IJPSR (2011), Vol. 2, Issue 9 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 28 May, 2011; received in revised form 29 June, 2011; accepted 18 August, 2011

OPTIMIZATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF LABETALOL HYDROCHLORIDE USING SIMPLEX CENTROID DESIGN

Ravi K. Barde*[1], Rahul K. Amrutkar [1], Minal R. Narkhede [1] and Jitendra Y. Nehete [2]

Department of Pharmaceutics, MGV's College of Pharmacy, Panchavati, Nasik-422 003, Maharashtra, India
Department of Pharmacognosy, MGV's College of Pharmacy, Panchavati, Nasik-422 003, Maharashtra, India

Keywords:

Labetalol Hydrochloride, Simplex Centroid design, Gastric floating drug delivery system, non-Fickian, HPMC, Carbopol, Gastro retentive drug delivery systems (GRDDS), Labetalol hydrochloride (LBT), Time required for 50% and 80% dissolution (t_{50} and t_{80})

Correspondence to Author:

Ravi K. Barde

Department of Pharmaceutics, MGV's College of Pharmacy, Panchavati, Nasik-422 003, Maharashtra, India

ABSTRACT

Labetalol Hydrochloride due to its pH dependant solubility in range of 6-10 shows 10-80% variability in bioavailability, used in treatment of hypertension. Due to its short half life i.e. 3-6 hrs, it is administered twice a daily. Therefore to improve bioavailability and patient compliance in this study attempt has been made to develop an oral floating tablet of Labetalol hydrochloride. An optimized floating drug delivery system (GFDDS) of Labetalol Hydrochloride was developed using simplex Centroid design. In this design Hydroxypropyl methyl cellulose K4M (X1), Carbopol 934P (X2), Sodium carboxymethylcellulose (X3) were used as independent variables and floating lag time,t_{50}% and t_{80}% as responses. In this design effervescent matrix tablets were prepared by combination of citric acid and sodium bicarbonate. Results of ANOVA indicated, low levels of X2 and X3, and high level of X1 should be used to manufacture the tablet formulations with desired *in vitro* floating time, t_{50}% and t_{80}%. Kinetics of drug release from tablet followed Korsmeyer–Peppas model by anomalous non-Fickian diffusion. It was concluded that gastro retentive tablet of Labetalol hydrochloride can be prepared via floating mechanism to increase residence time of drug in stomach and there by increasing its absorption. The present study demonstrates that use of simplex Centroid design in development of floating tablets with minimum experimentation.

INTRODUCTION: The aim of any drug delivery system is to afford a therapeutic amount of drug to the proper site in the body to attain promptly, and then maintain the desired drug concentration. Oral administration is the most convenient and commonly employed route of drug delivery for systemic action. Oral delivery of drugs is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc [1]. In oral drug delivery system not all drugs or therapeutic agents are absorbed uniformly throughout the gastrointestinal tract (GIT).

Some drugs are absorbed in a particular portion of GIT. One of the novel approaches in the area of oral sustained release drug delivery is gastro retentive drug delivery system (GRDDS) [2], indeed, for controlled release system; oral route of administration has received the more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes. For drugs with a narrow absorption window in the gastrointestinal tract or acting locally in the stomach, the challenging task is not only to prolong drug release but the retention of the dosage form in the upper gastrointestinal tract.

This results in a higher bioavailability, reduced time intervals for drug administration and thus a better patient compliance [3]. Gastro retentive drug delivery systems (GRDDS) mainly formulated with the aim of retaining the dosage form in the upper gastrointestinal tract i.e. stomach. GRDDS can remain in the gastric region for several hours, reducing degradation of drug liable to enzymatic metabolism in the intestinal condition increasing the amount of weakly basic drug in solution form and thus increasing the bioavailability. It has applications also for local drug delivery to the stomach and proximal small intestine. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems or by the simultaneous administration of pharmacological agents that delay gastric emptying [4].

Types of drugs which can benefit from using gastro retentive devices includes – [5]

1. Drugs acting locally in the stomach.
2. Drugs those are poorly soluble at an alkaline pH.
3. Drugs with a narrow window of absorption in small intestine.
4. Drugs that degrade in the colon.
5. Drugs that require good pharmacokinetic control.

Labetalol hydrochloride, 2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl]-benzamide, a non-selective α, β-adrenoceptor antagonist which is used in the treatment of hypertension. It is appreciably soluble in lower and higher pH solutions, with minimum solubility between pH 6 to 10. The drug shows variable bioavailability ranging from 10-80% which may be attributed to its instability in alkaline pH and poor absorption due to precipitation. It is administered in doses ranging from 50-200 mg twice a day due to its shorter half life of 3-6 hrs suggesting the need for sustained release formulation [6, 7].

The major objective of the present investigation was to develop a gastro retentive drug delivery system containing Labetalol Hydrochloride using simplex Centroid design as an optimization technique. The present study involved the design of Labetalol Hydrochloride gastric floating matrix tablets by combining three polymers: HPMC K4M, Carbopol 934P and Sodium carboxymethyl cellulose, and investigation of the combined effect of these polymers on the floating behavior and *in vitro* release pattern of the drug.

Experimental:

Materials: Labetalol hydrochloride was obtained as a gift sample (Mercury Labs. Ltd., Baroda, Gujarat, India). Hydroxypropyl methylcellulose K4M (HPMC K4M) and Carbopol 934P were received as gift samples from the Watson Pharma Pvt. Ltd (India). All other ingredients used were of analytical grade and were used as received.

Methods:

Formulation Design: For Simplex Centroid Design formulation design expert 8.0.4 software (stat-ease) demo version was used. In formulation amounts of HPMC K4M (X1), Carbopol 934P (X2) and Sodium carboxymethylcellulose (X3) were selected as independent variables. The floating lag time (FLT), and times required for 50% of drug release (t_{50}) and 80% of drug release (t_{80}) were selected as dependent variables. In this optimization study Quadratic mix order and Scheffe design model were used. A statistical model incorporating 7 interactive terms was used to evaluate the responses [8].

$$Y= b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X3+b_{13}X_1X_3 +b_{123}X_1X_2X_3$$

Where Y is the dependent variable, b0 is the arithmetic mean response of the 7 runs, and bi is the estimated coefficient for the factor Xi. The main effects (X_1, X_2, and X_3) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2, X_2X_3, X_1X_3, and $X_1X_2X_3$) show how the response changes when 2 or more factors are simultaneously changed.

Fabrication of Labetalol Hydrochloride floating tablets: LBT Floating tablets were formulated as per the formulations given in Table I. All the ingredients were weighed accurately. Drug was mixed with required quantity of all ingredients by geometric mixing. This blend was directly compressed into tablets using 10-mm flat-face round tooling on a Rimek-I

rotary tablet machine. Compression force was adjusted to obtain tablets with hardness in range of 5 to 6 kg/cm^2. Tablets weighed 300 mg, and were round flat-face with an average diameter of 10 ± 0.1mm and thickness of 3.4 ± 0.2 mm [9]. Formulations of the simplex centroid design batches (S1 to S7) are shown in **Table 1**.

TABLE 1: FORMULATION AND EVALUATION OF BATCHES IN SIMPLEX LATTICE DESIGN [12, 13]

Batch code	Transformed fractions of variables	Transformed fractions of variables	Transformed fractions of variables	F_{lag}±SD Sec.	t_{50}±SD Hr.	t_{80}±SD Hr.
	X1	X2	X3			
S1	1	0	0	32.8±2.1	8.2±0.8	10.5±2.0
S2	0	1	0	69.42±5.4	8±1.7	13.5±1.7
S3	0	0	1	42.3±2.8	8.7±1.2	13.2±2.2
S4	0.5	0.5	0	65±4.1	9.2±1.4	14.7±1.4
S5	0	0.5	0.5	47±2.4	9.8±1.2	14.6±2.2
S6	0.5	0	0.5	53.45±2.5	12±2.3	14.8±1.4
S7	0.33	0.33	0.33	40.67±2.1	8.3±1.2	14.1±1.3

Coded values	Actual values	Actual values	Actual values
	X1	X2	X3
0	40	30	15
1	80	70	45

Mean ± SD, n=3. All batches contained 85 mg Labetalol hydrochloride, 16.66% wt/wt of Sodium bicarbonate, 8.33% wt/wt of Citric acid, 1.66% wt/wt of talc, and 1.66% wt/wt of magnesium stearate. Average weight of each tablet was 300 mg. X_1 is the amount of HPMC K4 M (mg), X_2 is the amount of Carbopol 934 P (mg), and X_3 is the amount of sodium carboxy methyl cellulose (mg).

***In Vitro* Buoyancy Studies:** The *in vitro* buoyancy was determined by floating lag time as per the method described by Rosa *et al*, [10]. The tablets were placed in a 100-mL glass beaker containing simulated gastric fluid (SGF), pH 1.2, as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time.

***In Vitro* Dissolution Studies:** The *in vitro* dissolution study of Labetalol hydrochloride tablets was performed using USP apparatus fitted with paddles (100 rpm) at 37-C ± 0.5-C using SGF (pH 1.2; 900 ml) as a dissolution medium. At the predetermined time interval, 5-mL samples were withdrawn, filtered through a 0.45-μm membrane filter, diluted, and assayed at 302 nm using a Shimadzu UV/vis double-beam spectrophotometer.

Cumulative percentage drug release was calculated using an equation obtained from a calibration curve. The drug release profile is shown in **Figure 1**. The time required for 50% and 80% drug release was calculated [11].

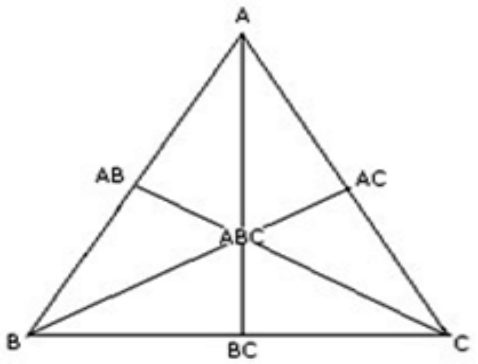

FIG. 1: EQUILATERAL TRIANGLE REPRESENTING SIMPLEX CENTROID DESIGN FOR 3 COMPONENTS (A, B, C)

Simplex Centroid Design [12, 13]: A simplex centroid design was adopted to optimize the formulation variables. In this design, 3 factors were evaluated by changing their concentrations simultaneously and keeping their total concentration constant. The simplex centroid design for a 3-component system is represented by an equilateral triangle in 2-dimensional space (**Figure 2**). Seven batches (S1-S7) were prepared: one at each vertex (A, B, C), one at the halfway point between vertices (AB, BC, AC), and one at the center point (ABC). Each vertex represents a formulation containing the maximum amount of 1 component, with the other 2 components at a minimum level.

The halfway point between the 2 vertices represents a formulation containing the average of the minimum and maximum amounts of the 2 ingredients represented by 2 vertices. The center point represents a formulation containing one third of each ingredient. The amounts of matrixing agent (HPMC K4 M, X1), Viscosity increasing agent (Carbopol 934 P, X2), and Gelling agent (Sodium carboxymethylcellulose, X3) were selected as independent variables. The floating lag time (Flag) and the time required for 50% (t50) and 80% drug dissolution (t80) were taken as responses.

Kinetic Modeling of Drug Release [12, 13, 14]: The dissolution profile of all the batches was fitted to various models such as zero-order, first-order, Hixon-Crowell, Korsmeyer and Peppas models to ascertain the kinetic modeling of drug release.

Statistical analysis: Statistical analysis of the simplex centroid design batches was performed by ANOVA. To evaluate the contribution of each factor with different levels to the response, the two-way analysis of variance ANOVA ($P<0.05$) was performed using the demo version DESIGN EXPERT 8.0.4 (STAT-EASE) software. The influence of each factor on the response, the response surface plots (graphically) were generated using the same demo version.

RESULTS: In the present investigation, combinations of three polymers were studied using the Quadratic design model. The mathematical models developed for all the dependent variables using statistical analysis software are shown in Equations (*1*)–(*3*):

F_{lag}= 50.92 + 37.87X1 + 68.99X2 + 45.16X3…… (1)

R= 0.5955

t_{50}=8.94+8.20X1+8.00X2+8.70X3+2.60X1X2+5.80X2X3+ 14.20X1X3−43.50X1X2X3…….. (2)

R=0.9703

t_{80}=13.39+10.52X1+13.52X2+13.22X3+9.13X1X2+4.16X 2X3+10.96X1X3…… (3)

R=0.9816

The floating lag time for all tablets was found to be below 69 seconds regardless of the concentration of polymers used, indicating insignificant effect of the concentration of polymers. Lower value of the correlation coefficient clearly indicates that the response is independent of the factors studied. This was due to evolution and entrapment of carbon dioxide inside the hydrated polymeric matrices, resulting from the interaction between the gas generating agent (NaHCO3) and dissolution medium (0.1 mol L^{-1} HCL, pH 1.2) which led to lowering of the density of matrices enabling the tablets to float.

The high values of correlation coefficient for t_{50}%, t_{80}%, indicate good fit between the dependent and independent variables. The polynomial equations can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). The values for Floating lag time (FLT), time required for 50% and 80% drug release ($t_{50\%}$ and $t_{80\%}$ respectively), for all 7 batches (S1-S7) showed a wide variation (**Table 2**).

TABLE 2: ANALYSIS OF VARIANCE FOR DEPENDENT VARIABLES FROM THE SIMPLEX CENTROID DESIGN

Source	SS	Df	MS	F value	Probability
FLT					
Regression	1198.89	2	599.44	5.89	0.0268
Residual	814.26	8	101.78		
Total	2013.15	10			
$t_{50\%}$					
Regression	13.22	6	2.20	21.76	0.0051
Residual	0.41	4	0.10		
Total	13.63	10			
$t_{80\%}$					
Regression	23.74	5	4.75	53.33	0.0002
Residual	0.45	5	0.089		
Total	24.48	10			

*df- indicates Degree of freedom; SS-Sum of square; MS- Mean of square; F- Fischer's ratio

In all Tablets batches (S1 to S7) floating lag time variation from 32 sec to 69 sec was observed. Floating lag time Polynomial equation (eq. 1) magnitudes of coefficients and mathematical signs suggested significant effect on floating lag time and varying amount of HPMC K14M, Carbopol 934P, Sodium carboxymethylcellulose. As the amount of HPMC K4M and sodium carboxy methyl cellulose increased, TFT increased; this is because of increased gel strength of matrices due to hydrophilic nature of HPMC which produces easy swelling of tablets, which prevents escape of evolved carbon dioxide from matrices, leading to decreased density. Also the amount of Carbopol 934 P increased, TFT increased this may be due to high affinity of carbopol towards water, which promotes water penetration into tablet matrices, leading to increased density.

Figure 2-(a) shows the 3D surface plot of the amount of HPMC K4M (X_1), of Carbopol 934P (X_2) and amount of sodium carboxymethylcellulose (X_3) versus FLT. The plot was drawn using Design Expert 8.0.4 (State Ease, Inc.). The data demonstrated that X_1, X_2 and X_3 affect the floating lag time. It may also be concluded that the high level of X_1 (amount of HPMC K4M) and the lower level of X_2 (amount of carbopol 934P) and X_3(amount of sodium carboxymethylcellulose) favor low floating lag time.

Time required release to 50% of drug ($t_{50\%}$) and time required release to 80% of drug ($t_{80\%}$) showed wide variation (Table 1). **Figure 2-(b) and Figure 2-(c)** shows the 3D surface plot of the amount of HPMC K4M (X_1), amount of Carbopol 934 P (X_2) and amount of sodium carboxy methyl cellulose (X_3) versus $t_{50\%}$ and $t_{80\%}$, respectively. The data clearly indicates the relationship between dependent ($t_{50\%}$ and $t_{80\%}$) and independent variables. The fitted equation relating the response $t_{50\%}$ and $t_{80\%}$ are shown in equations 2 and 3.

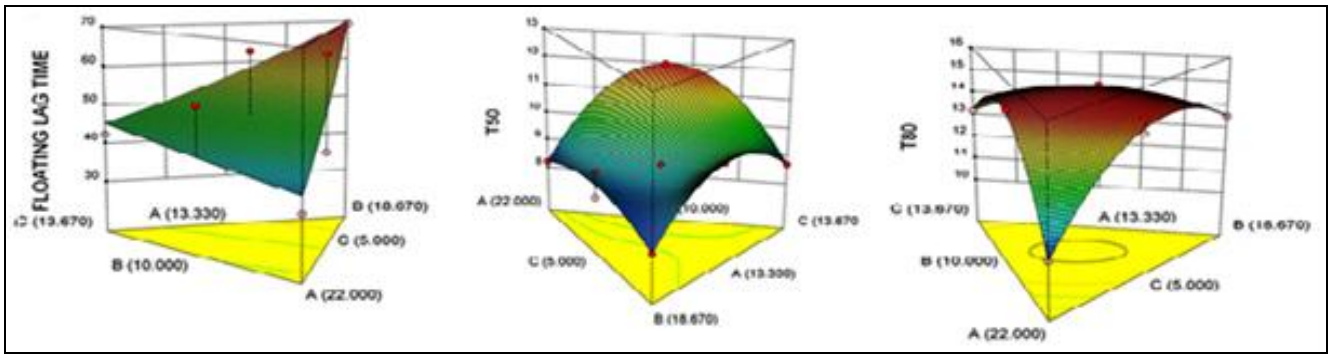

FIG. 2: RESPONSE SURFACE PLOT (3D) SHOWING THE EFFECT OF THE AMOUNT OF AMOUNT OF HPMC K4M, CARBOPOL 934P AND SODIUM CARBOXY METHYL CELLULOSE ON FLOATING LAG TIME, $T_{50\%}$ AND $T_{80\%}$ RESPECTIVELY

Data of $t_{50\%}$ and $t_{80\%}$ clearly indicated that as the amount of HPMC K4M and carbopol 934 P increased the time required to $t_{50\%}$ drug release increased. This may be due to high affinity of HPMC and carbopol toward water, which promotes water penetration into tablet matrices, leading to solubilization of Labetalol HCL. The high value of $X_1X_2X_3$ coefficient also suggests that the interaction between X_1, X_2 and X_3 has a significant effect on $t_{50\%}$. It can be concluded that the $t_{50\%}$ changed by appropriate selection of the X_1, X_2 and X_3 levels. Whereas high value of X_1X_3 coefficient suggests that the interaction between X_1 and X_3 has a significant effect on $t_{80\%}$. It can be concluded that the $t_{80\%}$ changed by appropriate selection of the X_1 and X_3 levels.

Kinetics of Drug Release: To study the release kinetics from hydrogel based matrix tablets, the release data were fitted to the well-known exponential equation (Korsmeyer–Peppas equation) and which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well known or when more than one type of release phenomenon is involved.

Figure 3 shows release profile of simplex centroid batches. Formulations S1, S2, S3, S4, S5, S6 exhibited anomalous (non Fickian transport) diffusion/polymer relaxation mechanism with a value ranging from 0.59 to 0.78. Whereas in case of formulations S7 exhibited zero-order release profile as their 'n' values were very close to 0.88.

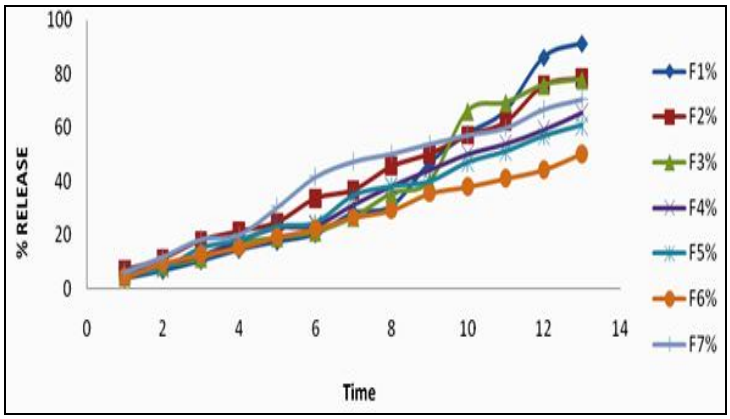

FIG. 3: RELEASE PROFILE OF SIMPLEX CENTROID DESIGN BATCHES

The results for optimized formulation with n value of 0.8776 confirmed that the formulation followed zero order kinetics indicating Labetalol hydrochloride release from controlled drug delivery system were by both diffusion and erosion mechanism.

DISCUSSION: An attempt was made to develop a gastro retentive drug delivery system of Labetalol HCL using HPMC K4M, Carbopol 934P,and Sodium carboxy methyl cellulose as matrixing agent, viscosity increasing agent, and gelling agent, respectively. A simplex centroid design was applied to investigate the combined effect of 3 formulation variables (i.e. amount of HPMC (X1), Carbopol 934P (X2), and sodium carboxymethyl cellulose (X3).

From the *in vitro* buoyancy studies, it was found that almost all the batches containing effervescent agent showed immediate floatation followed by floatation period of more than 18hr. The values of diffusion exponent 'n = 0.877 determined from the Korsmeyer-Peppas equations obtained from modeling of dissolution profiles showing percent drug release of a 90% indicates an anomalous transport mechanism and that the mass transfer follows a non Fickian model.

Results of multiple regression analysis indicated that high levels of X1 and low levels of X2 and X3 should be used to manufacture the tablet formulation with desired in vitro floating time and dissolution. A non Fickian diffusion was confirmed as the drug release mechanism from these tablets. This meant that water diffusion and the polymer rearrangement have essential roles in the drug release.

CONCLUSION: The effervescent based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of gel forming polymer (HPMC K4M) and gas generating agent sodium bicarbonate and citric acid were essential to achieve the *in-vitro* buoyancy. The drug release form the tablets were sufficiently sustained due to the presence of polymers. Labetalol hydrochloride floating tablet drug delivery system showed improved in-vitro bioavailability and extended drug release which may favor the reduced dose frequency and patient compliance.

From the results obtained, it was concluded that the formulation S1 is the best formulations as the extent of drug release was found to be around 90 %. This batch also showed immediate floatation and floatation duration of more than 18hr. The drug release model of this formulation complies with zero order kinetics. Based on the results we can certainly say that floating type gastro retentive drug delivery system holds a lot of potential for drug having solubility as well as stability problem in alkaline pH or which mainly absorb in acidic pH. We can certainly explore this drug delivery which may lead to improved bioavailability and ensured therapy with many existing drugs. It is the responsibility of future scientists working in this area to effectively use the potential of this drug delivery system for the benefit of mankind.

ACKNOWLEDGMENT: The authors are grateful to Mahatma Gandhi Vidyamandir's College of Pharmacy, Nasik, for providing essential laboratory conditions for present research work. Also an author acknowledges to Mercury labs Pvt. Ltd (Baroda, India), for providing gift sample of Labetalol HCL.

REFERENCES-

1. Jain N.K, Novel Drug Delivery System, CBS Publishers Delhi, 2nd edition, 2004; 1-42.
2. Londhe S, Gattani S , Surana S, Development of Floating Drug Delivery System with Biphasic Release for Verapamil Hydrochloride: In vitro and In Vivo Evaluation, Journal of Pharmaceutical Science and Technology Vol. 2 (11), 2010; 361-367.
3. Garse H, Vij M, Hirlekar R, Formulation and evaluation of Gastroretentive Dosage Form of Labetalol Hydrochloride, Arch Pharm Res vol 33 (3), 2010; 405-410.
4. Arora S, Ali J, Ahuja A, Khar R.K, Baboota S, Floating Drug Delivery System: A Review, AAPS PharmSciTech,6 ,2005; 47.
5. Gutierrez- Rocca, J., Omidian, H., Shah,K., Progresses in gastroretentive drug delivery, Pharm.Tech, 2003; 152-156.

6. Dollery C, Therapeutic drugs, Churchill Livingstone, 2nd edition, Volume 1, 1999; L1-L3.
7. Moffat A.C, Osselton M.D, Widdop B, Clarke's Analysis of Drugs and Poisons, vol-2, 1159-1160.
8. Prajapati S. T. *et al.* Gastric floating matrix tablets: Design and optimization using combination of polymers, Acta Pharm. 58**,** 2008; 221–229.
9. Prajapati S.T, Patel L.D, Patel C.N, Floating matrix tablets of domperidone: formulation and optimization using simplex lattice design, Thai J. Pharm Sci 33, 2009; 113-122.
10. M. Rosa, H. Zia and T. Rhodes, Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral application, Int. J. Pharm. 105, 1994; 65–70.
11. Patel D.M, Patel N.M, Pandya N.N, Formulation and Optimization of Carbamazepine Floating Tablets, Indian journal of Pharmaceutical sciences, Jan 2011, IP 117-199, 763-767.
12. Patel D.M, Patel N.M, Pandya N.N, Gastroretentive Drug Delivery System of Carbamazepine: Formulation optimization using Simplex Lattice Design: A Technical note, AAPS PharmSciTech, 2007; 8 (1), Article 11, E1-E5.
13. Jivani R R, Patel C.N, Jivani N.P, Design and Development of Self correcting Monolithic Gastroretentive Tablets of Baclofen, Scientia Pharmaceutica, 2009; 77, 651-667.
14. N. A. Peppas, Analysis of Fickian and non-Fickian drug release from polymers, Pharm. Acta Helv. 60, 1985; 110–111.

****