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Effect of Polymer Concentration on Drug Release in the Formulation of Controlled Release Tablets of Glipizide Using Novel Natural Polymers

Abstract

The objective of the present study was to develop Controlled release tablets of Glipizide using Natural polymers. The tablets were prepared with different ratios of Xanthan Gum, Guargum and Karaya Gum by direct compression technique. The solubility study of the Glipizide was conducted to select a suitable dissolution media for *in vitro* drug release studies. FTIR study revealed no considerable changes in IR peak of Glipizide and Hence no interaction between drug and the excipients. *In vitro* release from the formulation F5 was found to be 99.34 %. From all the results of dissolution data fitted to various drug release Kinetic equations. It was observed that highest correlation was found for Higuchi release kinetics mechanism.

Keywords : Glipizide , Xanthan Gum , Guar Gum, Karaya Gum and Controlled release tablets.

1. INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. 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.[1,2,3]

Controlled release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. Greater attention is paid on development of oral controlled release drug delivery systems due to flexibility in designing of dosage form. The main challenges to oral drug delivery systems are to deliver a drug at therapeutically effective rate to desirable site, modulation of GI transit time and minimization of first pass elimination. Control release dosage form provides better maintenance of optimal and effective drug level for prolonged duration with less dosing frequency and side effects.[4,5]

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms.[6]

The basic rationale of a controlled release drug delivery system is to optimize the biopharmaceutics, pharmacokinetics, and pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of disease condition in the shortest possible time by using smallest quantity of drug, administered by most suitable route. The immediate release drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. An ideal drug delivery system should deliver the drug at a rate dictated by the need of body over a specified period of treatment.

A controlled release drug delivery system is capable of achieving the following benefits over conventional dosage forms:[7]

- ✓ Total dose is low.
- ✓ Reduced GI side effects and other toxic effects.
- ✓ Reduced dosing frequency.
- ✓ Better patient acceptance and compliance.
- ✓ Less fluctuation in plasma drug levels.
- ✓ More uniform drug effect.
- ✓ Better stability of drug.

Aim of the study is to formulate Controlled release Tablets Of Glipizide by using different types of polymers like Xanthan gum ,Guar Gum and karaya gum for the Treatments Of hyperglycemia.

7. METHODOLOGY

1. Analytical method development:

a) Determination of absorption maxima:

10mg of Glipizide pure drug was dissolved in 10ml of Methanol (stock solution). 1ml of above solution was taken and made up to10ml by using 0.1 N HCl (100µg/ml).From this 1ml was taken and made up to 10 ml of 0.1 N HCl (10µg/ml) and the solution was scanned in the range of 200 – 400 nm. Similar procedure was repeated to pH 6.8 Phosphate buffer UV spectrum was taken using Double beam UV/VISspectrophotometer.

b) Preparation calibration curve:

10mg of Glipizide pure drug was dissolved in 10ml of Methanol (stock solution). 1ml of above solution was taken and made up to10ml by using 0.1 N HCl (100µg/ml). From this 1ml was taken and made up to 10 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 10, 20, 30, 40 and 50µg/ml of Glipized per ml of solution. The absorbance of the above dilutions was measured at 255nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and

Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2)which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer.

2. Preformulation parameters

Angle of repose:

The angle of repose was calculated using the following formula:

Tan θ = h / r Tan θ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Bulk density:

The bulk density was calculated using the formula:

Bulk Density = M / V_o

Where,

M = weight of sample

V_o = apparent volume of powder

Tapped density:

The tapped density was calculated, in gm per L, using the formula:

Tap= M / V

Where,

Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility:

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

3. Formulation development of Tablets:

All the formulations were prepared by direct compression. The tablets were prepared as per the procedure given below and aim is to prolong the release of Glipizide.

Procedure:

1) Glipizide and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined.The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\% \text{ Loss} = \frac{\text{Initial weight of tablet} - \text{Final weight of tablet}}{\text{Initial weight}} \times 100$$

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glipizide	5	5	5	5	5	5	5	5	5
Xanthan Gum	5	10	15	-	-	-	-	-	-
Guar Gum	-	-	-	5	10	15	-	-	-
karaya gum	-	-	-	-	-	-	5	10	15
Talc	7	7	7	7	7	7	7	7	7
Magnesium Stearate	7	7	7	7	7	7	7	7	7
Micro crystalline cellulose	76	71	66	76	71	66	76	71	66
Total weight	100	100	100	100	100	100	100	100	100

Formulation composition for tablets

Determination of drug content:
Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**
Dissolution parameters:
Apparatus --USP-II, Paddle Method

Dissolution Medium -- 0.1 N HCl , p H 6.8 Phophate buffer

RPM -- 50

Sampling intervals (hrs)--1,2,3,4,5,6,7,8,10,11,12

Temperature --37°c ± 0.5°c

Procedure:
900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HClwas removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at respective wavelength using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:
Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

4. Drug – Excipient compatibility studies
Fourier Transform Infrared (FTIR) spectroscopy:
The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FTIR analysis of the Pure drug and optimised formulation were carried out using an FTIR spectrophotometer (Bruker FT-IR - USA).

3. Results And Discussion

The present study was aimed to developing Controlled release tablets of Glipizide using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method
Graphs of Glipizide were taken in 0.1N HCl and in p H 6.8 phosphate buffer at255 nm and 260nm respectively.

Table 1 : Observations for graph of Glipizide in 0.1N HCl(255nm)

Conc [µg/mL]	Abs
0	0
10	0.157
20	0.349
30	0.548
40	0.763
50	0.957

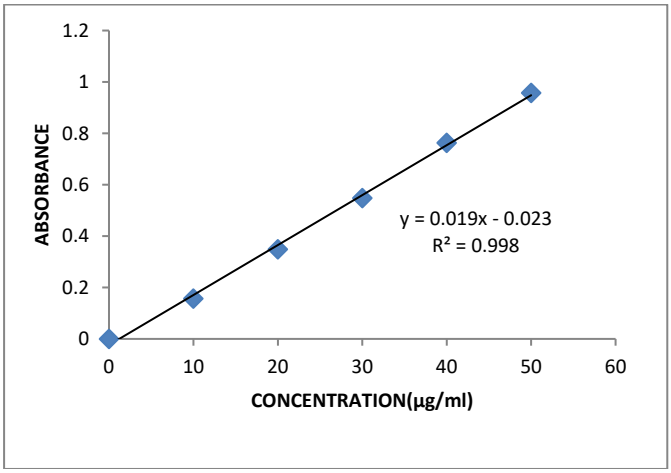

Figure 1 : Standard graph of Glipizide in 0.1N HCl (255nm)

Table 2 : Observations for graph of Glipized in p H 6.8 phosphate buffer (260nm)

Conc [µg/mL]	Abs
0	0
10	0.115
20	0.223
30	0.318
40	0.431
50	0.549

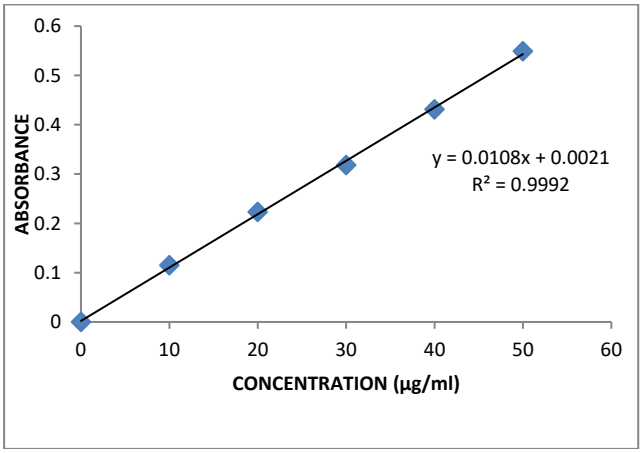

Figure 2 : Standard graph of Glipizide pH 6.8 phosphate buffer (260nm)

PREFORMULATION PARAMETERS OF POWDER BLEND

Table 3 :Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	27.08	0.664	0.823	19.32	1.07
F2	32.15	0.652	0.807	19.21	0.98
F3	37.39	0.662	0.901	26.53	0.95
F4	31.47	0.667	0.907	26.46	0.99
F5	31.09	0.624	0.801	22.10	1.10
F6	28.12	0.648	0.862	24.82	0.91
F7	26.89	0.681	0.887	23.22	0.98
F8	25.9	0.651	0.817	20.32	1.13
F9	24.70	0.672	0.826	18.64	1.18

Table 4 :*In vitro* quality control parameters for tablets

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	99.42	2.24	0.48	1.54	98.35
F2	98.73	2.43	0.65	1.85	99.48
F3	97.96	2.38	0.72	1.68	99.16
F4	96.45	2.54	0.57	1.52	99.65
F5	100.32	2.18	0.45	1.74	100.48
F6	101.68	2.49	0.67	1.66	97.65
F7	98.49	2.33	0.68	1.81	97.76
F8	95.67	2.29	0.82	1.65	98.46
F9	102.88	2.43	0.59	1.72	99.79

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.624to 0.681 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.801to 0.907showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 18.64 to 26.53 which shows that the powder has good flow properties.All the formulations has shown the hausner ratio ranging between 0.91 to 1.18 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 95.67 to 101.68mg, The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester. The results showed that the hardness of the tablets is in range of 2.18 to2.54 kg/cm^2,which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown .The result showed that thickness of the tablet is raging from 1.52 to1.85 mm.

Friability:

Tablets of each batch were evaluated for percentage friability and. The average friability of all the formulations lies in the range of 0.08±0.04 to0.72±0.03 which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table 5 : Dissolution Data of Glipizide Tablets F1-F9

TIME (HR)	CUMULATIVE PER								
	F1	F2	F3	F4					
0	0	0	0	0					
1	3.11	9.64	14.35	33.48	2				
2	9.54	13.83	17.58	49.66	3				
3	13.62	18.76	23.19	55.11	4				
4	18.22	21.53	27.38	63.92	5				
5	21.31	26.18	30.62	78.34	5				
6	23.04	33.68	33.97	82.88	6				
7	26.82	38.41	39.51	90.79	71.04	66.15	68.74	67.57	67.14
8	33.67	44.75	45.28	98.57	78.77	73.35	76.53	74.72	73.33
9	38.49	53.84	51.66		8				
10	51.77	65.28	71.42		8				
11	65.38	72.12	79.25		9				
12	73.44	81.07	85.33		9				

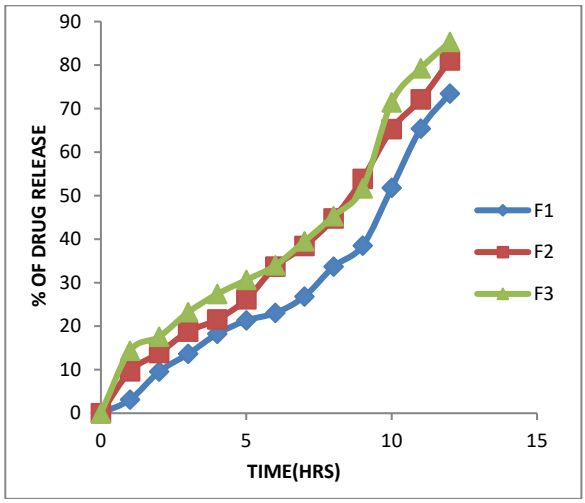

Figure 3 :Dissolution profile of Glipizide (F1, F2, F3 formulations).

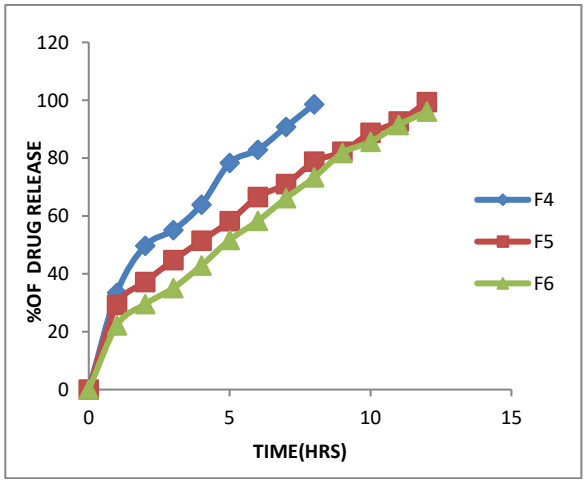

Figure 4 :Dissolution profile ofGlipizide (F4, F5, F6 formulations)

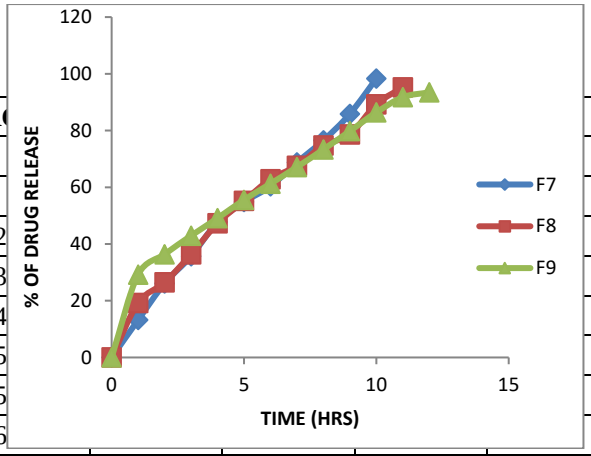

Figure 5 : Dissolution profile of Glipizide (F7, F8, F9 formulations)

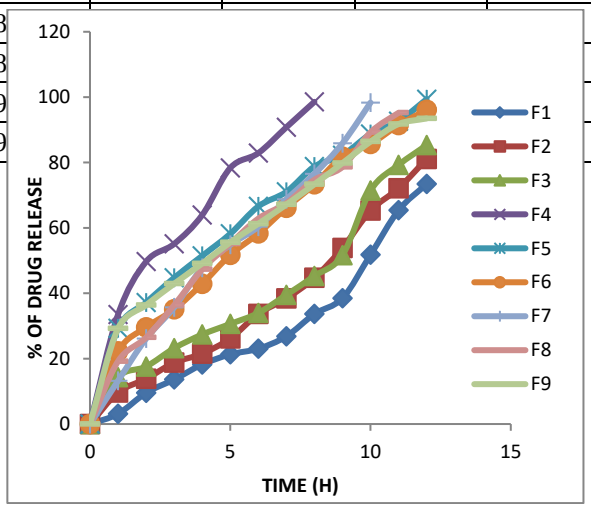

Figure 6 : Dissolution profile of Glipizide (F1-F9 formulations)

From the dissolution data, it was revealed that formulations prepared with Xanthan Gumretard the drug release up to 12 hrs.

Whereas the formulations prepared with Guar Gum were retarded the drug release in the concentration of 10 mg (F5 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.36% in 12 hours with good retardation.

Formulations prepared with karaya gum were revealed that increase in the concentration retards the drug release.

Among all formulationsF5 formulation was considered as optimised formulation. It was shown 99.36% drug release at 12hrs.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 6 :Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
29.24	1	1.000	1.466	0.000	1.850	29.240	0.0342	-0.534	70.76	4.642	4.136	0.505
37.17	2	1.414	1.570	0.301	1.798	18.585	0.0269	-0.430	62.83	4.642	3.975	0.666
44.73	3	1.732	1.651	0.477	1.742	14.910	0.0224	-0.349	55.27	4.642	3.809	0.832
51.44	4	2.000	1.711	0.602	1.686	12.860	0.0194	-0.289	48.56	4.642	3.648	0.993
58.19	5	2.236	1.765	0.699	1.621	11.638	0.0172	-0.235	41.81	4.642	3.471	1.171
66.57	6	2.449	1.823	0.778	1.524	11.095	0.0150	-0.177	33.43	4.642	3.221	1.420
71.04	7	2.646	1.852	0.845	1.462	10.149	0.0141	-0.148	28.96	4.642	3.071	1.571
78.77	8	2.828	1.896	0.903	1.327	9.846	0.0127	-0.104	21.23	4.642	2.769	1.873
82.22	9	3.000	1.915	0.954	1.250	9.136	0.0122	-0.085	17.78	4.642	2.610	2.032
88.73	10	3.162	1.948	1.000	1.052	8.873	0.0113	-0.052	11.27	4.642	2.242	2.400
92.65	11	3.317	1.967	1.041	0.866	8.423	0.0108	-0.033	7.35	4.642	1.944	2.697
99.36	12	3.464	1.997	1.079	-0.194	8.280	0.0101	-0.003	0.64	4.642	0.862	3.780

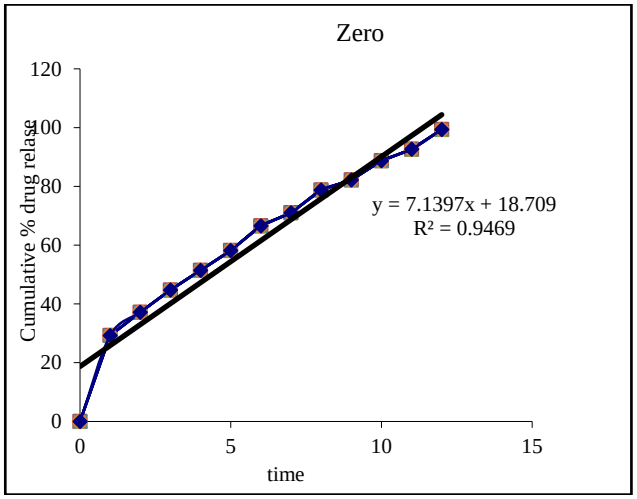

Figure 7 : Zero order release kinetics graph

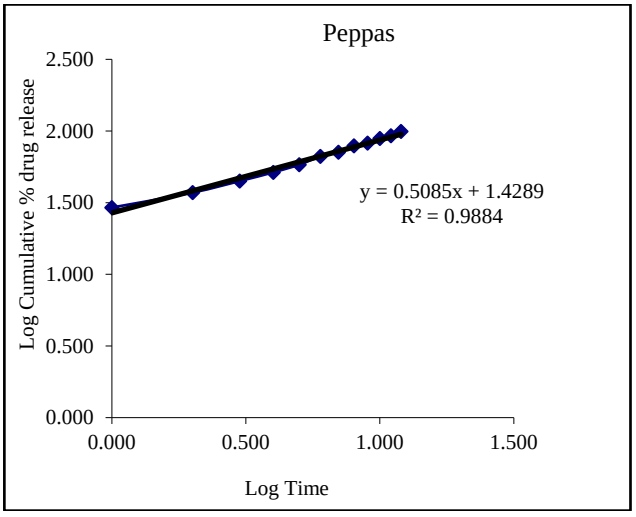

Figure 9 :Karsmayerpeppas graph

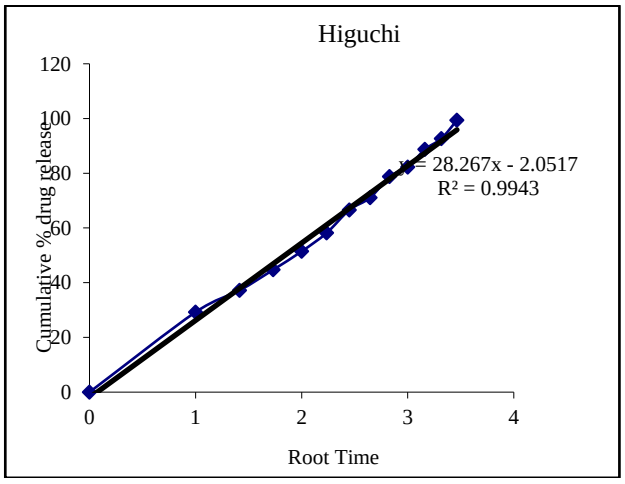

Figure 8 : Higuchi release kinetics graph

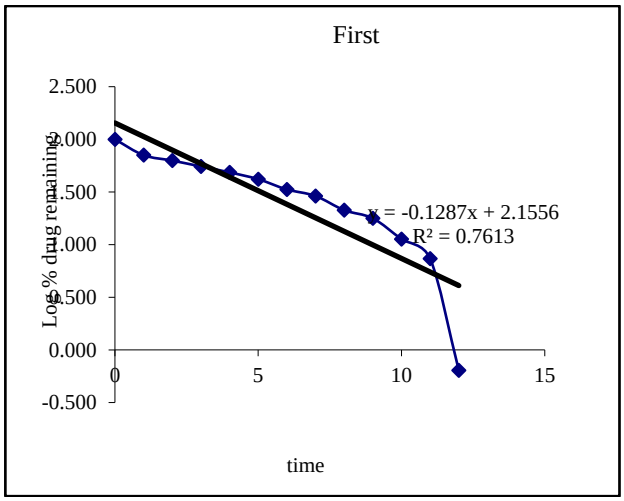

Figure 10 : First order release kinetics graph

Table 7: kinetics Correlation coefficient values

Release Kinetics	Correlation coefficient values
Zero order release kinetics	$R^2 = 0.946$
Higuchi release kinetics	$R^2 = 0.994$
Peppas release kinetics	$R^2 = 0.988$
First order release kinetics	$R^2 = 0.761$

The *in vitro* release data of best formulations (F5) were fitted into various kinetic models. Correlation coefficients of formulation F5 batch showed higher correlation with Higuchi release kinetics than Zero order,First order and Peppas release kinetics. So, predominant drug release mechanism is controlled release.

From the above graphs it was evident that the formulation F5 was followed Higuchi release kinetics.

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy:

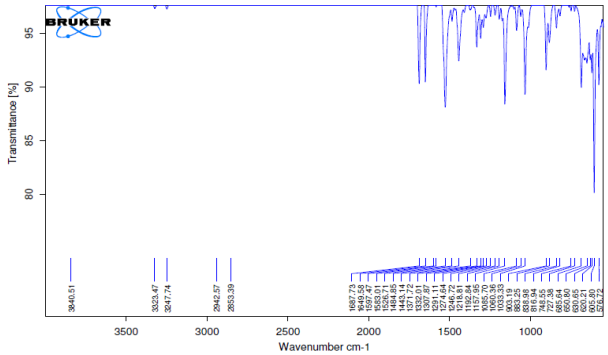

Figure 11 :FT-TR Spectrum of Glipizide pure drug.

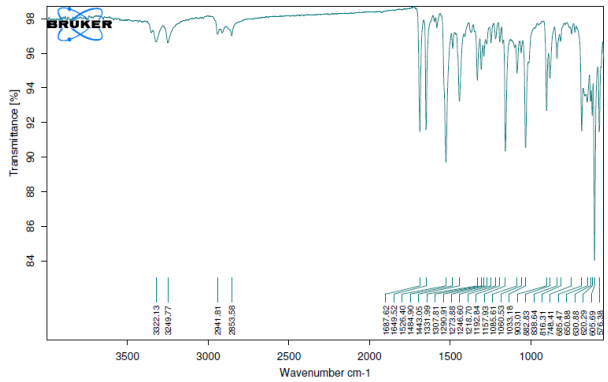

Figure 12: FT-IR Spectrum of Optimised Formulation

From the above studies it was found that there was no shifting in the majorpeaks which indicated that there were no significant interactions occurred between theGlipizide and excipients used in the preparation of different GlipizideControlled release formulations. Therefore the drug and excipients are compatible to form stable formulations under study. The FTIR spectra of Glipizide and physical mixtureused for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

9. Conclusion

In this study an effort was made to study controlled release Glipizide which can provide controlled drug release for up to 12hrs.Glipizide controlled release tablets were formulated and evaluated. Glipizide controlled tablets were prepared with different polymers like Xanthan gum ,Guar Gum and karaya gum. The pre-compression and the post compression parameters are found to be within the limits. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits.Whereas from the dissolution studies it was evident that the formulation F5 were optimized by conducting various trails. F5 was showed good drug release 99.36 % was up to 12hrs. It followed Higuchi release kineticsmechanism.

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