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Research Article

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Formulation of glibenclamide solid dispersions by solvent evaporation technique

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ABSTRACT

The problem of variable oral bioavailability of Glibenclamide (GB) a poorly water-soluble oral hypoglycemic agent has been examined and out the different techniques available like micronization, co-solvent, change in dielectric constant, chemical modification of drug and complexation methods, this work investigated the possibility of developing solid dispersions of glibenclamide with different hydrophilic carriers, such as PEG 6000, PVP K30, sorbitol, mannitol, mannitol, citric acid and urea in different concentrations (1:2.5, 1:5, 1:7.5, 1:10, 1:12.5 and 1:15) by solvent evaporation method. Solid dispersions obtained from PEG6000 (1:5) gave the best dissolution profile, showing double quantity of drug dissolved in 15 min as compared to pure glibenclamide (control).The FTIR spectra depicted possible interaction of drug and carrier while DSC and X-ray diffraction pattern indicated that the dispersion had an amorphous nature. The product was found to be stable and no significant alteration in the dissolution efficiency was observed after storage for 90 days at 45 ±2°C.

Key Words: Glibenclamide, solid dispersions, polyethylene glycol, PVP K30, solvent evaporation, dissolution rate.

INTRODUCTION

The satisfactory dissolution within the gastrointestinal tract is necessary for good bioavailability. The dissolution is the limiting factor for bioavailability. The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development [1]. Increasing numbers of compounds that are investigated have low aqueous solubility and fall in class II of the biopharmaceutical classification system [2]. Pharmaceutical scientists are applying a wide range of formulation approaches to improve the dissolution rate of poorly soluble drugs. Particle size reduction, leading to increased surface area, is a very promising approach to enhance dissolution rate and, thus, the bioavailability of poorly water- soluble compounds [3-6].

When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs.

The present study is based on the object of improving the bioavailability of poorly water soluble anti-diabetic drug glibenclamide, a second generation sulfonylurea [7] by preparing solid dispersion with hydrophilic polymers.

EXPERIMENTAL SECTION

The drug Glibenclamide BP was obtained as gift sample from Wokhardt Ltd., PVP-K 30, PEG-6000, Urea and Citric Acid were purchased from CDH, while Mannitol and Sorbitol was obtained from local market. All the chemicals were of commercial purity grade.

Preparation of Solid Dispersion Systems [8]
Various drug: carrier proportions *viz.* 1:2.5, 1:5, 1:7.5, 1:10, 1:12.5 and 1:15 (S1 to S6) were used, the fine powder of drug and carrier was accurately weighed and blended together in required ratio with a glass pestle and mortar, transferred to a beaker and ethanol was used as solvent. The mixture was stirred till the drug and carrier dissolved. The solvent was removed by evaporation at 50 °C and quick chilled on ice cooled surface to obtain a solid dispersion.

Drug Content [9, 10]
Drug content of solid dispersions was determined by taking powder (equivalent to 5 mg of glibenclamide) dissolving and carrying out HPLC analysis on $C_{18,}$ 100mm x 4.6mm, 5 µm (Spherisorb ODS 1) with mobile phase acetonitrile: water (47: 53 v/v) pH adjusted to 3.0 at a flow rate of 1.5 ml/min, injection volume of 20 µl and detection was done at 300 nm. Content of Glibenclamide was calculated using the area of principal peak by single-point standardization technique.

In vitro Dissolution Studies [9, 10]
The in vitro dissolution studies were carried out in 1000 ml of phosphate buffer (pH 7.5) using Paddles type BP Apparatus II (Distek 2100C, Universal Instrument) at 75 rpm and 37 ± 0.5 ºC. Aliquots (5ml) were withdrawn at 3, 6, 9, 12, 15, 30, and 45 minutes and fresh media was replaced after each withdrawal and analyzed by HPLC method. The cumulative percent drug dissolved in 45 min was recorded andplotted against time.

Infrared Spectroscopy [11, 12]
The solid state interactions between the drug and carrier in solid dispersions can be studied by Infrared spectroscopy. The finely powdered pure drug or drug carrier dispersion system was intimately mixed with potassium bromide and compressed into transparent pellet. I.R. spectra were obtained on a Shimadzu FTIR 8700 at 4000 to 450cm^{-1}.

Differential Scanning Calorimetry [13]
DSC thermograms of pure glibenclamide and that of their selected solid dispersions were obtained on a TA Instruments 2910, Modulated DSC instrument. About 2.5 mg of sample was taken in one of the matched aluminium pan and heated at the rate of 10 °C/ min with a continuous purge of argon (45 ml/min).

Powder X-Ray Diffraction Study [14, 15]
The powdered sample was spread on a graticule and pressed such that powder does not fall on keeping it vertical. The graticule was placed in sample holder and exposed to CuKα - radiation (40 KV, 40 mA), 2θ = 10° to 80° at a scanning speed 0.5 sec/step and step size 0.02° 2θ on a Bruker D8, Advance – Rotating anode X-ray generator instrument.

Stability Studies [16]
The physical changes in the dosage form upon storage may result in the change of crystal form and increase or decrease in dissolution rate and disintegration times leading to considerable bioavailability problems. Also there can appear serious chemical instability of the active ingredient leading to potency and safety concerns. The stability studies were therefore carried out by storage of the sample (2.5 g) in tightly closed glass bottles at 45 ± 2°C at ambient humidity for 90 days. After every 15 days the physical observation was made and drug content was determined by the HPLC method.

The effect of ageing on dissolution profile was also assessed by one point dissolution measurement by determining per cent dissolution at 45 min for the sample stored at 45 ± 2°C for three months.

RESULTS AND DISCUSSION

The solid dispersions were characterized using IR spectroscopy, differential scanning calorimetry and powder X-ray diffraction.

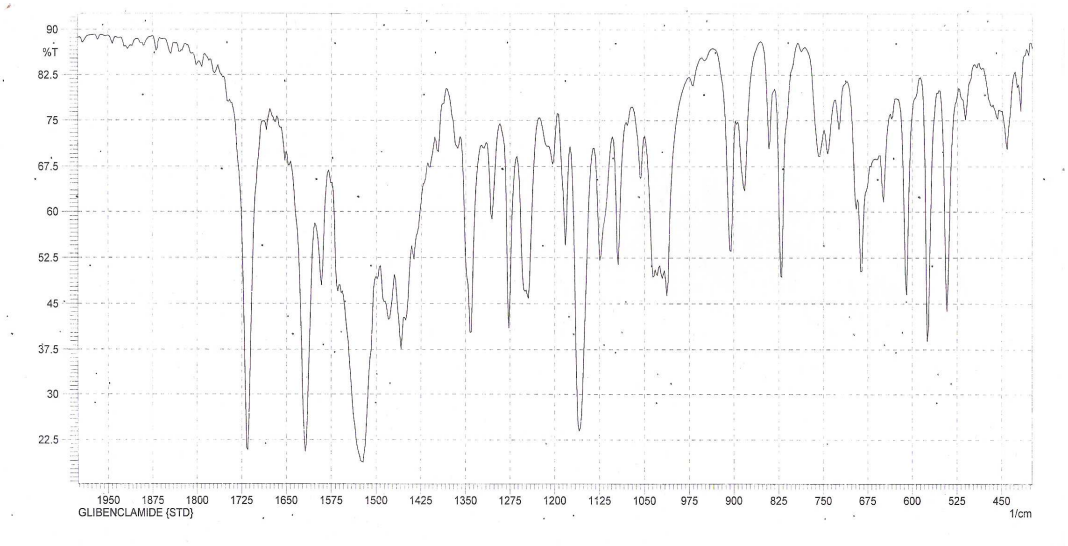
Table No.1: Dissolution (%) at 45 min, for solid dispersions prepared by solvent evaporation method

Drug/Carrier	Drug : Carrier Proportion/ Dissolution at 45 min					
	1:2.5	1:5	1:7.5	1:10	1:12.5	1:15
GB:PEG6000	GBP6S1 53.2%	GBP6S2 60.6%	GBP6S3 54.2%	GBP6S4 46.3%	GBP6S5 42.8%	GBP6S6 39.4%
GB:PVP K30	GBPVS1 40.8%	GBPVS2 45.3%	GBPVF3 50.1%	GBPVS4 58.0%	GBPVS5 53.2%	GBPVS6 53.0%
GB:MANNITOL	GBMNS1 43.3%	GBMNS2 45.1%	GBMNS3 44.3%	GBMNS4 46.2%	GBMNS5 45.6%	GBMNS6 45.0%
GB:SORBITOL	GBSRS1 44.1%	GBSRS2 45.0%	GBSRS3 45.1%	GBSRS4 46.2%	GBSRS5 45.0	GBSRS6 45.2%
GB:CITRIC ACID	GBCAS1 43.0%	GBCAS2 44.6%	GBCAS3 45.3%	GBCAS4 47.3%	GBCAS5 46.1%	GBCAS6 46.0%
GB:UREA	GBURS1 39.0%	GBURS2 40.0%	GBURS3 41.2%	GBURS4 42.8%	GBURS5 41.1%	GBURS6 41.0%

Table No.2: One point dissolution data (at 45 min.) of glibenclamide (control) and selected solid dispersions.

Name of Formulation	% drug dissolved in 45 min (after storage at 45 ± 2°C) at different time intervals (days)						
	0	**15**	**30**	**45**	**60**	**75**	**90**
GB(Control)	25.0	25.0	24.8	24.8	24.9	24.3	24.1
GBP6S2	60.6	60.5	60.5	60.3	60.3	60.2	59.8
GBPVS4	58.0	57.8	57.7	57.4	57.2	57.0	56.8
GBMNS4	46.2	46.0	45.6	45.6	45.3	45.0	44.1
GBSRS4	46.2	45.9	45.7	45.7	44.2	43.1	43.5
GBCAS4	47.3	47.0	46.9	46.6	46.1	45.8	45.1
GBURS4	42.8	42.6	42.1	41.6	41.3	41.1	40.3

Figure No.1: FTIR spectrum of pure glibenclamide-API



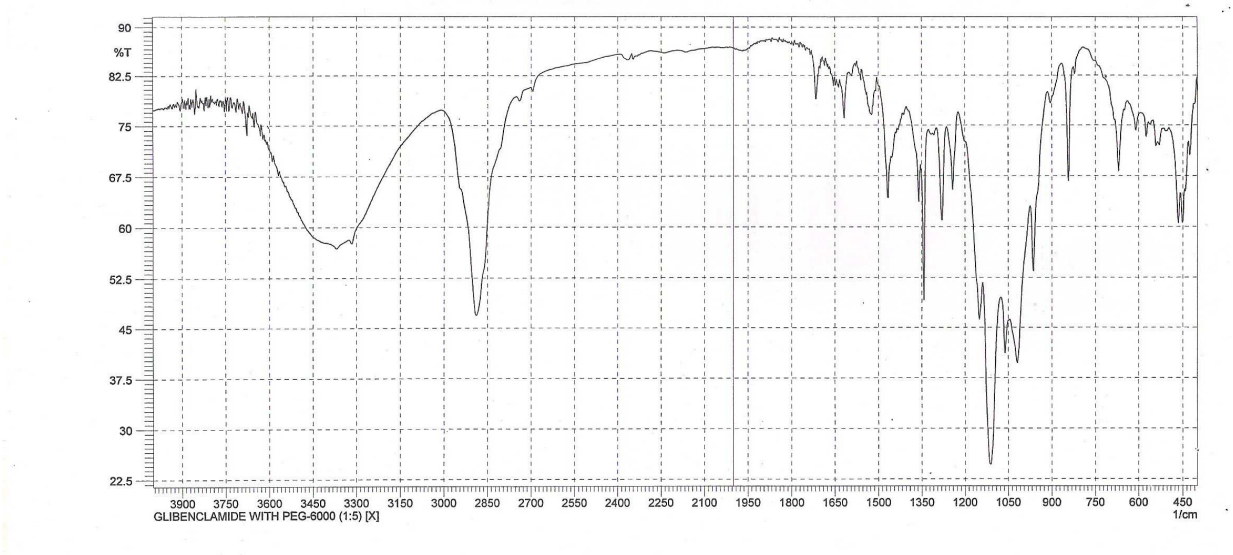
Drug Content

The solid dispersions of glibenclamide were prepared as a formulation approach to resolve the problem of poor aqueous solubility and consequent erratic bioavailability of this drug. Various hydrophilic carriers' *viz.* PEG 6000, PVPK30, sorbitol, citric acid, urea, and mannitol were used to prepare solid dispersions by solvent evaporation (co-precipitation) technique.

The drug content of each product was determined and found to be in the range of 97.0 to 100.1 % of the theoretical amount with low values of standard deviation indicating uniform distribution of drug in the solid dispersion products

prepared by various methods. ANOVA test ($p < 0.05$) indicated no significant difference between the percent drug content in different batches of solid dispersions prepared.

Figure No. 2: FTIR of solid dispersion of glibenclamide and PEG-6000



Dissolution Studies

Solid dispersion products prepared by using selected water soluble carriers with solvent evaporation methods showed enhancement of dissolution rate in comparison to pure drug as well as respective physical mixtures (1:10).
The data of single point cumulative dissolution at 45 min for the solid dispersion products showed that considerable enhancement in dissolution was observed in all cases but maximum enhancement was observed in solid dispersion of PEG 6000 (1:5) with respect to pure GB(Table 1). The results underline the importance of solid dispersion preparation and the influence of drug-carrier ratio on their dissolution rate. This suggests that formation of solid solution of drug in carrier or interaction at solid-state structure level probably through hydrogen bonding, dipole-dipole or induced dipole-dipole etc., may be responsible for improvement in the release rate from solid dispersions [17-20].

Characterization Studies

The IR spectrum of glibenclamide (standard) exhibited characteristics sharp peaks while in case of solid dispersion with PEG 6000 the peaks at 3313.5 & 3367.5 (N-H stretching) shifted to 3315.41 & 3369.41, and peak at 1157.2 has disappeared indicating a strong interaction between glibenclamide and PEG 6000 at molecular level. While all other major peaks of glibenclamide are present in the solid dispersions.

The DSC thermogram of solid dispersion product of glibenclamide and PEG 6000 showed only one peak at 62.94°C corresponding to melting of PEG 6000 while the melting endotherm of glibenclamide seen at 178°C in thermogram of pure glibenclamide was completely vanished indicating that either the glibenclamide existed in solid solution form or as a complex with PEG 6000.

Major peaks displayed in XRD pattern of pure glibenclamide disappeared in XRD pattern of glibenclamide-PEG6000 solid dispersion indicating existence of amorphous solid state of glibenclamide in the solid dispersion of glibenclamide-PEG 6000.While all the major peaks of glibenclamide are present in admixture of glibenclamide and PEG 6000.

Stability Studies of Glibenclamide and Selected Solid Dispersions

The degradation processes generally followed first order rate kinetics. The assay of solid dispersion sample (%drug remaining) after storage at 45±2^{o}C for 90 days, indicates that the formulations were fairly stable.

The solid dispersions of glibenclamide in polymeric hydrophilic matrices may show reduction in the dissolution rate upon aging [21]. It was assessed by single point dissolution study at 45 min after storage at 45 ± 2°C for 90 days (Table 2). The results indicate that the formulations were fairly stable and maintained their efficiency in terms of dissolution.
So, on the basis of dissolution study and stability study, solid dispersions prepared with PEG 6000 by using drug polymer ratio 1:5 (GBP6S2) exhibited the best performance, giving a percent of drug dissolved after 15 min more than 2 times higher than that from the pure glibenclamide.

Finally, the importance of selecting a suitable carrier and controlling factors such as drug-to-carrier ratio, and solid dispersion particle size, in order to maximize the drug dissolution rate improvement, has been pointed out.

Figure No.3: DSC curves of pure glibenclamide (GB), PEG6000 and solid dispersions (1:5 w/w ratios).

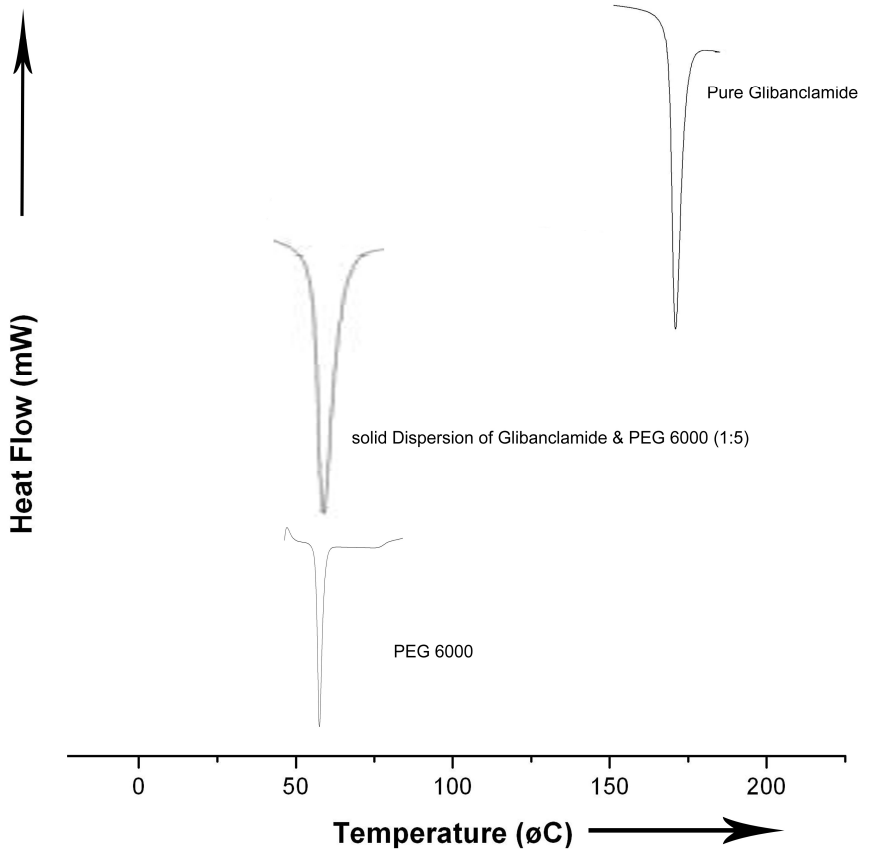


Figure No.4: Powder X-ray diffraction patterns of pure glibenclamide (GB), PEG6000, and solid dispersions (1:5 w/w ratios).

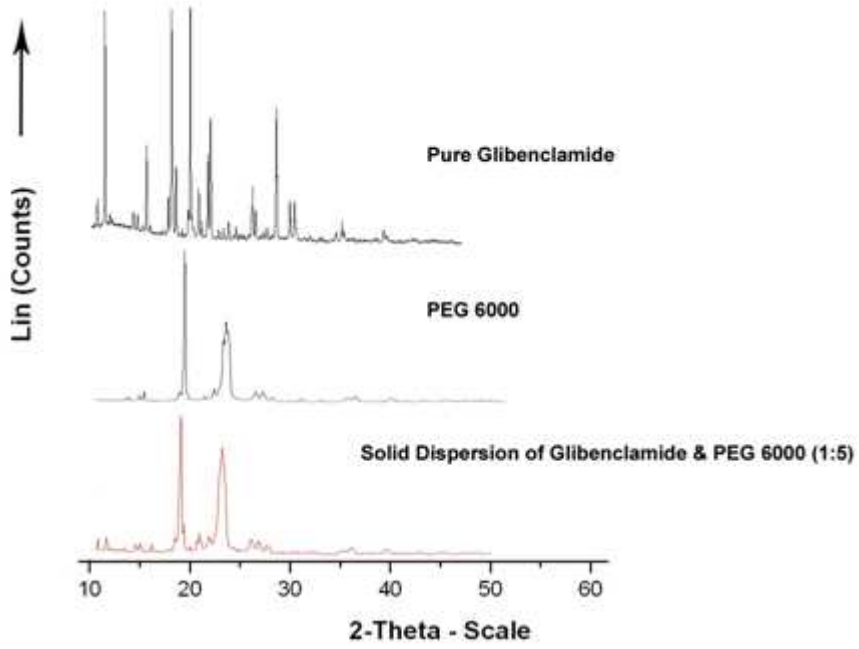


Figure No.5: Dissolution curves of glibenclamide (control) and physical mixtures (PM) of glibenclamide with different carriers (Ratio 1:10)

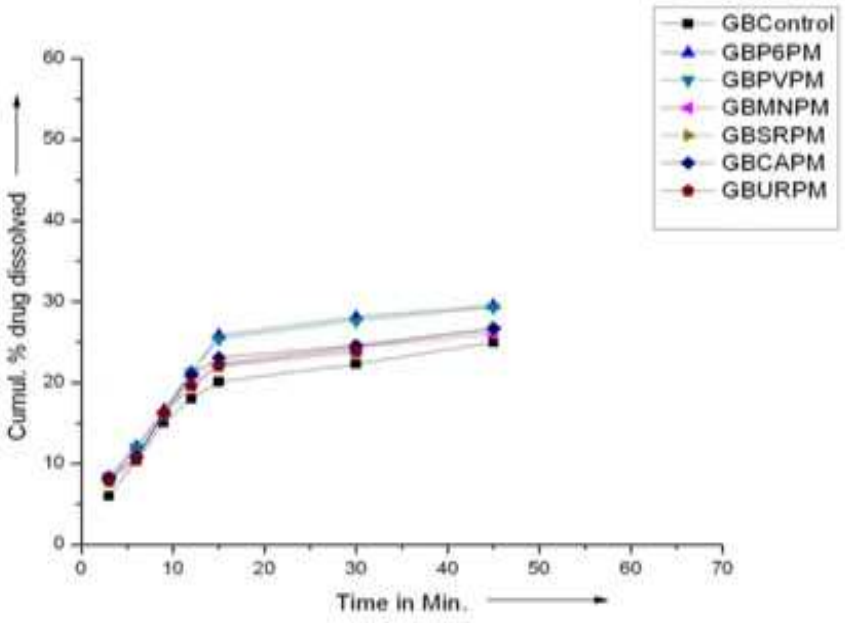
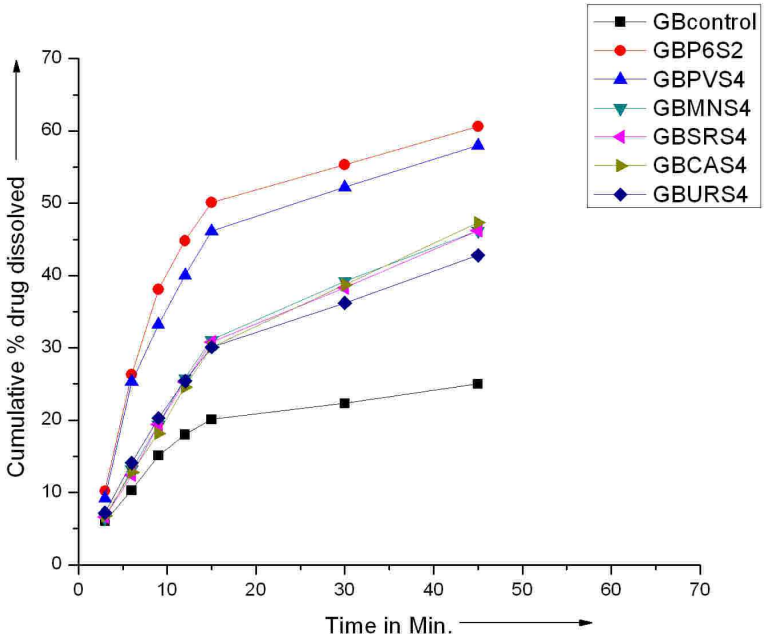


Figure No.6: Dissolution curves of pure glibenclamide (control) and best solid dispersion products of each carrier.



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