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DESIGN AND DEVELOPMENT OF FLOATING TABLETS OF DILTIAZEM HYDROCHLORIDE BY USING NATURAL POLYMERS

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ABSTRACT
The aim of present research work is to formulate and evaluate controlled release floating tablet of Diltiazem hydrochloride in view to enhance bioavailability and therapeutic action. The tablets were formulated by employing wet granulation method using PVP K 30 as binder and isopropyl alcohol as granulating fluid. The granules were evaluated for flow properties. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality. All the tablets were formulated using sodium bicarbonate as effervescent agent. All the prepared formulations floated immediately after placing into the beaker and the floating was maintained more than 14 hrs. It was observed that the carbon dioxide generated from sodium bicarbonate in presence of dissolution medium(0.1N HCL) was trapped in the polymer gel matrix formed by the hydration of polymer which decreases the density(<1) and makes the tablet buoyant. The correlation coefficient values (r) revealed that the dissolution profiles followed Zero order kinetics and the mechanism of drug release was governed by Peppas model. The n values are found to be more than 0.5 (n>0.5) indicted that the drug release was predominantly controlled by non fickian diffusion. Based on the release rate constant and % of drug release the formulations prepared with Moringa oleifera gumshown prolonged retarding nature compared with the formulations prepared with Aegle marmosa gum. Among all the formulations, F_3 formulation containing drug and Moringa oleifera gumin 1:1.5 ratio was found to be optimized formulations.

KEYWORDS: Diltiazem hydrochloride, Moringa oleifera gum, Aegle marmosa gum, Sodium bicarbonate.

INTRODUCTION
Diltiazem hydrochloride is a calcium channel blocker, an anti-hypertensive and anti-anginal drug, which undergoes extensive firstpass metabolism and display poor bioavailability.[1] It has an elimination half-life of 3 to 4.5 h and an absorption zone from the upper intestinal tract.[2]

Efficacy of the administered dose may get reduced due to incomplete drug release from the device above the absorption zone. The dosage is 30mg, 4 times a day and increased as necessary up to 360mg/day in divided doses.[3-4] Due to short half-life diltiazem hydrochloride require frequent administration. To reduce the dosing frequency and to improve the patient compliance, prolonged release dosage forms are required. These disadvantages can over come by developing a floating dosage form to be remained buoyant in the stomach.[5]

The gastroretentive drug delivery system can be retained in the stomach and assist in improving the oral sustained delivery of drugs. There is a need to investigate a number of indigenously available retardant material to make the concept of controlled release drug delivery more viable for the drug industry at more economical way. In the present study, natural polymers such as Moringa oleifera gum/Aegle marmosa gum were selected for the preparation of floating tablets of diltiazem hydrochloride. Sodium bicarbonate was used as gas generating agent. Tablets were prepared by wet granulation method using these polymers.

MATERIALS AND METHODS
Diltiazem hydrochloride was obtained as a gratis sample from Hetero labs, Hyderabad. Moringa oleifera gumand Aegle marmosa gum were purchased from Yucca enterprises, Mumbai. PVP K 30, Isopropyl alcohol and Sodium bicarbonate were purchased from Qualigens fine chemicals, Mumbai. All other ingredients were of analytical grade.

Preparation of Diltiazem hydrochloride floating tablets
Diltiazem hydrochloride was mixed with required quantities of Moringa oleifera gumand Aegle marmosa gum, Sodium bicarbonate and Citricacid by geometric

mixing. The tablets were formulated by employing wet granulation method using PVP K 30 as binder and isopropyl alcohol as granulating fluid. Magnesium stearate and talc were used as lubricant and glidant respectively. The final blend was compressed into tablets using 12 mm punches and corresponding dies on rotary tablet compression machine.[6] The composition of each formulation was given in Tables 1.

EVALUATION PARAMETERS

Flow properties of granules: The granules were evaluated for the bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose using standard reported methods.[7]

Evaluation of Diltiazem hydrochloride floating tablets

a) Hardness: The hardness of the tablet was measured by Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.[8] The hardness was measured in terms of kg/cm^2.

b) Weight variation: Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated.[8] The percent weight variation was calculated by using the following formula.

$$\% \text{ Weight Variation} = \frac{\text{Average Weight - Individual Weight}}{\text{Average Weight}} X100$$

c) Friability: The Roche friability test apparatus was used to determine the friability of the tablets. Thirteen pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.[8]

$$\text{Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X100$$

d) Swelling Index: Formulated tablets were weighed individually (W_0) and placed separately in Petri dish containing 50 ml of 0.1N Hydrochloric acid. The Petri dishes were placed in an incubator maintained at 37±0.5^{o}C. The tablets were removed from the petri dish, at predefined intervals of time and reweighed (Wt), and the % swelling index was calculated using the following formula[9]:

$$\% \ W_U = (Wt\text{-}Wo/Wo) \times 100$$

Where:

W_U – Water uptake

Wt – Weight of tablet at time t

Wo – Weight of tablet before immersion

e) In vitro buoyancy study: This test is characterized by floating lag time and total floating time. The test was performed using USP-Type II paddle apparatus using 900 ml of 0.1N Hydrochloric acid at paddle rotation of 100 rpm at 37 ± 0.5^{0}C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time.[10]

f) Drug content: 20 tablets were weighed and powdered the powder weight equivalent to 150mg of Ranitidine hydrochloride was dissolved in 100ml of 0.1N Hydrochloric acid and filtered. 5ml of this was diluted to 50ml with water and drug content was estimated at 237 nm by UV spectrophotometer.[11]

g) In vitro dissolution test: The release of Diltiazem hydrochloride from the tablet was studied using USP-Type II paddle apparatus. Drug release profile was carried out in 900 ml of 0.1N Hydrochloric acid maintained at 37 ± 0.5°C temperatures at 100 rpm. 5 ml of samples were withdrawn at regular time intervals. The samples was replaced by its equivalent volume of dissolution medium and was filtered through 0.45 µm Whatman filter paper and analyzed at 237nm by UV spectrophotometer.[12]

Drug Excipient Compatibility Studies

Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with Moringa oleifera gum/ Aegle marmosa gum used in tablet formulations.[13]

Stability studies of optimized floating matrix tablets

The optimized floating matrix tablets were separated in to two groups. Each group of formulations were placed separately in stability chamber which is maintained at 25±5^{o}C/60% RH and 40±5^{o}C/75% RH respectively for three months and every month the formulations from each group were subjected to dissolution studies and % drug release was calculated.[14]

RESULTS AND DISCUSSION

Floating tablets of Diltiazem hydrochloride were prepared by varying the concentration of Moringa oleifera gum (F_1-F_3) and Aegle marmosa gum (F_4-F_6). The formulated granules were evaluated for various flow properties. The bulk density for all the formulations ranged from 0.608to 0.616. The angle of repose for all the formulations was found to be in the range of $26^0 10^1$-$27^0\ 64^1$. The Carr's index for all the formulations ranged from 15.30 – 15.87%. The value of bulk density indicates good packing characters. The value of angle of repose (25^0-30^0) for all the formulations indicates good flow property. The value of Carr's index (10-16%) indicates free flowing material. The values of Hausner's ratio were found to be between 1.180-1.188. The powder blend with Hauser's ratio of 1.25 has good flow properties. So the values indicate that the granules had acceptable flow properties. The flow properties were shown in table 2.

Floating matrix tablets were evaluated for hardness and friability. The hardness was found to be in between 4.5 – 4.9 kg. The tablets satisfied friability requirement, as the

% friability values were less than 1%. The drug content estimations showed values in the range of 99.78 to 99.92%, which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeia limits of ±5% of the weight. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

All the tablets were formulated using sodium bicarbonate as effervescent agent. All the prepared formulations floated immediately after placing into the beaker and the floating was maintained more than 14 hrs. It was observed that the carbon dioxide generated from sodium bicarbonate in presence of dissolution medium(0.1N HCL) was trapped in the polymer gel matrix formed by the hydration of polymer which decreases the density(<1) and makes the tablet buoyant. The results of various physical properties and *invitro* buoyancy studies were tabulated in table 3.

In vitro dissolution studies of all the formulations of floating matrix tablets were carried out in 0.1N HCl. The study was performed for 12 hrs and the cumulative drug release was calculated. All the formulations remained floating and intact throughout the dissolution studies. The formulations(F_1-F_3) containing Moringa oleifera gumshowed decrease in drug release with increase in concentration of Cashew nut tree gum. The drug release from formulation F_3 containing drug and natural polymer in 1:1.5 ratio showed a maximum drug release at end of 12hours. The dissolution profile for the formulations F1-F3 was shown in figure 1. The formulations(F4-F6) containing Aegle marmosa gum showed decrease in drug release with increase in concentration of Aegle marmosa gum. The drug release from formulation F_6 containing drug and natural polymer in 1:1.5 ratio showed a maximum drug release at end of 11 hours. The dissolution profile for the formulations F4- F6 was shown in figure 2.To ascertain the mechanism of drug release, the dissolution data was analyzed by zero order, first order, and Higuchi and Peppas equations. The correlation coefficient values (r) revealed that the dissolution profiles followed Zero order kinetics and the mechanism of drug release was governed by Peppas model. The n values are found to be more than 0.5 (n>0.5) indicted that the drug release was predominantly controlled by non fickian diffusion. The in-vitro drug release kinetic data was shown in Table 4. The swelling index studies showed a gradual increase with increase in concentration of natural polymer and were shown in Table 5.The characteristics peaks confirmed the structure of Diltiazem hydrochloride. The same peaks were also reported in all drug loaded matrix tablet. There were no change or shifting of the characteristic peaks in matrix tablets suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in all formulations. Drug release from optimized formulations before and after storage under varying conditions were evaluated periodically at the regular interval of every month. The drug release profiles of all the formulations did not change significantly after storage at 25±2° C/60±5% RH and 40±2° C/75±5% RH for a period of 3 months. There is no significant difference in the drug content and release rate constants. The results indicated that the drug release from the optimized formulations were found to be quite stable.

From the above results,it is clearly evident that the invitro release of Diltiazem hydrochloride from the floating tablet was influenced by nature of natural polymer. Based on the release rate constant and % of drug release the formulations prepared with Cashew nut tree gum shown prolonged retarding nature compared with the formulations prepared with Aegle marmosa gum. Among all the formulations, F_3 formulation containing drug and Cashew nut tree gum in 1:1.5 ratio was found to be optimized formulations.

Table 1: Composition of Diltiazem hydrochloride floating tablets formulated with different natural polymers.

Ingredients	F_1(mg)	F_2(mg)	F_3(mg)	F_4(mg)	F_5(mg)	F_6(mg)
Diltiazem hydrochloride	90	90	90	90	90	90
Moringa oleifera gum	45	90	135			
Aegle marmosa gum				45	90	135
Micro crystaline cellulose	110	65	20	110	65	20
Sodium bicarbonate	50	50	50	50	50	50
Citricacid	25	25	25	25	25	25
Poly Vinyl Pyrolidine	20	20	20	20	20	20
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total weight	350	350	350	350	350	350

Table 2: Micromeritic properties of granules of Diltiazem hydrochloride floating tablets formulated with different concentrations of natural polymers.

Formulation code	Angle of repose (°)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio
F_1	27.16	0.539	0.623	13.48	1.155
F_2	26.81	0.531	0.612	13.23	1.152
F_3	26.37	0.521	0.594	12.28	1.140
F4	27.73	0.537	0.614	12.54	1.143
F5	26.82	0.529	0.604	12.41	1.141
F6	26.10	0.521	0.589	11.54	1.130

Table 3: Physical properties of Diltiazem hydrochloride floating tablets formulated with different concentrations of natural polymers.

Formulation	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating Lag time	Total floating time (hrs)
F_1	4.4±0.009	350.17±0.12	0.71±0.008	99.87±0.13	2.23 min	>14
F_2	4.6±0.011	350.14±0.15	0.59±0.012	99.75±0.14	2.05 min	>14
F_3	4.8±0.007	349.83±0.06	0.45±0.009	99.92±0.08	1.77 min	>14
F_4	4.3±0.005	350.18±0.11	0.69±0.008	99.89±0.11	2.38 min	>14
F_5	4.5±0.009	350.12±0.14	0.52±0.011	99.74±0.13	2.26 min	>14
F_6	4.7±0.011	349.86±0.08	0.39±0.009	99.91±0.11	1.88 min	>14

Table 4: *In vitro* drug release kinetic data of Diltiazem hydrochloride floating tablets formulated with different concentrations of natural polymers.

Formulation	Correlation Coefficient Value				Release Rate Constant (mg/hr)k_0	Exponential Coefficient (n)	T_{50} (hr)	T_{90} (hr)
	Zero Order	First Order	Matrix	Peppas				
F_1	0.9918	0.8208	0.9518	0.9961	9.18	0. 7555	4.9	8.8
F_2	0.9951	0.8098	0.9444	0.9964	8.18	0.7976	5.5	9.9
F_3	0.9986	0.7925	0.9354	0.9995	7.62	0.9576	5.9	10.6
F4	0.9984	0.7672	0.9586	0.9786	10.63	0.7199	4.23	7.5
F5	0.9896	0.8434	0.9570	0.9972	9.30	0.7605	4.8	8.6
F6	0.9933	0.7522	0.9501	0.9970	8.48	0.7908	5.3	9.6

Table 5: Swelling index values of Diltiazem hydrochloride floating tablets formulated with different concentrations of natural polymers.

Formulation code	Swelling index		
	Time in hours		
	after 1 hour	after 2 hours	after 8hours
F_1	53.46	73.67	144.58
F_2	55.21	81.12	153.29
F_3	59.79	92.56	167.44
F_4	50.13	68.52	137.57
F_5	54.17	79.45	148.36
F_6	58.43	88.74	161.25

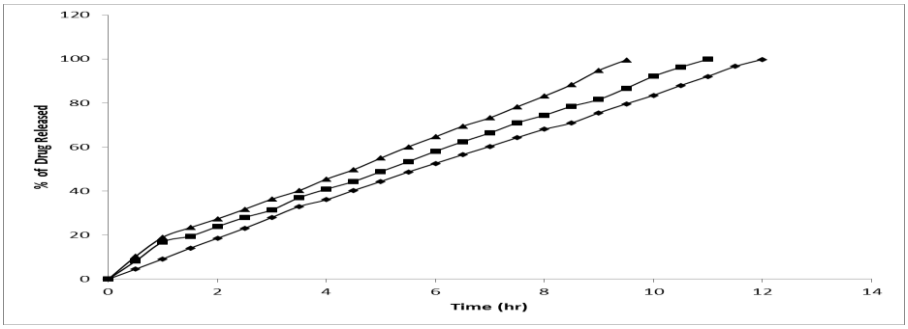

Figure 1: Comparative *in vitro* drug release profile of Diltiazem hydrochloride floating tablets formulated with different concentrations of Cashew nut tree gum.

(-♦-)Floating tablets formulated with drug and Cashew nut tree gum in 1:0.5 ratio
(-■-)Floating tablets formulated with drug and Cashew nut tree gum in 1:1 ratio
(-▲-) Floating tablets formulated with drug and Cashew nut tree gum in 1:1.5 ratio

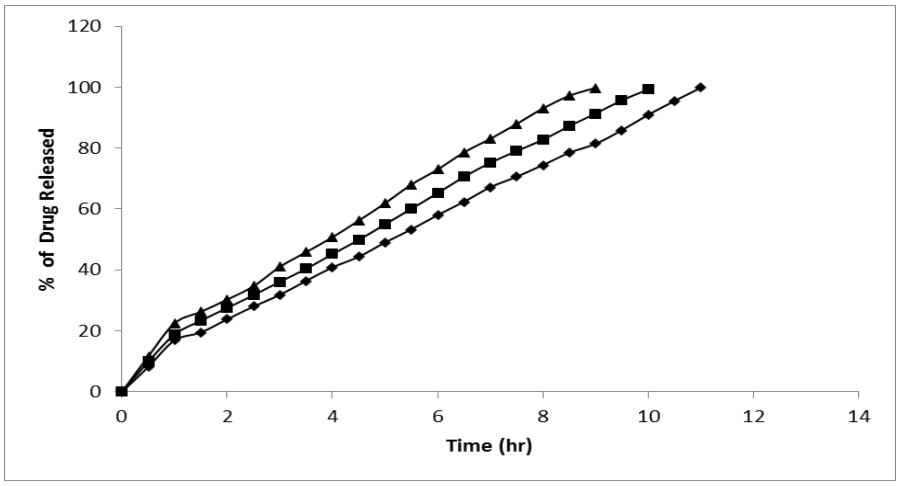

Figure 2: Comparative *in vitro* drug release profile of Diltiazem hydrochloride floating tablets formulated with different concentrations of Aegle marmelos gum.
(-♦-)Floating tablets formulated with drug and Aegle marmelos gum in 1:0.5 ratio
(-■-)Floating tablets formulated with drug and Aegle marmelos gum in 1:1 ratio
(-▲-) Floating tablets formulated with drug and Aegle marmelos gum in 1:1.5 ratio

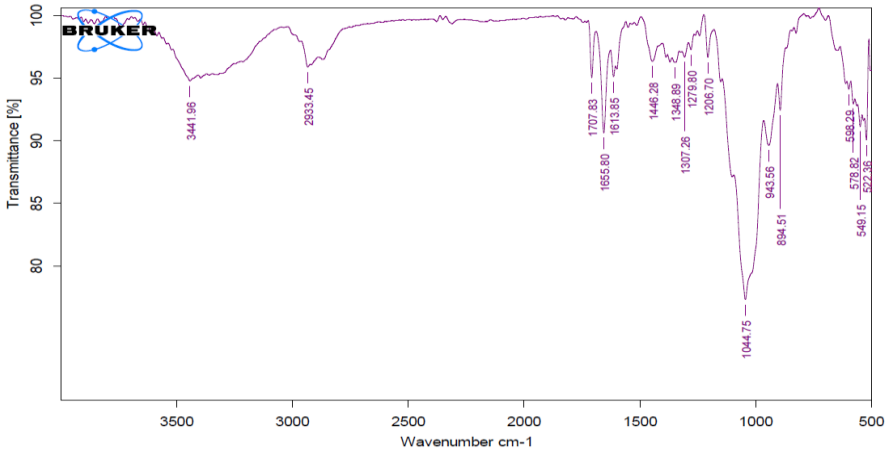

Figure 3: FTIR spectrum of Diltiazem hydrochloride.

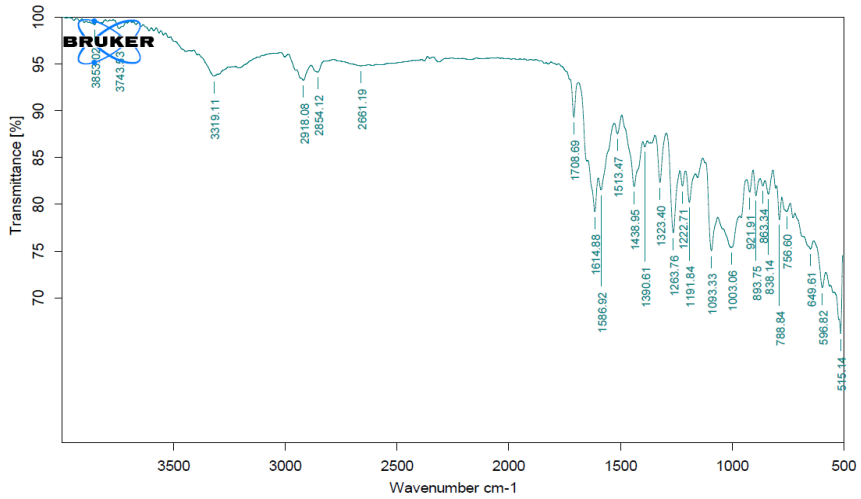

Figure 4: FTIR spectrum of Diltiazem hydrochloride floating tablet prepared with Cashew nut tree gum.

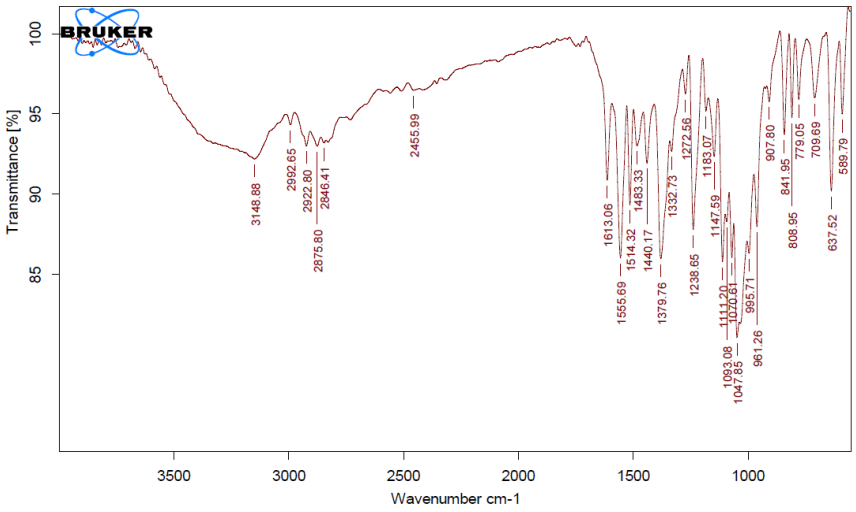

Figure 5: FTIR spectrum of Diltiazem hydrochloride floating tablet prepared with Aegle marmosa gum.

REFERENCES

1. Buckley MMT, Grant, S, Goa, KL, McTavish D, Sorkin EM. Diltiazem. A reappraisal of its pharmacological properties and therapeutic use. Drugs, 1990; 39: 757-806.
2. Chaffman M, Brogden RN. Diltiazem : A review of its pharmacological properties and therapeutic efficacy. Drugs, 1985; 29: 387-454.
3. Sadhana R Shahi, Vidya M. Madkar1, Prashant N Kshirsagar, S. S. Khadbadi. Development and evaluation of bilayer floating tablets of diltiazem hcl. Int J Pharm Pharm Sci., 2014; 6(2): 62-65.
4. Sailaja Gunnam, Chowdary K PR. Formulation and evaluation of diltiazem floating tablets employing a new modified starch – optimization by 2^3 factorial design. World Journal of Pharmacy and Pharmaceutical Sciences, 2014; 3(9): 1176-1187.
5. Lakshmi PK, T Shailaja, S Ramachandra, Y Sasi Bhushan. Formulation and In Vitro Evaluation of Gastro Retentive Delivery of Diltiazem Hydrochloride Using Natural Polymers. Int J Pharma Sci., 2013, 3(1): 129-135.
6. Chowdary KPR, Areefulla Hussainy S. Formulation and Evaluation of Floating Tablets of Diltiazem Employing HPMC K100M, Starch acetate and Carbopol 934P. RJPBCS, 2012; 3(1): 245-250.
7. Shivanand Pandey, Viral Devmurari1. Development and *In Vitro* Evaluation of Propranolol Hydrochloride Based Gastro-Retentive Floating Tablet. Der Pharmacia Lettre, 2010; 2 (1): 75-86.
8. Narendra C, Jain S, Srinath MS, Reddy SN, Sindhu A. Development of a Floating Dosage Form of Ranitidine Hydrochloride by Statistical Optimization Technique. J Young Pharm., 2010; 2(4): 342–349.
9. Swapna Velivela, Sashmitha Samuel.B, Konde Abbulu. Formulation and evaluation of floating ranitidine hydrochloride tablets by using moringa gum as a functionality carrier. Int. J. Pharm. Sci. Rev. Res., 2012; 16(2): 116-120.
10. Natasha Sharma, Neelam Balekar, Jain D K. Design and Development of Floating Tablet of Ranitidine Hydrochloride and Study the Effect of Formulation Variables. Indian Journal of Novel Drug delivery, 2011; 3(4): 296-302.
11. Narayana Charyulu R, Amit B. Patil, Lakshmi Deepika C.H, Prabhakar Prabhu, Shastry C.S. Development of gastro retentive floating matrix tablets of diltiazem hydrochloride. NUJHS, 2011; 1(3): 38-45.
12. Margret Chandira, Chandramohan, D. Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride. Der Pharmacia Lettre, 2009; 1(2): 25-38.
13. Prajapatia S, Patel L and Patel C. Floating matrix tablets of domperidone formulation and optimization using simplex lattice design**.** Iranian Journal of Pharmaceutical Research, 2011; 10(3): 447-455.
14. Sarojini Sarangapani, Manavalan Rajappan. Lansoprazole Release from a Floating Dosage Form based on the Natural Polymer of Delonix regia. International Journal of PharmTech Research, 2012; 4(3): 1084-1095.