



FORMULATION AND CHARACTERIZATION OF SOLID DISPERSIONS CONTAINING GLIBENCLAMIDE

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Received: 19 April 2010, Revised and Accepted: 03 May 2010

ABSTRACT

Solid dispersions of Glibenclamide in preparations containing from 30 to 80% w/w Poloxamer 407 were prepared by the fusion method. The solubility of the drug substance either alone or in solid dispersions was determined in pH 1.2 and 4.5 media (extraction fluid NFXII, without enzyme). A large increase in the solubility was noted from 80% w/w Poloxamer 407 preparation. A wettability study performed by measuring the contact angle on tablets of either drug substance or Poloxamer 407 or solid dispersions, revealed a minimal contact angle for the 80% w/w Poloxamer 407 solid dispersion (eutectic composition of Glibenclamide/ Poloxamer 407 phase diagram). Dissolution kinetic analysis performed at pH 1.2 on all solid dispersions, on the physical mixtures containing 70 and 80% w/w Poloxamer 407, and on Glibenclamide alone, showed a maximum release rate (100%) for the solid dispersions containing 70 and 80% w/w Poloxamer 407. The dissolution rate of the physical mixtures was faster than that of the drug substance alone but remained; however, lower than that of the solid dispersions, at the same composition. It was also observed that the dissolution rate, at pH 1.2 of the 70% w/w Poloxamer 407 solid dispersion was practically pH independent, which was not the case for the drug substance alone. The latter solid dispersion showed a slowing down of the dissolution kinetics after 3 months storage at 50° C whereas no change in the dissolution rate was observed following storage for 12 months at 25° C.

Keywords: Solid dispersion, Dissolution, Glibenclamide, Poloxamer 407

INTRODUCTION

Glibenclamide is a second generation sulphonylureas oral hypoglycemic agent used for the management of diabetes mellitus. It causes hypoglycemia by stimulating release of insulin from pancreatic β cells and by increasing the sensitivity of peripheral tissue to insulin¹. It is rapidly and well absorbed but may have wide inter- and intra-individual variability. Micronized glibenclamide is better absorbed and more effective at a lower dose than non-micronized Glibenclamide². Glibenclamide is partially soluble in water. The formation of amorphous forms to increase drug solubility and the reduction of particle size to expand surface area for dissolution and decrease the interfacial tension with the aid of a water-soluble carrier are among the possible mechanisms for increasing dissolution rates and improving bioavailability of poor water-soluble drugs³. Several methods can be employed to obtain a solid dispersion to improve solubility and bioavailability, such as fusion^{4, 5, 6}, fusion-dissolution⁷, dissolution/ solvent removal⁸, and spray drying⁹, depending on the characteristics of the drug and carrier.

In vitro dissolution testing can provide useful information regarding development of new products and quality control of candidate formulations.

This work aims at demonstrating the influence of solid dispersions made from Poloxamer 407 on improving dissolution kinetics of Glibenclamide a second generation sulfonylurea, which has poor aqueous solubility in gastric medium. The therapeutic efficacy of a drug depends first of all on its absorption by the gastrointestinal tract. However, for a drug substance to be absorbed, it needs to be solubilized. Among the most widely used methods are micronisation, use of surfactants and the formation of solid dispersions to modify the dissolution kinetics of poorly soluble drugs, to improve their bioavailability.

MATERIALS AND METHODS

The following chemicals were obtained from commercial suppliers and used as received: Glibenclamide (Cadila pharmaceuticals Ltd, India), Poloxamer 407 (BASF, Mount Olive, NJ, USA), potassium dihydrogen phosphate (SDS Company, Mumbai, India), sodium hydroxide (SDS Company, Mumbai, India). All solvents were of high-performance liquid chromatography (HPLC) grade.

Preparation of the physical mixtures and solid dispersions of Glibenclamide

Glibenclamide and Poloxamer 407 were thoroughly blended by triturating in a mortar for 5 min then sifted on a 250 μ m opening sieve. Four blends were so prepared with percentages of Poloxamer 407 corresponding to 30, 50, 70 and 80%. The solid dispersions were prepared according to the fusion method⁴. Each formulation of solid dispersion containing 5 mg glibenclamide, the required amount of Poloxamer 407 was weighed into a suitable glass beaker and heated to 60-65°C for Poloxamer 407 using a hot plate until melted. The required amount of glibenclamide powder is added to the molten vehicle with continuous stirring using a small magnetic bar. After complete dispersion of glibenclamide, the molten system was cooled at 20° C.

In vitro dissolution study

The dissolution test was carried out, using a USP XXIII. Paddle apparatus which was linked to a multi-tubing peristaltic pump ensuring a 7 ml/min flow interfaced with a Gilford automatic spectrometer, type Response II. The dissolution media was the extraction fluid NFXIT without enzyme: pH 1.2 (NaCl, 2 g; HCl, 7 ml; purified water, q.s. 1000 ml). 900 ml of dissolution medium was used; the stirring speed was 100 rpm and the temperature of the media was maintained at 37 \pm 0.5° C. Dissolution kinetic analyses were carried out at pH 1.2 on the drug substance alone, on the physical mixtures and on the solid dispersions. At specified time intervals up to 120 minutes, 5-mL samples were withdrawn and replaced with 5 mL fresh phosphate buffer. Samples were then filtered through a 0.45 μ m syringe filter. Analysis of Glibenclamide was performed using an HPLC method and UV/VIS (Shimadzu UV-1800) with a mobile phase of 0.02 M ammonium acetate in [methanol (30): acetonitrile (30): water (40)] at a flow rate of 1.0 mL/minute¹⁰. The column used was 5 μ m, 12.5 cm \times 4 mm ID, C18 and the detection wavelength was 240 nm.

Storage study

Solid dispersions containing 70% w/w of Poloxamer 407 were poured into amber glass bottles and stored in a humidity oven under the different conditions: (i) 12 months at 25° C and 45% RH; (ii) 6 months at 35° C and 45% RH; (iii) 3 months at 50° C and 45% RH.

Differential scanning calorimetry studies

Thermal properties of the untreated drug and the prepared solid dispersion were analyzed by DSC (TA Instruments, USA, and Model: SDT 2960). The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 350 °C at a heating rate of 10 °C/ min, using nitrogen as blanket gas.

FT-IR Studies

FT-IR spectra of prepared Lyophilized solid dispersion were recorded on Shimadzu FT IR – 8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 – 4000 cm⁻¹ at spectral resolution of 2 cm⁻² and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

X-ray powder diffraction analysis

Crystallinity of the drug and the samples was determined using the Philips Analytical XRD (Model: PW 3710, Holland) with copper target. The conditions were: 40 kV voltages; 30 mA current; at room temperature. The samples were loaded on to the diffractometer and scanned over a range of 2^θ values from 10 to 80 ° at a scan rate of 0.05 °/min.

RESULTS AND CONCLUSION

Content Uniformity

The content uniformities of glibenclamide were found to be in the range of 95.6–99.4%, 96.4–100.6%, and 96.0–101.4%, for physical mixture, Solid dispersion, and Plain drug, respectively. These values are within the acceptable range set in the USP. This test will eliminate the effect of overloading the capsule with more than 5 mg glibenclamide, which would give false results later in either an in vitro or in vivo study of the capsules as compared with the 5 mg Plain drug.

In vitro dissolution study

The releases of glibenclamide from the three products were plotted as percent amount glibenclamide released vs. time in minutes as shown in Figure. 1. Each value of the presented curve is the mean of six experiments. As shown in Figure. 1, more than 50% of glibenclamide was dissolved out of solid dispersion in the first 30 minutes, and more than 35% was dissolved out of physical mixture,

while only 17% was dissolved out of Plain drug. These results showed that both Physical mixture and solid dispersion have faster dissolution than the Plain drug. Also, after 90 minutes both Physical mixture and solid dispersion showed more amounts dissolved of Glibenclamide than the Plain drug. The rank of dissolution of the three products is as follows: solid dispersion > Physical mixture > Plain drug.

The rate of release of glibenclamide from solid dispersion made of Poloxamer 407 system is higher than the Plain drug. This may be due to the solubilizing effect of the carrier, its prevention of aggregation and agglomeration effect, and its improvement of wettability and dispersibility of drug from solid dispersion, which can result in increasing the dissolution rate of glibenclamide^{7, 1}. (Figure 1)

X ray diffraction

The relative intensity of most of the lines corresponding to Glibenclamide in the solid dispersion was less as compared to that of Glibenclamide alone. No significant difference in the reflections corresponding to the solid dispersion spectra (at the initial time point and after 12, 6 and 3 months at 30°θ) was observed, therefore, there is no crystalline modification of the solid dispersion with time when submitted to our accelerated ageing conditions (Figure 2).

DSC Study

Figure 3 represents the DSC study of Fenofibrate and Fenofibrate solid dispersions. The corresponding melting point depressions, enthalpy of fusion and degree of crystallinity are shown in figure. A depression in melting point of Glibenclamide was found in solid dispersions, which indicates an interaction of Glibenclamide with carrier molecule Poloxamer 407. The DSC thermograph of Glibenclamide solid dispersion formulation shows only endothermic peak; the absence of exothermic re-crystallization peak may be attributed to interaction between drug and polymers. (Figure 3)

FT-IR Study

State of drug molecule with the different hydrophilic polymers and surfactants was determined using FT-IR. Figure 3 shows IR spectra of Glibenclamide and prepared solid dispersion. IR-spectra of Glibenclamide and solid dispersion are exactly same, and there is no shift of peaks after adsorption of drug onto polymer and surfactants surface; indicating that there is no change in chemical structure of drug after preparing it into melt granules. (Figure 4)

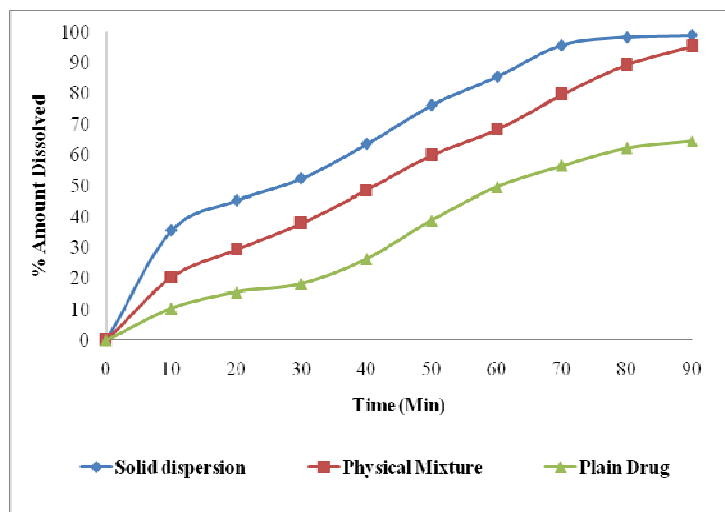


Fig. 1: Invitro dissolution profile of different glibenclamide formulations in solid dispersion, Physical mixture and Plain drug.

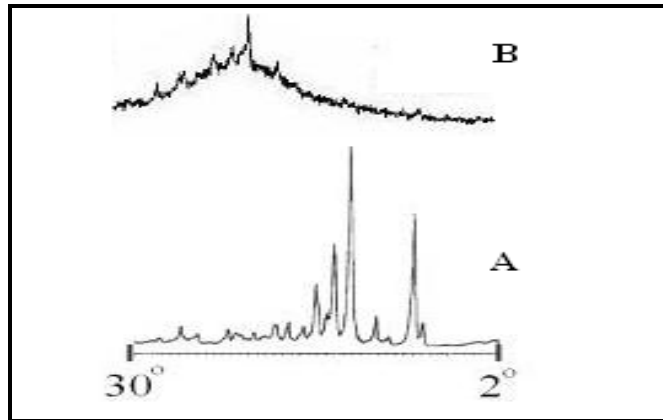


Fig. 2: Powder X-Ray Diffraction of (A) Plain drug (B) Solid dispersion with Poloxamer 407

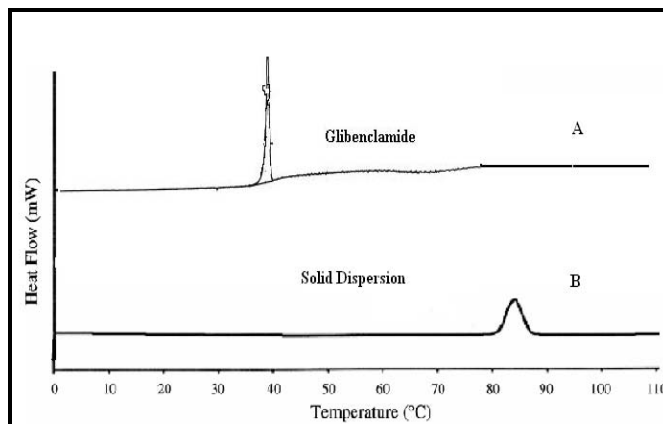


Fig. 3: DSC of (A) Plain drug (B) Solid dispersion with Poloxamer 407

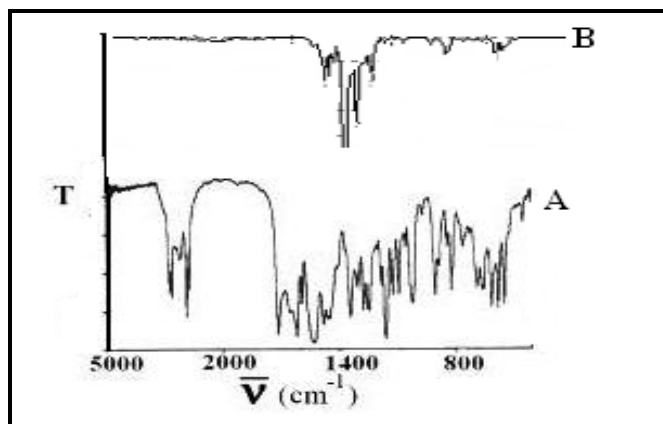


Fig. 4: FT-IR of (A) Plain drug (B) Solid Dispersion with Poloxamer 407

Storage study

Table 1 shows the results of storage of Solid dispersions containing 70% w/w of Poloxamer 407 were poured into amber glass bottles and stored in a humidity oven under the different conditions: (i) 12

months at 25° C and 45% RH; (ii) 6 months at 35° C and 45% RH; (iii) 3 months at 50° C and 45% RH. After storage in different conditions the content of drug was found in between 96.4–100.6% which was exactly in the range set in the USP. Therefore, there is no

effect of ageing in the content uniformity and stability of drug in the solid dispersion formulation and there is no degradation of drug compound during formulation of solid dispersion. (Table 1)

Table 1: % of drug present in the solid dispersion after storage at various conditions

Sr. No	Storage condition	% of drug present
1	25°C and 45% RH	98.35%
2	35°C and 45% RH	98.26%
3	50°C and 45% RH	97.86%

CONCLUSION

This present study showed that when glibenclamide was dispersed in a suitable water-soluble carrier Poloxamer 407 and its dissolution was enhanced compared with plain drug. The water soluble carrier may operate in the microenvironment (diffusion layer) immediately surrounding the drug particles in the early stage of dissolution, since the carrier completely dissolves in short time, enhancing the dissolution of drug. Therefore it is concluded that Poloxamer 407 was significantly improve the dissolution of glibenclamide in the solid dispersion system rather than physical mixtures of it.

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