World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Original Article

Formulation and *in-vitro* evaluation of pulsatile drug delivery system for eplerenone

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Received: 05-11-2020 / Revised Accepted: 30-11-2020 / Published: 30-11-2020

ABSTRACT

Eplerenone is a steroidal anti-mineralocorticoid of the spirolactone group that is used as an adjunct in the management of chronic heart failure and high blood pressure, particularly for patients with resistant hypertension due to elevated aldosterone. The present work is to develop and evaluation of press coated tablets of Eplerenone by using polymers like Ethyl cellulose, HPMC. From the reproducible results obtained from the executed trails of core and press coated tablets it can be concluded that F6 of core tablet and E2F6 of press coated tablet were maintained lag phase upto 6hrs and brust release was at 7^{th} hr and followed by maximum release at the end of 8^{th} hr, so it is selected as optimized formulations for designing Pulsatile device. Therefore the study proved that coated Eplerenone can be successfully used as a time dependent modified Chronopharmaceutical formulation.

Keywords: Eplerenone, Sodium starch glycolate, Ethyl cellulose, HPMC.

INTRODUCTION

Chronotherapeutics refer to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefit and minimum harm. A pulsatile dosage form, taken at bed time with a programmed start of drug release in the early morning hours, can prevent this.[1] By timing drug administration, plasma peak is obtained, at an optimal time. Number of doses per day can be reduced. When there are no symptoms there is no need of drugs. Saturable first pass metabolism and tolerance development can also be avoided.[2,3] Drug targeting to colon would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of disease that have peak symptoms in the early morning such as nocturnal asthma, angina, arthritis. Some orally administered drugs (eg. Metaprolol, Theophiline, Nifedipine, Isosorbide) may exhibit poor uptake in the upper regions of GIT or degrade in the presence of GIT enzymes. Better bioavailability can be achieved through colon-specific drug delivery. Colon targeting is also advantageous where delay in systemic absorption is therapeutically desirable.[3] A major objective of chronotherapy in

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How to Cite this Article: Vandlakonda Suresh Goud, GS Sharma, B Rajkamal. Formulation and *in-vitro* evaluation of pulsatile drug delivery system for eplerenone. World J Pharm Sci 2020; 8(12): 141-146.

the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome. The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets (press coated) and capsules. Delivery systems with a pulsatile pattern are receiving increasing interest for the development of dosage forms, because conventional systems with a continuous release are not ideal. Advantages of Press-coated pulsatile drug delivery systems can protect hygroscopic, light sensitive, acid labile drug, they are simple and cheap in making.[3,4]

This study focuses the development of press coated tablets of Eplerenone to treat congestive heart failure by direct compression method. Press coated tablet consists of rapid release core tablet & coated by HPMC, Ethyl cellulose which are used as drug release controlling polymer.

MATERIALS AND METHODS

Drug & excipient compatibility: 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. [6]

Formulation of Compressed Tablets of Eplerenone: The methodology adopted includes:-

1. Preparation of core tablets of Eplerenone
2. Coating of the core tablets

1. Formulation of core tablets of Eplerenone; The inner core tablets were prepared by using direct compression method as per the developed formulation table which was shown below. Accurately weighed amounts of Eplerenone, MCC, SSG, CCS, and Talc were dry blended for about 15min followed by addition of magnesium stearate. The mixture was then further blended for 10 min. Now the resultant powder blend was manually compressed using punching machine and finally the core tablet was obtained.[5,6] The content of each tablet is listed in Table-1.

2. Formulation of Eplerenone press-coated tablet: The optimized core tablets were coated with coating ingredients like HPMC K4M and Ethyl cellulose. Now accurately weighed amount of barrier layer material was transferred into a 12mm 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 12mm flat oval shape punch. The prepared tablet of each batch was evaluated for the tablet properties. [6, 8] The content of each tablet is listed in Table-2.

Characteristics of core tablet & Press coated tablets of Eplerenone: [5-9]
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.

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. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

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: Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. 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. Percentage of friability of the tablets of a badge can be finding by the following

Formula:

Percentage Friability $= W1 – W2/W1 \times 100$

Where,

W1 = weight of tablets before testing

W2 = weight of tablets after testing.

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 20 mg was weighed accurately and dissolved in 100ml of buffer used. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman's filter paper No.41. The absorbance of the diluted solutions was measured at 244 nm. The concentration of the drug was computed from the standard curve of the Eplerenone in 6.8 phosphate buffer.

Disintegration time: Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 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 1 liter beaker containing distilled water 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.

In-vitro **dissolution methods for press coated tablets:** Dissolution testing of pulsatile delivery systems with the conventional paddle method at 75 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 spectrophometer (PG Instruments T60) for the presence of the drug. Dissolution tests were performed in triplicate. Despite the 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 design.

RESULTS AND DISCUSSIONS

Evaluation of core tablet: Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Eplerenone) and optimized formulation (Eplerenone+ excipients) which indicates there are no physical changes. This can be observed in Figure-1, 2. Pre-compression parameters and post compression parameters of core and press coated tablets were found to be satisfactory. The percentage weight variations for all formulations were given. All the formulated (F1 to F6) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The measured hardness of tablets of all the formulations ranged between 3.09±0.06-3.98±0.82 kg/cm^2. This ensures good handling characteristics of all batches. The measured thickness & diameter of tablets of all the formulations ranged between 2.17±0.092 -2.54±0.043 mm & 8.02±0.004 - 8.09±0.009 mm respectively. Disintegration time was found between 32 – 78 seconds ensuring that all the cores of different formulations were rapid disintegrating type. The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable. The percentage of drug content for F1 to F6 was found to be between 97.98±0.87 % - 101.64±0.45 %.

Dissolution study of Eplerenone core tablet: Total 6 core tablets was formulated by using CCS and SSG as super disintegrants, among them F6 formulation containing 6% of CCS shows maximum drug release at the end of 45min. so f6 formulation is chosen as best formulation for formulating the press coated tablet. The results are shown in figure-3.

Evaluation of Press-coated tablets: Post-compression parameters of press coated tablets were found to be satisfactory and the results are shown in figure-4.

Invitro drug release studies of press coated tablets of Eplerenone: By comparing the drug release profiles of the formulations E1F6, E5F6, E3F6, E4F6, E5F6 the drug release was not lagged up to 5-6 hours. Among all the formulations E2F6 containing HPMC K15M: Ethyl cellulose (1:2) shows lag time for 6hours and complete drug was released at the end of 8hours. So E2F6 was considered as the optimized formulation, & the drug release kinetics were performed for the optimized formulation i.e., E2F6. The results are tabulated in Figure 2.

CONCLUSION

The aim of this study was to explore the feasibility of time dependent pulsatile drug delivery system of Eplerenone to high blood pressure. A satisfactory attempt was made to develop pulsatile system of Eplerenone and evaluated it. From the reproducible results obtained from the executed trails of core and press coated tablets it can be concluded that: Pre-compression parameters and post compression parameters of core and press coated tablets were

found to be satisfactory. On the basis of drug content, in-vitro release studies and its kinetic data F6 of core tablet and E2F6 of coated tablet were selected as optimized formulations for designing Pulsatile device. Therefore the study proved that coated Eplerenone can be successfully used as a time dependent modified Chronopharmaceutical formulation. Finally from the above results we can conclude that pulsatile drug delivery system of Eplerenone can be formulated using Ethyl cellulose and HPMC K4M.

Table 1: Formulation Table of Eplerenone Core Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Eplerenone	25	25	25	25	25	25
CCS	3	6	9	--	--	--
SSG	--	--	--	3	6	9
MCC	118	115	112	118	115	112
Mg. sterate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total	150	150	150	150	150	150

Table 2: Composition of press coated tablets of Eplerenone

Excipients	Formulation code				
	E1F6	E2F6	E3F6	E4F6	E5F6
Core (mg)	150	150	150	150	150
HPMC K4M (mg)	150	100	200	75	225
Ethyl cellulose (mg)	150	200	100	225	75
Total weight (mg)	450	450	450	450	450

Table 3: Evaluation of press coated tablets of Eplerenone

Formula code	Weight variation	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Diameter (mm)	Drug content (%)
E1F6	1.09±0.06	6.76±0.65	0.24±0.006	4.64±0.012	12.02±0.001	96.56±0.10
E2F6	2.23±0.04	6.38±0.09	0.14±0.004	4.82±0.019	12.09±0.006	98.09±0.26
E3F6	2.98±0.09	6.98±0.23	0.09±0.026	4.87±0.005	12.12±0.012	96.56±0.14
E4F6	3.09±0.02	6.97±0.62	0.34±0.091	4.58±0.092	12.20±0.098	99.57±0.43
E5F6	2.89±0.19	7.09±0.91	0.18±0.078	4.79±0.014	12.09±0.014	98.09±0.09

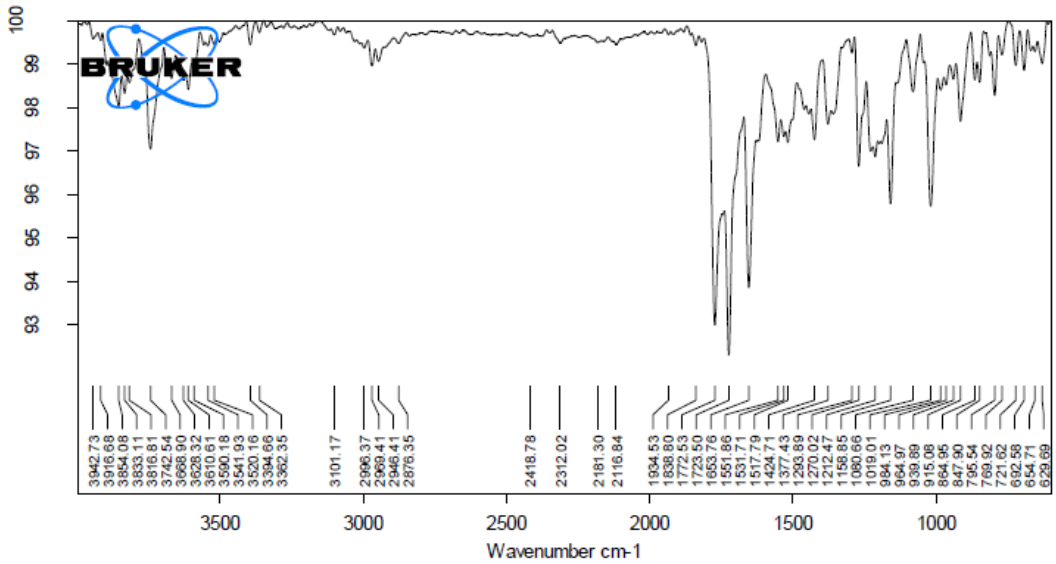

Figure 1: FTIR Spectrum of Eplerenone pure

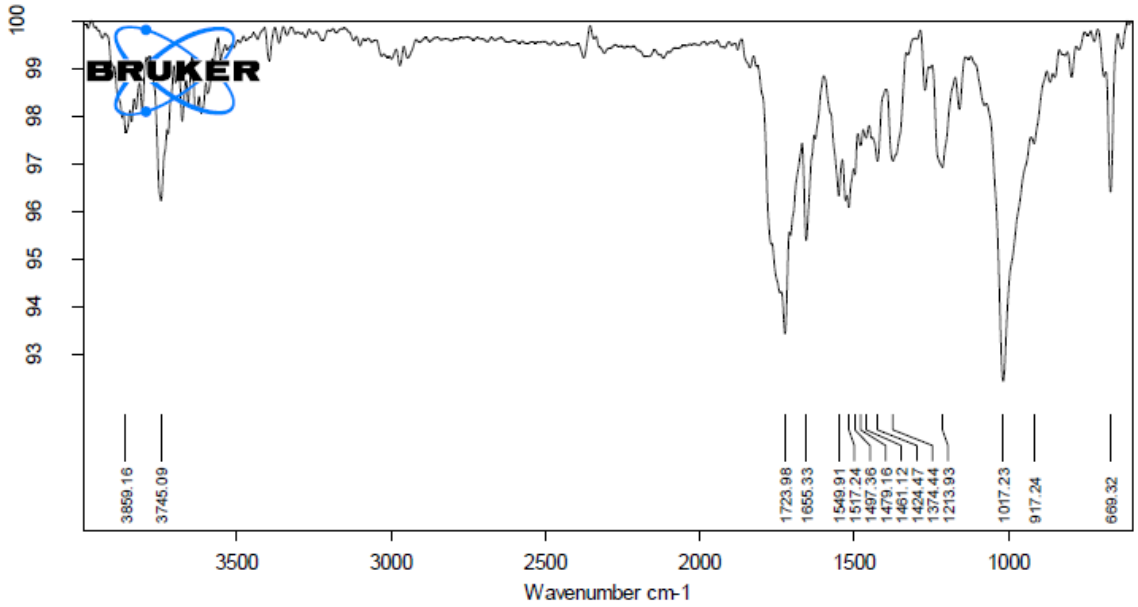

Figure 2: FTIR Spectrum of Eplerenone and Excipients

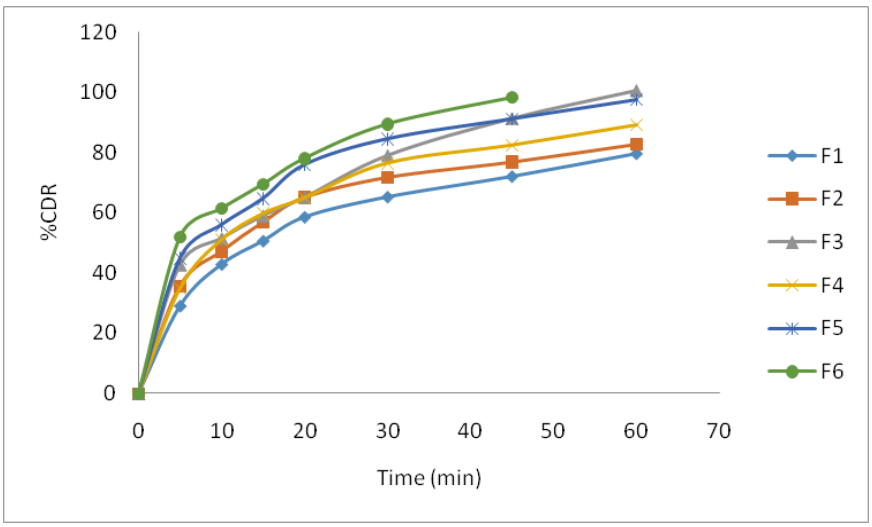

Figure 3: % CDR of Eplerenone core tablets F1 – F6

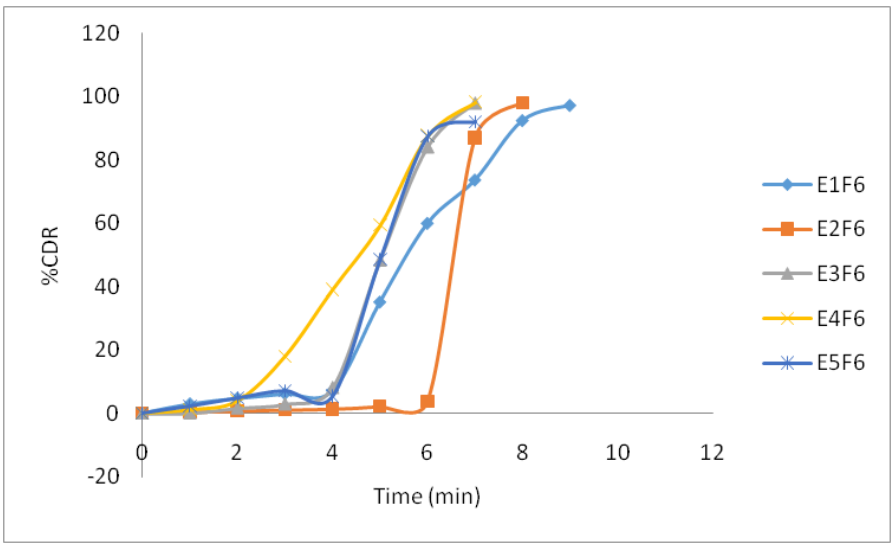

Figure 4: % CDR of Eplerenone press coated tablets E1F6- E5F6.

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