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Research Paper

Comparative Studies on Dissolution Enhancement of Glibenclamide in Solid Dispersions Made by Different Techniques

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Problems of poor and erratic bioavailability are associated with oral administration of Glibenclamide (GB) - a poorly water-soluble oral hypoglycemic agent. The paper deals with development of Solid dispersion formulations of GB to improve dissolution, using different water soluble hydrophilic carriers, such as PEG 6000, PVP K30, Mannitol, Sorbitol, Citric Acid and Urea, in different concentrations, by solvent evaporation and fusion methods. Phase analysis was performed by X-ray powder diffraction while infrared spectroscopy and differential scanning calorimetry (DSC) were used to study the nature of solid state interactions in solid dispersions. The X-ray diffraction studies indicated that the GB in dispersion had an amorphous nature further confirmed by missing melting endotherm of GB in the DSC thermograms of dispersions. No chemical interaction between the drug and carriers was observed. The effects of several variables related to solid dispersion preparation such as, solvent evaporation or fusion technique, drug-to-carrier ratio and type of carrier, on drug dissolution behaviour were investigated. Solid dispersions obtained from PEG 6000 (1:5) and PVPK 30 (1:10) by solvent evaporation technique showed 2 times higher dissolution at 15 min as against the pure glibenclamide (control).

Key word: Glibenclamide, solid dispersions, polyethylene glycol, PVP K30, mannitol, citric acid, sorbitol, urea, solvent evaporation, fusion, dissolution rate

INTRODUCTION

Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility properties. For poorly water-soluble drugs, the rate-determining step in the absorption process is usually dissolution of the drug[1]. Increased numbers of compounds that the investigation have low aqueous solubility and fall in class II of the biopharmaceutical classification system[2]. The dissolution is the limiting factor for bioavailability.

Enhancement of oral bioavailability of water insoluble drugs remains one of the most challenging of the drug development. Particle size reduction, leading to increased surface area, is a very promising approach to enhance dissolution rate and, thus, the bioavailability of poorly water-

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soluble compound[3-5]. According to the Noyes-Whitney equation, the rate of dissolution (dc/dt) depends on the effective surface area (A) of the drug particles[6].

The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by co-solvents, and particle size reduction[7]. Studies revealed that drugs in solid dispersion need not necessarily exit in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion[8-10]. 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.

Glibenclamide is a second generation sulfonylurea used in the treatment of noninsulin dependent diabetes mellitus.

Glibenclamide is practically insoluble in water leads to poor dissolution rate and subsequent decrease of its gastrointestinal absorption[11]. The aim of the present work was to address the problem of poor aqueous solubility of glibenclamide by using hydrophilic polymers as a carrier and formulate solid dispersions by applying different techniques.

MATERIALS AND METHODS

Glibenclamide BP was procured from Laboratori Guidotti. -Italy, PVP-K 30 from BASF, Germany; PEG-6000 from India Glycols Ltd, Urea from Universal Lab. Mumbai, Citric Acid from Rankem (RFCL Ltd, New Delhi), Mannitol and Sorbitol from RDPL, Jaipur and Ethanol from JPW, Jaipur as a gift sample. All the chemicals were of commercial purity grade.

Preparation of solid dispersion systems by solvent evaporation method[12]

Solid dispersions of glibenclamide (GB) were prepared in water soluble carriers like PEG 6000 (P6), sorbitol (SR), mannitol (MN), PVP K30 (PV), urea (UR) and citric acid (CA) by solvent evaporation method (S). Ethanol was chosen as solvent for evaporation method as both, the drug and carriers are soluble in it. 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 and was stirred with a glass rod till the drug and carrier dissolved in the ethanol. The solvent was evaporated by heating at 50°C on a thermostatically controlled hot plate cum magnetic stirrer with continuous

stirring. The co-precipitate was then powdered, uniformly mixed and sieved to 100 mesh fraction and stored in air-tight containers.

Preparation of solid dispersion systems by fusion method[13-15]

Solid dispersions of glibenclamide (GB) were prepared in water soluble carriers like PEG 6000 (P6), sorbitol (SR), mannitol (MN), PVP K30 (PV), urea (UR) and citric acid (CA) by fusion method (F). Various drug: carrier proportions *viz.* 1:2.5, 1:5, 1:7.5, 1:10, 1:12.5 and 1:15 (F1 to F6) were used.

The required weight of drug and carrier was blended together and transferred into porcelain dish and heated over an oil-bath at the melting point of the respective carrier (PEG 6000- 58-60° C, sorbitol-95-110° C, PVP K30-170^{o} C, citric acid-153^{o} C, mannitol-168^{o} C and urea-135^{o} C). The carriers were miscible with the drug in the melted state in all cases. The molten mass was immediately congealed. The hardened and dried mass was pulverized with a glass pestle and mortar and sieved to 100 mesh fractions and stored in air-tight containers.

Infrared Spectroscopy

Infrared spectroscopy was used to study solid state interactions between the drug and carrier in solid dispersions prepared by fusion and solvent evaporation methods. The sample was intimately mixed and ground with potassium bromide and was compressed into pellet. I.R. spectra were obtained on a Shimadzu FTIR 8700 at 4000 to 450 cm^{-1} [16, 17].

Differential scanning calorimetry

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 aluminum pan and heated at the rate of 10°C / min with a continuous purge of argon (45 ml/min) [18].

Powder X-ray diffraction study

Powder X-ray diffraction (XRD) spectra of pure glibenclamide, physical admixture of drug and polymer and that of their selected solid dispersions were obtained on a Bruker D8, Advance – Rotating anode X-ray generator instrument. 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.

Drug content determination[19,20]

Drug content of solid dispersions of glibenclamide prepared by different methods was determined as per BP-2005 using

powder of solid dispersions (equivalent to 5 mg of glibenclamide) was dissolved methanol and subjected to HPLC analysis using a stainless steel column (100 mm x 4.6 mm) packed with stationary phase C_{18} on 5 µm spherical particles (Spherisorb ODS 1) with mobile phase acetonitrile: water 47:53 v/v and 1.36 % w/v potassium dihydrogen ortho phosphate, 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.

In vitro dissolution rate studies[19, 20]

The in-vitro dissolution rate of pure glibenclamide sample (control), solid dispersion systems and physical mixtures of drug-carrier equivalent to 5 mg of glibenclamide were determined in 1000 ml of phosphate buffer solution of pH 7.5 using paddles type BP Apparatus II (Distek 2100C, Universal Instrument). The paddle speed was adjusted to 75 rpm and the dissolution medium was maintained at 37 ± 0.5 ºC. 5ml samples were withdrawn at 3, 6, 9, 12, 15, 30, and 45minutes and equal volume of fresh fluid was replaced after each withdrawal and analyzed for drug dissolved by the HPLC method. The cumulative percent drug dissolved was recorded and plotted against time.

Diffusion studies[21-25]

The solid dispersions of glibenclamide showing best dissolution in each category were subjected to diffusion studies. A dialysis membrane tubing 70, DM 003, MWCO 5000-7000, thickness 25 µm, average flat width 29.31 mm, average diameter 13.5 mm and capacity 2.41 ml/ cm (Himedia, Mumbai) was used in the diffusion study. 100 ml of mucosal fluid (PBS pH 7.4, containing 5 mg of drug or solid dispersion equivalent to 5 mg of drug) was taken and the temperature of the mucosal fluid was maintained at 37 + 0.5 °C, stirred gently with a magnetic stirrer at a constant slow speed. Five ml of serosal fluid (PBS pH 7.4, devoid of drug) was then placed into the open side of glass tube (serosal compartment).

The entire serosal fluid (5 ml) was withdrawn after diffusion for 3 minutes and 5 ml of fresh fluid was used to rinse the serosal side of the membrane and the rinsing was mixed with the withdrawn sample. Immediately after sampling and rinsing, fresh serosal fluid (5 ml) was placed in the serosal compartment and diffusion continued for next 3 minutes. The serosal compartment was sampled and rinsed every time at 3 min, 6 min, 9 min, 12 min, 15 min, 30 min and 45 minutes.

The samples of serosal fluid containing the diffused drug were analysed by the HPLC method and percent of drug diffused at

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different time intervals in each case was recorded.

Stability studies of solid dispersions [26-28]

Drugs and their selected solid dispersions (2.5 g) were stored separately in tightly closed glass bottles in an oven at 45 ± 2°C at ambient humidity.

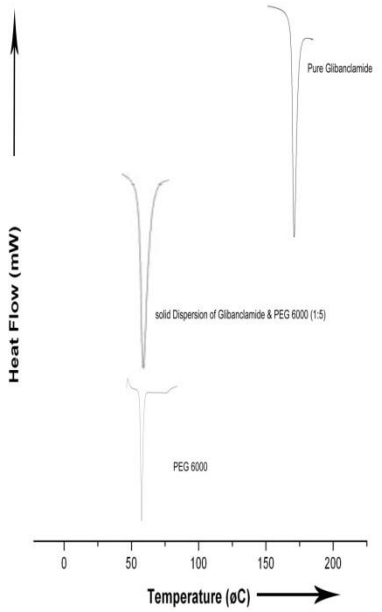

Fig.1: DSC Thermogram of Pure GB, PEG 6000 and SD (1:5)

An accurately weighed portion of each sample equivalent to 5 mg of drug was withdrawn from the sample kept at 45 °C, after every 15 days and drug content was determined by HPLC method. The per cent drug remaining after storage for up to three months at 45 ± 2°C temperature was determined.

RESULTS AND DISCUSSION

The solid dispersions were characterized using IR spectroscopy, differential scanning calorimetry and powder X-ray diffraction. IR spectra of solid dispersions of glibenclamide with PEG 6000 indicate a strong interaction between glibenclamide and PEG 6000 at molecular level. Further, the DSC thermogram depicted that glibenclamide existed in solid solution form or as a complex with PEG 6000 as melting endotherm of glibenclamide (178°C) completely vanished.

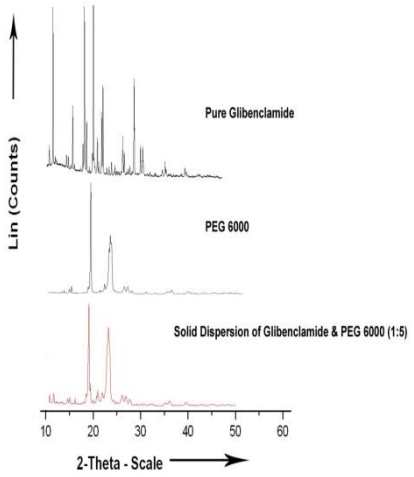

Fig.2: XRD Diffractogram of Pure GB, PEG 6000 and SD (1:5)

XRD diffractogram shows no major peak of pure crystalline substance indicating existence of amorphous state of glibenclamide (Fig. 1 & 2).

The IR of solid dispersion with PVP K30 shows a strong interaction between glibenclamide and PVP K30. In DSC, the melting endotherm of glibenclamide disappeared and crystal peaks of XRD pattern also vanished indicating of

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amorphous form of glibenclamide in the solid dispersion of glibenclamide-PVP K30 (Fig. 3 & 4).

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

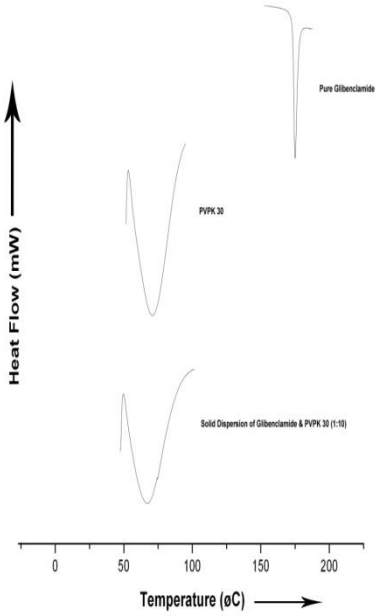

Fig.3: DSC Thermogram of Pure GB, PVP K30 and SD (1:10)

various methods. ANOVA test ($p < 0.05$) indicated no significant difference between the percent drug content in different batches of solid dispersions prepared.The diffusion studies of selected solid dispersions exhibited that the permeation of released drugs from solid dispersions was best (12.6%) for GBP6S2 as compared to pure GB (5.1%).

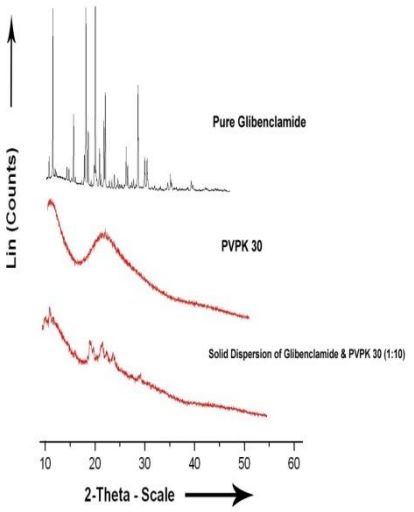

Fig. 4: XRD Diffractogram of Pure GB, PVP K30 and SD (1:10)

The dissolution profiles of solid dispersion products exhibited considerable enhancement in dissolution rate but maximum improvement was achieved for GBP6S2 (255%) and GBPVS4 (245%). These results showed the importance of using drug solid dispersions and the influence of drug–carrier ratio and their preparation method on their effectiveness. This suggests that formation of solid solution of drug in carrier or interaction at solid-state structure level probably through hydrogen bonding, dipole-dipole, induced dipole-dipole, non-dipole, complexation etc., may be responsible for improvement in the release from solid dispersions. Even the reduction in particle size of drug in case of co-precipitation with carrier or

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conversion of crystalline form of drug to amorphous form, improved wettability and solubilization effects associated with the carrier are considered the main ones responsible for enhanced dissolution of this poorly water soluble drug [29].

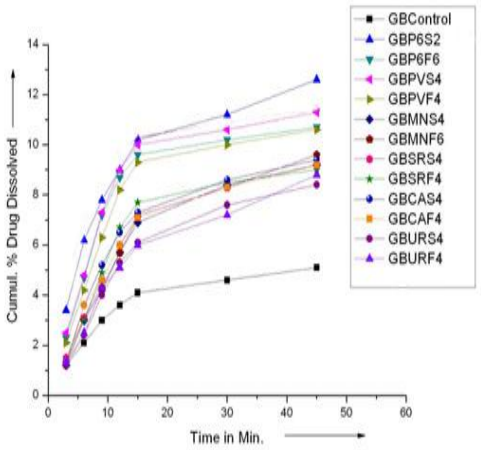

Fig.5: Diffusion Profile of Glibenclamide (control) and Selected Solid Dispersions

Stability data (%drug remaining after storage at 45±2°C for 90 days) indicates that the formulations were fairly stable. It is well known that drugs formulated in matrices can present a decrease in the solid dispersions in polymeric hydrophilic dissolution properties upon aging[30]. The change in per cent dissolution in 45 min after storage of solid dispersions for three months at 45 ± 2°C was observed. The results indicate that the formulations were fairly stable and maintained their efficiency in terms of dissolution.

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, mannitol, citric acid and urea were used to prepare solid dispersions by fusion and solvent evaporation (co-precipitation) techniques. Various solid dispersion products prepared by solvent evaporation and fusion methods showed enhancement of dissolution rate in comparison to pure drug as well as respective physical mixtures (1:10).

So, on the basis of dissolution study, diffusion study and stability study, solid dispersions prepared with PEG 6000 by using drug polymer ratio 1:5 by solvent evaporation method (GBP6S2) and PVP K30 by using drug polymer ratio 1:10 by solvent evaporation method (GBPVS4)

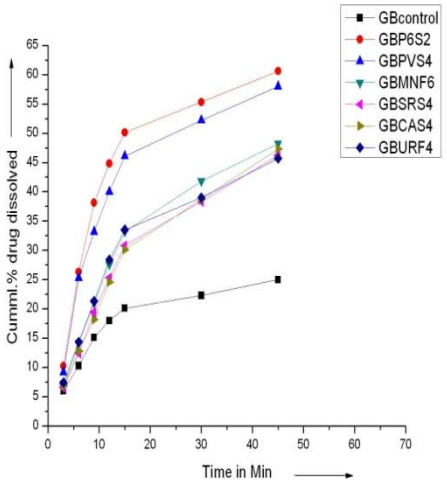

Fig. 6: Dissolution Profile of Glibenclamide (Control) and Selected Solid Dispersions

were found to exhibit the best performance, giving 2 times higher percent of drug dissolved in 15 min than that from the pure glibenclamide.

Finally, the importance of selecting a suitable carrier and controlling factors such as method of solid dispersion preparation, and drug-to-carrier ratio, and solid dispersion particle size, in order to maximize the drug dissolution rate improvement, has been pointed out. Based on the results of above investigations it can be concluded that the formulation of glibenclamide into solid dispersion with PEG6000 and PVP K30 carriers leads to particle size reduction. The molecular interaction existed in solid dispersions made from PEG6000 and PVP K30. These factors individually or in combination might have contributed for faster dissolution of glibenclamide from solid dispersions.

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