The Pharma Innovation Journal 2018; 7(5): 219-223

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(5): 219-223

www.thepharmajournal.com
Received: 02-03-2018
Accepted: 03-04-2018

AJ Chacko
Asst Professor, Dept of Pharmaceutical Sciences, RIMSR, CPAS, Puthuppally Campus. Kottayam. Kerala, India

Dr. Jyoti Harindran
Professor and head, Dept of Pharmaceutical Sciences, Cheruvandoor Campus. CPAS Kottayam. Kerala, India

Correspondence
AJ Chacko
Asst Professor, Dept of Pharmaceutical Sciences, RIMSR, CPAS, Puthuppally Campus. Kottayam. Kerala, India

Compression coated tablet of salbutamol sulphate for chronodelivery for nocturnal asthma

AJ Chacko and Dr. Jyoti Harindran

Abstract
The study was to develop and evaluate a compression coated tablet of salbutamol sulphate for chronotherapeutic delivery for nocturnal asthma. Incidence of asthma is greatest in the early hours and is referred as "morning dip". A formulation which could deliver the drug in the right concentration just prior to the attack could effectively control the disease. Sustaining drug release thereafter would further enable the dosage as once a day unit. The dosage consisted of a bilayered tablets prepared by direct compression. The core tablet contained 4mg salbutamol for sustained release and 2 mg for the burst release. The core was compression coated with a swellable polymer HPMC and further dip coated with Eudragit RS 100 and Eudragit RL 100 in the ratio 1:1, a pH independent semipermeable membrane to achieve a time lag of 5hrs for the initial burst release. The lag time was optimized Box-Behnken design. The developed system successfully released the initial dose after 5 hours and there after sustained for more than 12 hours. The drug release predominantly followed zero order kinetics. The Higuchi R2 values suggested that the drug release follows diffusion pattern. This dosage form would effectively control the nocturnal asthma.

Keywords: Chronotherapy, box-behnken design, optimization. compression coating, salbutamol, nocturnal asthma

1. Introduction
Chronopharmaceutic research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent in a rhythmic manner that ideally matches the biological requirement of the given disease. The physiological functions of an organism display a natural synchronization with an internal 24-h rhythmic clock (circadian rhythm) which is controlled by sleep wake cycle. Few of the physiological process likes lung function, heart rate, body temperature, liver function, blood flow and hormone release, exhibit a peak time of functionality that is in accordance with these rhythmic cycles[1]. Diseases associated with the above physiological functions, exhibit peak time of activity of function within a circadian rhythm.

Asthma is one of the most common ailments with the largest circadian variation. It is a disease of lung airways (bronchi) characterized by hyper-responsiveness to a variety of stimuli. Nocturnal asthma is defined as a variable night time exacerbation of the underlying asthma condition associated with increased airway responsiveness and worsening of lung functions. Generally, asthma attacks are more prevalent in early morning and generally referred as "morning dip". It is inconvenient for a patient to take medicine at midnight. In such condition, a delivery system that could release the drug at a predetermined time to guarantee therapeutic efficacy is a prerequisite[2]. This can be achieved by developing a pulsed release system capable of delivering the drug at the required time after a well-defined lag time.

The system consisted of a two layered core tablet of 2 mg salbutamol for burst release and 4mg for sustained release. This core tablet was compression coated with a swellable polymer, HPMC and further dip coated with a pH independent polymer eudragit RL 100: eudragit RS 100 (1:1) to achieve a time lag of 5hrs for the initial drug release[3]. Press-coating is relatively simple and economical and involve direct compression of both the core and the coat. Compression coating using hydrophilic cellulose derivatives is easy on both laboratory and industrial scale. Special large-scale manufacturing equipment are available for compression coating. The major drawbacks of this technique are the need of relatively large amounts of coating materials and difficulty to position the core tablet correctly to the center during the compression coating process [4].

2. Materials and Methods

2.1 Materials

Salbutamol sulphate was used as the model drug (gifted by SANCE Pharmaceuticals, Kerala) Potassium dihydrogen phthalate (central drug house, New Delhi). Polymers (yarrow chem., Mumbai-37) Ethanol (Pampa Sugar Mills, Thiruvalla). All the other chemicals and solvents were of reagent grade.

2.2 Preparation of bi-layered core tablets [5].

An optimal formula for the core tablet was arrived after performing various experimental trials. HPMC and guar gum were tried to achieving sustained release for about 12 hrs. Guar gum was found to be most suitable.

The sustained release layer of 50mg containing 4mg of salbutamol was compressed using the formula given in the table 1. The excipients were mixed together in geometrical dilution and passed through sieve no: 44 prior to compression. 50mg mixture was mildly compressed using 5mm flat punch on a rotary press. The second layer of 10mg formulation containing 2mg of the drug was filled over the first layer and again compressed mildly to get a bi-layered intact tablet.

Table 1: The ingredients for the bi-layered tablet

Immediate release layer.	Amount in one tablet (mg)
Salbutamol sulphate	2
Dextrose: Mannitol (1:1)	0.2
Lactose	7.8
Sustained release layer.	
Salbutamol sulphate	4
PVP K_{30}	0.25
Guar gum	45.25
Aerosol	0.5

2.3 Evaluations of bi-layered core tablet [5, 6].

The compressed bi-layered core tablets were evaluated for all the parameters specified for tablets like thickness, diameter, weight variation etc. The dissolution studies were also conducted on the core tablet to confirm the immediate and sustained release for about 12hrs.

2.4 Compression coating of the core tablet [7, 8].

The 5mm bi-layered core tablets were compression coated using 8mm flat punches in a rotary press. The coating material HPMC: lactose mixture (in the ratio 140:0/ 120:20/ 100:40) was loaded in the hopper. The die fill weight was adjusted to 140 mg at weight control cam. A specially designed device was placed after the weight control cam so that 50% of the coating material filled in the die was ejected out during the passage of lower punch over the 'device'. The ejected coating material was set aside on the die table. The machine was stopped and the bi-layered core tablet was manually placed at the center of the die fill. The lower punch was brought down and the coating material set aside on the die table was refilled into the die cavity over the core tablet. The machine was then run to get the compression coated tablet with a uniform coating all around. The cycle was continued to get more compression coated tablets.

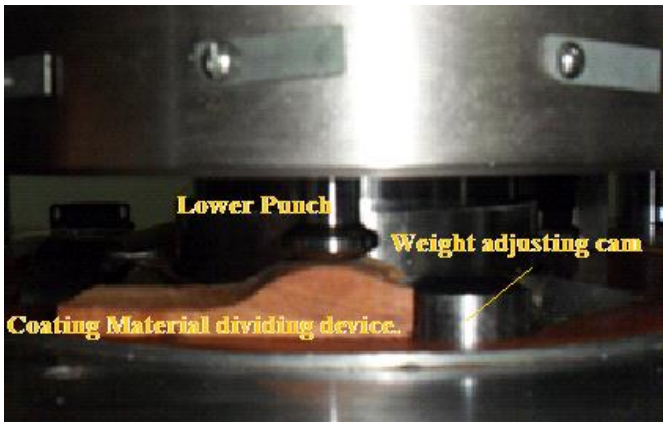

Fig 1: Modified tablet punching machine

2.5 Dip coating of compression coated tablet [9].

The compression coated tablets were further dip coated with a polymeric layer of Eudragit RS 100 and Eudragit RL 100 in the ratio 1:1. Dibutyl phthalate is used as plasticizer. The polymers were dissolved in acetone to get 10, 15 and 20% solutions. The coating solution was kept closed on ice bath throughout the process to prevent the evaporation of acetone thereby maintaining the polymer concentration constant. The dip coated tablets were first air dried and further dried in an oven at 40 ℃ for 1hour to remove the residual solvent. Varying levels of coating were given by changing the number of dips the tablets in the coating solution. The numbers of dips assigned were 2, 3 and 4.

2.6 Optimization of the formulations by Box-Behnken design [10].

2.6.1 Experimental design.

The preliminary studies revealed that the three important factors which affect the time lag of salbutamol release were amount of HPMC the swellable layer, concentration of coating polymer (Eudragit RS 100 : Eudragit RL 100) and the coating levels. Hence these 3 factors were selected as the independent variables for the optimization. All the other factors were kept constant throughout. For the optimization, a three- factor, and three-level seventeen run 'Box-Behnken' design was employed using statistical software. The response variable was lag time in the drug release in hours. The variables at three level was to check the possible non-linearity of the influences. The independent factors, dependent variables and the levels used in the design are listed in the table 2:

Table 2: List of factors and responses with their levels and constraints

Factors	**Levels used**		
	1	**0**	**-1**
X1 = Amount of HPMC (mg)	100	120	140
X2 = Conc of polymer (%)	10	20	30
X3 = Coating level (dips)	2	3	4
Responses	Constraint		
Y1 = Lag time (hours)	5 hours		

Table 3: Formula by Box- Behnken experimental design

Formln Code	Amt of HPMC code/mg	Conc. of Eudragit code/mg	Coating Level. code/dip
F1	0/120	1/20	1/4
F2	-1/100	1/20	0/3
F3	-1/100	-1/10	0/3
F4	0/120	-1/10	1/4
F5	1/140	0/15	-1/2
F6	0/120	0/15	0/3
F7	0/120	0/15	0/3
F8	1/140	1/20	0/3
F9	-1/100	0/15	1/4
F10	1/140	0/15	1/4
F11	0/120	0/15	0/3
F12	0/120	1/20	-1/2
F13	1/140	-1/10	0/3
F14	0/120	0/15	0/3
F15	-1/100	0/15	-1/2
F16	0/120	0/15	0/3
F17	0/120	-1/10	-1/2

2.6.2 Outer coat rupture test [11, 12].

Pulsatile release tablets were visually observed for the rupture simultaneously during the dissolution studies of the tablet. The rupture time was taken as the lag time. The lag time was defined as the time point, when the outer coating ruptured due to swelling of the underneath HPMC layer.

2.6.3 *In-vitro* dissolution testing [13].

The dissolution was first carried out in 900ml of 0.1 N HCl containing 1% sodium lauryl sulphate in USP II apparatus at 100 RPM for 2 hours, followed by phosphate buffer pH 6.8 both equilibrated to 37±0.50C. Aliquots were withdrawn at predetermined time intervals for 17 hours and analyzed spectrophotometrically.

2.6.4 Development of the optimum batch.

The outer coat rupture time of the seventeen trials were fed in to the statistical software for Box- Behnken design (Design expert version 9). Based on the input, the software suggested an optimum composition to attain the lag time 5 hours. The suggested composition was then formulated.

2.6.5 Evaluations of the optimal formula

The optimal formula prepared was evaluated for various parameters like thickness, diameter, hardness, friability, weight variation. The invitro dissolution studies were also performed for 17 hours and the lag time and the drug release also were determined. The results obtained were compared with the predicted values suggested by the software.

2.6.6 Mechanism of drug release.

A drug release mechanism of the optimized formula was determined by fitting the drug release data to various the kinetic models.

The dosage was designed with 2mg (33.33%) of salbutamol for immediate release and 4mg (66.67%) as a part of matrix material for sustained release. The release mechanism was determined with respect to the matrix part which was the sustainable part of the dosage form.

The kinetic study was based on the following assumption.

1. Time commenced only when the cumulative release reached 2mg (33.33%).
2. This 2mg was subtracted from each of the cumulative drug release value.

2.7. Stability studies [5]

The optimized batch was monitored up to 6 months at accelerated conditions of temperature and relative humidity (40±2 °C/75±5%RH) to check the stability.

3. Results and Discussion.

3.1 Evaluation of bi-layered core tablet

Table 4: Evaluation of bi-layered core tablet

Thickness (mm)	Diameter (mm)	weight variation %	Drug content %
2.56±0.03	5.01±0.03	2.64±1.13	100.06±2.606

*Mean ± SD; n=10.

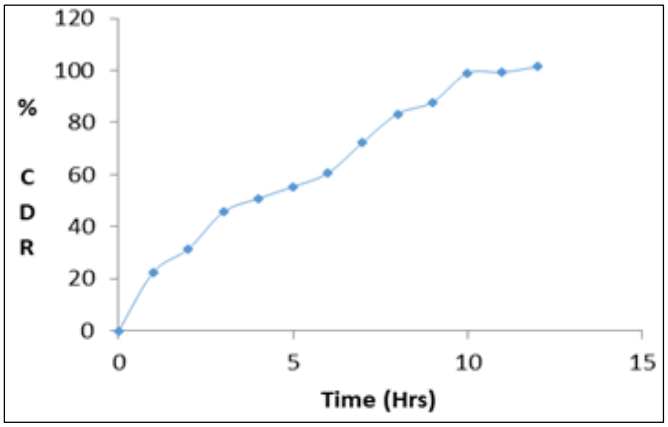

Fig 2: The dissolution profile of bi-layered core tablet confirming immediate release followed by the sustained release

3.2 Optimization design.

A three factor three level, Box-Behnken design was used for the optimization. The design consists of a replicated center point and a set of point lying at the midpoint of each edge of the multidimensional cube that defines the region of interest. The nonlinear computer generated quadratic model is given as

$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_{12} + b_{22}X_{22} + b_{33}X_{32} + E$

Where

Y = the measured response associated with each factor level combination.

b_0 = intercept.

B_1 to b_{33} are regression coefficients computed from the observed experimental values of Y X_1, X_2 and X_3 = coded levels of independent variables

E = error term

ANOVA was applied to estimate the significance of model at the 5% significance level. At 5% level of significance a model was considered significant if the p-value is less than 0.05

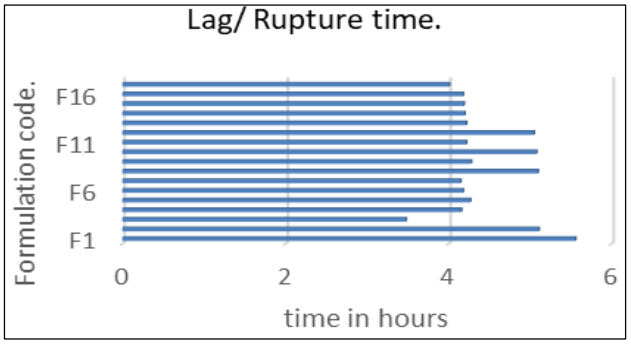

Fig 3: The repture or lag time

Table 5: ANOVA summery of all responses

Source	Y1	
	F-value	P-value
Model	260.1247	<0.0001*
X_1	168.9114	<0.0001*
X_2	1564.309	<0.0001*
X_3	154.6295	<0.0001*
$X_1 X_2$	70.48915	<0.0001*
$X_1 X_3$	66.73042	<0.0001*
$X_2 X_3$	15.76866	0.005386
X_1^2	1.437506	0.269551
X_2^2	150.2422	<0.0001*
X_3^2	128.2806	<0.0001*

* Significant at 5% level

The Model F-value of 260.12 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. Values of "Prob > F" less than 0.05 indicate model terms are significant. The coefficients of X_1, X_2, X_3, $X_1 X_2$, $X_2 X_3$, $X_1 X_3$, X_{12}, X_{22} and X_{32} have significant effects on coat rupture. Mathematical relationship in the form of polynomial equation for the measured responses was obtained with the statistical software.

$$Y1 = 4.186 + 0.2025X_1 + 0.61625X_2 + 0.19375X_3 - 0.185X1X_2 + 0.18X1X_3 + 0.0875\ X_2X_3 + 0.02575X_1^2 + 0.26325X_2^2 + 0.24325X_3^2$$

The equation represents the quantitative effect of variable (X_1, X_2, and X_3) and their interactions on the responses. Coefficients with more than one factor term and those with higher order term represent interaction terms and quadratic relationships respectively. A positive sign represents a synergistic effect, while a negative sign indicates an antagonistic effect.

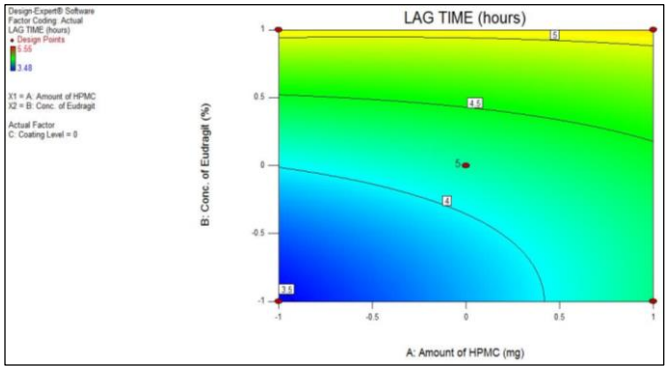

Fig 4: Contour plot for the effect of amount of HPMC and Eudragit concentration on lag time

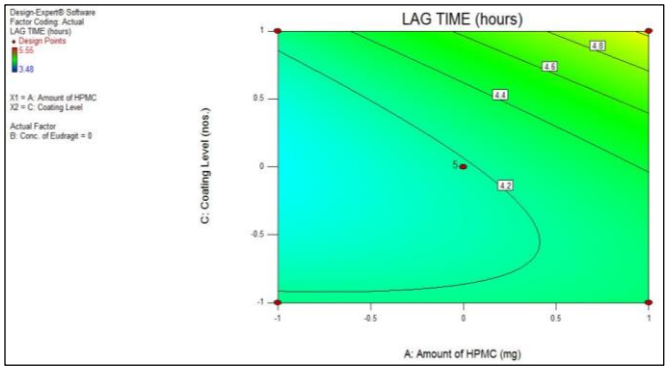

Fig 5: Contour plot for the effect of Amount of HPMC and coating level on lag time

3.2 Development of the optimum batch

Based on the statistical evaluations the software suggested a number of solutions for compression coating and selected one as the optimal composition.

Table 6: Composition of the optimum batch

Ingredients	Core tablet	Amt of HPMC	Conc of Eudragits	Coating level
Quantity	60 mg	120mg	20mg	4 dips

The bilayer core tablet was compression coated with the optimal composition suggested by the software. The predicted lag time was 5hrs.

3.3 Evaluations of the optimum batch.

The powder blend for coating was evaluated for the bulk density, tapped density, Carr's index, Hausners ratio & Angle of repose. The compressed core tablets were then evaluated for the various parameters including thickness, diameter, weight variation, friability and hardness. All the parameters were found to be within acceptable limits.

Table 7: Evaluation of powder blend for coating

Bulk Density	Tapped Density	Carr's index	Hausners ratio	Angle of repose
0.58±0.001	0.72±0.009	19.44±1.11	1.24±0.02	39.46±0.53

The results confirmed that the powder blend for compression coating have moderate flow properties.

Table 8: Evaluation of compression coated tablet

Thickness Mm	Diameter mm	Wt variation %	Hardness Kg/cm²	Friability %
6.6±2.3	8.01±0.05	4.47±1.83	3.6±0.3	0.72±0.85

*Mean ± SD; n=10.

Table 9: Evaluation of bi-layered core tablet

Thickness (mm)	Diameter (mm)	weight variation %	Drug content %
2.56±0.03	5.01±0.03	2.64±1.13	100.06±2.606

*Mean ± SD; n=10.

3.4 *In-vitro* dissolution testing of the optimized batch.

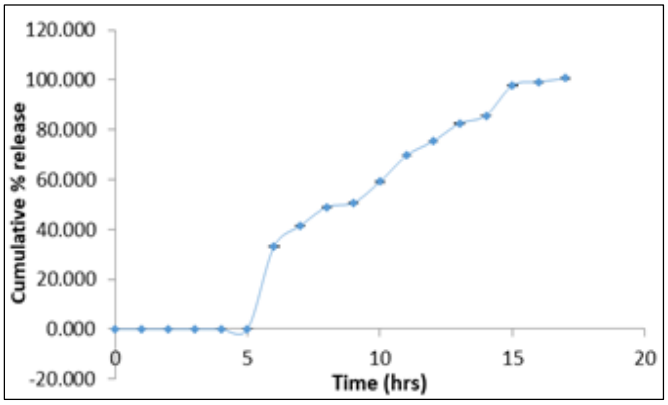

Fig 6: Dissolution profile of optimum formula

3.5 Mechanism of drug release

A drug release mechanism of the optimized formula was determined by fitting the drug release data to various the kinetic models.

Table 10: Release kinetics data of optimized batch

Time (hr)	Cumulative drug release (mg)	Cumulative drug release less 2mg in burst release layer (mg)	% cumulative release from the matrix layer.	Time for kinetic studies.
0	0	0	0	-
1	0	0	0	-
2	0	0	0	-
3	0	0	0	-
4	0	0	0	-
5	0	0	0	0
6	1.987	0	0	1
7	2.492	0.492	12.3	2
8	2.941	0.941	23.52	3
9	3.042	1.042	26.05	4
10	3.55	1.55	38.75	5
11	4.181	2.181	54.54	6
12	4.521	2.521	63.02	7
13	4.950	2.950	73.75	8
14	5.147	3.147	78.67	9
15	5.87	3.87	96.75	10
16	5.95	3.95	98.75	11
17	6.03	4.03	100.75	12

The correlation coefficient (R^2) values for various release models: zero-order, first order, Higuchi model and Korsmeyer Peppas model were determined.

Table 11: Kinetics of Salbutamol sulphate release

Zero order R^2	First order R2	Higuchi R2	Peppas R2/ n	
0.981	0.903	0.977	0.976	1.284

The drug release predominantly followed zero order kinetics. The Higuchi R^2 values suggested that the drug release follows diffusion pattern. Release exponent n, was >1, for the batch suggesting anomalous diffusion, non Fickian and super case II transport mechanism.

4. Conclusion

A compression coated tablet for chronotherapeutic drug release was designed and optimized successfully. The 60mg core tablet consisted of two layers was prepared by direct compression, 10mg layer for immediate and 50mg layer for sustained release. The core tablet was evaluated and confirmed for its immediate and sustained release property. The core tablet was then compression coated with a swellable layer of HPMC: lactose blend using a special device ensuring the division of coating material equally for the lower and upper layer. The so coated tablet was further dip coated with eudragit RS100: eudragit RL100 to get a pH independent semipermeable membrane. The coat rupture time was optimized using Box-Behnken design. The drug release predominantly followed zero order kinetics. The Higuchi R^2 values suggested that the drug release follows diffusion pattern with non Fickian and super case II transport mechanism.

Accelerated stability study was conducted as per ICH guidelines for 6 months and was found stable. The designed dosage form if taken at bed time could release the first dose as a burst in the early hours of morning around 3-4am and thereafter sustain the effect for 10 hours. This dosage form effectively controls the “nocturnal asthma”.

5. References

1. Ashwini D, Asif K, Mv R, Mitul P, Omkar D. Chronotherapy: A novel drug delivery system. Int J Res ayurveda Pharm. 2011; 2(6):1692-700.
2. Bansal J, Malviya R, Kumar Sharma P. Circadian Cycle and Chronotherapy: Role in the Treatment of Various Biological Disorders. World Appl Sci J, 2014; 32(5):825-38.
3. Asiniparthi M, Donti V. Formulation and Evaluation of Chronomodulated Drug Delivery of Montelukast Sodium. Glob J Pharm Pharm Sci. 2016; 1(1):1-8.
4. Anal AK. Time-Controlled Pulsatile Delivery Systems for Bioactive Compounds. Recent Pat Drug Deliv Formul. 2007; 1:73-9.
5. Janugade BU. patil ss. Formulation and evaluation of press-coated montelukast sodium tablets for pulsatile drug delivery system. Int J ChemTech Res. 2009; 1(3):690-5.
6. Akshay Ramesh K, SA R, Mohd A, Kamath KK. Formulation and evaluation of pulsatile drug delivery system containing indomethacin using natural polymers. Int J Pharm [Internet]. Available from. 2013; 4(2):111-4 www.irjponline.com
7. Amit Bhat KPR, Chowdary SRH, Design LN. characterization of chronopharmaceutical drug delivery of theophylline. Int J Pharm Sci Res. 2011; 2(4):1023-30.
8. Jitendra K, Patel MMPAAB. Development and evaluation of time controlled pulsatile drug delivery. Int J Curr Res Chem Pharm Sci Res. 2015; 2(1):46-50.
9. Fan T, Weis YW. An investigation of pulsatile release tablets with ethyl cellulose and eudragit L as film coating materials and cross-linked polyvinyl pyrrolidone in core tablets. J Control Release. 2001; 7:245-51.
10. Kim MS, Kim JS, You YH, Park HJ, Lee S, Park JS *et al*. Development and optimization of a novel oral controlled delivery system for tamsulosin hydrochloride using response surface methodology. Int J Pharm. 2007; 341(1):97-104.
11. Sungthangieen s, putipipatkhachom RB. Development of pulsatile release tablets with swelling and rupturable layers. J Control Release. 2004; 95:145-59.
12. Lin HL, Lin SY, Lin YK, Ho HO, Lo YW, Sheu MT. Release characteristics and *in vitro-in vivo* correlation of pulsatile pattern for a pulsatile drug delivery system activated by membrane rupture via osmotic pressure and swelling. Eur J Pharm Biopharm. 2008; 70(1):289-301.
13. Dharmeshkumar Patel, Patel MR, Patel NMP KR. Formulation and *In-vitro* Evaluation of Pulsatile Release Tablet of Lornoxicam. Am J PharmTech Res. 2012; 2(3):842-55.