Original Article

DRUG RELEASE AND SWELLING KINETIC STUDIES OF GLIPIZIDE SUSTAINED RELEASE MATRIX TABLET – WET GRANULATION METHOD

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Abstract

The aim of present study was to prepare and characterize sustained release glipizide matrix tablet using synthetic (Sodium alginate, carbopol) and natural (chitosan, xanthan gum) polymers as a cost effective, nontoxic, easily available, hydrophilic matrix system when compared with extensively investigated hydrophilic matrices [sodium alginate], [carbopol]. Matrix tablets of Glipizide (dose 10mg) were prepared by wet granulation method at different ratios of 1:5,1:6,1:7,1:8 (Drug: polymers) . Release kinetics was studied using United states of Pharmacopeia (USP)-22 type I dissolution apparatus. Further more *in vitro* and *in vivo* datas of newly formulated sustained-release Glipizide tablets were compared with conventional marketed tablet (Glipizide,India). The *in vitro* release study revealed that formulation containing chitosan showed sustained release of 96.4% up to 12 h. Sustained release formulation of Glipizide containing chitosan showed good bioavailability and pharmacokinetic profile from the *in vivo* study carried out on rat. Thus the results suggest the developed sustained-release tablets of Glipizide performed therapeutically better than conventional dosage forms, leading to improved bioavailability, therapeutic efficacy with better patient compliance.

Key words: glipizide, sodium alginate, carbopol, chitosan, xanthan gum,

Introduction

Increased complications and expense involved in marketing of new drug entities has focused greater attention on development of sustained release (SR) or controlled release (CR) drug delivery systems[1]. Sustained or controlled release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half - life drugs, decreased toxicity and reduction of required dose, optimized therapy and better patient compliance[2, 3]. Matrix type sustained delivery systems are popular because of their ease of manufactures. It is controlled mainly by the type and proportion of the polymers used in the preparation. Hydrophilic polymer matrix is widely used for formulating a sustained release dosage form[4,5]. The hydrophilic polymer selected for the present study are Hydrophilic polymer matrix system are widely used for designing oral sustained release delivery systems because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance in the gastrointestinal tract at any biological pH and provide good bioavailability of the active ingredient. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic matrix. For such drugs it becomes essential to include hydrophobic polymers in the matrix system.

Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes[6]. It is used adjunct to diet to the management of type II (non-insulin dependent) diabetes mellitus in patients whose hyperglycemia cannot be controlled by diet and exercise alone. Glipizide stimulates insulin secretion from the cells of pancreatic islets tissue, increases the concentration of insulin in the pancreatic vein and may increase the number of insulin receptors. Glipizide is a weak acid (pKa = 5.9) practically insoluble in water and acidic environment and highly permeable (class II) drug according to the Biopharmaceutical Classification System (BCS)[8]. The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life of 2- 4 hours[8]. Glipizide is reported to have a short biological half-life (3.4±0.7 h) requiring it to be administered in 2 to 3 doses of 2.5 to10 mg per day[9]. SR formulations that would maintain plasma levels of drug for 8 to 12 hrs might be sufficient for once a day dosing for glipizide. SR products are needed for glipizide to prolong its duration of action and to improve patient compliance[10].

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Materials and methods

Materials

Glipizide gift sample from Micro Labs, Hosur. Sodium alginate, carbopol chitosan , xanthan gum Gift sample from S.D fine chemicals., Mumbai. Magnesium stearate, talc, colloidal silicon dioxide, was of AR Grade.

Methods

Preparation of matrix tablets

Matrix tablets were prepared by wet granulation method. Accurate quantities of all ingredients for different were weighed. For each formulation, specific and accurate quantities were blended uniformly and passed through sieve No.20. Starch mucilage was used as a binder .The aggregates formed after addition of binder were initially dried 5-10 min to reduce moisture level and to prevent sticking with the sieve. The aggregates were passed through sieve # 16 mesh to get granules. The granules were finally dried at 50^0 c for 10-15 min to reduce moisture content to 2-5%. Magnesium stearate and talc were used for lubrication. After lubrication the formulations were evaluated for bulk density and compressibility. Same method followed for all formulations (FI, FII, FIII, FIV, and up to FXVI). The formulation manuals for all formulation are given in Table 1. Prior to the compression the granules were evaluated for several tests.

Table 01 : Formulation Manuals

F.No.	Glipizide	Sodium alginate	Carbopol	Chitosan	Xanthan gum	Lactose	Starch paste	Magnesium stearate	Colloidal silicon dioxide	Total weight (Mg)
F-I	10	50	-	-	-	115	q.s	15	10	200
F-II	10	60	-	-	-	105	q.s	15	10	200
F-III	10	70	-	-	-	95	q.s	15	10	200
F-IV	10	80	-	-	-	85	q.s	15	10	200
F-V	10	-	50	-	-	115	q.s	15	10	200
F-VI	10	-	60	-	-	105	q.s	15	10	200
F-VII	10	-	70	-	-	95	q.s	15	10	200
F-VIII	10	-	80	-	-	85	q.s	15	10	200
F-IX	10	-	-	50	-	115	q.s	15	10	200
F-X	10	-	-	60	-	105	q.s	15	10	200
F-XI	10	-	-	70	-	95	q.s	15	10	200
F-XII	10	-	-	80	-	85	q.s	15	10	200
F-XIII	10	-	-	-	50	115	q.s	15	10	200
F-XIV	10	-	-	-	60	105	q.s	15	10	200
F-XV	10	-	-	-	70	95	q.s	15	10	200
F-XVI	10	-	-	-	80	85	q.s	15	10	200

Evaluation of granules

Angle of repose

The angle of repose of granules was determined by the funnel method. [11]The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation .
Given in table 02

Bulk density

Both loose Bulk density (LBD) and tapped density (TBD) were determined. A calculated quantity of 2 gm of powder from each formula was introduced into a measuring cylinder and tapped for certain time until no further change in volume was noted. LBD and TBD were calculated using the following formula. The results are given in table 02

Compressibility index

The compressibility Index[12] of the granules was determined by Carr's compressibility index. The results are given in table 02.

Total porosity(Hausners ratio's)

Total Porosity was determined by measuring the volume occupied by a selected weight of a powder (V bulk) and the true volume of the granules V the space occupied by the powder exclusive of spaces greater than the intermolecular space[13]. The results are given in table 02.

Drug content

20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 15mg of glipizide was taken and dissolved in 30 ml of methanol with gentle heating on a water bath, cool and add sufficient amount of methanol is added to produce 50 ml. filter and dilute to 5 ml of the filtrate to 50ml with methanol. The absorbance was measured spectrophotometrically at 274 nm after suitable dilution.

Evaluations of tablets

Thickness

The thickness of the tablets were determined using a Digital Caliper (Mitutoyo, Digimatic Caliper, New Delhi, India) 20 tablets from each batch were used and average values were calculated. The results are given in table 03.

Weight variation test

To study the weight variation, 20 tablets of each formulation were selected at random and average weight was determined. Not more than 2 of the individual weights may deviate from the average weight by more than the % deviation and none should deviate by more than twice that of the percentage (Limit for not more than 130 to 324 mg is 7.5 %.). The results are given in table no: 3

Hardness and friability

For each formulation, the hardness and friability of 20 tablets each were determined using the Monsanto Hardness Tester and Roche Friabilator (Cadmach, Ahmedabad, India). The results are given in table 03.

In vitro drug release studies

The *in vitro* dissolution studies were performed using USP - 22 type I dissolution (Electro Lab, TDT -08 L, Mumbai, India) apparatus 37±5°C, at 50 rpm. Using 900 ml of 0.1 N HCl for first 2 hr and phosphate buffer of pH 6.8 from 2-12 hr. An aliquot (5 ml) of the sample solution was withdrawn at predetermined time intervals , filtered through a membrane filter, diluted suitably and analyzed spectrophotometrically at 274 nm (Shimadzu Model 1601). The results are given in table no: 4

Optimum release profile

Optimum release profile for once daily SR formulation was calculated by the Equation 3 using available pharmacokinetic data [14].

$$Dt = Dose\ (1 + 0.693 \times t / t\ ½)$$

(Equation 1)

Where Dt is total dose of drug, dose is dose of the immediate release part, t is time duringwhich the sustained release is desired (12 h) and t ½ is half -life of the drug (3 h). The optimum formulation was selected on the above equation so that it could attain complete and controlled drug release upon "trading off" various response variables; the following maximizing criteria were adopted.

Kinetic release profile

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models, zero order. As cumulative amount of drug released Vs time, C= Ko.t

first order as log cumulative percentage of drug remaining *vs.* time,

$$Log\ C = Log\ Co - kt / 2.303$$

Higuchi's model as cumulative percentage of drug released Vs. square root o f time.

$$Q = kt^{½}$$

Where

- 'Ko' is the zero -order rate constant expressed in units of concentration / time and 't' is the time in hours. A graph of concentration Vs time would yield a straight line with a slope equal to Ko and intercept the origin of the axes [15].
- 'Co' is the initial concentration of drug, 'k' is the first order constant, and t is the time.
- 'K' is the constant, reflecting the design variables of the system and 't' is the time in hours. These models fail to explain drug release mechanisms due to the swelling (upon hydration) along with gradual erosion of the matrix.

Therefore the dissolution data was also fitted to the well known Koresmeyer- peppas equation[16]

$$Log\ (Mt/Ma) = log\ K + n\ Logt$$

Hixon and crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particle, the data were plotted using Hixon and crowell rate equation. The graph was plotted by cubic root of % drug remaining Vs time in hours.

$$Qo^{1/3} - Qt^{1/3} = K_{HC}\ Xt$$

Which is often used to describe the drug release behavior from polymer systems?

Where

- 'Mt' is the amount of the drug release at time't',
- 'Ma' is the amount of drug release after infinite time and
- 'K' is a release rate constant incorporating structural and geometric characteristic of the tablet and 'n' is the diffusion exponent indications of the mechanism of drug release.

A value of n=0.45 indicates Fickian (case -I) release: >0.45 but <0.89 for non-Fickian (Anomalous) release and >0.89 indicates case II type of release.

Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both erosion and diffusion controlled drug release. The results are given in table no: 5

***In vivo* pharmacokinetic study (Experimental procedure)**

Anti diabetic activity[17]

Study in normal rats: A group of ten albino rats weighing between 250-300 g were administered with 2 mg/kg weight Glipizide orally, for two consecutive days. Blood samples withdrawn from retro orbital puncture at 0,1,2,4,6 and 12 hours intervals. Blood samples were analysed for blood glucose levels by GOD/POD method using commercial glucose kits for serum Glipizide concentration by HPLC method.

Study in diabetic rats: diabetes was induced by the administration of alloxan monohydrate in the two doses i.e 100 mg and 50 mg/kg body weight, intraperitoneally for two consecutive days. A group of 10 rats with blood glucose levels above 250 mg/dL was selected for the study. The similar to the one conducted in normal rats was repeated in diabetic group. The results are given in table no: 6

Estimation of Glipizide SR by HPLC Method

Test solution- dissolve 25 mg of s the substance under examination in 100ml of mobile phase. A stainless steel column 15cm X 4.6 mm packed with octa decylsilyl silica.

Mobile phase- mixture of 17 volumes of acetonitrile and 83 volumes of 0.35 percent w/v of dipotassium hydrogen phosphatewas taken and adjust to pH 8.0 with orthophosphoric acid.
The results are given in table and fig no: 7, 8 & 6. The concentration[18] of glipzide SR tablet at sampling points were utilized for calculating pharmacokinetic parameters using PK summit solutions (software for calculations)

The relative bioavailability was calculated by using the following equation

$$\text{Relative bioavailability} = \frac{(AUCo - a)\ F4\ Ho, L}{(AUCo - a)\ Std\ Glipizide\ SR}$$

Accelerated stability studies[19]
Tablets from optimized formulated batch F10 was packed in an air tight high density polythene bottles and kept at 45 °C with 75±5% RH for 45 days as per International Congress on Harmonization states (ICH) guidelines. Samples were withdrawn at 0, 15, 30 and 45 days of storage and evaluated for appearance, hardness and drug content. The results are given in table 09 & 07.

Comparison of Dissolution profile between Optimized Formulation and Marketed Product

It was done as per procedure given as per *in vitro* release in this section. Graph of cumulative percentage drug release Vs time (hour) for both the optimized formulation and marketed product was plotted. The results are given in table 10 and fig no 8

Result and Discussion

Glipizide raw material passed all the tests for identification, Percentage purity of raw material was determined to be % w/w.

Physical compatibility Studies
The physical compatibility test between drug and other tablet components was carried out at 25-30^{0}C and 75% R.H for 45 days.

The mixture does not show any visible change, thus indicating drug and other tablet components do not have any physical incompatibility.

Drug- Excipient interaction
The drug polymer interaction was studied by comparing the FTIR spectrum of the formulations F1 to F16 with that of Glipizide RS. Thus the comparison shows that there is no drug interaction between the drug and other ingredients of formulation including excipients and such as lactose, starch, talc etc.

Fig no: 1 FT IR Spectrum of Glipizide

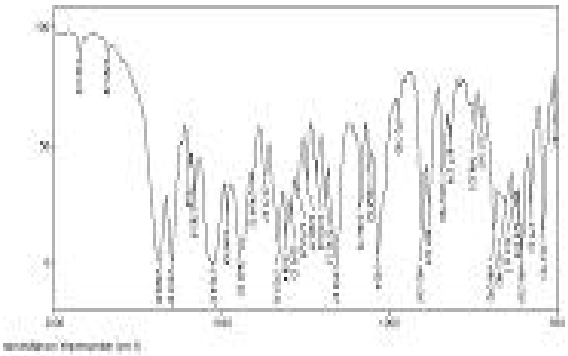


Fig no: 2 FT IR Spectrum of Sodium alginate

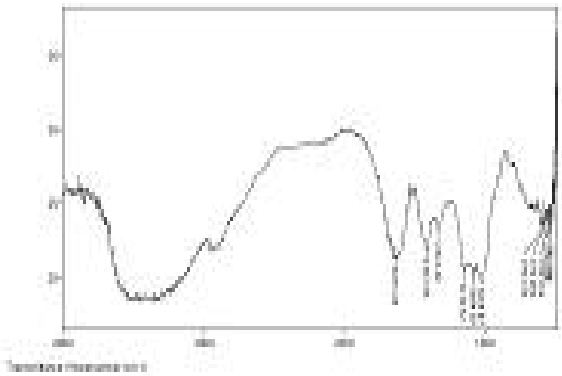


Fig no: 3 FT IR Spectrum of Carbopol

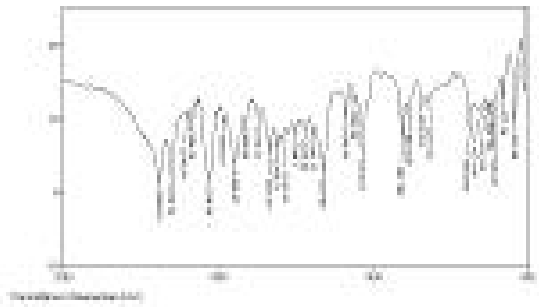


Fig no: 4 FT IR Spectrum of Xanthan gum

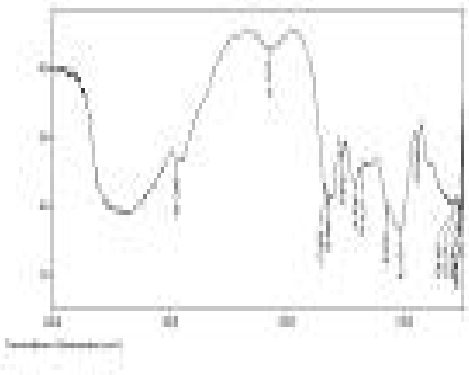
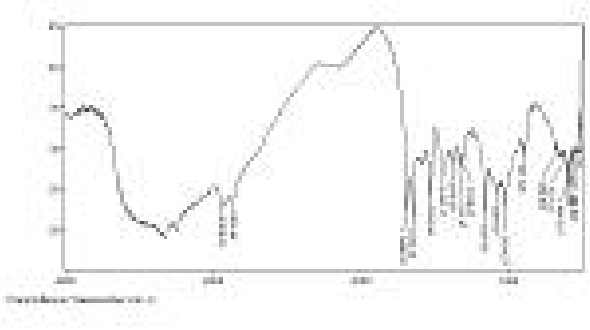


Fig no: 5 FT IR Spectrum of Chitosan



Physical Properties of Granules

Glipizide powder and the prepared granules were evaluated for angle of repose, bulk density, hausner's ratio and compressibility index. Results of evaluation of granules are as follows,

Table no: 2 Evaluation of granules

S.No.	Formulation	Bulk Density (gm/ml)	Angle of repose	Carr's index (%)	Hausner's Ratio
1	FA1	0.450	30°42'	12.25	1.13
2	FA2	0.462	30°40'	14.36	1.16
3	FA3	0.456	30°48'	15.42	1.15
4	FA4	0.458	30°62'	14.36	1.14
5	FA5	0.464	30°40'	12.36	1.12
6	FA6	0.470	30°42'	15.42	1.13
7	FA7	0.472	30°44'	12.68	1.15
8	FA8	0.468	31°12'	14.62	1.13
9	FA9	0.468	30°60	13.85	1.14
10	FA10	0.476	30°42'	14.28	1.16
11	FA11	0.498	30°44'	12.98	1.15
12	FA12	0.472	30°39'	15.00	1.15
13	FA13	0.478	30°42'	13.62	1.12
14	FA14	0.478	30°39'	14.06	1.14
15	FA15	0.476	31°08'	12.98	1.12
16	FA16	0.472	30°42'	15.02	1.13

Loss on drying

Loss on drying was determined as per procedure given in material and methodology section.

Physical compatibility test

Physical compatibility test was determined as per procedure given in material and methodology section. The study implies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description.

Test	Specification	Observation
Granules ready for compression	Not more than 0.5%	0.39%

Further to this all the formulated tablets designed as FA1, FA2, FA3, FA4, FA5, FA6, FA7, FA8, FA9, FA10, FA11, FA12, FA13, FA14, FA15, FA16 were evaluated for its following physicochemical character

Physical Properties of Tablets

Table no: 3 Evaluation of tablets

S.No	Formulations	Thickness (mm)	Uniformity weight (mg)	Hardness (kg/cm²)	Friability (%w/w)
1	FA1	5.01	205	4.8	0.721
2	FA2	5.01	201	4.5	0.221
3	FA3	5.02	206	4.4	0.482
4	FA4	5.01	202	4.1	0.324
5	FA5	5.01	205	4.2	0.148
6	FA6	5.02	200	4.4	0.421
7	FA7	5.01	202	4.2	0.324
8	FA8	5.03	205	4.1	0.289
9	FA9	5.01	207	4.4	0.385
10	FA10	5.02	201	4.3	0.412
11	FA11	5.01	206	4.6	0.396
12	FA12	5.01	202	4.1	0.401
13	FA13	5.01	203	4.6	0.298
14	FA14	5.01	202	4.4	0.412
15	FA15	5.02	205	4.5	0.326
16	FA16	5.01	203	4.3	0.312
17	Marketed	5.01	221	5.1	0.286

***In Vitro* Release Studies**

The *in vitro* dissolution studies were performed using USP-22 type I dissolution (Electro Lab, TDT -08 L, Mumbai, India) apparatus 37±5°C, at 50 rpm. Using 900 ml of 0.1N HCl for first 2 hr and phosphate buffer of pH 6.8 from 2-12 hr. An aliquot (5 ml) of the sample solution was withdrawn at predetermined time intervals , filtered through a membrane filter, diluted suitably and analyzed spectrophotometrically at 274nm (Shimadzu Model 1601).

Table no:4 *invitro* drug release studies F1-F16

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
0.5	4.02±0.12	5.04±0.12	4.02±0.12	3.52±0.12	3.02± 0.08	3.02± 0.10	2.51± 0.10	2.51± 0.10	3.52± 0.12	4.02± 0.10	3.02± 0.15	3.02± 0.12	4.02± 0.12	3.52± 0.12	3.52± 0.12	3.52± 0.12
1.0	6.06±0.13	6.57±0.09	5.56± 0.013	4.55± 0.13	4.55± 0.11	4.55± 0.11	5.05± 0.12	5.55± 0.12	5.05± 0.12	5.56± 0.11	5.05± 0.12	5.05± 0.11	5.56± 0.15	5.56± 0.11	5.05± 0.11	5.05± 0.15
1.5	9.12±0.09	6.57±0.08	9.12±0.11	8.61±0.11	10.12±0.10	10.12±0.12	9.61±0.11	11.13±0.11	12.14±0.15	14.16±0.15	10.62±0.10	12.13±0.12	9.63± 0.11	9.12±0.15	14.15±0.15	13.86± 0.12
2	16.74±0.10	15.24±0.11	12.20±0.10	14.68±0.09	16.22±0.11	14.21±0.11	15.21±0.11	13.21±0.12	17.25±0.11	19.01±0.09	17.24±0.12	19.77±0.13	14.72±0.15	13.71±0.11	27.33±0.10	25.66± 0.12
3	25.25±0.11	18.92±0.09	17.62±0.09	19.52±0.10	18.27±0.11	21.74±0.12	25.54±0.09	20.79±0.09	20.20±0.12	23.74±0.10	21.77±0.12	25.91±0.12	18.90±0.12	19.84±0.15	24.08±0.12	33.58± 0.13
4	32.36±0.12	23.14±0.12	21.51±0.08	26.91±0.11	21.22±0.12	33.89±0.10	33.60±0.10	31.34±0.11	25.99±0.14	29.57±0.12	30.12±0.11	31.44±0.14	23.76±0.11	25.02±0.12	32.76±0.12	36.93± 0.09
5	41.72±0.08	32.13±0.13	30.82±0.09	36.88±0.12	28.30±0.11	41.68±0.11	39.80±0.11	37.86±0.12	32.80±0.15	35.43±0.11	32.82±0.12	40.16±0.11	30.22±0.11	33.07±0.15	44.02±0.15	41.25± 0.08
6	48.91±0.09	47.82±0.09	38.58±0.10	40.25±0.14	33.53±0.09	48.88±0.10	42.57±0.10	47.57±0.14	41.85±0.17	39.11±0.14	42.18±0.11	46.08±0.12	37.35±0.12	37.05±0.12	51.23±0.14	50.34± 0.11
7	54.16±0.09	54.42±0.12	48.93±0.09	50.50±0.15	40.99±0.10	59.91±0.09	54.85±0.11	57.30±0.09	50.63±0.11	48.19±0.12	50.53±0.10	49.82±0.11	43.26±0.10	42.64±0.13	60.38±0.10	54.09± 0.10
8	62.46±0.12	66.75±0.08	53.31±0.11	58.16±0.09	53.88±0.10	65.94±0.09	73.52±0.12	65.88±0.14	59.45±0.12	53.84±0.13	55.36±0.12	54.52±0.15	46.03±0.11	49.52±0.11	67.36±0.090	66.74± 0.09
9	73.88±0.08	72.82±0.12	62.15±0.12	63.54±0.09	67.79±0.08	71.27±0.08	78.99±0.11	70.35±0.12	66.74±0.09	61.10±0.12	69.91±0.11	69.70±0.18	68.13±0.10	54.22±0.12	77.86±0.11	77.23± 0.08
10	81.88±0.09	81.45±0.08	74.21±0.11	77.19±0.12	76.08±0.09	80.30±0.10	84.05±0.09	78.97±0.11	75.97±0.10	70.29±0.13	74.09±0.10	72.93±0.11	77.68±0.11	69.08±0.14	86.51±0.15	86.83± 0.12
11	90.56±0.09	87.59±0.12	83.80±0.12	84.89±0.10	87.26±0.10	87.39±0.11	93.19±0.08	86.36±0.13	84.30±0.09	87.77±0.11	83.36±0.11	84.41±0.12	90.14±0.15	78.64±0.12	91.41±0.10	90.15± 0.13
12	96.43±0.12	97.88±0.12	95.33±0.11	95.17±0.09	95.65±0.10	99.57±0.12	97.49±0.08	96.65±0.09	97.74±0.08	98.93±0.09	96.16±0.11	94.68±0.09	97.59±0.14	98.70±0.10	96.97±0.09	97.28± 0.08

***In vitro* Kinetic study**

The *in vitro* data of optimized formulation F10 for zero and first order, higuchi and Korsmayer peppas equation were the observed slop values and regression co-efficient .The result of table showed that the formulation F10 follow zero order and release mechanism of drug through polymeric membrane was observed anomalous transport (Non-fickian) diffusion, which is also confirmed by koresmeyer-peppas plot.

Table no: 5 *invitro* kinetic studies

Formulation	Regression coefficient of Zero order kinetics	Regression coefficient of first order kinetics	Order of release
The drug sustained release tablets	0.9965	0.6853	Zero order

***In vivo* pharmacokinetic study:**

Table No: 6 Blood Glucose Level Time In Hours

Time (Hours)	1	2	3	6	8	12	Mean ± SEM
Control	0	91.00	90.25	88.0	87.0	87.0	88.5±0.71
Test-A	0	210.0	201.0	160.5	137.3	129.0	166.3±13.2
Test-B	0	207.0	199.5	160.5	135.5	125.0	164.8±13.3
Test-C	0	205.0	197.5	159.5	134.3	123.0	163.3±13.2
Standard	0	201.0	193.5	154.5	128.8	122.0	159.0±13.5

Relative bioavailability

In vivo pharmacokinetic study (approval from the IACE/XIII / 02 /CLBMCP/ 2009-2010 dated 15/10/09) carried out albino rats. *In-vivo* release characteristics of F10with that of marketed Glipizide SR. Plasma concentration was determined by established high performance liquid chromatography method.

Table no: 7 *in vivo* pharmacokinetic study of HPLC

Time in hrs	Test F (mcg/ml)	Marketed F (mcg/ml)
0	0	0
1	14.25	12.25
2	24.4	22.63
3	35.05	35
4	42.66	40.1
5	62.3	60.52
6	85	52.32
8	63.41	48.37
12	40.23	37.74

Fig no: 6

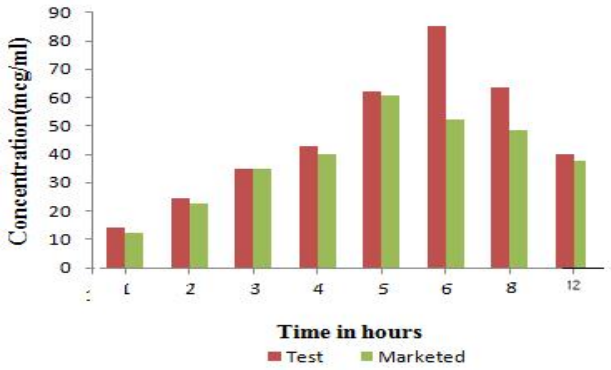


Table no: 8 Pharmacokinetic parameters

Parameters	Units	F10	Marketed F
C max	Mcg/ml	85	60.5
t max	Hrs	6	5
AUC 0-α	Mcg-hr/ml	93.0	1083
AUMC 0-α	Mcg-hr* hr/ml	17327	11254
MRT	mr	4.2	4.1

The results were analysed by student 't' test F10 and marketed formulation. Therefore F10 performs. Significantly better than marketed formulation.

The relative bioavailability = 1.16.

Stability studies (As Per ICH Guidelines)

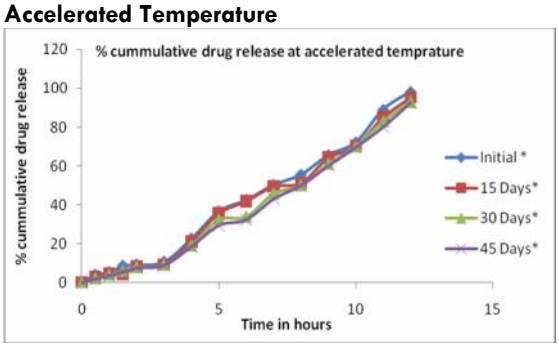
Dissolution data cumulative drug released for optimized formulation. Dissolution data of stability sample was also performed at room temperature 30^{0}C±2^{0}C / 65% RH±5% and 40^{0}C±20^{0}C / 75% RH±5% accelerated temperature for 45 days. The product was evaluated Friability, hardness, weight variation, thickness, drug content an *in vitro* release study.

Test	Inference
Hardness Weight variation Thickness Friability	Complies with the stability condition

Table no: 9
Comparison of dissolution data of stability sample at Accelerated temperature

Time (hrs)	Initial *	15 Days*	30 Days*	45 Days*
0.5	3.93	2.89	2.12	2.02
1	5.26	4.56	4.01	3.59
1.5	8.56	4.25	5.98	5.58
2	9.18	8.25	8.01	7.59
3	10.65	9.24	9.15	9.01
4	22.59	21.12	19.02	18.59
5	36.67	35.74	32.54	29.48
6	42.53	41.98	33.96	32.42
7	50.29	49.58	45.90	43.06
8	55.59	51.25	50.12	49.98
9	65.64	64.25	61.25	60.12
10	72.25	70.15	70.12	69.58
11	89.10	85.19	83.15	80.01
12	98.36	95.29	93.25	92.56

Fig no: 7 Percentages Cumulative Drug Release at Accelerated Temperature



Comparison of Dissolution Profile between Optimized Formulation and marketed product

The comparison of dissolution profile between optimized formulation F10 and marketed product was done as per procedure given as per *in vitro* release in material and methodology section. Graph of cumulative percentage drug release Vs time (hour) for both the optimized formulation F10 and Marketed product was plotted

Fig no: 8

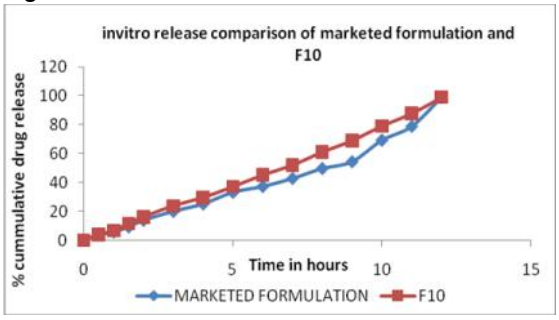


Table no: 10 %cumulative drug release comparison of Marketed and Test formulation

Percent cumulative drug release for marketed product		
Time in hr	Marketed formulation	F10 formulation
0.5	3.52	4.02
1.0	5.56	6.56
1.5	9.12	11.60
2	13.71	16.10
3	19.84	23.74
4	25.02	29.58
5	33.07	37.03
6	37.05	45.10
7	42.64	52.03
8	49.52	61.03
9	54.22	69.02
10	69.08	79.09
11	78.64	87.78
12	98.70	98.93

Conclusion

From the results and discussions, amongst, the 16 different formulations designate as F-I,F-II,F-III,F-IV,F-V,F-VI,F-VII,F-VIII,F-IX,F-X,F-XI,F-XII,F-XIII, F-XIV,F-XV and F-XVI the formulation in terms of sustained release and maximum percentage drug release, and the results are comparable with that of marketed formulation. This was further ascertained by the *in vivo* studies in rat models where formulation F10 has got no similar profile with that of the marketed formulation. To conclude, chitosan at a concentration ratio of 1:6 is suitable for preparing sustained release matrix tablets of glipizide SR.

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