

DEVELOPMENT OF GASTRORETENTIVE OPTIMIZED ONCE A DAY FLOATING AND/OR BIOADHESIVE TABLET OF ALFUZOSIN

JADHAV KHANDERAO R.*¹, PAWAR ASHISH Y.² & TALELE GOKUL S.³

¹Department of Pharmaceutical Sciences, JJT Univesity, Rajasthan, India. ²Department of Pharmaceutics, MGV's Pharmacy College, Nashik, Maharashtra, India. ³Department of Pharmaceutical Chemistry, NGSPM's College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.
 Email: krjadhav25@gmail.com

Received: 18 June 2013, Revised and Accepted: 10 July 2013

ABSTRACT

A novel extended release Alfuzosin hydrochloride (HCL) tablet formulation which possesses a unique combination of floatation and bioadhesion for prolonged residence in the stomach has been developed. Alfuzosin HCl is a selective α -adrenergic antagonist used against benign prostatic hyperplasia (BPH). The usual dose of immediate release Alfuzosin HCl tablet is 2.5mg thrice a day. Therefore, there is need to formulate once daily sustained release tablet of Alfuzosin HCl which is convenient for older patients. In this work floating and/or bioadhesive tablets were prepared by direct compression method which is economical and easy to scale up. Polymers like Hydroxy propyl methyl cellulose (HPMC K100M), Carbopol 934P, Sodium carboxyl methyl cellulose (Na CMC) & Sodium bicarbonate in different ratios. Formulations were evaluated for *in vitro* drug release profile, swelling characteristics and *in vitro* bioadhesion property. Sustained drug release with floating duration up to 24hrs and high bioadhesive strength was observed in case of Optimized formulation.

Keywords: Alfuzosin, Gastro retentive, Optimized, Controlled release.

INTRODUCTION

Oral sustained release systems continue to be the most popular ones among all drug delivery systems due to their several advantages over the conventional systems like; Improved patient compliance, less frequent dosing, reduction in fluctuation of steady state plasma levels, reduction in health care cost through improved therapy and shorter treatment period [1, 2] and patentability and opportunity for extending product life-cycle [3]. However, the problem frequently encountered with oral sustained release dosage forms is inability to increase the residence time of the dosage form in stomach and proximal portion of the small intestine, due to the rapid gastrointestinal transit phenomenon of stomach which may consequently diminish the extent of absorption of many drugs since most of the drug entities are absorbed from the upper part of intestine. Therefore it would be beneficial to develop sustained release formulations which remain at the absorption site for an extended period of time. Several approaches have emerged to prolong the residence time of the dosage form at the absorption site and oral sustained release bioadhesive floating system are one of the approach.

Alfuzosin HCl is a selective α -adrenergic antagonist used against benign prostatic hyperplasia (BPH). It is freely soluble in water and readily absorbed from proximal part of gastrointestinal tract after oral administration [7,8]. The pK_a of the drug is 8.1 and elimination half-life of immediate release (marketed) tablet is 3-5h. The usual dose of immediate release Alfuzosin HCl tablet is 2.5mg thrice a day. Marketed (U.S.) alfuzosin tablet is a three layered geomatrix tablet

that requires special facility high cost and complex operation than conventional formulation. Therefore, there is need to formulate once daily sustained release tablet of Alfuzosin HCl which is convenient for older patients. In this work floating and/or bioadhesive tablets were prepared by direct compression method which is economical and easy to scale up.

EXPERIMENTAL

Materials

Alfuzosin HCl was obtained as gift sample from Hetero Drugs Ltd (Baddi), HPMC K100M from Colorcon Ltd., Goa, SCMC from Lupin Pharmaceuticals, Pune. Other materials used were of AR Grade and were purchased from Modern Science Apparatus, Nasik.

Experimental design [9-10]

Formulation & development

A 3² full-factorial design was applied in the present study. In this design two factors were evaluated at 3 different levels and experimental trials were performed at all 9 possible combinations. The amount of release rate modifying HPMC K100M (X1) and amount of bioadhesive polymer SCMC (X2) were selected as independent variables while t50%, t90%, floating lag time and detachment force were selected as dependent variables. The formulations are shown in Table 1.

Table 1: Formulations of Factorial design

Ingredients	FT-1	FT-2	FT-3	FT-4	FT-5	FT-6	FT-7	FT-8	FT-9
Alfuzosin HCl	10	10	10	10	10	10	10	10	10
HPMCK 100M	120	90	60	120	90	60	120	90	60
Carbopol 934P	90	90	90	60	60	60	30	30	30
NaCMC	20	20	20	20	20	20	20	20	20
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Citric acid	25	25	25	25	25	25	25	25	25
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total weight	320	290	260	290	260	230	260	230	200

Preparation of Tablets

The direct compression technique was followed to manufacture tablets for all batches containing Alfuzosin HCl, HPMC K100M, CP934P, NaCMC; Sodium bicarbonate was passed through # 36 sieves. Magnesium stearate and Citric acid were passed through # 60 sieves. Weighed amounts of drug as well as all other ingredients were transferred into polythene bag and blended for 10 minutes. The blend was compressed using 10-station rotary press using round shaped punches. Punches measuring 8 & 10 mm diameter were used for compression of the tablets. Compression force for all the tablets was adjusted to get tablets of hardness 7-9 kg/cm².

Evaluation of Tablets

Evaluation of Tablet characteristics

All tablets were tested for appearance, colour and odour. Tablets were also evaluated for hardness (Pfizer type hardness tester General Machines, Ahmedabad, India), friability (Roche friabilator Remi Electronics, Mumbai, India), content uniformity and thickness.

Determination of Floating Behavior of Tablets: [8]

1. Floating (buoyancy) lag time (FLT) of tablets

The buoyancy lag time was determined using a 500 ml beaker containing 0.1N HCl. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as floating lag time (FLT).

2. The buoyancy (Floating) duration

Duration of buoyancy is the time for which the tablet constantly floats on the surface of the medium. The duration of buoyancy was measured using a 500 ml beaker containing 0.1NHCl.

Ex-vivo Mucoadhesion Measurement of Tablets: [11-12]

Ex-vivo mucoadhesion measurement was done using modified balance method. Briefly, Pieces of goat fundus 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 fundus 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 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 (Fig.1). The bioadhesive force, expressed as the detachment stress in dyne/cm², was determined from the minimum weight required to detach the two vials using the following equation,

$$\text{Detachment stress (dyne/cm}^2\text{)} = m \cdot g / A$$

(Where, m-balance weight, A-area of surface, g-acceleration due to gravity)

Determination of Swelling Index of Tablets:

The swelling index of preweighed tablet was determined using USP type I dissolution apparatus (DISSO 2000 LABINDIA) at 50 rpm and 0.1 N HCl was used as medium; temperature was maintained at 37± 0.5°C. At selected time intervals, the specimens were removed, wiped gently with a tissue paper to remove surface water and weighed. Swelling characteristics of the tablet was expressed in terms of swelling index which was calculated by using following formula.

$$\% \text{ of hydration} = (W_2 - W_1) \times 100 / W_1$$

Where W₁- initial weight of tablet, W₂- weight of disc after specified time interval.

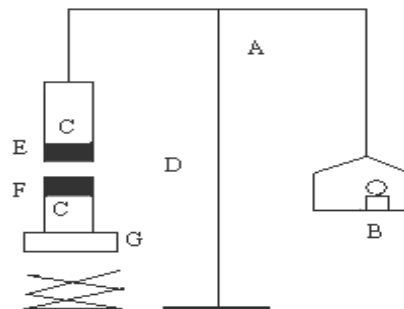


Figure 1: Modified balance for the measurement of bioadhesive strength B, weights; C, glass vial; D, Bioadhesive tablet; E, Intestine tissue; F, supportive adhesive tape; G, height adjustable pan

Determination of Matrix erosion [11-12]

The swollen tablets in swelling study at 24 hours were dried at 60°C in vacuum oven subsequently dried in desiccators for 2 days and reweighed (W₃). Matrix erosion at 24h was calculated by using following formula,

$$DS = (W_1 - W_3) \times 100 / W_1$$

Where, W₁- initial weight of tablet, W₃ = Weight of tablets dried at 60°C for 24 hrs in vacuum oven.

In-vitro drug release [11-12]

In-vitro drug release study of the samples was carried out using USP - type II dissolution apparatus (Peddle type). The dissolution medium, 900 ml of simulated gastric fluid (without enzyme), was placed into the dissolution flask maintaining the temperature of 37 ± 0.5 °C and rpm of 100. One Alfuzosin HCl matrix tablet was placed in each basket of the dissolution apparatus. The apparatus was allowed to run for 24 hours. Samples measuring 5 ml were withdrawn after every 1 hour up to 24 hours manually and samples were filtered. The fresh dissolution medium was replaced every time with the same quantity of the sample withdrawn. Collected samples were analyzed at 245 nm using 0.1 N HCl as blank. The cumulative percentage drug release was calculated using PCP Disso v3 software.

Stability study

The optimized formulation was wrapped in aluminum foil and subjected to 40 ± 0.5°C temperature in oven for the period of three month. The formulation was analyzed for organoleptic characteristics, hardness, drug content and dissolution.

RESULTS AND DISCUSSION

Evaluation of tablets

The tablet formulations were subjected to various evaluation tests, such as thickness, diameter, uniformity of weight, drug content, hardness, friability, and in-vitro dissolution. The results for all the formulations are shown in Table 2. The thickness of all the formulations were varied with drug: polymer ratio it ranges from 3.01-3.96 mm. The weight variation test was carried out as per official method and the average percentage deviation of all the formulation was found to be within the limit (as per pharmacopeial standard the deviation should not be more than 5% for tablet having weight 350 mg) i.e. less than 5%. The content uniformity test was also carried out as per official method and it was found that different batches shows good content uniformity. It was found that all batches

shows percent drug content more than 95%. The tablet hardness of all the formulations was determined and it was found in the range 3.5-5 kg/cm². Another measure of tablet hardness was the friability.

Compressed tablets that lose less than 1 % of their weight are generally considered acceptable. For all formulation tried here the weight loss was less than 1 % hence acceptable

Table 2: Evaluation of Final Formulation Tablets

Batch Code	Hardness Kg/cm ²	Friability (%)	Uniformity of weight	Thickness (mm)	Drug Content (%)
1	3.5±0.41	0.2559	310±0.13	3.96±0.032	99.54±0.32
2	3.8±0.27	0.1870	284±0.21	3.54±0.011	99.42±0.45
3	4±0.31	0.275	253±0.11	3.35±0.043	98.35±0.12
4	4.2±0.3	0.4760	285±0.37	3.53±0.129	98.55±0.56
5	4±0.45	0.104	254±0.18	3.36±0.05	99.38±0.23
6	4.5±0.35	0.329	225±0.15	3.1±0.083	99.24±0.75
7	4.5±0.4	0.149	252±0.16	3.32±0.074	99.96±0.85
8	4.3±0.51	0.335	224±0.14	3.12±0.012	99.86±0.64
9	4.6±0.12	0.2885	198±0.18	3.01±0.024	99.69±0.89

Determination of Floating Behavior

An effervescent floating drug delivery was used to achieve in vitro buoyancy. All tablet batches (F1 to F9) exhibited satisfactory floatation ability and remained buoyant for more than 15h in dissolution medium (0.1 N HCl). Floating lag time (FLT), for all batches (F1 to F9) was found between 20± 0.79 - 51± 0.86sec Table 3. These results indicate that the buoyancy lag-time was satisfactory.

Table 3: Floating lag time (FLT) of different formulations (n=3)

Formulation	Floating Lag Time (FLT) (sec) Mean ± SD	Formulation	Floating Lag Time (FLT) (sec) Mean ± SD
F1	32± 0.59	F6	40± 0.52
F2	42± 1.922	F7	12± 0.82
F3	51± 0.86	F8	22± 1.23
F4	20± 0.79	F9	29± 0.92
F5	35± 1.12		

Buoyancy (Floating) duration

From Table 4, it has been observed that as the conc. of CP934P increases, the TFT is decreases. F7 has highest TFT observed 26 ± 0.82h & F3 has lowest TFT 14 ± 0.86h

Table 4: Total Floating Time

Formulation	Total Floating Time (TLT) (h) Mean ± SD	Formulation	Total Floating Time (TLT) (h) Mean ± SD
F1	16± 0.59	F6	17± 0.52
F2	15± 0.922	F7	26± 0.82
F3	14± 0.86	F8	24± 0.63
F4	22± 0.79	F9	22± 0.92
F5	19± 0.52		

Ex-vivo Mucoadhesion Measurement:

Table 5, shows the detachment force of tablet CP934P, HPMC K100M & NaCMC exhibiting inheritant bioadhesion were chosen as drug retreading polymer it was observed that optimized formulation have adhesion force 3430 dyne/cm²

Table 5: Detachment force of different formulations (n=3)

Formulation	Bioadhesion Strength (dyne/cm ²) Mean ± SD	Formulation	Bioadhesion Strength (dyne/cm ²) Mean ± SD
F1	6460 ± 1.053	F6	4020 ± 1.153
F2	6040 ± 1.352	F7	3430 ± 6.53
F3	5570 ± 7.54	F8	3090 ± 1.228

F4	4830 ± 1.708	F9	2650 ± 1.081
F5	4450 ± 1.328		

In general it does not seem that mucoadhesive polymers are able to control and slowdown significantly the gastrointestinal transit time of solid dosage form, the bioadhesion tendency of CP934P, HPMC K100M could possibly to some extent, assist the tablet to remain in upper gastrointestinal tract and enhance gastro retention. From above study it was found that polymers shows difference in their bioadhesion in order of,

CP934P>HPMC K100M

Determination of Swelling Index

From, Fig 2 it was observed that F7 has significant % swelling index due high conc. of HPMC K100M. Swelling is vital factor to ensure buoyancy, drug dissolution and also influence drug release kinetics. A greater extent of swelling is observed with highest conc. of HPMC K100M led to an increase in tablet dimension thus increase in diffusion pathway and decrease in drug release. Also this higher water content predicts the higher penetration of the gastric fluid into the tablet leading to faster generation of CO₂ and thus reducing the floating lag time. %Swelling index was calculated at 4, 8, 16, 24h; it has been observed that increase in %S.I. with time. HPMC K100M has contributed in swelling property also prevent tablet from disintegration. HPMC K100M swells immediately and this will be assisted by NaCMC while CP 934P will swells continuously over the 24h.

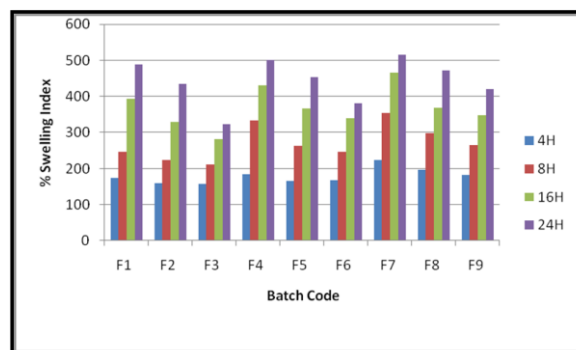


Figure 2: Swelling indices of different formulations

In vitro Drug release study

From Figure 3 & Figure 4 it was observed that (F1, F4, F7) conc. of CP934P increased the drug release decreased. HPMC K100M swells immediately increase diffusional path length led to increase in tablet dimension thus decrease in dissolution rate. Formulations (F1, F2, and F3) have highest drug release retardant ability.

Thus it has been concluded that all formulations have good drug release retarding ability and prevent initial burst release of drug. Tablet containing highest amount of HPMC K100M retains matrix integrity intact but as far as concerned with (F1 & F4) which having high and medium conc. level respectively of CP934P couldn't remain buoyant for 24h due to immediate swelling of CP934P and then sank to the bottom. Fixed conc. of NaCMC used for aiding buoyancy as well as bioadhesive property to the final formulation. F7 shows 99.69% drug release over 24h. It has significant % swelling index and also maintained matrix integrity for 24h. These findings are in compliance with the ability of HPMC to form complex matrix network which leads to increase in the diffusion path so the amount of drug released decreases.

Data treatment

The dissolution data of batches F1 to F9 was fitted to Zero order, First order, Higuchi and Korsmeyer-Peppas models. The coefficient of correlation (R^2) value was used as criteria to choose the best model to describe drug release from the tablets.

In case of all the formulations the R^2 values were higher for zero order model than for First order model indicating that the drug release from the formulation followed zero order kinetics.

The n value 0.8566 obtained from the drug release data to the K-Peppas equation, indicated that the drug release mechanism from these tablets was diffusion and erosion controlled. The values of ' n ' in Peppas model also indicated that all the formulations followed diffusion and anomalous release; this indicated that the drug released is controlled by both diffusion and erosion.

Optimization data analysis

Response surface methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices. Based on the principle of design of experiments (DOE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations and mapping of the response over the experimental domain to determine the optimum formulation(s). The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms. Various RSM computations for the current optimization study were performed employing Design Expert software. Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented as Equation below

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_1X_2 + \beta_4X_1^2 + \beta_5X_2^2$$

where, β_0 is the intercept representing the arithmetic average of all quantitative outcomes of 9 runs; β_1 to β_5 are the coefficients computed from the observed experimental values of Y ; and X_1 and X_2 are the coded levels of the independent variable(s). The terms X_1X_2 represents the interaction. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). The analysis of variance (ANOVA) is performed to identify the insignificant factors and reduce the equation in order to get better fit and the best formulation possible.

Model assessment for the dependent variables

Model for T_{25}

After putting the data in Design Expert software, Fit summary applied to data in that linear model had been suggested by the software so as per this model the equation is as follows Model equation in coded terms (Figure 3)

T_{25} follows Linear Model

$$y = 4.0666 + 0.6666 \text{ HPM K100M} + 0.6333 \text{ CP934P}$$

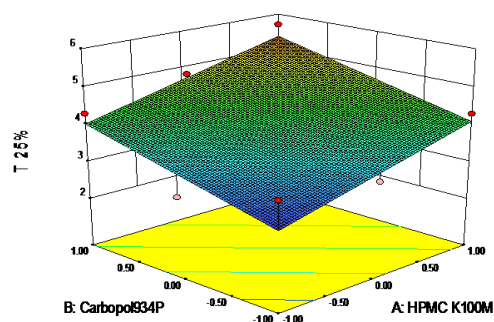


Figure 3: 3-D Response plot of $T_{25\%}$

The result of multiple linear regression analysis (linear model) reveals that, on increasing the concentration of HPMC K100M & CP934P, $t_{25\%}$ is increased.

Model for T_{90}

After putting the data in Design Expert software, Fit summary applied to data in that linear model had been suggested by the software so as per this model the equation is as follows.

Model equation in coded terms (Figure 4)

T_{90} follows Linear kinetic model

$$y = 22.8111 + 2.4660 \text{ HPMC K100M} + 5.6660 \text{ CP934P}$$

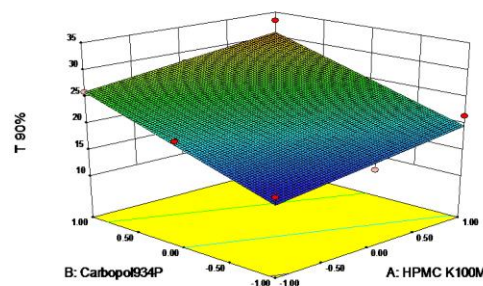


Figure 4: 3-D Response plot of $T_{90\%}$

The result of multiple linear regression analysis (linear model) reveals that, on increasing the concentration of HPMC K100M & CP934P, $t_{90\%}$ is increased

Model for FLT

After putting the data in Design Expert software, Fit summary applied to data in that Linear model had been suggested by the software so as per this model the equation is as follows

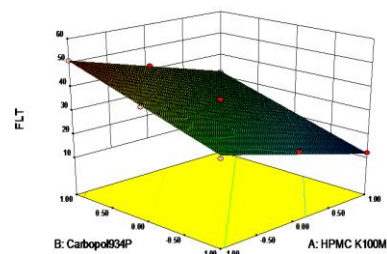


Figure 5: 3-D Response plot of FLT

Model equation in coded terms (Figure 5)

FLT follows Linear Model

$$y = 31.4444 - 9.3333 \text{ HPMC K100M} + 10.3333 \text{ CP934P}$$

The result of multiple linear regression analysis (linear model) reveals that, on increasing the concentration of HPMC, FLT is decreased and reverse is true for CP934P; as the signs are bears negative & positive respectively

Model for Swelling Index

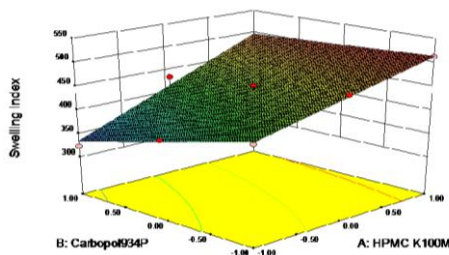


Figure 6: 3-D Response plot of Swelling Index

Swelling Index Follows 2FI Kinetic Model (Figure 6)

Table 6: Proposed optimized formulation by Design Expert software

Name	Goal	Lower Limit	Upper limit	Low Wt.	Upper Wt.	Imp
HPMC K100M	Is In range	-1	1	1	1	3
CP934P	Is In Range	-1	1	1	1	3
T25%	Is In Range	3h	4.5h	1	1	3
T90%	Is In Range	15.9h	22h	1	1	3
FLT	Minimize	12Sec	55sec	1	1	3
%Swelling Index	Maximize	322.87	512.03	1	1	3

Table 7: Composition of optimized formulation(F7)

Optimized formulation	Alfuzosin HCl	HPMC K100M	CP934P	Sod. Bicarbonate	Citric Acid	Mg- stearate	NaCMC	Total
Quantity (mg)	10	120	30	50	25	05	20	260

Tablets were compressed with hardness 4.5±0.5 kg/cm². Thickness of tablets was found to be 3.32 ± 0.6 mm. Tablet weight was found to be 252±0.16 mg. Content uniformity was found to be 99.96+0.85. All results obtained were complies with the official standards. The comparison between predicted values and experimental values was carried out (Table 8).

Table 8: Predicted and experimental values obtained for different responses of optimised formulation (F7)

Responses	Predicted values	Experimental values
t ₅₀ (hrs)	4.0929	4.3
t ₉₀ (hrs)	19.5972	20.1
Floating Lag Time (min)	11.9487	12
%Swelling index	513.155	515.03

Stability Studies

Short-term accelerated stability data obtained for optimized formulation revealed that drug content, thickness, hardness, in-vitro dissolution were within the acceptable limit. All results obtained were complies with the official standards. The thickness of F7 was found to be 3.32 ± 0.6 mm. Tablet weight was found to be 252±0.16 mg. Content uniformity was found to be 99.96+0.85 Short term stability testing was carried out for the optimized formulation (F7). The results for the dissolution profile are as depicted in the graph.

$$Y=442.5322+62.6166HPMC$$

$$K100M-26.4483CP934P+18.4425HPMC K100M.CP934P$$

The result of multiple linear regression analysis (2FI model) reveals that, on increasing the concentration of HPMC; %Swelling Index is increased and reverse is true for CP934P; as the signs are bears positive and negative respectively

Optimization Result

The optimization was performed on the basis of response surface modeling by using the numerical and graphical optimization method. Desirability is an objective function that ranges from zero outside of the limits to one at the goal. The numerical optimization finds a point that maximizes the desirability function. The characteristics of a goal may be altered by adjusting the weight or importance. For several responses and factors, all goals get combined into one desirability function. The goal of optimization is to find a good set of conditions that will meet all the goals.

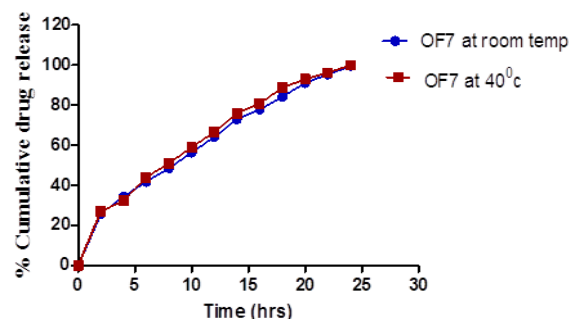


Figure 7: Dissolution profiles of F7 at room temperature and OF7 at 40°C

REFERENCES

1. Antonios GM, Nicolas AP. Bioadhesive analysis of controlled release system: An experimental method for testing the adhesion of micro particulate with mucus. J.Control Release. 1990; 12: 31-37.
2. McKinney Jw, Kolenge JJ, Repka MA, Zange R. Hot melt extrusion technology. In Swarbrick J, Boylan JC, editors. Encyclopedia of pharmaceutical technology. 2nd ed, New York: Marcel Dekker Inc. 2005; 19: 221-226.
3. Hong SI, Oh SY. Dissolution kinetics & physical characterization of three layer tablet with poly (ethylene oxide) corer matrix capped by Carbopol. Int. J. Pharm. 2008; 356: 121-129.

4. Hoffman BB. Catecholamines, sympathomimetics drugs, and adrenergic receptor antagonists. In Hardman JG, Limbird LE, editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed, New York: McGraw-Hill, 2001; 255-256.
5. Chavanpati MD, Jain P. & Vavia P.R., Development of sustained release gastroretentive dosage form of Ofloxacin, In vitro-in vivo evaluation, Int. J. Pharm. 2005; 304: 178-184.
6. Hardman JG & Limbird LE Eds, Goodman & Gilman's The pharmacological basis of therapeutics, 10th edition, McGraw Hill, 2002; 288-916.
7. Quan Liu, Reza Fassihi, Zero order delivery of highly soluble low dose drug alfuzosin HCl via gastro-retentive system International journal of Pharmaceutics. 2008; 348: 27-34.
8. David R.P. Extended Release Alfuzosin HCl: A New Alpha-Adrenergic Receptor Antagonist for Symptomatic Benign Prostatic Hyperplasia The American Journal of Geriatric Pharmacotherapy. 2004; 23: 75-83.
9. Gohel M, Patel M, Amin A, Agrawal R, Dave R, Bariya N. Formulation Design and Optimization of Mouth Dissolve Tablets of Nimesulide using Vacuum Drying Technique. AAPS PharmSciTech, 2004; 5; 1-6.
10. Bhalekar MR, Madgulkar AR, Sheladiya DD, Kshirsagar SJ, Wable ND, Desale SS. Statistical Optimization of Sustained Release Venlafaxine HCl Wax Matrix Tablet. Indian J. Pharm. Sci. 2008; 70: 472-476.
11. Grabovac V, Guggi D, Bernkop-Schnurch A. Comparison of the mucoadhesive properties of various polymers. Adv. Drug Delivery Reviews. 2005; 57: 1713-1723.
12. Craig A. Comparison of different in vitro methods for measuring mucoadhesive performance. Eur J Pharm Biopharm. 1997; 44: 159-167.