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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEMS OF GLIPIZIDE FOR THE MANAGEMENT OF TYPE-II DIABETES MELLITUS

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ABSTRACT

The objective of the present study was to fabricate and evaluate a chronomodulated pulsatile drug delivery system to maintain the blood glucose level by releasing the drug at a predetermined time interval. The basic design of the system consisted of a glipizide microspheres filled in a formaldehyde treated impermeable gelatin capsule body which is plugged with a bilayer tablet plug (glipizide in fast releasing layer and erodible polymer plug made of 20% guar gum). Plugs were prepared by direct compression method using super disintegrant (Croscarmellose) in fast releasing layer and different percentage of guar gum in erodible tablet layer. The microspheres were successfully prepared from ethylcellulose and eudragit using emulsification-solvent evaporation method. Formaldehyde treated capsules, bilayered tablet plugs and microspheres were evaluated for various parameters. A chronomodulated pulsatile drug delivery system containing glipizide bilayer tablet and glipizide microspheres was prepared and was evaluated for weight variation and *in vitro* drug release studies. The results concluded the programmable pulsatile release has been achieved with modified pulsincap of Glipizide. Formulation F_G-2, F_G -5, F_G -8 and F_G -11 were chosen as best formulations. The dosage form can be taken half an hour before the breakfast and will deliver its first pulse as an immediate dose (5 mg) within 30 minutes and second pulse of sustained release microspheres (equivalent to 10 mg Glipizide) during noon which will maintain the drug concentration throughout the day till mid night and thus consistent with the demands of the chronotherapeutic drug delivery.

Keywords: Pulsincap, chronomodulated, glipizide, guar gum, croscarmellose.

INTRODUCTION

The oral route of drug delivery in general is considered the favourite means of drug administration. Conventional drug delivery systems for controlled release are based on single or multiple unit reservoir or matrix system. These are design to deliver constant drug levels over an extended period of time. Pulsatile systems are basically time controlled drug delivery systems which are designed to mimic the circadian rhythm of the body and deliver the drug at a specific time (after a programmed lag phase) as the pathophysiological conditions of disease required, resulting in improvement of patient compliance and therapeutic efficacy[1-5].

Need for study:

Diabetes mellitus (DM) is characterized by high levels of blood glucose due to defects in insulin production, insulin action, or both. Type-II DM (non-insulin dependent diabetes mellitus) occurs due to insulin resistance and relative insulin deficiency. Oral sulfonylurea's therapy remains a cornerstone for the treatment of diabetes. Sulfonylurea's acts through insulin release by inhibiting the K_{ATP} channel of the pancreatic ß-cells. Glipizide belongs to sulfonylurea class and is an oral rapid- and short-acting anti-diabetic drug. It is an effective oral anti-diabetic (100 times more potent than Tolbutamide in evoking pancreatic secretion of insulin)[6-8]. Owing to its short biological half life (3.4 ± 0.7 h), there is an urgent need of such a delivery system which can overcome its multidosing per day through delayed release and extended half life. Thus, development of multiunit pulsatile dosage form would be the advantageous.

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MATERIALS AND METHODS

Materials:

Glipizide was obtained as a gift sample from USV Ltd, Baddi. Ethyl cellulose and croscarmellose were procured from HiMedia Laboratories Pvt. Ltd., Mumbai. Eudragit S-100 and L-100 were obtained as a gift sample from Evonik Degussa India Private Limited, Mumbai. Disodium hydrogen phosphate, potassium dihydrogen phosphate, acetone, chloroform, petroleum ether and n-Hexane were purchased from Merck India Pvt. Ltd., Mumbai. Guar gum, PVP, cellulose acetate phthalate, sodium hydroxide was purchased from CDH (P) Ltd., New Delhi. Lactose, magnesium stearate, sodium chloride, span-80 and tween-80 were procured from Loba Chemie Pvt. Ltd., Mumbai.

Preparation of impermeable capsule body[9,10]:

Hard gelatin capsules of size 0 were taken 50 in number. Their bodies were separated from the caps. 25 ml of 15% v/v formaldehyde was taken into desiccator and a pinch of $KMnO_4$ was added, to generate formalin vapours. The desiccator was tightly closed. The reaction was conducted for 12 hours; after which the capsule bodies were removed. The capsule bodies were dried for 30 minutes at 50°C to ensure the completion of reaction between gelatin and formaldehyde vapours. To facilitate removal of residual formaldehyde the bodies were then dried at room temperature. Tests like identification attributes (transparency, lockable type, odour, nature), visual defects, dimensions and solubility studies of the treated capsules were conducted on prepared impermeable capsule body.

Preparation of microspheres of Glipizide:

Microspheres were prepared by using emulsification-solvent evaporation method. Accurately weighed 1 gm polymer (Ethyl cellulose/Eudragit L-100:S-100) was dissolved in 100 ml of solvent (Chloroform/Acetone) to form a homogenous polymer solution. Core material, i.e. Glipizide was added to the polymer solution and mixed thoroughly. This organic phase was slowly poured into continuous phase (200 ml of aqueous phase containing emulsifier i.e. 0.5 %w/v of Sodium CMC / 200 ml of liquid paraffin) containing 1% w/w of surfactant (Tween-80/Span-80) with stirring at 1000 rpm to form a smooth emulsion. Thereafter, it was allowed to reach room temperature and stirring was continued until residual chloroform/acetone was evaporated and smooth-walls, rigid and discrete microspheres were formed. The microspheres were collected by decantation and the product was washed with water/petroleum ether (40-60°C), four times and dried at room temperature for 3 hours. The microspheres were then stored in a desiccator over fused calcium chloride.

Microspheres were evaluated for particle size (using optical microscopy), flow properties, surface morphology (SEM), percentage practical yield and percentage drug content. To carry out drug content, in a 100 ml volumetric flask microspheres equivalent to 10mg of Glipizide were taken and the volume was made up to mark with pH 6.8 phosphate buffer. The flask was shaken for 12 hours using a mechanical shaker. Then the solution was filtered and appropriate dilutions were made from the filtrate and absorbance was measured at 226 nm.

Table 1: Drug Polymer Ratio for Eudragit and Ethyl cellulose microspheres of Glipizide

Ingredients	Formulations			
	G_M-1	G_M-2	G_M-3	G_M-4
Glipizide	0.5 gm	1 gm	0.5 gm	1 gm
Eudragit	1 gm	1 gm	---	---
Span-80	2ml	2ml	---	---
Liquid Paraffin	200 ml	200 ml	---	---
Ethyl cellulose	---	---	1 gm	1 gm
Tween-80	---	---	2ml	2ml
Aqueous solution (0.5%w/v Sodium CMC)	---	---	200 ml	200 ml

Preparation of glipizide bilayered tablet plug:

Bilayered tablet plugs of glipizide were prepared by the direct compression method.

1. **Formulation of the fast release layer:** The dose of the formulation for fast release was 5mg. The polymers, drug and other excipients for fast releasing layers were passed through sieve #60 before their use in the formulation. The blend is mixed properly.
2. **Formulation of erodible tablet layer:** The formulations containing 16, 20 and 30% of Guar gum were prepared and excipients like lactose was added up to 99%. Each formulation was mixed for 10 minutes, followed by addition of 1% magnesium stearate to each blend. The resultant blends were mixed for 5 minutes.

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Table 2: The composition of Bilayer Tablet Plugs

Formulation / Ingredients	G-1 (mg)	G-2 (mg)	G-3 (mg)	G-4 (mg)	G-5 (mg)	G-6 (mg)	G-7 (mg)	G-8 (mg)	G-9 (mg)	G-10 (mg)	G-11 (mg)	G-12 (mg)
Fast Release Layer												
Glipizide	5	5	5	5	5	5	5	5	5	5	5	5
MCC	---	86	85	84	---	86	85	84	---	86	85	84
Croscarmellose sodium	----	4	5	6	----	4	5	6	----	4	5	6
PVP K-30	---	3	3	3	---	3	3	3	---	3	3	3
Aerosil	---	1	1	1	---	1	1	1	---	1	1	1
Lactose	66	---	---	---	66	---	---	---	66	---	---	---
Starch	25	---	---	---	25	---	---	---	25	---	---	---
Mg. Stearate	2	1	1	1	2	1	1	1	2	1	1	1
Talc	2	---	---	---	2	---	---	---	2	---	---	---
Amaranth	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Erodible Tablet Layer												
Guar Gum	32	32	32	32	40	40	40	40	60	60	60	60
Lactose	164	164	164	164	156	156	156	156	136	136	136	136
Mg. Stearate	4	4	4	4	4	4	4	4	4	4	4	4

3. **Compression of bilayered tablet plugs:** The blends of erodible tablet plug containing 16, 20 and 30% of Guar Gum were separately compressed lightly using a Rotary Tablet Compression Machine using 6.5 mm round, flat and plain punches. Over this compressed layer, required quantity of the fast release layer containing drug was placed and compressed (hardness in the range of 4.5-5.5 kg/cm^2) to form a Glipizide Bilayered Tablet Plugs. The composition of all formulations is provided in table 2.

Pre-compression Studies were conducted. Compressed bilayered tablet plugs were evaluated for parameters like hardness, weight variation, uniformity of thickness, friability test, erosion time, percentage drug content and *in vitro* drug release studies.

Assembly of pulsatile drug delivery system containing glipizide[11,12]:

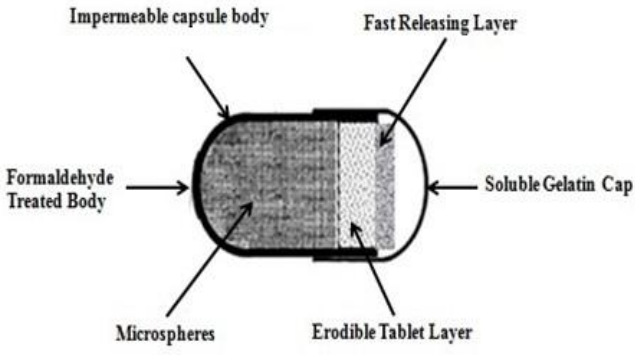

Figure 1: Overview of designed pulsatile device

A chronomodulated Pulsatile (modified pulsincap) drug delivery system containing Glipizide Bilayer Tablet and Glipizide microspheres was prepared for the time-controlled release of both drugs in combination. Overview of designed pulsatile device is shown in Figure 01.

Procedure for assembly of pulsatile (modified pulsincap) drug delivery system:

Formaldehyde treated hard gelatin capsules of size '0' were chosen for the formulation. The bodies and caps were separated manually. Microspheres equivalent to 10 mg of Glipizide and lactose was filled in capsule body and then plugged with bilayered tablet plugs containing Guar Gum of various compositions and then capped with soluble gelatin cap. The whole system thus produced is modified pulsincap.

Glipizide bilayered tablet plug containing fast releasing layer (5 mg glipizide and five percent croscarmellose sodium as super disintegrant) and erodible tablet layer containing 16%, 20% and 30% of Guar Gum has been used for preparing pulsatile (modified pulsincap) drug delivery system containing Glipizide microspheres (equivalent to 10 mg).

In bilayered tablet layer, there will be fast release of Glipizide (5 mg) followed by a slow erodible polymer (guar gum). Sampling was stopped after 0.5 hours (i.e. after release of Glipizide from fast releasing layer) and again started 0.5 hours before the expelling time of plugs (i.e. sampling started after 4, 5 and 6.5 hour for formulations containing 16%, 20% and 30% guar gum plug respectively). The composition for modified pulsatile device containing Glipizide Bilayer tablet and Glipizide microspheres is illustrated in the following table 3. Formulation F_G-1 to F_G-3, F_G-4 to F_G-6, F_G-7 to F_G-9 and F_G-10 to F_G-12 contains Glipizide: Ethylcellulose (0.5:1), Glipizide: Ethylcellulose (1:1), Glipizide: Eudragit (0.5:1) and Glipizide:Eudragit (0.5:1) respectively.

Table 3: Composition for modified pulsatile device containing Glipizide microspheres

Batch code	Wt. of empty body (mg)	Wt. of Microspheres (mg)	Percentage of Guar Gum used in plugs	Lactose	Total wt. of assembled capsule after CAP coating (mg)
F_G-1	43.0	31	16%	200	622
F_G-2	41.0	31	20%	200	620
F_G-3	43.0	31	30%	200	623
F_G-4	39.0	21	16%	200	611
F_G-5	40.0	21	20%	200	609
F_G-6	41.0	21	30%	200	608
F_G-7	41.0	31	16%	200	619
F_G-8	43.0	31	20%	200	621
F_G-9	42.0	31	30%	200	620
F_G-10	43.0	21	16%	200	608
F_G-11	42.0	21	20%	200	610
F_G-12	41.0	21	30%	200	607

Stability Studies[13]:

ICH Tripartite Guidelines have established that long term stability testing should be done at 25°C / 60% RH; stress testing should be done at 40°C / 75% RH for 6 months. If significant change occurs at these stress conditions, then the formulation should be tested at an intermediate condition i.e. 30°C / 75% RH.

RESULT AND DISCUSSIONS

Impermeable capsule body

Impermeable capsule body was successfully obtained. Formaldehyde treated empty capsules were evaluated for various parameters and results are as follows:-

1. **Identification attributes:** They were no significant changes in the capsules except for the stickiness.
2. **Visual defects:** In about 50 capsule bodies treated with formaldehyde five were found to shrink or distorted.
3. **Dimensions:** The '0' size capsule bodies showed a significant decrease in length and diameter. The following measurements were taken before and after formaldehyde treatment of capsule body.

Average capsule length:

- Before formaldehyde treatment (untreated cap and body): 18.5 ± 0.101 mm
- After formaldehyde treatment (treated body and untreated cap): 17.5 ± 0.116 mm

Average diameter of capsule body:

- Before formaldehyde treatment: 6.5 ± 0.097 mm
- After formaldehyde treatment: 6.3 ± 0.072 mm

Average length of capsule body:

- Before formaldehyde treatment: 16.0 ± 0.088 mm
- After formaldehyde treatment: 15.0 ± 0.069 mm

4. **Solubility studies for the treated capsules:** The treated capsules were subjected to solubility studies for 24 hours in different buffers, the following observations were made:

- In the case of normal capsules, both cap and body dissolved within 15 minutes.
- In the case of formaldehyde treated capsules, the cap dissolved within 15 minutes; whereas the capsule remained intact for about 24 hours. This was attributable to the cross linking of gelatin which prevented the disintegration of the capsule body.

Microspheres of glipizide

Microspheres were successfully prepared. The prepared microspheres were examined under an optical microscope. From SEM (Figure 02), it was observed that the prepared microspheres were spherical with smooth surface; might be due to complete homogeneity of drug and polymers. Eudragit microspheres had mean particle size of ranged between 30-55 µm; while the ethylcellulose microspheres were ranged between 38-61 µm.

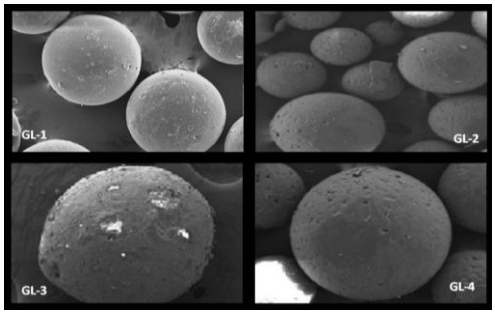

Figure 2: Scanning Electron Micrographs of glipizide microspheres
a) GL-1, b) GL-2, c) GL-3 and d) GL-4

Results of flow property, percentage yields and percentage drug content of glipizide microspheres are shown in table 4. All the formulations showed good flow properties. The value of the angle of repose between 21-28°θ indicates that the flow of the particles was reasonable and the microspheres were found to be fit in respect to flow ability and were thus suitable for further processing in the filling of the capsules. The mean percentage practical yield for all the formulation G_M -1 to 4 was greater than 91%. It was observed that there was a positive correlation between the solid content and the percentage yield, which can be explained by the fact that, though a constant material is

always lost in processing. This loss is proportionately less significant when the solid content is more. The drug content was found to be very high in all the cases i.e. all the formulations showed percentage drug content in the range of 96-98%.

Table 4: Flow property, % yields and % drug content of Glipizide microspheres

Formulation	Angle of Repose*	% Drug content*	% Yield*
G_M -1	28.83 ± 0.5830	98.38 ± 0.7378	93.11 ± 0.5639
G_M -2	23.17 ± 0.6740	97.51 ± 0.5682	91.68 ± 0.8392
G_M -3	25.79 ± 0.4317	96.74 ± 0.4973	94.42 ± 1.0523
G_M-4	21.51 ± 0.4842	96.49 ± 0.6119	92.74 ± 0.3850

**Each value is the mean ± SD; n=3*

Bilayered tablet plugs

Bilayered Tablet Plugs were successfully prepared by direct compression method. Tablets were then stored in a desiccators over fused calcium chloride till further evaluations. The results of pre-compression studies are presented in table 5 and it shows that the results obtained for all formulations are in conformity with their flow rates. Both Hausner's ratio and Carr's index of all formulations indicate good and excellent flow respectively.

The measured hardness of tablets of all formulations ranged between 5.28 ± 0.1643 to 5.46 ± 0.1342 Kg/cm^2. These ensure good handling characteristics of all batches. All the formulated plugs passed the test as the percentage weight variation was within the pharmacopoeial limits. It was found out; the weights of all tablets were uniform with low standard deviation values. Thickness of tablets was found in a range 5.97 ± 0.0891 mm to 6.04 ± 0.1350 mm. The percentage friability was less than one percent in all formulations, indicating is within the prescribed limits. The results of friability indicate that the tablets possess good mechanical strength. A result of erosion time/disintegration time is shown in table 6. From erosion time, it was found Guar Gum disintegrate slowly and take more time to erode as compared to other formulations. Among all the formulations, formulations containing 16% Guar Gum tablet plugs erode fast than others because of less concentration of this polymer. It was observed as the concentration of polymer increases erosion time increases. The content of Glipizide in each preparation was assayed by UV spectroscopy. The drug content was found to be very high in all the cases in a range between 96.6 ± 0.1643% to 99.2 ± 0.0512%. The assay values were between 95% and 98% of the theoretical values.

Table 5: Pre-compression studies of fast releasing layer

Bulk density* (gm/ml)	Tapped density* (gm/ml)	Carr's index* (%)	Hausner ratio*	Angle of repose* (˚θ)
Fast releasing layer containing Glipizide lactose granules (G-1, G-5, G-9)				
0.461 ± 0.011	0.566 ± 0.006	18.44 ± 1.305	1.226 ± 0.012	26.630 ± 0.872
Fast releasing layer containing 4% Croscarmellose (G-2, G-6, G-9)				
0.415 ± 0.016	0.498 ± 0.009	16.60 ± 0.739	1.199 ± 0.017	25.712 ± 0.683
Fast releasing layer containing 5% Croscarmellose (G-3, G-7, G-11)				
0.444 ± 0.026	0.544 ± 0.011	18.23 ± 0.928	1.223 ± 0.026	26.787 ± 0.914
Fast releasing layer containing 6% Croscarmellose (G-4, G-8, G-12)				
0.437 ± 0.019	0.529 ± 0.015	17.46 ± 1.218	1.212 ± 0.031	27.163± 0.846

**Average ± SD of 3 determinations*

Table 6: Results of erosion time and percentage drug content of different formulations of bilayered tablet plug

Code	Erosion Time of Fast releasing layer (Coloured Layer) (min)	Erosion Time of Erodible polymer layer (hr)	Percentage Drug content* (%)
G-1	3.59 ± 0.151	4.54 ± 0.392	97.2 ± 0.2859
G-2	0.85 ± 0.253	4.56 ± 0.288	96.6 ± 0.1643
G-3	0.67 ± 0.121	4.59 ± 0.153	99.2 ± 0.1305
G-4	1.27 ± 0.163	4.52 ± 0.034	98.3 ± 0.0797
G-5	3.62 ± 0.142	5.62 ± 0.191	98.4 ± 0.1014
G-6	0.85 ± 0.211	5.58 ± 0.113	98.6 ± 0.0512
G-7	0.65 ± 0.194	5.59 ± 0.218	98.2 ± 0.0568
G-8	1.29 ± 0.136	5.61 ± 0.104	98.4 ± 0.0960
G-9	3.83 ± 0.294	6.63 ± 0.099	97.6 ± 0.0911
G-10	0.83 ± 0.183	6.62 ± 0.111	97.2 ± 0.1190
G-11	0.65 ± 0.314	6.61 ± 0.429	98.8 ± 0.0854
G-12	1.28 ± 0.384	6.65 ± 0.183	99.2 ± 0.0512

**Average ± SD of 3 determinations*

In vitro drug release studies were performed using USP-XXIII dissolution assembly. *In vitro* percentage drug release data are given in table 7. *In vitro* dissolution studies of formulations containing Glipizide lactose granules (starch as a disintegrant) were carried out and it showed approximately 98% of drug release after 30 minutes. Among all the formulations, formulations containing super disintegrant croscarmellose five percent show fast drug release than other formulations. Croscarmellose swells faster and cause fast disintegration of tablets. It was observed that the formulations containing croscarmellose six percent show slower release of drug. This is due to the reason that croscarmellose is effective at low concentrations only (0.5-5%)[14].

Table 7: Percentage Cumulative Drug Release data of Glipizide from formulations

Time (min)	Percentage Cumulative Drug Release*											
	G-1	G-2	G-3	G-4	G-5	G-6	G-7	G-8	G-9	G-10	G-11	G-12
0	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00
2.5	18.89 ± 0.25	38.88 ± 0.36	43.19 ± 0.26	32.21 ± 0.47	19.43 ± 0.03	39.04 ± 0.15	42.97 ± 0.45	31.91 ± 0.59	18.56 ± 0.30	38.04 ± 0.15	42.32 ± 0.28	32.08 ± 0.65
5	33.49 ± 0.13	60.36 ± 0.35	65.78 ± 0.23	52.20 ± 0.39	33.64 ± 0.41	59.98 ± 1.46	66.18 ± 0.51	55.69 ± 0.64	32.78 ± 0.33	59.08 ± 0.96	65.51 ± 0.47	51.95 ± 0.66
10	53.10 ± 0.17	79.20 ± 0.47	88.23 ± 0.35	71.09 ± 0.28	54.12 ± 0.51	78.84 ± 0.64	89.03 ± 0.56	71.54 ± 0.42	52.26 ± 0.37	79.61 ± 0.87	87.88 ± 0.57	70.83 ± 0.52
15	68.55 ± 0.83	89.95 ± 0.26	96.61 ± 0.24	83.99 ± 0.39	69.05 ± 0.31	89.15 ± 0.20	96.74 ± 0.58	83.71 ± 0.40	67.71 ± 0.42	89.94 ± 0.32	95.56 ± 0.44	83.56 ± 0.42
20	80.31 ± 0.18	95.38 ± 0.29	99.59 ± 0.41	91.00 ± 0.42	80.63 ± 0.20	94.86 ± 0.47	99.55 ± 0.09	90.46 ± 0.57	81.05 ± 0.29	95.21 ± 0.24	99.15 ± 0.37	90.53 ± 0.30
25	90.28 ± 0.29	99.27 ± 0.13	---	96.90 ± 0.19	90.81 ± 0.14	99.61 ± 0.16	---	97.23 ± 0.53	90.02 ± 0.39	99.36 ± 0.33	---	97.15 ±0.67
30	98.02 ± 0.58	---	---	---	98.26 ± 0.63	---	---	---	98.67 ± 0.45	---	---	---

**Average ± SD of 3 determinations*

Pulsatile (modified pulsincap) drug delivery system containing glipizide

Pulsatile drug delivery system of Anti-Diabetic Drug (Glipizide) was successfully prepared. All the formulated capsules passed the test since the percentage weight variation was within the pharmacopoeial limits. *In vitro* dissolution profile of pulsincap formulations during 16 hours studies was found to have an efficient time controlled release of Glipizide.

The percentage cumulative drug release for all formulations (F_{AL}-1 to F_{AL}-12) is illustrated in Figure 03-06. It was observed that the fast releasing layer of Bilayered tablet plug shows *in vitro* release of 5 mg of drug within 30 minutes and later the drug release from Glipizide microspheres occur after a lag time period of 4.5-7 hours.

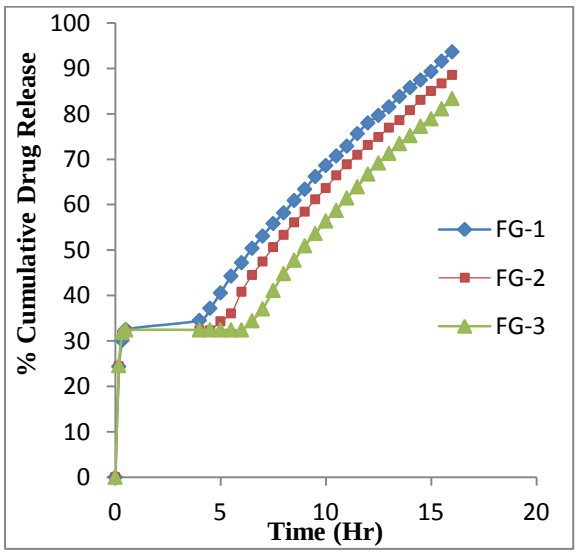

Figure 3: *In vitro* drug release profile of formulation F_G-1 to F_G-3

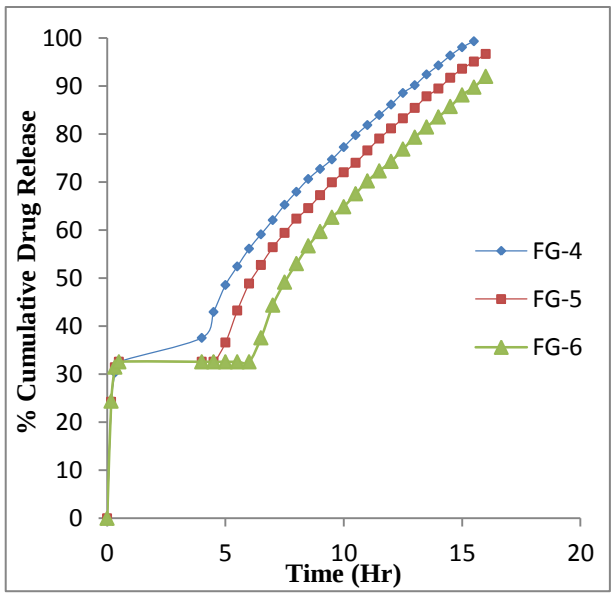

Figure 4: *In vitro* drug release profile of formulation F_G-4 to F_G-6

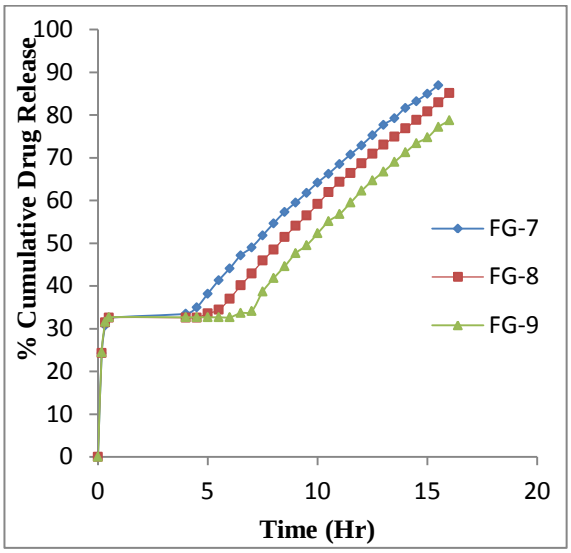

Figure 5: *In vitro* drug release profile of formulation F_G-7 to F_G-9

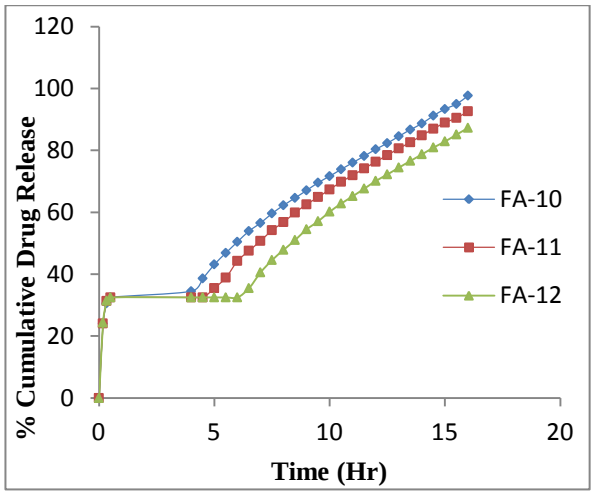

Figure 6: *In vitro* drug release profile of formulation F_G-10 to F_G-12

The drug release from the formulations was dependent on the type of hydrogel plug present in the Pulsincap device. The formulations with the plug with 30% Guar Gum showed more lag time 7 hours this was due to the higher viscosity of Guar Gum which swell slowly and to a greater extend producing a viscous gel which holds the capsule body for a longer time as compared to the hydrogel plugs containing 16% guar gum plugs which takes up water fast, disintegrates faster and showed less lag time of 4.5 hours.

During dissolution studies, it was observed that, after the releases of immediate dose of Glipizide (5 mg) from bilayered tablet plug in simulated gastric fluid; the exposed polymer plug start absorbing the surrounding fluids, swollen and released the drug through the swollen matrix. After complete wetting of the plug, it formed a soft mass and then easily ejected out of the capsule body; releasing the Glipizide microspheres into the simulated colonic fluid with pH 6.8. Among all the formulations, formulations containing Glipizide: Eudragit 0.5:1 microspheres (F_G-7 to F_G-9) showed slow drug releases after controlled lag time.

Based on the *in vitro* drug release data, considering the highest regression values the best fitting model for Glipizide in all formulations was Higuchi-Matrix with an exception of F_G-9 where First order was the best fitting model for Glipizide.

Stability Studies

The results of stability studies of Glipizide Pulsatile drug delivery system showed no significant change with respect to physical appearance, drug content and *in vitro* drug release at the end of six months. Aging did not alter the drug release profiles of any of the formulations significantly at the end of the storage period.

CONCLUSION

In the present study, a time-controlled chronomodulated pulsatile drug delivery system of Glipizide containing an immediate release dose and Glipizide microspheres for sustained release of the drug after a desired lag time was successfully developed. It has been concluded from the investigation that pulsincap dosage form of glipizide could be effectively control the blood glucose levels throughout the day in respect to release of two pulses i.e. first pulse of immediate dose (equivalent to 5 mg Glipizide) after administration before breakfast and second pulse of sustained release microspheres (equivalent to 10 mg Glipizide) during noon which will maintain the drug concentration throughout the day till mid night. Hence it is considered to be suitable for the diabetic patient to manage postprandial blood glucose levels.

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DECLARATION OF INTERERST

Authors show no conflict of interest.

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