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FORMULATION AND INVITRO EVALUATION OF GLICLAZIDE FLOATING PULSATILE DRUG DELIVERY SYSTEM

R. Karthiga[1]*, Dr. G. Mariyappan[2], Dr. J. Karthi[3], Murugan Muthukrishnan[4], Prakash Murugan[5]

Department of Pharmaceutics, Pallavan Pharmacy College, Kolivakkam, Kanchipuran, Tamil Nadu.

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***Corresponding Author**

R. Karthiga

Department of Pharmaceutics, Pallavan Pharmacy College, Kolivakkam, kanchipuran, Tamil Nadu.

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ABSTRACT

Drug delivery systems based on chronotherapy are designed to facilitate medication release with circadian rhythm-dependent medical conditions such non-insulin-dependent diabetic mellitus (NIDDM). An acceptable choice for pulsatile administration to treat early-morning hyperglycemia is gliclazide, a short-acting sulfonylurea. The goal of the current study was to create and assess a time-dependent floating pulsatile drug delivery system for gliclazide that offers a predetermined lag time followed by quick drug release. Superdisintegrants such as sodium starch glycolate, crospovidone XL, and croscarmellose sodium were incorporated in the formulation of a rapid-release core tablet. While floating layers have been developed by press-coating low-density polymers like Carbomer 974P and HPMC E15LV, time-dependent barrier layers were created using several grades of HPMC (K4M, K15M, and K100M). The physicochemical characteristics, drug content, in vitro buoyancy, dissolving behavior, release kinetics, and stability of the formulations had been evaluated. FTIR analyses established the absence of drug-excipient incompatibility. Within five minutes, core formulation T6 confirmed significant drug release. The improved floating pulsatile formulation (F5P6T6) demonstrated a burst release of more than 80%, a consistent lag time of 5–8 hours, as well as adequate buoyancy. The Korsmeyer-Peppas model was followed by drug release, suggesting anomalous transport. Studies on stability revealed no notable improvements. A promising

chronopharmaceutical technique to achieve successful NIDDM control has been proved by the established system.

KEYWORDS: Gliclazide, Pulsatile drug delivery system, Floating tablets, Chronotherapy and Non-insulin-dependent diabetes mellitus

INTRODUCTION

Diabetes mellitus is known to be a chronic metabolic disease, which is recognized by the presence of elevated blood glucose levels due to an impairment in the secretion, action, or both of insulin.[1] Non-insulin-dependent diabetes mellitus (NIDDM), also known as type 2 diabetes mellitus, has been known to comprise the greatest proportion of diabetic patients.[2] Moreover, the condition has been observed to be accompanied by complications that include both micro- and macro-angiopathies due to its long duration. Glycemic control has been considered a difficult task, especially due to the circadian rhythm of glucose metabolism.[3]

Evidence indicates that blood glucose concentrations follow sharp circadian rhythms, characterized specifically by morning hyperglycemia; this is seen especially in diabetic patients and is referred to as the "dawn phenomenon."[4] Current conventional immediate release and sustained release oral antidiabetic drug delivery systems do not align drug release with biological rhythms, thereby leading to poor drug efficacy and an incidence of hypoglycemia episodes when chronobiological drug delivery systems that release drugs accordinging to circadian rhythms of the biological system are utilized.[5]

Pulsatile drug delivery systems (PDDS): These are designed for a programmable lag time followed by instant and complete drug release.[6] These are especially useful for time-specific drug delivery for drugs like antidiabetics, for which drug release is desirable during the early hours of the morning. The floating pulsatile system is an advancement because it enhances gastric residence time and ensures a fixed lag time because of its unvarying passage through the gastrointestinal tract.[7]

Gliclazide is a second generation sulphonylurea and is widely used for managing NIDDM.[8] 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 and gastroretentive delivery. In fact, the timed release of this drug can improve its potency because the drug concentration can be released in the blood according to the blood glucose levels.

Hydroxypropyl Methyl Cellulose, or HPMC, is a hydrophilic polymer that is abundantly used as a controlled and time-related drug delivery system because of its improved swelling capacity, gel forming ability, and release retardation properties. HPMC of varying viscosities is also useful for modulating the drug delivery profiles.[9] Also, Carbomer and HPMC E15LV, which have lower densities, can introduce buoyancy to float the drug delivery system.[10]

Although there has been tremendous work on chronotherapeutic formulations, relatively few formulations have investigated the dual approach of time-dependent as well as floating pulsatile systems for Gliclazide. Hence, it becomes important to develop and evaluate a floating pulsatile drug delivery system of Gliclazide by employing the press coating method to achieve the desired lag time with rapid release, as desired by chronotherapeutic treatment in the management of NIDDM.

MATERIALS AND METHODS

Materials

Gliclazide samples were provided as gift samples by Sai Mirra Innopharm Pvt. Ltd.,. Microcrystalline cellulose (MCC), polyvinylpyrrolidone (PVP K30), sodium starch glycolate, crospovidone, croscarmellose sodium, colloidal anhydrous silica, and magnesium stearate were of pharmacopeial grade and were used as such. Sodium bicarbonate and citric acid were gas-generating agents in floating layer formulation. Hydroxypropyl methylcellulose (HPMC K100M and HPMC E3), Ethyl cellulose (7 cps), xanthan gum, and Eudragit RL/RS were used as release retarding agents and polymer coatings. Ethanol and isopropyl alcohol are solvents in coating and formulation. All materials and reagents being used in this experiment are of analytical or pharmacopeial grade and meet pharmacopeial standards.

METHODS

Preparation of the Rapid Release Core Tablet (RRCT)

Gliclazide core tablets were produced using the wet granulation technique in a rapid mixer granulator. Gliclazide and microcrystalline cellulose (MCC 101) were sifted through a #40 mesh sieve and mixed as a dry mix for 5 minutes at low speed. A binder solution was prepared by dissolving polyvinylpyrrolidone (PVP K30) in isopropyl alcohol and added to the dry mix in small amounts, about 70% of the total added at this stage followed by the remaining amount, till a uniform wet mass was formed. Wet granules were dried in a fluid bed dryer, air drying for 10 minutes without heating followed by drying at 40-50°C till an active substance loss of 1.0-2.0% w/w was reached. Sifted dried granules were milled to

produce granules of uniform size and further mixed for 10 minutes with sodium starch glycolate, crospovidone, croscarmellose sodium, sodium bicarbonate, citric acid anhydrous, and colloidal anhydrous silica. Magnesium stearate previously sifted through a #60 mesh sieve was added as a lubricant for an additional 3 minutes. These mixtures were compressed into 8.0 mm diameter plain surface core tablets using a rotary tablet compression machine.

Table No. 1: Formulation table of Gliclazide core tablet.

S.NO	Ingredients	T1 (mg)	T2 (mg)	T3 (mg)	T4 (mg)	T5 (mg)	T6 (mg)
1	Gliclazide	80	80	80	80	80	80
2	Microcrystalline Cellulose (MCC)	50.5	43	50.5	43	50.5	43
3	Polyvinylpyrrolidone (PVP K30)	6	6	6	6	6	6
4	Iso Propyl Alcohol	18	18	18	18	18	18
5	Sodium Starch Glycolate	7.5	15	-	-	-	-
6	Crospovidone	-	-	7.5	15	-	-
7	Croscarmellose Sodium	-	-	-	-	7.5	15
8	Colloidal Anhydrous Silica	3	3	3	3	3	3
9	Magnesium Stearate	3	3	3	3	3	3
Total weight of tablet (mg)		150	150	150	150	150	150

Preparation of Pulsatile Release Tablets

Pulsatile Release Tablets (PRTs) were produced using the optimized formulation for the rapid-release core tablet (F6) developed for quick release, following the dry press-coating method. Chronotropic Coating Blends (200 mg) containing either HPMC K4M, HPMC K15M, or HPMC K100M, Microcrystalline Cellulose (MCC 102), and Magnesium Stearate were produced by pre-sieving the polymers and MCC through a #40 mesh sieve, while Magnesium Stearate was sifted through a #60 mesh sieve. Sifted Polymer mixtures and MCC were mixed together in the double-cone blender for 10 minutes, followed by lubrication for another 3 minutes with Magnesium Stearate. For tableting, the two-step process involving press-coating with an 11.0 mm die was used, whereby 100 mg of the blend was filled into the die, followed by the center placement of the Rapid Release Core Tablet, with minimal compression, followed by the addition of another 100 mg of the blend before final tablet compression. Various polymer grades and concentrations were tested for their effect in modulating the Lag Time and Pulsatile Release characteristics of Gliclazide.

Table No. 2: Composition Chronotropic Layer or Pulsatile Release Tablet (PRT).

Ingredients (mg)	P1T6	P2T6	P3T6	P4T6	P5T6	P6T6
HPMC K4M	100	110	-	-	-	-
HPMC K15M	-	-	100	110	-	-
HPMC K100M	-	-	-	-	100	110
MCC 102	95	85	95	85	95	85
Magnesium stearate	5	5	5	5	5	5
Total Tablet weight (mg)	200	200	200	200	200	200

Preparation of Floating Pulsatile Release Tablets

For the purpose of this research, the optimized pulsatile release tablet formulation (P6F6) core was used as the core for preparing FPRTs through the dry press-coating process. To make the outer FPRTs, the outer FPRT formulation (150 mg) was prepared as a blend of the buoyant polymer HPMC E15LV or Carbomer 974P, gas-generating substances sodium bicarbonate and citric acid, Pearlitol 100SD as the filler, and magnesium stearate as the lubricant. All of these components, except for magnesium stearate, were sifted through a #24 mesh sieve, while the other component was sifted using a #60 mesh sieve. These sifted materials, apart from magnesium stearate, were physically mixed for 10 min using the double cone blender, followed by lubrication with magnesium stearate for an added 3 min. For the process of press-coating, an 11.0 mm die was used. This process started with the filling of 75 mg of the FPRT formulation blend into the die, followed by the centralized placement of the optimized PRT (P6F6) core tablet and lightly pressing down to hold the coating material in place, followed by the addition of the remaining 75 mg of the blend and pressing. Various FPRTs with different formulations were prepared to optimize the FPRT for buoyancy, lag time, and pulsatile drug-release character.

Table No. 3: Compositions of outer Floating Layer or Floating pulsatile release tablets (FPRT).

Ingredients (mg)	F1P6T6	F2P6T6	F3P6T6	F4P6T6	F5P6T6	F6P6T6
Carbomer 974P	60	70	80	-	-	-
HPMC E15LV	-	-	-	60	70	80
Sodium Bicarbonate	30	30	30	30	30	30
Citric acid	15	15	15	15	15	15
Pearlitol 100SD	45	35	25	45	35	25
Total weight(mg)	150	80	70	150	150	150

Analytical method development

Determination of Absorption Maxima (λmax) of Gliclazide

The UV–Visible spectrophotometer was used to determine the absorption maxima (λmax) of Gliclazide. The required amount of accurately weighed 10 mg of Gliclazide was dissolved in a methanol and the volume was made up to 100 mL to obtain a 100 µg/mL stock solution. Further appropriate dilution from this stock solution was prepared to obtain a concentration within the linear range of the instrument. The prepared solution was then scanned on a UV–Visible spectrophotometer in the range of 200–400 nm against the corresponding solvent blank. The wavelength where maximum absorbance was observed was noted down as the λmax of Gliclazide and further used during quantitative analysis.[11]

Evaluation Of Gliclazide Floating pulsatile Tablets

The prepared Gliclazide pulsatile floating tablets were characterized for different physicochemical and function-related parameters like tablet thickness, hardness, weight variation, friability, and content uniformity using official pharmacopeial methods. In-vitro buoyancy evaluations were carried out to measure the floating lag time and total floating time in 0.1 N HCl, and the in-vitro dissolution studies were carried out using USP type II (paddle) apparatus at predetermined conditions to examine the pulsatile release characteristics after the lag period. The results obtained from the dissolution studies were further used to determine the release kinetics of the drug, and the results obtained were used to determine the release mechanism. Fourier Transform Infra-Red (FTIR) analysis was further used to measure the excipient and drug interaction. Accelerated stability studies were further used to determine the stability parameters like physical appearance, content, buoyancy, and dissolution characteristics.

In-Vitro Buoyancy Studies

The in-vitro buoyancy studies were carried out for determining the floating lag time (FLT) and total floating time (TFT) for Gliclazide floating pulsatile tablets. The table was placed inside a 100 mL glass boiling tube filled with a fixed amount of simulated gastric fluid (0.1 N hydrochloric acid, USP). The room temperature was maintained. The floating lag time was determined as the time the table takes to reach the surface of the fluid, until it started floating. The total floating time was set as the time for which it continuously stayed buoyant on the surface layer. The time, when the outer layer of the floating mass burst, separating the core

tablet from the press coating, was considered as the fixed off release time, which was set as the total floating time.[12]

In-Vitro Dissolution Study

In-vitro dissolution analysis of Gliclazide core tablets (CT) and pulsatile release tablets (PRT) was carried out using USP Apparatus-II (paddle method) at an operational speed of 100 rpm. A dissolution medium of 900 mL phosphate buffer pH 7.4 was used, and it was prepared by adding 50 mL of 0.2M solution of potassium dihydrogen phosphate and 39.5 mL of 0.2M solution of sodium hydroxide and then volume adjusted with purified water. Additionally, the temperature of the dissolution medium was adjusted at 37 ± 0.5°C during the experiment. For the assessment of core tablets, samples were taken at 45 minutes, and for the PRT, samples were taken at the 1st, 3rd, 5th, and 8th hours and also at the 12th hour until the full release of the drug. For the sampling of dissolution profiles, an amount of sample was taken from a point mid-way between the surface of dissolution medium and paddle. Furthermore, it was filtered through a 0.45µm membrane after discarding the first 5 mL and then appropriately diluted using the dissolution medium. Additionally, the amount of Gliclazide released was determined using a UV-VISIBLE spectrophotometer based on absorbance at 226nm using dissolution medium as the blank. Additionally, the standard solution was prepared by dissolving an accurately weighed quantity of Gliclazide working standard in methanol and then further diluted using dissolution medium so as to obtain the desired concentration. Additionally, the amount of drug released was expressed as percentage of the labeled claim using the standard calibration method, and all tests were performed in triplicates.[13]

RESULTS AND DISSCUSION

Pre-Compression parameters

Table No. 4: Pre-compression Parameters for Gliclazide Lubricated Blend.

S.No	FORMULATION CODE	T1	T2	T3	T4	T5	T6
1	BULK DENSITY (g/mL)	0.421	0.478	0.493	0.578	0.556	0.559
2	TAPPED DENSITY (g/mL)	0.589	0.66	0.652	0.687	0.663	0.682
3	HAUSNER'S RATIO	1.39	1.38	1.32	1.18	1.19	1.22
4	COMPRESSIBILITY INDEX (%)	28.52	27.57	24.38	23.56	16.13	18.03
5	ANGLE OF REPOSE (Ɵ)	47 º 12'	46º 75'	41º 20'	35º 35'	37º 45'	36º 70'
6	FLOW PROPERTY	POOR	POOR	PASSABLE	GOOD	GOOD	GOOD

Determination of Absorption Maxima for Gliclazide

Measurement of absorption maxima: The spectrum for the working standards is determined by scanning from 200-400 nm with the reagent blank. The λmax is identified, and further studies are presently pursued at this same wavelength. The spectra obtained showed a peak, which indicated the maximum absorbance (λmax) is usually around 226 nm. The λmax for this study was identified, and these wavelengths were assigned for the UV tests.

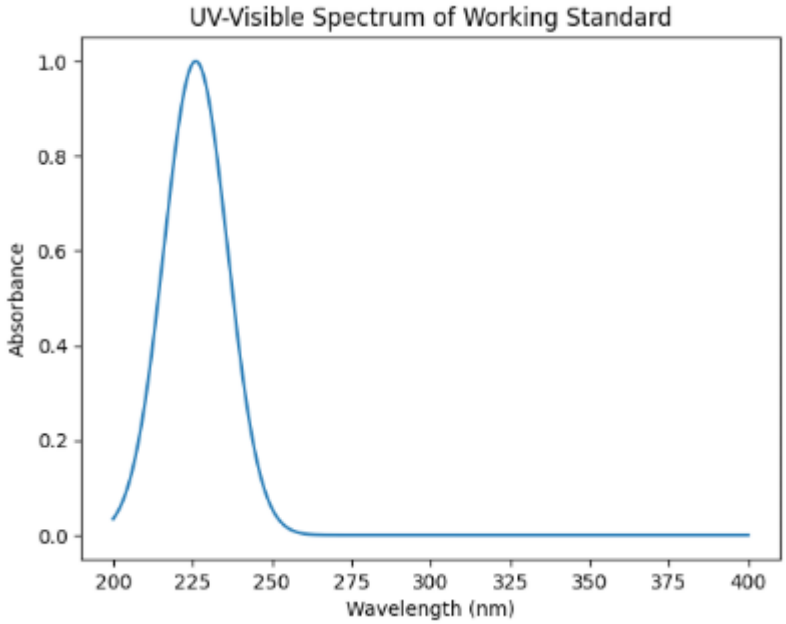

Fig. No. 1: absorption maximum (λmax).

Drug–Excipient Compatibility Studies by FTIR

Compatibility of the drug-excipients was carried out through the application of Fourier Transform Infrared (FTIR) Spectroscopy techniques.[14] Pure samples of Gliclazide as well as physical mixtures of Gliclazide and certain excipients (in appropriate ratios) were investigated. The mixtures were ground using potassium bromide (KBr) and then pressed into transparent pellets using a hydraulic press. The FTIR spectra were scanned between the wavenumbers of 4000 and 400 cm^{-1} using an FTIR spectrophotometer. The spectra of the physical mixtures were then overlaid with the spectra of the pure sample of Gliclazide in the search for marked shifts, absorption, or the appearance of new peaks indicative of drug-excipient interactions.

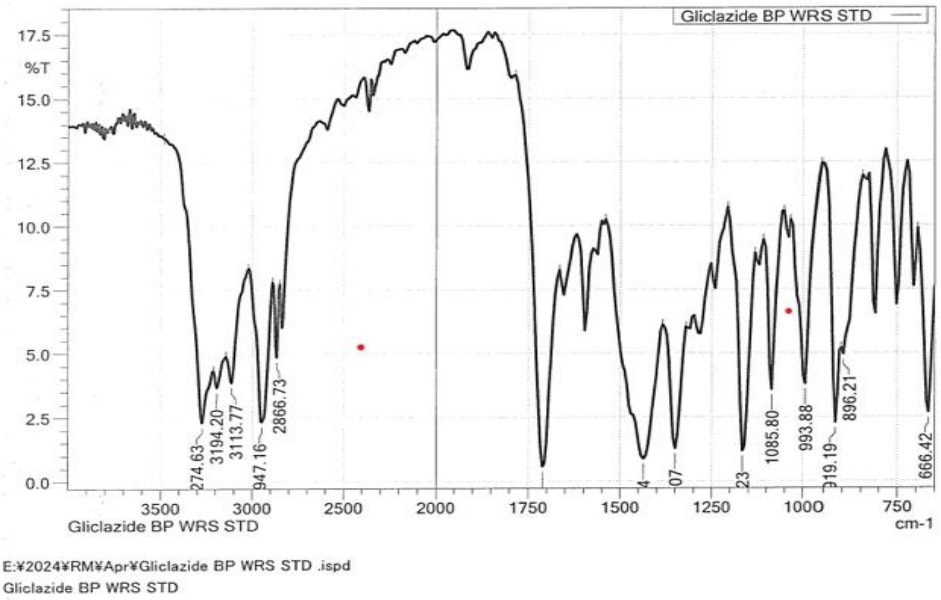

Fig. No. 2: FTIR Spectra of pure Gliclazide.

The FTIR Spectra of Gliclazide and the combination of drug and excepients shows nosignificant interaction between drug and excepients.

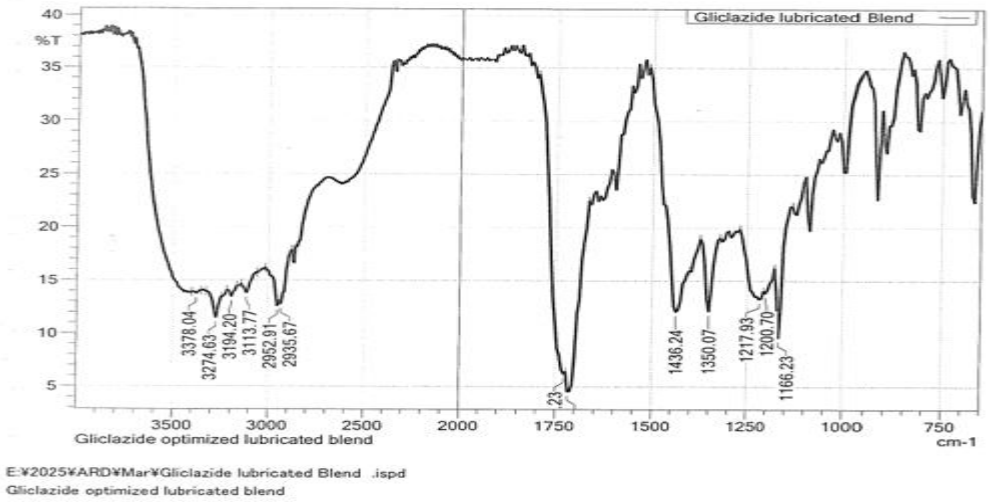

Fig No. 3: FTIR Spectrum of Gliclazide best formulation.

Drug and excipient compatibility testing under accelerated environmental conditions (40°C / 75% RH)

The drug-excipient compatibility study under accelerated stability conditions for a period of four weeks was conducted at 40°C ± 2°C and 75% ± 5% relative humidity. Under such conditions, different drug-excipient mixes were preserved, and their physical attributes were evaluated from time to time at pre-arranged times against their original baseline information for any change in appearance, colour, and other physicochemical properties. Compatibility

and stability could be ensured only by such an investigation, which can identify negative interactions under stressed conditions.

Post compression parameters

Table No. 5: Evaluation Of Gliclazide Floating Pulsatile Core Tablets (T1 to T6).

Tests	Specifications	T1	T2	T3	T4	T5	T6
Description	Whight colored circular shaped uncoated Tablet	Complies	Complies	Complies	Complies	Complies	Complies
Average weight (mg)	150mg ± 7.5%	153	151	155	154	153	152
Thickness (mm)	3.50 ± 0.2	3.55	3.51	3.51	3.53	3.53	3.51
Hardness (kg/cm2)	NLT 3.0	5.5	5	5.75	5.45	5.35	5.75
Friability(% w/w)	NMT 1%	0.07	0.1	0.1	0.1	0.13	0.11
Disintegration Time	NMT 15 Minutes	02’20”	02’55”	03’10”	02’50”	02’00”	01’18”
Weight variation (n=20)	± 5% from the average weight	-2.5 to +3.1	-2.7 to +2.9	-2.7 to +2.5	-2.7 to +2.5	-3.0 to +2.7	-2.3 to +2.9
Assay							
Gliclazide	90 – 110%	96.90%	98.20%	97.10%	98.10%	98.70%	98.10%

Tablet No. 6: Evaluation Of Gliclazide Pulsatile Release Tablet (PRT) (P1T6 to P6T6).

Tests	Specifications	P1T6	P2T6	P3T6	P4F6	P5F6	P6F6
Description	White colored Capsule shaped uncoated Tablet	Complies	Complies	Complies	Complies	Complies	Complies
Average weight (mg)	350 mg ± 3%	357	351	353	355	356	352
Thickness (mm)	4.7 ± 0.2 mm	4.75	4.7	4.79	4.74	4.73	4.71
Weight variation (n=20)	± 5% from the average weight	-2.5 to +3.1	-2.7 to +2.9	-2.7 to +2.5	-2.7 to +2.5	-3.0 to +2.7	-2.3 to +2.9

Table No. 7: In-Vitro Evaluation Of Gliclazide Pulsatile Release Tablet (PRT) (P1T6 to P6T6).

Time (hr)	P1T6	P2T6	P3T6	P4T6	P5T6	P6T6
0	0	0	0	0	0	0
1	39.88 ± 3.33	21.59 ± 3.25	10.19± 1.29	8.23 ± 1.35	2.73 ± 0.85	0.7±0.17
3	37.62 ± 5.52	27.72 ± 5.42	18.62 ± 5.21	15.30 ± 3.56	2.35 ± 1.46	1.05± 0.37
5	85.81 ± 5.75	75.73 ± 5.45	68.73 ± 4.84	57.86 ± 5.11	4.85 ± 2.81	2.23± 1.43
8	91.91± 6.71	93.67± 7.51	87.97± 4.71	93.19± 4.67	95.64± 4.17	94.53± 2.85
12	96.14± 4.51	95.21± 5.71	95.26± 4.41	95.63 ± 3.35	96.46± 4.51	98.69± 2.55

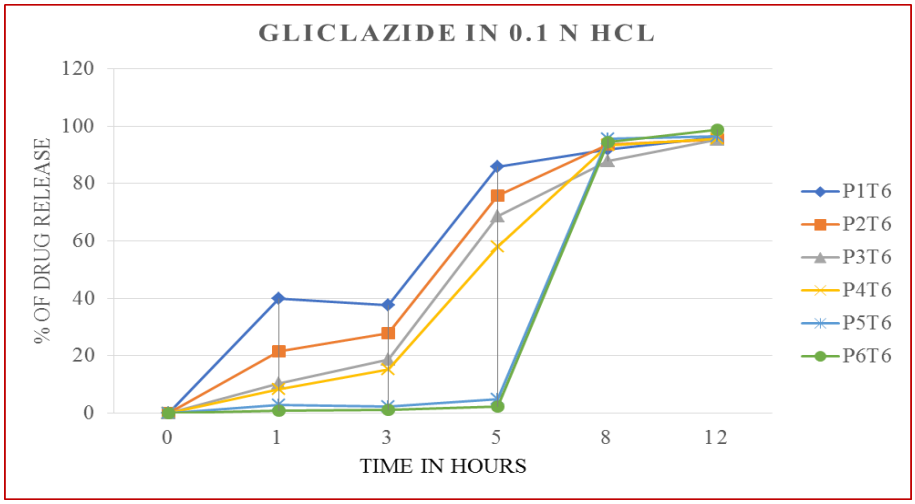

Fig No. 4: In-Vitro Evaluation Of Gliclazide Pulsatile Release Tablet (PRT) (P1T6 to P6T6).

DISCUSSION

Results from the in-vitro drug release studies carried out on Gliclazide Pulsatile Release Tablets (PRTs) formulation P1F6 to P6F6 indicated that the percentage drug release varied from 0.7% to 98.69%, thus showing a considerable variation in drug release among the formulations. However, of all the formulations, formulation P6F6 was ideal with a minimum variation and was able to satisfy the official acceptance criteria of percentage drug release thus qualifying to be identified as an optimized formulation that could be suitable for developing a floating pulsatile tablet system.

Table No. 8: Evaluation Of Gliclazide Floating Pulsatile Release Tablet (FPRT) (F1P6T6 to F6P6T6).

Tests	Specifications	F1P6T6	F1P6T6	F1P6T6	F4P6T6	F4P6T6	F4P6T6
Description	White colored Capsule shaped uncoated Tablet	Complies	Complies	Complies	Complies	Complies	Complies
Average weight (mg)	500 mg ± 5%	503	505	501	507	504	501
Thickness (mm)	5.0 ± 0.2 mm	5.15	5.05	5.01	5.15	5.1	5.1
Weight variation (n=20)	± 5% from the average weight	-2.5 to +3.1	-2.7 to +2.9	-2.7 to +2.5	-2.7 to +2.5	-3.0 to +2.7	-2.3 to +2.9

Floating test

In 0.1 N HCl immersion at 37^0C, tablets showed buoyant and no disintegration. The floating time in excess of 6 hours belongs to tablets of formulations F1P6T6 to F3P6T6. The total

floating time in excess of 10 hours belongs to tablets of formulations F4P6T6, F5P6T6, and F6P6T6. The floating time in excess of 1 minute belongs to tablets of formulations F1 to F6.

Table No. 9: Evaluation of Floating test.

Parameters	Formulation code					
	F1P6T6	F2P6T6	F3P6T6	F4P6T6	F5P6T6	F6P6T6
Floating Lag Time or Buoyancy Lag Time (≤300 sec)	45	42	40	27	18	20
Total Floating Time (≥12 hours)	>6	>6	>6	>10	>10	>10

Table No. 10: In *vitro* dissolution profile of Floating pulsatile tablet F1P6T6 to F6P6T6.

Time (hr)	F1P6T6	F2P6T6	F3P6T6	F4P6T6	F5P6T6	F6P6T6
0	0	0	0	0	0	0
1	38.28 ± 0.23	17.49 ± 0.15	4.19± 0.09	3.13 ± 0.15	0.73 ± 0.15	0.8±0.15
3	34.42 ± 0.42	25.52 ± 032	13.32 ± 012	8.10 ± 0.26	1.02 ± 0.26	1.2± 0.07
5	86.31 ± 0.45	71.23 ± 0.25	64.63 ± 0.15	59.80 ± 0.31	3.24 ± 0.31	3.83± 0.83
8	92.91± 0.51	91.07± 0.71	89.07± 0.81	91.49± 0.67	97.74± 0.97	86.13± 0.25
12	95.54± 0.81	96.21± 0.61	95.07± 0.81	96.13 ± 0.15	99.65± 1.31	96.64± 0.51

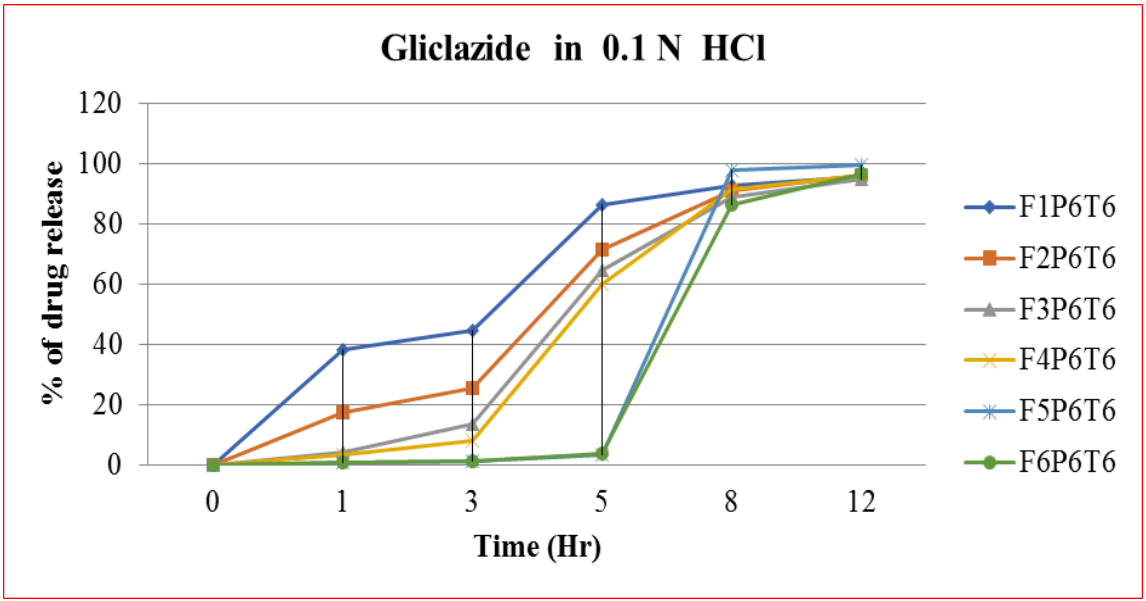

Fig. No.5: In vitro dissolution profile of Floating pulsatile tablet F1P6T6 to F6P6T6.

Optimized Floating Pulsatile Formulation Performance

The optimized formulation F5P6T6 had excellent floating properties with a very low floating lag time and buoyancy of more than 12 hours, which guaranteed the floating system for its increased gastric retention. The formulation achieved the pulsatile release profile of interest-a burst release of over 80% after an 8-hour lag period-and this hence meets the

chronotherapeutic needs of Gliclazide in the treatment of diabetes mellitus. Dissolution data of F5P6T6 analysed using different kinetic models suggested that the Korsmeyer-Peppas model (n = 0.686) best described the drug release from this formulation.

SUMMERY AND CONCLUSION

Croscarmellose sodium was found to be the most effective superdisintegrant, showing higher dissolution ability compared with crospovidone and sodium starch glycolate. For the rapidly release core tablets, formulation T6 with 10% croscarmellose sodium was found to release quickly within 2 minutes and was thus chosen as the optimized RRCT. For the pulsatile release tablets, HPMC grades K4M, K15M, and K100M CR Premium could be used effectively to get a desired lag time. The HPMC press-coated tablets weighing between 100 and 110 mg could effectively release doses and satisfy the USP acceptance specifications, and formulation P6T6 was found to give the best lag time control and desired burst release, and it was thus found to be the optimized pulsatile delivery system. To increase the lag time inside the stomach, floating pulsatile release tablets could be designed using lower-density materials. Among these, formulation F5P6T6 possessed the best floating properties, possessing a shortest floating lag time and maintaining the buoyancy for over 12 hours. The optimized floating pulsatile release tablets possessed a pulsatile burst release of over 80% post 8-hour lag, thus meeting the chronotherapeutic need of Gliclazide drug delivery. The drug release kinetics of F5P6T6 followed Korsmeyer and Peppas equations (n=0.686), signifying the anomalous diffusion process, which follows a non-Fickian diffusion pattern. The results of the storage test proved that this formulation possessed excellent stability, and the values of the physio parameters, floating, and dissolution remains unchanged.

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