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Formulation and *In-Vitro* Evaluation of Floating Pulsatile Drug Delivery System of Ivabradine

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ABSTRACT

The aim of present investigation was to develop press coated tablets for Floating pulsatile drug delivery of Ivabradine used for is a medication used for the symptomatic management of stable heart-related chest pain and heart failure not fully managed by beta blockers. The drug delivery system was designed to deliver the drug such a time when it could be needful of patient conditions. The press coated tablets containing Ivabradine in the inner core were formulated by direct compression method with an outer coating of different amount of HPMCK200 M. The release profile of press coated tablet exhibited a lag time. The optimized batch F9 gave good drug release of 99.58 %.

Keywords: Ivabradine, Eudragit, EC, HPMCK200M

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1. INTRODUCTION

In recent years, a major goal for the drug delivery research is turned towards the development of efficacious drug delivery systems with already existing active ingredients in case of new drug discovery. Many of pharmaceutical therapeutic agents are mostly effective when made available at constant rates or near to absorption sites. Much effort has been going on to develop sophisticated drug delivery systems such as osmotic devices for oral application. Oral drug delivery system is more favored on popular controlled drug delivery system in pharmaceutical research and development (R&D) business due to increase in awareness of medical and pharmaceutical community about the importance of safe and effective use of drug. This system aims to maintain plasma drug concentration within the therapeutic window for long period of time.[1]

2. MATERIALS AND METHODS

Materials: Ivabradine was obtained as a gift sample from Biocon Limited., Crospovidone, Sodium starch glycolate, Croscarmellose sodium and Sodium carbonate was obtained from Yarrow chem products. Mumbai, Avicel-P^{H}102, Magnesium stearate, Talc, Lactose was purchased from Signet chemicals, Mumbai.

Methods:

2.1. Analytical method development:

a) Preparation of calibration curve in 0.1N HCL:

10mg of Ivabradine pure drug was dissolved in 10ml of methanol (stock solution 1). 1ml of solution was taken and make up with10ml of 0.1N HCL (100µg/ml) stock-2. From this 1ml was taken and make up with 10 ml of 0.1N HCL (10µg/ml) stock-3. The above stock-II solution was subsequently diluted with 0.1N HCL to obtain series of dilutions containing and 2,4,6,8 and 10µg/ml of solution. The absorbance of the above dilutions was measured at 286 nm for 0.1N HCL by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

Preparation calibration curve in pH 6.8 phosphate buffer:

10mg of Ivabradine pure drug was dissolved in 10ml of methanol (stock solution 1). 1ml of solution was taken and make up with10ml of 6.8 Phosphate buffer (100µg/ml) i.e. stock-2. From this 1ml was taken and make up with 10 ml of 6.8 Phosphate buffer (10µg/ml) i.e. stock-3. The above stock-II solution was subsequently diluted with 6.8 Phosphate buffer to obtain series of dilutions Containing and2, 4, 6, 8

and 10µg/ml of solution. The absorbance of the above dilutions was measured at 286 nm for 6.8 Phosphate buffer by using UV-Spectrophotometer taking 6.8 Phosphate buffer as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

2.2. Drug – Excipient compatibility studies: [2-5]

Fourier Transform Infrared (FTIR) spectroscopy:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-1}.

2.3. Formulation development of Tablets: [6-15]

Formulation of core tablets by direct compression:

The inner core tablets were prepared by using direct compression method. Powder mixtures of Ivabradine, microcrystalline cellulose, CCS, Talc, ingredients were dry blended for 20 min. followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 60mg of resultant powder blend was manually compressed using, Lab press Limited, India with a 6mm punch and die to obtain the core tablet.

Formulation of mixed blend for barrier layer:

The various formulation compositions containing Eudragit S-100, Ethyl cellulose, HPMC-K200M, Magnesium stearate, talc and Microcrystalline cellulose. Different compositions were weighed dry blended at about 10 min. and used as press coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Preparation of press-coated tablets:

The core tablets were press-coated with 120 mg of mixed blend. 100 mg of barrier layer material was weighed and transferred into a 7mm die then the core tablet was placed manually at the center. The remaining of the barrier layer materiel was added into the die and compressed by using Lab press Limited, India.

Table 1: Formulation development of core tablets

Ingredients	C1	C2	C3
Ivabradine	5	5	5
Croscarmellose sodium	10	15	20
Microcrystalline cellulose	26	21	16
PVP k 30	15	15	15
Magnesium stearate	3	3	3
Talc	1	1	1
Total weight	60	60	60

Table 2: Formulations for press coated tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Eudragit S-100	10	20	30	--	--	--	--	--	--
Ethyl Celluose (EC)	--	--	--	10	20	30	--	--	--
HPMC K200M	--	--	--	--	--	--	10	20	30
PVP K30	15	15	15	15	15	15	15	15	15
Sodium bicarbonate	10	10	10	10	10	10	10	10	10
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Microcrystalline cellulose	81	71	61	81	71	61	81	71	61
Talc	1	1	1	1	1	1	1	1	1
Total weight (mg)	120	120	120	120	120	120	120	120	120

3. RESULTS AND DISCUSSION

Present study was done on pulsatile tablets with different formulations F1 to F9. Formulations had weight ratio of polymers like Eudragit S-100, Ethyl cellulose, HPMC K200M along with various excipients. Ethyl cellulose is an insoluble.

3.1 Preformulation Studies:

Standard graph of Ivabradine in 0.1N HCL:

Ivabradine showed maximum absorbance in 0.1N HCL at 286 nm. The solution obeyed Beer-Lambert's law for concentration range of 0µg/mL to 10µg/mL with regression coefficient of 0.998. Standard curve of Ivabradine prepared in 0.1N HCL.

Table 3: Calibration data of Ivabradine in 0.1N HCL

Concentration [µg/ml]	Absorbance
0	0
2	0.177
4	0.369
6	0.557
8	0.743
10	0.934

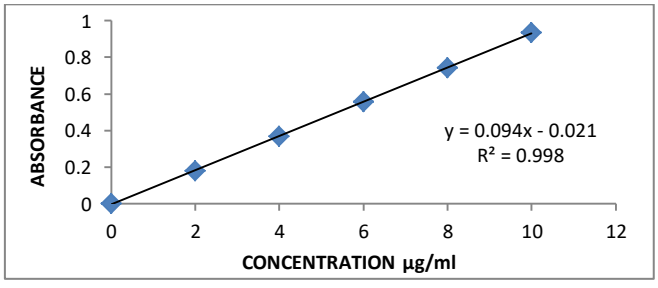

Fig. 1: Standard Graph of Ivabradine in 0.1N HCL

3.2: FT-IR (Fourier Transform Infrared Spectrophotometry)

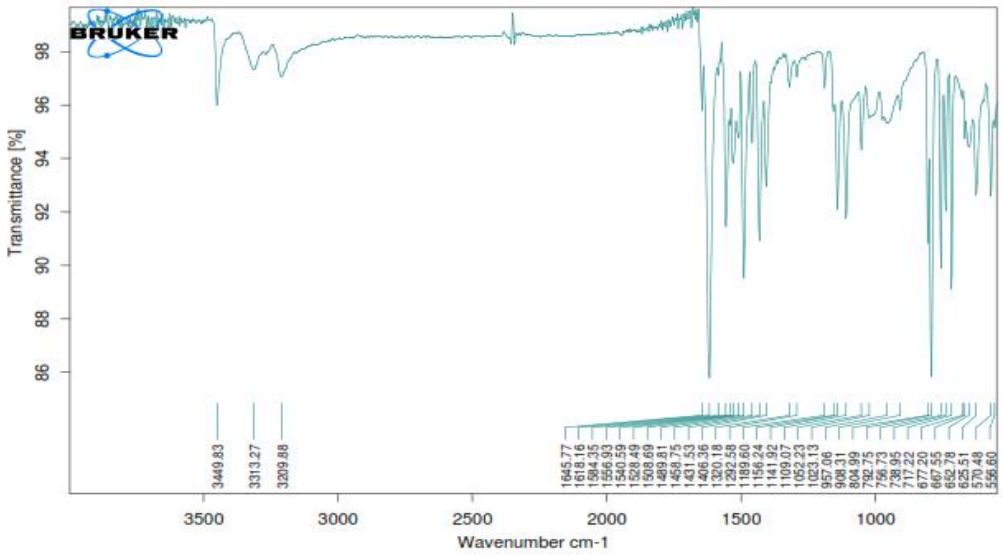

Fig. 2: FTIR spectra of Ivabradine pure drug

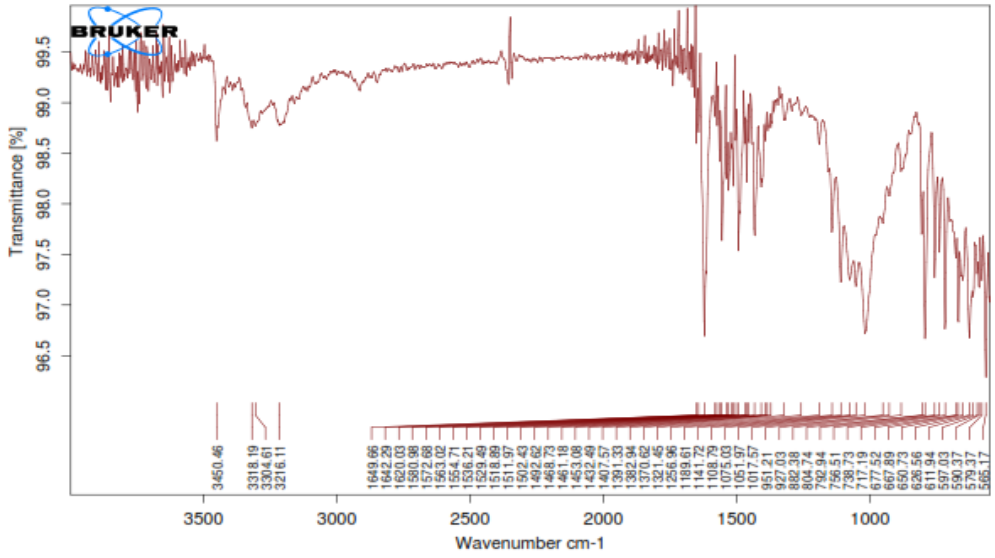

Fig. 3: FTIR spectra of Optimized Formula

The spectra for pure Ivabradine and for the physical mixture of Ivabradine and all the polymers were determined to check the intactness of the drug in the polymer mixture using FTIR Spectrophotometer.

The comparative FTIR studies of Drug and excipients combination had shown negligible variation in the values as compared with that of only pure form of Drug. Therefore it implies good compatibility of drug and excipients.

From the above table, the wave number of mixture of drug with excipients is within the range of wave number of pure drug. This implies that the excipients are compatible with the drug since their combination did not alter the functional groups of pure drug

Table 4: Pre compression parameters of Cap core tablets

Formulation Code	Angle of repose (^{O}) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
C1	26.29	0.34	0.38	10.52	1.11
C2	27.29	0.33	0.38	13.15	1.15
C3	28.29	0.34	0.38	13.14	1.14

Tablet powder blend was subjected to various pre formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.33 to 0.34 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.38 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 10.52 to 13.15 which were showed that the powder has good flow properties. All the formulations has shown the hausner ratio ranging from 0 to 1.15 indicating the powder has good flow properties.

Table 5: Post compression parameters of Core tablet:

Formulation code	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In-vitro* disintegration time (min)
C1	59.12	1.13	0.24	0.345	98.18	15
C2	60.28	1.25	0.18	0.287	99.27	10
C3	60.77	1.34	0.22	0.321	99.13	18

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Weight variation and thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance. The average tablet weight of all the formulations was found to be between 9.12 to 60.77. The maximum allowed percentage weight variation for tablets weighing <80 mg is 10% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 0.287 to 0.345.

Hardness and friability:

All the formulations were evaluated for their hardness, using monsanto hardness tester. The average hardness for all the formulations was found to be between (1.13– 1.34) Kg/cm^2 which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator. The average percentage friability for all the formulations was between 0.18-0.24 which was found to be within the limit.

Drug content: The drug content values for all the formulations were found to be in the range of 98.18 to 99.27. According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the formulations comply with the standards given in IP.

***In-vitro* disintegrating time:** The *in vitro* disintegration time values for all the formulations were found to be in the range of 10 to 18 mins.

Table 6: Pre compression Parameters of Ivabradine coated Tablets

rmulation code	Angle of repose (^{O})	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	17.10	0.318	0.38	16.31	1.19
F2	28.97	0.342	0.4	15.0	1.17
F3	18.19	0.34	0.43	20.93	1.26
F4	22.61	0.36	0.42	14.28	1.16
F5	26.56	0.33	0.41	19.06	1.24
F6	23.10	0.33	0.42	22.35	1.28
F7	19.85	0.33	0.41	19.51	1.24
F8	21.80	0.32	0.42	24.70	1.32
F9	17.74	0.33	0.4	17.5	1.21

Tablet powder blend was subjected to various pre formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.32 – 0.342 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.38 - 0.43 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 14 to 24 which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0.16 to 1.32 indicating the powder has good flow properties.

Table 7: Post compression parameters of Coated tablet

Formulation code	Average Weight (mg)	Hardness (kg/cm2)	Thickness	Friability (%loss)	Drug content (%)	Floating lag time (min)	Total Floating Time (Hrs)
F1	178.28±0.12	5.82±0.22	2.12±0.78	0.54±0.28	99.28	3.2	5
F2	180.03±0.95	5.66±0.51	2.67±0.64	0.23±0.34	98.12	3.4	10
F3	176.98±0.74	5.09±0.95	1.85±0.48	0.47±0.94	99.73	3.8	12
F4	180.57±0.64	5.16±0.46	2.45±0.32	0.61±0.47	100.01	3.1	5
F5	179.48±0.37	5.77±0.37	1.98±0.17	0.44±0.85	97.42	3.6	10
F6	178.61±0.56	5.62±0.55	2.12±0.95	0.50±0.24	99.35	3.2	12
F7	176.38±0.33	5.94±0.48	2.44±0.81	0.38±0.95	98.75	2.6	8
F8	177.73±0.76	5.81±0.72	2.89±0.99	0.31±0.81	99.41	2.0	11
F9	180.05±0.84	5.19±0.22	3.18±0.75	0.55±0.76	99.27	3.4	12

***In-Vitro* Drug Release Studies of Ivabradine core tablet:** *In vitro* dissolution studies of Ivabradine core tablets were performed using USP XXIII Type II rotating paddle dissolution apparatus by using phosphate buffer (pH 6.8) as a dissolution medium. From formulation C1-C3 Ivabradine core tablets, C2 showed faster drug release than the other formulations. Faster drug release can be correlated with the high disintegration time. So, C2 formulation was selected as best formulation for further press coating and enteric coating formulations.

Table 8: Drug release of Ivabradine core tablets

Time (min)	C1	C2	C3
0	0	0	0
5	12.82	18.98	7.98
10	22.08	35.48	10.14
15	37.41	55.58	36.98
20	67.66	82.31	58.9
30	91.2	96.88	92.53
45	94.6	98.86	96.66
60	96.92	99.76	98.27

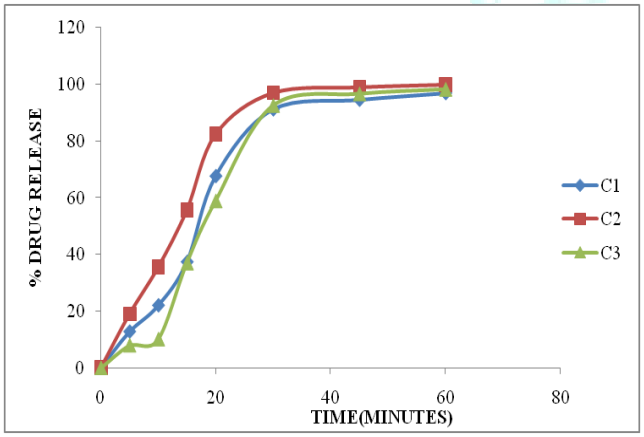

Fig. 4: Cumulative % drug released of Ivabradine core tablets

***In vitro* drug release study of Ivabradine pulsatile tablets:**

The time dependent pulsatile tablets were prepared by using different concentrations of Eudragit S-100. The formulation C2 showed maximum drug release at immediately. So, C2 formulation was selected as best formulation for further press coating and enteric coating formulations.

Table 9: Cumulative % drug Release of Coated Ivabradine Tablets containing Eudragit S-100

Time (hr)	F1	F2	F3
0	0	0	0
0.5	0.14	0.13	0.12
1	0.18	0.19	0.22
2	0.25	0.21	5.43
3	28.54	25.29	15.68
4	50.34	30.18	24.32
5	98.37	41.72	30.62
6	---	51.31	39.57
7	---	60.34	44.28
8	---	72.48	50.02
9	---	88.68	61.25
10	---	100.64	77.31
11	---	---	84.92
12	---	---	95.45

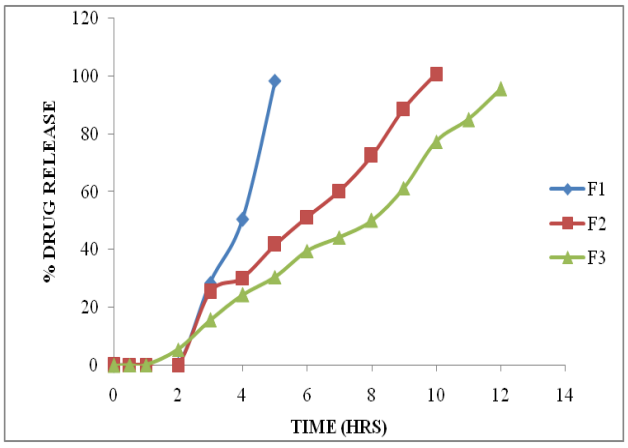

Fig. 5: Cumulative % drug release study of Ivabradine pulsatile tablets (F1, F2 & F3)

Table 10: Cumulative % drug Release of Coated Ivabradine Tablets containing Ethyl cellulose

Time (Hrs)	F4	F5	F6
0	0	0	0
0.5	0.28	0.12	0.11
1	12.56	0.19	0.17
2	28.18	1.95	1.35
3	50.34	10.12	9.38
4	85.17	21.23	20.38
5	90.61	30.22	28.39
6	99.76	39.15	35.59
7	---	43.52	40.38
8	---	49.06	52.12
9	---	55.79	64.21
10	---	75.34	74.86
11	---	94.25	80.67
12	---	---	94.76

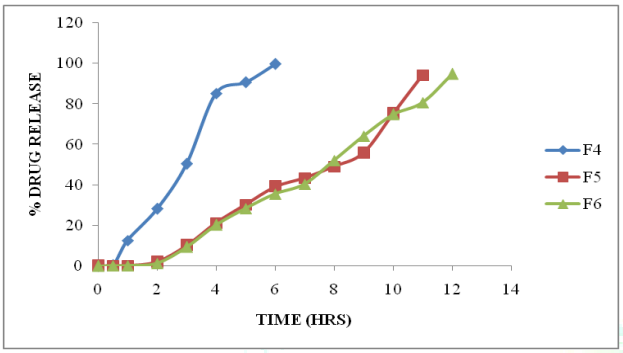

Fig. 6: Cumulative % drug release study of Ivabradine pulsatile tablets (F4, F5 & F6

Table 11: Cumulative % drug Release of Coated Ivabradine Tablets containing HPMC K200M

Time (Hrs)	F7	F8	F9
0	0	0	0
0.5	0.19	0.16	0.12
1	0.65	0.54	0.54
2	1.95	1.84	0.59
3	5.39	14.74	19.74
4	13.73	20.38	25.38
5	27.37	38.48	36.48
6	41.38	47.48	45.48
7	63.83	50.29	52.29
8	80.29	61.27	66.27
9	96.38	79.38	71.38
10	---	86.39	78.39
11	---	96.28	86.28
12	---	---	99.58

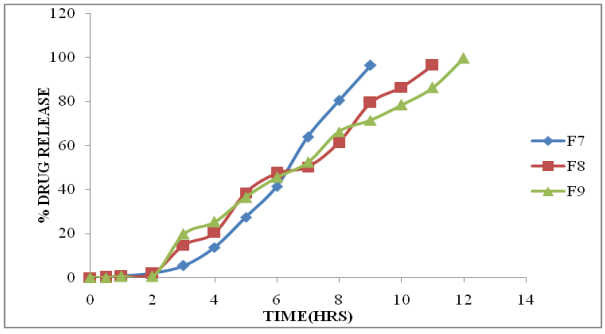

Fig. 7: Cumulative % drug release study of Ivabradine pulsatile tablets (F7, F8, F9)

4. CONCLUSION

Ivabradine Pulsatile dosage form was formulated by press coating technique. The lag time and time controlled release behavior of Ivabradine from press coated tablets could be modulated by varying the concentration of polymer in outer coating layer and thickness if compression coating. From formulation C1-C3 Ivabradine core tablets, C2 showed faster drug release than the other formulations. Faster drug release can be correlated with the less disintegration time. So, C2 formulation was selected as best formulation for further press coating and enteric coating formulations. Among All Formulations F9 was showed maximum % drug release 99.58% at 12 hours. Hence F9 Formulation was considered as optimized Formulation.

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REFERENCES

1. Chien YW. Oral drug delivery and delivery system in novel drug de livery Systems, ed, 50, Marcel Dekker publication, New York, 19 92.
2. Ramesh D, Parmar, Rajesh K, Parikh, Vidyasagar G, Dhaval, Pulsatile drug delivery systems, International journal of pharmaceutical sciences and nanotechnology, 2014; 8(10):605-611.
3. Hiralal S. Chaudhari, Mahadev S. Lohar, Amol S. Amritkar, Dinesh K. Jain, Dheeraj T. Baviskar, Pulsatile drug delivery system, International journal of pharmaceutical sciences review and research, 2011; 8(2):160-169.
4. S. Keerthi, Vijay Bhaskar Reddy, Gopal Muralidharan, Formulation and evaluation of pulsatile drug delivery system of anti-asthmatic drug, Am. J. Pharmtech res., 2014; 4(1):797-809.
5. Chikhalikar SS, Wakade RB, Floating Drug Delivery System - An Approach to Oral Controlled Drug Delivery, International Journal of Pharm. Tech Research, 2012; 4(4):1812-26.
6. Tripathi GK, Singh S, Formulation and In-vitro evaluation of pH sensitive oil entrapped polymeric blended buoyant beads of Amoxicillin, Scholars Research Library, 2010; 2 (2):131-38.
7. Burns SJ, Attwood D, Barnwell SG, Assessment of a dissolution vessel designed for use with floating and erodible dosage forms, International Journal of Pharmaceutics, 1998; 160:213–18.
8. Kharia A.A, Hiremath SN, Singhai AK, Jain SK, Design and optimization of floating drug delivery system of acyclovir, Indian Journal of Pharmaceutical Sciences, 2010; 72(5):599-606.
9. Mathur P, Verma N, Floating drug delivery system: An innovative acceptable approach in gastroretentive drug delivery, Scholars Research Library, 2010; 2(2):257-70.
10. Chandel A, Chauhan K, Parashar B, Kumar H and Arora S: Floating drug delivery systems: A better approach. International Current Pharmaceutical Journal 2012; 1(5):110-18.
11. Shah SH, Patel JK, Patel NV, Stomach specific floating drug delivery system: A review, International Journal of Pharmaceutical Technology and Research, 2009; 1(3):623-33.
12. Gopalakrishnan S, Chenthilnathan A, Floating drug delivery system: A review, Journal of Pharmaceutical Science and Technology, 2011; 3(2): 548- 54.
13. Vedha H, Chaudhary J, The recent developments on gastric floating drug delivery system: An overview, Journal of Pharmaceutical Technology and Research, 2010; 2(1):524-34.
14. Arunachalam A, Kishan GK, Floating drug delivery system: A review, International Journal of Research in Pharmaceutical Sciences, 2011; 2(1): 76-78.
15. Sinduri P, Vyshali P, Formulation and In-Vitro Evaluation of Pulsatile Drug Delivery Tablets of Zaltoprofen, International Research Journal of Pharmaceutical and Biosciences, 2017; 4 (2):8-17.