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Research Article

Formulation and Evaluation of Glimepiride Solid Dispersion Tablets for Their Solubility Enhancement

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ABSTRACT

Glimepiride (GMP) is poorly water soluble drug, so solubility is the main constraint for its oral bioavailability. The objective of the research project is to enhance of the solubility of Glimepiride by using solid dispersion technique. The polymers used were Poloxamer 188 and Poloxamer 407 and solid dispersions were prepared by kneading method. The solubility study was carried out to study the effect of polymers on solubility of Glimepiride. The prepared solid dispersions were characterized by In-vitro solubility Study, %Drug content; Fourier transforms spectroscopy (FTIR), In vitro drug dissolution to identify the physicochemical interaction between drug and excipients. The dissolution studies of solid dispersion were performed by using USP II apparatus. The solid dispersion prepared with Poloxamer 188 showed better drug release as compared to solid dispersion prepared with Poloxamer 407. The drug release profile of F5 batch with Poloxamer 188 was 98.20±0.19 in 60 min. and drug release profile of F11 batch with Poloxamer 407 was 97.39±0.18 in 60 min. in pH 7.4. The results of dissolution studies and stability study the kneading method prepared solid dispersion by using Poloxamer 188 (Batch F5) was selected for tablet formulation. Tablet formulations were prepared by direct compression technique and developed tablet formulations were evaluated for various pharmaceutical characteristics viz. hardness, % friability, weight variation, drug content, in-vitro dissolution profiles. Thus Results showed that the solid dispersion technique by using poloxamer successfully used for enhancing the solubility of Glimepiride.

Keywords: Glimepiride, poloxamer 188, poloxamer 407, solid dispersions, solid dispersion tablets.

1. INTRODUCTION

More than 40 percent of the drug coming from high-throughput screening are poorly soluble in water compounds with poor Solubility are increasingly posing challenges in the development of new drugs, since a large number of drugs coming directly from synthesis or from high throughput screening have a very poor solubility. It is well known that drug efficacy can be severely limited by poor aqueous solubility, leading to low dissolution rate and thus results in low absorption in the gastrointestinal tract after oral administration hence comprising oral bioavaibility. The ability to increase aqueous solubility is thus a valuable aid to increase the efficacy for certain drugs [1].

The Biopharmaceutical Classification system divides drugs into four classes depending on *in vitro* and *in vivo* permeability data [2]. Four classes of compound can be distinguished: I (high solubility, high permeability), II (low solubility, high permeability), III (high solubility, low permeability) and IV (low solubility and low permeability). Class I compounds are typical examples for waiving bioequivalence studies. In the selection process, new chemical compound with low aqueous solubility and low permeability are preferably filtered out since they might pose problems during pharmaceutical development.

For class II drugs dissolution /solubility and for Class III drug permeability limits the oral drug absorption. It is obvious that class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption than their ability to permeate through the intestinal epithelia. There are several pharmaceutical strategies available to improve the aqueous solubility of poorly soluble drugs: solid dispersion, solubilization using surfactant, the use of co-solvent, reduction of particle size, hydrotropy and the use of aqueous soluble derivatives or salts [3].Among all technique solid dispersion (SD), is the most efficient technique from the dispersion in carrier more specially define the system has the dispersion of the one or more active ingredient in an inert matrix at solid state perform by melting method, solvent evaporation method and melting solvent [4]. Since long, many investigators have studied SDs of poorly water-soluble drugs with various pharmacologically inert carriers to increase the dissolution and oral absorption of poorly water soluble drugs, however, only a few system are useful commercially [5].

Poloxamer have been recently widely used as wetting and solubilizing agents as well as surface adsorption excipients. They have been employed to enhance the solubility, dissolution and bioavailability of many hydrophobic drugs using various techniques, for some drugs, the improvement in solubility using Poloxamer was higher compared to the other meltable

polymers such as PEGs and complex forming agents such as cyclodextrin. In the present study, Poloxamer was thus empirically selected as a hydrophilic carrier for its excellent surfactant properties and oral safety [6].

The main possibilities for improving dissolution according to analysis are to increase the surface area available for dissolution rate by decreasing the particle size of the solid compound and or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink condition for dissolution and last but definitely not least, to improve the apparent solubility of drug under physiologically relevant condition [7].

Solid dispersion(SD) technique are developing to modify the physicochemical and biopharmaceutical properties of drug, for above mentioned techniques BCS Class II drugs are selected because low solubility and high permeability like antidiabetic drugs. Antidiabetic drugs to be absorbed must be present in the form of an aqueous solution at the site of absorption for their hypoglycemic activity so solubility enhancement technique s are more essential for drugs like Glimepiride (GMP) 3-ethyl-4-methyl-N-{2-[4-({[(4methylcyclohexyl) carbamoyl]amino} sulfonyl) phenyl] ethyl, is thiozolidinedioneantidiabetic agent that depends on the presence of insulin for its mechanism of action lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cell.

Glimepiride (GMP) is classified under class II according to biopharmaceutical classification system [8].The drug shows low, pH dependent solubility. In aqueous media, glimepiride exhibits very poor solubility at 37°C (<0.004 mg/ml). In media pH>7, solubility of drug is slightly increased. This poor solubility may cause poor dissolution and unpredicted bioavailability. It is practically insoluble in water and other aqueous media. However, the drawback of this potentially useful hypoglycemic agent is that it is highly hydrophobic and practically insoluble in water [9].

The presented research work thus deals with the techniques of enhancement of solubility as well as dissolution and bioavaibility of poorly aqueous soluble drugs like Glimepiride.

2. MATERIAL AND METHODS

GMP was obtained from Cipala Pharmaceuticals Ltd. Mumbai as a gift sample; PXM 188 was obtained from Alembic pharmaceutical Pvt. Ltd. Badodara, and PXM 407 Alembic pharmaceutical Pvt. Ltd. Badodara. Polyvinyl Pyrollidone, Lactose, Sodium Starch glycolate and Magnesium stearate were obtained from Loba Chemie Pvt. Ltd, Mumbai, India.

2.1. Preparation of physical mixture [10]

A physical mixture of Glimepiride with Poloxamer 188 or Poloxamer 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. This mixture was then subsequently passed through mesh no. 40 and stored in a dessicator for 48 h.

2.2. Preparation of Solid Dispersion [10]

The Kneading method (KM) was used for the preparation of solid dispersion. Six different drugs: Carrier ratios (1:1, 1:2, 1:3, 1:4, 1:5, and 1:6.) were used. F1 to F6 corresponds to preparations containing Poloxamer 188 and F7 to F12 correspond to preparations containing Poloxamer 407. Glimepiride and Poloxamer 188 or 407 were weighed according to these weighed ratios. Glimepiride and Poloxamer were triturated using a small volume of isopropyl alcohol to give 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 mesh no. 30, stored in a vacuum desiccator (48 h) and passed through sieve no. 60 before packaging in an airtight container.

2.3. Determination of drug content [11]

The drug content was calculated by dissolving solid dispersion equivalent to 2 mg of Glimepiride was transferred to 100 ml volumetric flask and dissolved in minimum amount of methanol; and the volume was made up to 100 ml with phosphate buffer (pH 7.4) and then solution was filter through 0.45-µm membrane filter paper and assayed for drug content using UV double beam spectrophotometer at 228 nm.

2.4. Solubility Determination [12]

Phase solubility was performed as described by Higuchi and Connors. Excess amount of solid dispersion 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 no 40. The filtrate was analyzedspectrophotometrically at 228 nm. Shaking was continued until three consecutive reading were the same.

2.5. Fourier transforms infra-red spectroscopy [13]

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.

2.6. *In vitro* drug release [14]

Accurately weighed preparations equivalent to 2 mg of Glimepiride were added to 900 ml of dissolution media (7.4 phosphate buffer) contained in USP dissolution apparatus II and

stirred at a speed of 50 rpm at 37±0.5°C. Five milliliter aliquots were withdrawn at 10, 20, 30, 40, 50 60 minute and replaced by 5 ml of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution at 228 nm using UV-visible spectrophotometer against the blank. The dissolution of pure Glimepiride was done similarly.

2.7. Formulation and evaluation of Glimepiride solid dispersions tablets

2.7.1. Evaluation of blends [15]

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced. The various characteristics of blends tested are bulk density, tapped density, compressibility index, Hausner ratio, and angle of repose.

2.7.2. Preparation of Tablets of Solid Dispersions

Tablets containing equivalent to 2 mg of Glimepiride solid dispersion (F5) were prepared by direct compression. The blend was compressed on a 16 station rotary machine using round shaped, concave punches. The composition of tablet is given in Table No. 1.

Table No.1: Composition of Tablet Formulation

Ingredients	Formulation (mg)
Solid dispersion	12
Polyvinyl Pyrollidone	08
Lactose	110
Sodium Starch glycolate	18
Magnesium stearate	02

2.7.3. *Evaluation of glimepiride solid dispersion Tablets [16]*

All prepared tablets were evaluated for drug content, friability, hardness and weight variation and *in vitro* drug dissolution. Friability was determined using Roche friabilator. Hardness was measured using Pfizer hardness tester.

2.7.4. Content Uniformity of Tablets

Ten tablets were weighed and crushed in a small mortar. The fine powder equivalent to 2 mg of Glimepiride was transferred to 100 ml volumetric flask containing 10 ml of methanol and dissolved. The volume was made up to 100 ml with NaOH. The solution was filter through 0.45-µm membrane filter paper. One ml of this solution was diluted 100 times and the absorbance was measured at 228 nm.

2.7.5. In vitro drug dissolution

Glimepiride formulated tablet were added to 900 ml of dissolution media (pH 7.4 phosphate buffer) contained in USP dissolution apparatus II and stirred at a speed of 50 rpm at 37 ± 0.5°C. Five milliliter aliquots were withdrawn at 10, 20, 30, 40, 50, 60 minute and replaced by 5 ml of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution at 228 nm using UV-visible spectrophotometer against the blank. The dissolution of pure Glimepiride was done similarly.

3. RESULTS AND DISCUSSION

3.1. Drug content estimation

The drug content of Glimepiride solid dispersion was found to be in range 97.59 to 99.82 and these values are within the acceptable range. Low values of standard deviation in respect of with respect to drug content, as given in Table No. 2, indicating uniform drug distribution in all the solid dispersions.

Table No. 2: Evaluation of % Drug content and solubility Study

Formulation Code	%Drug content	Solubility mg/ml
Pure drug	-	0.0074
PM 1	98.95	0.013
PM 2	91.92	0.011
F1	98.24	0.126
F2	97.59	0.167
F3	97.96	0.212
F4	98.67	0.235
F5	**99.82**	**0.345**
F6	99.26	0.320
F7	97.62	0.074
F8	97.90	0.125
F9	97.92	0.202
F10	98.33	0.282
F11	**99.63**	**0.324**
F12	98.82	0.314

3.2. Solubility Studies

The solubility profile of Glimepiride was found to be 0.0074mg/ml suggesting a strong need to enhance the solubility and dissolution of Glimepiride. Therefore, a solid dispersion technique using Poloxamer 188 and Poloxamer 407 was employed for solubility and dissolution enhancement of Glimepiride in the present investigation. The improvement in solubility was observed with for all solid dispersion, Increase in weight fraction of surface-active carrier resulted in an increase in the solubility of all dispersions. Maximum solubility enhancement was found in 1:5 ratio of Glimepiride:

Poloxamer 188 prepared by the kneading method.ie 0.345mg/ml Enhancement in saturation solubility was found to be in order of Poloxamer 188>Poloxamer 407, Solubility study as given in Table No. 2.

3.3. Fourier transforms infra-red spectroscopy of solid dispersion

FT-IR spectra of Glimepiride, Poloxamer and Solid dispersion (1:5). Characteristic peaks of Glimepiride at 3344(3300-3500) (N-H), 2900(2850-3000) (C-H), 2900(3300-2500) (O-H), 1427 and 1342(1350-1550) (N=O), 1072(1220-1020) (C-N) and 1033(1000-1300) (C-O) were observed.

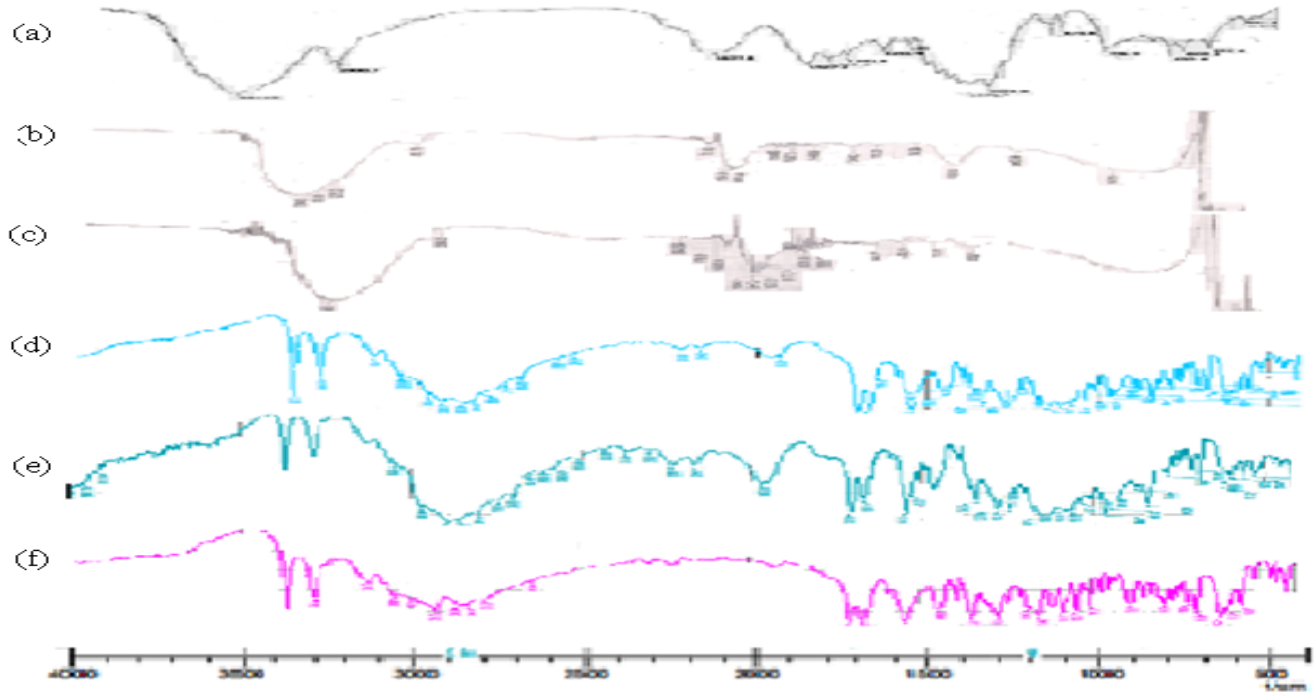

Fig. 1: FT-IR of (a) Glimepiride; (b) Poloxamer 188; (c) Poloxamer 407; (d) Physical mixture of Glimepiride with PXM 188; (e) Physical mixture of Glimepiride with PXM 407; (f) Solid dispersion with PXM 188

Due to similarities in molecular structure, of Poloxamer 188 and Poloxamer 407 showed similar absorption bands, in which characteristic peaks of OH stretching (3443/cm), CH stretching (2880/cm), C-H bending (1477/cm), C-H bending (1452/cm) respectively for Poloxamer-188 and Poloxamer-407 and R-O stretching (1097/cm) were observed. All solid dispersion showed peaks of Glimepiride (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 dispersion.

3.4. In vitro drug dissolution studies

The in vitro release profile of Glimepiride from Poloxamer 188 and Poloxamer 407 solid dispersions (prepared by the kneading method) and physical mixture formulation are shown in fig. 2 and 3, and the graph for the comparison of the cumulative percent release is illustrated in figure no.4. According to observations, drug dissolution was increased gradually with increasing the concentration of both the grades of Poloxamer up to a certain limit, and after that then it almost becomes constant. The dissolution of drug from solid dispersion was found to be faster than that from physical mixtures and drug this may be due to the molecular and colloidal dispersion of drug in hydrophilic carrier matrix of poloxamer.

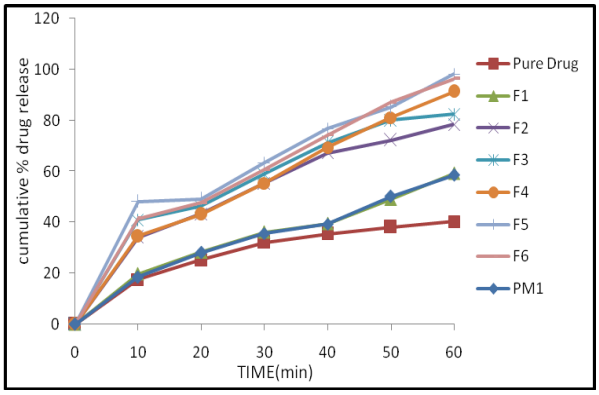

Fig. 2: In vitro drug release of Glimepiride in pH 7.4 phosphate buffer from solid dispersion and physical mixtures of glimepirie - PXM 188 systems

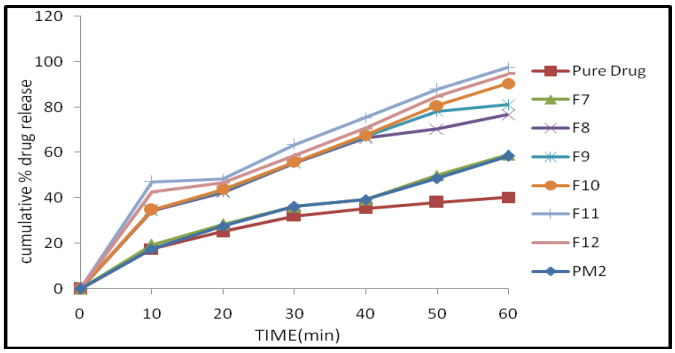

Fig. 3: In vitro drug release of Glimepiride in pH 7.4 phosphate buffer from solid dispersion and physical mixtures of glimepirie - PXM 188 systems

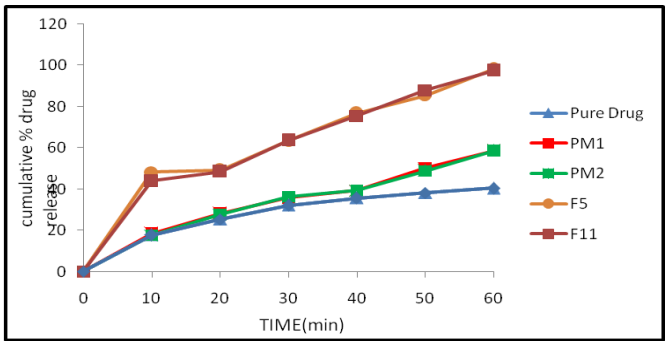

Fig. 4: Comparative dissolution profiles of glimepiride in pH 7.4 phosphate buffer from physical mixtures and solid dispersions prepared using PXM 188 and PXM 407

3.5. Evaluation of the solid dispersion tablet dosage form

3.5.1. Pre compression Evaluation of Drug- Excipients blend

The results of pre compression evaluation of Drug-Excipients blend are given in Table no. 3. The value of angle of repose was found to be below 30 which indicate good flow property. The bulk density and tapped density value was found to be less than one. Similarly the percentage compressibility (Carr's Index) value for all batches was less than 16 % which also indicate that all batches of tablet blend have good flow property.

Table no.3: Evaluation of Solid Dispersion Drug- Excipients blend

Parameters	Formulation
Angle of Repose (θ)	25.11
Bulk Density (g/ml)	0.54
Tapped Density (g/ml)	0.58
% Compressibility	6.89
Hausner Ratio	1.07

3.5.2. Post Compression Evaluation of Marketed & Formulated Tablet

The result of post compression evaluation of formulated tablet is given in Table no. 4.

Table no. 4: Post Compression Evaluation of Formulated Tablet

Parameters	Formulated Tablet
Weight Uniformity (mg)	149.5 ± 0.45mg
Content Uniformity (%)	99.23 %
Friability (%)	0.5 ± 0.50
Hardness (kg/cm^2)	3.9 ± 0.36kg/cm^2

3.5.3. Dissolution Study of Tablet

The formulated tablets were subjected to dissolution study in pH 7.4. Phosphate buffer is given in Figure no. 5

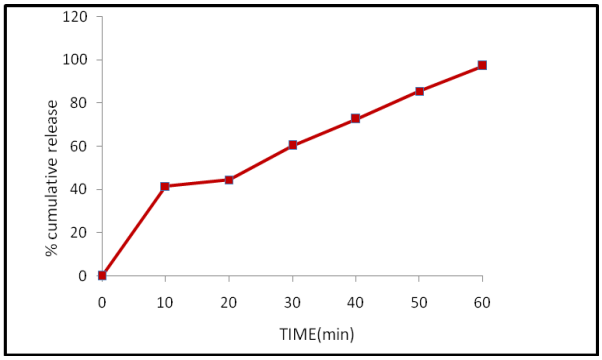

Fig.5: In-vitro drug release profile of formulated tablet

When the mixture comes in contact with water, the polymer particles might have hydrated rapidly into polymeric solution, solubilizing the adjacent drug particles and subsequently releasing the drug into the medium. Reason for improvement of Glimepiride release from solid dispersion with the increasing ratio of Poloxamer 188 and Poloxamer 407 is that at low concentrations, approximating those at which more conventional nonionic detergents from micelles, the poloxamer monomers are thought to form monomolecular micelles by through a change in configuration in solution. At higher concentration, these monomolecular micelles associate to form aggregates of varying size, which have the ability to solubilized drugs to a larger extent.

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

4. CONCLUSION

The dissolution rate of Glimepiride was increased by solid dispersions prepared by the kneading technique by using poloxamers, without any physical and chemical interaction. Solid dispersions of Poloxamer 188 with Glimepride showed a enhancement in dissolution profile as compare to physical mixtures as well as solid dispersion with poloxamer 407.and whole in-vitro studies proved that Glimepride :Poloxamer 188,1:5 ratio showed best results among all formulations.and tablets prepared by that blend also showed better dissolution profile and not affected by mechanical shocks while compression.

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