Original Article

Noval Treatment in Hypertension

Radadia Ashwinbhai Arjanbhai[1]*, Dr. Satyajit Sahoo[2], Dr. Nizant Oza[3], Chodvadiya Chandrika Upendra[4], Dobariya Vithal Dhirubhai[5], Darji Yogeshkumar Govindbhai[6], Vijay K Patel[7]

[1*,4,5,6]Research Scholar, Research Development and Innovation Centre C. U. Shah University Wadhwancity – 363 030
[2,3]Profesor, Research Development and Innovation Centre C. U. Shah University Wadhwancity – 363 030
[7]Associate professor, Sharda school of Pharmacy, Pethapur, Gandhinagar

***Corresponding Author:-** Radadia Ashwinbhai Arjanbhai

*Research Scholar Research Development and Innovation Centre C. U. Shah University, Wadhwancity – 363 030, Ph. 9327770619
Email: drharaj@yahoo.com
DOI:10.47750/pnr.2023.14.S01.116

Abstract

Formulation and evaluation of floating pulsatile drug delivery system for chronotherapy of hypertension. It is aimed to modulate the pulsatile release profile from time lagged coating using single or a combination of rupturable and erodible polymer.To prepare enalapril maleate core tablets by wet granulation method.To prepare press coated pulsatile tablets by direct compression method.

Keywords: ENALAPRIL MALEATE angiotensin I–converting enzyme

INTRODUCTION:

Several controlled release preparations present numerous problems such as resistance drug tolerance and activation of the physiological system due to long term constant drug concentrations in the blood and tissues. In addition, sustained and controlled release devices are not applicable in some cases like time-programmed administration of hormones and many drugs.

Recent studies also reveal that the body's biological rhythm may affect biological functions such as heart rate, blood pressure, body temperature, blood plasma concentration, intraocular pressure, stroke volume. The symptoms of many diseases, such as bronchial asthma, myocardial infarction, angina pectoris, hypertension, and rheumatic disease have followed the body's biological rhythm. which require different amounts of drug at expected times within the circadian cycle. Pulsatile drug delivery system has fulfilled this requirement.

Pulsatile Drug Delivery System can deliver the correct amount of medication at the desired location at the optimal time for maximum effect against disease, thereby enhancing therapeutic efficacy and improving patient compliance. Heart rate and blood pressure both exhibit a strong circadian pattern with values for blood pressure, double product typically peaking in the early morning period compare with till late afternoon, and then drops off during night (hypertension).

MATERIALS AND METHODS:

The combination of floating and pulsatile principle are very well suitable for site and time specific oral drug delivery have recently been of greater interest in pharmaceutical field to achieve improved therapeutic efficacy. The floating pulsatile delivery provides various advantages such as nearly constant drug level at the site of action, avoidance of undesirable side effects, reduce dose, increased gastric residence of the dosage form.

After review of patents we can concluded that pulsatile drug delivery systems offer the delivery of drugs exhibiting chronopharmacological behavior, necessity of night time dosing, etc. There is a need for new delivery systems that can provide increased therapeutic benefits to the patients to match with circadian rhythm of body. This technique overcomes first pass metabolism and proves most beneficial when taken at bedtime.

Thus it concluded that the pulsatile delivery system release the drug at specific time and at specific site to improves the bioavailability, reduce dosing frequency and hence increase patient compliance and this correlates well with the rational for selection of project.

Drug excipient compatibility study:

Compatibility of Enalapril maleate with respective polymes that is HPMC E5, E15 and E50, individual excipients was established by infrared absorption spectral analysis (FTIR). Any changes in the chemical composition after combination with the excipients were investigated with IR spectral analysis.

Differential scanning calorimetry:

The DSC thermogram were recorded using a differential scanning calorimetry (DSC 60, Shimadzu). Approximately 2-5 mg of each sample was heated in a piece red aluminium pan from 50-300 °C at a heating rate of 10°C/min. under a stream of nitrogen at rate 10 ml/min.

EVALUATION PARAMETERS[19,26,27,43]:

Evaluation of powder blend:

Angle of repose:

It is used to estimate the flow property of material. The angle of repose less than 30º indicates good flow property of material. The angle of repose of powder blend was determined by funnel method. The accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the granules. The powder was allowed to flow through funnel to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation (Tan θ = h/r) where, h=height and r=radius of powder cone

Bulk density:

Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder was determined.
Bulk density = weight / bulk volume

Tapped density:

The measuring cylinder containing a known mass of powder blend was tapped for a fixed number of times as per USP apparatus-11. The minimum volume occupied by the powder after tapping was measured.
Tapped density = weight/tapped volume

Compressibility index: Compressibility index is calculated as follows Tapped density- Bulk density/ Tapped density*100
The value below 16% indicates a powder with good flow characteristics where as above 25% indicates poor flowability.

Hausner's Ratio:

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 – 1.5.it is the determined by the ratio of tapped density and bulk density.

Evaluation of RRCT:

Weight variation test:

Weight variation was carried out by taking 20 tablets and weighed and the average weight was taken. Then the tablets were weighed individually. The percentage weight variation of each tablet from average weight was calculated using the following formula %Deviation=Individual weight-Average weight/Individual weight * 100

Tablet dosage form assay (Drug Content):

Twenty tablets were powdered, and 10 mg equivalent weight of Enalapril maleate tablet powder was accurately weighed and transferred into a 100 ml volumetric flask and dissolved with buffer solution. The solution in the volumetric flask was filtered and Pipette out 0.5 ml from above solution into 10 ml volumetric flask and make up with 1 ml FeCl3, 1 ml potassium ferricyanide, kept aside for 10 min. and 1 ml conc. HCl and mark with distilled water . Then, analyzed spectrophotometrically at 778 nm.

Hardness test:

The hardness of the tablet was measured using a Pfizer hardness tester. It is expressed in Kg/cm^3.

Friability test:

The friability of the tablet was measured using Roche friabilator. It is expressed in percentage (%). 5 tablets were weighed and transferred to the Friabilator. The friabilator was operated at 25 rpm for 4 min. The tablets were weighed again. The % friability was then calculated by
% Friability= Initial weight – Final weight / Initial weight * 100

In vitro disintegration test:

In vitro disintegration time of tablets from each formulation was determined by using digital tablet disintegration apparatus. In vitro disintegration test was carried out at 37 ± 2 in 900 ml. Acid buffer pH 1.2.

Evaluation of Floating Pulsatile Tablet:

Buoyancy determination:

The buoyancy test of floating pulsatile release tablet was studied by placing them in 900 ml beaker containing Buffer pH 1.2, then tablet from same batches were placed in dissolution test apparatus containing buffer pH 1.2, maintained at 37±0.1 ºC and agitated at 50 rpm. The floating onset time (time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation.

Drug release lag time:
The lag time is the time interval between the dosage forms is placed into the aqueous environment and drug get to release from its dosage form after rupturing or eroding outer layer. It should be determined during the invitro drug release study.

In vitro dissolution studies:
The in vitro dissolution studies were carried out in acid buffer pH 1.2.(900 ml) at 37 ± 0.5 C using USP dissolution apparatus type II. The speed of rotation was maintained at 50 rpm. Aliquots of dissolution medium were withdrawn at predetermined time interval and content of Enalapril Maleate was determined by using UV Spectrophotometer.

Optimization by using 3^2 full factorial Experimental Design:
It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man, hours and raw materials. Traditionally pharmaceutical formulations after developed by changing one variable at a time by trial and error method which is time consuming in nature and requires a lot of imaginative efforts. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interaction. The number of experiments required for these studies is dependent on the number of independent variables selected.

Stability study of floating pulsatile tablet:
The optimized formulation was subjected for accelerated stability studies as per ICH guidelines Q1A (R2) by keeping sample in stability chamber. The formulation was stored at different storage conditions like 40±2 ºC / 75±5 % RH for 30 days.
The formulation was subjected to different tests such as drug release lag time and in vitro drug release study.

Analysis of drug candidate:
Drug characterization
UV Characterization
Enalapril maleate shows maximum absorbance at wavelength maxima at 760 nm by uv- visible method.

FTIR Spectra[25],[26]
The IR spectrum of pure drug was having the same peak as of pure drug spectra in standard.

calibration curve of enalapril maleate
A representative spectrum of enalapril maleate showing wavelength maxima at 760 nm for concentration of 5 µg/ml are shown in figure.

Preparation of calibration curve
Enalapril maleate exhibits maximum absorbance at 760 nm and obeyed beer's law in range of 1-5 µg/ml. The result of calibration curve preparation are shown below.

DISCUSSION:-
From this preliminary test, it should concluded that core tablet have ability to disintegrate rapidly which fulfill the requirement for pulsatile drug delivery. so this formulation can be used for development of floating pulsatile tablet.

Evaluation of factorial batches
Angle of repose less than 30 º indicates good flow property. Compressibility index up to 16% indicates good compressibility and value obtained showed satisfied flow property

Evaluation of post compressional parameter
The hardness value of formulation were within the range 3-5 kg/cm^3. Friability values of all formulation less than 1%. According to USP, less than 10 % weight variation is acceptable in the tablet formulation having avg. weight less than 130 mg.

Evaluation of pulsatile release tablet
Evaluation of preliminary trial batches

DISCUSSION:-
Drug release lag time is most important parameter in pulsatile drug delivery system. Drug release lag time more than 6 hrs is requirement or criteria for pulsatile delivery. So from this batches of floating pulsatile tablet it should concluded that if only HPMC E5 or HPMC E15 are used for pulsatile release coating layer give drug release lag time 96 min. and 331 min. which can not fulfill criteria for pulsatile. And HPMC E50 give lag time more than expected outcome which can not able to give suitable drug release at specific time. But when combination of HPMC E5 and HPMC E15 can be used than it will give drug release lag time 456 min. which fulfill criteria of pulsatile delivery. So weight ratio of HPMC E5 and HPMC E15 are used for development of floating pulsatile tablet.

Statistical Optimization

Fitting of data to the model

A two-factor, three-level full factorial statistical experimental design requires 9 experiments. All the responses observed for 9 formulations prepared were simultaneously fit to quadratic model using Design Expert 9.0.2.0. It was observed that the best fit model was quadratic model and the comparative values of R2, SD, and %CV are given in table along with the regression equation generated for each response as shown in table. A positive value represents an effect that favours the optimization, while a negative value indicates an inverse relationship between the factor and the response. It is evident that both independent variables, viz., Weight ratio of HPMC E5: HPMC E15 (X1) and Conc. of SSG (X2) have positive effects on the responses, viz., Y1 (Drug release lag time) and Y2 (% CDR at 8 h).

Validation of experimental model

For the checkpoint formula, the results of the dependent variables Y1 (Drug release lag time) and Y2 (%Drug Release at 8 h) were found to be within limits. Table 5.25 shows the predicted and experimental values for all the response variables, and the percentage bias. Percentage bias is helpful in establishing the validity of generated equations and to describe the domain of applicability of RSM model.

Stability Study of optimised batch

After one month stability study of optimized formulation, values of parameters like drug release lag time and % cumulative drug release at 8 hr. were almost similar to the initial values. There was no significant change in any value so formulation is stable.

Comparision with marketed product

Comparision of optimized batch formulation with marketed product of enalapril maleate uncoated tablet.

DISCUSSION:

From the in-vitro release study of marketed product, it can be concluded that the marketed product released maximum drug within 30 minute and when it compared with selected formulation of pulsatile tablet, it released maximum drug at 8 hrs. Hence, it can be concluded that marketed product was immediate release tablet and selected formulation was controlled released tablet.

CONCLUSION:-

The present investigation deals with the formulation and development of floating pulsatile drug delivery system for chronotherapy of hypertension using polymers such as HPMC E5, HPMC E15 and HPMC E50. Combination of HPMC E5 and HPMC E15 were used as release rate controlling polymer for maintaining of drug release lag time. So thus Enalapril maleate could be successfully delivered to provide chrono pharmacotherapy if taken at bed time and gives early morning release during that time worsening of condition.

From the evaluation parameter of trial batches it should be concluded that if the concentration of polymer increases or using high viscosity grade polymer than drug release lag time will be increases.

The formulation was optimized using two factor and three level factorial design. The amount of independent variables like weight ratio of polymer HPMC E5: HPMC E15 (X1) and concentration of SSG (X2) showed effect on dependent variables like drug release lag time (Y1) and % drug release (Y2) at 8 hr. Response surface methodology was used to predict levels of factor X1 and X2 to obtain optimization of formulation. From the results of factorial batches, it should be concluded that weight ratio of polymer increase than lag time increase and conc. of SSG increase than % drug release increase. After 1 month stability of optimized batch it should be concluded that there is no significant change in lag time and % drug release.

REFERENCES:

1. Khochage SR, Bhutkar MA, Indryani R, "A Review On Pulsatile Drug Delivery System." Am. J. Pharm Tech Res.**2013**,3,18-35.
2. Anantha NR, Bairi AG, "A Review on - Recent advances in oral pulsatile drug delivery." J. Adv. Pharm. Sci..**2011**,1,133-145.
3. Haribansh NS, Shivangi S, Sunil S, Ajit KY, "Pulsatile drug delivery system: Drugs used in the pulsatile formulations." Res. J. Pharma Dosage Forms and Technology.**2013,**5,115-121.
4. Hitesh S, Jignesh T, Jainish P, "Floating pulsatile drug delivery system: A Review." Uni. J. Pharmacy.**2013,**2,6-13.
5. Supriya S, Ashwini D, Tejal B, Chaitali S, "Technologies in pulsatile drug delivery system." Int. J. Adva. in Pharmacy, Biology and Chemistry.**2012**,1,438-445.
6. Nayana DP, Bari MM, Barhate SD, "A Review on novel approach pulsatile drug delivery system" Int. J. Pharm. Sci. Rev. Res.**2013**,21,209-222.
7. Ganesh R, Ganesh B, Siddheshwar D, Amol T, "Pulsatile drug delivery system: Current scenario" Int. J. Pharma and Bio Sci.**2011**,2,332-343.
8. Ramon CH, Diana EA, Carlos C, "Chronotherapy of hypertension: Administration time dependent effects of treatment on the circadian pattern of blood pressure" Adv. Drug Delivery Rev.**2007**,59,923-939.
9. Francesco P, Bjorn L, "Chronobiology and chronotherapy of ischemic heart disease" Adv. Drug Delivery Rev.**2007**,59,952-965.
10. Harshida GP, Karishma P, Upadhyay UM, Viral HS, "Chrono modulated drug delivery system: A Review" Pharmacy Rev. & Res.**2013**,3,26-32.
11. Asim SM, Nikhil B, Kazi MK, "Drug delivery system based on chronobiology-A Review" J. Controlled Release.**2010**,147,314-325.
12. Maroni A, Lucia Z, Maria DDC, Giulia L, Andrea G, "Oral pulsatile delivery: Rationale and chrono pharmaceutical formulations." Int. J.

Pharma.**2010,**398,1-8.
13. Shan-Yang L and Yoshiaki K, "Current status and approaches to developing press-coated chrono delivery drug systems." J. Controlled Release.**2012**,157,331-353.
14. Usha YN, Gopal VS, Yogendra N, Ranjith KA, "Chronotherapeutic drug delivery for early morning surge in blood pressure: A programmable delivery system" J. Controlled Release.**2009**,136,125-131.
15. Badoni A, Ojha A, Gnanarajan G, Kothiyal P, "Review on gastro retentive drug delivery system" The Pharma Innovation.**2012**,1,32-42.
16. Pallavi P, Vijay S, Lalit S, "A review on floating type gastroretentive drug delivery system" Int. Res. J. Pharmacy.**2012**,3,37-43.
17. Vairappan K, Ayarivan P, Viswanadhan VP, Krishnamoorthi M, "Enhancement of drug bioavailability by floating drug delivery system- A Review" Int. J. Drug Delivery.**2011**,3,558-570.
18. Srisagul S and Pornsak S, "Design and evaluation of floating multi layer coated tablets based on gas formation." European J. Pharma. Biopharm..**2008**,69,255-263.
19. Hao Z, Xuetao J, Lingshan K, Shen G, "Design and evaluation of dry coated drug delivery system with floating-pulsatile release." J. Pharm. Sci.**2007**,97,263-273.
20. Andrea G, Luca P, Anastasia F, Maria ES, "Oral pulsatile delivery systems based on swellable hydrophilic polymers." European J. Pharma. and Biopharm.**2008**,68,11-18.
21. Rujivipat S and Bodmeier R, "Modified release from hydroxypropyl methylcellulose compression-coated tablets" Int. J. Pharma.**2010**,402,72-77.
22. Efentakis M, Koligliati S, Vlachou M, "Design and evaluation of a dry coated drug delivery system with an impermeable cup, swellable top layer and pulsatile release." Int. J. Pharma.**2006**,311,147-156.
23. Bussemera T, Peppas NA, Bodmeier R, "Evaluation of the swelling, hydration and rupturing properties of the swelling layer of a rupturable pulsatile drug delivery system." European J. Pharma. and Biopharm.**2003**,56,261-270.