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Original Article

DESIGN, DEVELOPMENT AND *IN VITRO* EVALUATION OF COMBINED FLOATING-BIOADHESIVE DRUG DELIVERY SYSTEMS OF ATENOLOL

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ABSTRACT

Objective: A combination of the Floating-Bioadhesive system will overcome the drawbacks of floating & bioadhesive systems if used alone and will have a significant effect on improving the therapeutic effect of the drug involved. The present study involves the formulation and *in vitro* evaluation of atenolol floating-Bioadhesive tablet for prolonged residence in the stomach for the treatment of hypertension.

Methods: The tablets were prepared by direct compression method using directly compressible polymers such as, Hydroxy Propyl Methyl Cellulose (HPMC) K15M, Guar gum, Carbopol, and sodium alginate. The tablets were evaluated for buoyancy test, mucoadhesion force, swelling study, drug content, e*x-vivo* mucoadhesion strength and *in-vitro* release profile. Sodium bicarbonate was used for producing the effervescent base for the buoyancy of tablets.

Results: Formulation batch contains sodium alginate which has shown highest percentage cumulative drug release up to 99.12%. No significant change was observed in physical appearance, drug content, float ability or *in vitro* dissolution pattern after storage at 45 °C/75% RH for three months.

Conclusion: In this present research work it was concluded that the cumulative drug release increased when the viscosity and concentration of the polymer was increased. The swelling properties were increased with increasing polymer concentration and contributed to the drug release from the tablet matrix.

Keywords: Hypertension, *Ex vivo* mucoadhesion strength, Carbopol, Atenolol.

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 a prolonged residence time in the stomach [1]. Atenolol is a cardioselective β-blocker widely prescribed for an asymptomatic condition such as hypertension. It is poorly absorbed from the lower gastrointestinal tract. The oral bioavailability of atenolol was reported to be 50% [2]. The human jejunal permeability and extent of absorption is low [3]. Thus, it seems that an in gastric residence time may increase the extent of absorption and bioavailability of the drug. The recommended adult oral dosage of atenolol is 50 mg twice daily for the effective treatment of hypertension. However, fluctuations of drug concentration in plasma may occur, resulting in side effects or a reduction in drug concentration at receptor side. As the drug is effective when the plasma fluctuations are minimized, therefore sustained release dosage form of atenolol is desirable. The short biological half-life of drug (6 to 8 h) also favors the development of sustained release formulations. In this study, an effervescent floating system and bioadhesive 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 [4]. A floating-Bioadhesive system would overcome these drawbacks of floating and Bioadhesive systems and would have a significant effect on improving the therapeutic effect of the drug involved [5]. The present study involves the formulation and *in vitro* evaluation of atenolol floating-Bioadhesive tablet for prolonged residence in the stomach for the treatment of Hypertension.

MATERIALS AND METHODS

Atenolol was supplied as a gift sample from GVK Pharma, Hyderabad. Micro Crystalline Cellulose (MCC), HPMC K15M and Sodium alginate were brought from Signet chemical corporation, Mumbai. Sodium bicarbonate and Carbopol obtained from Loba Chem. Pvt. Ltd., Mumbai. Guar gum was supplied from Noveon chemicals, Mumbai.

Pre-formulation studies

Drug-excipient compatibility studies

The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, easy to administer and safe. The compatibility studies provide the framework for the drugs combination with excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes after it has been subjected to processing steps during formulation of tablets. Compatibility studies were carried out by mixing definite proportions of drug and excipient and kept in glass vials, which are stored at 55 °C (2 w) and 40±2 °C/75±5 % RH (4 w)[6].

Differential scanning calorimetry (DSC)

The DSC analysis was carried out using Differential Scanning Calorimeter (SDT 2960 TA Instrument, USA). Samples were placed in a platinum crucible, and the DSC thermograms were recorded at a heating rate of 10 °C/min in the rage 20 °C to 350 °C, at a nitrogen flow of 20 ml/min.

Calibration curves for atenolol

A standard graph of pure drug in the suitable medium was prepared by plotting the concentration on X-axis and absorbance on Y-axis. An accurately weighed 100 mg of Atenolol was dissolved in 0.1N HCl as per I. P and make up the volume up to 100 ml in a volumetric flask, (Stock Solution I: 1 mg/ml or 1000 µg/ml). From this stock solution I, 10 ml of solution was pipetted out and make up the volume up to 100 ml (Stock Solution II: 100µg/ml). Then the aliquots were prepared, whose concentration ranging from 10 to 50 µg/ml and the absorbance were measured at 275 nm by using UV Spectro-photometer (Elico) against the reagent blank. The coefficient of variation and correlation coefficient were determined.

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.

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

Where, *D*f= Poured bulk or bulk density, *D*0 = Tapped or consolidated bulk density.

Preparation of floating-bioadhesive tablets

All the floating-bioadhesive tablets were fabricated by using direct compression technique. HPMC K15M, Gaur gum, Carbopol, Sodium alginate, Sodium bicarbonate, Talc, Magnesium Stearate, Citric acid and microcrystalline cellulose were blended homogeneously in a mortar. The blended mixture was passed through Sieve 60. Finally, talc and magnesium stearate was added and blended. The homogeneously blended mixture was compressed in a 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.

Evaluation of tablet

Density measurement of tablet

The 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 Vernier caliper) using the mathematical equation for a cylinder (V = π × r 2 × h). The tablets with ~1 g/cm^3 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 900 ml of 0.1N HCl solutions. Then note the time in minutes for each tablet 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 ℃. 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 224 nm. Tablets were also examined with regard to their weight variation (*n* = 10), friability (*n* = 10) and hardness (*n* = 3) [10].

***In vitro* bio-adhesion study**

The bioadhesive 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 N/M^2, was determined from the minimum weight required to detach the two vials using the following equation [11].

$$\text{Bioadhesive force (N/M}^2\text{)} = \frac{\text{m x g}}{\text{A}}$$

***Ex vivo* mucoadhesive time**

A modified balance method [12] was used for determining the *ex vivo* Mucoadhesive strength. Fresh sheep mucosa was obtained from a local slaughterhouse and used within 2 h 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 min 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.

***In vitro* dissolution studies**

The release rate of Atenolol from floating-bioadhesive 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 ℃ and 50 r/min. A sample (5 ml) 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 275 nm.

Stability studies

The stability studies were carried out according to ICH and WHO guidelines [13] to assess the drug and formulation stability. Optimized F9 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 mo. At the end of the study period, samples were analyzed for buoyancy lag time, *ex vivo* mucoadhesion time, and bioadhesive force and drug release characteristics.

RESULTS

Floating-bioadhesive tablets of atenolol were mainly prepared by using different polymer like HPMC-K15M, sodium alginate, guar gum and Carbo pol either alone or in combination (table 1). The compatibility studies provide the framework for the drugs combination with excipients in the fabrication of the dosage form. No significant change in peak pattern in the IR spectra of pure Drug and combination of the drug with polymer indicates no interaction

between pure drug and polymer (fig. 1-5). The DSC analysis was carried out using Differential Scanning Calorimeter (SDT 2960 TA Instrument, USA). Samples were placed in a platinum crucible, and the DSC thermo grams were recorded at a heating rate of 10 °C/min in the range 20 °C to 350 °C, at a nitrogen flow of 20 ml/min. (fig. 6).

The effervescent base of tablets was prepared by using sodium bicarbonate. The tablets were fabricated using direct compression technique. The pre-blended powders were characterized with respect to the angle of repose, bulk density, tap density and Carr's index (table 2).

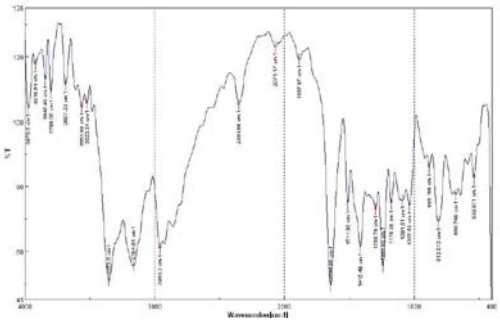

Fig. 1: FTIR spectra of Atenolol

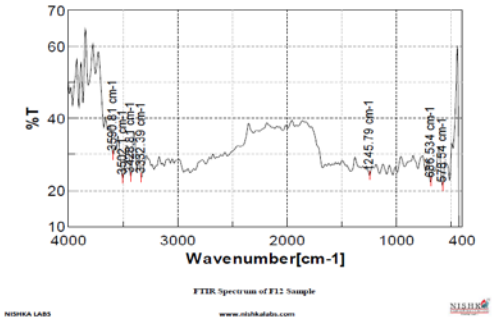

Fig. 2: FTIR spectra of formulation (F12)

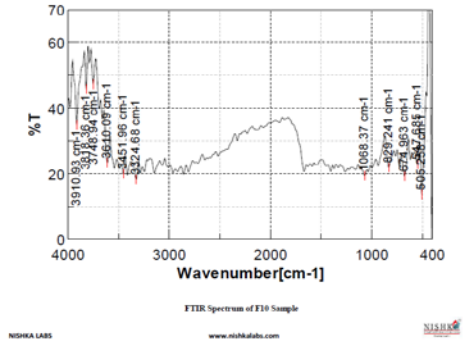

Fig. 3: FTIR spectra of formulation (F10)

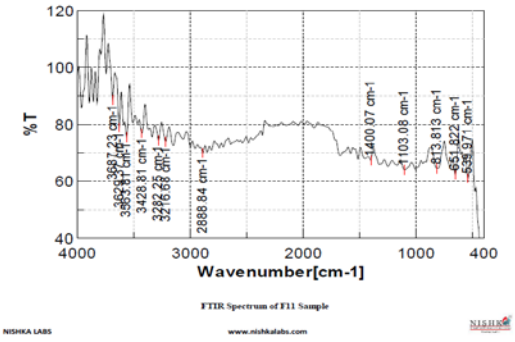

Fig. 4: FTIR spectra of formulation (F11)

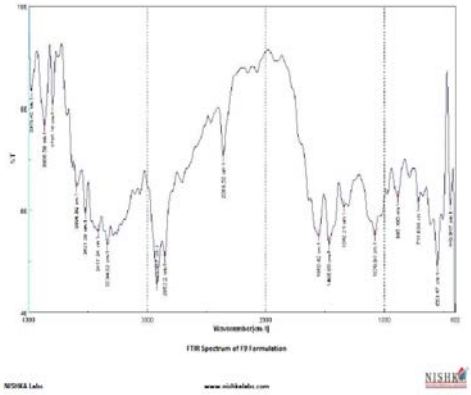

Fig. 5: FTIR spectra of formulation (F9)

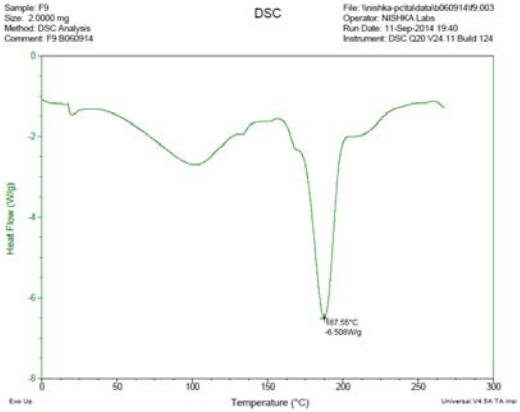

Fig. 6: DSC of formulation (F9)

Table 1: Formulation of floating-bioadhesive tablets of atenolol

Formulation batches	Atenolol (mg)	HPMC (K15M)	Guar gum (mg)	Sodium alginate (mg)	Carbopol (mg)	MCC (mg)	$NaHCo_3$ (mg)	Citric acid	Talc (mg)
F1	50	70	30	-	-	55	65	26	4
F2	50	75	25	-	-	55	65	26	4
F3	50	80	20	-	-	55	65	26	4
F4	50	70	-	30	-	55	65	26	4
F5	50	75	-	25	-	55	65	26	4
F6	50	80	-	20	-	55	65	26	4
F7	50	70	-	-	30	55	65	26	4
F8	50	75	-	-	25	55	65	26	4
F9	50	80	-	-	20	55	65	26	4
F10	50	70	25	25	-	45	65	26	4
F11	50	75	-	25	25	45	65	26	4
F12	50	80	25	-	25	45	65	26	4

HPMC-Hydroxy Propyl Methyl Cellulose, SCMC-Sodium Carboxy Methyl Cellulose, MCC-Micro Crystalline Cellulose, MS-Magnesium Stearate.

The Micromeritic properties of the drug and polymers were done by evaluating them for the physical characteristics such as Bulk density, Tapped density, Compressibility index, Hausner's ratio and Angle of repose. All batches have excellent flow properties.

The angle of repose for all the batches of powder indicates 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, Mucoadhesive 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/m^2) and drug content (>90%). The floating lag time for all formulations was found to be less than 5 min (table 3). Examination of tablets from each formulation showed concave shape with no cracks having a white color.

Table 2: Characterization of pre compressed powder blend

Formulation batches	Bulk density(mg/ml)*	Tapped density(mg/ml)*	Hausner's ratio	Carr's index %	Angle of repose*
F1	341±2.0	394±1.8	1.1554	13.45	23.9±1.3
F2	311±3.2	368±2.8	1.183	15.48	26.1±2.6
F3	350±2.8	402±1.2	1.148	12.94	25.5±1.5
F4	350±1.6	410±2.2	1.178	14.63	20.4±1.7
F5	300±1.2	343±1.6	1.147	12.53	19.5±3.2
F6	375±1.6	445±1.4	1.187	15.73	26.7±3.3
F7	468±2.3	538±3.1	1.151	12.32	23±1.4
F8	416±3.1	482±3.3	1.158	13.69	24.3±1.3
F9	357±2.1	421±2.3	1.179	18.09	18.5±1.1
F10	326±2.2	398±2.1	1.221	16.3	24.6±1.2
F11	341±1.4	407±2.7	1.193	16.21	28±2.1
F12	349±2.1	431±2.8	1.235	19.02	29±1.7

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

The thickness of tablets ranged from 3.22±0.01 to 3.38±0.03. All formulations showed uniform thickness. In weight variation test, the pharmacopeia limit for percent deviation for tablets of more than 300 mg is±5%. The average percent deviation of all tablets was found to be within limits, and hence all formulations pass the weight variation test. The drug content was found to be uniform among all formulations 98.19% to 100.85%. the hardness of the tablets was found to be between 5.5±0.03 to 5.9±0.01 kg/m. The friability was found to be 0.34±0.01% to 0.79±0.03%.

The muco-adhesion characteristic was found more in F12. This formulation contains guar gum and sodium alginate polymers which have high adhesion properties (table 4). Swelling index was calculated with respect to time (fig. 7).

Table 3: Evaluation of floating-bioadhesive tablet of atenolol*

Formulation batches	Hardness (kg/m^2)	% Drug content	Buoyancy lag time (sec)	Weight variation	Friability %	*Ex-Vivo* Mucoadhesive time (hours)
F1	5.7±0.3	99.90%	18±0.7	Passes	0.67%	10±0.3
F2	5.9±0.2	98.39%	13±0.9	Passes	0.68%	10.3±0.1
F3	5.6±0.4	99.77%	22±1.2	Passes	0.33%	8.1±0.7
F4	5.8±0.1	100.36%	10±1.7	Passes	0.34%	9.7±0.6
F5	5.4±0.5	98.33%	19±1.6	Passes	0.68%	10.3±0.4
F6	5.7±0.3	100.06%	12±0.8	Passes	0.70%	10.7±0.3
F7	5.8±0.2	98.19%	18±1.6	Passes	0.71%	10.8±0.5
F8	5.9±0.1	97.41%	52±0.9	Passes	0.68%	9.2±0.6
F9	5.6±0.3	100.85%	9±0.9	Passes	0.68%	9.8±0.8
F10	5.5±0.4	99.93%	28±1.2	Passes	0.64%	10.1±0.4
F11	5.5±0.3	98.72%	14±1.7	Passes	0.67%	11.2±0.9
F12	5.8±0.1	99.63%	33±1.6	Passes	0.66%	11.5±0.5

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

Table 4: Mucoadhesion study of floating-bioadhesive tablets of atenolol

Formulations	Mucoadhesion value
F1	4.6906 N
F2	3.9768N
F3	3.467N
F4	4.2828N
F5	4.1808N
F6	5.0985
F7	4.0788N
F8	3.8768N
F9	4.3847N
F10	3.9768N
F11	3.7729N
F12	5.6084N

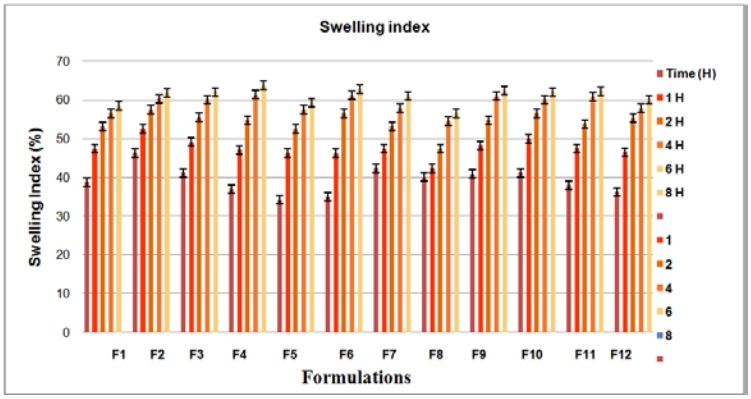

Fig. 7: Swelling index of all formulations

The release of atenolol from bioadhesive floating tablets varied according to the type of and concentrations of polymers. Formulations F1, F2, and F3 containing drug and guar gum in the ratios of 2:1, 1:1 and 2:3 had a % cumulative release of 91.45%, 86.67% and 87.49% in 12 h respectively. Which showed that guar gum was helpful in retarding the drug release (fig. 8). The hydrogel were not entangled in the chain of polymers, but discrete microgels made up of many polymer particles in which the drug was dispersed. The hydrogel remains intact and continuously diffuses through the gel layer at a uniform rate. Formulations F4, F5 and F6 containing drug and carbopol 974P in the ratios of 2:1, 1:1 and 2:3 had a % cumulative release of 85.5%, 90.12% and 91.67% in 12h respectively (fig. 9), which shows that the drug was released in a controlled manner.

The hydrogel remains intact when dissolved in water and there was a uniform release of the drug. This may be because of high viscosity and less solubility. Formulations F7, F8, and F9 containing drug and sodium alginate in the ratios of 2:1, 1:1 and 2:3 had a cumulative drug release of 96.04%, 96.17% and 99.12% in 12h respectively. The release profile was shown in fig. 22. These formulations showed faster release than Carbopol 940P and guar gum formulations, this might be due to the low viscosity of the polymer (fig. 10). Formulations F10 containing drug, guar gum and sodium alginate formulation F11 containing drug, guar gum and Carbopol and F12 containing drug, sodium alginate and Carbopol in the ratios of 2:1:1, 2:1:1 and 2:1:1 respectively showed % cumulative release of 93.92%, 94.43% and 94.22% in 12h respectively and the results shown in fig. 11.

Formulation F9 contains polymer sodium alginate which has shown highest % cumulative drug release up to 99.12%.

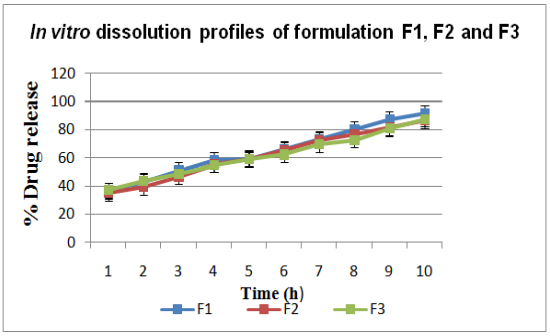

Fig. 8: Dissolution profile of formulations F1, F2, F3

Results of stability studies of formulation F9 indicate that it is stable at 40 °C,75%±5% relative humidity as there was no significant difference observed for dissolution, floating time Mucoadhesive force and *ex-vivo* mucoadhesion time.(fig. 12 and 13).

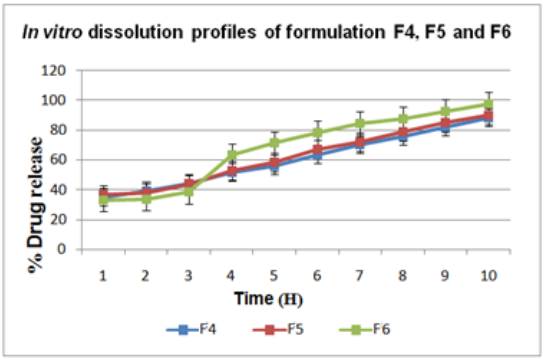

Fig. 9: Dissolution profile of formulations F4, F5, F6

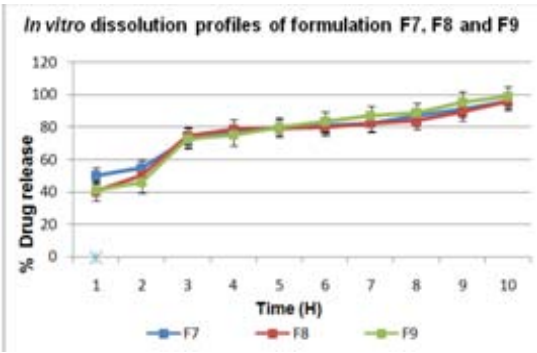

Fig. 10: Dissolution profile of formulations F7, F8 and F9

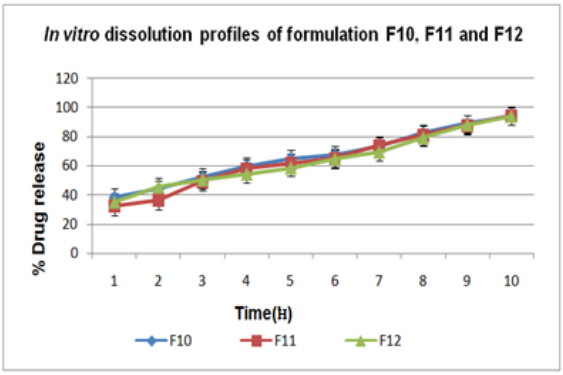

Fig. 11: Dissolution profile of formulations F10, F11, F12

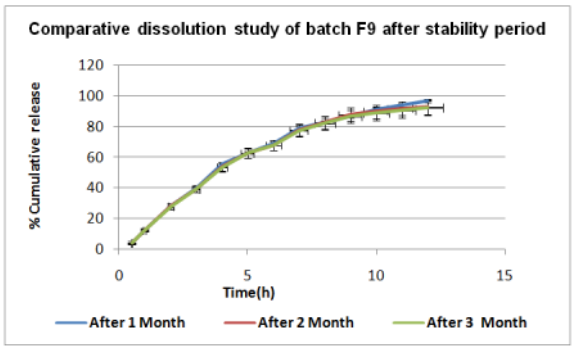

Fig. 12: Comparative dissolution study of batch F9 after stability period

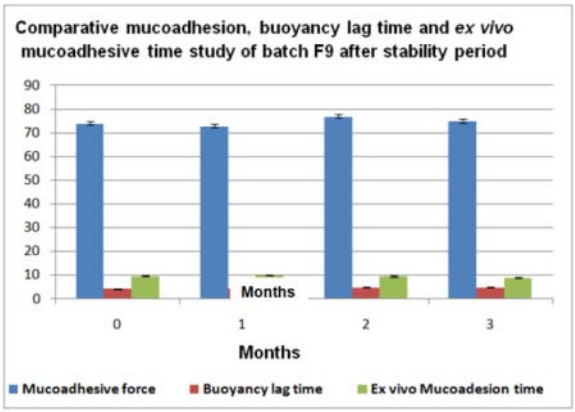

Fig. 13: Comparative mucoadhesion, Buoyancy lag time and *ex vivo* mucoadhesive time study of batch F9 after stability period

DISCUSSION

Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopeia and standard reference. Results of floating behavior indicated that all batches show floating time less than a minute and floating duration for more than 12 h. Results of swelling characteristics and *in vitro* dissolution study indicated that batch (F9) was having considerable swelling index and desirable dissolution. Inter-particulate interactions that influence the bulking properties of a powder are powder flow. A comparison of bulk density and tapped density can give a measure of the relative importance of this in a given powder; such a comparison is often used as an index of the ability of the powder flow. From the study it was found that maximum liquid uptake and swelling of the polymer was achieved up to 10hr and then gradually decreased. Maximum swelling was observed in formulation (F9). It was also observed that cumulative drug release increased when the viscosity and concentration of the polymer was increased.

From previous work [14] on the gastro retentive floating tablet of atenolol it was concluded that the swelling index may be increased as the concentration of guar gum increases, but in the present work it was found out that the swelling index may directly relates the viscosity as well as the concentration of the polymers.

From previous work [15] it was mentioned the floating lag time gradually decreases with increase in concentration of sodium bicarbonate, but in the present work it was found that the floating lag time may also depend upon the concentration, type as well as the viscosity of the polymer used.

CONCLUSION

From the research work it was concluded that batch F9 had considerable floating and swelling behaviors with good release pattern. Tablets of batch F9 were selected as optimum batch.

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CONFLICT OF INTERESTS

Declared none

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