Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Formulation development and evaluation of delayed-release tablets of montelukast sodium

Gaurav Agarwal[1]*, Pawan Kumar[1], Shipli Agarwal[1],MurthyDwibhashyam V.S.N.[2], Nagappa A.N.[3]*

1 Department of Faculty of Pharmacy, RPIIT Technical and Medical Campus, Karnal (Haryana) India
2 Formulation Development Lab, Aurobindo Pharma Limited Research Center-1, Hyderabad,Telangana, India.
3 Amity Institute of Pharmacy, Amity University of Madhya Pradesh, Maharajapura, Gwalior, 474005 , India.

ARTICLE HISTORY

Received: 14.06.2018

Accepted: 12.08.2018

Available online: 30.09.2018

Keywords:

Nocturnal asthma, Chronotherapeutic drug delivery systems, Delayed-release tablets.

***Corresponding author:**

Email : anantha1232000@gmail.com; gbitsian@yahoo.com
Tel.: +91 - 7015848427

ABSTRACT

Worsening of asthma at night is commonly referred as nocturnal asthma (night-time asthma). It is believed that a rise in plasma histamine concentration at night causes nocturnal asthma. Leukotriene anatagonists are of specific use in the treatment of nocturnal asthma. Montelukast Sodium is an orally active compound that binds with high affinity and selectivity to the CysLT1 receptor. Chronotherapeutic Drug Delivery Systems refers to a treatment method in which in-vivo drug availability is timed to match circadian rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. Considering the circadian rhythm of nocturnal Asthma, an attempt is made in the current study to develop a delayed-release tablet formulation of Montelukast Sodium as an approach of chronotherapeutic drug delivery system. A calibration curve was plotted at various concentrations of the drug substance. The observed results indicated a positive correlation(correlation coefficient R2 =0.999 and regressed equation y = 0.037x + 0.007) between concentration and absorbance. Optimized formulation was seal coated and enteric coated and evaluated for in-vitro drug release properties in 0.1M HCl followed by pH 6.8 Phosphate buffer and 0.1M HCl followed by 0.5% SDS solution. The drug release profile in 0.5% SDS aqueous solution differed from that in 6.8 pH phosphate buffer. Drug release started lately in 0.5% SDS solution compared to that in pH 6.8 phosphate buffer. However, drug release was relatively more in 0.5% SDS solution than in 6.8 pH phosphate buffer.

INTRODUCTION

Circadian rhythms are endogenous oscillations that occur with a periodicity of about 24 hours. Circadian rhythm regulates many functions of the human body such as metabolism, physiology, behaviour, sleep pattern and hormone production [1]. Some diseases that follow circadian rhythms include cardiovascular diseases, asthma, arthritis, ulcers, diabetes etc. Chronotherapeutic Drug Delivery Systems refers to a treatment method in which in-vivo drug availability is timed to match circadian rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. Chronotherapeutic Drug Delivery Systems are gaining importance in the field of pharmaceutical drug delivery technology as these systems reduce dosing frequency, toxicity and deliver the drug that matches the circadian rhythm of that particular disease when the symptoms are maximum to worse [2]. Finally, patient is benefited due the effectiveness of the delivery system and improvement in the patient compliance because of the convenient time of dosage form administration.

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, coughing, particularly at night or in the morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment [3]. Worsening of asthma at night is commonly referred as nocturnal asthma (nighttime asthma). Based on a literature report, it is postulated that a rise in plasma histamine concentration at night causes nocturnal asthma [4].

Several medications are available currently for effective treatment of Asthma such as inhaled and oral steroids, leukotriene antagonists and long acting beta-2 agonists. Leukotriene anatagonists are of specific use in the treatment of nocturnal asthma. Leukotriene LTC_4, LTD_4, and LTE_4, collectively termed the cysteinylleukotrienes (cys-LTs), are peptide-conjugated lipids that are prominent products of activated eosinophils, basophils, mast cells (MCs), and macrophages. ThecysLTs produce their biological actions by binding and activating specific receptors located on the cell membranes of target cells. Two subtypes of cysLT receptor have been pharmacologically characterized $cysLT_1$ and $cysLT_2$. Although $cysLT_1$ has been identified in a number of both animal and human cell types, $cysLT_2$ has yet to be found in human airway smooth muscle [5]. CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early and late-phase reactions and are associated with symptoms of allergic rhinitis.

Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or -adrenergic receptor). Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity [6]. Montelukast sodium is available on the market in conventional dosage forms such as oral granules, chewable tablets and film-coated tablets. Considering the circadian rhythm of the Asthma, various approaches have been reported in the literature for effective delivery of Montelukast Sodium [7-9]. An attempt is made in the current study to develop a delayed-release tablet formulation of Montelukast Sodium as an approach of chronotherapeutic drug delivery system. Various placebo formulations are made initially and characterized for physical parameters such as hardness and friability. After satisfactory physical properties are achieved, formulations are made with inclusion of the drug substance Montelukast Sodium. These formulations are seal coated and enteric coated and evaluated for in-vitro drug release properties.

MATERIALS AND METHODS

Materials:

Montelukast Sodium was procured from MorepenPharma Ltd., India. Hypromellose (6 cPs) was procured from TaianRuitai Cellulose Co. Ltd., China. All Microcrystalline Cellulose grades (PH 101, PH 102 and PH 103) were procured from Amisi Drug and Chemical Ltd., India. Isopropyl alcohol was procured from Divis Labs Ltd. India. Poly(methacylic acid-co-ethyl acrylate) 1:1 (Eudragit L 100-55) was procured from Yarrow Chem. Products, India. Dibutylsebacate was procured from Sigma-Aldrich. Hydrochloric Acid was procured from Rankem, India. n-Hexane was procured from S.D.Fine Chemicals, India. Sodium dodecyl sulfate (SDS) was procured from Sigma-Aldrich. Methanol was procured from Rankem, India. Croscarmellose sodium was procured from Rajesh Chemicals, India. Low substituted Hydroxypropyl cellulose (L-HPC) and Magnesium stearate were procured from HimediaChem Lab, India. Lactose grades Pharmatose DCL-15 and Pharmatose DCL-21 were procured from Tiwari Chemicals, India. Sunset Yellow was procured from Narmada Color (P) Ltd., India.All organic solvents were of high performance liquid chromatography (HPLC) grade. All other chemicals were of reagentgrade. All excipients used were of USNF grade. Drug substance was of USP grade.

Methods:

Preparation of standard plot by UV spectrophotometer:

Standard plot in the concentration range of 2-12 µg/ml was obtained by using stock solution of Montelukast Sodium prepared by dissolving 100 mg of drug in 100 ml of methanol in a100 ml volumetric flask (stock solution). Stock solution was further diluted with methanol to prepare the concentrations mentioned in table 1. These solutions were analyzed spectrophotometrically at 282nm. Plot was prepared in triplicate. The obtained resultsare presented in table 1 and figure1.

Method of preparation of Montelukast Sodium tablets:

Montelukast sodium tablets are prepared by direct

Table 1 : Initial placebo trials executed during formulation development

Ingredient	Placebo Batch Number Quantity (mg/Tablet)							
	MK-1A	MK-2A	MK-2B	MK-2C	MK-3A	MK-3B	MK-3C	MK-4A
Pharmatose DCL-15	100.0	94.65	89.15	85.35	98.65	89.05	74.15	--
Pharmatose DCL-21	--	--	--	--	--	--	--	74.15
MCC PH 101	20.5	25.15	30.5	34.6	--	--	--	--
MCC PH 102	--	--	--	--	20.6	30.6	45.5	45.5
L-HPC	2.5	3.1	3.1	2.8	3.5	3.1	3.1	3.1
Croscarmellose sodium	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Magnesium stearate	0.5	0.6	0.75	0.75	0.75	0.75	0.75	0.75
Total weight (mg)	130	130	130	130	130	130	130	130

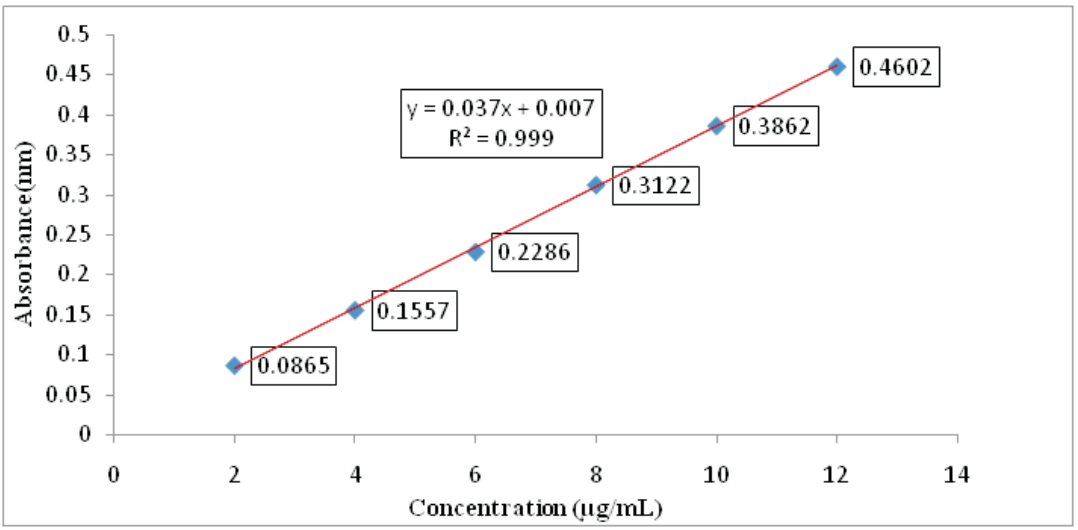

Figure 1 : Standard curve of Montelukast sodium in methanol at 282nm

compression method, which is by far the simplest means of production of a pharmaceutical tablet. It only requires that the active ingredient is properly blended with appropriate excipients before compression. Apart from simplicity of formulation and manufacture, the key advantage of direct compression includes reduced capital, labour and energy cost for manufacturing and avoidance of water granulation for water sensitive drug substances [10-11].For placebo tablets preparation, all excipients, except Magnesium stearate were passed through ASTM #30 mesh. Magnesium stearate was passed through ASTM #60 mesh. All the excipients, except Magnesium stearate mere mixed well for about 10 minutes and lubricated with Magnesium stearate for about 3 minutes. For Montelukast tablets preparation, Montelukast Sodium was passed through ASTM #80 mesh. All excipients, except Magnesium stearate were passed through ASTM #30 mesh. Magnesium stearate was passed through ASTM #60 mesh. Montelukast sodium and excipient blend were mixed geometrically and mixed well for about 5-10 minutes at each blending and lubricated with Magnesium stearate for about 3 minutes.

Method of preparation ofseal coating dispersion:

Required quantity of Isopropyl alcohol (IPA) was taken in a vessel.Required quantity of coloring material and Titanium dioxide were added to the IPA and mixed well with the help of a stirrer. Required quantity of Hypromellose (6 cPs) was added to the dispersion and mixed well.Required quantity of methylene chloride was added to the solution to make 10% w/v dispersion and mixed well. IPA and methylene chloride ratio was 40:60.

Method of preparation of enteric coating dispersion:

Required quantity of IPA was taken in a vessel. Required quantity of plasticizer (dibutylsebacate) was added to it and mixed well with the help of a stirrer. Enteric coating polymer Eudragit L 100-55 was added to it and mixed well. Required quantity of purified water was added to it and mixed well. IPA and water ratio was about 94:6.

Method of seal coating and enteric coating on core tablets:

Enteric coating on core tablets was done in two steps. Initially the core tablets were seal coated with seal coating dispersion till required weight build up is achieved as per batch formula.Seal coated tablets were enteric coated withenteric coating dispersion. Both these coatings were performed using a pan coater using suitable coating parameters as required for the respective processes.

Method of pre-compression evaluation of powder:

Flow properties:

Angle of repose

Angle of repose was calculated from three averages using following formula.

$= \tan^{1} h/r$

Where,

= angle of repose

h = height of powder cone

r = radius of the powder cone

Bulk Density (B.D)

Bulk density was calculated using the following formula.

$$\text{Bulk Density (g/mL)} = \frac{\text{Weight of sample (g)}}{\text{Volume occupied by sample (mL)}}$$

Tapped density (T.D)

Volume occupied by the sample after tapping was recorded and tapped density was calculated using the following formula.

$$\text{Tapped Density (g/mL)} = \frac{\text{Weight of sample (g)}}{\text{Volume occupied by tapped sample (mL)}}$$

Compressibility Index (Carr's Index)

Compressibility index of the powder blend was calculated using the following formula.

$$\text{Compressibility Index (Carr's Index)} = \frac{\text{T.D - B.D}}{\text{T.D}} \times 100$$

Hausner ratio

It provides an indication of the degree of densification which could result fromvibration of the feed hopper.Hausner ratio of the powder blend was calculated by using the following formula.

$$\text{Hausner Ratio} = \frac{T.D}{B.D}$$

Drug content determination (Assay):

Drug content in final lubricated blend (for compression) was determined by following method. Prepare standard solution and sample solution as given below.

Preparation of sample solution(10µg/mL): Dissolve quantity of powder (mixed blend) containing the equivalent of 25 mg Montelukast Sodium in 100ml methanol by using volumetric flask.Take 2mL of it and further dilute with methanol in 50mL volumetric flask to prepare 10µg/mL solution.

Preparation of standard solution (10µg/mL): Dissolve 25 mg Montelukast Sodium (working standard) in 100 mL methanol by using volumetric flask.Take 2mL of it and further dilute with methanol in 50mL volumetric flask to prepare 10µg/mL solution. Both sample and standard solutions were analyzed spectrophotometrically at 282nm and the readings were recorded. Drug content was calculated by using the following formula.

Assay (% Drug Content) =

$$\frac{aborbance\ of\ samle}{aborbance\ of\ \ standard} \times \frac{w1}{100} \times \frac{2}{50} \times \frac{100}{w2} \times \frac{50}{2} \times \frac{p}{100} \times F \times Average\ Weig\sqcap t$$

w1 = weight of standard

w2 = weight of sample

P = potency of drug

F = equivalent factor of drug for its salt form

Method of post compression evaluation of tablets

Hardness: Tablets require certain amount of strengthor hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packaging and shipping.Tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability: It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. It is expressed in percentage (%). Twenty tablets were initially weighed (W1) and transferred into friabilator. Initial the friabilator was operated at 25 rpm for 4 minutes or ran up to 100 revolutions. The tablets were weighed again (W2). The percentage friability was then calculated by the following formula.

Friability of less than 1% is considered acceptable.

$$\text{Friability} = \frac{\text{Initial weight(W1)} - \text{Final weight(W2)}}{\text{Initial weight(W1)}} \times 100$$

Thickness: The thickness of the tablet in mm was measured by using Digital Vernier calipers.

Disintegration Test: Disintegration time (D.T) of tablet was measured by using disintegration test apparatus, in which six tablets from each formulation were placed into basket assembly and the test was runat temperature of 37± 2ºC.

Dissolution test: In-vitro dissolution studies were performed at 37±0.5ºC using 900 mL, 0.1M Hydrochloric acid (HCl) for acid stage and 0.5% w/v aqueous solution of Sodium Dodecyl Sulphate(SDS)-for buffer stage, USP Type II (Paddle method). 5mL sample was collected at each specified interval of time and replaced by fresh medium. The standard solution was prepared by first dilution in methanol and second in dissolution medium. The samples and standard were analyzedspectrophotometrically at 282nm and % of drug release was calculated accordingly.

Method evaluation of enteric coated tablets:

DT: DT of enteric coating tablets wasmeasured in two stages. In first stage, DT was examined in 0.1M HCI for 1 hour and during this time period no unit should show evidence of disintegration, cracking or softening.In the second stage, DT of same tablets was examined in pH 6.8 Phosphate buffer. All units should disintegrate within 45 minutes.

Dissolution test: Dissolution test of enteric coatedtablets was carried outin two stages. In first stage, dissolution of enteric

Table 2 : Initial trials executed for tablet core formulation development

Ingredient	Batch Number Quantity (mg/Tablet)				
	MK-5A	MK-6A	MK-6B	MK-7A	MK-8A
Montelukast Sodium	5.2	5.2	5.2	5.2	5.2
Pharmatose DCL-21	74.15	82.0	92.6	86.1	86.1
MCC PH 102	40.3	30.45	20.45	24.45	24.45
L-HPC	3.1	3.1	2.5	3.5	3.5
Croscarmellose sodium	6.5	8.5	8.5	10.0	10.0
Magnesium stearate	0.75	0.75	0.75	0.75	0.75
Tablet weight (mg)	130	130	130	130	130

Table 3 : Formulation composition of final enteric coated tablets

Ingredient	Batch Number Quantity (mg/Tablet)
	MK-9A
Core Tablet of Batch NumberMK-8A	130
SEAL COATING	
Hypromellose, 6 cPs	1.30
Sunset Yellow	0.03
Titanium dioxide	0.67
Isopropyl alcohol	Q.S
Methylene chloride	Q.S
ENTERIC COATING	
Eudragit L100-55	18
Dibutylsebacate	4
Isopropyl alcohol	Q.S
Purified Water	Q.S
Tablet weight (mg)	154.0

Table 4 : Standard curve data of Montelukast Sodium

Concentration(µg/mL)	Absorbance	Statistical data
2	0.0865	
4	0.1557	
6	0.2286	Y=0.037x+0.007
8	0.3122	$R^2 = 0.999$
10	0.3862	
12	0.4602	

Table 5 : Results of pre-compression and post-compression evaluation parameters of the formulation blendsand tablets with Montelukast Sodium.

B. No.	Angle of repose (°)	Hausner ratio	Compressibility Index (%)	Average weight (mg)	Weight Variation (Max. % deviation)	Thickness (mm)	Hardness (Kg/cm3)	Friability	D.T (min.)
MK-5A	34.75	1.19	15.96	132.6	2.5	3.2±0.1	1.6	0.21	14 - 16
MK-6A	34.48	--	--	132.8	3.8	3.2±0.1	1.4	0.35	8 - 10
MK-6B	34.63	--	--	132.4	3.2	3.2±0.1	1.2	0.85	3 - 4
MK-7A	34.34	--	--	132.2	3.0	3.2±0.1	1.4	0.28	2
MK-8A	34.26	--	--	133	3.2	3.2±0.1	1.4	0.28	2
MK-9A	34.38	--	--	133	3.2	3.2±0.1	1.4	0.25	2

Table 6 : Inferences of pre-compression and post-compression evaluation parameters of the formulation blends and tablets with Montelukast Sodium.

B. No.	Inferences/Observations
MK-5A	Blend has good flow characteristics. All the studied parameters were satisfactory, except D.T.
MK-6A	Blend has good flow characteristics. All the studied parameters were satisfactory, except D.T.
MK-6B	Blend has good flow characteristics. D.T was improved. But, other physical parameters such as hardness and friability were affected and the same are to improved.
MK-7A	Blend has good flow characteristics. D.T was improved. Other physical parameters such as hardness and friability were also improved.
MK-8A	It was reproducibility batch of MK-7A, with a slight modification of the process (Montelukast Sodium was passed through ASTM #120 mesh). Blend has good flow characteristics. D.T was improved. Other physical parameters such as hardness and friability were also improved.
MK-9A	It was reproducibility batch of MK-8A. Blend has good flow characteristics. All physical parameters were satisfactory.

Table 7 : Results of In-vitro dissolution profile of the final enteric coated formulation in pH 6.8 Phosphate buffer.

Time (min.)	Visual observation	% Drug Release
5	No change	1.2±0.24
10	No change	4.30±0.20
15	Tablets swollen	10.68±0.31
20	Cracking occurred in coating	19.98±0.52
25	Disintegration started	32.60±0.45
30	Disintegration continued	50.72±0.36
35	Completely disintegrated	66.34±0.62
40	Powder was left	86.92±0.5
45	Powder was left	84.65±0.42
50	Powder was left	83.94±0.48

coated tablets wasexamined in 0.1M HCI for 2 hours.It was followed by dissolution test of the same tablets in pH 6.8 Phosphate buffer/0.5% SDS in water for 1 hour. Dissolution specifications like type,temperature conditions, volume of medium andstirrer speed were maintained same as described in dissolution test for uncoated tablets.

Formulation and development

Selection of excipients: Excipients used in present research work were selected based on product monograph of US Reference Listed Drug product of Montelukast Sodium tablets and granules [12].

Following table (Table 1) describes the initial placebo trials executed during formulation development.

Following table (Table 2) describes the initial trials executed for tablet core formulation development.

The optimized core formulation was seal coated and enteric coated as mentioned in the table (Table 3.) given below.

RESULT

It can be inferred from the dissolution data that the drug release profile of enteric coated Montelukast Sodium tablet in 0.5% SDS aqueous solution differs from that in 6.8 pH phosphate buffer. Drug release started lately in 0.5% SDS solution compared to that in pH 6.8 phosphate buffer. However, drug release was relatively more in 0.5% SDS solution than in 6.8 pH phosphate buffer.The studied enteric coated tablet would resist drug release in the acidic environment and would release the drug after the formulation reaches enteron with a pH of ≥ pH 5.5, where in the enteric polymer dissolves and drug releasesthere upon. This type of drug delivery would be of specific advantage in the treatment of diseases such as nocturnal asthma, where in, the patient can take the medicine before bed and the activity would start after a lag time of approx. 2-3 hrs. Present study was focused more on the development of core tablets. A single coating trial was carried out and the drug release profile was evaluated. Further formulation trials are required to be carried out with respect to seal coating and enteric coating and to develop optimum formulation which is a robust and stable.

DISCUSSION

A standard curve of montelukast sodium was made in methanol at 282 nm by using UV spectrophotometer. The standard regressed data of montelukast sodium shown in Table 1and graphically depicted in figure 1. The observed results

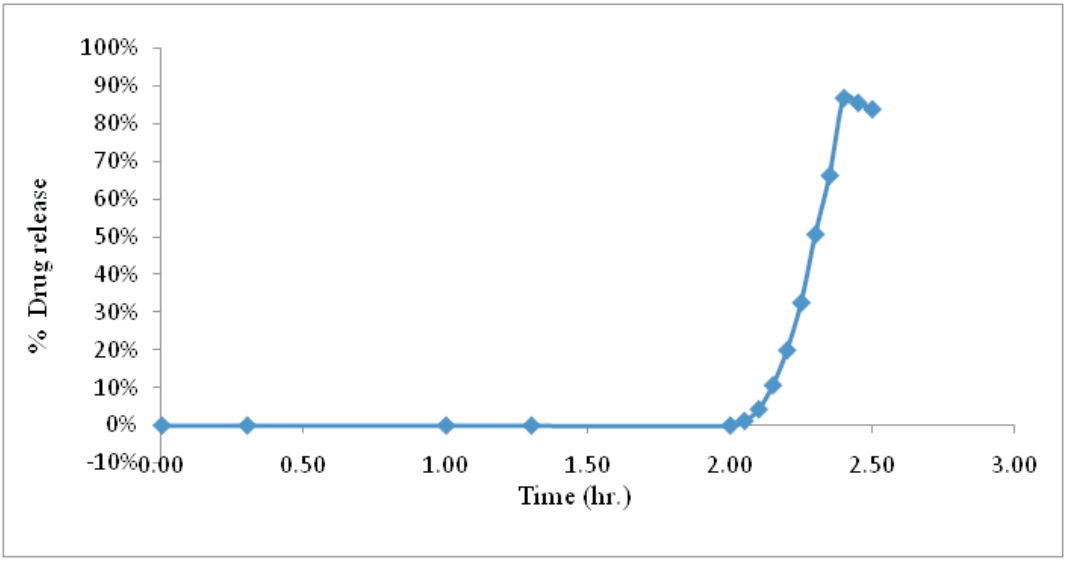

Figure 2 : Dissolution profile of enteric coated tablet of B. No. MK-9A in 0.1 M HCl (initial two hours) followed by pH 6.8 phosphate buffer.

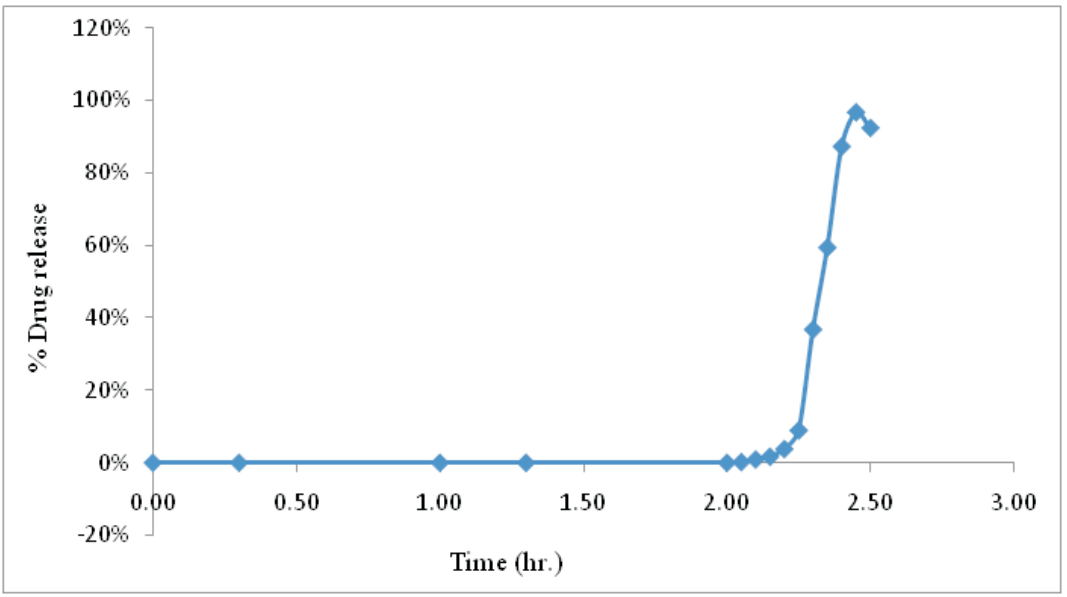

Figure 3 : Dissolution profile of enteric coated tablet of B. No. MK-9A in 0.1 M HCl (initial two hours) followed by 0.5% SDS solution.

Table 8 : Results of In-vitro dissolution profile of the final enteric coated formulation in 0.1M HCl.

Time (hr.)	Visual observation	% Drug release
0.5	No change	0.00
1	No change	0.00
1.5	No change	0.00
2	No change	0.00

indicated a positive correlation(correlation coefficient R^2 =0.999 and regressed equation y = 0.037x + 0.007) between concentration and absorbance.

Placebo trial blends and tablets (B. No. MK-1A to MK-4A) were evaluated for pre-compression parameters and post-compression parameters. The results are given the following table (Table 5)

The inferences/observations, based on the observations of the pre-compression and post-compression evaluation parameters of the placebo trial blends and tablets are tabulated below (Table 6)

Formulation trials were taken including drug substance Montelukast Sodium in the selected placebo formulation. Results ofpre-compression and post-compression evaluation parameters of these formulation blends and tablets were given. Inferences

from these studies are given in the following table (Table 7).

Formulation B.No. MK-9A was further evaluated for chemical parameters at various stages of the formulation and the results are tabulated below (Table 8).

In-vitro dissolution profile of the final enteric coated formulation was studied in 0.1M HCl followed by pH 6.8 Phosphate buffer and the results are indicated in the following figure 2.

Based on literature[13], 0.5% SDS aqueous solution was evaluated instead of pH 6.8 Phosphate buffer.In-vitro dissolution profile of the final enteric coated formulation was studied in 0.1M HCl followed by 0.5% SDS solution and the results are indicated in the following figure 3.

CONCLUSION

The studied enteric coated tablet would resist drug release in the acidic environment and would release the drug after the formulation reaches enteron with a pH of ≥ pH 5.5, where in the enteric polymer dissolves and drug releases there upon. This type of drug delivery would be of specific advantage in the treatment of diseases such as nocturnal asthma, where in, the patient can take the medicine before bed and the activity would start after a lag time of approx. 2-3 hrs. Present study was focused more on the development of core tablets. A single coating trial was carried out and the drug release profile was evaluated. Further formulation trials are required to be carried out with respect to seal coating and enteric coating and to develop optimum formulation which is a robust and stable.

REFERENCES

1. Sachin S, Neeraj K. Pulsatile Drug Delivery: Current Scenario, Current Research and Information Pharm. Sci. 2007:8(2):27-33.
2. Sunil S.A, Srikanth M.V, Rao N.S, Uhumwangho M.U, Latha K, Murthy K.V. Chronotherapeutic drug delivery systems: an approach to circadian rhythms diseases. Curr. Drug Deliv. 2011:8(6):622-633.
3. Bhave S, Pemde H.K. Current Management: Asthma. Apollo Medicine, 2005:2(4): 334-341.
4. Barnes P.J, Fitzgerald G, Brown M, Dollery C. Nocturnal asthma and change in circulation epinephrine, histamine and cortisol. N. Engl. I. Med. 1980: 303: 263-267.
5. Kanaoka Y, Boyce J.A. CysteinylLeukotrienes and Their Receptors: Cellular Distribution and Function in Immune and Inflammatory Responses. J. Immunol. 2004: 173(3):1503-1510.
6. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021409s036lbl.pdf
7. Patil S.V, Patil S.S, Sahoo S.K, Janugade B.U. Formulation and evaluation of press-coated montelukast sodium tablets for pulsatile drug delivery system. Pharmaceut. Anal. Acta. 2014: 5 (3):130.
8. Ranjan O.P, Nayak U.Y, Reddy M.S, Dengale S.J, Musmade P.B, UdupaN.Osmotically controlled pulsatile release capsule of montelukast sodium for chronotherapy: statistical optimization, in vitro and in vivo evaluation. Drug Deliv. 2014:21(7):509-518.
9. Popova T, Petkova V, Dimitrov M. Formulation Approaches To Pulsatile-Release Chronotherapeutical Drug Delivery System with Montelukast Sodium. WJPPS. 2016:5(6): 1-17.
10. Brahmankar DB, Jaiswal SB. Biopharmaceutics and Pharmacokinetic, A treatise. 1st ed.VallabhPrakashan, New delhi, 1995. 335357.
11. Udupa N, Venkatesh, Mutalik S, Venugopal K. Nimesulide dispersible tablets from direct compression method. Ind. Drugs. 2001: 38:208-210.
12. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020829s069,020830s071,021409s047lbl.pdf
13. https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm