International Journal of Medicine and Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ijmpr

R E S E A R C H A R T I C L E

Formulation and Evaluation of Atenolol floating Drug Delivery Systems

Tharun D*, N. Devanna, Thirumalesh Naik SB, Siva Kumari K, Hindustan Abdul Ahad, Maddileti R

Jawaharlal Nehru Technological University Ananthapur, Oil Technological and Pharmaceutical Research Institute, Ananthapuramu, Andhra Pradesh, India -515001

A B S T R A C T

Gastro retentive drug delivery is apracticeto extend stomach retaining and aiming stomach site for local or systemic effects. Atenolol is a cardio selective β_1 blocker used in the treatment of angina pectoris and hypertension, which has a biological half-life of 6 h with a dose of 50-100 mg daily. It is considered as an ideal drug for designing of gastro retentive floating drug delivery system because of its poor absorption. The use of HPMC, Carbopol 934P, polymer matrices has become extremely popular in controlling the release rate of drugs from solid dosage forms. Effervescent floating tablets of Atenolol was prepared by direct compression method using different hydrophilic polymers and tablets were evaluated for hardness, friability, weight variation, drug content uniformity, swelling index, *in-vitro* floating studies, drug-polymer interaction and *in-vitro* drug release. Based on the experimental results the formulated tablets show non-fickian diffusion and controlled zero order kinetic. Formulation (F-7) showed the better drug release for a period of 12 h dissolution in 0.1N HCl.

Keywords: Atenolol, HPMC, FDDS, Gastro retentive, buoyant.

A R T I C L E I N F O

***Corresponding Author**
Tharun D
Jawaharlal Nehru Technological University Ananthapur,
Oil Technological and Pharmaceutical Research Institute, Ananthapuramu,
Andhra Pradesh, India -515001
MS-ID: IJMPR3613

PAPER QR-CODE

A R T I C L E H I S T O R Y: Received 25 February 2018, **Accepted** 29 March 2018, **Available Online** 10 April 2018

Citation: Tharun D, *et al.* Formulation and Evaluation of Atenolol floating Drug Delivery Systems. *Int. J. Med. Pharm. Res., 2018, 6(1): 72-78.*

C O N T E N T S

1. Introduction

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects[1-3]. Atenolol, an antihypertensive drug was chosen as a model drug because of its poor bioavailability (40-50%) and has elimination half-life of 6-7

h. Its dose is 50-100 mg daily in divided doses. The major site of absorption is stomach. The floating tablets were formulated to increase the gastric residence time and extended the drug release and to improve the bioavailability of drug. Hydrophilic swellable polymers viz., HPMC K100M, Carbopol 934P were used as release retarding material to control the drug release. $NaHCO_3$ (14%) as gas generating agent by tablet weight basis, citric acid (5%)as an acidifier to neutralize the base released from the $NaHCO_3$ on reaction with aqueous medium. MCC as a filler to increase the tablet mass, PVP K30(4%) as binding agent, magnesium stearate & talc as lubricant and glidants respectively [4].The use of HPMC, Carbopol 934 P polymer matrices has become extremely popular in controlling the release rate of drugs from solid dosage forms. These systems are attractive from economic as well as process development view point. In the present study, an attempt was made to prepare effervescent floating tablets of Atenolol by direct compression method using different hydrophilic polymers as matrix material. Direct compression technique is scientifically and economically appealing [5].

2. Materials and Methods

Atenolol was gifted from Micro Labs Pvt. Ltd Bangalore. Carbopol-934P was procured form SD fine-chemicals Ltd, Mumbai. HPMC K100M was obtained from Yarrow chem products, Mumbai, MCC and PVP K30 were from Elegant Drugs Pvt. Ltd, Hubli. Sodium bicarbonate, Citric acid, magnesium stearate, Talc and Hydrochloric acid were obtained from Finar Chemicals Limited, Ahemadabad. Double distilled water was used when ever needed.

Preformulation Studies

Preparation of calibration curve: An accurately weighed quantity of Atenolol (50mg) was dissolved in 50mL 0.1N HCl. From this stock solution, transfer 1mL into 50mL volumetric flask and make up the volume to 50mL with 0.1N HCl to get concentration of 20µg/mL. From the above solution transfer 1mL, 2mL, 3mL, 4mL, 5mL, solution then transferred to 10mL volumetric flask and diluted upto 10mL to get 2, 4, 6, 8 and 10 µg/mL concentrations respectively [6]. The absorbance of these solutions were determined in UV spectrophotometer at 225nm and calibration curve was plotted (table 1 and fig.1).

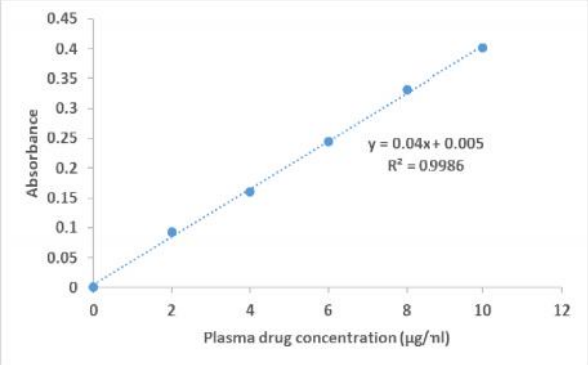

Figure 1: Calibration curve of Atenolol

It can be concluded that linear range for atenolol was observed in 0.1N HCl, while the regression was 0.9986.

Table 1: Absorbance for calibration curve of atenolol

Concentration (µg/mL)	Absorbance
0	0.000±0.00
2	0.093±0.01
4	0.161±0.01
6	0.245±0.02
8	0.331±0.02
10	0.401±0.01

All values mentioned as mean±SD; Number of trials (N)=3

Flow properties:

The prepared blend was evaluated for flow properties[7-9].

Angle of Repose:

It is defined as the maximum angle possible between the surface of the pile of granules or powder and the horizontal plane, which used to quantify the frictional forces that leads to improper flow.

Bulk density:

It includes interparticulate void volume and density of powder which can be determined by passing into 50 mL of graduated cylinder. Unsettled volume of powder was taken to be nearest graduated units. It can be calculated through formula

$$\text{Bulk density} = (\text{Weight of the powder blend}) / (\text{Bulk volume})$$

Tapped density:

The cylinder used for bulk density is concerned for tapped density by specific volume. The changes in the volume were calculated by using the following formula

$$\text{Tapped density} = (\text{Weight of the powder blend}) / (\text{Tapped volume})$$

Compressibility index

Based on the apparent bulk density and the tapped density, the percentage compressibility of the powder mixture was determined by the following formula.

$$C_I = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped Density}} \times 100$$

Hausner's ratio

It indicates flow properties of granules and is measured by the ratio of tapped density to bulk density.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Formulation of Dosage Forms

All the ingredients were weighed accurately and individually passed through sieve no # 60.The components were blended together according to their ascending order of weight in a poly bag for 10min, to ensure homogenous mixing. Magnesium stearate and talc were added to the above blend as flow promoters [10].The floating tablets of atenolol were prepared by different polymer concentrations of 20%, 30% & 40% and the total tablet weight is maintained at 200 mg. Which is prepared by direct compression method by rotary tablet punching machine. The formulations shown in table 2.

Evaluation of Floating Drug Delivery Systems of Atenolol

Post-compression evaluation parameters

After tablet compression the following tests were performed for tablets [11-15].

Tablet hardness

The hardness of each batch of tablet was checked by using Monsanto hardness tester in terms of kg/cm^2. Three tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

Friability

10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

$$\text{friability} = \frac{(w_1 - w_2)}{w_1} \times 100$$

Where: w_1= weight of the tablet before test.

w_2 = weight of the tablet after test

Uniformity of weight

Twenty tablets were selected randomly, weighed individually and average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than the percentage shown in the table and none should deviate by more than twice that percentage.

Content uniformity:

20 tablets were weighed and powdered, 100mg of drug equivalent weight was weighed accurately and dissolved in 100mL of 0.1N HCl. Then transfer 1mL of above solution into 100mL volumetric flask and make up the volume with 0.1N HCl. The absorbance of the diluted solutions was measured at 225nm. The drug concentration was computed from the standard curve of the atenolol in 0.1N HCl.

Swelling studies:

One tablet from each formulation was weighed and kept in Petri dish containing 50 mL of 0.1N HCl solution. At specified time intervals tablets were withdrawn and excess 0.1N HCl was blotted with tissue paper and weighed and % of weight gained was calculated by using following formula.

$$\text{Swelling index (\%)} = \frac{M_t - M_0}{M_0} \text{ X } 100$$

Where, M_t – weight of tablets at time't'; M_0 – weight of tablets at time '0'.

Floating lag time determination and Total floating time:

Each formulated tablets were placed in a 900 mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the floating lag time.

***In-Vitro* dissolution studies**

Tablets were introduced into dissolution test-II apparatus which was set at 50rpm and 5 mL of sample was withdrawn for every hour up to 12 h and analyzed by UV-Visible spectrophotometer at 225nm with 0.1N HCl as blank.

***In-Vitro* drug release kinetics**

The *in vitro* drug release data was subjected to various pharmacokinetic models [16 and17].

Zero order release

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented as

$$Q = Q_0 + K_0 t$$

Where Q is the amount of drug released,Q_0 is the initial amount of drug in solution and K_0 is the zero order release constant

First order release

To study the first order release rate kinetics, the release rate data were fitted into the following equation,

$$\text{LogC} = \text{LogC}_o - kt / 2.303$$

Where C is the amount of drug released at time t, C_o is the initial amount of drug in the solution and K_1 is the first order release constant.

Higuchi Model: A large number of modified release dosage form contain some sort of matrix system. In such instances, the drug dissolves from the matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled) and thus the following relationship applies as formula

$$Q = k_2 t^{1/2}$$

Where Q is the percent of drug release at time t, and k_2 is the diffusion rate constant. In higuchi model, a plot of % drug unreleased (released) versus square root of time is linear

Korsmeyer-Peppas model

$$M_t / M_\infty = Kt^n$$

Where M_t / M_∞ is fraction of drug released at time t, k: is the rate constant and n: is the release exponent. The n value is used to characterize different release mechanisms. Fickian (case I) behavior indicates that the drug partially diffuses through the swollen polymer matrix and partly through the water filled pores and channels in the matrix channel. While non fickian(anomolous) behavior indicates that the drug partially diffuses through the swollen polymer matrix and also partly through the gradually expanding hydrated and eroding matrix with increasing diffusional path.

3. Results and Discussion

Compatibility studies:

FTIR studies: FTIR was acquired with KBr (pellet) method. The sample powder of drugs and excipient mixture of were prepared and placed on glass plate and apply the infra-red beam to record the spectra. The mixture spectra were compared with that of the original spectra. The characteristic peaks of pure atenolol and its blend was shown in table 3. The spectra were shown in fig 2 and 3.

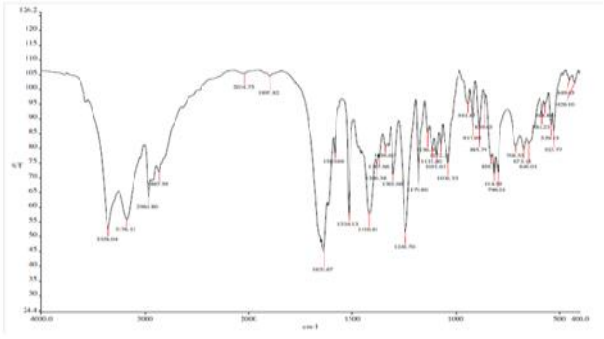

Figure 2: FTIR spectra of pure atenolol

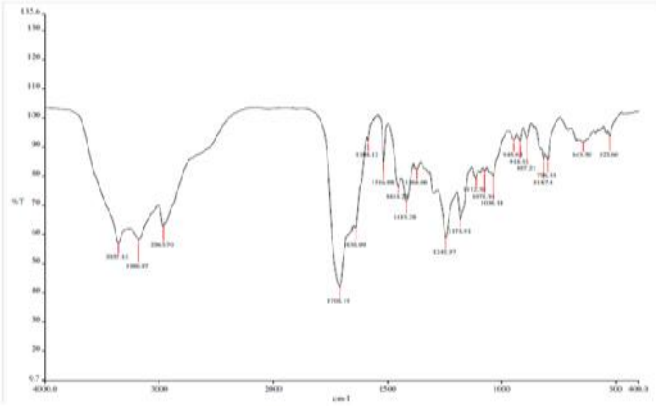

Figure 3: FTIR spectra of formulation blend

The results were represented, the high and low values of angle of repose were 31^0.86' and 27^0.61' for F-6 & F-1 respectively. For all the formulations, the flow of powder blend was good. The high and low values of bulk densities and tapped densities were observed in F-5 &F-10 respectively. The high and low values of compressibility index were observed for F-6 & F-1 respectively. F-1&F-5 shows high and low values of Hausner's ratio.The drug blend shown excellent flow properties. The compressibility index and hasners ratio indicates the good compression properties of the prepared blend. The results of post-compression evaluation parameters were shown in table 4.

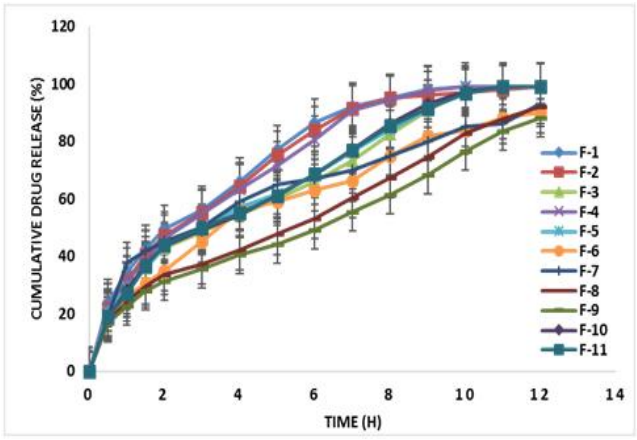

Figure 4: In-Vitro drug release of all formulations

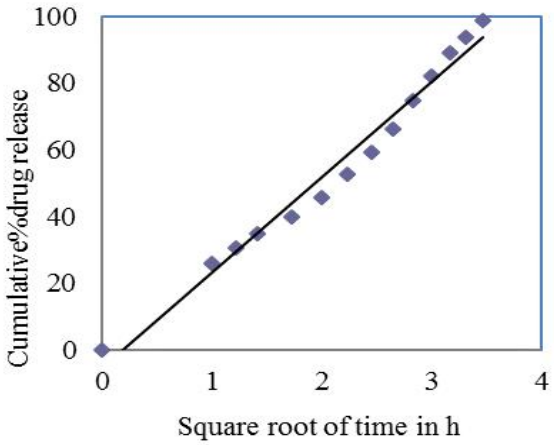

Figure 5: Higuchi plot for F-7

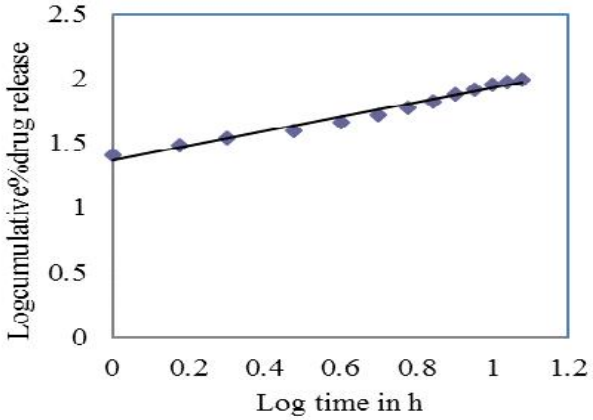

Figure 6: Korsmeyer-peppas plot for F-7

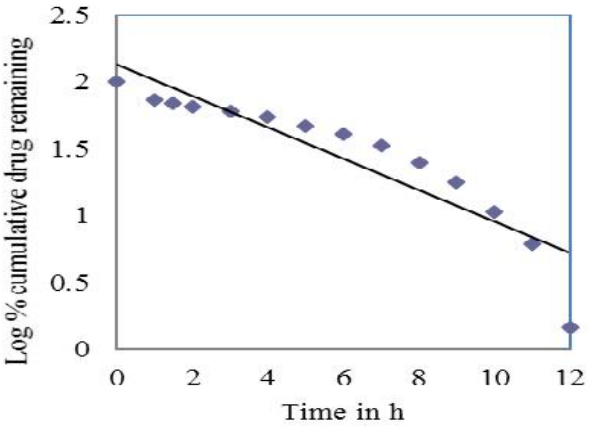

Figure 7: First order plot for F-7

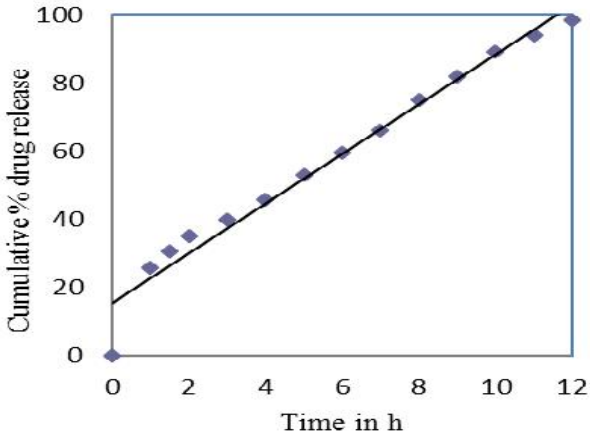

Figure 8: Zero order plot for F-7

All formulated tablets were found to be uniform with respect to hardness (4 to 6.5 kg/cm^2). The friability (0.25 to 0.50%). Weight variation was found within prescribed IP limits (±7.5%). Drug content (95.23 to 101.23%) was found uniform within the batches of different tablets. These values were shown in table 5. On comparing the swelling indices of different floating formulations, it was observed that, the viscosity of the polymer had major influence on swelling process. The prepared tablets shown good swelling properties and these values shown in table 6.

Table 2: Formulation of atenolol floating tablet

Ingredients (mg)	Formulations										
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11
Atenolol	50	50	50	50	50	50	50	50	50	50	50
HPMC K100M	40	60	80	--	--	--	40	26.6	20	53.2	60
Carbopol 934P	--	--	--	40	60	80	40	53.2	60	26.6	20
$NaHCO_3$	28	28	28	28	28	28	28	28	28	28	28
Citric acid	10	10	10	10	10	10	10	10	10	10	10
PVP K30	8	8	8	8	8	8	8	8	8	8	8
Microcrystalline cellulose	58	38	18	58	38	18	18	18	18	18	18
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200	200	200	200

Table 3: Characteristic peaks of pure atenolol and its blend

Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})		Conformation
			Atenolol	Blend	
C=C	Stretching	1500	1516.13	1516.08	Aromatic
C-O	Stretching	1100	1112.40	1112.39	Secondary alcohol
O-H	Bending	1350-1260	1339.62	1368.06	
C-O	Stretching	1270-1200	1242.70	1242.97	Ether
N-H	Stretching	3310-3140	3176.12	3180.87	Secondary amine
N-H	Stretching	3350	3355.50	3357.12	Primary amide

Table 4: Post-compression evaluation parameters

Formulation	Angle of repose (^{0})	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index (%)	Hausners Ratio
F-1	27^0.61'±0.525	0.425±0.002	0.524±0.003	18.89±0.300	1.232±0.005
F-2	29^0.37'±0.287	0.392±0.001	0.479±0.001	18.16±0.173	1.221±0.003
F-3	29^0.82'±0.255	0.442±0.001	0.542±0.001	18.45±0.255	1.225±0.004
F-4	28^0.41'±0.811	0.417±0.001	0.501±0.001	16.76±0.115	1.201±0.002
F-5	29^0.36'±0.510	0.467±0.002	0.562±0.002	16.90±0.242	1.181±0.042
F-6	31^0.86'±0.559	0.459±0.002	0.546±0.001	15.93±0.207	1.189±0.004
F-7	30^0.36'±0.542	0.425±0.002	0.524±0.003	18.89±0.300	1.232±0.005
F-8	30^0.66'±0.271	0.412±0.002	0.496±0.004	16.93±0.372	1.203±0.009
F-9	33^0.05'±1.146	0.426±0.001	0.519±0.003	17.01±0.503	1.205±0.008
F-10	28^0.76'±0.346	0.395±0.028	0.476±0.002	17.34±0.215	1.209±0.006
F-11	30^0.08'±0.686	0.424±0.004	0.513±0.001	17.01±0.611	1.205±0.009
All values mentioned as mean±SD; Number of trials (N)=3					

Table 5: Post-compression evaluation parameters

Formulation	Hardness (Kg/cm)	Friability (%)	Deviation in Weight (%)	Drug content (%)
F-1	4.5±0.32	0.45±0.02	1.22±0.11	98.2±1.65
F-2	5.0±0.52	0.49±0.00	1.17±0.32	99.43±2.35
F-3	5.0±0.33	0.41±0.02	1.37±0.33	98.01±2.21
F-4	5.5±0.23	0.39±0.02	1.41±0.69	101.23±3.25
F-5	5.5±0.44	0.34±0.01	1.44±0.18	98.04±3.84
F-6	6.5±0.18	0.28±0.01	1.38±0.43	95.08±0.93
F-7	5.5±0.25	0.38±0.01	1.22±0.16	100.73±2.34
F-8	5.5±0.14	0.30±0.01	1.23±0.03	99.83±4.27
F-9	6.0±0.35	0.25±0.02	1.33±0.22	95.93±0.91
F-10	5.5±0.23	0.50±0.01	1.22±0.15	95.23±2.25
F-11	5.5±0.06	0.48±0.01	1.27±0.15	96.1±0.57
All values mentioned as mean±SD; Number of trials (N)=3				

Table 6: Swelling indices of all formulations

Formulation	Time (h)	Swelling index (%)
F-1	7±0.8	133.61±0.83
F-2	8±0.2	148.85±0.84
F-3	10±0.1	168.72±0.57
F-4	9±0.3	192.07±0.25
F-5	10±0.4	236.12±0.48
F-6	12±0.2	290.31±0.86
F-7	12±0.8	240.25±0.37
F-8	12±0.8	255.06±0.58
F-9	12±0.5	270.49±0.92
F-10	10±0.6	215.35±0.81
F-11	10±0.5	225.53±0.39

All values mentioned as mean±SD; Number of trials (N)=3

All the formulations were showed the floating lag time and good retain ability on the surface of gastric fluids. These values represented in table 7.All the formulations were showed the floating lag time less than two minutes and their duration of flotation were more than 12 h.

Table 7: Data for floating lag time and total floating time

Formulation	Floating lag time (sec)	Total floating time (h)
F-1	95	>12
F-2	110	>12
F-3	50	>12
F-4	80	>12
F-5	67	>12
F-6	28	>12
F-7	48	>12
F-8	40	>12
F-9	65	>12
F-10	52	>12
F-11	45	>12

All values mentioned as mean±SD; Number of trials (N)=3

The prepared gastro retentive formulations shown good drug release patterns (Fig.4). The release data was further evaluated by plotting various pharmacokinetic plots and the release from the dosage form is by non fickian mechanism (table 8 and fig 5-8).

Table 8: *In-Vitro* drug release kinetic data of all formulations

Formulation	Zero order		First order		Higuchi		Korsmeyer-peppas		Drug release mechanism
	r^2	Slope	r^2	Slope	r^2	Slope	r^2	Diffusion exponent(n)	
F-1	0.933	12.07	0.765	-0.214	0.989	35.834	0.986	0.515	Non-fickian
F-2	0.938	10.86	0.850	-0.187	0.995	34.846	0.995	0.535	Non-fickian
F-3	0.944	8.212	0.804	-0.128	0.985	29.631	0.984	0.508	Non-fickian
F-4	0.930	9.718	0.934	-0.163	0.996	33.484	0.997	0.525	Non-fickian
F-5	0.939	8.249	0.849	-0.128	0.992	29.942	0.991	0.503	Non-fickian
F-6	0.919	5.999	0.990	-0.062	0.999	24.423	0.998	0.485	Non-fickian
F-7	0.970	7.289	0.833	-0.117	0.978	28.586	0.978	0.551	Non-fickian
F-8	0.968	6.694	0.919	-0.079	0.971	26.188	0.968	0.534	Non-fickian
F-9	0.966	6.277	0.921	-0.065	0.964	24.489	0.965	0.532	Non-fickian
F-10	0.943	8.406	0.874	-0.131	0.988	30.382	0.985	0.514	Non-fickian
F-11	0.941	8.326	0.892	-0.123	0.990	30.168	0.986	0.520	Non-fickian

4. Conclusion

The present investigation citric acid and sodium bicarbonate system helps the dosage form to buyout in gastric fluid and the incorporated HPMC and Carbopol 934P are good polymer matrices for controlled drug delivery for prolonged period of time.

5. References

[1] Nayak A, Maji R, Das B. "Gastro retentive drug delivery systems: a review". Asian J Pharm Clin Res 2010; 3(1): 1-10.

[2] Samyuktha RB, Vedha HB, Reddy B, Punitha S. Parimaladevi. "The recent developments on gastric floating Drug delivery systems: an overview". Int J Pharm Tech Res 2010; 2(1): 33-45.

[3] Fell JT. "Targeting of drugs and delivery systems to specific sites in the gastrointestinal tract". J Anat 1996; 189: 517-19.

[4] Arora S, Ali J, Abuja A, Char RK, Baboota S. "Floating drug delivery systems: A Review". AAPS Pharm Sci Tech 2005; 6(3): E372-90.

[5] Tripati KD. Essential Medical Pharmacology. 7th Edition. Jaypee Publishers, New Delhi, India. 2008; 772-775.

[6] Karam MA, Ali M, Mostafa I and Mustafa B, development and validation uv spectrophotometric method for determination of atenolol in pure materials and pharmaceutical dosage, Indo American Journal of Pharmaceutical Research, 2017; 7 (4), 8179-8184.

[7] Indian pharmacopoeia, 5th edition. Published by the Indian pharmacopoeia commission, 2007; 2: 1391-1392.

[8] Lachman, Lieberman HA, and Lachman KJL. The theory and practice of industrial pharmacy, 3rdedition. Lea andfebiger, Philadelphia USA. 1991; 327-29.

[9] Aaaa

[10] Hindustan Abdul Ahad, Sreeramulu J, Preparation and in vitro evaluation of altered density gastro retentive microspheres of Famotidine with synthetic and natural polymers, Der Pharmacia Sinica, 2011; 2 (2): 110-118.

[11] Oth M, Franz M, Timmermans J, Moes A. "The bilayer floating capsule: a stomach-directed drug delivery system misoprostol". Pharm Res 1992; 9: 298-302.

[12] Mazer N, Abisch E, Gfeller JC, Laplanche R, Bauerfeind P, Cucala M, Lukachich M, Blum A. "Intragastric behaviour and absorption kinetics of a normal and floating modified-release capsules of isradipine under fasted and fed conditions". J Pharm Sci 1988; 8: 647-57.

[13] Hindustan AA, Preparation and evaluation of famotidine high density gastro retentive microspheres with synthetic and natural polymers, J. of Pharma. Education and Research, 2011; 2 (1)1, 54-60.

[14] Sangekar S, Vadino WA, Chaudry I, Parr A, Beihn R, Digenis G. "Evaluation of the effect of food and specific gravity of the tablets on gastric retention time". Int. Pharm 1987; 35: 187-91.

[15] Abdul AH, Chitta SK, Kishore KR. Novel approach in Ranitidine Hydrochloride Effervescent Oral Floating Technique, Journal of Pharmacy Research, 2011; 4 (1),104-106.

[16] Higuchi T. Mechanism of sustained action medication. J. Pharm. Sci. 1963; 52, 1145-1149.

[17] Korsmeyer RW, Gunny R, Doelker EM, Buri P and Peppas NA. Int. J. Pharm, 1983; 15:25-35.