FORMULATION AND IN VITRO EVALUATION OF BUPROPION PRESS COATED TABLETS

Shaik Rasheed* G.Archana

Department of pharmaceutics, Srikrishna devaraya University College of Pharmaceutical Sciences

Rasheedsk1798@gmail.com archana.pharma156@gmail.com

ABSTRACT:

The purpose of the present study was to design and evaluate an Oral, site specific, Pulsatile drug delivery system containing Bupropion Press Coated Tablets as a model drug. The powder blend containing Bupropion, ludiflash, lycoat, MCC and talc was prepared and evaluated for flow properties and FTIR studies. From the obtained results, F4 powder blend formulation was selected for further fabrication of pulsatile capsules. Hydrogel plug was formulated in a lone and in combination of hydrophobic polymer like ethyl cellulose with hydrophilic polymers like HPMC K15M in 1:1, 1:2, and 2:1 ratio to maintain a suitable lag period. Invitro release studies of pulsatile device revealed that increasing hydrophilic polymer content resulted in delayed release of Bupropion from the pulsincap after a predetermined lag time of 9hrs. Based on Invitro studies performed, B5F4 was found to be optimized formulation.

KEY WORDS: *Oral, site specific, Pulsatile drug delivery system,Bupropion,Tablets.*

INTRODUCTION:

Controlled drug delivery systems have acquired a centre stage in the arena of pharmaceutical research and development sector. Such systems offer temporal and /or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of patentability. Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for obvious advantages of oral route of drug administration. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern known as "pulsatile release.

Chronotherapeutics is a branch of pharmaceutics devoted to design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Ideally chronopharmaceutical drug delivery system (ChrDDS) should embody time-controlled and site specific drug delivery system.

In this century, the pharmaceutical industry is caught between pressure to keep prices down and the increasing cost of successful drug discovery and development. In the form of an NDDS or ChrDDS, an existing drug molecule can "get a new life" thereby increasing its market value and competitiveness and extending patent life.

Among modified- release oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsative) and site-specific delivery of drugs. In particular, systems for delayed release are meant to deliver the active principle after a programmed time period following administration. These systems constitute a relatively new class of devices the importance of which is especially connected with the recent advances in chronopharmacology. It is by now well-known that the symptomatology of a large number of pathologies as well as the pharmacokinetics and pharmacodynamics of several drugs follow temporal rhythms, often resulting in circadian variations. Therefore, the possibility of exploiting delayed release to perform.

Chronotherapy is quite appealing for those diseases, the symptoms of which occur mainly at night time or in the early morning, such as bronchial asthma, angina pectoris and rheumatoid arthritis. The delay in the onset of release has so far mainly been achieved through osmotic mechanisms, hydrophilic or hydrophobic layers, coating a drug- loaded core and swellable or erodible plugs sealing a drug containing insoluble capsule [body1-6.]

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. Most conventional oral controlled release drug delivery systems release the drug with constant or variable release rates. A pulsatile release profile is characterized by a time period of no release

(lag time) followed by a rapid and complete release.The present study was to design and evaluate an Oral, site specific, Pulsatile drug delivery system containing Bupropion Press Coated Tablets as a model drug.

Materials and Methodology:

1.1DEVELOPMENT OF CALIBRATION CURVE

a) Preparation of Standard Calibration Curve of Bupropion in 0.1 N HCL

10mg of Bupropion was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 0.1 N HCL buffer to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with 0.1 N HCL buffer to get 5 to 30 µg/ml of Bupropion. The absorbance of the solution were measured against 0.1 N HCL buffer as blank at 252 nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

b. Preparation of Standard Calibration Curve of Bupropion in 6.8 pH phosphate buffer

10mg of Bupropion was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8 pH phosphate buffer to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with 6.8 pH phosphate buffer to get 5 to 30 µg/ml of Bupropion. The absorbance of the solution were measured against 6.8 pH phosphate buffer as blank at 252 nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

1.2. Compatibility Studies

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. [7-10]

1.3. FLOW PROPERTIES OF API:

Bulk Density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve#20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/cc and is given by:

$$Db = m/Vo$$

Where,

m = mass of the powder

Vo = bulk volume of powder

Tapped density (Dt): It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between the two tapped volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. . It is expressed in g/cc and is given by:

$$Dt = m/Vi$$

Where,
m = mass of the powder
Vi = tapped volume of powder

Angle of Repose (θ): This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \theta = h/r$$

(Or)

$$\theta = \tan^{-1}(h/r)$$

Where,
θ = angle of repose
h = height of the heap r = radius of the heap

Compressibility Index: The flowability of powder can be evaluated by comparing the bulk density (Db) and tapped density (Dt) of powder and the rate at which it packed down. Compressibility index is calculated by:
Where,

$$\text{Compressibility index (\%)} = Dt - Db/Dt \times 100$$

Db = Bulk density
Dt = Tapped density

Hausner's Ratio: It is the ratio of tapped density to the bulk density. It is given by:

$$\text{Hausner's ratio} = Dt / Db$$

Dt = Tapped density Db = Bulk density
The flow properties of API alone and along with excipients i.e., powder blend was calculated by using the above formulae and the type of flow can be compared by using the following standard specifications were shown in table 1.

Table 1 Standard specifications for comparison of flow properties

S.No	Flow property	Angle of repose	Carr's Index	Hausner's ratio
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair	36-40	16-20	1.19-1.25
4.	Passable	41-45	21-25	1.26-1.36
5.	Poor	46-55	26-31	1.35-1.45
6.	Very poor	56-65	32-37	1.46-1.59
7.	Very very poor	>66	>38	>1.6

1.4. Pulsincap Desingning [11-13]:

Designing or preparation of pulsincap capsules involves 3 steps:

i. Preparation of cross-linked gelatin capsule.
ii. Preparation of powder blends for filling into capsules.
iii. Formulation of pulsincap of Bupropion.

i. Preparation of Cross-Linked Gelatin Capsule:

Formaldehyde treatment:

About 100 hard gelatin capsules size '0' were taken. Their bodies were separated from the caps and placed on a wire mesh. The bodies which were placed on a wire mesh were spread as a single layer. 25 ml of 15% v/v of formaldehyde solution was prepared and placed in a desiccators. To this 5 g of potassium permanganate was added. The wire mesh containing the bodies of the capsules was kept on the top of desiccators' containing formaldehyde liquid at the bottom in equilibrium with its vapor and immediately the desiccators' was tightly closed and sealed. The bodies of capsules were made to react with formaldehyde vapors by exposing them for varying periods of time viz., 2, 4, 6, 8, 10hrs. Then they were removed and kept on a filter paper and dried for 24 hrs to ensure completion of reaction between gelatin and formaldehyde vapors, afterwards the capsules were kept in an open atmosphere, to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated cap and stored in a polythene bag.

Use of Formaldehyde treatment:

The main aim of formaldehyde treatment was to modify the solubility of hard gelatin capsules. Cross-linking of gelatin molecules was achieved by exposing to formalin vapors. Cross-linking involves the reaction of amino groups in gelatin molecular chain with aldehyde groups of formaldehyde by a "Schiff's base condensation" so that the gelatin becomes water insoluble. Formaldehyde reacts with gelatin forming an irreversible complex. The primary amine group

present in gelatin reacts with formaldehyde making it irreversibly bound. Potassium permanganate was added to formaldehyde solution so that formalin vapors were produced. When bodies of hard gelatin capsule were exposed to formaldehyde vapors for different periods of time in a closed dessicator, vapor gets equilibrated with formaldehyde liquid and therefore makes the gelatin water insoluble.

ii. Preparation of Bupropion Tablet For Filling Into Capsules:

All the ingredients were passed through # 60 mesh sieve separately. The drug & M C C were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#44 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3-4 kg/cm^2 for all batches. The weight of the tablets was kept constant for all formulations F1 to F8 (100 mg).

Table 5.4 Formulation table for preparation of blend for filling of Bupropion pulsincap

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Bupropion	150	150	150	150	150	150	150	150
Ludiflash	5	10	15	20	--	--	--	--
Lycoat	--	--	--	--	5	10	15	20
MCC	90	85	80	75	90	85	80	75
Mg. sterate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total	250	250	250	250	250	250	250	250

iii. Formulation of Pulsincap of Bupropion:

iv.

The modified release pulsincaps containing 4 mg of Bupropion were prepared by using different excipients and polymers in varying ratios. The formaldehyde treated capsule bodies which were exposed to 6 hrs was optimized and chosen for the pulsincap formulation based on disintegration time. Optimized formulation of Bupropion tablet was filed into the capsule body. For hydrogel plug formulation, the plug was prepared by using the combination of Ethyl cellulose: HPMC K15M in varying ratios. Initially the total weight of the plug was taken as 100 mg alone and the ratio of hydrophobic & hydrophilic polymer as 1:1, 1:2 and 2:1

1.5. Evaluation of tablets:[14-18]

Tablet Dimensions:

Thickness and diameter were measured using a calibrated vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability test:

The friability of tablets was determined by using electrolab friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_I) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_F). The % friability was then calculated by –

$\%F = 100\ (1-W_I/W_F)$

% Friability of tablets less than 1% was considered acceptable.

Weight Variation Test:

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet according to U.S. Pharmacopoeia. Table 2: The following percentage deviation in weight variation was allowed.

Average weight of a tablet	Percentage deviation
130 mg or less	±10
>130mg and <324mg	±7.5
324 mg or more	±5

In all formulations, the tablet weight is 100 mg, hence 10% maximum difference allowed.

Test for Content Uniformity:

Tablet containing 150mg of drug was dissolved in 50ml of 6.8 pH buffer in volumetric flask. The drug was allowed to dissolve in the solvent. The solution was filtered, 2ml of filtrate was taken in 10ml of volumetric flask and diluted up to mark with distilled water and analyzed spectrophotometrically at 252 nm. The concentration of Bupropion was obtained by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each formulation batch.

In vitro Disintegration Time:

Tablet was added to 900ml of distilled water at 37±0.5ºC. Time required for complete dispersion of a tablet was measured.

1.6 In vitro Dissolution Study

In vitro dissolution of Bupropion tablets was studied in USP XXIV dissolution test apparatus. 900 ml Phosphate buffer 6.8 (simulated fluid) was used as dissolution medium. The stirrer was adjusted to rotate at 100 RPM. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 252 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent Bupropion released was calculated and plotted against time.

1.7 Method of preparation of Pulsincap dosage form:

I. Preparation of powder blend:

- Hard gelatin capsules of 'size 0' which were hardened with formaldehyde treatment for 6hrs were chosen for the formulation. The bodies and caps separated manually. Optimized formulation F4 was fitted at the bottom of the capsule body.

II. Preparation of Hydrogel plug:

- Plug was prepared as a compressed tablet and placed at the opening of capsule body. The capsule body was closed by a cap.
- Hydrogel plug was prepared by using different polymers like Ethyl cellulose, HPMC at different concentrations.
- A combination of hydrophobic and hydrophilic polymers were used viz., Ethyl cellulose: HPMC, in different ratios like 1:1, 1:2 and 2:1.
- A tight fit between the plug and impermeable capsule shell is essential to regulate water penetration into the capsule content and the drug release prior to complete erosion of plug material. Ideally plug should erode only from the surface exposed to the release medium.
- Plug ejection can be done by swelling on contact with aqueous fluids (or) pushing out by increased internal pressure (or) erosion (or) by enzyme degradation.

III. Capsule filling:

- Homogeneous mixture of drug and excipients were filled into the 6^{th} hr formaldehyde treated capsule body manually by filling method.
- Then, hydrogel plug in the form of a tablet is placed above the mixture i.e., at the opening of capsule body
- The capsule body was closed by a cap.

IV. Capsule sealing:

- The joint of the treated capsule body and untreated cap of the capsules was sealed with a small amount of 1% ethyl cellulose ethanolic solution.

.

1.8. Evaluation Of Pulsincap Dosage Form:[19-21]

In-vitro release studies:

Dissolution study was carried out to measure the release rate of the drug from the pulsincap formulation. *In-vitro* dissolution profile of each formulation was determined by employing

USP I apparatus by rotating basket method. In order to stimulate the pH changes along GI tract 2 different dissolution media with pH 1.2, 6.8, 2 buffers were sequentially used, and therefore referred to as "Sequential pH change method". The dissolution media were maintained at a temperature of 37 ± 0.5ºC throughout the experiment and the speed of rotation of basket maintained at 100 rpm. 900ml of dissolution medium was used at each time. Bupropion Pulsincaps was placed in basket in each dissolution vessel to prevent floating. While performing experiments, stimulated gastric fluid (SGF) pH 1.2 buffer was first used for 2 hrs (since the average gastric emptying time is 2hrs) and then removed and the fresh stimulated intestinal fluid (SIF) pH 6.8 buffer was added and used for remaining hours. 5 ml samples of dissolution fluid were withdrawn at predetermined time intervals with the help of a syringe. The volume withdrawn at each time interval was replaced with 5ml of fresh dissolution medium maintained at same temperature. The filtered samples were suitably diluted whenever necessary and assayed for Bupropion by measuring absorbance at 252 nm, by UV absorption spectroscopy. % CDR was calculated over the sampling times.

Table 3: Dissolution specifications of Bupropion

Vessel temperature	37 □ 0.5ºC
Bath temperature	□ 0.5ºC

1.9.Release Kinetics:[22-25]

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. Mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient(R) value in various models. The models with high 'R-value is considered as the best fit on the release data.

Various mathematical models are:

i. Zero order release model
ii. First order release model
iii. Higuchi release model
iv. Korsmeyer – peppas release model

Zero Order Release Equation: The equation for zero order release is

$$Q_t = Q_o + K_o t$$

Where ,

Q_O = Initial amount of drug

Q_t = Cumulative amount of drug release at time "t" K_O= Zero order release constant

T= Time in hours

The zero-order kinetics describes the systems in which the drug release rate is independent of its concentration of the dissolved substance. A graph is plotted between the time taken on x-axis and the cumulative percentage of drug release on y-axis and it gives a straight line.

First Order Release Equation: The first order release equation is

$$\text{Log } Q_t = \text{Log } Q_o + K_t / 2.303$$

Where,

Q_O = Initial amount of drug

Q_t = Cumulative amount of drug release at time "t" K= First order release constant

T= Time in hours

Here, the drug release rate depends on its concentration .The first order kinetics describes the systems in which the drug release rate is concentration dependent. A graph is plotted between the time taken on x-axis and the log % of drug release on y-axis and it gives a straight line.

Higuchi Release Equation: The Higuchi release equation is

$$Q_t = K_H \sqrt{t}$$

Where ,

Q = Cumulative amount of drug release at time "t" K_H = Higuchi constant

T = Time in hrs

Higuchi described the release of drug from an insoluble matrix as square root of time dependent process. A graph is plotted between the square root of time taken on x-axis and the cumulative percentage of drug release on y-axis and it gives it a straight line.

$$F = M_t / M = K_m t^n$$

Korsmeyer -Peppas Release Equation: The Korsmeyer –Peppas equation

Where,

F = fraction of drug released at time't' M_t = amount of drug released at time 't' M = total amount of drug in dosage form K_m= kinetic constant

n = diffusion or release exponent

A graph is plotted between the log time taken on x-axis and the log percentage of drug release on y-axis and it gives a straight line.

Table 4: Diffusion exponents and solute release mechanism

Diffusion (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
4	Anomalous (non fickian) diffusion
0.89	Case- transport
n>0.89	Super case-II transport

RESULTS AND DISCUSSION:

2.1 a. Preparation of Standard Calibration Curve of Bupropion in 0.1 N HCL

Table 5: Calibration data of Bupropion in 0.1N HCl.

Conc (µg/ml)	Absorbance
0	0
5	0.163±0.012
10	0.303±0.012
15	0.446±0.012
20	0.563±0.012
25	0.698±0.012
30	0.841±0.012

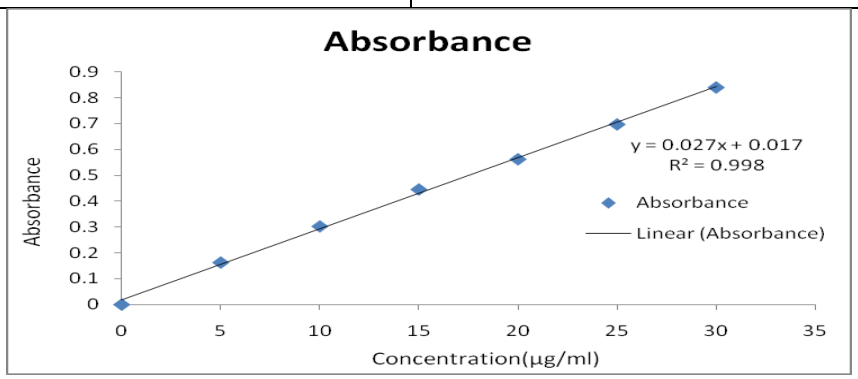

Fig 1: calibration curve of Bupropion with 0.1N HCl

2.1.b Preparation of Standard Calibration Curve of Bupropion in 6.8 pH phosphate buffer

Table 6: Calibration data of Bupropion in pH 6.8 phosphate buffer.

Conc (µg/ml)	Absobance
0	0
5	0.175±0.012
10	0.332±0.017
15	0.484±0.025

20	0.644±0.077
25	0.796±0.014
30	0.942±0.010

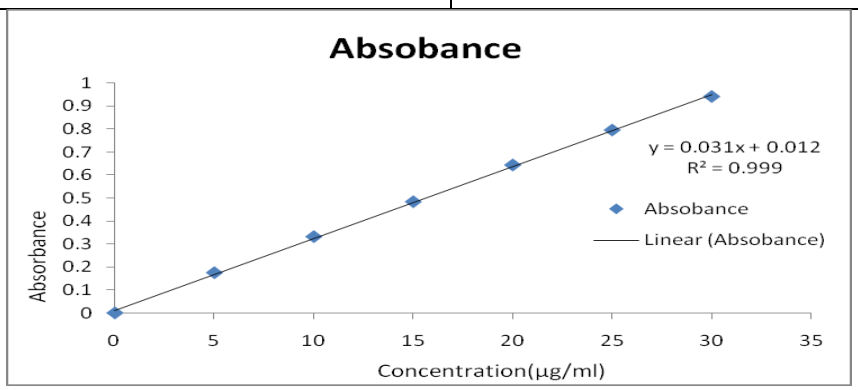

Fig 2: calibration curve of Bupropion with 0.1N HCl

The results of calinration curve of bupropion was showed in table 5 and 6; figure 1 and 2. The linearity was found to be in the range of 5-30µg/ml in pH 6.8 buffer and 0.1N HCl. The regression value was closer to 1 indicating the method obeyed Beer-lambert's law.

2.2 Drug-Excipient compatibility studies:

The IR spectrum of pure drug was found to be similar to the standard spectrum of Bupropion. From the spectra of Bupropion, combination of Bupropion with polymers, it was observed that all characteristic peaks of Bupropion were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and polymers. FTIR spectra of Bupropion, and Optimized formulation are shown in Figure respectively.

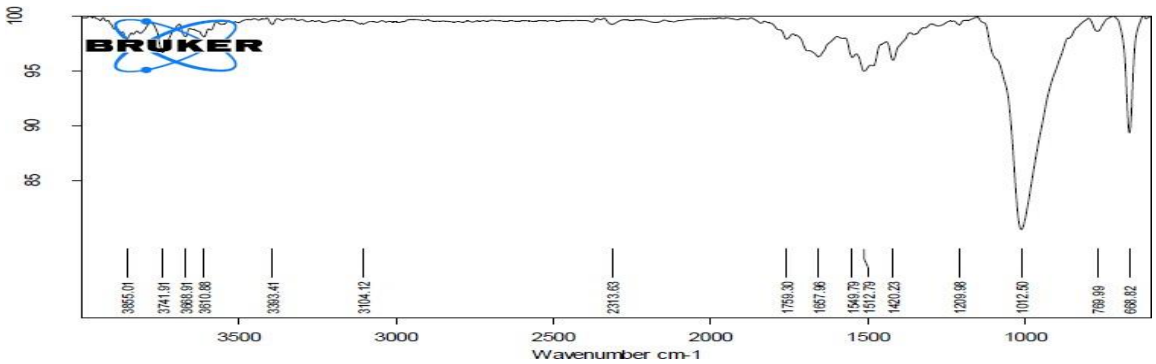

Fig 3: FTIR Spectrum of pure drug

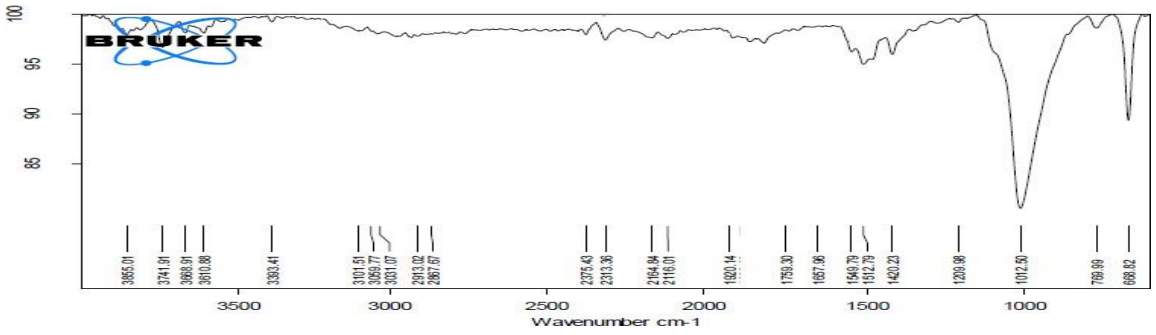

Fig 4: FTIR Spectrum of pure drug and Excipient**s**

2.3 Flow properties of powder blend:

Table 7: Flow properties of powder blend

Formulation Code	Angle of Repose±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	Hausner's ratio±SD
F1	27.85±0.15	0.373±0.15	0.470±0.86	14.61±0.02	1.20±0.53
F2	25.28±0.18	0.387±0.23	0.484±0.24	17.54±0.52	1.29±0.49
F3	29.32±0.63	0.353±0.78	0.468±0.39	15.74±0.36	1.28±0.63
F4	28.51±0.85	0.398±0.64	0.489±0.15	14.31±0.98	1.11±0.18
F5	27.12±0.21	0.375±0.26	0.462±0.50	17.25±0.42	1.15±0.42
F6	29.47±0.15	0.369±0.41	0.452±0.26	18.84±0.15	1.22±0.15
F7	27.54±0.24	0.372±0.28	0.453±0.30	19.68±0.15	1.20±0.24
F6	28.42±0.14	0.375±0.35	0.472±0.18	14.79±0.15	1.24±0.17

The angle of repose of different formulations was ≤ 29.47 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.364g/cm^3 to 0.389g/cm^3. Tapped density was found between 0.442g/cm^3 to 0.481g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 15.25- 18.54 and Hausner's ratio from 1.18-1.23 which reveals that the blends have good flow character.

2.5 Characterization of Tablets Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table.

Table 8: Characterization Bupropion Tablets

Formulation code	%Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness	Friability (%)	Disintegrating time(sec)	Drug content (%)
F1	2.42	2.43	8.10	3.8	0.70	20	95.15
F2	0.77	2.40	8.37	3.9	0.40	16	98.24
F3	2.12	2.58	8.21	3.8	0.64	29	96.75
F4	2.45	2.52	8.21	4.1	0.76	10	97.07
F5	2.26	2.30	8.20	3.7	0.98	21	99.80
F6	2.05	2.33	8.17	3.2	0.84	18	98. 57
F7	2.17	2.41	8.17	3.1	0.72	17	95.45
F8	2.60	2.36	8.17	3.4	0.68	19	100.44

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3-4 kg/cm^2.All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 –F8 and considered to be satisfactory ensuring that all the formulations are mechanically stable. The drug content values for all the formulations (F1-F8) was found to be in the range of 95-100%.

2.6 Dissolution studies of the tablets:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release.

Table 9: % Cumulative drug release of formulations F1-F8

Time(mins)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	15.25	27.36	40.18	44.18	25.48	35.08	45.89	42.89
10	27.76	40.42	55.83	58.83	37.82	40.48	58.24	55.24
15	38.23	55.35	63.45	68.49	47.45	48.05	69.42	64.42
20	42.48	65.63	76.62	82.65	58.21	64.78	74.19	76.19
30	60.52	78.49	89.42	92.48	61.48	75.36	80.46	85.46
40	76.43	85.31	94.42	99.51	70.82	85.09	89.78	96.53
50	82.75	93.53	97.51		78.49	90.31	96.53	
60	96.41				84.46	95.75		

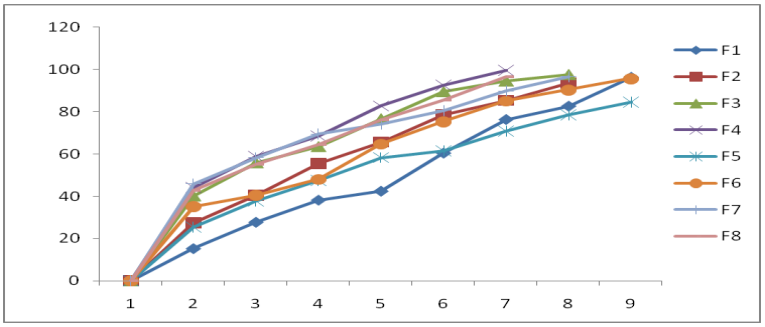

Fig 5: In vitro drug release of formulations F1-F8

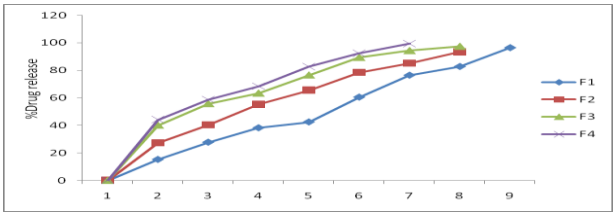

Fig 6: In vitro drug release of formulations F1-F4

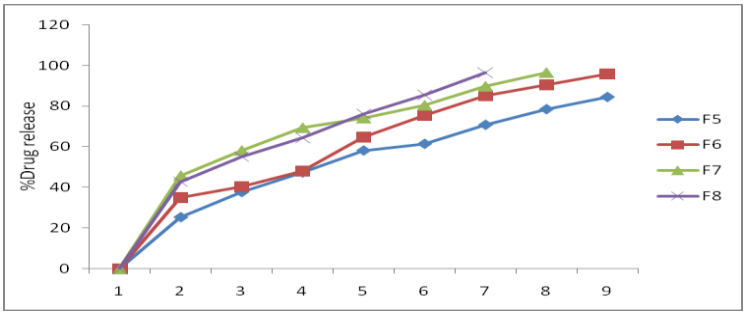

Fig 7: In vitro drug release of formulations F5-F8

The results of % Cumulative drug release of formulations F1-F8 were shown in table 9 and were shown in figure 5- 7. From the in vitro drug release in studies it was observed that the formulations containing ludiflash as a super disintegrant in different concentrations like 2, 4, 6 and 8%, reveals that the increased in the super disintegrant concentration decreases the drug release time and the F4 formulation containing ludiflash 8% concentration shows maximum amount of drug release (99.51%) at the end of 40 mins.

Whereas formulations containing lycoat as a super disintegrant in different concentrations like 2,4, 6 and 8%, reveals that the increased in the super disintegrant concentration decreases the drug release time and the F8 formulation containing lycoat with 8% concentartion shows maximum amount of drug release (96.53%) at the end of 40 mins.

So, F4 formulation containing 8% concentration of ludiflash shows max. release within 40 mins so that it is choosen as optimized formulation.

2.7 Evaluation of Formaldehyde Treated Capsules:

Physical tests:

- **Identification attributes:** The size '0' capsules chosen were opaque, with white colored body and red cap. The normal capsule bodies were soft and sticky when touched with wet hand. After treating with formaldehyde, there were no significant changes in the physical appearance of the capsules except for the stickiness. The body of capsule was hard and non-sticking even when touched with wet hand due to treatment with the formaldehyde.
- **Visual defects:** Among 100 capsules body which were treated with formaldehyde, about 15 to 20 capsule bodies showed visual defects. They were found to be shrunk and distortion into different shapes due to the complete loss of moisture.

Dimensions: Dimensional examination was done by using vernier calipers.

Average capsule length:

Before formaldehyde treatment (untreated cap and body) : 20.7 mm
After formaldehyde treatment(treated body and untreated cap) : 19.8 mm

Average diameter of capsule body:

Before formaldehyde treatment : 7.3 mm
After formaldehyde treatment : 6.9 mm

Average length of capsule body:

Before formaldehyde treatment : 17.9 mm
After formaldehyde treatment : 17.2 mm

Discussion: On formaldehyde treatment, the "0" size capsules bodies showed a significant decreases in length and diameter and attained hardness.

Chemical test:

- **Qualitative test for free formaldehyde:** The formaldehyde treated capsules were tested for the presence of free formaldehyde by comparing color of sample solution with standard solution. It was found that the sample solution was not more intensity colored than the standard solution inferring that less than 20µg/ml of free formaldehyde was present in 25 capsule bodies.

Limit test for the presence of residual formaldehyde, indicated that the amount of formaldehyde present in treated capsules was well within limits.Optimization of formaldehyde treated capsule bodies exposed at various time intervals viz., 2, 4, 6, 8, 10hrs:

Table 10: Disintegration test for Treated Capsules

Code	Disintegration Time (hrs)	
	1.2 pH (2hrs)	6.8 pH (upto 24hrs)
(2rd hr)	2	_
(4th hr)	2	1
(6th hr)	2	7
(8th hr)	2	9
(10th hr)	2	12

Based on the disintegration studies, it was observed that the 6th hr treated capsule (F9) remained intact for 7 hrs so lag time was maintained. F10, F11 remain intact for 9, 12 hrs respectively and therefore they were not selected for the formulation because the required lag time was 6hrs. As the required lag time is 6hrs, F9 (6th hr treated capsule) was selected as optimized time for formaldehyde treatment for further studies.

2.8 Invitro release studies:

Dissolution study was carried out to measure the release rate of drug from prepared pulsincap formulation using USP I dissolution apparatus at 37^0C using 2 different dissolution media of pH 1.2, pH 6.8 phosphate buffers in order to mimic in vivo GIT conditions. Initially first 2hrs of dissolution was conducted in pH 1.2 buffer, followed by 10hrs of dissolution study in pH 6.8 phosphate buffer .

Table 11: *Invitro* dissolution data of formulations B1F4 to B5F4

Time (hrs)	B1F4	B2F4	B3F4	B4F4	B5F4
0	0	0	0	0	0
1	32.43	25.52	30.52	22.69	24.26
2	49.63	32.86	45.95	34.63	32.96
3	55.35	42.29	50.26	40.98	44.45
4	64.63	59.49	60.39	55.43	52.42
5	79.43	69.35	72.45	64.86	60.89
6	90.63	78.12	82.96	78.05	72.56
7		89.01	95.43	85.49	85.46
8				97.42	95.63
9					99.78
10					

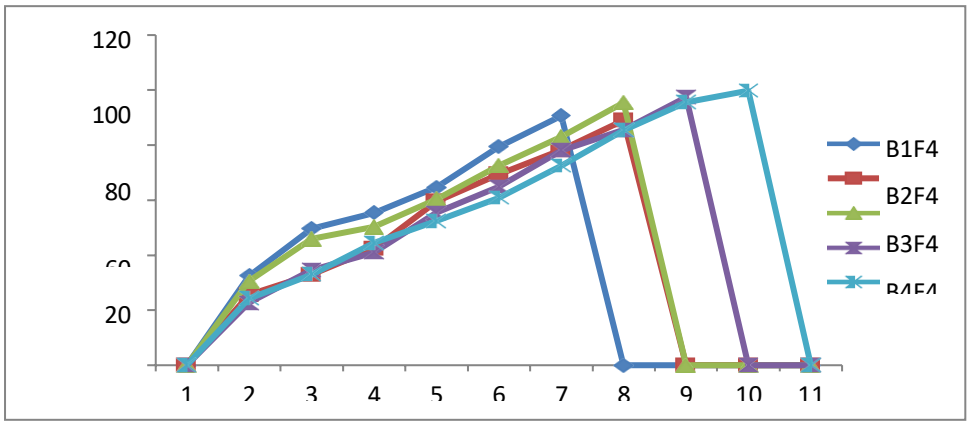

Figure 8: Dissolution plots for formulations B1F4 to B5F4

All the 5 formulations of Bupropion pulsincaps were subjected to dissolution studies. Formulations B1F4, B2F4, B3F4, B4F4, B5F4, contain the hydrogel plug with alone and combination of hydrophobic polymer and Hydrophilic polymer i.e., Ethyl cellulose: HPMC in the ratio of 1:1, 1:2 and 2:1 of total 100 mg weight of the plug.

It was observed that a proper lag time of 6 hours was maintained with minimal upper GIT drug release for the combination of Ethyl cellulose and HPMC K15M hydrogel plug in the 2:1. It was observed that as the concentration of Hydrophilic polymer was increased the release rate of drug was delayed and finally burst release of drug from the formulation occurred after lag time. So basing on these observations, of all the 5 pulsincap formulations, B5F4 formulation containing hydrogel plug of ethyl cellulose & HPMC K15M in 2:1 ratio was selected as optimized pulsincap formulation.

2.9 RELEASE KINETICS:

Dissolution data was fitted in Zero order, First order, Higuchi's and koresmayer peppas equations. The regression coefficient "R" values for zero order, first order, higuchi's and peppas for formulation P5F4 was found to be 0.966, 0.835, 0.982, and 0.606 respectively.

The 'n' value is 1.302 for the optimised formulation P5F4 i.e., n value was >0.89 this indicates Super case II transport.

ZERO ORDER:

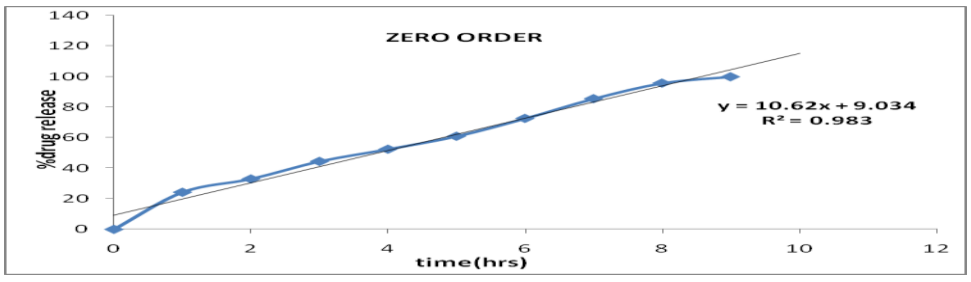

Figure 9: Zero order plot for optimized formulation B5F4

FIRST ORDER:

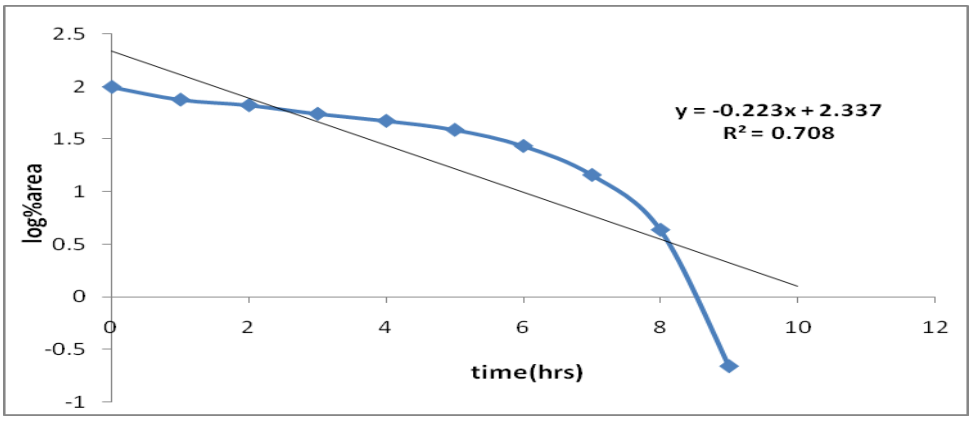

Figure 10: First order plot for optimized formulation B5F4

HIGUCHI PLOT:

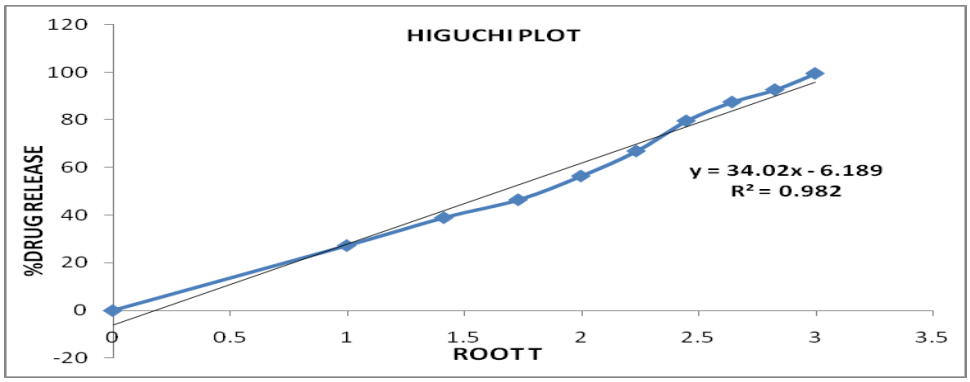

Figure 11: Higuchi's order plot for optimized formulation B5F4

PEPPAS PLOT:

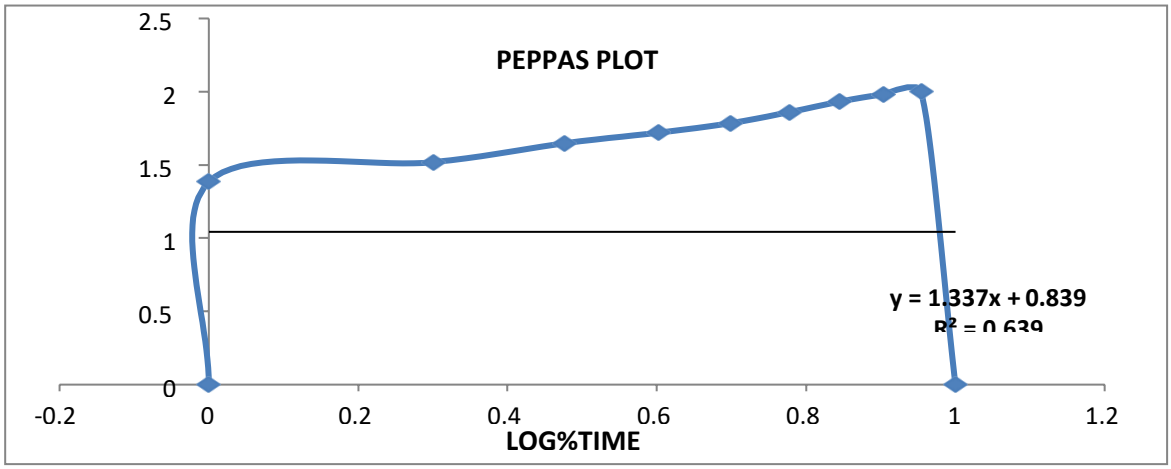

Figure 112: Koresmayer peppas order plot for optimized formulation B5F4

Table 12: Correlation coefficient "R" values of B5F4 optimized formulation

Models	R values
Zero order	0.983
First order	0.708
Higuchi	0.982
Koresmayer peppas	0.639
Peppas "n"	1.337

To analyze the mechanism of drug release from optimized P5F4 pulsincap formulation, data obtained from the drug release studies was subjected to different kinetic treatments. The correlation coefficient (R^2) was used as indicator of the best fitting for each of the models considered. The drug release kinetics for the optimized formulation P5F4 followed the zero-order kinetics and follows super case II transport mechanism.

CONCLUSION:

The aim of this study was to explore the feasibility of time specific pulsatile drug delivery system of Bupropion to treat blood clot, and to lower the risk of stroke, heart attack. The solubility studies of empty gelatin capsule bodies, which were cross linked with formaldehyde treatment, revealed that they are intact for 24 hrs, and hence suitable for colon targeting.The polymers like HPMC K15M, and Ethylcellulose can be used as hydrogel plugs to delay the release of Bupropion.The result of micromeritic properties showed good flow property of the powder blend indicating uniform distribution of drug within the various batches of capsule with negligible loss during the formulation stage.In conclusion, this system can be considered as one of the promising formulation technique for preparing time specific drug delivery systems and in Chronotherapeutic management. From the preliminary trials it was concluded that it is possible to formulate the pulsatile drug delivery system by the design of time modified chronopharmaceutical formulation.

REFFERENCES:

1. Sharagil L, Pony S. applied Bio-pharmaceutics and Pharmacokinetics. 5th ed. Singapur ; 2005: p. 481-2.
2. Robert W, Thomas P. Drug therapy for hypercholestemia and Dyslipidemia.In: Goodmen and Gilmans. The pharmacological basis of therapeutics. 10th ed. 2003: McGraw- hill. Medical publishing division p. 971-972.
3. Filippatos TD, Derdemezis CS, Elisaf MS. Department of Internal Medicine, School of Medicine, University of Loannina Greece. Available from: articles\Diet for hyperlipidemia.mht.
4. Scott MG. Atherogenic dyslipidemia associated with metabolic syndrome and Insulin resistance. vol 8. Suppl 1.

5. Bi-Botti CY. Chronopharmaceutics: Gimmick or clinically relevant approach to drug delivery- A Review. J Control Rel. 2004 Aug; 98(3):337-353.
6. Jain NK. Controlled and novel drug delivery. 1 st Ed. New Delhi: CBS Publishers; 2002.
7. Iskakov RM1, Kikuchi A, Okano T.,Time-programmed pulsatile release of dextran from calcium-alginate gel beads coated with carboxy-n-propylacrylamide copolymers. J Control Release. 2002 Apr 23;80(1-3):57-68.
8. Bhupendra Singh1*, Dr. Suresh Purohit2, Geetanjali Saini1, Dr. Anil Bhandari3, Deepak Awasthi1.,colon specific chronotherapeutic drug delivery for nocturnal asthma: eudragit s-100 coated calcium alginate gel beads-entrapped salbutamol sulphate. International Journal of Pharmacy and Pharmaceutical Sciences ISSN- 0975-1491 Vol 5, Suppl 2, 2013.
9. Bussemer T1, Dashevsky A, Bodmeier R.A pulsatile drug delivery system based on rupturable coated hard gelatin capsules. J Control Release. 2003 Dec 12;93(3):331-9.
10. Ranjan, O.P., Nayak, U.Y., Reddy, M.S. et al. Optimization of Chronomodulated Delivery System Coated with a Blend of Ethyl Cellulose and Eudragit L100 by Central Composite
11. Martin R J, Schlegel S B. Chronobiology of Asthma. Am. J. Respir. Crit. Care Med. 1998;158: 1002–1007.
12. Lieberman HA, Lachman L and Schwartz JB. Pharmaceuticaldosage forms: Tablets. Marcel Dekker, New York. 1990: 201- 43.
13. Kulkarni PA, Jaiswal M, Jawale SB, Shirolkar SV, Kasture PV. Development and evaluation of press coated tablets for chronopharmaceutical drug delivery using gellable and permeable polymers. Der Pharmacia Lettre. 2010; 2(4): 482-97.
14. Ansel HC, Allen LV, Popovich NG, Capsules and Tablets, in Pharmaceutical Dosage Forms and Drug Delivery Systems, Lippincott Williams & Wilkins, Philadelphia. 7th edn. 2002; Page no: 204–209.
15. Iskakov RM1, Kikuchi A, Okano T.,Time-programmed pulsatile release of dextran from calcium-alginate gel beads coated with carboxy-n-propylacrylamide copolymers. J Control Release. 2002 Apr 23;80(1-3):57-68.
16. Bhupendra Singh1*, Dr. Suresh Purohit2, Geetanjali Saini1, Dr. Anil Bhandari3, Deepak Awasthi1.,colon specific chronotherapeutic drug delivery for nocturnal asthma: eudragit s-100 coated calcium alginate gel beads-entrapped salbutamol sulphate. International Journal of Pharmacy and Pharmaceutical Sciences ISSN- 0975-1491 Vol 5, Suppl 2, 2013.
17. Bussemer T1, Dashevsky A, Bodmeier R.A pulsatile drug delivery system based on rupturable coated hard gelatin capsules. J Control Release. 2003 Dec 12;93(3):331-9.
18. Ranjan, O.P., Nayak, U.Y., Reddy, M.S. et al. Optimization of Chronomodulated Delivery System Coated with a Blend of Ethyl Cellulose and Eudragit L100 by Central Composite.
19. Costa P, Lobo JMS. Divisability of diltiazem matrix sustained release tablets. Pharmaceutical Development and Technology.2001; 6 (3): 343-51.
20. Raghavendra rao N G, Suryakar V B. Formulation and evaluation of montelukast sodium mucoadhesive buccal patches for chronic asthma attacks. International Journal of Pharma and Bio Sciences 2010;1(2):1-14.
21. Kanaka Durga Devi N, Sai Mrudula B, Prameela Rani A. Chronomodulated drug delivery system of Montelukast sodium. Der Pharmacia Lettre 2010; 2(5): 316-329.
22. Dash S, Murthy PN, Nath L and Chowdhury P: Kinetic modeling on drug release from

controlled drug delivery systems. Acta Poloniae Pharmaceutica - Drug Research 2010; 67: 217-223.
23. Modasiya Moin K. And Patel Vishnu M.: Pulsatile Drug Delivery System for Colon – A Review. International Journal of Research in Pharmaceutical and Biomedical Sciences 2011; 2(3): 934-941.
24. Akila Ramanathan and Sreeja Sreekumar G.*Development of chronomodulated drug delivery system of Pravastatin sodium for the treatment of hypercholesterolemia, Der Pharmacia Sinica, 2014, 5(5):36-41.
25. Mahmoud Teaima etal, Promising Swellable Floating Bupropion Tablets: Formulation, in vitro/in vivo Evaluation and Comparative Pharmacokinetic Study in Human Volunteers, 14: 2741–2757.2020