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Enhancement of Solubility and Bioavailability of Glimepiride Using Solid Dispersion Technique

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ABSTRACT

The poor aqueous solubility of Glimepiride is the major factor limiting its oral bioavailability. The objective of the work is to enhance the solubility of Glimepiride, there by its bioavailability by using solid dispersion technique. Solid dispersions of Glimepiride were prepared by using Poly vinyl Pyrrolidone (PVP K30), by solvent evaporation method in different ratios of 1:0.5, 1:1, 1:3, 1:5 respectively and evaluated for its *in vitro & in vivo* release along with Mdsc & FTIR. The equilibrium solubility of solid dispersions was determined in water to study the effect of PVP K30 on solubility of Glimepiride. In Vitro dissolution studies were conducted in water from solid dispersions equivalent to 4 mg of Glimepiride. Protocol bound in vivo studies were conducted in non diabetic rats with the best formulation. Two groups of rats (6 rats in each group) were orally fed Glimepiride as plain drug dispersion (control group) & as drug: PVP K30 solid dispersion (test group). The fall in blood glucose level was monitored over 24 hours. Successful conversion of the crystalline Glimepiride to amorphous solid dispersion was achieved at 1:5 level of drug to PVP K30 (F_4). The solid dispersion prepared with PVP K30 at 1:5 level (F_4) showed a 4 folds enhancement in aqueous solubility of the drug. So the *in vivo* studies conducted with 1:5 drug to PVP K30 (F_4) solid dispersion, the best formulation, it was observed that the fall in the test group is significantly faster and more intense as compared to the control group. The above study shows that solid dispersion of Glimepiride offers an simple and attractive solution to increase the solubility of the poorly water soluble drug and thereby improve its oral bioavailability.

Key words: Glimepiride, Poly vinyl Pyrrolidone (PVP K30), Solid dispersions (SD)

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INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development are intended to be used as a solid dosage form that originate an effective and after oral administration [1, 2]. In fact, most NCEs are poorly water-soluble drugs and are not well absorbed after oral administration which can detract from the drug's inherent efficacy [3, 4]. Consequently, if these drugs are not completely released in the gastrointestinal area, they will have a low bioavailability [5]. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs[6]. The techniques/approaches that have commonly been used to overcome drawbacks associated with poorly water-soluble drugs, in general includes micronization, salt formation, use of surfactants and use of prodrug [7]. However, all these techniques have potential limitations. Solid dispersion is the most successful strategy to improve drug release of poorly soluble drugs. Solid dispersion improves the solubility through decreased particle size, increased surface area, improved wettability and increased amorphous state of water insoluble compound [8]. Sekiguchi and Obi first introduced the concept of using solid dispersions to improve bioavailability of poorly water soluble drug in 1961. Chiou and Riegelman defined the term solid dispersion as "a dispersion of one or more active ingredients in an inert carrier or matrix, prepared by the melting, solvent evaporation method, or melting solvent method [9]. Solid dispersion (SD) technique has been widely used to improve the solubility, dissolution rate and oral absorption of poorly water-soluble drugs [10, 11]. Glimepiride (a BCS class II drug) is a third generation of sulfonyl urea oral anti diabetic drug having high permeability and low solubility. Low water soluble drugs often exhibit low dissolution profile and oral bioavailability problems [12, 13]. Therefore, the objective of the present study was to improve *in vitro* dissolution profile, there by bioavailability of Glimepiride using solid dispersions by solvent evaporation method.

MATRERIALS AND METHOD

Chemicals and Reagents:

Glimepiride USP (EMCO Industries, Hyderabad), Poly vinyl Pyrrolidone USP (PVP K 30, - Ashland Specialty Chemicals Ltd, USA), All other chemicals and reagents used were of Analytical grade from Merck. Purified water USP (from Millipore system) was used wherever required.

Preparation of solid dispersion:

Solid dispersions were prepared by solvent evaporation method using poly vinyl pyrrolidone (PVP K30) at 1:0.5, 1:1, 1:3, 1:5 ratios. Glimepiride was dissolved in the solvent (Dichloromethane), and then the polymer was also allowed to dissolve completely in the same drug-solvent mixture and allowed the mixture for solvent evaporation by transferring it into china dishes at room temperature (static). Then the solidified mixture was scrapped from the dishes and pulverized using mortar & pestle, sieved and stored.

Table 1: Formulation of Solid Dispersion

Ingredients	**Formulations**			
	F_1 1:0.5	**F_2 1:1**	**F_3 1:3**	**F_4 1:5**
Drug (Glm) (mg)	100	100	100	100
Polymer (PVP K30) (mg)	50	100	300	500
Dichloromethane (ml)	25	25	25	25

Differential Scanning Calorimetry

Thermal curves of each sample were recorded by simultaneous Differential scanning Calorimeter (TA Instruments Q 1000). Each sample (approximately 2.5 mg) were scanned in hermetic pan made of aluminum at 10°C /min over the range of 50°C -300°C with an empty aluminum pan used as reference. Samples were heated under nitrogen atmosphere (flow rate of N_2 - 50 ml/min).

Equilibrium Solubility Studies

Equilibrium solubility studies were conducted in order to find out the solubility of the solid dispersions in water, by dissolving solid dispersions equivalent to 10 mg of the drug in 25 ml of distilled water. This solution was sonicated for 1hr and filtered through Whatmann filter paper 44.The filtered solution was analyzed for drug release from the solid dispersion by Uv-Visible spectrophotometer at 225 nm.

Drug Content

The drug content was determined by accurately weighing out solid dispersion equivalent to 10 mg of Glimepiride in a 100 ml volumetric flask. Approximately 70 ml of Methanol was added and sonicated for 30 minutes. The volume was made up to 100 ml with Methanol and filtered. An aliquote equivalent to 100 µg of the drug was transferred to a 10 ml volumetric flask and volume was made upto 10 ml with Methanol. The absorbance was measured at 225 nm and the value was compared with that of a standard 10 µg/ml solution.

Each analysis was carried out in triplicate. The concentration was determined and % drug content was calculated.

In Vitro Release Studies of Solid Dispersions

The solid dispersion powder was weighed accurately equivalent to 4mg of the drug. This weighed powder was allowed to undergo dissolution in USP apparatus I (basket) for 1 hr at 50 rpm in 900 ml distilled water. Sample of the dissolution media were removed at predetermined time interval (0, 5, 10, 15, 30, 45, 60 min).Withdrawn samples were analyzed at 225 nm.

In Vivo Studies*:*

Protocol (Approval No: MRCP/CPCSEA/IAEC/2012-13/MPC/4) bound in vivo studies were conducted in order to evaluate the in vivo efficacy of Glimepiride solid dispersions. This study was conducted by using optimized solid dispersion of Glimepiride with poly vinyl pyrrolidone (PVP K30) (F_4), which has given the best in vitro dissolution profile.

For this study 12 rats of Wistar strain, Albino species were selected which were weighed approximately 200gm & above.

Procedure:

1. Albino rats of approximate 200 gram weight are selected for this study.
2. The rats are divided into 2 groups of n=6 in each group.
3. Group I fed with plain Glimepiride dispersion (Reference) and Group II fed with the solid dispersion (Test product)
4. After overnight fasting (water ad lib), the rats are weighed on the morning of the dosing
5. T-0 blood samples are drawn from the tail vein of the rat and evaluated for basal blood glucose levels from each rat.
6. The dose was given as an aqueous dispersion of the drug in 10% HPMC
7. The calculated dose was fed to each rat using gastric lavage
8. The blood samples (0.5ml) are drawn from the tail vein at, T_{30}, T_{60}, T_{120}, T_{240}, T_{480} and T_{1440} minutes and evaluated for fall in BGL using Glucometer.

RESULTS AND DISCUSSION

DSC:

DSC studies were performed on the plain drug and on freshly prepared solid dispersions at 1:0.5, 1:1, 1:3 and 1:5 proportions in order to study the interaction between Glimepiride and the carrier at different ratios in the solid state. Glimepiride exhibited a single sharp melting endothermic peak at 210°C. Solid dispersion of Glimepiride and PVP K30 lead to further decrease or broadening of this melting endothermic peak. The melting peak of Glimepiride disappeared or appeared as broad peak in case of drug molecule bound to the carrier in the solid state as in case of solid dispersion of

PVP K-30 at its 1:5 ratio. There is no significant difference between DSC thermograms of solid dispersion of Glimepiride with PVP K 30 at 1:0.5, 1:1 ratios & its plain drug.

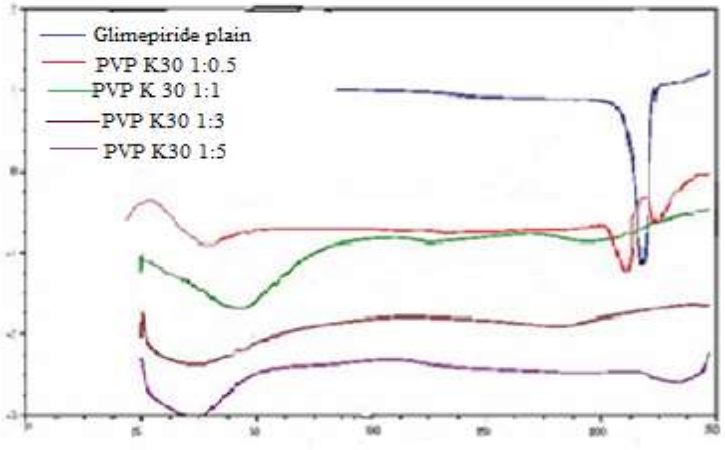

Figure 1 DSC Thermogram of Glimepiride & Its Solid Dispersions

Equilibrium Solubility Studies of solid dispersions In Water:

The equilibrium solubility studies which were conducted to determine the effect of polymer on the solubility of the Glimepiride in water shows that solubility of drug was more at 1:5 proportion (F_4), where in case of rest of proportions(F_1, F_2, F_3); the solubility was not much significant.

Drug Content:

The drug content of the solid dispersions of Glimepiride at all proportions was evaluated and found to be in the range of 97% to 100%, which intimates that the drug was distributed uniformly in solid dispersions. The drug content of each formulation is as follows:

Table 2: Equilibrium Solubility & Drug Content Studies of Solid Dispersions

S. No.	Formulations	Drug release (µg/ml)	Drug content (%)
1	Plain drug	1.32	--
2	F_1	2.86	97.2
3	F_2	3.23	98.3
4	F_3	3.78	98.74
5	F_4	6.20	99.45

In Vitro Release Studies of Solid Dispersions

Table 3: Dissolution data of Glimepiride & Its Solid Dispersions with PVP K30 at Different Ratios in Water: (n =3)

Mean Percentage release of the drug:

S. No	Time(min)	Plain drug	F_1	F_2	F_3	F_4
1	0	0	0	0	0	0
2	5	15.3	6.1	7.3	26.6	68
3	10	18.6	6.6	9.6	33.3	74.0
4	15	21.3	8.4	11.6	35.1	74.2
5	30	21.8	11.6	16.6	35.6	74.5
6	45	22.6	17.3	17	38	74.8
7	60	24	25	25.6	38.6	75.08

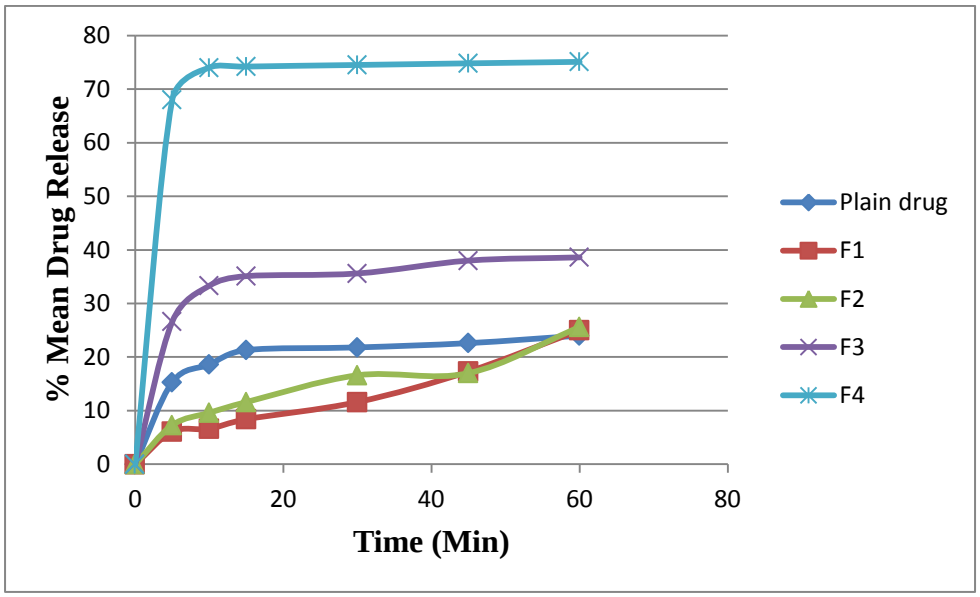

Figure 2 Dissolution Profile of Glimepiride Solid Dispersions in Water (n=3)

In vitro studies were conducted for the prepared solid dispersions in comparison with the plain drug in water for 1 hr using USP apparatus I (basket). From the studies it was proved that the drug release was more with the F_4 which was 75% for 1hr, the maximum release, compared to plain drug, which was 24% for 1hr. It has shown a 4 fold increase in the drug release with that of plain drug.

Next to F_4, F_3 has given better result, where as F_2 & F_1 (26 & 25% respectively) didn't show the significant increase in the drug release compared to the plain drug.

The order was as follows:

$F_4 > F_3 > F_2 > F_1$

D_5, D_{30}, D_{60}, were computed to compare the relative performance of all formulations.

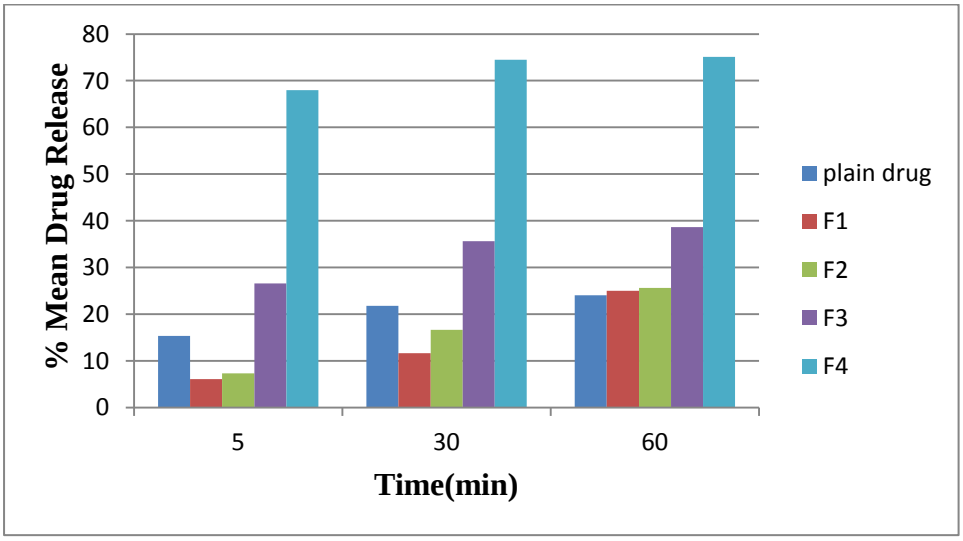

Figure 3: Comparisons of D_5, D_{30}, D_{60} of Different Solid Dispersions of Glimepiride In Water

The rate & extent of the drug release from different solid dispersions is depicted in the above chart. From the above chart it was observed that the F_4 formulation is the potent compared to others.

IN VIVO STUDIES:

Table 4: Blood Glucose Levels Of Control & Test Rats

Group No.	Rat no.	Body weight(gm)	Blood glucose levels (mg/dl) at different time intervals						
			T_0	T_{30}	T_{60}	T_{120}	T_{240}	T_{480}	T_{1440}
I(control)	1	179	50	43	35	28	28	39	52
	2	209	65	57	49	41	43	49	64
	3	215	69	62	54	47	49	55	70
	4	210	70	63	56	49	51	59	74
	5	225	61	54	47	41	41	50	62
	6	217	72	65	58	52	54	62	71
II(test)	1a	345	70	55	47	31	47	58	75
	2a	275	80	64	55	39	54	66	79
	3a	240	68	53	45	31	47	58	69
	4a	217	74	58	50	35	49	60	76
	5a	260	99	83	74	58	76	85	108
	6a	231	76	62	54	37	57	71	82

From the in vitro studies it was proved to be F_4 was the best formulation. In order to prove its bioavailability, in vivo studies were conducted on albino rats for 24 hrs with only the F_4 formulation. The in vivo studies also proved that F_4 was the potent formulation which has enhanced its bioavailability when compared to the plain drug. There was a rapid fall in blood glucose levels (BGL) in the test rats when compared to control rats, which indicates its enhanced efficacy.

CONTROL:

Table 5: Mean & Δ Blood Glucose Levels (BGL)

Time(hrs)	Mean	Standard deviation	variance	ΔBGL (mg/dl)
0	64.5	8.11	65.9	64.5
0.5	57.3	8.11	65.8	7.2
1.0	49.8	8.37	70.1	14.7
2.0	43	8.5	73.2	21.5
4.0	44	8.9	80.8	20.5
8.0	52	7.7	60.8	12.5
24	65.8	8.3	69.7	- 1.3

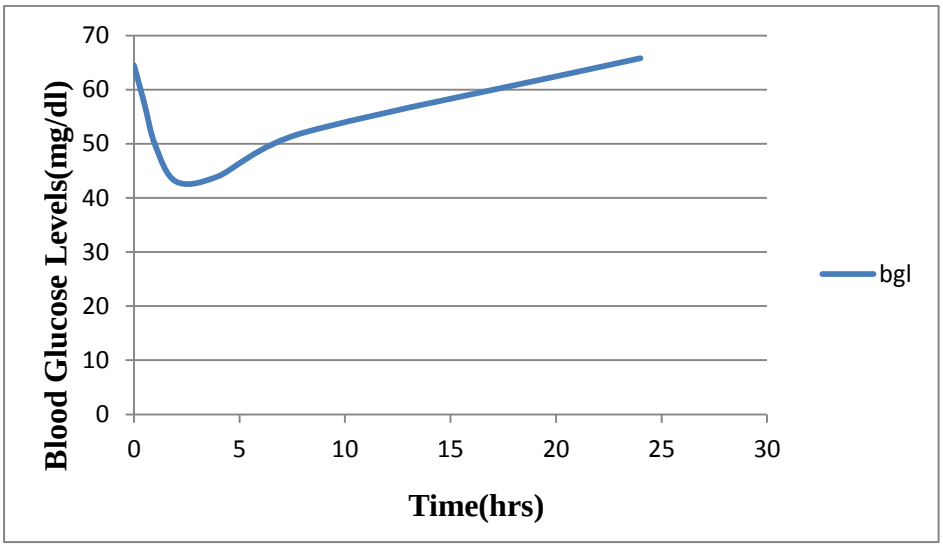

Figure 4 Fall In Blood Glucose Levels In Control Rats

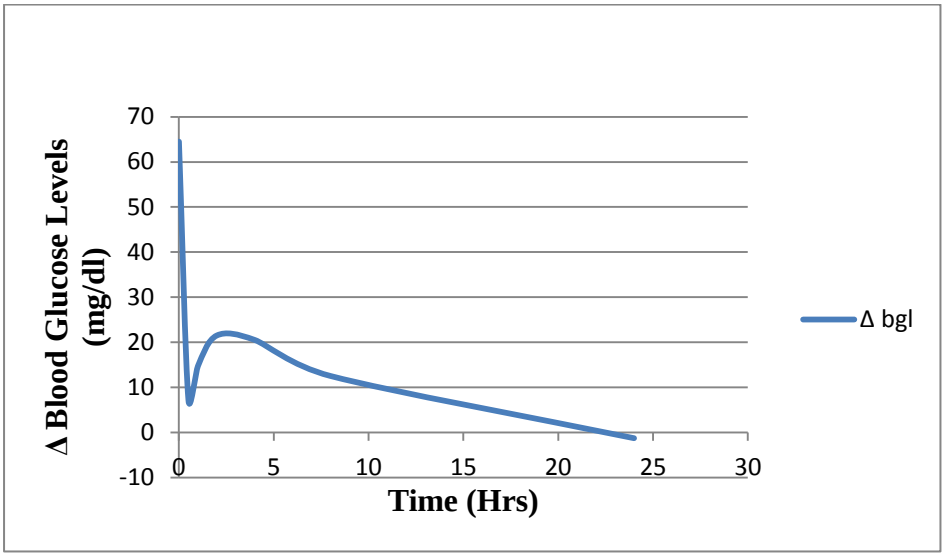

Figure 5 Δ BGL Fall in Control

TEST*:*

Table 6: Mean & Δ Blood Glucose Levels (BGL)

Time(hrs)	Mean	Standard deviation	variance	Δ BGL(mg/dl)
0	77.8	11.2	125.7	77.8
0.5	62.5	10.8	117.9	15.3
1.0	54.1	10.4	109.3	23.7
2.0	38.5	10.07	101.5	39.3
4.0	55	11.04	122	22.8
8.0	66.3	10.4	109.8	11.5
24.0	81.5	13.6	187.5	-3.7

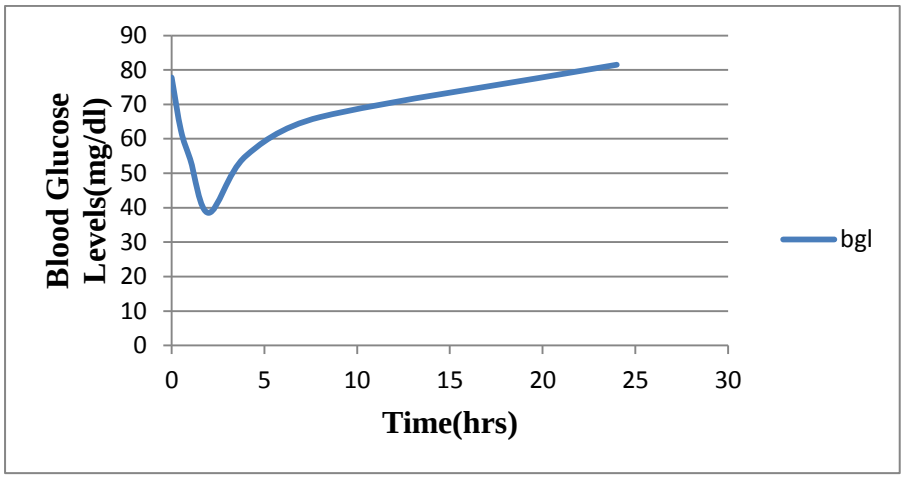

Figure 6 Fall In Blood Glucose Levels In Test Group

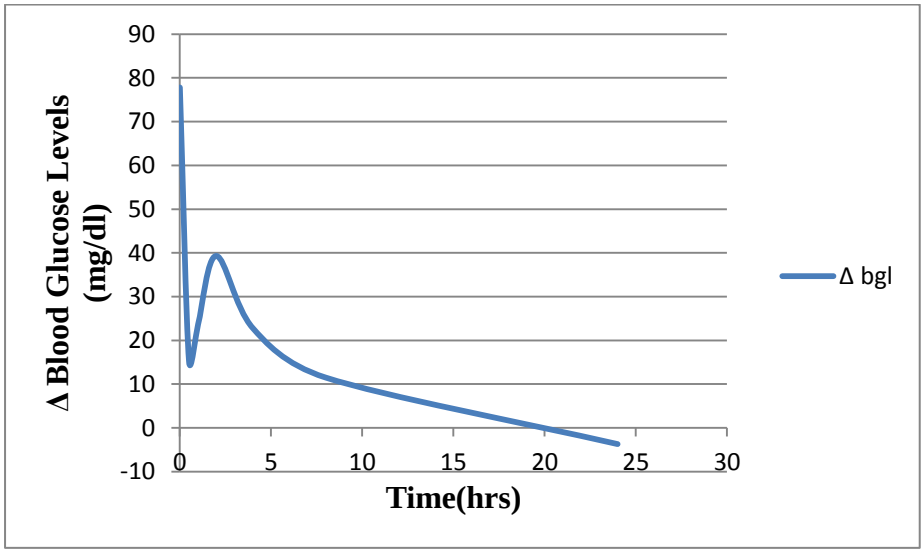

Figure 7: Δ BGL Fall In Test Group

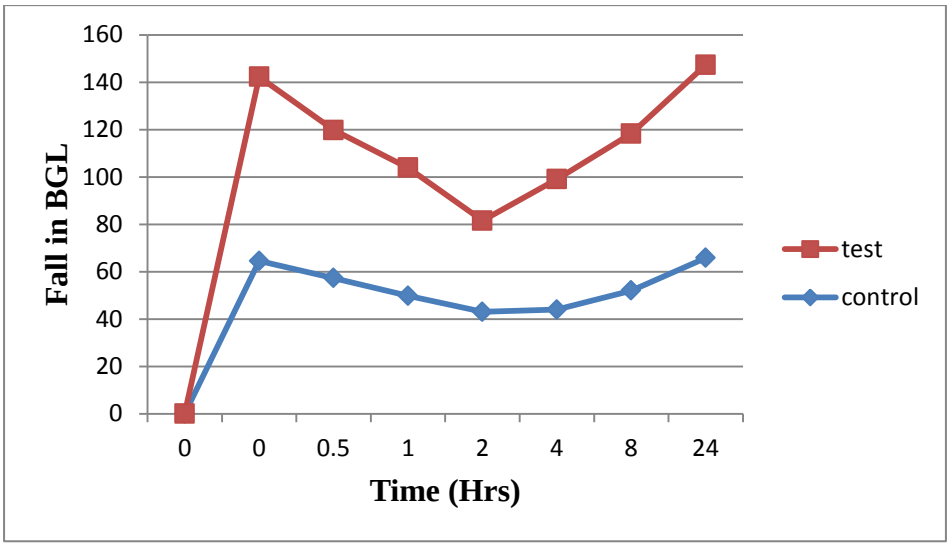

Figure 8: Comparison of Fall In BGL Of Control & Test

The difference in fall in BGL of control & test can be observed from the above figures. Comparison of test and control was performed using ANOVA as listed in table 7 which is significant.

Table 7: Comparison of Control & Test Using Anova:

ANOVA	Sum of squares(Ss)	Degree of freedom (DF)	Mean Squares (MS)	F	P
Between	251.09	1	251.09	2.62	0.131
Within	1146.62	12	95.5		
Total	1397.71	13			

CONCLUSION

In the present work, amorphous solid dispersion of Glimepiride was evaluated in an approach to enhance aqueous solubility of the drug. From this study it was proved to be solid dispersion technique can potentially enhance the solubility, thereby bioavailability of the poorly aqueous soluble drugs. From the *in vitro* studies it was observed that the F_4 formulation was the best formulation of all which was continued for its *in vivo* studies. From the *in vivo studies* it was observed that the test group shows a significant steeper fall in blood glucose levels as compared to control. However the T_{max} is not significantly affected. This indicates that solid dispersion can potentially enhance the oral bioavailability of the drug. Stability studies and in depth in vivo experiments need to be done in order to successfully complete the study.

Abbreviations:

GLM : Glimepiride

SD : solid dispersion

PVP : Poly Vinyl Pyrrolidone

BGL : Blood Glucose Levels

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