Design, Formulation and Evaluation of Atenolol Gastro Retentive Floating Tablets

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Abstract

The main objective of present research work is to formulate the floating tablets of atenolol using 3^2 factorial design. Atenolol, β-blocker belongs to Biopharmaceutical Classification System Class-III. The floating tablets of atenolol were prepared employing different concentrations of hydroxypropyl methylcellulose (HPMC) K15M and sodium bicarbonate in different combinations by direct compression technique using 3^2 factorial design. The concentration of HPMC K15M and sodium bicarbonate required to achieve desired drug release was selected as independent variables, X_1 and X_2, respectively, whereas time required for 10% of drug dissolution ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$), and 90% ($t_{90\%}$) were selected as dependent variables. Totally, nine formulations were designed and are evaluated for hardness, friability, thickness, % drug content, floating lag time, *in vitro* drug release. From the results, concluded that all the formulation were found to be within the pharmacopoeial limits and the *in vitro* dissolution profiles of all formulations were fitted into different Kinetic models, the statistical parameters like intercept (a), slope (b) and regression coefficient (*r*) were calculated. Polynomial equations were developed for $t_{10\%}, t_{50\%}, t_{75\%}, t_{90\%}$. Validity of developed polynomial equations was verified by designing 2 checkpoint formulations (C_1, C_2). According to SUPAC guidelines the formulation (F_8) containing combination of 25% HPMC K15M and 3.75% sodium bicarbonate, is the most similar formulation (similarity factor f_2 = 87.797, dissimilarity factor f_1 = 2.248 and no significant difference, t = 0.098) to marketed product (BETACARD). The selected formulation (F_8) follows Higuchi's kinetics, and the mechanism of drug release was found to be non-Fickian diffusion (n = 1.029, Super Case-II transport).

Key words: 3^2 factorial design, atenolol, floating lag time, gastro retentive floating tablet, hydroxypropyl methyl cellulose K15M, non-Fickian diffusion mechanism, sodium bicarbonate, SUPAC

INTRODUCTION

Oral administration is the most convenient, widely used route for both conventional and novel drug delivery systems, and preferred route of drug delivery for systemic action. Tablets are the most popular oral solid formulations available in the market and are preferred by patients and physicians alike. There are many reasons for this, not the least of which would include acceptance by the patient and ease of administration, patient compliance and flexibility in formulation, etc. From immediate release to site-specific delivery, oral dosage forms have really progressed.

In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and, therefore, have several disadvantages.[1] However, when administered orally, many therapeutic agents are subjected to extensive pre-systemic elimination by gastrointestinal degradation and/or first-pass hepatic metabolism as a result of which low systemic bioavailability and shorter duration of therapeutic activity and formation of inactive or toxic metabolites.[2]

Rapid gastrointestinal transit can result in incomplete drug release from a device above the absorption zone, leading to the diminished efficacy of the administered dose. Therefore, different approaches have been proposed to retain the dosage form in the stomach. These include bio adhesive systems, swelling and expanding systems and floating systems. Large single-unit dosage forms undergo significant swelling after oral administration, and the swollen matrix inhibits gastric emptying even when the pyloric sphincter is in an uncontracted state.[3] Gastric floating drug delivery system (GFDDS) can overcome at least some of these problems and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. The GFDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug.

Gastroretentive dosage forms significantly extend the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance.[4,5] Such retention systems are important for those drug that are degraded in the intestine like antacids or certain antibiotics, enzymes that act locally in the stomach. These systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract, thus ensuring optimal bioavailability.

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, the goal in the designing sustained/controlled drug delivery system is to reduce the dosing frequency or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery.[3]

Since the early 1950s, the application of polymeric materials for medical purposes is growing very fast. Polymers have been used in the medical field for a large extent.[4] Natural polymers remain attractive primarily because they are inexpensive, readily available, be capable of chemical modifications, non-carcinogenicity, mucoadhesivity, biodegradable, biocompatible, high drug holding capacity, and high thermal stability and easy of compression.[5] This led to its application as excipient in hydrophilic drug delivery system. The various natural gums and mucilages have been examined as polymers for sustained drug release in the last few decades for example; sodium bicarbonate, tragacanth gum, xanthan gum, pectin, alginates, etc. In the development of a gastro-retentive floating tablet dosage form. Availability of wide variety of polymer and frequent dosing interval helps the scientist to develop sustained release product. cellulose derivatives such as carboxymethylcellulose (CMC), sodium CMC, hydroxyproyl cellulose, and hydroxypropyl methylcellulose (HPMC) have been extensively studied as the polymer in the Floating tablet formulations along with gas

generating agent like $NaHCO_3$.[6] These polymers are most preferred because of its cost effectiveness, broad regulatory acceptance, non-toxic and easy of compression. These dosage forms are available in the extended release, targeted release, delayed release, prolonged action dosage form. Some factors like molecular size, diffusivity, pKa-ionization constant, release rate, dose, and stability, duration of action, absorption window, therapeutic index, protein binding, and metabolism affect the design of sustained release formulation. The future of sustained-release products is promising in some area like chronopharmacokinetic system, targeted drug delivery system, mucoadhesive system, particulate system that provide high promise and acceptability.

Developing floating formulations Biopharmaceutical Classification System Class-III drugs has become a challenge to the pharmaceutical technologists. Fast release drug generally causes toxicity if not formulated as extended release dosage form. Among various formulation approaches, in controlling the release of water-soluble drugs, the development of sustained release coated granules has a unique advantage of lessening the chance of dose dumping which is a major problem when the highly water-soluble drug is formulated as matrix tablets.

Oral sustained release dosage form by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic, or oxidative reactions occurred during processing of dosage forms.[7]

The selection of the drug candidates for floating drug delivery system needs consideration of several biopharmaceutical, pharmacokinetic and pharmacodynamic properties of the drug molecule.[8]

In the present study, a gastro-retentive floating dosage form of atenolol has been developed that makes less frequent administering of the drug also to improve bioavailability.

Atenolol is a cardioselective β-blocker, selective $β_1$ adrenergic antagonist it is widely used in the treatment of hypertension and angina pectoris. The chemical name of atenolol is 4-[2-hydroxy-3-[(1-methyl ethyl)amino]propoxy] benzene acetamide. Undergoes little or no hepatic first pass metabolism and its elimination half-life is 6-7 h. The present modes of administration of atenolol are oral and parenteral. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 50% while the remaining is excreted unchanged in feces. The human jejunal permeability and extent of absorption are low. 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.[9] The short biological half-life of drug (6-8 h) also favors the development of sustained release formulations.

The gastro-retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.

Thus, there is a need to maintain atenolol at its steady state plasma concentration. Hence, the study was carried out to formulate and evaluate floating dosage form of atenolol as a model drug and had aim that final batch formulation parameters should show prolong drug release.

Development of dosage form depends on chemical nature of the drug/polymers, matrix structure, swelling, diffusion, erosion, release mechanism, and the *in vivo* environment.

It is an important issue is to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. For this purpose, response surface methodology (RSM) utilizing a polynomial equation has been widely used. Different types of RSM designs include 3-level factorial design, central composite design, Box-Behnken design, and D-optimal design. RSM is used when only a few significant factors are involved in experimental optimization. The technique requires less experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating sustained release dosage forms.[10-13]

Hence, an attempt is made in this research work to formulate floating tablets of atenolol using HPMC K15M and sodium bicarbonate. Instead of the normal and trial method, a standard statistical tool design of experiments is employed to study the effect of formulation variables on the release properties.

Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The floating tablets formulation by direct compression method is most acceptable in large scale production.

A 3^2 full factorial design was employed to systematically study the drug release profile. A 3^2 full factorial design was employed to investigate the effect of two independent variables (factors), i.e., the amounts of HPMC K15M and sodium bicarbonate on the dependent variables, i.e., $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$ (Time taken to release 10%, 50% 75%, 90%, respectively).

MATERIALS AND METHODS

Materials used in this study were obtained from the different sources. Atenolol was a gift sample from Aurobindo Pharma Ltd, Hyderabad, India. HPMC K15M from colorcon, sodium bicarbonate, Di-Calcium Phosphate were procured from Loba Chemie Pvt. Ltd, Mumbai. Other excipients such as stearic acid, citric acid, aerosil, and talc were procured from S.D. Fine Chem. Ltd., Mumbai, Maharashtra, India.

Formulation development of atenolol sustained-release tablets

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses.[14]

A selected three level, two-factor experimental design (3^2 factorial design) describe the proportion in which the independent variables HPMC K15M and sodium bicarbonate were used in the formulation of atenolol floating tablets. The time required for 10% ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$), and 90% ($t_{90\%}$) drug dissolution were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($P < 0.05$) for Final Equations. Polynomial equations were developed for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (step-wise backward Linear Regression Analysis).

The three levels of factor X_1 (HPMC K15M) at a concentration of 25%, 31.25%, 37.25%. three levels of factor X_2 (sodium bicarbonate) at a concentration of 3.75%, 7.5%, 11.25% (% with respect to total tablet weight) was taken as the rationale for the design of the Atenolol floating tablet formulation. Totally, nine Atenolol floating tablet formulations were prepared employing selected combinations of the two factors, i.e., X_1, X_2 as per 3^2 Factorial and evaluated to find out the significance of combined effects of X_1, X_2 to select the best combination and the concentration required to achieve the desired prolonged release of drug (by providing gastro retentivity) from the dosage form.

Preparation of atenolol floating tablets

All the ingredients were accurately weighed and passed through mesh # 60. To mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 min then sodium bicarbonate, talc and aerosil were mixed one by one. After thoroughly mixing these ingredients, the powder blend was passed through # 44 mesh. Powder blend was compressed by using rotary tablet punching machine (RIMEK), Ahmedabad). Compressed tablets were examined as per official standards and unofficial tests. Tablets were packaged in well closed light resistance and moisture proof containers.

Experimental design

Experimental design utilized in present investigation for the optimization of excipients concentration such as concentration of HPMC K15M was taken as X_1 and concentration of sodium bicarbonate was taken as X_2. Experimental design was given in Table 1. Three levels for the concentration of HPMC K15M were selected and coded as $-1 = 25\%$, $0 = 31.25\%$, $+1 = 37.5\%$. Three levels for the concentration of sodium bicarbonate were selected and coded as $-1 = 3.75\%$, $0 = 7.5\%$, $+1 = 11.25\%$. Formulae for all the experimental batches were given in Table 2.[15]

Evaluation of atenololsustained release tablets

Hardness[16]

The hardness of the tablets was tested by diametric compression using a monsanto hardness tester. A tablet hardness of about 2-4 kg/cm² is considered adequate for mechanical stability.

Friability[16]

The friability of the tablets was measured in a Roche friabilator (Camp-Bell Electronics, Mumbai, Maharashtra, India). Tablets of a known weight (W_0) or a sample of 20 tablets are deducted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

Friability (%) = [(Initial weight−Final weight)/(Initial weight)] × 100

Content uniformity[16]

In this test, 20 tablets were randomly selected, and the percent drug content was determined, the tablets contained not less than 85% or more than 115% of the labeled drug content can be considered as the test was passed.

Assay[17]

The drug content in each formulation was determined by triturating 20 tablets, and powder equivalent to average weight was added in 100 ml of 0.1 N hydrochloric acid, followed by stirring. The solution was filtered through a 0.45 µ membrane filter, diluted suitably, and the absorbance of the resultant solution was measured spectrophotometrically at 224 nm using 0.1 N hydrochloric acid as blank.

Thickness

Thickness of the all tablet formulations was measured using vernier calipers by placing tablet between two arms of the vernier calipers.[16]

In vitro buoyancy studies

The tablets were placed in a 100 mL beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.[18,19]

In vitro dissolution study[20]

The *In vitro* dissolution study for the atenolol floating tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium

Table 1: Experimental design layout

Formulation code	X_1	X_2
F_1	1	1
F_2	1	0
F_3	1	−1
F_4	0	1
F_5	0	0
F_6	0	−1
F_7	−1	1
F_8	−1	0
F_9	−1	−1

F_1-F_9: Factorial formulations

Table 2: Formulae for the preparation of atenolol floating tablets as per experimental design

Name of ingredients	Quantity of ingredients per each tablet (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Atenolol	50	50	50	50	50	50	50	50	50
HPMC K15M	150	150	150	125	125	125	100	100	100
Sodium bicarbonate	45	30	15	45	30	15	45	30	15
Di calcium phosphate	97	112	127	112	137	152	147	162	177
Stearic acid	40	40	40	40	40	40	40	40	40
Citric acid	10	10	10	10	10	10	10	10	10
Aerosil	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Total weight	400	400	400	400	400	400	400	400	400

HPMC: Hydroxypropyl methylcellulose

at 50 rpm and temperature $37 \pm 0.5°C$. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with the same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 224 nm using UV-Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate ($n = 3$).

Kinetic modeling of drug release[21-24]

The dissolution profile of all the formulations was fitted into zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to ascertain the kinetic modeling of drug release.

RESULTS AND DISCUSSION

Gastro retentive floating tablets of atenolol were prepared and optimized by 3^2 factorial design to select the best combination of different release rate modifiers, HPMC K15M, sodium bicarbonate and also to achieve the desired prolonged release of drug from the dosage form (by retaining drug at gastric environment). The two-factorial parameters involved in the development of formulations are quantity of HPMC K15M and sodium bicarbonate polymers as independent variables (X_1, X_2), and *In vitro* dissolution parameters such as $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ as dependent variables Totally, nine formulations were prepared using 3 levels of 2 factors and all the formulations containing 50 mg of Atenolol were prepared as a floating tablet dosage form by direct compression technique as per the formulae given in Table 2.

All the prepared tablets were evaluated for different post-compression parameters, drug content, mean hardness, friability, mean thickness, mean diameter, floating lag time as per official methods, and results are given in Table 3. The hardness of tablets was in the range of 4.49-4.69 Kg/cm². Weight loss in the friability test was less than 0.68%. Drug content of prepared tablets was within acceptance range only.

Results for all Post-compression parameters were tabulated or shown in Table 3. *In vitro* dissolution studies were performed for prepared tablets using 0.1 N HCl as a dissolution media at 50 rpm and temperature $37 \pm 0.5°C$. The *in vitro* dissolution profiles of tablets are shown in Figure 1 and the dissolution parameters are given in Table 4. Cumulative % drug release of factorial design formulations F_1-F_9 at 10 Hr were found to be in the range of 72.91-100.80 %. From the results, it reveals that as the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent ($NaHCO_3$) increases the drug release increases and at the same time floating lags time decreases.

Therefore, required release of drug can be obtained by manipulating the composition of HPMC K15M and sodium bicarbonate.

Many variations were observed in the $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ due to formulation variables. Formulation F_8 containing 100 mg of HPMC K15M, 30 mg of sodium bicarbonate showed promising dissolution parameter ($t_{10\% =}$ 0.418 h, $t_{50\% =}$ 2.747 h, $t_{75\% =}$ 5.494 h, $t_{90\% =}$ 9.128 h) which meets the objective of work by providing more gastric retentivity and maximum drug release. The difference in burst effect of the initial time is a result of the difference in the viscosity of the polymeric mixtures. Dortunc and Gunal have reported that increased viscosity resulted in a
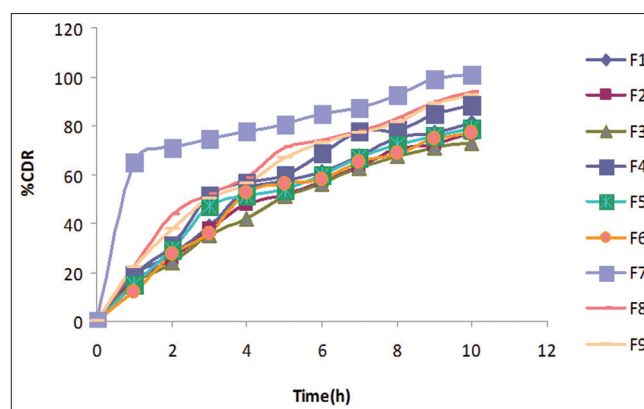

Figure 1: Comparative zero order plots for F_1-F_9

Table 3: Post-compression parameters for the formulations						
Formulation code	**Hardness (kg/cm²)**	**Floating lag time (min)**	**Diameter (mm)**	**Thickness (mm)**	**Friability (%)**	**Weight variation**	**Drug content (%)**
F_1	4.66	1.1	9.94	4.66	0.64	400.07	95.55
F_2	4.67	3.5	9.96	4.67	0.62	400.32	95.77
F_3	4.69	4.3	9.97	4.68	0.57	400.05	95.72
F_4	4.51	0.9	9.95	4.51	0.69	400.60	93.49
F_5	4.59	3.2	9.98	4.59	0.65	400.45	95.70
F_6	4.62	4.1	10.05	4.62	0.53	400.90	97.15
F_7	4.42	0.3	10.00	4.42	0.68	400.23	94.57
F_8	4.49	2.9	10.02	4.49	0.61	400.66	97.09
F_9	4.54	3.8	10.01	4.54	0.55	400.03	96.83

F_1-F_9: Factorial formulations

corresponding decrease in the drug release, which might be due to the result of thicker gel layer formulation.[25]

The *in vitro* dissolution data of atenolol floating formulations was subjected to the goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to assess the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4 and plots shown in Figures 1-4. It was observed from the above that dissolution of all the tablets followed first order kinetics with co-efficient of determination (R^2) values in the range of 0.872-0.998. The values of r of factorial formulations for Higuchi's equation was found to be in the range of 0.931-0.997, which shows that the dissolution data/drug release fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values ranges from 0.809 to 1.056 that shows non-Fickian diffusion mechanism (Super Case-II Transport). Polynomial equations were derived for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ values by backward stepwise linear regression analysis using PCP Disso software and Contour plots, Response surface plots were constructed using SIGMAPLOT V13 software. The Response surface plots and Contour plots

were shown in Figures 5-12 for t10% to t90% using X1 and X2 on both the axes. The dissolution data (Kinetic parameters) of factorial formulations F1 to F9 are shown in Table 5.

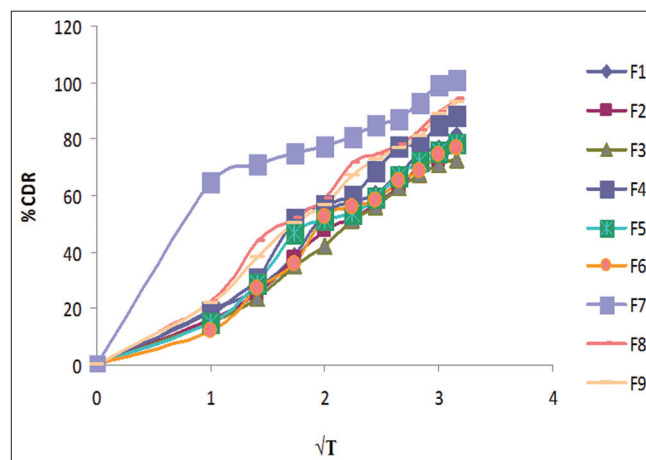Polynomial equation for 3² full factorial designs is given in Equation:
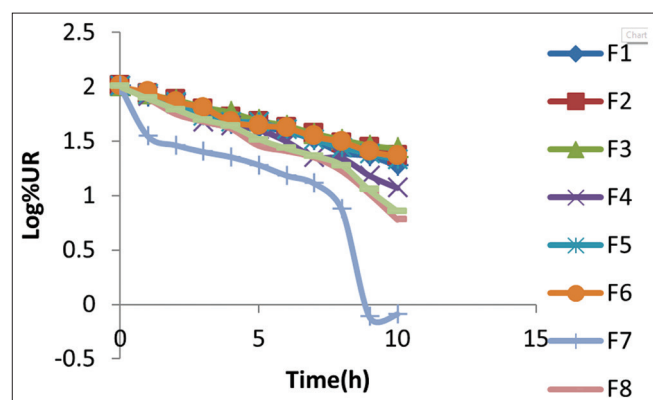

Figure 3: Comparative Higuchi plots for F_1-F_9

Figure 4: Comparative Korsmeyer–Peppas plots for F_1-F_9

Figure 2: Comparative first order plots for F_1-F_9

Formulation code	Zero order			First order			Higuchi			Korsmeyer–Peppas		
	a	b	r	a	b	r	a	b	r	a	b	r
F_1	12.134	7.713	0.969	1.992	0.071	0.996	5.284	27.408	0.991	0.959	1.056	0.938
F_2	10.577	7.330	0.975	1.991	0.063	0.998	5.716	25.920	0.992	0.934	1.050	0.941
F_3	9.402	7.168	0.978	1.991	0.058	0.998	6.300	25.234	0.991	0.909	1.059	0.949
F_4	14.530	8.269	0.961	2.004	0.090	0.994	4.639	29.625	0.991	0.998	1.062	0.919
F_5	12.924	7.403	0.959	1.978	0.066	0.994	4.295	26.553	0.990	0.965	1.043	0.914
F_6	10.516	7.484	0.965	1.989	0.064	0.994	6.388	26.596	0.986	0.901	1.104	0.924
F_7	42.206	6.711	0.808	1.926	0.159	0.872	20.915	26.853	0.931	1.300	0.809	0.822
F_8	18.631	8.402	0.952	2.018	0.110	0.984	1.682	30.512	0.995	1.056	1.029	0.890
F_9	16.334	8.466	0.964	2.026	0.105	0.986	3.459	30.413	0.997	1.031	1.044	0.910
MP	19.614	8.484	0.951	2.028	0.118	0.982	1.058	30.889	0.996	1.070	1.023	0.888

Table 4: Regression analysis data of 3² factorial design formulations of atenolol

F_1-F_9: Factorial formulations, *r*: Correlation coefficient, a: Intercept, b: Slope, MP: Marketed product

$$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2$$

Where, Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated co-efficient for factor X_1.

Table 5: Dissolution parameters of atenolol floating tablets 3^2 full factorial design batches

Formulation code	Kinetic parameters			
	$t_{10\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
F_1	0.641	4.215	8.429	14.005
F_2	0.731	4.811	9.621	15.985
F_3	0.784	5.157	10.314	17.137
F_4	0.511	3.361	6.721	11.167
F_5	0.694	4.567	9.133	15.175
F_6	0.716	4.709	9.418	15.649
F_7	0.287	1.888	3.775	6.273
F_8	0.418	2.747	5.494	9.128
F_9	0.437	2.876	5.751	9.555
MP	0.387	2.546	5.093	8.462

F_1-F_9: Factorial formulations, MP: Marketed product

The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. Validity of derived equations was verified by preparing two checkpoint formulations of Intermediate concentration (C_1,C_2) C_1 is X_1=-0.5 X_2=-0.5 and C_2 is X_1=0.5, X_2=0.5.

The equations for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ developed as follows:

$$Y_1 = 0.580 + 0.169X_1 - 0.083X_2 + 0.002X_1X_2 - 0.0907\ X_1^2 - 0.052X_2^2 (\text{for } t_{10\%})$$

$$Y_2 = 3.815 + 1.112X_1 - 0.546X_2 + 0.012X_1X_2 - 0.597\ X_1^2 - 0.341X_2^2 (\text{for } t_{50\%})$$

$$Y_3 = 7.628 + 2.224X_1 - 1.093X_2 + 0.023X_1X_2 - 1.193\ X_1^2 - 681X_2^2\ (\text{for } t_{75\%})$$

Figure 5: Response surface plot for $t_{10\%}$

Figure 7: Response surface plot for $t_{50\%}$

Figure 6: Contour plot for $t_{10\%}$

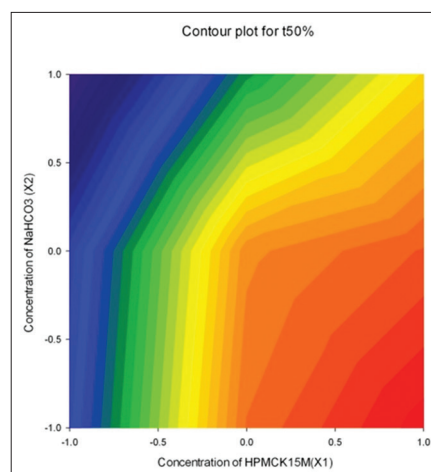**Figure 8:** Contour plot for $t_{50\%}$

$$Y_4 = 12.675 + 3.695X_1 - 1.816X_2 + 0.0375X_1X_2 - 1.983\ X_1^2$$
$$- 1.132X_2^2\ (\text{for } t_{90\%})$$

The positive sign for co-efficient of X_1 in Y_1, Y_2, Y_3, and Y_4 equations indicates that, as the concentration of HPMC K15M increases, $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ value increases. In other words, the data demonstrate that both X_1 (amount of HPMC K15M) and X_2 (amount of sodium bicarbonate) affect the time required for drug release ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$). From the results, it can be concluded that, as the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent ($NaHCO_3$) increases the drug release increases, drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels.

The dissolution parameters for predicted from the polynomial equations derived and those actual observed from experimental results are summarized in Table 6. The closeness of predicted and observed values for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ indicates the validity of derived equations for dependent variables. The contour plots were presented to show the effects of X_1 and X_2 on $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$. The final best (optimized) formulation (F_8) is compared with marketed product (BETACARD) shows similarity factor (f_2) 87.797, difference factor (f_1) 2.225 (There is no significant difference in drug release because t_{cal} is <0.05).

CONCLUSION

The present research work envisages the applicability of rate retarding agent and Gas generating agent such as HPMC

Table 6: Dissolution parameters for predicted and observed values for check point formulations

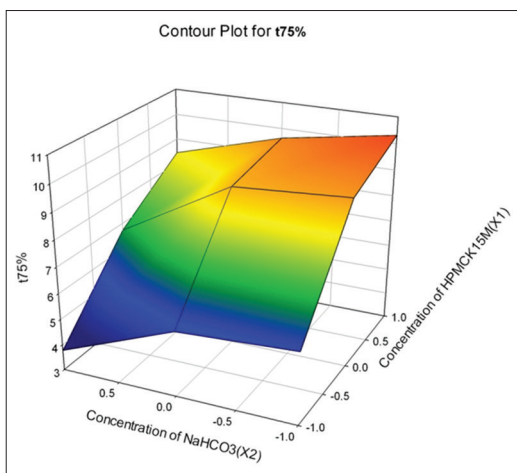| Formulation code	Predicted value				Actual observed value			
	$t_{10\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)	$t_{10\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
C1	0.502	3.300	6.600	10.966	0.505	3.303	6.602	10.970
C2	0.588	3.867	7.731	12.845	0.588	3.870	7.735	12.848

Figure 9: Response surface plot for $t_{75\%}$

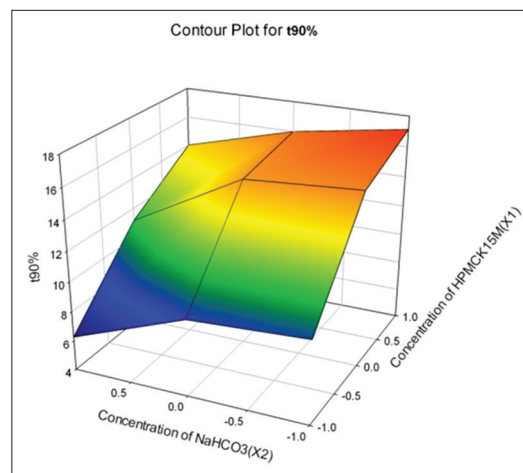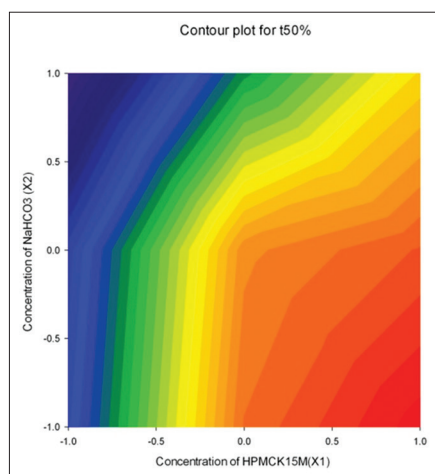**Figure 11:** Response surface plot for $t_{90\%}$

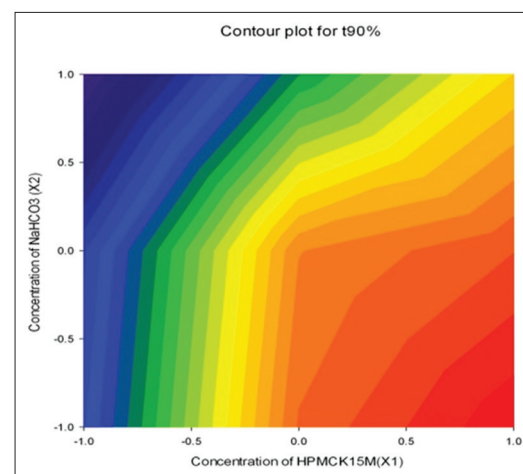**Figure 10:** Contour plot for $t_{75\%}$

Figure 12: Contour plot for $t_{90\%}$

K15M and sodium bicarbonate respectively in the design and development of Gastro Retentive Floating tablet formulations of Atenolol utilizing the 3^2 factorial design. From the results, it was clearly understand that As the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent ($NaHCO_3$) increases the drug release increases and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired floating delivery of the drug for longer periods. The optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to be non-Fickian diffusion (Super Case-II Transport), first order release type, controlled by diffusion through the swollen matrix. On the basis of evaluation parameters, the optimized formulation F_8 may be used once a day administration in the management of hypertension and angina pectoris.

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