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FORMULATION DEVELOPMENT AND EVALUATION OPULSATILE DRUG DELIVERY SYSTEM OF HYDROCHLOROTHIAZIDE

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Abstract:

The study aimed to develop and evaluate a pulsatile drug delivery system (PDDS) for Hydrochlorothiazide, a thiazide diuretic commonly used for managing hypertension and edema. The PDDS was designed to synchronize drug release with the body's circadian rhythm, targeting early morning peaks in blood pressure. Using the wet granulation method, core tablets were formulated using various super disintegrants (Lycoat, Sodium starch glycolate, and Ludiflash). These tablets were then coated with natural and synthetic polymers, including Xanthan gum, Karaya gum, HPMC K4M, and HPMC K15M, to control the release profile. The formulations were evaluated for pre- and post-compression parameters, drug content uniformity, in vitro drug release, and dissolution kinetics. The optimized core tablet formulation (F9) and coated tablet formulation (C7F9) were identified based on their ability to maintain a lag phase followed by a burst release at the desired time, which was confirmed by release kinetics analysis indicating a first-order release mechanism and super case II transport. The study concludes that the PDDS developed for Hydrochlorothiazide can effectively provide a time-dependent release profile, making it suitable for chronotherapy in hypertension management.

Keywords: Pulsatile drug delivery system, Hydrochlorothiazide, Chronotherapy, Wet granulation, Super disintegrants, Xanthan gum, Karaya gum, HPMC, In vitro release, Dissolution kinetics.

Introduction

Pulsatile drug delivery systems (PDDS) are advanced pharmaceutical technologies designed to release drugs in a time-controlled manner, aligning with the body's circadian rhythms or specific pathophysiological needs, thus enhancing therapeutic efficacy and reducing side effects. These systems are particularly beneficial for diseases that follow predictable patterns, such as asthma, arthritis, and cardiovascular disorders, where drug release is timed to

coincide with disease exacerbation periods. PDDS can be classified into time-controlled, stimulus-induced, and externally regulated systems, each offering unique mechanisms to achieve the desired drug release profile. Technologies like multi-particulate systems, capsular systems, and osmotic devices are commonly employed to achieve pulsatile release, providing significant advancements over traditional drug delivery methods. The clinical potential of PDDS is supported by various studies demonstrating improved patient compliance and therapeutic outcomes, making them a promising approach for tailored and effective disease management. [1-4]

Hydrochlorothiazide is the most commonly prescribed thiazide diuretic. It is indicated to treat edema and hypertension. Hydrochlorothiazide use is common but declining in favour of angiotensin-converting enzyme inhibitors. Many combination products are available containing hydrochlorothiazide and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Hydrochlorothiazide is indicated alone or in combination for the management of edema associated with congestive heart failure, hepatic cirrhosis, nephrotic syndrome, acute glomerulonephritis, chronic renal failure, and corticosteroid and estrogen therapy. Hydrochlorothiazide is also indicated alone or in combination for the management of hypertension. [5,6]

Materials and Methodology

Materials

The materials used in the formulation include hydrochlorothiazide (provided as a gift sample), Lycoat, SSG, Ludiflash, MCC, talc, and magnesium stearate, all sourced from B.M.R Chemicals in Hyderabad. Additionally, xanthan gum, karaya gum, HPMC K4M, and HPMC K15M were obtained from Narmada Chemicals. These materials are essential for formulating pharmaceutical products, each contributing properties such as film-forming ability, binder functionality, flow enhancement, and lubrication, depending on their intended use in the formulation process.

Preparation of Standard Calibration Curve of Hydrochlorothiazide in 0.1 N HCL

10mg of Hydrochlorothiazide was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 0.1 N HCL buffer to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with 0.1 N HCL buffer to get 2 to 12µg/ml of Hydrochlorothiazide. The absorbance of the solution was measured against 0.1 N HCL buffer as blank at 238nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.[7,8]

Preparation of Standard Calibration Curve of Hydrochlorothiazide in 6.8 pH. Buffer

10mg of Hydrochlorothiazide was accurately weighed and transferred into a 10ml volumetric flask. It was dissolved and diluted to volume with 6.8 phosphate buffer to give a stock solution

containing 1000µg/ml. The standard stock solution was then serially diluted with 6.8 phosphate buffer to get 2 to 10µg/ml of Hydrochlorothiazide. The absorbance of the solution was measured against 6.8 phosphate buffer as blank at 238nm using a UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve**.**

Preformulation studies [9-18]

It is an essential prerequisite in the development of any drug delivery system. The drug underwent Preformulation studies, which included melting point determination, solubility studies, and compatibility studies.

Determination of Melting Point

The melting point of Hydrochlorothiazide was determined by the capillary method. Fine powder of Hydrochlorothiazide was filled in a glass capillary tube (previously sealed at one end). The capillary tube was tied to a thermometer and placed in the Thais tube, which was set on fire. The powder's melting temperature was noticed.

Solubility studies

The solubility of Hydrochlorothiazide was determined in pH 1.2, 6.8, and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amounts of Hydrochlorothiazide in different beakers containing the solvents. The mixtures were shaken for 24 hrs. at regular intervals. The solutions were filtered by using Whattmann's filter paper grade no. 41. The filtered solutions were analyzed spectrophotometrically at 238 nm.

FTIR analysis:

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

Table 1: Formulation Table of Core Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hydrochlorothiazide	60	60	60	60	60	60	60	60	60
Lycoat	2	4	6	--	--	--	--	--	--
SSG	--	--	--	2	4	6	--	--	--
Ludiflash	--	--	--	--	--	--	2	4	6
MCC	32	30	28	32	30	28	32	30	28
Starch Solution (5%)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Mg. Stearate	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2
Total wt	100	100	100	100	100	100	100	100	100

Formulation of core tablet of Hydrochlorothiazide

Fast-dissolving Hydrochlorothiazide tablets were prepared using different super disintegrants: Lycoat, Sodium starch glycolate, and Ludiflash by wet granulation method. To prepare tablets previously sieved (Sieve no. 50), ingredients were mixed according to a formula specified in the formulation, as shown in the table. Starch was dissolved in isopropyl alcohol (IPA) to prepare a 5% alcoholic solution and added to the above mixture to form a lump-like mass. This was passed through (Sieve no.16) to prepare granules. The granules were dried at 60^0C for 15-20 minutes and then passed through (Sieve no. 20) for re-granulation. Superdisintegrants were added as intragranular. Finally, magnesium stearate and talc were mixed well into the above mixture. Then 100mg of the granules were punched to form tablets.

Formulation of tablets of Hydrochlorothiazide

The optimized core tablets were coated with coating ingredients like Xanthan gum, Karaya gum. Now accurately weighed amount of barrier layer material was transferred into a 16mm die then the core tablet was placed manually at the center. The remaining amount of the barrier layer material was added into the die and compressed. Compression of tablets was done in rotary compression tablet machine using 16.4x8mm flat oval shape punch. The prepared tablet of each batch was evaluated for the tablet properties.

Evaluation of Tablet Properties

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.[19-28]

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.

Tablet 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

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.

$$\text{Friability} = \frac{\textit{Initial weight of tablet} - \textit{Final weight of tablets}}{\textit{Initial weight of tablet}} \boldsymbol{x100} \quad \%$$

Tablet 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 200 mg was weighed accurately and dissolved in 100ml of buffer. The solution was shaken thoroughly. The un-dissolved matter was removed by filtration through Whitman's filter paper No.41. Then, the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 238 nm. The concentration of the drug was computed from the standard curve of the Hydrochlorothiazide in 6.8 phosphate buffer.

Disintegration time

Tablet disintegration is an essential step in drug absorption. The disintegration test was conducted in the Electro lab USP disintegration test apparatus. It consists of 6 glass tubes, which are 3 inches long, open at the top, and held against a ten 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 a 1-liter beaker containing 6.8 phosphate buffer solution 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.

Invitro Dissolution time

The tablet was introduced into the basket of the Lab India DS8000 USP dissolution test apparatus and set in motion. Five ml of sample was withdrawn for half an hour at 5-minute intervals. The samples withdrawn were analyzed by UV spectrophotometer for the presence of the drug using buffer solution as a blank.

Table 2: Composition of compression coated tablets

Formulation	C1F9	C2F9	C3F9	C4F9	C5F9	C6F9	C7F9	C8F9
Core Tablet	20%	20%	20%	20%	20%	20%	20%	20%
Xanthan gum	40%	50%	32.5%	42.5%	-	-	-	-
Karaya gum	40%	30%	42.5%	32.5%	-	-	-	-
HPMC K 4M	-	-	-	-	40%	50%	32.5%	42.5%
HPMC K 15M	-	-	-	-	40%	30%	42.5%	32.5%
Total weight	500	500	500	500	500	500	500	500

Evaluation of Pulsatile Drug Delivery Systems

Characteristics of coated tablets of Hydrochlorothiazide

Characteristics of tablets of Hydrochlorothiazide, such as hardness and disintegration tests, were conducted. 3 tablets were taken, and the hardness of formulations was determined by using a Monsanto hardness tester. An average of three determinations was noted down. 6 tablets were taken in the Electro lab USP Disintegration test apparatus, and the disintegration time of the tablets was determined using a pH 6.8 buffer. The thickness of coated Hydrochlorothiazide tablet formulations was determined by using digital Vernier calipers. 3 tablets of each type of coated formulation were determined for thickness, and the average thickness of the formulation was determined. Similarly, the thickness of the coating on the formulation was determined by deducting the thickness of the core tablets from the thickness of the coated formulation. A successful Pulsatile drug delivery system is one that remains intact in the physiological environment of the stomach and small intestine for up to six hours, releasing no or minimum amount of drug, but completely releases the drug after six hours.

***In-vitro* Dissolution methods:**

Dissolution testing of pulsatile delivery systems with the conventional paddle method at 50 rpm and 37±0.5°C has usually been conducted in different buffers for different periods of time to simulate the GI tract pH and transit time that the pulsatile delivery system might encounter *in-vivo.* The ability of the coats/carriers to remain intact in the physiological environment of the stomach and small intestine is generally assessed by conducting drug release studies in 0.1N HCL for 2 hours (mean gastric emptying time) and in pH 6.8 phosphate buffer for remaining hours (mean small intestinal transit time) using USP

dissolution rate test apparatus. The samples were withdrawn at regular intervals and analyzed by UV spectrophotometer (PG Instruments T60) for the presence of the drug. Dissolution tests were performed in triplicate.

Despite its simplicity and convenience, conventional dissolution testing primarily provides essential information on the processing specifications of a Pulsatile drug delivery system rather than on the validity of the system's design.

Release Kinetic Models

The data obtained were fitted to a zero-order, first-order, Higuchi matrix, Korsmeyer's-Peppas, and Hixson Crowell model to analyze the mechanism for the drug release and drug release rate kinetics of the dosage form. By comparing the R-values obtained, the best-fit model was selected.

Result & Discussion

Solubility

The solubility of a substance in different buffer solutions is crucial for understanding its dissolution and absorption characteristics in pharmaceutical formulations. This study evaluated the substance's solubility in three different buffer solutions: 0.1N HCl, pH 6.8 buffer, and pH 7.4 buffer. The results indicate varying solubilities, with 0.1N HCl showing the lowest solubility at 0.106 mg/ml, pH 6.8 buffer demonstrating the highest solubility at 0.256 mg/ml, and pH 7.4 buffer having an intermediate solubility of 0.194 mg/ml. These findings are essential for formulating dosage forms that optimize drug dissolution and ensure adequate bioavailability based on the pH conditions encountered in different parts of the gastrointestinal tract or other biological environments.

Preparation of Standard Calibration Curve of Hydrochlorothiazide in 0.1N HCL

Table 3: Calibration Curve of Hydrochlorothiazide in 0.1N HCL

S.NO	CONC	ABS
1	0	0
2	2	0.056
3	4	0.132
4	6	0.202
5	8	0.276
6	10	0.346
7	12	0.418

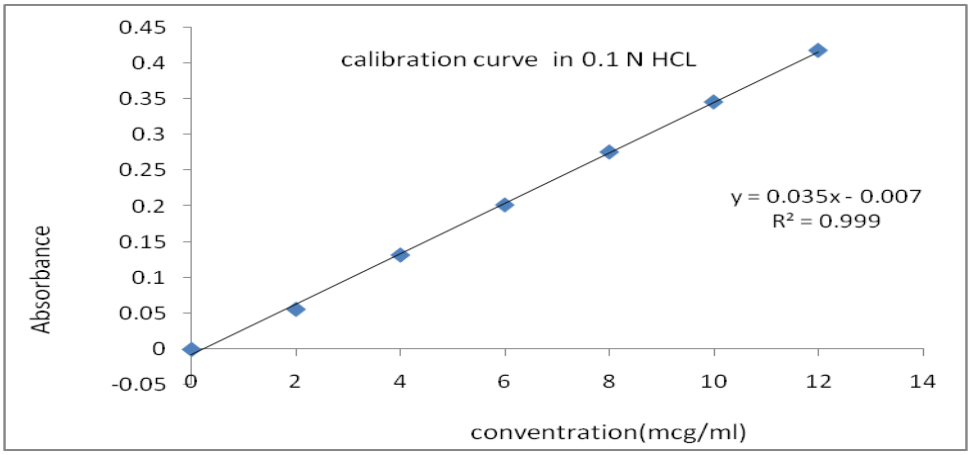

Fig 1.Calibration Curve of Hydrochlorothiazide in 6.8 ph buffer

Table 4: Standard Calibration Curve of Hydrochlorothiazide at 238 nm

S.NO	CONC	ABS
1	0	0
2	2	0.173
3	4	0.358
4	6	0.535
5	8	0.694
6	10	0.847
7	12	1.026

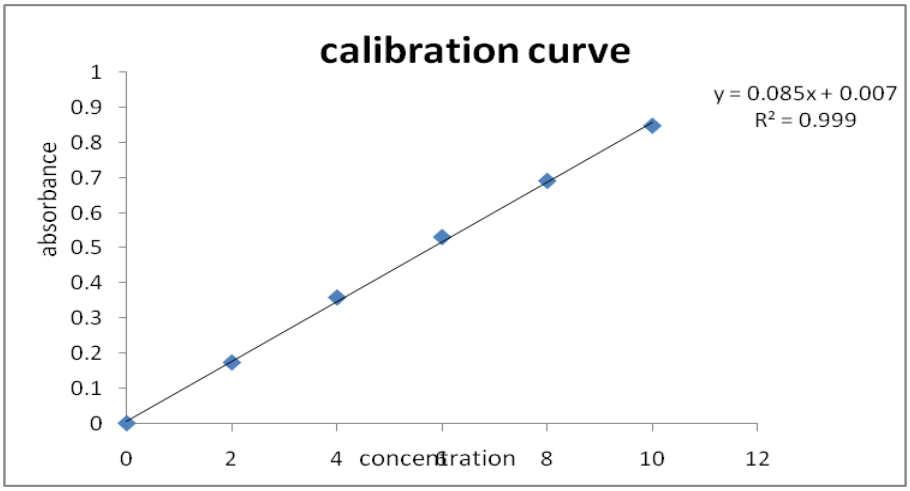

Fig 2: Calibration curve of Hydrochlorothiazide

Compatibility Studies

Compatibility with excipients was confirmed by FTIR studies. The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

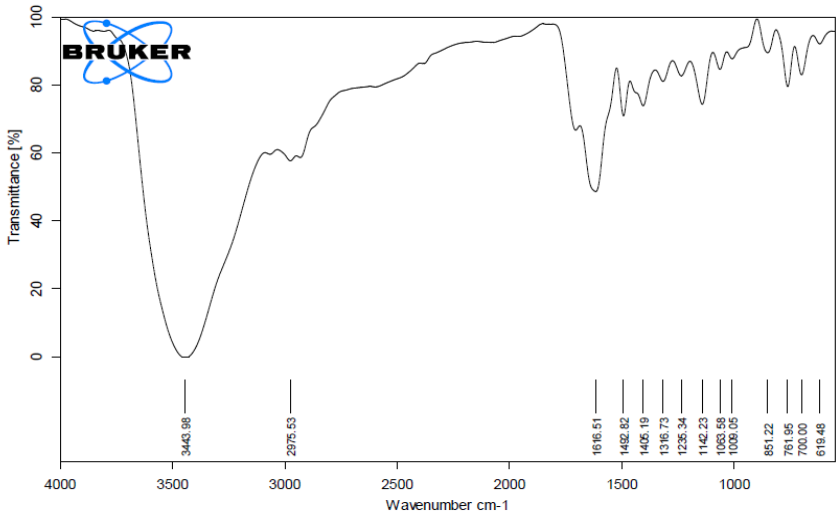

Fig 3: FTIR Spectrum of Hydrochlorothiazide pure

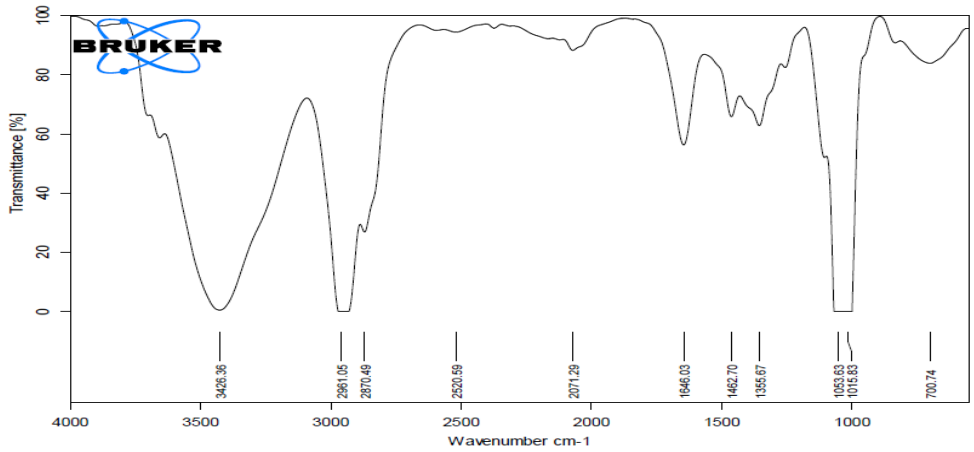

Fig.4 FTIR Spectrum of Hydrochlorothiazide and Excipients

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug and optimized formulation (Hydrochlorothiazide + excipients) which indicates there are no physical changes

Table 5: Pre Compression parameters

Formulation Code	Derived properties		Flow properties		
	Tapped density (mean±SD)	Bulk density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.48±0.01	0.56±0.015	26.38±0.30	14.28±1.02	1.16±0.06
F2	0.46±0.01	0.52±0.02	27.42±0.39	11.53±1.26	1.13±0.03
F3	0.42±0.04	0.48±0.01	24.02±0.68	12.58±2.08	1.14±0.05
F4	0.46±0.02	0.54±0.015	26.26±0.96	14.81±1.28	1.12±0.02
F5	0.52±0.6	0.60±0.03	30.68±0.73	13.33±1.86	1.17±0.04
F6	0.49±0.2	0.58±0.006	29.26±0.36	15.51±1.96	1.18±0.05
F7	0.42±0.08	0.48±0.04	24.02±0.68	12.58±2.08	1.14±0.05
F8	0.52±0.12	0.60±0.03	30.68±0.73	13.33±1.86	1.17±0.04
F9	0.42±0.06	0.48±0.01	24.02±0.52	12.58±1.08	1.14±1.05

The angle of repose of different formulations was ≤ 30.68 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.42g/cm^3 to 0.52g/cm^3.Tapped density was found between 0.48g/cm^3 to 0.60g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.53-15.518 and Hausner's ratio from 1.12-1.18 which reveals that the blends have good flow character.

Table 6: Post Compression Parameters of core tablet

Formula	Post compression parameters of core tablet				
	Avg. Wt (mg)	**Hardness(kg/cm^2)**	**Thickness(mm)**	**Friability(%)**	**Disintegration time(secs)**
F1	99.12	3.34	3.41	0.23	86
F2	98.97	3.12	3.69	0.41	63
F3	97.56	3.30	3.97	0.77	47
F4	98.56	3.20	3.55	0.54	79
F5	99.23	3.33	3.36	0.63	58
F6	99.78	3.45	3.64	0.70	39
F7	98.89	3.36	3.40	0.19	71
F8	98.55	3.55	3.39	0.35	53
F9	99.41	4.02	3.77	0.48	30

Table 7: Evaluation of Physical Parameters of Compressed Tablets of Hydrochlorothiazide

Formula	**Weight variation (mean ± SD, mg)**	**Hardness**	**Friability (%)**	**Thickness**
C1F9	492.30±0.11	5.12	0.89	4.78
C2F9	497.56±1.20	5.30	0.78	4.85
C3F9	495.66±2.59	5.16	0.65	4.69
C4F9	498.98±0.45	5.20	0.26	4.70
C5F9	497.79±1.03	5.23	0.78	4.75

C6F9	498.80±1.30	5.22	0.96	4.72
C7F9	497.56±2.18	5.36	0.78	4.85
C8F9	498.98±1.26	5.24	0.26	4.70

Table 8: Content uniformity of different formula (F1 to F9)

Formulation code	Drug content
F1	91.02±0.15
F2	90.23±0.79
F3	93.30±0.26
F4	91.22±0.33
F5	92.56±0.45
F6	95.69±0.98
F7	97.41±0.77
F8	95.59±0.44
F9	98.86±0.32

Table 9: Cumulative percent drug release of core Hydrochlorothiazide tablets of different formulations (F1 to F9)

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	25.57	27.78	33.56	30.48	36.60	42.26	52.74	43.26	47.13
10	34.49	39.90	42.02	41.79	49.98	53.36	63.60	59.69	62.22
15	52.11	57.15	61.19	50.80	65.54	72.20	75.09	66.78	84.14
20	69.90	73.30	76.62	61.60	79.59	84.47	82.97	79.04	91.10
25	76.65	82.20	85.59	72.79	88.80	96.66	87.58	92.41	99.45
30	87.19	91.16	97.40	84.63	97.19	99.24	93.30	98.91	
45	95.50	98.07		92.77			99.78		

60									

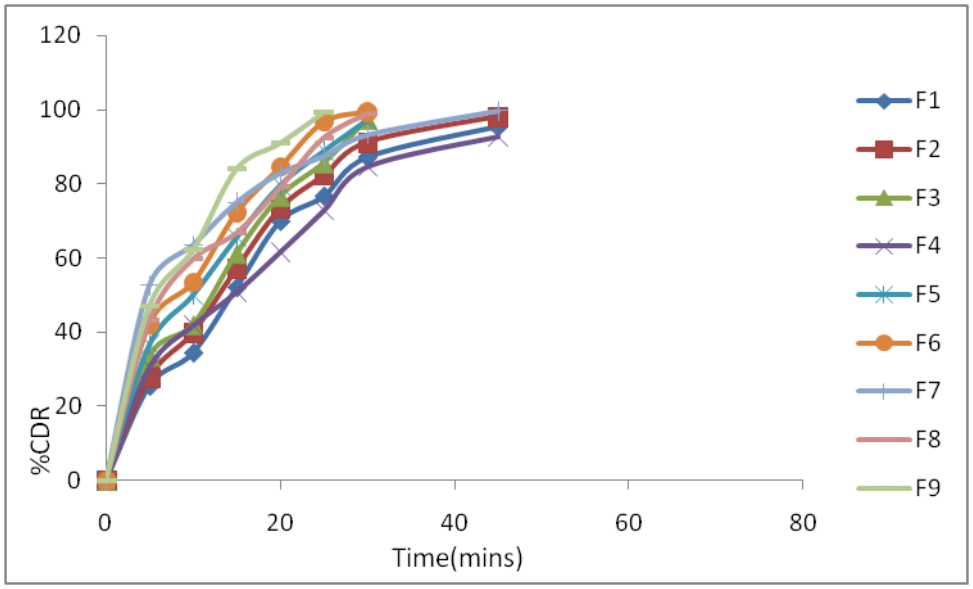

Fig 5: Cumulative percentage drug release of core formulation F1 – F9

Drug Release Kinetics Mechanisms

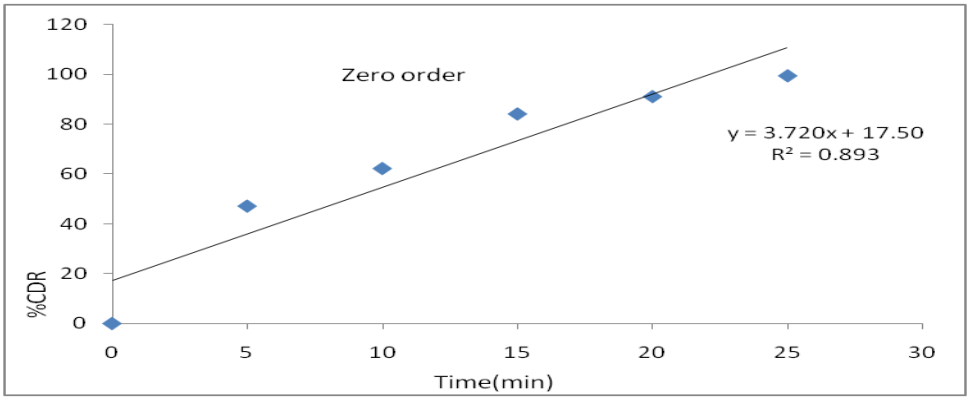

Fig 6: Zero Order Release Kinetics for Best Formulation (F9)

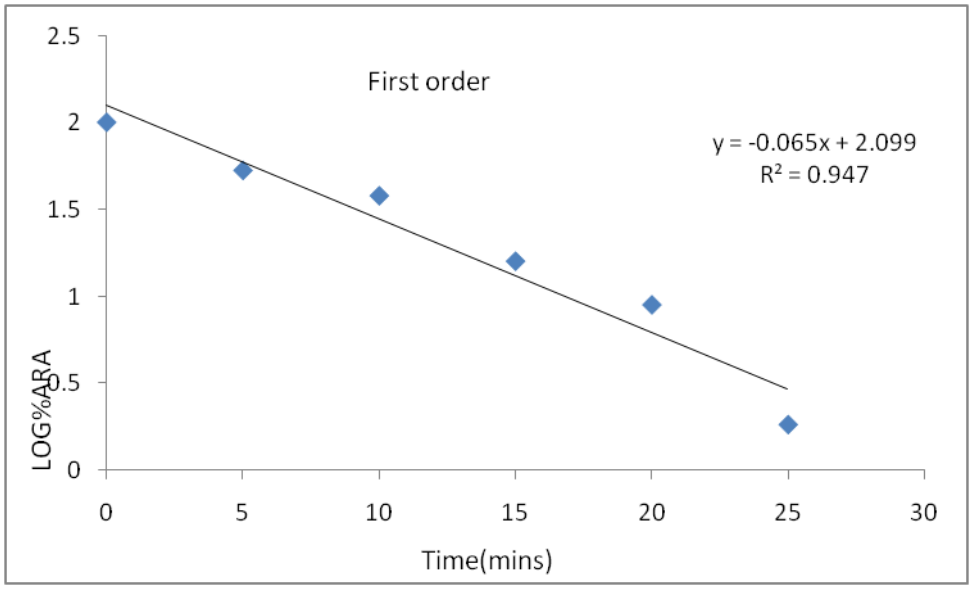

Fig.7 : First Order Release Kinetics For Best Formulation (F9)

Table 10: *in-vitro* drug release mechanism of best core formulation

Batch	**Zero Order**	**First Order**
Code	**r^2**	**r^2**
F9	0.893	0.947

Table 11: Cumulative % drug release of coated different formulation (C1F9 to C8F9)

Time(HRS)	**C1F9**	**C2F9**	**C3F9**	**C4F9**	**C5F9**	**C6F9**	**C7F9**	**C8F9**
0	0	0	0	0	0	0	0	0
1	0.54	0.22	0.41	0.51	0.89	0.55	0.28	0.41
2	0.63	0.64	0.97	0.77	1.36	1.23	0.56	0.77
3	2.03	0.84	1.75	3.69	4.47	5.60	1.81	3.69
4	4.12	1.97	2.98	8.79	9.98	10.23	2.24	8.79
5	19.65	13.36	13.69	26.65	26.6	21.36	6.65	26.65
6	32.30	74.46	38.79	48.87	47.48	34.45	58.87	48.87
7	44.47	85.97	52.65	66.30	69.14	66.54	86.30	66.30

8	74.12	98.89	68.78	87.90	87.19	80.21	97.90	87.90
9	84.20	--	79.96	99.02	95.24	96.54	99.86	92.64
10	98.46	--	92.64	--	100.01	98.26	-	96.22

From the Invitro drug release studies of the press coated tablets of Hydrochlorothiazide it was observed that the formulation C1F9 containing xanthan gum and Karaya gum releases maximum drug at the end of 10 hours due to the high polymer concentrations of xanthan gum and Karaya gum.

whereas the formulation C2F9 containing xanthan gum and Karaya gum in 50% and 30% concentration releases maximum drug at the end of 8 hours and it maintains lag phase for 6hours, but this formulation didn't shows repeatability. So this formulation didn't considered as the best formulation.

whereas the formulation C3F9 containing 32.5% and 42.5% of xanthan gum and Karaya gum concentrations releases maximum drug at the end of 10 hours due to the higher Karaya gum concentration.

whereas by changing the concentrations of the polymers as in case of C3F9 to C4F9 viceversa the drug release was shown at the end of 9 hours.

By considering the all formulations it was considered that none of the above formulations didn't follow lag phase.

So the further trials which were performed using synthetic polymers shown drug release as follows.

C4F9 to C8F9 formulations were formulated as the same concentrations of natural polymers among them, C7F9 formulation was considered as the best formulation, as it maintains lg phase for upto 6hours and the maximum drug was released at the end of 9hours, due to higher polymer concentration of HPMC K15M.

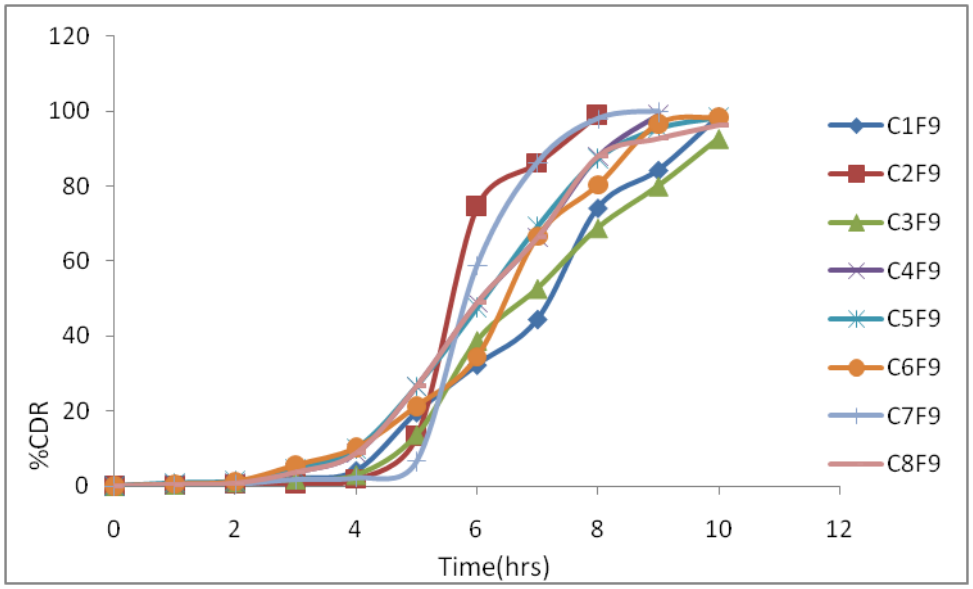

Fig .8: Cumulative percentage drug release of coated formulation C1F9-C8F9

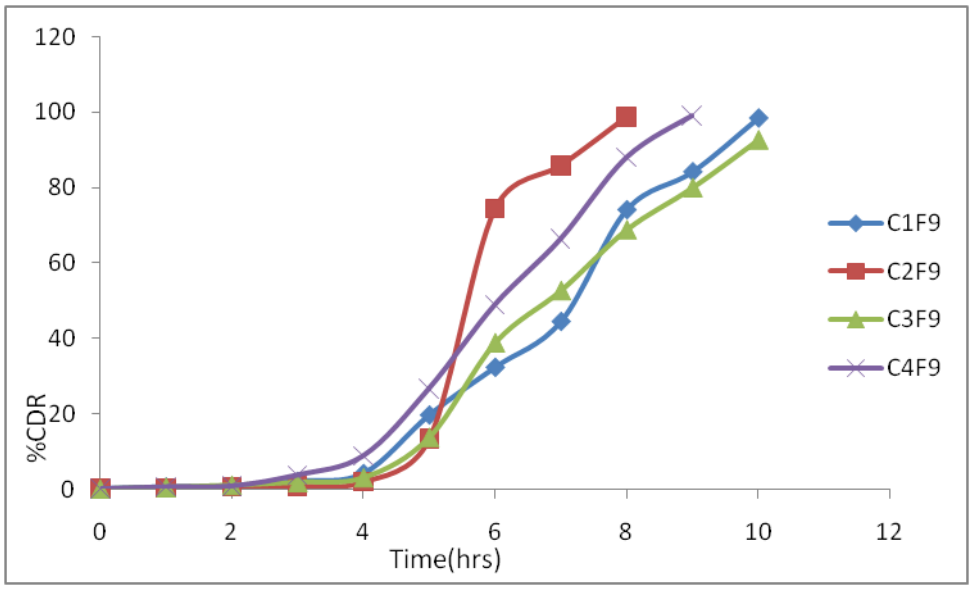

Fig 9: Cumulative percentage drug release of coated formulation C1F9 –C4F9

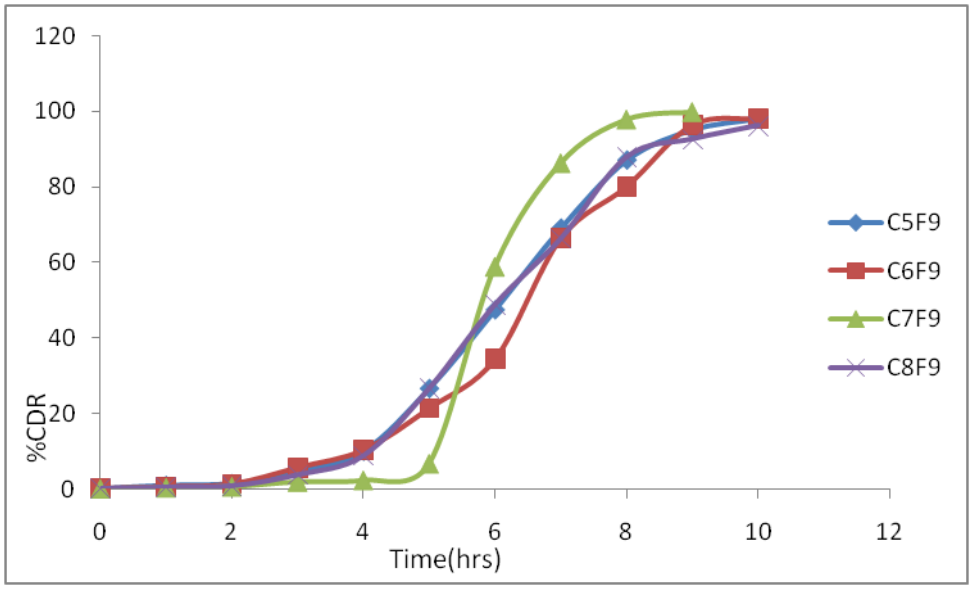

Fig.10: Cumulative percentage drug release of coated formulation C5F9-C8F9

Drug Release Kinetics Mechanisms:

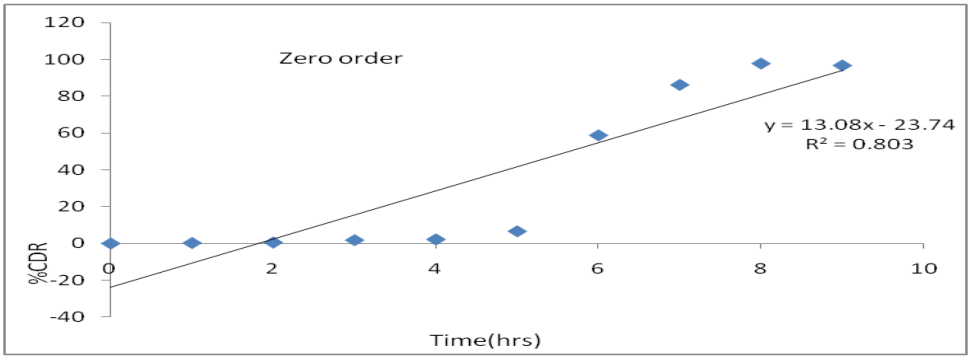

Fig.11: Zero order release kinetics for best formulation (C7F9)

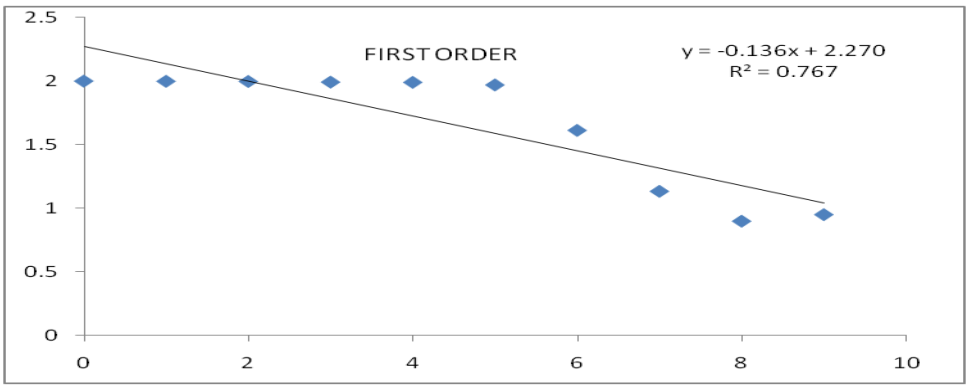

Fig.12 : First order release kinetics for best formulation (C7F9)

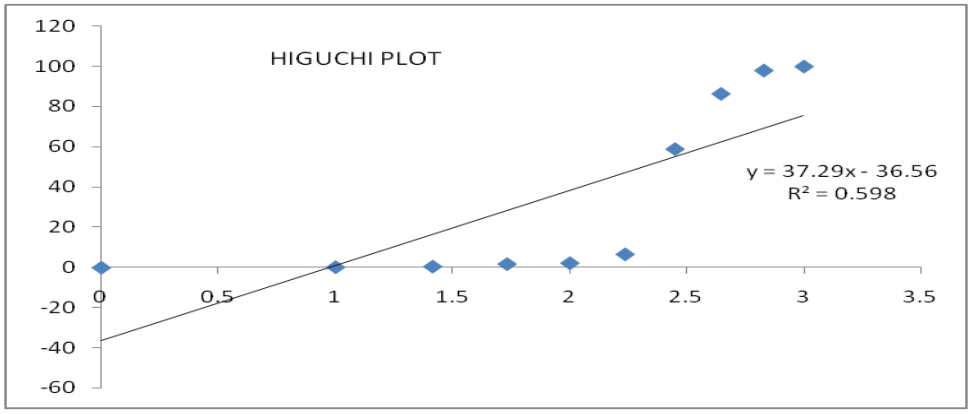

Fig.13: Higuchi plot of C7F9

Table 12: *in-vitro* drug release mechanism of best formulation

Batch	**Zero Order**	**First Order**	**Higuchi**	**Peppas**	**Peppas**
Code	**r^2**	**r^2**	**r^2**	**r^2**	**n**
C3F9	0.803	0.767	0.598	0.832	2.602

From the drug release kinetics of the press coated tablet, it was concluded that the formulation C7F9 maintained a lag phase for 5 hours, and the drug release bursts at the end of 6 hours, and it releases the maximum drug release at the end of 9 hours. It follows first order drug

release and follows super caseII transport mechanism.

Conclusion

Based on the reproducible results obtained from the experiments conducted, it can be concluded that formulations F9 of the core tablet and C3F9 of the coated tablet were selected as the optimised formulations for designing a pulsatile drug delivery device for hydrochlorothiazide. These selections were based on criteria such as drug content uniformity, in-vitro release profiles, and kinetic data analysis. The study demonstrates that the coated formulation of hydrochlorothiazide can effectively serve as a time-dependent modified chrono pharmaceutical formulation, releasing the drug in a controlled manner over a specific period. Overall, the results affirm that a pulsatile drug delivery system for hydrochlorothiazide can be successfully formulated using the polymers and techniques described in the study, paving the way for potential applications in achieving targeted drug release profiles and therapeutic outcomes.

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