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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF COMBINED FLOATING-MUCOADESIVE TABLET OF METOPROLOL SUCCINATE

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ABSTRACT

A new drug delivery system for a water-soluble beta-blocker drug, Metoprolol Succinate, was developed utilizing both the concepts of adhesiveness and of flotation, in order to obtain a unique drug delivery system which could remain in the stomach for a much longer period of time. Floating-Mucoadesive tablets of Metoprolol Succinate were developed to prolong its release and improve bioavailability by avoidance of first pass metabolism during the treatment of chronic hypertension. Tablets were prepared by direct compression using directly compressible polymers such as HPMC K4M, HPMC K15M, Sodium CMC and Carbopol 940P and were evaluated for buoyancy test, mucoadhesion force, swelling study, drug content, *Ex vivo* mucoadhesion strength and *in-vitro* release profile. Sodium bicarbonate was used for producing effervescent base for buoyancy of tablets. Result indicated that release of Formulations best fitted square root kinetics. The swelling properties were increased with increasing polymer concentration and contributed to the drug release from the tablet matrix. No significant change was observed in physical appearance, drug content, floatability or *in vitro* dissolution pattern after storage at 45 °C / 75% RH for three months.

Keywords: Metoprolol Succinate, Floating–Mucoadesive, *Ex vivo* mucoadhesion strength

INTRODUCTION

Many orally-administered drugs display poor bioavailability when administered as conventional dosage form, i.e. the rate and extent to which the drugs are absorbed is less than desirable. With several drugs, absorption may be as little as 30% or less of the orally administered dose. To compensate for this effect, a very large dose is often administered so that absorption of the therapeutically required quantity of the drug can occur.

This technique may prove costly with expensive drugs; and the unabsorbed drug may also have undesirable side effect within the gastrointestinal tract. In addition, poorly absorbed drug often display large inter and intra subject variability in bioavailability. This problem may be overcome by modified release drug delivery system with prolonged residence time in the stomach[1]. Metoprolol Succinate (MS) is a β1-selective adrenergic blocking agent.[2]When MS conventional tablets are administered with food rather than on an empty stomach, peak plasma concentrations are higher and the extent of absorption of the drug is increased.

The maintenance of a constant plasma level of a cardiovascular drug is important in ensuring the desired therapeutic response. Since the half-life of MS is ~3 to 4 hours[3] ,multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance. It has also been reported that MT absorption in the duodenum and jejunum is directly proportional to the dose availability.[4]In this study, an effervescent floating system and a bio adhesion system were used in combination. Floating dosage forms are meant to remain floating on the gastric fluid when the stomach is full after a meal. However, as the stomach empties and the tablet reaches the pylorus, the buoyancy of the dosage form may be reduced. It may be that the dosage form will then pass through the pylorus into the small intestine. Thus, the buoyancy of an FDDS in the stomach may be limited to only 3–4 h. Furthermore, floating systems do not always release the drug at the intended site. In a bioadhesive drug delivery system, it is quite likely that the system becomes dislodged from the stomach mucosa wall when the system is full and the semi-liquid contents are churning around due to the effect of peristalsis [5]. A floating-Mucoadesive system would overcome these drawbacks of floating and Mucoadesive systems and would have a significant effect on improving the therapeutic effect of the drug involved[6].The present study involves the formulation and in vitro evaluation of Metoprolol Succinate floating- Mucoadesive tablet for prolonged residence in stomach for the treatment of Hypertension.

MATERIALS AND METHODS

Metoprolol Succinate was supplied as a gift sample from IPCA Lab Ltd., Ratlam. Carbopol 940P and Sodium CMCwere brought from S.D. Fine-Chem. Ltd., Mumbai, hydroxyl propyl methyl cellulose K4 andK15 obtained from Loba-Chem. Pvt. Ltd., Mumbai. Sodium bicarbonate was supplied from Titan Biotech Limited, Rajasthan.

Preparation of floating-mucoadhesive tablets

All the floating-Mucoadesive tablets were fabricated by using direct compression technique.MS, HPMC K4M, HPMC K15M,SCMC, Carbopol 940P and MCC were blended homogeneously in mortar (Table 1). Blended mixture was passed through Sieve 60, finally Sodium bicarbonate and magnesium stearate was added and blended. The homogeneously blended mixture was compressed in rotary tablet press with the 8 mm concaves punch. The tablet hardness was in the range 5-6 kg/cm^2 tested on Monsanto tablet hardness tester.

Characterization of pre compressed powder blend

The characteristic parameters of the powders were evaluated. (Table No.2) The angle of repose was determined by the funnel method. The bulk density and tapped density were determined by the cylinder method and Carr's index was calculated using the following equation.

$$\text{Carr's index} = Df - D0/Df \times 100$$

Where, Df= Poured bulk or bulk density, $D0$ = Tapped or consolidated bulk density

Evaluation of tablet

Density measurement of tablet

Density of tablets was calculated from their volumes and masses in triplicate. The volume V of the cylindrical tablets were calculated from their height h and radius r (both determined with a verniar caliper) using the mathematical equation for a cylinder ($V = \pi \times r\ 2 \times h$). The tablets with ~1 g/cm3 density or less were chosen for further studies[7].

Determination of floating capacity

Three individual tablets from each formulation were put in an individual flask containing 900ml of 0.1N Hcl solutions. Then note time in minutes for each tablets to go from the bottom to the top of

the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) were measured. The sample mean and standard deviation were calculated[8].

Swelling characteristics

The swelling properties of matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml 0.1N Hcl at 37 ± 0.5°C. The tablets were removed periodically from the dissolution medium and, after removing free water, the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU %) according to the equation[9].

$$WU\% = \frac{\text{Weight of the swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

Drug content and physical evaluation

The drug content of the tablets was determined using 0.1N Hcl as a solvent, and the samples were analyzed spectrophotometrically (Shimadzu, SPD-10AVP, Kyoto, Japan).at 224nm. Tablets were also examined with regard to their weight variation (n = 10), friability (n = 10) and hardness (n = 3)[10].

***In vitro* mucoadhesion study**

The Mucoadesive forces of the bilayer tablets were determined by the measuring device shown in Fig. 1. Pieces of sheep funds tissue were stored frozen in saline solution and thawed to room temperature immediately before use. At the time of testing a section of tissue (E) was transferred, keeping the mucosal side out, to the upper glass vial (C) using a rubber band and an aluminum cap. The diameter of each exposed mucosal membrane was 1.1 cm. The vials with the funds tissue were stored at 37°C for 10 min. Next, one vial with a section of tissue (E) was connected to the balance (A) and the other vial was fixed on a height-adjustable pan (F). A bilayer tablet (D) was applied to the lower vial with the help of two pieces of adhesive tape. The height of the vial was adjusted so that the tablet could adhere to the mucosal tissues in the vial. A constant weight (10 g) was placed on the upper vial and applied for 2 min, after which it was removed and the upper vial was then connected to the balance. Weights (B) were added at a constant rate to the pan on the other side of the modified balance of the device until the two vials were separated. The bioadhesive force, expressed as the detachment stress in dyne/cm2, was determined from the minimum weight required to detach the two vials using the following equation[11].

Mucoadesive force (dyne/cm2) = $m \cdot g / A$

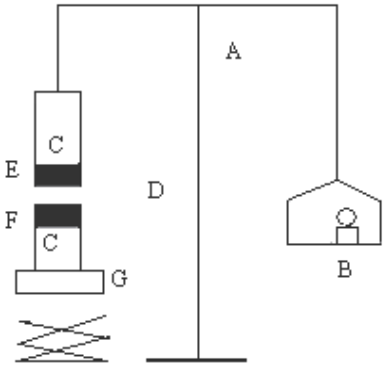

Fig. 1: Mucoadesive force measuring device

A, modified balance; B, weights; C, glass vial; D, Bioadhesive bilayer tablet; E, Intestine tissue; F, supportive adhesive tape; G, height adjustable pan[24]

***Ex vivo*Mucoadesive time**

A modified balance method was used for determining the *ex vivo*Mucoadesive strength[12] ·Fresh sheep mucosa was obtained from a local slaughter house and used within 2 hours of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. The sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with 0.1N Hcl, at 37°C± 1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive. The two sides of the balance were made equal before the study, by keeping a 5-g weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This Mucoadesive strength gave the Mucoadesive strength of the bioadhesive tablet in grams.

***In vitro* dissolution studies**

The release rate of Metoprolol Succinate from floating-Mucoadesive tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml 0.1N Hcl, at 37 ± 0.5°C and 50 r/min. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman filter paper and the absorbance of these solutions was measured at 224 nm.

Data analysis

To analyse the mechanism of release and release rate kinetics of the dosage form, the data obtained were evaluated according the relationship proposed by Korsemeyer et al., as in following equation[13]

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

Stability studies

The stability studies were carried out according to ICH and WHO guidelines [14] to assess the drug and formulation stability. Optimized B5 formulations were sealed in aluminum packaging having a polyethylene coating on the inside. Samples were kept in a humidity chamber maintained at 45°C and 75% RH for 3 months. At the end of the study period, samples were analyzed for buoyancy lag-time, *Ex vivo* mucoadhesion time, and Mucoadesive force and drug release characteristics.

RESULTS AND DISCUSSION

Floating-Mucoadesive tablets of Metoprolol Succinatewere mainly prepared by using different polymer like HPMC-K4M, HPMC-K15M, SCMC and Cabopol-940P either alone or in combination (Table 1). Effervescent base of tablets were prepared by using sodium bicarbonate. The tablets were fabricated using direct compression technique. The preblended powders of the sustained release layer were characterized with respect to the angle of repose, bulk density, tap density and Carr's index (Table 2).

The angle of repose for all the batches of powders indicating satisfactory flow behavior. Table 2 shows that, as the concentration of polymer increases, the angle of repose and Carr's index increases. The formulated tablets were subjected for various evaluation parameters like hardness, thickness, density, weight variation, drug content, floating capability, Mucoadesive force, ex-vivo mucoadhesion time and dissolution study. Our experimental results (Table 3) revealed that all the formulated tablets were of good quality with regard to hardness (5- 6 kg/cm2), density (~ 1 g/cm3), drug content (> 90%) and floating lag time (4-6 min). in vitro mucoadhesion study reveals that as the conc. of Carbopol 940P decreased the Mucoadesive strength decreased in combination with HPMC-K4M, HPMC-K15M and SCMC respectively (Fig 2).

Table 1: Formulation of floating-mucoadesive tablet of Metoprolol succinate

Formulation batches	Metoprolol succinate (mg)	Carbopol 940P (mg)	HPMC K-4M (mg)	HPMC K-15M (mg)	SCMC (mg)	MCC (mg)	$NaHCo_3$ (mg)	Talc (mg)
F1	50	10	-	-	-	105	30	5
F2	50	-	35	-	-	80	30	5
F3	50	-	-	35	-	80	30	5
F4	50	-	-	-	35	80	30	5
F5	50	7.5	27.5	-	-	80	30	5
F6	50	5	30	-	-	80	30	5
F7	50	2.5	32.5	-	-	80	30	5
F8	50	7.5	-	27.5	-	80	30	5
F9	50	5	-	30	-	80	30	5
F10	50	2.5	-	32.5	-	80	30	5
F11	50	7.5	-	-	27.5	80	30	5
F12	50	5	-	-	30	80	30	5
F13	50	2.5	-	-	32.5	80	30	5

SCMC-Sodium Carboxy Methyl Cellulose ; MCC-Micro Crystalline Cellulose

Table 2: Characterization of pre compressed powder blend*

Formulation batches	Angle of repose(^{0})	Bulk density (gm/ml)	Tap density (gm/ml)	Carr's index
F1	18.6±1.3	0.613	0.792	22.6±2.0
F2	18.2±2.6	0.622	0.795	21.7±3.2
F3	18.8±1.5	0.598	0.773	22.6±2.8
F4	20.4±1.7	0.625	0.833	24.2±1.6
F5	23±3.2	0.638	0.909	31.2±1.2
F6	19.4±3.3	0.594	0.769	23.5±1.6
F7	16.7±1.4	0.612	0.763	19.7±2.3
F8	16.3±1.3	0.605	0.752	19.5±3.1
F9	11.2±1.1	0.622	0.713	12.7±2.1
F10	14.1±1.2	0.587	0.699	16.3±2.2
F11	13.3±2.1	0.598	0.705	15.1±1.4
F12	18.6±1.7	0.613	0.794	22.7±2.1
F13	17.1±1.2	0.631	0.796	20.7±3.2

*Each sample was analyzed in triplicate (n = 3).

Table 3: Evaluation of floating-mucoadesive tablet of Metoprolol succinate*

Formulation batches	Hardness (kg/cm^2)	% Drug content	Buoyancy lag time (min)	Ex-Vivo Mucoadesive time (hours)
F1	6.2± 0.2	99.4±0.5	5.2±0.7	10±0.3
F2	5.3±0.3	100.05±0.7	4.7±0.9	10.3±0.1
F3	5.5±0.2	100.12±0.8	4.9±1.2	8.1±0.7
F4	5.4±0.2	98.8±0.4	5.2±1.7	9.7±0.6
F5	5.8±0.3	98.97±0.5	5.1±1.6	10.3±0.4
F6	5.3±0.4	99.98±0.4	4.7±0.8	10.7±0.3
F7	5.4±0.5	100.42±0.5	5.0±1.6	10.8±0.5
F8	5.1±0.2	102.45±0.3	5.7±0.9	9.2±0.6
F9	5.8±0.2	100.69±0.4	5.2±0.9	9.8±0.8
F10	5.6±0.3	98.35±0.5	5.3±1.2	10.1±0.4
F11	5.7±0.4	99.23±0.4	5.7±1.7	11.2±0.9
F12	5.2±0.5	103.42±0.5	5.9±1.6	11.5±0.5
F13	5.4±0.2	98.99±0.3	5.4±0.8	11.7±0.3

*Each sample was analyzed in triplicate (n = 3)

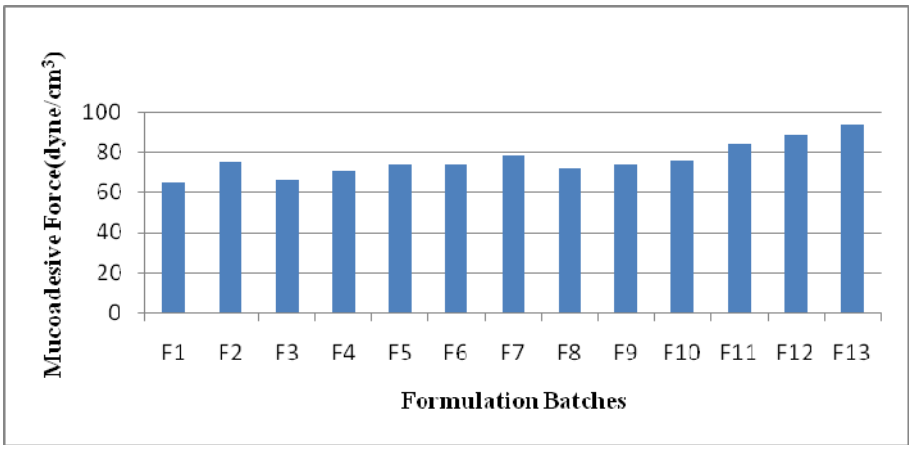

Fig. 2: Mucoadhesion study of floating-mucoadesive tablet of Metoprolol succinate

Swelling index was calculated with respect to time. Maximum swelling was seen with the batches F5, F8, F11 containing Carbopol 940P (7.5%) in combination with 27.5% HPMC-K4M, HPMC-K15M and SCMC respectively (Fig .3). *Invitro* drug release showed (Fig.4, 5, 6 and 7) that the release increased with decrease conc. of Carbopol 940P.

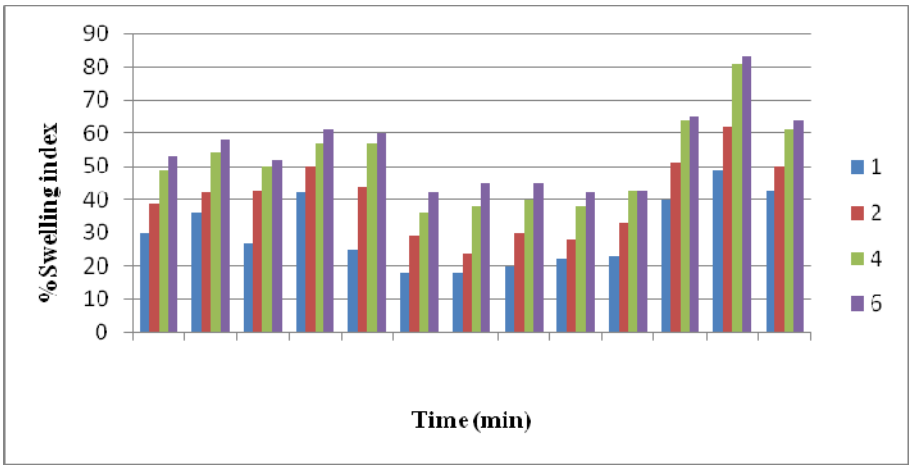

Fig. 3: Swelling study of all formulations

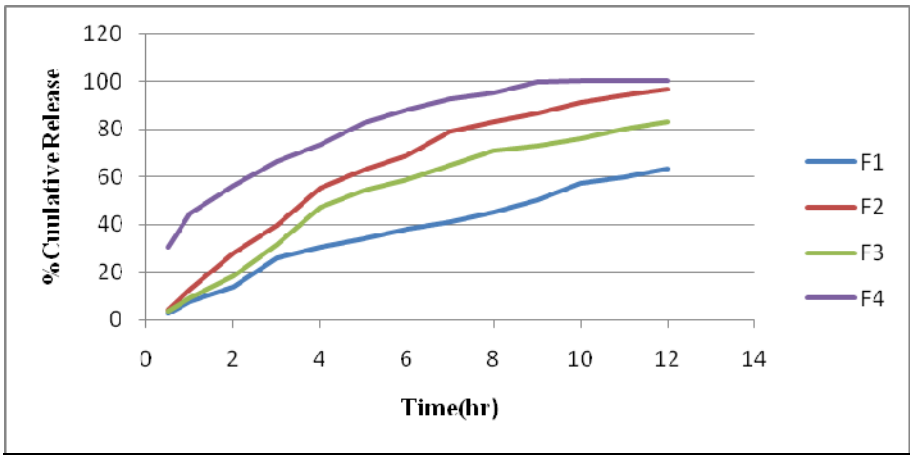

Fig. 4: % Cumulative release of Metoprolol succinate floating-mucoadesive tablets comprising of carbopol 940P, HPMC K4M, HPMC K15M, sodium CMC

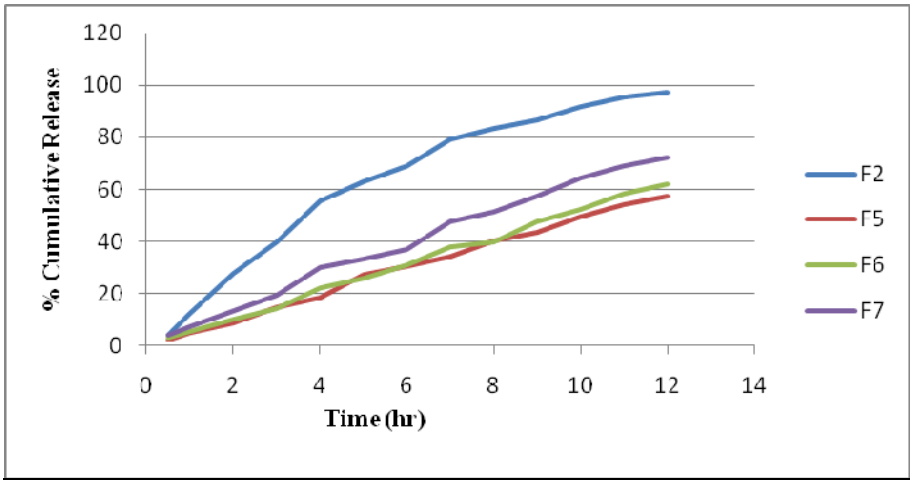

Fig. 5: % Cumulative release of Metoprolol succinate floating-mucoadesive tablets comprising of HPMC K4M and Carbopol 940P

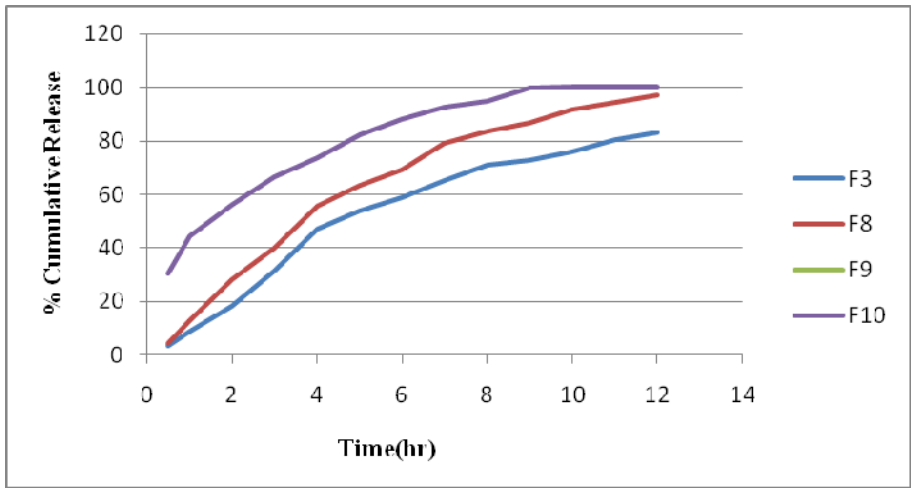

Fig. 6: % Cumulative release of Metoprolol succinate floating-mucoadesive tablets comprising of HPMC K15M and Carbopol 940P

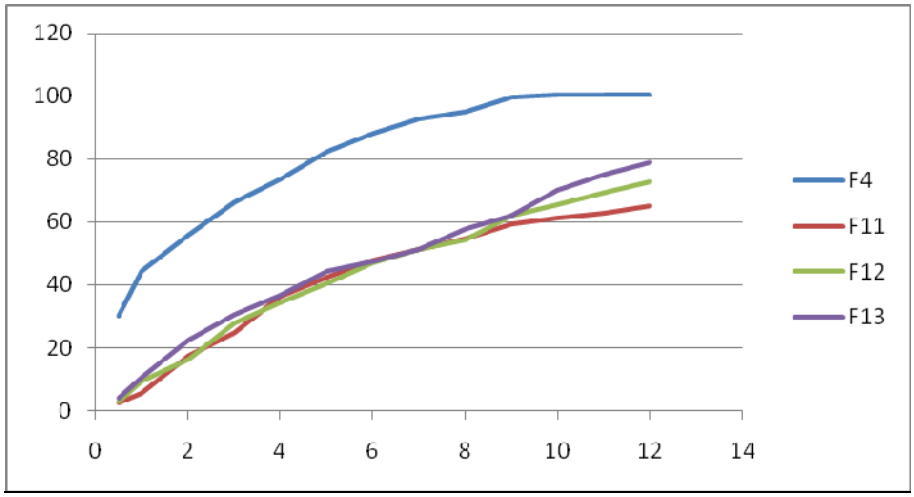

Fig. 7: % Cumulative release of Metoprolol succinate floating-mucoadesive tablets comprising of sodium CMC and carbopol 940P

This was shown by the release pattern of bathes F5, F6, F7, F8, F9, F10, F12 and F13. HPMC are more hydrophilic then Carbopol, this can be shown by the release pattern of the batches F1, F2, F3 and F4.The maximum drug release and fast release was obtained with the formulations contains the Sodium CMC in the more amount then the other polymer or as alone, this was due to high swelling capacity of the polymer. Kinetic models describe drug release from immediate and modified releasedosage forms. To predict the mechanism of diffusional release, equation $Mt / M\infty = kt^n$ was used. Consideringthe *n* values calculated for the studied tablets (Table 4), different kinetic was applied to interpret the release rate of Metoprolol from Floating-Mucoadesive tablets of batch F2 the coefficient of determination were (r^2) determined (Table 5)

Result indicated that release of F2 best fitted square root kinetics. Formulation F2 was selected as a most promising formulation for further study depending on its swelling study, Mucoadesive force and drug release properties. Results of stability studies of formulation F2 indicate that it is stable at 40^0c,75%±5% relative humidity as there was no significant difference observed for dissolution, floating time Mucoadesive force and ex-vivo mucoadhesion time.(Fig . 8 and 9).

Table 4: Estimated value of n, k and regression (r) of log (M_t/M_∞)

Formulation Batches	n	K	r^2
F1	0.9761	6.6603	0.9873
F2	0.9852	11.6478	0.9841
F3	1.0324	8.8045	0.9890
F4	0.3694	47.8195	0.9642
F5	1.0586	4.4086	0.9980
F6	0.9908	5.2373	0.9980
F7	0.9263	7.5029	0.9985
F8	1.1176	3.5178	0.9935
F9	1.1281	3.5434	0.9991
F10	1.0807	4.9700	0.9982
F11	1.0847	6.3978	0.9853

Table 5: Kinetic assessment of release data (r^2) of F2

Kinetic order	r^2(F2)
Zero order Kinetic	0.9691
First Order kinetic	0.9899
Square root kinetic	0.9979

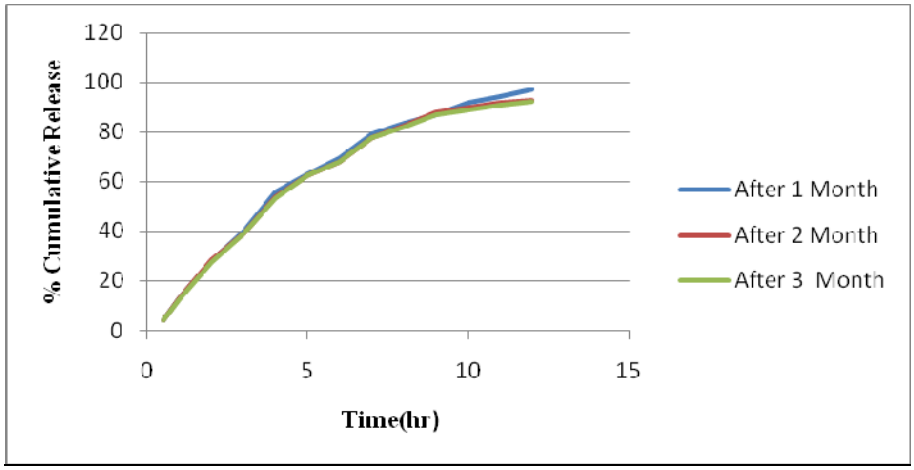

Fig 8: Comparative dissolution study of batch F2 after stability period

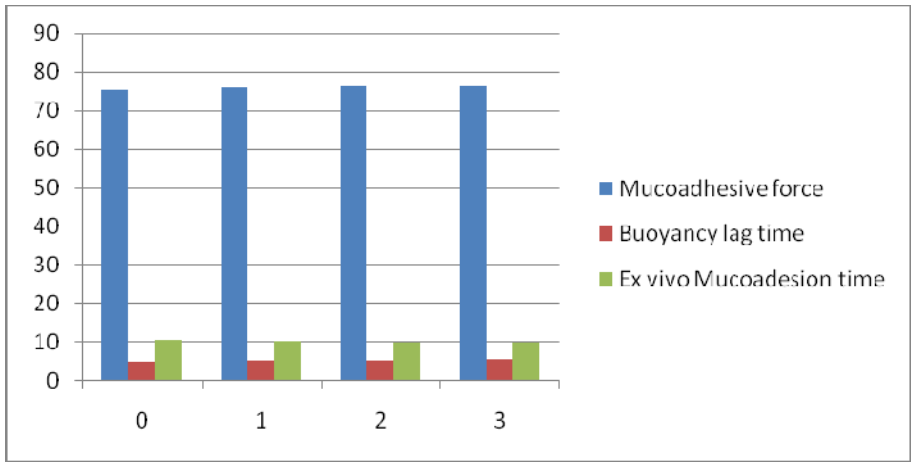

Fig 9: Comparative mucoadhesion, buoyancy lag time and *ex vivo* mucoadesive time study of batch F2 after stability period

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