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# Formulation and Evaluation of Pulsatile Release Tablets of Meloxicam

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## ABSTRACT

The aim of the present work is to develop a pH and time dependent pulsatile release tablets of Meloxicam for delivering the drug into colon. The system consists of a drug containing core, coated by a combination of natural polymer locust bean gum and hydroxy propyl methyl cellulose (HPMCK100M) in various proportions to control the onset of release. The whole system was coated with Methacrylic acid copolymers to prevent the drug release in stomach and also to prolong the lag time. Meloxicam was used as a model drug and varying combinations of locust bean gum and HPMCK100M were used to achieve the desired lag time before rapid and complete release of drug in colon takes place. It was observed that the lag time depends on the coating ratio of LBG and HPMC and also on press coating weight. The drug release was to be increased by 15-30% in the presence of colonic microbial flora. The present study demonstrates that the Meloxicam enteric coated tablets could be successfully formulated as a pulsatile drug delivery by the design of a time and $P^H$ dependent Chronotherapeutic formulation.

**Keywords:** Pulsatile drug delivery, Meloxicam, Locust bean gum, Chronotherapeutics, hydroxy propyl methyl cellulose, Methacrylic acid copolymers, press and enteric coated tablets.

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## INTRODUCTION

Oral controlled drug delivery systems are known to provide a zero order or first order release in which the drug is released at a substantially steady state per unit time. These dosage forms are satisfactory for the administration of most drugs. But there are certain conditions which demand release of drug after a lag time i. e., chronopharmacotherapy of some diseases show circadian rhythms[1] in their pathophysiology. Recent studies have revealed that disease has predictable cyclic rhythms and the timing of medication regimen could improve out come in selected chronic conditions. Oral time controlled pulsatile release formulations possess the interesting characteristic that is the capability of giving one or more instant and transit release pulses at a predetermined time period after a desired lag time or at specific sites. A timed release formulation could allow drug release and a greater plasma drug concentration specifically when clinical signs are developed or aggravated. Disease conditions such as early morning symptoms of asthma, arthritis, heart attacks and myocardial infarction, a time controlled pulsatile drug delivery system offer more benefits [2,3]. In rheumatoid arthritis symptoms are more exaggerated in the early morning [4,5] and night time medication is more beneficial [6].

Meloxicam is a member of enolic acid group of non steroidal anti-inflammatory drugs(NSAIDs) and is used to treat arthritis and primary dysmenorrheal. Specific Meloxicam uses include the relief of symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis symptoms, osteoarthritic symptoms and pain or inflammation caused by other conditions.

A number of oral systems are available through which a pulsatile release pattern can be achieved. Most systems contain a drug reservoir, surrounded by a barrier which erodes dissolves [7, 8] or ruptures. Many authors have reported that the compression coating with hydrogel around core tablet achieves better timed release or colon specific drug delivery. A dry coated tablet was recently renewed has a novel system to deliver a drug in a pulsatile way at predetermined times following oral administration [9,10]. Press coating technique is advantageous because the tablets can be prepared with various characteristics suitable for a number of uses [11-13]. Natural polymers that have been used previously to prepare press coated colon specific tablet dosage forms include guar gum, pectin, Chitosan and *Delonix regia* gum [14].

In the present study we have developed a pH and time dependent press coated pulsatile drug delivery system using natural polymer like *locust bean* gum. The delivery system using Meloxicam as a model drug, is made of three compartments, i.e., a drug containing core tablet and two layers of coating (the outer enteric film coating layer and the inner press coating layer)

which could have minimum influence on gastric emptying time on drug release and to reach the colon safely.

## MATERIALS AND METHOD

### Materials

Meloxicam ( Dr. Reddy's Laboratories Ltd., Hyderabad, India), Eudragit L100 and S100(Rohm Pharma, Germany) and Hydroxy propyl methyl cellulose(HPMCK100M) (Colorcon Pvt. Ltd., Goa, India) were kindly supplied as gift samples. Locust bean gum (LBG) was obtained from Hi-media chemicals Pvt. Ltd., Ahmadabad, India. Spray dried lactose and crosspovidone were obtained as gift samples from RIKON Pharmaceuticals, Hyderabad. Magnesium stearate and talc were obtained from S. D Fine chemicals Pvt. Ltd., Mumbai.

### Methods

### Preparation of core tablets

The core tablets were prepared by direct compression method followed by press coating and enteric coating. Meloxicam, spray dried lactose, cross povidone, magnesium sterate and talc were mixed according to geometric dilution method. 100 mg of powder blend was compressed using 5mm flat and plain faced punches and die cavity on a single station tablet machine (Cadmach, Ahmadabad).

### Evaluation of core tablets:

These prepared core tablets were evaluated for weight variation, hardness, friability, thickness, drug content uniformity and dissolution studies.

### Preparation of enteric coated timed release press coated tablets

### Press coating of core tablets

Press coating of tablets was done according to the method previously reported by [15]. LBG and HPMC were passed through a 120 mesh sieve and half of the total quantity of coating powder blend was filled in die cavity to make a powder bed at the bottom. The previously compressed tablet using 5mm flat punches and die cavities were then placed in the centre on the above powder blend. The remaining powder was filled in the die and the content was compressed using a flat punch of 10mm in diameter, as given in table 2. The formulated press coated tablets were evaluated for their physical properties(Table 3).

**Table 1: Formulation of press coated Meloxicam tablets**

| Formulation code | LBG-HPMC (%) | Coating weight(mg) |
|---|---|---|
| F1 | 40-60 | 200 |
| F2 | 40-60 | 250 |

| | | |
|---|---|---|
| F3 | 40-60 | 300 |
| F4 | 50-50 | 200 |
| F5 | 50-50 | 250 |
| F6 | 50-50 | 300 |
| F7 | 60-40 | 200 |
| F8 | 60-40 | 250 |
| F9 | 60-40 | 300 |
| F10 | 75-25 | 200 |
| F11 | 75-25 | 250 |
| F12 | 75-25 | 300 |
| F13 | 80-20 | 200 |
| F14 | 80-20 | 250 |
| F15 | 80-20 | 300 |

**Table 2: composition of core, press coated and Press coated enteric tablets**

| Variable | Composition | PCC Tablet | PCEC Tablet |
|---|---|---|---|
| Core tablet | Meloxicam | 7.5 | 7.5 |
| | Spray dried lacose | 65.5 | 65.5 |
| | Microcrystalline cellulose | 20 | 20 |
| | Crosspovidone | 4 | 4 |
| | Magnesium stearate | 2 | 2 |
| | Talc | 1 | 1 |
| Timed release layer | LBG | 133 | 133 |
| | HPMCK 100M | 47 | 47 |
| Enteric coating layer | Eudragit L100 | - | 14,75 |
| | Eudragit S 100 | - | 30.25 |
| | Dibutyl pthalate | - | 5 |
| Total (mg) | | 300 | 350 |

**Enteric coating of Press coated tablets**

The core tablets were coated in a conventional coating pan. The enteric coating solution was prepared by dissolving 5% w/v Eudragit L100: S100(1:2 ratio) containing 5%v/v dibutyl phthalate as a plasticizer in isopropyl alcohol solution. Coating of tablets was done at a rotating pan speed of 15rpm at a drying temperature of 55°C. The coated tablets were dried at 45°C for 24 hrs. The formulation is given in table 2.

**Method to test LBG-HPMC coat erosion**

The compressed tablets were subjected for erosion study [16]. The USP dissolution apparatus 2 was used at stirring rate of 50rpm or 100 rpm at 37±0.5°C. The dissolution test was performed using 1.2 pH buffer for 2h. At the end of 2h the medium was replaced with 7.4 phosphate buffer and the test was continued for 3h. Finally medium was replaced with 6.8 pH phosphate buffer and the study was continued for the remaining time. After 5h 3-4ml of diluted caecal contents were added to the dissolution vessels and the study was continued for 12h. All the experiments were

performed by continuously supplying nitrogen into dissolution vessels. Tablets were dried overnight at 45°C in hot air oven and the remaining tablet mass was determined gravimetrically.

**In vitro dissolution studies of press coated enteric coated core tablets**

In vitro dissolution studies were conducted at three stages to evaluate drug release profile. First on core tablets, second on press coated ones and third on press coated enteric coated core tablets in sequence. The dissolution study was performed according to the method described in United States Pharmacopoeia. The type 2 apparatus (paddle method) was used with 900ml of dissolution fluid with a rotating speed of 100rpsm at 37±0.5°C. The in vitro drug release test was performed for 2h at 1.2 pH buffer, 3h in pH 7.4 phosphate buffer [17](average small intestine transit time)and the remaining 7h in 6.8 pH phosphate buffer [18]. To evaluate the effect of enzymes on drug release rate at the end of 5h, freshly prepared 3ml of 4%w/v of rat caecal [19] content was added with previously bubbled nitrogen to maintain anaerobic condition. The samples were withdrawn at predetermined time intervals and assayed for the amount of Meloxicam release using UV Spectrophotometer at a ƛmax of 364nm.

## RESULTS AND DISUCSSION

In the present investigation to develop a pulsatile release drug delivery system is designed into three steps. Then they were evaluated at each stage.

**In-vitro characterization of core tablets and press coated tablets**

**Table 3: Physical properties of Meloxicam core and press coated tablets.**

| Code | Weight (mg) | Hardness (Kg/cm2) | Friability (%) | Drug content (%) |
|---|---|---|---|---|
| Core | 100±0.8 | 5.0±0.61 | 0.4 | 94.2±1.02 |
| F1 | 301±1.52 | 5.2±0.28 | 0.2 | 95.3±0.61 |
| F2 | 352±1.28 | 4.8±0.32 | 0.2 | 96.2±1.74 |
| F3 | 403±1.76 | 4.9±0.22 | 0.3 | 95.8±1.24 |
| F4 | 305±1.69 | 5.4±0.16 | 0.5 | 94.8±1.36 |
| F5 | 355±1.84 | 4.4±0.24 | 0.6 | 97.2±1.28 |
| F6 | 403±1.28 | 4.2±0.36 | 0.6 | 98.3±1.04 |
| F7 | 302±1.46 | 4.3±0.46 | 0.7 | 96.4±1.26 |
| F8 | 351±1.58 | 4.6±0.42 | 0.8 | 97.3±1.32 |
| F9 | 402±1.44 | 4.7±0.16 | 0.8 | 98.3±1.42 |
| F10 | 303±1.18 | 4.8±0.22 | 0.2 | 99.7±1.02 |
| F11 | 353±2.01 | 4.9±0.12 | 0.3 | 96.4±0.76 |
| F12 | 404±1.88 | 5.0±0.76 | 0.4 | 95.8±1.08 |
| F13 | 301±1.7 | 5.2±0.82 | 0.5 | 94.8±1.22 |
| F14 | 355±2.12 | 5.1±0.68 | 0.7 | 93.4±1.33 |
| F15 | 404±1.96 | 5.0±0.22 | 0.6 | 94.5±1.23 |

The core tablets and press coated tablets were prepared by direct compression method and were evaluated for quality control tests such as weight variation, hardness, friability, drug content uniformity and in vitro drug release. All the formulated core tablets comply with the Pharmacopoeial limits. The physical properties of core and press coated tablets are shown in table. 3.

**In vitro dissolution profile of core tablets:**

The dissolution studies were carried out for core tablets at pH 7.4 and pH 6.8 phosphate buffers to determine the release profile of core tablets in both media. It was observed that more than 75% drug was released within 5 min and 100% drug release within 15 min(figure 1).

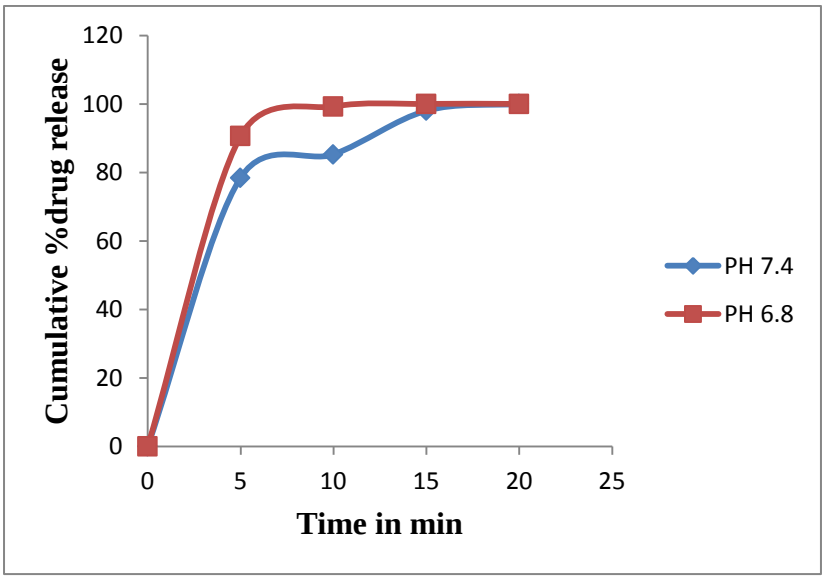


**Figure 1: In-vitro release profile of Meloxicam core tablets in PH 7.4 & PH 6.8 phosphate buffer solutions**

**In vitro release studies of press coated enteric coated tablets**

The press coated enteric coated tablets were studied for their dissolution profiles at pH 1.2 buffer for 2h, at pH 7.4 phosphate buffer for 3h and at pH 6.8 phosphate buffer for the remaining period .These studies were performed with or without rat caecal content to determine the effect of colonic bacteria on the release of the drug. Core tablets were press coated with the same weight at various LBG to HPMC polymer ratios and with different weights at the same ratio (table.1) and release profiles are shown in figure 2-4. Figure. 5 shows the effect of the presence of rat caecal content on the drug release profiles from the press coated enteric coated tablets.

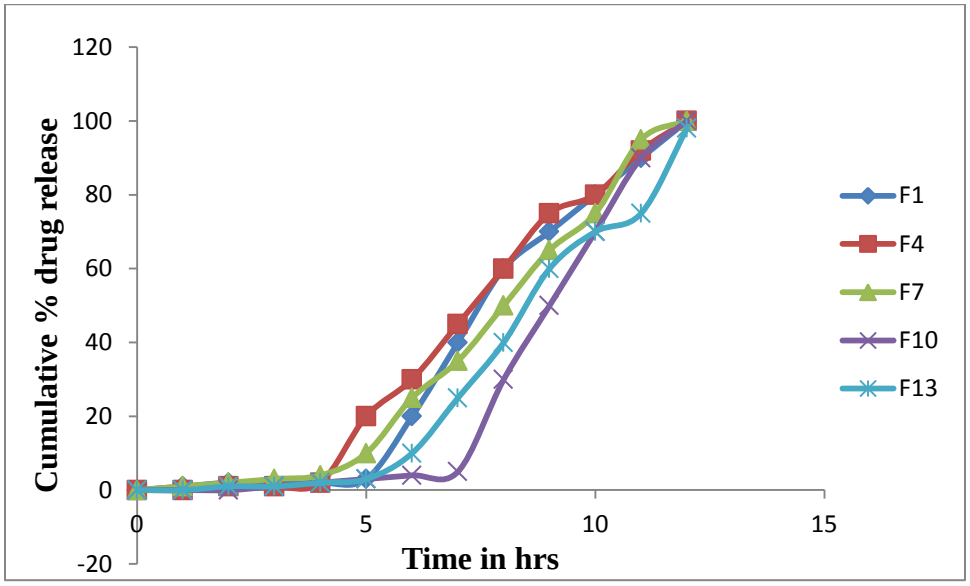


**Figure 2: In-vitro drug release profiles of press coated tablets (200mg) at PH 1.2, pH 7.4 and PH 6.8 buffer solutions .**

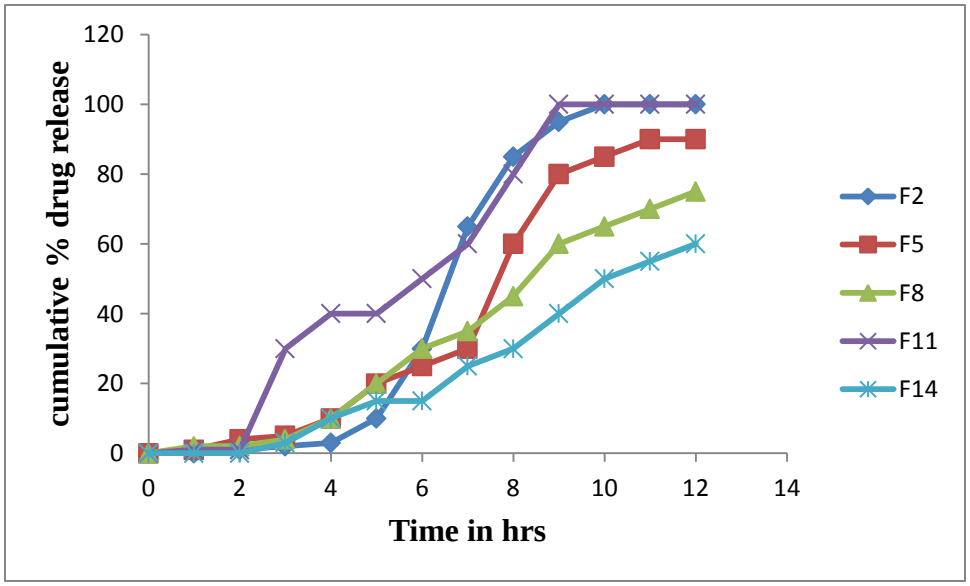


**Figure 3: In-vitro drug release profiles of Meloxicam press coated tablets (250 mg) at PH 1.2, PH 7.4 and PH 6.8 buffer solutions.**

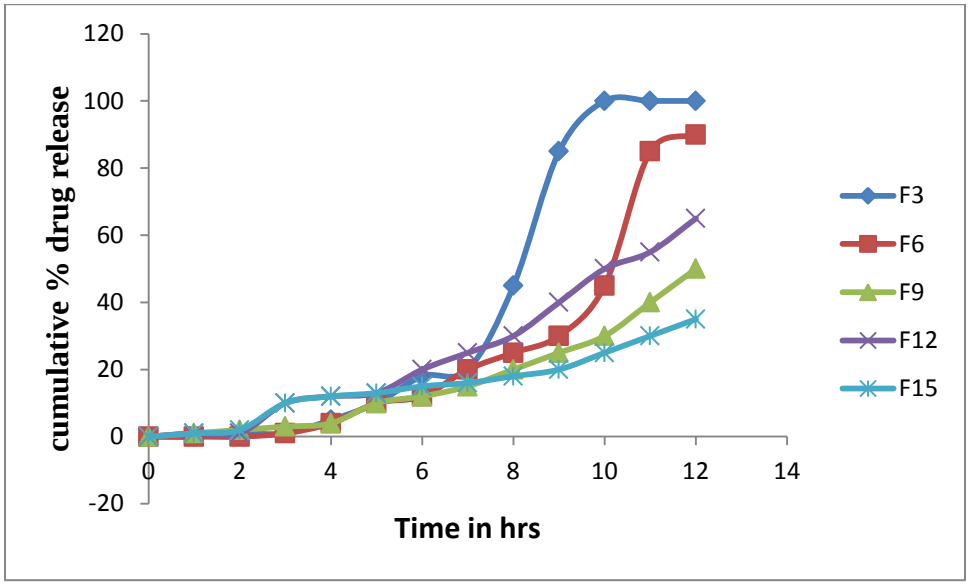


**Figure 4: In-vitro drug release profiles of Meloxicam press coated tablets (300 mg) at PH 1.2, PH 7.4 and PH 6.8 buffer solutions.**

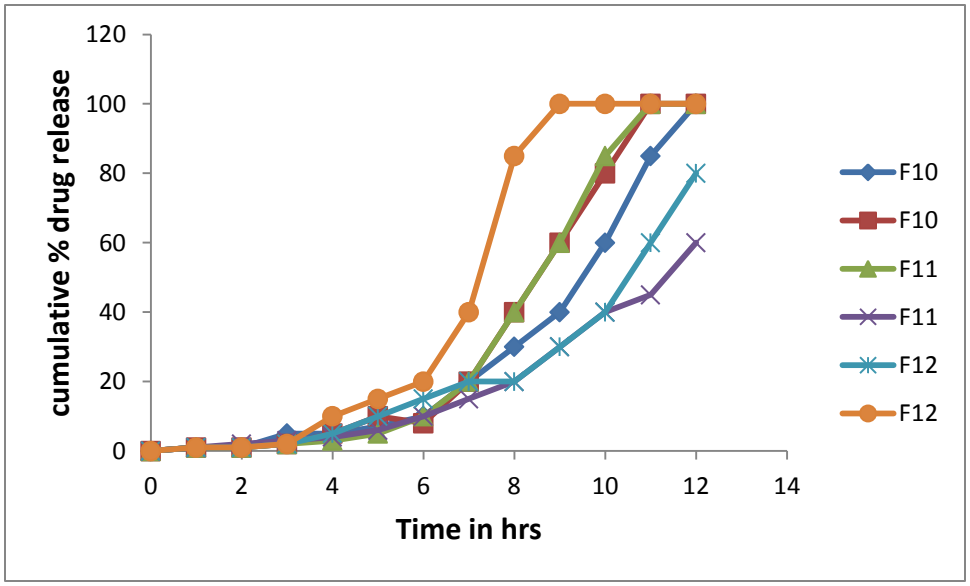


**Figure 5: In-vitro drug release profiles of press coated enteric coated tablets (250 mg) at PH 1.2, PH 7.4 & PH 6.8 Buffer solutions with or without rat caecal contents**

**Coat erosion study**

The natural polymer locust bean gum shows the property of coat erosion. This study was performed at pH 7.4 and pH 6.8 phosphate buffer solutions. This study was also conducted to find the effect of bacteria on the coat erosion. The results coat erosion with or without rat caecal content are shown in figure 6.

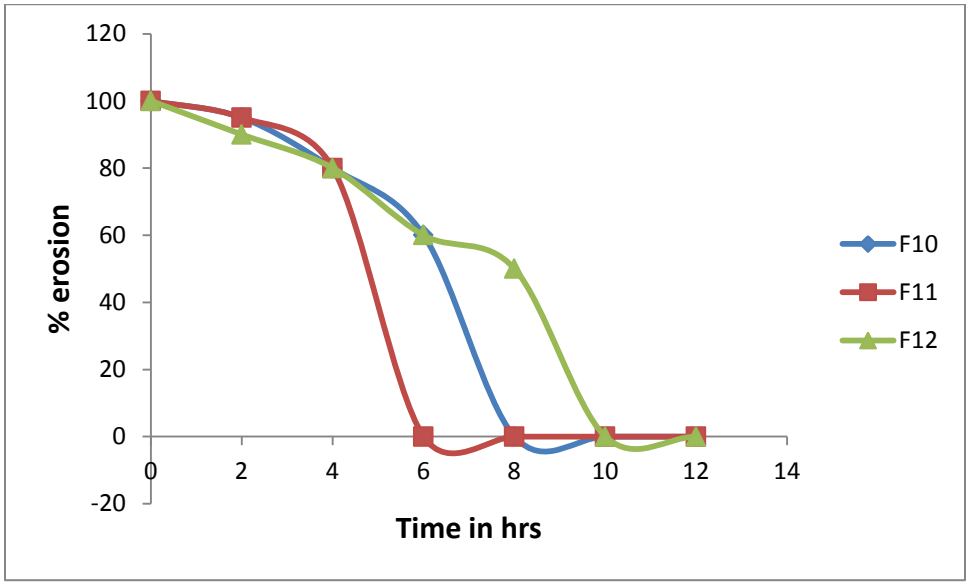


**Figure 6: coat erosion in the absence of rat Caecal content**

On the basis of desired lag time(6h)and later pulsatile release (figure 4), F10 was selected as optimized formulation. Core tablets show almost similar % of drug release in both pH 7.4 and pH 6.8 phosphate buffers. In both media core tablets have shown complete drug release within 15 min which indicate rapid release of the drug satisfying the requirement of pulsatile drug delivery system. The release of the drug from all the batches mentioned in figs2-4 shows that coat erosion decreases and drug release retards as the coating weight increases. This may be due to decrease proportion of LBG and increased proportion of HPMC. As the proportion of HPMC increases more than 40%w/v the drug release became slow and it behaves as a sustained drug delivery system. Lag time was found to be increased with increased in HPMC concentration .On the other hand as the proportion of LBG increases above 75% w/w lag time was found to be decreased due to erosion of the polymer. LBG is a natural polymer that show the biodegradation property by colonic microbial flora, hence we have attempted to find out the effect of colonic microbial flora on the drug release. The F10 formulation was selected as optimized formulation from the In-vitro drug release studies. LBG polymer also have good swelling property in all the 3 media and hence enteric coating of the press coated layer of the system could be useful to increase the lag time. Eudragit L100 and S100 are the PH sensitive copolymers used in 1:2 w/w ratios that dissolve at PH 6.8. Thus the prepared formulation is useful in such away that when it administered at bed time it may release the drug during morning hours to get relief from early morning pains of rheumatoid arthritis .

## CONCLUSION

present study confirms that Meloxicam could be delivered as a pulsatile release dosage form by formulating into PH dependent press coated, enteric coated tablet using a combination of natural polymer LBG and HPMC K 100 M. the optimized formulation showed a desired lag time of 6 hour before rapid and transient release of the drug. Thus if the formulation is administered at bed time it may release the drug between 4 to 6 am when the symptoms of rheumatoid arthritis are at its peak .

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