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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF COLON TARGETED DRUG DELIVERY SYSTEM CONTAINING ANTI DIABETIC AGENT

[1*]Teelavath Vijayakumari, [1]Mangilal, T., [2]Shyamsunder, R., [2]Jayaprakash, D., [2]Ravindranath, A. and [2]Rao Patnaik, K. S. K.

[1]Department of Pharmaceutics, KGR Institute of Technology and Management, Rampally, Keesara, R.R Dist-501301, Telangana, India
[2]Department of Pharmacy, University College of Technology, Osmania University, Hyderabad, Telangana, India

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ABSTRACT

The main aim of the present Investigation was to develop colon targeted matrix tablets of Glipizide using various concentrations of selected polymers are Hydroxy propyl methyl cellulose, Ethyl cellulose and Guar gum. Tablets were prepared by direct compression method and both pre-compression and post- compression parameters for all batches showed the suitable ranges. Short term accelerated stability studies are performed according to ICH guidelines temperature of $40^0 \pm 2^0$ and relative humidity of 75%±5% RH to study any physical changes and chemical decomposition of the drug, in this concern no formulation shown any physical or chemical changes. The compatibility of drugs, polymers and excipients were studied by FT-IR Spectroscopy and the results showed that the drug was compatible with polymers and all excipients. Interaction between drug and optimized formulations were acertain by DSC Thermographs and the results showed that there is no interaction. Dissolution studies were performed for 12 hours in 1. 2 pH, 7.4 pH, 6.8 pH, respectively in phosphate buffer at the temperature of 37 ± 0.5^0C at 100rpm. The dissolution data so obtained was fitted to various mathematical kinetic models and the drug release followed mixed order and Higuchi's model. To study release mechanism of the drug from matrices the data were fitted to Koresmeyer-Peppas model. *In –vitro* release profile of Glipizide from all polymers which are used in study showed that drug increasing the concentration of polymers resulted in a reduction in the release rate of the drug. A formulation containing combination of polymers showed that the drug release profile for Glipizide about 38.72% after 12 hrs, 40.66% after 12 hrs, 45.45% after 12 hrs for all formulations, this is an indicative of the retardation of drug release when polymer combination was changed.

INTRODUCTION

An appropriately designed controlled release drug delivery system can be major advances to solve problems with targeting drugs to a specific tissue or organ and controlling the rate of drug delivery to the target tissue or organ. The matrix tablets are an interesting option to develop an oral controlled release formulation. The present investigation mainly focuses on oral controlled release dosage forms and which type of polymers is suitable to formulate matrix tablets. Conventional dosage form releases the drug immediately and showing large distribution to all organs, so there is need to target the drug to specific sign with specific concentration. Colon targeted matrix tablet is one control release dosage form which release the drug in a continuous manner to the colon. The release of drug takes by both dissolution as well as diffusion control mechanism to maintain the plasma concentration of the drug for an extended period of time with minimized local or systemic unwanted effects (Vinod Dube *et al*., 2011). The delivery of drugs to the colon for systemic action or a local effect is valuable in a variety of situations; these include treatment of the topical diseases these are Chron's disease, ulcerative colitis and infectious disease for colon, irritable colon syndrome, colon cancer and potentially for the oral delivery of peptides. Colon targeting glipizide via oral route can be reached by different approaches and different formulation system, for which the drug release is control by different pH conditions, transit time and microbial flora (Poonam Kushwaha *et al*., 2010: Dinesh Kaushik *et al.,* 2009: Nitin Saigal *et al*., 2009). Glipizide is an antidiabetic agent and one of the most commonly prescribed drug for the treatment of patients with type II diabetes mellitus. In spite of its favorable clinical response in chronic therapy with Glipizide, suffers from certain specific problems of high dose (1.5-2.0 g/day),

Corresponding author: Teelavath Vijayakumari,
Department of Pharmaceutics, KGR Institute of Technology and Management, Rampally, Keesara, R.R Dist-501301, Telangana, India.

half life is about 1.5-4 hours, low bioavailability (60%) and the high incidence of GI side effects (25% cases).

The situation is complicated further with a decrease in absorption of the drug with food that delays t_{max} up to 40 mins, (Tapan Kumar *et al*., 2007: Margret Chandira *et al*., 2010: Basavaraj *et al*., 2011). The primary objective of present investigation is to develop control release matrix tablets of Glipizide to improve bioavailability, to prevent changes of concentration of the drug in plasma, to reduce the dose dumping and to examine the effects of combination of polymers on *in-vitro* drug release. Glipizide matrix tablets were prepared by using polymers such as Guar gum, Ethyl cellulose, Hydroxy propyl methyl cellulose are used in combination to study the drug release kinetics and find out the effects of the polymer with the Glipizide (Bagyalakshmi *et al*., 2011; Kamlesh *et al.,* 2011; Akash Yadhav *et al*., 2011)

MATERIALS AND METHODS

Glipizide was a gift sample from Sun Pharmaceutical Industries Ltd, India. Hydroxy propyl methyl cellulos, Ethyl cellulose, Guar gum from Loba Chemie, India**,** microcrystalline cellulose, magnesium stearate and talc from S.D. Fine Chem. Ltd, Mumbai, India. Other materials and solvents were used analytical grade. *In-vitro* analysis of the prepared tablets was carried out as per the requirements of official pharmacopoeia for matrix tablets.

Standard Curve for Glipizide 100 mg of Glipizide was accurately weighed and dissolved in 100 ml of distilled water to prepare the first stock solution that is pH 1.2. 1ml of above solution was taken and diluted to 100 ml with the same solvent to prepare second stock solution. The aliquot amount of stock solution II was further diluted with first stock solution to get 1, 2 , 3, 4, 5, 6µgs of drug per ml of the final solution. After that the absorbance was measured with a UV spectrophotometer at 233nm against pH 1.2 as a blank. The same procedure was repeated by phosphate buffer pH 7.4 and 6.8. The absorbance obtained were shown in Tables 2-4. Calibration curve was plotted and shown in Figures 1-3 respectively.

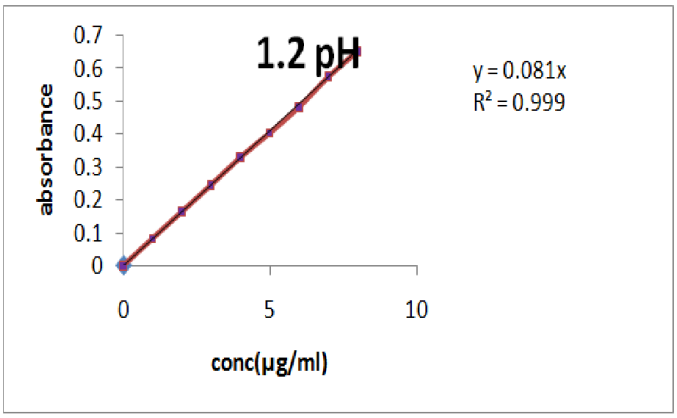

Fig. 1. Calibration curve of glipizide in 1.2 pH buffer

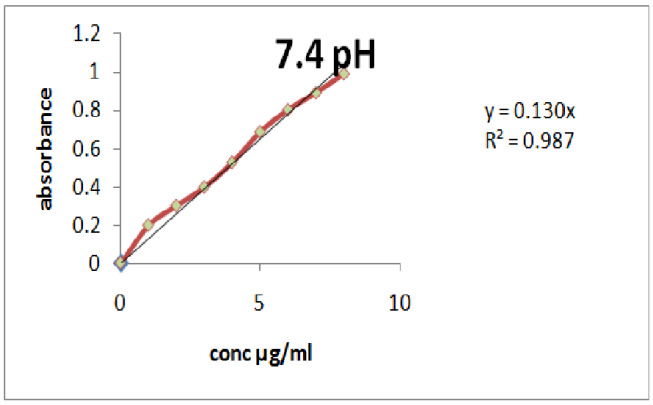

Fig. 2. Calibration curve of glipizide in 7.4 pH buffer

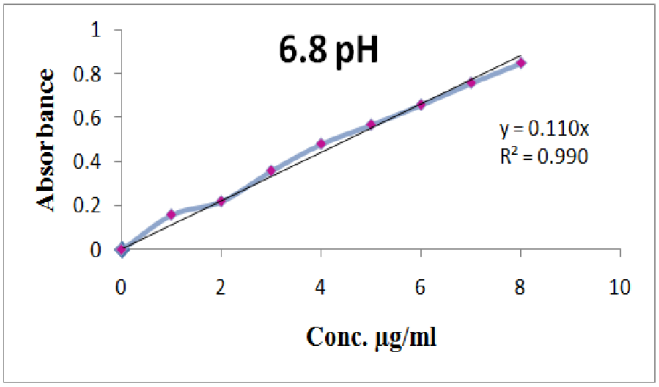

Fig. 3. Calibration curve of glipizide in 6.8 pH buffer

Preparation of Glipizide succinate

Glipizide was dissolved in methanol and water of ratio 5:1 with constant stirring. A solution of succinic acid in ethanol was added for one hour drop wise under a nitrogen atmosphere temperature at 20ºC. Crystallization of salt commenced shortly after the addition of the succinic acid solution. The crystals was filtered off, washed with ethanol and dried under vacuum to form the Glipizide succinate (2:1). The obtained salt was free flowing with a melting point of 205-208^{0}C (Sanket D Gandhi *et al.,* 2010).

FTIR studies

The I.R. spectrum of Glipizide, Polymers and optimized formulations were recorded individually. The disc was made using 1 mg of each samples in 100 mg potassium bromide individually and the spectras were recorded between 4000 cm^{-1} – 400 cm^{-1} using Shimadzu FTIR Spectrophotometer and results were shown in Figures 4 –12 (Pavia *et al.,* 2002)

Differential Scanning Calorimetry

DSC Thermographs of Glipizide and optimized formulations were recorded individually between 30.0^{o}C to 300.0^{o}C at the rate of 20.0^{o}C per minute under the environment of nitrogen and the results are provided in Figures 13 and 14 (Beckett and Stenlake, 2004).

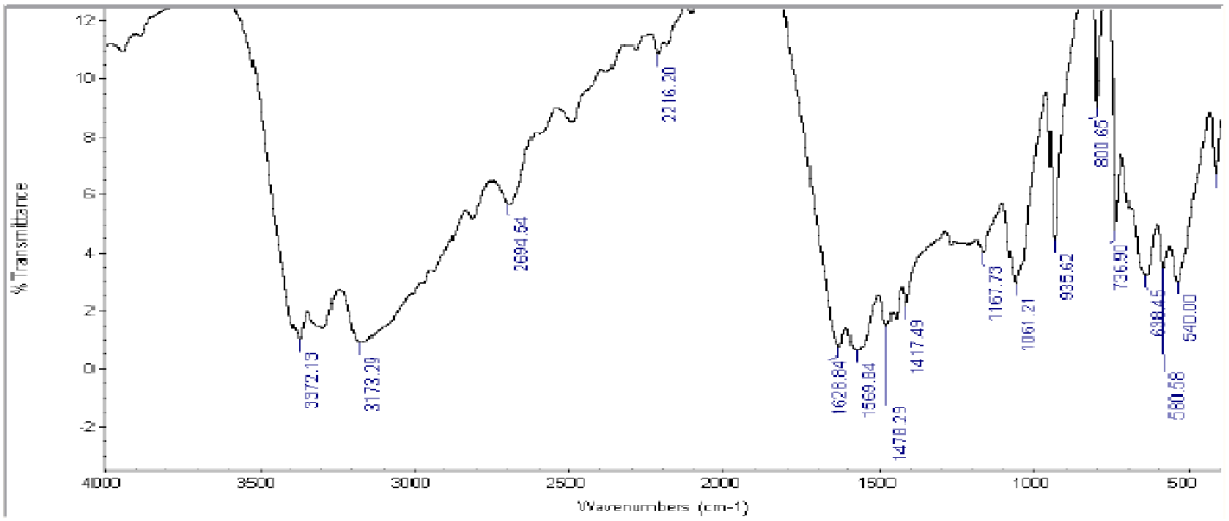

Fig. 4 FT-IR spectra of Glipizide

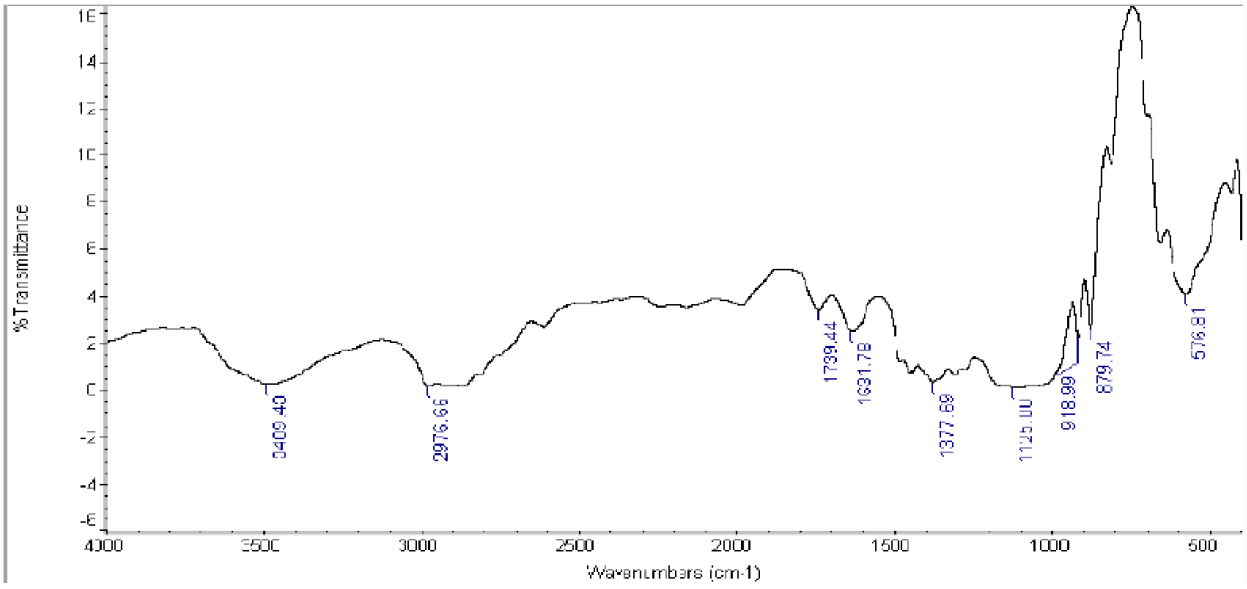

Fig. 5. FT-IR spectra of ethyl cellulose

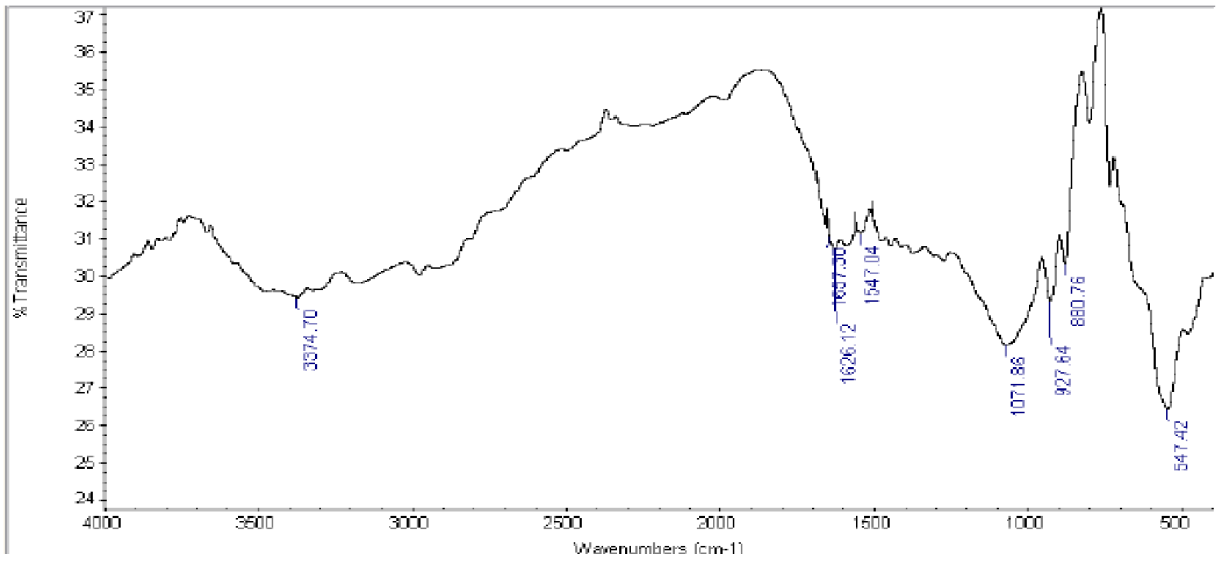

Fig. 6. FT-IR spectra of glipizide with ethyl cellulose

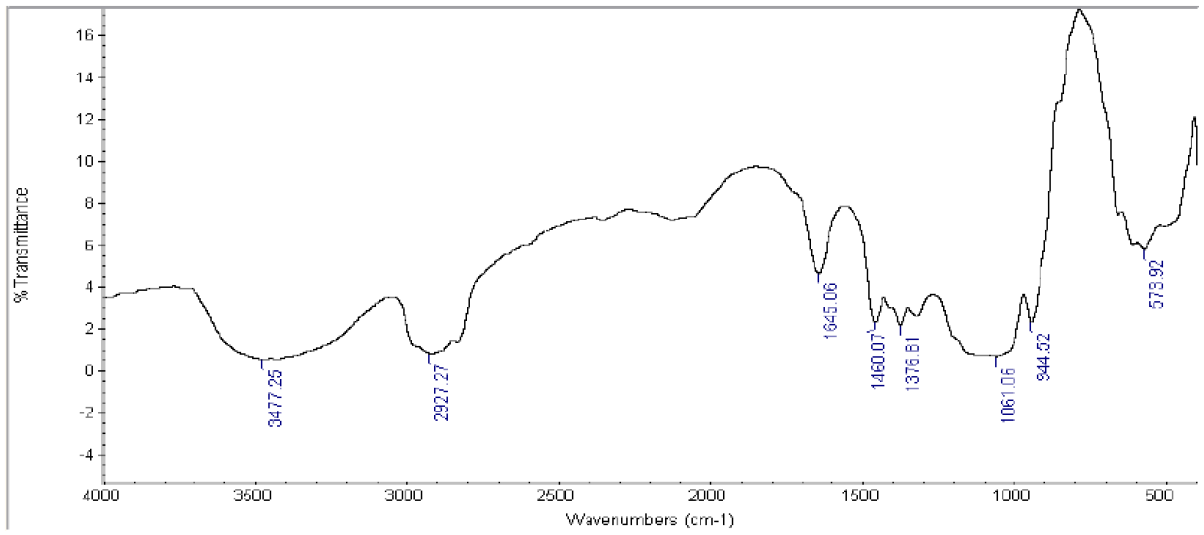

Fig. 7. FT-IR spectra of hpmc

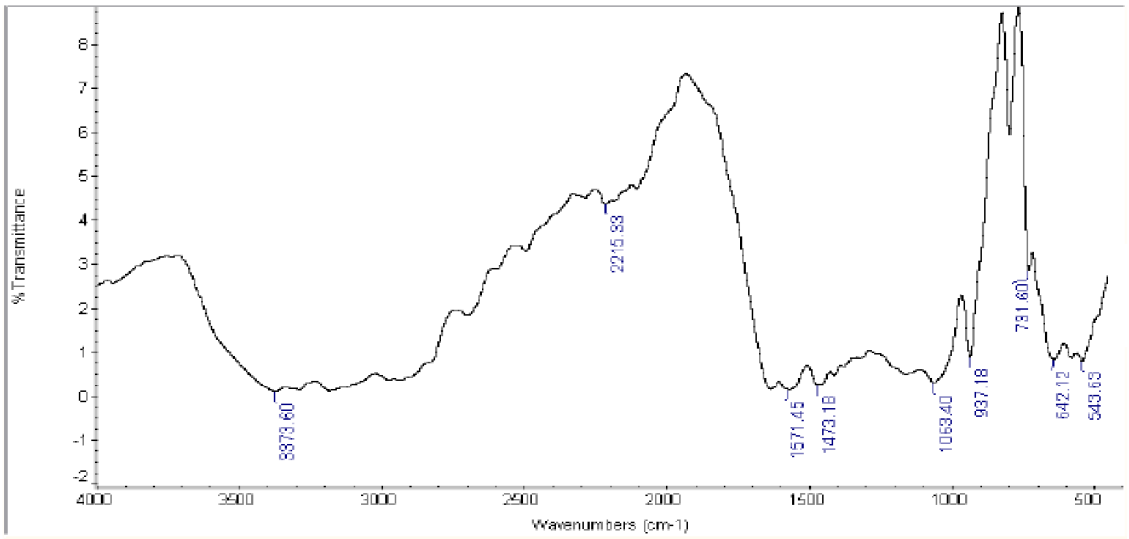

Fig. 8. FT-IR spectra of glipizide with hpmc

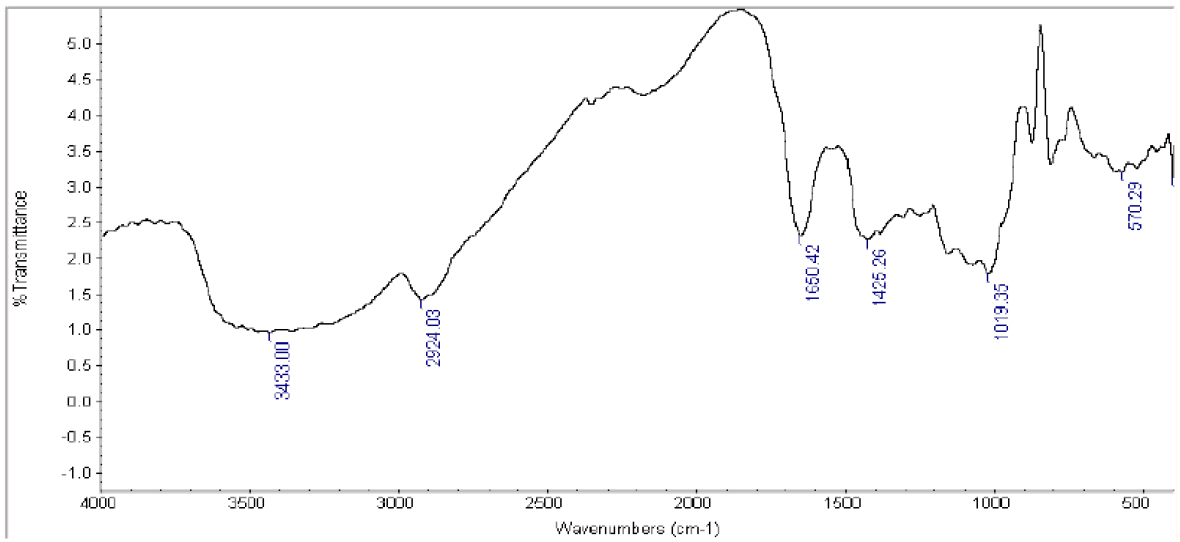

Fig. 9. FT-IR spectra of guar gum

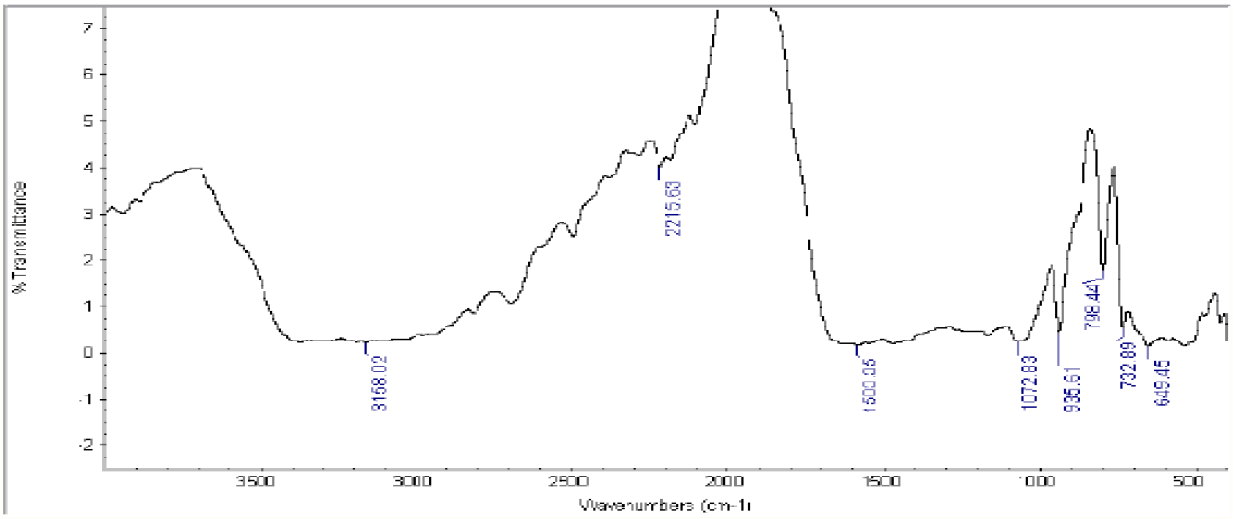

Fig. 10. FT-IR of glipizide with guar gum

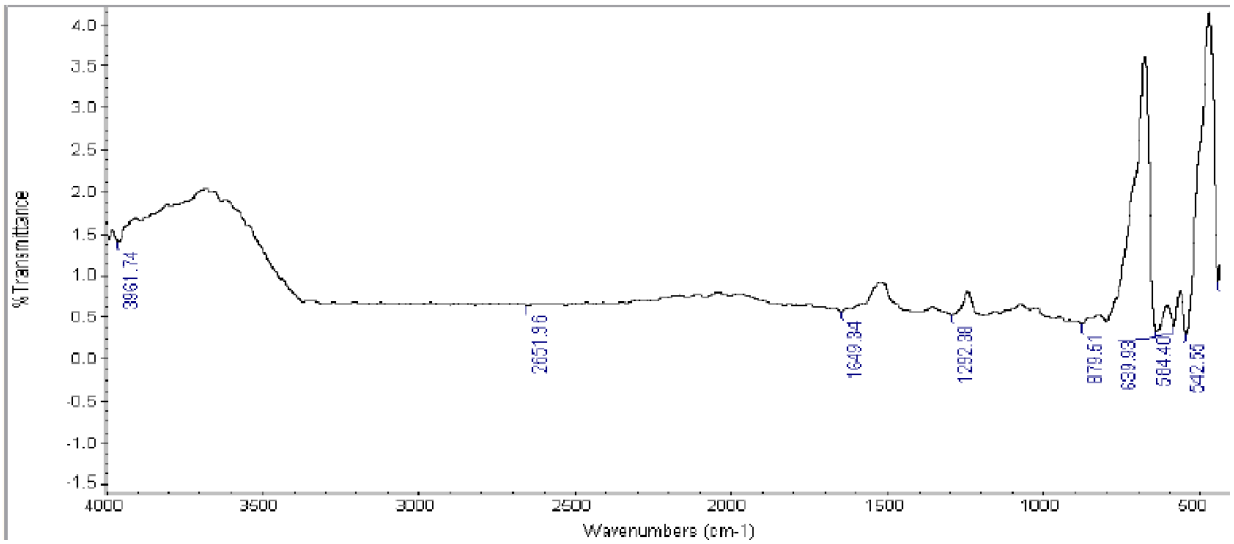

Fig. 11. FT-IR spectra of succinic acid

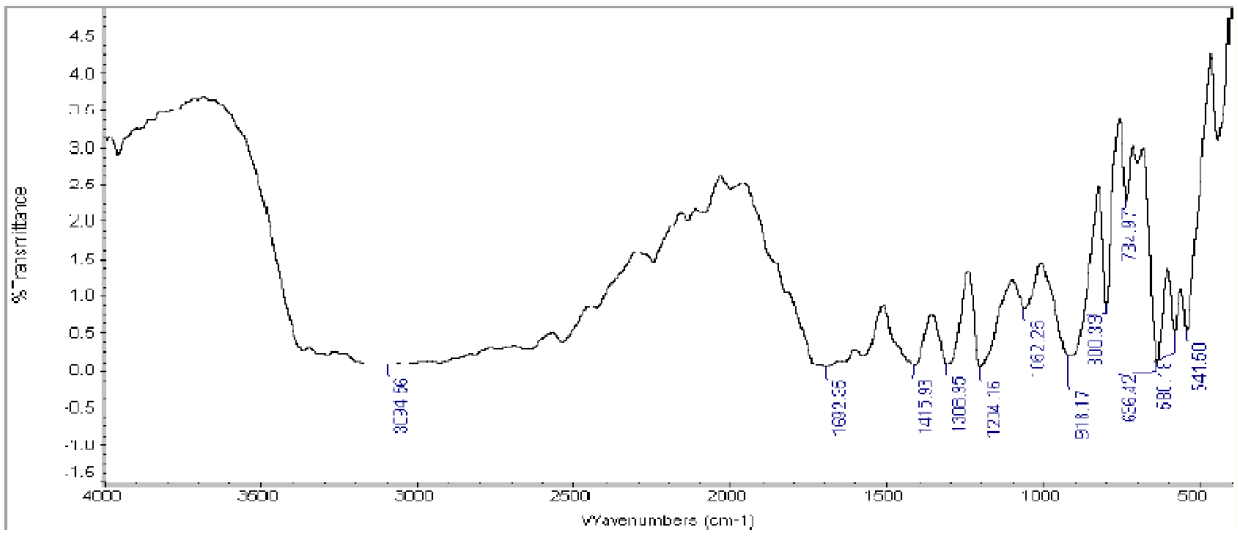

Fig. 12. FT-IR spectra of glipizide with succinic acid

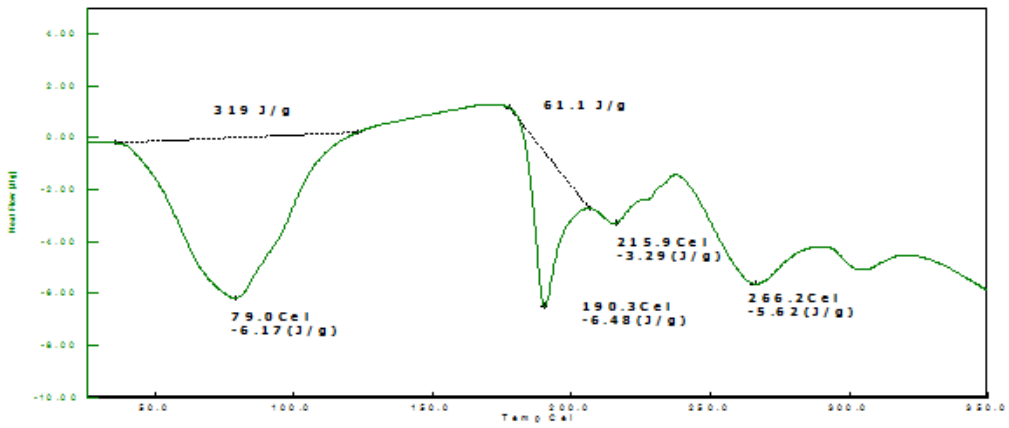

Fig. 13. Themogram of drug glipizide

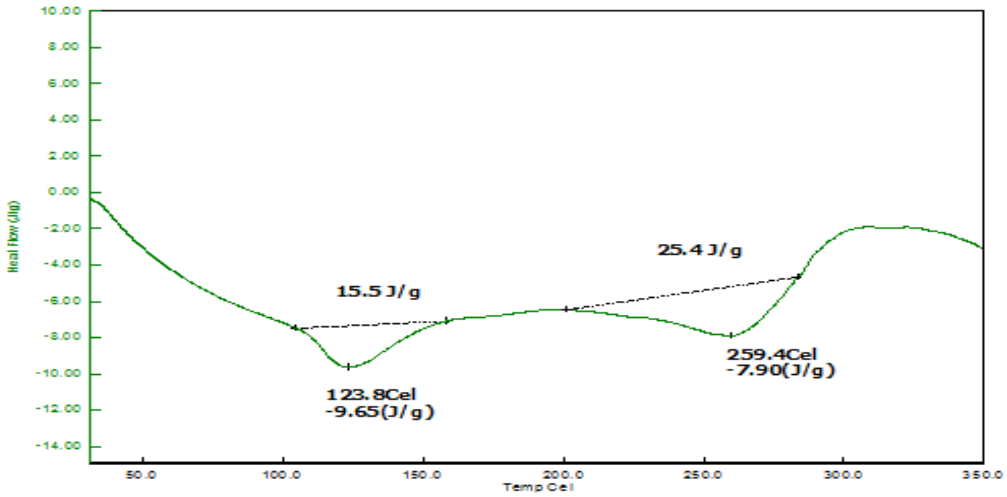

Figure 14. Themogram of optimized formulation

Preparation of Glipizide Matrix Tablets

Glipizide and all Excipients was selected for final weights of formulation (f1-f12) for the compression of matrix tablets as shown in Table 1

Evaluation for pre-compression parameters (Aulton, 2002)

Angle of repose The static angle of repose θ was measured according to the fixed funnel and freestanding cone method. A funnel was clamped with its tip 2 cm above a graph paper placed on a flat horizontal surface. The granules were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameters of the base of the powder cones were determined and the tangent of the angle of repose was calculated using the following equation:

$\tan \theta = h / r,$

$\theta = \tan^{-1}[h/r]$

Where

θ = Angle of repose

h = Height in cm

r = Radius.

Five measurements were made for each sample and results were shown in Table 5.

Bulk Density (D_b) It was measured by pouring the weighed powder into a measuring cylinder and the volume was calculated by using following equation and the results were depicted in Table 6:

D_b = (Mass powder)/Bulk volume of the powder

Tapped density (D_t) The tapped volume was measured by tapping the powder to constant volume and calculated by using following equation and the results were depicted in Table 6:

D_t = (Mass of powder)/(Tapped volume of the powder)

Carr's index It helps in measuring the force required to break the friction between the particles and the hopper and it is calculated by using following formula and results were shown in Table 6:

Carr's index= (Tapped density-Bulk density)/(Tapped de ensity) X100

Hausner's Ratio It reveals the flow property of the powder material. It is the ratio of tapped density to bulk density of the

powder and measured by employing the following formula and results were depicted in Table 6.
Hausner ratio = D_t / D_b

Where
D_t = Tapped density
D_b = Bulk density

Preparation of Glipizide matrix tablets

Matrix tablets containing 500mg of Glipizide along with various amounts of polymers and other excipients were prepared by direct compression technique. In this first step, the drug and ingredients with the exception of magnesium stearate were blended in a tubular mixer for 5 minutes and magnesium stearate was added. The desired amount of the blend was directly compressed into tablets using rotary tablet compression machine (Multi punch machine). Before compression, the surface of the die and punch were lubricated with magnesium stearate and all the preparations were stored in airtight container at room temperature for further studies.

Evaluation of glipizide matrix tablets

The matrix tablets prepared were evaluated for the following parameters (Lachman *et al.,* 1991)

Weight Variation Test 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method given in IP and results were shown in Table 6.

Hardness Hardness, which is now more appropriately called crushing strength is expressed usually as the load (force) required to crush a tablet placed between two jaws forcing each other, one of which moves towards the other. Tablet hardness usually affects drug dissolution and release and it may affect bioavailability. Hardness determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet punching machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Twenty tablets were randomly selected and each tablet was tested for hardness using Digital Hardness Tester results were as shown in Table 6.

Friability
20 tablets were weighed then placed in the friabilator chamber. The tablets were subjected to combined effect of abrasion and shocks by utilizing a plastic chamber that revolve at a speed of 25 rpm drop form a height of 6// per revolution for 4 minutes. The 20 tablets were then collected and cleaned with a brush and weighed. The percentage of weight loss was calculated using the following formula and the values are presented in Table 6.

%Loss = (weight before – weight after)/(weight before)X100

Drug Content

Standard solution 100 mg of pure Glipizide drug was dissolved in water in a volumetric flask and the volume was made up to 100ml mark with the same solvent and sonicated for 5 minutes.

Sample solution

20 tablets from each batch were randomly selected and were weighed accurately and then finely powdered. To a powder equivalent to 100mg of Glipizide about 70ml of water was added and dissolved with the aid of shaker for 15 minutes sufficient quantities of water was added to produce 100ml in a volumetric flask mixed well and filtered. To 1ml of the filtrate methanol was added to produce 100ml. The absorbance of the resulting solution was measured at the 233nm using blank in the reference cell.

***In-vitro* Dissolution studies**

The prepared Glipizide matrix tablets were evaluated for their integrity in the physiological environment of the stomach and small intestine under conditions mimicking mouth to colon transit. The water bath was thermo stated at $37^0C \pm 0.5^0C$. The paddle was set to rotate at 100 rpm. At every 1 hour samples of 5ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant and maintain sink conditions and the sample solution was analyzed at 233nm by using double beam U.V-Visible spectrophotometer (SHIMADZU-1700). The amount of drug present in the samples was calculated with the help of calibration curve constructed from standard (Indian pharmacopoeia *et al*., 2010).

***In-vitro* release rates of glipizide matrix tablets (Korsemeyer *et al.,* 1983)**

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treated as follows and results were given in Figures 20-24:

- Zero- order Kinetic model – Cumulative % drug released versus Time.
- First- order Kinetic model –Log cumulative % drug remaining versus Time.
- Higuchi's model-Cumulative % drug released versus the square root of time.
- 4.Korsmeyer equation/Peppa's model-Log cumulative percent drug release versus log time.

Stability studies

The optimized formulation was subjected for two month stability study, according to ICH guidelines. The selected formulations these which are involved in the study were packed in aluminium foils.

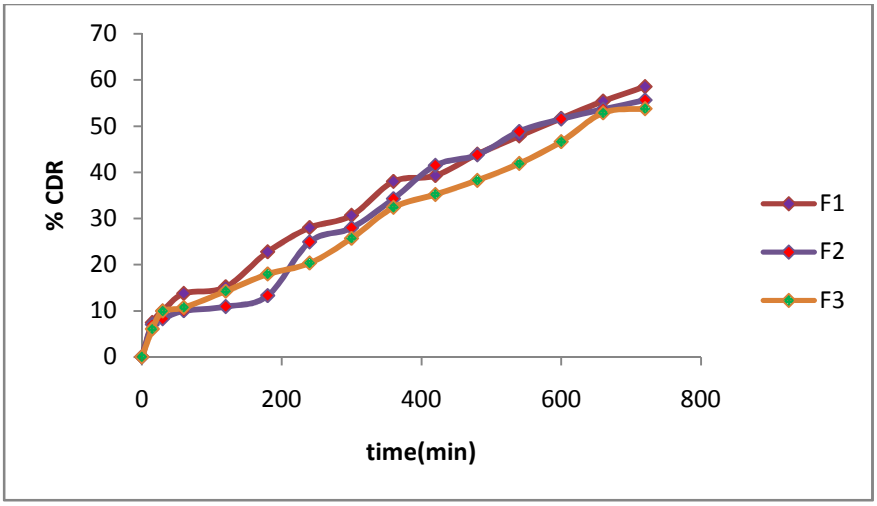

Fig. 15. Comparision of Cumulative% Release Vs Time Profile of Formulations F1, F2 And F3

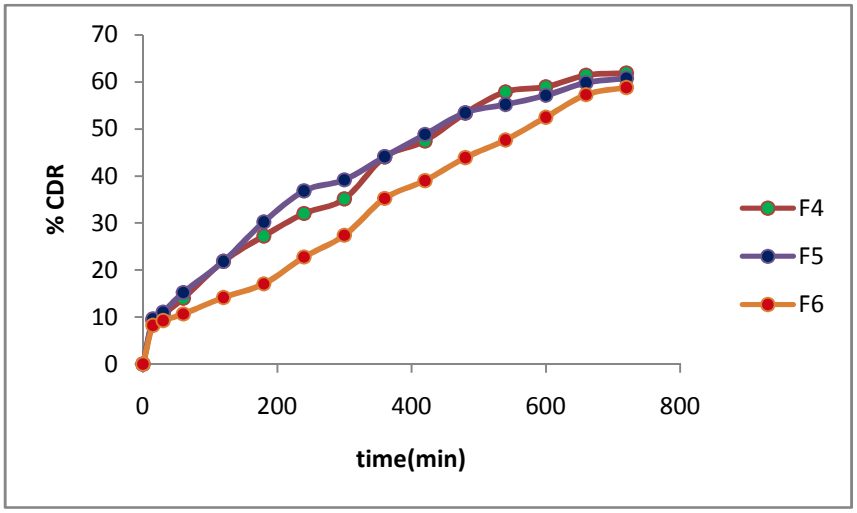

Fig. 16. Comparision of cumulative% release vs time profile of formulations f4, f5 and f6

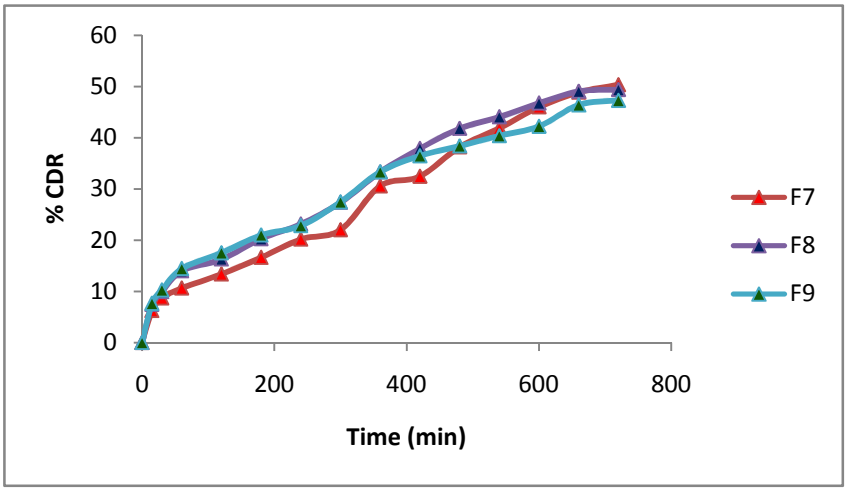

Fig. 17. Comparision of cumulative% release vs time profile of formulations f7, f8 and f9

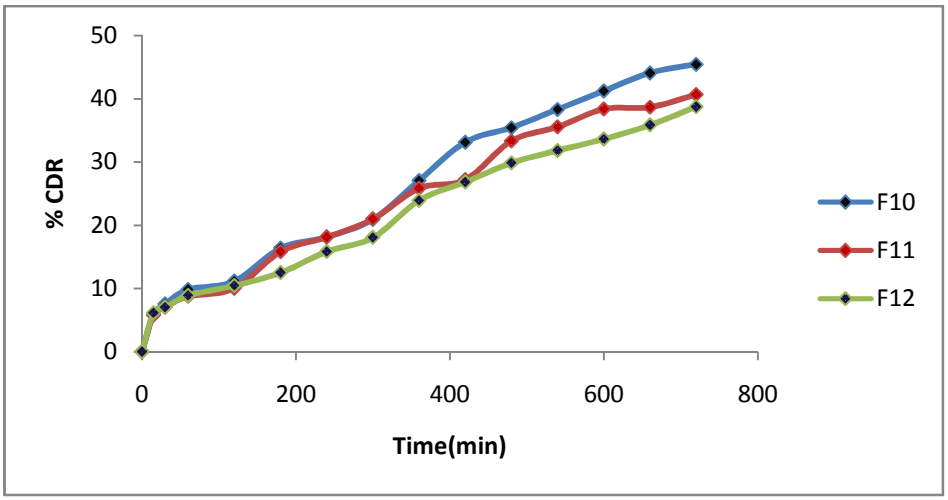

Fig. 18. Comparison of cumulative% release vs time profile of formulations f10, f11 and f12

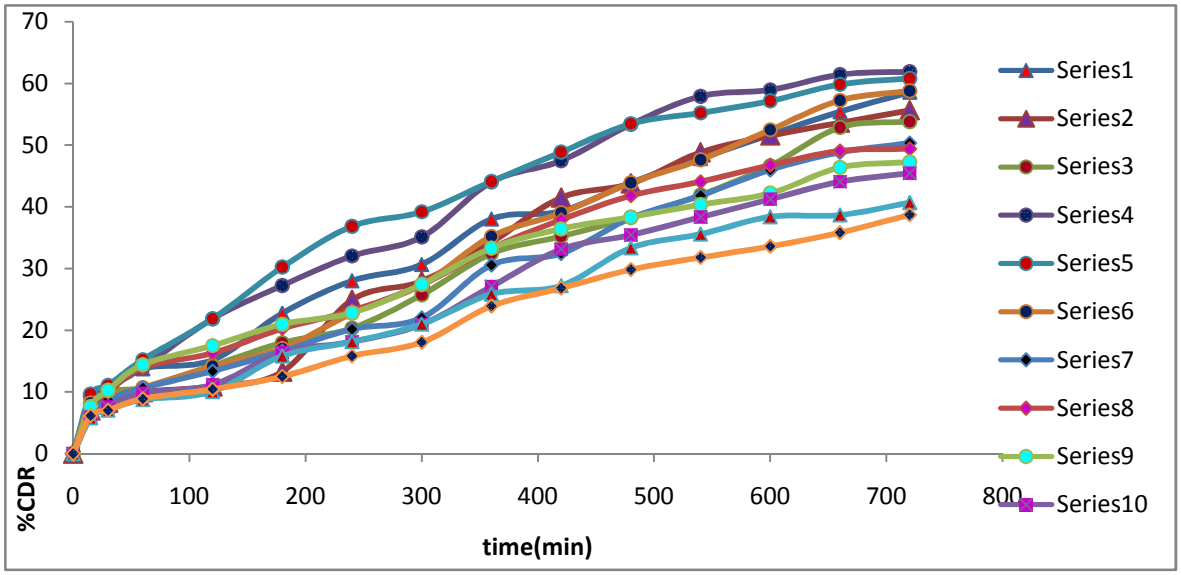

Fig. 19. Comparision of cumulative% release vs time profile of formulations f1-f12

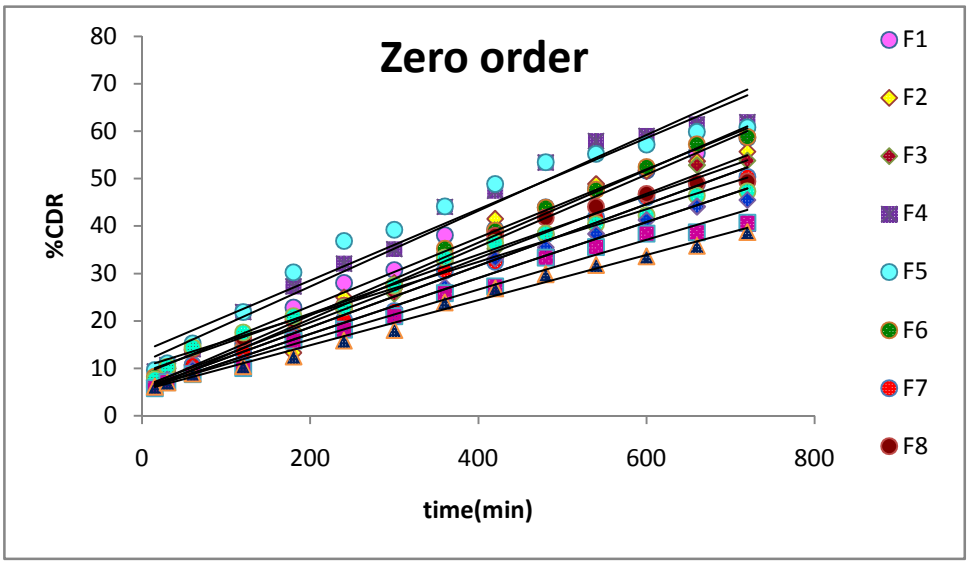

Fig. 20. Comparative zero order release profile of formulations (f1 to f12)

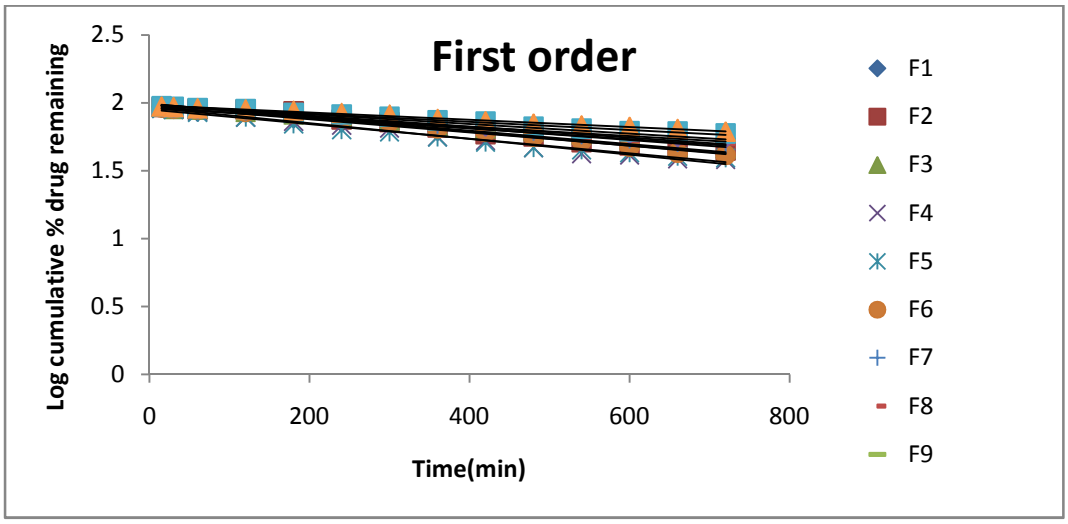

Fig. 21. Comparative first order release profile of formulations (f1 to f12)

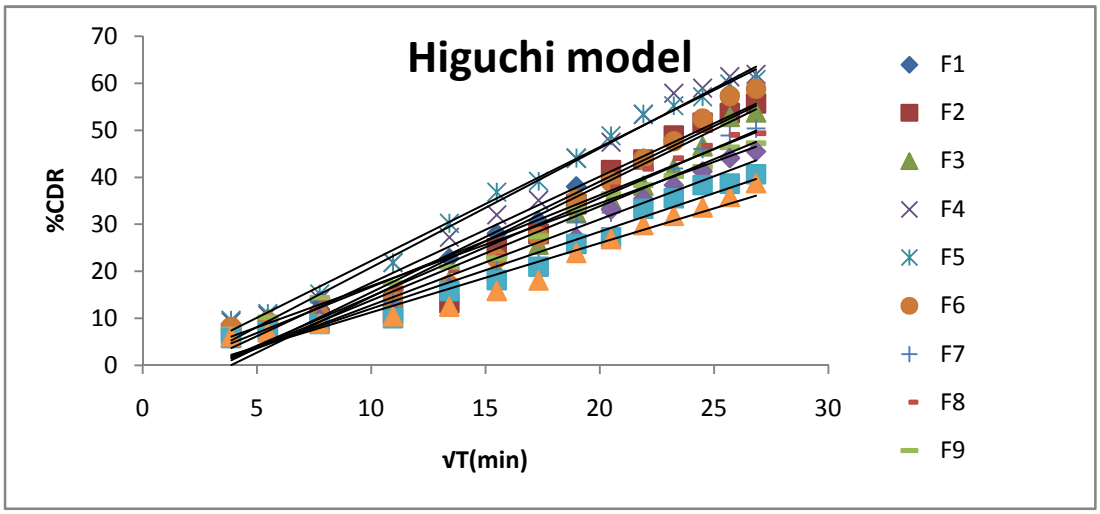

Fig. 22. Comparative higuchi release profile o formulations (f1 to f12)

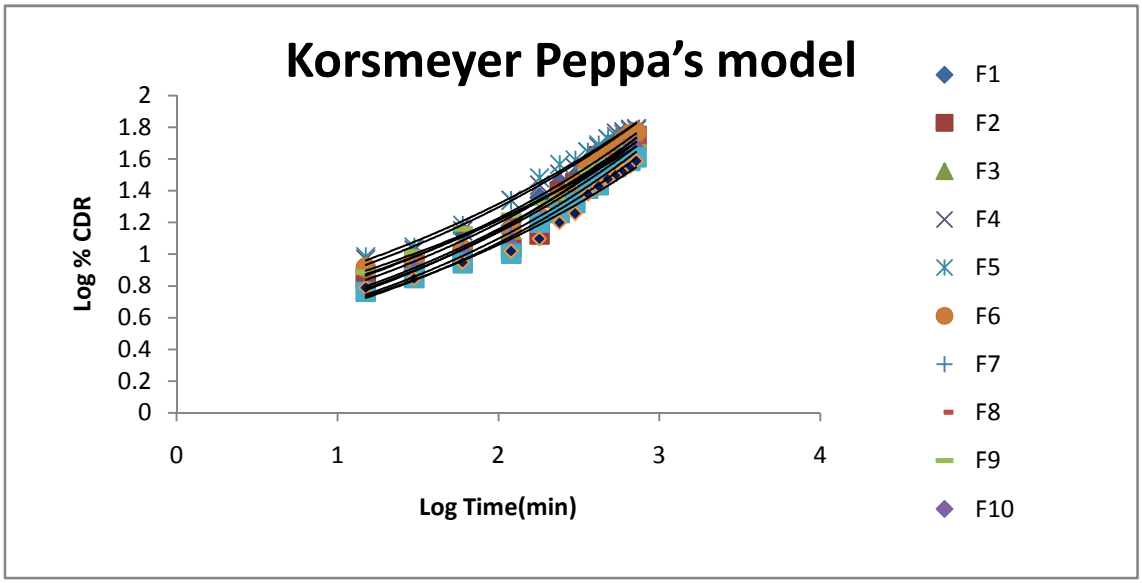

Fig. 23. Comparative hixson crowel cube root release profile of formulation (f1to f12)

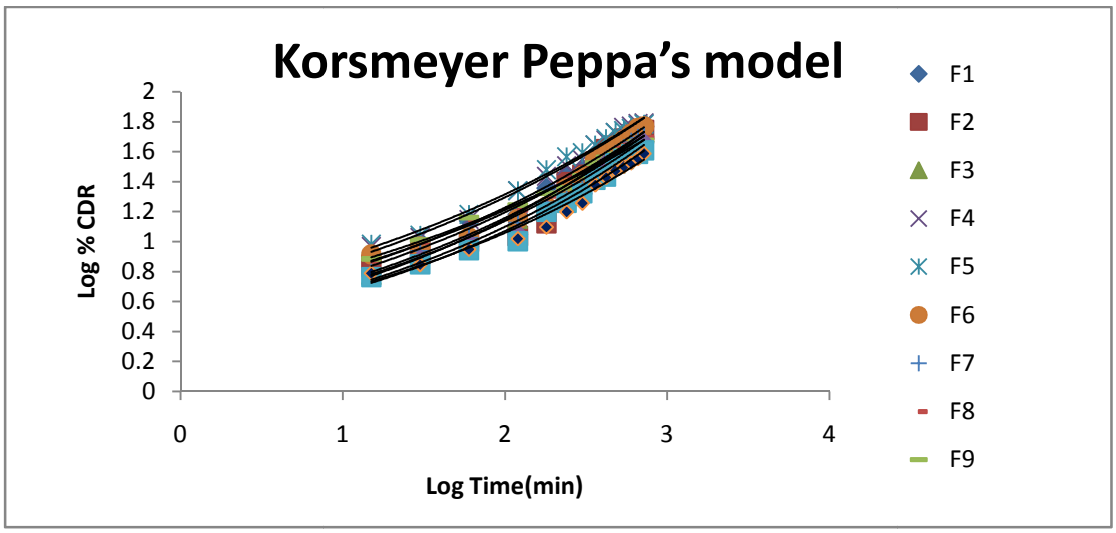

Fig. 24. Comparative korsmeyer-peppas release profile of formulation (f1 to f12)

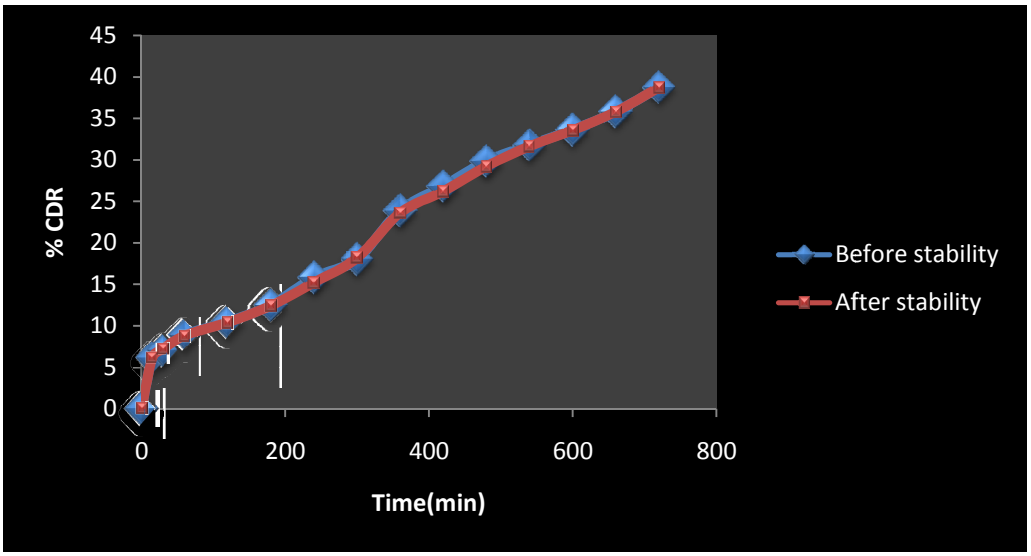

Fig. 25. Cumulative % drug release of f11 (stability studies) at room temperature

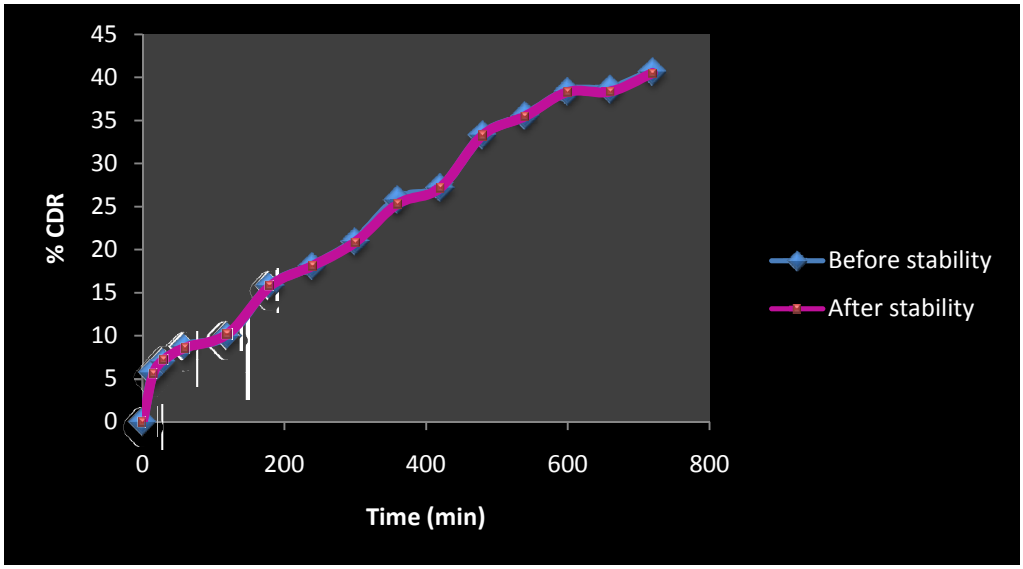

Fig. 26. Cumulative % drug release of f12 (stability studies) at room temperature

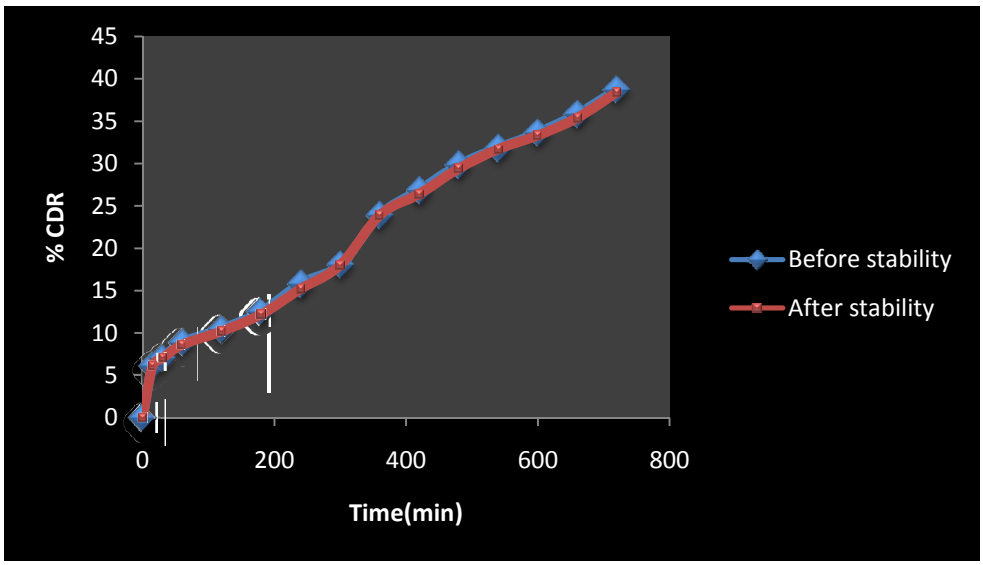

Fig. 27. Cumulative % drug release of f11 (stability studies) AT 40ºC/75%RH

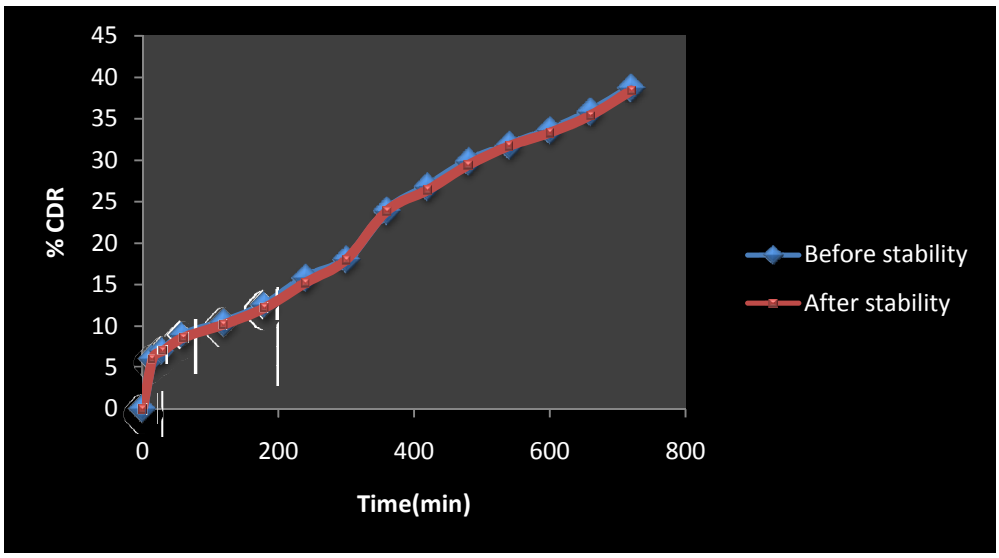

Fig. 28 Cumulative % drug release OF F12 (stability studies) AT 40ºC/75% RH

They were then stored at 25ºC and 60% RH, 30ºC and 65% RH, 40ºC and 75% RH for 3 months and evaluated for their permeation study and results were shown in Tables 9-11 and Figures 25-28 (ICH *et al*., 2008).

RESULTS AND DISCUSSION

Calibration Curve of Glipizide

The absorbance was measured in a UV spectrophotometer at 233 nm. The obtained absorbance were shown in Table 2 and graph plotted was shown in the Figure 1 and standard calibration curve with slope 0.081 and regression value R^2 of 0.999 was obtained. The absorbance was measured in a UV spectrophotometer at 233 nm. The obtained absorbance were shown in Table 3 and graph plotted was shown in the Figure 2. Standard calibration curve with slope 0.130 and regression value R^2 of 0.989 was obtained and all above results were comparable with standard data.

Calibration Curve of Glipizide in 6.8 pH buffer

The absorbance was measured in a UV spectrophotometer at 233nm against 6.8 pH buffer. The absorbance so obtained were tabulated in Table 4 and Calibration curve was plotted and shown in Figure 3 and standard calibration curve with slope 0.110 and regression value R^2 of 0.991 was obtained were comparable with standard data.

FT-IR spectrum and DSC Study

Drug and polymers were identified and conformed from the peak values by performing FT-IR studies and results were shown in Figures 4-12. The FT-IR spectrum not shown the presence of any additional peaks for new functional groups, indicating that no chemical interaction between drug and polymers.

Table 1. Formulations containing and various concentrations of excipients

Ingredients	F1 (mg/tab)	F2 (mg/tab)	F3 (mg/tab)	F4 (mg/tab)	F5 (mg/tab)	F6 (mg/tab)	F7 (mg/tab)	F8 (mg/tab)	F9 (mg/tab)	F10 (mg/tab)	F11 (mg/tab)	F12 (mg/tab)
	500	500	500	500	500	500	500	500	500	500	500	500
Ethyl cellulose	150	100	75	-	-	-	-	-	-	75	-	75
HPMC	-	-	-	75	150	100	-	-	-	75	75	-
Guar gum	-	-	-	-	-	-	75	100	150	-	75	75
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Talc	5	5	5	5	5	5	5	5	5	5	5	5
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	850	850	850	850	850	850	850	850	850	850	850	850

Table 2. Spectrophotometric data for the estimation of glipizide in 1.2 pH

S.No	CONC (µg/ml)	ABSORBANCE			AVG	S.D
		Trial 1	Trial 2	Trial 3		
1	0	0	0	0	0	0
2	1	0.081	0.089	0.081	0.0836	0.0046
3	2	0.163	0.169	0.163	0.1650	0.0034
4	3	0.243	0.254	0.243	0.2466	0.0063
5	4	0.325	0.343	0.325	0.3310	0.0103
6	5	0.406	0.403	0.406	0.4050	0.0017
7	6	0.482	0.489	0.482	0.4843	0.0040
8	7	0.565	0.599	0.599	0.5763	0.0196
9	8	0.648	0.667	0.667	0.6543	0.0109

Table 3. Spectrophotometric data for the estimation of glipizide in 1.2 pH

S.No	CONC (µg/ml)	ABSORBANCE			AVG	S.D
		Trial 1	Trial 2	Trial 3		
1	0	0	0	0	0	0
2	1	0.199	0.198	0.199	0.1986	0.0005
3	2	0.298	0.296	0.310	0.3013	0.0075
4	3	0.398	0.397	0.398	0.3980	0.0010
5	4	0.499	0.587	0.527	0.5276	0.0513
6	5	0.689	0.697	0.688	0.6888	0.0085
7	6	0.789	0.799	0.804	0.8043	0.0181
8	7	0.893	0.897	0.893	0.8931	0.0041
9	8	0.986	0.993	0.992	0.9925	0.0056

Table 4. Spectrophotometric data for the estimation of glipizide in 6.8 pH

S.No	CONC (µg/ml)	ABSORBANCE			AVG	S.D
		Trial 1	Trial 2	Trial 3		
1	0	0	0	0	0	0
2	1	0.199	0.198	0.198	0.1590	0.0005
3	2	0.266	0.247	0.204	0.2198	0.0391
4	3	0.319	0.367	0.384	0.3582	0.0312
5	4	0.461	0.489	0.492	0.4812	0.0141
6	5	0.529	0.587	0.567	0.5683	0.0274
7	6	0.643	0.699	0.668	0.6584	0.0326
8	7	0.701	0.788	0.789	0.7582	0.0409
9	8	0.801	0.832	0.868	0.8488	0.0402

Table 5. Pre compression evaluation parameters

Formulation	Bulk density(gm/cc)	Tapped density(gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.750±0.0020	0.8486±0.0051	11.624±0.310	1.131±0.0039	18.79±1.09
F2	0.654±0.0135	0.7416±0.0210	11.762±0.679	1.133±0.0087	20.64±0.629
F3	0.730±0.0015	0.8456±0.0102	13.628±1.228	1.157±0.0163	22.43±1.060
F4	0.624±0.0011	0.7113±0.0120	12.212±1.631	1.139±0.0212	20.26±1.692
F5	0.693±0.0035	0.793±0.0030	12.568±0.116	1.143±0.0015	21.58±1.030
F6	0.716±0.0052	0.838±0.0056	14.588±1.070	1.170±0.0147	22.45±1.062
F7	0.648±0.0045	0.734±0.0034	11.715±0.683	1.132±0.0087	20.02±1.486
F8	0.655±0.0030	0.754±0.0026	13.089±0.507	1.150±0.0067	27.02±0.470
F9	0.626±0.0023	0.727±0.0040	13.923±0.608	1.161±0.0082	26.95±1.291
F10	0.621±0.0079	0.721±0.0102	13.893±1.966	1.161±0.0262	24.93±1.095
F11	0.654±0.0026	0.754±0.0026	13.262±0.046	1.152±0.0006	25.54±1.015
F12	0.6266±0.0236	0.728±0.0168	13.978±1.131	1.162±0.0178	25.34±1.58

DSC thermogram showed that there was no any major difference in onset temperature and peak temperature, when compared with pure drug thermogram, results were shown in Figures 13 and 14. No interaction was found between drug and polymers and the characteristic peak of drug is not observed in the formulation. Hence it indicates the physical nature of the drug is not changed in the formulation, it indicating that no significant change in the chemical integrity of the drug.

Preformulation studies

Melting Point Determination Melting point of Glipizide was determined by standard method as capillary method and was found to be in the range 205-208^{0}C, which complied with IP standards, thus indicating the purity of the drug sample as the same compared with the standard.

Flow properties

Angle of repose: All formulations were between 18-27, shown in Table 5, indicating reasonable flow property and all formulations were found to fit with respect to flow property.

Carr's index: was between 11 to13 shown in Table 5, indicating all formulations was found to be within the limits.

Hausner's Ratio: was between 1.131 to 1.170 shown in Table 5, indicating that all formulations was found to be within the limits.

Post compression evaluation parameters

Weight variation: The weight variation for all formulations was shown in Table 6. The results of weight variation of tablets in all formulations were found to be in the range of 847.80±0.603 to 853.2±1.362 mg indicating that the weight variation is within the pharmacopoeial limits.

Hardness: The hardness for all formulations were shown in the 6, hardness was found to be in the range of 6.2±0.34 to 6.59±0.1 indicating that is within the pharmacopoeia limits.

Friability: The friability of all formulations was shown in the Table 6 and ranges from 0.0133±0.003 to 0.097±0.0209 indicating that the variability of all formulations was less than 1%.

Thickness: Thickness of all formulations was depicted in the Table 6. The results thickness of all formulations found to be in the range of 4.11±0.18 to 4.78±0.20.

Drug content: The percentage drug content of all formulations was found in the range of 97.06±0.92 to 100.15±0.52, which was all within the acceptable limits of official standards.

***In vitro* drug release studies**

The *in-vitro* release study was carried out in three different dissolution media, namely, in simulated gastric fluid at pH 1.2 for 2 hrs then replaced by simulated intestinal fluid for next 3 hrs at 7.4pH and then followed by simulated colonic fluid at 6.8 pH for next 7hrs.

Table 6. Results of post compression characteristics

Formulation	Bulk density(gm/cc)	Tapped density(gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	853.2±1.362	6.3±0.07	0.0507±0.017	4.11±0.18	99.03±1.67
F2	852.68±2.116	6.32±0.09	0.0387±0.016	4.70±0.22	99.15±0.89
F3	852.18±0.560	6.5±0.17	0.040±0.0147	4.54±0.18	98.98±0.77
F4	852.57±1.019	6.2±0.34	0.0524±0.025	4.78±0.20	99.80±0.13
F5	851.08±1.060	6.4±0.35	0.0370±0.0178	4.56±0.18	100.25±0.08
F6	850.51±0.896	6.59±0.1	0.097±0.0209	4.11±0.11	97.06±0.92
F7	848.60±0.976	6.5±0.17	0.024±0.0120	4.54±0.21	99.82±1.35
F8	848.55±1.02	6.4±0.04	0.0250±0.0167	4.70±0.16	100.06±0.77
F9	849.20±0.577	6.3±0.05	0.0133±0.003	4.16±0.20	99.92±0.20
F10	850.16±1.486	6.5±0.17	0.0383±0.0086	4.52±0.22	98.37±0.67
F11	847.80±0.603	6.4±0.04	0.0407±0.0057	4.72±0.10	100.7±0.52
F12	851.92±0.545	6.2±0.34	0.0233±0.0174	4.28±0.18	99.87±0.052

Table 7. Cumulative percentage drug release of f1 to f12

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
15	7.4444	7.000	6.0333	9.2777	9.6444	8.222	6.222	7.444	7.655	5.9111	5.788	6.1444
30	9.930	8.261	9.9224	10.607	11.053	9.267	8.701	9.9302	10.264	7.5661	7.054	7.0230
60	13.762	9.973	10.721	13.999	15.225	10.652	10.638	13.985	14.432	9.8413	8.7600	8.8840
120	15.172	10.917	14.258	21.854	21.865	14.155	13.363	16.284	17.512	11.162	10.041	10.455
180	22.755	13.284	17.949	27.238	30.226	17.056	16.622	20.270	20.975	16.390	15.820	12.502
240	28.003	24.918	20.332	32.026	36.831	22.757	20.175	23.151	22.821	18.141	18.123	15.824
300	30.649	27.962	25.704	35.109	39.179	27.382	22.016	27.362	27.445	20.941	20.991	18.057
360	38.010	34.271	32.403	44.024	44.100	35.210	30.563	33.295	33.309	27.084	25.838	23.914
420	39.281	41.494	35.198	47.455	48.840	39.002	32.448	37.894	36.436	33.123	27.207	26.826
480	43.912	43.766	38.253	53.358	53.442	43.878	38.188	41.782	38.352	35.430	33.430	29.836
540	47.832	48.831	41.896	57.901	55.204	47.634	41.832	44.054	40.359	38.323	35.555	31.798
600	51.690	51.550	46.623	58.951	57.137	52.474	45.985	46.746	42.213	41.230	38.346	33.606
660	55.404	53.628	52.847	61.395	59.816	57.257	48.852	49.043	46.367	44.070	38.653	35.832
720	58.565	55.635	53.786	61.887	60.790	58.792	50.342	49.388	47.269	45.453	40.660	38.725

Table 8. Mathematical modeling and drug release kinetics of formulation f1 tof12

Formulation code	Drug Release Kinetics					
	R^2	R^2	R^2		n	R^2
F1	0.991	0.995	0.978	0.996	0.422	0.990
F2	0.977	0.983	0.945	0.983	0.437	0.937
F3	0.994	0.984	0.952	0.989	0.467	0.979
F4	0.972	0.988	0.984	0.985	0.499	0.992
F5	0.953	0.985	0.993	0.977	0.483	0.991
F6	0.994	0.985	0.946	0.990	0.432	0.959
F7	0.991	0.985	0.947	0.989	0.454	0.982
F8	0.982	0.989	0.974	0.988	0.498	0.990
F9	0.979	0.991	0.984	0.988	0.474	0.993
F10	0.989	0.989	0.954	0.990	0.428	0.981
F11	0.987	0.989	0.964	0.989	0.473	0.979
F12	0.990	0.991	0.951	0.991	0.442	0.967

Table 9. Drug content data after stability study

S.No	Time	Formulation (Content estimation in%) at room temperature		Formulation (Content estimation in%) at 40ºC/75%RH	
		F11	F12	F11	F12
1	15 Days	98.95	99.85	98.83	99.76
2	30 Days	98.49	98.99	98.36	98.89
3	45 Days	98.38	98.78	98.26	98.72
4	60 Days	98.24	98.62	97.45	98.58

Table 10. *In-vitro* drug release of tablets stability study of formulation f11 and f12 at room temperature

Time in min	F11 Formulation		F12 Formulation	
	Before stability studies	After stability studies	Before stability studies	After stability studies
0	0	0	0	0
15	5.788889	5.739	6.144444	6.132
30	7.054383	7.0118	7.023025	7.194
60	8.760062	8.6953	8.884074	8.878
120	10.04167	10.0124	10.45525	10.491
180	15.82072	15.7654	12.5024	12.432
240	18.12303	18.1636	15.82471	15.289
300	20.99149	20.937	18.0574	18.174
360	25.83897	25.7456	23.9146	23.634
420	27.20716	27.143	26.82687	26.213
480	33.32761	33.284	29.83642	29.256
540	35.55397	35.456	31.79824	31.624
600	38.36443	38.267	33.60642	33.554
660	38.65306	38.196	35.83278	35.779
720	40.66034	40.598	38.72506	38.756

Table 11. *In-vitro* drug release of tablets stability study of formulation F11 AND F12 AT 4OºC/75%RH

Time in min	F11 Formulation		F12 Formulation	
	Before stability studies	After stability studies	Before stability studies	After stability studies
0	0	0	0	0
15	5.788889	5.601	6.144444	6.132
30	7.054383	7.196	7.023025	7.194
60	8.760062	8.593	8.884074	8.845
120	10.04167	10.256	10.45525	10.435
180	15.82072	15.763	12.5024	12.467
240	18.12303	18.112	15.82471	15.236
300	20.99149	20.847	18.0574	18.174
360	25.83897	25.298	23.9146	23.667
420	27.20716	27.165	26.82687	26.287
480	33.32761	33.284	29.83642	29.297
540	35.55397	35.4858	31.79824	31.623
600	38.36443	38.394	33.60642	33.554
660	38.65306	38.343	35.83278	35.779
720	40.66034	40.532	38.72506	38.723

The amount of drug released from formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12 in gastric condition after 2hrs were 15.15%, 10.91%, 14.26%, 21.84%, 21.85%, 14.155%, 13.35%, 16.27, 17.51%, 11.16%, 10.05% and 10.44% respectively.

The amount of drug released from formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12 in intestinal condition after 3hrs were 30.63%, 27.95%, 25.71%, 35.11%, 39.16%, 27.37%, 22.00%, 27.35%, 27.44%, 20.95%, 20.98% and 18.04% respectively.

The amount of drug released from formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12 in the colonic fluid after 7hrs were 58.55%, 55.64%, 53.77%, 61.87%, 60.80%, 58.80%, 50.35%, 49.37%.47.25%, 45.45% 40.66%, and 38.71%, respectively and results showed in Table 7 and Figures 15-19,indicating that the drug release from the formulations decreased with an increase in the amount of polymer added in each formulation. Formulation F11 and F12 shows slow release compared to all formulations and found to be good candidate for colonic drug delivery.

Release kinetics of Glipizide

All the formulations shown linearity with respect to zero order and first order kinetics as shown in Table 8 and Figures 20-24. The regression values of the Zero order kinetics of Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12 were 0.992, 0.977, 0.995, 0.971, 0.954, 0.994, 0.991, 0.982, 0.979, 0.989, 0.987 and 0.995 respectively. The regression values of first order kinetics of Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12 were 0.995, 0.983, 0.985, 0.988, 0.985, 0.986, 0.985, 0.989, 0.988, 0.992, 0.989 and 0.993 respectively. From the regression values was found that the drug release follows mixed order kinetics.

To ascertain the drug release mechanism, the *in-vitro* data were also subjected to Higuchi's model. R^2 values of formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12 were 0.977, 0.946, 0.953, 0.985, 0.994, 0.945, 0.947, 0.973, 0.985, 0.954, 0.966 and 0.952 respectively. The formulations were subjected to Peppas plots, 'n' value ranges from 0.422 to 0.499 indicating that the drug release was by non-Fickian diffusion mechanism.

Stability studies

After the stability studies the formulations were subjected to content estimation and the results were shown in Tables 9-11 and Figures 25-28. The best formulations F11 and F12 subjected to stability studies at 40^0C /75% RH and room temperature for 2 months. Then the tablets were analyzed for physical change, drug content estimation and *in-vitro* dissolution studies at an interval of 15 days. Results were showed that after analyzed there was no change in case of physical appearance, no significant differences in the drug content and dissolution study. Comparison of drug release profiles of formulations before stability and after stability was shown in the Tables 9 and 11. It was found that formulations were stable throughout the study period.

Conclusion

Glipizide, an oral hypoglycemic agent, is one of the most commonly prescribed drug for the treatment of patients with type II diabetes mellitus (Non- Insulin Dependent Diabetes Mellitus), and belongs to class II of Biopharmaceutical classification System (BCS).All the prepared formulations were evaluated for both pre-compression and post-compression parameters such as tablet thickness, hardness, friability, weight variation and drug content, the values obtained were found to be satisfactory and they comply with pharmacopoeial standards. The i*n-vitro* drug release was studied with USP Type-II dissolution apparatus in different pH conditions like simulated gastric fluid pH 1.2, intestine fluid pH 7.4 and simulated colonic fluid pH 6.8 for a period of 12hrs. The results of dissolution studies indicated that formulations F11 and F12 produced better control in colonic conditions with 40.65% and 38.71% of drug release over a period of 12hrs in comparison to other formulations. The dissolution data so obtained was fitted to various mathematical kinetic models and the drug release followed mixed order and Higuchi's model. To study release mechanism of the drug from matrices the data were fitted to Koresmeyer-Peppas model and the release mechanism involved was non-Ficknian diffused (Anomalous transportation).

From above highlight it can be concluded that the polymer plays a major role in the design of Control Drug Delivery System with matrix tablets. The study reveals that the release of drug was low when the matrix tablet contained polymers with increasing concentration and combination. Hence it clearly indicated that the necessity of combining different classes of polymer to get an acceptable pharmacokinetic profile in the fluctuating *in vivo* environment.

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