Journal of PharmaSciTech
ISSN: 2231 3788 (Print)
2321 4376 (Online)
Research Article

Non Effervescent Floating Matrix Tablets of Atenolol: Formulation and Optimization using Box Behnken Design

Gayatri C. Patel, Ankita U. Patel*, Dinesh R. Shah

Maliba Pharmacy College, Surat - 394350, Gujarat, India

Correspondence: ankitapatel_0910@yahoo.com (Tel.+9194262 56571)

Abstract

Gastroretentive drug delivery systems have shown to be of a better significance in controlling the release rate for drug having site specific absorption. The aim of the present investigation was to develop non effervescent floating matrix tablets of atenolol. Since atenolol is a BCS class III drug, aim was to get controlled release and also to increase permeability *in vivo*. So, non effervescent floating matrix tablet was prepared using lipophilic surfactant and hydrophilic polymers. The prepared hot melt granules (HMG) were characterized by Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) and X-ray diffraction (XRD). There was no incompatibility observed in HMG. The HMG based floating matrix tablets were optimized by Box Behnken design to study the effect of independent variables, i.e. drug: lipophilic polymer ratio (X_1), drug: total polymer ratio (X_2) and hydrophilic polymer I: hydrophilic polymer II ratio (X_3) on dependent variables like % drug released at 1, 6 and 10 h. All batches showed good floating properties with total floating time more than 12 h. From the regression analysis, it was observed that all three independent variables show significant effect on the response variables. There was no significant change after 6 months of stability study of optimized batch.

Keywords: Atenolol, Box Behnken design, Controlled release, Floating tablets, Gastroretentive drug delivery system, Non effervescent system

Introduction

The drug bioavailability of pharmaceutical dosage forms is influenced by various factors. One of the important factors is the gastric residence time (GRT) of the dosage forms [1]. The gastric emptying process from the stomach to small intestine generally lasts from a few minutes to 12 h. This variability leads to an unpredictable bioavailability of an orally administered dosage form. Furthermore, the short gastric emptying time can result in an incomplete release of drug from the drug delivery system, leading to a diminished efficacy of the administered dose [2].

The aim of oral controlled release drug delivery system is to achieve better bioavailability and release drug from the system, which should be predictable and reproducible [3, 4]. Gastroretentive drug delivery systems can remain in the gastric region for several h and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment [5, 6]. It has applications also for local drug delivery to the stomach and proximal small intestine.

Atenolol is a hydrophilic Cardio selective ß-1 adrenergic receptor blocker devoid of intrinsic sympathomimetic and membrane stabilizing activity. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 50%, while the remaining is excreted unchanged in faeces [7, 8, 9]. This is because of its poor absorption in the lower gastrointestinal tract. It undergoes little or no hepatic first pass metabolism and its elimination half-life is 6 to 8 h [10, 11, 12]. An intubation technique in humans showed that atenolol absorption is greater in the jejunum than in the ileum. Furthermore, the human jejunum permeability and the extent of absorption are already low for this drug [13, 14]. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, result in either in the manifestation of side effects or reduction in drug concentration at the receptor site [15, 16]. Thus, it seems that an increase in GRT may increase the extent of absorption and bioavailability of the drug. Therefore, it is selected as a suitable drug for the design of a gastroretentive drug delivery system (GRDDS) with a view to improving its oral bioavailability.

Garg and Gupta [17] classified the gastroretentive dosage forms into four main classes: (i) floating systems, (ii) expandable systems, (iii) bioadhesive systems and (iv) high density systems. Floating systems are of two types: (A) Effervescent systems, depending on the generation of carbon dioxide gas upon contact with gastric fluids, and (B) Non effervescent systems. The non effervescent systems can be further divided into four sub-types, including hydrodynamically balanced systems, micro porous compartment systems, alginate beads and hollow microspheres/microballoons. In addition, super-porous hydrogels and magnetic systems were described.

Floating drug delivery system (FDDS) or hydrodynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach. As suggested by Singh and Kim [18], floating drug delivery is of particular interest for drugs which: (a) act locally in the stomach; (b) are primarily absorbed in the stomach; (c) are poorly soluble at an alkaline pH; (d) have a narrow window of absorption; and (e) are unstable in the intestinal or colonic environment.

The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release [19, 20]. Gastric floating drug delivery system releases the drug in the stomach and upper gastrointestinal tract and provide ample opportunity of absorption in the stomach and upper gastrointestinal tract.

The objective of the present investigation was to develop non effervescent floating matrix tablets of atenolol. Since atenolol is BCS class III drug, the aim was to get controlled release and tablet should release more than 90% of drug within 12 h but not more than 90% drug release within 10 h.

Materials and methods

Materials

Atenolol (Vapi Care Ltd., Vapi) was used as a model drug. Stearic acid (S D fine chem. Limited, Mumbai), Precirol ATO 5 (Gatteffose, Germany) and Glyceryl mono stearate (Yarrow Chem Products, Mumbai) were used as lipophilic surfactants. HPMC K4M, HPMC

K15M and HPMC K100M (Colorcon Asia Pvt. Ltd.) were used as hydrophilic swelling polymers. Microcrystalline cellulose PH101 (S D fine chem. Limited, Mumbai) was used as an additive. Talc and Magnesium stearate (S D fine chem. Limited, Mumbai) were used as a glidant and lubricant respectively.

Preparation, characterization and evaluation of hot melt granules (HMG) of atenolol

Preparation of hot melts granules of atenolol

Preliminary screening was done to select an appropriate lipophilic surfactant (LS) for the preparation of hot melt granules. For this study three LSs were selected, namely stearic acid, glyceryl monosterate and precirol ATO. Granules containing Atenolol were prepared using the melt granulation technique. The drug-LS ratio 1:1 was used.

Preparation of cream

The ingredients used for the preparation of cream have been mentioned in Table 1.

Method

In preparation of HMG, first lipid was melted in a porcelain dish at their respective melting temperature and the quantity of drug was added to melted mass, mixed well and cooled to room temperature. The mass was passed through a sieve 60# to obtain uniform size granules.

Characterization of HMG

The following analytical techniques were used to characterize the optimized HMG.

Differential scanning calorimetry (DSC)

Thermograms of samples were obtained using Perkins Elmer, Pyris 6DSC instrument. The samples were hermetically sealed in an aluminium pan and heated at a constant rate of 10°C min^{-1} over a temperature range of 25°C to 300°C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 40 ml min^{-1}.

Fourier transform infrared (FTIR) spectroscopy

HMG were powdered and ground with KBr and analyzed using Fourier transform infrared spectroscopy (FTIR) (Shimadzu FTIR-8400S with IR solution software). Data were collected over a spectral region from 4000 to 400 cm^{-1}.

X-ray diffraction (XRD) study

X-ray Diffraction of HMG was carried out using a Phillips PW 3710 scanner, IW 1830 generator with the CuKα anode at a voltage of 40 KV and a current of 30 MA and at a scan range of 1° min^{-1} from 2θ range from 0° to 50°.

Evaluation of HMG

Drug content

HMG equivalent to 10 mg of Atenolol was extracted with methanol. The solution was filtered through Whatman grade No. 1 filter paper. The sample was analyzed for drug content by a UV spectrophotometer (Shimadzu UV-1800 UV/Vis double-beam spectrophotometer) at 275nm after suitable dilutions. Determinations were performed in triplicate.

$$\% \text{ Drug content} = \frac{\text{Actual drug content}}{\text{Total drug amount taken}} \times 100 \quad \text{Eq.(1)}$$

Percentage yield

The percentage yield of prepared granules was calculated using the following equation,

$$\% \text{ Yield} = \frac{\text{Practical weight of HMG}}{\text{Theoretical weight of granules}} \times 100 \quad \text{Eq.(2)}$$

Flow property

The prepared HMG was evaluated for flow property parameters like bulk density, tapped density, Compressibility index, Hausner's ratio and angle of repose. All parameters were evaluated in triplicate.

***In vitro* evaluation of floating ability**

HMG equivalent to 50 mg of Atenolol were placed in 900 ml of simulated gastric fluid (SGF, pH 1.2) in a vessel which was maintained at 37 ± 0.5°C and stirred at 50 RPM in a USP XXIII paddle apparatus (Dissolution Test Apparatus-TDT 06T). Floating lag time and total floating time of the granules were measured.

Preparation and evaluation floating tablets

Optimization of variables using Box Behnken design

A Box Behnken design was used in the present study. In this design three factors were evaluated each of three levels and experimental trials were performed for all possible combinations. The ratio of (i) Drug: Stearic acid ratio (X_1), (ii) Drug: Total polymer ratio (X_2) and (iii) HPMC K4M: HPMC K100M ratio (X_3) was chosen as independent variables while % cumulative drug release at 1 h (Q_1), % cumulative drug release at 6 h (Q_6) and % cumulative drug release at 10 h (Q_{10}) were taken as dependent variables.The non-linear computer generated quadratic model is given as,

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 \quad \text{Eq. (3)}$$

Independent and dependent variables are given in Table 1.

Table 1: Independent and dependent variables

Independent variables	Variable level		
	Low (-1)	**Medium (0)**	**High (1)**
Drug : Stearic acid	1:0.5	1:1	1:15
Drug : Total polymer	1 : 1	1 : 15	1 : 2
HPMC K4M : HPMC K100M	25* : 75*	50* : 50*	75* : 25*

Dependent variables	
1.	% Cumulative release at 1 h (Q_1 in %)
2.	% Cumulative release at 6 h (Q_6 in %)
3.	% Cumulative release at 10 h (Q_{10} in %)

[*25%, 50% and 75% of total polymer]

Fabrication of atenolol floating matrix tablets

All the ingredients were passed from sieve no. 20# (Table 2).

A geometric mixture of hydrophilic polymers (HPMC K4M and HPMC K100M) and MCC PH 101 were added extra granularly in prepared HMG and mixed them properly. Talc (1%) and magnesium stearate (1%) were added at the last. The mass ready for compression was direct compressed using multi punch tablet compression machine (Rimek mini press-I) equipped with 9.0 mm diameter concave punches. Each tablet weighing 250 mg contains 50 mg of atenolol. Compression pressure was adjusted to obtain tablets with hardness in a range of 4-5 kg/cm^2. Prepared formulation batches were evaluated for weight variation, drug content, thickness, hardness, friability test, floating behaviour, tablet density, swelling study and *in vitro* dissolution study.

Physicochemical properties of powder blend ready for compression

The blend ready for compression was evaluated for evaluation parameters like flow property and drug content.

Evaluation of atenolol floating matrix tablets

Physicochemical properties

The prepared tablets were evaluated for physicochemical parameters like weight variation, thickness, hardness, friability test, etc [21, 22, 23].

Table 2: Composition of tablet formulations investigated in the present study

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Intragranular															
Atenolol	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Stearic acid	25	75	25	75	25	75	25	75	50	50	50	50	50	50	50
Extragranular															
HPMC K4M	25	25	50	50	18.75	18.75	56.25	56.25	12.5	25	37.5	75	37.5	37.5	37.5
HPMC K100M	25	25	50	50	56.25	56.25	18.75	18.75	37.5	75	12.5	25	37.5	37.5	37.5
MC	120	70	70	20	95	45	95	45	95	45	95	45	70	70	70
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mg stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250

Tablet density

The tablet will only float when its density is less than that of gastric fluid (~1.004) [24]. The density was determined using following relationship,

$$D = m/V \quad \text{Eq. (4)}$$

$$\text{Where, } V = \pi r^2 h \quad \text{Eq. (5)}$$

Where, V = volume of tablet (cm^3)

π = constant (3.14)

r = radius of tablet (cm)

h = crown thickness of tablet (gm/cm^3)

m = mass of tablet

Drug content

Ten tablets were finely powdered, quantities of the powder equivalent to 50 mg of atenolol were accurately weighed and transferred to a 100 ml of volumetric flask containing methanol and mixed thoroughly. The solution was made up to volume and filtered. Appropriate dilutions were made using methanol and absorbance of the resulting solution was measured at the maximum at 275 nm using a UV spectrophotometer.

Swelling index

For each formulation batch one tablet was weighed and placed in a petri plate containing 25mL of SGF pH 1.2. Tablets were taken out carefully after each h up to 12 h, blotted with filter paper to remove the water present on the surface and weighed accurately. All experiments were done in triplicate **[**25, 26**]**. Percentage swelling (swelling index) was calculated using following formula,

$$\text{Swelling index} = \frac{\text{Wet weight of the tablet - Dry weight of the tablet}}{\text{Dry weight of the tablet}} \times 100 \quad \text{Eq.(6)}$$

***In vitro* buoyancy study**

A floating behaviour study was carried out in a USP XXIII dissolution apparatus type II (Paddle) at a speed 50 RPM in 900 ml SGF at 37±0.5 °C for 12 h to mimic *in vivo* conditions[27]. The floating behaviour of the tablets was visually determined, in triplicate. The floating lag time (the time between tablet introduction and its buoyancy) and total floating duration (the time during which tablet remains buoyant) were recorded.

***In vitro* dissolution studies**

The release rate of atenolol from floating matrix tablets ($n = 3$) was determined using the Dissolution Test Apparatus II (paddle method). The dissolution test was performed using 900 ml of simulated gastric fluid (SGF) without the enzyme (pH 1.2), at 37±0.5 °C and 50 RPM. A 10 ml sample was withdrawn from the dissolution apparatus hly for 12 h, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 μm membrane filter and diluted to a suitable concentration with SGF (pH 1.2). Absorbance of this solution was measured at 274 nm wavelength using a UV/Vis spectrophotometer [21, 23]. The cumulative drug release was calculated using the equation generated from Beer Lambert's calibration curve in the linear range of 25-175 $\mu g\ ml^{-1}$. FLT and TFT of the tablets were measured during dissolution studies. Also, the drug stability in dissolution medium SGF pH 1.2 was checked for a period of 12 h.

Kinetic modelling and mechanism of drug release

Dissolution profile of all batches was fitted to various models such as zero order, first order, Higuchi [28], Hixson Crowell, Korsemeyer and Peppas [29] to ascertain kinetics of drug release. The method described by Korsemeyer and Peppas was used to describe the mechanism of drug release.

Statistical analysis

Response surface modeling and evaluation of the quality of fit of the model for the current study were performed employing Design Expert® software (Version 8.0.1, Stat-Ease Inc., Minneapolis, MN).

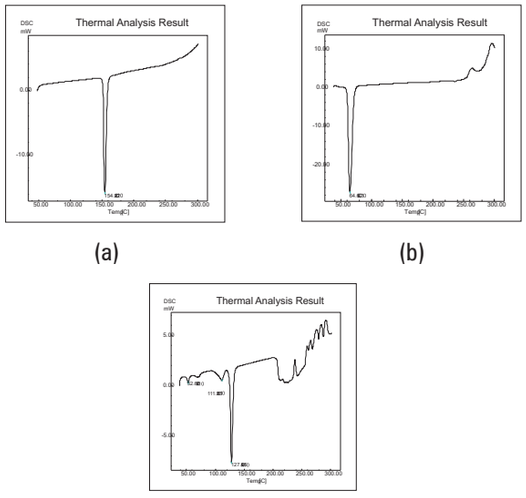
Stability study

Stability study of the optimized floating matrix tablet was carried out as per ICH guidelines at 40°C±2°C/75%±5% RH [30]. Physical appearance, hardness, floating time, drug content and *in vitro* release study were carried out over a period of 6 months at different time intervals of 0, 1, 3 and 6 months.

Results and discussion

Thermal analysis, FTIR spectroscopy and X-ray solid state characterization studies

DSC studies were performed to investigate the physical state of the drug within the LS matrix.



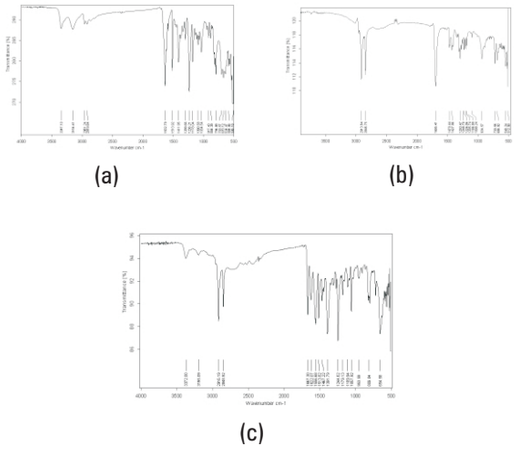
(a) (b)

(c)

Figure 1: Differential scanning calorimetric thermograms of (a) Atenolol, (b) Stearic acid and (c) HMG of atenolol with stearic acid

As it can be seen in Figure 1a and Figure 1b the DSC thermogram of pure drug and stearic acid showed a sharp melting peak at 154.22°C and 64.62°C respectively was indicating their crystalline and anhydrous nature. The DSC scan of the dispersion (Figure 1c) showed melting endotherm at 127.86°C. The shifts of the melting endothermic peak can be attributed to possible drug-stearic acid complex formation without any changes in the crystal modification.

The IR spectrum of atenolol, stearic acid and HMG of atenolol with stearic acid are shown in Figure 2. FTIR spectra of HMG of atenolol with stearic acid show all the characteristic peaks of atenolol.



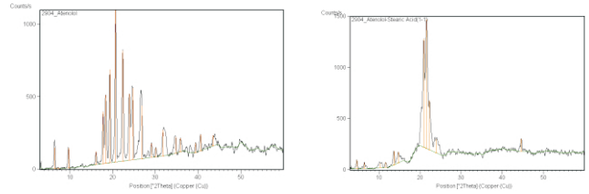
(a) (b)

(c)

Figure 2: FTIR spectra of (a) Atenolol, (b) Stearic acid and (c) HMG of atenolol with stearic acid

Thus, it can be interpreted that HMG merely formed the granules of atenolol with stearic acid.

To perform the crystalline nature of atenolol in granules, XRD analysis was performed. The diffractogram of atenolol and HMG are shown in Figure 3.



(a) (b)

Figure 3: X-ray diffractogram of (a) Atenolol and (b) HMG of atenolol with stearic acid.

Diffractogram (intensity vs 2θ°) of atenolol showed a high-intensity peak at 2θ values of 20.668, 22.353 and 19.297 which confirms its crystalline nature. In the spectra of HMG of atenolol with stearic acid showed numerous sharp and intense peaks. Here there is a decrease in number of peaks, might be due to the formation of complex between mutable binder and atenolol.

Physicochemical properties of HMG

Preliminary trials were done on selection of lipophilic surfactant for the preparation of floating matrix tablet of atenolol. The rationale behind the selection of LS was to control the drug release of highly acid soluble [31] drug atenolol and also to improve *in vivo* permeability. Dispersion of LS with atenolol was prepared by hot melt granulation method. HMGs were evaluated for their appearance, flow properties, *in vitro* floating ability, drug content and yield (Table 3).

Table 3: Physicochemical properties of HMG

Parameters	Lipophilic surfactant		
	Stearic acid	**Precirol ATO 5**	**GMS**
Content uniformity	99.88%	97.59%	96.33%
% Yield	99.97%	96.5%	90%
Flow property	Excellent	Good	Good
	FLT: 1.22 sec	FLT: 1.67 sec	FLT: 1.88 sec
In vitro floating ability	Total floating time: >12 h	Total floating time: >12 h	Total floating time: >12 h

From the results of drug content, it is reflected that the drug is uniformly dispersed with LS. Flow properties determination has helped to access the compressibility of prepared granules for the preparation floating matrix tablets. Table 3 showed the evaluation parameters of the prepared batches of HMG. It was found that granules prepared with stearic acid possessed all parameters in the satisfactory range. So stearic acid was optimized for the further preparation of tablets.

Physicochemical properties of powder blend ready for compression

The blend ready for compression was evaluated for evaluation parameters like flow property and drug content. Results are shown in Table 4.

Table 4: Evaluation of powder blend ready for compression

Batch no.	Angle of Repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	% Compressibility	Hausner's ratio	Drug content (%)
F1	26.10±1.04	0.34±.02	0.39±.04	12.82	1.14	98.15±0.32
F2	22.78±1.38	0.37±.04	0.43±.04	13.95	1.16	98.89±0.45
F3	24.70±1.42	0.33±.02	0.39±.02	15.38	1.18	97.96±0.19
F4	25.64±1.47	0.35±.04	0.41±.03	14.63	1.17	99.07±0.25
F5	23.27±1.24	0.35±.04	0.42±.03	16.67	1.14	97.78±0.27
F6	25.17±1.05	0.36±.03	0.41±.04	12.20	1.19	100.00±0.33
F7	22.94±1.68	0.37±.03	0.44±.02	15.91	1.19	100.56±0.48
F8	24.54±1.52	0.36±.02	0.42±.04	14.29	1.17	101.30±0.28
F9	24.54±1.96	0.34±.03	0.40±.03	15.00	1.18	98.52±0.34
F10	23.91±1.76	0.33±.04	0.38±.03	13.16	1.15	100.74±0.19
F11	24.70±1.34	0.36±.02	0.42±.02	14.29	1.17	98.33±0.14
F12	23.59±1.56	0.36±.02	0.41±.03	12.20	1.14	99.81±0.52
F13	23.75±1.48	0.35±.04	0.41±.04	14.63	1.17	99.26±0.34
F14	23.70±1.55	0.35±.03	0.41±.02	14.63	1.17	99.78±0.56
F15	23.65±1.68	0.35±.03	0.41±.02	14.63	1.17	99.96±0.44

Angle of repose of all batches varies from 22.94 to 25.64. Angle of repose less than 30 indicates good flow property. Compressibility index vary from 12.20% to 15.91%. Compressibility index 12 to 16% indicates good compressibility. Hausner's ratio varies from 1.14 to 1.19. Hausner's ratio less than 1.25 indicates good compressibility. Here all these results showed excellent flow property and compressibility which is favourable for direct compression. Drug content of batches F1-F15 varies from 97.78% to 101.30% indicates passes the all batches as per pharmacopoeial limit. Particle size of all batches ranges from 150-200 μm.

Physicochemical properties of floating matrix tablets of atenolol

The physicochemical properties of the tablets are summarized in Table 5. Microscopic examination of tablets from each batch showed white, circular and concave tablets with no cracks. The thickness of all tablet batches ranged from 4.61 - 4.93 mm. The measured hardness of tablets of each batch ranged between 4.27 - 4.79 kg/cm^2.

Table 5: Physicochemical properties of prepared atenolol floating matrix tablets

Batch no.	Average weight (mg) (n=20)	Thickness (mm) (n=5)	Hardness (kg/cm^3) (n=5)	Friability (%) (n=26)	Tablet density (gm/cm^3)	Assay (%) (n=20)	FLT (sec.) (n=10)	Total floating duration (h)
F1	250.1±2.88	4.84±0.01	4.67±0.12	0.79	0.88	99.80±0.10	1.33±0.58	9
F2	250.0±2.31	4.86±0.02	4.30±0.10	0.68	0.92	98.32±0.20	2.00±0.10	11
F3	249.7±2.75	4.87±0.01	4.79±0.06	0.65	0.87	100.44±0.23	1.33±0.58	>12
F4	250.9±2.38	4.61±0.01	4.50±0.10	0.54	0.96	99.61±0.33	1.67±0.58	>12
F5	250.4±2.99	4.88±0.02	4.43±0.21	0.74	0.98	99.21±0.19	2.33±0.58	>12
F6	250.3±3.27	4.72±0.01	4.43±0.12	0.660	0.91	98.68±0.22	1.67±1.15	>12
F7	249.4±2.84	4.93±0.01	4.70±0.10	0.69	0.88	100.34±0.30	1.33±0.58	>12
F8	250.3±2.58	4.74±0.02	4.27±0.06	0.62	0.95	100.81±0.36	1.33±0.58	>12
F9	249.8±2.25	4.75±0.006	4.50±0.06	0.76	0.93	99.48±0.20	1.67±0.58	>12
F10	250.1±2.96	4.87±0.010	4.57±0.06	0.61	0.89	98.24±0.31	1.67±1.15	>12
F11	250.0±3.20	4.77±0.006	4.33±0.21	0.75	0.90	100.48±0.44	1.33±0.58	>12
F12	250.2±2.49	4.74±0.015	4.77±0.12	0.57	0.86	99.83±0.31	1.67±0.58	>12
F13	249.9±2.60	4.74±0.006	4.43±0.21	0.68	0.92	99.35±0.31	1.33±0.56	>12
F14	250.5±2.96	4.73±0.010	4.57±0.06	0.66	0.94	100.17±0.37	1.33±0.56	>12
F15	250.0±2.60	4.74±0.006	4.63±0.15	0.65	0.93	99.43±0.22	1.33±0.56	>12

This ensures good handling characteristics of all batches. All the tablet formulae showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability. The weight of the tablets ranged from 249.4 - 250.9 mg. So, all tablets passed the weight variation test as the % weight variation was within the pharmacopoeial limits of 7.5% of the weight. Drug uniformity results were found to be good among different batches; the percentage of drug content ranged from 98.24±0.31% to100.81±0.36%. The percentage friability for all formulae was less than 1%, indicating good mechanical resistance. All batches showed density less than 1.0 g/cm^3.

Swelling index

The hydration ability of the formula is important because it influences: (i) tablet buoyancy, (ii) adhesion ability of swellable polymers as HPMC K4M and/or HPMC K100M in contact with the test fluid and (iii) drug release kinetics.

Plot of %swelling index against time (h) is depicted in Figure 4.

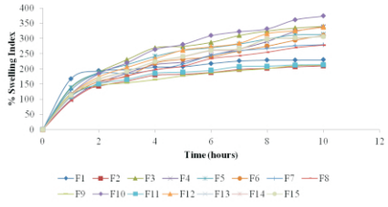


Figure 4: Swelling index of batches F1 - F15

Swelling increases as the time passes because the polymer gradually absorbs water due to hydrophilicity of polymer. The outer most hydrophilic polymer hydrates and swells and a gel barrier are formed on the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling, release process is repeated towards new exposed surfaces, thus maintaining the integrity of the dosage form.

In the present study, the higher swelling index was found in tablets of batch F10 containing higher concentrations of HPMC K4M (25mg) and HPMC K100M (75mg). Thus, the viscosity of the polymer had a major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that a linear relationship exists between swelling process and viscosity of polymer.

Floating lag time and duration

In the study it was observed that the tablets of all batches showed good floating characteristics after buoyancy lag time due to lower the density of tablets than gastric fluid (~1.004 g/cm^3). All tablets float within 1-3 Sec without sinking. From the results of total floating time it can be concluded that all batches showed a good duration of floating i.e. floating time more than 12 h.

***In vitro* dissolution study**

In vitro drug release data and profile of prepared tablets are shown in Figure 5. It is clear that all formulae succeeded in controlling the rate of

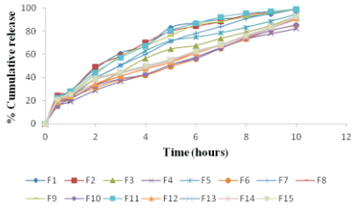


Figure 5: In vitro drug release profile of batches F1 - F15

drug release for 12 h. However, the drug release rate was dependent on the type and concentration of the investigated polymer(s).

In the present study, HPMC K4M and HPMC K100M are hydrophilic in nature while stearic acid is hydrophobic. The concentration of steric acid affects drug release. The release rate in F4, F6 and F8 (75mg stearic acid) showed good sustaining effect in comparison to F1, F3, F5 and F7 (25 mg stearic acid). From the result data of *in vitro* dissolution study, it can be concluded that drug release decreased with increased concentration of stearic acid, which prohibited penetration of dissolution medium into the hydrophilic matrix.

The concentration of HPMC K4M and HPMC K100M also affect drug release. As the amount of total polymer increases, the drug release decrease. HPMC K100M is more viscous than HPMC K4M, so as the amount of HPMC K100M increases, the drug release decreases.

The higher viscosity of HPMC K100M would promote the formation of highly viscous gels upon contact with aqueous fluids. This would promote retardation of the drug release rate. In a parallel line, Siepmann and Peppas suggested that the drug release from HPMC matrices is sequentially governed as follows: (i) At the beginning, steep water concentration gradients are formed at the polymer/water interface resulting in water imbibition into the matrix. (ii) Due to the imbibition of water, HPMC swells resulting in dramatic changes of polymer and drug concentrations and increasing the dimensions of the system. (iii) Upon contact with water, the drug dissolves and diffuses out of the device due to concentration gradients. (iv) Water content increases, the diffusion coefficient of the drug increases substantially.

From the result, it was concluded that the concentration of hydrophilic polymers (HPMC K4M and HPMC K100M) along with lipophilic surfactant (stearic acid) was sufficient to retard the atenolol release upto 12 h.

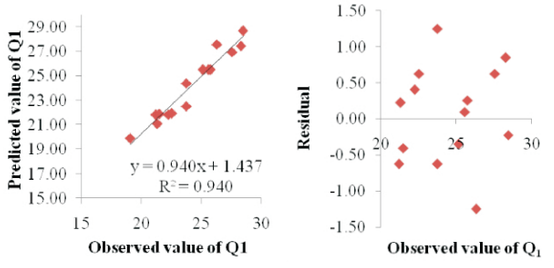
Kinetic modelling and mechanism of drug release

The drug release from the polymeric systems is mostly by diffusion and is best described by Fickian diffusion. Korsmeyer and Peppas equation superposes two apparently independent mechanisms of drug transport, Fickian diffusion and a case-II transport, for the description of drug release from a swelling polymer. For a matrix tablet, when n takes the value of 0.45 it indicates diffusion-controlled drug release and for the value more than 0.89, it indicates swelling-controlled drug release. Values of n between 0.45 and 0.89 can be regarded as an indicator for both the phenomena (anomalous transport). The value of n with the corresponding correlation coefficients for all the formulae is shown in Table 6.

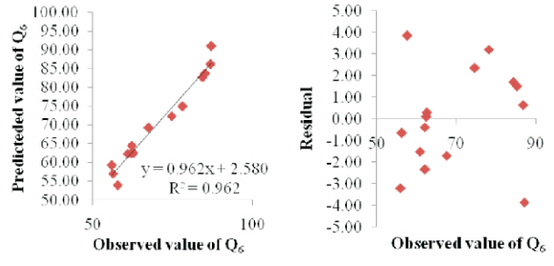
Table 6: Mathematical modelling and release kinetics of atenolol from the prepared floating tablets

Batch no.	Zero order kinetics	Higuchi kinetics	First order kinetic	Hixon Crowel kinetic	Korsmeyer Peppas		Mechanism of drug release
	R^2	R^2	R^2	R^2	R^2	N	
F1	0.8659	0.9583	0.5551	0.9082	0.7239	0.576	Non-Fickian
F2	0.8827	0.9671	0.5603	0.9238	0.7044	0.522	Non-Fickian
F3	0.9691	0.9943	0.7302	0.9551	0.8313	0.560	Non-Fickian

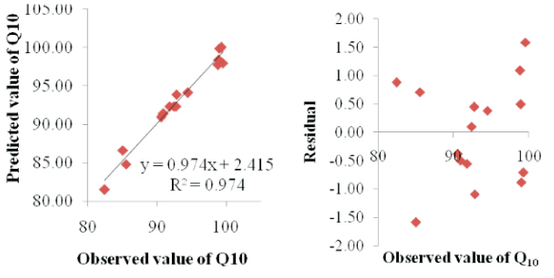
Batch no.	Zero order kinetics	Higuchi kinetics	First order kinetic	Hixon Crowel kinetic	Korsmeyer Peppas		Mechanism of drug release
	R^2	R^2	R^2	R^2	R^2	N	
F4	0.9909	0.9878	0.8178	0.9872	0.8838	0.550	Non-Fickian
F5	0.9317	0.9890	0.6547	0.8674	0.8091	0.623	Non-Fickian
F6	0.9943	0.9739	0.8298	0.9715	0.8532	0.466	Non-Fickian
F7	0.9311	0.9868	0.6630	0.9313	0.8000	0.579	Non-Fickian
F8	0.9908	0.9868	0.7891	0.9681	0.8482	0.502	Non-Fickian
F9	0.8898	0.9721	0.5937	0.9192	0.7617	0.628	Non-Fickian
F10	0.9892	0.9826	0.8032	0.9812	0.8712	0.523	Non-Fickian
F11	0.8774	0.9624	0.5788	0.9399	0.7286	0.534	Non-Fickian
F12	0.9933	0.9809	0.7938	0.9580	0.8309	0.459	Non-Fickian
F13	0.9922	0.9789	0.7699	0.9033	0.8052	0.439	Fickian
F14	0.9930	0.9790	0.7753	0.9045	0.8105	0.442	Fickian
F15	0.9922	0.9797	0.7664	0.9021	0.7982	0.431	Fickian



(a)



(b)



(c)

Figure 6: Linear and residual plots between observed and predicted values of (a) Y1 (Q_1), (b) Y2 (Q_6), (c) Y3 (Q_{10})

Upon comparison of observed responses with that of anticipated responses, the prediction error varies between -1.25 to +1.25, -3.85 to +3.85 and -1.59 to + 1.59 for Y_1, Y_2 and Y_3 respectively. The linear correlation plots drawn between predicted and observed responses shows values of R^2, which are 0.940, 0.962 and 0.974 for Y1, Y2 and Y3 indicating excellent goodness of fit. The corresponding residual plots show nearly uniform and random scatter around the mean values of response variables.

In the present investigation, three factors were evaluated each of three levels and experimental trials were performed for all possible combinations using the Box Behnken design. In this design three factors were evaluated each of three levels and experimental trials were performed for all possible combinations. The mathematical models developed for all the dependent variables using statistical analysis software are shown in Equations (*7*) - (*9*):

Factorial equation for Q_1

$$Y1 = 25.48 - 0.60X_1 - 3.16X_2 + 0.63X_3 - 0.35X_1X_2 - 0.64X_1X_3 + 0.08X_2X_3 - 1.95X_1^2 - 0.50X_2^2 - 1.02X_3^2 \quad \text{Eq. (7)}$$

$R^2 = 0.9405$

The amount of drug released at 1 h from the F1-F15 batches of floating matrix tablet varied from 19.07% to 28.45%. **This showed best fit to the model.** From the P-value, it was concluded X_2 has the prominent effect **($P < 0.05$)** on the Q_1 than X_1 and X_3. (A negative sign of X_1, X_2 and X_3 in the regression equation indicate the response value decreases as the amount of factors increases and positive sign of X_1, X_2 and X_3 in the regression equation indicate the response value increases as the amount of factors increases.)

Factorial equation for Q_6

$$Y2 = 62.44 - 5.90X_1 - 12.62X_2 + 1.97X_3 - 1.77X_1X_2 + 0.68X_1X_3 + 0.73X_2X_3 - 3.6X_1^2 - 8.15X_2^2 - 1.73X_3^2 \quad \text{Eq. (8)}$$

$R^2 = 0.9629$

The amount of drug released at 6 h from the F1-F15 batches of floating matrix tablet varied from 56.03% to 87.1%. This showed best fit to the model. From the P-value, it was concluded that X_1 ($P < 0.05$) and X_2 ($P < 0.05$) both have the prominent effect on the Q_6 than X_3.

The amount of drug released at 6 h from the F1-F15 batches of floating matrix tablet varied from 56.03% to 87.1%. This showed best fit to the model. From the P-value, it was concluded that X_1 ($P < 0.05$) and X_2

($P < 0.05$) and X_3 **($P < 0.05$)** have the prominent effect on the Q_{10}.

The optimization of formulation was carried out by plotting contour plots (3-D) and surface plots (2-D) for all observed dependent variables. Here, contour plots and surface plots were drawn using the design expert 7.1.6 software. These types of plots are useful in a study of the effects of two factors on the response at one time. In all presented plots, the third factor was kept at a constant level. Various contour plots and response surface plots are depicted Figures 7(a-c) for Q_1, Q_6 and Q_{10} respectively.

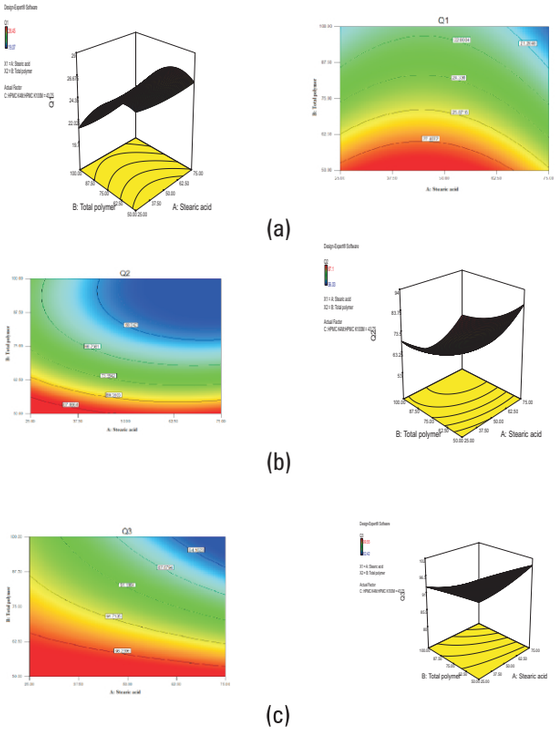


Figure 7: Contour plots and 3 D surface plot for (a) Q_1, (b) Q_6 and (c)Q_{10}

Figure 7a shows the response surface plot, which displays the effect of X_1, and X_2 on the Q_1 (Y1). From the figure, at a fixed percent of X_3, increasing X_1 up to 75 (level 1) along with increasing X_2 up to 100 (level 1) results in decreasing Q_1 of the formulation to 21.While using the low level (level -1) of X_1 along with decreasing X_2 (level -1) results in increasing the Q_1 of the formulation to 27. From the figure it was concluded that, X_1 has a more prominent effect on Q_1 than X_2.

Figure 7b shows the response surface plot, which displays the effect of X_1, and X_2 on the Q_1 (Y1). From the figure, at a fixed percent of X_3, increasing X_1 up to 75 (level 1) along with increasing X_2 up to 100 (level 1) results in decreasing Q_1 of the formulation to 60.While using the low level (level -1) of X_1 along with decreasing X_2 (level -1) results in increasing the Q_1 of the formulation to 87. From the figure it was concluded that, X_1 has a more prominent effect on Q_2 than X_2.

Figure 7c shows the response surface plot, which displays the effect of X_1, and X_2 on the Q_1 (Y1). From the figure, at a fixed percent of X_3, increasing X_1 up to 75 (level 1) along with increasing X_2 up to 100 (level 1) results in decreasing Q_1 of the formulation to 64.While using the low level (level -1) of X_1 along with decreasing X_2 (level -1) results in increasing the Q_1 of the formulation to 96. From the figure it was concluded that, X_1 has a more prominent effect on Q_2 than X_2.

Optimization of floating matrix tablets

Upon 'trading of' various response variables and comprehensive evaluation of feasibility search and exhaustive grid search, the formulation composition with 53.33 mg of hydrophobic polymer and 96.67mg hydrophilic was found to fulfil the maximum requisite of an optimum formulation. So we found total two batches F10 and F12 which satisfied the values obtained from overlay plot [X1 (Stearic acid) = 53.33mg and X2 (HPMC K4M + HPMC K100M) = 96.67 mg]. But from the % cumulative drug release study and data of kinetic modelling the optimized batch was found to be F10.

Stability study

Tablets were evaluated periodically (0, 1, 2 and 3 months) for appearance, hardness, friability, swelling index, floating test, drug content and in vitro drug release. Results of stability study are given in Table 7.

Table 7: Results of stability study of optimized batch

Tested after time (days)	Hardness (kg/cm2)	Swelling index	Floating test		Drug Content (%)	(%) Drug release
			FLT (sec)	TFT (h)		
At 25°C and 40% RH						
0	4.57	373.41	1	>24	98.24	93.19
1	4.56	371.56	2	>24	98.20	93.00
2	4.54	372.65	2	>24	97.53	92.45
3	4.53	370.78	1	>24	96.56	91.26
At 40°C and 75% RH						
0	4.57	373.41	1	>24	98.24	93.19
1	4.55	372.54	1	>24	97.42	92.96
2	4.54	370.45	2	>24	96.86	92.24
3	4.52	370.86	2	>24	95.99	91.78

No significant changes were observed in physical appearance, hardness, drug content, *in vitro* release study and total floating time during the study period.

Conclusion

The present investigation deals with the formulation development and optimization of non effervescent based floating matrix tablet of atenolol using HMG of Atenolol with stearic acid. Combination of HPMC K4M and HPMC K100M were used as the release rate controlling polymers. Optimization was done using Box Behnken design at 3 levels and 3 factors. From the polynomial equation and contour plots generated, all 3 independent factors showed significant effect on dependent variables. The controlled release of Atenolol was observed and good fit to the zero order and Higuchi model was demonstrated. The optimized batch F10 (50 mg of stearic acid, 25 mg of HPMC K4M and 75 mg of HPMC K100M) exhibited the hypothesis criteria. Thus the non effervescent floating matrix tablets using HMG is suitable to get site specific delivery and controlled release.

Acknowledgement

We sincerely thank to Vapi Care Ltd, Vapi, India who gifted drug sample. We also thankful to Dr. Shailesh A. Shah, Head of the P. G. Dept., for valuable advice and suggestions.

Conflict of Interest: The authors confirm that this article content has no conflict of interest.

References

[1] Desai S, Bolton S. A floating controlled-release drug delivery systems: *in vitro - in vivo* evaluation. Pharm Res 1993; 10:1321-25.

[2] Chueh HR, Zia H, Rhodes CT. Optimization of sotalol floating and bioadhesive extended release tablet formulations. Drug Dev Ind Pharm 1995; 21:1725-47.

[3] Hoffmann A. Pharmacodynamic aspects of sustained release preparations. Adv Drug Deliv 1998; 33:185-99.

[4] Stanley SD, Lisbeth I. Drug delivery system for challenging molecules. Int J Pharm 1998; 176:1-8.

[5] Prajapati ST, Patel LD, Patel DM. Gastric floating matrix tablets: design and optimization using a combination of polymers. Acta Pharm 2008; 58:221-9.

[6] Sauzet C, Claeys-Bruno M, Nicolas M, et al. An innovative floating gastro retentive dosage system: formulation and *in vitro* evaluation. Int J Pharm 2009; 378:23-9.

[7] Doller C. Therapeutic Drugs, 1st ed. Edinburgh: Curchill Livingstone; 1999; p. 224-7.

[8] Hoffman BB. Catecholamines, sympathomimetics drugs, and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, editors. Goodman Gilman's: The Pharmacological Basis of Therapeutics, 10th ed.; New York: McGraw Hill, 2001.

[9] Lorey K. Analytical profile of drug substances, 12th ed.; Vol. 13. New Deli: Reed Elsevier, India Pvt. Ltd; 2005, p. 2-25.

[10] Kirch W, Gorg KG. Clinical pharmacokinetics of atenolol-a review. Eur J Drug Met Pharmacokinet 1982; 7:81-91.

[11] Melander A, Stenberg P, Liedholm H, et al. Food-induced reduction in bioavailability of atenolol. Eur J Clin Pharmacol 1979; 16:327-30.

[12] Srivastava AK, Wadhwa S, Ridhurkar D, et al. Oral sustained delivery of atenolol from floating matrix tablets formulation and *in vitro* evaluation. Drug Dev Ind Pharm 2005; 31:367-74

[13] Amidon GL, Lennernas H, Shah VP, et al. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res 1995; 12:413-20.

[14] Sutcliffe FA, Riley SA, Lynch J, et al. Comparative absorption of drugs from jejunum and ileum of rat and human. In: Third Conference on Drug Absorption, Conference Edimburg, 1988, 37.

[15] Sastry SV, Reddy IK, Khan MA. Atenolol gastrointestinal therapeutic system: Optimization of formulation variables using response surface methodology. J Control Release 1997; 45:121-30.

[16] Vaithiyalingam SR, Sastry SV, Dehon RH, et al. Long-term stability characterization of a controlled release gastrointestinal therapeutic system coated with a cellulose acetate pseudolatex. Pharmazie 2001; 56:66-9.

[17] Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop J Pharm Res 2008; 7:1055-66.

[18] Singh BN and Kim KH, "Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention", J Control Release 2000; 63:235-59.

[19] Arora S, Ali J, Ahuja A, et al. Floating drug delivery systems of celecoxib. AAPS PharmSciTech 2005; 6:372-90.

[20] Narayana CR, Basavaraj BV, Madhavan, V. Microballoons of Famotidine: A non-effervescent gastroretentive controlled drug delivery system using Eudragit L-100. Der Pharmacia Lettre 2010; 2:176-89.

[21] Lachman L, Liberman HA, Kanig JL. The Theory and Practice of industrial Pharmacy, 3rd ed.; Varghese Publishing House: Bombay, 1987, p 297-300.

[22] Martin A. Micromeretics, In: Martin A, Ed. Physical Pharmacy, Baltimores, MD: Lippincott Williams and Wilkins, 2001, pp 423-54.

[23] Indian Pharmacopoeia, Government of India, Ministry of Health and Family welfare, The Indian pharmacopoeia commission, Ghaziabad, 2007, 1:182-3.

[24] Maru AD, Lalla JK. Intragastric floating tablets as novel oral drug delivery systems. Indian drugs 1987; 25:57-69.

[25] Bhosale UV, Kusum Devi, Jain N, et al. Effect of polymer concentration and viscosity grade on Atenolol release from gastric floating drug delivery system. Indian J Pharma Educ Res 2010; 44:267-73.

[26] Wang L, Tang X. A novel ketoconazole bioadhesive effervescent tablet for vaginal delivery: design, *in vitro* and *in vivo* evaluation. Int J Pharm 2008; 350:181-7.

[27] Rosa M, Zia H, Rhodes T. Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral application. Int J Pharm 1994; 105:65-70.

[28] Higuchi T. Mechanism of sustained action medication. J Pharm Sci 1963; 52:1145-49.

[29] Korsmeyer RW, Gurny R., Docler E, et al. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm 1983; 15:25-35.

[30] Mathews BR. Regulatory aspects of stability testing in Europe. Drug Dev Ind Pharm 1999; 25:831-56.

[31] National Center for Biotechnology Information, U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD20894, USA Refer:https://pubchem.ncbi.nlm.nih.gov/compound/atenolol#section=Depositor-Supplied-Synonyms