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FORMULATION AND INVITRO EVALUATION OF PULSINCAP TECHNOLOGY OF INDOMETHACIN

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Abstract:

The purpose of the present study was to design and evaluate an Oral, site specific, Pulsatile drug delivery system containing Indomethacin as a model drug, which can be time dependent manner, to modulate the drug level in synchrony is a member of the drug class known as statins It is used for lowering cholesterol based on Chronopharmaceutical considerations.

The basic design consists of an insoluble hard gelatin capsule body, filled with powder blend and sealed with a hydrogel plug. The powder blend containing Indomethacin, ludiflash, lycoat, SSG, MCC and talc was prepared and evaluated for flow properties and FTIR studies. From the obtained results, F12 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 and it was found that the drug release was controlled by the proportion of polymers used.

The prepared formulations were evaluated for drug content, weight variation and Invitro release studies. FTIR studies confirmed that there was no interaction between drug and polymers and Invitro release studies of pulsatile device revealed that increasing hydrophillic polymer content resulted in delayed release of Indomethacin from the pulsincap after a predetermined lag time of 6hrs. Based on invitro studies performed, P5F12 was found to be optimized formulation.

Key words: *Pulsatile system; time dependent delivery; Indomethacin; Chronopharmaceutics; Invitro release studies.*

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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" [1-4].

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, cardio vascular diseases, hyper cholesterolemia, ulcer and neurological disorder [5-9].

Indomethacin is a nonsteroidal anti-inflammatory (NSAID) used for symptomatic management of chronic musculoskeletal pain conditions and to induce closure of a hemodynamically significant patent ductus arteriosus in premature infants [10].

METHODOLOGY:

Materials

Indomethacin analytical grade gifted from Yarrow Chem. Ltd., Mumbai, lycoat, Hydroxy Propyl Methyl Cellulose Ethyl cellulose, Microcrystalline Cellulose Magnesium Stearate Talc and other products were purchased from S.D fine chemicals.

Pre-formulation studies [11-14]:

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 Indomethacin 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 undissolved solute particles.

Drug-Excipient compatibility studies:

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 Indomethacin, physical mixture of Indomethacin and for the best formulation.

Standard calibration curve for Indomethacin:

Indomethacin standard calibration curve was plotted in pH 7.2 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 7.2 buffer. This gives a solution having concentration of 1000 µg/mL of Indomethacin 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 7.2, 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 7.2 buffer, to produce 3, 6, 9, 12, 15, and 18µg/ml solution respectively. The absorbance was measured at 317 nm using UV spectrophotometer.

Similarly Indomethacin standard graphs were plotted in pH 1.2 buffers.

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:

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

Where,
Db = Bulk density
Dt = Tapped density

Hausner's Ratio:

It is the ratio of tapped density to the bulk density. It is given by:

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

Where,
Dt = Tapped density
Db = Bulk density

Desingning or preparation of pulsincap [15-19]:
Designing or preparation of pulsincap capsules involves 3 steps:

A. Preparation of cross-linked gelatin capsule.
B. Preparation of powder blends for filling into capsules.
C. Formulation of pulsincap of Indomethacin.

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 desiccator. 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.

Optimization of formaldehyde treated capsule bodies exposed at various time intervals viz., 2, 4, 6, 8, 10hrs:-
Formaldehyde treated capsule bodies which were exposed at various time intervals viz., 2, 4, 6, 8, 10hrs were optimized by conducting Disintegration test. Disintegration test was carried out by using Hiccon disintegration test apparatus. pH 1.2, pH 7.2, buffers were used as medium and maintained at 37°C throughout the experiment. The time at which the capsules disintegrate are noted.

Preparation of indomethacin tablet for filling into capsules:
All the ingredients were passed through # 60 mesh sieve separately. The drug & MCC 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 F12 (100 mg). Then performed the entire evaluation test for determine optimized formulation which is used to prepare pulsincap of indomethacin (Table 1)

Table 1: Formulae for preparation of blend for filling of Indomethacin pulsincap

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	25	25	25	25	25	25	25	25	25	25	25	**25**
Ludiflash	4	8	12	16	--	--	--	--	--	--	--	**--**
SSG	--	--	--	--	4	8	12	16	--	--	--	
Lycoat	--	--	--	--	--	--	--	--	4	8	12	**16**
MCC	65	61	57	53	65	61	57	53	65	61	57	**53**
Mg. sterate	4	4	4	4	4	4	4	4	4	4	4	**4**
Talc	2	2	2	2	2	2	2	2	2	2	2	**2**
Total	100	100	100	100	100	100	100	100	100	100	100	**100**

Evaluation of tablets:
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 electro lab 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.

Test for Content Uniformity :

Tablet containing 10mg 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 317 nm. The concentration of Indomethacin was obtained by using standard calibration curve of the drug.

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.

In vitro Dissolution Study:

In vitro dissolution of Indomethacin tablets was studied in USP XXIV dissolution test apparatus. 900ml Phosphate buffer 7.2 (simulated fluid) was used as dissolution medium. The stirrer was adjusted to rotate at 1 0 0 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 317 nm . The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent Indomethacin released was calculated and plotted against time.

Formulation of pulsincap of indomethacin:

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 Indomethacin 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:

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. 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. 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 7.2 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 measuring absorbance at 318 nm, by UV absorption spectroscopy. %CDR was calculated over the sampling times.

RESULT AND DISCUSSION:

Preformulation studies:

Solubility:

It was determined as per standard procedure. The results are given in Table 2

Table 2: Solubility studies of Indomethacin in various solvents

Solvent	Solubility (µg/mL)
0.1 N HCL	1.168
6.8pH buffer	0.858
7.2pH buffer	1.248

Drug-Excipient compatibility studies:

From the spectra of Indomethacin, combination of Indomethacin with polymers, it was observed that all characteristic peaks of Indomethacin were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and polymers (Figure 1, 2).

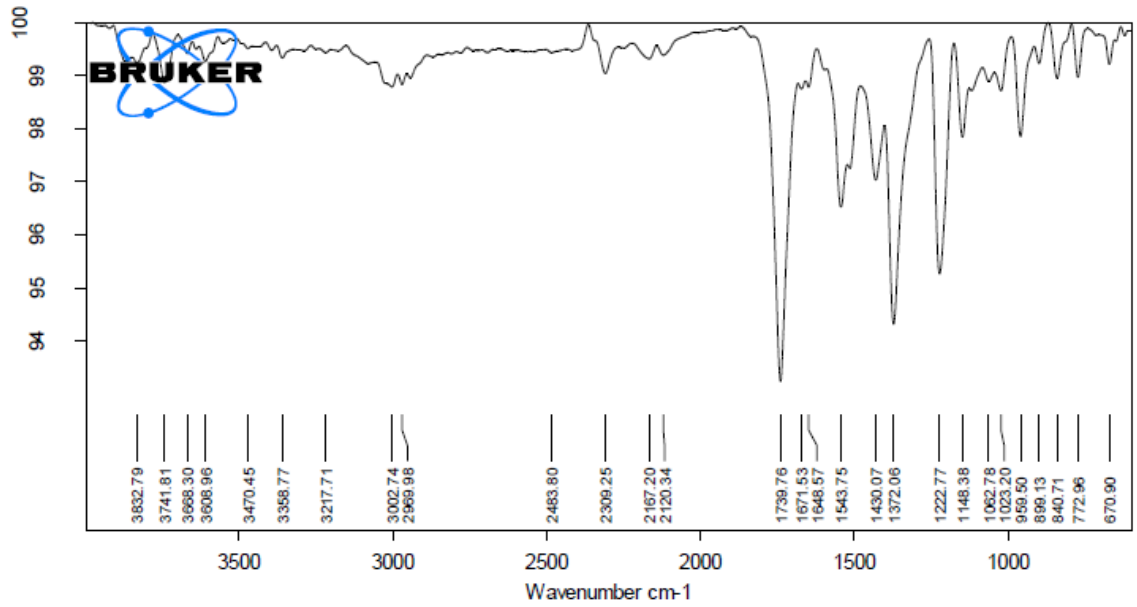

Figure 1: FTIR spectrum of Indomethacin

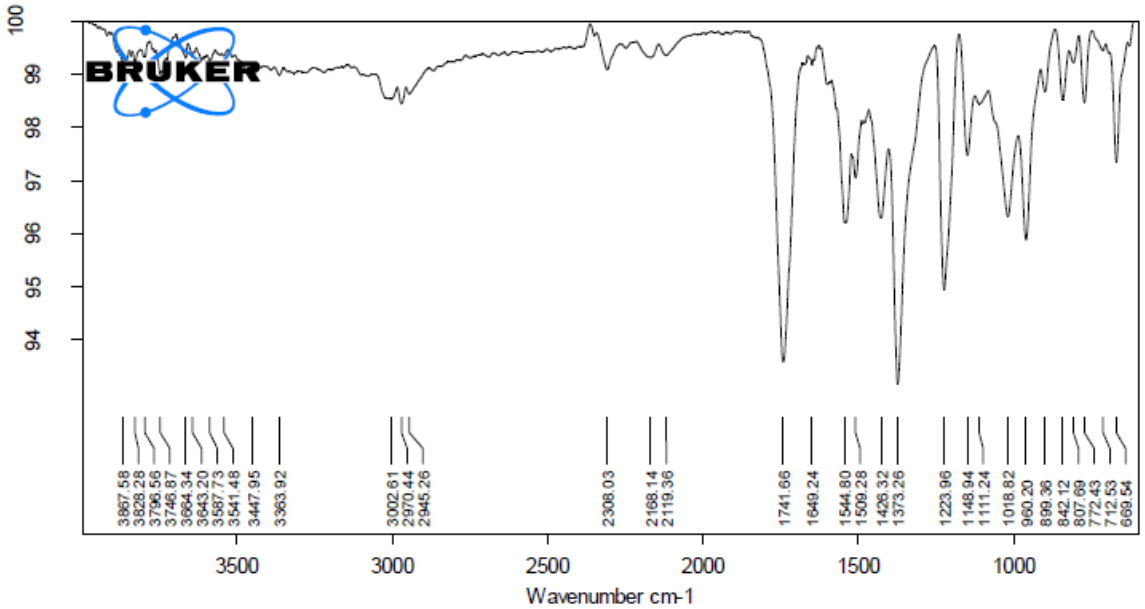

Figure 2: FTIR Spectrum of optimized formulation

Flow properties of powder blend:

The angle of repose of different formulations was ≤ 29.84 which indicates that material had good flow property. The bulk density of blend was found between 0.365±0.17g/cm^3 to 0.421±0.14g/cm^3.Tapped density was found between 0.451±0.19g/cm^3 to 0.492±0.11g/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±0.42-18.65±0.57 and Hausner's ratio from 1.18-1.29 which reveals that the blends have good flow character (Table 3).

Table 3: Flow property 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	29.84±0.16	0.395±0.15	0.468±0.16	15.60±0.02	1.18±0.12
F2	26.49±0.24	0.387±0.23	0.475±0.14	18.53±0.52	1.23±0.19
F3	29.43±0.85	0.395±0.14	0.467±0.15	15.42±0.98	1.18±0.18
F4	28.51±0.63	0.375±0.18	0.451±0.19	16.85±0.36	1.20±0.13
F5	29.12±0.21	0.389±0.16	0.459±0.10	15.25±0.42	1.18±0.12
F6	27.46±0.14	0.384±0.14	0.462±0.16	16.88±0.15	1.20±0.15
F7	29.75±0.45	0.376±0.14	0.487±0.18	17.54±0.24	1.22±0.12
F8	27.16±0.27	0.398±0.18	0.492±0.11	18.65±0.57	1.26±0.19
F9	25.47±0.49	0.421±0.14	0.456±0.18	16.58±0.64	
F10	26.58±0.56	0.405±0.14	0.471±0.14	18.21±0.45	1.21±0.14
F11	28.17±0.51	0.365±0.17	0.468±0.16	17.61±0.26	1.29±0.11
F12	26.74±0.39	0.384±0.14	0.489±0.18	18.54±0.48	1.24±0.10

Post Compression parameters

All formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are within the acceptable limits (Table 4).

Table 4: Post Compression Parameters of Indomethacin Tablets

Formulation code	%Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness	Friability (%)	Disintegrating time(sec)	Drug content (%)
F1	100.14	3.43	8.10	6.8	0.70	20	96.15
F2	102.51	3.40	8.37	5.9	0.40	16	98.24
F3	99.84	3.50	8.20	5.1	0.75	19	98.06
F4	97.65	3.57	8.20	6.8	0.65	29	95.76
F5	103.18	3.30	8.20	5.7	0.98	21	99.32
F6	101.75	3.43	8.17	5.2	0.74	18	98.75
F7	98.45	3.84	8.54	6.1	0.42	15	97.47
F8	101.24	4.21	8.46	5.9	0.61	18	96.85
F9	103.85	3.84	8.61	6.2	0.75	24	99.51
F10	99.58	4.10	8.51	5.8	0.41	16	98.45
F11	102.15	4.19	8.65	6.3	0.62	18	100.21
F12	100.15	4.25	8.47	6.4	0.36	11	99.64

Dissolution studies of the tablets:
From the in vitro drug release studies, it was observed that the F12 formulation containing 8% concentration of Lycoat shows max release within 40mins so that it is chosen as optimized formulation (Figure 3).

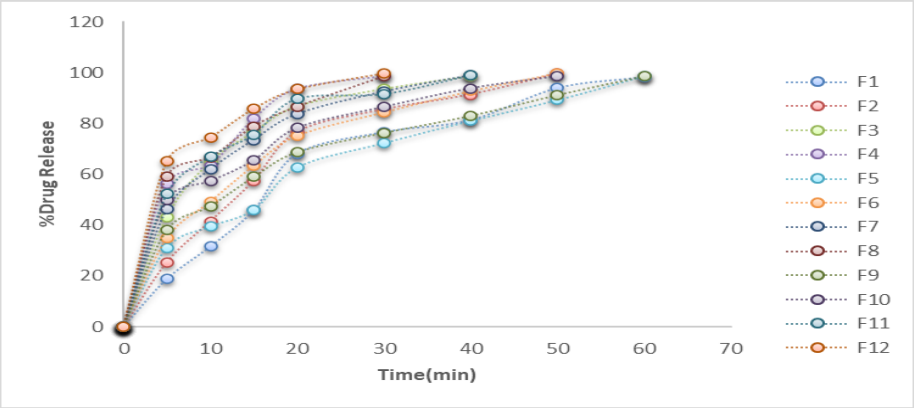

Figure 3: Invitro drug release of F1-F12 Formulations

EVALUATION OF FORMALDEHYDE TREATED CAPSULES
Optimization of formaldehyde treated capsule bodies exposed at various time intervals viz., 2, 4, 6, 8, 10hrs
Based on the disintegration studies, it was observed that the 6th hr treated capsule (F15) remained intact for 6 hrs so lag time was maintained. F16, F17 remain intact for 9, 12 hrs respectively therefore they were not selected for the formulation because the required lag time was 6hrs. As the required lag time is 6hrs, F15 was selected as optimized time for formaldehyde treatment for further studies (Table 5).

Table 5: Disintegration test of formaldehyde treated capsules:

Code	Disintegration Time (hrs)	
	1.2 pH (2hrs)	7.2 pH (up to 24hrs)
F13(2rd hr)	2	_
F14(4th hr)	2	1
F15 (6th hr)	2	6
F16 (8th hr)	2	9
F17 (10th hr)	2	12

Invitro release studies of pulsincap:
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 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 7.2 phosphate buffer.

All the 5 formulations of Indomethacin pulsincaps were maintained proper lag time of 6 hours.
Of all the 5 pulsincap formulations, P5F12 formulation containing hydrogel plug of ethyl cellulose & HPMC K15M in 2:1 ratio was release the drug up to 9 hrs. so it is selected as optimized pulsincap formulation (Figure 4).

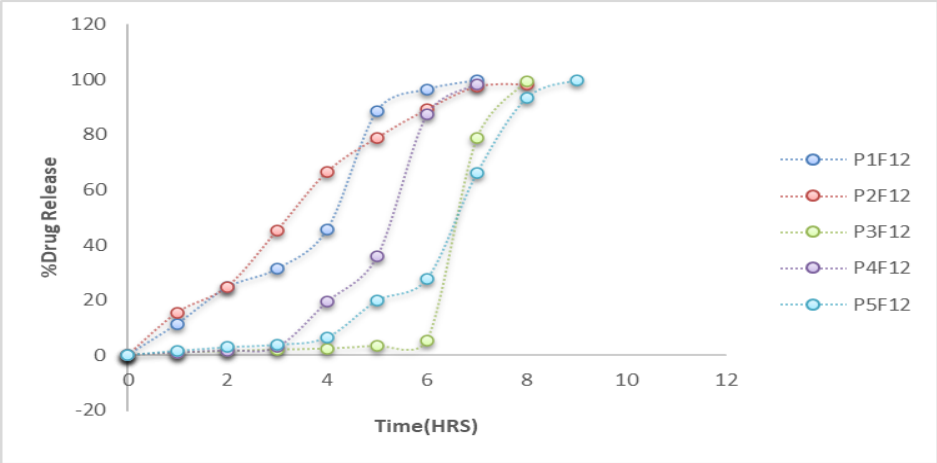

Figure 4: Dissolution plots for Formulations P1F12 TO P5F12

CONCLUSION:

The aim of this study was to explore the feasibility of time specific pulsatile drug delivery system of Indomethacin 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 Indomethacin 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. Polymers like HPMC K15M, and Ethylcellulose can be used as hydrogel plugs to delay the release of Indomethacin. The result of micrometric 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.

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