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Research

Preparation and in vitro evaluation of nabumetone colon target drug delivery system

P. Jeykumar[1], G. Mariyappan[2], J. Karthik[3]

[1]Department of Pharmaceutics, Pallavan Pharmacy college, Kanchipuram, Tamil Nadu, India
[2]Professor & Head, Department of Pharmaceutics, Pallavan Pharmacy college, Kanchipuram, Tamil Nadu, India
[3]Principal & Professor, Department of Pharmacognosy, Pallavan Pharmacy college, Kanchipuram, Tamil Nadu, India.

*Author for Correspondence: P. Jeykumar
Email: vivekmpharm17@gmail.com

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Abstract

The aim of the present study is to formulate and evaluate pulsincap dosage form containing Nabumetone which may be targeted to colon for to treat osteoarthritis and rheumatoid arthritis. A controlled onset, pulsatile, chronopharmaceutical drug delivery system of Nabumetone was developed for, to delay the release of drug and hence delay the onset of drug action. To minimize the frequency of drug administration by developing a once daily therapy administered at bedtime and Patient convenience and compliance could be achieved. The formulations were subjected to flow properties and FTIR study. Based on the results obtained F12 containing 8% Croscarmellose sodium was considered as the optimum powder blend for fabrication of pulsincap capsule. 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, P5F12 formulation containing hydrogel plug of ethyl cellulose & HPMC K15M in 2:1 ratio was selected as optimized pulsincap formulation. In conclusion, this system can be considered as one of the promising formulation techniques 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.

Keywords: Nabumetone, pulsincap, Colon drug delivery, chronopharmaceutical, rheumatoid arthritis.

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"[1].

Traditionally, drug delivery has meant getting a simple chemical absorbed predictably from the gut or from site of injection. A second-generation drug delivery goal has been the perfection of continuous, constant rate (zero order) delivery of bioactive agents. However, living organisms are not "zero order" in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drugs at predictably different times within the circadian cycle in order to maximize desired and minimize undesired drug effects. Due to advances in chronobiology, chronopharmacology and global market constraints, the traditional goal of pharmaceutics (eg. design drug delivery system with a constant release rate) is becoming obsolete. However, the major bottleneck in the development of drug delivery systems that match circadian rhythms (chronopharmaceutical drug delivery systems: ChrDDS) may be the availability of appropriate technology. The diseases currently targeted for chronopharmaceutical formulation or those for which there are enough scientific back grounds to justify ChrDDS compared to the conventional drug administration approach. These include asthma, arthritis, duodenal ulcer, cancer, diabetics, cardiovascular diseases, hyper cholesterolemia, ulcer and neurological disorder[2].

Chronotherapeutics refer to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefit and minimum harm[3].

A pulsatile dosage form, taken at bed time with a programmed start of drug release in the early morning hours, can prevent this. By timing drug administration, plasma peak is obtained, at an optimal time. Number of doses per day can be reduced. When there are no symptoms there is no need of drugs. Saturable first pass metabolism and tolerance development can also be avoided[4].

Drug targeting to colon would prove useful where intentional delayed drug. Absorption is desired from therapeutic point of view in the treatment of disease that have peak symptoms in the early morning such as nocturnal asthma, angina, arthritis[5,6]. Some orally administered drugs (eg. Metaprolol, Theophiline, Nifedipine, Isosorbide) may exhibit poor uptake in the upper regions of GIT or degrade in the presence of GIT enzymes[7]. Better bioavailability can be achieved through colon-specific drug delivery. Colon targeting is also advantageous where delay in systemic absorption is therapeutically desirable[8].

The emerging role of biorhythms in optimizing drug therapy

The presence of circadian rhythms in human health and illness has been alluded to since the time of Hippocrates. However, it was not until the 1960's that a large variety of physiologic functions and biologic rhythms were described. Biologic variations have now been reported for several physiologic processes and play an important role in the manifestation of many illnesses. The past decade has witnessed rapid advances in the field of chronobiology, which are now being incorporated into clinical medicine, pharmacology and pharmacy practice. A number of chronotherapeutics medications, aiming at synchronizing medications and the intrinsic biorhythms of disease have been developed by novel drug delivery technology. In some cases, conventional medications are being administered according to circadian rhythms[9].

Important findings from the new science of chronobiology- the scientific study of biological rhythms- clearly revealed that biological functions and processes are not static over time. Rather, they are variable in a predictable manner as rhythms of defined period. Some of the rhythms that affect our bodies include[10],

- **Ultradian,** which are cycles shorter than a day (for e.g. the millisecond it takes for a neuron to fire or a 90-minute sleep cycle)
- **Circadian,** which lasts about 24 hrs (such as sleeping and walking patterns)
- **Infradian,** referring to cycles longer than 24 hrs (for e.g. monthly menstruation)
- **Seasonal,** such as Seasonal Effective Disorder (SAD), which causes depression in susceptible people during the short days of winter [11].

Chronotherapeutics: therapy in synchrony with biorhythms

Chronotherapeutics co-ordinates drug delivery with human biological rhythms and holds huge promise in areas of pain management and treatment of asthma, heart disease and cancer. The coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed chronotherapy[12].

Chronotherapeutics, or delivery of medication in concentrations that vary according to physiological need at different times during the dosing period, is a relatively new practice in clinical medicine and thus many physicians are unfamiliar with this intriguing area of medicine. It is important that physicians understand the advantages of Chronotherapy, so that they can make well- informed decisions on which therapeutic strategies are best for their patients- traditional ones or chronotherapies.

The goal of chronotherapeutics is to synchronize the timing of treatment with the intrinsic timing of illness. Theoretically, optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ the most appropriate time. In contrast, many side effects can be minimized if a drug is not given when it is not needed. Unlike homeostatic formulations, which provide relatively constant plasma drug levels over 24 hrs, chronotherapeutics formulations may use various release mechanisms e.g. Time-delay coatings (Covera-HSTM), osmotic pump mechanisms (COER-24TM), and matrix systems (GeminexTM), that provide for varying levels throughout the day.

A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome. The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets and capsules. In most cases, however, special drug delivery technology must be relied upon to synchronize drug concentrations to rhythms in disease activity[13].

Pulsatile drug delivery systems

New global trends in drug discovery and development

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 body[14].

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.

MATERIALS AND METHODS

The following materials of Pharma grade or the best possible Laboratory Reagent (LR) were used as supplied by the manufacturer. The API, polymers, other excipients, reagents used for the development of formulation are given below in Table.

Table 1: List of chemicals used with grade and supplier

Sl. no.	Materials used	Grade	Manufacturer
1.	Nabumetone	Pharma Grade	Pragathi Organics Pvt. Ltd,hyderabd
2.	Ludiflash	LR	S d fine chemical Ltd, Mumbai
3.	Lycoat	LR	S d Fine chemical Ltd, Mumbai
4.	Microcrystalline cellulose	LR	Lobachemiepvt.ltd
5.	Talc	LR	Lobachemiepvt.ltd

6.	Ethyl cellulose	LR	Otto Chemicals, Mumbai
7.	HPMC K15M	LR	Otto Chemicals, Mumbai
8.	Magnesium sterate	LR	Lobachemiepvt.ltd, Mumbai
9.	Formaldehyde	LR	Qualigens fine chemicals,Mumbai
10.	Potassium permanganate	LR	Qualigens fine chemicals,Mumbai
11.	Hydrochloric acid	LR	S d fine chemical Ltd,Mumbai
12.	Potassium dihydrogen Phosphate	LR	Qualigens fine chemicals,Mumbai
13.	Methanol	LR	S d fine chemical Ltd, Mumbai
14.	Sodium hydroxide pellets	LR	Qualigens fine chemicals,Mumbai

METHODOLOGY

Preformulation studies: [15-18]

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It is one of the important prerequisites in development of any drug delivery system. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. Characterization of the drug is a very important step at the preformulation phase of product development followed by studying the properties of the excipients and their compatibility. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced.
The following are the various preformulation studies:

Solubility

Solubility is defined as amount of substance that passes into solution to achieve a saturated solution at constant temperature and pressure. The solvents used are water and methanol. Solubility was determined by adding Nabumetone in small incremental amount to a test tube containing fixed quantity of different solvents. After each addition, the system was vigorously shaken and examined visually for any un dissolved solute particles.

Drug-Excipient compatibility studies

To know the chemical compatibility of the drug spectroscopic technique that is FTIR studies were used. The FTIR spectra were recorded using an IR spectrophotometer (IR-Affinity-1, Shimadzu, Japan). The IR spectra for the samples were obtained by KBr disk method. The samples were prepared by grinding the pure drug, polymer and physical mixture with KBr separately. The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000- 600 cm-1. FTIR study was carried on Nabumetone, physical mixture of Nabumetone and for the best formulation.

UV spectroscopy

The main step in preformulation is to establish a simple analytical method so that all future measurements can be quantitative. Most drugs absorb light in ultraviolet wavelengths (190-400nm), since they are generally aromatic or contain double bonds.10 mg of Nabumetone was accurately weighed on an electronic balance and dissolved in 2 ml methanol and volume was made upto 10ml with buffer which gives 1000µg/mL (stock solution I). From the stock solution I, 1 ml is pippetted out then transfer to 10mL volumetric flask and volume was made upto 10mL with buffer which gives 100 µg/mL. From 100 µg/mL, 1mL was pippeted out and volume was made upto 10ml with buffer to give 10 µg/mL and scanned on a UV scanner between 2000-400nm. The maxima obtained in the graph were considered as λmax for the Nabumetone in respective buffers.

Standard calibration curve for Nabumetone

Nabumetone standard calibration curve was plotted in pH 1.2 buffer. Accurately weighed amount of 10 mg of drug was transferred into a 10 ml volumetric flask and the primary stock solution was prepared by making up volume to 10 ml with pH 1.2 buffer. This gives a solution having concentration of 1000 µg/mL of Nabumetone in stock solution. From this primary stock solution 1 ml was transferred into another 10 ml volumetric flask and made up to 10 ml with pH 1.2, from this secondary stock 0.3, 0.6, 0.9, 1.2, 1.5, and 1.8ml was taken separately and made up to 10 ml with pH 1.2 buffer, to produce 3, 6, 9, 12, 15, and 18µg/ml solution respectively. The absorbance was measured at 332nm using UV spectrophotometer. Similarly, Nabumetone standard graphs were plotted in pH 7.4 phosphate buffer and pH 7.4 phosphate buffer by following the above procedure.

Formulation of pulsincap of nabumetone

The modified release pulsincaps containing 10mg of Nabumetone 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 Nabumetone 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.

Evaluation of pulsincap dosage form:[19-22]

Invitro release studies

Dissolution study was carried out to measure the release rate of the drug from the pulsincap formulation. Invitro 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, 7.4, 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. Nabumetone 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 7.4 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 Nabumetone by measuring absorbance at 332 nm, by UV absorption spectroscopy. %CDR was calculated over the sampling times.

Table 2: Dissolution specifications of Nabumetone

Vessel temperature	37 ± 0.5ºC
Bath temperature	38 ± 0.5ºC
Dissolution media	pH 1.2, pH 7.4
Volume of dissolution media	900 ml
Aliquot withdrawn	5 ml
Aliquot replaced	5 ml of the fresh solution
Dissolution apparatus	USP type I (Basket)
Speed	100RPM

RESULTS AND DISCUSSION

Pre formulation studies

Solubility: It was determined as per standard procedure. The results are given in Table.

Table 3: Solubility studies of Nabumetone in various solvents.

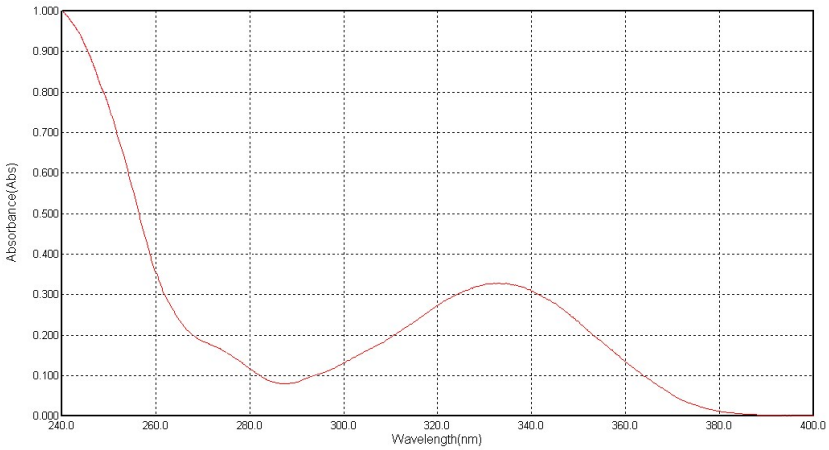
Solvent	Solubility (µg/mL)
0.1 N HCL	1.214±0.027
6.8pH buffer	0.962±0.054
7.4 pH buffer	1.283±0.036

Discussion: The solubility of Nabumetone was occurs more on 7.4 pH phosphate buffer with compare of 6.8 pH phosphate buffer and 0.1 N HCl solution.

Melting point: The melting point of Nabumetone was found to be 80 – 83^{0}C

Determination of λ max of Nabumetone

The λ max of Nabumetone was estimated by carrying out UV scan between the wavelength 200 to 400 nm which gave a highest peak at 332 nm and the same was selected for Nabumetone.



The maximum absorbance was found to be at 332 nm.

Calibration curve of Nabumetone

Table 4: Calibration data of Nabumetone in 0.1N HCl

Conc (µg/ml)	Absorbance
0	0
5	0.124±0.021
10	0.251±0.021
15	0.372±0.021
20	0.486±0.021
25	0.598±0.021
30	0.726±0.021

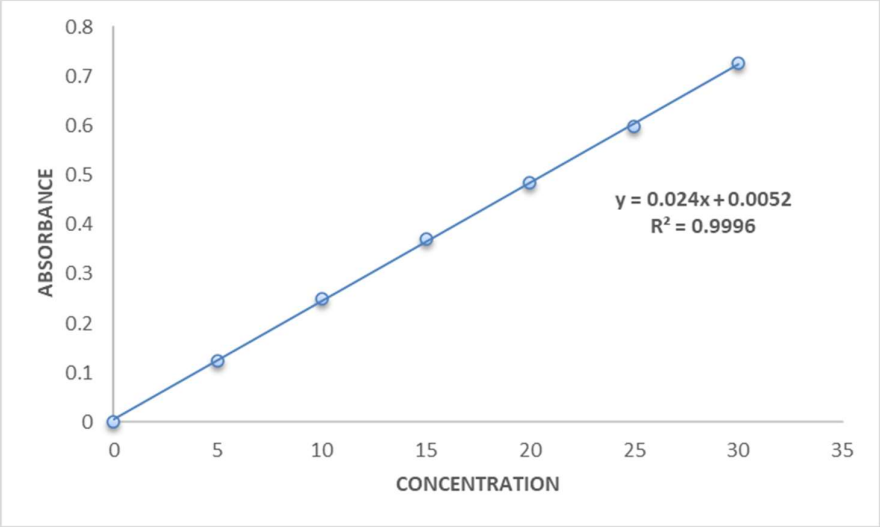


Fig 1: Calibration curve of Nabumetone with 0.1N HCl

Table 5: Calibration data of Nabumetone in pH 7.4 phosphate buffer.

Conc (µg/ml)	Absorbance
0	0
5	0.142±0.026
10	0.249±0.026
15	0.372±0.026

20	0.484±0.026
25	0.596±0.026
30	0.712±0.026

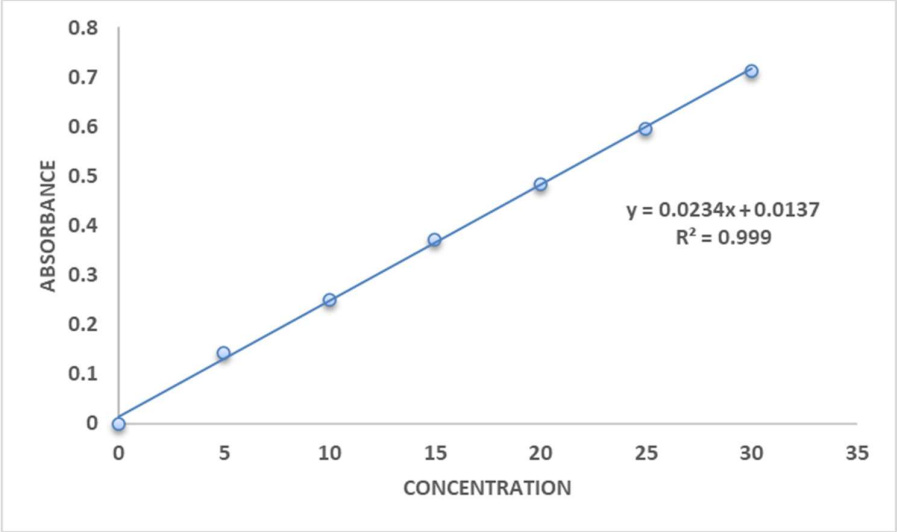


Fig 2: Calibration curve of Nabumetone with 7.4 pH Buffer

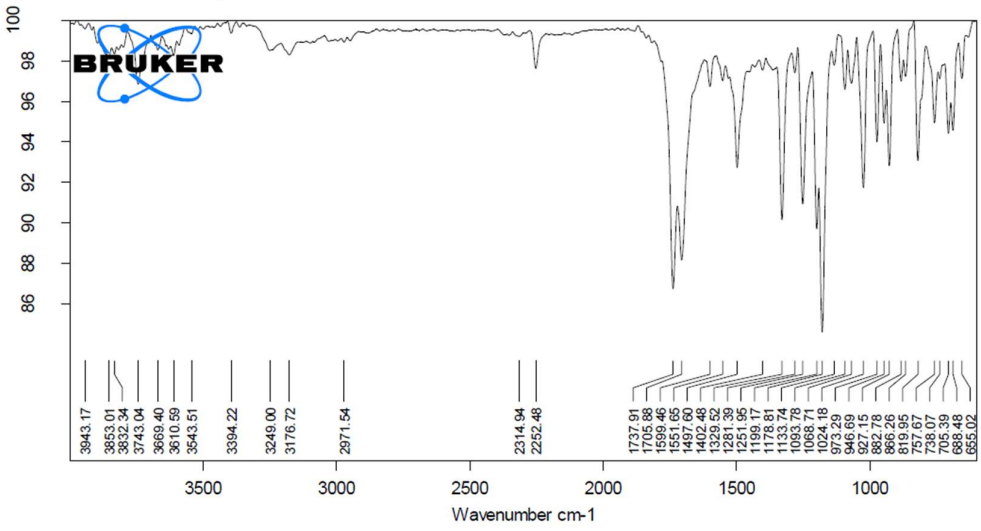
The linearity was found to be in the range of 5-30µg/ml in pH 7.4 buffer and 0.1N HCl. The regression value was closer to 1 indicating the method obeyed Beer-lambert's law.

FTIR

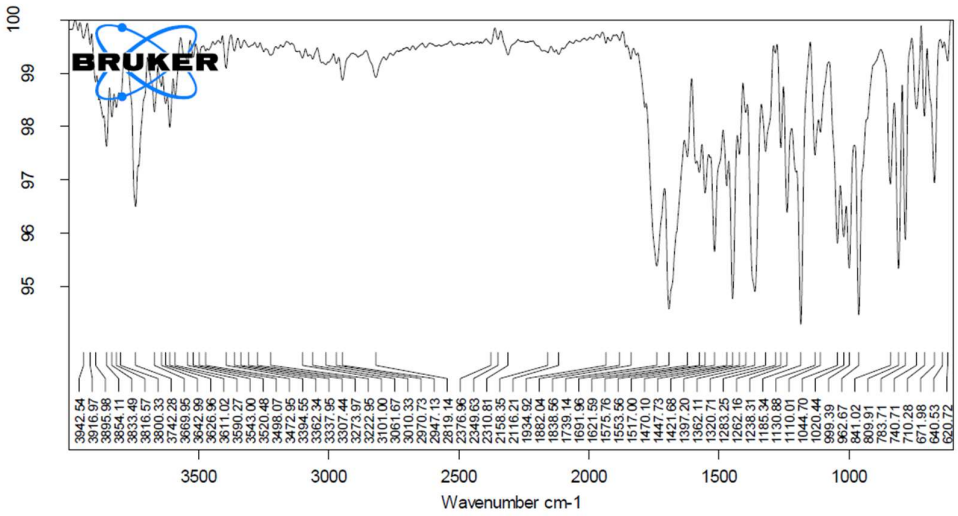
Drug-Excipient compatibility studies

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

FTIR Spectra of Pure drug



FTIR Spectra of Drug and Excipients



Form the drug excipients compatibility studies we observe that there are no interactions between the pure drug and (drug+ excipients) which indicates there are no physical changes.

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 6: Characterization Nabumetone Tablets

Formulation code	%Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness	Friability (%)	Disintegrating time(sec)	Drug content (%)
F1	150.21	3.94	9.34	5.7	0.57	14	95.28
F2	149.25	3.51	8.48	5.9	0.46	15	97.14
F3	151.26	3.48	9.25	6.2	0.75	20	96.39
F4	148.21	3.57	9.62	4.5	0.85	13	99.42
F5	152.78	3.68	9.47	4.6	0.54	21	98.34
F6	150.18	3.75	8.38	4.8	0.68	16	96.81
F7	152.19	3.68	9.42	5.1	0.61	19	97.32
F9	148.26	3.82	8.19	5.2	0.78	17	98.45
F10	151.47	3.84	9.57	5.7	0.65	16	98.56
F11	148.21	3.85	8.41	5.6	0.74	14	97.58
F12	150.62	3.74	9.68	5.8	0.84	11	99.45

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found in between 4-6.5 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 –F12 and considered to be satisfactory ensuring that all the formulations are mechanically stable. The drug content values for all the formulations (F1-F12) were found to be in the range of 95-100%.

Dissolution studies of the tablets

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

Table 7: % Cumulative drug release of formulations F1-F12

Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	**0**
5	18.74	27.36	36.18	44.28	25.48	38.08	48.89	49.89	19.28	25.36	42.18	**48.28**
10	26.41	45.42	48.83	59.34	39.82	45.48	57.24	55.24	28.41	46.42	58.83	**61.34**
15	35.36	62.35	56.49	67.25	45.45	53.05	73.42	67.42	37.36	57.35	66.49	**68.25**
20	45.74	82.63	75.65	88.66	59.21	69.78	75.19	78.19	45.74	78.63	74.65	**82.66**
30	59.25	87.49	85.48	92.25	65.48	79.36	86.46	86.46	59.25	87.49	85.48	**93.84**
40	77.17	91.31	93.41	99.15	71.82	88.09	93.78	98.53	76.17	92.31	93.41	**99.26**
50	89.75	98.83	99.14		85.49	92.31	98.53		88.75	98.53	99.14	
60	98.41				97.46	98.75			98.41			

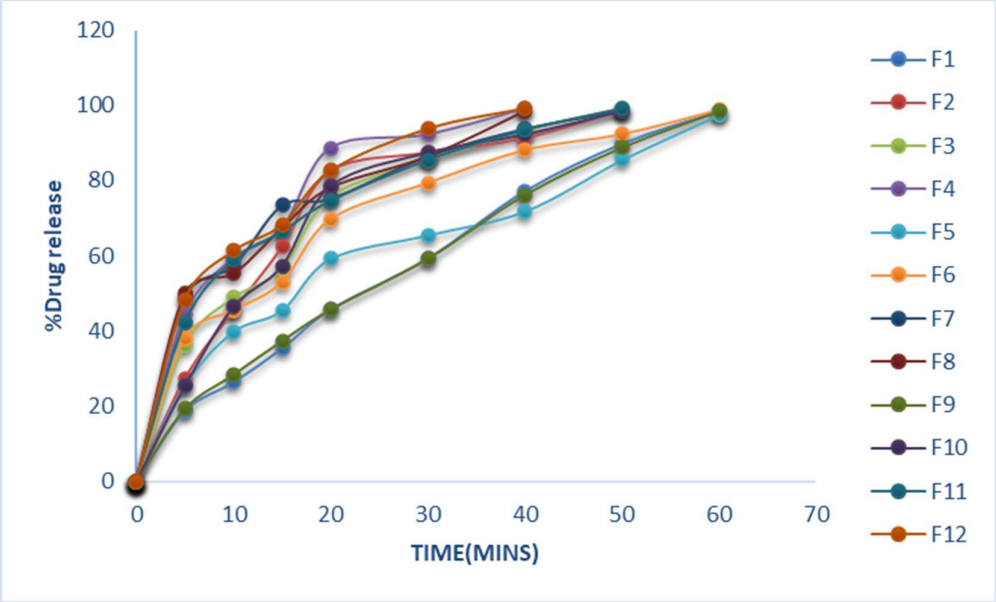


Fig 3: In vitro drug release of formulations F1-F12

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 (99.15%) 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 (98.53%) at the end of 40 mins. Whereas formulations containing Croscarmellose sodium 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% concentration shows maximum amount of drug release (99.26%) at the end of 40 mins. So, F12 formulation containing 8% concentration of Croscarmellose sodium shows max. release within 40 mins so that it is chosen as optimized formulation.

Table 8: Disintegration test for Treated Capsules

Code	Disintegration Time (hrs)	
	1.2 pH (2hrs)	7.4.8 pH (upto 24hrs)
F13 (2rd hr)	2	
F14 (4th hr)	2	1
F15 (6th hr)	2	7
F16 (8th hr)	2	9

F17 (10th hr)	2	12

Based on the disintegration studies, it was observed that the 6th hr treated capsule (F13) remained intact for 7 hrs so lag time was maintained. F15, F16 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, F13 (6th hr treated capsule) was selected as optimized time for formaldehyde treatment for further studies.

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^{0}C using 2 different dissolution media of pH 1.2, pH 7.4 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 7.4 phosphate buffer.

Table 9: *Invitro* dissolution data of formulations P1F12 to P5F12

Time (hrs)	P1F12	P2F12	P3F12	P4F12	P5F12
0	0	0	0	0	0
1	0	0	0	0	0
2	0	0	0	0	0
3	68.47	0	0	0	0
4	75.21	78.85	0	0	0
5	91.63	89.12	82.45	0	0
6		98.24	92.26	79.28	0
7			98.37	88.49	89.21
8				98.21	95.28
9					99.62
10					

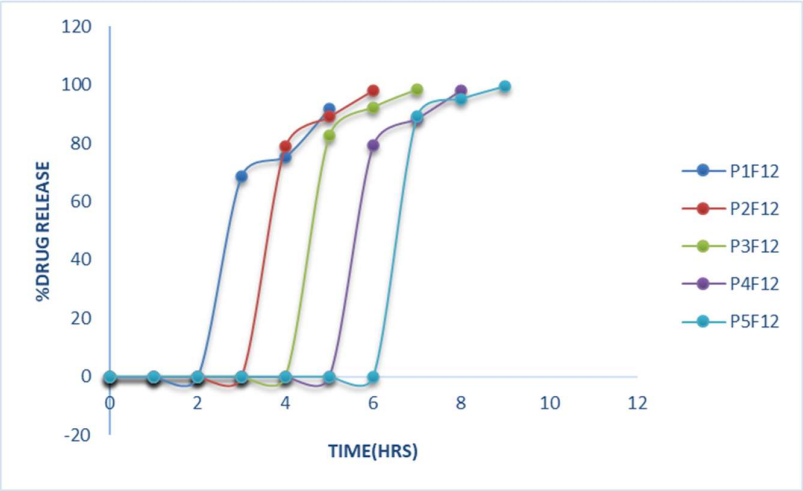


Fig 4: Dissolution plots for formulations P1F4 to P5F4

All the 5 formulations of Nabumetone pulsincaps were subjected to dissolution studies. Formulations P1F4, P2F4, P3F4, P4F4, P5F4, 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, P5F4 formulation containing hydrogel plug of ethyl cellulose & HPMC K15M in 2:1 ratio was selected as optimized pulsincap formulation.

Release Kinetics[23-24]

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 optimized formulation P5F4 i.e., n value was >0.89 this indicates Super case II transport.

Table 10: Correlation coefficient "R" values of P5F4 optimized formulation

Models	R values
Zero order	0.647
First order	0.338
Higuchi	0.448
Koresmayer peppas	0.455
Peppas "n"	1.811

To analyze the mechanism of drug release from optimized P5F12 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 P5F12 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 Nabumetone to treat blood clot, and to lower the risk of stroke, heart attack. From the results obtained from executed experiments it can be concluded that the Preformulation studies like pH, solubility and UV-analysis of Nabumetone were compiling with BP standards. The FTIR Spectra revealed that, there was no interaction between polymer and drug. 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 Ethyl cellulose can be used as hydrogel plugs to delay the release of Nabumetone. 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 techniques 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.

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