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Formulation and Evaluation of Sustained Release Matrix Tablets Glimipride

Ch. Saibabu, Konuri Deepika*, and Karavadi Thejomoorthy

Department of Pharmaceutics, Malineni Lakshmaiah College of Pharmacy, Kanumalla, Singarayakonda-523101

ABSTRACT

The aim of the study is to formulate sustained release matrix tablets of Glimepiride with different polymers and choosing the best formulation. To perform preformulation studies like flowing properties & bulking density for powders of drug and polymers.To formulate matrix tablets of Glimepiride by wet granulation method by using different polymers like Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose (HPC).To evaluate prepared formulations for physical parameters like weight variation, friability, and hardness etc.To study swelling index behavior of selected formulation. To study *in-vitro* drug release performance of different tablets formulations. To study the effect of different polymers on drug release. To ascertain the release mechanics and kinetics of drug release from compressed matrix tablets. To perform stability studies as per International Conference on Harmonization (ICH) guidelines.

Key words: Glimepride, Hydroxy Propyl Methyl Cellulose K4M, Hydroxy Propyl Cellulose 75-100, Di-calcium Phosphate, PVP K30, Magnesium Stearate and Colloidal silicon dioxide.

Introduction

Pharmaceutical products designed 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[1-5] such a

1) Drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance [6-9.]

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

3) The unavoidable fluctuations in the drug concentration may lead to under

medication or overmedication as the steady state concentration (CSS) values fall or rise beyond the therapeutic range.

4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication

occurs. In this type of controlled drug delivery system, the drug reservoir results from the homogeneous dispersion of the drug particles in either a lipophilic or a hydrophilic polymer matrix. The modified-release delivery systems may be divided conveniently into four categories[10-15]

MATERIALS AND METHODS

Glimepride were obtained from Naprod Life Sciences, Mumbai Indion resins 204, Hydroxy Propyl Methyl Cellulose K4M, Hydroxy Propyl Cellulose 75-100, Di-calcium Phosphate were obtained from Qualigenes fine chemicals. PVP K30, Magnesium Stearate and Colloidal silicon dioxide were obtained from S.D. Fine Chemicals, Mumbai

Preparation of sustained release matrix tablets of Glimepiride with HPMC/HPC or both retarding material.

Weigh and shift the Glimepiride, Di-Calcium phosphate through mesh # 40. Weigh the PVP K-30 and dissolve in water by means of mechanical stirrer. Dry mix the step one material in planetary mixer for 10 min. Add the above binder solution into it with in 2-3 min run the planetary mixer at slow speed for 8-10 min and at high speed for 2-3 min. Add extra water if require.Semidry granules at 60 0C for 30-40 min, passed through mesh #20, again dry

it till LOD (2-3%). Weigh the HPC 75-100, HPMC K-4M, magnesium stearate and aerosol passed through mesh #40. Lubricate it for 5 min with step 4 blend and check the blend parameter.Compressed tablet using punch size 10 mm with 16 station compressed machine.And finally check in process parameter.

Composition of Matrix tablets of Glimepiride

Ingredients (mg/tablet)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Glimepiride	2	2	2	2	2	2	2	2	2
HPC 75-100	60	70	80	---	---	---	30	30	30
HPMC K4M	---	---	---	60	70	80	30	40	50
Di-calcium Phosphate	215	205	195	215	205	195	215	205	195
PVP K30	10	10	10	10	10	10	10	10	10
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Aerosil	1	1	1	1	1	1	1	1	1
Water	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

Determination of Dissolution Pattern: -

Freshly prepared test media of 900 ml was placed in dissolution vessels of dissolution test apparatus USP XXIV model. Six samples of the matrix tablet of Glimepiride (after weighing) was placed in 6 different jar containing dissolution media and temperature was maintained at 37.5 ±10C and paddle was rotated at the speed of 100 rpm. At the specified time interval withdraw 5 ml sample solution from each vessel and filter. Further dilute the sample upto 25ml with dissolution medium. Then measure the absorbance of standard and sample solution in 1 cm cell on a suitable UV spectrophotometer at 226 nm and 290 nm, using dissolution as blank. Correct the absorbance obtained at 226 nm by subtracting the absorbance obtained at 290 nm. Record the absorbance and calculate the percentage of Glimepiride dissolved in dissolution media by using following formula.

RESULTS & DISCUSSION

CALIBRATION CURVE.

Standard Calibration Curve of Glimepiride in phosphate buffer pH 7.4:-

Standard calibration curve of Glimepiride was drawn by plotting absorbance v/s concentration. The absorbance values are tabulated in Table 6. Standard calibration curve of Glimepiride in the Beer's range between 5-25 µg/ml is shown in Fig below

Calibration data of Glimepiride in phosphate buffer pH 7.4 at 226 nm and 290 nm.

S. No.	Concentration(µg/ml)	Absorbance*
1	0	0
2	5	0.108
3	10	0.224
4	15	0.339
5	20	0.423
6	25	0.552

*Average of 3 determinations

The linear regression analysis for standard curve in phosphate buffer pH 7.4:-

The linear regression analysis was done on absorbance data points. The results are as follows:

The Slope = 0.022

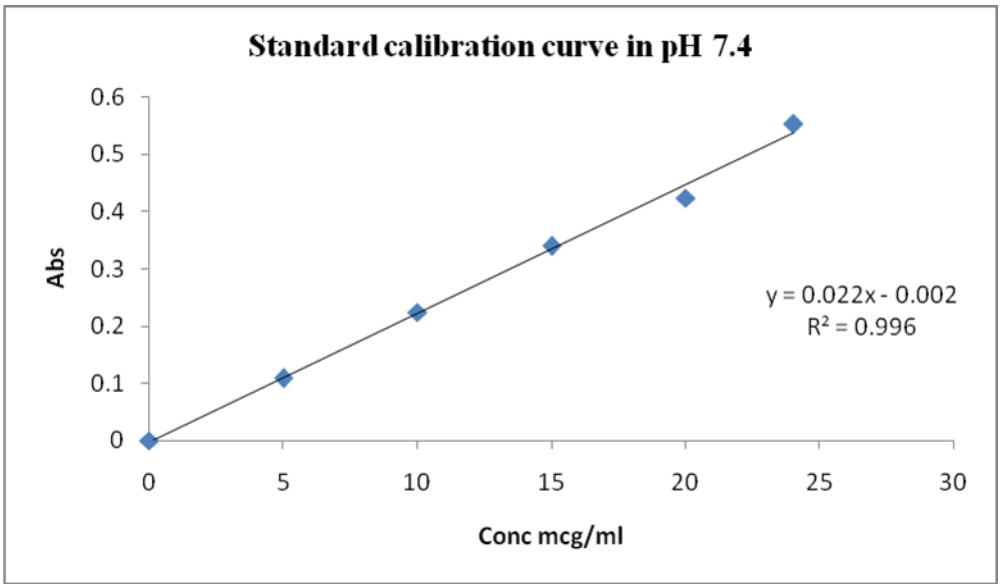
The intercept = 0 .002

The correlation coefficient = 0.996

A straight-line equation (y = mx + c) was generated to facilitate the calculation for amount of drug. The equation is as follows.

Absorbance = 0.022 x Concentration

Standard calibration curve for Glimepiride in phosphate buffer pH 7.4 at 226 nm and 290 nm.



II. COMPATIBILITY STUDY:-

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied making a KBr disc. The characteristic absorption peaks of Glimepiride were obtained at different wave numbers in different samples. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. The spectra for all formulations are shown below.

The spectral details for all types of formulations are shown as follows

A. Pure drug Glimepiride.

IR Spectrum	S.No	(KBr Disc) peaks at	Indications
	1.	3272 cm-1	NH, str.
	2.	3118 cm-1	CH, str Ar

	3.	2931 cm-1	CH str. CH3
	4.	1708 cm-1	C=O str.
	5.	1438,1352 cm-1	C=C str.
	6.	1163 cm-1	C-N str

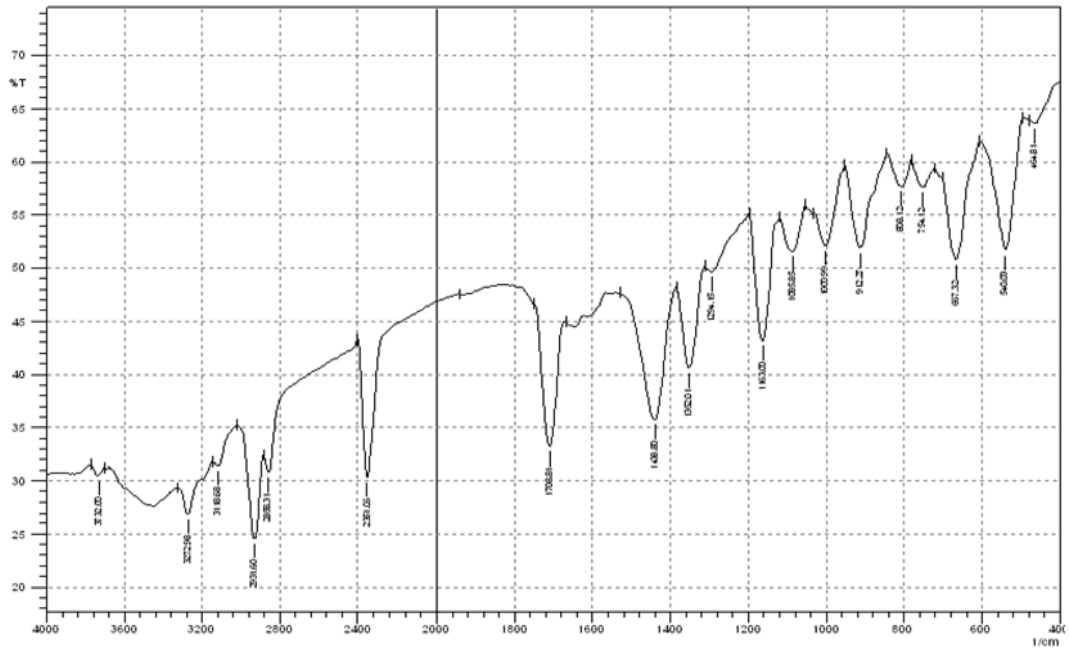
B. Glimepiride + HPC 75-100

IR Spectrum	S.No	(KBr Disc) peaks at	Indications
	1.	3771 - 3190 cm-1	NH, str.
	2.	2939 cm-1	CH, str. CH3
	3.	1708 cm-1	C=C, str,
	4.	1436, 1348 cm-1	C=C, str
	5.	1160, cm-1	C- N str

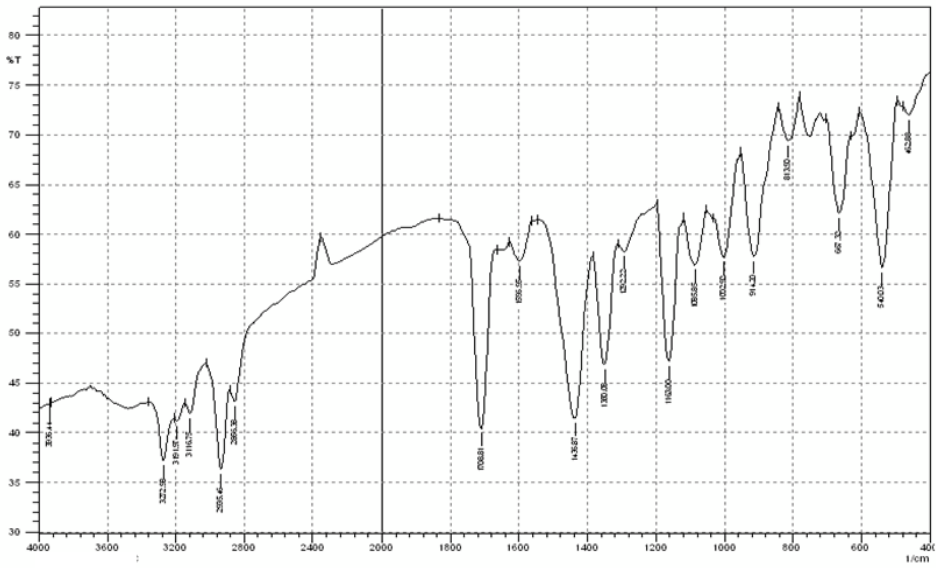
C. Glimepiride + HPMC

IR Spectrum	S.No	(KBr Disc) peaks at	Indications
	1.	3272 cm-1	NH, str
	2.	3116 cm-1	CH, st. Ar
	3.	2935 cm-1	CH str, CH3
	4.	1708 cm-1	C=O, str
	5.	1596, 1436 cm-1	C=C str
	6.	1163 cm-1	C-N str

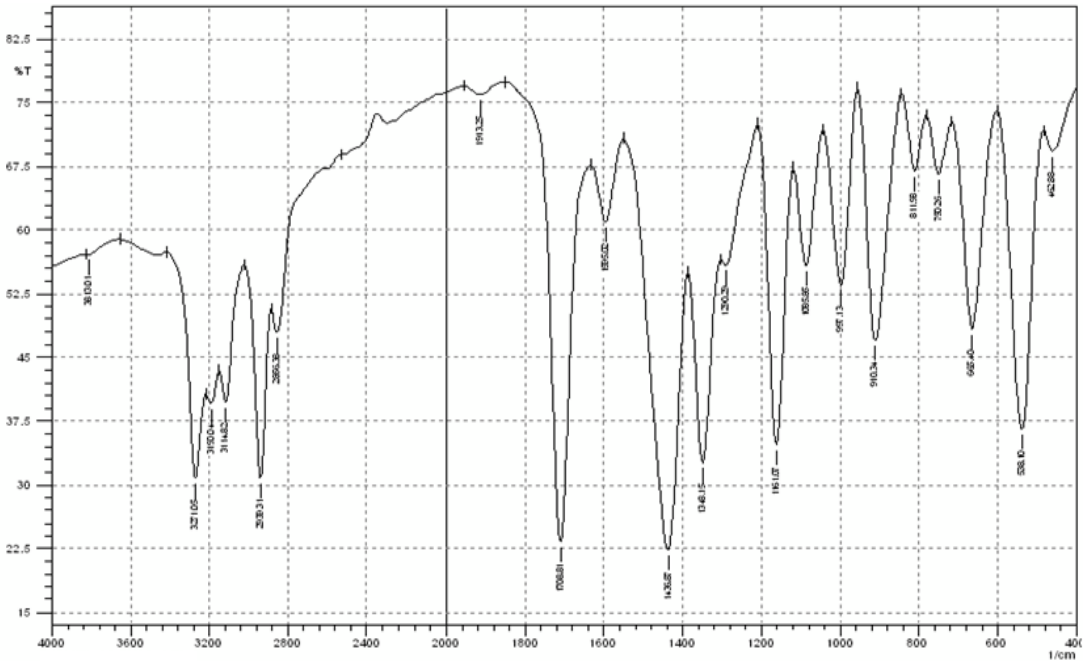
IR Spectrum of Glimepiride Pure drug



IR Spectrum of Glimepiride + HPMC K4M



IR Spectrum of Glimepiride+ HPC 75-100



Physical Properties of all granules

Formulations	Angle of repose (θ)	Compressibility Index or Carr's Index (%)	Hausner's ratio	Drug uniformity* (%)
F1	280.95′	15.15	1.178	98.94±0.40
F2	290.56′	15.38	1.182	97.31±0.32
F3	250.94′	16.42	1.196	99.75±0.33
F4	230.96′	16.92	1.204	96.31±0.41
F5	240.14′	16.42	1.196	98.69±0.22
F6	250.91′	16.67	1.2	99.75±0.34
F7	220.69′	14.28	1.167	99.75±0.21
F8	230.58′	16.67	1.2	98.94±0.25
F9	250.95′	14.92	1.175	99.75±0.34

*mean±SD, n=3.

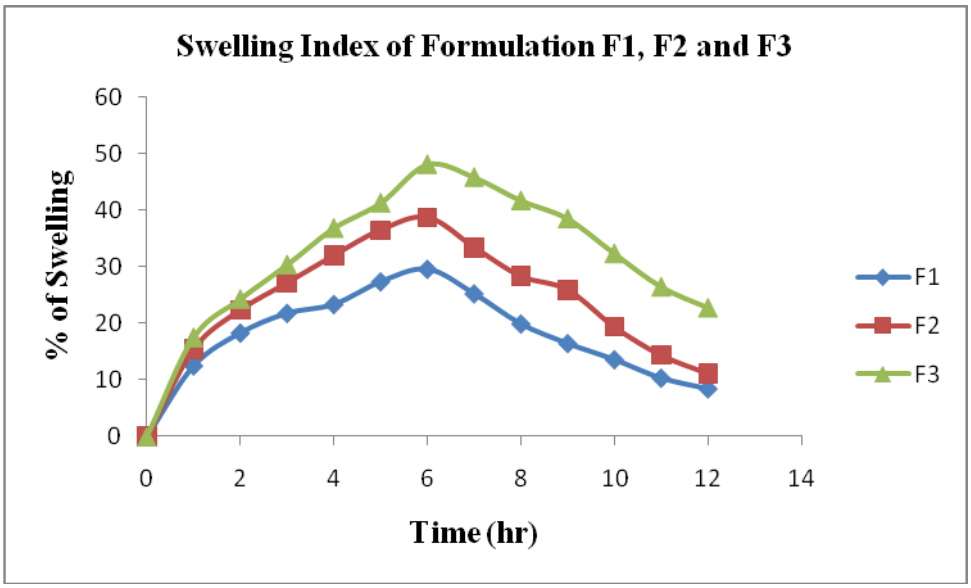
Physical Properties of all Formulations.

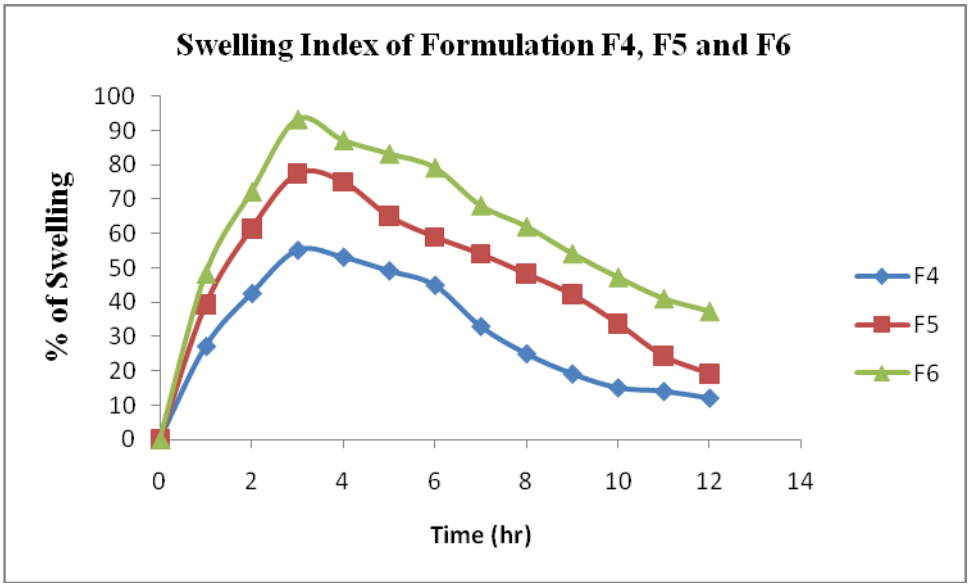
Formulations	Diameter* (mm)	Thickness* (mm)	#Weight variation (mg)	Hardness* (kg /cm2)	Friability (%)	Drug content* (%)
F1	10.05±0.030	4.45±0.11	351±5	5.1 ± 0.12	0.191	97.00±0.24
F2	10.06±0.040	4.50±0.04	350±5	5.5 ± 0.24	0.290	98.90±0.22
F3	10.04±0.030	4.49±0.05	354±5	5.8 ± 0.21	0.146	97.86±0.34
F4	10.02±0.030	4.45±0.12	345±5	5 .2± 0.23	0.149	98.75±0.32
F5	10.02±0.054	4.46±0.03	347±5	5.9 ± 0.12	0.145	96.26±0.46
F6	10.05±0.064	4.54±0.23	351±5	6.1 ± 0.14	0.191	98.45±0.26
F7	10.07±0.022	4.52 ±0.2	352±5	5.2 ± 0.18	0.193	98.00±0.28
F8	10.05±0.035	4.51±0.12	349±5	5.4 ± 0.22	0.146	99.72±0.30
F9	10.04±0.059	4.53 ±0.3	348±5	6 .1± 0.21	0.191	98.82±0.34

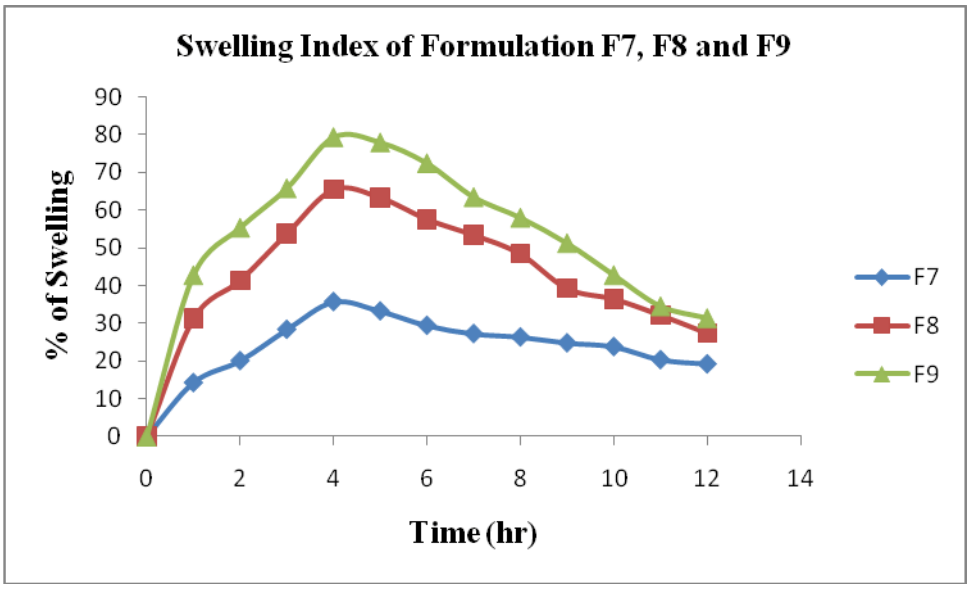
* mean ±SD, n=6. # mean ±SD, n=20.

Swelling Index Behavior Study of selected Formulations*

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	12.5	15.45	17.56	27.2	39.2	48.32	14.3	31.21	42.76
2	18.3	22.34	24.34	42.6	61.34	72.21	20.09	41.4	55.34
3	21.78	27.14	30.4	55.2	77.34	93.32	28.34	53.8	65.76
4	23.34	31.98	36.87	53.2	75.03	87.23	35.67	65.5	79.3
5	27.34	36.45	41.34	49.2	65.03	83.32	33.21	63.3	77.9
6	29.56	38.67	48.14	45.01	59	79.24	29.4	57.6	72.4
7	25.23	33.4	45.87	33.01	54.02	68.21	27.23	53.4	63.45
8	19.9	28.3	41.76	25.03	48.23	62.1	26.34	48.43	57.98
9	16.45	25.9	38.56	19.14	42.21	54.21	24.8	39.23	51.23
10	13.6	19.34	32.4	15.09	33.8	47.28	23.8	36.45	42.8
11	10.34	14.34	26.5	14.06	24.27	41.09	20.35	32.2	34.54
12	8.45	11.1	22.8	12.08	19.2	37.4	19.23	27.4	31.4







***In vitro* drug release for all tablets formulation**

TIME (Hrs)	FORMULATIONS									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**Amaryl**
0	0	0	0	0	0	0	0	0	0	0
1	19.772	15	16.363	20.454	18.409	12.613	16.704	15	12.272	12.272
2	42.272	26.590	28.636	44.659	32.045	23.522	31.704	28.636	22.5	23.522
3	61.363	42.613	40.227	66.136	41.931	33.068	48.068	38.181	31.363	33.409
4	82.840	61.022	53.863	82.5	55.227	45.340	62.045	49.090	47.045	47.045
6	97.840	82.840	73.295	99.204	68.522	61.022	83.863	64.431	62.386	64.772
8	97.840	98.522	85.568	99.204	82.840	80.454	98.181	83.522	80.113	80.454

10	97.840	98.522	98.181	99.204	97.840	88.295	98.181	97.840	90	88.636
12	97.840	98.522	98.181	99.204	97.840	98.181	98.181	97.840	99.204	98.522

DISCUSSION OF RESULTS

The goal of any drug delivery system is to provide a therapeutic amount of drug to the target site in the body and also to achieve and maintain the desired plasma concentration of the drug for a particular period of time. The goals of sustained drug delivery are to conserve and maintain effective drug concentration, eliminate night time dosage, improve compliance and decrease side effects thus, optimizing drug therapy.

In present investigation an attempt has been made to design and develop some Glimepiride matrix tablets using Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose and their combination as release retarding polymers. Glimepiride is oral hypoglycaemic drug which lowers blood glucose level and has been selected to prepare sustained release dosage forms.

1. Glimepiride sustained release matrix tablet were prepared using Hydorxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose and their combination as base polymer by wet granulation method.
2. IR spectral analysis showed that characteristic peak of Glimepiride pure drug was retained in the spectra of all the formulations indicating the intactness of the drug in all the formulations.
3. The prepared tablets were evaluated for number of parameters like thickness, diameter, weight variation, swelling index and *in vitro* release studies.
4. All the prepared tablets were of smooth surface and elegant texture.
5. The tablets prepared were checked visually for its appearance & surface texture.
6. The weights of the tablets were in the range of 250 ± 5 mg. The thickness of the tablet was in the range of 4.45 ± 0.11 to 4.51 ± 0.12 mm.

As the time increases, the swelling index was increased later on it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. Comparison between Hydroxy Propyl Cellulose and Hydroxy Propyl Methyl Cellulose has been observed that swelling index is more in Hydroxy Propyl Methyl Cellulose. Drug content uniformity study showed uniform dispersion of the drug throughout the formulation in the range of 97.00 ±0.24 to 99.72 ±0.30 %.

7. The maximum drug release was found to be 98.18% over a period of 12 hours in HPMC K4M based tablets (F6). Similarly maximum drug release was found to be 99.20% over a period of 12 hours in HPC 75-100 & HPMC K4M based tablets (F9) and maximum drug release was found to be 98.52% over a period of 12 hours in marketed formulation Amaryl. This indicates that the minimum quantity of HPC 75-100 and maximum quantity of HPMC required to prepare the sustain release matrix tablets of Glimepiride

8. The formulations were also subjected to model fitting analysis to know the order and mechanism of drug release from the formulations by treating the data according to zero – order, *first – order*, *Higuchi* and peppas equations. The data clearly shows that, the release kinetics revealed that the formulations containing HPMC K4M follows *first – order* drug release with non-fickian diffusion, formulation containing HPC 75-100 & HPMC K4M follows *first – order* drug release with non-fickian diffusion and the marketed sample Amaryl follows *first – order* drug release with non-fickian diffusion. Sustained Release matrix tablets of Glimepiride were formulated and evaluated.

Conclusion

Glimepiride tablets were prepared using HPMC K4M and HPC 75-100 as release retardant materials by Wet Granulation method. By increasing the polymer concentration there is decrease in rate of drug release. By comparing all the formulations, formulation (F9) containing minimum amount of Hydroxypropylcellulose and maximum amount of Hydroxypropylmethylcellulose showed better sustained release.The tablets showed a sustained release profile in-vitro without the burst release of the drug.

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