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FORMULATION AND IN-VITRO EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF ATENOLOL

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ABSTRACT

The main purpose of present investigation was to formulate and evaluate a pulsatile drug delivery system of drug Atenolol to achieve it's time specific release. Pulsatile Drug Delivery System (PDDS) deliver the drug at the right time, at right site of action and in right amount which provides more benefits than conventional dosage forms consequently increasing patient compliance. These systems are designed according to circadian rhythms of the body and the drug is released rapidly and completely as a pulse after lag time. Firstly, Fast disintegrating core tablet of Atenolol was prepared by direct compression technique using Microcrystalline Cellulose (MCC), Sodium Starch Glycollate (SSG), Lactose, Talc and Magnesium stearate. Then core tablet was coated with mixture of Ethyl Cellulose (EC), a hydrophobic polymer and Hydroxypropyl Methyl Cellulose (HPMC), a hydrophilic polymer by press coating technique. Mixtures of different weight ratio of Hydroxypropyl Methyl Cellulose (HPMC K4M) and Ethyl Cellulose (100:0, 80:20, 60:40, 50:50, 40:60, 20:80 and 0:100) were pressed coated over Atenolol core tablets to release Atenolol after a desired lag time of 6 hours. Pre-compression parameters and post-compression parameters of formulated tablets were evaluated. Among different formulation prepared by using different weight ratios of Hydroxypropyl Methyl Cellulose (HPMC K4M) and Ethyl Cellulose the optimum result was achieved in formulation containing 50:50 weight ratios. This is applicable formulation for pulsatile drug delivery of Atenolol in hypertension. Thus Pulsatile drug delivery system of Atenolol and other drugs can be developed using equal mixture of Hydroxypropyl Methyl Cellulose and Ethyl Cellulose.

KEYWORDS: Pulsatile drug delivery system, Atenolol, Hydroxypropyl methyl cellulose, Ethyl cellulose, Core tablet and Press coating technique.

INTRODUCTION

Oral drug delivery system is the fast growing, largest and the oldest segment of the total drug delivery market.[1] Over the past two decades, the pharmaceutical market has been demonstrating increased prefer ability for controlled and targeted drug delivery system. Such system has been focused on constant, variable; sustain drug release delivery system targeting the therapeutic agent to specific site/organ.[2] Studies have revealed that disease has a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of a 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 lag time. Such systems are called pulsatile drug delivery system.[3] Pulsatile drug delivery system is promising in such diseases like asthma, myocardial infarction, peptic ulcer, hypercholesterolemia.[4] Advantages of pulsatile drug delivery are extended day time or night time activity, reduced side effects, reduce dosage frequency, reduction in dose size, improved patient compliance, lower daily cost to patient, drug adapts to suit circadian rhythms of body functions or diseases, drug targeting to specific site like colon, protection of mucosa from irritating drugs, drug loss is prevented by extensive first pass metabolism etc. Disadvantages of pulsatile drug delivery system are lack of manufacturing reproducibility and efficacy, larger number of variables, multiple formulation steps, higher cost of production, need of advanced technology, trained/skilled person needed for manufacturing. Necessities of PDDS includes first pass metabolism, bilological tolerence, special chronopharmacological needs, local therapeutic need, gastric irritation or drug istability gastric fluid.[5] Pulsatile drug delivery system is divided into two distinct types, the time controlled drug delivery system and site specific drug delivery system.[6] This study is focused on development of pulsatile release formulation of atenolol based on swelling and erodible membrane system which helps release of the drug only after predetermined lag time.

MATERIALS AND METHODS

Materials

The drug molecule Atenolol along with other ingredients such as Sodium Starch Glycolate, Microcrystalline Cellulose, Lactose, Magnesium Stearate and Talc were also obtained as a gift samples from Lomus Pharmaceuticals Pvt. Ltd, Gothatar, Bhaktapur, Nepal. Other

materials such as Hydroxypropyl Methyl Cellulose, Ethyl Cellulose, Hydrochloric acid and Sodium hydroxide were provided by research laboratory of National Model College for Advance Learning (NMCAL).

Methods

Analytical method development

Weighed amount of Atenolol was dissolved in 0.1 N HCL and diluted accordingly to get final solution containing 0.01% of atenolol solution. The solution was filtered and subjected to scanning between 200-400 nm and absorption maximum was determined.

Analytical method validation

Analytical method was validated for accuracy, precision, specificity, limit of detection, limit of quantitation and linearity.[7]

Preparation of atenolol core tablets

The core tablets of Atenolol were prepared by direct compression method. An optimized core tablet was formulated using various concentration of ingredient. An accurately weighed quantity of Atenolol, Microcrystalline Cellulose, Sodium Starch Glycolate, Talc (2% w/w) and Magnesium stearate (1% w/w) were passed through sieve no. 24 and mixed by triturating in a mortar and pestle for 10 minutes. The resultant powder mixture were compressed into tablets (average weight = 125 mg) by 7 mm standard concave punch using rotatory tableting machine.

Preparation of press coated tablets

The core tablets were compressed coated with 300 mg of coating material containing different weight ratios (w/w) 0f HPMC K4M and ethyl cellulose. The weight ratio of HPMC K4 M and EC were used for the compression coating. Weighed amount of coating material, 1% magnesium stearate and 2% talc were passed through sieve no. 24 separately and blended using mortar and pestle for 10 minutes. 150 mg weight of the coating material first placed into the die cavity (diameter 12 mm). Then, the core tablet was carefully placed on it manually at the center of the die. The remaining 150mg of the coating material was added into the die and the coating material was then compressed around the core tablet using 12 mm standard concave punch using rotatory tableting machine.[8]

Table 1: Formulation of pulsatile drug delivery tablet (mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7
Composition of core tablet							
Atenolol	50	50	50	50	50	50	50
Microcrystalline Cellulose	47	47	47	47	47	47	47
Sodium Starch Glycollate	6	6	6	6	6	6	6
Lactose	18	18	18	18	18	18	18
Talc	3	3	3	3	3	3	3
Magnesium stearate	1	1	1	1	1	1	1
Composition of press coated tablet							
Hydroxypropyl Methyl Cellulose K4M	291	233	175	145.5	116	58	0
Ethyl Cellulose	0	58	116	145.5	175	233	291
Talc	3	3	3	3	3	3	3
Magnesium Stearate	6	6	6	6	6	6	6
Total Weight (mg)	425	425	425	425	425	425	425

Evaluation of pre-compression parameters of powder blend

The flow properties of powder blend were characterized in terms of Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio.[9,10]

Investigation of post compression parameters

The post compression parameters will be characterized in terms of Weight variation test, Hardness, Thickness, Friability and Swelling Index.[8]

Estimation of drug content

Twenty tablets were weighed and powdered. A quantity of powder containing 0.1.g equivalent of Atenolol was shaken with 150ml of methanol for 15 minutes, diluted to 250 ml with methanol. It was filtered through sintered glass funnel. 25 ml of the filtrate was diluted to 100 ml with methanol to produce a solution containing 0.01% w/v of atenolol. The absorbance of the resulting solution was measured at 275 nm.[11]

$$\text{Assay}=\frac{Absorbance}{E^{1\%}}\times\frac{Dilution}{wt.taken}\times\frac{Avg\ wt.}{100} \qquad \ldots 1$$

In-vitro drug release

The in-vitro release of Atenolol tablets was performed using IP dissolution apparatus type 1 (Paddle). The test was carried out in 1000ml 0f 0.1 for 2 hr. and 7.4 pH phosphate buffer solution for subsequent hours. The test was performed at a temperature of 37± 0.5°c and 50 rpm for 10 hours. Tablets were in dissolution jar and samples were taken at one hour intervals. The samples were withdrawn and filtered. The solution was replaced with the same dissolution medium. The samples were analyzed for Atenolol at 275nm by using UV

Spectrophotometer. The in-vitro release of marketed product was carried out in the similar manner and the results were compared.

$$\%\text{Drug release} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times \frac{\text{Standard dilution}}{\text{Sample dilution}} \times \text{Potency} \quad \text{....2}$$

RESULT AND DISCUSSION

Determination of λ max of Atenolol in 0.1 N HCL

The λ max of atenolol in 0.1 N HCL was found to be 275nm.

Analytical Method Validation

The method was found accurate with % recovery of 98.6%, 99.5% and 101.5% respectively for three different concentrations. The method was also precise with mean RSD value of 0.153 which was less than 2%. The method was specific for Atenolol. The limit of detection of atenolol is 0.361µg/ml. The limit of quantification of Atenolol is 1.09µg/ml. The range of concentration detected was found to be 1.09µg/ml to 193.88µg/ml. The value of correlation coefficient (R^2) was determined to be 0.996.

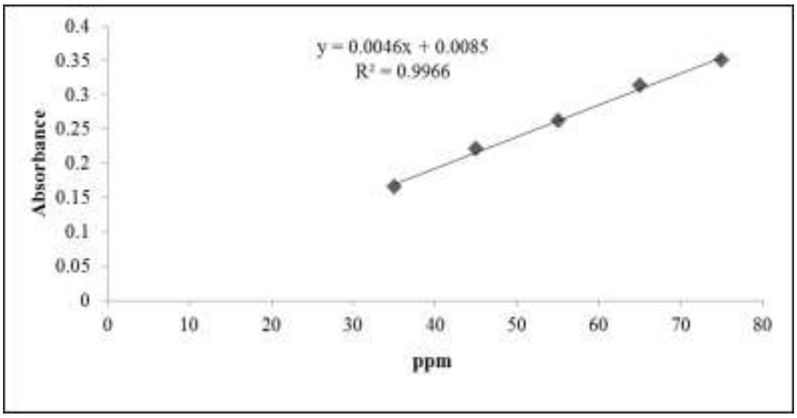

Figure 1: Linearity graph of different concentration

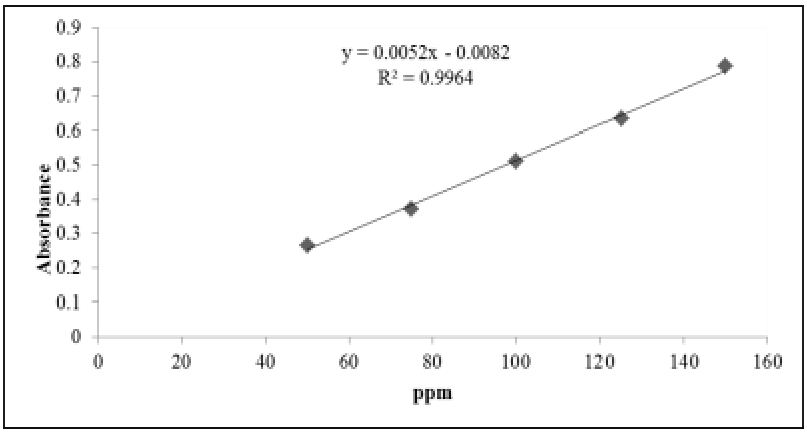

Figure 2: Standard calibration curve of Atenolol Standard in 0.1N HCL

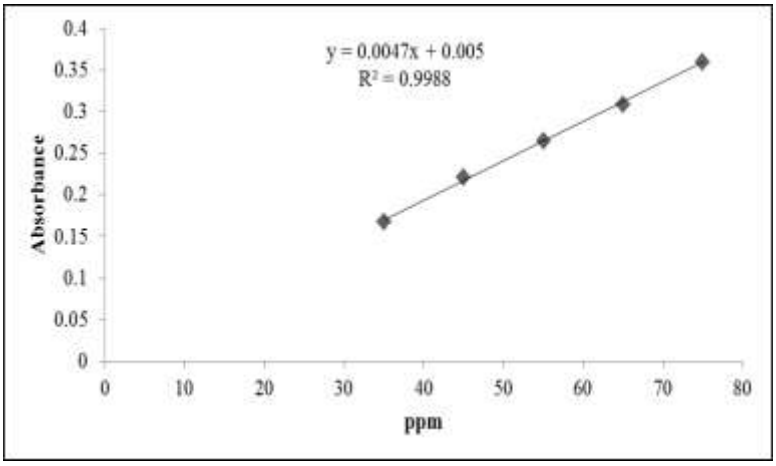

Figure 3: Standard calibration curve of Atenolol Standard in7.4 pH phosphate buffer

Pre compression parameter

The Pre compression parameters were evaluated by finding the Angle of repose, Tapped density, Bulk density, Carr's index and Hausner's ratio.

Table 2: Pre compression parameters of the formulated Atenolol pulsatile release tablets

Formulation	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio
Core	39.48	0.49	0.574	14.63	1.170
F1	38.3	0.56	0.658	14.89	1.175
F2	37.6	0.556	0.645	13.79	1.165
F3	39.01	0.604	0.717	15.79	1.187
F4	37.95	0.596	0.707	15.70	1.186
F5	36.68	0.588	0.70	16.0	1.190
F6	39.35	0.606	0.721	15.95	1.189
F7	38.1	0.568	0.677	16.07	1.191

Post compression parameters

Table 3: Post compression parameter of Atenolol pulsatile release tablets

Formulation	Weight variation (mg) N =20	Hardness (kg/m^2) N=6	Thickness (mm) N=6	Assay (%) N=3	Friability (%) N=10
Core	123.58±4.27	4.01±0.24	3.02±0.01	99.5±0.23	0.3
F1	426.22±3.662	9.02±0.28	6.04±0.056	101.5±0.34	0.40
F2	424.91±3.127	10.05±0.77	6.04±0.042	99.5±0.282	0.21
F3	420.3±3.24	9.05±0.35	6.04±0.056	96.0±0.141	0.52
F4	418.0±2.46	9.75±0.35	6.04±0.049	101.93.±0.98	0.37
F5	422.35±4.20	10.04±0.70	6.03±0.042	97±0.989	0.45
F6	424.47±3.88	9.57±0.09	6.02±0.014	99.9±0.707	0.42
F7	423.77±3.72	8.75±0.35	5.75±0.070	100.4±0.424	0.6

Swelling index

The swelling of tablet was progressive and reached maximum at 10-12 hrs.

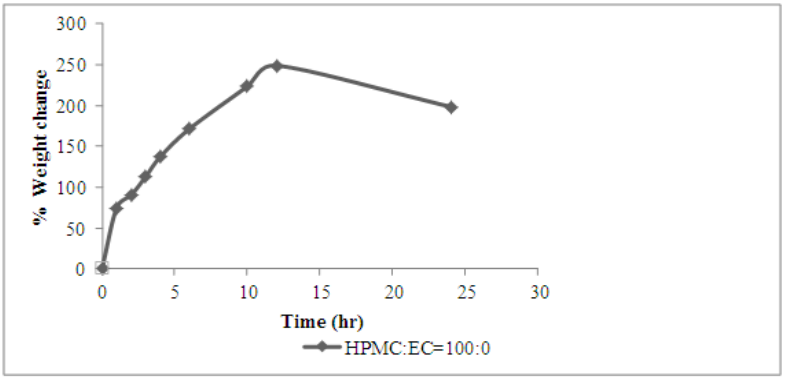

Figure 4: Swelling index of HPMC only

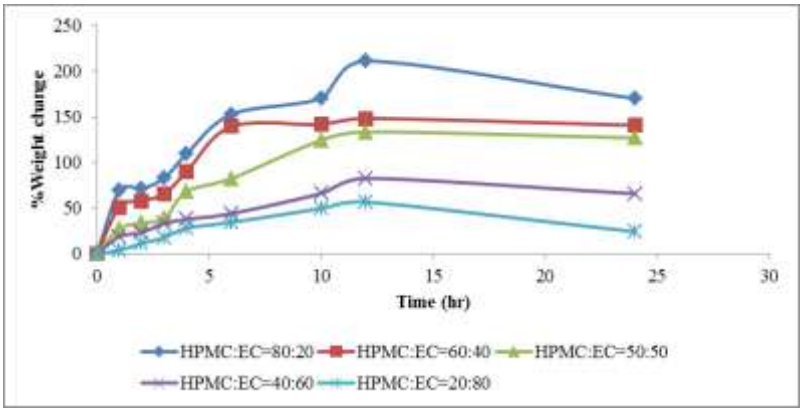

Figure 5: Swelling index of different grades of HPMC and EC

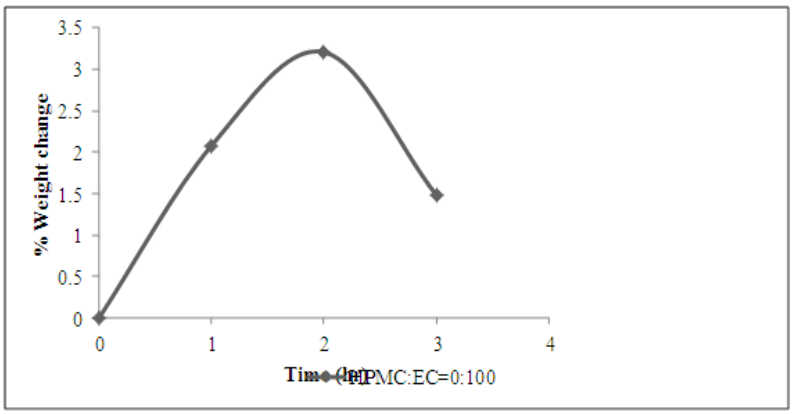

Figure 6: Swelling index of EC only

Swelling study of press coated tablets indicate that combination of EC and HPMC K4M, when used have better capacity to protect the drug from being released in the upper parts of the GIT than HPMC K4M alone compression coated tablet. This may be due to HPMC K4M

is more hydrophilic as swelling index is better for HPMC K4M. As the amount of HPMC K4M increases swelling of tablet increases. F1 batch having high amount of HPMC K4M (having HPMC K4M alone) was showed high percentage of swelling (248.9%). HPMC K4M alone released the drug relatively at higher rate than combination of EC and HPMC K4M because it formed weak swellable layer, which could rupture easily upon exposure to the dissolution medium. While F7 batch having EC alone could not maintain the integrity, and it divided into two equal half and negligible sign of swelling. Batches F2 to F6 showed that as the amount of EC is increased in the mixture of HPMC K4M and EC, %swelling of tablet decreases because of EC retards the swelling of HPMC K4M. EC retard the hydration of HPMC K4M and maintain the integrity of swellable layer of HPMC K4M.[12]

Assay

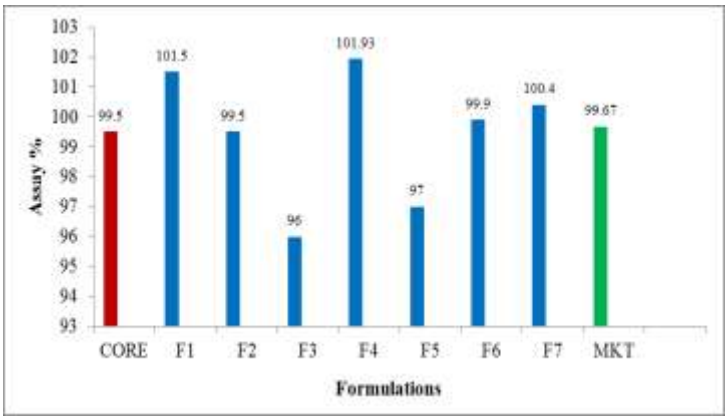

Figure 7: Assay percentages of different formulated batches and marketed sample.

The assay percentages of all the formulated batches were found in the range of 96% to 104% which was within the limit.

In-vitro dissolution study

Drug release of core tablets

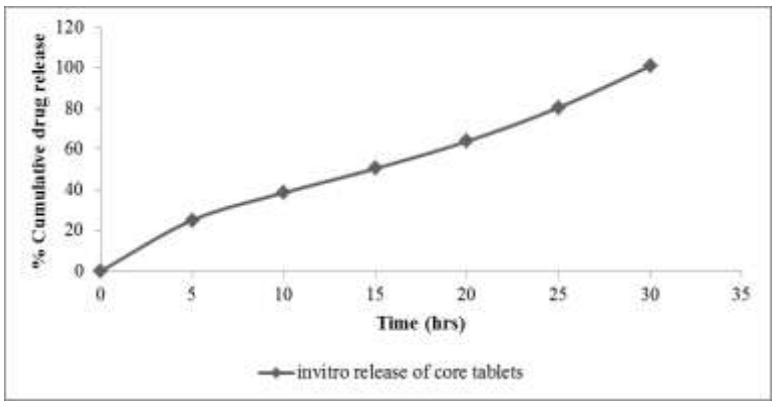

Figure 8: Cumulative % drug release of core tablets

The core tablet of Atenolol is fast disintegrating tablet. When the tablet comes in contact with dissolution medium it gets rapidly disintegrated. Thus it shows 100% drug release within 30 minutes upon contact with dissolution medium.

Effect of different ratio of HPMC K4M and EC

Effect of HPMC K4M alone (HPMC: EC= 100:0)

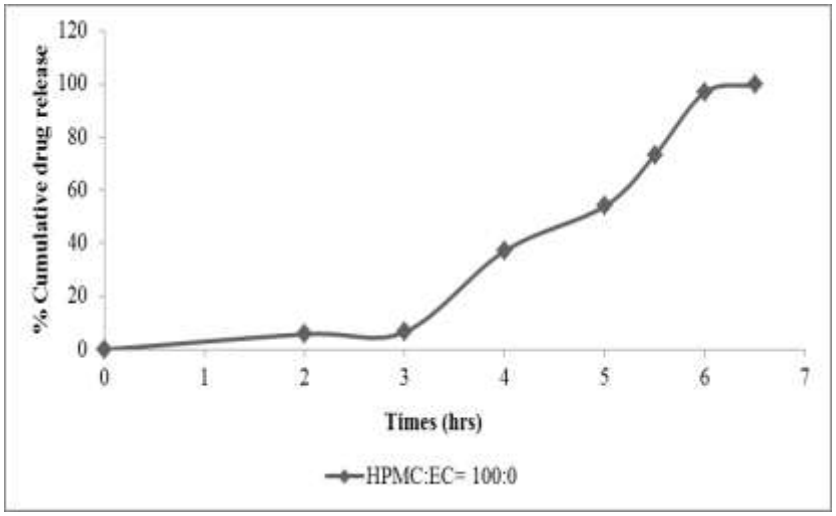

Figure 9: Cumulative % drug release of formulation containing coating polymers (HPMC K4M: EC = 100:0)

The weight ratio of HPMC K4M and EC (100:0) showed the lag time of 3 hours and the release was increased rapidly which showed the complete release at 7 hours.

Effect of HPMC K4M and EC (HPMC K4M: EC= 80:20)

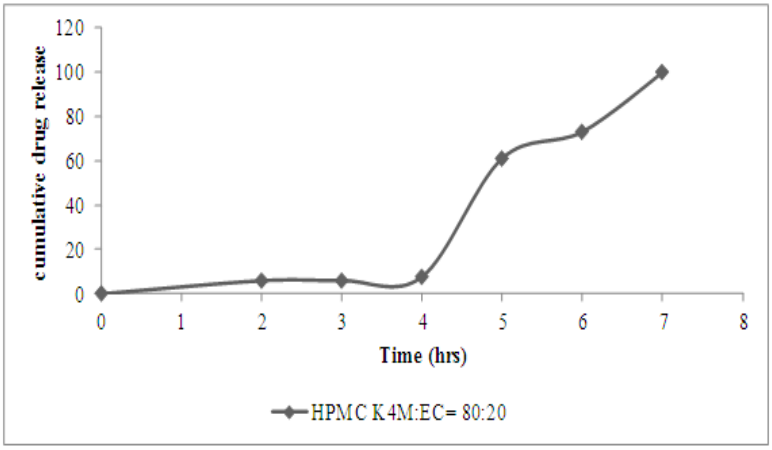

Figure 10: Cumulative % release of formulation containing coating polymers HPMC K4M: EC (80:20)

The weight ratio (HPMC K4M and EC = 80:20) showed the lag time of 4 hours and release was rapid after lag time and showed the complete drug release within 7 hours.

HPMC K4M and EC (60:40)

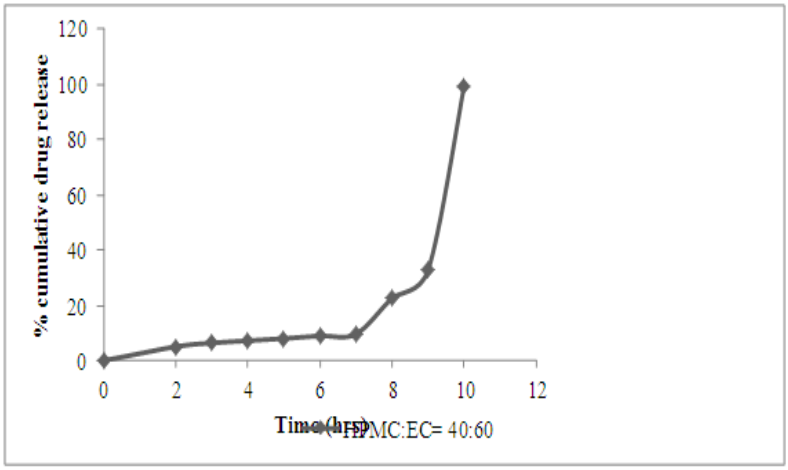

Figure 11: Cumulative % release of formulation containing coating polymers HPMC K4M: EC (60:40)

The weight ratio (HPMC K4M and EC = 60:40) showed the lag time of 7 hours and complete release was within 10 hours.

Effect of HPMC K4M and EC (50:50)

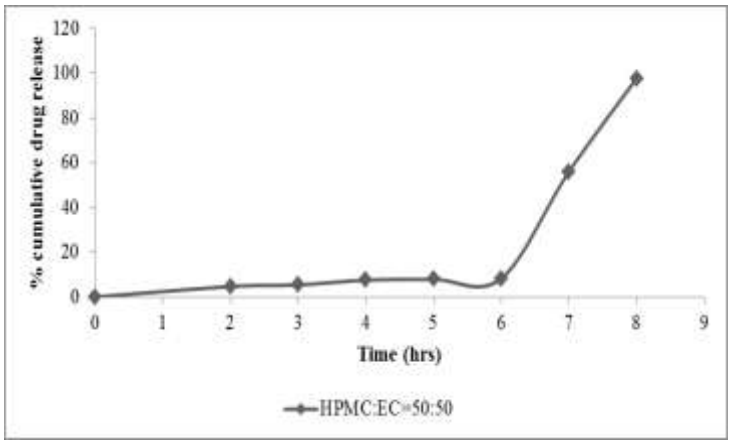

Figure 12: Cumulative % release of formulation containing coating polymers HPMC K4M: EC (50:50)

The weight ratio (HPMC K4M and EC= 50:50) showed the lag time of 6 hours and complete release was within 8 hours.

Effect of HPMC K4M and EC (40:60)

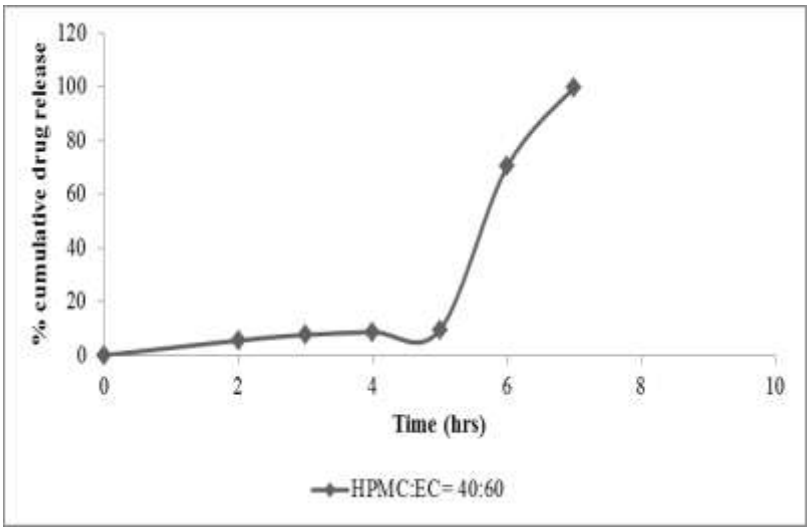

Figure 13: Cumulative % release of formulation containing coating polymers HPMC K4M: EC (40:60)

The weight ratio (HPMC K4M and EC= 40:60) showed the lag time of 5 hours and complete release was within 8 hours.

Effect of HPMC K4M and EC (20:80)

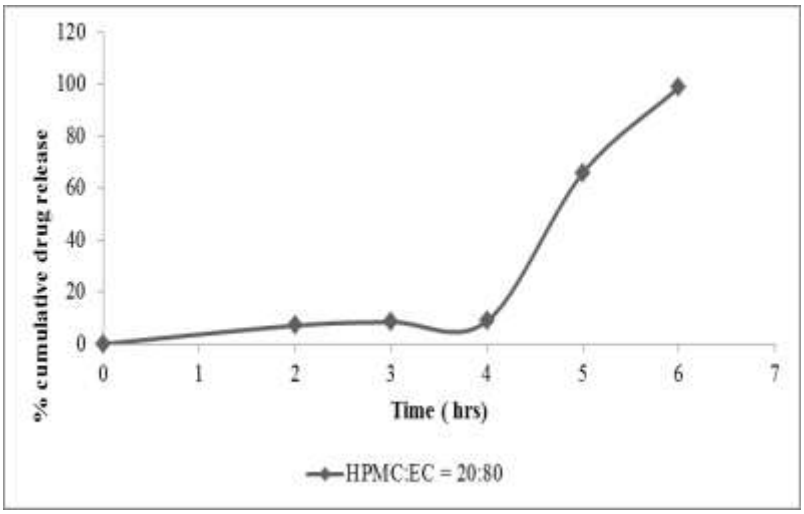

Figure 14: Cumulative % release of formulation containing coating polymers HPMC K4M: EC (20:80)

The weight ratio (HPMC K4M and EC= 20:80) showed the lag time of 4 hours and complete release was within 6 hours.

Effect of HPMC K4M and EC (0:100)

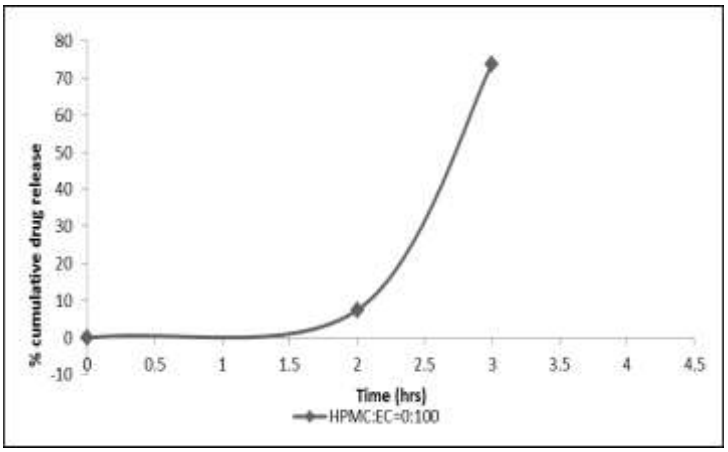

Figure 15: Cumulative % release of formulation containing coating polymers HPMC K4M: EC (0:100)

The weight ratio (HPMC K4M and EC= 0:100) showed the lag time of 2 hours and complete release was within 3 hours due to cracking.

In time controlled press coated tablets, drug containing core compressed with the outer barrier layer l, it prevents the rapid drug release from core tablets. The drug will not be released unless the coat is broken. When the dissolution medium reaches the core after eroding or rupturing the outer barrier layer rapid drug release was observed. The release profile of compression coated tablet exhibited lag time followed by burst release, in which the outer shell break into two halves.[12]

Press coated tablet (F1 to F7 formulations) showed distinct lag time. When HPMC K4M was used alone (F1), it showed the lag time of only 3 hours. This is probably because of mechanism of producing a lag time of this formulation was based upon the hydration and swelling of outer barrier layer or water penetration through outer barrier layer.[13]

When HPMC K4M was used alone, it formed mechanically weak swellable layer, which could rupture easily upon exposure to the dissolution medium and resulting development of internal pressure within tablet core and drug release was initiated. Hydrophilic polymer (HPMC K4M) alone for controlling the drug release of highly water soluble drugs like atenolol is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel layer.

With ethyl cellulose alone (F7), showed lowest lag time of two hours as compared to any weight ratio of mixture of HPMC K4 M and EC. EC has no swelling property and is hydrophobic and cracking of tablet occurs as it has no push effect like HPMC. EC exhibiting a porous structure, the porosity is proportional to the proportion of ethyl cellulose. Ethyl cellulose is semipermeable in nature, although it is naturally insoluble in water, controls the passage of water inside the core, core swells and ruptures the EC coat. Water penetrates faster the coating layer of the core tablet when used alone. After hydration of core, the drug was released.[14]

When ethyl cellulose was used in combination with HPMC K4 M, it causes synchronization between swelling and erosion of the polymer in maintaining a constant gel formation for a longer period of time.[14] Upon contact with dissolution medium HPMC K4M hydrated and formed compact with ethyl cellulose. The hydrophobicity of ethyl cellulose retards the hydration of HPMC K4M. Therefore the dissolution medium did not penetrate the outer coating layer, but the coating eroded slowly. The active erosion rate of outer barrier layer depends upon the composition of the formulation which determines the lag time of press coated tablet.[15]

The combination of HPMC K4M and EC showed the synergistic effect on lag time. The finding indicates that the lag time of press coated tablet can be modulated from 4 hours to 6 hours by combining with EC and HPMC K4M in different weight ratio. System was found to be satisfactory in terms of release of the drug after the predetermined lag time of 6 hrs. This is shown by the formulation F4 (HPMC K4M:EC = 50:50). Thus the dosage form can bet taken at bed time, so that the content will be release in the morning hours, i.e. at the time when the symptom is more progressive. The release was rapid after the completion of lag time. Lag time can be controlled by adjusting the mixture containing different weight ratio of HPMC K4M and EC.

CONCLUSION

The promising pulsatile drug release of atenolol is successfully achieved by press coating technique using combination of time dependent rupturable and erodible polymers. Ethyl Cellulose was chosen because of its rupturable behavior and HPMC K4M was selected because of its swelling and erodible behavior. Atenolol press coated tablet was prepared using different weight ratios (W/W) of HPMC K4M and EC. The formulation F4 achieved a burst release after 6 hr. which is applicable pulsatile drug delivery system of atenolol.

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