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FORMULATION AND *IN-VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF GLICLAZIDE

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ABSTRACT

The sustained release matrix tablets of gliclazide were prepared by direct compression technique using synthetic polymers like hydroxypropyl methylcellulose, and ethyl cellulose as release retardant polymers. In this work, only physiochemical characterization such as angle of repose, Carr's index, hausner ratio, weight variation, hardness, thickness, friability, drug content and *in vitro* evaluation of matrix tablet of gliclazide was performed. Along with *in vitro* studies, *in vivo* studies of drug is most important.

NEED AND OBJECTIVE

1. To perform pre formulation studies like flowing properties & bulking densityfor powders of drug and polymers.
2. To formulate matrix tablets of Gliclazide by wet granulation method by usingdifferent polymers like HPMC, HPC.
3. To evaluate prepared formulations for physical parameters like weight variation, friability, and hardness etc.
4. To study *in-vitro* drug release performance of different tablets formulations.
5. To study the effect of different polymers on drug release.
6. To ascertain the release mechanics and kinetics of drug release fromcompressed matrix tablets.
7. To perform stability studies as per ICH guidelines.

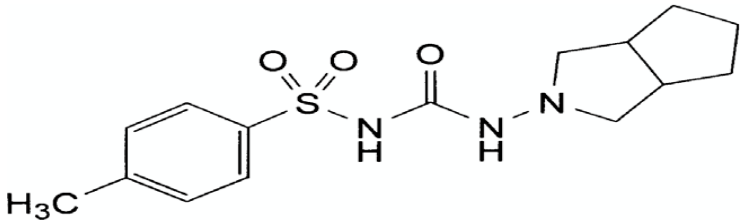
Plan of Work

The present work was carried out to design and evaluate sustained-release tablets of Gliclazide, an anti diabetic drug. The sustained-release matrix tablets were prepared by direct

compression method using HPMC K100M, ethyl cellulose, PVP K30, magnesium stearate and lactose keeping in view the objectives described above the following plan of work was adopted.

Drug Profile

GLICLAZIDE



Gliclazide, 1-(3-azabicyclo (3.3.0) oct-3-yl)-3-*p*tolylsulphonylurea is an oral hypoglycemic agent used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It contains not less than 99.0% and not more than the equivalent of 101.0% of 1-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-3-[(4-methylphenyl)sulphonyl]urea, calculated with reference to the dried substance.

MATERIALS AND METHOD

Table 1: List of Materials.

S.No.	Name of Ingredients
1	Gliclazide
2	HPMC K100M
3	Ethyl cellulose
4	Polyvinyl pyrrolidone K30
5	Magnesium stearate
6	Lactose
7	Aerosol
8	Isopropyl alcohol

Table 2: List of materials with source.

S.No.	Name of Ingredients	Name of supplier
1	Gliclazide	Sunglow pharmaceuticals, Puducherry.
2	HPMC K100M	Tristar formulations Pvt. Ltd., Puducherry.
3	Ethyl cellulose	Tristar formulations Pvt. Ltd., Puducherry.
4	Polyvinyl pyrrolidone K30	Nickon laboratories Pvt. Ltd., Puducherry.
5	Magnesium stearate	Loba chemie Pvt.Ltd., Mumbai.
6	Lactose	Loba chemie Pvt.Ltd., Mumbai.
7	aerosol	S d fine-chem limited, Mumbai.
8	Isopropyl alcohol	Qualigens fine chemicals, Mumbai.

Equipments used

Table 3: List of equipments with model/make.

S.No.	Equipment	Model/ Make
1	Electronic balance	Shimadzu BL-220H, Japan.
2	Bulk density apparatus	Indolabs VTAP/MATIC-II, Chennai.
3	Standard sieves	Jayant scientific, India.
4	Hot air oven	Precision scientific Co., Chennai.
5	Sixteen punch tablet compression Machine	Cadmach, Ahmadabad, India.
6	Friability apparatus	Veego scientific VFT-DV, Mumbai.
7	Hardness tester	Monsanto
8	Vernier caliper	Indolabs, Mitutoyo.
9	Humidity chamber	Labtech, Ambala.
10	USP dissolution test apparatus Type I	Veego scientific VDA-8DR, Mumbai.
11	UV-Visible spectrophotometer	Elico-SL 159 UV-Visible spectrophotometer, Japan.
12	FTIR spectrophotometer	Shimadzu, Japan.
13	Differential scanning calorimeter	Shimadzu, Japan.

Formulation of Gliclazide sustained release matrix tablets

All the ingredients mentioned in Table were pre-weighed and passed through mesh #60 separately. The drug and polymer were blended first in mortar and pestle then the remaining ingredients are added in that and blended for 15 minutes and the blend is finally passed through mesh #20 and used for evaluation of flow characteristic.

Table 4: Composition of gliclazide SR matrix tablets.

Ingredients(mg)	LF1	LF2	LF3	LF4	LF5	LF6	LF7	LF8	LF9
Gliclazide	60	60	60	60	60	60	60	60	60
HPMC K100M	35	70	105	-	-	-	17.5	35	52.5
Ethyl cellulose	-	-	-	35	70	105	17.5	35	52.5
Lactose	240	205	170	240	205	170	240	205	170
Polyvinyl pyrrolidone-k30	10	10	10	10	10	10	10	10	10
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Aerosol	1	1	1	1	1	1	1	1	1
Isopropyl alcohol	**Q.S**	**Q.S**	**Q.S**	**Q.S**	**Q.S**	**Q.S**	**Q.S**	**Q.S**	**Q.S**
Total weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

All the quantities are expressed as mg per tablet.

RESULTS AND DISCUSSION

Preformulation parameters

Identification of drug

Identification by FTIR spectroscopy

The FTIR spectrum of gliclazide was shown in Figure 1 and the interpretations of FTIR

frequencies were showed in Table 5.

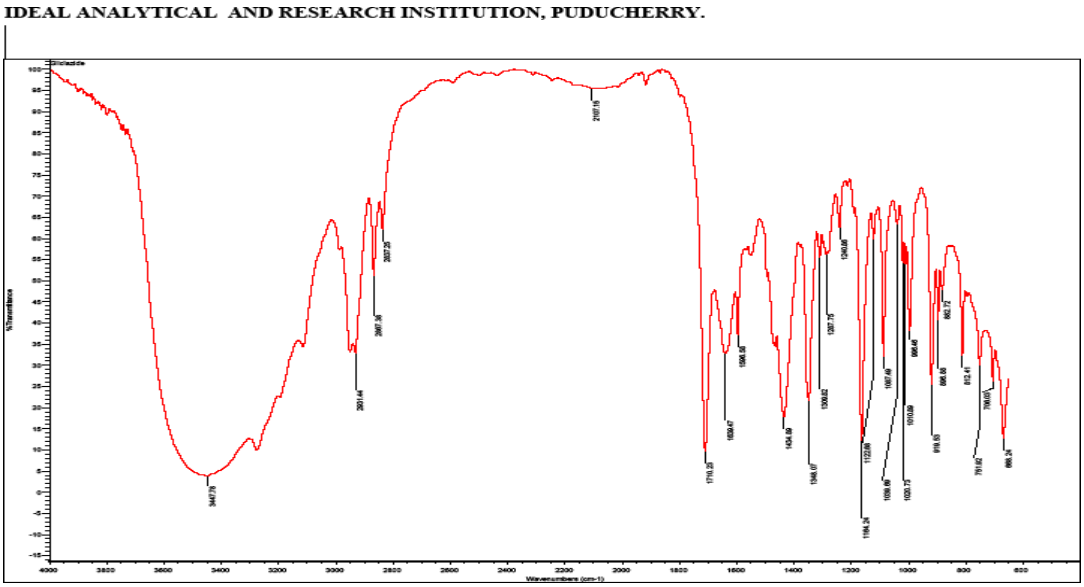


Figure 1: FTIR spectrum of gliclazide.

➢ **Interpretation of FTIR Spectrum**

Major functional groups present in gliclazide shows characteristic peaks in FTIR spectrum. Table 8.1 shows peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of gliclazide. Hence, the sample was confirmed as gliclazide.

Table 6: Characteristic frequencies in FTIR spectrum of gliclazide.

Wave No.(cm^{-1})	Functional group
3447.78	N-H stretching
2931.44	CH3 asymmetric stretching
2867.38	CH3 absorption
1710.23	C-O stretching
1639.47	NH2 deformation
1596.58	C=C stretching
1348.07	C-C stretching
1164.24	C-N stretching

Solubility study

Table 7: Solubility of gliclazide in different solvents.

Name of solvents	Solubility
Distilled water	InSoluble
Methanol	Sparingly soluble
0.1N HCl	Freely Soluble
Dichloro methane (or) methylenechloride	Freely Soluble

Phosphate buffer (pH 7.4)	Freely Soluble
Acetone	Soluble

Analytical methods

Determination of absorption maximum in 0.1 N HCl

The absorption maximum for gliclazide was found to be 281 nm.

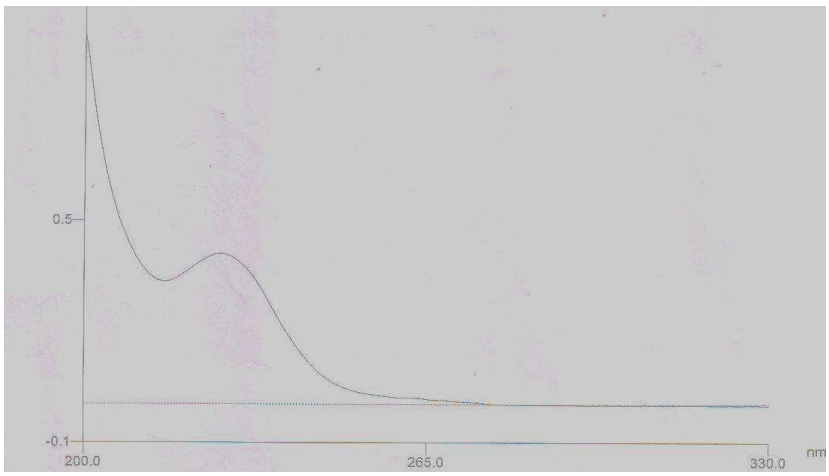


Figure 2: λ_{max} observed for gliclazide in 0.1N HCl.

Determination of absorption maximum in pH 7.4 phosphate buffer

The absorption maximum of gliclazide was found to be 225.5 nm.

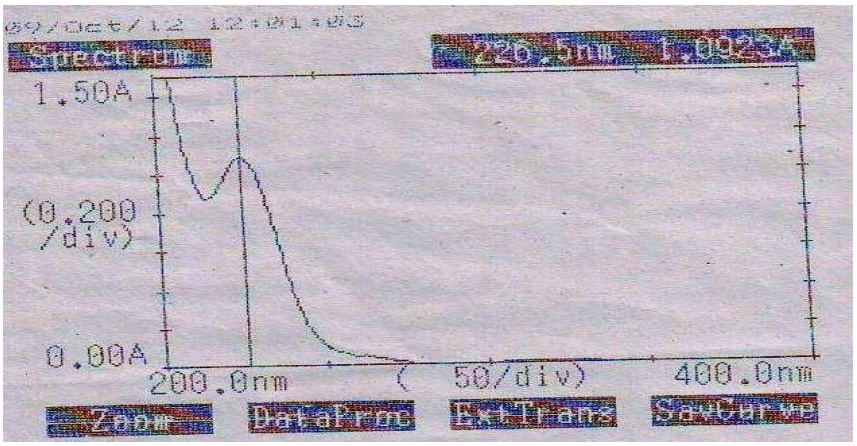


Figure 3: λ_{max} observed for gliclazide in pH 7.4 phosphate buffer.

Preparation of standard curve of gliclazide in 0.1 N HCl

UV absorption spectrum of gliclazide in 0.1N HCl showed λ_{max} at 281 nm. Absorbance obtained for various concentrations of gliclazide in 0.1N HCl are given in Table 8.3. The curve of absorbance versus concentration for gliclazide was found to be linear in the concentration range of 0–30 µg/ ml. The drug obeys Beer- Lambert's law in the range of 0–30 µg/ ml.

Table 9: Concentration and absorbance of gliclazide in 0.1N HCl.

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	5	0.304
3	10	0.597
4	15	0.901
5	20	1.173
6	25	1.472
7	30	1.760

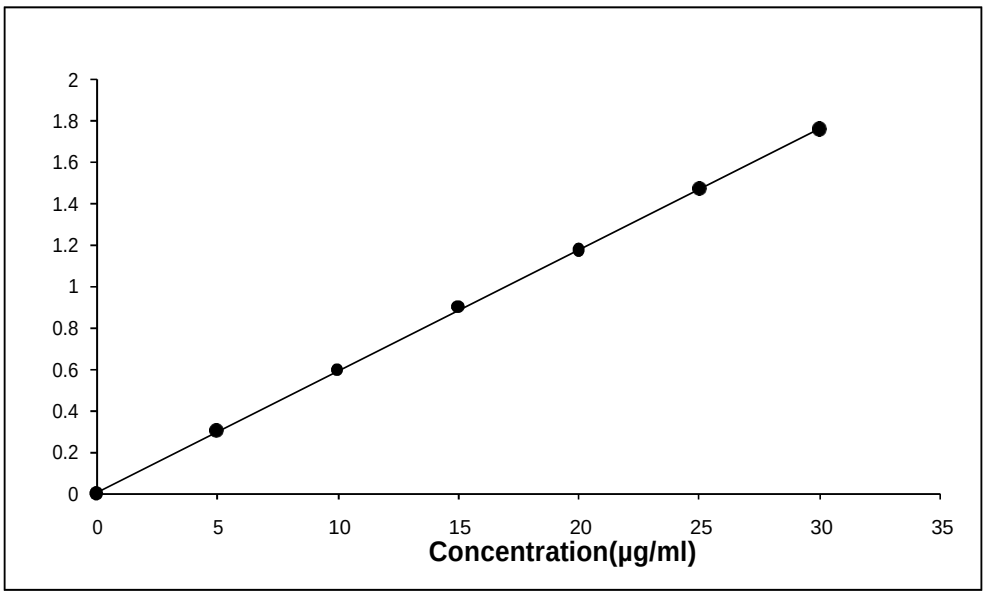


Figure 4: Calibration curve of gliclazide in 0.1N HCl.

Table 10: Calibration parameter values in 0.1 N HCl.

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.9999
2	Slope (m)	0.0585
3	Intercept (c)	0.0090

Preparation of standard curve of gliclazide in pH 7.4 phosphate buffer

UV absorption spectrum of gliclazide in pH 7.4 showed λ_{max} at 225.5 nm. Absorbance obtained for various concentrations of gliclazide in pH 7.4 are given in Table 8.5. The curve of absorbance versus concentration for gliclazide was found tobe linear in the concentration range of 0–30 µg/ ml. The drug obeys Beer- Lambert's law in the range of 0–30 µg/ ml.

Table 11: Concentration and absorbance of gliclazide in pH 7.4 phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	5	0.210
3	10	0.409

4	15	0.592
5	20	0.788
6	25	0.981
7	30	1.183

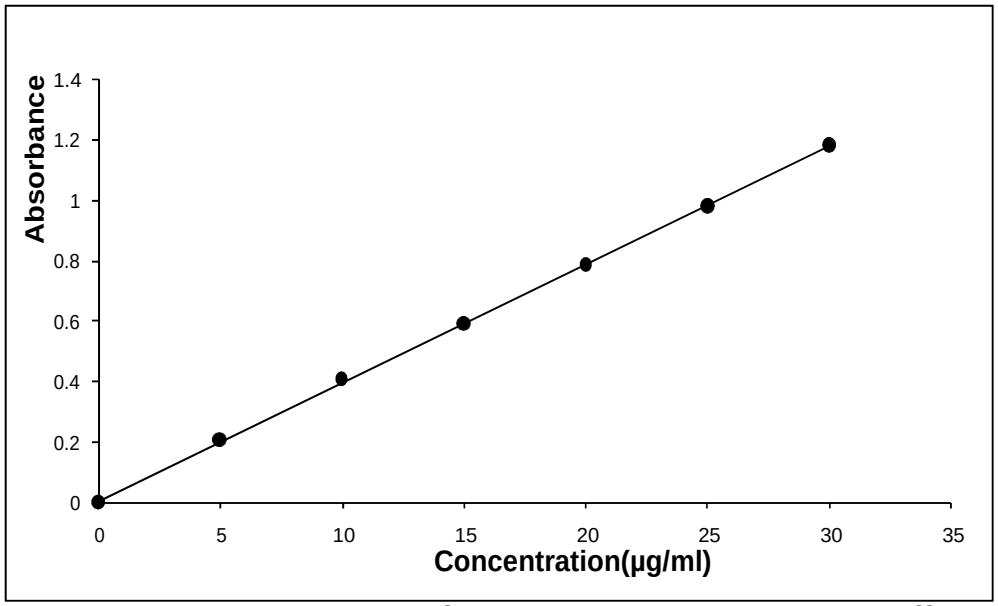


Figure 5: Calibration curve of gliclazide in pH 7.4 phosphate buffer.

Table 12: Calibration parameter values in pH 7.4 phosphate buffer.

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.9999
2	Slope (m)	0.0391
3	Intercept (c)	0.0086

Percentage purity of drug

The percentage purity of drug was calculated by using calibration curve method. The percentage purity of drug was found in official limits.

Table 13: Percentage purity of gliclazide in pure drug.

S. No.	Percentage purity (%)	Average percentage purity (%)
1	99.79	100.13 ± 0.30
2	100.29	
3	100.33	

The reported percentage purity for gliclazide in IP 2007 is 97 to 102%.

Compatibility testing of drug with polymer

Compatibility of drug and polymers was found to be as following methods such as Fourier transform infrared spectroscopy and differential scanning calorimetry.

Fourier transform infrared spectroscopy

The FTIR spectrums of gliclazide with different polymers used in formulationare shown in Figures 6, 7 and Table 8.

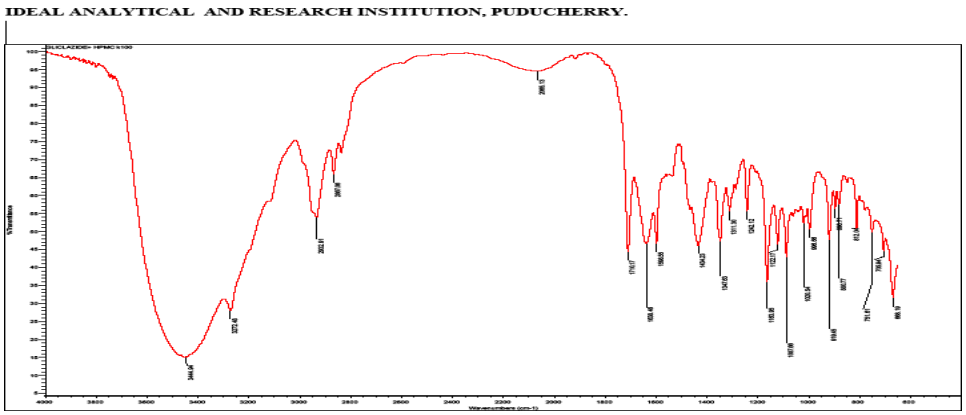


Figure 6: FTIR spectrum of gliclazide with HPMC K100M.

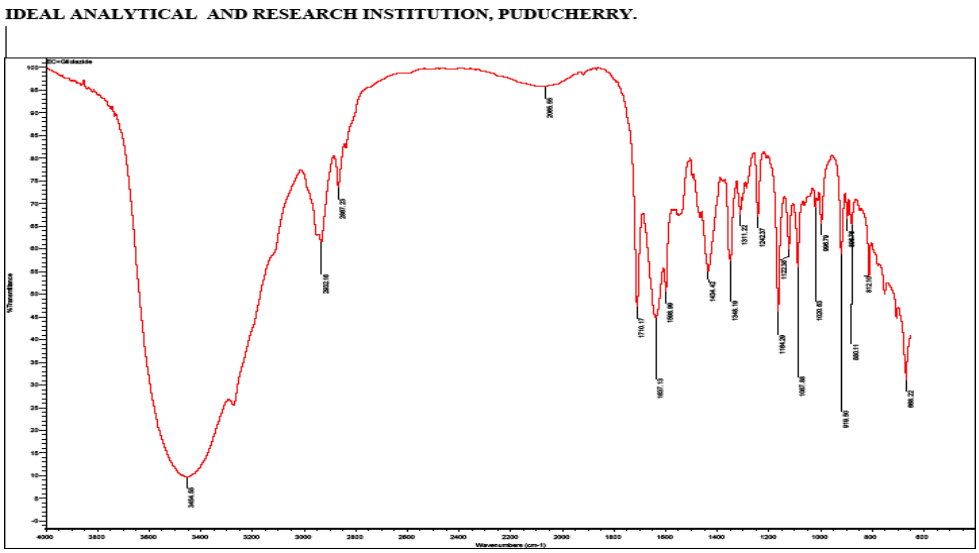


Figure 7: FTIR spectrum of gliclazide with ethyl cellulose.

Table 14: FTIR peak observed for gliclazide with different polymers used in formulations.

Functional groups	Peaks observed [Wave No. (cm^{-1})]		
	GLI + HPMC K100M	GLICLAZIDE	GLI + Ethyl cellulose
N-H stretching	3444.94	3447.78	3454.55
CH3 asymmetric stretching	2932.91	2931.44	2932.16
CH2 absorption	2867.06	2867.38	2867.23
C-O stretching	1710.17	1710.23	1710.17
NH2 deformation	1638.46	1639.47	1637.13

C=C stretching	1598.55	1596.58	1598.99
C-C stretching	1347.63	1348.07	1348.19
C-N stretching	1163.95	1164.24	1164.29

According to Table 14 and Figures 1, 6, and 7, FTIR spectrum showed that there was no major difference in peak when compared between pure drug of gliclazide and gliclazide with different polymers. Therefore it could indicate that therewas no incompatibility between drug and different polymers.

Differential scanning calorimetry

The compatibility and interactions between drug and polymers were checked using differential scanning calorimetry and the results were shown in Figures 8, 9 and 10.

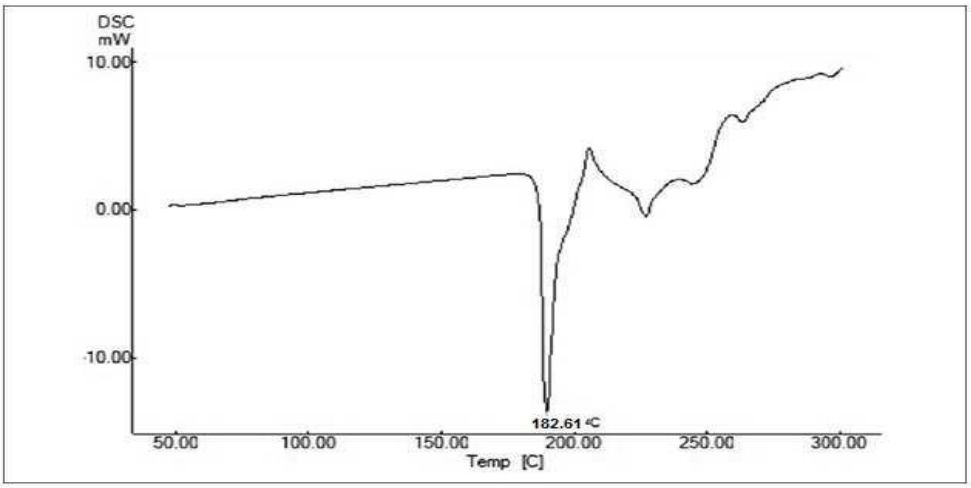


Figure 8: DSC thermal analysis of gliclazide.

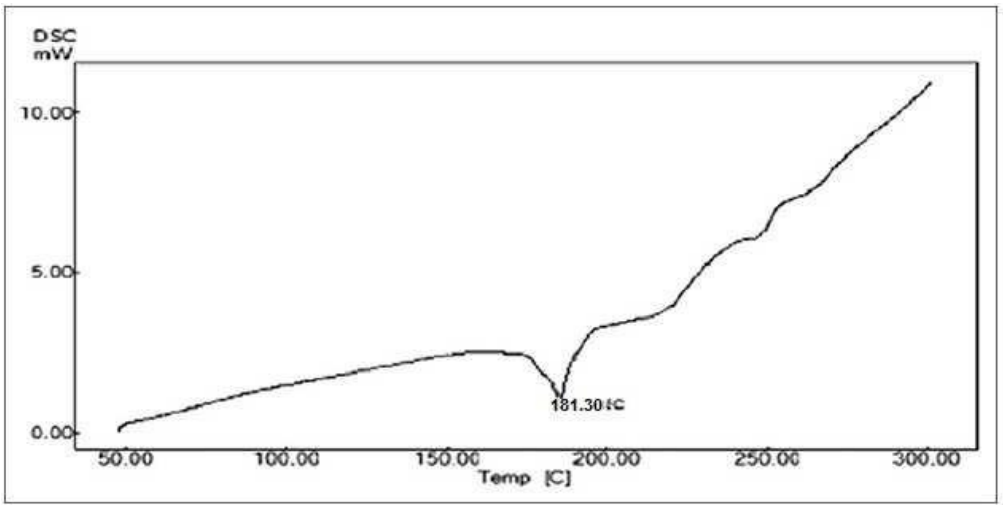


Figure 9: DSC thermal analysis of gliclazide + HPMC K100M.

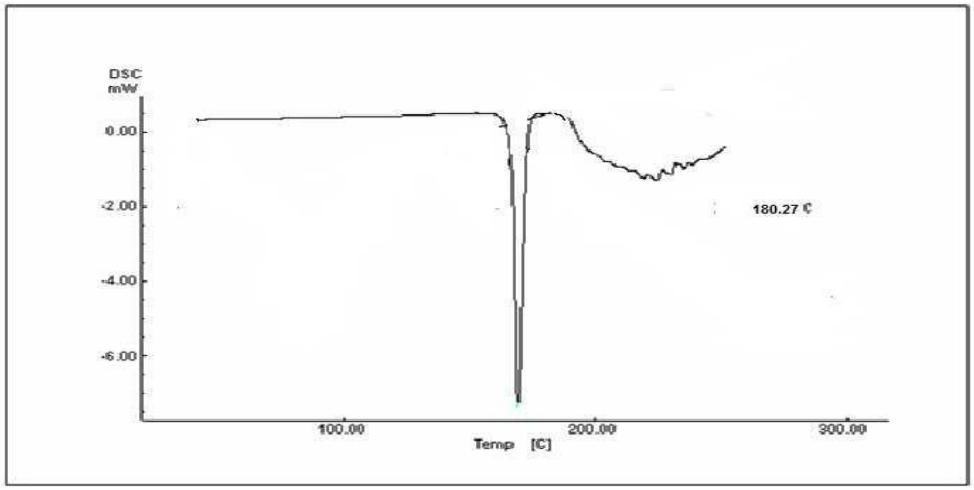


Figure 10: DSC thermal analysis of gliclazide + ethyl cellulose According to Figures 9 to 12 and Table 15, DSC thermogram showed that there was no major difference in onset temperature, end set temperature and peak temperature when compared with pure drug thermogram. Therefore it could indicate that there was no incompatibility between drug and different polymers.

Table 15: DSC thermogram parameters of gliclazide with various polymers.

S. No.	DSC thermogram	Onset temperature (°C)	Peak temperature (°C)	End set temperature (°C)
1	Gliclazide	180.42	182.61	184.62
2	Gliclazide + HPMC K100M	178.70	181.30	183.81
3	Gliclazide + Ethylcellulose	177.75	180.27	184.59

Evaluation of powder blends

The blended powders of different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio. The results of these evaluations were as follows.

Angle of repose

Angle of repose ranged from 23.20° ± 0.61 to 24.49° ± 0.36. The results were found to be below 25° and hence the blend was found to have excellent flowability. (Table No. 16).

Table 16: Flow characteristics of powder blends.

Formulation Code	Angle of repose (^{0})*	Loose bulk density (g/ml)*	Tappedbulk density (g/ml)*	Hausner ratio*	Carr's index (%)*
GF1	24.19±0.98	0.638±0.00	0.730±0.00	1.13±0.00	12.147±0.30
GF2	24.48±0.17	0.538±0.00	0.616±0.06	1.09±0.02	10.333±0.33
GF3	23.36±0.98	0.481±0.01	0.547±0.04	1.10±0.00	9.736±1.14
GF4	23.44±0.73	0.547±0.00	0.721±0.02	1.24±0.10	14.505±2.20
GF5	24.05±0.19	0.572±0.00	0.682±0.00	1.22±0.03	16.256±0.61
GF6	23.30±0.17	0.616±0.00	0.778±0.00	1.21±0.00	16.582±0.09
GF7	23.93±0.77	0.561±0.01	0.691±0.00	1.20±0.06	13.586±2.66
GF8	23.20±0.61	0.590±0.01	0.646±0.00	1.11±0.00	12.038±1.50
GF9	24.49±0.36	0.602±0.01	0.636±0.00	1.16±0.17	15.236±0.47

*All the values were expressed as mean± SD, n=3

Loose bulk density and tapped bulk density

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.481 ± 0.01 to 0.638 ± 0.00 g/ml; and 0.547 ± 0.04 to 0.778 ± 0.00 g/ml respectively. (Table No. 16).

Compressibility index (Carr's index)

The compressibility index (%) ranged from 9.736 ± 1.14 to 16.582 ± 0.09 (Table No.16). The blend was found to have excellent flowing property as the resultwere found to be below 15%.

Hausner ratio

The Hausner ratio ranged from 1.09 ± 0.02 to 1.24 ± 0.10, (Table No.16).

The result indicates the free flowing properties of the powders.

Evaluation of sustained release matrix tablets

Appearance

Surface nature of tablets was observed visually and it was concluded they did not show any defects such as capping, chipping and lamination.

Physico-chemical characteristics

The physical characteristics of gliclazide matrix tablets (GF1 toGF9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and the results were shown in table 17.

Dimension (Thickness and Diameter)

The size (diameter) of the tablets was found to be in the range from 11.17±0.01 mm to 11.20

± 0.01 and thickness between 4.32 ± 0.06 to 4.58 ± 0.04 mm.

Tablet hardness

The hardness of tablets was found to be in the range from 5.1 ± 0.10 kg/cm^2 to 6.3 ± 0.10 kg/cm^2. This indicates good mechanical strength of tablet.

Percent friability

Percentage friability of all the formulations was found to be in the range from 0.418±0.04 to 0.846±0.09%. This indicates good handling property of the prepared matrix tablet.

Table 17: Physico-chemical parameters of gliclazide matrix tablets.

F. Code	Dimension		Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%w/w)
	Diameter (mm)	Thickness (mm)				
GF1	11.20±0.01	4.44±0.02	5.2±0.10	0.704±0.07	348.15±1.47	99.00±1.55
GF2	11.19±0.02	4.37±0.06	5.5±0.30	0.774±0.07	348.70±2.42	101.00±2.20
GF3	11.20±0.01	4.57±0.06	5.1±0.10	0.846±0.09	348.70±2.42	99.55±1.10
GF4	11.19±0.01	4.32±0.06	5.8±0.10	0.634±0.05	347.05±3.25	101.00±2.20
GF5	11.17±0.01	4.34±0.07	6.1±0.26	0.677±0.06	347.10±3.88	99.75±0.55
GF6	11.17±0.04	4.40±0.09	5.2±0.20	0.418±0.04	347.05±3.25	102±2.20
GF7	11.19±0.01	4.58±0.04	5.9±0.43	0.705±0.10	347.30±3.10	99.50±3.00
GF8	11.19±0.01	4.54±0.02	5.2±0.17	0.805±0.07	347.70±2.31	99.23±1.13
GF9	11.18±0.01	4.46±0.06	6.3±0.10	0.631±0.06	348.45±2.06	98.56±1.12

All the values were expressed as mean ± SD, n=3

Weight variation

A tablet is designed to contain a specific amount of drug. When the average weight of the tablet is 400 mg, the pharmacopoeial limit for percentage deviation is ± 5%. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test forweight variation according to the pharmacopoeial specifications IP 2007.

Drug Content

The drug content of all the formulation was found to be in the range from 98.56 ± 1.55 to 102 ± 2.20 % w/w, which was within the specified limit as per IP2007.

***In vitro* dissolution studies**

Table 18: Results of *in vitro* release studies of gliclazide sustained release matrix tablets.

S. No	Time in hours	Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1	09.21 ±0.11	12.4 ±1.54	14.5 ±1.04	16.7± 1.54	14.4± 1.56	15.6± 0.45	9.4 ±2.78	6.81± 0.45	8.8± 1.54
2	2	19.89 ±1.23	36.8 ±1.89	29.3 ±2.66	34.8± 0.61	38.7 ±1.05	30..4± 0.15	17.8 ±1.96	13.73 ±0.55	15.7 ±1.45
3	3	49.30 ±2.54	48.5 ±2.54	37.7 ±0.20	58.6± 0.02	52.9± 3.51	38.9± 1.63	29.6 ±0.12	38.6 ±0.56	26.4 ±1.52
4	4	75.00 ±1.56	68.4 ±1.65	49.7 ±1.53	79.5± 0.91	63.3 ±1.55	51.1± 3.55	47.7 ±0.56	49.2 ±0.22	33.8 ±0.01
5	5	93.10 ±2.57	79.3 ±0.22	64.2 ±2.01	92.1± 0.78	71.5 ±0.45	65.3± 2.23	68.9 ±1.56	56.9± 1.51	48.1 ±0.12
6	6	93.30 ±0.23	81.5 ±2.55	76.5 ±2.50	92.6± 0.51	84.6 ±0.61	77.5± 1.25	79.3 ±3.45	69.8 ±1.02	57.9 ±0.65
7	7	93.60 ±1.54	94.0 ±0.23	87.6 ±1.21	93.1± 0.05	93.8 ±0.49	88.9± 061	84.6± 1.56	76.4 ±2.55	66.6 ±0.54
8	8	93.90 ±2.45	94.8 ±2.55	95.6 ±0.54	93.9± 0.07	94.9 ±0.61	96.0± 0.74	95.0 ±1.26	85.1 ±2.16	78.6 ±1.55
9	9	94.10 ±2.77	95.4 ±2.54	95.8 ±0.26	94.3 ±048	95.2 ±1.54	96.2± 0.07	95.2 ±0.16	97.3 ±2.55	83.5 ±0.65
10	10	94.30 ±2.54	95.6 ±2.54	96.1 ±0.50	94.6± 0.52	95.8 ±0.91	96.5± 0.21	95.5 ±1.51	97.5 ±2.16	98.2 ±0.55

*All values are expressed as mean ± S.D. n=3.

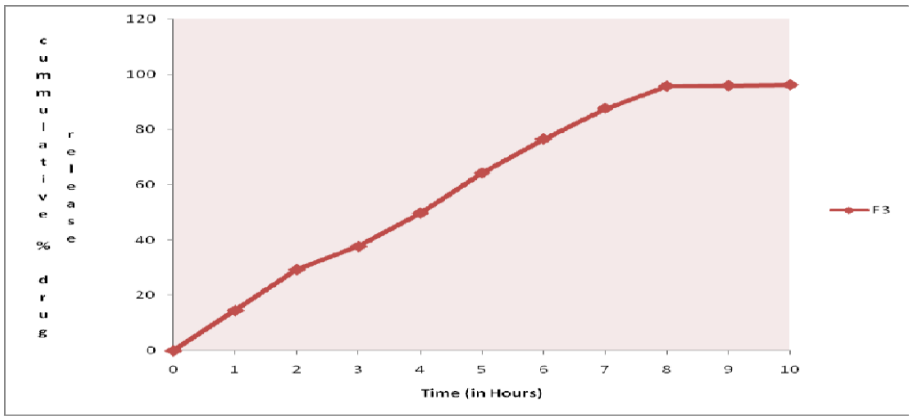


Figure 11: *In vitro* drug release profile of formulation GF1.

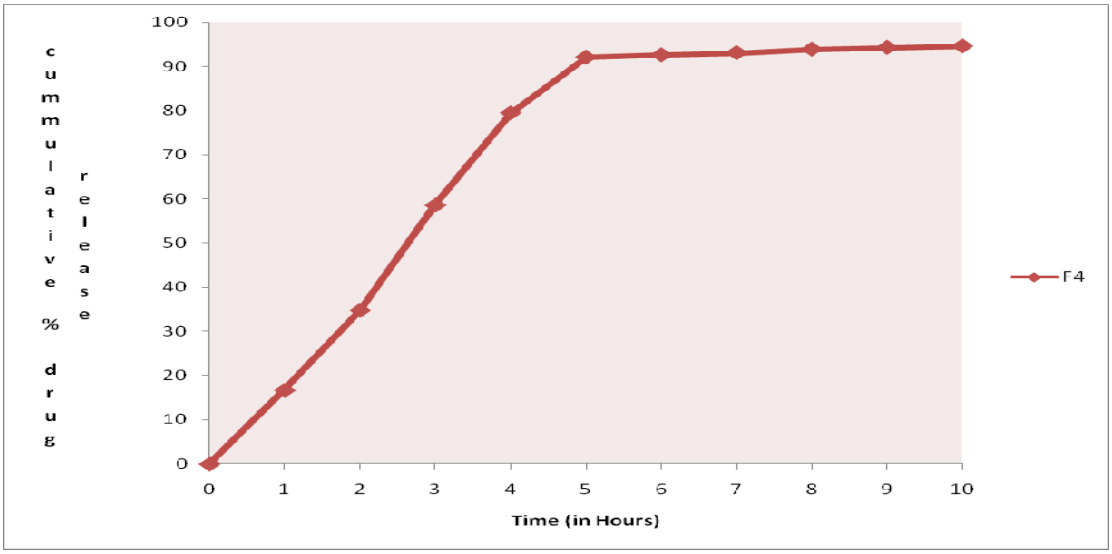
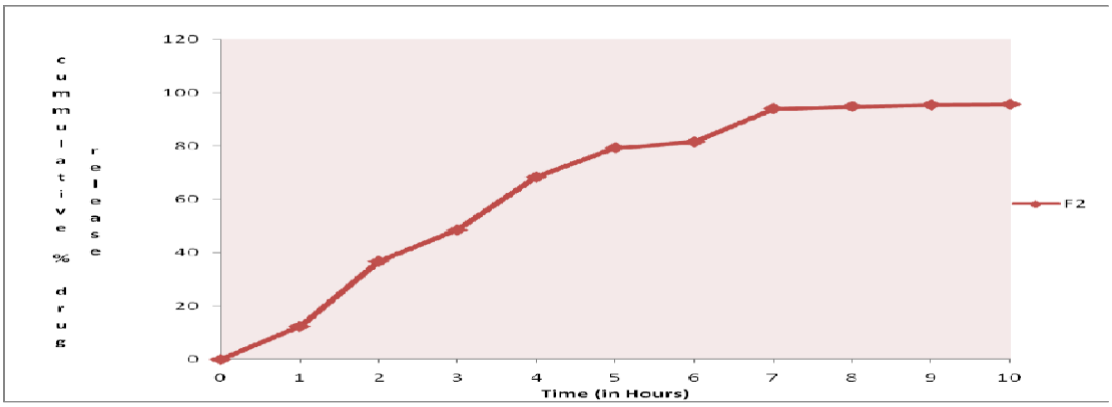


Figure 13: *In vitro* drug release profile of formulation GF3.



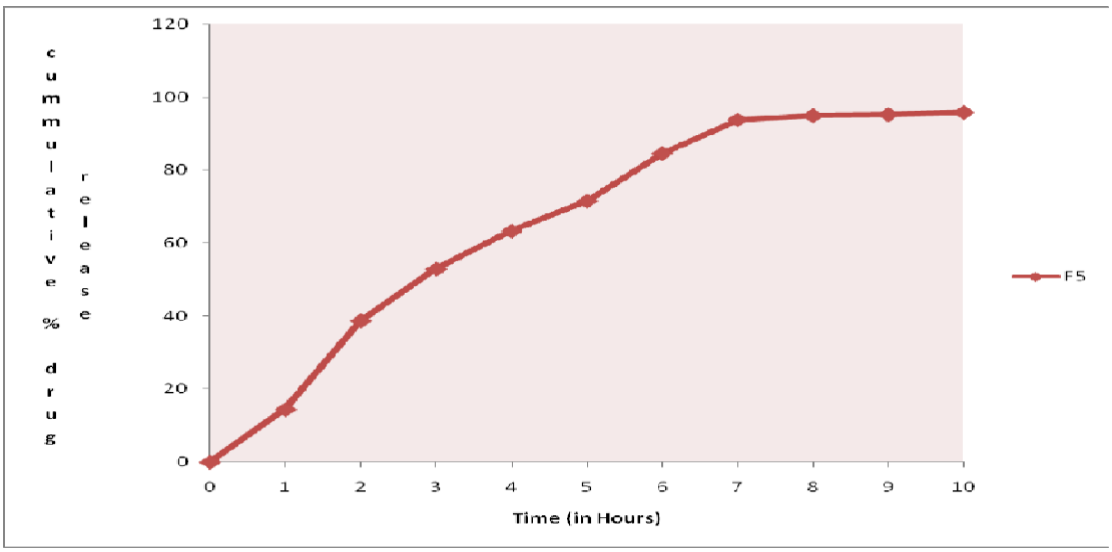


Figure 15: *In vitro* drug release profile of formulation GF5.

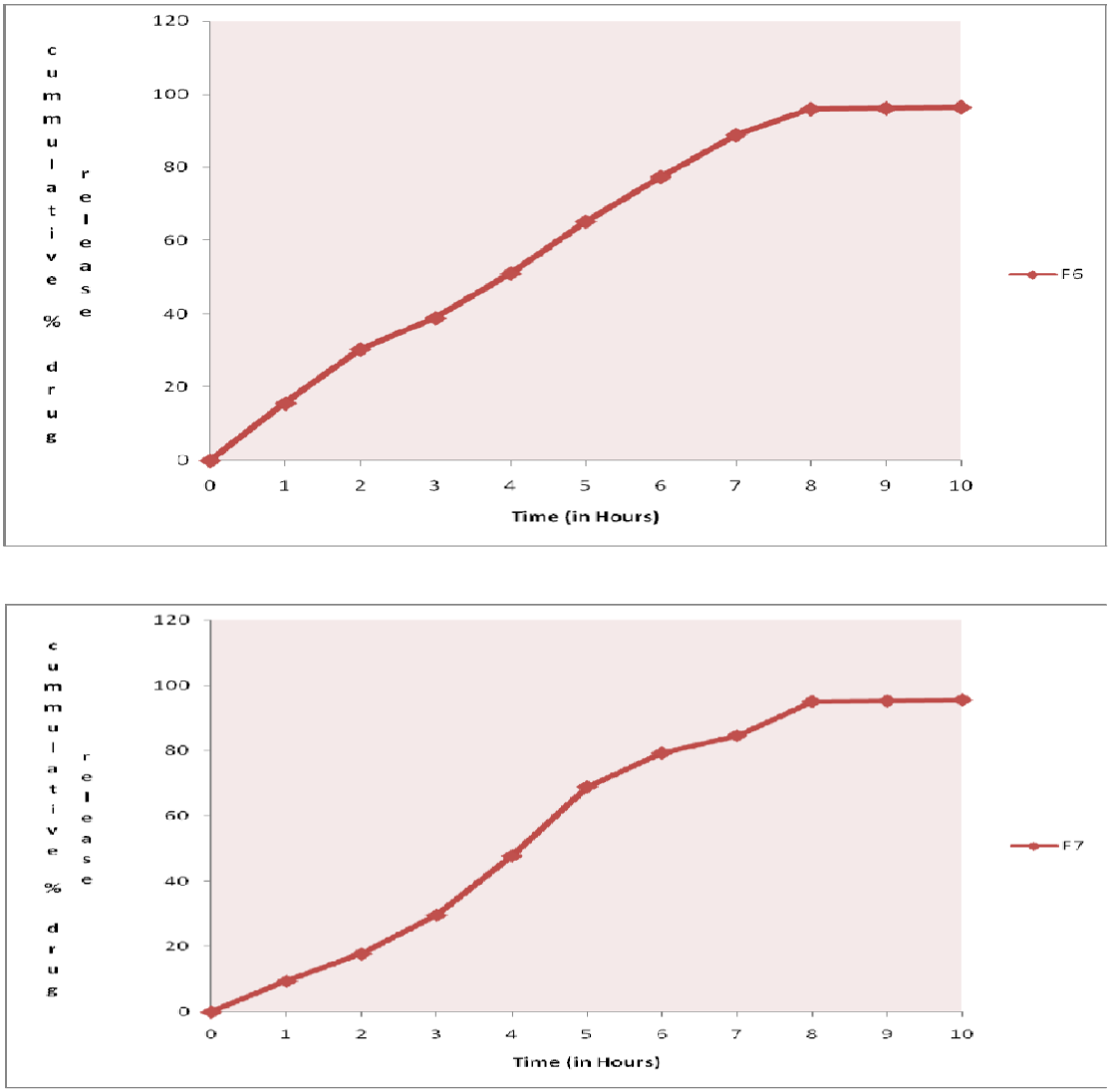
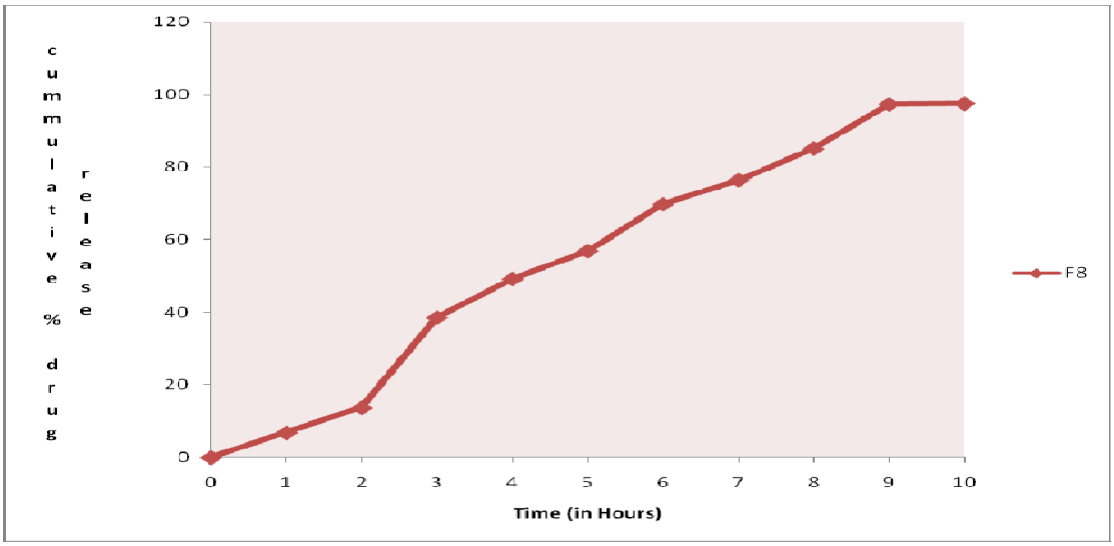


Figure 17: *In vitro* drug release profile of formulation GF7.



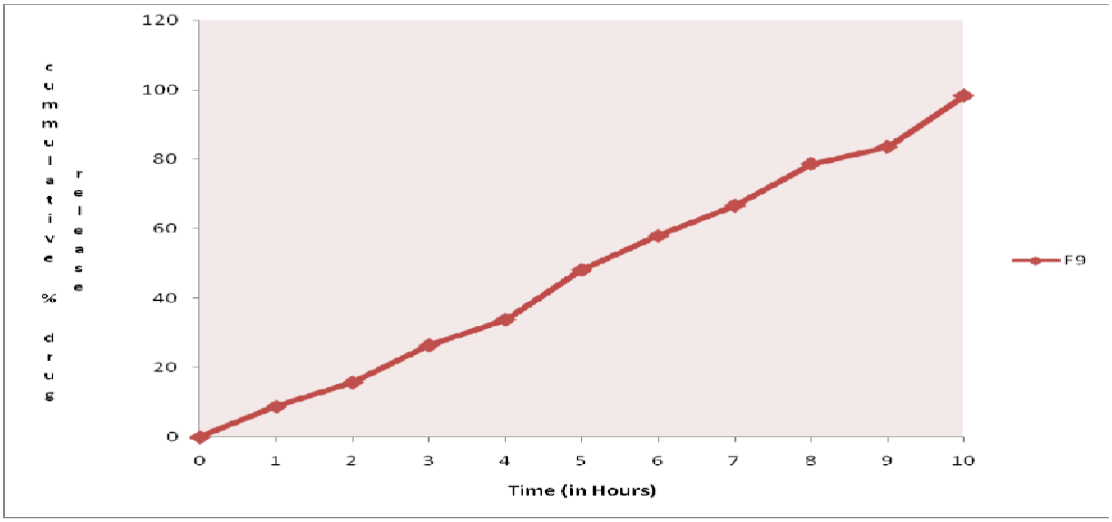


Figure 19: *In vitro* drug release profile of formulation GF9.

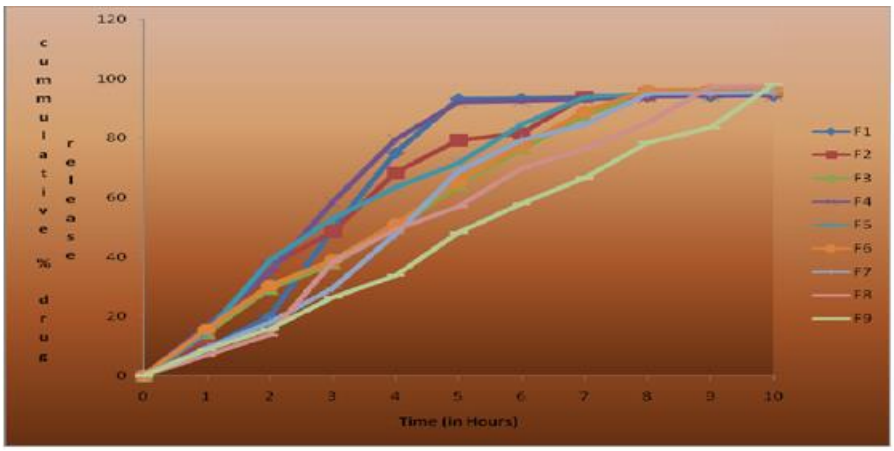


Figure 20: *In vitro* drug release profile of formulations GF1 to GF9.

Gliclazide drug was soluble in phosphate buffers and its release from the matrix was largely dependent on the polymer swelling, drug diffusion and matrix erosion. The concentration of polymer in the matrix tablet was a key factor in sustaining the drug release.

Various sustained release formulations were formulated with HPMC K100M, and ethyl cellulose polymer alone; polyvinyl pyrrolidone as binder and lactose was used as diluents.

The variation in drug release was due to different types of polymers and different concentrations of polymer in all the nine formulations. It is expected that the developed formulations should have the following theoretical drug release profile.

The drug released from formulation GF1 to GF3 containing HPMC K100M at three concentration levels of 10%, 20%, 30% were found to be 94.30 ± 2.54, 95.60 ± 2.54, and

96.1 ± 0.50 % for gliclazide respectively at the end of 10 hours. It was shown in Figures (8, 9 and 10).

The drug released from formulation GF4 to GF6 containing ethyl cellulose at three concentration levels of 10%, 20%, 30% were found to be 94.6 ± 0.50, 95.8 ± 0.91 and 96.5. ± 0.21% for gliclazide respectively at the end of 10 hours. It was shown in Figures (11, 12 and 13).

The drug released from formulation GF7 to GF9 containing both HPMCK100M and ethyl cellulose at three concentration levels of 10%, 20%, 30% were found to be 95.5 ± 1.51, 97.5 ± 2.16 and 98.2 ± 0.55% for gliclazide respectively at the end of 10 hours. It was shown in Figures (14,.5 and 16).

The drug release rate from HPMC K100M matrix was found to be less as compared to and ethyl cellulose. This might be due to slow hydration of matrix and its property to form a thick gel layer, it's due to slow erosion of matrix and its property which retard the drug release from the tablet for long duration.

The overall release rate of gliclazide from ethylcellulose matrices are significantly higher than that from HPMC K100M matrices were shown in Figure 17. These results are indicating that HPMC K100M has higher drug retarding ability for long duration than ethylcellulose.

In addition to concentration of polymer, the type and viscosity of polymer also influences drug release. When drug release data obtained from dissolution study of different polymers at 10%, 20% and 30% concentration is plotted against time respectively, it was observed that low concentration of polymer induces more drug release. High concentration of polymer should be retarding the drug release for longerperiod of time.

From the above study, the formulation GF9 was concluded as the best formulation among all the nine formulation of this series. Hence the formulation GF9 was selected for further stability study.

Kinetics of *in vitro* drug release

In order to investigate the release mechanism, the data were fitted to models representing first order, zero order, higuchi and korsmeyer- Peppas. The linear regression analysis shown as 'r'

values in Table 8.22, demonstrated that all theformulated tablets follows korsmeyer- Peppas release kinetics. The result obtainedwas shown in Figures 21 to 29.

Table 19: Different kinetic models for gliclazide matrix tablets (GF1 to GF9)

F. Code	Zero Order	First order	Higuchi	Korsemeyer- Peppas		Best fit model
	R^2	R^2	R^2	R^2	n	
GF1	0.978	0.918	0.970	0.987	0.720	Peppas
GF2	0.988	0.895	0.950	0.989	0.749	Peppas
GF3	0.988	0.927	0.945	0.992	0.759	Peppas
GF4	0.981	0.849	0.967	0.986	0.698	Peppas
GF5	0.986	0.890	0.962	0.989	0.731	Peppas
GF6	0.989	0.899	0.955	0.990	0.743	Peppas
GF7	0.983	0.888	0.967	0.987	0.726	Peppas
GF8	0.988	0.892	0.957	0.989	0.736	Peppas
GF9	0.989	0.922	0.955	0.990	0.759	Peppas

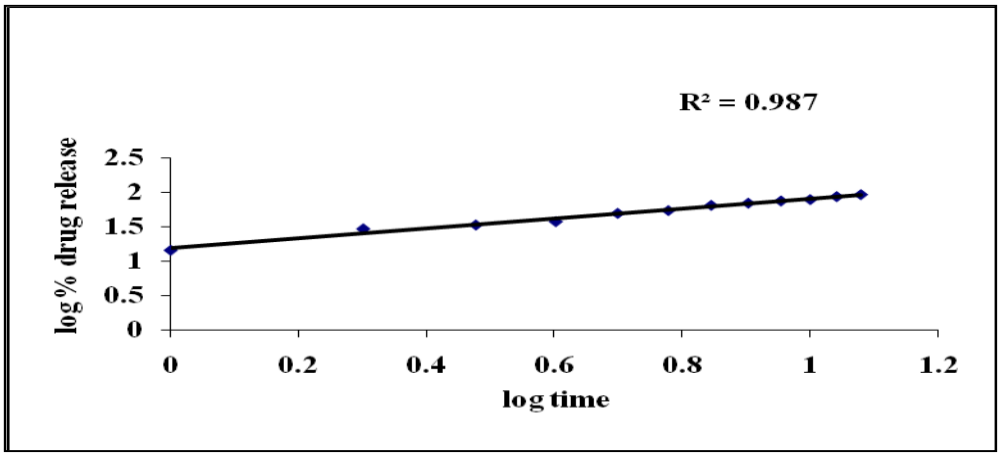


Figure 21: Best fit model (Peppas) of formulation GF1.

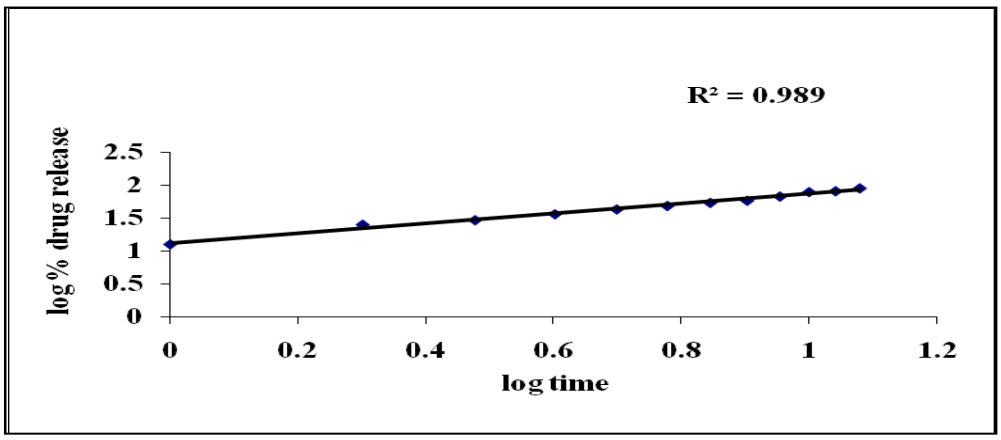


Figure 22: Best fit model (Peppas) of formulation GF2.

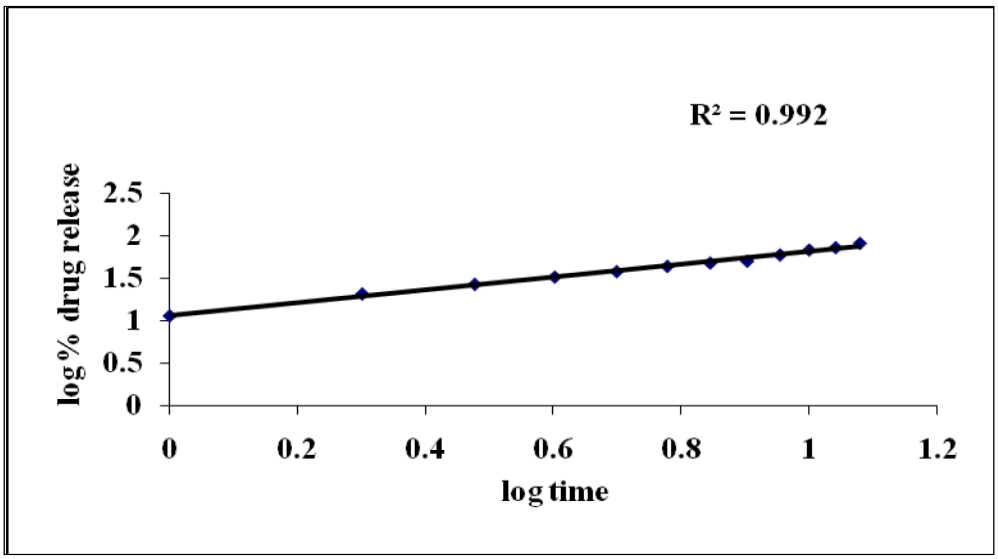


Figure 23: Best fit model (Peppas) of formulation GF3.

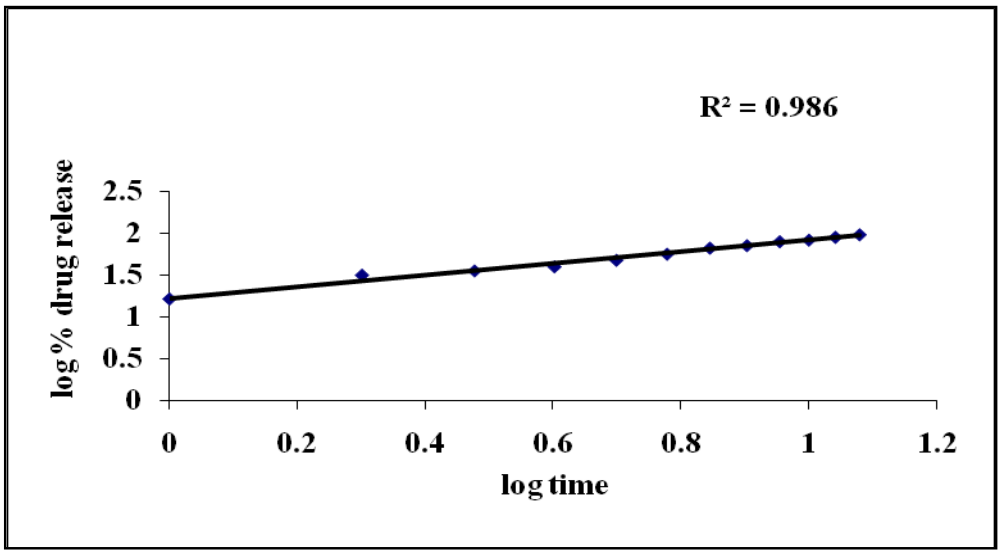


Figure 24: Best fit model (Peppas) of formulation GF4.

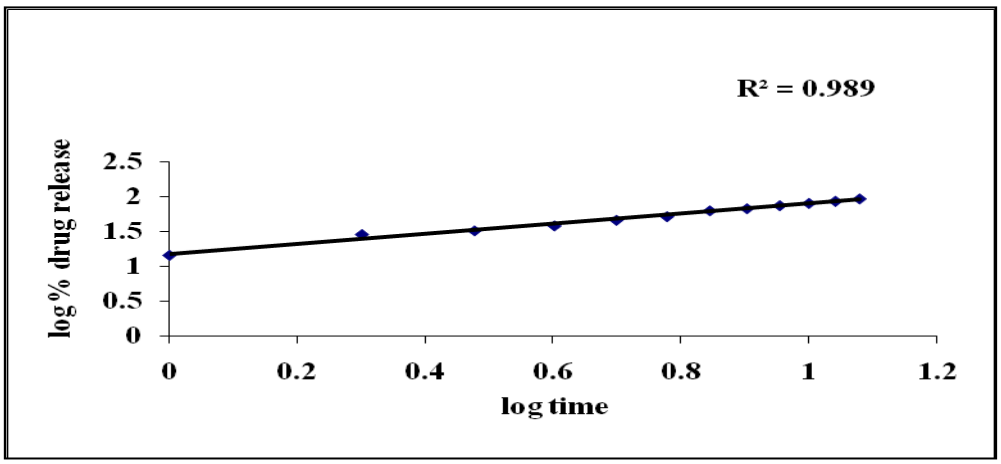


Figure 25: Best fit model (Peppas) of formulation GF5.

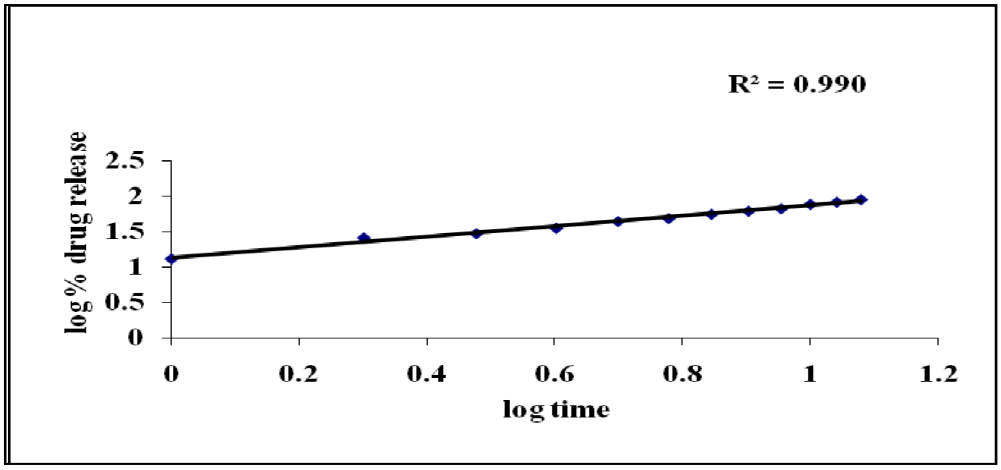


Figure 26: Best fit model (Peppas) of formulation GF6.

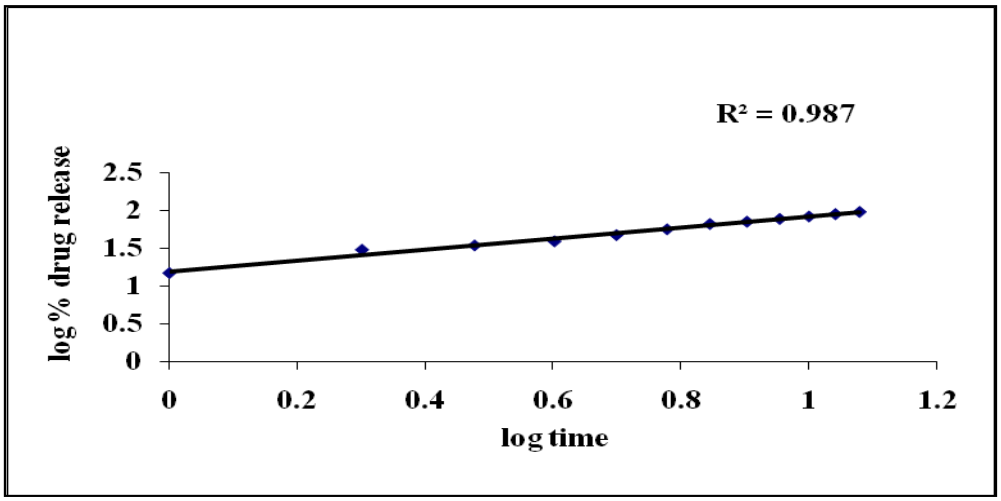


Figure 27: Best fit model (Peppas) of formulation GF7.

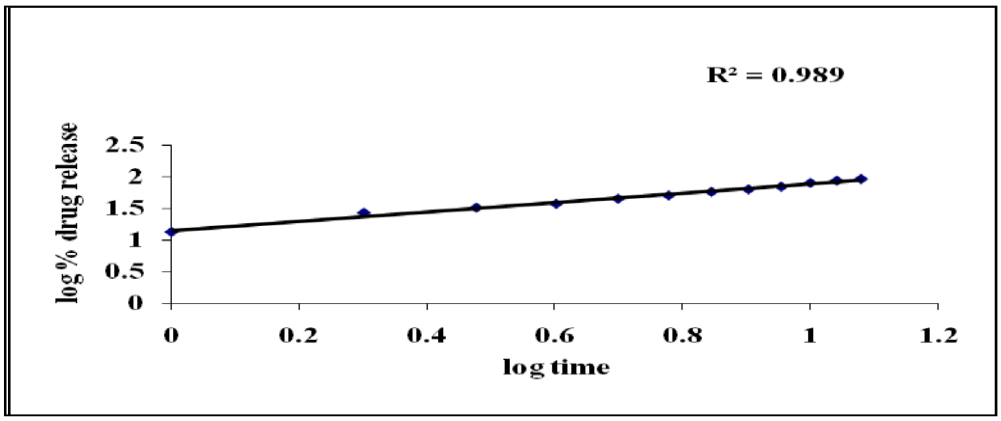


Figure 28: Best fit model (Peppas) of formulation GF8.

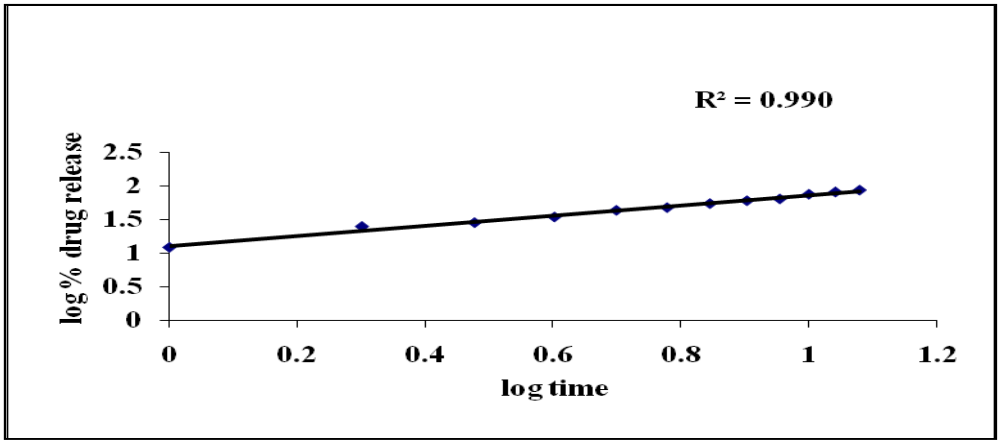


Figure 29: Best fit model (Peppas) of formulation GF9.

Further, to understand the drug release mechanism, the data were fitted to korsmeyer- Peppas exponent equation, when n < 0.45 indicates fickian drug release. For 0.45 < n < 0.89 as anomalous diffusion (non-fickian). In the present study also it was observed that almost all the formulated tablets followed anomalous diffusion mechanism, which indicates the drug release through diffusion coupled with erosion.

Stability study

After exposure to accelerated stability conditions the formulation was analyzed for various evaluation parameters; results were shown in Table 8.23 and Figures 8.39, 8.40 and 8.41.

Table 20: Stability studies of best formulation (GF9).

Stability chamber	Time	Appearance	Hardness (kg/cm²)	Friability(%)	Drug content (%)	%drug release
	Initial	White	6.30±0.10	0.631±0.06	98.56±1.12	98.2±0.55
40±2°C with	1st month	No change	6.25±0.32	0.627±0.09	98.39±0.55	97.8±0.23
75±5°%RH	2nd month	No change	6.23±0.09	0.622±0.05	97.94±0.20	97.3±0.02
	3rd month	No change	6.18±0.06	0.614±0.10	97.63±0.08	96.9±0.30

*All the values were expressed as mean± S.D., n=3.

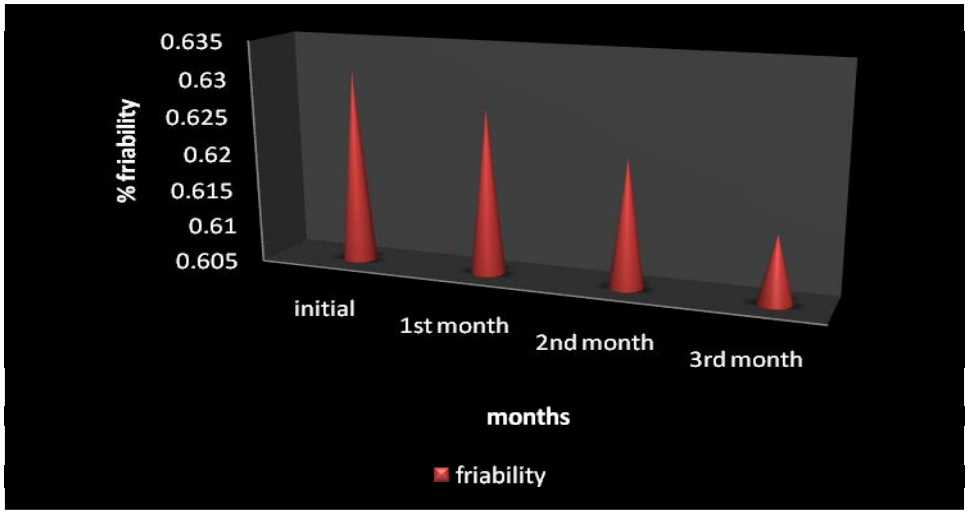


Figure 30: Comparison for friability before and after stability studies of bestformulation GF9.

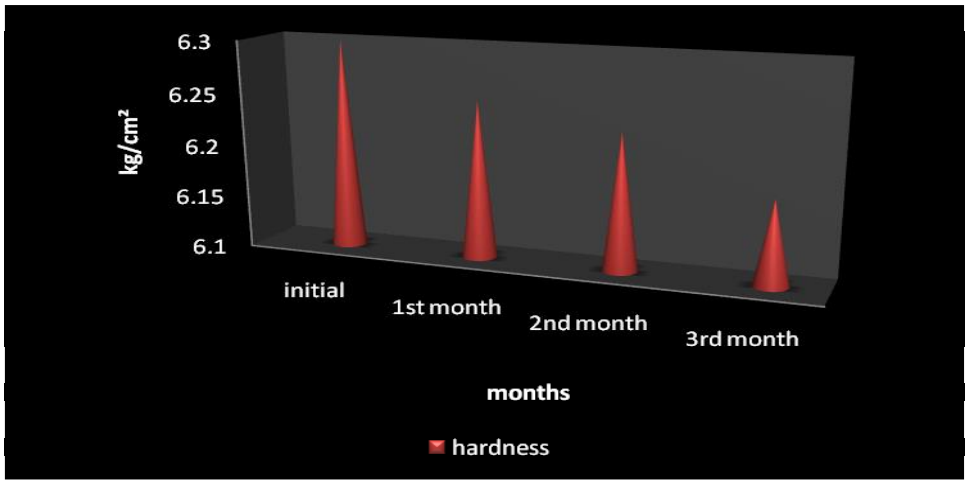


Figure 31: Comparison for hardness before and after stability studies of best formulation GF9.

Figure 32: Comparison for drug content before and after stability studies of best formulation GF9.

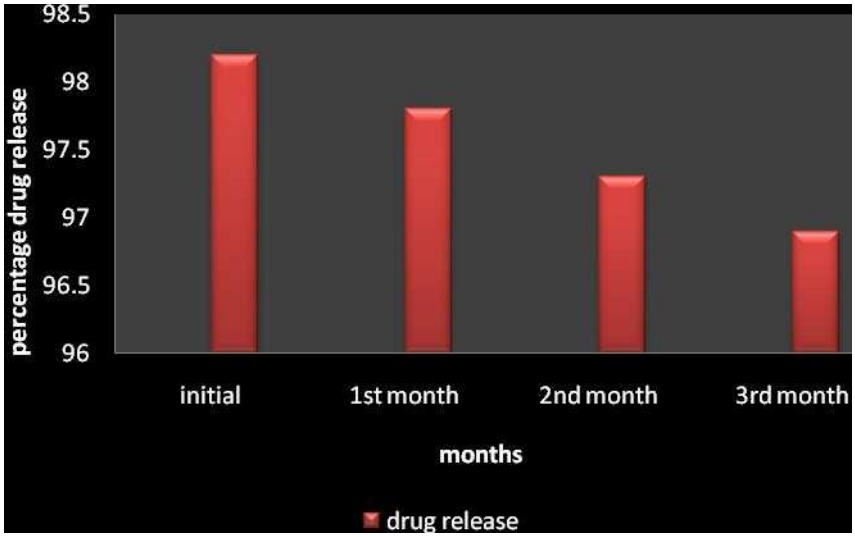


Figure 33 Comparisons for *in vitro* drug release profile of before and after stability studies of best formulation GF9.

From the above studies there was no significance differences was initiate between the evaluated data from initial and after stability studies and all the values were found to be accepting limits. The best formulation was showed adequatephysical stability at $40^{o}C \pm 2^{o}C$ at 75% ± 5% relative humidity.

SUMMARY AND CONCLUSION

Gliclazide was chosen as a drug having soluble in intestinal pH. Gliclazide plays a major role in treatment of Diabetic mellitus type2. The drug half-life in plasma is 10.4 hours. It is bound to plasma proteins 85 to 95%. Gliclazide is rapidly absorbed with a bioavailability of over 97% following oral ingestion, hence it was considered as an good candidate for the design of oral sustained release dosage form.

In the present study, an attempt was made to formulate the oral sustained release matrix tablets of gliclazide to provide a dosage form for prolonged period of time, in order to improve efficacy, reduce the frequency of total dose and better patient compliance. Infrared spectroscopy and differential scanning calorimetric analysis confirmed the absence of any drug polymer interaction.

The sustained release matrix tablets were prepared by the direct compression method using different polymers like hydroxypropyl methylcellulose, and ethylcellulose as release retardant polymers. The powders were evaluated for angle of repose, bulk density, compressibility index and hausner's ratio. All the tests revealed that powders showed

excellent flow properties.

The resulting monolithic tablets were evaluated for thickness, diameter, weight variation test, hardness, friability and drug content. All the tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopoeial standards. The *in vitro* release profiles from tablets of drug and different polymer ratio were applied on various kinetic models. *In vitro* release studies revealed that the release rate was decreased with increase in polymer proportion.

In the present studies, matrix formulation GF9 containing HPMC K100M and ethyl cellulose were probably showing maximum retardation of drug release and it shows anomalous diffusion mechanism, for these reasons, it was considered that the formulation GF9 as best formulation among all the nine formulations. Based onrelease exponent (n) values, it was concluded that mechanism of drug release was found to be diffusion coupled with erosion (anomalous transport mechanism).

From the stability studies, there was no significance difference in hardness, friability, drug content and *in vitro* release profile for the best formulation.

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