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**Research**

# Formulation and evaluation of flurbiprofen pulsincap colon Target drug delivery

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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 Flurbiprofen 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 chrono pharmaceutical 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 Flurbiprofen, SSG, Lycoat, Ludiflash, MCC, Magnesium stearate 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 lactose with hydrophilic polymers like HPMC K15M in 1:1, 1:2, and 2:1 ratios 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 hydrophilic polymer content resulted in delayed release of Flurbiprofen from the pulsincap after a predetermined lag time of 6hrs. Based on *invitro* studies performed, C5F8 was found to be optimized formulation.

**Keywords:** Pulsatile system; time dependent delivery; Flurbiprofen; Chrono pharmaceutics; *In vitro* release studies.

## 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, cardio vascular diseases, hyper cholesterolemia, ulcer and neurological disorder[2].

If the organization in time of living systems including man is borne in mind, it is easy to conceive that not only must the right amount of the right substance be at the right place but also this must occur at the right time. In the last decade numerous studies in animals as well as clinical studies have provided convincing evidence, that the pharmacokinetics and /or the drug's side effects can be modified by the circadian time and/ or the timing of drug application with in 24 hrs of a day[3].

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[4]. 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[5].

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[6,7]. 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[8]. Better bioavailability can be achieved through colon-specific drug delivery. Colon targeting is also advantageous where delay in systemic absorption is therapeutically desirable[9].

**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[13].

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[14],

- **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.

**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[18].

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[19].

**Chronopharmaceutics**

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.

## MATERIALS

Flurbiprofen -Pharma Grade Pragathi Organics Pvt. Ltd,hyderabd , Ludiflash-S d fine chemical Ltd, Mumbai, Lycoat -S d Fine chemical Ltd, Mumbai, Microcrystalline cellulose-Lobachemiepvt.ltd, Talc-Lobachemiepvt.ltd, Lactose-Otto Chemicals, Mumbai, SSG-Otto Chemicals, Mumbai, Magnesium sterate-Lobachemiepvt.ltd, Mumbai, Formaldehyde-Qualigens fine chemicals,Mumbai, Potassium permanganate-Qualigens fine chemicals,Mum Bai, Hydrochloric acid-S d fine chemical Ltd,Mumbai, Potassium dihydrogen Phosphate-Qualigens fine chemicals,Mumbai, Methanol-S d fine chemical Ltd, Mumbai, Sodium hydroxide pellets-Qualigens fine chemicals, Mumbai.

## METHODOLOGY

**Preformulation studies: [86-89]**

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 Flurbiprofen 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 Flurbiprofen , physical mixture of Flurbiprofen 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 Flurbiprofen 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 $\lambda_{max}$ for the Flurbiprofen in respective buffers.

**Standard calibration curve for Flurbiprofen**

Flurbiprofen 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 Flurbiprofen 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 247 nm using UV spectrophotometer. Similarly, Flurbiprofen standard graphs were plotted in pH 7.4 phosphate buffer and pH 7.4 phosphate buffer by following the above procedure.

## RESULTS AND DISCUSSION

**Preformulation studies**

**Solubility**

It was determined as per standard procedure. The results are given in Table 1.

**Table 1: Solubility studies of Flurbiprofen in various solvents**

| Solvent | Solubility (µg/mL) |
|---|---|
| 0.1 N HCL | 1.153 |
| 6.8pH buffer | 0.948 |
| 7.4pH buffer | 1.426 |

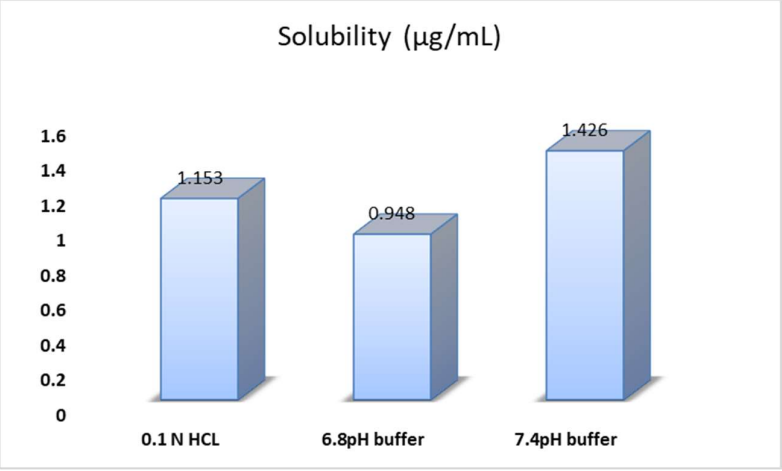


**Fig 1: Solubility studies of Flurbiprofen in various solvents**

Flurbiprofen was found to be more soluble in 7.4 pH buffer when comparted to other buffers.

**Drug-Excipient compatibility studies**

The IR spectrum of pure drug was found to be similar to the standard spectrum of Flurbiprofen . The spectrum of Flurbiprofen shows the following functional groups at their frequencies shown in Fig 1. From the spectra of Flurbiprofen , combination of Flurbiprofen with polymers, it was observed that all characteristic peaks of Flurbiprofen were not altered and present without alteration in the combination spectrum, thus

indicating compatibility of the drug and polymers. FTIR spectra of Flurbiprofen , and Optimized formulation are shown in Figure 2, 3 respectively.

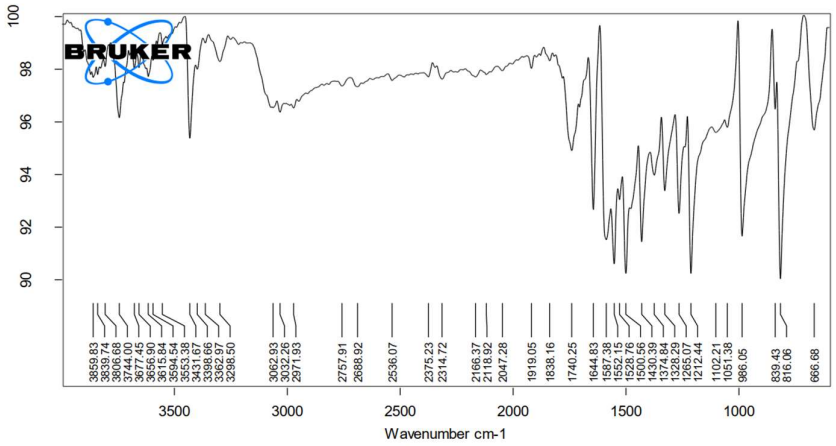


**Fig 2: FTIR spectrum of Flurbiprofen**

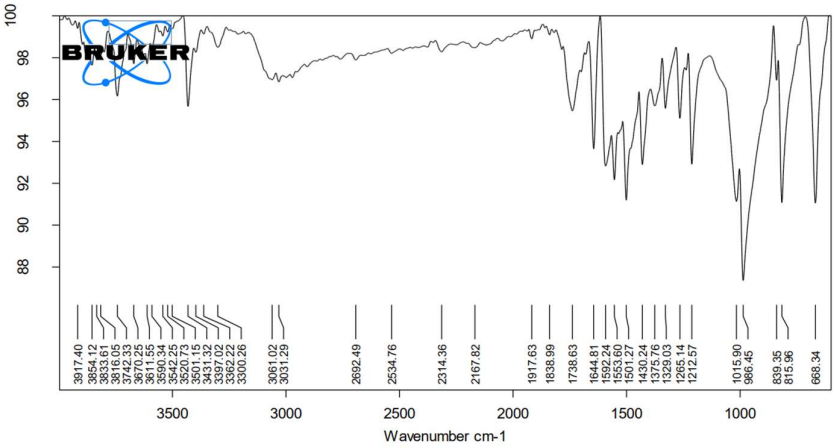


**Fig 3: FTIR Spectrum of optimized formulation**

Chemical interaction between drug and the polymeric material was studied by using FTIR. There was no difference between the IR patterns of Flurbiprofen , physical mixture of Flurbiprofen and Flurbiprofen optimized formulation.

**$\lambda_{max}$ Determination of Flurbiprofen**

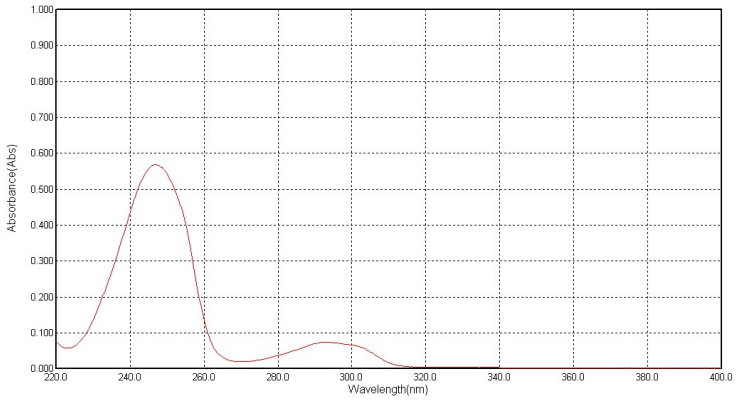


**Fig 4: $\lambda_{max}$ Determination of Flurbiprofen**

**Standard Calibration Curve**

The standard calibration curve of Flurbiprofen was developed in different pH media such as pH 1.2, and pH 7.4 phosphate buffer. Two buffers were selected in order to mimic the in-vivo conditions of the GIT.

**Standard Calibration Curve in 1.2 pH**

Standard graph of Flurbiprofen showed linearity at the concentration range of 3-18µg with correlation coefficient of 0.999.

**Table 2: Data for calibration curve of Flurbiprofen in pH 1.2 at 246 nm**

| Concentration (µg/mL) | Absorbance |
|---|---|
| 0 | 0 |
| 3 | 0.143 |
| 6 | 0.285 |
| 9 | 0.421 |
| 12 | 0.536 |
| 15 | 0.668 |
| 18 | 0.798 |

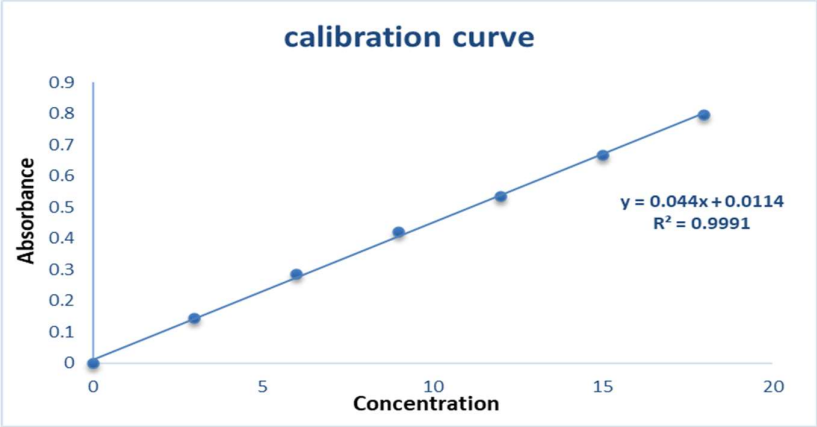


**Fig 5: Standard Calibration Curve of Flurbiprofen in pH 1.2 at 246 nm**

**Standard Calibration Curve in 6.8 pH phosphate buffer**

Standard graph of Flurbiprofen in pH 7.4 phosphate buffer shows linearity in the concentration range of 3-18 µg with correlation coefficient of 0.999.

**Table 3: Data for calibration curve of Flurbiprofen in pH 7.4 at 247 nm**

| Concentration (µg/mL) | Absorbance |
|---|---|
| 0 | 0 |
| 3 | 0.156 |
| 6 | 0.298 |
| 9 | 0.436 |
| 12 | 0.575 |
| 15 | 0.735 |
| 18 | 0.865 |

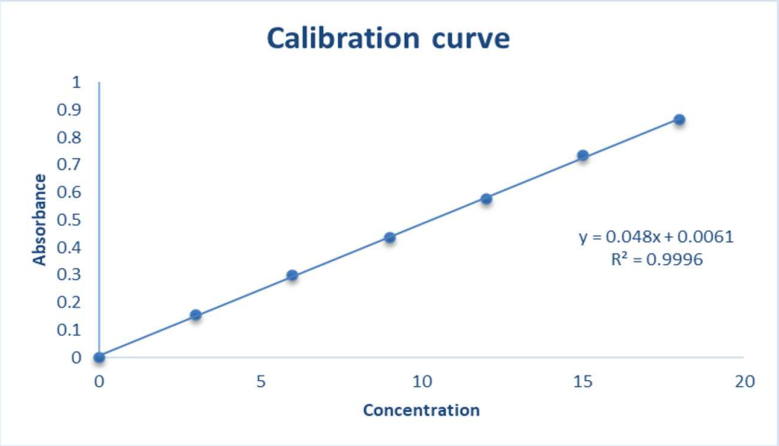


**Fig 6: Standard Calibration Curve of Flurbiprofen in pH 7.4 at 247 nm**

**Flow properties of powder blend**

**Table 4: 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** | 28.47±0.16 | 0.431±0.15 | 0.521±0.26 | 16.25±0.02 | 1.19±0.62 |
| **F2** | 27.25±0.24 | 0.425±0.23 | 0.503±0.24 | 17.47±0.52 | 1.22±0.59 |
| **F3** | 28.78±0.85 | 0.398±0.14 | 0.498±0.15 | 14.29±0.98 | 1.21±0.18 |
| **F4** | 27.26±0.63 | 0.402±0.28 | 0.476±0.39 | 15.35±0.36 | 1.17±0.63 |
| **F5** | 26.84±0.21 | 0.421±0.26 | 0.495±0.20 | 14.41±0.42 | 1.16±0.42 |
| **F6** | 29.61±0.14 | 0.431±0.14 | 0.484±0.16 | 17.25±0.15 | 1.18±0.15 |
| **F7** | 28.45±0.25 | 0.398±0.25 | 0.498±0.18 | 16.16±0.14 | 1.21±0.19 |
| **F8** | 25.26±0.33 | 0.401±0.19 | 0.465±0.21 | 15.39±0.24 | 1.17±0.24 |
| **F9** | 26.46±0.74 | 0.398±0.12 | 0.461±0.20 | 16.01±0.14 | 1.14±0.15 |
| **F10** | 27.62±0.51 | 0.421±0.28 | 0.436±0.19 | 15.25±0.26 | 1.23±0.21 |
| **F11** | 28.89±0.32 | 0.412±0.19 | 0.474±0.18 | 18.15±0.38 | 1.19±0.17 |
| **F12** | 29.37±0.75 | 0.406±0.26 | 0.468±0.21 | 17.65±0.24 | 1.16±0.16 |

The angle of repose of different formulations was ≤ 29.37±0.75which 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 0.398±0.14 g/cm$^3$ to 0.431±0.15g/cm$^3$.Tapped density was found between 0.436±0.19 g/cm$^3$ to 0.521±0.26g/cm$^3$.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 14.41±0.42-18.15±0.38 and Hausner's ratio from 1.14±0.15-1.23±0.21 which reveals that the blends have good flow character.

**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 5: Characterization Flurbiprofen Tablets**

| Formulation code | %Weight variation (mg) | Thickness (mm) | Hardness | Friability (%) | Disintegrating Time (sec) | Drug content (%) |
|---|---|---|---|---|---|---|
| **F1** | 250.14±1.21 | 3.15±0.47 | 4.25±0.84 | 0.68±0.21 | 22±1.2 | 96.15±1.24 |
| **F2** | 248.16±1.28 | 3.29±0.56 | 4.64±0.47 | 0.55±0.17 | 18±1.4 | 97.24±1.84 |
| **F3** | 247.68±1.47 | 3.37±0.48 | 4.12±0.82 | 0.79±0.09 | 16±1.47 | 98.06±1.47 |
| **F4** | 253.14±1.63 | 3.18±0.84 | 4.81±0.69 | 0.66±0.10 | 28±1.26 | 96.76±1.26 |
| **F5** | 251.12±1.42 | 3.25±0.62 | 4.74±0.84 | 0.45±0.14 | 22±1.47 | 97.32±1.88 |
| **F6** | 250.61±1.36 | 3.39±0.67 | 4.22±0.75 | 0.78±0.16 | 17±1.25 | 98.35±1.65 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **F7** | 253.15±1.28 | 3.17±0.85 | 4.43±0.85 | 0.72±0.21 | 19±1.56 | 96.35±1.47 |
| **F8** | 250.01±0.86 | 3.84±0.94 | 4.96±0.86 | 0.76±0.27 | 10±1.27 | 98.84±1.75 |
| **F9** | 247.52±1.24 | 3.24±0.36 | 3.91±0.64 | 0.85±0.18 | 15±1.11 | 95.74±1.19 |
| **F10** | 248.57±0.89 | 3.21±0.75 | 3.88±0.85 | 0.73±0.11 | 16±1.26 | 96.25±1.36 |
| **F11** | 251.24±1.05 | 3.16±0.61 | 4.52±0.97 | 0.92±0.18 | 14±1.54 | 97.65±1.84 |
| **F12** | 252.36±0.98 | 3.19±0.74 | 4.16±0.84 | 0.86±0.12 | 15±1.24 | 97.48±1.26 |

Hardness of the tablet was acceptable and uniform from batch-to-batch variation, which was found to be 3.88±0.85-4.96±0.86kg/cm$^2$. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeia 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 95.74±1.19-98.84±1.75%.

**Dissolution studies of the tablets**

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

**Table 6: % Cumulative drug release of formulations F1-F12**

| Time (mins) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5** | 18.85 ±1.24 | 27.36 ±1.36 | 48.18 ±1.24 | 55.75 ±1.47 | 26.21 ±1.20 | 37.26 ±1.20 | 45.89 ±1.24 | 58.15 ±1.21 | 25.48 ±1.57 | 32.08 ±1.21 | 45.89 ±1.26 | 52.36 ±1.14 |
| **10** | 32.86 ±1.68 | 41.42 ±1.47 | 54.83 ±1.67 | 66.26 ±1.25 | 47.23 ±1.75 | 51.15 ±0.98 | 61.24 ±1.74 | 69.48 ±1.24 | 34.82 ±1.11 | 43.48 ±1.21 | 59.24 ±1.27 | 65.26 ±1.51 |
| **15** | 47.63 ±1.45 | 53.35 ±1.28 | 69.49 ±1.36 | 73.12 ±1.67 | 55.15 ±1.68 | 59.42 ±1.11 | 68.42 ±1.58 | 77.26 ±1.51 | 49.45 ±1.04 | 53.05 ±1.45 | 67.42 ±1.54 | 74.12 ±1.74 |
| **20** | 65.48 ±1.28 | 72.63 ±1.67 | 76.65 ±1.78 | 87.36 ±1.26 | 63.42 ±1.65 | 64.36 ±1.01 | 77.19 ±1.21 | 88.74 ±1.77 | 54.21 ±1.21 | 65.78 ±1.24 | 75.19 ±1.21 | 86.36 ±1.52 |
| **30** | 73.52 ±1.67 | 81.49 ±1.21 | 85.48 ±1.28 | 93.14 ±1.74 | 68.26 ±1.25 | 73.25 ±1.28 | 90.46 ±1.51 | 95.25 ±1.52 | 66.48 ±1.74 | 76.36 ±1.64 | 85.46 ±1.54 | 89.14 ±1.62 |
| **40** | 88.43 ±1.84 | 90.31 ±1.61 | 92.51 ±1.67 | 98.58 ±1.62 | 77.24 ±1.20 | 81.15 ±1.64 | 97.78 ±1.24 | 99.16 ±1.21 | 72.82 ±1.52 | 84.09 ±1.54 | 92.78 ±1.31 | 98.86 ±1.47 |
| **50** | 95.75 ±1.75 | 93.53 ±1.84 | 98.88 ±1.14 | | 89.62 ±1.75 | 90.26 ±1.25 | 98.53 ±1.74 | | 86.49 ±1.21 | 92.31 ±1.12 | 98.53 ±1.47 | |
| **60** | 98.11 ±1.85 | 98.38 ±1.36 | | | 97.25 ±1.68 | 99.84 ±1.21 | | | 97.46 ±1.91 | 99.75 ±1.27 | | |

From the in vitro drug release in studies, it was observed that the formulations containing SSG as a super disintegrant in different concentrations like 20,40,60,80 mg reveals that the increased in the super disintegrant concentration decreases the drug release time and the F4 formulation containing SSG 80mg concentration shows maximum amount of drug release (98.58±1.62%) at the end of 40mins. Whereas formulations containing lycoat as a super disintegrant in different concentrations like 20,40,60,80mg reveals that the increased in the super disintegrant concentration decreases the drug release time and the F8 formulation containing lycoat with 80mg concentration shows maximum amount of drug release (99.16±1.21) at the end of 40mins. And formulations containing ludiflash as a super disintegrant in different concentrations like 20,40,60,80mg reveals that the increased in the super disintegrant concentration decreases the drug release time and the F8 formulation containing ludiflash with 80mg concentration shows maximum amount of drug release (98.86±1.47%) at the end of 40mins. So, F8 formulation containing 80mg concentration of lycoat shows max. release 99.16±1.21% within 40mins so that it is chosen as optimized formulation.

**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) : 22.4 mm

After formaldehyde treatment (treated body and untreated cap) : 20.4 mm

**Average diameter of capsule body**

Before formaldehyde treatment : 7.8 mm

After formaldehyde treatment : 7.0 mm

**Average length of capsule body**

Before formaldehyde treatment : 18.7 mm

After formaldehyde treatment : 17.7 mm

On formaldehyde treatment, the "0" size capsules bodies showed a significant decrease 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 7: Disintegration test for Treated Capsules**

| Code | Disintegration Time (hrs) | |
|---|---|---|
| | 1.2 pH (2hrs) | 7.4 pH (upto 24hrs) |
| **Capsule 1 (2rdhr)** | 2 | _ |
| **Capsule 2 (4thhr)** | 2 | 1 |
| **Capsule 3 (6thhr)** | 2 | 5 |
| **Capsule 4 (8thhr)** | 2 | 7 |
| **Capsule 5 (10thhr)** | 2 | 12 |

Basing on the disintegration studies, it was observed that the 6th hr treated capsule 1 remained intact for 7 hrs so lag time was maintained. Capsule 4,5 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, capsule 3 (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 8: *Invitro* dissolution data of formulations C1F8 to C5F8**

| Time (hrs.) | C1F8 | C2F8 | C3F8 | C4F8 | C5F8 |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | **0** |
| 1 | 07.17 | 09.21 | 0.18 | 0.85 | **0.57** |
| 2 | 15.25 | 18.18 | 1.45 | 1.45 | **0.96** |
| 3 | 21.75 | 37.75 | 4.76 | 2.62 | **1.45** |
| 4 | 37.18 | 45.26 | 8.59 | 15.81 | **3.84** |
| 5 | 75.45 | 68.15 | 12.34 | 28.74 | **4.67** |
| 6 | 89.16 | 85.24 | 19.15 | 85.25 | **6.98** |
| 7 | 97.24 | 91.47 | 54.85 | 98.85 | **85.29** |
| 8 | | 98.84 | 88.28 | | **99.85** |

| | |
|---|---|
| 9 | 98.47 |
| 10 | |

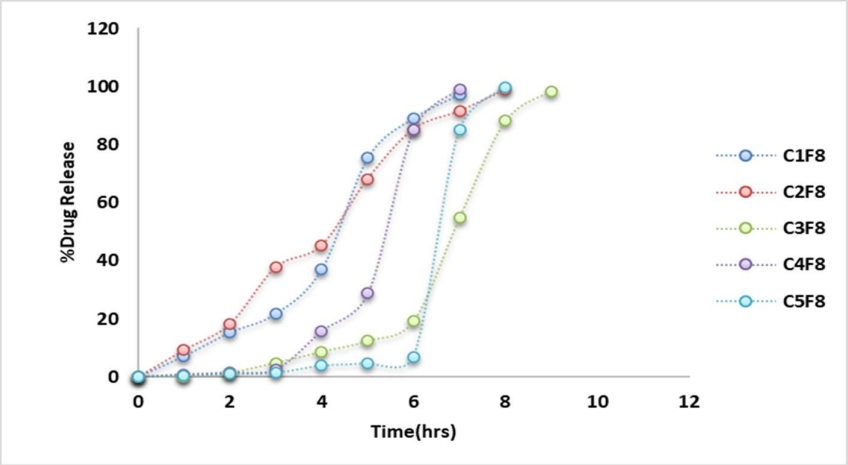


**Fig 7: Dissolution plots for formulations C1F12 to C5F12**

All the 5 formulations of Flurbiprofen pulsincaps were subjected to dissolution studies. Formulations C1F8, C2F8, C3F8, C4F8, & C5F8, contain the hydrogel plug with alone and combination of hydrophobic polymer and Hydrophilic polymer i.e., Lactose: HPMC in the ratio of 1:1, 2:1 & 1:2 of total 100mg 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 Lactose 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, C5F8 formulation containing hydrogel plug of Lactose & HPMC K15M in 2:1 ratio was selected as optimized pulsincap formulation.

**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 C5F8 was found to be 0.585, 0.449,0.389 and 0.743 respectively.

**Table 9: Correlation coefficient "R" values of C5F8 optimized formulation**

| Models | R values |
|---|---|
| Zero order | 0.585 |
| First order | 0.449 |
| Higuchi | 0.389 |
| Koresmayer peppas | 0.743 |

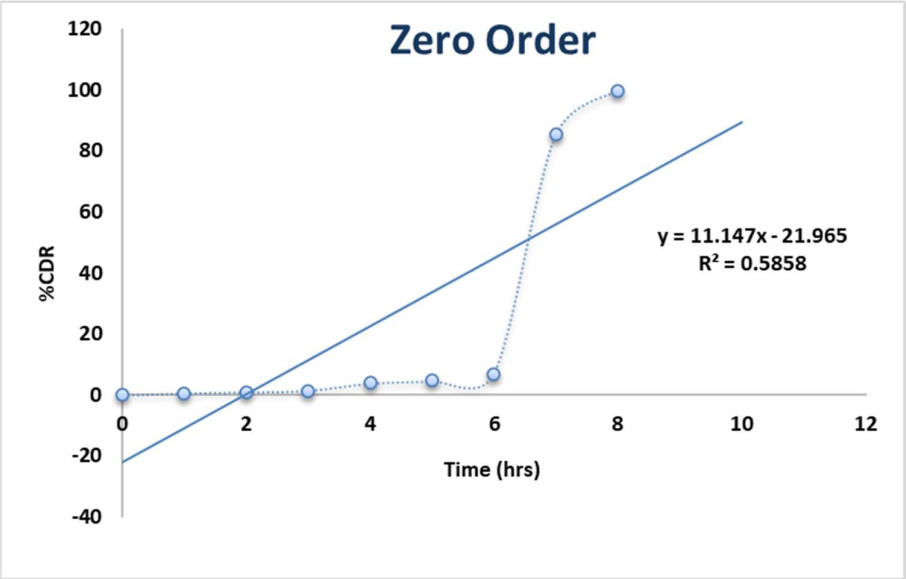


**Fig 8: Zero order plot for optimized formulation C5F8**

To analyze the mechanism of drug release from optimized C5F8 pulsincap formulation, data obtained from the drug release studies was subjected to different kinetic treatments. The correlation coefficient (R) was used as indicator of the best fitting for each of the models considered. The drug release kinetics for the optimized formulation C5F8 followed the zero order 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 Flurbiprofen 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 Pre formulation studies like solubility and UV-analysis of Flurbiprofen was 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 Lactose can be used as hydrogel plugs to delay the release of Flurbiprofen. 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 chrono pharmaceutical formulation.

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