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RESEARCH ARTICLE

Formulation and Evaluation of Sustained Release Mucoadhesive Atenolol Tablets for Gastric Retention

Sunena Jha[1*], Arun Nanda[2]

1 Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar,(125001), India

2 Department of Pharmaceutical Sciences, Maharishi Dayanand University, Rohtak (124001), India.

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ABSTRACT

An oral sustained release gastroretentive dosage form comes out as better alternative for drugs having narrow absorption window. Atenolol conventional tablets have been reported by many scientists to exhibit poor oral bioavailability and fluctuations in plasma drug concentration. This results, either in precipitation of side effects or reduction in drug concentration at the target site. Thus objective of present study was to develop, optimize and evaluate a gastroretentive, mucoadhesive tablet for sustained release. A 2^2 factorial design was employed to systematically study the drug release profile and bioadhesive strength. Sodium carboxymethyl cellulose (CMC) and carbopol 934P were selected as independent variables. Tablets were prepared by direct compression and were evaluated for tablets characteristics, swelling study, adhesion strength and percent drug released. Optimized formulation was compared with marketed formulation (ATEN-50). In vitro wash off test was applied to study the gastroretentive behavior.Tablets prepared show good tablet characteristics, optimum swelling behavior and high adhesion strength. The optimized batch follows zero order drug release profile with non fickian transport mechanism. The mucoadhesion time for optimised batch (M4) was found to be more than four hours and compared with plain tablet which was found to be very less (less than half hour).Thus, the gastroretension by mucoadhesion proven to be a potential tool for drug atenolol which improves its bioavailability with reduction in dosing frequency and dose related side effects.

Keywords: Mucoadhesion, Gastroretentive drug delivery,Atenolol HCl, Carbopol 934P, Sodium Carboxymethyl Cellulose (CMC), Factorial design.

1. INTRODUCTION

Amongst the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the Gastro intestinal tract (GIT) is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, (*e.g.,* gastro retentive dosage forms (GRDFs)), will provide us advanced and better therapeutic opportunities. Gastroretentive systems, mainly mucoadhesive drug delivery systems have emerged as an efficient means for enhancing the bioavailability of drugs having narrow absorption window (1,2,3). Atenolol is a β-blocker, is used widely in various cardiovascular diseases, *e.g.,* hypertesion, angina pectoris, arrhythmias, myocardial infarction and in prophylactic treatment of migrane. Oral absorption of atenolol is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Thus atenolol gastroretentive drug delivery system would give better therapeutic results (4). Carbopol 943P and sodium carboxy methylcellulose, both have good mucoadhesive potential (5). Many hydrophilic polymers adhere to mucosal surfaces as they attract water from the mucus gel layer adherent to the epithelial surface. This is the simplest mechanism of adhesion and has been defined as "adhesion by hydration". Several types of adhesive force, e.g. hydrogen bonding between the adherent polymer and the substrate, i.e. mucus, are involved in mucoadhesion at the molecular level. Carbopol polymers have been

*Corresponding author: Sunena Jha | Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar,(125001), India | Email: garhwal_s@rediffmail.com

demonstrated to create a tenacious bond with the mucus membrane resulting in strong bioadhesion (6). In brief gastroretentive dosage forms with the development of novel, advanced and mucosa-compatible polymers, are providing new commercial and clinical opportunities for delivery of drugs with narrow absorption window at the target site. These tailored polymers offer better opportunities for and broader applicability to highly variable and challenging drugs and therapy of various gastrointestinal disorders (7).

2. MATERIALS AND METHODS

2.1. Materials

Atenolol HCl was obtained as a gift sample from Yarrow Chem. Products, Mumbai. Carbopol, sodium CMC, magnesium stearate and talc were supplied by Loba Chemie Pvt. Ltd., Mumbai. All other chemicals were of analytical grade and were used as such.

2.2. METHODS

2.2.1. IDENTIFICATION OF DRUG:

Ultraviolet spectroscopy: Solutions of atenolol concentration ranging from 5-35 mcg/ml is prepared with double distilled water. The absorbance of these solution were measured at 223 nm in 1 cm cell against a reagent blank (distilled water) using Systronics UV/Visible Double Beam Spectrophotometer. A mean of five readings were obtained and the method of linear regression was applied on the data. A standard curve was constructed by the plotting absorbance versus concentration in microgram/ml. The results are compiled in Table 1 and plotted in Figure 1.

S.No.	Concentration (micrograms/ml)	Mean absorbance (experimental)	Absorbance (by regression)
1	5	0.118	0.154
2	10	0.314	0.314
3	15	0.513	0.474
4	20	0.661	0.634
5	25	0.831	0.794
6	30	0.916	0.954
7	35	1.114	1.114

Table 1: Absorbance profile of atenolol hcl in water at 223 nm (N=5)

2.2.2. Preparation of mucoadhesive tablets:

The matrix tablets were prepared by direct compression method by rotary tableting machine (PHARMAC-076, Manufactured by- Pharmaceutical machinery manufacturing works, Indore-452006) using 12mm round, concave punches. Lactose is used as diluent. Mixture of talc and magnesium stearate (2:1) was used as lubricant. All the component were sieved (250 micro meter) separately and mixed by spatulation method in mortar and pastel.

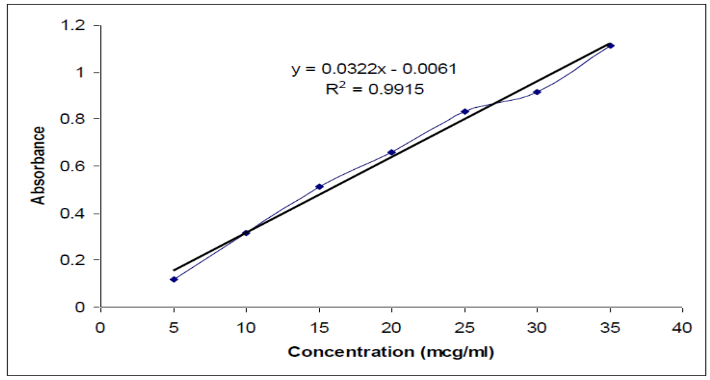

Fig 1: The standard curve of atenolol hcl in water by UV spectroscopy

Batch	Factor-(carbopol 934)	Factor-B(sod.CMC)	Mucoadhesion time(min)
A	0% (minimum)	0% (minimum)	1
B	40% maximum)	0% (minimum)	180
C	0% (minimum)	40% (maximum)	30
D	40% maximum)	40% (maximum)	220

Table 2: Ratio of carbopol 934 and sodium CMC in various formulations

2.2.3. EVALUATION OF TABLETS

Tablet characterstics:

Formulated matrix tablets were evaluated for thickness using vernier caliper, weight variation, hardness (Monsanto hardness tester), friability (Roche friabilator) and drug content (8).

***In-vitro* dissolution studies:**

Dissolution studies were carried out using USP dissolution (paddle type six basket) apparatus at 50 rpm and temperature 37±0.5^{0}C. Each beaker contains 900ml of distilled water and a single tablet. Samples of 1 ml were taken from the medium at the definite time intervals and the volume replaced with an equivalent amount of the plain dissolution medium. The samples were analyzed spectrophotometrically at 223nm (9).

Drug release kinetics study:

Zero- order release model, first- order release model, Higuchi drug release model and Ritger- Peppas model were applied on the dissolution profile data of batch M4 mucoadhesive tablets (10,11).

Comparative studies:

Mucoadhesive tablet M4 versus marketed immediate release tablet (ATEN-50; Cadila):

Dissolution studies were performed for marketed immediate release tablet {ATEN-50 (50 mg) Cadila} by using same procedure as described above.

Ingredient	Batch-A	Batch-B	Batch-C	Batch-D
Lactose	485	285	285	85
Carbopol-934	--	200	--	200
Sodium CMC	--	--	200	200
Magnesium stearate	5	5	5	5
Talc	10	10	10	10
Total	500	500	500	500

Table 3: Complete formula of various formulations (mg)

Batch	Carbopol	Mucoadhesion time (min)
M1	10%	25
M2	20%	40
M3	30%	105
M4	40%	180

Table 4: Percentage of carbopol 934 in various batches of optimized mucoadhesive formulations

Ingredients	Quantity (mg)			
	M1 (10%)	M2 (20%)	M3 (30%)	M4 (40%)
Atenolol	50	50	50	50
Lactose	385	335	285	235
Carbopol-934	50	100	150	200
Magnesium stearate	5	5	5	5
Talc	10	10	10	10
Total	500	500	500	500

Table 5: Complete formula of different batches of optimized mucoadhesive tablets

Time (hrs)	Cumulative percentage drug release			
	Batch M1	Batch M2	Batch M3	Batch M4
0.25	27.28	15	8.46	5.6
0.5	69.72	30.25	15	8.9
0.75	80.26	64.49	22	10.9
1	91.34	75.56	37.98	13.2
2	96.99	86.98	60.26	23.62
4	98.89	97.45	84.63	46.98
6	99.12	98.78	96.46	71.26
8	99.78	100.1	98.29	95.63

Table 6: Cumulative percentage drug release of different batches of optimized mucoadhesive tablets (N=3)

Swelling Index of tablets (batch M4);

Mucoadhesive tablets were weighed individually (W_0) and placed separately in petri dishes contains distilled water. At regular 1-hour time intervals until 6 hours, the tablet was removed from the petri dish and excess surface water was removed carefully using filter paper. The swollen tablet was then reweighed (W_t), and the swelling index (SI) was calculated using the following formula (12):

$$SI = \frac{W_t - W_0}{W_0}$$

Where W_0 and W_t is weight of tablets at 0 and t time.

This procedure was performed for 6 tablets of the batch. The Swelling index of mucoadhesive tablets at different time intervals are given in Table 9.

S. No.	Time(hrs)	Square root of time (hrs)	%age cumulative Drug Release	Log %age cumulative Drug Release	Log time (min)
1	0.25	0.5	5.6	0.748	1.176
2	0.5	0.707	8.9	0.949	1.477
3	0.75	0.866	10.9	1.037	1653
4	01	01	13.2	1.120	1.788
5	02	1.414	23.62	1.373	2.079
6	04	02	46.98	1.671	2.38
7	06	2.449	71.26	1.852	2.556
8	08	2.828	95.63	1.980	2.681

Table 7: Kinetic analysis of the mucoadhesive Formulation M4

Release model	Correlation coefficient
Zero order	0.9989
First order	0.7395
Higuchi release model	0.9311

Table 8: Correlation coefficient observed from different release models for optimized mucoadhesive formulation M4, as fitted for various patterns of drug release

Time (hrs)	% Cumulative drug release	
	ATEN-50	Mucoadhesive formulation M4
0.25	81.5	5.6
0.5	94.15	8.9
0.75	96.88	10.9
1	98.12	13.2
2	98.67	23.62
4	98.92	46.98
8	99.45	95.63

Table 9: Comparative drug release profile of atenolol hydrochloride immediate release tablet (ATEN-50; Cadila) and mucoadhesive formulation M4

Time (hrs)	Swelling index
0	0
1	0.2
2	0.43
3	0.551
4	0.734
5	0.952
6	1.35

Table 10: Swelling index of mucoadhesive tablets

In - vitro mucoadhesion study (*In-vitro* wash-off test):

The mucoadhesive property of the tablet was evaluated by an *in-vitro* adhesion testing method known as the wash-off method. Freshly excised piece of intestinal mucosa (2×2 cm) from sheep was mounted on to the glass slide (3×1 inch) with cyanoacrylate glue. The tablet was sticked to the tissue by applying slight pressure with thumb and the support was tied to the paddle with cotton thread of a USP dissolution apparatus containing 900ml of distilled water and rotated at the speed of 25 rpm. When the dissolution apparatus was operated, the tissue was given a slow, regular rotation in the test fluid (distilled water) at 37^0C contained in the vessel. The test was conducted till the tablet remain sticked to the tissue. The time of adherence is noted known as mucoadhesion time (13). In-vitro wash off test for measurement of mucoadhesion time using sheep intestine is shown in *Figure 9* .

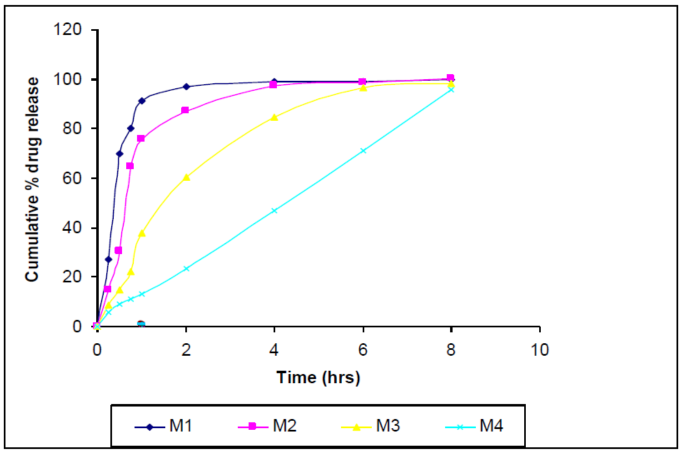

Figure 2: Cumulative percentage drug release of different batches of mucoadhesive formulations

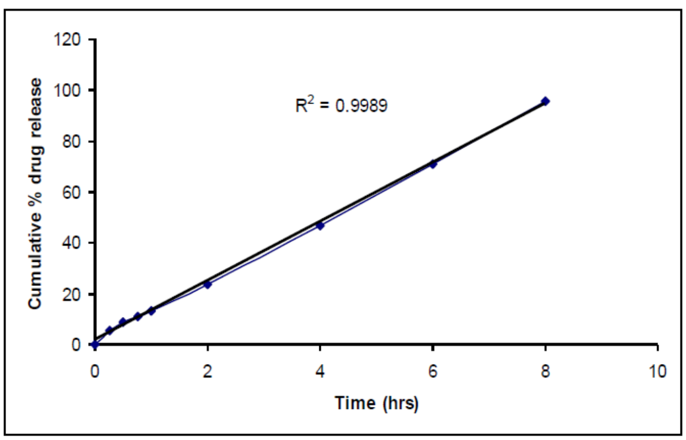

Figure 3: Zero order release model for optimized formulation M4

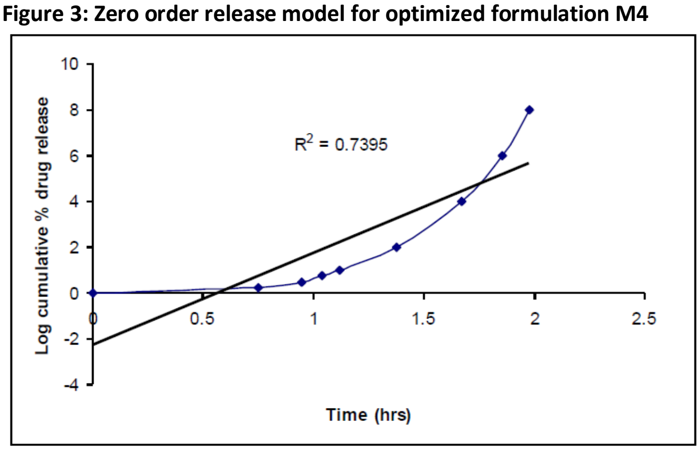

Figure 4: First order release model for optimized formulation M4

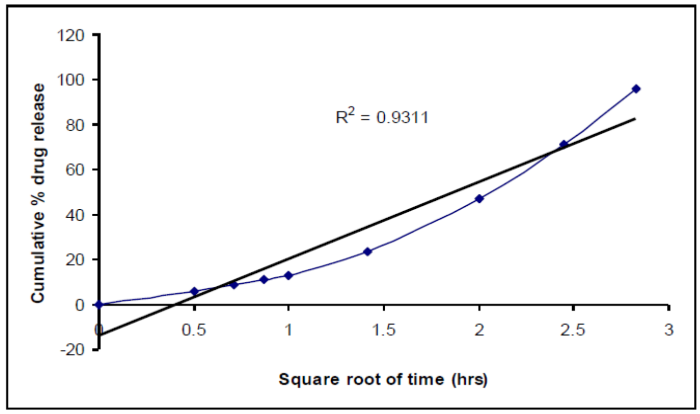

Figure 5: Higuchi release model for optimized formulation M4

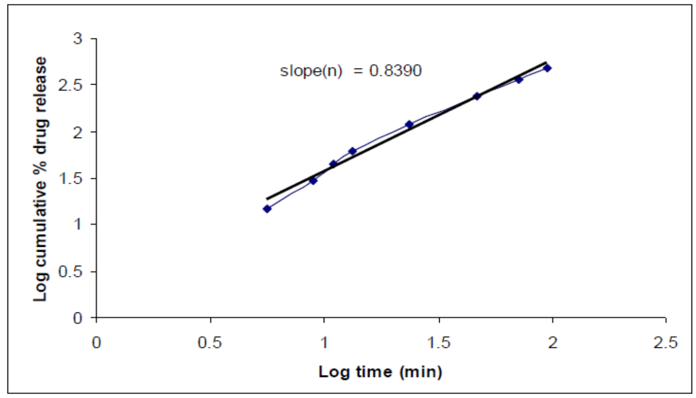

Figure 6: Ritger- Peppas model for optimized formulation M4

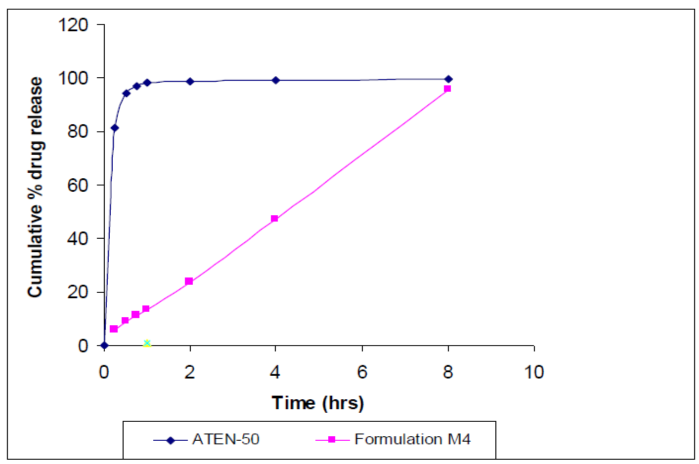

Figure 7: Comparative drug release profile of atenolol hydrochloride immediate release tablet (ATEN-50; Cadila) and mucoadhesive formulation M4

Figure 8: *In-vitro* wash off test – measurement of mucoadhesion time using sheep intestine

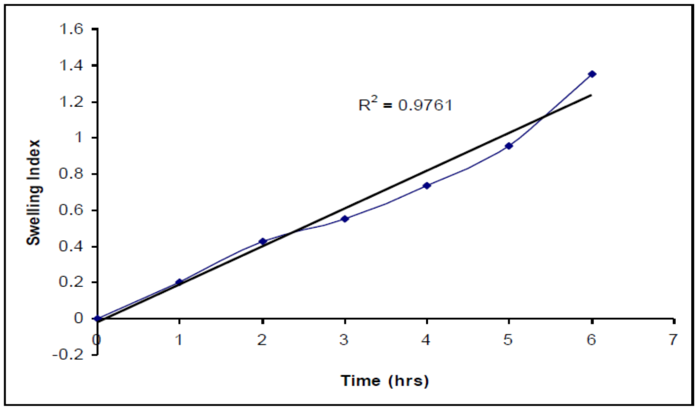

Figure 9: Swelling index of mucoadhesive tablets

3. RESULTS AND DISCUSSION

The present study is an attempt to develop, optimize and evaluate a suitable gastro retentive drug delivery system using atenonol as model drug.

Optimization of drug formulation using factorial design (2^2):

In the start of study three batches were made, ratio of carbopol-934 (factor-A) and sodium CMC (factor-B) in various batches are given in *Table 1* and complete formula of various formulations is given in *Table 2*. Effects of factor-A and factor-B and their interaction were calculated using (2^2) factorial design (14). Furthermore evaluation was done by in vitro dissolution study and results are given in *table 3.* Mucoadhesion time for Carbopol-934 is much higher than Sodium CMC. As effect of carbopol-934 is much more than sodium CMC and their magnitude of interaction (5.5%) is very less so final formulation prepared for further study was chosen that only contain Carbopol-934(10-40%).Finally four batches of mucoadhesive formulations were made with carbopol (10-40%) as given in *table 4 and 5.*

Effect of factor A (*i.e.,* carbopol) on mucoadhesion time:

= 1/2[(ab+a)-(b+1)]
= 1/2[(220+180)-(30+1)]
= 1/2[400-31]
= 1/2[369]
= 184.5

Effect of factor B (*i.e.,* Sodium CMC) on mucoadhesion time:

= 1/2[(ab+a)-(b+1)]
= 1/2[(220+30)-(180+1)]
= 1/2[(250-181)]
= ½[69]
= 34.5

Carbopol-934 has got more significant effect on mucoadhesion time.

Magnitude of interaction

= ½[(1+ab)-(a+b)]
= ½[(1+220)-(180+30)]
= ½[221-210]
= ½[11]
= 5.5

Drug release Study:

Drug release pattern show that percentage drug release at different time intervals goes on decreasing as the carbopol concentration increases. From the study of mucoadhesion time and drug release pattern for different batches of mucoadhesive tablets we find batch that M4 was the best formulation having 180 minutes of mucoadhesion time and 95% of drug release in eight hours. Cumulative percentage release of drug for different batches are given in *table 6* and shown in *figure 2*.

Drug release kinetics of mucoadhesive formulation:

The mucoadhesive formulation follows zero order drug release profile, which will describe the sustained drug release profile of mucoadhesive formulation. From Ritger-Peppas model value of n found to be 0.839 which is in between 0.5 and 1, so follow non-Fickian transport for drug release. Kinetic analysis data and values of correlation coefficients are given in *table 7;8* respectively and figures 3; 4; 5;6.

Comparative study:

Marketed immediate release tablet (ATEN-50; Cadila) release 94.15 % of drug in the first half hour whereas mucoadhesive tablet (M4) release 95.63 % of drug in eight hours. Comparative drug release profile of atenolol hydrochloride immediate release tablet (ATEN-50; Cadila) and mucoadhesive formulation M4 are given *Table 9* and shown in *Figure 7.*

***Ex- vivo* mucoadhesion study:**

The mucoadhesion time for mucoadhesive tablet (M4) was found to be more than four hours. Mucoadhesion time for plain tablets was found to be very less (less than half hour) as compared to formulated tablet. In-vitro wash off test for measurement of mucoadhesion time using sheep intestine is shown in *Figure 8.*

Swelling index:

Swelling index of tablets was found to be increasing 0.2 to 1.35 with time (up to 6 hrs). It shows that tablets have good swelling power. The Swelling index of mucoadhesive tablets at different time intervals are given in *Table 10* and shown in *Figure9.*

Weight variation: It was observed that no single tablet was out of limit (±5%).

Hardness: The hardness of tablets was found in range 6.6 to 8.1 with Pfizer tablet hardness tester.

Friability: The friability of tablets was found to be 0.0107, which is acceptable, as per prevalent practice (less than 1%).

4. DISCUSSION

The mucoadhesive matrix tablets of atenolol with carbopol 934P, using 2^2 factorial design were formulated and evaluated. Mucoadhesive strength was increases with increase in the polymer concentration. The optimized formulation containing 40% carbopol 943P exhibits good mucoadhesive potential. The *in vitro* release kinetics studies reveal that all formulations fits well with zero order kinetics and the mechanism of drug release is non-Fickian diffusion.It may prove to be more productive than conventional tablets by virtue of prolongation of drug residence time in GI tract. Such formulation would serve as a platform for design of gastroretentive drug delivery systems.

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Conflict of Interest: None Declared

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