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RESEARCH ARTICLE

In Vitro Studies for the Formulation and Evaluation of Pulsincap of Ibuprofen for Arthritis

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ABSTRACT

The objective of the present study was to develop colon targeted pulsatile drug delivery system of ibuprofen for the treatment of arthritis. Drug excipients interaction was carried by UV spectroscopy, FTIR, swelling index, in vitro studies by dissolution. Ibuprofen granules were prepared by wet granulation method. When different ratio used as a hit and trial method based on results obtained from initial trials (f1-f10) pulsatile capsule formulation design with hydrogel plug. The formulation evaluated for chronokinetics and *in vitro* studies based on physiochemical parameters and polymers ratio used. It was found that increase in the ratio of the polymer results to decrease the pulsincap properties and release of active ingredient content will also varied. Present f1 batch conducted that successfully targeted to colon in the treatment of arthritis. Drug release over the period of 5-16hr can be achieved from formaldehyde treated hard gelatine capsule and hydrogel plug.

KEYWORDS

Pulsatile, Colon Targeted, Ibuprofen Chronokinetic, Chronotherapeutics

INTRODUCTION

Chronopharmacotherapy

Chronopharmacotherapy is the cure of pharmaceutical disorders by control release drug delivery system or pulsatile drug delivery system according to circadian rhythm of disease by increasing therapeutic outcome and decreasing side effects of drug because chronopharmaceutics drugs design to release drug within short period of time immediately after a predetermined lag time.[1-2]

Chronopharmaceutics

Chronopharmaceutics is define as a branch of pharmaceutics devoted to the design and evaluation of drug delivery system, that release a drug content immediately after a predetermined lag time at a circadian rhythm to receive the pharmacological requirement for the given drug.[3]

Pulsatile drug delivery system is a controlled drug delivery system, this system are produced to make time predetermined and site predetermined delivery of active drug according to circadian rhythm of the body.[4]

Pulsatile drug delivery system has most popular form of controlled drug delivery system because conventional system with continuous release are not ideal because it cause many side effect and adverse effect on human body. These system are beneficial for the drug having chrono-pharmacological behaviour.[5-6]

Colon targeted drug delivery system may be develop to release the drug within a short period of time after predetermined leg time at specific sit.[7]

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Control drug delivery system would also useful when delay absorption required from the therapeutic use for the treatment of disease that have peak symptoms in the early morning and that represent circadian rhythm such as arthritis, peptic ulcer, migrant angina pectoris migraine etc.

Pulsatile drug delivery also known as chronotherapeutics drug delivery system, colon targeted drug delivery system, sustained and controlled release drug delivery system are provide prolonged therapeutic effect, reduced the GIT toxic effect and dosing frequency and compliance. The drug Ibuprofen (RS)-2(4-(2-methylpropyl)phenyl) propanoic acid is practically insoluble in water, but very soluble in organic solvent like ethanol, methanol acetone and dichloromethane having 87%-100% oral administration bioavailability, 98% protein binding, metabolised in liver, 1.3-3hr biological half life and 95% excrete from urine. Ibuprofen is a non- steroidal anti- inflammatory drug (NSAIDs) having good chronopharmaceutical properties that is helpful for preparation of pulsincap drug delivery system which used in the treatment of disease required presence of drug in the body according to circadian rhythm after predetermined lag time. Here control release drug delivery system prepared by pulsincap method by using different polymers ratio of HPMC, magnesium stearate, and polyethyelene oxide and granulating agent as ethanol.

Mode of Action of Ibuprofen Use as Active Ingredient

Ibuprofen is a non-steroidal anti inflammatory drug (NSAID) non-selective cyclo-oxygenase (COX) inhibitor which responsible for conversion of arachidonic acid into prostaglandin H_2 (PGH_2). Prostaglandin cause pain, inflammation and fever in the body. Ibuprofen also inhibit conversion of some prostaglandin H_2into thromboxane which responsible for blood clotting.[8]

MATERIAL AND METHODS

Ibuprofen and HPMCK was gift sample by Lloyd School of Pharmacy Greater Noida (UP), India. Ethanol, HPMCK, magnesium stearate was supplied by SK traders New Delhi. All other chemical used of analytical grade.

Drug-Characterization

UV Spectroscopy

Calibration curve of ibuprofen was plotted with water, pH 1.2, 7.4 and 6.8 buffer with different concentration (1, 2, 3, 4, 5µg/ml) of the solution was taken at wavelength 248 nm against the blank solution (UV spectroscopy 400-200nm).[9]

FT-IR Spectroscopy

Infrared spectroscopy was used to determine drug excipients interaction using FTIR spectrometer (4100) at 2000-400cm^{-1}.[9]

Drug Excipient Interaction Study

Fourier Transform Infrared Spectroscopy

The IR spectra of Ibuprofen, polymer and resulting formulation were recorded by Fourier transform infrared spectroscopy using the range 2000-400cm^{-1}. The sample was mix with dry powder potassium bromide in 1:10 ratio and prepared pallets. Then these pallets disc was placed in IR spectrophotometer and IR spectra was recorded.[9]

Formulation

Treatment of Hard Gelatine Capsule

For the treatment of hard gelatine capsules, take zero size hard gelatine capsules and removes the bodies from cap. Take formaldehyde in petridish, put in desiccator, place bodies removed from cap in petridish containing formaldehyde and closed tightly the lid of desiccator for 12-14 hr. After 12-14 hr open lid of desiccator remove bodies from petridish and dried at $50^{O}C$ for 30 minutes. After completion of reaction between gelatine and formaldehyde store treated bodies at room temperature in poly beg.[10-13]

Preparation of Hydrogel Plug

For preparation of pulsing cap take equal amount of HPMCK 50 mg and methyl cellulose 50 mg compressed by 7mm punches and dies in a rotary tablet punching machine. The hydrogel plug store at room temperature in poly beg.

Formulation of Ibuprofen Granules

Ibuprofen granules were prepared by wet granulation method. Take 300 mg Ibuprofen and different polymers ratio (show in table 1) used to preparation of Ibuprofen granules for pulsincap study. Polymers like HPMCK, Mg stearate and polyethylene oxide mix, sieved with 60 no. mesh size and add Ibuprofen. The powder were blend and make a wet mass by using ethyl alcohol as granulating agent. The wet mass was passed through a mesh and granules were dried at $50^{O}C$ for 1 hr.

Preparation of Pulsincap Drug Delivery System

Prepared ibuprofen Granules filling in zero size formaldehyde treated insoluble hard gelatine capsule bodies. After granules, insert prepared hydrogel plug 100 mg into capsule bodies and then finally soluble caps fitted to the capsule bodies.

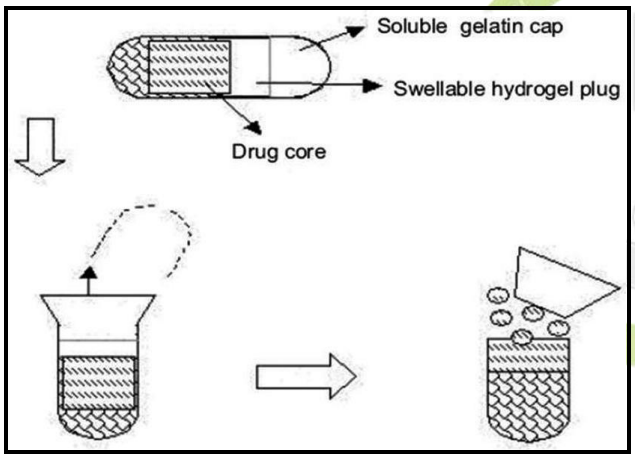

Figure 1: Pulsatile drug delivery system

Evaluation Parameters

Capsule Bodies

Length and Width Testing

Various test carried out of formaldehyde treated and untreated capsule bodies like diameter and length by dial calliper.[10-13]

Solubility Testing

After formaldehyde treatment the capsule bodies were tested in 0.1N HCl. Time recorded at which bodies dissolve or form fluffy mass was happen.[10-13]

Test for Free Formaldehyde

Take 25-30 formaldehyde treated capsules bodies, cut into small parts and taken into a beaker containing 30-40 ml de-mineral water (DM water) and stirrer for about 1 hr. Take resultant solution into 100ml volumetric flask and make-up the volume up to 100 ml. Take 2 ml solution from resultant solution into glass test tube add 4 ml DM water and 4 ml acetone. The resulting solution was less intense than standard solution which prepared same manner as test solution. Examine both test tube containing test and standard solution on their vertical axis.[14]

Evaluation of Hydrogel Plug

Hardness, thickness and lag time testing parameter were evaluated for hydrogel plug. Lag time performed using USP2 dissolution apparatus in 6.8pH phosphate buffer for 10 hr and observed drug dissolution rate.

Evaluation of Ibuprofen Granules

Prepared granules evaluated for bulk density, tapped density, angle of repose, flow rate, compressibility index etc.[15]

Bulk Density

It is the density of any material in gm/ml determined by without tapping of material in a graduate measuring cylinder. Calculated by

Bulk density = weight of microspheres in gm/volume in ml consumed by microspheres

Tapped Density

It is the density of any material in gm/ml determined by tapping of material in a graduate measuring cylinder. Calculate by

Tapped density = weight of microspheres in gm/volume in ml after tapping

Angle of Repose

Angle of repose used to determined flow properties of powder or granules measure in degree, calculated by

$$\text{Tan } \Theta = 2H/D$$

Where

H = standing height

D = diameter of the microspheres heap formed on a graph paper

Flow Rate (Compressibility Index)

Flow rate of microspheres determine by compressibility index (I) equation

$$I = [1-V/V_O] \times 100$$

Where,

V = volume occupied by sample after tapping

V_O = volume before tapping

When value of I below than 15% show good flow properties and when value of I above 25% show poor flow properties.

Evaluation of Prepared Pulsatile drug Delivery System

Uniformity of Weight

Take 10 capsules were selected from each batch and weight together and then take filled and empty weight of each capsule and determine weight variation of pulsincap capsule by subtracting empty capsule weight from filled weight of capsules.

Swelling Index

Hydrogen plug were tested for swelling index using disintegration apparatus in phosphate buffer pH6.8. Tablet weight and placed in USP disintegration apparatus for predetermined interval. Tablets were remove, release excess fluid and reweight. And calculate from given swelling index formula.

$$\% \text{ water uptake} = w_s\text{-}w_{i/}w_p \text{ x } 100$$

Where,

w_s- Weight of swollen matrix at time t

w_i - initial weight of matrix

w_p - weight of polymer in the matrix

Drug Content

Take 10pulsincap capsule, Remove content and powdered by mortar pastel. Take 100mg content in 100ml volumetric flask, add 10ml methanol to dissolve Ibuprofen and make up the volume up to 100 ml with phosphate buffer pH 6.8,filter through 0.45µm filter paper, Suitably dilute and drug content was determine by UV spectroscopy at 248nm wavelength.

Disintegration Time

Disintegration time were determined in USP disintegration test apparatus. Disintegration time noted at which pulsatile capsule disintegrate or make fluffy mass.

In-Vitro Dissolution Study

In vitro dissolution study were determine by using USP dissolution test apparatus, first of all prepared phosphate buffer of pH6.8 for dissolution media. Fill 900ml dissolution media in USP type-1 (basket system) dissolution apparatus set 100rpm for predetermined time interval at 37±0.5^{O}C temperature. After each predetermined time interval withdraw 5ml of dissolution fluid and replace with fresh dissolution medium, maintain same temperature condition. Filtered sample, dilute suitably and assayed for ibuprofen pulsincap at 248nm λmax. All the absorbance takes by three times and determine mean value of absorbance.

Analysis of Dissolution Data

Obtained dissolution data fitted into zero order[16], first order[17-18], higuchi[19] and erosin[20] equation. To determine drug release properties of pulsatile drug delivery system.

Zero Order Release Pharmacokinetics

It define a linear relationship between the fraction of drug release versus time

$$Q = K_O t$$

Where,

Q - Fraction of drug release at time t

K_O- zero order release rate constant

A plot between drug release versus time will be linear.

First Order Release Kinetics

Wagner assumed that the exposed surface area of a tablet decrease exponentially with time during dissolution process. The most slow drug release formulation describe by first order kinetics

First order equation is

$(I-Q) = -K_1t$

Where,

Q- Fraction of drug release at time t

K_1- first order kinetics

Logarithmic plot of the fraction of drug release verses time remain liner if drug release follow first order kinetics.

Higuchi Equation

It define a linear dependence of the active fraction release per unit of surface (Q) on the square root of time

$$Q = K_2t^{1/2}$$

RESULTS AND DISCUSSION

Where,

K_2-release rate constant

A plot of the fraction of the drug released against root of time will be linear if the drug release follow higuchi equation.

Erosion Equation

This equation define the drug release based on erosion alone

$$Q = 1-(1-K_3t)^3$$

Where,

Q-fraction of drug release at time t

K_3- release rate constant

The plot between $[1-(1-Q)^{1/3}]$ against time follows erosion equation.

Table1: Formula for the Preparation of Ibuprofen Pulsatile Capsule

S. No	Ingredient	Qty (mg)									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Ibuprofen	300	300	300	300	300	300	300	300	300	300
2	HPMCK	10	20	30	40	50	60	70	80	90	100
3	Mg stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
4	Polyethylene oxide	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Table 2: Composition for Pulsincap Drug Delivery System

Formulation code	Wt. of empty body (mg)	Wt. of granules (mg)	Hydrogel plug (100mg)	Wt. of cap (mg)	Total wt. of capsule (mg)
F1	58.82	313.4	99.41	39.43	511.76
F2	59.64	323.6	98.64	38.61	520.49
F3	59.24	334.5	101.3	39.61	534.65
F4	59.86	344.6	100.6	38.64	543.7
F5	60.03	354.2	100.7	39.43	544.36
F6	59.21	362.9	99.61	38.58	560.30
F7	59.45	372.8	99.41	38.64	570.30
F8	60.43	383.7	99.24	38.71	582.08
F9	60.04	394.4	98.41	38.79	591.49
F10	58.93	413.6	99.74	38.13	610.4

Table 3: Drug Content in Various Ibuprofen Pulsatile Capsule

S. No.	Formulation code	Drug content (%)
1.	F1	98.35
2.	F2	98.13
3.	F3	97.65
4.	F4	98.45
5.	F5	96.56
6.	F6	97.72
7.	F7	96.76
8.	F8	98.76
9.	F9	98.47
10.	F10	97.43

Table 4: Dissolution Data of Various Ibuprofen Pulsatile Capsule (F1-F10)

S. No	Time (hr)	% Drug Release									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	1	12.24	10.45	9.36	9.02	8.52	7.73	7.13	7.42	5.92	4.91
2.	2	25.61	21.64	17.41	16.21	16.04	15.64	14.61	13.81	12.15	10.62
3.	3	38.45	30.51	26.41	24.21	23.61	22.84	22.04	21.65	20.04	18.64
4.	4	46.97	44.36	31.56	30.82	28.41	27.09	27.64	26.58	25.10	24.61
5.	5	56.91	52.91	39.51	38.42	38.11	37.23	36.24	36.01	35.61	34.24
6.	6	65.76	61.42	47.64	45.21	44.91	44.16	43.68	42.21	40.35	48.26
7.	7	74.93	73.61	59.51	57.61	57.18	56.58	55.39	54.59	52.19	50.51
8	8	86.47	80.61	70.36	68.59	67.02	66.72	65.93	65.21	63.40	60.21
9.	9	93.45	83.41	82.76	82.21	80.06	78.51	76.21	75.93	73.24	68.32
10.	10	96.82	90.52	86.36	84.24	81.51	80.13	78.13	76.82	74.61	72.36

In drug dissolution study of pulsincap drug delivery system indicate that drug release from pulsincap was uniform over the period of 10hr (table 4) this is due to different polymer concentration of HPMCK in a range 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 mg, use in the formulation of ibuprofen granules which filled in formaldehyde treated capsules range from f1 to f10.The soluble cap of capsule which dissolve in phosphate buffer and then the polymer plug absorbed the surrounding fluid, swelled and released the drug through the swollen matrix. After complete swollen of plug, it ejected out of the capsules body, released drug into colon fluid from the ibuprofen granules. This in-vitro dissolution data show that increasing the HPMCK polymer cause decreasing drug release profile of pulsatile drug delivery system.

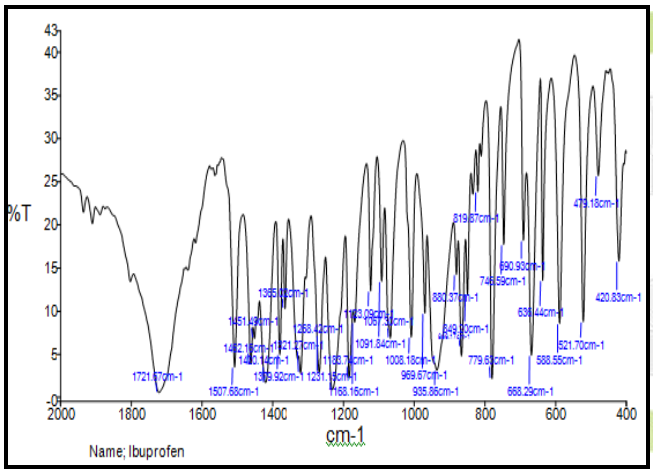

Figure 2: FTIR spectrum of Ibuprofen

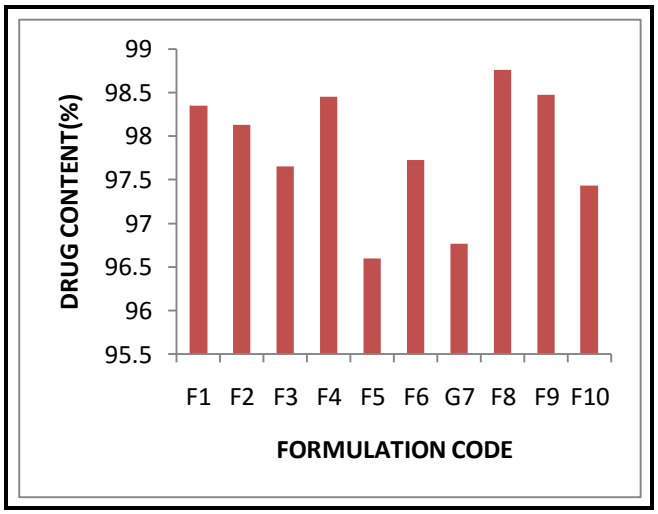

Figure 3: Histogram of percentage drug content of formulation f1-f10

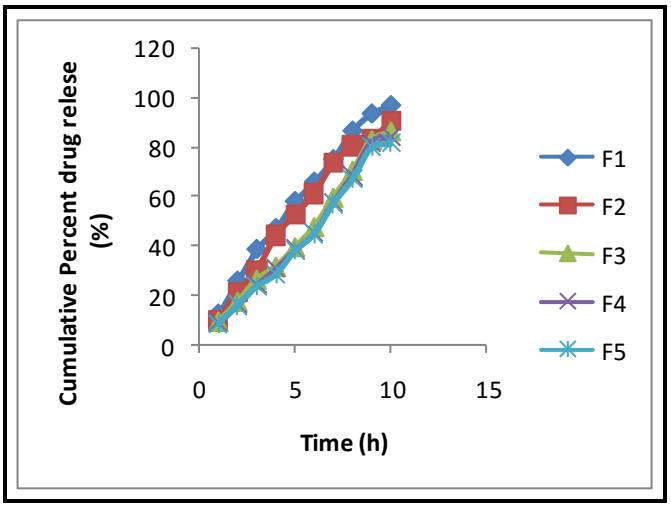

Figure 4: Dissolution plots of ibuprofen pulsatile capsules (F1-F5)

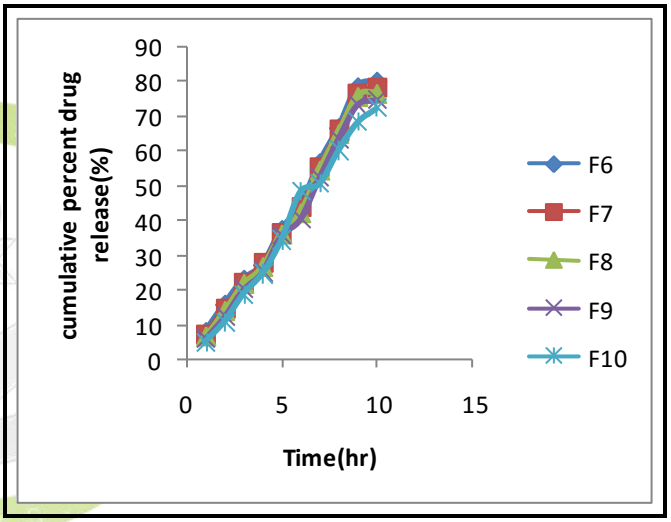

Figure 5: Dissolution plots of Ibuprofen pulsatile capsule (F6-F10)

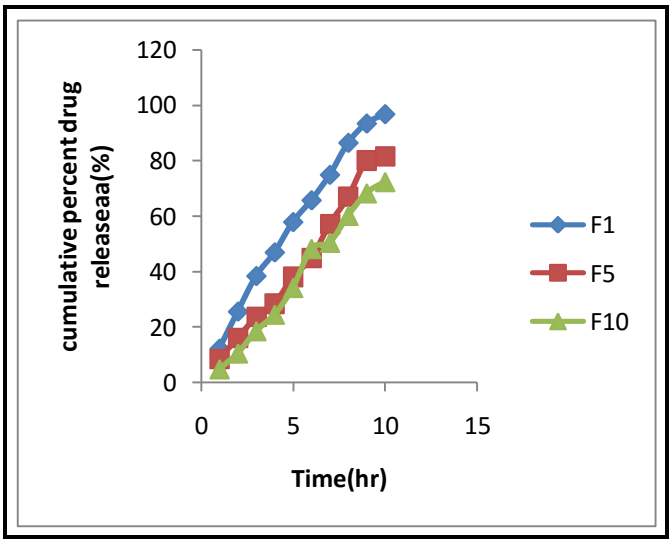

Figure 6: dissolution plots for various ibuprofen pulsatile capsules

CONCLUSION

Pulsatile drug delivery system is specially design to colon targeted drug delivery system to maintain the chronopharmacological anti-arthritis action of drug.

We prepared 10 batch of pulsatile drug having different polymer concentration in a range 10-100mg having code f1-f10.

Their in-vitro dissolution properties check in phosphate buffer pH6.8 at 37±0.5ºC in USP dissolution apparatus type 1 (basket system). Withdraw selected volume of sample fluids after predetermined time interval dilute accordingly and note reading using UV spectroscopy at 248nm and make dissolution data for f1 to f10 batch of 10 hr. This data show drug releasing properties decrease from f1 to f 10.

From these formulation f1 show good drug release profile after a lag time over a period of time 10 hr at specific site of action.

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