INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

FORMULATION AND EVALUATION OF CONTROLLED DRUG RELEASE TABLET OF ATENOLOL

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ABSTRACT
The role of chronotherapeutics in hypertension and anti-inflammatory management is based on the recognition that blood pressure and pain does not remain constant throughout the day. Instead, it tends to be higher in the early morning hours and lower in the evening hours. The aim of the present study was to design time controlled tablet of Atenolol, as chronopharmaceuticaldrug delivery system by compression coating. Formulation design involves coating polymers HPMC K05:EC (ratio - 1:1,1:2,2:1 w/w) and HPMC K05:CA (ratio - 1:1,1:2,2:1 w/w)were exploited for their pulsatile drug release ability. The basic idea behind the dosage form development is to investigate effect of coating design on lag time and drug release from press-coated pulsatile release tablet. Coating materials were evaluated for pre-compression parameters like bulk density, tapped density, Angle of repose, Compressibility index, Hausner's ratio and also evaluated the tablet for hardness, thickness, friability, weight variation, swelling index, drug content, In vitro drug release, drug excipient compatability studies. The Formulation was optimized on basis of acceptable tablet properties and in vitro drug release. The results indicate that Formulation F9, F14 for Atenolol press-coated tablets achieve a burst release after 7.45 & 8hrs lag time which is applicable pulsatile drug delivery for hypertension.

Key Words: Atenolol, HPMC K05, pulsatile release tablet.

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INTRODUCTION
Pulsatile drug delivery systems (PDDS) (or) Cracking drug delivery systems (CDDS) can be classified in site specific and time controlled systems.Drug release from site specific systems depends on the environment in the GIT. Eg:-on pH, presence of enzymes, and the pressure in the GIT.Time controlled pulsatile delivery has been achieved mainly with drug containing cores, which are covered with release Controlling layers.The cores serves as a reservoir, which protects the core from environment, eg:- water, acidic pH and enzymes, until the drug is released after the lag phase.The coatings can erode/ dissolve, rupture (or) alter their permeability at the required time.The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease.Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. There is a constant need for new drug delivery systems that can provide

increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by deliveringdrug at the right time, right place and in right amounts, holds good promises of benefits to the patients suffering from chronic problems like arthritis, asthma, hypertension etc. Various methodologies are employed for developing pulsatile drug delivery like time controlled, stimuli induced externally related system and multiparticulate drug delivery system. These considerations, along with the potential therapeutic benefits of pulsatile drug delivery systems, should ensure that the current high level of interest in this area would stretch well into future and ensures the betterment of quality life [1-6].Atenolol is used in treatment of hypertension and it is an oral antihypertensive in the form of tablets. Basing on its solubility and permeability characteristics, it is aBCS class ΠI drug. Hence, we wanted to formulate controlled drug release formulation.

MATERIALS AND METHODS

Method of Preparation of Core Tablets by Solvent deposition technique

Core tablets were prepared by solvent deposition technique. The solvent deposited systems were prepared in various ratios (1:0.5, 1:1, 1:1.5 and 1:2) on weight basis as given in the table-1.Required amount of Atenolol was taken in a china dish and dissolved in 5 ml methanol. Then required amount of β-Cyclodextrin was added to the above mixture. Solvent was evaporated by placing on hot plate with continuous stirring. This process was continued until we get a white powder. This solvent deposited system was passed through sieve number 100 and stored in a self-sealable cover till further use.

Table-1 Quantities of Atenolol and β-Cyclodextrin taken to prepare Solvent Deposited System

S.NO	Formulation	Amount of Atenolol (mg)	Amount of β-Cyclodextrin (mg)	Technique
1	SDS1	100	50	SDS
2	SDS2	100	100	SDS
3	SDS3	100	150	SDS
4	SDS4	100	200	SDS
SDS: Solvent Deposited System				

The core tablets of atenolol were prepared by direct compression method. An optimized core tablet was formulated using various ratios of Atenolol and β-Cyclodextrin (SDS). The weight equivalent to the dose required for the tablet was weighed from the SDS mixture and passed through 40# to obtain uniform sized powder particles and then add accurately weighed quantities of microcrystalline cellulose, mixed well for 15 min. Add talc (2% w/w) (40#) into it and mix well for 10 min. Add magnesium stearate (1% w/w) (40#) into it and mix for 5 min. The resultant powder mixtures were compressed into tablets (average tablet weight = 90 mg) by 9 mm standard concave plain punches using rotary tableting machine. The prepared atenolol core tablets were tested for *in vitro* dissolution study.Coat was prepared by using polymers like HPMC, Ethyl cellulose and Cellulose acetate. Various ratios were prepared to obtain a coat to release the drug after a required time.

Preparation of atenolol press coated tablets

The core tablets were compression coated with 150 mg of coating material containingdifferent weight ratios of HPMC K05, EC and HPMC K05, Cellulose acetate. The weight ratios of HPMC K05, EC and HPMC K05, Cellulose acetate were used for the compression coating. 43 % of (64.5 mg) weight of coating material was first placed into die cavity (diameter 9 mm). Then, the core tablet was carefully placed on it manually at the center of the die. The remaining 57 % of (85.5 mg) of the coating material was added into the die and the coating material was then compressed around the core tablet by 9 mmstandard concave plain punches using rotary tabletingmachine.The prepared compression coated

ISSN: 2395-0536 Impact Factor- 2.90*

atenolol tablets were tested for weight variation, hardness, thickness, drug content, friability and *in vitro* dissolution study [7].

Disintegration Time

Tablet disintegration testing is used as a quality-assurance measure. It is not a true predictor of how well the dosage form will release its active ingredient *in vivo*. The United States Pharmacopoeia (USP) sets standards for tablet disintegration testing. The apparatus is relatively simple. It consists of a basket rack holding six plastic tubes open at the top and bottom. The bottom is covered with a 10 mesh screen. The rack is immersed in a suitable liquid at 37 degrees C. It moves up and down at a specified rate. One tablet is placed into each tube and the time to disintegrate and fall through the screen is noted.

Dissolution rate studies for Atenolol

The dissolution rate testing of different Atenolol formulations (table) was studied using USP XXII dissolution rate testing apparatus, (basket type). The basket was rotated at a speed of 50 rpm and the dissolution fluid (900 ml of 0.1N HCl , 6.8 pH phosphate buffer) was maintained at a temperature of 37.50 ± 0.5^0c. At specific time intervals a 5 ml aliquot of dissolved medium was withdrawn and was replaced with fresh quantity of dissolution medium. The samples were suitably diluted with dissolution medium and assayed for Atenolol content by measuring the absorbance at 228 nm using U.V Spectrophotometer. The percent of Atenolol dissolved at various time intervals was calculated and plotted against time [8, 9].

RESULTS AND DISCUSSION

The results of different tests carried are given in below table-2

Table-2 Evaluation of post compression parameters of F9

S.NO	Parameter	Result
1	Hardness ($Kg/cm^{2)}$	5.6 kg/cm^2
2	Weight variation (mg) for (average of 10 tablets)	0.23± 5%
3	Friability (%)	0.12 %
4	Dissolution time	Breaks after a lag time of 7.45hrs
5	%Swellability studies	116.45%
6	Thickness(mm)	4.1 ± 0.05
7	Drug content	97%

Different ratios of HPMC; Ethyl cellulose and HPMC; Cellulose acetate were used to optimize the formula for compression coating by using Riboflavin as model drug. The ratios were changed systematically to obtain a perfect ratio of coat so that final dosage form cracks after a lag time of 7.45 to 8.00 hrs.Core formula was optimized by determining its disintegration time. For normal core formula satisfactory results were not obtained so that atenolol solvent deposited systems were prepared by using β-Cyclodextrin and Methanol and finally core containing drug and β-Cyclodextrin in the ratio of 1:1.5 get released within 30 mins.The best formula**(F9)** that cracks after a lag time of 7.45hrs consists of polymers HPMC K05 and Ethyl cellulose in the ratio1:1(75:75) and released the drug from the inner core of the tablet within 30 min completely (Fig-1).The best formula**(F14)** that cracks after a lag time of 8.00hrs consists of polymers HPMC K05 and Cellulose acetate in the ratio1:1(75:75) and released the drug from the inner core of the tablet within 30 min completely (Fig-2).

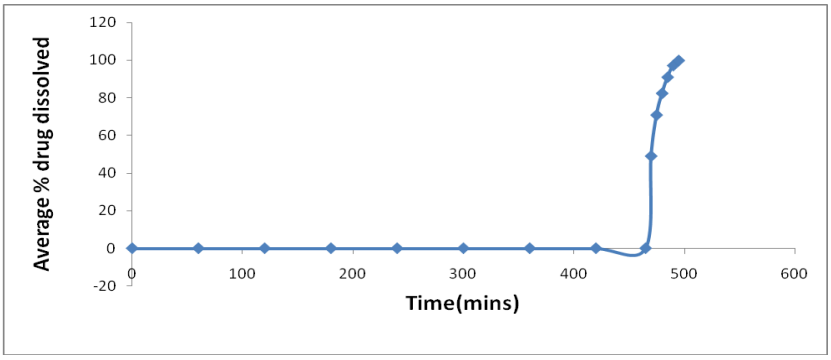

Fig-1 Dissolution of F9

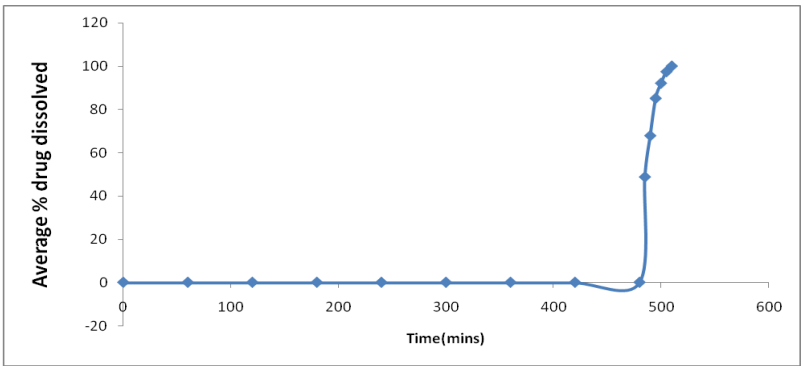

Fig-2 Dissolution profile of F14

CONCLUSION

Core formula was optimized by determining its disintegration time. For normal core formula satisfactory results were not obtained so that atenolol solvent deposited systems were prepared by using β-Cyclodextrin and Methanol and finally core containing drug and β-Cyclodextrin in the ratio of 1:1.5 get released within 30 mins.With the optimized core formula various formulas were prepared by using different ratios of coat and the tablets were prepared by compression coating technique and analyzed by dissolution studies by using 0.1N HCl for 2 hrs and P^H 6.8 buffer for next 6 hrs.From the results we obtained two formulas with two different polymers and their lag time was maintained for 7.45 hrs and 8.00 hrs. i.e., they cracked after 7.45 and 8.00hrs and released the drug from the inner core of the tablet within 30 min completely.The best formula(F9) that cracks after a lag time of 7.45hrs consists of polymers HPMC K05 and Ethyl cellulose in the ratio1:1(75:75) and released the drug from the inner core of the tablet within 30 min completely.The best formula(F14) that cracks after a lag time of 8.00hrs consists of polymers HPMC K05 and Cellulose acetate in the ratio1:1(75:75) and released the drug from the inner core of the tablet within 30 min completely.

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