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DEVELOPMENT AND *IN-VITRO* EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM FOR GLICLAZIDE

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Abstract:

Gliclazide is a second generation sulphonylurea and is widely used for managing NIDDM. The drug has a short biologic life and the absorption in the gastrointestinal tract is site specific. Thus, Gliclazide is an ideal drug for pulsatile drug delivery. The present work is to develop and evaluation of pulsin cap technology by using polymers like Ethyl cellulose, HPMC. From the reproducible results obtained from the executed trails of core and pulsin cap it can be concluded that F12 of core tablet and C3F4 of press pulsincap formulation maintained lag phase upto 6hrs and brust release was at 7th hr and followed by maximum release at the end of 8th hr, so it is selected as optimized formulations for designing Pulsatile device. Therefore the study proved that pulsincap formulation of Gliclazide can be successfully used as a time dependent modified Chronopharmaceutical formulation.

Keywords: Gliclazide, Sodium starch glycolate, Lycoat, Crospovidone, Ethyl cellulose.

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INTRODUCTION:

Chronotherapeutics refer to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefit and minimum harm. A pulsatile dosage form, taken at bed time with a programmed start of drug release in the early morning hours, can prevent this.[1] By timing drug administration, plasma peak is obtained, at an optimal time. Number of doses per day can be reduced. When there are no symptoms there is no need of drugs. Saturable first pass metabolism and tolerance development can also be avoided.[2,3] Some orally administered drugs (eg. Glicazide, Theophiline, Nifedipine, Isosorbide) may exhibit poor uptake in the upper regions of GIT or degrade in the presence of GIT enzymes. Better bioavailability can be achieved through colon-specific drug delivery. Colon targeting is also advantageous where delay in systemic absorption is therapeutically desirable.[3] A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome. The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets (press coated) and capsules. Delivery systems with a pulsatile pattern are receiving increasing interest for the development of dosage forms, because conventional systems with a continuous release are not ideal. Advantages of pulsatile drug delivery systems can protect hygroscopic, light sensitive, acid labile drug, they are simple and cheap in making.[3,4]

This study focuses the development of press coated tablets of Gliclazide to treat NIDDM. Pulsin cap formulation consists of rapid release core tablet & Pre coated formaldehyde capsule shells wih HPMC, Ethyl cellulose which are used as drug release controlling polymer.

MATERIALS AND METHODS:

MATERIALS

The chemicals used in the present study were procured from reputed manufacturers and were of suitable pharmaceutical or laboratory grade. Gliclazide (Pharma Grade) was obtained from Hetero Labs Limited, Nakkapally. Sodium starch glycolate, Crospovidone, Lycot, Microcrystalline cellulose, Talc, Ethyl cellulose, HPMC K15M, Magnesium stearate, Formaldehyde, Potassium permanganate, and Methanol were procured from DFE Pharma, BASF, Roquette Frères, Crest Cellulose Pvt. Ltd., Imerys, Colorcon, Otto Chemicals (Mumbai), Peter Greven (Netherlands), Qualigens Fine Chemicals (Mumbai), and S.D. Fine Chemicals Ltd. (Mumbai), respectively. All the chemicals and excipients used in the study were of laboratory reagent (LR) grade unless otherwise specified and were used as received without further purification.

METHODOLOGY

DRUG & EXCIPIENT COMPATIBILITY:

The drug-polymer interactions were studied by FTIR spectrometer, Shimadzu 8400 S. 2% (w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem. Ltd., Mumbai, India) was mixed with dry KBr. The mixture was ground into a fine powder using mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned 10 times at a resolution of 2 cm–1 using Happ-Genzel apodization. The characteristic peaks were recorded. [6]

DESIGNING OF PULSINCAP:[10-16]

The methodology adopted includes:-

A.Preparation of cross-linked gelatin capsule.

B.Preparation of core ablet for filling into capsules.

C.Formulation of pulsincap of Gliclazide.

A. PREPARATION OF CROSS-LINKED GELATIN CAPSULE:

FORMALDEHYDE TREATMENT:

About 100 hard gelatin capsules size '0' were taken. Their bodies were separated from the caps and placed on a wire mesh. The bodies which were placed on a wire mesh were spread as a single layer. 25 ml of 15% v/v of formaldehyde solution was prepared and placed in a desiccator. To this 5 g of potassium permanganate was added. The wire mesh containing the bodies of the capsules was kept on the top of desiccators' containing formaldehyde liquid at the bottom in equilibrium with its vapor and immediately the desiccators' was tightly closed and sealed. The bodies of capsules were made to react with formaldehyde vapors by exposing them for varying periods of time viz., 2, 4, 6, 8, 10hrs. Then they were removed and kept on a filter paper and dried for 24 hrs to ensure completion of reaction between gelatin and formaldehyde vapors, afterwards the capsules were kept in an open atmosphere, to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated cap and stored in a polythene bag.

B. PREPARATION OF GLICLAZIDE CORE TABLET FOR FILLING INTO CAPSULES:

Gliclazide core tablets were produced using the wet granulation technique by using microcrystalline cellulose (MCC 101) Povidone(K30), isopropyl alcohol,Sodium starchglycolae, lycoat kollidon CL, Colloidal silicon dioxide (Aerosil 200) and Magnesium stearate.A binder solution was prepared

by dissolving Povidone(K30) in isopropyl alcohol and added to the dry mix in small amounts, till a uniform wet mass was formed. Wet granules were dried in a fluid bed dryer, air drying for 30 minutes without heating followed by drying at 40-50°C till an active substance loss of 1.0-2.0% w/w was reached. Dried granules were Sifed through #30 mesh. Sifted Disintegrant (Sodium starch glycolae/lycoat/kollidon CL) through #30 mesh and added o dried granules & blended for 10 minutes. Sifed Colloidal silicon dioxide (Aerosil 200) through #60 mesh & added to the above step.Sifted Magnesium stearate hrough #60 mesh & added to the above step & lubricated the blend for 5 minues.The mixture was then further blended for 10 min. Now the resultant powder blend was manually compressed using punching machine and finally the core tablet was obtained.[5,6] The content of each tablet is listed in Table-1.

Table 1: Formulation Table of Eplerenone Core Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Gliclazide	80	80	80	80	80	80	80	80	80	80	80	80
MCC	61	58	55	52	61	58	55	52	61	58	55	52
Povidone K30	3	3	3	3	3	3	3	3	3	3	3	3
Isoproyl Alcohol	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Sodium starch glycolate	3	6	9	12	--	--	--	--	--	--	--	--
Crospovidone (Kollidon CL)	--	--	--	--	3	6	9	12	--	--	--	--
Lycoat	--	--	--	--	--	--	--	--	3	6	9	12
Colloidal silicondioxide (Aerosil 200)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Tablet weight(mg)	150	150	150	150	150	150	150	150	150	150	150	150

C. FORMULATION OF PULSINCAP OF GLICLAZIDE:

The modified release pulsincaps containing 80 mg of Gliclazide were prepared by using different excipients and polymers in varying ratios. The formaldehyde treated capsule bodies which were exposed to 6 hrs was optimized and chosen for the pulsincap formulation based on disintegration time. Optimized formulation of Gliclazide tablet was filed into the capsule body. For hydrogel plug formulation, the plug was prepared by using the individual polymer and combination of Ethyl cellulose: HPMC K15M in varying ratios of hydrogel plugs. Initially the total weight of the plug was taken as 100 mg alone and the ratio of hydrophobic & hydrophilic polymer as 1:1, 1:2 and 2:1

The prepared tablet of each batch was evaluated for the tablet properties. [6, 8] The content of each tablet is listed in Table-2.

Table 2: Composition of Pulsincap of Gliclazide

Ingredients	C1F4	C2F4	C3F4	C4F4	C5F4
Core Tablet	150mg	150mg	150mg	150mg	150mg
Ethyl Cellulose	100 mg	-	200 mg	100 mg	100 mg
HPMC K15M	-	100 mg	100 mg	200 mg	100 mg

EVALUATION OF GLICLAZIDE CORE TABLET [5-9]

Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and in-vitro drug release with different media.

WEIGHT VARIATION

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

HARDNESS

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

FRIABILITY

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. 20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded. Percentage of friability of the tablets of a badge can be finding by the following

Formula:

Percentage Friability $= W1 – W2/W1 \times 100$

Where,

W1 = weight of tablets before testing

W2 = weight of tablets after testing.

THICKNESS

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation.

CONTENT UNIFORMITY

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 20 mg was weighed accurately and dissolved in 100ml of buffer used. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman's filter paper No.41. The absorbance of the diluted solutions was measured at 244 nm. The concentration of the drug was computed from the standard curve of the Glicazide in 6.8 phosphate buffer.

DISINTEGRATION TIME

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in 1 liter beaker containing distilled water at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

***IN VITRO* DISSOLUTION STUDY OF CORE TABLET**

In Vitro dissolution of Gliclazide tablets was studied in USP XXIV dissolution test apparatus by using USP Type-I 'Basket apparatus. 900 ml Phosphate buffer 6.8 (simulated fluid) was used as dissolution medium. The stirrer was adjusted to rotate at 100 rpm. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 230 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent Gliclazide released was calculated and plotted against time.

***IN-VITRO* RELEASE STUDIES OF PULSINCAP**

Dissolution study was carried out to measure the release rate of the drug from the pulsincap formulation. *In-vitro* dissolution profile of each formulation was determined by employing USP Type-I 'Basket apparatus' by rotating basket method. In order to stimulate the pH changes along GI tract 2 different dissolution media with pH 1.2, 6.8, 2 buffers were sequentially used, and therefore referred to as "Sequential pH change method". The dissolution media were maintained at a temperature of 37 ± 0.5ºC throughout the experiment and the speed of rotation of basket maintained at 100 rpm. 900ml of dissolution medium was used at each time. Gliclazide Pulsincaps was placed in basket in each dissolution vessel to prevent floating. While performing experiments, stimulated gastric fluid (SGF) pH 1.2 buffer was first used for 2 hrs. (since

the average gastric emptying time is 2hrs) and then removed and the fresh stimulated intestinal fluid (SIF) pH 6.8 buffer was added and used for remaining hours. 5 ml samples of dissolution fluid were withdrawn at predetermined time intervals with the help of a syringe. The volume withdrawn at each time interval was replaced with 5ml of fresh dissolution medium maintained at same temperature. The filtered samples were suitably diluted whenever necessary and assayed for Gliclazideby measuring absorbance at 230 nm, by UV absorption spectroscopy. % CDR was calculated over the sampling times.

RESULTS AND DISCUSSION:

DRUG & EXCIPIENT COMPATIBILITY:

From the drug excipients compatibility studies, we observe that there are no interactions between the pure drug and drug with excipients which indicates there are no physical changes and he funcional gropus like N-H secondary amine/amide groups(3400 - 3270 cm^{-1}),carbonyl group(1710 - 1650 cm^{-1}),sulfonyl group(1355 and 1160 cm^{-1}) are intact.

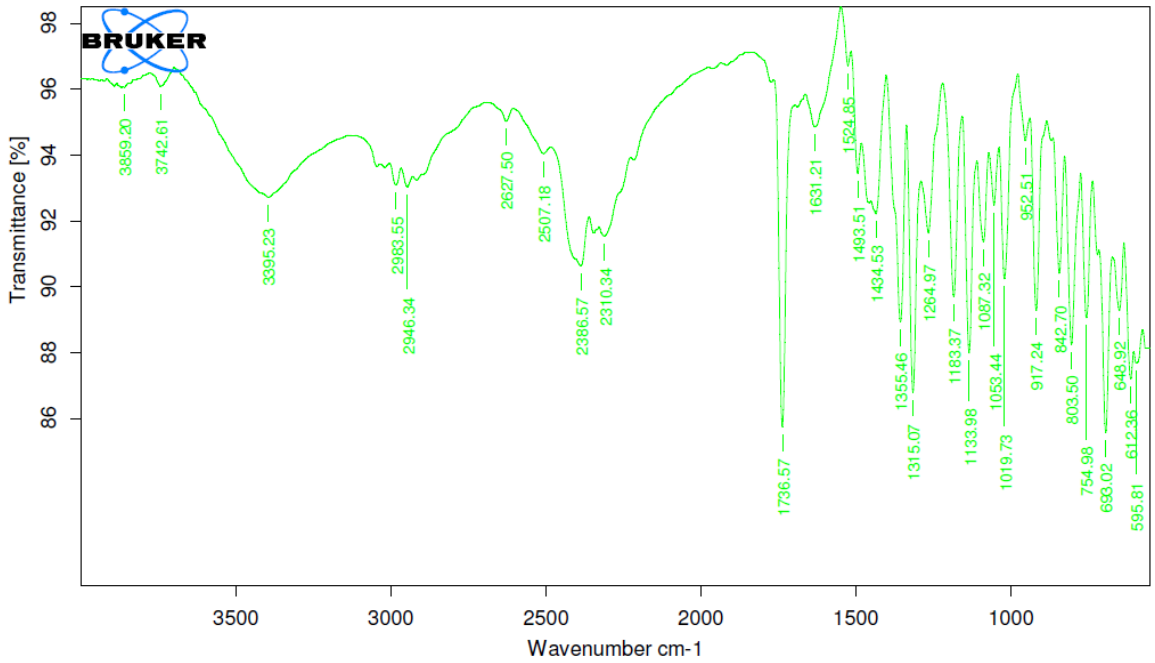

Figure 1: FTIR Spectrum of Gliclazide pure

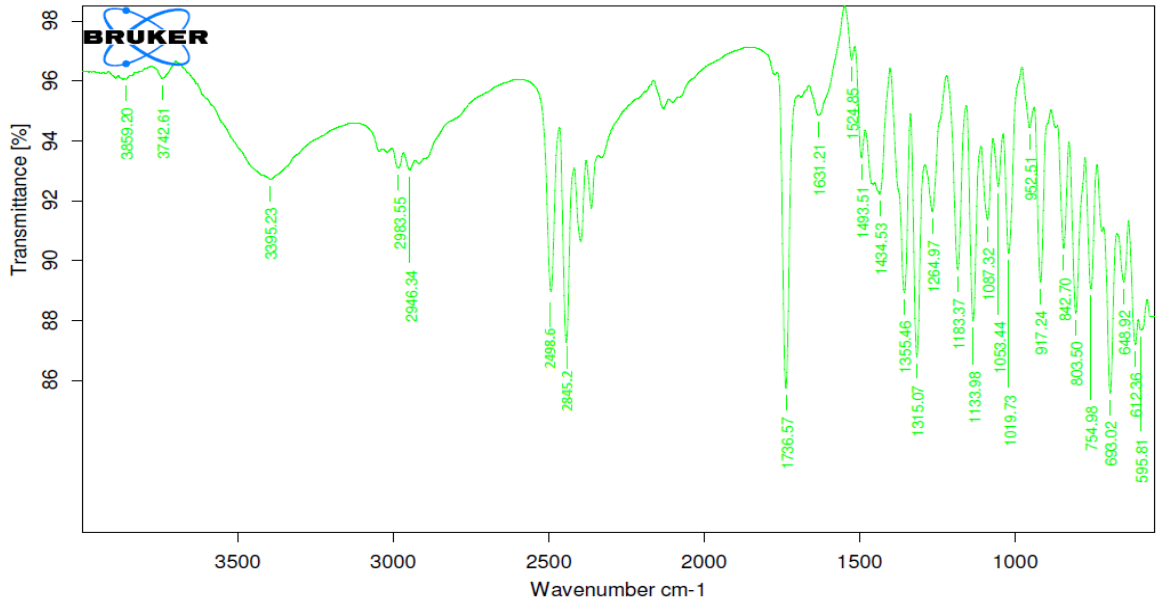

Figure 2: FTIR Spectrum of Gliclazide and Excipients

EVALUATION OF GLICLAZIDE CORE TABLET :

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Gliclazide) and optimized formulation (Gliclazide+ excipients) which indicates there are no physical changes. This can be observed in Figure-1, 2. Pre-compression parameters and post compression parameters of core and press coated tablets were found to be satisfactory. The percentage weight variations for all formulations were given. All the formulated (F1 to F12) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The measured hardness of tablets of all the formulations ranged between 4.08-5.12 kg/cm^2. This ensures good handling characteristics of all batches. The measured thickness & diameter of tablets of all the formulations ranged between 2.12-2.69 mm & 6.05-6.12 mm respectively. Disintegration time was found between 18-35 seconds ensuring that all the cores of different formulations were rapid disintegrating type. The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable. The percentage of drug content for F1 to F12 was found to be between 96.86% - 99.15%.

Table 3: Evaluation of press coated tablets of Glicazide

Formulation code	%Weight variation	Thickness (mm)	Diameter (mm)	Hardness	Friability (%)	Disintegrating time(sec)	Drug content
F1	151.28	2.48	6.12	4.54	0.75	29	95.45
F2	149.02	2.12	6.08	4.28	0.68	25	97.12
F3	155.28	2.34	6.05	5.12	0.55	20	98.27
F4	151.20	2.15	6.12	5.10	0.43	18	99.15
F5	150.28	2.37	6.08	4.82	0.86	35	98.42
F6	151.22	2.25	6.10	5.10	0.73	31	97.28
F7	148.26	2.69	6.04	5.08	0.69	27	97.24
F8	150.22	2.41	6.02	5.04	0.51	22	98.18
F9	151.65	2.26	6.04	4.84	0.96	38	98.21
F10	149.68	2.45	6.05	4.56	0.76	35	98.10
F11	150.22	2.75	6.08	4.08	0.65	30	96.86
F12	151.26	2.36	6.10	4.68	0.59	24	98.15

***INVITRO* DISSOLUTION STUDY OF GLICAZIDE CORE TABLET:**

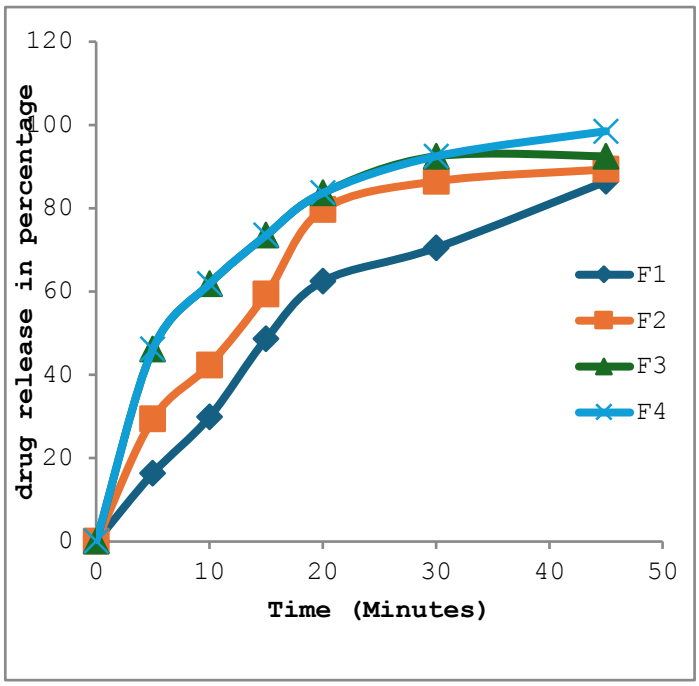

Fig:3 *In Vitro* drug release of formulations F1-F4

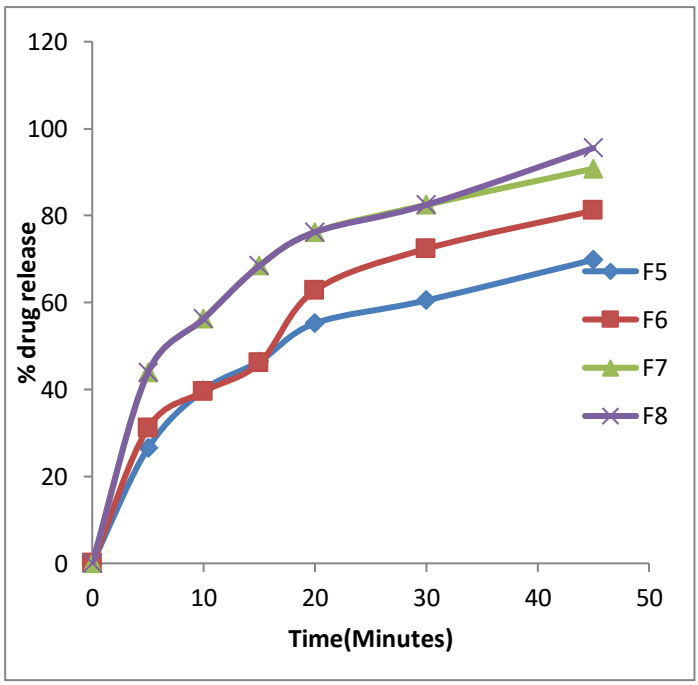

Fig:4 *In Vitro* drug release of formulations F5-F8

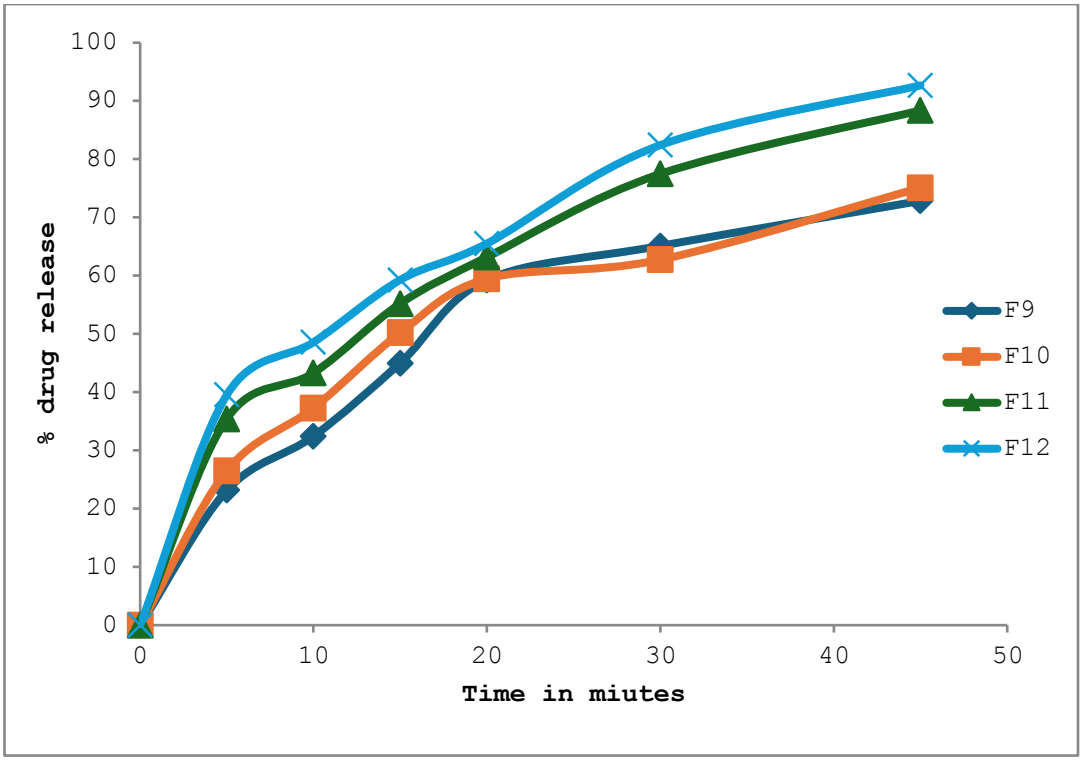

Fig:5 *In Vitro* drug release of formulations F9-F12

Total 12 core tablets was formulated by using Sodium starch glycolate, lycoat kollidon CLas super disintegrants, among them F12 formulation containing 12mg of Sodium starch glycolate shows maximum drug release at the end of 45min. so F12 formulation is chosen as best formulation for formulating the pulsin cap formualation. The results are shown in Table-3.

***IN VITRO* DISSOLUTION STUDY OF PULSINCAP:**

By comparing the drug release profiles of the formulations C1F4, C2F4, C3F4, C4F4, C5F4 the drug release was not lagged up to 5-6 hours. Among all the formulations C3F4 containing HPMC K15M: Ethyl cellulose (1:2) shows lag time for 6hours and complete drug was released at the end of 8hours. So C3F4 was considered as the optimized formulation, & the drug release kinetics were performed for the optimized formulation i.e., C3F4. The results are tabulated in Figure 6.

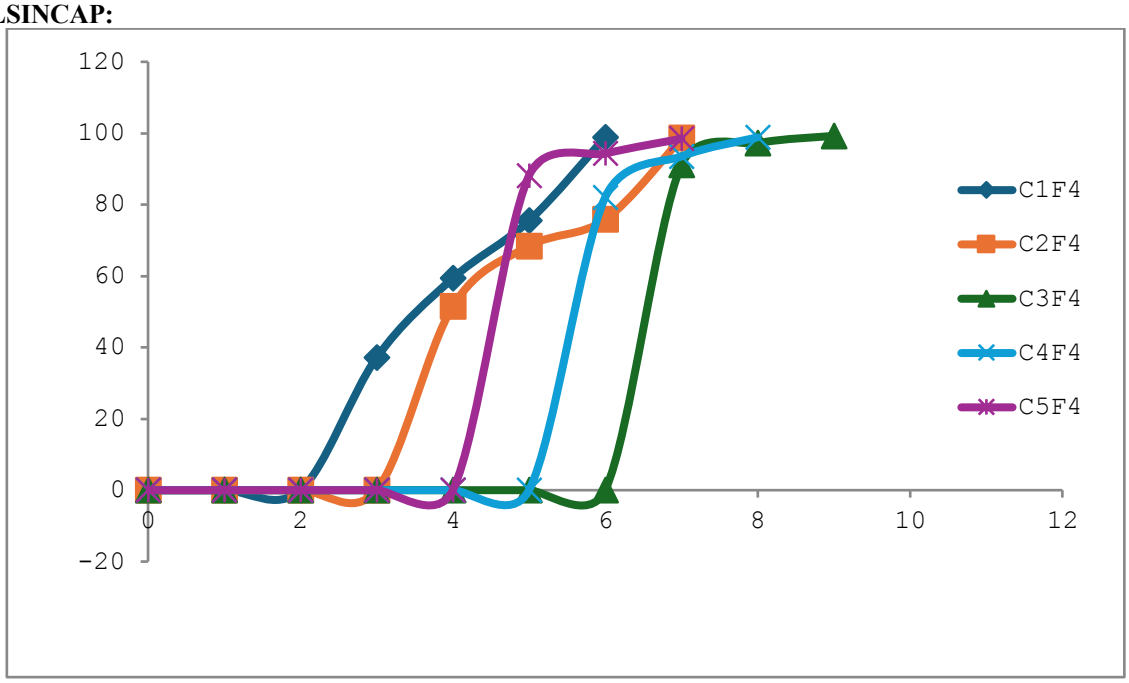

Figure 6: % CDR of Gliclazide Pulsin caps of formulaions C1F4-F5F4

CONCLUSION:

The aim of this study was to explore the feasibility of time dependent pulsatile drug delivery system of Gliclazide to treat Non-Insulin-Dependent Diabetes Mellitus. A satisfactory attempt was made to develop pulsatile system of gliclazide and evaluated it. From the reproducible results obtained from the executed trails of core and press coated tablets it can be concluded that: Pre-compression parameters and post compression parameters of core and pulsin caps were found to be satisfactory. On the basis of drug content, in-vitro release studies and its kinetic data F4 of core tablet and C3F4 of pulsincap were selected as optimized formulations for designing Pulsatile device. Therefore the study proved that coated Gliclazide can be successfully used as a time dependent modified Chronopharmaceutical formulation. Finally from the above results we can conclude that pulsatile drug delivery system of Gliclazide can be formulated using Ethyl cellulose and HPMC K15M.

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