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DESIGN, DEVELOPMENT AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF EPROSARTAN MESYLATE FOR CHRONOPHARMACOTHERAPHY

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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 based on a core-in-cup dry coated tablet, where a core tablet surrounded on the bottom and circumference wall with inactive material. The system consists of three parts, a core tablet, containing the active ingredient, an impermeable outer shell and top cover layer of hydrophilic polymer. 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, 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 FT-IR. From the obtained results, it was found that the order of sustaining capacity of pulsatile device is, HPMC K4M > Sodium CMC > Sodium alginate.

KEYWORDS

Pulsatile drug delivery system, Eprosartan Mesylate, HPMC K4M, EC and Compression coating.

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INTRODUCTION

Pulsatile Drug delivery systems 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, GIT 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 hr 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 Comes after midnight or early in mornings. So 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 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]. Eprosartan Mesylate (EM) (Figure No.2), 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].

MATERIALS

Eprosartan Mesylate was obtained as gift sample from Life Care Laboratories Pvt. Ltd. Hyderabad; 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.

METHODS

Preformulation Study[14]

Drug Characterization

Characterization of drug was done to check whether the obtained sample is in pure form or not. Eprosartan Mesylate sample was subjected for various tests like solubility, melting point, UV, FTIR analysis.

Polymer Characterization

Characterization of polymers was 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.

Compatibility Study

Infrared spectra analysis

IR spectroscopy was also 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.

Preparation of Eprosartan Mesylate Compression Coated Tablet

Preparation of Core Tablet

The inner core tablets were prepared by using direct compression method. Powder mixture of Eprosartan Mesylate, sodium starch glycolate, microcrystalline cellulose and lactose ingredients were dry blended for 20 mins. Followed by addition of magnesium stearate. The mixture was then further blended for 10 mins; 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 the table no-, 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 10mm flat punch. (Rimek Mini Press-I), to produce the desired core-in-cup system. The above procedure was repeated by using different hydrophilic swellable polymer (SA, HPMC K4M, SCMC) in different concentrations as given in Table No.1.

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.

Evaluation of Press-Coated Tablet

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

Evaluation of Pre compression Parameter for both core and coat material

Bulk density

250 ml of measuring cylinder was taken and 100 gm 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.

$$\text{Bulk density} = \text{Mass} / \text{volume}$$

Tapped Density

250 ml of the measuring cylinder was taken and 100 gm 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.

a)

b)

$$\text{Tapped density} = \text{Mass of powder} / \text{tapped volume}$$

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.

$$\text{Carr's index} = [\text{tapped density} - \text{bulk density} / \text{tapped density}] \times 100$$

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.

$$\text{Hausner's ratio} = \text{tapped density} / \text{bulk density}$$

Angle of repose

Angle of repose was determined according to USP 2007 method, funnel was taken and it is fixed at 1cm 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

R = diameter formed by powder.

Evaluation of core tablet and compression coated tablet of Eprosartan Mesylate

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.

$$\%\ \text{loss} = [\text{Final wt. of tablets} - \text{Initial wt. of tablets} / \text{Initial wt. of tablets}] \times 100$$

Weight variation

20 tablets were selected randomly and average weight was calculated, nost more than 2 tablets from this average weight should not be deviate shown in table. The test was performed According to the Indian Pharmacopoeia 2010 and results were recorded in Table No.15 and 18. Weight variation was calculated by using following formula.

$$\%\text{weight variation} = [\text{Weight of single tablet} - \text{Average weight of tablet} / \text{Average weight of tablet}] \times 100$$

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.

Diameter and thickness of core tablet

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

Disintegration test for core tablet of Eprosartan Mesylate

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

Dissolution testing of core tablet of Eprosartan Mesylate

Dissolution testing of core tablet of Eprosartan Mesylate was performed by using pH 6.8 phosphate buffers and 0.35% w/v Tween20 as dissolution medium. Dissolution study was carried out for about 30 min. at 370 C and 50 rpm by using USP type II apparatus. 5ml 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).

***In vitro* dissolution testing of compression coated tablet of Eprosartan Mesylate 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 500ml 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 hrs because gastric emptying time is 2 hrs, then that medium was replaced with pH 6.8 phosphate buffer and testing carried out for 3 hrs because intestinal emptying time is 3 hrs, 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 ±0.50 C. The rotation speed was kept at 50rpm for dissolution testing. Each sample was tested for its absorbance at 233 nm by using UV spectrophotometer.

Assay of the Eprosartan Mesylate compression coated tablet

Ten tablets were weighed and powdered. An amount of powder equivalent to 8 mg of Eprosartan Mesylate was dissolved in 100 ml of phosphate buffer [pH 6.8]. It was shaken by mechanical means for 1 hr. Then it was filtered through a whatsman filter paper. From this resulted solution 1ml 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^{0}C and RH 75±5%.

RESULTS AND DISCUSSION

Evaluation of Eprosartan Mesylate

Calibration curve for the estimation of Eprosartan Mesylate was constructed in Methanol and 7.4 pH buffer at 233 nm. The method obeyed Beer's Lambert law in range of 2-22 mcg/ml. as shown in Table No.3 and Figure No.2 and 3.

Pre-Compression Parameters

Powder ready for compression containing drug and various excipients 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 Preformulation parameters are given in Table No.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 Preformulation parameters are given in Table No.4 and 6.

***In-vitro* Drug Release Studies**

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 than calculated. The result obtained in the in vitro dissolution studies for all the formulations are reported in Table No.7 to 9.

Formulations with Sodium alginate

With formulations ESA-1 (30mg), ESA-2 (60mg), ESA-3 (90mg) and ESA-4 (120mg) the lag time was 1hr, 2hr, 3hr and 4hr respectively. And drug release was found 97.48%, 97.02%, 98.04% 97.19% respectively (Table No.7).

Formulation with HPMC

With formulation EHP-1 (30mg), EHP-2 (60mg), EHP-3 (90mg) and EHP-4 (120mg) the lag time was 3hr, 4hr, 5hr, and 6hr respectively. And drug release was found 96.92%, 97.19%, 97.08%, 97.96% respectively (Table No.8).

Formulations with sodium CMC

With formulations ESCMC-1(30 mg), ESCMC-2 (60 mg), ESCMC-3(90mg) and ESCMC-4 (120 mg) the lag time was 2hr, 3hr, 4hr, and 5hr respectively. And drug release was found 97.70%, 96.37%, 95.97%, 96.51% respectively (Table No.9).

In vitro dissolution results elicited that the fast and complete drug release after lag time was observed in all formulations. But maximum lag time (6hr) was observed in formulation EHP-4. Hence EHP-4 was considered as the optimum formulation.

IR Studies

Identification of pure drug

The IR spectrum of pure drug was found to similar to the standard spectrum of Eprosartan Mesylate. The spectrum of Eprosartan Mesylate shows the following functional groups at their frequencies. The drug Eprosartan Mesylate taken is ionic form of potassium salt. Since this compound contains -OH residue can formed sodium salt very easily. The presence of hydroxyl group in the molecule is indicated by the exhibition of strong absorption peak at 3350 cm^{-1} responsible for the presence of -OH functionality in the molecule that drug is combination of aromatic C-H as well as aliphatic C-H which is indicated by the absorption peaks at 320 cm^{-1}, 2930 cm^{-1}, and 2840 cm^{-1}since it contains no. Of C=N absorption peaks at 5020 cm^{-1} and 1455 cm^{-1} indicating that this drug molecule contains C=N moieties. Hence it must be hydrophilic molecule as shown in Figure No.4.

Compatibility Study

From the spectra it was observed that all the characteristic peaks of Eprosartan Mesylate were present in the combination spectrum, thus indicating compatibility of the drug and polymer. I.R. spectra of pure drug Eprosartan Mesylate, polymers Sodium alginate, HPMC K4M, and Sodium CMC and also the combination of Eprosartan Mesylate and polymers are shown in IR spectrum Figure No.5-7.

Table No.1: Formulation of Core -In-Cup Pulsatile Tablets

S.No	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
1	Eprosartan Mesylate	50	50	50	50	50	50	50	50	50	50	50	50
2	Ethyl Cellulose	160	160	160	160	160	160	160	160	160	160	160	160
3	Sodium Alginate	30	60	90	120	-	-	-	-	-	-	-	-
4	HPMC-K4M					30	60	90	120	-	-	-	-
5	SCMC	-	-			-	-	-	-	30	60	90	120
6	**Total**	**240**	**270**	**300**	**330**	**240**	**270**	**300**	**330**	**240**	**270**	**300**	**330**

Table No.2: Preformulation study of Eprosartan Mesylate

S.No	Parameter	Observation	Standard
1	Solubility Study of Eprosartan Mesylate	Practically insoluble in water, sparingly soluble in methanol	Practically insoluble in water, sparingly soluble in methanol
2	Loss of Drying	0.3%	NMT 0.5%
3	λ_{max} of Eprosartan Mesylate	234nm	233nm
4	Melting point of Eprosartan Mesylate	248-251°C	250°C

Table No.3: Standard Calibration data of Eprosartan Mesylate in Methanol and in pH 7.4 buffer

S.No	Concentration (mcg/ml)	Absorbance (mm) [Methanol]	Absorbance (nm) [pH 7.4 buffer]
1	0.000	0.000	0.000
2	4.000	0.168	0.144
3	8.000	0.332	0.318
4	12.000	0.488	0.455
5	16.000	0.650	0.609
6	20.000	0.796	0.759

Table No.4: Pre Compression and Post-Compression parameters

S.No	Pre-Compression Parameter	Observation	Post-Compression Parameter	Observation
1	Angle of Repose (θ)	24^0	Thickness*	2.32±0.45 mm
2	Loose bulk density	0.416±0.15gm/cm^3	Hardness*	2.50±0.25 kg/cm^2
3	Tapped bulk density	0.454±0.20gm/cm^3	Average Weight	49.16±0.47 mg
4	Compressibility Index (%)	8.338±0.58 (%)	Friability (%)	0.741±0.78 (%)

***Average of three replicates**

Table No.5: Pre-Compression Parameters for core-in-cup tablets

S.No	Formulation (degree) code	Bulk density* (g/cc) SD	Tapped density(g/cc) SD	Angle of repose* SD	Carr's index*(%) SD
1	ESA-1	0.5434±0.10	0.6341±0.02	25.28±1.23	14.3037±1.58
2	ESA-2	0.5212±0.02	0.6294±0.01	27.20±1.41	17.1909±1.22
3	ESA-3	0.5137±0.07	0.6098±0.01	25.14±0.57	15.7592±0.63
4	ESA-4	0.5098±0.01	0.5998±0.02	24.19±0.69	15.0050±0.58**L**
5	HP-1	0.5438±0.09	0.6401±0.02	26.41±1.20	15.044±0.60**L**
6	HP-2	0.5345±0.15	0.6296±0.03	28.56±1.55	15.1048±0.75**L**
7	HP-3	0.5121±0.02	0.6210±0.02	25.71±1.42	17.5362±1.23**L**
8	HP-4	0.5342±0.13	0.6408±0.01	26.38±1.35	16.6354±0.67
9	ESCMC-1	0.5088±0.01	0.5941±0.01	26.01±0.13	14.3578±1.51
10	ESCMC-2	0.5147±0.02	0.6091±0.02	27.01±1.21	15.4982±1.59
11	ESCMC-3	0.5218±0.03	0.6218±0.02	25.08±1.07	16.0823±1.19
12	ESCMC-4	0.5401±0.04	0.6387±0.02	28.46±1.26	15.4376±1.08

***Average of three replicates**

Table No.6: Post-Compression Parameters for core-in-cup tablets

S.No	Formulation Code	Hardness (kg/mg^2) SD	Thickness (mm) SD	Friability (%) SD	Weight Variation SD	Drug Content (%) SD
1	ESA-1	5.50	3.32±0.04	0.72±0.08	241.5±13	97.56±2.03
2	ESA-2	5.60	4.81±0.03	0.74±0.07	273.5±0.6	98.67±1.8
3	ESA-3	6.50	5.25±0.08	0.74±0.08	299±0.07	97.67±23
4	ESA-4	6.51	5.81±0.03	0.75±0.07	332±0.08	99.01±0.09
5	EHP-1	6.00	4.12±0.04	0.73±0.09	243±0.05	97.78±1.18
6	EHP-2	5.50	4.35±0.07	0.73±0.02	268.4±0.06	98.89±1.06
7	EHP-3	8.00	5.22±0.03	0.77±0.04	301.8±0.07	99.01±0.25
8	EHP-4	8.50	5.83±0.09	0.79±0.01	332.4±0.7	97.23±1.25
9	ESCMC-1	4.50	4.10±0.09	0.69±0.09	242±0.08	97.99±1.89
10	ESCMC-2	4.50	4.35±0.07	0.68±0.07	271.5±0.6	97.98±1.06
11	ESCMC-3	5.50	5.32±0.03	0.75±0.08	310±0.07	98.89±1.06
12	ESCMC-4	6.59	5.83±0.09	0.83±0.07	335±0.08	99.01±0.25

***Average of three replicates**

Table No.7: *In-vitro* release profile of ESA-1, 2, 3, 4 containing 30, 60, 90,120 mg Sodium alginate

S.No	Time(T) Log Time Hrs	Cum% Drug release ±SD ESA-1	Cum % Dug release ±SD ESA-2	Cum %Drug release ±SD ESA-3	Cum % Drug release ±SD ESA-4
1	0	0	0	0	0
2	1.0	0.00	0.00	0.00	0.00
3	2.0	7.0±0.03	0.00	0.00	0.00
4	3.0	21.58±1.13	10.56±0.18	0.00	0.00
5	4.0	82.42±0.09	25.96±0.98	9.517±0.35	0.00
6	5.0	89.83±1.17	81.93±0.16	30.42±0.56	12.73±0.65
7	6.0	95.21±0.12	88.93±0.48	49.06±0.93	27.07±0.87
8	7.0	97.48±0.89	96.00±0.89	78.67±0.63	43.77±0.54
9	8.0	---	97.02±0.79	96.00±1.02	88.27±0.73
10	9.0	---	---	98.04±0.75	95.14±0.42
11	10.0	---	---	---	97.19±0.24

All values are represented as mean standard deviation (n=3)

Table No.8: *In-vitro* release profile of EHP-1, 2, 3, 4 containing 30, 60, 90, 120 mg HPMC K4M

S.No	Time(T) Log Time hrs	Cum% Drug release ±SD EHP-1	Cum %Drug release±SD EHP-2	Cum % Drug release±SD EHP-3	Cum % Drug release±SD EHP-4
1	0	0	0	0	0
2	1.0	0.00	0.00	0.00	0.00
3	2.0	0.00	0.00	0.00	0.00
4	3.0	0.00	0.00	0.00	0.00
5	4.0	8.5±0.26	0.00	0.00	0.00
6	5.0	19.29±0.82	8.23±0.42	0.00	0.00
7	6.0	83.81±0.69	28.51±0.57	7.9±0.87	70.00
8	7.0	94.84±0.74	69.51±0.64	22.49±0.46	6.0±0.52
9	8.0	96.92±0.12	96.16±0.73	81.93±0.58	17.2±0.36
10	9.0	---	97.19±0.79	96.05±0.98	88.39±0.38
11	10.0	---	---	97.08±0.63	95.87±0.96
12	11.0	---	---	---	97.96±0.88

All values are represented as mean standard deviation (n=3)

Table No.9: *In-vitro* release profile of ESCMC-1, 2, 3, 4 containing 30, 60, 90, 120 mg Sodium CMC

S.No	Time(T) Hrs	Cum % Dug release ±SD ESCMC-1	Cum %Drug release ±SD ESCMC-2	Cum %Drug release ±SD ESCMC-3	Cum %Drug release ±SD ESCMC-1
1	0	0	0	0	0
2	1.0	0.00	0.00	0.00	0.00
3	2.0	0.00	0.00	0.00	0.00
4	3.0	5.10±0.34	0.00	0.00	0.00
5	4.0	18.12±0.48	6.817±0.17	0.00	0.00
6	5.0	46.55±0.64	12.09±0.34	5.0±0.13	0.00
7	6.0	78.50±0.80	47.83±0.51	26.36±0.62	8.61±0.12
8	7.0	96.96±0.96	87.96±0.85	46.36±0.39	18.21±0.25
9	8.0	97.70±1.12	95.32±0.19	85.21±0.52	84.01±0.97
10	9.0	---	96.37±0.38	94.94±0.65	94.44±0.93
11	10.0	---	---	95.97±0.78	95.48±0.45
12	11.0	---	---	---	96.51±0.38

All values are represented as mean standard deviation (n=3)

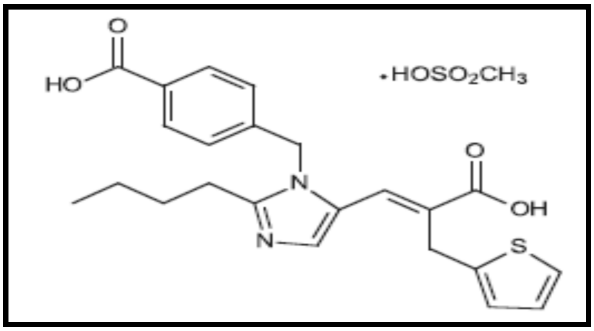

Figure No.1: Chemical structure of Eprosartan Mesylate

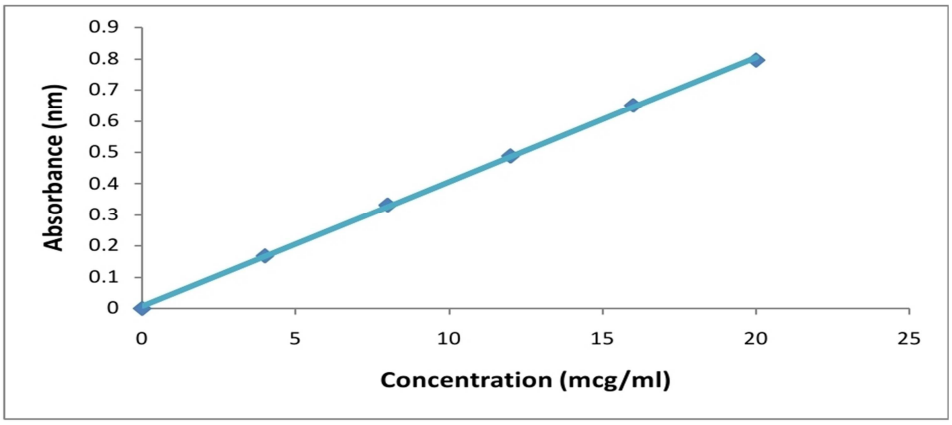

Figure No.2: Standard Calibration Curve of Eprosartan Mesylate in Methanol (λ_{max} 233 nm)

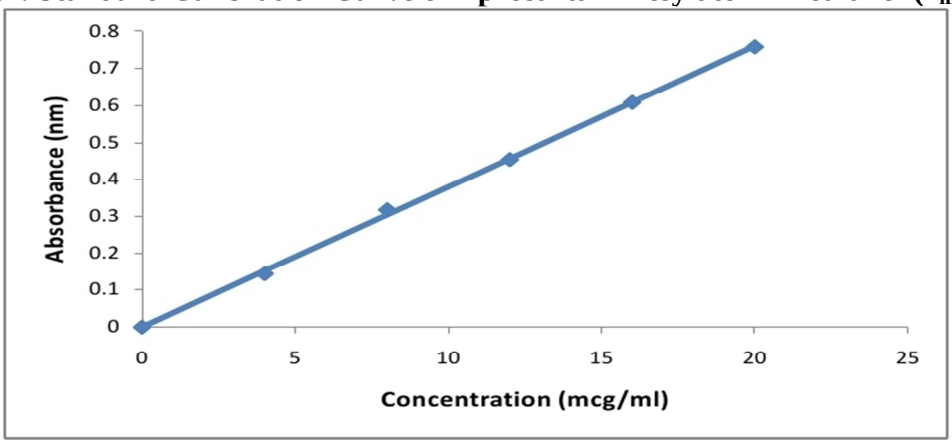

Figure No.3: Standard Calibration Curve of Eprosartan Mesylate in pH 7.4 buffer

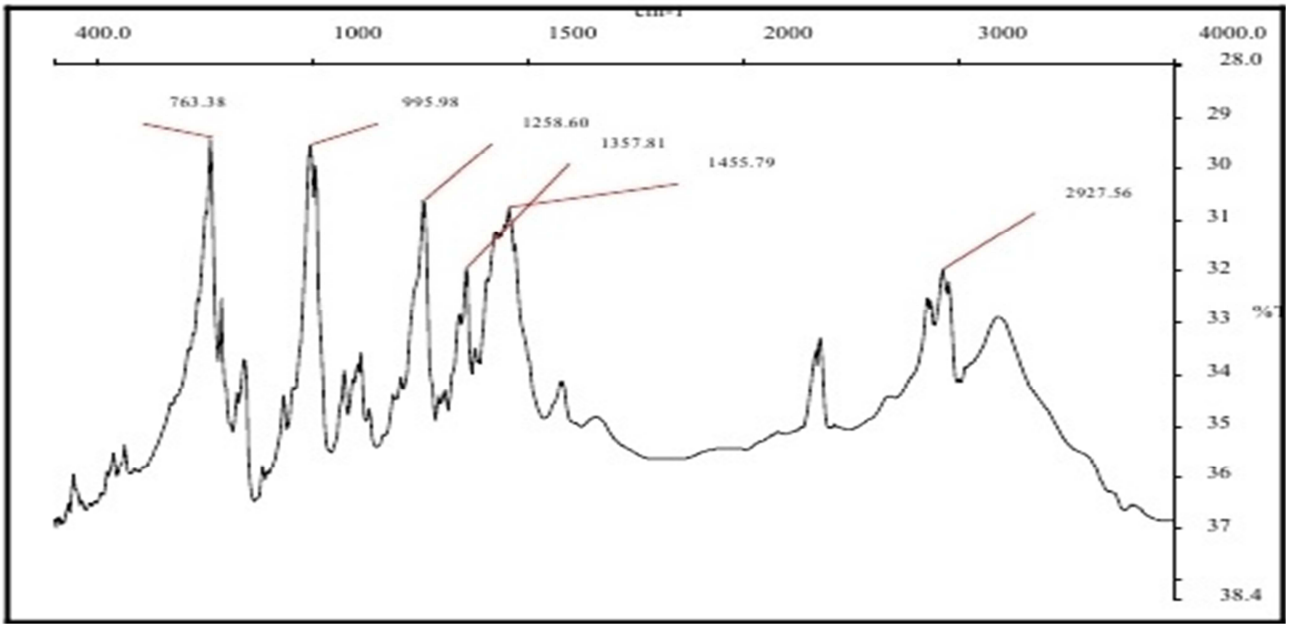

Figure No.4: IR.Spectrum of pure Eprosartan Mesylate

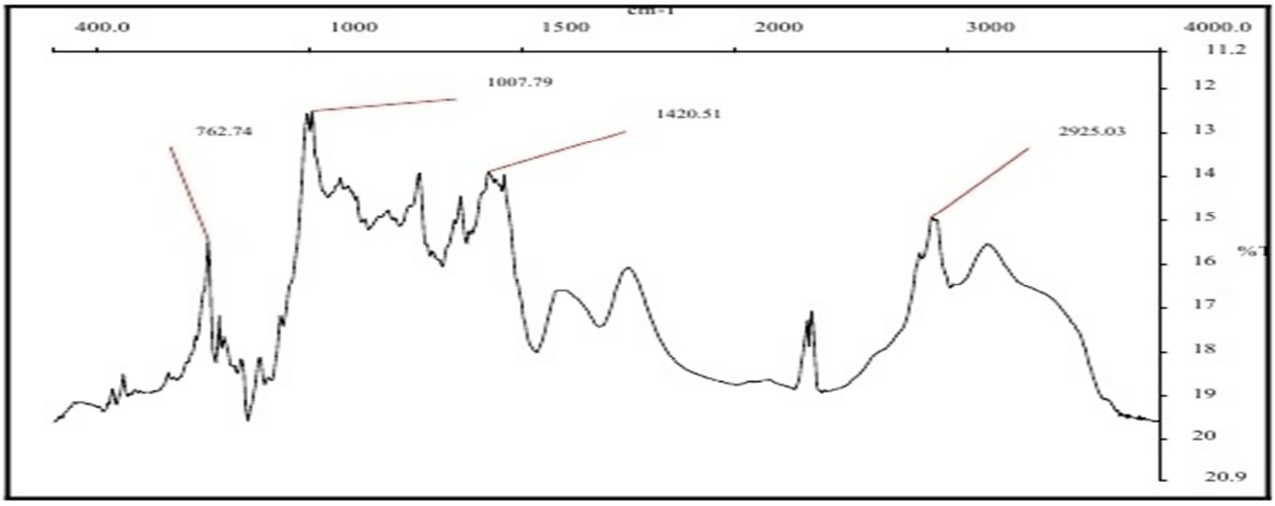

Figure No.5: IR. Spectrum of Eprosartan Mesylate + Cellulose acetate propionate +Sodium alginate

Figure No.6: IR. Spectrum of Eprosartan Mesylate + Cellulose acetate propionate +HPMC K4M

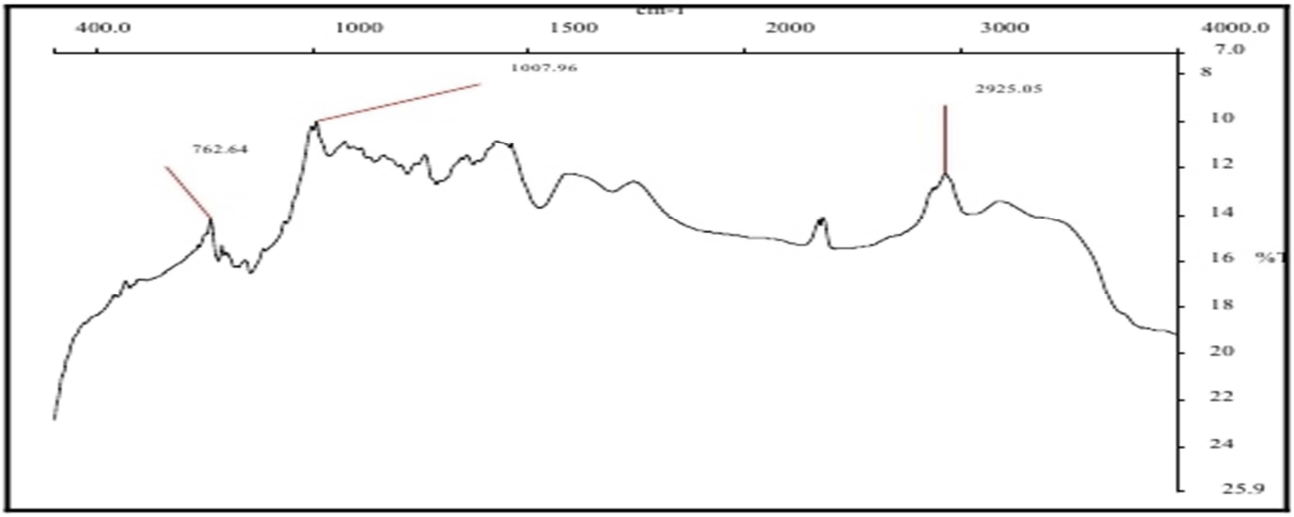

Figure No.7: IR. Spectrum of Eprosartan Mesylate + Cellulose acetate propionate + Sodium CMC

CONCLUSION

The data obtained from the study of "Formulation and evaluation of Eprosartan Mesylate pulsatile drug delivery system for effective treatment of hypertension" reveals following conclusion: Pulsatile Tablets of Eprosartan Mesylate were successfully prepared by direct compression method. flow properties and uniformity of all the prepared tablets were good as indicated by good bulk density, tapped density, low angle of repose (<30), low compressibility index (i<35). The percentage deviation of average weight of the prepared tablets showed between 0.03 to 1.22 which indicated weight uniformity within the batches prepared. The hardness of the prepared tablets was found to be in the range 2.5 to 8.5 kg/cm^2. The thicknesses of the prepared pulsatile tablets by all formulations were found in between 2.32 to 5.83 mm. The friability values of the prepared pulsatile tablets were found to be less than 1%. The drug content of pulsatile tablets was uniform in all the formulations and was between 97.23 to 99.01%. FT-IR spectrums of physically mixture of Eprosartan Mesylate and polymer revealed that the drug and polymers were satisfactorily compatible without any significant change in the chemical nature of the drug. The in vitro drug release from Eprosartan Mesylate pulsatile drug delivery system prepared by direct compression method was found to be in the range of 95.97 to 98.04%. 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. Sodium CMC 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 > Sodium CMC > Sodium alginate. On the basis of drug content, IR study, *in vitro* drug release study and its kinetic release data, EHP-4 was 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.

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CONFLICT OF INTEREST

None declared.

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