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Research Article

EVALUATION OF A NOVEL, NATURAL BADAM GUM AS A SUSTAINED RELEASE AND MUCOADHESIVE COMPONENT OF ATENOLOL BUCCAL TABLETS

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ABSTRACT

The present study was demonstrated to evaluate the mucoadhesive and sustained release properties of the badam gum obtained from the *Prunus amygdalus*. mucooadhesive tablets were prepared by directly compressing atenolol with badam gum in a concentration of 0, 15, 25, 35, 45 and 55mg. They were coated with 5% w/v ethylcellulose on all but one face. The force of detachment for the mucoadhesive buccal tablets increased with increase in concentration of badam gum. An *in vitro* study was carried out using phosphate buffer at pH 6.8. The cumulative percentage release of atenolol was decreased with increase in concentrations of badam gum. The release data were fitted to $M_t/M_\infty = Kt^n$ simple equation. The release characteristic has shown a non-fickian mechanism of release in formulation containing 35, 45 and 55mg of badam gum. An *in vivo* study was conducted with the prepared formulation in sixteen healthy human volunteers to determine the plasma concentration of atenolol at 0, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours. The bioavailability ($AUC_{0\text{-}t^*}$ ng.hr/ml) of the buccal atenolol tablet (F_4, F_5 and F_6) and oral (F_7) was found to be 2226.6 ± 228, 3251.9 ± 409, 3379.8 ± 269 and 1732 ± 96 ng.hr/ml respectively. These results showed that badam gum in the concentration of 45 and 55mg not only release the atenolol unidirectionally from buccal tablets, but also exhibited sufficient mucoadhesive properties for clinical applications.

Keywords: Buccal delivery, Badam gum, Atenolol, Bioavailability study

INTRODUCTION

Extensive efforts have recently been focused on targeting a drug in a particular region of the body for extended period of time, not only for local targeting of drugs but also for the better control of systemic drug delivery. The concept of mucosal adhesives are synthetic or natural polymers which interact with the mucus layer covering the mucosal epithelial surface and mucin molecules constituting a major part of mucus. The concept of mucoadhesive has alerted many investigators to the possibility that these polymers can be used to overcome physiological barriers in long-term drug delivery. They render the treatment more effective and safe, not only for topical disorders but also for systemic problems. A variety of drug substances have been administered by buccal route. Examples include peptide like TRH (Thyrotropin Releasing Hormone), calcitonin, buserelin and oxytocin, analgesic such as morphine and vasodilators such as nitroglycerin. [1,2] The present investigation was aimed at using the inexpensive, naturally and abundantly available badam gum as a mucoadhesive component in buccal tablets. Badam gum is a natural polymer, it is obtained mostly from the trunk of *prunus amygdalus* (Family: Rosaceae). It consists of L-arabinose (4 parts), D-xylose (2 parts), D-galactose (3 parts), D-glucouronic acid (1 part) and Aldobio uroic acid.[3,4] Atenolol is an adrenergic selective β_1-receptor antagonist, practically sparingly soluble in water, soluble in dehydrated alcohol, slightly soluble in dicholoromethane, and is rapidly but incompletely absorbed after oral administration. It has low bioavailability due to 35-50% of oral dose being excreted in the urine and 30-50% in the faeces, in 24 hours.[5,6] The aim of the present study was to evaluate the natural polymers badam gum in the concentration of 15, 25, 35, 45 and 55mg as a mucoadhesive component in buccal tablets, following their application to the buccal mucosa. The release characteristics of atenolol buccal tablets were compared with oral formulation. In addition the bioadhesive strength was reflected by the force of detachment of these buccal tablets was quantititated by *in vitro* using freshly excised pig buccal membrane as a model biological interface. The overall goal associated with the present study was not to determine that a conventional drug substance could be administered via the buccal route but to demonstrate the utility of a new, heretofore untested natural polymer to serve as a mucoadhesive tablet excipient.

MATERIALS AND METHODS

Atenolol was obtained as a gift sample from Torrent Pharmaceuticals, Ahmedabad, India. Badam gum was obtained from local market, Coimbatore, India. Microcrystalline cellulose, magnesium stearate and ethyl cellulose were purchased from Loba chemie, Mumbai, India.

Acute toxicity study for badam gum

Wistar rats (150-200g) maintained at standard laboratory conditions were used. A total of five animals were used which received a single oral dose (2000mg/kg**)** badam gum. Animals were kept overnight fasting prior to drug administration. After the administration of the polymer, food was withheld for further 3-4 hours. Animals were observed individually at least one during the first 30 minutes after dosing, periodically during the first 24 hours and up to 14 days after drug administration (OECD guidelines).

Evalution of gum

Organoleptic evaluation, physical evaluation, determination of ash value and microbial count of badam gum were performed according to Indian Pharmacopeia.[7]

Method of preparation of Bilayered Buccal Tablet

Preparation of buccal tablet

The mucoadhesive layer containing atenolol (10mg) was prepared by using various concentration of badam gum. The compositions of the different formulations were represented in Table 1. The various components of the each formula were weighed, mixed and pass through the mesh to ensure complete mixing. The average weight of about 150mg were separately weighed and compressed using a 13mm diameter of a die on an infra red hydraulic pellet press (Kimaya Engineers, India) using a force of 8 tonnes for 60 seconds. The prepared mucoadhesive tablets were 13.32mm in diameter and 1.10mm in thickness.[8,9]

Formation of backing layer to the mucoadhesive layer

The backing layer was made up of ethyl cellulose. The solution was prepared by dissolving 5% w/v of ethyl cellulose in choloform. The prepared solution was sprayed on to one surface of the mucoadhesive layer leaving the other side free. Then it was air dried at room temperature. The double-layered structure design was expected to provide drug delivery in a unidirectional fashion to the

mucosa. It avoids loss of drug to wash out saliva and the swelling profile of the buccal tablet can be changed dramatically by the amount of backing material and those changes could alter drug release profile.[10]

Table 1: Composition of Mucoadhesive layer of Buccal tablets of Atenolol with Badam gum

Formulation	Atenolol (mg)	Badam gum(mg)	Microcrystalline cellulose (mg)	Magnesium stearate (mg)
F1	10	0	139	1
F2	10	15	124	1
F3	10	25	114	1
F4	10	35	104	1
F5	10	45	94	1
F6	10	55	84	1

Evaluation of the Prepared Tablets

Weight uniformity

The weight of each of ten randomly selected tablets of each formulation was determined by using an electronic balance (Precisa 205 A Balances, Switzerland).[11]

Hardness and friability testing

Hardness and friability of each ten randomly, selected tablets of each formulation were determined using the Erweka hardness tester (TBH 30) and the Erweka friabilator (GmbH, Germany) respectively.[11]

Drug content uniformity

Ten randomly selected tablets of each formulation were weighed accurately and powered. Powder equivalent to 10mg of atenolol was transferred into a 10ml of volumetric flask containing 50ml, of phosphate buffer pH 6.8, sonicated for 30min, and stirred continuously for 8 hrs on a magnetic stirrer. The volume was made up to 100ml with phosphate buffer pH 6.8, and the absorbances were measured in a UV Spectrophotometer at 274nm (Shimadzu, UV Spectrophotometer, Tokyo, Japan). Concentrations of atenolol were calculated from standard calibration curve of atenolol phosphate buffer pH 6.8 without interference excipients.[11]

Infrared (IR) absorption Spectroscopy

To investigate any possible interaction between the drug and the utilized buccoadhesive material, the IR spectra of pure atenolol and its physical mixture (1:1) with badam gum were carried out using JASCO FTIR 410. The samples were prepared as KBr disks compressed under a pressure of 6 Ton / nm^2. The wave number selected range between 400 and 4000 cm^{-1}.

Bioadhesion Studies

In vitro bioadhesion study

Satisfactory bioadhesion is essential for the successful application of a buccal bioadhesive drug delivery system. It implied the strength of attachment of the dosage form to the biological tissue. Several techniques for *in vitro* determination of bioadhesion have been reported, which included tensile testing, shear stress testing, adhesion weight method, fluorescent probe method, flow channel techniques and colloidal gold staining method. In our study the polymers were evaluated using a $TA.XT_2$ texture analyzer equipment pig buccal mucosa as a model tissue under simulated buccal conditions.[12,13,14]

Bioadhesion measurement

A $TA.XT_2$ texture analyzer (Stable Micro System, Haslemere, Surrey, U.K.) equipped with a 5kg load cell was employed to determine the bioadhesion using pig buccal mucosa as the model tissue. The buccal mucosa was stored frozen in a simulated saliva solution (2.38g of Na_2HPO_4, 0.19g KH_2PO_4 and 8g NaCl in 1000ml of distilled water at pH 6.75) and thawed to room temperature before used. The pig buccal mucosa was mounted onto a cylindrical Perspex support of 2cm diameter and 4cm length and secured with a string. A foam tape was placed underneath the porcine buccal mucosa on the Perspex support at the cross-sectional end to provide cushioning effect. The pig buccal mucosa was further secured by placing an aluminum cap over the Perspex support. A circular hole of 17mm diameter was made on the top of the cap to expose the buccal membrane for contact with the tablet during measurements. The whole Perspex support was then positioned at the bottom of the measuring system and held in place by a clamp. Tablet was fixed to another Perspex support of similar dimension using a double-sided tape and the support was then screwed on to the upper probe of the instrument. These two Perspex supports were aligned to ensure that the tablet would come into direct contact with the exposed surface of buccal mucosa when the upper tablet support was lowered. All measurements were conducted at a room temperature of 25°C and relative humidity of 50-60%. During measurement, 200µl of simulated saliva solution was evenly spread on the surface of tissues. The upper Perspex support was lowered at a speed of 1.0 mm/s until contact was made with the tissue and the contact force of 0.5N was applied. At various contact times 5, 10, 15, 20, 25 and 30 seconds the detachment force in 'N' was measured.

Swelling study

Swelling index of the tablet was evaluated for six tablets of each formulation. These were weighed and placed separately in pre-weighed basket made of stainless steel mesh. The total weight was recorded (W_2). This basket was placed in a plastic vessel containing 4ml of demineralized water and placed in an incubator at 37°C. At time intervals 0.5, 1, 2, 3 and 4hrs excess water was carefully removed and the swollen tablets were weighed (W_2). The swelling index was determined from the formula.[13]

Swelling study = $(W_2-W_1)/W_1$

Surface pH of the tablet

The surface pH of the tablet was determined to investigate the effect of pH on the bioadhesion and possible side effects of the tablets *in vivo*. This was determined by allowing the tablet to swell in 1.0ml of demineralized water (pH 6.8 ± 0.06) for 2hrs. A combined glass pH electrode was brought in contact of the swollen tablet and the pH was measured after 1min equilibration.[15]

***In vitro* drug release studies**

It has been reported that the normal pH of the human saliva varies from 5.8 to 7.8 with an average of 6.8. So the release studies were conducted in the pH 6.8 to find out the amount of drug release into the solution from the buccal tablet before diffusion through the membrane. For the dissolution study of buccal tablets a specially designed glass cylinder closed at one end and opened at the other end was employed. This glass cylinder allows the tablets to dissolve from the fixed place with out any movement (since the tablet should release the drug from a fixed area in the buccal region).[16,17]

Atenolol buccal tablet

Release of Atenolol from buccal tablets was studied in phosphate buffer of pH 6.8 (250ml) using a USP XXI / XXII dissolution rate apparatus Mumbai, with a paddle rotating at a rate of 75 RPM and at 37 ± 0.5°C, samples were withdrawn through a filter (0.45µm) at different time interval and were assayed at 274nm for atenolol using Jasco V530, 1400 UV visible double beam spectrophotometer. The drug release experiments were conducted in triplicate.

In Vivo Bioavailability Studies

Protocol

Each study was carried out in 16 healthy male volunteers of 20-23 years of age and 55-70kg weights were selected. A complete crossover design is employed in which each subject receives the test product and the reference product. Their liver and kidney functions were assessed to be normal by clinical and standard biochemical investigation. None of the subjects used alcohol or tobacco or had not taken any medication for a week prior to study. The purpose of the study was fully explained and each volunteer had given his written consent and was approved by the ethical committee of the institution.

Volunteers were fasted overnight and zero hour blood samples were collected early in the morning from each volunteer. For oral administration one tablet containing the drug (10mg atenolol) was administered at 8 hours along with 200ml of water. The mouth was rinsed with an additional 100ml of water, which was also swallowed. Food was with held for a period of 2 hours. The samples of blood were collected at various time intervals. Blood samples obtained were immediately centrifuged and the plasma was separated and stored at -20˚C for analysis. For buccal administration, buccal tablet was placed in the buccal cavity, while the subjects were in a sitting position. Samples of blood (5ml) were collected at various time intervals. Blood samples were immediately centrifuged and the plasma was separated, the drug was extracted and analyzed by spectrofluorimetrically[18]

Statistical Analysis

The results obtained for *in vivo* studies were subjected to statistical analysis using a computer program instat (Graph Pad) for one way analysis of variance ($p < 0.01$) followed by Dunnett's test.

RESULTS AND DISCUSSION

Microbial count of gum

None of the colonies were recovered from the dishes representing the intial 1:10 dilution of substances; express the result as "less than 10 microorganism per gram of the substance".

Acute toxicity study for badam gum

The results indicated that the polymer up to a dose of 2000mg/kg was non lethal. The LD_{50} of the badam gum falls under class 4 values as per the OECD guidelines. The biological evaluation was carried out at 2000mg/kg dose levels.

Infrared (IR) absorption spectroscopy

The IR Spectra did not show any significant differences from those obtained for pure sample. These obtained results indicated that there was no positive evidence for the interaction between the drug and the polymers more than hydrogen bonding (if any), which may have occurred between donating and accepting groups of both the drug and the polymers.

Evaluation of tablets

The composition of the buccal tablet was shown in Table – 1. In that, microcrystalline cellulose is added as a direct compression adjuvant, since the Badam gum does not produce sufficient hardness. The hardness of the prepared tablets was varied between 4.7 and 5.0 kg/cm2 and friability ranged between 0.5 and 0.7%. Tablet weight varied between 147.2 and 150.6mg and the assay content of atenolol varied between 98.8 and 99.7%. Thus all the parameters of the compressed tablets were practically within control.

Bioadhesion study

A profile showing the mean value of the force of detachment of atenolol buccal tablets containing various concentration of badam gum, following their application to excised pig buccal mucosa is shown in Fig. 1. It can be noted that the mean values of the force of detachment increased with time and reached a plateau at later time points. The mean values of the forces of detachment were greater for formulation containing 55mg of badam gum and the bioadhesive strength increased with increase in the concentration of badam gum.

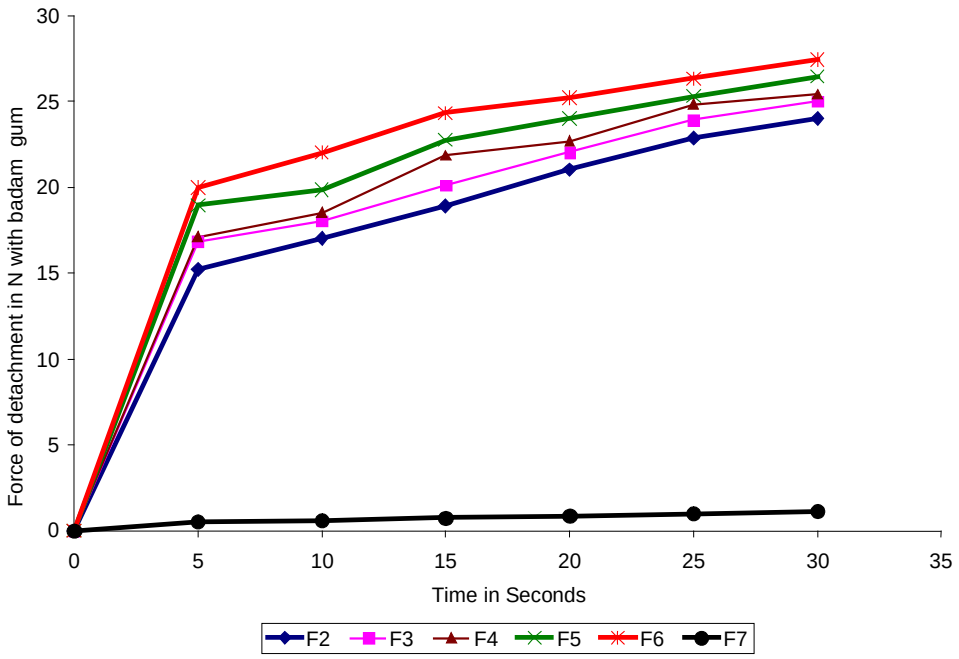

Fig. 1: The force of detachment from pig intestine for directly compressed Atenolol Buccal tablets containing 15, 25, 35, 45 and 55 mg of Badam gum. All data points represent the mean value ± standard deviation of three experiments

Swelling index

The swelling index for the various formulations was shown in Fig. 2. These profiles indicate the uptake of water into the tablet matrix producing an increase in weight. Formulations F2, F3, F4, F5 and F6 take up water over the first half an hour and the tablets were intact throughout study. Formulation F4, F5 and F6 were found to absorb more than the rest of the formulation, exhibited 'n' value characteristic of non-Fickian release mechanism involving a combination of both diffusion and chain relaxation.These results suggested that formulation F5 and F6 containing 45 and 55mg of badam gum is the suitable concentration for the hydrophilic swellable matrix in order to achieve controlled drug release.

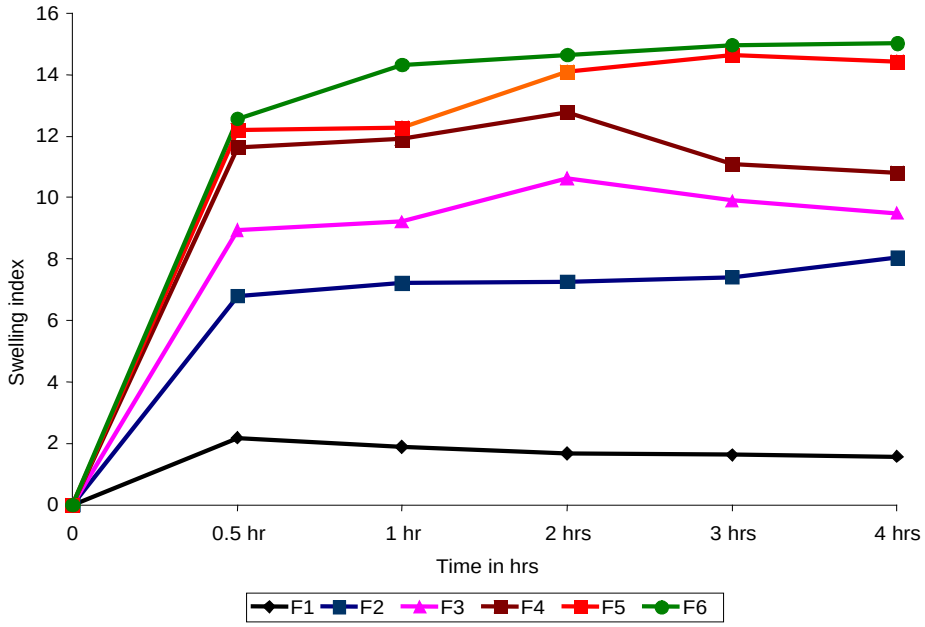

Fig. 2: Swelling index of Atenolol Buccal tablets using badam gum

Surface pH

The surface pH of the tablets has been given in table – 2. The surface pH of all the formulation was found to be within the pH range of 5-7 (Salivary pH) and hence these formulations do not produce any irritation in the buccal cavity.

Drug release characteristics

The drug release profiles from the prepared atenolol buccal tablets containing various concentration of badam gum are shown in Fig. 3. Atenolol was more rapidly released from F2, F3 and F4 with almost 97.01±0.13, 89.12±0.54 and 86.13±0.64 within 15th hour respectively. Increase in concentration of badam gum decreased the release of atenolol.

Table 2: Surface ph of the Atenolol Buccal tablets containing badam gum

Drug + polymer	Formulation	Surface pH
	F1	6.8
Atenolol	F2	6.6
+	F3	6.4
Badam gum	F4	6.2
	F5	5.9
	F6	5.7

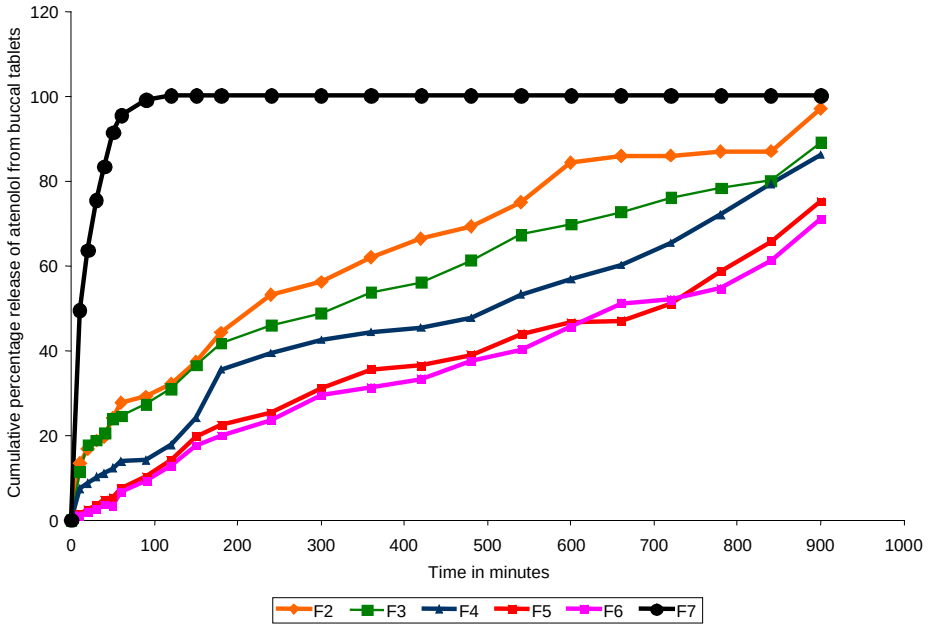

Fig. 3: Cumulative mean (±s.d) percentage release of Atenolol from directly compressed Buccal tablets containing 15,25,35,45 and 55mg of badam gum in phosphate buffer ph 6.8

Drug release kinetics

To examine the release mechanism of atenolol from the prepared bioadhesive tablets, the results were analysed according to the following equation.

$$M_t/M_\infty = Kt^n$$

Where M_t/M_∞ is the fractional drug released at time t, K is the kinetic constant incorporating structural and geometrical characteristics of drug/polymer system (device) and n is the diffusional exponent that characterizes the mechanism of drug release. For non-Fickian release, the n value falls between 0.5 and 1.0 (0.5<n<1.0)

Whereas in the case of Fickian diffusion, n = 0.5, for zero order release (case II transport) n = 1 and for supercase II transport, n>1. The values of n as estimated by linear regression of log M_t/ M_∞ vs log (t) of different formulations was shown in Table – 3

Table 3: Kinetic release constants (K), and diffusion exponents (N) after fitting the release data to the simple power law (Log M_T / M_∞ Vs Log T)

Drug+Polymer	Formulation code	n value	K value	Release Characteristics
Atenolol + Badam gum	F1	0.2985	26.4084	-
	F2	0.4677	3.9178	-
	F3	0.4319	4.2950	-
	F4	0.5690	1.5132	Non- Fickian
	F5	0.8755	0.2024	Non- Fickian
	F6	0.9430	0.1271	Non- Fickian

n^a = the diffusion release exponent, indicative of the release mechanism; n = 0.5 for Fickian diffusion mechanism; n = 1 for zero order release (case II transport); n lies between 0.5 and 1.0 (0.5<n<1) for non-Fickian (anomalous) release and n>1for super case II transport.

Data analysis

The data obtained from dissolution kinetic studies were analysed using PCP Disso V2.08 software. Dissolution profiles for badam gum in Fig. 3 demonstrate the rapid release of atenolol from the 15 and 25mg, badam gum formulations as a result of tablet erosion and disintegration. Formulation F4, F5 and F6 containing 35, 45 and 55mg badam gum demonstrate slower atenolol release compared with formulation F2 and F3 is due to the combination of swelling and erosion in the matrix. The obtained value for formulation F4, F5 and F6 of 'n' was 0.5690, 0.8755 and 0.9430 respectively. These indicate the non-fickian release kinetics, involving a combination of both diffusion and chain relaxation mechanism. But formulations F2 and F3 cannot follow any of the release characteristics.

$T_{50\%}$ and $T_{90\%}$ release of atenolol

The time for 50% ($T_{50\%}$) and 90% ($T_{90\%}$) release of atenolol from the prepared buccal tablets were estimated by linear regression of log M_t/ M_∞ Vs log (t) of different formulations are shown in Table – 4. The results clearly indicate, increasing the half life ($T_{50\%}$) of atenolol release from the prepared tablets by increasing the concentration of badam gum.

Table 4: Time (H) for 50% and 90% Atenolol release from the prepared Buccal tablets

Drug + Polymer	Formulation code	$T_{50\%}$	$T_{90\%}$
Atenolol + Badam gum	F1	0.32	1.04
	F2	3.88	12.58
	F3	4.89	19.10
	F4	7.71	24.99
	F5	9.01	27.63

	F6	9.41	27.54

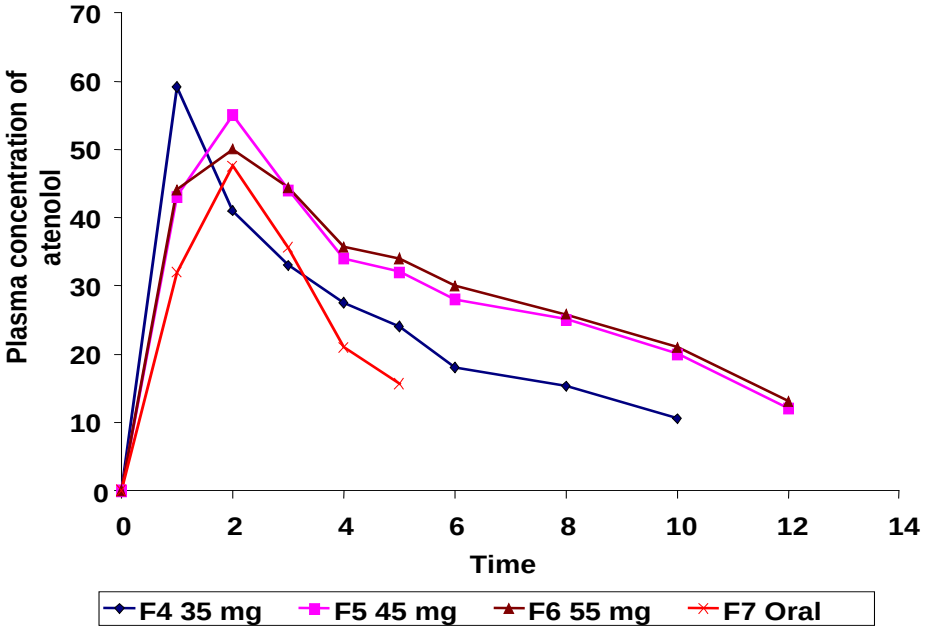

Fig. 4: Plasma profiles of Atenolol in healthy human volunteers from directly compressed Buccal tablets containing 35, 45 and 55 mg of Badam gum and oral tablet

***In vivo* bioavailability study**

The mean plasma profiles of atenolol from the prepared buccal tablets in comparison with the formulated oral tablets are shown in Fig.4. The relevant pharmacokientic parameters are listed in Table 5. The plasma profiles exhibited a higher C_{max} with a faster decline in the plasma concentrations for the formulated buccal tablet F4, but exhibited a lesser C_{max} and more sustained levels for prepared buccal tablets F5 and F6. It has been observed that, by increasing the badam gum content C_{max} was decreased and T_{max} was increased (Table 5). This could be attributed to the slower. *in vitro* release of the drug by increasing the badam gum concentration. For F4, F5 and F6 the mean C_{max} values were 592.61 ± 89, 551.02 ± 32 and 500.61 ± 30 and the mean T_{max} values were 1 ± 0.0, 2 ± 0.0 and 2 ± 0.0 respectively . The higher the C_{max} and less T_{max} value for formulation, F4 is due to the faster release of the drug from the polymer. The area under the curve (AUC) for the various formulations F4, F5 and F6 were found to be 2226.6 ± 228, 3251.9 ± 409 and 3379.8 ±269 respectively. The higher $AUC_{o\text{-}t^*}$ values of the prepared formulations F5 and F6 were due to the slow release of the drug by the polymer. All the formulated buccal tablets showed higher AUC than the formulated oral tablets. This could be attributed to the avoidance of first pass metabolism by the buccal dosage form. The mean residence time (MRT) for the various formulations is increased from 10.77 ± 0.27h to 17.54 ± 0.26 on increasing the concentration of polymer.

Table 6 presents the statistical analysis of the obtained pharmacokinetic parameters C_{max} and $AUC_{0\text{-}t^*}$ were significantly (P< 0.01) affected (p<0.01) by the type and composition of the prepared buccal tablets, which could be attributed to the difference in the *in vitro* release of the drug.

Table 5: Pharmacokinetic parameters of Atenolol directly compressed Buccal tablets obtained from *In Vivo* studies carried out in healthy human volunteers

Pharmacokinetic Parameters	F4 35 mg BG	F5 45 mg BG	F6 55 mg BG	F7 (Oral tablet)
C_{max} ng /ml	592.61±89	551.02±32	500.61±30	475.6 ±112.4
T_{max} (h)	1±0.0	2±0.0	2±0.0	2±0.0
Kel (h)	0.082±0.19	0.055±0.04	0.048±0.006	0.293±0.013
T ½ (h)	8.38±0.83	12.397±1.06	14.34±0.21	2.36±0.40
$AUC_{0\text{-}t^*}$ (ng. h/ ml)	2226.6±228	3251.9±409	3379.8±269	1732±96
AUC_{0} - ∝* (ng.h/ml)	3501.7±180	5409.5±592	6083.7±480	2091±8.88
$AUMC_{0\text{-}t^*}$ ($ng.h^2$/ml)	9534.2 ±253	17251±229	18225.8±184	4068.4±61
MRT	10.77±0.27	15.12±1.01	17.54±0.26	3.56±0.35

Table 6: Instat (Graph PAD) One- way Analysis of variance of the in vivo characteristics of Buccal tablets contain Badam gum and Oral tablets

Formulation	Pharmacokinetic parameters	
	Cmax	T max

F4	592.61± 89	2226.6±228
F5	551.02±32	3251.9±409
F6	500.61±30	3379.8±269
F7 oral	475.6±112.4	1732±96

Values are mean ± SEM (n = 16 in each group)

Statistical analysis was performed using Instat (Graph Pad) one -way analysis of variance (ANOVA)

*P< 0.01 Vs oral tablets

CONCLUSION

Formulations F5 and F6 contains 45 and 55mg of badam gum exhibited a lesser C_{max} and more sustained release then the other formulations. All the formulated buccal tablets showed higher AUC than the formulated oral tablets. This could be attributed to the avoidance of first pass metabolism by the buccal dosage form.

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