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A Path for Horizing Your Innovative Work

DESIGN AND DEVELOPMENT OF FLOATING PULSATILE DRUG DELIVERY SYSTEM USING MELOXICAM

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Abstract: The main objective of the present study was to develop single-unit floating-pulsatile drug delivery system for obtaining no drug release during floating and in the proximal small intestine followed by pulsed drug release in distal small intestine to achieve chronotherapeutic release of meloxicame for treatment of rheumatoid arthritis, osteoarthritis, spondylytis and to improve the patient compliance. The objective of present investigation was to prepare and evaluate a floating pulsatile drug delivery system of Meloxicam. The prepared floating pulsatile delivery system consisted of three different parts: a core tablet, containing the active ingredient, an erodible outer shell and a top cover buoyant layer. The rapid release core tablet (RRCT) was prepared by using superdisintegrants along with active ingredient. Dry coating of optimized RRCT was done by using different grades of hydroxyl propyl methyl cellulose (HPMC) E5, E15, and E50 and upper most buoyant layer was prepared with HPMC K15M and sodium bicarbonate. Developed formulations were evaluated for their physical characteristics, drug content, in vitro disintegration time, in vitro drug release profile (lag time), floating lag time, floating time . On the basis of these evaluation parameters it was found that optimized floating pulsatile release formulation (FPRT) F8 showed floating lag time of 4 min, floating time of 12 hrs and release lag time of 6 hrs. The F8 formulation showed compliance with chronotherapeutic objective of rheumatoid arthritis.

Keywords: Gastric residence time, Meloxicam, Rheumatoid arthritis, Lag time, Floating lag time, Floating drug delivery system, Chronotherapeutic.

INTRODUCTION

Chronopharmacotherapy, the drug regime based on circadian rhythm, regulates many body functions in human beings, viz., metabolism, physiology, behavior, sleep patterns, hormone production, etc. Human beings greatly vary in their biochemical and physiologic status over a 24-hour period due to the existence of a number of circadian rhythms.

Various diseases like asthma has been reported to have increased airway responsiveness and worsening of lung function measured over a 24-hour cycle will show a characteristic circadian rhythm with the peak during the afternoon and the trough in the early hours of the morning [1, 2, 3].

Heart rate and blood pressure both exhibit a strong circadian pattern with values for blood pressure, double product typically peaking in the Early morning period compare with till late afternoon, and then drops off during night (hypertension), [4, 5, 6] gastric acidity was observed toward an increase in intragastric acidity during the time period from the middle of the night to the early dawn, and toward a decrease in intragastric acidity during the early morning, [7.8,9] rheumatoid arthritis feel more pain in the morning hours show circadian variation that demand time-dependant drug release for effective drug action, for example, more pain with morning body stiffness, asthma, and heart attack in early hours of the day.[10]Circadian rhythm disturbances are observed in children with attention-deficit/hyperactivity disorder and sleep onset insomnia [11].

The floating pulsatile concept was thus applied to increase the gastric residence of the dosage form having lag phase followed by a burst release in either stomach or distal part of small intestine. A combination of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in upper GI tract after a defined time period of no drug release. [12]

Krogel and Bodmeier developed floating and pulsatile drug delivery systems based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating.[13] Studies identified important core and coating properties for the two systems.

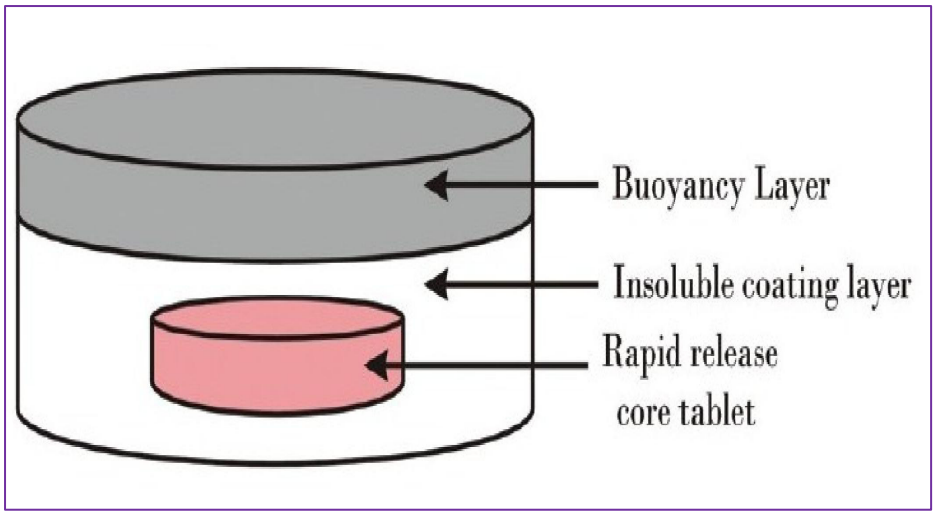


Figure 1. Design of floating pulsatile release tablet of Meloxicam

Different methods are developed to prepare time- and site-specific drug release of Meloxicam for chronopharmacotherapy in rheumatoid arthritis.

The pulsatile release system with various lag times was prepared by compression with different erodible polymeric layers. Combined usage of hydroxypropyl methylcellulose (HPMC) and carbomer in a gastric floating or mucoadhesive drug delivery system has been reported [14, 15] to improve the floating properties or mucoadhesiveness of the combined system. The novel system could result in (1) a floating dosage form with a prolonged gastric residence time and in (2) a pulsatile dosage form, in which the drug is released rapidly in a time-controlled manner after rupturing of the coating.

The floating pulsatile drug delivery system was designed such that rapid release core tablet of Meloxicam was dry coated by the layer of HPMC to impart pulsatile release characteristics and the top cover buoyant layer ensured the floating of the system (figure 1). Developed formulations were evaluated for buoyancy studies, drug release studies and floating lag time studies.

MATERIALS AND METHODS

Hot melt method

In hot melt method, the carriers such as PEG 6000 and PEG 4000 were selected. The drug to polymer ratio was kept 1:1, 1:4 and 1:8. The carrier was first melted in the china dish

at about 60 ^{0}C and the drug was dispersed in the molten mixture with constant stirring. The dispersion was poured immediately into the molds (specially designed for filling into the capsule) and cooled immediately. The effect of 1 % w/w polysorbid 80 (Tween - 80) on the solubility of Meloxicam was also investigated by adding the 1 % w/w Tween 80 into the molten mixture with constant stirring followed by repeating the above procedure. The solid dispersions obtained from this method were tacky enough. Addition adsorbents like lactose, powdered citric acid did not improve its tacky nature. Hence it was poured into the molds designed to fill into the capsule. Physical mixtures Meloxicam and carriers were also prepared by mixing physically the powdered carrier with the drug.

Solvent evaporation method

In solvent evaporation method, drug and the carrier were dissolved in alcohol and the adsorbent like micro crystalline cellulose (MCC) were dispersed in the same medium with constant stirring. Alcohol was evaporated under low pressure to get the solid dispersion. In this method, PEG 6000, PEG 4000 and PVP-K-30[6] were used as carriers and MCC was used as adsorbent. Drug: carrier: adsorbent ratio was kept 1: 2: 1. The product obtained was free flowing unlike the solid dispersions obtained by hot melt method. The solid dispersions showing good water solubility from the above methods were further studied evaluated.

Preparation of Rapid Release Core Tablet (RRCT)

Meloxicam RRCTs were prepared by wet granulation method (table 1). All the ingredients were passed through 60 # mesh sieve separately and collected. The ingredients were weighed and mixed in a geometrical order. Then the mixture was wetted with a solution of PVP K-30 (10% w/v in ethanol). The wetted mass was again passed through 22 # mesh sieve. The granules were dried in a circulating hot air oven (40 ºC) for 6h and compressed by using 6 mm size punch to get a tablet of 60 mg weight using single punch tablet machine.

The physical characteristics such as thickness, diameter, hardness and weight variation test were evaluated according to the Indian Pharmacopoeia (IP) 1996

In vitro disintegrating time

In vitro disintegration time of six tablets from each formulation was determined by using digital tablet disintegration apparatus (Electrolab, ED- 2L). *In vitro* disintegration test was carried out at 37 ± 2 ^{0}C in 900 ml 0.1N HCl.

In vitro dissolution studies

The *in vitro* dissolution studies were carried out in 0.1N HCl (900 ml) at 37 ± 0.5^{o}C using USP dissolution apparatus type II. The speed of rotation was maintained at 50 rpm. Aliquots of dissolution medium were withdrawn at predetermined time interval and content of Meloxicam was determined by using UV spectrophotometer at 274 nm. The dissolution studies were conducted in triplicate.

Preparation of the Pulsatile Release Tablet (PRT)

The optimized RRCT was used for preparation of PRTs. Dry coating of optimized RRCT was done by using different grades of HPMC (E5, E15 and E50) at different concentrations (table 3). Final weight of tablet was adjusted to 360 mg. Dry coated tablet was prepared by placing 50% of pulsatile release layer in 10 mm die and RRCT was placed on it. Further remaining quantity of pulsatile release layer was added in cavity so as to cover the RRCT and finally compressed by using single punch tablet machine.

Evaluation of PRT

The formulated PRTs were evaluated for parameters like thickness, diameter, hardness and *in vitro* drug release (lag time). The optimization was done based on these results.

Preparation of Floating Pulsatile Release Tablet (FPRT)

The composition of buoyant layer was optimized by using 3^2 full factorial design (table 5). In this study, two factors were evaluated each at three levels and experimental trials were performed at all nine possible combinations. The amounts of HPMC (X1) and sodium bicarbonate (X2) were selected as independent variables.

All the nine possible combinations of buoyant powder were filled into the die individually, followed by addition of optimized PRT and finally compression was done. These nine formulations were studied and optimized for floating lag time and floating time.

Evaluation of FPRT

FPRTs were evaluated for parameters like thickness, diameter, hardness, floating lag time, floating time and in vivo animal study. *In vitro* floating behavior of FPRT was studied by using dissolution apparatus type II in 900ml 0.1N HCl at 37 ± 0.50C. The speed of rotation was maintained at 50 rpm. The floating lag time (the period between placing FPRT in the medium and buoyancy) and floating duration of FPRT were determined by visual observation.

Stability studies

A short-term stability study on optimized FPRT was carried out by storing the tablets at 40 ^{0}C/ 75% RH over a 6 months period according to ICH guidelines[16] . At the end of six months time interval, the tablets were examined for any physical characteristics, drug content, *in vitro* drug release (lag time), floating lag time and floating duration. Statistical analysis was performed on the drug content data and drug release parameters by using 't' test.

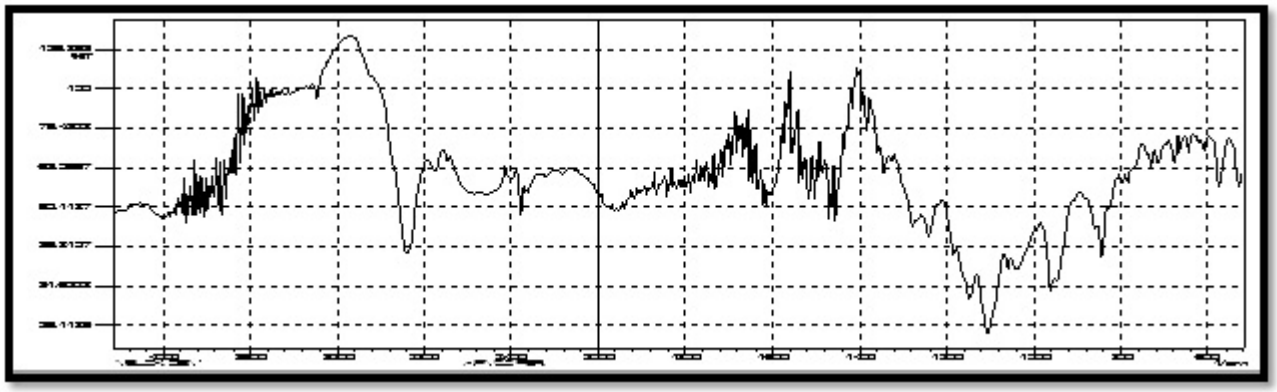
RESULTS AND DISCUSSION

Rapid Release Core Tablet (RRCT) Characterization

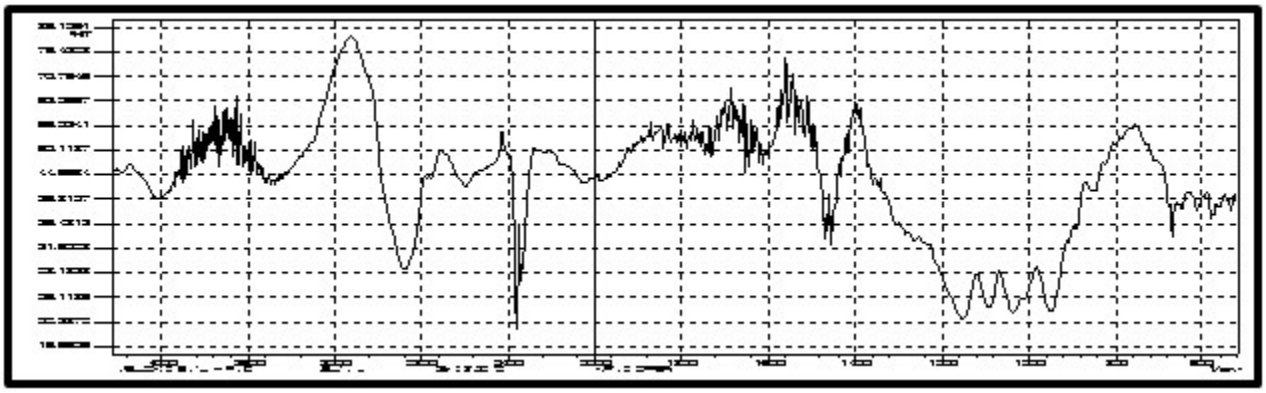
Drug- Excipient interaction study

Infrared spectroscopy was used as means of studying drug-excipients interactions. It was found that there was no chemical interaction between Meloxicam and excipients used because there were no changes in the characteristic peaks of Meloxicam in the IR spectra of mixture of drug and excipients as compared to IR spectra of pure drug.

IR Spectroscopy of pure drug



Pure drug + Excipients



Eight formulations of Meloxicam RRCTs with varying concentration of croscarmellose sodium (RR1- RR4), crospovidone (RR5- RR8) were evaluated for tablet dimensions, hardness, weight variation, uniformity of content, *in vitro* disintegration time and *in vitro* drug release study. It was found that all RRCTs showed tablet dimensions, hardness, weight variation, uniformity of content, *in vitro* disintegration time within the prescribed range as given in IP (table 7).

***In vitro* drug release of RRCT**

In this study formulations containing crospovidone (RR5-RR8) showed fast drug release than the formulation containing croscarmellose sodium (figure 3). This may be because of the fact that crospovidone probably made larger pores with continuous network or skeleton providing enough pressure for faster disintegration and it also had capability to swell at least twice of its original volume when in contact with dissolution fluid[16]. Among eight formulations of Meloxicam RRCTs, it was observed that formulations containing crospovidone in concentration 5% (RR8) showed satisfactory hardness, uniformity of content , lowest disintegration time and highest drug release (table 7). So RR8 was considered as optimized formulation and was taken for further studies

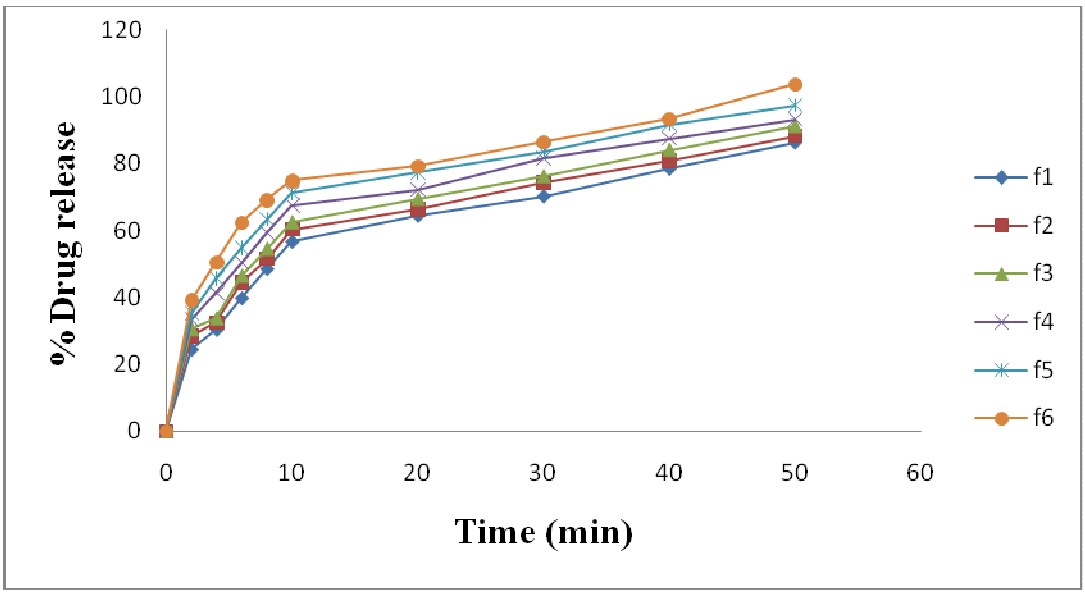


Figure 2. *In Vitro* Drug Release Profile of Meloxicam from RRCT Croscarmelose Sodium and Crospovidone

Pulsatile Release Tablet (PRT) Characterization

Physical characteristics of PRT

For PRT characterization, total 18 formulations containing varying concentration (200- 300 mg) of HPMC E5, E15 and E50 were evaluated for thickness, diameter, hardness and drug release profile in terms of lag time. It was found that all PRT formulations showed satisfactory features in terms of thickness, diameter and hardness (table 8).

***In vitro* drug release (lag time) study**

In vitro drug release (lag time) study of 18 formulations, showed differences in drug release (lag time) as shown in table 4. All the formulations coated with HPMC E5 and E15 have given the lag time of less than 3 hr and 5 hr respectively which was considered to be unsuitable for chronotherapeutic objective. The formulations coated with HPMC E50 in concentration of 280 mg showed sufficient lag time as compared to formulations coated with HPMC E5 and E15 with same concentration.

In this study (lag time) as the coated tablet i.e. PRT was placed in the dissolution medium, it was observed that the hydrophilic polymeric layer started erosion, which underwent progressive modification in terms of thickness and consistency. In the second phase of the dissolution procedure, the coating layer gradually started to erode

up to a limiting thickness. After this stage, a shell was ruptured under the pressure applied by the swelling of the core tablet and M was released. All of this process contributed to a lag time capable of exhibiting a pulsatile release of the drug. The drug release profiles relevant to the coated tablet showed that a lag phase was followed by the quick delivery of the drug. As the formulation coated with HPMC E50 in concentration of 280 mg showed sufficient lag time as compared to other formulations, this formulation was considered as optimized formulation for FPRT.

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Floating Pulsatile Release Tablet (FPRT) Characterization

The composition of buoyant layer was prepared by using 32 full factorial design and evaluated for thickness, diameter, hardness, floating lag time and for floating time. It was found that all tablets form FPRT composition showed satisfactory results in terms of thickness, diameter and hardness (table 10).

Floating lag time and floating time study

In this study floating lag time for all compositions of FPRTs were found to be less than 14 minutes and floating time more than 12 hr (table 10).

Here FPRT with highest concentration of HPMC K15 M and sodium bicarbonate (F8) was selected for chronotherapy of rheumatoid arthritis because it showed least floating lag time of 4.6 minutes and highest floating time of 12 hr.

HPMC, a non ionic polymer with unique physicochemical properties, is used frequently as a controlled release polymer in swellable

hydrophilic matrices. The popularity of this polymer may be attributed to its nontoxic nature and being relatively inexpensive. Sodium bicarbonate was included as a gas generating agent and this compound generates carbon dioxide on the reaction with acidic aqueous media, which help the tablet to become buoyant and remain entrapped in the gel layer. The amount of X1 (HPMC) and the X2 (Sodium bicarbonate) were chosen as independent variables in 3^2factorial design. A statistical model used was

$$Y= bo +b1x1+b2x2+b12x1x2+b11x1x1+b22x2x2$$

Where Y is the dependent variable, bo is the arithmetic mean response of the nine runs, and b1 is the estimated coefficient for the factor x1. The main effects (x1 x2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (x1 x2) showed how the response changes when two factors are changed simultaneously. The polynomial Terms (x1 x1, x2) are included to investigate nonlinearity.

From the data of floating lag time parameters for factorial composition F1 to F9; polynomial equation for dependent variable has been derived using Design Expert software. The equation derived for floating lag time was

$$Y\ 9.03-1.42\ x1-\ 1.53\ x2+1.12\ x1x2+1.35\ x1x1+0.50x2x2$$

In equation (3), negative sign for coefficient of x1 and x2 indicates that as the concentration of HPMC corresponding response surface plot and contour plot are given in figure 3 and 4.

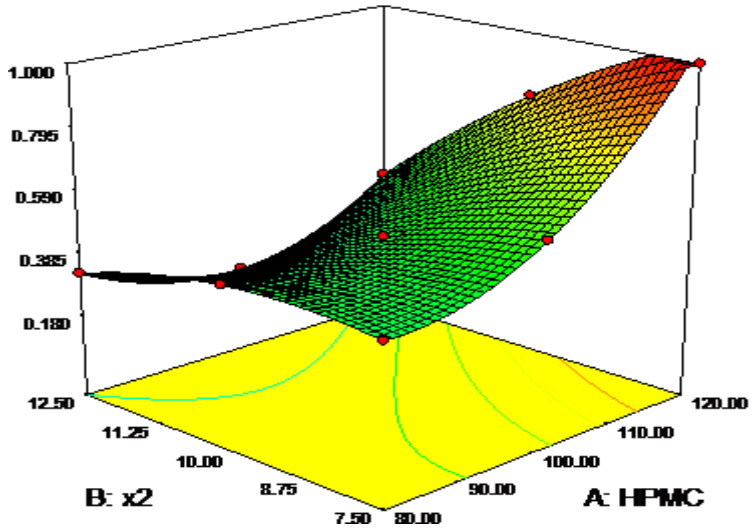

Figure 3. Response surface plot showing effect of factorial variables on floating lag time

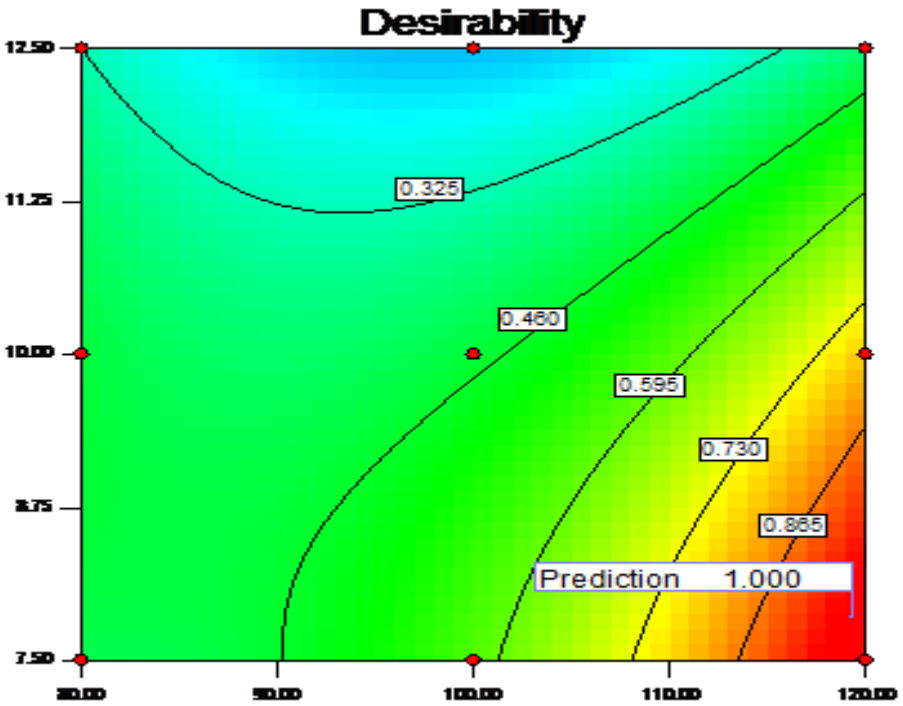

Figure 4. Contour plot showing relationship between various levels of HPMC and NaHCO3 to attain fixed value of floating lag time.

Stability studies

Short-term stability studies of the optimized FPRT (F8) indicated that there were no significant changes ($p<0.05$) in physical parameters, *in vitro* dissolution studies, floating lag time and floating time at the end of six months period (table 11).

CONCLUSION

A chronotherapy based FPRT of Meloxicam was successfully developed. Taking into consideration the chronotherapy of rheumatoid arthritis, FPRT with highest concentration of HPMC K15M and sodium bicarbonate in buoyant layer and 280 mg concentration of HPMC E50 in pulsatile layer (formulation F8) gave satisfactory release lag time of 6 hr, 4.6 minutes floating lag time and more than 12 hr floating time

Table 1.

Formulation of RRCT of Meloxicam

Ingredients (mg)	RR1	RR2	RR3	RR4	RR5	RR6
Meloxicam	30	30	30	30	30	30
Cross carmalose sodium	1	1.6	2.2	-	-	-
Crospovidone				1	1.6	2.2
MCC	29	28.4	27.8	29	28.4	27.8
Total Weight (mg)	60	60	60	60	60	60

Table 2.
Blend Evaluation of Formulation

Parameters	F1	F2	F3	F4	F5	F6
Angle of repose	24.89	26.45	24.23	28.34	27.63	24.85
Loose bulk density(g/ml)	0.524	0.5282	0.523	0.587	0.487	0.527
Tapped bulk density(g/ml)	0.582	0.674	0.523	0.613	0.675	0.584
Compressibility index (%)	17.09	14.72	15.83	17.09	16.41	13.83

Table 3.

Composition of PRT of Meloxicam

polymer	Concentration in mg/tablet					
HPMC E5	200	220	240	260	280	300
HPMC E15	200	220	240	260	280	300
HPMC E50	200	220	240	260	280	300

Table 4.

Solubility data of pure drug and solid dispersion(SD)

Sr. No	Type	Carrier	Grade	D:C Ratios	Solubility (µ/ml)
1	Pure drug		A		8.2
2	SD: Hot melt method	PEG 6000	B	1:1	28.25
			C	1:4	49.87
			D	1:8	97.56
		PEG 4000	E	1:1	17.2
			F	1:4	23.58
			G	1:8	38.4
3	SD:solvent evaporation method	PEG 6000	H	1:2:1	13.4

	PEG 4000	I	1:2:1	11.7

Table 5.

IR Range of Drug and Excipients

Inference	Reported frequency(cm^{-1})	Observed frequency(cm^{-1})
N-H Stretch	3290-3370	3280
Aromatic C-H Stretch	2930-3050	2950 , 3030
s=o stretch	1080- 1160	1100
C=O Stretch of quinoline	1610-1640	1620
C-N Stretch	1410-1500	1450,1510

Table 6.
Evaluation of RRCT of Meloxicam

F.C	Thickness (mm) n=5	Diameter (mm) n=5	Hardness (kg/cm^2) n=6	*In vitro* disintegration time (sec) n=6
RR1	1.5±0.14	5±0	2.4±0.16	66
RR2	1.5±0.16	5±0	2.52±0.056	59
RR3	1.5±0.14	5±0	2.43±0.12	48
RR4	1.5±0.17	5±0	2.35±0.14	31
RR5	1.5±0.16	5±0	2.4±0.16	25
RR6	1.5±0.15	5±0	2.36±0.14	18

Table 7.

***In Vitro* Drug Release of RRCT of Meloxicam**

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	24.45	28.49	30.58	33.34	35.38	39.24
4	30.36	32.49	33.78	41.35	45.69	50.59
6	39.78	44.54	46.48	50.36	54.84	62.55
8	48.57	51.54	54.58	59.46	63.38	69.21
10	56.68	60.39	62.47	67.46	71.31	74.93
20	64.47	66.39	69.49	72.26	77.41	79.39
30	70.29	74.45	76.23	81.58	83.46	86.62
40	78.54	80.9	84.14	87.53	91.69	93.58
50	86.38	88.34	91.25	93.22	97.38	98.8

Table 8.

Evaluation of Meloxicam PRT

F.C	Thickness (mm)n=5	Diameter (mm)n=5	Hardness (kg/cm)n=6	Lag Time (min)n=3
$E5_{200}$	2.98±0.006	11±0	3.8±0.2	48
$E5_{220}$	3.24±0.01	10.99±0.01	3.6±0.1	69
$E5_{240}$	3.49±0.05	11±0	3.6±0.1	110
$E5_{260}$	3.79±0.01	11±0	3.5±0.1	136
$E5_{280}$	3.98±0.01	10.92±0.08	3.7±0.2	169
$E5_{300}$	4.22±0.01	10.98±	3.5±0.1	195
$E15_{200}$	2.98±0.006	11±0	3.6±0.1	146
$E15_{220}$	3.24±0.01	11±0	3.5±0.1	186
$E15_{240}$	3.49±0.05	11±0	3.8±0.2	205
$E15_{260}$	3.79±0.01	10.99±0.01	3.7±0.2	235
$E15_{280}$	3.98±0.01	10.96±0.04	3.6±0.1	268
$E15_{300}$	4.22±0.01	10.96±0.04	3.2±0.08	310
$E50_{200}$	2.98±0.006	11±0	3.8±0.2	248
$E50_{220}$	3.24±0.01	11±0	3.6±0.1	259
$E50_{240}$	3.49±0.05	10.99±0.01	3.5±0.1	319
$E50_{260}$	3.79±0.01	10.99±0.01	3.5±0.1	334
$E50_{280}$	3.98±0.01	10.98±0.02	3.6±0.1	360
$E50_{300}$	4.22±0.01	10.96±0.04	3.8±0.2	390

Table 9.

Coded levels as per 3^2 full factorial designs with observed responses

Coded values	Actual	Values
	X1	X2
-1	80	7.5
0	100	10
+1	120	12.5

X1- HPMC K15; X2- Sodium bicarbonate

F.C	X1	X2	Thickness (mm) n=5	Diameter (mm) n=5	Hardness (kg/cm^2)	Floating lag time (min)n=5	Floting time(h)n=3
F1	-1	-1	3.8±0.05	11±0	4.8±0.10	13.8±0.05	>12
F2	-1	0	3.8±0.05	11±0	4.8±0.10	10.4±0.05	>12
F3	-1	+1	3.8±0.05	11±0	4.6±0.08	8.5±0.05	>12
F4	0	-1	3.8±0.05	11±0	5.0±0.10	6.1±0.05	>12
F5	0	0	3.8±0.05	11±0	5.2±0.12	9.4±0.05	>12
F6	0	+1	3.8±0.05	11±0	5.0±0.10	12.6±0.05	>12
F7	+1	-1	3.9±0	10.96±0.04	4.9±0.09	5.8±0.05	>12
F8	+1	0	3.8±0.05	11±0	5.2±0.12	4.6±0.05	>12
F9	+1	+1	3.9±0	10.99±0.01	5.0±0.10	9.4±0.05	>12

Table 10.

Evaluation of FPRT (F8) after short term stability period

Parameters	Before	After
Thickness(mm)	3.8±0.05	3.9±0.08
Diameter(mm)	11±0	11±0
Hardness(kg/cm2)	5.2±0.12	5.3±0.17
In vitro drug release (lag time) in min	360	360
Drug release (%)	98.8	93.8
Floating lag time (min)	4.6±0.05	4.6±0.05
Floating time (h)	>12	>12

REFERNCES

1. Groning R and Heun G: Dosage forms with controlled gastrointestinal passage - studies on the absorption of nitrofurantion. Int J Pharm 1989; 56: 111-6.

2. Clark TJ: Diurnal Rhythm of Asthma. Chest 1987; 91: 137S-41.

3. Karras DJ, D'Alonzo GE and Heilpern KL: Is Circadian Variation in Asthma Severity Relevant in the Emergency Department. Ann Emerg Med 1995; 26: 558-62

4. Pickering TG and James GD: Determinants and consequences of the diurnal rhythm of blood pressure. Am J Hypertens 1993; 6: 166S-9S.

5. Massin MM, Maeyns K, Withofs N, Ravet F and Gérard P: Circadian rhythm of heart rate and heart rate variability. Arch Dis Child 2000; 83: 179-2.

6. Qureshi J, Amir M, Ahuja A, Baboota S and Ali J: Chronomodulated Drug Delivery System of Salbutamol Sulphate for the Treatment of Nocturnal Asthma. Indian J Pharm Sci 2008; 70: 351-6.

7. Saitoh T, Watanabe Y, Kubo Y, Shinagawa M, Otsuka K and Ohkawa SI: Intragastric acidity and circadian rhythm. Biomed Pharmacotherapy 2001; 55: 138-41.

8. Moore JG and Englert E: Circadian rhythm of gastric acid secretion in man. Nature 1970; 226: 1261-2.

9. Roy P and Shahiwala A: Statistical optimization of ranitidine HCl floating pulsatile delivery system for chronotherapy of nocturnal acid breakthrough. Eur J Pharm Sci 2009; 37: 363-9.

10. Survase S and Kumar N: Pulsatile Drug Delivery: Current Scenario. Curr Res Infor Pharm Sci 2007; 8: 27-3.

11. Van Veen MM, Sandra Kooij JJ, Marije Boonstra A, Gordijn MC and Van Someren EJ: Delayed circadian rhythm in adults with attention-deficit/hyperactivity disorder and chronic sleep-onset insomnia. Biol Psychiatry 2010; 67: 1091-6.

12. Shivkumar HG, Gwda DO and Kumar Pramod TM: Floating Controlled Drug Delivery Systems For Prolong Gastric Residence. Indian J Pharm Educ 2004; 38: 172-9.

13. Krögel I and Bodmeier R: Floating or pulsatile drug delivery systems based on coated effervescent cores. Int J Pharm 1999; 187: 175-4.

14. Li S, Lin S, Daggy B P, Mirchandani H L and Chien Y W: Effect of HPMC and Carbopol on the release and floating properties of Gastric Floating Drug Delivery System using factorial design. Int J Pharm 2003; 253: 13-22.

15. Karavas E, Georgarakis E and Bikiaris D: Application of PVP/HPMC miscible blends with enhanced mucoadhesive properties for adjusting drug release in predictable pulsatile chronotherapeutics. Eur J Pharm Biopharm 2006; 64:115-6.

16. International Conferences on Harmonization. Stability testing of new Drug Substances and Products. Q 1 A (R2). **2003** [cited 2009 Sept 10]; Available from http://www.emea.europa.eu

17. RC Rowe, P Sheskey and P Weller: Handbook of Pharmaceutical Excipients, 4th Edition, Pharmaceutical Press Publishers, Great Britain, **2005**; pp. 139-146