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Formulation and characterization of floating tablets for site specific sustained release of metoprolol succinate

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ABSTRACT

The present study was undertaken to formulate a floating matrix for site specific sustained release of Metoprolol Succinate in stomach with the aid of polymers HPMC K4M, Carbopol 934P and natural polysaccharide Xanthine gum as release modifiers. Metoprolol Succinate, β1-selective adrenergic receptor- blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The short half-life of Metoprolol Succinate, need of multiple administrations during therapy and hence, absorption window in the small intestine, warrants the gastric retarded sustained release formulation. Ten formulations of Metoprolol Succinate floating tablets had been done by employing various combinations and concentration of release modifying polymers. The tablets were evaluated for uniformity in weight, hardness, friability, content uniformity, Swelling index and in vitro release study. It was found that the Metoprolol Succinate floating tablets optimized formulation F3 had good floating characters and sustained the release of the drug for about 53.13±1.26% over 12 hrs. The release of drug from the formulations follows zero order, non-fickian mechanism except F3 where it follows supercase II model. The optimized formulation subjected for short term stability studies.

Keywords: Metoprolol Succinate, Floating Tablets, Gastric Retarding, Sustained Release, Hypertension.

INTRODUCTION

For any therapeutic molecule oral delivery of the drugs is the most preferable route due to the ease of administration, patient compliance and flexibility in formulation, etc. Furthermore oral controlled release dosage forms have been widely used to improve the therapy of many important medications having a short half life by reducing the multiple administrations. But many of the therapeutic agents have a narrow therapeutic window in the upper part of intestine for which the absorption of drug from sustained release formulations depends upon the various factors such as gastric emptying, intestinal transit time, drug release from the dosage form and site of absorption of drugs [1]. Hence, the real challenge in the development of an oral sustained drug delivery system is not just to control the drug release, but also to prolong the presence of the dosage form in the stomach or the upper small intestine until all the drug is completely released in the desired period of time [2].

The extent of absorption is determined by the GI transit time (GITT) of the dosage form rather than its Release properties or delivery profile. Generally, the GITT of many dosage forms is relatively short (8–12 h), which in turn impedes the formulation of a once daily dosage form [3]. Many of the approaches such as intra-gastric floating systems [2, 3], mucoadhesive systems [4, 5], swelling and expanding systems [6], high density systems [7, 8], ion exchange resins [9], osmotic regulated systems [10] and low density super porous systems[4] has been done to enhance the residence of a drug delivery system in the upper part of the gastrointestinal tract (GIT). Among them, Floating Drug Delivery Systems (FDDS), also called hydrodynamically balanced system (HBS), is an effective technology to prolong the gastric residence time [11]. This technology is suitable for drugs with an absorption window [12] in the stomach or in the upper part of the small intestine, drugs acting locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid. FDDS have a bulk density lower than the gastric fluid and thus remain buoyant in the stomach, without affecting the gastric emptying rate for a prolonged period of time.

Metoprolol succinate [MS] ((+)-1-(isopropyl amino)-3-[p-(2-methoxyethyl)]-2-propanol succinate) is a β_1- selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. Hence the drug has relatively short half-life about 4-6hrs, in the normal course of therapy multiple administration is required every 4-6hrs, thus justifies the use of sustained release formulation for prolonged action and to improve patient compliance. [13]

MATERIALS AND METHODS

Materials:

Metoprolol Succinate [MS] gift sample was provided by ipca labs, Mumbai. HPMC K4M, Xanthan Gum, Carbopol 934 P, Sodium Bicarbonate, Sodium Carboxy Methyl Cellulose, Aspartam, Magnesium Stearate were purchased form commercial supplier. All the materials had been used without any further modification.

Methods:

Preparation of MS Floating Tablet:

Different compositions of floating tablets of MS with different composition of polymers as shown in Table-1 were prepared by the direct compression method. All ingredients were weighed, Sieved through #60 and mixed with mortar to get homogeneous Blend. Magnesium stearate which previously sieved through #100 was added as a lubricant and the tablets have been compressed on a tablet machine (Rimack, 10 Station) using 10 mm flat beveled edge punches.

Tabe-1: Formulation of MS Floating Tablets

NAME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Metoprolol Succinate	100	100	100	100	100	100	100	100	100	100
Xanthan Gum	25	25	50	50	25	25	50	50	-	-
Carbopol 934 P	-	-	-	-	160	100	160	100	60	120
HPMC K4M	160	100	160	100	-	-	-	-	120	60
Sodium bicarbonate	50	50	50	50	50	50	50	50	50	50
Sodium Carboxy Methyl Cellulose	60	120	35	95	60	120	35	95	65	65
Aspartam	20	20	20	20	20	20	20	20	20	20
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5
Total	420	420	420	420	420	420	420	420	420	420

All the ingredients are incorporated in weights (mg)

Characterization of granules

The characteristic parameters of the granules were evaluated. The angle of repose and flow rate were determined by the Fixed funnel method. The bulk density and tapped density were determined by the cylinder method. Compressibility Index and Hausner's ratio were calculated to evaluate the micromeritics of the powder.

Evaluation of MS floating tablets

Drug Content Uniformity (Assay)

Three tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 100 mg was transferred to a 100 ml volumetric flask containing 100 ml of methanol. It was shaken by mechanical means for 15min. Then it was filtered through a # 45µm filter paper and diluted to 10 ml with simulated intestinal fluid without enzymes and absorbance was measured against blank at 222 nm.

Swelling characteristics
The swelling properties of polymer matrix containing the drug were determined by placing the tablet in the dissolution test apparatus, in 900 ml 0.1 mol/l HCL at $37^{o}\pm0.5^{o}C$. The tablets were withdrawn periodically, the excess free water was removed and the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU%) according to the equation [14].

$$WU\,\% = \frac{w_t - w_0}{w_0} \times 100$$

Where,
Wt = weight of the dosage form at time t.
W_0 = initial weight of dosage form

Measurement of tablet density
To check the floating behavior of tablets the apparent densities of the tablets was calculated from their mass and volume. The volume of the tablets were calculated from their heights 'h' and radii 'r' (both determined by using a micrometer gauge by using the mathematical equation for a cylinder {$V= \pi r^2 h$}.

Buoyancy Study
The In vitro floating behavior of tablet was studied by placing the tablet in 500 ml container filled with 300 ml Simulated Gastric Fluid (SGF) without enzymes (pH=1.2) as a medium and the time taken by tablet to float on the surface was recorded as floating lag time (FLT) and the total duration of time in which the tablet was floated in the dissolution medium was the total floating time (TFT) and were determined by visual observation.

***In - vitro* drug release study**
Release study of floating tablets was carried out in 900 ml of 0.1N HCl buffer of pH=1.2 dissolution medium using USP apparatus II at 37°C with paddle speed at 75 rpm. The floating tablets of metoprolol succinate were weighed and dropped into the dissolution medium. During the dissolution study, every time 5 ml of aliquots of dissolution medium was withdrawn and replaced with 5 ml of fresh medium kept at 37°C. These samples were filtered and the required dilutions were made with the 0.1N HCl solution of pH1.2 and then analysed at 222.0 nm using UV-visible spectrophotometer.

Drug Release modeling
The release mechanisms described by several linear and non - linear kinetic models as follows:

Zero order kinetics [15, 16]
Drug dissolution of pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

$$W_0 - W_t = K_0 t$$

Where, W_0 is the initial amount of drug in the pharmaceutical dosage form, Wt is the amount of drug in the pharmaceutical dosage form at time t, and k is a proportionality constant.

Dividing this equation by W_0 and simplifying:

$$f_t = k_0 t$$

Where, $f_t = 1 - (W_t / W_0)$ and ft represents the fraction of drug dissolved in time t and K_0 the apparent dissolution rate constant or zero order release constant

First order kinetics [15, 16]
This type of model to analyse drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model:

$$\text{Log } Q_t = \text{Log } Q_0 + K_1\, t/2.303$$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release rate constant.

Higuchi Model [15, 16]

$$Q_t = K_H t^{1/2}$$

Where, Q_t = the amount of drug released at time t and K_H = the Higuchi release rate; this is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square root of time versus the concentration indicates that the drug release follows strict Fickian diffusion

Korsmeyer Peppas model [15, 16]
Korsmeyer developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$Q_t/Q_\alpha = K_K t^n$$

Where, K_K is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanisms shown in Table-2. The Release exponent can be obtained from the slope and the Constant (K) obtained from the intercept of the graph between logarithmic versions of left side of the equation versus log t

Table- 2: Various drug transport mechanisms

Release exponents(n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian dissusion	$t^{0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

Stability studies
Short-term stability studies were performed at a temperature of 45±1^{0}C/75±5%RH over a period of three months (Sameeksha Pvt.Ltd,) on the promising HBS tablet formulation (F3). The samples were analysed at periodical intervals for any qualitative and quantitative changes. At the end of three months, in vitro floating studies and in vitro release study were performed. The similarity factor (f_2) was calculated to assess the acceptance of the stability of dosage form against storage condition.[16].

$$F_2 = 50.\ \mathrm{Log}\ \{[1+ (1/n) \textstyle\sum_{t=1}^{n} (R_t-T_t)^2]^{-0.5}.100\}$$

Where, f_2 is a similarity factor between two dissolution profile, n= number of time points, R_t and T_t are drug release of reference and test at time t.

Table-3: Pre compression and Post compression Evaluation results of MS Floating Tablet

Code	Angle of repose (θ)*	Bulk density (g/cc)*	Tap density (g/cc)*	Caar's index	Hausner's ratio	Weight variation (%) **	Friability (%) **	Hardness (kg/cm^2)*	Content uniformity* (%)
F1	27.5±0.31	0.42±0.05	0.45±0.03	11.9	1.13	418.65±2.29	0.46±0.12	5.5±0.47	99±0.56
F2	27.8±0.15	0.39±0.04	0.43±0.05	11.6.	1.13	421.50±1.73	0.52±0.06	6.0±0.32	98.01±0.41
F3	28.1±0.11	0.38±0.06	0.43±0.08	13.1	1.15	419.55±1.18	0.41±0.11	6.0±0.54	98.05±0.72
F4	27.9±0.13	0.39±0.03	0.44±0.04	12.3	1.14	419.65±1.49	0.36±0.09	5.5±0.42	97.19±0.35
F5	27.2±0.41	0.37±0.02	0.41±0.02	11.9	1.13	420.55±1.18	0.69±0.08	5.8±0.35	98.08±0.19
F6	28.5±0.34	0.36±0.01	0.40±0.04	13.05	1.15	421.62±1.29	0.49±0.02	5.9±0.38	99.05±0.56
F7	27.8±0.28	0.36±0.08	0.42±0.06	13 .08	1.16	420.99±1.85	0.55±0.11	6.0±0.34	98.25±0.78
F8	28.2±0.32	0.35±0.05	0.40±0.04	10.3	1.11	419.76±1.06	0.46±0.14	5.6±0.62	97.95±0.85
F9	27.4±0.18	0.39±0.06	0.42±0.04	10.37	1.11	421.78±2.18	0.62±0.08	6.1±0.39	98.48±1.19
F10	27.5±0.27	0.37±0.04	0.41±0.06	12.4	1.14	418.12±1.92	0.49±0.10	6.0±0.35	99.55±0.96

**All the value represents mean values with ± Standa rd Deviation, n=3.*
***All the value represents mean values with ± Stand ard Deviation, n=10.*

RESULTS AND DISCUSSION

Pre compression Evaluation

Before the tablets compressed the powder blend of all the formulations were evaluated for various physical characteristics like Angle of repose, Bulk Density, Tapped Density, Compressibility index and Housner's ratio to verify its fitness for tablet preparation (Table-3). The result of Angle of repose for the powder blend varied from 27.2±0.41 to 28.5±0.34 which indicates the powder blends have good flow property. The bulk density values varies from 0.36 to 0.42 g/cc and the tapped density values ranging from 0.40 to 0.45 g/cc which influenced by the availability of various polymers in the formulations. The powder blend has the compressibility index between 10.3 to 13.1 and the Hausner's ratio 1.11 to 1.15 confirmed about the compaction behavior. Overall, the prepared powder blend has good flow ability and compression behavior.

Evaluation of MS Tablet

The physical evaluation for the MS tablet has been done and the results were displayed in table-3. The average weight of the tablets varied from 418.12±1.92 to 421.78±2.18 mg and no tablet is out the range of ± 5% of the tablet weight. The friability results of the formulations were ≤ 0.69±0.08 % W/W of the tablet weight which passed the official limits. The tablets have the minimum hardness of 5.5±0.47 kg/cm^2 and a maximum of 6.1±0.39 kg/cm^2. The assay value of the tablets was varied from 97.19±0.35 to 99.55±0.96 % W/W which falls within the range of official limits. Overall, the physical characteristics of the MS tablets were satisfied the specifications required.

Swelling Characteristics

The results of the swelling nature of the MS floating tablets were shown in Fig.1, by plotting Time (hrs) Vs % Water uptake. The rate of swelling were varied among the tablets which, influenced by the type and quantity of hydrophilic polymers incorporated in the formulations. The swelling results indicate that the hydrophilic polymers added in the tablet formulations tend to absorb the water rapidly until to its maximum limit that forced faster increase in the tablet weight. Over some period the weight of the tablets remains unchanged because of no further absorption of water occurred. Later, the weight of the tablets gradually reduced probably due to the erosion of the swollen matrix.

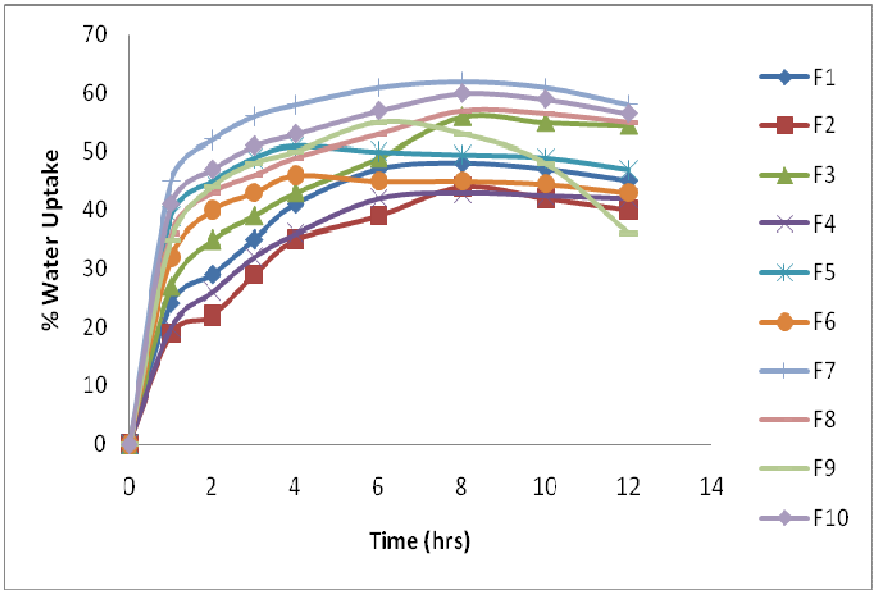

Fig.1: Plot of Swelling Index of MS Floating Tablets

Tablet Density and Buoyancy Study

Tablet density is an important parameter for the floating of the matrix on the aqueous fluid. The floating studies were performed by using specified medium and the table-3. Hence the initial density of the tablet exceeds SGF density it sinks when placed in the fixed volume of medium. Later the tablets start to float on the medium because of the change in tablet density, which driven by the swelling of tablets by absorbing the water from the medium. Further the sodium bicarbonate liberates the gas will accelerate the buoyancy of the tablet. All the tablet formula

shows Acceptable FLT among them F10 showed least FLT values about 45 Sec, the highest TFT was observed as >24 hrs for the formulationsF1,F3, F5, F6, F7 and F8. Contrastingly F9 showed least TFT values as around 10 hrs may be the reason that absences of Xanthine gum which retards the erosion.

Table-3: Results of Tablet Density and Buoyancy Studies

Batch	Tablet Density (gm/cc)	Buoyancy Lag Time (Sec.)	Total Floating Time (Hrs)
F1	1.183	68	>24
F2	1.194	74	>18
F3	1.180	62	>24
F4	1.202	69	> 12
F5	1.191	60	>24
F6	1.186	67	>24
F7	1.196	42	>24
F8	1.186	58	>24
F9	1.180	61	>10
F10	1.183	45	>18

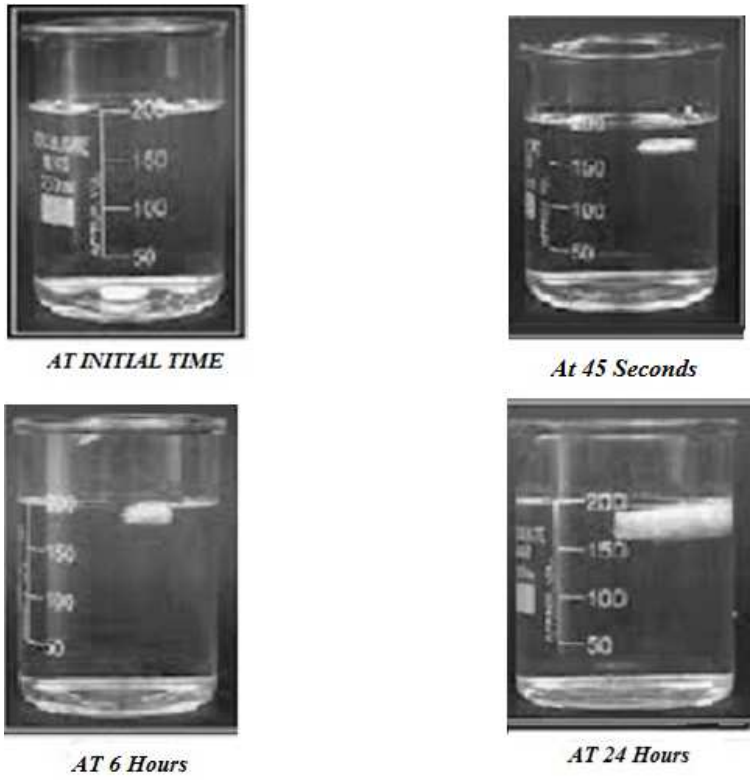

Fig.2: *in vitro* Buoyancy Study of MS Floating Tablet

Invitro release studies

The results of in vitro dissolution studies of the MS floating tablets were performed as prescribed and the results were shown in Fig.3. The rate of release of the drug from the floating matrix is proportionate to the quantity of rate controlling polymers availed in the formulations. All the formulations released the drug in its individual rate gradually with respect the time. Among all formulations, the drug release was sustained in F3 which contains the highest composition of Xanthine gum and HPMC K4M. The other formulations contained a reduced quantity of the HPMC K4M and Xanthine gum had a faster drug release than F10. Also the formulation F7 contains the maximum quantity of Xanthine gum and Carbopol released the sustained rate but faster than of F10. These results elucidate that though the quantity of Xanthine gum had the significant role in release rate of drug and HPMC K4M dominates

the drug release sustaining than carbopol. The desired rate of release may be obtained by varying the composition of rate controlling plymers in the formulation.

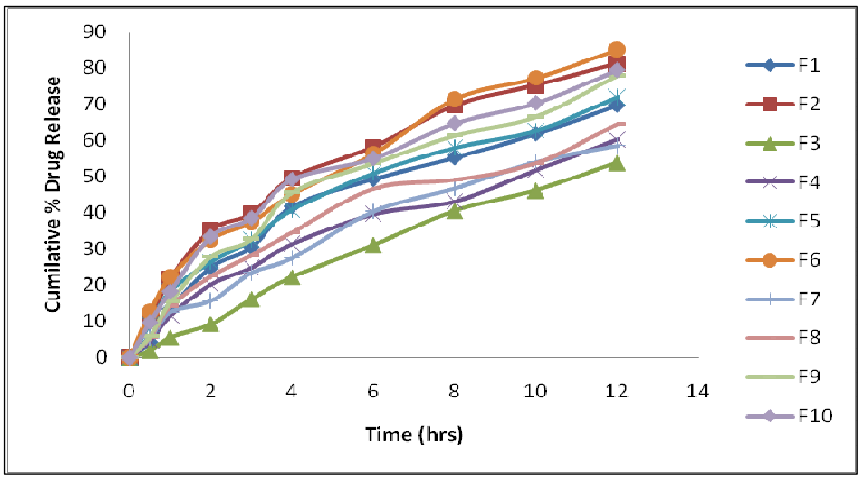

Fig.3: Results of In vitro Dissolution study of MS Floating Tablets

Table-4: Release kinetics parameter for Metoprolol Succinate Floating Tablets

Formulation	Parameter	First Order	Zero order	Higuchis Plot	Korsmeyers-Peppas
	r^2	0.849	0.926	0.983	0.942
F1	**k**	-	-	-	1.046
	n	-	-	-	0.808
	r^2	0.849	0.911	0.992	0.971
F2	**k**	-	-	-	1.294
	n	-	-	-	0.609
	r^2	0.775	0.99	0.95	0.986
F3	**k**	-	-	-	0.668
	n	-	-	-	1.037
	r^2	0.733	0.954	0.985	0.969
F4	**k**	-	-	-	1.001
	n	-	-	-	0.75
	r^2	0.778	0.933	0.994	0.985
F5	**k**	-	-	-	1.214
	n	-	-	-	0.613
	r^2	0.826	0.947	0.993	0.993
F6	**k**	-	-	-	1.31
	n	-	-	-	0.582
	r^2	0.803	0.967	0.979	0.983
F7	**k**	-	-	-	1.008
	n	-	-	-	0.731
	r^2	0.722	0.932	0.985	0.964
F8	**k**	-	-	-	1.08
	n	-	-	-	0.708
	r^2	0.703	0.932	0.984	0.959
F9	**k**	-	-	-	1.129
	n	-	-	-	0.755
	r^2	0.731	0.911	0.989	0.973
F10	**k**	-	-	-	1.256
	n	-	-	-	0.629

Release Mechanism

In order to understand the release mechanism of drug release from the floating matrix, the in vitro release data of formulations were fitted to various release models and the results of slope and regression coefficient (**R^2**) were shown in the table. The results illustrate that the drug release from the formulations best fitted to zero order kinetics. The regression values of Higuchi's plot suggest that the formulations release the drug as like diffusion controlled release mechanism. The n-value of kosmeyers-Peppas plot confers that all the formulations non-fickian release except F3 which follows supercase II type release.

Stability Study

The stability studies were carried out on the formulation F3. The formulations were stored at 40 ± 2°C/75 ± 5% RH for 3 months to assess their long term stability. The protocol of the stability studies conformed to WHO guidelines for stability testing of protocols intended for the global market. After an interval of 7, 15, 30, 60 and 90 days, samples were withdrawn and retested for hardness, drug content, buoyancy lag-time and Total Floating time (Table-5). The comparative in vitro dissolution profiles of the formulation F3 at 0 day and after 90days were shown in Fig.4. The similarity factor f_2 value was found as 89.71 which indicated that, the floating matrix doesn't have change in release profile during the test period, concluded the formulations remained stable throughout the test period.

Table-5: Results of Stability Studies

Days	Hardness (kg/cm2)	Assay (%)	BLT (Sec)	TFT (hrs)
0	6	98.05	62	>24
7	5.9	98.02	62	>24
15	5.9	97.98	64	>24
21	5.9	97.98	64	>24
30	5.8	97.95	65	>24
60	5.8	97.91	66	>24
90	5.7	97.9	67	>24

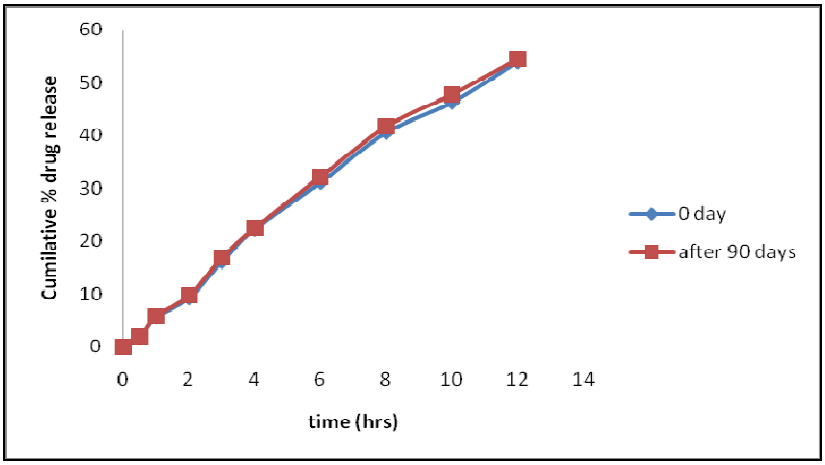

Fig.4: Comparative Dissolution profile of F3 before and after Stability study

CONCLUSION

MS Floating tablets were prepared by direct compression method using different Polymers HPMC K4M and Carbopol 934 in combination with Xanthane Gum by direct compression technique. All the formulations had satisfactory pre compression and post compression results. Optimized formulation F3 had good floating characters and release the drug sustained over 12 hrs. The release of drug from the formulations follows zero order, non-fickian mechanism except F3 where it follows supercase II model. Short term stability studies results confirmed that the formulation was stable under storage condition.

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