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Formulation and Evaluation of Press Coated Pulsatile Tablet of Valsartan.

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ABSTRACT:

The present study described the preparation of the valsartan (model drug) core-in-cup pulsatile release tablets based on pulse release pattern intended for chronotherapy in hypertension. By using different polymers with various combinations fails to give desired lag time. Then by various trials, ethyl cellulose and polyethylene oxide shows desired lag time. Hydrophilic polymers used were essential for achieving the desired release pattern. The combination of hydrophobic polymer (ethyl cellulose) and hydrophilic polymer (polyethylene oxide) gave optimum release profile by providing initial swelling in acidic pH followed by a pulse release after specific lag time. From the disintegration test of core tablets it was concluded that croscarmellose sodium (8%) show least disintegration time. In trial-1 in ethyl cellulose is used as impermeable cup and L-HPC as top layer, it showed lag time of 1-3 hrs which is not desired lag time because of top layer of hydrophilic polymer L-HPC it gets solubilise quickly and exposes tablet. In trial-2 ethyl cellulose and polyox-301, it showed lag time of 1-3 hrs which is not desired lag time because of erodible nature of polyox 301 it get eroded in contacts with dissolution media. In trial-3 ethyl cellulose and polyox-303, it showed lag time of 2-5 hrs which is desired lag time because of swelling nature of polyox 303 it get swelled in contacts with dissolution media and after lag time it exposes tablet. In impermeable cup method the concentration of hydrophobic polymer do not affect the release profile after fix concentration however the lag time increases and drug release decreases with increasing concentration of hydrophilic polymer.

KEYWORDS: Valsartan, Microcrystalline cellulose, Croscarmellose sodium, Ethyl cellulose, L-Hydroxy Propyl Cellulose, Polyox 301, Polyox 303

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1.INTRODUCTION

Today, a pharmaceutical scientist is well versed with the fact that the overall action of a drug molecule is not merely dependent on its inherent therapeutic activity, rather on the efficiency of its delivery at the site of action. An increasing appreciation of the latter has led to the evolution and development of several drug delivery systems (DDS), aimed at performance enhancement of the potential drug molecules. Thorough understanding of the disease physiology is required before designing the pulsatile drug delivery system. Diseases where rhythmic circadian organization of the body plays an important role; pharmacokinetics and/or pharmacodynamics of the drugs are not constant within 24 hr. Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. In case of cardiovascular diseases, several functions (e.g., blood pressure, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood.

Circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type-I diabetes has been well exploited. Furthermore diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various complications. A circadian rhythm occurs during hepatic cholesterol synthesis. In case of arthritis there is a circadian rhythm in the plasma concentration of C- reactive protein and interleukin-6 of patients with rheumatoid arthritis.^{3,11}

2. MATERIAL AND METHOD:

Valsartan was obtained by Cipla Pvt Ltd, Microcrystalline cellulose and croscarmellose sodium were procure from ozone international Pvt Ltd, Ethyl cellulose was obtained from S.D Fine chemicals Pvt Ltd, L-hydroxy propyl cellulose were procured from Colorcon Asia Pvt. Ltd, Polyox 301 and polyox 303 were obtained from Dow chemicals.

METHOD:***Formulation Development:******2.1. Preparation of rapid release core tablets (RRCT)***

The rapid release core tablets were prepared using a compression machines (Lab Press) with suitable flat punches. The core was made of the suitable mixture of powder blends of valsartan, Microcrystalline Cellulose (MCC, Avicel PH-101), Croscarmellose Sodium (Ac-Di-Sol), Magnesium Stearate & Talc was used in different batches. All above ingredients were dry blended for 20 minutes followed by addition of Magnesium Stearate & Talc. The mixture was then further blended for 10 minutes. The 100mg of the resultant mixture then directly compressed at a suitable pressure for 1 minute using 6 mm punch and die.

Table no. 1: Composition of core tablet

Formulation Code	Drug (mg)	Microcrystalline Cellulose	Croscarmellose sodium	Magnesium Stearate(mg)	Total
C1	40	57	1	2	100
C2	40	56	2	2	100
C3	40	54	4	2	100
C4	40	52	6	2	100
C5	40	50	8	2	100

3. FORMULATION DESIGN OF PRESS COATED TABLETS:***3.1. Preparation of Press Coated Tablets by Impermeable Cup Shaped Method:***

An impermeable coating cup consisting of ethyl cellulose was applied in the bottom and around the core tablet. The ethyl cellulose powder was filled into a die of 10mm diameter and then was gently compacted to make a powder bed with a flat surface. The core tablet was in turn carefully placed in center of powder bed next the die was filled with the reminder of the coating powder so that surrounding surfaces of the core tablet was fully covered. On the top hydrophilic polymer was added and last bed was compressed to produce the desired core-in-cup system.

3.2. Trial 1 (EC: L-HPC)

In this trial the bottom layer was prepared by hydrophobic polymer ethyl cellulose and upper layer is hydrophilic polymer L-HPC.

Table no 2. Composition of core-in-cup tablet (F1-F3)

Formulation		Coating Material		
Batch code	Core tablet weight (mg)	Coating material In cup shape (Ethyl cellulose)	Coating material in upper layer (L-HPC)	Total
F1	100	150	100	350
F2	100	150	150	400
F3	100	150	150	400

3.3. Trial 2 (EC: POLYOXY WSR-301):

In this trial the bottom layer was prepared by hydrophobic polymer ethyl cellulose and upper layer is hydrophilic polymer Polyox 301.

Table No.3: Composition of core-in-cup tablet (F4-F6)

Formulation		Coating material		
Batch code	Core tablet Weight(mg)	Coating material In cup shape (Ethyl cellulose)	Coating material In upper layer (Polyox 301)	Total
F4	100	150	100	350
F5	100	150	125	375
F6	100	150	150	400

3.4. Trial 3 (EC: POLYOX WSR-303):

In this trial the bottom layer was prepared by hydrophobic polymer ethyl cellulose and upper layer is hydrophilic polymer Polyox 303

Table No.4: Composition of core-in-cup tablet (F7-F9):

Formulation		Coating material		
Batch code	Core tablet Weight(mg)	Coating material In cup shape (Ethyl cellulose)	Coating material In upper layer (Polyox 303)	Total
F4	100	150	100	350
F5	100	150	125	375
F6	100	150	150	400

4. EVALUATION OF PRESS COATED TABLETS:

4.1. Thickness:

Thickness of tablets was determined using Vernier caliper. Five tablets from batch were used and average values were calculated.

4.2. Average Weight:

To determine average weight, each tablet from formulation was weighed using an electronic balance.

4.3. Hardness:

The hardness was tested using Monsanto tester. The force is measured in kilograms/cm².

4.4. Uniformity of Content:

The tablet from each batch was powdered individually and a quantity equivalent to 40 mg of valsartan was accurately weighed and dissolved in a suitable volume of 6.8 pH phosphate buffer. After making suitable dilutions the final solution was analyzed spectrophotometrically at λ max of drug.

4.5. Friability:

For each formulation, the friability of 6 tablets was determined by using the *Roche friabilator*.

4.6. In-Vitro Drug Release Studies:

In-vitro drug testing of the core tablets was carried out using a USP Type II (rotating paddle) dissolution apparatus at $37 \pm 0.5^\circ\text{C}$ in 900 mL phosphate buffer (pH 6.8) and a stirring rate of 50 rpm. The in-vitro release studies for core-in-cup of valsartan tablets were carried out using USP Type II (rotating paddle) dissolution apparatus in 900 mL of 0.1N HCl (pH 1.2) for 2h, followed by 900 mL of phosphate buffer (pH 6.8). The study was performed at $37 \pm 0.5^\circ\text{C}$ at a stirring rate of 50 rpm. At different time intervals, 2 mL sample was withdrawn, filtered through a Whatman filter paper no. 41 and analyzed at 248 nm. Each withdrawn sample was compensated with 2 mL of the fresh corresponding medium.

4.7. Stability Study:

After determining the drug content, the optimized batches of tablet were monitored up to 1 month at accelerated stability conditions of temperature and relative humidity ($40 \pm 2^\circ\text{C}$ and $75\% \pm 5\%$ RH). Samples were withdrawn after one month and characterized for appearance, weigh variation,

thickness, hardness, drug content and *in-vitro* drug release. The choice of appropriate storage condition during accelerated stability study is necessary to predict the long-term stability of valsartan core-in-cup tablet. The humidity during storage is also extremely important, considering the hygroscopic nature of hydrophilic polymers.

5. RESULTS AND DISCUSSION:

5.1 Pre-compression Parameters of Core Tablets:

The results of angle of repose, bulk density, tapped density and compressibility index indicates that powder blend has passable flow property with good compressibility and suitable for direct compression method.

Table No.5: Pre-compression parameters of core tablets.

Batch code	Bulk density	Tapped density	Hausner's ratio	Compressibility Index	Angle of Repose
C1	0.506±0.013	0.625±0.01	1.23 ±0.03	19.04±2.16	24.07±0.87
C2	0.484±0.007	0.585±0.018	1.20 ±0.04	20.86±2.80	24.41±1.15
C3	0.464±0.006	0.592±0.020	1.27 ±0.02	21.62±3.52	23.98±0.28
C4	0.457±0.011	0.579±0.009	1.26 ±0.01	21.07±0.98	23.76±0.28
C5	0.502±0.015	0.597±0.010	1.18 ±0.04	15.91±2.24	24.63±0.49

Bulk & tapped density was found to be between 0.484-0.506, 0.579-0.625 respectively. Hausner's ratio in between 1.18-1.27, which shows good flow property of powder. Compressibility index also shows good flow of powder. Angle of repose in between 23.76-24.63, which shows excellent flow property.

5.2 Characterization of Valsartan Core Tablet:

The core tablets were subjected for weight variation, diameter, thickness, hardness friability and percentage drug contents were found to be within acceptable limit.

Table No.6: Characterization of valsartan core table:

Batch Code	Weight Variation (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Drug Content (%)
C1	99.58±0.35	6.02±0.007	2.94±0.005	4.50±0.50	0.350±0.051	99.56±0.68
C2	99.60±0.36	6.02±0.011	2.96±0.016	4.33±0.03	0.361±0.031	98.80±0.72
C3	99.70±0.31	6.01±0.015	2.91±0.014	4.00±0.00	0.328±0.039	98.33±0.11
C4	99.70±0.31	6.01±0.011	2.92±0.008	4.00±0.50	0.348±0.042	98.26±0.30
C5	99.61±0.39	6.02±0.008	2.90±0.008	3.83±0.23	0.308±0.045	98.93±0.30

5.3 Disintegration Time:

Press coated tablet gives a burst release after predetermined lag time. For this core tablets must have least possible disintegration time. Hence, superdisintegrant was tried at different concentration ranges and subjected to disintegration test.

Table no.7 Batch Code

Batch Code	Disintegration time (sec)
C1	128
C2	120
C3	105
C4	90
C5	80

5.4. In-Vitro Dissolution of Valsartan Core Tablets:

The effect of croscarmellose sodium (C1-C4) level on drug release profile from uncoated tablet was determined. It was found that formulation containing highest amount of croscarmellose sodium (C4) showed fast disintegration and drug release 97% in one hour.

Table No.8: Percentage drug release from valsartan core tablet (cross carmellose sodium C1-C5) (n=3)

Time in min	C1	C2	C3	C4	C5
2	31.13±0.56	31.53±0.55	33.51±0.67	37.87±0.57	38.67±0.59
4	32.67±0.62	33.47±0.54	35.47±0.75	45.43±0.60	48.43±0.60
6	34.61±0.64	36.21±0.60	35.47±0.75	50.69±0.62	55.34±0.59
8	36.18±0.67	38.59±0.56	42.23±0.74	53.63±0.63	59.32±0.62
10	40.54±0.72	44.16±0.68	46.65±0.57	57.38±0.64	63.11±0.61
15	46.13±0.74	49.40±0.67	50.72±0.76	59.58±0.59	67.22±0.63
20	47.81±0.76	51.51±0.74	53.25±0.67	62.20±0.67	69.76±0.65
30	50.69±0.78	54.04±0.74	56.19±0.63	64.83±0.61	72.34±0.63
40	56.07±0.80	59.06±0.69	65.08±0.64	68.45±0.63	78.64±0.64
50	60.50±0.84	59.06±0.69	68.04±0.63	75.78±0.60	89.03±0.62
60	67.08±0.86	69.05±0.76	73.67±0.64	80.78±0.62	97.56±0.63

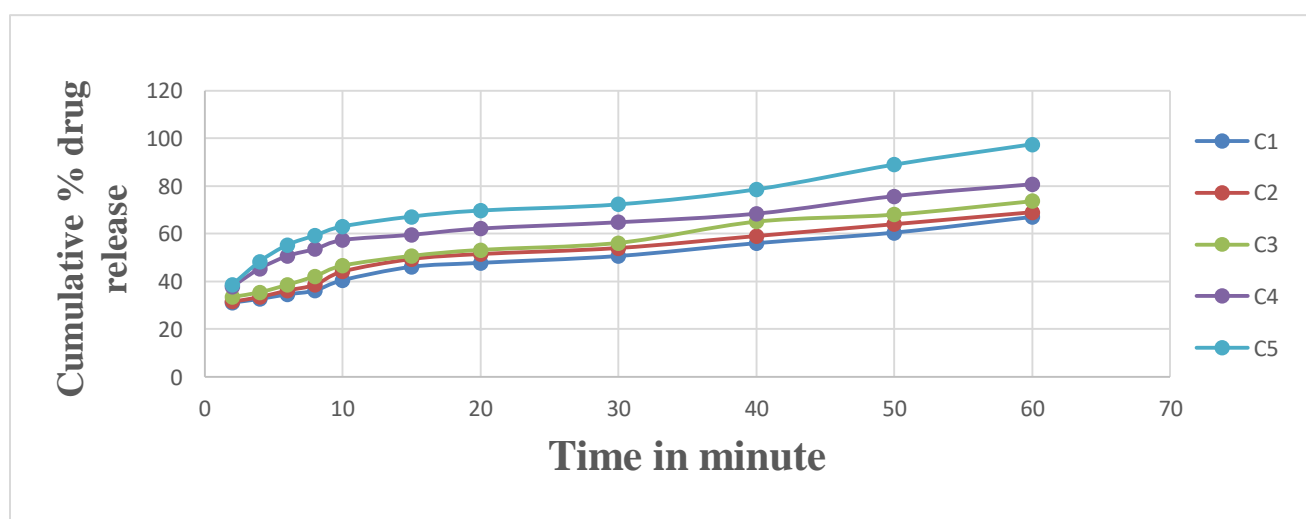


Figure No.1: Dissolution profile of core tablet (C1-C5).

**5.5. Evaluation of Press Coated Tablets (By impermeable cup shaped method):
Trial 1 to 3**

Table No.9: Evaluation of press coated tablets

Formulation	Weight Variation (mg)	Diameter(mm)	Thickness (mm)	Hardness(kg/cm ²)	Friability	% Drug content
F1	349.58±0.35	10.02±0.007	5.0±0.04	4.7±0.2	0.50±0.14	99.32±0.1
F2	374.68±0.36	10.02±0.011	4.9±0.03	4.5±0.1	0.54±0.11	98.45±0.2
F3	399.47±0.31	10.01±0.015	4.8±0.03	4.4±0.3	0.52±0.13	98.66±0.1
F4	349.70±0.31	10.00±0.011	5.0±0.04	4.5±0.2	0.54±0.14	99.89±0.1
F5	374.43±0.32	10.03±0.006	4.9±0.01	4.6±0.4	0.51±0.11	99.30±0.3
F6	399.55±0.34	10.01±0.012	4.8±0.11	4.3±0.5	0.53±0.12	99.23±0.2
F7	349.01±0.59	10.02±0.022	4.9±0.01	4.5±0.3	0.52±0.14	98.33±0.4
F8	374.82±0.62	10.01±0.014	5.0±0.01	4.4±0.2	0.52±0.12	99.44±0.2
F9	399.43±0.78	10.02±0.018	5.0±0.01	4.5±0.1	0.5±0.10	99.68±0.1

The data obtained from post-compression parameter such as weight variation, hardness, friability, and drug content are shown in Table No.25. Weight variation was found to be within USP limit. In all formulation, the hardness test indicates good mechanical strength. Hardness was ranged from 4.3-4.7 Kg/cm². Friability was ranged from 0.54-0.50 Friability is less than 1% which indicate that tablets had good mechanical resistance. The diameter was found to be within the range 10.01-10.03 mm. Drug content was observed within the range 98-99%.
5.6. In-vitro drug Release Studies: Trial 1 (EC: L-HPC):

Table No.10:Percentage drug release of Batch F1-F3 (n=3)

Time in Hr.	% Release of Individual Batch		
	F1	F2	F3
1	0	0	0
2	18.67±0.65	0	0
3	33.46±0.49	24.79±0.78	0
4	55.78±0.56	43.71±0.64	59.03±0.82
5	69.34±0.60	87.02±0.65	80.98±0.78
6	86.57±0.72	91.21±0.73	87.02±0.65
7	98.28±0.65	95.34±0.68	96.80±0.62

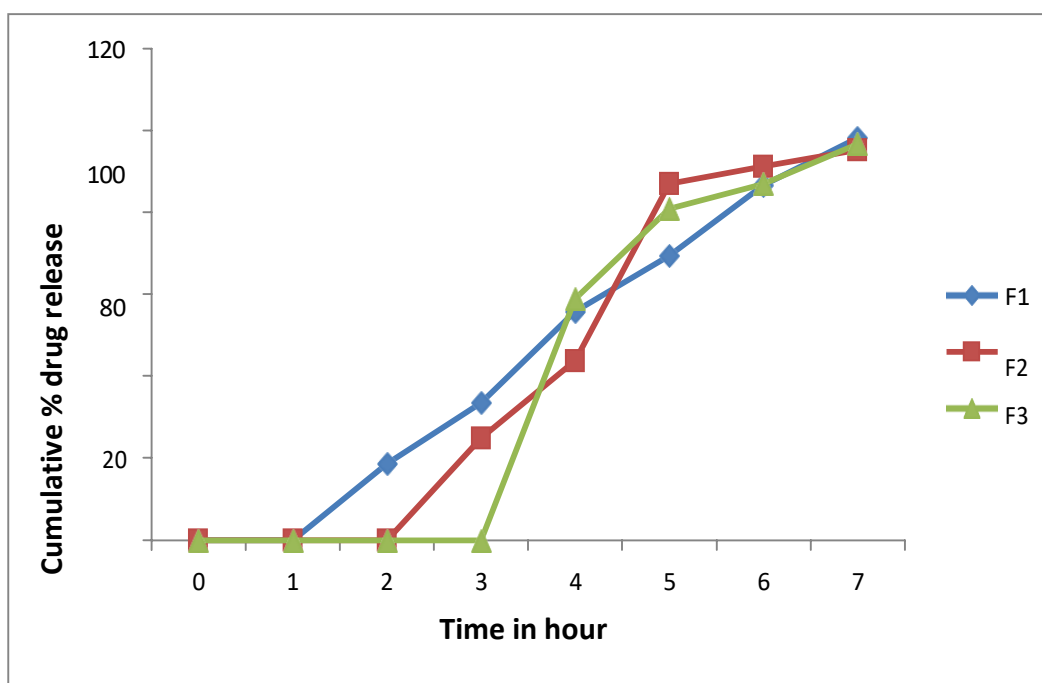
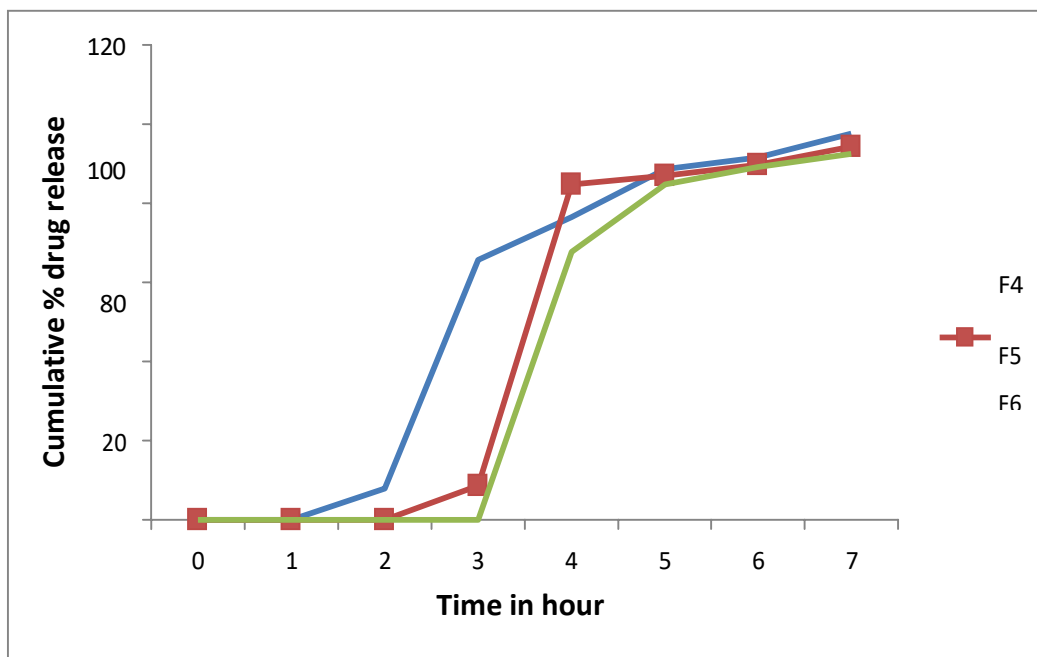


Figure No.2: Dissolution profile of batch F1-F3

In this upper layer of tablet contain L-HPC and rest portion of tablet was made up of Ethyl cellulose. In contacts with dissolution media L-HPC get eroded slowly. This cause's dissolution media to enter into core tablet resulting in bursting of tablet due to pressure develop by super disintegrant. It showed that lag time increases with increasing concentration of L-HPC. Hence, we can say that lag time is directly proportional to the thickness of top layer.

Trial 2 (EC: POLYOX 301)**Table No.11:Percentage drug release of Batch F4-F6(n=3)**

Time in Hr.	% Release of Individual Batch		
	F4	F5	F6
1	0	0	0
2	7.89±0.67	0	0
3	65.69±0.76	8.53±0.68	0
4	76.45±0.75	84.78±0.79	67.63±0.69
5	88.56±0.63	86.91±0.74	84.64±0.79
6	91.45±0.48	89.67±0.84	89.14±0.67
7	97.58±0.59	94.34±0.42	92.34±0.82

**Figure No.3:Dissolution profile of batch F4-F6**

After observation we can say that polyox 301 is good but not best to give required lag time. In this upper layer of tablet containing polyox 301 and due to erodible nature of polyox 301 in contacts with dissolution media it gets eroded slowly from top layer. This causes dissolution media to enter into core tablet resulting in bursting of tablet due to development of pressure by superdisintegrant, it showed lag

time of 3 hr. It showed that lag time increases with increasing concentration of polyox 301.

Trial:3 (EC: POLYOX 303)

Table No.12: Percentage drug release of Batch F7-F9 (n=3)

	% Release of Individual Batch		
	F7	F8	F9
1	0	0	0
2	0	0	0
3	24.79±0.59	0	0
4	43.71±0.78	49.03±0.87	0
5	84.02±0.92	78.98±0.72	0
6	89.21±0.68	90.02±0.56	12.055±0.67
7	92.34±0.84	94.80±0.65	98.255±0.84

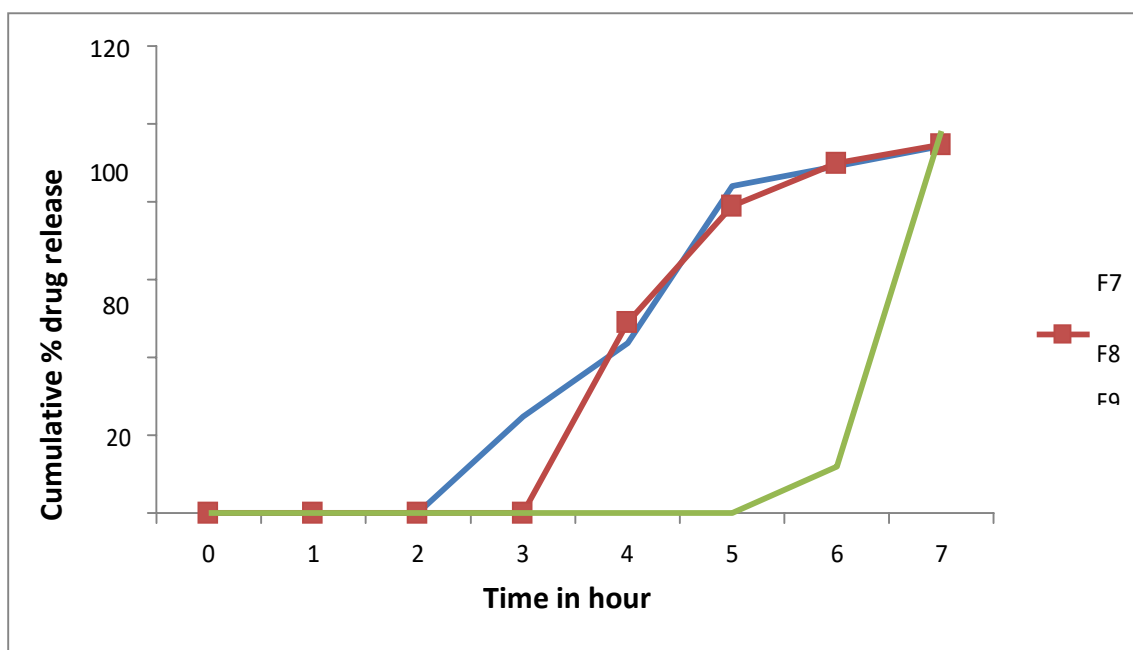


Figure No.4: Dissolution profile of batch F7-F9.

After observation of unsatisfactory result of polyox 301 we can proceed for higher grade of polyox 303. Which showed lag time of 5 hr. in this upper layer of tablet containing Polyox 303 and due

to swellable nature of polyox 303 in contacts with dissolution media it get swelled slowly from top layer. This cause's dissolution media gets enter into core tablet due to development of pressure by superdisintegrant resulting in bursting of tablet. It showed that lag time increases with increasing concentration of polyox 303.

5.7. Comparison between F3, F6 and F9:

Table No.13: Comparison between F3, F6 & F9

Time in Hrs	% Release of Individual Batch		
	F3	F6	F9
1	0	0	0
2	0	0	0
3	0	0	0
4	59.03±0.82	67.63±0.69	0
5	80.98±0.78	84.64±0.79	0
6	87.02±0.65	89.14±0.67	12.055±0.67
7	96.80±0.62	92.34±0.82	98.255±0.84

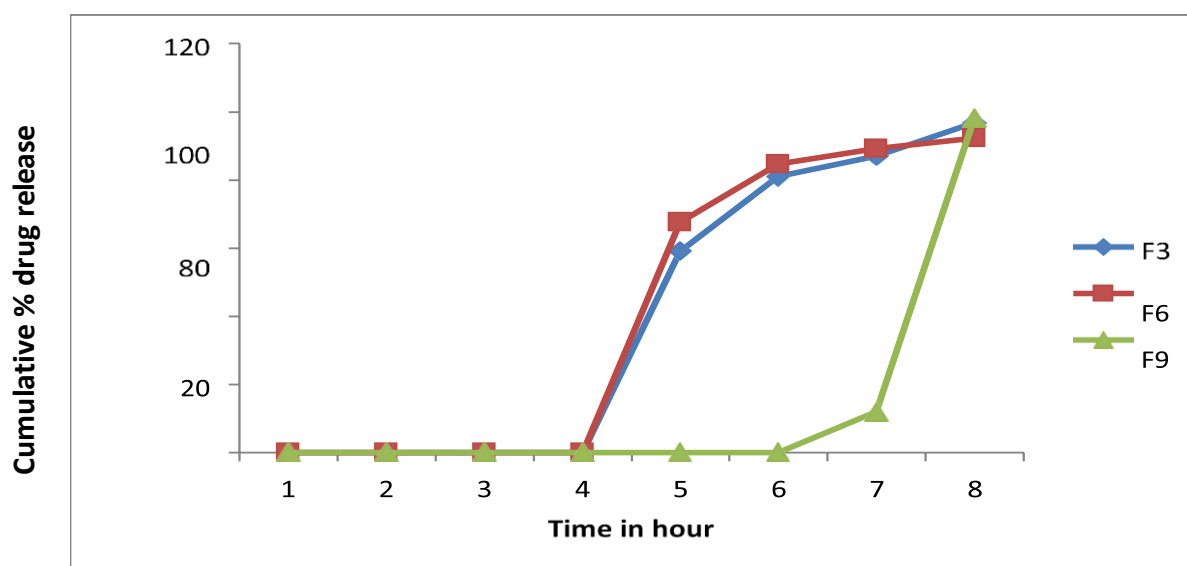


Figure No.5: Dissolution Profile of Comparison between F3, F6, and F9

In batch F3 ethyl cellulose as impermeable cup and L-HPC as top layer. It showed bursting effect at 3 hr. Batch F6 contain hydrophilic polymer polyox 301. Polyox 301 have low molecular weight and erodible in nature. Due to this it gets eroded slowly in contacts with dissolution media & after lag time (3hr.) upper polyox 301 gets removed completely and released drug. Batch F9 showed slow release because it contains high media, due to high molecular weight it requires more pressure to bust the outer layer and releases drug after lag time.

5.8. In-vitro release Kinetics and Mechanism:

To know the release mechanism and kinetics of optimized formulations (F9) were attempted to fit into mathematical models and n , R^2 values for zero order, first order, matrix, Korsmeyer-Peppas and Hixon- Crowel models were represented in Table No.14

Table No.14: In-vitro Drug Release Kinetics of F9 formulation.

Models	R^2 Value	K value
Zero order	0.5611	5.4296
1 st order	0.5217	- 0.2080
Matrix	0.4217	10.3393
Korsmeyer- Peppas	0.7337	0.0000
Hixon- Crowel	0.5329	- 0.0388

Observation of all the R^2 values indicated that the highest R^2 (0.7337) and n (5.5185) values was found for Korsmeyer- Peppas release which are shows in Table No.13 and Figure No.14

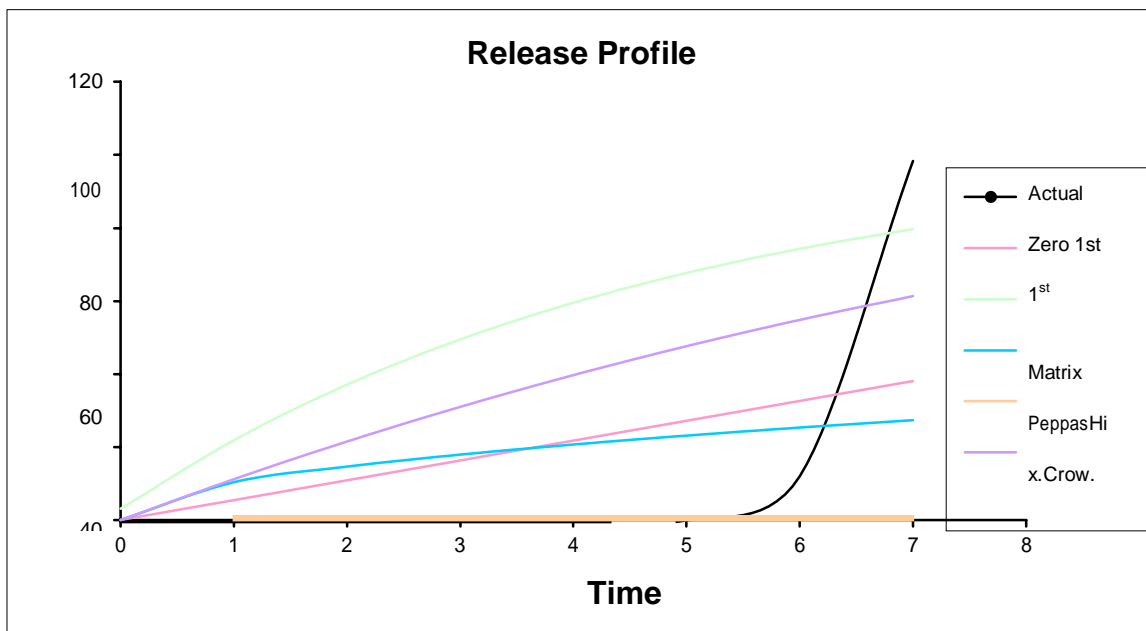


Figure No.6: *In-vitro* Drug Release Kinetics of F9 formulation.

6. DISCUSSION:

Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of the desired effect. This condition demands release of drug as a 'pulse' after a lag time and has to be designed in such a way that a complete and rapid drug release should follow the lag time. Such systems are called as pulsatile drug delivery systems or time-controlled systems.

Hypertension is influenced by circadian rhythm. It rises in the morning on awakening and is maximum during day time activities. Morning may be a factor in the higher incidence of acute attack of hypertension.

7. CONCLUSION:

The present study described the preparation of the valsartan (model drug) core-in-cup pulsatile release tablets based on pulse release pattern intended for chronotherapy in hypertension. By using different polymers with various combinations fails to give desired lag time. Then by various trials, ethyl cellulose and polyethylene oxide show desired lag time. Hydrophilic polymers used were essential for achieving the desired release pattern. The combination of hydrophobic polymer (ethyl cellulose) and hydrophilic polymer (polyethylene oxide) gave optimum release profile by providing initial swelling in

acidic pH followed by a pulse release after specific lag time. From the disintegration test of core tablets, it was concluded that croscarmellose sodium (8%) show least disintegration time. In trial-1 in ethyl cellulose is used as impermeable cup and L-HPC as top layer, it showed lag time of 1-3 hrs which is not desired lag time because of top layer of hydrophilic polymer L-HPC it gets solubilise quickly and exposes tablet. In trial-2 ethyl cellulose and polyox-301, it showed lag time of 1-3 hrs which is not desired lag time because of erodible nature of polyox 301 it gets eroded in contacts with dissolution media. In trial-3 ethyl cellulose and polyox-303, it showed lag time of 2-5 hrs which is desired lag time because of swelling nature of polyox 303 it gets swelled in contacts with dissolution media and after lag time it exposes tablet. In impermeable cup method the concentration of hydrophobic polymer does not affect the release profile after fix concentration however the lag time increases and drug release decreases with increasing concentration of hydrophilic polymer.

REFERENCES:

1. Prajapati BG, Patei GN, Solanki HK. Formulation and Stastical Optimization of Time Controlled Pulsatile Release Propranolol Hydrochloride Compressed Coated Tablet. E-Journal of Scientific Technology.2010; 5:4.
2. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Special Indian Ed., CBS Publisher and Distributors, Mumbai.2009; 171-195, 293-373.
3. Chein YW, Novel Drug Delivery Systems, 2nd Ed., New York, Marcel Dekker, Inc., 1992; 1-134, 139-192.
4. Marikki Halsas, Development and Biopharmaceutical Evaluation of Press-Coated Tablets Taking Account of Circadian Rhythms of Disease, Division of Biopharmaceutics and Pharmacokinetics Department of Pharmacy, University of Helsinki.
5. Survase S, Kumar N, Pulsatile Drug Delivery: Current Scenario, Current Research & Information on Pharmaceutical Sciences. 2007; 8(2): 27-33.
6. Prasanthi NL, Swathi G, Manikiran SS, Chrono therapeutics: A New Vista in Novel Drug Delivery Systems, International Journal of Pharmaceutical Sciences Review and Research, 2011; 6(2): 66-75.
7. Rasve G, Borade G, Deshmukh S, Tagalpallewar A, Pulsatile Drug Delivery System: Current Scenario, International Journal of Pharma and Bio Sciences.2011;2(3):332-343.
8. Ravikumar Reddy J. et al, Review On: Pulsatile Drug Delivery Systems, J.Pharm. Sci. & Res.2009; 1(4): 109-115.

9. Kumar A, Ranga S, Pulsatile Drug Delivery System: Method and Technology Review, International Journal of Drug Development & Research.2012;4(4): 95-107.
10. D'Souza A, Sutar PS, Nadgouda S, Karigar AA, The Use of Chronotherapeutics In Design of Pulsatile Delivery System- A Review, Journal of Pharmaceutical and Scientific Innovation.2012; 50-55.
11. Asija R, Patel J, Asija S, A Novel Approach: Pulsatile Drug Delivery System, International Research Journal of Pharmacy.2012; 3(9):44-49.
12. Parmar RD, Parikh RK, Vidyasagar G, Patel DV, Patel CJ, Patel BD, Pulsatile Drug Delivery Systems: An Overview, International Journal of Pharmaceutical Sciences and Nanotechnology.2009;2(3):605-614.
13. Devdhawala MG, Seth AK, Current Status of Chronotherapeutic Drug Delivery System: An Overview, Journal of Chemical and Pharmaceutical Research. 2003; 2(3):312-328.
14. Patel D, Patel A, Solanki T, Bharadia PD, Pandya VM, Modi DA, Advance in Time Controlled and Site-Specific Drug Delivery, JPI'S Journal of Pharmaceutics and Cosmetology.2011;1(4):31-41.
15. Kalantzi LE, Karavas E, Koutris EX, Bikiaris DN, Recent Advances in Oral Pulsatile Drug Delivery, Recent Patents on Drug Delivery & Formulation.2009; 3(1):49-63.
16. Bose S, Bogner RH, Solventless Pharmaceutical Coating Processes: A Review, Pharmaceutical Development and Technology.2007;12:115-131.
17. Dabhi C, Randale S, Belgamwar V, Gattani S, Tekade A, Predictable Pulsatile Release of Tramadol Hydrochloride for Chronotherapeutics of Arthritis.2010;273-281.
18. Jagdale S, Sali M, Barahate A, Chabukswar A, Design and Evaluation of Enteric Press Coated Tablet for Pulsatile Delivery of Atenolol, International Journal of Pharma Word Research.2010; 1-14.
19. Bhat A, Chowdary K, Shobharani.R, Narasu L, Formulation and Evaluation of Chronopharmaceutical Drug Delivery of Theophylline for Nocturnal Asthma, International Journal of Pharmacy and Pharmaceutical Sciences.2011; 3(2):183-85.
20. Sadaphal K, Thakare V, Gandhi B, Tekade B, Formulation and Evaluation of Pulsatile Drug Delivery System for Chronobiological Disorder: Asthma, International Journal of Drug Delivery.2011;348-356.
21. Bussemerra T, Peppasb NA, Bodmeiera CD, Evaluation of The Swelling, Hydration and Rupturing Properties of The Swelling Layer of a Rupturable Pulsatile Drug Delivery System, European Journal of Pharmaceutics and Biopharmaceutics.2003; 56:261-70.

22. Janugade B, Patil S, Patil S, Lade P, Formulation and Evaluation of Press-Coated Montelukast Sodium Tablets for Pulsatile Drug Delivery System, International Journal of Chemtech Research.2009;1(3):690-91.
23. Moon A, Kondawar M, Shah R, Formulation and Evaluation of Press-Coated Indomethacin Tablets for Pulsatile Drug Delivery System, Journal of Pharmacy Research.2011;4(3): 564-66.
24. Kulkarni P, Jaiswal M, Jawale S, Shirolkar S, Kasture P, Development and Evaluation of Press Coated Tablets for Chronopharmaceutical Drug Delivery Using Gellable and Permeable Polymers, Scholars Research Library.2010;2(4):482-97.
25. Rasve G, Borade G, Deshmukh S, Tagalpallewar A, Pulsatile Drug Delivery System: Current Scenario, International Journal of Pharma and Bio Sciences.2011;2(3):332-43.
26. Monica R, Gajanan P, Borate S, Ranpise A, Mandage Y, Design Evaluation and Comparative Study of Pulsatile Release from Tablet and Capsule Dosage Forms, Iranian Journal of Pharmaceutical Sciences.2009;5(3):119-28.
27. Agrawal SS, Dadarwal S, Madan M, Formulation and *In-Vitro* Characterization of Chronopharmaceutical Drug Delivery System of Metoprolol Tartrate Using Hydroxypropyl Cellulose, Journal of Chronotherapy and Drug Delivery.2011; 2(2):95-101.
28. Efentakis M, Koligliati S, Vlachou M, Design and Evaluation of a Dry Coated Drug Delivery System with An Impermeable Cup, Swellable Top Layer and Pulsatile Release, International Journal of Pharmaceutics.2006;311:147-156.
29. Fan T, Wei S, Yan W, Chen D, An Investigation of Pulsatile Release Tablets with Ethylcellulose and Eudragit L as Film Coating Materials and Cross-Linked Polyvinyl pyrrolidone In the Core Tablets, J. Control. Release.2001;245-251.
30. Rane A, Gattani S, Kadam V, Tekade A, Formulation and Evaluation of Press Coated Tablets for Pulsatile Drug Delivery Using Hydrophilic and Hydrophobic Polymers, Chem. Pharm. Bull.2009; 57(11):1213-217.
31. Baviskar DT, Jain DK, Novel Drug Delivery System, 1st Ed., NiraliPrakashan, India.2012; 11.14-11.27.
32. Usha Yogendra Nayak, Gopal Venkatesh Shavi, Yogendra Nayak, Ranjith Kumar Averinen A, Srinivas Mutalik B, Sreenivasa Meka Reddy A, Purshottam Das Gupta and Nayanabhirama Udupa, Chronotherapeutic drug delivery for early morning surge in blood pressure: A programmable delivery system, Journal of Controlled Release.2009;136: 125-131.

33. Sweetman CS, Martindale: The Complete Drug Reference, 33rd Ed., Pharmaceutical press; London.2002;787,988.
 34. Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins, USA, Vol 2, (2006), 1357.
 35. The Merck Index, By Merck Research Laboratories, 13th Edition, (2001), 9987
 36. <https://www.drugbank.com>.
 37. Indian Pharmacopoeia, Ministry of Health and Family Welfare, Government of India, 6th Ed., Published by The Indian Pharmacopoeia Commission, Ghaziabad, 2010;Vol III:2286-2287.
 38. Efentakis M, Koligliati S, Vlacho M, Design and Evaluation of a Dry Coated Drug Le Release, International Journal of Pharmaceutics.2006; 311:147-156.
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