FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF GLIPIZIDE BY MEANS OF FACTORIAL DESIGN

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Abstract

Present study was conducted to develop formulation of Glipizide using high viscosity grades of hydroxypropyl methylcellulose (hydrophilic). All the polymers were incorporated separately in the matrix system using wet granulation technique. $A3^2$ full factorial design was employed for the optimization of formulation. The granules were prepared by wet granulation method and thereby formulated as F_1 to F_9 by using the above bring up polymers with other ingredients. The granules of different formulations were evaluated for angle of repose, loose bulk density and tapped density, compressibility index, and drug content. Technological characterizations thickness, diameter, weight variation test, drug content, hardness, and friability were conceded with the formulated matrix tablet and *in- vitro* drug release was measured by means of dissolution apparatus USP *Type II* (paddle) using the phosphate buffer pH 7.4. Formulation F_8 was subjected to stability was accomplished studies for three months at 30^0C/65%RH and 40^0C/75%RH. The kinetic release model showed that the release of drug follows zero order kinetic. Thus the result suggest the developed sustained release tablets of Glipizide performed therapeutically better than conventional dosage form, leading to increased half-life, therapeutic efficacy with better patient compliance.

Key word: Glipizide, HPMC, Matrix Tablet, Wet granulation, Sustained release.

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Introduction [1,2]

Pharmaceutical product design for oral delivery, are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations. Drug with short half-life requires frequent administration, which increases the chances of missing dose of leading to poor patient compliance. A typical peak valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead to under medication or over medication as the C_{ss} values fall or rise beyond the therapeutic range. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever over medication occurs.

Materials and methods

Materials

Glipizide, HPMC K100MCR, HPMC K4M, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide, Isopropyl Alcohol, and PVP-K30 all materials are procured from S. Kant Healthcare, Vapi.

Methods

Compressed tablet using punch size 8 mm with 12 station compressed machine [Rimek Mini Press 2] Check in process parameter. 3^2 randomized full factorial designs were applied in the present study. In this design 2 factors will be evaluated, each at 3 levels, and experimental trials will be performed at all 9 possible combinations.

Table 1: composition of Matrix tablets of Glipizide

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
	mg/tablet								
Glipizide	10	10	10	10	10	10	10	10	10
HPMC K100MCR	20	20	20	30	30	30	40	40	40
HPMC K4M	25	35	45	25	35	45	25	35	45
MCC	136	126	116	126	116	106	116	106	96
PVP K- 30	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Magnesium stearate	2	2	2	2	2	2	2	2	2
IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	200	200	200	200	200	200	200	200	200

Stability Study for Optimized Formulation: [12, 13]

Table 2: Evaluation for physical properties of optimized formulation kept for stability at 400C /75%RH

Parameter	1 Month	2 Month	3Month
Appearance	White	White	White
Thickness	3.66±0.07	3.62±0.04	3.74±0.02
Hardness	7.24±0.07	6.83±0.03	7.51±0.08
Drug content	98.0±0.90	98.3±0.40	97.6±0.52

Table 3: Evaluation for physical properties of optimized formulation kept for stability at 30^0C /65%RH

Parameter	1 Month	2 Month	3Month
Appearance	White	White	White
Thickness	3.64±0.08	3.65±0.03	3.62±0.06
Hardness	7.41±0.02	7.0±0.08	6.85±0.03
Drug content	98.0±0.84	96.3±0.52	98.4±0.20

Result and Discussion

Melting point

Melting point of was found to be in the range of 206-209°C, while in the standard it is reported in the range of 208-209°C. So it can be concluded that Glipizide was in pure state.

Table 4: Me lting point of Glipizide

Sr. No.	Parameters	Glipizide
1	Melting point(Test sample)	206-209^{0}C
2	Melting point (Reference)	208-209^{0}C

FTIR Study for Drug + HPMC K 100 MCR

Compatibility for Glipizide was carried out with potential formulation excipients to determine possibility of any drug –drug excipients interaction/incompatibility.

FTIR spectrums are shown in Figure. FTIR shows no evidence of any significant interaction between drug and HPMC K100MCR and HPMCK4MCR.

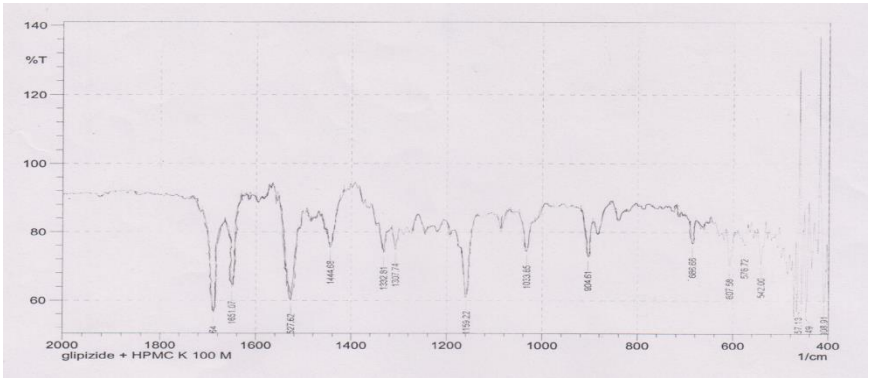


Figure 1: IR spectra of HPMC K 100 MCR+DRUG

The specific peaks obtained are repeated in Table.

FTIR Study for drug + HPMC K 4 M

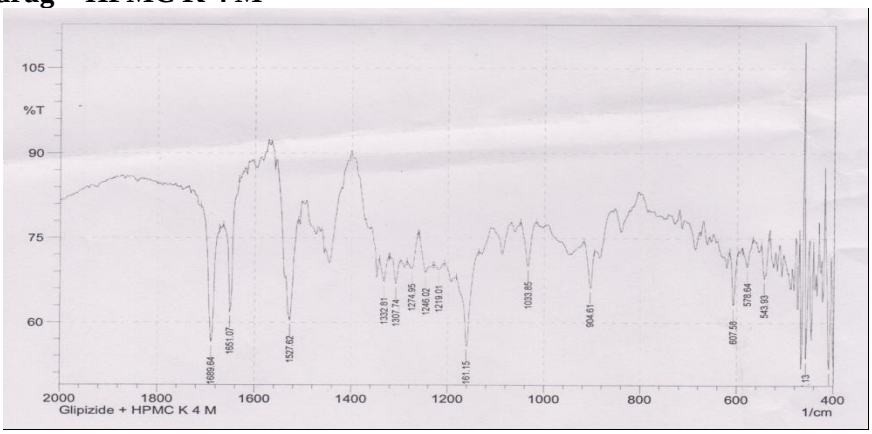


Figure 2: IR spectra of HPMC K 4 M+DRUG

The specific peaks obtained are repeated in Table.

Differential Scanning Calorimetry (DSC)

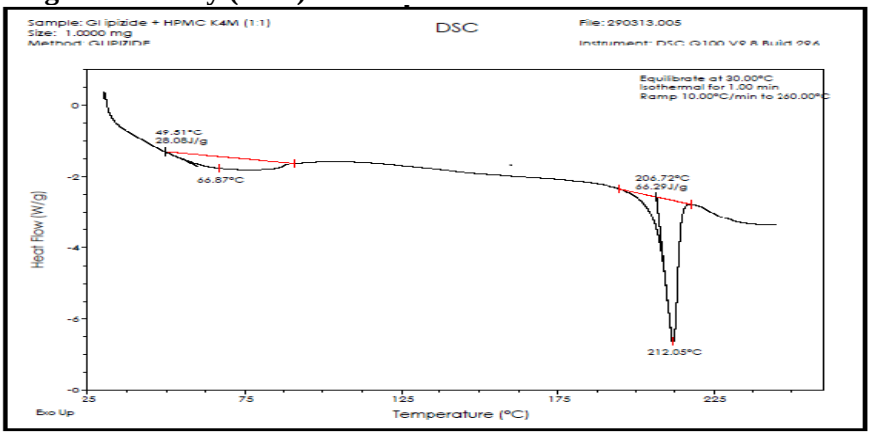


Figure 3: DSC thermograms for Mixture of Glipizide+ HPMC K4M

The DSC thermogram of Glipizide + HPMC K4M was a sharp endothermic peak at 210°C corresponding to the melting transition temperature and decomposition of Glipizide. Such sharp endothermic peak signifies that Glipizide used was in pure state.

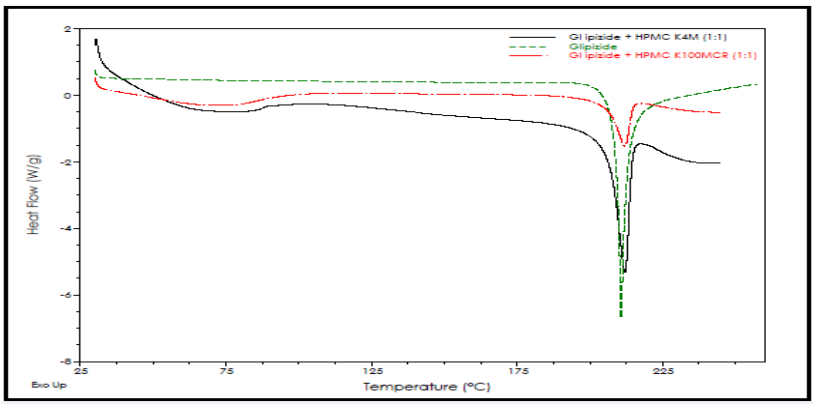


Figure 4: DSC thermograms for Mixture.

Effect of temperature and humidity conditions (Drug – Excipient compatibility Study)

Formulation and Development

Dose Selection

Dose of Glipizide prescribe is 10 mg once daily for sustained release tablet which is safe and effective**.**

Evaluation parameter for F1-F9 formulation

Pre Compression Study

The Angle of repose, Loose bulk density, tapped bulk density, Compressibility index and Hauser's ratio of all the formulations (F1 to F9) were determined and the results obtained are mentioned in the **Table 5** the angle of repose above the $22^0.69$ -$29^0.56$ have flowability shows passable test as per pharmacopeia powder having compressibility more than 14- 28 %- 16.92% powder also shows fair result to passable all the properties of granules which obtained are acceptable for wet granulation of matrix tablet.

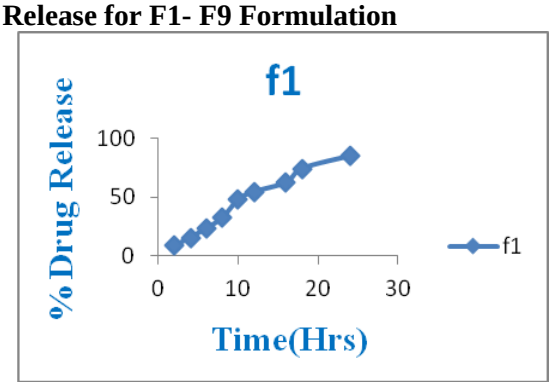
Table 5: Evaluation parameter of granules

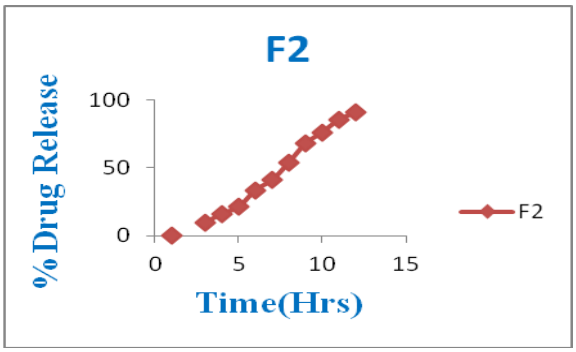
Formulation Code	Angle of Repose (o)	LBD (gm/cm2)	TBD (Gm/cm^2)	Compressibility Index (%)	Hausner's Ratio
F1	28^0.95±0.45	0.375±0.006	0.479±0.025	21.71±4.47	1.17±0.07
F2	29^0.56±0.55	0.387±.005	0.506±0.005	25.83±1.76	1.18±0.03
F3	25^0.94±0.32	0.394±.009	0.504±0.007	21.82±0.62	1.19±0.01
F4	23^0.96±0.40	0.349±0.005	0.456±0.004	23.46±0.81	1.20±0.01
F5	24^0.14±0.26	0.366±0.004	0.482±0.004	24.06±1.69	1.19±0.02
F6	25^0.91±0.45	0.375±0.004	0.482±0.026	22.19±4.32	1.20±0.06
F7	22^0.69±0.81	0.338±0.002	0.440±0.001	23.18±0.44	1.16±0.007
F8	28^0.58±0.7	0.337±0.003	0.458±0.003	26.41±0.38	1.20±0.007
F9	25^0.95±0.25	0.353±0.005	0.470±0.002	24.89±1.42	1.17±0.02

*All values are mean ± SD, (n =3).

Post Compression Study

Drug Release for F1- F9 Formulation





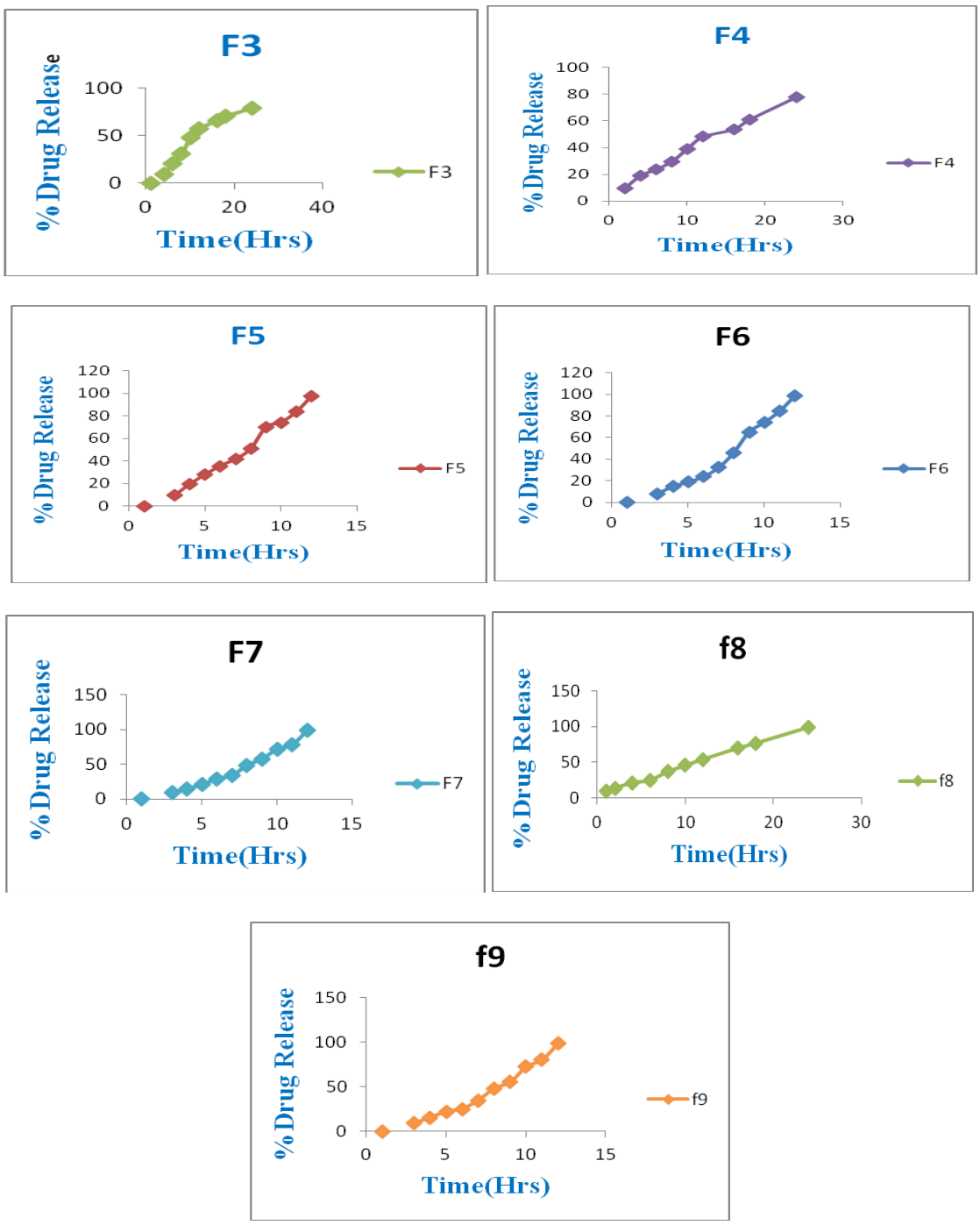


Figure 5: % Drug Release for F1- F9 Formulation

Table 6: Dissolution model for F1- F9 Formulation for r^2 value

Sr. No	Zero order model	First-order model	Higuchi model	Kosmeyer-Peppas model	Hixon-Crowel model
1	0.9727	0.9616	0.9688	0.7836	0.9931
2	0.9528	0.9779	0.9578	0.7836	0.9854
3	0.9196	0.9756	0.9844	0.7836	0.9934
4	0.9821	0.8756	0.9525	0.7836	0.9481
5	0.9661	0.8900	0.9660	0.7836	0.9699
6	0.9769	0.8234	0.9185	0.7836	0.9407
7	0.9920	0.7717	0.9424	0.7836	0.9207
8	0.9960	0.7203	0.9341	0.7836	0.8915
9	0.9922	0.7736	0.9332	0.7836	0.9190
Best fitted model was found to be zero order kinetic model.					

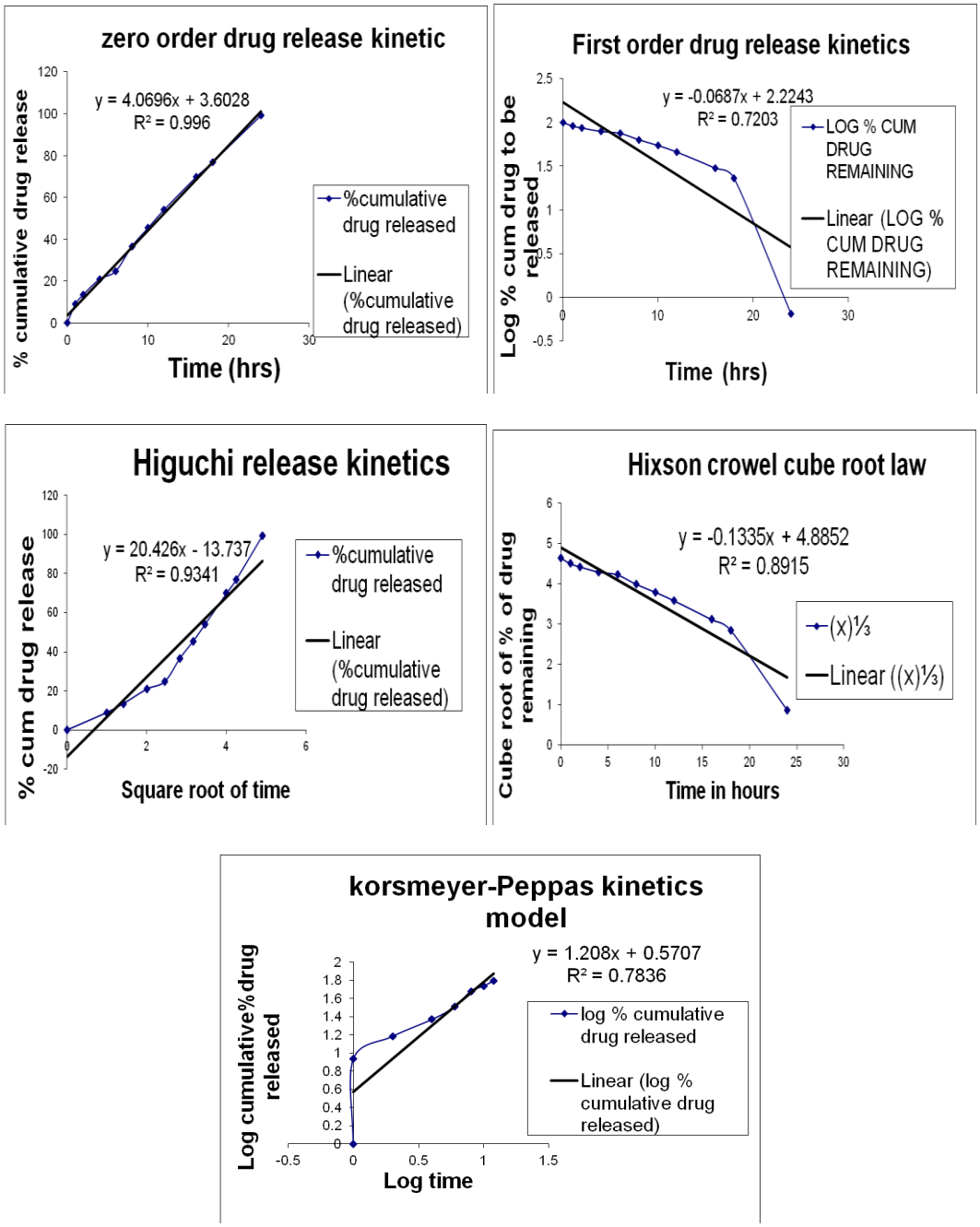


Figure 6: Dissolution Model of optimized Batch F8

Table 7: Cumulative % drug released of stability Studies 40ºC/ 75 % RH

Cumulative % drug released (mean ±S.D.)			
Time(Hr)	**1 month**	**2 month**	**3 month**
1	8.25±2.3	9.22± 1.07	10.4± 0.23
2	14.43±0.2	16.34± 2.62	15.14± 0.39
4	25.84±0.9	24.74± 0.34	28.61± 0.24
6	37.4±0.8	35.05± 0.25	42.32± 0.75
8	46.32±1.6	44.1± 0.53	54.84± 0.79
10	53.97±1.2	52.78± 0.77	61.60± 1.19
12	65.08±0.6	63.06± 0.38	72.07± 0.73
16	77.21±0.5	79.23±2.1	83.12±0.43
18	88.4±0.2	86.2±1.3	89.3±0.43
24	99.21±0.4	97.4±0.4	98.34±0.43

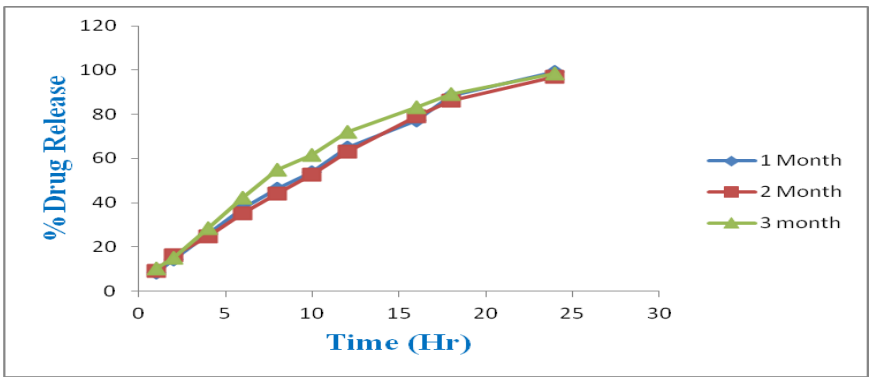


Figure 7:Cumulative % drug release of stability Studies 40ºC/75% RH

Table 8: Cumulative % drug released of stability Study30ºC/ 65 % RH

Cumulative % drug released (mean ±S.D.)			
Time (Hr.)	**1 month**	**2 month**	**3 month**
1	9.86± 0.95	10.04±0.12	10.68± 0.23
2	17.49± 0.44	16.32± 0.16	17.57± 0.39
4	29.53± 0.32	22.37± 0.33	28.73± 0.24
6	38.62± 0.58	33.64± 0.10	36.14± 0.75
8	49.12± 0.52	42.00± 0.40	48.25± 0.79
10	56.48± 2.18	56.52± 5.86	59.64± 1.19
12	68.22± 0.51	65.1± 2.62	70.41± 0.73
16	77.00±0.33	78.82±0.33	81.50±0.32
18	86.09±0.13	88.27±0.12	87.04±0.08
24	99.30±0.85	98.35±0.55	98.22±0.42

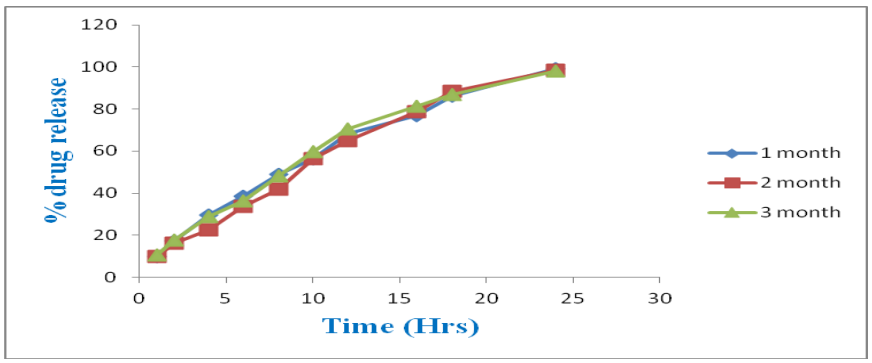


Figure 8: Cumulative % drug release of stability study 30ºC/ 65 % RH

Summary and Conclusion

In present investigation an attempt has been made to design and develop Glipizide matrix tablets using combination of hydroxypropyl methylcellulose K100MCR and hydroxypropyl methylcellulose K 4 M as release retarding polymers. Glipizide is an oral hypoglycemic drug which lowers blood glucose level and has been selected to prepare sustained release dosage forms. Glipizide sustained release matrix tablet were prepared using combination of hydroxypropyl methylcellulose K100MCR and hydroxypropyl methylcellulose K4M as base polymer by wet granulation method. FT-IR spectral analysis showed that characteristic peak of Glipizide pure drug was retained in the spectra of all the formulations indicating the intactness of the drug in all the formulations. The prepared tablets were evaluated for number of parameters like thickness, diameter, weight variation, swelling index and *in -vitro* release studies. All the prepared tablets were of smooth surface and elegant texture. The prepared tablets were checked visually for its appearance & surface texture. The prepared granules were evaluated for various flow-ability parameter the Hausner's ratio was found in the range 1.16±0.007 to 1.20±0.01, compressibility index were found to be in the range 21.71±4.47 to 26.41±0.38, and angle of repose were in the range in respectively

220.69±0.81 to 290.56±0.55 in the formulate F1 to F8 respectively. The weights of the tablets were in the range of 200±8 mg. The thickness of the tablet was in the range of 3.62±0.01 to 3.66±0.06 mm. As the time increases, the swelling index was increased; later on it decrease gradually due to dissolution of outermost- gelled layer of tablet into dissolution medium. Drug content uniformity study showed uniform dispersion of the drug throughout the formulation in the range of 96.8±0.99 99.9±0.57%. The maximum drug release was found to be 99.35 % over a period of 24 hours in combination of HPMC K100MCR and HPMC K4M, and best fit model was found to be zero order, and drug release kinetic study showed all formulation follows anomalous behavior or non-Fickian transport These values are fitted to the Zero order plot and its regression values are ranges from 0.9196 to 0.9960, as its value nearer to the '1' it was conformed as it follows for anomalous behavior or non – Fickian transport. Stability studies reveled that there were no significant changes in physical properties and drug content of formulation F8 the selected formulation was stable. It can be concluded that combination of HPMC K100MCR and HPMC K4M can be used as an effective matrix former to sustain the release of Glipizide for an extended period of 24 hrs.

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