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Development and Evaluation of Pulsatile Drug Delivery System of Eprosartan Mesylate

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ABSTRACT

The chronopharmacotherapy drug delivery system is widely used for treatment of diseases occurs due to circadian changes in the body. This system is aims to release drugs at a programmed pattern i.e., at appropriate time and/or at appropriate site of action. In this investigation, a novel oral pulsatile drug delivery system (PDDS) based on a core-in-cup dry coated tablet. The core containing eprosartan mesylate as a bioactive compound was prepared by direct compression method and evaluated for thickness, hardness, weight variation and friability. The impermeable coating cup consisted of hydrophobic polymer of cellulose acetate propionate, and the top cover layer of hydrophilic swellable materials (sodium alginate, hydroxypropyl methylcellulose [HPMC] K4M, sodium carboxy methylcellulose) were used in different concentration. The tablets prepared were evaluated for micromeritic properties, hardness, thickness, weight variation, friability, drug content uniformity and in-vitro drug release study. The drug-excipients study was carried out by using Fourier transform infrared. From the obtained results, it was found that the order of sustaining capacity of pulsatile device is, HPMC K4M >sodium carboxymethyl cellulose >sodium alginate.

Key words: *Pulsatile drug delivery system, Eprosartan mesylate, Direct compression, Ultraviolet, Fourier transform infrared.*

1. INTRODUCTION

Pulsatile drug delivery systems (PDDS) are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. Pulsatile drug delivery systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastrointestinal tract motility, etc. These systems are designed for chronopharmacotherapy, which is based on the circadian rhythm of the body. In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. Control release systems for 12 or 24 h drug release are not suitable for diseases, which follow circadian variation [1-3]. An ideal drug delivery system should be able to deliver an adequate amount of drug for an extended period of time for its optimum therapeutic activity. Most drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. To overcome such problems greater attention has been focused on sustained release drug delivery system [4,5]. Hypertension or congestive heart failure mostly will come after midnight or early in mornings. Hence, it is important to control the blood pressure at that particular time, if not control may lead to increase in blood pressure and finally heart failure, which may causes death also. This can be done by using antihypertensive drugs, which can lower the blood pressure at that time [6]. Eprosartan mesylate (EM) is an antihypertensive drug which is the angiotensin II receptor blockers. It can blocks the angiotensin II receptor in vascular smooth muscles and adrenal gland, producing decrease in blood pressure and avoids vasoconstriction and aldosterone secretion. The effect of drug is essential after some lag time, thus it can be achieved by using the time and pH dependent polymer coating [7,8]. EM (Figure 1), mono-methane sulfonate salt of (E)-2-butyl-1-(p-carboxybenzyl)-α-2-thienylmethylimid-azole-5-acrylic acid, is a non-biphenyl non-tetrazole angiotensin II receptor (AT1) antagonist [9,10].

2. EXPERIMENTAL

2.1. Materials

EM was obtained as gift sample from Life Care Laboratories Pvt. Ltd. Hyderabad; hydroxypropyl

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methylcellulose (HPMC) K4M from Healthcaps India Ltd. Chandigarh, ethyl cellulose and cellulose acetate propionate was obtained from SD Fine Limited, Mumbai. All other solvents and reagents used were of analytical grade.

2.2. Methods

2.2.1. Preformulation study

A. Drug characterization: Characterization of drug was done to check whether the obtained sample is in pure form or not. EM sample was subjected for various tests such as solubility, melting point, ultraviolet (UV), Fourier transform infrared (FTIR) analysis.
B. Polymer characterization: Characterization of polymers were done to check whether the obtained sample is in pure form or not. All polymer samples were subjected for various tests like solubility, melting point, UV, FTIR analysis.
C. Compatibility study: IR spectroscopy was used to determine the molecular interaction between polymer and drug. All physical mixtures and drug sample were mixed with dried KBR in ratio 1.100. Then small fraction of mixture was compressed on automatic IR press at pressure 10 tones to form transparent pellet. Then the IR spectrum of pellet was taken on FTIR spectrophotometer.

2.2.2. Preparation of EM compression coated tablet

Preparation of core tablet: The inner core tablets were prepared by using direct compression method. Powder mixture of EM, sodium starch glycolate, microcrystalline cellulose and lactose ingredients were dry blended for 20 min followed by addition of magnesium stearate. The mixture was then further blended for 10 min; 100 mg of resultant powder blend was manually compressed with 6 mm punch and die to obtain the core tablet (Rimek Mini Press-I).

Preparation of core-in-cup pulsatile tablets by direct compression method: As given in Table 1, an impermeable coating cup consisting of cellulose acetate propionate was applied under the bottom and around the core tablet. The cellulose acetate propionate powder (100 mg) was filled into a die of 10 mm diameter and then gently compacted to make a powder bed with a flat surface. The core tablet was carefully placed in the center of the powder bed; the die was filled with the remaining quantity of coating powder (60 mg) so that the surrounding surfaces of the core tablet were fully covered. On the top, hydrophilic polymer was added and the bed was compressed directly by using 10 mm flat punch (Rimek Mini Press-I), to produce the desired core-in-cup system. The above procedure was repeated by using different hydrophilic sweallable polymer (SA, HPMC K4M, sodium carboxymethyl cellulose [SCMC]) in different concentrations as given in Table 1.

2.3. Evaluation of Pre Compression Parameter of Powder Blend

The flow properties of granules were characterized in terms of angle of repose, Carr index and Hausner's ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner's ratio were calculated.

2.4. Evaluation of Press-coated Tablet

Tablets from all the formulations were evaluated for various properties like hardness, Friability and weight variation.

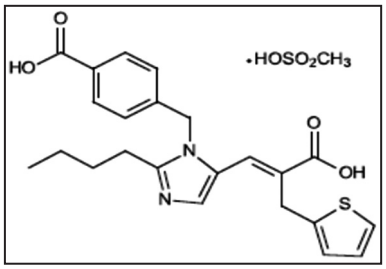

Figure 1: Chemical structure of eprosartan mesylate.

Table 1: Formulation of core-in-cup pulsatile tablets.

Ingrediens (mg)	ESA-1	ESA-2	ESA-3	ESA-4	EHP-1	EHP-2	EHP-3	EHP-4	ESCMC-1	ESCMC-2	ESCMC-3	ESCMC-4
Eprosartan mesylate	50	50	50	50	50	50	50	50	50	50	50	50
Ethyl cellulose	160	160	160	160	160	160	160	160	160	160	160	160
Sodium alginate	30	60	90	120	-	-	-	-	-	-	-	-
HPMC-K4M					30	60	90	120	-	-	-	-
SCMC	-	-			-	-	-	-	30	60	90	120
Total	240	270	300	330	240	270	300	330	240	270	300	330

EM: Eprosartan mesylate, CMC: Carboxymethyl cellulose, HPMC: Hydroxypropyl methylcellulose

2.5. Evaluation of Pre Compression Parameter for both Core and Coat Material

2.5.1. Bulk density

A volume of 250 ml of measuring cylinder was taken and 100 g of powder of all batches were weighed and passed through the sieves and filled into the cylinder and their volumes were noted down and bulk density was calculated. The formula used for calculation is as follow.

Bulk density = Mass/volume

2.5.2. Tapped density

250 ml of the measuring cylinder was taken and 100 g of the powder of all batches were weighed and filled into the cylinder, volume of powder measured and noted then that cylinder was tapped about 300 times and again volume of powder measured and tapped density of powder calculated by following formula.

Tapped density = Mass of powder/tapped volume

2.5.3. Carr's index

Carr's index of the powder was determined for determination of flow of the powder, for the calculation of Carr's index it requires tapped density and bulk density. Formula for the calculation of the Carr's index is given below:

Carr's index = (tapped density − bulk density/tapped density) × 100

2.5.4. Hausner's ratio

Hausner's ratio gives information about flow ability of the powder, for the determination of the Hausner's ratio it requires tapped density and bulk density.

Hausner's ratio = tapped density/bulk density

2.5.5. Angle of repose

Angle of repose was determined according to USP 2007 method, funnel was taken and it is fixed at 1 cm height on the stand. One cotton was placed at the orifice of the funnel and on that cotton a constant powder weight was placed. The cotton was removed and the diameter formed by powder and height formed by the pile of the powder was measured and angle of repose was calculated from the following formula.

$\tan^{-1} [\theta] = h/r$

Where h = height formed by the pile of the powder and R = diameter formed by powder.

2.6. Evaluation of Core Tablet and Compression Coated Tablet of EM

2.6.1. Friability testing

20 tablets were taken, it is weighed and initial weight was noted then it was placed into the Roche friabilator and test was performed for 4 min by using 25 rpm after that tablets were weighed and friability was calculated by using following formula.

% loss = (Final weight of tablets – Initial weight of tablets/Initial weight of tablets) × 100

2.6.2. Weight variation

20 tablets were selected randomly and average weight was calculated, not more than 2 tablets from this average weight should not be deviate shown in Table 4. The test was performed According to the Indian Pharmacopoeia 2010 and results were recorded in table 15 and 18. Weight variation was calculated by using following formula.

% weight variation = (Weight of single tablet – Average weight of tablet/Average weight of tablet) × 100

2.6.3. Hardness testing

The crushing strength kg/cm^2 of prepared tablets was determined for tablets by using Monsanto hardness tester. A tablet is placed between the anvils and the crushing strength, which causes the tablet to break, is recorded. Average of three readings was taken and results were tabulated.

2.6.4. Diameter and thickness of core tablet

The diameter and thickness of core tablet were measured by using Vernier caliper.

2.6.5. Disintegration test for core tablet of EM

Disintegration test on core tablet of EM was performed by using distilled water as media. 6 core tablets of EM were taken and placed in 6 respective tubes of disintegration apparatus and disintegration time of core tablet was measured.

2.6.6. Dissolution testing of core tablet of EM

Dissolution testing of core tablet of EM was performed by using pH 6.8 phosphate buffers and 0.35% w/v Tween 20 as dissolution medium. Dissolution study was carried out for about 30 min. at 37°C and 50 rpm by using USP Type II apparatus. 5 ml sample were removed from dissolution medium at every 5 min. and its absorbance was checked by using UV (Systronics India Limited UV-Vis Spectrometer-2203).

2.7. In vitro Dissolution Testing of Compression Coated Tablet of EM in Phosphate Buffer pH 1.2, 6.8, and 7.4

Dissolution testing was carried out by using USP Type II dissolution apparatus [Lab India]. Dissolution medium used for the testing were 500 ml phosphate buffer pH 1.2, pH 6.8, pH 7.4 each. Compression coated tablet was placed in pH 1.2 phosphate buffer for 2 h because gastric emptying time is 2 h, then that medium was replaced with pH 6.8 phosphate

buffer and testing carried out for 3 h because intestinal emptying time is 3 h, after that pH 6.8 was replaced by using pH 7.4 phosphate buffer and testing carried out. Samples of 5 ml were withdrawn after every hour, filtered with Whatman's filter paper and replaced with 5 ml of fresh dissolution medium. The Temperature condition used for dissolution testing was 37.5±0.5°C. The rotation speed was kept at 50 rpm for dissolution testing. Each sample was tested for its absorbance at 233 nm by using UV spectrophotometer.

Assay of the EM compression coated tablet: Ten tablets were weighed and powdered. An amount of powder equivalent to 8 mg of EM was dissolved in 100 ml of phosphate buffer [pH 6.8]. It was shaken by mechanical means for 1 h. Then it was filtered through a Whatsman filter paper. From this resulted solution 1 ml was taken, diluted to 100 ml with phosphate buffer of pH 6.8 and absorbance was measured against blank at 234 nm using UV-Visible spectrophotometer. From the absorbance values, amount of drug present in the given tablet was calculated using calibration curve. Procedure was repeated by using two or more tablets from the same formulation and the average value of all three tablets were calculated.

Stability study: Stability of a drug has been defined as the ability of a particular formulation in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The best formulation was kept for stability study in stability chamber for period of 3 months at temperature 45±2°C and RH 75±5%.

3. RESULTS AND DISCUSSION

3. 1. Preformulation Study

Preformulation study of EM drug was carried out (Table 2):

Identification of pure drug: The IR spectrum of the pure drug was to be similar to the standard spectrum of EM (Figure 4).

Solubility study: Sparingly soluble in methanol, practically insoluble in water.

Melting point determination: Melting point of EM was found to be in the range of 248-250°C with decomposition as reported in pharmacopoeia, thus indicating the purity of the drug sample.

Compatibility study: From the spectra of pure drug and combination of drug with polymers, it was observed that all characteristic peaks of EM were present in the combination spectrum, thus indicating compatibility of the drug and polymer. IR spectra of pure drug EM, polymers sodium alginate, HPMC K4M, and SCMC and also the combination of EM and polymers are shown in IR spectrum Figures 5-7.

3.2. Evaluation of EM

Standard calibration curve of EM: Calibration curve for the estimation of EM was constructed in methanol and 7.4 pH buffer at 233 nm. The method obeyed Beer's Lambert law in a range of 2-22 mcg/ml. As shown in Table 3 and Figures 2 and 3.

3.3. Evaluation of EM Powder and Core Tablet

Pre-compression parameters: Powder ready for compression containing drug and various excipients

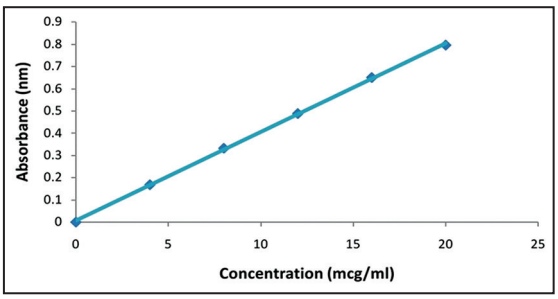

Figure 2: Standard calibration curve of eprosartan mesylate in methanol (λ_{max} 233 nm).

Table 2: Preformulation study of EM.

Parameter	Observation	Standard
Solubility study of EM	Practically insoluble in water, sparingly soluble in methanol	Practically insoluble in water, sparingly soluble in methanol
Loss of drying	0.3%	NMT 0.5%
λ_{max} of EM	234 nm	233 nm
Melting point of EM	248-251°C	250°C

EM: Eprosartan mesylate

Table 3: Standard calibration data of EM in methanol and in pH 7.4 buffer.

Concentration (mcg/ml)	Absorbance (mm) (methanol)	Absorbance (nm) (pH 7.4 buffer)
0.000	0.000	0.000
4.000	0.168	0.144
8.000	0.332	0.318
12.000	0.488	0.455
16.000	0.650	0.609
20.000	0.796	0.759

EM: Eprosartan mesylate

were subjected for pre-compression parameters (Micrometric properties) to study the flow properties of granules, to achieve uniformity of tablet weight. The results of all the pre-formulation parameters are given in Tables 4 and 5.

Post-compression parameters: Powder ready for compression containing drug and various excipients were subjected for post-compression parameters to study the hardness, thickness, friability test, weight variation and drug content uniformity of tablets. The results of all the pre-formulation parameters are given in Tables 4 and 6.

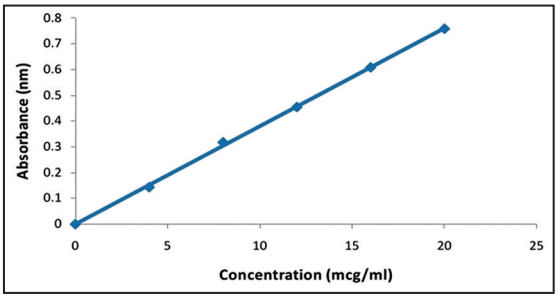

Figure 3: Standard calibration curve of eprosartan mesylate in pH 7.4 buffer.

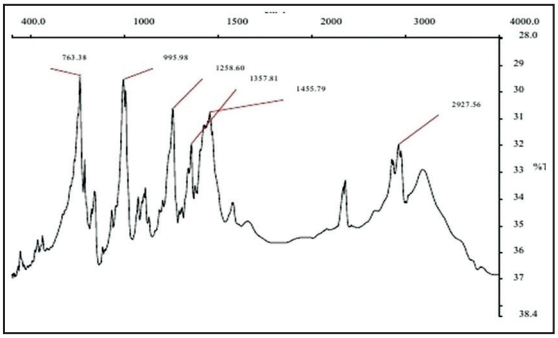

Figure 4: Infrared spectrum of pure eprosartan mesylate.

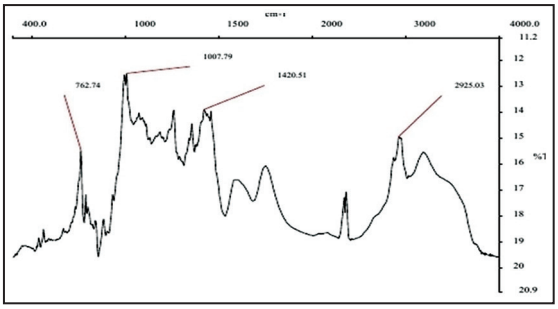

Figure 5: Infrared spectrum of eprosartan mesylate+CAP+SA.

3.4. Evaluation of In-vitro Drug Release of Prepared Pulsatile Tablet

The formulation was subjected *in vitro* study using USP paddle type-II apparatus (DR-6, dissolution test apparatus) at 100 rpm and 37±0.5. Phosphate buffer (pH 7.4) was used as the dissolution medium. The study was carried out in triplicate. Cumulative drug released was calculated for different time intervals of sample withdrawn. Cumulative % drug release and % drug remained were then calculated. The result obtained in the *in vitro* dissolution studies for all the formulations are reported in Tables 7-9.

3.5. IR - Studies

From the spectra of pure drug and the combination of the drug with polymers, it was observed that

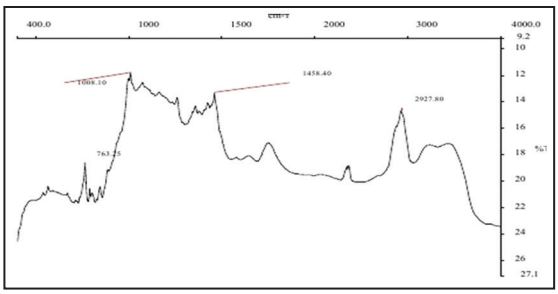

Figure 6: Infrared spectrum of eprosartan mesylate+CAP+hydroxypropyl methylcellulose K4M.

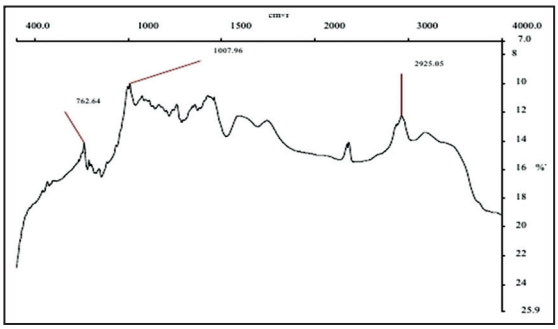

Figure 7: Infrared spectrum of eprosartan mesylate+CAP+sodium carboxymethyl cellulose.

Table 4: Pre-compression and post-compression parameters.

Pre-compression parameter	Observation	Post-compression parameter	Observation
Angle of repose (θ)	240	Thickness*	2.32±0.45 mm
Loose bulk density	0.416±0.15 g/cm^3	Hardness*	2.50±0.25 kg/cm^2
Tapped bulk density	0.454±0.20 g/cm^3	Average weight	49.16±0.47 mg
Compressibility index (%)	8.338±0.58	Friability	0.741±0.78

*Average of three replicates

Table 5: Pre-compression parameters for core-in-cup tablets.

Formulation (degree) code	Bulk density* (g/cc) SD	Tapped density (g/cc) SD	Angle of repose* SD	Carr's index* (%) SD
ESA-1	0.5434±0.10	0.6341±0.02	25.28±1.23	14.3037±1.58
ESA-2	0.5212±0.02	0.6294±0.01	27.20±1.41	17.1909±1.22
ESA-3	0.5137±0.07	0.6098±0.01	25.14±0.57	15.7592±0.63
ESA-4	0.5098±0.01	0.5998±0.02	24.19±0.69	15.0050±0.58L
HP-1	0.5438±0.09	0.6401±0.02	26.41±1.20	15.044±0.60L
HP-2	0.5345±0.15	0.6296±0.03	28.56±1.55	15.1048±0.75L
HP-3	0.5121±0.02	0.6210±0.02	25.71±1.42	17.5362±1.23L
HP-4	0.5342±0.13	0.6408±0.01	26.38±1.35	16.6354±0.67
ESCMC-1	0.5088±0.01	0.5941±0.01	26.01±0.13	14.3578±1.51
ESCMC-2	0.5147±0.02	0.6091±0.02	27.01±1.21	15.4982±1.59
ESCMC-3	0.5218±0.03	0.6218±0.02	25.08±1.07	16.0823±1.19
ESCMC-4	0.5401±0.04	0.6387±0.02	28.46±1.26	15.4376±1.08

*Average of three replicates. SD: Standard deviation, CMC: Carboxymethyl cellulose

Table 6: Post-compression parameters for core-in-cup tablets.

Formulation code	Hardness (kg/mg^2) SD	Thickness (mm) SD	Friability (%) SD	Weight variation SD	Drug content (%) SD
ESA-1	5.50	3.32±0.04	0.72±0.08	241.5±13	97.56±2.03
ESA-2	5.60	4.81±0.03	0.74±0.07	273.5±0.6	98.67±1.8
ESA-3	6.50	5.25±0.08	0.74±0.08	299±0.07	97.67±23
ESA-4	6.51	5.81±0.03	0.75±0.07	332±0.08	99.01±0.09
EHP-1	6.00	4.12±0.04	0.73±0.09	243±0.05	97.78±1.18
EHP-2	5.50	4.35±0.07	0.73±0.02	268.4±0.06	98.89±1.06
EHP-3	8.00	5.22±0.03	0.77±0.04	301.8±0.07	99.01±0.25
EHP-4	8.50	5.83±0.09	0.79±0.01	332.4±0.7	97.23±1.25
ESCMC-1	4.50	4.10±0.09	0.69±0.09	242±0.08	97.99±1.89
ESCMC-2	4.50	4.35±0.07	0.68±0.07	271.5±0.6	97.98±1.06
ESCMC-3	5.50	5.32±0.03	0.75±0.08	310±0.07	98.89±1.06
ESCMC-4	6.59	5.83±0.09	0.83±0.07	335±0.08	99.01±0.25

SD: Standard deviation, CMC: Carboxymethyl cellulose

all the characteristic peak of EM were present in the combination spectrum, thus indicating the compatibility of the drug and polymer.

4. CONCLUSION

The data obtained from the study of "Formulation and evaluation of EM pulsatile drug delivery system for effective treatment of hypertension" reveals following conclusion: Pulsatile Tablets of EM were successfully prepared by direct compression method. FTIR spectrums of physically mixture of EM and polymer revealed that the drug and polymers were satisfactorily compatible without any significant change in the chemical nature of the drug. The quantity of material in the top layer, polymer characteristics and drug solubility are important factors in controlling the lag time and drug release. The lag time increases by increasing the quantity of the hydrophilic top cover layer. In contrast, drug release was found to decrease. Thus, it was concluded that the erodible polymeric material as a top layer, regulate the performance of the system. The polymers contained in the top layer reported considerable differences. HPMC K4M exhibited the greatest top layer swelling, maximum gel thickness and lag time from the system. SCMC showed an intermediate behavior while SA, with the smallest swelling and gel thickness as well as the shortest lag time which exhibits much faster release i.e., HPMC K4M > SCMC > sodium alginate. On the basis of drug content, IR study, *in vitro* drug release study and its kinetic release data, EHP-4 was

Table 7: *In-vitro* release profile of ESA-1, 2, 3, 4 containing 30, 60, 90,120 mg sodium alginate.

Time (T) log time h	Cum% drug release ±SD			
	ESA-1	ESA-2	ESA-3	ESA-4
0	0	0	0	0
1.0	0.00	0.00	0.00	0.00
2.0	7.0±0.03	0.00	0.00	0.00
3.0	21.58±1.13	10.56±0.18	0.00	0.00
4.0	82.42±0.09	25.96±0.98	9.517±0.35	0.00
5.0	89.83±1.17	81.93±0.16	30.42±0.56	12.73±0.65
6.0	95.21±0.12	88.93±0.48	49.06±0.93	27.07±0.87
7.0	97.48±0.89	96.00±0.89	78.67±0.63	43.77±0.54
8.0		97.02±0.79	96.00±1.02	88.27±0.73
9.0			98.04±0.75	95.14±0.42
10.0				97.19±0.24

All values are represented as mean SD (n=3),
SD: Standard deviation

Table 8: *In-vitro* release profile of EHP-1, 2, 3, 4 containing 30, 60, 90,120 mg HPMC K4M.

Time (T) log time h	Cum% drug release ±SD			
	EHP-1	EHP-2	EHP-3	EHP-4
0	0	0	0	0
1.0	0.00	0.00	0.00	0.00
2.0	0.00	0.00	0.00	0.00
3.0	0.00	0.00	0.00	0.00
4.0	8.5±0.26	0.00	0.00	0.00
5.0	19.29±0.82	8.23±0.42	0.00	0.00
6.0	83.81±0.69	28.51±0.57	7.9±0.87	70.00
7.0	94.84±0.74	69.51±0.64	22.49±0.46	6.0±0.52
8.0	96.92±0.12	96.16±0.73	81.93±0.58	17.2±0.36
9.0		97.19±0.79	96.05±0.98	88.39±0.38
10.0			97.08±0.63	95.87±0.96
11.0				97.96±0.88

All values are represented as mean SD (n=3), SD: Standard deviation, HPMC: Hydroxypropyl methylcellulose

selected as an optimized formulation for designing pulsatile device. Hence, finally it was concluded that the prepared pulsatile drug delivery system can be considered as one of the promising formulation technique for chronotherapeutics management of hypertension.

5. ACKNOWLEDGMENTS

The authors reported no conflict of interest. The authors alone are responsible for the content and writing of the paper and no funding has been received on this work. Ethical Approval was not require.

Table 9: *In-vitro* release profile of ESCMC-1, 2, 3, 4 containing 30, 60, 90,120 mg sodium CMC.

Time (T) h	Cum % drug release ±SD			
	ESCMC-1	ESCMC-2	ESCMC-3	ESCMC-1
0	0	0	0	0
1.0	0.00	0.00	0.00	0.00
2.0	0.00	0.00	0.00	0.00
3.0	5.10±0.34	0.00	0.00	0.00
4.0	18.12±0.48	6.817±0.17	0.00	0.00
5.0	46.55±0.64	12.09±0.34	5.0±0.13	0.00
6.0	78.50±0.80	47.83±0.51	26.36±0.62	8.61±0.12
7.0	96.96±0.96	87.96±0.85	46.36±0.39	18.21±0.25
8.0	97.70±1.12	95.32±0.19	85.21±0.52	84.01±0.97
9.0		96.37±0.38	94.94±0.65	94.44±0.93
10.0			95.97±0.78	95.48±0.45
11.0				96.51±0.38

All values are represented as mean SD (n=3).
SD: Standard deviation, CMC: Carboxymethyl cellulose

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