Development and Evaluation of A Pulsatile Drug Delivery System For Chronotherapeutic Drug Delivery

Geetanjalli Arjun Bargal*[1], Dr. Paresh Mahaparale[2], Laxman Chintaman Sapkal[3], Prof. Amol Arunrao Wadhave[4]

[1]Research Scholer, Government College of Pharmacy, Dr.BAM University, Chh.Sambhajinagar. Email id: bgeet1595@gmail.com
[2]Associate Professor, Government College of Pharmacy, Dr.BAM University, Chh. Sambhajinagar.
[3]Research Scholer, Y.B.College of Pharmacy, Dr.BAM University, Chh. Sambhajinagar.

ABSTRACT:

Pulsatile drug delivery systems (PDDS) are advanced drug delivery approaches designed to release a therapeutic agent after a predetermined lag time, followed by a rapid or controlled release phase. Such systems are particularly useful for chronotherapy, where drug release needs to be synchronized with the temporal pattern of disease symptoms. The present study focuses on the design, formulation, and optimization of a polymer-based pulsatile drug delivery system intended to achieve time-controlled drug release. The formulation was developed using suitable hydrophilic and/or hydrophobic polymers to provide an effective barrier around the drug-containing core and to regulate the lag time. Different formulation variables, including polymer type, polymer concentration, coating thickness, and drug-to-polymer ratio, were investigated to optimize the desired release characteristics. The prepared formulations were evaluated for physical characteristics, drug content, lag time, and in-vitro drug release behavior. Optimization was performed by assessing the influence of formulation variables on the lag time and subsequent drug-release profile. The optimized formulation was expected to exhibit a predetermined lag period followed by rapid and reproducible drug release, demonstrating the potential of polymer-based systems for chronomodulated drug delivery. The developed approach may provide a promising platform for improving therapeutic outcomes in diseases exhibiting time-dependent or circadian patterns of symptoms.

KEYWORDS: Pulsatile drug delivery system, polymer-based drug delivery, controlled release, chronotherapy, lag time, drug release, formulation optimization.

INTRODUCTION:

Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of the (sustained release), thereby ensuring sustained therapeutic action. But there are certain conditions which demand release of drug after a lag time. i.e. Chronopharmacotherapy of diseases which shows Circadian rhythms in their pathophysiology. These conditions demand release of drug after lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such release pattern is known as 'Pulsatile Release'. Here constant drug level is not preferred, but need a pulse of therapeutic concentration in a periodic manner that complete and rapid drug release following lag time

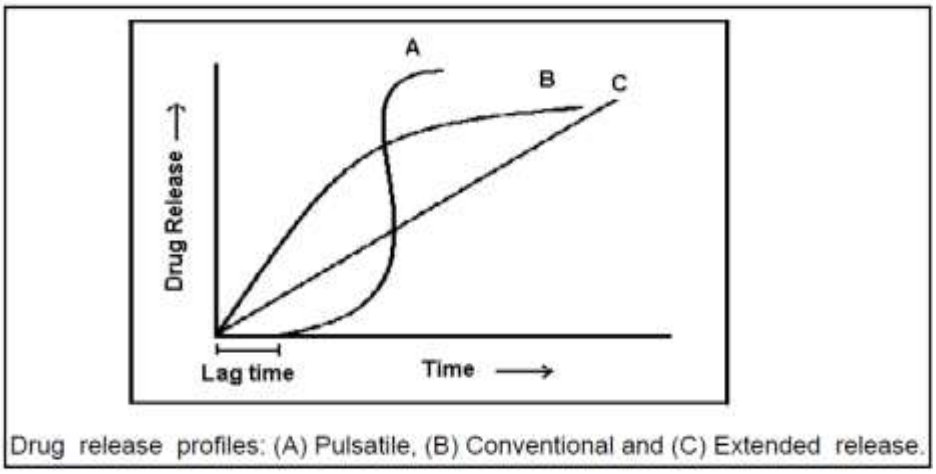

Figure 1: Drug Release Profile

To introduce the pulsatile drug delivery system, it is imp to know following concepts.

1.1 BIOLOGICAL RHYTHMS:

Table 1: Biological Rhythms

Period (τ)	Major rhythmic components
Short (τ <0.5h)	0.1s< τ <1s ,τ≈min Pulsatiles
Intermediate (0.5h <τ <6 days)	Ultradian (0.5h <τ < 20h) Circadian (20h <τ < 28h) Infradian (28h<τ <6 days
Long (τ >6 days)	Circasepatan(τ≈7days) Circamensual(τ≈ 30 days) Circannual(τ≈ 1year)

Circardian rhythm - circardian rhythm is any biological process that displays an endogeneous, entrainable oscillation of about 24hrs . these 24hours rhythm are driven by a circardian clock , and they have been widely observed in plants , animals ,fungi and cyanobacteria. Circadian - "Circa" means about and "dies" means day.

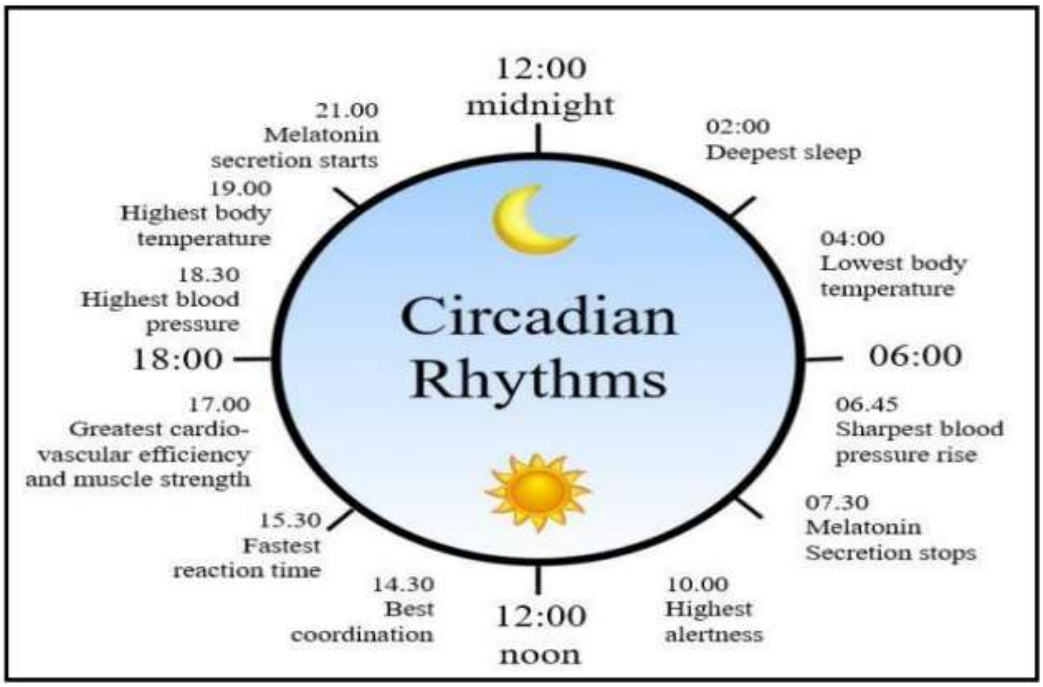

Figure 2: Circadian Rhythms

PULSATILE DRUG DELIVERY SYSTEM:

1. Pulsatile systems are gaining a lot of interest as they deliver the drug at the wright site of action at the wright time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance.
2. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time.

3. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. These systems are designed according to the circadian rhythm of the body.

NEED OF PULSATILE DRUG DELIVERY

1 First pass metabolism: Some drugs, such as beta blockers and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

2 Biological tolerance: Drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitro-glycerine, salbutamol sulphate.

3 Special chronopharmacological needs: Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

4 Local therapeutic need: For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect.

5 Gastric irritation or drug instability in gastric fluid: Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (e.g., peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting.

DISEASES REQUIRING PULSATILE DRUG DELIVERY:

Sr.no	Diseases	Chronological behaviour	Drug used
1	Peptic ulcer	Acid secretion higher in afternoon & at night	H_2 blokers
2	Asthama	Precipitation of attack during night or at early morning hour	B_2 Agonist, Antihistaminics
3	Cardiovascular diseases	BP is at its lowest during sleep cycle & rises steeply during early morning awakening period	Nitro-glycerine, Ca^+ channel blocker, ACE inhibitors
4	Arthritis	Pain in the morning and more pain at night	NSAIDS, Glucocorticoids
5	Hyperchole-sterolemia	Cholesterol synthesis is higher during night than day	HMG co-A enzyme Inhibitor
6	Diabetis mellitus	Increase in blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
7	Attention deficit disorders	Increase DOPA level in afternoon	Methylphenidate

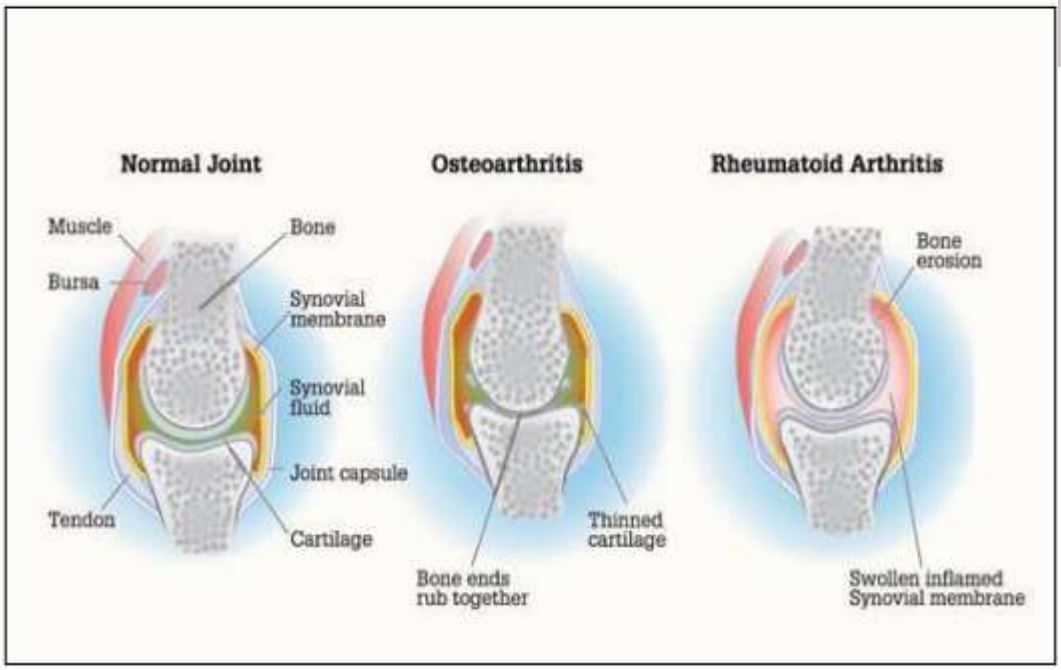

Figure 3: Normal and Arthritic joint

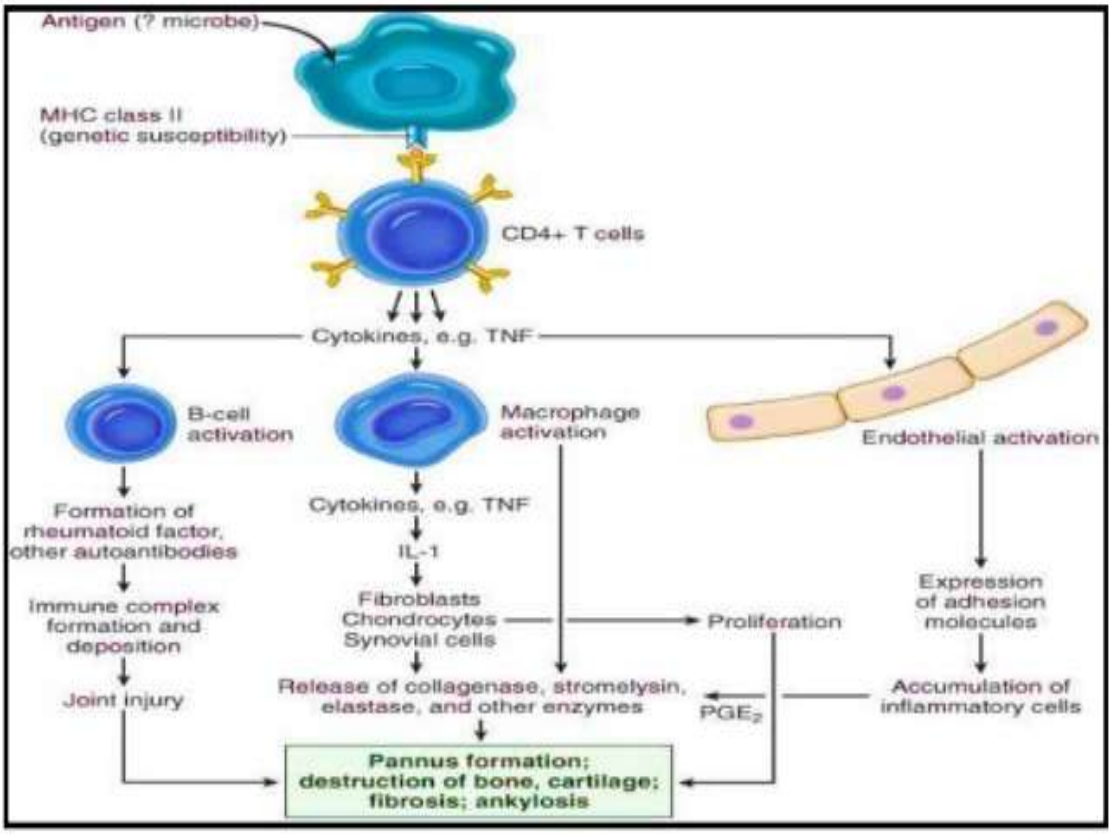

Figure 4: Pathophysiology of RA

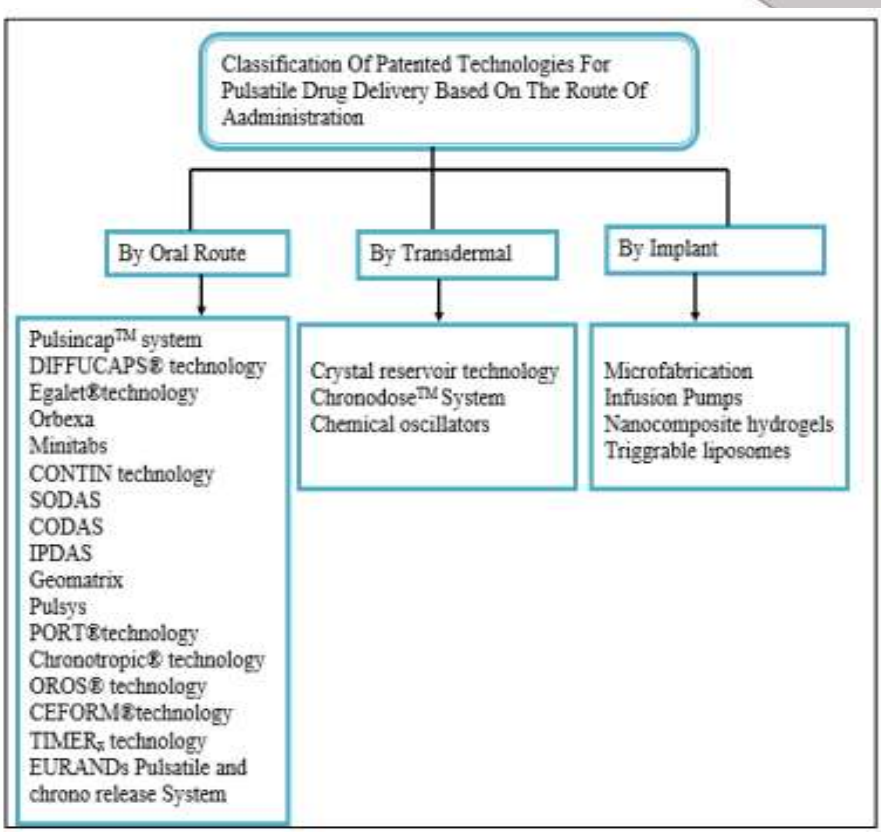

Figure 5. Marketed Techniques of Pulsatile Drug Delivery

EXPERIMENTAL WORKS:

Table 1: Formulation Design of Preliminary batches (screening of polymer)

Formulation Code	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
Drug	15	15	15	15	15	15	15	15	15	15		
SSG	-	-	6	10	-	-	6	10	-	-	6	10
NaCl	-	30	40	50	-	30	40	50	-	30	40	50
MCC	135	105	89	73	135	105	89	73	135	105	89	73
Weightof Physical blend (mg)	150	150	150	150	150	150	150	150	150	150	150	150
HPMC K4M plug	120	120	120	120								
PolyoxN80 plug					120	120	120	120				
HPMC K15M plug									120	120	120	120
Total wt.(mg)	270	270	270	270	270	270	270	270	270	270	270	270

Table 2: Formulation design of preliminary batches for screening of polymer weight and osmogene concentration

Formulation	P13	P14	P15	P16	P17	P18	P19	P20	P21
Drug	15	15	15	15	15	15	15	15	15
SSG	10	10	10	10	10	10	10	10	10
NaCl	30	40	50	30	40	50	30	40	50
MCC	95	85	75	95	85	75	95	85	75
Weight of Physical blend (mg)	150	150	150	150	150	150	150	150	150
HPMCK15M Plug	90	90	90						
				120	120	120			
							150	150	150
Total wt.(mg)	240	240	240	270	270	270	300	300	300

Table 3: Preliminary batches for study of effect of bulking agen

Formulation	P22	P23	P24	P25
Drug	15	15	15	15
SSG	10	10	10	10
NaCl	40	50	40	50
MCC	85	85	85	85
Weight of Physical blend (mg)	150	150	150	150
HPMCK15M+MCC Plug	90+30	90+30		
HPMCK15M+MCC plug			105+15	105+15
Total wt.(mg)	280	280	280	280

Table 4: Factorial design batches of meloxicam with coded and actual level

Factors	HPMC K15			NaCl		
Coded levels	-1	0	+1	-1	0	+1
Actual level (mg)	110	120	130	35	40	45

Variable	Batch								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
X_1	-1	-1	-1	0	0	0	+1	+1	+1
X_2	-1	0	+1	-1	0	+1	-1	0	+1

RESULT AND DISCUSSION:

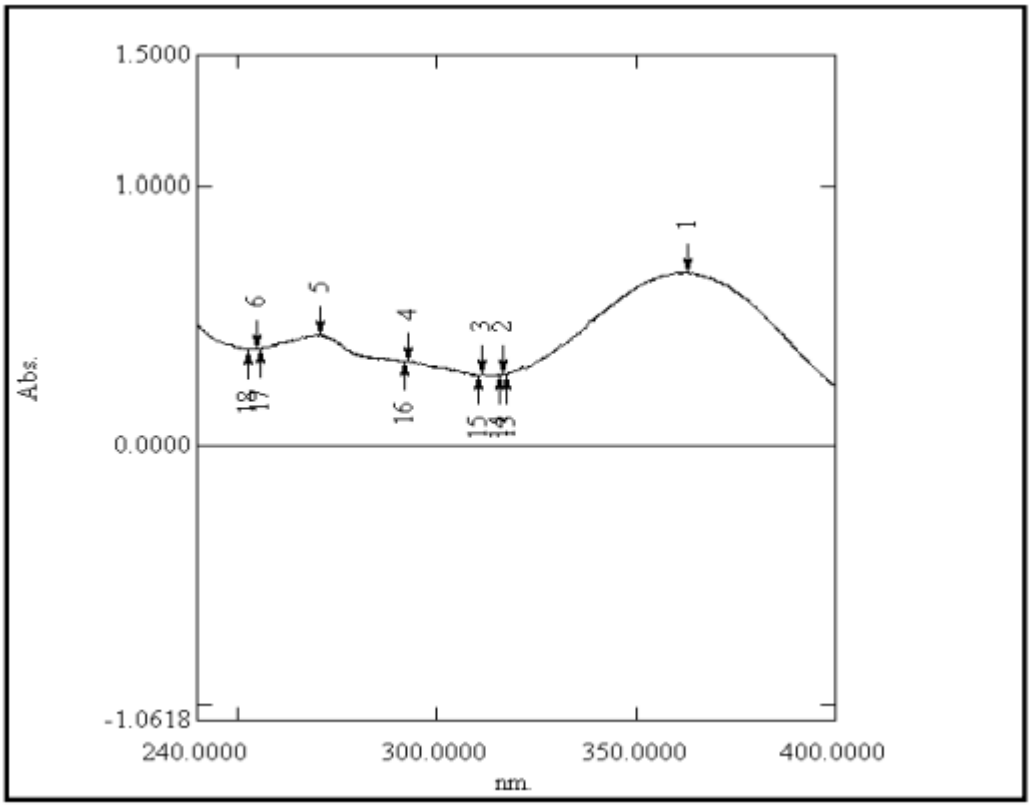

Figure 6: UV Spectrum of Meloxicam

Table 5: Calibration Curve of Meloxicam in pH 1.2 (0.1 N HCl)

Sr. No	Concentration (ppm)	Absorbance
1	2	0.24
2	4	0.43
3	6	0.64
4	8	0.86
5	10	1.15
6	12	1.51

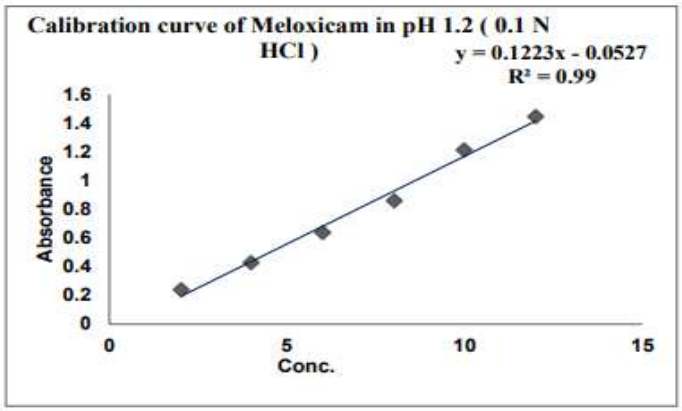

Figure 7: Calibration curve of Meloxicam in pH 1.2 (0.1 N HCl)

Table 6: Calibration for meloxicam in phosphate buffer pH6.8

Sr. no.	Concentration (ppm)	Absorbance in pH 6.8
1	2	0.13
2	4	0.25
3	6	0.39
4	8	0.52
5	10	0.64
6	15	0.95
7	20	1.24

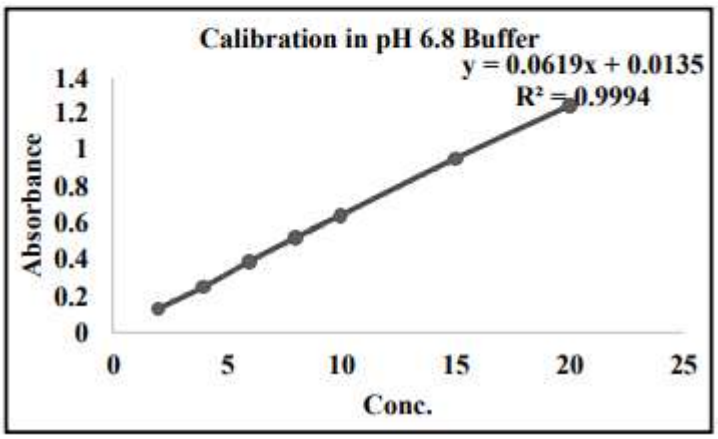

Figure 8: Calibration curve of Meloxicam in Phosphate buffer 6.8

IR ANALYSIS: IDENTIFICATION OF MELOXICAM USING IR SPECTROSCOPY

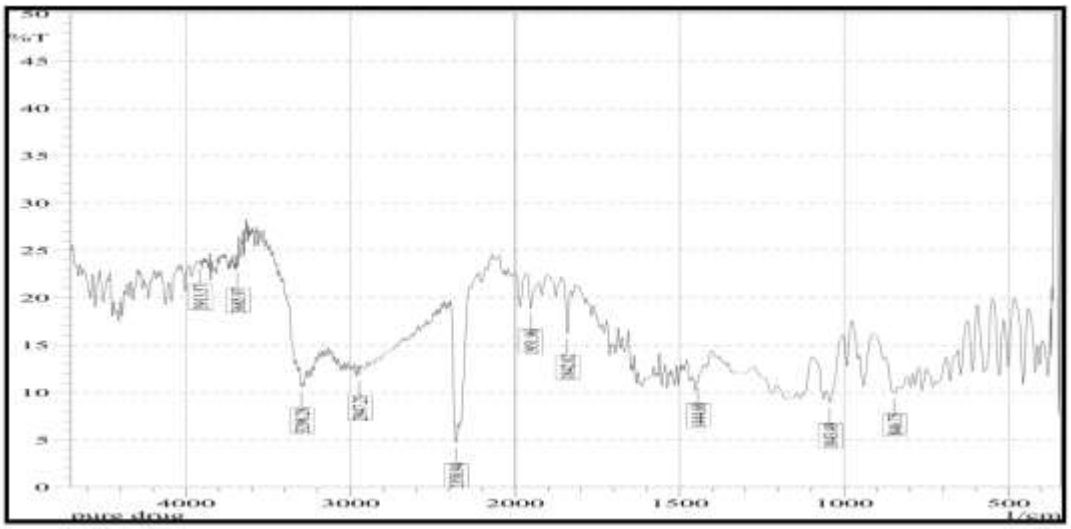

Figure 9: IR Spectra of Meloxicam

Table 7: Solubility study of crosslinked gelatine capsules

Formaldehyde concentration %W/V	Time of exposure (hr)	Observation in dissolution media		
		0.1 N HCl	Phosphate Buffer pH7.4	Phosphate Buffer Ph6.8
5%	6	Soften in 1hr	Soften in 90min	Soften in 90min
	9	Soften in 3hr	Soften in 3hr	Soften in 3hr
	12	Soften in 4hr	Soften in 4hr	Soften in 4hr
10%	6	Soften in 4hr	Soften in 4hr	Soften in 4hr
	9	Soften in 5hr	Soften in 5hr	Soften in 5hr
	12	Soften in 7hr	Soften in 6hr	Soften in 6hr
15%	6	Soften in 8hr	Soften in 9hr	Soften in 9hr
	9	Soften in 9hr	Soften in 10hr	Soften in 10hr
	12	Soften in 12hr	Soften in 14hr	Soften in 14hr

Table 8: Evaluation of Hydrogel plug

Weight (mg)	Thickness (mm)	Hardness(kg/cm^2)	Lagtime (hrs)	Swelling index(%)
90	2.3±0.02	3.2±0.20	4.5	52±0.23
90	2.1±0.03	3.3±0.54	4	52±0.22
90	2.1±0.02	3.2±0.69	3.5	52±0.19
120	2.8±0.04	3.3±0.33	8.5	52±0.25
120	2.6±0.06	3.2±0.10	8	53±0.21
120	2.6±0.01	3.5±0.40	7.5	53±0.22
150	3.1±0.02	3.4±0.46	9.5	55±0.18
150	3.1±0.06	3.3±0.45	9	55±0.31
150	3.0±0.03	3.2±0.33	8.5	55±0.25

*All values are Mean ±SD

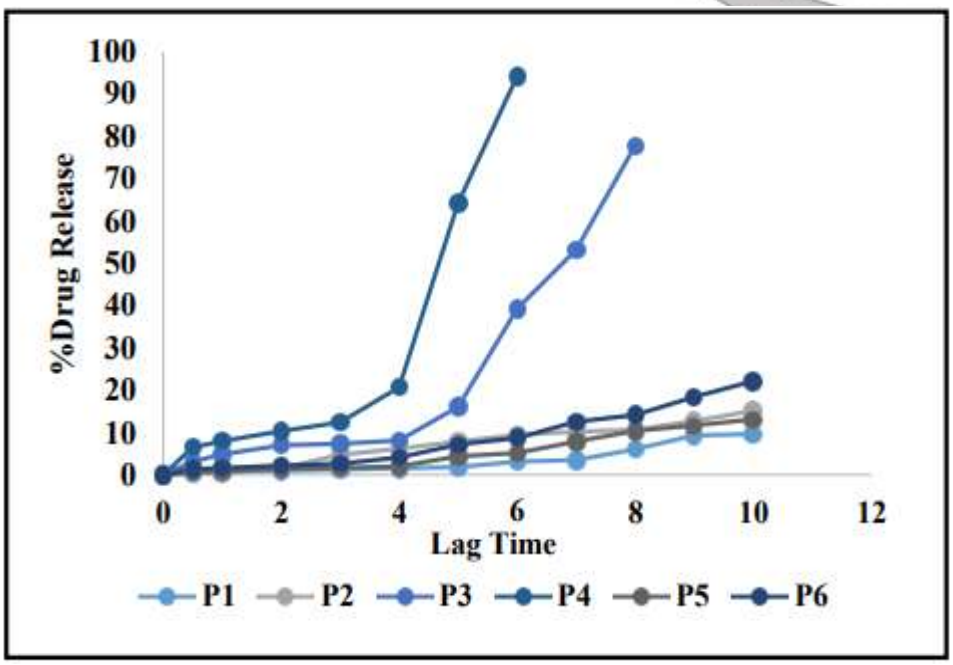

Figure 10: In vitro drug release of preliminary batches P1-P6 for screening of polymer.

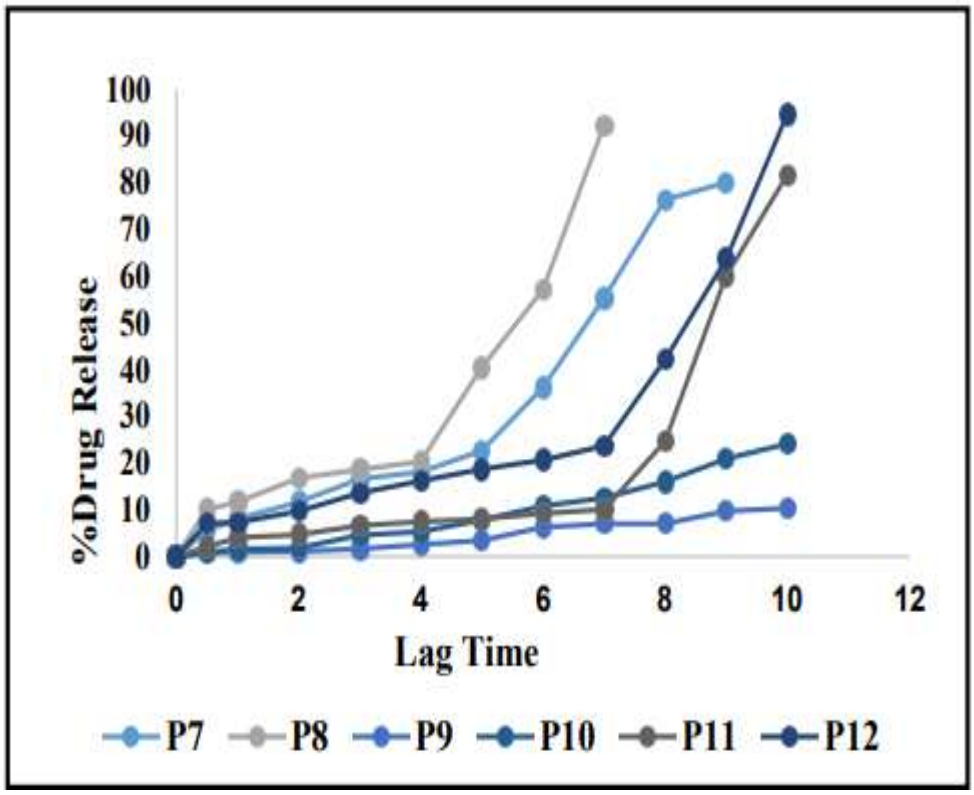

Figure 11: In vitro drug release of preliminary batches P7-P12 for screening of polymer.

Table 9: In-vitro drug release of factorial formulations

Time (Hr)	FORMULATION								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	0.64	0.46	0.53	0.72	0.57	1.02	1.60	1.54	1.68
2	0.85	0.56	0.58	0.96	0.73	1.57	2.23	2.20	2.53
3	1.86	1.08	0.96	1.27	1.08	2.05	5.72	5.90	5.31
4	1.94	1.75	1.75	3.19	1.842	3.62	6.30	6.79	8.27
5	2.90	2.17	1.81	7.59	3.38	5.92	49.50	45.55	41.73
6	3.57	2.72	2.54	41.18	6.09	8.10	68.04	75.92	80.02
7	5.55	4.05	3.02	78.09	43.32	55.34	102.9	98.09	95.86
8	6.24	5.98	5.91	92.24	78.72	96.79			
9	51.90	35.94	45.90		98.18				
10	84.27	83.31	82.52						

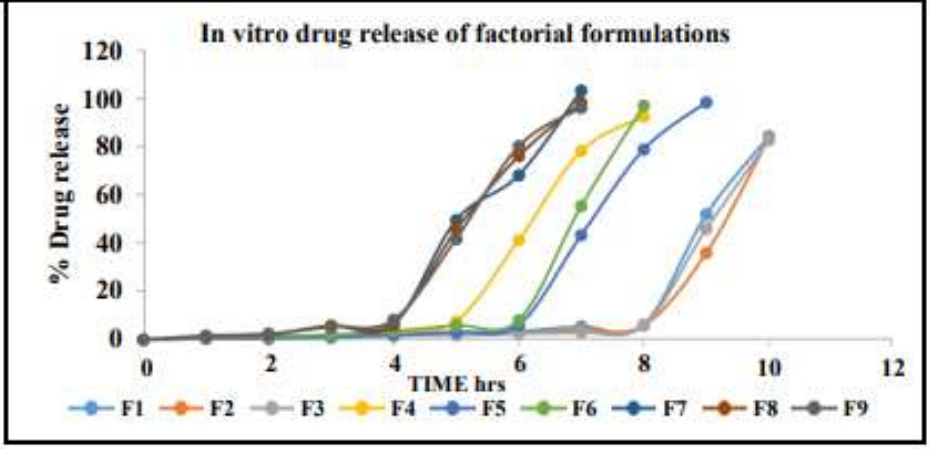

Figure 12: In vitro drug release of factorial formulations

Table 10: ANOVA for % Drug Release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	355.54	2	177.77	11.52	0.0088	Significant
A-Conc.of HPMC K 15M	351.14	1	351.14	22.75	0.0031	
B-Conc. of NaCl	4.40	1	4.40	0.2853	0.6124	
Residual	92.59	6	15.43			
Cor Total	448.13	8				

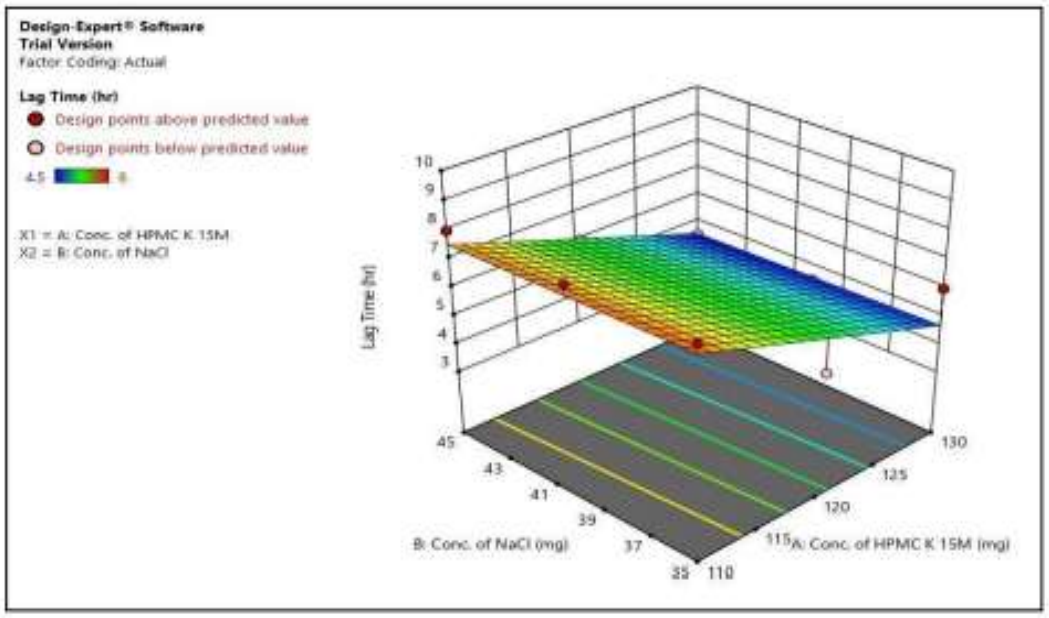

Figure 13: Response surface 3D plot of Lag Time

SUMMARY:

The work was initiated with thorough literature survey on pulsatile drug delivery, pathogenesis of Rheumatoid arthritis (RA), and treatments available for RA. Most of the treatments available do not consider the circadian rhythm in pathogenesis of the disease. The available treatment with non-steroidal anti-inflammatory agents shows adverse side effects on long term therapy such as gastric irritation. The adverse effects can be minimised if the therapy is syncronised with the peak time of symptoms. This can be achieved by chronotherapy. From the investigations following conclusions were drawn: ¬ In preformulation study identification of Meloxicam was done and it was found that meloxicam shows melting point of 2540C, and wavelength of maximum362 nm in phosphate buffer pH 6.8, Characterization of FTIR peaks shows all functional groups of meloxicam. ¬ FTIR data confirm that there is no chemical interaction of the drug with the other components used in the formulation. ¬ Calibration curve of meloxicam was performed on Methanolic HCl (1:1mix) and phosphate buffer pH 6.8 which can be used for drug quantification in dissolution analysis.

FUTURE PROSPECTIVE:

The optimized formulation F5 & F6 should be further evaluated for in vivo drug release followed by IVIVC .

REFERENCES:

1 Matholiya, C. R.; Dedakia, A. S. An Approach For Controlled Drug Delivery : As Pulsatile Drug Delivery System. Int. Bull. Drug Res. (3), 1–21.

2 Bathe, A. D. M. and R. S.; Department. An Updated Review on Pulsatile Drug Delivery System. Int. J. Adv. Pharm. 2015, 4 (4).

3 Rewar, S.; Bk, B.; Shakya, V.; Cj, S.; Sharma, M. New Approaches in Pulsatile Drug Delivery System : A Review. Int. J. Pharm. Biol. Arch. 2014, 5 (2), 27–43.

4 Nagar, M.; Singhai, S.; Chopra, V. S.; Gautam, N.; Trivedi, P. Chronotropic Systems ; an Emerging Trend in Drug Delivery for Pulsed Release in Chrono pharmacotherapy. Int. J. Pharm. Clin. Res. 2010 2 (1), 10–19.

5 Gs, S.; Mv, S.; Mu, U.; Ks, P. K.; Kv, M. Recent Trends in Pulsatile Drug Delivery Systems - A Review. Int. J. Drug Deliv. 2010, 2, 200–212.

6 Singh, N.; Gill, V.; Gill, P.; Singh, S. Chrono pharmaceutical Drug Delivery System-A Guided Therapy. Int. Res. J. Pharm. Appl. Sci. 2013, 3 (4), 84–87.

7 Khan, V. M. and A. B. Chronotherapeutics In Development Of Pulsatile Delivery Systems. Int. Jouranl Pharm. Sci. Res. 2012, 3 (11), 4086–4095.

8 Patel.V.P.; M, S. M. Pulsatile Drug Delivery System for Treatment of Various Inflammatory Disorders : A Review. Int. J. Drug Dev. Res. 2012, 4 (3), 67–87.

9 Karale, P.; Education, P.; Education, P. Pros and Cons of Pulsatile Drug Delivery System. Int. Jouranl Pharm. Drug Anal. 2015, No. August.
10 Vinupama, S.; K, S. S. K.; Keerthi, T. S.; K, S. K. S. Pulsatile Drug Delivery System : A Review. Internatinal Bull. Drug Res. 1 (1), 19–31.
11 Bhatia, S.; Kumar, B. Oral Chronotherapeutics: Future of Drug Delivery Systems. Int. J. Sci. c Study 2014, 2 (4), 4–7.
12 Surendra, P.; Shirisha, V.; Phanidra, V.; Keerthi, G. R. A Review Articles On Pulsatile Drug Delivery System. Int. J. Res. Pharm. Nano Sci. 2013, 2 (4), 471–477.
13 Shidhaye, S.; Dhone, A.; Budhkar, T.; Surve, C. Technologies in Pulsatile Drug Delivery System. Int. J. Adv. Pharmacy, Biol. Chem. 2012, 1 (4), 438–445.
14 Singh, A.; Dubey, H.; Shukla, I.; Singh, D. P. Pulsatile Drug Delivery System : An Approach of Medication according to Circadian Rhythm. J. Appl. Pharm. Sci. 2012, 2 (3), 166–176.