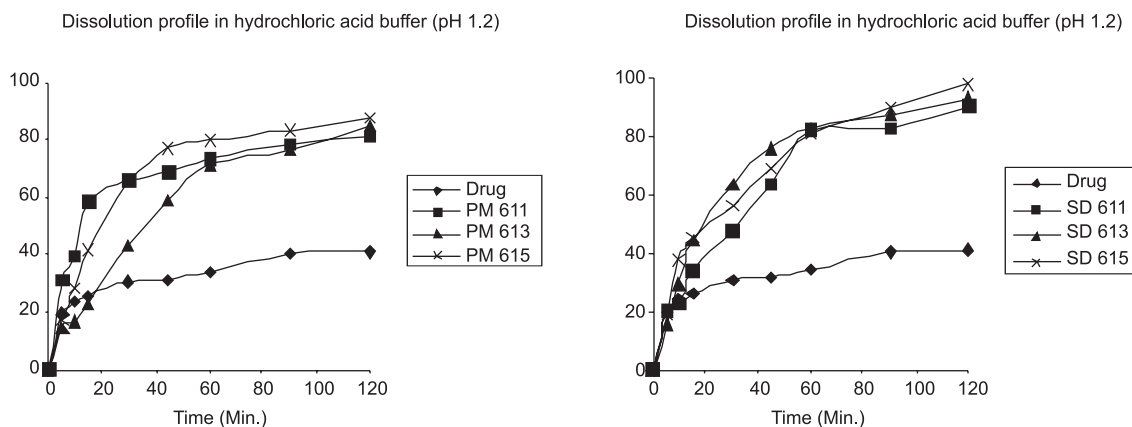


FIGURE 1 - % drug release in hydrochloric acid buffer (pH 1.2). PM 611, PM 613 and PM 615 indicates physical mixtures of drug: PEG 6000 at 1:1, 1:3 and 1:5 ratios. SD 611, SD 613 and SD 615 indicate solid dispersions of drug: PEG 6000 at 1:1, 1:3 and 1:5 ratios.

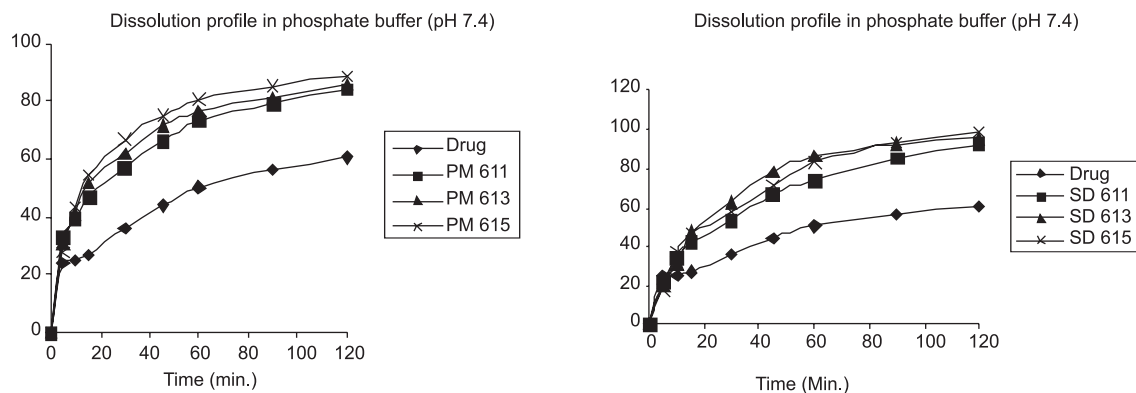


FIGURE 2 - % drug release in phosphate buffer (pH 7.4). PM 611, PM 613 and PM 615 indicates physical mixtures of drug: PEG 6000 at 1:1, 1:3 and 1:5 ratios. SD 611, SD 613 and SD 615 indicate solid dispersions of drug: PEG 6000 at 1:1, 1:3 and 1:5 ratios.

The results indicated that, as the concentration of polymer in the dispersed system increases, dissolution of poorly soluble drug also increases. In all cases, solid dispersions exhibited faster and almost complete dissolution compared to the pure drug and its corresponding physical mixtures. The possible mechanisms responsible for increased dissolution could be reduction of crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, and conversion of the drug to an amorphous state (De-sai, Liu, 2005; Ozkan, 2000).

FT-IR study

The FT-IR spectrum of Gliclazide showed a sharp concave curve at 1709 cm^{-1} for the carbonyl group. For the sulphonyl group bands, the spectrum showed stretching peak at 1164 cm^{-1} and 1350 cm^{-1} and a peak at 3272 cm^{-1} evidenced the amino group. The spectrum of PEG 6000 showed important peaks at 3425 cm^{-1} (O-H stretch), at 1109 cm^{-1} (C-O-C stretch) and at 2889 cm^{-1} (C-H stretch). Consequently, the FT-IR spectra of both solid dispersion and physical mixture seemed to be only the summation of Gliclazide and PEG 6000 spectra. These results suggested

that there was no interaction between Gliclazide and PEG 6000. The results are given in Figure 3.

DSC

Gliclazide showed an endothermic reaction and its melting peak was at $172.3\text{ }^{\circ}\text{C}$. The thermal behavior of PEG 6000 exhibited a sharp endothermic peak at $62.2\text{ }^{\circ}\text{C}$. A slight difference was evident in the thermograms of the physical mixture and solid dispersion, showing a single sharp melting peak at $60.2\text{ }^{\circ}\text{C}$ and $60.5\text{ }^{\circ}\text{C}$, respectively. The complete disappearance of Gliclazide melting peak observed in both PM and SD was attributable to the complete miscibility of the drug in the melted carrier. The enthalpy of melting of drug in solid dispersion (ΔH_f : -151.5 J/g) was gradually decreased compared to the drug (ΔH_f : -126.9 J/g). This phenomenon could be attributed to the amorphous form of the drug in solid dispersion. The results are given in Figure 4.

X-ray diffractometry study

Numerous diffraction peaks of gliclazide observed at 2θ of 10.5, 15.0, 16.7, 17.0, 17.8, 18.1, 18.4, 20.8, 21.1, 22.0, and 26.2 indicated the presence of crystallinity. Pure PEG 6000 showed two peaks with highest intensity at

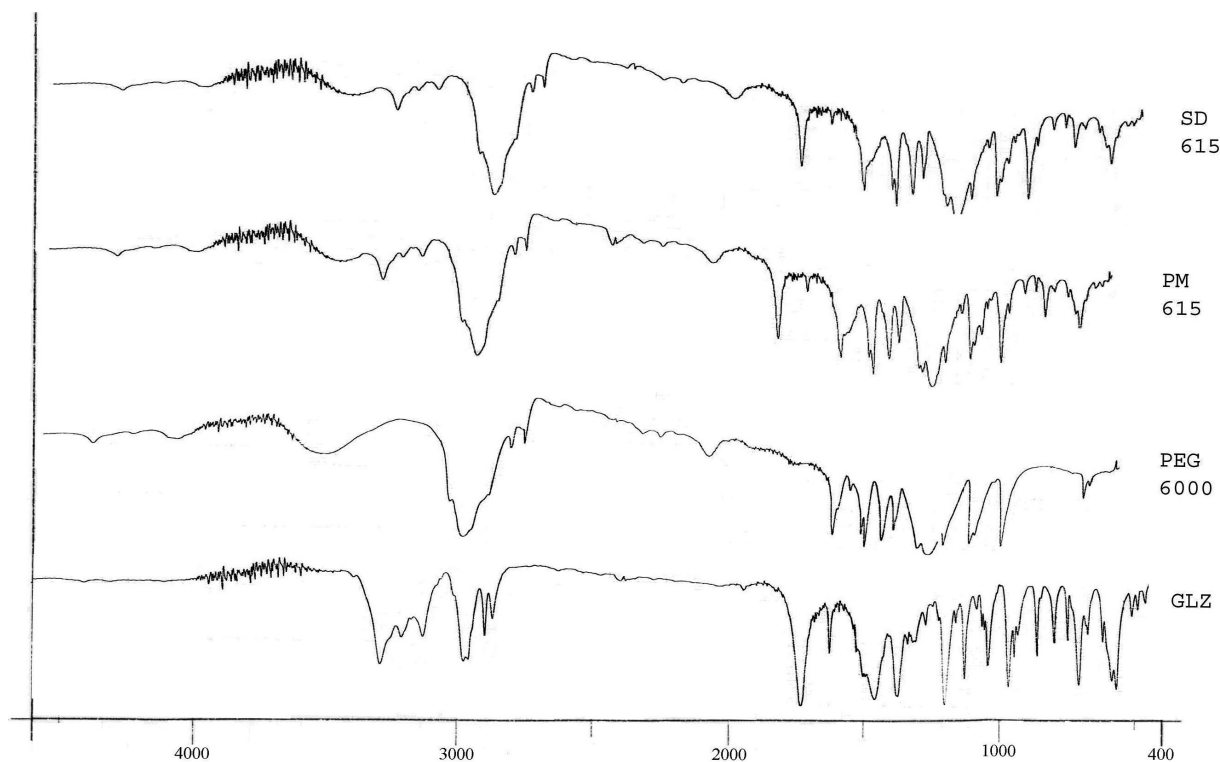


FIGURE 3 - FT-IR spectrum of Gliclazide, PEG 6000, their physical mixture and solid dispersion.

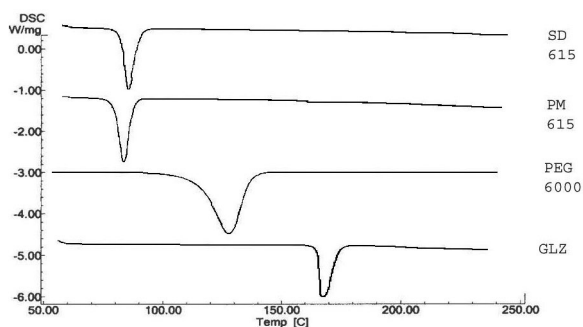


FIGURE 4 - DSC scans of Gliclazide, PEG 6000, their physical mixture and solid dispersion

2θ of 19.3 and 23.4, along with other peaks at 2θ of 13.7 and 27.4. The physical mixture showed peaks of PEG 6000 along with low intensity peaks of Gliclazide. The diffraction pattern of the solid dispersion showed peaks of Gliclazide of lower intensity. Some peaks shown by pure Gliclazide were also found to be absent, and the intensity of peaks observed was markedly reduced in the XRD spectrum of the solid dispersion. The results indicated that the drug in solid dispersion was present in an amorphous state. Results are given in Figure 5.

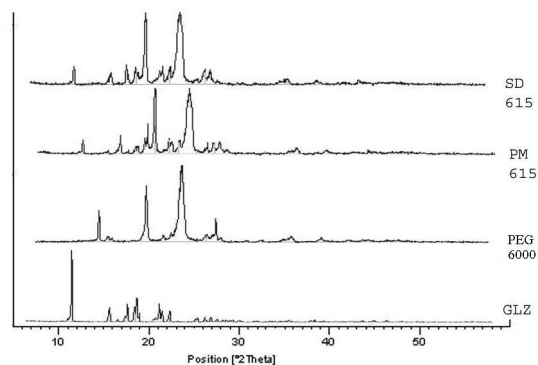


FIGURE 5 - XRD pattern of Gliclazide, PEG 6000, their physical mixture and solid dispersion

CONCLUSION

The approach of the present work was to characterize the solid dispersion of a Class II drug (Biopharmaceutic Classification System) and study its effect on dissolution. Infra-red spectroscopy studies indicated no interaction between drug and carrier. The drug was completely miscible in water-soluble carrier. The enthalpy of melting of the drug in solid dispersion was gradually decreased compared to pure drug, as revealed by DSC thermograms. The XRD study showed that the drug was present in amorphous form. The study showed increased dissolution rate

with the formation of solid dispersion. Solid dispersion performed better than the corresponding physical mixture while physical mixture performed better than the pure drug. The mechanisms responsible for this improvement could be a solubilization effect of the carrier, miscibility of the drug in melted carrier, and conversion of the drug from crystalline to amorphous form.

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