Effect of different polymers on release of the sustained release tablets of the glipizide

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ABSTRACT

Sustained release delivery systems have shown to be of better significance in release rate for drug. The present work was an attempt to study the effect of different polymers like HPMC – K100M, HPMC – K15M, Chitosan, and Aloe mucilage on release of the sustained release tablets of the Glipizide. The formulations were prepared with the polymers in different ratios with the drug (drug: polymer, 1:6, 1:7, 1:8) by wet granulation method. Sustained release tablets of Glipizide which on oral administration prolongs its release thereby increasing bioavailability, diminishing side effects and enhanced patient compliance. The prepared formulations were evaluated with pre-compression parameters like bulk density, compressibility index, hausner's ratio, angle of repose and post-compression parameters like weight variation, thickness, hardness, friability. In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II at 50 rpm. The dissolution medium consisted of 900 ml of pH 7.4 phosphate buffer, maintained at 37 ± 0.5^{0} C. Among all the formulation the HPMC – K100M shows the better retarding of drug release from the Glipizide sustained release tablets.

Key words: Glipizide, HPMC – K100M, HPMC – K15M, Chitosan, Aloe mucilage, sustained release, *in-vitro* dissolution.

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INTRODUCTION

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages [1]. Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs[2]. Diabetes a global public health problem is a chronic disease and is now growing as an epidemic in both developed and developing countries. Around 150 million people suffer from diabetes in the world out of which above 35 million are Indians. Current drugs used for managing TYPE II Diabetes and its precursor syndromes, such as insulin resistance, fall within five classes of compound such as the Biguanides, Thiazolidinediones, Sulfonylurea's, Benzoic acid derivatives and alpha glycosidase inhibitors.

Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes. Glipizide, is an effective oral antidiabetic (100 times more potent than tolbutamide in evoking

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pancreatic secretion of insulin [3,4] requires controlled release formulation owing to its short biological half-life [5] of 3.4 ± 0.7 h and is rapidly eliminated). Hence sustained release formulation is needed for glipizide for better control of blood glucose levels to prevent hypoglycemia and enhance clinical efficiency, to reduce G.I disturbances and to enhance patient compliance. A few controlled release formulations of glipizide are available commercially.

The major objective of the present study is to design and evaluate glipizide sustained release tablets by using the different polymers. Another objective of the study is to compare the release-retarding efficiency of these four polymers for controlled release of glipizide

EXPERIMENTAL SECTION

2.1Materials
Glipizide is a gift sample from Kekole pharma Pvt ltd, Hyderabad. HPMC – K100M was brought from Dr.Reddy's laboratory Hyderabad, HPMC – K15M, Chitosan, MCC, Magnesium stearate, Colloidal silicon dioxide from Finar chemicals Ltd, Ahmadabad, Pectin from Burgoyne burbidges & co, Mumbai, PVP-K30 Accord labs,Secunderbad

2.2. Compatability studies
Compatibility studies of pure drug Glipizide with polymers was carried out prior to the formulation of tablets. IR spectra of pure drug and polymers were taken, which were depicted in Figures 1-5. All the characteristic peaks of Glipizide were present in spectra at respective wavelengths. Thus, indicating compatibility between drug and polymers. It shows that there was no significant change in the chemical integrity of the drug.

2.3. Preparation of tablets
Sustained release tablets each containing 10 mg of Glipizide were formulated with (i) HPMC K100M (ii) HPMC K15M (iii) Chitosan (iv) Aloe mucilage (v) Pectin as rate-controlling polymers. All formulations were prepared with the polymers in different ratios with the drug (drug: polymer, 1:6, 1:7, 1:8) by wet granulation method. The SR tablets were prepared as per the formulae given in (Table 1). Accurate quantities of all ingredients were weighed. The MCC, Polymer and the drug were passed through the # 40 and collected separately in polybags. The required quantities of medicament and matrix materials were mixed thoroughly in a mortar by following geometric dilution. The polymer solution (prepared by dissolving the PVPK-30 in water) was added to and mixed thoroughly to form dough mass. The mass was passed through mesh#10 to obtain wet granules. The wet granules were dried at 55°C±5°C to get the LOD limit 1.5 to 2. The dried granules were passed through mesh#20 to break the aggregates. The lubricants talc and magnesium stearate were passed through mesh no. 60 onto dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary multi-station tablet-punching Machinery United technician corp. Delhi.) to a hardness of 4-5 kg/cm2, using 8 mm round and flat punches.

2.4. Evaluation of granules
The angle of repose was measured by using funnel method, which indicates the flow ability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= weight of the powder / volume of the packing. TBD= weight of the powder / tapped volume of the packing. Compressibility index [18] of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100.The physical properties of granules were shown in Table 3.

2.5. Evaluation of tablets
Hardness of the tablets was tested using a Monsanto Hardness Tester. Friability of the tablets was determined in a Roche Friabilator. Disintegration times were determined in various dissolution fluids viz., distilled water and pH 7.4 phosphate buffer using Electrolab tablet disintegration apparatus.

2.6. Estimation of glipizide
Glipizide content of the matrix tablets was estimated by UV spectrophotometric method [6] based on the measurement of absorbance at 223 nm in phosphate buffer of pH 7.4. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range 1-10 µg/ml. When standard drug solution was assayed repeatedly (n=6), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.6 and 0.8 %, respectively.

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2.7. In-vitro release studies
Drug release studies from the SR tablets was studied using 8 station dissolution rate test apparatus (Lab India) employing a paddle stirrer at 50 rpm and at 37±1°C. Phosphate buffer of pH 7.4 (900 ml) was used as dissolution fluid. Samples of 5 ml of each were withdrawn at different time intervals over a period of 24 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 223 nm for glipizide using a Shimadzu UV-150 double beam UV-spectrophotometer. The drug release experiments were conducted in triplicate.

RESULTS AND DISCUSSION

The SR tablets were prepared by conventional wet granulation method as per formulae given in (Table 1). Formulations SR F1 to SR F3 contained HPMCK100M, Formulations SR F4 to SR F6 contained HPMCK15M, Formulations SR F7 to SR F9 contained Chitosan, Formulations SR F10 to SR F12 contained Aloe mucilage [7], and Formulations SR F13 to SR F15 contained Pectin. The HPMCK100M [8] exhibited excellent release retarding properties in matrix tablets for controlled release. All the prepared tablets were evaluated for physical properties and drug release characteristics.

Table 1: FORMULATION OF GLIPIZIDE MATRIX TABLETS

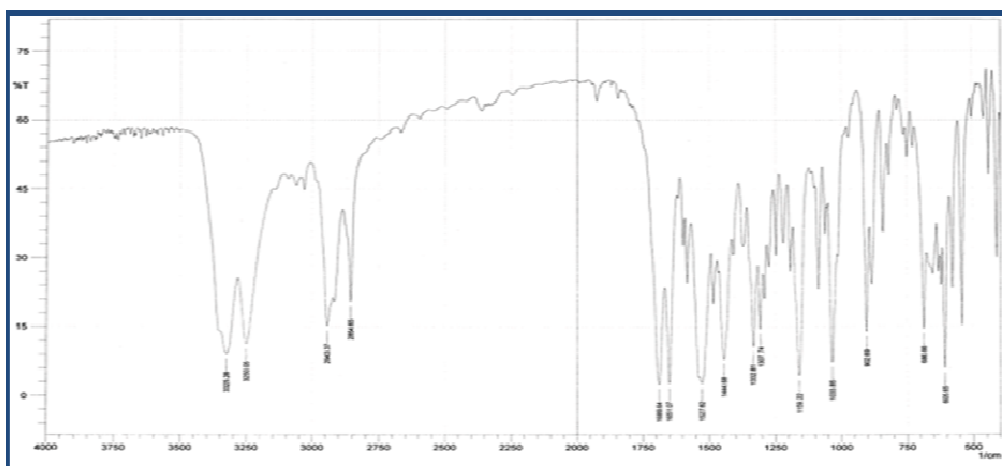| F. NO	Glipizide (Mg)	HPMC K100M (%)	HPMC K15M (%)	Chitosan (%)	Aloe mucilage(%)	Pectin (%)	MCC	PVP	Magnesium stearate	Colloidal silicon dioxide
SRF1	10	-	-	60	-	-	105	5	10	10
SRF2	10	-	-	70	-	-	95	5	10	10
SRF3	10	-	-	80	-	-	85	5	10	10
SRF4	10	-	-	-	-	60	105	5	10	10
SRF5	10	-	-	-	-	70	95	5	10	10
SRF6	10	-	-	-	-	80	85	5	10	10
SRF7	10	60	-	-	-	-	105	5	10	10
SRF8	10	70	-	-	-	-	95	5	10	10
SRF9	10	80	-	-	-	-	85	5	10	10
SRF10	10	-	60	-	-	-	105	5	10	10
SRF11	10	-	70	-	-	-	95	5	10	10
SRF12	10	-	80	-	-	-	85	5	10	10
SRF13	10	-	-	-	60	-	105	5	10	10
SRF14	10	-	-	-	70	-	95	5	10	10
SRF15	10	-	-	-	80	-	85	5	10	10

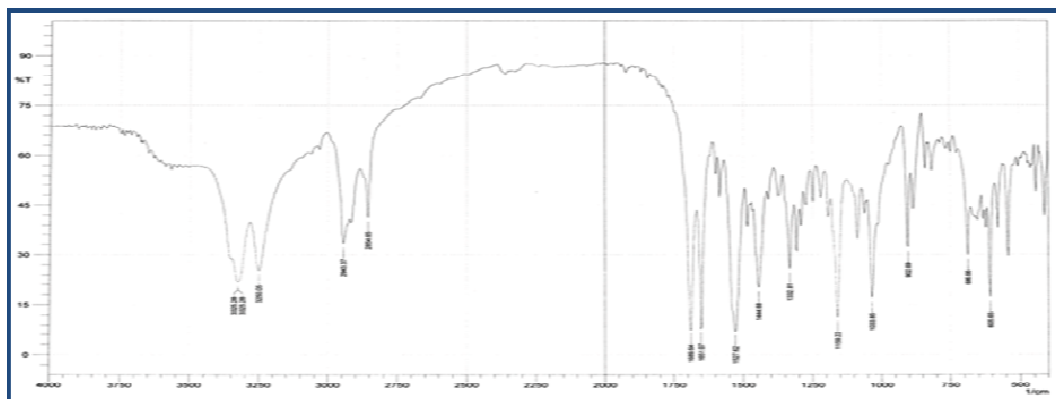**Figure. 1: Infrared Spectrum of pure Glipizide**

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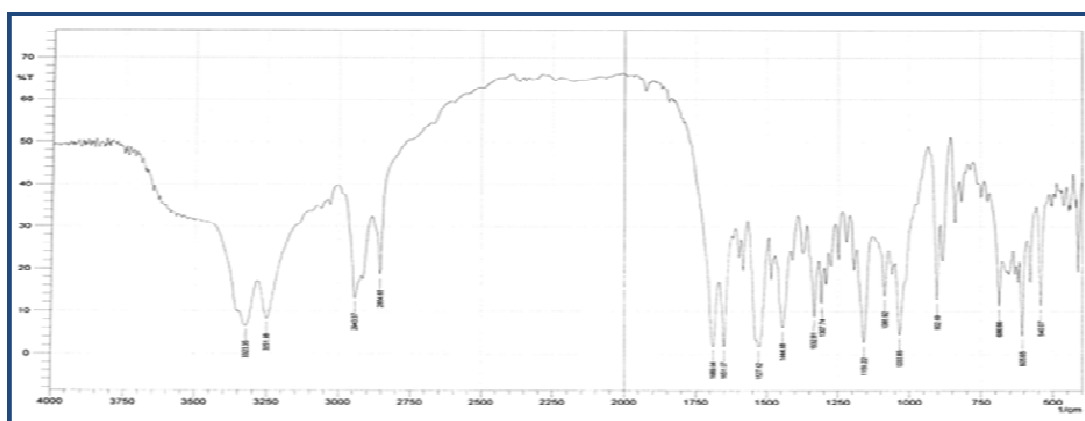**Figure 2: Infrared Spectrum of Glipizide + Chitosan + pectin**

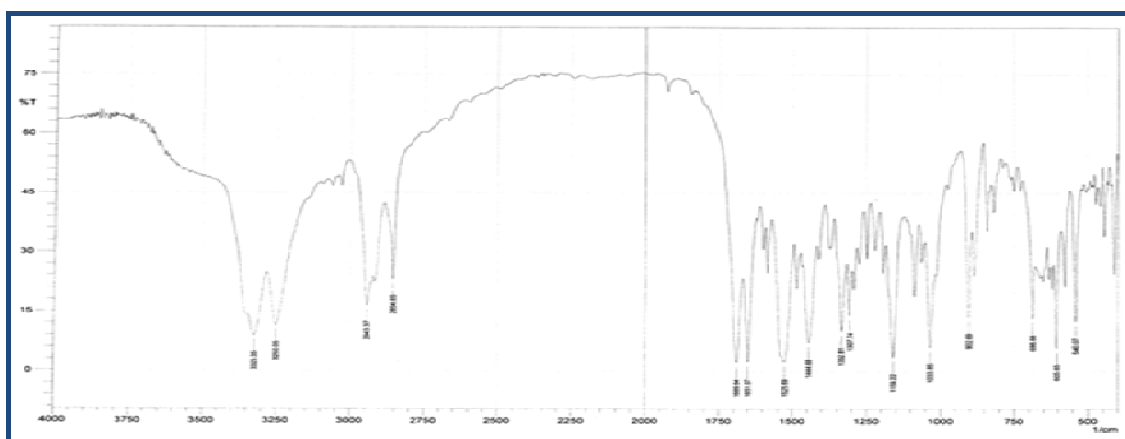**Figure 3: Infrared Spectrum of Glipizide + HPMC K100M + HPMC 15M**

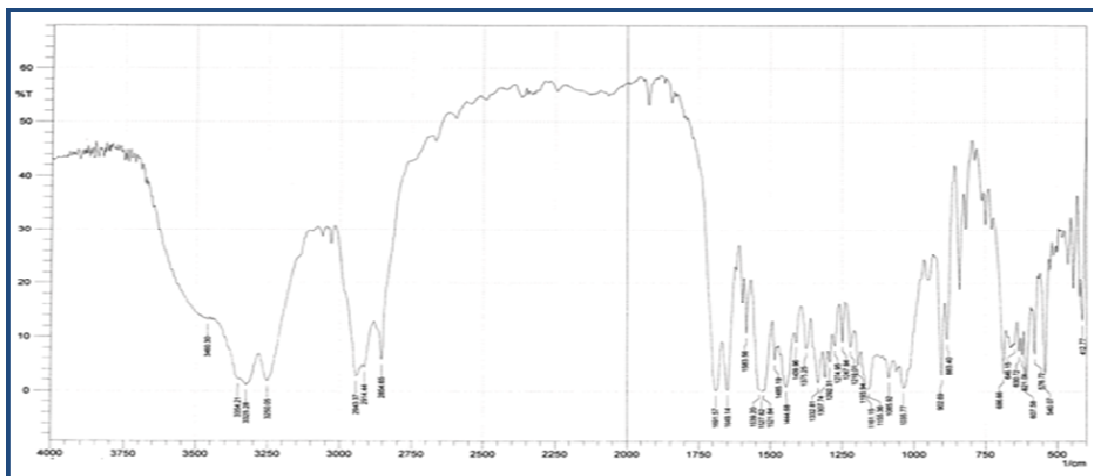**Figure 4: Infrared Spectrum of Glipizide + Aloe barbadensis Miller leaves mucilage**

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Figure 8: Infrared Spectrum of Glipizide + all polymers

Table 2: Functional groups of Infrared spectroscopy

S. No.	Groups	Peaks (cm^{-1})
1	-C=O, amide	1689 cm^{-1}
2	-C=O, urea	1661 cm^{-1}
3	Ar-CH stretching	1525 cm^{-1}
4	Ar-CH Bending	1443 cm^{-1}
5	SO$_2$NH	1159 cm^{-1}

Table 3: Pre-Compression Parameters of Designed Formulations (F1 to F15)

S. No.	Formulation code	Bulk Density (gm/ml)	Angle of Repose (θ)	Carr's index (%)	Hausner's Ratio
1	F1	0.43	29.42	12.5	1.16
2	F2	0.37	27.62	13.36	1.14
3	F3	0.39	28.12	12.42	1.12
4	F4	0.36	28.44	14.36	1.15
5	F5	0.37	29.44	15.02	1.13
6	F6	0.44	29.40	15.42	1.13
7	F7	0.476	29.39	14.28	1.14
8	F8	0.52	26.08	13.85	1.12
9	F9	0.42	25.12	13.32	1.15
10	F10	0.498	26.42	12.98	1.13
11	F11	0.470	25.08	12.68	1.13
12	F12	0.48	24.12	12.36	1.14
13	F13	0.50	27.32	11.66	1.16
14	F14	0.54	28.13	11.12	1.14
15	F15	0.48	28.06	12.32	1.15

The tablet characteristics are given in the (Table 3). All the tablets prepared contained glipizide within in 100 ± 5% of the labeled claim. Hardness of the tablets was in the range 4-5 kg/cm2. Weight loss in the friability test was < 1.0% in all the cases. All the tablets were found to be non- disintegrating in water and aqueous acidic (pH 1.2) and alkaline (pH 7.4) fluids.

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Table 4: Post-Compression Parameters of Designed Formulations (F1 to F15)

S. No.	Formulation code	Thickness (mm)	Uniformity weight (mg)	Hardness (kg/cm2)	Friability (%)	Drug Content (%)
1	F1	4.11	201	4.5	0.496	95.13
2	F2	4.32	203	4.7	0.324	96.86
3	F3	4.21	202	4.5	0.413	98.33
4	F4	4.13	199	4.1	0.582	96.20
5	F5	4.45	198	4.3	0.513	95.67
6	F6	4.31	200	4.5	0.348	97.13
7	F7	4.11	203	4.7	0.489	98.00
8	F8	4.53	205	4.2	0.546	96.34
9	F9	4.22	201	4.1	0.426	95.44
10	F10	4.33	201	4.5	0.652	96.76
11	F11	4.42	203	4.4	0.526	98.12
12	F12	4.23	202	4.5	0.562	96.87
13	F13	4.52	205	4.7	0.453	96.00
14	F14	4.43	201	4.6	0.314	97.83
15	F15	4.23	202	4.7	0.445	99.88

Table5: *In vitro* dissolution data for formulations F1 to F7

S. NO	TIME (hrs)	F1	F2	F3	F4	F5	F6	F7
1	1	4.02	5.04	4.02	3.52	3.02	3.56	2.51
2	2	6.06	6.57	5.56	4.22	4.55	5.67	5.05
3	3	9.12	10.57	9.12	10.61	10.12	10.12	9.61
4	4	16.74	15.24	12.2	18.68	18.22	20.34	15.21
5	5	25.25	18.92	17.62	25.53	30.22	31.67	25.54
6	6	32.36	23.14	21.51	36.91	38.30	44.45	33.60
7	7	41.72	32.13	30.82	42.88	46.53	50.78	45.80
8	8	48.91	47.82	38.58	56.25	54.23	62.88	55.57
9	9	54.16	54.42	48.93	68.78	68.88	70.91	68.55
10	10	62.46	66.75	53.31	75.16	76.79	81.94	77.52
11	11	73.88	72.82	62.15	86.54	86.08	88.27	89.99
12	12	82.34	79.45	75.21	99.19	97.67	94.30	99.56

Table 6: *In vitro* dissolution data for formulations F8 to F15

S. No.	TIME(hrs)	F8	F9	F10	F11	F12	F13	F14	F15
1	1	2.51	3.52	4.12	3.56	3.45	4.78	3.52	3.52
2	2	5.55	5.89	5.56	5.89	12.13	7.34	6.65	6.87
3	3	11.13	12.14	14.16	10.67	19.77	11.45	9.67	14.15
4	4	13.21	17.25	24.61	18.45	25.91	19.56	13.89	20.67
5	5	20.79	20.20	33.74	23.78	31.44	29.67	19.45	27.45
6	6	31.34	28.99	42.57	31.45	40.16	36.55	25.02	32.45
7	7	42.86	37.80	50.43	42.67	46.45	43.12	33.07	44.02
8	8	51.57	51.84	62.18	50.56	57.83	53.78	46.78	57.23
9	9	67.88	62.67	69.53	65.37	65.78	64.33	58.89	68.38
10	10	75.35	71.74	78.36	79.91	72.45	78.45	70.78	77.54
11	11	87.97	85.97	89.91	84.99	83.56	89.45	86.86	86.76
12	12	96.67	92.78	98.67	94.67	91.41	102.45	96.55	94.67

Glipizide release from the SR tablets prepared was studied in phosphate buffer of pH 7.4. The release profiles are given in (Figure.6, Figure.7 and Fig.8). Glipizide release from all the SR tablets prepared was slow and spread over more than 12h and depended on the polymer. Among all the formulation F3 shows more retarding of the drug release in 12hrs, where as the drug release from other formulations was faster when compared to the other formulations. It was found that the cumulative percentage of drug release decreases with increase in the polymer concentration. The regression coefficients obtained for zero order kinetics[9] were found to be higher (R^2: 0.982 to 0.996) when compared with those of first order kinetics (R^2: 0.664 to 0.886), indicating that drug released from all formulation is Zero order kinetics (Table 4). To evaluate drug release mechanism from the matrix tablets, plots of cumulative percentage release vs square root of time as per Higuchi's equation [10] were constructed. These plots were found to be linear with all the formulations (R^2: 0.917 to 0.978) indicating that the drug release from the matrix tablets was diffusion controlled. To confirm the diffusion mechanism the data were fit into korsmeyer et al's

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equation[11] [12]. All the formulation shows good linearity (R^2 : 0.984 to 0.990), with the slope (*n*) values 1.029 to 1.079, indicating release mechanism was Super Case-II transport. But it cannot be concluded that release was totally based on diffusion, which generally in the case in Higuchi's square root equation. Based on swelling and erosion studies, it was concluded that matrix tablets undergo swelling as well as erosion during the dissolution study, which indicates that polymer relaxation had a role in drug release mechanism. However, it can be concluded that effect of release kinetics was found to be diffusion[14] coupled with erosion.
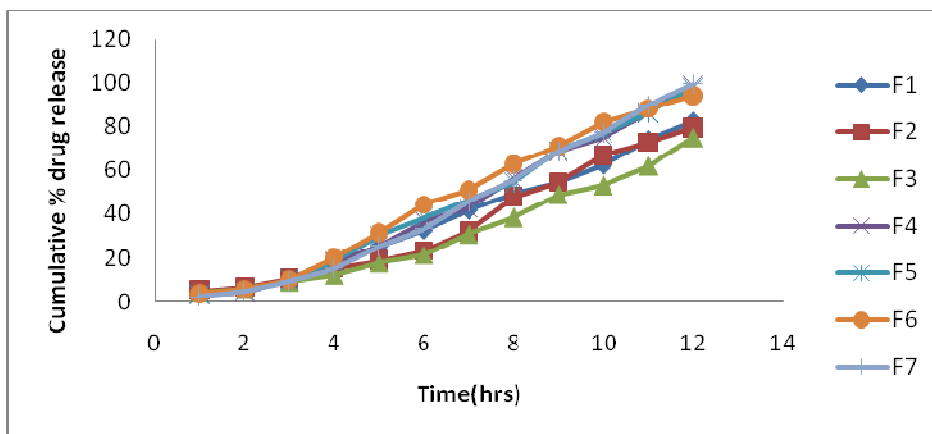

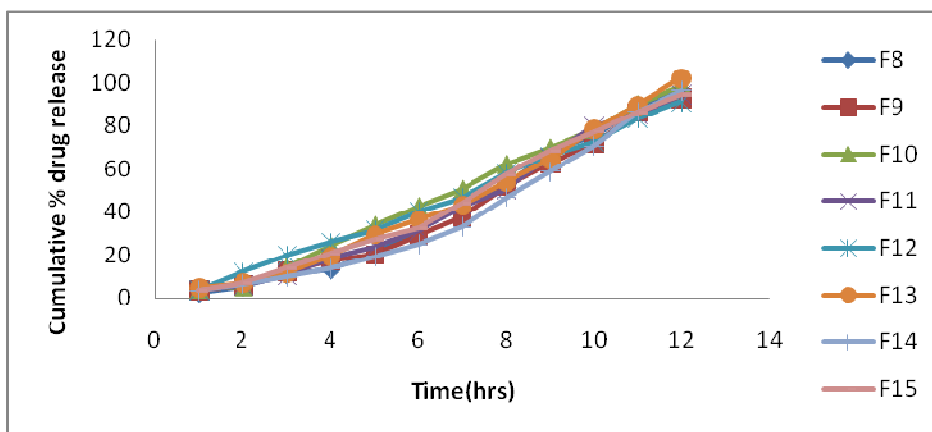**Figure 6: Comparative dissolution profiles for formulations (F1 to F7)**

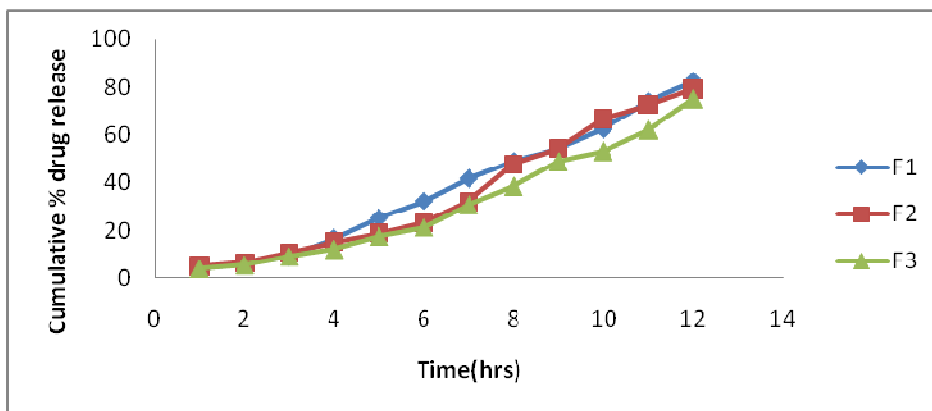**Figure 7: Comparative dissolution profiles for formulations (F8 to F15)**

Figure 8: Comparative dissolution profiles for formulations (F1 to F3)

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Table 4: Release kinetics parameters of designed controlled release matrix tablets of Glipizide

Formulations	Zero order equation	First order equation	Higuchi's equation		Korsemeyer's equation
	Regression coefficient R^2	Regression coefficient R^2	Regression coefficient R^2	Slope (n)	Regression coefficient R^2
F1	0.982	0.664	0.917	1.04261	0.985
F2	0.996	0.864	0.978	1.07984	0.994
F3	0.996	0.834	0.979	1.02949	0.990

CONCLUSION

From the above observations it is concluded that slow and controlled release of Glipizide over a period of 12 hours was obtained from matrix tablets (F1 to F15). Among all the formulation, F3 shows that 75.21% of drug release at the end of 12 hours. The cumulative percentage drug was decreased by increase in polymer concentration[13]. The mechanism of drug was diffusion coupled with erosion. The stability studies show that there was no significant change in hardness, friability, and drug content of selected formulation F3. The controlled and efficient drug delivery system developed in the present study will maintain plasma Glipizide levels better, which will overcome the drawbacks associated with the conventional therapy.

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