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Development and Evaluation of Mucoadhesive Tablets of Atenolol and its B-Cyclodextrin Complex

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Abstract

Drug delivery via the buccal mucosa offers a novel route of drug administration. The route has been tried for systemic delivery of a number of drug candidates since it overcomes first pass metabolism, gastrointestinal irritation and bioavailability and also for local delivery of drugs. Atenolol is an antihypertensive agent wildly used as a first line treatment for hypertension. It has half life 6-7 h. The drug is incompletely absorbing about 50 % but most of the absorbed drug reaches to the systemic circulation. Therefore it was planned in this investigation to develop controlled release mucoadhesive buccal tablets containing antihypertensive agent, atenolol to release the drug unidirectionallly in buccal cavity for extended periods of time for improvement in bioavailability, to reduce the dosing frequency and to improve the patient compliance. Also, it was planned to evaluate such mucoadhesive buccal tablets for their various pre-compression and compression characteristics, *in vitro* drug release kinetics and stability of the dosage forms.

Keyword: Mucoadhesive tablet, atenolol, β-cyclodextrin, xanthan gum, carbopol 934p

INTRODUCTION

Today, a pharmaceutical scientist is well versed with the fact that the overall action of a drug molecule is not merely dependent on its inherent therapeutic activity, rather on the efficiency of its delivery at the site of action. Many drug delivery systems (DDS) are aimed to sustain drug blood concentration and controlling the rate of drug delivery to the target tissue, but mucoadhesion is one of the most prominent and latest systems in the design of buccal drug delivery systems. It prolongs the residence time of the dosage form at the site of application or absorption and facilitates an intimate contact of the dosage form with the underline absorption surface and thus contributes to improved and / or better therapeutic performance of the drug. In recent years many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, gastrointestinal, rectal and vaginal routes for both systemic and local effects.[1]

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. An ideal DDS should aid in the optimization of drug therapy by delivering an appropriate amount to the intended site and at a desired rate. By and large, a DDS may be employed for spatial placement (i.e. targeting a drug to a specific organ or tissue) or temporal delivery (i.e., controlling the rate of drug delivery to the target tissue). [2]

Buccal route provides one of the potential route for typically large, hydrophilic and unstable proteins, oligonucleotide, and polysaccharides as well as conventional small drug molecule. The oral cavity can be used for local and systemic therapy. Examples of local therapy would be the treatment of oral infections, dental caries, mouth ulcers and stomatitis. The buccal route is of particular interest with regard to systemic delivery of small molecule that are subjected to first pass metabolism of protein and peptides.[3]

Atenolol is a selective β-blocker used for treatment of hypertension. The systemic bioavailability of atenolol following oral administration is 50 %. Over 85% of intravenous dose is excreted in urine within 24 hr compared with 50% of an oral route. Plasma half life of atenolol is 6- 7 hours, molecular weight 266.34, and it does not have objectionable taste.[4] Therefore the present work was planned to develop mucoadhesive controlled release tablet of atenolol. Solubility enhancement of drug was done by β-CD complexation which increases the bioavailability of drug.

MATERIALS AND METHODS

Material

Atenolol was provided as gift sample from Blue-cross Pharmaceutical Pvt, Ltd, (Nashik, India). β-cyclodextrin, Carbopol 934P, Xanthan gum were obtained from Glenmark pharmaceuticals, (Nashik). Magnesium stearate, talc, mannitol was procured from S.D. fine chemicals Ltd.

Biological tissue used

The buccal mucosa of goat obtained from local slaughter house.

METHODS:

Preparation and characterization of β-Cyclodextrin complex [6]

Physical mixture

The complex was made by two methods kneading and co-precipitation method. The physical mixture of atenolol and β-cyclodextrin in 1:1 and 1:2 molar ratio was prepared by mixing individually components that had previously been sieved through sieve no 60.

Kneading method

The inclusion complex was prepared by the β-CD, not by dissolving but kneaded like a pest with small amount of water to which the cyclodextrin has been added. Drug component can be dissolved in small amount of methanol in which β-CD has been suspended. After 4 hours of grinding of paste in mortar results in evaporation of solvent and formation of powder like complex. The complex was pulverized and passed through sieve no 100 and stored in dessicator until further use.

Co-precipitation method

Inclusion complex was prepared by dissolving cyclodextrin in water and drug was dissolved in methanol at room temperature. Different molar ratios that are 1:1 and 1:2 were taken. The mixture was stirred at room temperature, for 1 hr and then slowly evaporated on boiling water bath. The inclusion complex was slowly precipitated as crystalline powder pulverized and passed through sieve no 100 and stored in dessicator till free from any traces of organic solvent.

Characterization of atenolol-β-CD complex

Phase solubility study [7]

Phase solubility study was performed by method previously reported by Higuchi and Connors (1965). Briefly excess amount of atenolol 50 mg were added to 20 ml of aqueous solution. It is vigorously shaken at 25±1⁰ C for 1 day. After equilibrium was attained the sample were filtered through a 0.45 μm Millipore membrane filter and diluted with same solution. The concentration was determined spectrophotomertically, at λ_{max} 224 nm.

Infra-red spectrum [8, 9]

The studies were carried out using IR 84005 Shimadzu, Japan. The infra red spectrum of atenolol was recorded with KBr disc over the wave number of 4000 to 400 cm^{-1} by using Infra red spectroscopy.

Differential scanning Calorimetry[10]

The formation of inclusion complex was conformed using a Mettler Toledo differential scanning calorimeter equipped to a computerized data station. The sample of pure drug, physical mixture of complex, and complex prepared by kneading and co-precipitation method was weighed and heated at a scanning rate of 10°C/min between 40 and 200°C and 40 ml/min of nitrogen flow.

Powder X-ray diffraction [10]

The powder x-ray diffraction was recorded using Bruker AXS, D8, Advance SAIF, Kochi, at 3-80 ^{0} C (2θ) at room temperature. The diffractogram were recorded with a step width 0.020 0 (2θ) and count time 32.8 sec per step.

Preparation of mucoadhesive buccal tablets of atenolol

Mucoadhesive tablets of atenolol were prepared by direct compression method. All the ingredients as mention in table 1 were weighed accurately and passed through sieve no.120 and blended thoroughly to obtain uniform mixing. The powder blend were evaluated for its rheological characteristics and then compressed on 10 station pilot press using 8 mm flat faced punches. The machine was adjusted to produce an approximate weight of 200 mg tablet. The composition of all formulation was shown in table 1.

Formulation	F1	F2	F3	F4	F5	F6*	F7*
Ingredient							
Atenolol	50	50	50	50	50	-	-
β-CD complex equivalent to 50 mg of drug	-	-	-	-	-	476	476
Xanthan gum	40	40	40	60	60	60	60
Carbopol 934 p	-	40	60	40	60	40	40
Talc	2	2	2	2	2	6.5	6.5
Mg stearate	2	2	2	2	2	6.5	6.5
Mannitol	106	66	46	46	26	41	41
Total wt (mg)	200	200	200	200	200	650	650

Table 1 : Formulation table for mucoadhesive tablets of atenolol
* 650 mg tablet prepared with atenolol: β-CD complex equivalent to 50 mg of atenolol

Evaluation of powder blend [10]

There are many formulations and process variables involved in mixing step and all these can affect characteristics of blend produced. Angle of repose, bulk density, true density and percent compressibility index have been measured which are given in table 3.

Bulk density

Bulk density was determined by placing the powder blend in a measuring cylinder and the total volume was noted. The weight of powder bed was determined. Bulk density was calculated by using the formula.

Bulk density= Total weight of powder/granules
$$\overline{\text{Total volume of powder/granules}}$$

Average of three bulk densities of powder were taken and tabulated. (n = 3).

Tapped density

The tapped density was obtained by dividing the mass of powder by the tapped volume in cm^3. The powder blend carefully introduced into graduated measuring cylinder. The cylinder was tapped on surface 100times from a height of 1 inch. After tapping volume was noted. Tapped density can be calculated by using following formula

Tapped density= Mass/ Tapped volume

Average of three bulk densities of powder were taken and tabulated. (n = 3).

Compressibility index

It helps in measuring the force requires to break the friction between the particles and hopper. The flow property of a powder can be easily measured with the help of compressibility. Compressibility index was determined by placing the powder in a measuring cylinder and the volume (V_0) was noted before tapping. After 100 tapings again volume (V) was noticed.

Compressibility index = $(1- V/ V_0) \times 100$

V_0 = volume of powder before tapping.

V = volume of powder after 100 tappings.

Average of three compressibility in-dices of powder readings were taken and tabulated (n = 3).

Hausner's ratio

It is the ratio of tapped density to bulk density. Hausner's ratio is an ease of powder flow; it is calculated by following formula.

Hausner's ratio= Tapped density / Bulk density

Angle of repose (°θ)

Angle of repose was determined by measuring the height and radius of the heap of the powder bed. A cut stem funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the plane. Powder was placed in the funnel and allowed to flow freely. With the help of vernier calibre the height and radius of the heap were measured and noted. Average of triplicate reading were noted (n = 3)

tan θ = h /r

h = height of heap of powder/granule blend.

r = radius of heap of powder/granule blend.

Evaluation of mucoadhesive tablets:

Weight uniformity:

Ten tablets were taken and weighed individually. Average weight was calculated standard deviation was computed.

Thickness test:

The tablets were evaluated for their thickness using a micrometer. Average of three readings were taken and the results were tabulated (n = 3).

Hardness test:

The tablets were evaluated for their hardness using Pfizer hardness tester. Average of three reading were taken and tabulated (n = 3).

Surface pH: [11]

Three tablets were allowed to swell for four hour in simulated saliva fluid . pH was found out by placing the electrode of pH meter just in contact with the surface of the tablets. Average of three readings was computed.

Drug content uniformity:[13]

From each batch three randomly selected tablets were weighed accurately and powdered in a glass mortar with pestle. Powder equivalent to 10 mg of drug was transferred into 10 ml volumetric flask containing 10 ml of pH 6.8 phosphate buffer and kept aside with constant shaking for 24 h to extract the total drug present in the tablet. Then the solution was filtered and the volume was made with phosphate buffer and analyzed for drug content at λ_{max} of 224 nm against drug devoid phosphate buffer as blank. Averages of triplicate readings were taken. The content of drug was calculated using standard graph.

Swelling studies: [12]

Preparation of simulated saliva solution:

Weigh accurately 2.38g of Na_2HPO_4, 0.19 g KH_2PO_4, 8.00g NaCl and dissolve in 1000 ml of distilled water to produce simulated saliva solution; finally adjusted the pH with phosphoric acid to 6.75.

Three tablets were weighed individually (W_1) and immersed in a petridishes containing simulated saliva fluid (pH 6.75) for predetermined times (15min, 30 min,1, 2, 3, 4, 5, 6, 7, 8h). After immersion tablets were wiped off by the excess surface water by the use of filter paper and weighed (W_2). The % swelling index was calculated by:

% Swelling Index = [W_2- W_1] / W_2 x 100

Where W_1 is the initial weight of the tablet and W_2 is the weight of the tablet after the particular swelling time interval.

Mucoadhesive strength [13]

Mucoadhesive strength was conducted on modified physical balance. The equipment was fabricated by us in the laboratory as polypropylene disc (A), also locally fabricated. The apparatus consist of a modified double-beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This was kept in beaker filled with buffer media pH 6.75, which

was then placed below right side of the balance. The right pan (D) was replaced with a lighter pan so that, the left pan weighs more than the right pan. The lower polypropylene block was intended to hold the mucosal tissue (B) of goat cheek pouch and to be placed in a beaker containing simulated saliva solution pH 6.75 (C). Goat cheek pouch was obtained commercially; the cheek pouch was collected into a sterile container containing sterile buffer solution of pH 6.75. The cheek pouch brought was stored in a refrigerator until use. The following procedure was used for all the test formulations using the above equipment. The cheek pouch was removed from refrigerator and allowed to attain equilibrium with ambient conditions in the laboratory. The goat cheek pouch was carefully excised, without removing connective and adipose tissue and washed with simulated saliva solution. The tissue was stored in fresh simulated saliva solution. Immediately afterwards the membrane was placed over the surface of lower polypropylene cylinder (B) and secured. This assembly was placed into beaker containing simulated saliva solution pH 6.75 at 37 ± 2°C. From each batch, one tablet at a time was taken and stuck to the lower surface of polypropylene cylinder with a standard cynoacrylate adhesive. The beaker containing mucosal tissue secured upon lower cylinder (B), was manipulated over the base of the balance so that, the mucosal tissue is exactly below the upper cylinder (A). The exposed part of the tablet was wetted with a drop of simulated saliva solution, and then a weight of 20 gms was placed above the expanded cap, left for 10 minutes. After which the tablet binds with mucin. The weight was removed. Then slowly and gradually weights were added on the right side pan till the tablet separates from the mucosal surface/ membrane. The weight required for complete detachment is noted (W_1) (W_1-5.25gm) gives force required for detachment expressed in weight in grams. Procedure was repeated for two more tablets. Average was computed and recorded.

***In vitro* release method for atenolol tablets:** [14]

The drug release profile was studied using USP dissolution testing apparatus method II using a paddle at 50 rpm. 500ml dissolution fluid, pH 6.8 phosphate buffer, was used and a temperature of 37 ± 0.5°C was maintained. 5ml aliquots at 0 min, 15 min, 30 min, 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12 h respectively were pipette out and the same volume was replaced with pH 6.8 phosphate buffer . Absorbance was measured at λ_{max} 224nm and from which percentage of atenolol was calculated using calibration curve. The procedure was repeated for three more tablets similarly and average was computed.

Drug release kinetics: [15, 16, 17]

In the present work the data obtained from drug release was fitted to various kinetic equations to find the mechanism of drug release from controlled release mucoadhesive tablets.

Stability studies [18]

The mucoadhesive tablets were subjected for a period of three months as per ICH guideline at the 40^0C temperature and relative humidity 75% RH. The samples were withdrawn at 7 days, 15 days, 1, 2, 3 months for given temperature condition. The formulations were evaluated mainly for drug content at the predetermined intervals.

**RESULT AND DISCUSSION**

Phase solubility study:

The solubility of atenolol and its β- cyclodextrin complex was taken in solvent like water and pH 6.8 phosphate buffer. The Solubility of pure drug in water was 1.0588 mg/ml and in pH 6.8 phosphate buffer 1.018 mg/ml. Complex prepared by 1:2 ratio shows greater solubility than 1:1. Hence 1:2 ratio were selected for further tablet compression of optimized batches.

| Solvent used	1:1 Ratio		1:2 Ratio	
	Water (mg/ml)	pH 6.8 phosphate buffer (mg/ml)	Water (mg/ml)	pH 6.8 phosphate buffer (mg/ml)
Drug	1.0588	1.018	1.0588	1.0188
Complex by kneading method	2.64	2.81	2.75	2.88
Complex by co-precipitation method	2.51	2.95	2.91	2.96

Table 1 : Phase solubility study

Infra-red spectroscopy:

It is a useful technique to assess the interaction and complex formation between drug molecule and β-CD in solid state. This allows detection of complex formation in solid phase and to point out the implication of different functional groups of the guest and host molecule in the inclusion process, by analysing significant changes in shape and position of absorbance bands. Shift or intensity changes in the characteristic band of pure substance are considered as evidence of the complex existence. The spectra of drug shows sharp peak at 3354 cm^{-1} which was broaden in complex spectra by shift in spectra. This shows that there is formation of complex. Peak of 3174 cm^{-1} present in drug spectra is totally absent in the spectra of complex because of the host guest complex formation with β-CD. The NH_2-CO band shows sharp peak at 1415 cm^{-1} in drug spectra. In the complex reduction in intensity

band due to restriction to vibration imposed by host molecule when it was enclosed in β-CD.
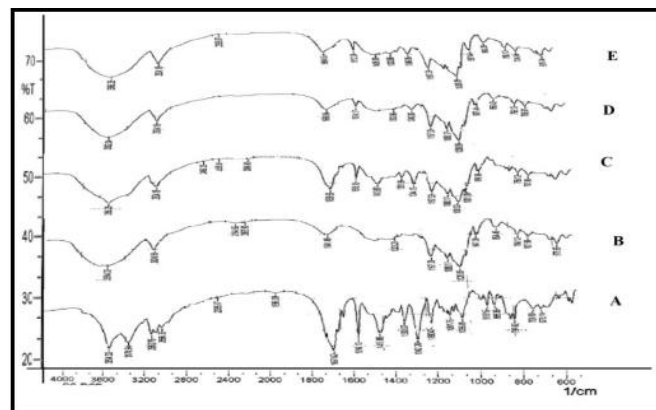
Figure 1: IR spectra of a) Atenolol, b) β-cyclodextrin, c) Physical mixture, d) Kneading complex, e) Co-precipitation complex.

Differential scanning Calorimetry:

Thermal behaviour of cyclodextrin inclusion complex was studied using DSC in order to confirm formation of β-cyclodextrin complex. The DSC thermogram of atenolol show an endothermic peak at 154.23 ^{0}C corresponding to its melting point. The β-CD show broad endothermic peak which is nearer to 100 due to release of water molecule. The physical mixture of complex show two endothermic peak at 95^0 and 151^0 C, which are shifted from original value. Thermal curve of complex prepared by kneading shows curve at 92 ^{0} C, and co-precipitation complex shows peak at 66^0C. The complete disappearance of atenolol indicates that there is formation of complex.
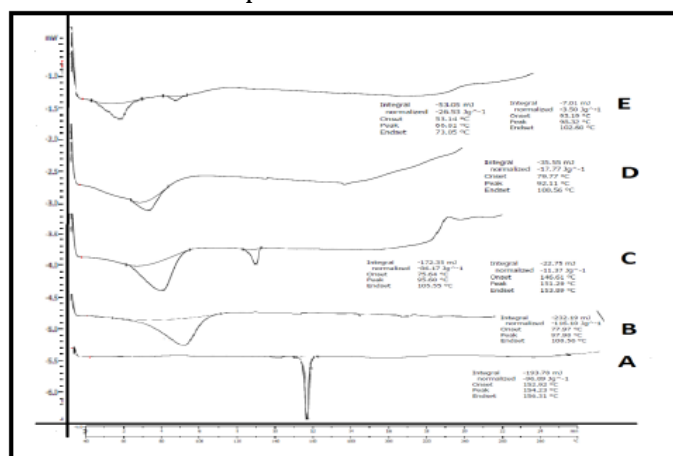
Figure 2: DSC thermograms of a) Atenolol, b)β-cyclodextrin, c) Physical mixture, d) Kneading   complex, e) Co-precipitation complex

Powder X-ray diffraction

Powder x-ray study was used to measure crystallanity of the formed inclusion complexes. A change in crystallanity of drug indicates complex formation by appearance of new or at least deviation from original pattern. X-ray diffractometry studies for atenolol and β-CD revels that they are present in purely crystalline

form. The physical mixture was interpreted as superposition of atenolol and amorphous β-CD. Drug shows diffraction peak at 2θ= 20.49.In case of inclusion complex prepared by kneading method there was decrease in intensity of atenolol. It shows peak at 2θ=18.78. On the other hand the graph shows the deviation of peaks from original in complex prepared by co-precipitation method at 2θ=18.40. It shows that some molecule of atenolol incorporated in β-CD cavity. The formation of amorphous state proves that the drug formed complex with β-CD.
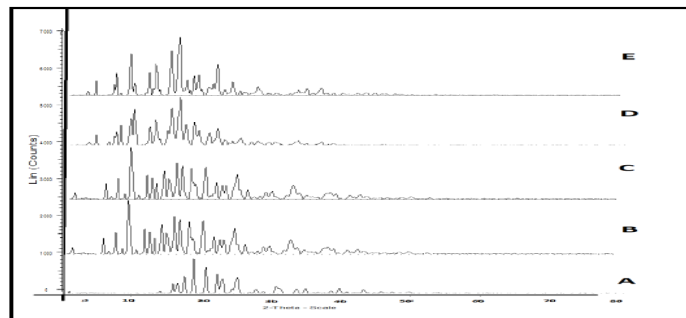
Figure 3: Powder x-ray diffraction pattern of a) Atenolol, b)β-cyclodextrin, c) Physical mixture, d) Kneading complex, e) Co-precipitation complex

Formulation code	Bulk density (gm/ml)	Tapped Density (gm/ml)	Angle of repose	Compressibility Index	Haussnes ratio
F1	0.37±0.008	0.47±0.01	30.81	14.18	1.12
F2	0.34±0.003	0.40±0.009	32.66	14.98	1.13
F3	0.31±0.005	0.41±0.009	30.96	15.20	1.11
F4	0.35±0.001	0.42±0.008	31.40	12.74	1.16
F5	0.37±0.007	0.40±0.009	29.57	13.57	1.14
F6 *	0.35±0.002	0.40±0.001	30.11	16.2	1.12
F7 *	0.36±0.006	0.46±0.005	29.23	13.56	1.14

Table 3: Flow properties of prepared mucoadhesive tablets of atenolol

Evaluation of mucoadhesive tablets

The controlled release mucoadhesive tablets were evaluated for thickness, hardness, weight variation, friability, mucoadhesive strength, swelling study, drug content are summarised in table 4.

Hardness:

The hardness of tablet from F1 to F5, F6* and F7* were 3±0.072 to 4.5±0.050 kg/cm2, 4.5±0.10 and 5±0.78 which indicating good binding and satisfactory strength of tablet.

Thickness:

The thickness of tablet was found to be in between 2.77±0.067 to 2.79±0.031for F1 to F5 batch, and F6*, F7* batch shows thickness 5.73±0.049, 5.68±0.023.

Weight variation:

Weight of tablets was found to be uniform with low standard deviation values from 196±1.67 mg to 198.33±1.6 mg and the weight formulated tablets of the atenolol β-cyclodextrin complex (F6*, F7*) was found to be 648±1.44 mg and 649.8±1.28 mg. The prepared formulations comply with the weight variation test as per IP. The results are given in table 4.

Friability:

The percent friability for formulations (F1 to F5, F6* and F7*) 0.002 ±0.0013 to 0.5872±0.00023. The % friability was less than 1% for all formulation.

Drug content:

The drug content for all formulation was found in the range of 98.20±0.44 to 102.37±0.20. The result was found within the pharmacopoeial limit.

Surface pH

The surface pH for all formulation was found in between 6.45±0.09 to 6.9±0.64. The acceptable pH of saliva in range 5-7. The surface pH was found for all formulations within the limit.

Formulation code	Hardness	Thickness (mm)	Weight variation	% Friability	%Drug content	Surface pH
F1	3±0.072	2.79±0.031	198.06±1.3	0.0506±0.0009	100.34±1.02	6.84±0.21
F2	4.5±0.01	2.78±0.042	198.33±1.6	0.1006±0.00127	98.20±0.44	6.47±0.44
F3	4.5±0.003	2.79±0.031	197.33±1.4	0.0507±0.00050	101.94±0.16	6.79±0.12
F4	4.5±0.020	2.78±0.042	196±1.67	0.002 ±0.0013	102.37±0.20	6.45±0.09
F5	4.5±0.055	2.77±0.067	197.23±1.7	0.0509±0.00002	100.95±0.63	6.8± 0.40
F6*	4.5±0.10	5.73±0.049	648±1.44	0.05006±0.0007	99.41±0.29	6.9±0.11
F7*	5±0.78	5.77±0.005	649.8±1.28	0.5872±0.00023	100.05±0.34	6.9±0.64

Table 4: Evaluation table of mucoadhesive tablets of atenolol

Swelling study-
The swelling index of all formulation was found in the range of 20.11±0.31to 81.60±0.27 for 8 hr. Swelling studies indicate that swelling index of F6 and F7 was found to be higher followed by F5 >F4 >F3 >F2 >F1. Swelling of tablet increases with increase in polymer concentration.

Hr	1	2	3	4	5	6	7	8
F1	31.90±0.60	40.21±0.78	48.57±0.95	55.79±0.05	61.46±0.56	66.88±0.89	70.80±0.43	72.71±0.15
F2	23.06±0.05	30.35±0.25	36.88±0.90	41.01±0.65	46.49±0.52	49.29±0.44	52.16±0.27	54.42±0.11
F3	15.53±0.15	19.14±0.40	24.95±0.78	27.28±0.32	31.43±0.14	34.05±0.65	36.07±0.54	38.06±0.23
F4	41.15±0.25	47.48±0.91	53.08±0.83	58.40±0.57	64.62±0.72	67.83±0.24	69.20±0.22	72.88±0.34
F5	28.01±0.21	39.87±0.86	49.91±0.43	58.52±0.61	65.38±0.28	72.17±0.16	75.07±0.15	80.31±0.07
F6*	17.66±0.02	26.34±0.22	35.07±0.09	46.89±0.18	58.51±0.43	64.88±0.11	77.48±0.69	82.92±0.55
F7*	20.11±0.31	28.44±0.58	41.88±0.38	53.87±0.28	63.90±0.03	69.34±0.27	75.91±0.32	81.60±0.27

Table 5: Swelling study

***In-vitro* drug release study:**
The drug release profile was studied using USP dissolution testing apparatus II using a paddle at 50 rpm. 500ml dissolution fluid, pH 6.8 phosphate buffer, was used and a temperature of $37 \pm 0.5°C$ was maintained. 5ml aliquots at 0 min, 15 min, 30 min, 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, and 12h respectively were pipette out. Absorbance was measured at λmax 224nm and from which percentage of atenolol was calculated using calibration curve. The *in-vitro* cumulative drug release for formulation F1 to F5, F6* and F7* at 12 hr showed 68.84, 76.18, 80.53, 65.35, 78.37, 93.3, and 97.68% shown in fig 6.
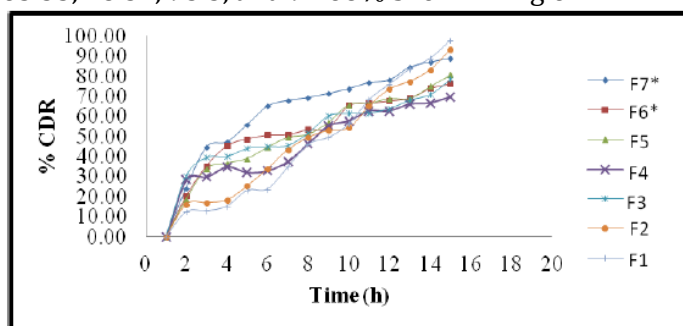
Figure 4: *In-vitro* drug release of formulation F1 to F5, F6* and F7*

Kinetic treatment to dissolution data:
The dissolution data from the batches were was fitted to zero order and Korsemeyer's peppas model and the result are shown in table. The release of atenolol in all formulation was best explained by higuchi, as the plot show higher regression coefficient and follow Korsemeyer's peppas model. A good compliance with higuchi equation indicates that drug release from all formulation were nearly shows matrix drug release. The next best fit was Korsemeyer's Peppas model (average=0.996). The calculated diffusion exponent (n) were found between 0.507 to 0.642 which indicates a combination of diffusion and swelling controlled release mechanism and drug release was highly influenced by swelling and gradual erosion of the tablets. It was concluded in a study that formulations (F1 to F5, F6* and F7*) exhibited anomalous (non fickian) diffusion.

Formulation	Zero order plot	First order	Higuchi	Korsemeyer's n	Peppas plot R²	Mechanism of drug release
F1	0.62	0.77	0.903	0.86	0.577	
F2	0.76	0.93	0.903	0.84	0.546	
F3	0.81	0.98	0.975	0.92	0.507	Non-fickian diffusion
F4	0.87	0.95	0.945	0.85	0.522	
F5	0.73	0.96	0.895	0.76	0.519	
F6*	0.99	0.92	0.963	0.93	0.612	
F7*	0.91	0.92	0.932	0.93	0.642	

Table 7: Kinetic data for all mucoadhesive tablets of formulation F1 to F5, F6*, F7*

Stability studies
The stability studies were carried out for F6 and F7 formulations according to ICH guidelines at temperature of 40°C with 75 % relative humidity (RH) for 3 months. The results showed that there was no considerable difference in drug content as shown in table.

Formulation code	8 days	15 days	1 month	2 month	3 month
F6*	99.41 %	99.41 %	99.38 %	99.30 %	99.25 %
F7*	100.05 %	100.05 %	100.05 %	100.01 %	100 %

Table 8: Stability study

CONCLUSION:

The current studies are aimed at successful development and optimization of mucoadhesive tablets of atenolol for the systemic treatment of hypertension with high regulation of the release rate. Based on the in vitro dissolution studies, it was found that formulation (F4) showed maximum drug release in 12 hrs. Therefore this formulation was optimized by complexing the atenolol with β-cyclodextrin (1:2 molar ratio) which was resulted in increase the dissolution rate of the formulation F6* and F7*.

Stability studies were performed for all formulations as per ICH guidelines, for drug content. The formulations showed no significant variations in the drug content and they were stable for specified time period. It was concluded that the mucoadhesive controlled release tablets of atenolol may be a good choice to bypass the extensive hepatic first pass metabolism with atenolol tablets and atenolol with β-cyclodextrin to improve the bioavailability of drug through buccal mucosa.

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