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Development of Pulsatile System of Nabumetone for Effective Management of Colonic Spasms

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ABSTRACT

In the present study, an attempt was made to develop pulsatile system of Nabumetone for effective management of colonic spasms. We tried to explore the feasibility of time dependent pulsatile drug delivery system of nabumentone to treat colon spasms. And also to prepare enteric coated tablets consisting of super disintegrates by direct compression method and to evaluate for their quick release properties and disintegration. Literature review has proved that Nabumetone , which undergoes hepatic biotransformation, 6- methoxy -2-naptthylacetic acid a protein inhibitor of prostaglandin synthesis through binding COX-1 and COX-2 receptors. Explosol used as super disintegrant and hydroxy propyl methyl cellulose (HPMC K100M), Eudragit as film former. Drug and excipients are studied for pulsatile release of precompressional tablets by using FT-IR spectrophotometry. Tablets were prepared by direct compression method. Evaluation of tablets by pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and post compressional parameters namely thickness, weight variation , Hardness, friability, dissolution studies, assement of kinetics of dissolution, zero order model, first order model, Higuci model, Korsmeyer-peppas model and stability studies were determined. All the obtained results from the tests were found to be within permissible limit. From the overall results, we can conclude that pulsatile tablets of nabumetone would deliver the drug according to the need of the patient for control of sever colon spasms.

Keywords: Colon drug delivery system, Nabumetone, colonic spasms

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INTRODUCTION

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug, route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons:

1. Less diversity, and intensity of digestive enzymes,
2. Comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability.
3. And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers.

On vast review the immense important of oral and other therapeutic systems in human use have validated the concept that controlled continuous drug release can minimize the daily dose of a drug required to maintain the required therapeutic effect. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal. Drug preparation for intrarectal administration is supplied as solutions, foam, and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application.

The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity. Because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low.

The human colon has over 400 distinct species of bacteria as resident flora, among the reactions carried out by these gut flora are azo reduction and enzymatic cleavage i.e. glycosides. These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules such as insulin by oral administration[1-4]. Target sites, colonic disease conditions, and drugs used for treatment are shown in Table 1[5]

Table 1: List of diseases occurring in colon and drugs used in treatment-I:

Target sites	Disease conditions	Drugs& active agents
Topical action	Inflammatory bowel disease Irritable bowel disease Crohn's disease	Hydrocrotisone, olsalazine, budenoside, prednisolone, balsalazide.
Local action	Pancreatacomy and cystic fibrosis, colorectal cancer	Digestive enzyme supplements, 5-flourouracil.
Systemic action	To prevent gastric irritation To prevent first pass	NSAIDS Steroids

CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery[6]. Drug Carrier is another factor which influences CDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems[6].

Several factors like properties of drug, delivery system, interaction with GIT contents play a major role in the successful delivery of drug. The luminal fluid in the colon plays a major role in the absorption of the drugs. The luminal fluid in the colon is less compared to the small intestine. The drug should be in soluble state for the successful absorption. The low contents of the colon effects the absorption of low soluble drugs. To prevent the decreased availability of low soluble drugs the drug should be delivered in pre solubilized form. The key factors to be considered while targeting the drug to the specific organ like colon are pH of GIT, drug solubility, contents of GIT, microbial flora, transit time of the intestine, etc. Pulsatile drug delivery is time and site specific drug delivery, thus providing spatial and temporal delivery and increasing patient compliance.

Pulsatile drug delivery is defined as the rapid and transient release of certain amount of molecules, within a short time period immediately after a predetermined off-released period, i.e., lag time, or these systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time, i.e., a period of no drug release. Such a release pattern is known as pulsatile release[7,8,9,10,11].

There are certain conditions for which such a release pattern is not suitable that demand release of a drug after a lag time. In other words, they require pulsatile drug delivery system (PDDS). The pulsatile system is gaining a lot of interest, as the drug is released completely after defined lag time Figure 1.

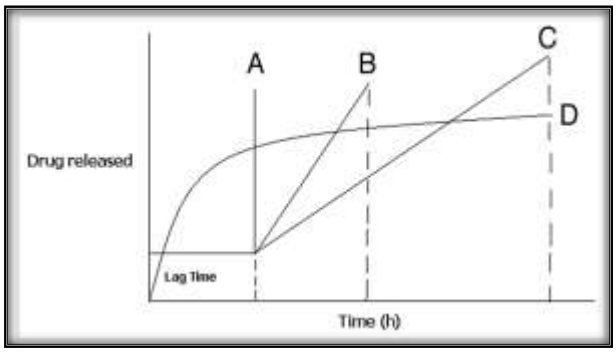

Figure 1: Schematic representation of different drug delivery systems

A) Sigmoidal release after lag time; B) delayed release after lag time; C) sustained release after lag time and D) extended release without lag time.

Humans exhibit endogenous circadian rhythms that are regulated by the master circadian clock of the body, the supra-chiasmatic nucleus. There are many other conditions that demand pulsatile release, like many body functions that follow circadian rhythms, such as secretion of hormones including follicle stimulating hormone (FSH), luteinizing hormone (LH), luteinizing hormone releasing hormone (LHRH), estrogen and progesterone], acid secretion in the stomach, gastric emptying and gastrointestinal blood transfusion. The lag time is essential for drugs that undergo degradation in gastric acidic medium (e.g., peptide drug) and irritate the gastric mucosa or induce nausea and vomiting. Targeting a drug to a distal organ of gastrointestinal tract (GIT), like the colon, requires that the release is prevented in the two-third portion of the GIT.

There are numerous advantages of the pulsatile drug delivery systems. Some of them are enlisted as below:

- These systems can be used for extended day time or night time activity.
- They reduce the dose frequency, dose size and cost, which ultimately reduce side effects, thereby improving patient compliance.
- Drug adapts to suit circadian rhythms of body functions or diseases.

- Drug targeting to a specific site, like the colon, can be achieved.
- They protect mucosa from irritating drugs.
- Drug loss by extensive first pass metabolism is prevented.
- They provide constant drug levels at the site of action and prevent the peak-valley fluctuations.[12]

Disadvantages

- Low drug loading capacity and incomplete release of drug.
- Multiple manufacturing steps.

Pulsatile drug delivery system:

A pulsatile drug release, where the drug is released rapidly after a well defined lag-time, could be advantageous for many drugs or therapies. Pulsatile release systems can be classified in multiple-pulse and single-pulse systems. A popular class of single-pulse systems is that of rupturable dosage forms. Other systems consist of a drug-containing core, covered by a swelling layer and an outer insoluble, but semi permeable polymer coating or membrane. The lag time prior to the rupture is mainly controlled by:

- The permeation and mechanical properties of the polymer coating and
- The swelling behavior of the swelling layer.

As it is frequently found in the living body, many vital functions are regulated by pulsed or transient release of bioactive substances at a specific site and time. Thus it is important to develop new drug delivery systems to achieve pulsed delivery of a certain amount of drugs in order to mimic the function of the living systems, while minimizing undesired side effects. Special attention has been given to the thermally responsive poly (N isopropylacrylamide) and its derivative hydro gels. Therefore, Pulsatile drug delivery is one such systems that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension etc. Various techniques are available for the Pulsatile delivery like pH dependent systems, time dependent systems, micro-flora activated systems etc. which can be designed as per the physiology of disease and properties of the drug molecule. The focus of the present review is primarily on the Pulsatile drug delivery methodologies and the upcoming technologies, which are being exploited on an industrial scale.

Classification of Pulsatile Drug Delivery Systems:

Pulsatile drug delivery systems can be classified in to three categories:

A) Time-controlled pulsatile release systems

i. Drug delivery systems with an erodible layer.

- Bulk eroding system
- Surface eroding system

ii. Drug delivery systems with a rupturable coating layer.

iii. Capsule-shaped system provided with release controlling plug

B) Stimuli-induced pulsatile release systems:

i. Thermo responsive pulsatile release.

ii. Chemical Stimuli induced pulsatile release.

C) Externally regulated pulsatile release systems:

i. Electrically regulated systems.

ii. Ultrasonically regulated systems

iii. Magnetically regulated systems.

General considerations in colon targeted drug delivery:

Formulations for colonic delivery are, in general, delayed-release dosage forms which may be designed either to provide a 'burst release' or a sustained/prolonged release once they reach the colon. The proper selection of a formulation approach is dependent upon several important factors, which are listed below:

Pathology and pattern of the disease, especially the affected parts of the lower GI tract or, physiological composition of the healthy colon if the formulation is not intended for localized treatment.

Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery.

Colon related diseases:

Irritable bowel syndrome:

Irritable bowel syndrome is most commonly associated with the specific condition of intestinal spasms. IBS has many causes, including an abnormal functioning of the digestive muscles and a limited ability to move or stretch the intestines. Intestinal infections can cause cramping to develop after the initial illness has passed. Foods such as vegetables, fruits, and dairy products can bring on spasms. Beverages, such as carbonated and caffeinated drinks, can also be IBS triggers. Patients with IBS may experience worsening intestinal spasms if they are also suffering from depression, stress or anxiety, as these emotional states can affect intestinal movement. Stress control and a

healthy diet can help improve digestion. People under the age of 35, women and individuals with a family history of the condition have an increased risk of developing IBS.

Inflammatory Bowel Disease (IBD):

Inflammatory bowel disease or IBD is a collective term encompassing related but distinct chronic inflammatory disorders of the gastrointestinal tract such as Crohn's disease, ulcerative colitis (UC), indeterminate colitis, microscopic colitis and collagenous colitis. Crohn's disease and ulcerative colitis are the most common diseases. Another chronic disorder of the gastrointestinal tract is irritable bowel syndrome (IBS). For most patients, IBD and IBS are chronic conditions with symptoms lasting for months to years. Inflammatory bowel diseases such as ulcerative colitis and Crohn's disease are serious intestinal diseases that can ultimately lead to the surgical removal of the colon.

Ulcerative Colitis:

Ulcerative colitis is a chronic inflammation of the large intestine (colon). It is a disease that causes inflammation and sores called ulcers, in the lining of the rectum and colon. Ulcers form at sites where inflammation has killed the cells that usually line the colon, then bleed and produce pus. Ulcerative colitis is closely related to another condition of inflammation of the intestines called Crohn's disease. Together, they are frequently referred to as inflammatory bowel disease (IBD).

Table 2: List of some important Marketed Pulsatile technologies:

Technology	Mechanism	Active drug
PULSYS®	Time controlled systems	Amoxicillin
UNIPHYL®	Externally regulated systems	Theophylline
RITALINA®	Osmotically regulated systems	Methyl phenidate
CODAS®	Multi particular pH regulated systems	Verapamil HCl
DIFFUCAPS®	Multi particular systems	Verapamil HCl

MATERIALS AND METHOD

Nabumetone was obtained from Sravani pharma Pvt ltd, Lactose was collected from Qualigens fine chemicals, Mumbai, Xanthan gum, HPMC K100 M, KPMCK30 M, PVP K30, Magnesium Stearate, Talc were purchased Central Drug House(P).Ltd, New Delhi .Sodium hydroxide, Sodium dihydrogen phosphate, Hydrochloric acid were purchased from Qualigens fine chemicals, Mumbai.

Preparation of Standard Stock Solutions:

Preparation of Standard Stock Solutions of Nabumetone in 0.1N HCl:

Stock solution of Nabumetone (1000 µg/mL) was prepared by dissolving 100 mg of drug in 100 ml of volumetric flask containing 50 mL of 0.1N HCl. The solution was sonicated for about 15

minutes and then made up to 100ml with 0.1N HCl. From the stock solution, 1mL was pipette out and transferred into the 10mL volumetric flask to get 100 µg/mL concentrations. From the second dilution 0.2, 0.4, 0.6, 0.8, 1.0, 1.2 mL was pipette out and transferred into the six 10mL volumetric flask and make up to 10 mL with 0.1N HCl, to get 2, 4, 6, 8, 10 & 12 µg /mL concentrations respectively. All the samples were filtered and analyzed by UV spectrophotometer at wavelengths of 241 nm

Preparation of Standard Stock Solutions of Nabumetone in Phosphate Buffer pH 6.8:

Stock solution of Nabumetone (1000 µg/mL) was prepared by dissolving 100 mg of drug in 100 ml of volumetric flask containing 50 mL of Phosphate Buffer pH6.8. The solution was sonicated for about 15 minutes and then made up to 100ml with Phosphate Buffer pH 6.8. From the stock solution, 1mL was pipette out and transferred into the 10mL volumetric flask to get 100 µg/mL concentrations. From the second dilution, dilution 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2mL was pipette out and transferred into the six 10mL volumetric flask and make up to 10 mL with Phosphate Buffer pH 6.8, to get dilution 2, 4, 6, 8, 10 & 12 µg /mL concentrations respectively. All the samples were filtered and analyzed by UV spectrophotometer at wavelengths of 241 nm.

Formulation of Pulsatile release Tablets of Pre compressional studies:

Drug and the excipients are studied for their compatibility using FT- IR spectrophotometry.

Preparation of core tablet:

Nabumetone tablet core were prepared by direct compression. Nabumetone & excipients were weighed as per formulae given in Table 3 and then passed through a sieve No 100. Nabumetone, Sodium starch glycolate and HPMC K 100Mwere mixed in geometric proportion and blended for 30 minute. To this homogeneous blend, magnesium stearate (1% w/w) and talc (2% w/w) were added and blended for 10 minute. Core tablets (diameter, 8 mm; average tablet weight, 80mg) were compressed within 8 mm of punches on Shakthi 10 station compression machine under a common compression force of 3-4 Kg/cm^2

Table 3: Formulation code for tablet core

S.No	Ingredients	Quantities Per Tablet
1	Nabumetone	500
2	HPMC K 100M	25
3	Sodium Starch Glycolate	75
4	Magnesium Stearate	1
5	Talc	2

Preparation of compression coated tablet:

Six mm diameter drug cores were compression-coated in to coated tablets with coating level 0, 5,

10, 15 %. The weight ratios of Eudragit L 100: ethyl cellulose and Eudragit S 100: ethyl cellulose, according to the formulation table. Compression coated tablet were prepared by first filling half of the polymer blend in the die cavity, then centrally positioning the tablet core on the powder bed followed by filling the remaining half of the polymer blend on top. Then compressed Shakthi 10 station compression machine with a compression force to obtain tablets with hardness in the range of at 6-7 Kg/cm^2.

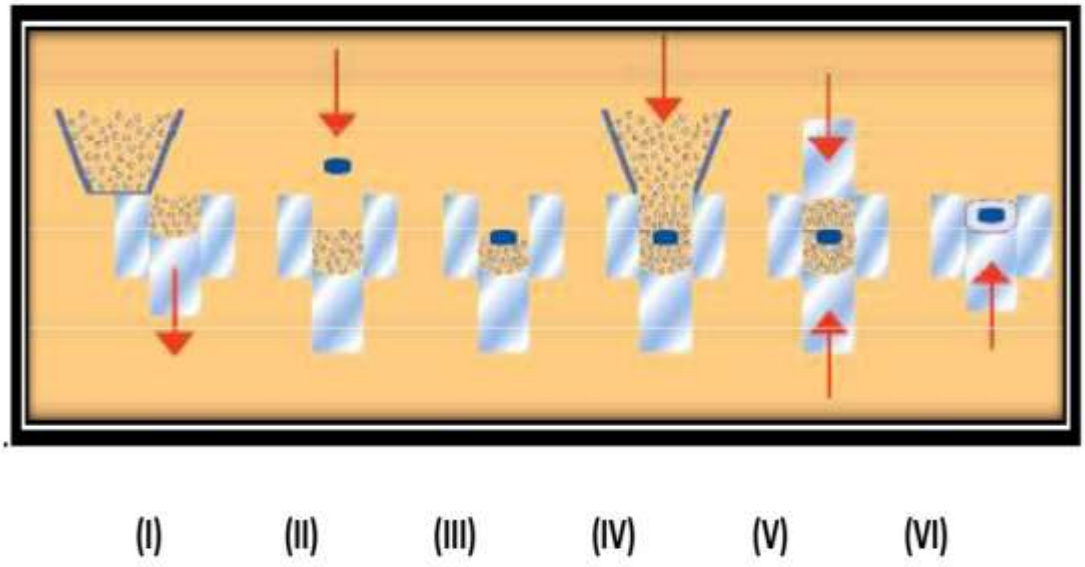

Figure 2: Compression coating of pulsatile tablet:

I) Filling of die with coat material; II) Placing Core Tablet III) Pre-compression IV) filling with coat layer V) Final Compression with desired hardness VI) Coated tablet

Table 4: Formulation Codes for Compression coating of Polymers

Formulation Code	Eudragit L 100	Ethyl Cellulose
EL1	0	15
EL 2	5	10
EL 3	10	5
EL 4	7.5	7.5
Formulation Code	**Eudragit S 100**	**Ethyl Cellulose**
ES 1	5	10
ES 2	10	5
ES 3	7.5	7.5

Taken in % weight of finished tablet

Evaluation of tablets[13,14,15,16,17,18,19]**:**

the prepared direct compression tablet were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and post compressional parameters -thickness was recorded using vernier caliper, weight variation , Hardness of the tablets was tested by Monsanto hardness tester, friability were found by Roche friabilator (Electrolab, Mumbai, India),

***In vitro* release studies**[13,20,21,22]**:**

composition of the coat and core to coat ratio interfere drug release profile of tablet were studied using USP type II apparatus in 900ml medium at 37±0.5 ° C at a rotation speed of 100 rpm. With the medium change method, the release was performed in pH 1.2 for 2 h followed by pH 6.8 containing 1% sodium lauryl sulphate for 10 hr. Five milliliter sample was withdrawn at pre-determined time interval(1, 2, 3,4,5,6,8,10 and 12 hr) and replaced by the fresh dissolution medium. All the samples were filtered and analyzed by UV spectrophotometer at wavelengths of 241 nm.

Kinetics Analysis of dissolution data [23,24,25]**:**

The release data obtained, for selected batch (s), were treated according to zero order model, first order model, Higuci model. Korsmeyer-peppas equation models to determine the release rate and mechanism of drug release from polymeric system.

Stability studies: Short-term stability studies were performed at a temperature of 45°±1°Cover a period of seven weeks (45 days) on the promising optimized formulation. Sufficient number of tablets (15) were packed in amber colored screw capped bottles and kept in humidity chamber and maintained at 45°±1°C. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, color, dissolution test and *in vitro* studies were performed to determine the drug release profiles.

RESULTS AND DISCUSSION:

Construction of Standard Plot for Nabumetone in 0.1 N HCl and phosphate buffer pH 6.8:

Standard plots of Nabumetone in 0.1N HCl (pH 1.2) showed good linearity with r^2value of 0.9996, which suggest that it obeys the "Beer – Lambert" law. The standard graphs in pH 6.8 phosphate buffer showed r^2 values of 0.999 at Wavelength 241 nm. Standard calibration curve values were shown in Table.5 Calibration curves were shown in Figure 3

Table 5: Standard plots of Nabumetone in 0.1N HCl (pH 1.2)

Concentration	Absorbance
0	0
2	0.122 ± 0.001
4	0.252 ± 0.003
6	0.390 ± 0.005
8	0.505 ± 0.003
10	0.625 ± 0.002
12	0.756 ± 0.006

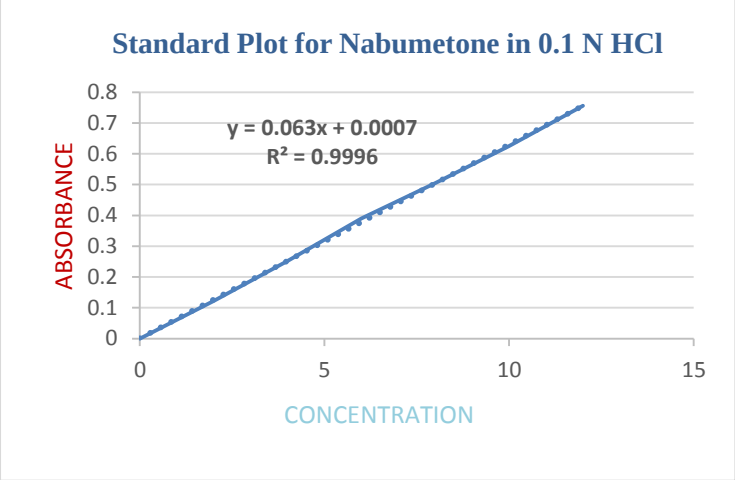

Figure 3: Standard plots of Nabumetone in 0.1N HCl (pH 1.2)

Table 6: Standard plots of Nabumetone in Phosphate buffer pH 6.8

Concentration	Absorbance
0	0
2	0.142 ± 0.002
4	0.282 ± 0.022
6	0.412 ± 0.002
8	0.525 ± 0.008
10	0.655 ± 0.007
12	0.786 ± 0.001

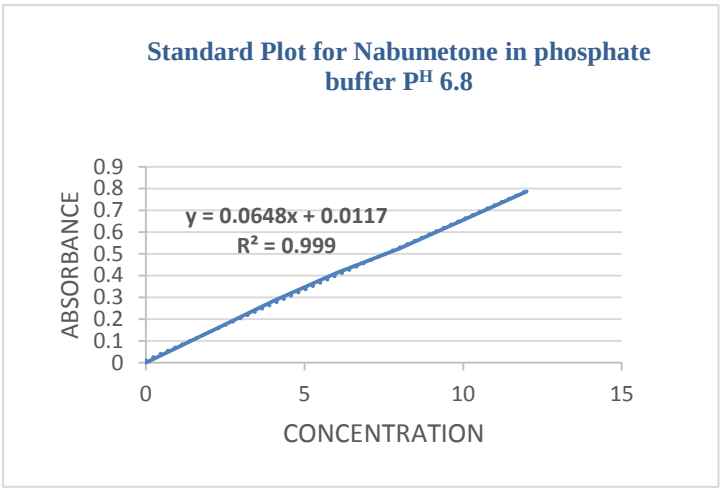

Figure 4: Standard plots of Nabumetone in Phosphate buffer pH 6.8

Characterization of Powder blend for Tablet Core: The powder blend was studied for various pre-compressional properties, like angle of repose, bulk density, Hausner ratio all the observed values, the powder blend shows good flow properties with values in optimum range.

Table 7: Physical properties of powder mixture for core

Angle of repose	Bulk Density	Compressibility Index	Hausner Ratio
24.26	0.342 gm/cm^3	13.33	1.15

Characterization of compressed tablet core:

The powder blend was then processed for punching:

Table 8: Physical properties of tablet core

Hardness	Friability	Weight variation	Disintegration time(min)	Drug Content
5.47 ± 0.52	0.28 ± 0.02	600.52 ± 1.56	4.03 ± 0.24	101.40 ± 0.38

The compressed core tablet has showed optimum Hardness (5.47 ± 0.52), friability (0.28 ± 0.02), disintegration time (4.03 ± 0.24). The weight variation was also found to be within the limits of official pharmacopeia.

The drug content in the tablets was found to be (101.40 ± 0.38)., which complies with pharmacopeial requirements of greater than 70 % (> 70%).

Characterization of Pulsatile tablets:

Physical Characterization of Pulsatile tablets:

The core of the tablet is then coated with the polymers Eudragit L100 or Eudragit S100 and Ethyl cellulose at various ratios as per formulation table: The formulated coated pulsatile tablets were evaluated for various physical characteristics like hardness, thickness & drug content all the values obtained are within the optimum range as per compendia.

Table 9: Physical properties of compression coated tablet

Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Drug Content (%)
Ethyl Cellulose			
EC 1	7.02 ± 0.5	5.64 ± 0.4	99.83 ± 0.47
Eudragit L 100			
EL 1	6.23 ± 0.2	5.89 ± 0.1	100.25 ± 0.63
EL 2	6.45 ± 0.3	5.78 ± 0.33	101.65 ± 0.52
EL 3	6.62 ± 0.15	5.97 ± 0.2	101.44 ± 0.78
Eudragit S 100			
ES 1	6.45 ± 0.2	5.63 ± 0.15	100.84 ± 0.23
ES 2	6.76 ± 0.21	5.48 ± 0.2	101.21 ± 0.45
ES 3	6.48 ± 0.33	5.72 ± 0.3	101.33 ± 0.42

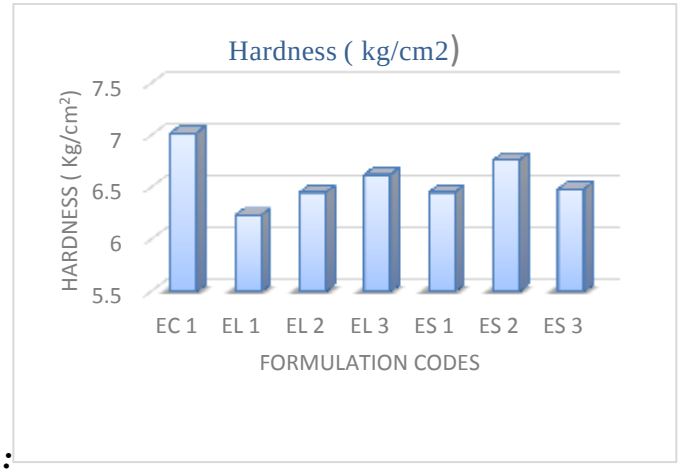

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Figure 5: Hardness of Compression coated Pulsatile Tablets

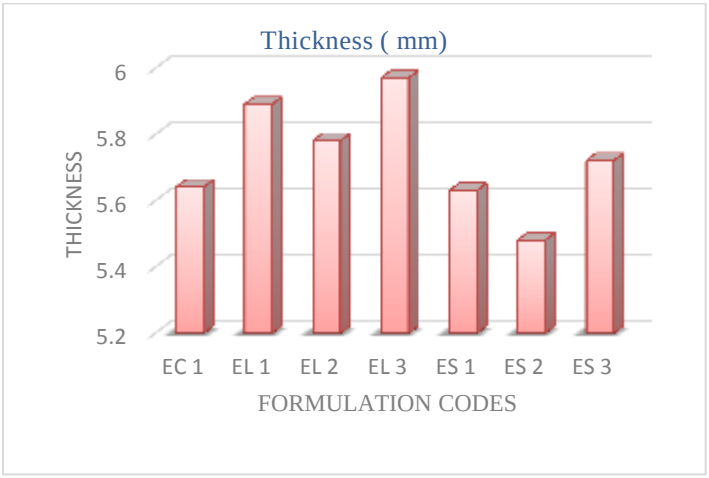

Figure 6: Thickness of Compression coated Pulsatile Tablets

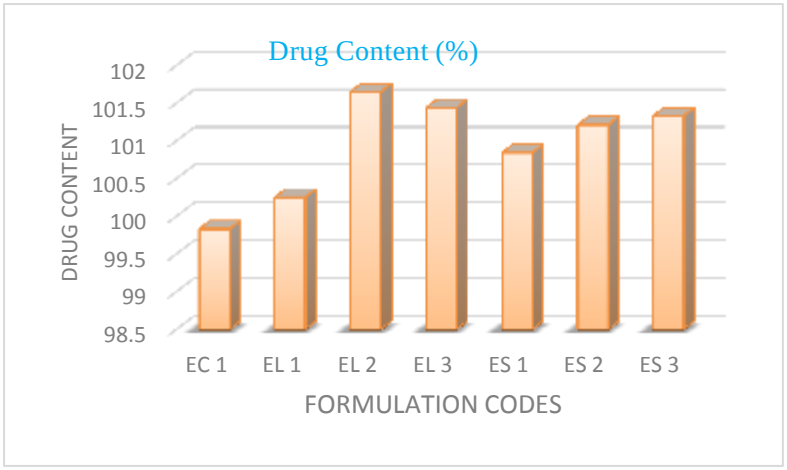

Figure 7: Drug Content of Compression coated Pulsatile Tablets

The pulsatile tablet has showed Hardness values in range of 6.23 - 7.02 kg/ cm^2, which is found to be in the optimum range for the controlled release pulsatile tablets. The thickness of the tablets was

found to be in range of 5.48 -5.86 mm. The drug content in all the formulations on an average was found to be 101%, satisfying the compendia requirement of greater than 70%.

Characterization of dissolution profiles:

In vitro release profiles for tablets with Eudragit L100& Ethyl cellulose:

Table 10: Dissolution Profiles of compression coated tablet with Eudragit L100 & Ethyl cellulose

Time (Hrs)	EC1(only Ethyl Cellulose)	Eudragit L100 (EL 1)	Eudragit L100(EL 2)	Eudragit L100(EL 3)
0	0	0	0	0
1	0	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
2	0.1 ± 0.01	0.3 ± 0.01	0.6 ± 0.01	0.4 ± 0.01
3	2.31 ± 0.14	8.45 ± 0.74	9.78 ± 0.67	12.63 ± 0.32
4	14.56 ± 0.82	24.52 ± 0.56	29.89 ± 0.78	27.52 ± 0.84
5	28.44 ± 0.98	38.71 ± 0.67	42.63 ± 0.59	40.36 ± 0.65
6	34.75 ± 1.14	48.43 ± 0.37	50.99 ± 1.12	48.69 ± 1.12
8	45.68 ± 1.26	63.27 ± 1.02	72.33 ± 1.26	70.48 ± 1.22
10	58.94 ± 1.95	74.32 ± 1.43	86.97 ± 0.52	85.37 ± 1.17
12	65.63 ± 1.09	86.32 ± 1.06	97.40 ± 0.97	95.98 ± 1.24

In vitro release profiles for tablets with Eudragit S 100& Ethyl cellulose:

Table 11: Dissolution Profiles of compression coated tablet with Eudragit S 100 & Ethyl cellulose:

Time (Hrs)	Eudragit S100 (ES 1)	Eudragit S100 (ES 2)	Eudragit S 100(ES 3)
0	0	0	0
1	0.03 ± 0.01	0.03 ± 0.01	0.05 ± 0.01
2	0.5 ± 0.01	0.8 ± 0.01	0.6 ± 0 .01
3	9.12 ± 0.12	12.32 ± 0.32	10.12 ± 0.18
4	25.96 ± 0.78	28.63 ± 0.41	27.96 ± 0.36
5	40.35 ± 0.96	44.78 ± 0.56	43.94 ± 0.58
6	50.67 ± 1.02	58.62 ± 0.48	54.89 ± 0.45
8	65.88 ± 1.08	76.47 ± 0.92	73.38 ± 0.98
10	76.98 ± 1.15	89.65 ± 1.02	82.89 ± 0.97
12	88.32 ± 1.06	98.12 ± 0.97	97.08 ± 1.24

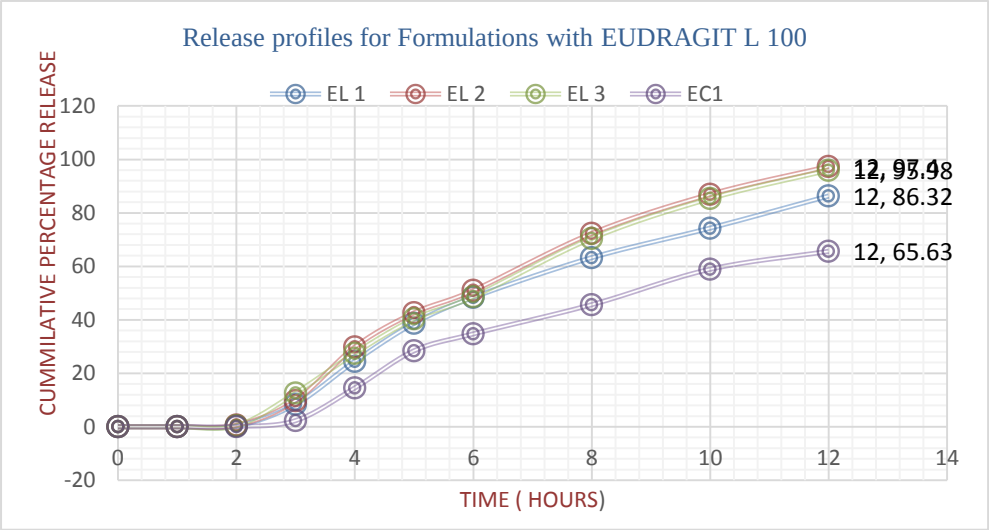

Figure 8: Dissolution Profiles of Compression coated Pulsatile Tablets with Eudragit L 100 & *EC*

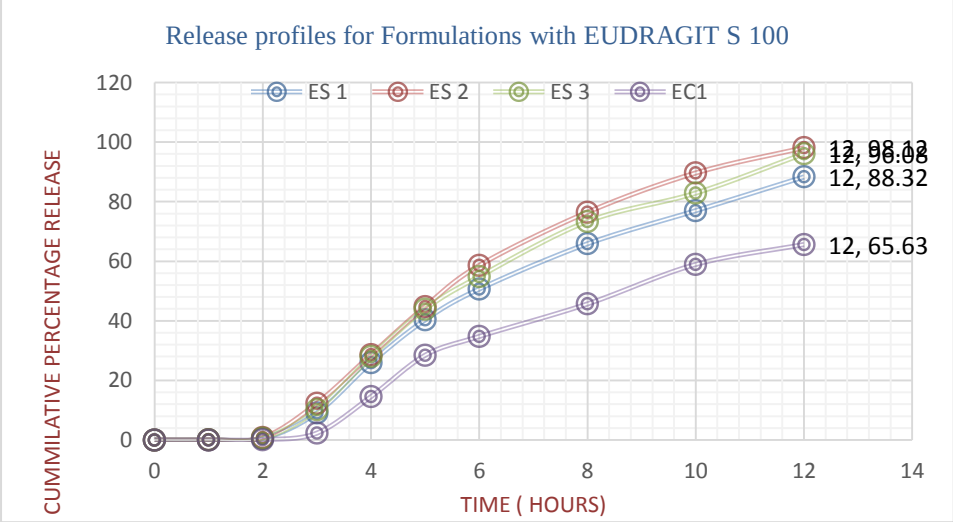

Figure 9: Dissolution Profiles of Compression coated Pulsatile Tablets with Eudragit S 100 & EC

The evaluation of release profile is recommended as an important tool in the development and optimization of drug formulations. Release studies of core tablet were carried out in 0.1 N HCl for 2 hours followed by a study for about 12 hours in pH 6.8 phosphate buffer.

All the formulations showed very insignificant or no release in the 0.1 N HCl, and for about 2 hours the tablet coat remained intact without rupturing releasing no drug into the media dissolution media. As the time progresses and when the dissolution media was changed to phosphate buffer pH 6.8. The tablets started slow drug release progressing up to 12 hours to release maximum amount of drugs from the formulations.

Formulation EC 1, coated with ethyl cellulose showed very poor release profiles releasing only 65.63 % drug at the end of 12th hour. Formulations EL 1, EL 2, EL 3 showed release of 86.32 %, 97.40 % and 95.98 % of drug at the end of 12th hour. Formulations ES 1, ES 2, ES 3 showed a release profile of 88.32%, 98.12% & 97.08 % drug release at the end of 12th hour.

This shows that the drug release could be modified by adjusting the ratio of these two polymers in combination. When a tablet comes in contact with the dissolution media, water influx was through the highly permeable rupturable hydrophobic layer (Ethyl cellulose, Eudragit L, Eudragit S) which leads to swelling and erosion of hydrophilic layer (HPMC K100M). HPMC K100M forms a very viscous gel layer which will reduce the seepage of dissolution fluid into the core tablets and thereby retards the drug release. When HPMC K100M swells to a maximum extent, it expands and creates pores on the surface facilitating the dissolution media to enter into a reservoir (core). Core containing sodium starch glycolate as a super-disintegrant and swelling in nature develops a pressure from inside the reservoirs finally leading to rupture of the coat layer. Water influx was through the semipermeable rupturable outer coating which leads to the expansion and erosion of an intermediate layer, which ultimately resulted in rupture of the outer coating. The drug was released within a short time after a definite lag time period. The lag time of the tablet decreased with increasing level of ethyl cellulose coat, and increase in concentration of Eudragit L 100 and Eudragit S 100. In-vitro dissolution studies revealed that there was no drug release until the coat ruptures.

Characterization of drug release kinetics:

The mechanism and kinetics of drug release of Nabumetone is determined by the application of zero order, first order, Higuchi, and Korsmeyer- peppas kinetics as

Table 12: Release Kinetic Profiles of compression coated tablet

Formulation Code	Kinetic Model				
	Zero order	First Order	Higuchi	Korsmeyer- peppas	Peppas (n)
Ethyl Cellulose	0.856	0.843	0.882	0.896	2.901
Eudragit L 100 (EL 1)	0.957	0.987	0.986	0.988	1.514
Eudragit L 100 (EL 2)	0.962	0.925	0.996	0.998	1.498
Eudragit L 100 (EL 3)	0.968	0.942	0.983	0.995	1.390
eudragit S 100 (ES 1)	0.972	0.988	0.983	0.998	1.482
Eudragit S 100 (ES 2)	0.947	0.936	0.980	0.991	1.412
Eudragit S 100 (ES 3)	0.948	0.937	0.981	0.997	1.476

From the assessment of dissolution kinetics it for various release models it was found that the formulation Eudragit S 100 ***(*ES 1)**shows better dissolution profiles and the release follows

diffusion by Super Case II transport mechanism interpreted from the slope value of the Korsmeyer- peppas plot.

Formulation Eudragit S 100 (ES 1) was selected to be the optimized formulation: Formulation Eudragit S 100 **(**ES1) was selected to be the optimized formulation, as it is showing more controlled release and releasing maximum up to 89% drug at the end of 12th hour

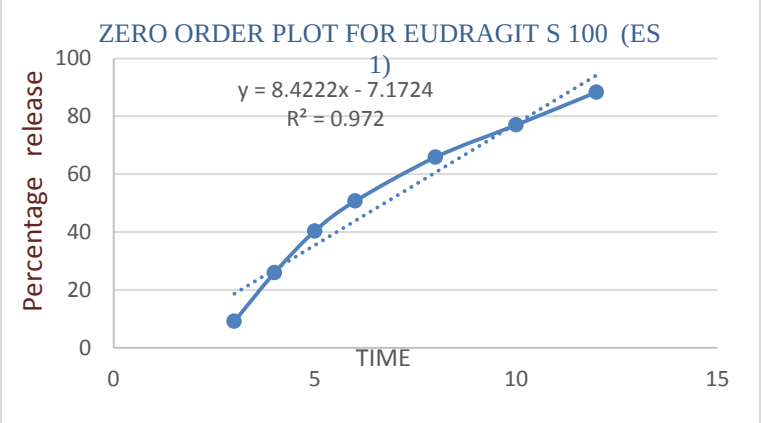

Figure 10: Zero order plot for Eudragit S 100 (ES 1)

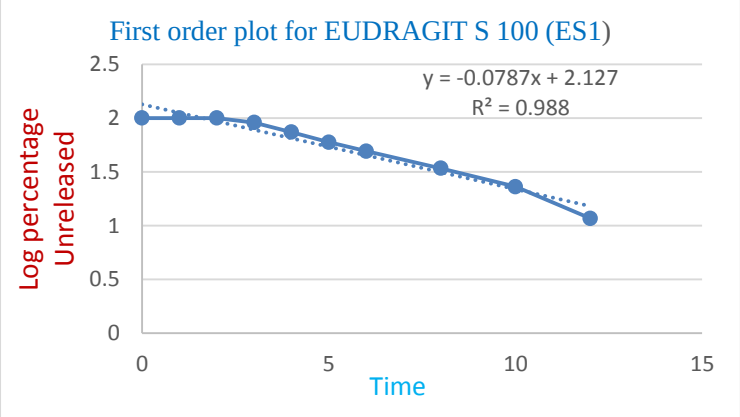

Figure 11: First order plot for Eudragit S 100 (ES 1)

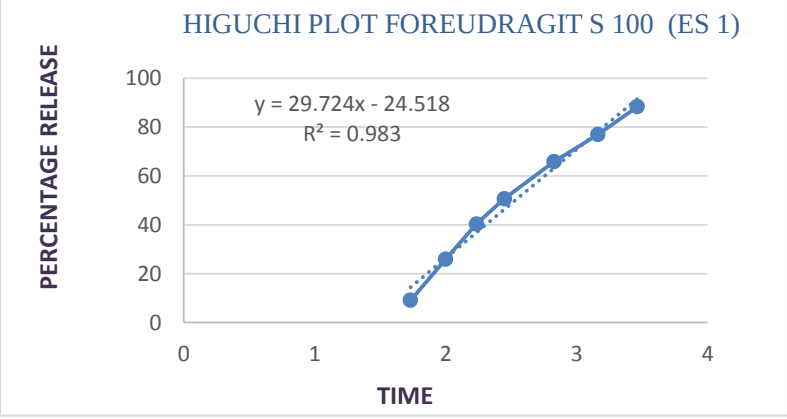

Figure 12: Higuchi plot for Eudragit S 100 (ES1)

Stability Studies:

Table 13: Stability Studies on Optimized formulation

Formulation code	Test Period (days)	Hardness (Kg/cm^2)	Friability	Drug Content	Drug release at end of 12th h.
EUDRAGIT S 100 (ES 1)	7	6.45 ± 0.2	5.63 ± 0.15	101.44 ± 0.78	88.32
	14	6.36 ± 0.21	5.58 ± 0.2	101.41 ± 0.45	88.24
	21	6.38 ± 0.33	5.52 ± 0.3	101.34 ± 0.88	88.65
	28	6.32 ± 0.22	5.47 ± 0.5	101.24 ± 0.68	87.93
	35	6.36 ± 0.15	5.46 ± 0.12	101.24 ± 0.68	87.90
	45	6.30 ± 0.30	5.45 ± 0.33	101.22 ± 0.41	87.88

Pre formulation studies:

FT-IR Studies: Physical mixture of drug (Nabumetone) and optimized formulation was treated under FT-IR spectrophotometer and the spectra obtained were analyzed.

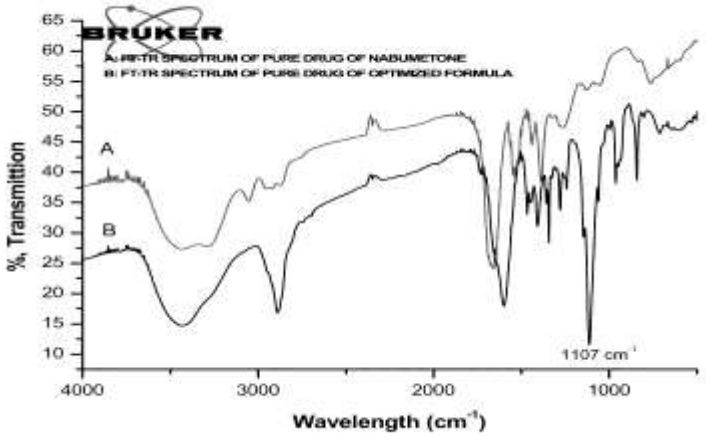

Figure: 13: FT-IR spectra for drug and Optimized formulation mixture

CONCLUSION:

The pulsatile drug delivery system is a ability to explore the feasibility of time dependent drug delivery. The rational design of chronotherapeutic drug delivery system of Nabumetone was successfully prepared which provided desired lag time for time controlled pulsatile release of Nabumetone useful for chrono pharmaceutics of colon spasms. From the above the results and discussion, thus pulsatile tablets of Nabumetone would deliver the drug according to the need of the patient for control of severe colon spasms.

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