wjpmr, 2024, 10(1), 203-211

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

FORMULATION AND IN-VITRO EVALUATION OF INCLUSION COMPLEX TABLETS OF WATER INSOLUBLE DRUG GLIPIZIDE

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Article Received on 19/11/2023 **Article Revised on 09/12/2023** **Article Accepted on 29/12/2023**

ABSTRACT

Glipizide is an oral quick and short acting anti diabetic drug from the sulfonylurea class. It is classified as a second generation sulfonylurea, which means that it undergoes enter hepatic circulation. Second-generation sulfonylureas are both more potent and have shorter half lives than the first generation sulfonylureas. The rationale of this study was to enhance the solubility & dissolution of the Glipizide by preparing its complex with water soluble polymers such as PEG 4000 and PEG 6000 were selected as carriers. In the present study attempt has been made to prepare, formulate and characterize inclusion complexes of Glipizide with PEG 4000 and PEG 6000. The inclusion complexes were prepared by two methods viz. Physical method and Kneading method. The inclusion complex containing Glipizide: PEG 4000 and PEG 6000 were further formulated into Tablets by Direct Compression Technique using microcrystalline cellulose, Magnesium stearate and Aerosil. The prepared Tablets were characterized using FTIR and DSC and finally the prepared Tablets Were Evaluated for various pharmaceutical characteristics viz. Hardness, % Friability, thickness, Weight Variation, Drug Content and In-vitro Dissolution profiles. The results of stability studies revealed no change in physical appearance, hardness, thickness, drug content and in vitro dissolution profiles, thus indicating that formulation GF4 was stable.

KEYWORDS: Glipizide, PEG 4000, PEG 6000, Inclusion Complexation, Direct compressed Tablets, Microcrystalline cellulose.

INTRODUCTION

Medicine release is a pivotal and limiting step for oral medicine bioavailability, particularly for medicines with low gastrointestinal solubility and high permeability. By perfecting the medicine release profile of these medicines, it's possible to enhance their bioavailability and reduce their side goods. Solid dissipations are one of the most successful strategies to ameliorate the medicine release of inadequately answerable drugs. Presenting the emulsion as the molecular dissipation combining the benefits of an original increase in the solubility (within the solid result) and maximizing the face area of the emulsion that comes in contact with the dissolution medium as the carrier dissolves. The large face area of the performing suspense should affect in an enhanced dissolution rate and thereby bettered bioavailability.[1]

The two areas of pharmaceutical exploration that concentrate on perfecting the oral bioavailability of active agents include enhancing solubility and dissolution rate of inadequately water-answerable medicines and enhancing the permeability of inadequately passable medicines.

The advantage of solid dissipations over other approaches is that numerous of the carriers that can be applied are formerly considerably used in the pharmaceutical assiduity as excipients, so fresh toxin studies over and beyond what's needed for the medicine itself shouldn't be needed. The possibility of combining several carriers to produce an optimized product farther extends the range of possibilities for formulation.[2]

Glipizide is an effective anti-diabetic drug which belongs to second generation sulphonyl urea and can lower the blood glucose levels in humans by stimulating the release of insulin from pancreas and is typically prescribed to treat Type II diabetes (Non-Insulin Dependent Diabetes Mellitus). Its short biological half-life, 3.4 h, necessitates that it has to be administrated with doses of 2.5–10mg twice or thrice daily. The maintenance dose is 2.5 to 40 mg per day. Total daily doses above 15 mg/day should be divided and administered twice a day.[3-5]

Polyethylene glycols (PEGs) are semi-crystalline polymers that have been used extensively in the SDs

preparation for their wetting, solubilizing, and surface active properties. They have been reported to enhance the solubility, dissolution, and bioavailability of many poorly water soluble drugs using various techniques including melting agglomeration and melting.[5] The extent of their absorption appears to be dependent on their molecular weights. Complete absorptions have been reported for PEGs with lower molecular weights. However, the absorption is much more limited in the case of PEGs with high molecular weights. A particular advantage of PEGs for the formation of SDs is that they also have good solubility in many organic solvents. These relatively low melting points of PEGs are advantageous in the manufacture of SDs by the melting method.[1-3] In this study, to improve its solubility, dissolution, bioavailability, and low melting temperature IB were utilized to make SDs with PEG 4000 and 6000. The SDs was evaluated for their *in vitro* dissolution properties. PEG 4000 and 6000 was empirically selected as a mutable polymer for its low melting point, surfactant properties, and oral safety.[6]

Experimental

MATERIALS AND METHOD

Glipizide was a gift sample obtained from M/s. Amsal Chem Pvt. Ltd. Mumbai, India. And all other excipients such as PEG 4000 and PEG 6000, microcrystalline cellulose, Aerosil and Magnesium stearate were procured from M/s. Yarrow Chem Products., Mumbai, India.

Scanning of Glipizide in phosphate buffer pH 7.4

50 mg of Glipizide was accurately weighed in to 50 ml volumetric flask and dissolved in small quantity of phosphate buffer pH 7.4. The volume was made up with the buffer to 50ml to produce stock solution having a concentration of 1mg/ml. A standard solution having a concentration of 20 mcg/ml was prepared by appropriately diluting the stock solution. The standard solution was scanned between the wavelength ranges of 200 to 350 nm in Shimadzu UV spectrophotometer to determine the wavelength of maximum absorbance. The UV spectrum of Glipizide in phosphate buffer pH 7.4 is shown in Figure No. 1.

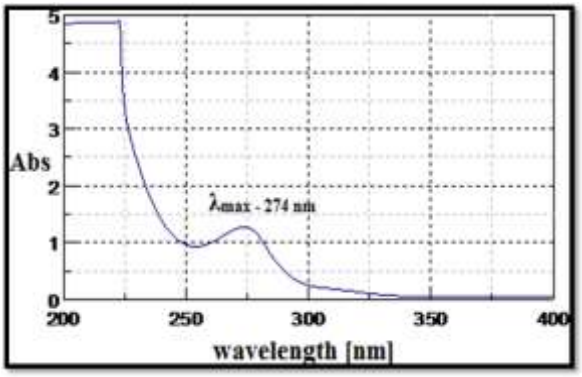

Figure No. 1: UV spectrum of Glipizide in phosphate buffer pH 7.4.

Preparation of standard solution

50 mg of the pure drug was accurately weighed and dissolved in methanol and the volume was made up to 50 ml with methanol to give standard stock solution of 1000 µg/ml. Aliquots of standard stock solution were suitably diluted with distilled water to get working standard solutions of concentration of 5, 10, 15, 20, 25, 30, 35 and 40 µg/ml. These were scanned in the wavelength range 200-400 nm. Table No. 1.

Table No. 1: Table for standard graph of glipizide.

SL. No.	Concentration of Drug (µg/ml)	Absorbance at 274 nm
1	0	0
2	5	0.109
3	10	0.223
4	15	0.339
5	20	0.448
6	25	0.561
7	30	0.671
8	35	0.790
9	40	0.900

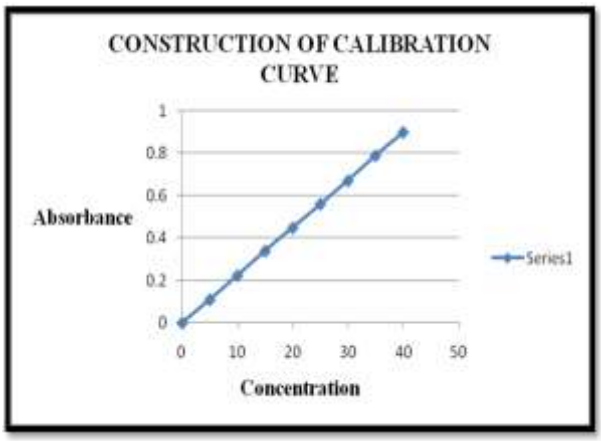

Figure No. 2: Standard graph of glipizide.

Phase solubility studies

Phase solubility studies were carried out according to the method reported by Higuchi and Connors. An excess of Glipizide (200 mg) was added to 15 ml portions of distilled water, each containing variable amount of PEG 4000 or PEG 6000 such as 0, 1, 3, 6, 9, 12, and 15 x 10-3 moles/liter. All the above solutions with variable amount of PEG 4000 or PEG 6000 were shaken for 72 hours. After shaking, the solutions were filtered and their absorbance was noted at 274 nm.[6] The solubility of the Glipizide in every PEG 4000 or PEG 6000 solution was calculated and phase solubility diagram was drawn between the solubility of Glipizide and different concentrations of PEG 4000 or PEG 6000.

Preparation of PEG 4000 and PEG 6000 **Inclusion Complexes**

Physical mixture

Glipizide with PEG 4000 in different molar ratios (i.e. 1:1M, 1:2M 2:1M) and with PEG 6000 in ratio (i.e. 1:1M, 1:2M 2:1M) were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 80 and stored in a desiccator. Table No. 2.

Kneading method

Glipizide with PEG 4000 in different molar ratios (i.e. 1:1M, 1:2M 2:1M) and with PEG 6000 in ratio (i.e. 1:1M, 1:2M 2:1M) were added to the mortar, and triturated in a mortar with 10 ml of distilled water. The thick Slurry was kneaded for 45 minutes and dried at 55^{o}C. The kneaded product passed through mesh no 100 and stored in desiccators. Table No. 2.

Table No. 2: Different Formulations of Glipizide with PEG 4000 and PEG 6000 in Molar Ratio.

Method	Drug to carrier Complex	Drug to Carrier Ratio	Code for Complex	Code for Tablet Formulation
Physical Mixture	GPZD : PEG 4000	1:1	G_1	GF_1
	GPZD : PEG 4000	1:2	G_2	GF_2
	GPZD : PEG 4000	2:1	G_3	GF_3
Kneading Method	GPZD : PEG 4000	1:1	G_4	GF_4
	GPZD : PEG 4000	1:2	G_5	GF_5
	GPZD : PEG 4000	2:1	G_6	GF_6
Physical Mixture	GPZD : PEG 6000	1:1	G_7	GF_7
	GPZD : PEG 6000	1:2	G_8	GF_8
	GPZD : PEG 6000	2:1	G_9	GF_9
Kneading Method	GPZD : PEG 6000	1:1	G_{10}	GF_{10}
	GPZD : PEG 6000	1:2	G_{11}	GF_{11}
	GPZD : PEG 6000	2:1	G_{12}	GF_{12}
Pure Drug Glipizide			G_0	GF_0

Determination of drug content[8]

The percent drug content of each solid dispersion, was determined using powder equivalent to 50 mg Glipizide and was dissolved in minimum amount of methanol and volume was made up to mark 100ml using pH 7.4 phosphates buffer. The solution was then filtered through Whatman filter paper no. 42 and required dilution were being made and assayed for drug content using UV double beam spectrophotometer at 274 nm. Three replicates were prepared and average value was reported.

Fourier transform infrared spectroscopy (FTIR) studies

The FTIR spectra of the drug, PEG-4000, PEG-6000 and solid dispersion in different ratio were recorded with FTIR spectrophotometer (Jasco V-6001). The samples were prepared by using potassium bromide and scanned for the absorbance at 4000-400/cm.

Formulation of glipizide inclusion complexes tablets

Preparation of tablet by direct compression

The active ingredient i.e. Glipizide with PEG 4000 and PEG 6000 (1: 1M) (1:2M) (2:1M) and each separately along with micro crystalline cellulose, Aerosil and Magnesium Stearate were blended together by dry mixing in a laboratory mixer (poly bag) for 10 minutes. The mixture was then compressed using 8 mm Flat Faced punches and dies set (Pilot Press 10 station) at compression force 6 ton. The formulation of the tablet is listed in above Table and the amount of Glipizide is equivalent to 30 mg per tablet. Table No. 3.

Table No. 3: Formulation table showing various compositions.

Name	GF1	GF2	GF3	GF4	GF5	GF6	GF7	GF8	GF9	GF10	GF11	GF12	GF13
	Physical Mixture			Kneading Method			Physical Mixture			Kneading Method			
Glipizide + PEG 4000	60	90	90	60	90	90	-	-	-	-	-	-	
Glipizide + PE 6000	-	-	-	-	-	-	60	90	90	60	90	90	
Glipizide	-	-	-	-	-	-	-	-	-	-	-	-	30
MCC	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Aerosil	3	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3	3

Evaluation of glipizide inclusion complexes tablets[9]

The prepared Glipizide tablets were evaluated for weight variation, hardness and friability. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2. The hardness of 6 tablets was determined using the Monsanto hardness tester. Friability was determined by first weighing 10 tablets after dusting and placing them in a friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablet was recorded and the percent friability was calculated. With the help of Vernier caliper thickness of the tablet is calculated.

***In vitro* dissolution studies for glipizide inclusion complexes tablets[10]**

In-vitro dissolution of Glipizide Tablet was studied in USP XXIV dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of phosphate buffer of pH 7.4 was used as dissolution medium. The stirrer was adjusted rotate at 75 rpm. The temperature of dissolution media was previously warmed to 37 ± 0.5°C and was maintained throughout the experiment. 1 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 274 nm after suitable dilution with phosphate buffer pH 7.4. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Percentage amount of GF released was calculated and plotted against time.

Stability studies glipizide inclusion complexes tablets

The optimized formulation was subjected for six-month stability study according to ICH guidelines**.** The selected formulations GF4 were packed in aluminum foils, which were in wide mouth bottles closed tightly. They were then stored at Room Temperature 40ºC / 75% RH for 6 months and evaluated for their permeation study.[8]

RESULT AND DISCUSSION

Fourier transform infrared spectroscopy (FTIR) spectrum of glipizide showed characteristic bands at 1689 cm1 which is due to C = O stretch of amides, a band at 1151 cm1 is present because of C-N stretching vibrations of amines, bands at 1653 cm1, and 1444 cm1 were assigned to C = C stretching of aromatic ring, a peak observed at 1663 cm1 attributed to C = N stretching, strong band at 1540 cm1 was assigned to N-H bending vibrations. A band at 3325 cm1 could probably be assigned to N-H stretching vibrations. A band present at 1033 cm1 is due to S = O. stretching, strong band at 1540 cm1 was assigned to N-H bending vibrations. A band at 3325 cm1 could probably be assigned to N-H stretching vibrations. A band present at 1033 cm1 is due to S = O. All graphs are shown in Fig. No. 3 to 6.

Samples were weighed (2 mg) and with 10 mg of potassium bromide. The samples were then compressed using a hydraulic press to obtain a translucent pellet. The pellet was placed in Fourier transform infrared spectrometer (Model-8400-S, Shimadzu, Japan), and the samples were scanned between 4000.

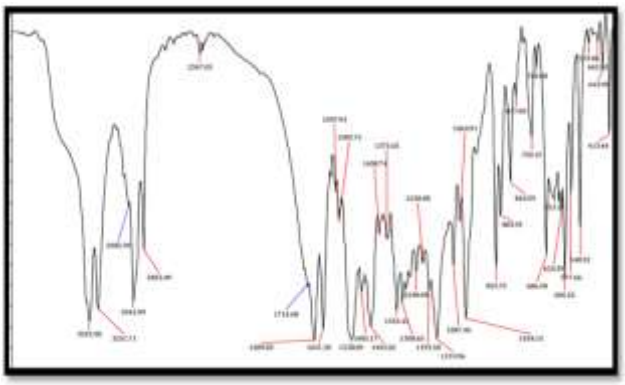

Figure No. 3: FTIR Spectra of glipizide.

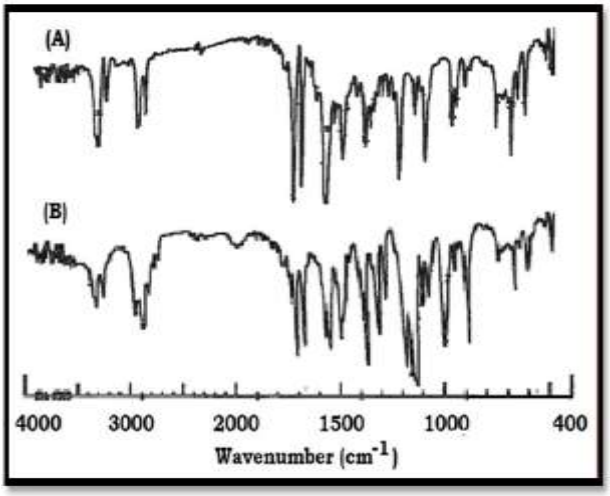

Figure No. 4: FTIR Spectra of A-PEG 4000 and B-PEG 6000.

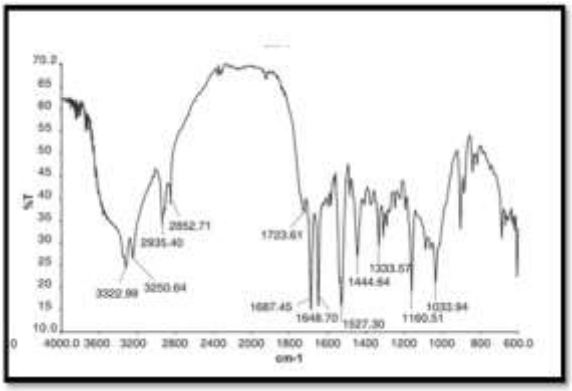

Figure No. 5: FTIR Spectra of Glipizide with PEG 4000.

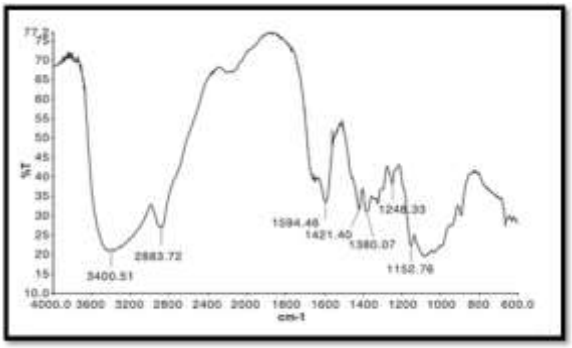

Figure No. 6: FTIR Spectra of Glipizide with PEG 6000.

Evaluation of Post-Compression

Table No. 4: Evaluation of Post-Compression Physical Parameters of Glipizide Inclusion Complexes Table with Marketed Tablet Glynase XL 10.

Formulation Code	Hardness Kg/cm^2	Thickness mm	Friability %	Weight Variation mg (%)	Drug Content (%)
GF_1	3.2 ± 0.22	2.1 ± 0.13	0.27 ± 0.11	152 ±0.07	98.01±0.11
GF_2	3.3 ± 0.36	2.2 ± 0.12	0.35 ± 0.17	150 ± 0.01	98.11 ± 0.12
GF_3	3.3 ± 0.52	2.0 ± 0.14	0.16 ± 0.13	153 ± 0.04	98.32 ± 0.15
GF_4	3.1 ± 0.55	2.1 ± 0.15	0.22 ± 0.11	157 ± 0.03	99.52 ± 0.20
GF_5	3.0 ± 0.36	2.2 ± 0.19	0.34 ± 0.l2	155 ± 0.02	99.32 ± 0.15
GF_6	3.2 ± 0.14	2.0 ± 0.14	0.50 ± 0.18	159 ± 0.05	99.14 ± 0.07
GF_7	3.3 ± 0.27	2.1 ± 0.15	0.32 ± 0.10	157 ± 0.07	97.51 ± 0.13
GF_8	3.2 ± 0.23	2.2 ± 0.15	0.27 ± 0.l2	155 ± 0.05	97.72±0.12
GF_9	3.2 ± 0.25	2.0 ± 0.19	0.22 ± 0.14	152 ± 0.05	98.15±O.16
GF_{10}	3.3 ± 0.24	2.1 ± 0.34	0.31 ± 0.12	150 ± 0.15	96.26±0.15
GF_{11}	3.3 ± 0.06	2.1 ± 0.12	0.29 ± 0.37	149 ± 0.09	98.87±0.45
GF_{12}	3.2 ± 0.16	2.1 ± 0.24	0.26 ± 0.21	151 ± 0.17	97.23±0.27
Marketed Tablet	3.2 ± 0.32	2.2 ± 0.26	0.24 ± 0.24	150 ± 0.34	99.42±0.45

- The measured hardness of the formulated tablets (GF1 to GF12) ranged between 3.0 ± 0.36 kg/cm2 to 3.1 ± 0.55 kg/cm2
- Thickness of the formulation was measured with Vernier Caliper. The measured thickness of matrix tablets of each formulation ranged between 2.1 ± 0.12 mm to 2.2 ± 0.26 mm.
- The values of friability test were tabulated in above table within the pharmacoepeial limit.
- All the formulated tablets (GF1 to GF12) passed weight variation test as the % weight variation 149 ± 0.09 to 157 ± 0.07 mg was within the Pharmacopeial limits.
- The percentage of drug content was found to be between 97.23±0.27% to 99.52 ± 0.20%. It complies with official specifications and signifies the well entrapment efficiency of prepared formulation.

All above results are shown in Table No. 4.

In- vitro Drug Dissolution

Table No. 5: In- vitro Drug Dissolution Profile of different formulation with Marketed Tablet Glynase XL 10 in Phosphate Buffer pH 7.4.

Time (min)	Percent drug release												
	Gf1	Gf2	Gf3	Gf4	Gf5	Gf6	Gf7	Gf8	Gf9	Gf10	Gf11	Gf12	Mt
0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	13.31	7.71	10.60	19.40	6.10	11.32	21.32	14.20	21.11	23.21	26.09	22.11	15.27
30	25.63	12.60	16.20	34.60	12.45	23.75	32.70	24.70	31.25	34.2	35.25	34.51	28.34
60	31.71	19.40	28.10	41.32	23.10	32.64	34.17	33.10	43.27	46.25	46.21	46.21	39.28
90	38.27	28.10	39.20	55.38	35.20	44.83	53.80	46.70	56.27	55.12	56.27	57.47	50.21
120	44.53	36.47	48.00	64.30	42.70	56.17	60.10	55.30	64.19	64.34	65.55	68.27	61.29
150	56.85	48.40	59.20	75.63	54.20	68.41	73.20	69.37	77.43	76.34	73.29	81.39	73.65
180	65.72	59.20	69.30	83.70	61.30	81.33	81.20	79.63	83.31	84.56	82.21	90.64	82.77
240	73.14	71.14	75.60	94.91	72.30	90.62	92.91	88.67	92.44	90.23	91.44	93.20	93.23

Dissolution data and % release of the various Glipizide Inclusion Complexes Tablets is indicated in table No. 5. The formulated Glipizide Inclusion Complexes Tablelets released the drug for 4 hours (formulations: GF1 to GF12 and Marketed Tablet Glynase XL 10). All the formulations (GF1 to GF12) showed marked variation in the drug release at the end of 4 hours. Formulation GF4 showed the highest release rate (94.91%) and formulation GF2 least release rate (71.14%) at the end of 4 hours. Among all 12 formulations (GF1 to GF12), the 3 formulations (GF7, GF9 and GF12) gives good release as compared to other formulations. As per the drug content and dissolution studies are concerned, it indicated that GF4 formulation gives best drug content and shows best dissolution release. Marketed Tablet Glynase XL 10 gives 93.23% drug release. The comparative graphs of the i*n- vitro* dissolution studies of Glipizide tablets % release are shown in figure. No. 7 to 9.

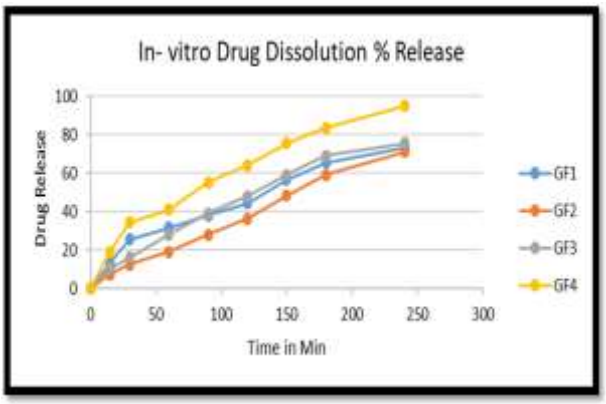

Figure No. 7: Dissolution profile of GF1 to GF4.

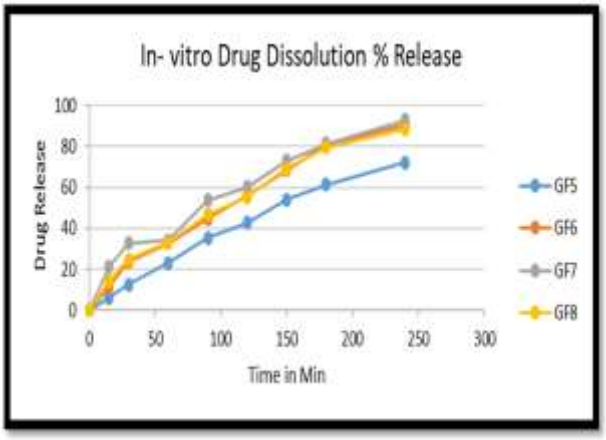

Figure No. 8: Dissolution profile of GF5 to GF8.

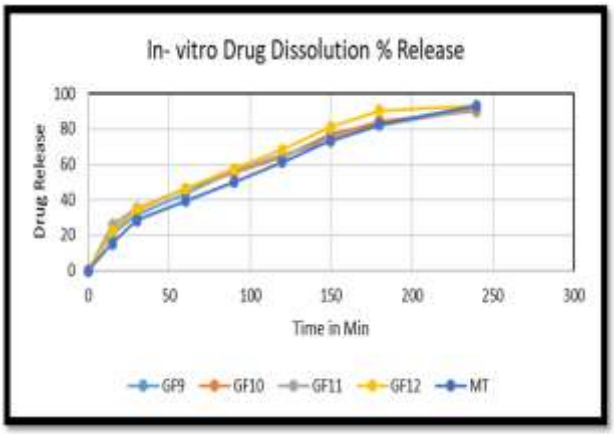

Figure No. 9: Dissolution profile of GF9 to GF10 and (MT) Marketed Tablet Glynase XL 10.

Short term stability studies at room temperature and at 40°c

Stability studies: The selected formulation GF4 Glipizide Inclusion Complexes Table was subjected to accelerated stability studies for 6 months at Room Temperature and 40^0C / 75% RH, in vitro permeation study was performed on first day, one month, three months and six month showed negligible change in permeation profile. The formulation subjected for stability studies was found to have no change in the physical appearance and drug content. The Dissolution studies of both Percent Drug Release Stored at Room Temperature and Percent Drug Release Stored at 40°C are showed negligible changes. All results are shown in Table No. 6 to 8.

Table No. 6: Evaluation of GF4 Glipizide Inclusion Complexes Table 10 at Room Temperature and at 40°C.

	Hardness Kg/cm^2	Thickness mm	Friability %	Weight Variation mg (%)	Drug Content (%)
Stored at Room Temperature	3.1 ± 0.26	2.1 ± 0.17	0.27 ± 0.12	154 ±0.35	98.01±0.11
Stored at 40°C	3.1 ± 0.18	2.1 ± 0.14	0.30 ± 0.10	149 ± 0.21	97.81 ± 0.12

Table No. 7: In- vitro Drug Dissolution GF4 Glipizide Inclusion Complexes Table at Room Temperature and at 40°C in Phosphate Buffer pH 7.4.

Time (Min)	Percent Drug Release Stored at Room Temperature	Percent Drug Release Stored at 40°C
0	0	0
15	15.40	14.57
30	28.60	26.38
60	40.32	37.42
90	52.38	48.62
120	61.30	60.22
150	73.63	71.56
180	84.70	81.44
240	93.91	91.64

Table No. 8: Percent Drug Content of GF4 Glipizide Inclusion Complexes Table at Room Temperature and at 40°C.

Time	Percent Drug Content at Room Temperature	Percent Drug Content at 40°C
First Day	99.14	99.14
One Month	98.87	98.21
Three Month	98.23	90.10
Six Month	98.04	97.62

CONCLUSION

PEG-4000, PEG-6000 can be used to prepare inclusion complexes of Glipizide with improved solubility of the drug. Glipizide formed inclusion complexes with PEG-4000, PEG-6000 in 1:1 1:2 and 2:1 M ratio. All inclusion complexes showed increasein and similar dissolution rate with compare to Marketed Tablet Glynase XL 10. The inclusion complex prepared with PEG-4000 by kneading method (GF_4**)** showed highest enhancement in dissolution profile.

Acknowledgements

The authors are thankful to MEWAR UNIVERSITY, Gangrar, Chittorgarh Rajasthan, India for providing the facilities to carry out the work.

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