RESEARCH ARTICLE

Enhancement of solubility and dissolution of glipizide by solid dispersion (kneading) technique

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Glipizide is a poorly water-soluble (BCS class II) antidiabetic drug. Due to the poor water solubility of this drug, its bioavailability is dissolution rate-limited. The purpose of this study was is to increase the solubility of Glipizide (GZ) in aqueous media by solid dispersion (SDs) technique with Poloxamer (PXM) 188 and Poloxamer (PXM) 407 by using the kneading method. The GZ-PXM solid dispersion system was characterized by dDifferential scanning calorimetry (DSC), X-ray powder diffraction (XRD) analysis, Fourier transform-infrared spectroscopy (FT-IR) and Scanning electron microscopy (SEM), and *in vitro* dissolution studies. No chemical interaction was found between GZ and PXM 188 or PXM 407. The results from DSC, XRD and SEM studies show that PXM 188 or PXM 407 inhibits the crystallization of GZ. The SDs prepared in this study were found to have better dissolution rates in comparisoncompared to intact GZ and physical mixture of PXM 188 or PXM 407 and GZ. It was found that the optimum weight ratio for drug: Carrier is 1:5 for PXM 188 and 1:6 for PXM 407.

Key words: *Glipizide, kneading, poloxamer, solid dispersion*

INTRODUCTION

Poorly water-soluble compounds have solubility- and dissolution-related bioavailability problems.[1] The absorption of such compounds when presented in the crystalline state to the gastrointestinal tract is typically dissolution rate-limited, and the dissolution rate is directly proportional to the solubility of the compound. The compounds are typically BCS class II or class IV compounds.[2] The rate and extent of absorption of class II compounds is highly dependent on the performance of the formulated product. These drugs can be successfully formulated for oral administration, with formulation design to ensure consistent bioavailability.[3]

Solid dispersions are one of the most promising strategies to improve the solubility and dissolution rate of poorly water-soluble drugs.[4] By reducing the drug particle size to the absolute minimum, and hencethereby improving drug wettability, bioavailability may can be significantly improved. They are usually presented as amorphous products. Recently, surfactants have been included to stabilize the formulations; thus avoidingthis avoids drug recrystallization, thereby and potentiating their solubility.[5,6]

The term "'solid dispersion'" has been utilized to describe a family of dosage forms, whereby the drug is dispersed in a biological inert matrix, usually with a viewin order to enhanceing the oral bioavailability. More specifically, Chiou and Regelman (1971), define these systems as "the dispersion of one or more active ingredient in an inert matrix at solid-state prepared by the melting (Fusion), solvent or melting solvent method".[7,8]

Glipizide is oral hypoglycemic agent that is, 100 times more potent than Tolbutamide, which is used for treatment of type II diabetes mellitus.[9] As per BP, It GZ is practically insoluble in water; because of its poor aqueous solubility (classified as BCS class II drug), conventional GZ dosage form show absorption problem, and its dissolutions is are considered to be a rate determining step in its absorption from gastrointestinal tract.[10,11] During high blood glucose level conditions, an antidiabetic drug should show quick and high oral bioavailability, which can be achieved by high aqueous solubility. Many hydrophilic excipients like PEG4000, PEG 6000, urea, Mannitol, PVP and poloxamers can be used to enhance the dissolution of drugs.[11,12]

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The aim of present study was is to enhance the aqueous solubility and oral bioavailability of GZ by solid dispersions technique using water soluble carriers like such as PXM 188 and PXM 407 by the kneading method.

MATERIALS AND METHODS

Glipizide was obtained from Glenmark Pharmaceuticals Ltd. Baddi as a gift sample; poloxamer 188 and Poloxamer 407 were obtained from Signet Chemicals Pvt. Ltd., Mumbai. All other chemicals used were of analytical grade.

Preparation of physical mixture

A Pphysical mixture (PM) of GZ with PXM 188 or PXM 407 in 1:1 ratio was prepared by thoroughly mixing the accurately weighed quantity of drug and carrier in by using glass mortar and pestle for 5 min. whichThis mixture was then subsequently passed through meshs no. 40 and stored in a dessicator for 48 h.

Preparation of solid dispersions[12,13]

The Kneading method (KM) was used for the preparation of solid dispersion (SD). Eight different drug: Carrier ratios (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 and 1:8) were used. GZ1 to GZ8 correspond to preparations containing PXM 188, and GZ9 to GZ16 correspond to preparations containing PXM 407. Glipizide and PXM 188 or 407 were weighed according to these weighed ratios. GZ and PXM were triturated using a small volume of methanol-water (1:1) solution to give obtain a thick paste, which was kneaded for 30 minutes and then dried at 40° C in an oven. The dried mass was then pulverized, passed through 30 mesh no. 30, stored in a vacuum desiccator (48 h) and passed through 60 mesh no. 60 before packaging in an airtight container.

Determination of drug content[14]

The drug content was calculated by dissolving SDs equivalent to 10 mg drug into a 100 ml volumetric flask and dissolved in minimum amount of methanol; and the volume was made up to the mark with using phosphate buffer (pH 7.4) and then filtered through 0.45-μ filter and assayed for drug content using UV double beam (Shimadzu) spectrophotometer at 275 nm. Three replicates were prepared, and the average drug contents were estimated in the prepared solid dispersion.

Actual drug content was calculated for all batches using the equation:

$$\text{Drug content } (\%) = \frac{G_{act}}{G_{sd}} \times 100$$

Where G*act* is Actual GZ Content in weighed quantity of solid dispersion, and G*sd* is theoretical amount of GZ in SD.

Phase solubility study

Phase solubility was performed as described by Higuchi and Connors. Excess amount of SDs were added to 25 ml phosphate buffer (pH 7.4) taken in a stoppered conical flasks, and mixture were shaken for 24 hrs in a rotary flask shaker. After shaking to achieve attain equilibrium, 2 ml aliquots were withdrawn at 1 hr intervals and filtered through Whatman filter paper (0.45 μ). The filtrate was analysed spectrophotometrically at 275 nm. Shaking was continued until three consecutive reading were the same.[15]

Fourier transform infra-red spectroscopy

FT-IR spectra were recorded on the sample prepared in KBr disks (2 mg sample in 200 mg KBr) using Shimadzu Fourier Transform Infra-Red spectrophotometer. The scanning range was 500-4000/cm with a resolution of 4/cm.

Differential scanning calorimetry analysis

The thermal analyses were carried out with a Sshimadzu DSC 60 (Japan). All accurately weighed samples were placed in sealed aluminum pans and heated at a rate of 100°C /min in the temperature range of 30-300°C temperature range under a nitrogen flow rate of 20 ml/min.

Powder X-ray diffraction

XRD patterns were recorded using Philips PW 1729 X-ray generator (Computer 1710). Powder X-ray diffraction patterns were traced for glipizide, various carriers and solid dispersions SDs. The position and intensities of diffraction peaks were considered for the identification and comparison of crystallinity of the drug or carrier.

Scanning electron microscopy

The external morphology of solid dispersions SDs was analyzed by using a scanning Electron Microscope (SEM). The morphology of pure drug, PM and SDs was examined under a scanning electron microscope SEM – JSM 6100 JEOL JAPAN.

In vitro drug release

Accurately weighed preparations equivalent to 10 mg of glipizide were added to 900 ml of dissolution media (7.4 phosphate buffer) contained in USP dissolution apparatus II (Paddle type) and stirred at a speed of 50 rpm at 37 ± 0.5°C. Five milliliter aliquots were withdrawn at 2, 4, 6, 8, 10, 15, 20, 25, 30 minutes and replaced by 5 ml of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution (if required) at 275 nm using UV-visible spectrophotometer against the blank. The dissolution of pure glipizide was done similarly. The release profile data was analyzed for cumulative percent dissolved at different time intervals and for dissolution efficiency at 6 and 10 minutes.[16]

RESULT AND DISCUSSION

All physical mixtures and solid dispersions SDs were easy to prepare and reproducible.

Drug content estimation

The drug content of GZ solid dispersion was found to be in range 97.24 ± 0.64 to 100.01 ± 0.01 and these values are

within the acceptable range. Low values of standard deviation in respect ofwith respect to drug content, as given in Table 1, indicating indicate uniform drug distribution in all the solid dispersionsSDs.

Solubility studies

The solubility profile of GZ was found to be 4.01 μg/ml, and drug release was found to be only 38.97% during *in vitro* dissolution study, suggesting a strong need to enhance the solubility and dissolution of GZ. Therefore, a solid dispersion technique using PXM 188 and PXM 407 was employed for solubility and dissolution enhancement of GZ in the present investigation. The improvement in solubility was observed with for all physical mixtures and solid dispersionsSDs. Increase in weight fraction of surface-active carrier resulted in an increase in the solubility of all solid dispersions. Maximum solubility enhancement was found in 1:8 ratio of GZ: PXM 188 prepared by the kneading method. Enhancement in saturation solubility was found to be in order of PXM 188 > PXM 407.

FT-IR spectroscopy

FT-IR spectra of GZ, PXM, physical mixture and SDs (1:5 and 1:6) are illustrated in Figure 1. Characteristic peaks of GZ at 3249/cm (aromatic C-H stretching), 3324/cm (N-H stretching), 1689/cm (C=O stretching), 1550/cm (C=C stretching) and 2939/cm (C-H aliphatic stretching) were observed.

Due to similarities in molecular structure, of PXM 188 and PXM 407 showed similar absorption bands, in which characteristic peaks of OH stretching (3000/cm), CH stretching (2400/cm), CH_2 bending (1400/cm), and R-O stretching (1200/cm) were observed. All physical mixtures and solid dispersions SDs showed peaks of GZ (pure) and carriers. As the carrier concentration was increased, the intensities of carrier peaks also increased while with the decrease in the intensities of the drug peaks decreased. These results indicate that there is no chemical interaction between drug and carrier when formed as solid dispersionSD.

Differential scanning calorimetry

The DSC thermograms of GZ, PXM 188, and PXM 407, and physical mixtures of GZ and with polymers, and SDs are shown in Figure 2. Pure GZ showed the sharp endotherm peak at 205°C, corresponding to melting point of GZ. Such melting peak with GZ-PXM 188 or GZ-PXM 407 physical mixture as well as SDs shifts the melting endotherm to lower temperatures for 201.12°C, 198.73°C, 190.83°C and 192.36°C for GZ- PXM 188 physical mixture, GZ-PXM 407 physical mixture, solid dispersionSD with PXM 188, and solid dispersionSD with PXM 188, respectively. No melting endotherm of solid dispersions corresponding to pure GZ was observed. It shows the peak at a lower temperature at about approximately 190.83°C; and hence, we can be conclude that GZ completely dissolved completely in the polymer below the melting temperature of crystalline GZ. The SDs with PXM 188 (GZ5) shows

Table 1: Evaluation of physical mixtures and solid dispersions SDs of glipizide

Formulation code	% Drug content*	Solubility mg/ml)	DE_6	DE_{10}
GZ PURE	-	0.004	26.73	36.11
PM 1	98.94 ± 0.12	0.012	31.72	36.95
PM 2	97.92 ± 0.82	0.011	33.73	41.57
GZ 1	99.44 ± 0.32	0.072	40.60	46.16
GZ 2	97.90 ± 0.14	0.123	41.39	46.17
GZ 3	97.62 ± 0. 76	0.183	41.65	46.42
GZ 4	98.93 ± 0.91	0.200	41.93	46.95
GZ 5	99.92 ± 0.79	0.240	47.68	48.70
GZ 6	99.84 ± 0.59	0.305	46.26	47.98
GZ 7	98.33 ± 0.03	0.322	45.34	47.04
GZ 8	97.92 ± 1.14	0.354	45.12	47.29
GZ 9	98.91 ± 0.91	0.124	34.13	42.79
GZ 10	99.11 ± 0.11	0.165	42.21	44.62
GZ 11	97.24 ± 0.64	0.210	34.53	43.42
GZ 12	97.96 ± 1.21	0.233	34.83	44.65
GZ 13	100.01 ± 0.01	0.279	34.44	40.37
GZ 14	99.43 ± 0.27	0.312	43.93	48.46
GZ 15	98.67 ± 0.73	0.318	40.24	42.83
GZ 16	97.59 ± 0.17	0.343	40.56	43.83

*Data are expressed as mean ± S.D. (n = 3)

the almost disappearance of that the drug peak almost disappears, suggesting two possibilities-, namely, amorphous precipitation of the drug and better solubilization in carrier.

X-ray diffraction

The XRD patterns of GZ, GZ-PXM 188 and GZ-PXM 407 physical mixture, and GZ-PXM 188 or GZ-PXM 407 SDs were are shown in Figure 3. In the X-ray differactogram of pure GZ, a sharp peak is presented at a diffraction angle (2θ), are presented and it confirms that the drug is in the crystalline form. Typical diffraction peaks of GZ in physical mixture indicating indicate the presence of free crystalline drugs, which were revealed by few broad peaks of low intensity which that emerged on the background of PXM as an amorphous carrier. The reduction in intensity and number of typical diffraction peaks of GZ in SD X-ray diffractogram suggests the reduction in the crystalline nature of drug.

Scanning electron microscopy

SEMScanning electron micrographs of pure glipizide, pure poloxamer PXM 188 and SDs (GZ5) are shown in Figure 4. Glipizide was present in a crystal form. Poloxamer 188 was present in globular form. The surface morphology of SDs indicates that glipizide was adsorbed into the PXM 188 and homogeneously dispersed into the polymer. SEM pictures images suggested that the individual surface properties of PXM 188 and GZ were lost during kneading and the formation of effective SD systems. These findings demonstrated that the drug was thoroughly mixed in the carriers with the a negligible loss of little crystallinity.

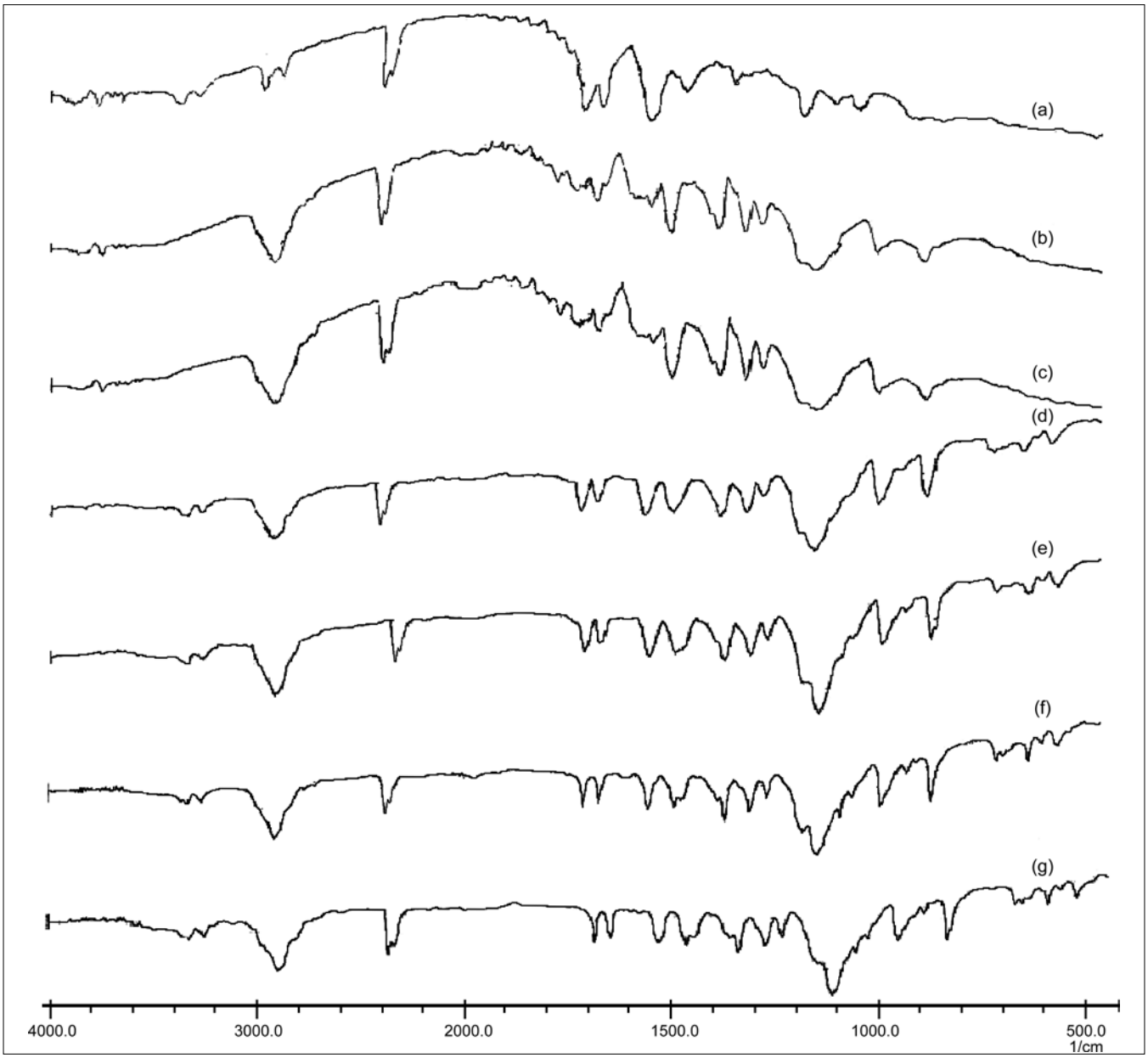

Figure 1: FT-IR of GZ, pure carriers, physical mixtures and different solid dispersion systems (a) GZ; (b) PXM 188; (c) PXM 407; (d) Physical mixture of GZ with PXM 188; (e) Physical mixture of GZ with PXM 407; (f) Solid dispersion with PXM 188; (g) Solid dispersion with PXM 407

***In vitro* dissolution studies**

The *in vitro* release profile of GZ from PXM 188 and PXM 407 solid dispersionsSDs (prepared by the kneading method) and physical mixture formulations are shown in Figures 5 and 6, and the graph for the comparison of the cumulative percent release is illustrated in Figure 7. According to observations, drug release was increased with increasing the concentration of both the grades of poloxamer (i.e., PXM 188 and PXM 407) up to a certain limit, and after thatthen it almost becomes constant. Drug release from SDs and physical mixtures was faster thaen that from the pure drug. The dissolution of drug from solid dispersionsSDs was found to be faster than that from physical mixtures; this may be due to the molecular and colloidal dispersion of drug in hydrophilic carrier matrix of poloxamers.

Several mechanisms may be possible formight have lead to the enhanced release of GZ in the solid dispersion formulation with the water soluble polymeric surfactants PXM 188 and PXM 407: The reduction of crystallinity of drug resulting in improved release (supported by X-ray diffraction); reduction of particle size to expand the surface area for dissolution solubilizing effect of PXM is likely to occur through the following mechanism. In the dry state, drug particles were in close contact or adhered to the polymer particles as a result of mixing (supported

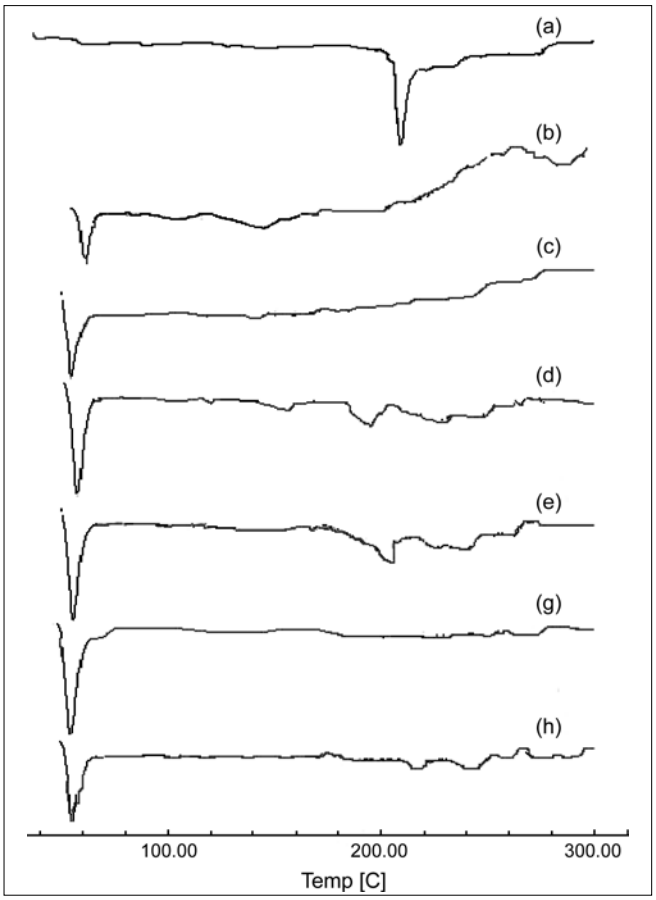

Figure 2: DSC thermograms of glipizide and solid dispersion with different carriers (a) GZ; (b) PXM 188; (c) PXM 407; (d) Physical mixture of GZ with PXM 188; (e) Physical mixture of GZ with PXM 407; (f) Solid dispersion with PXM 188; (g) Solid dispersion with PXM 407

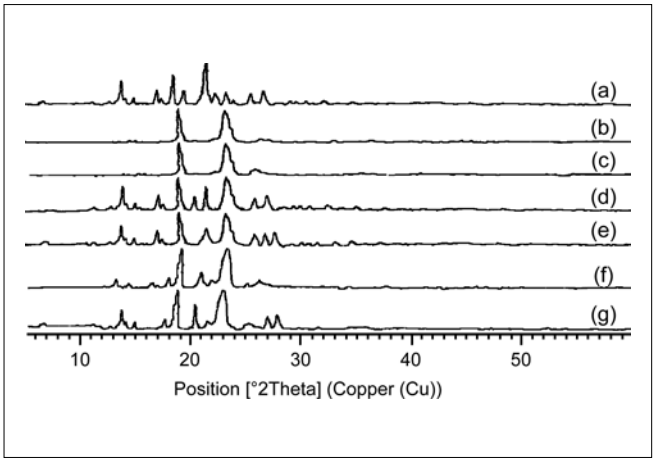

Figure 3: XRD patterns of GZ and solid dispersions with different carriers: (a) GZ; (b) PXM 188; (c) PXM 407; (d) Physical mixture of GZ with PXM 188; (e) Physical mixture of GZ with PXM 407; (f) Solid dispersion with PXM 188; (g) Solid dispersion with PXM 407

by SEM). When the mixture comes in contact with water, the polymer particles might have hydrated rapidly into the polymer solution, solubilizing the adjacent drug particles and subsequently releasing the drug into the medium.

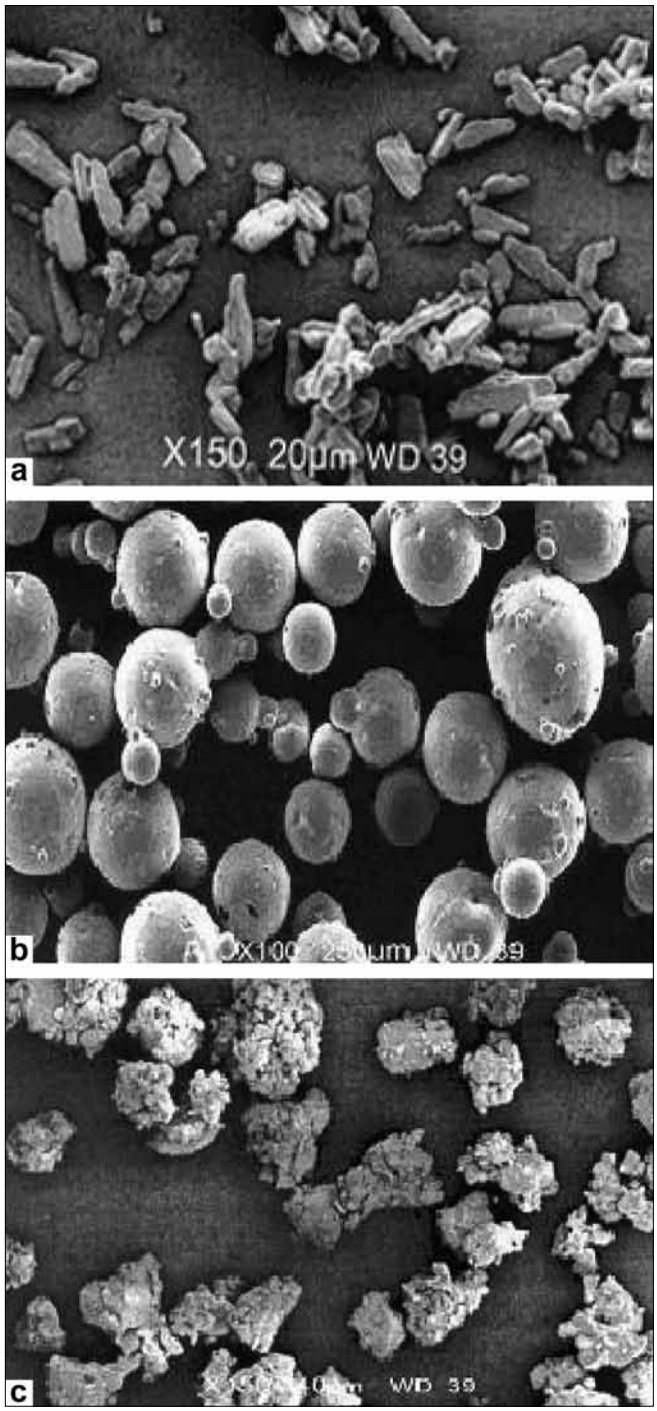

Figure 4: Scanning electron micrographs (SEM): (a) GZ; (b) PXM 188 and (c) GZ 5 solid dispersions

Reason for the increase of GZ release from solid dispersionSD with the increasing ratio of PXM 188 and PXM 407 is that at low concentrations, approximating those at which more conventional nonionic detergents form micelles, the poloxamer monomers are thought to form monomolecular micelles by through a change in configuration in solution. At higher concentrations, these monomolecular micelles associate to form aggregates of varying size, which have the ability to solubilize drugs to a larger extent.

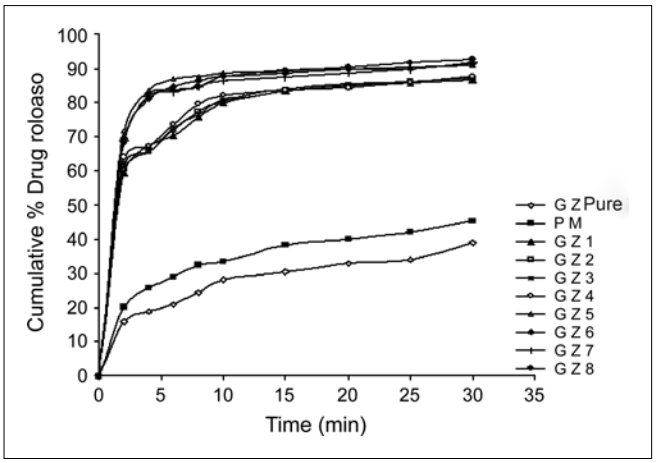

Figure 5: *In vitro* drug release of GZ in pH 7.4 phosphate buffer (pH 7.4) from solid dispersions and physical mixtures of GZ- PXM 188 systems

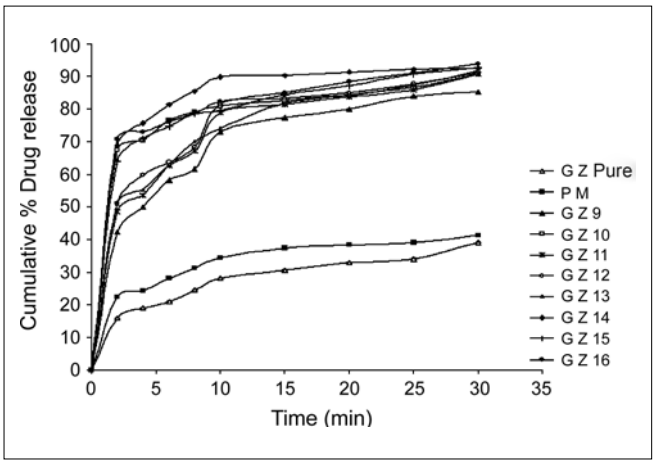

Figure 6: *In vitro* drug release of GZ in pH 7.4 phosphate buffer (pH 7.4) from solid dispersions and physical mixtures of GZ- PXM 407 systems

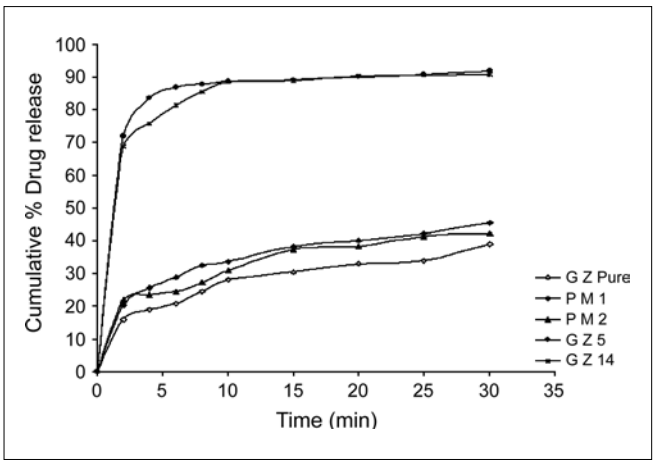

Figure 7: Comparative dissolution profiles of GZ in pH 7.4 phosphate buffer (pH 7.4) from physical mixtures and solid dispersions prepared using PXM 188 and PXM 407

Dissolution efficiency of pure GZ and all the solid dispersion formulations at 6 minutes and 10 minutes were calculated which is as shown in Table 1. The dissolution efficiency increased in all the formulations As with the increase in the dissolution time was increased from 6 to 10 minutes, the dissolution efficiency was increased in all the formulations. Among the formulations, GZ5 has shown maximum dissolution efficiencies of 47.68% and 48.70% at six minutes6 min (DE_6) and ten minutes10 min (DE_{10}) respectively.

In vitro drug release study indicates that PXM 188 showsn better dissolution efficiency than PXM 407. This behavior further could be explained further by the physico-chemical properties of these both poloxamers. PXM 188 is composed of more hydrophilic polyethylene glycol polymers than PXM 407. This composition leads to a higher Hydrophilic lipophilic balance (HLB) value and has a greater tendency to solubilize into the water thaen PXM 407.

CONCLUSION

The dissolution rate of glipizide was increased from solid dispersions prepared by the kneading technique by using poloxamers without any physical and chemical interaction. Solid dispersion showed more a greater increase in the dissolution of glipizide than from a physical mixture. Solid dispersion of Glipizide-PXM 188 showed faster release than from that of PXM 407 solid dispersions. Solid dispersion of Glipizide: PXM 188 (1:5) showed the maximum dissolution efficiency among all solid dispersions and physical mixtures.

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