

Evaluation of a Novel, Natural Locust Bean Gum as a Sustained Release and Mucoadhesive Component of Tizanidine Hcl Buccal Tablets

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ABSTRACT

Mucoadhesive polymers that bind to the gastric mucin or epithelial cell surface are useful in drug delivery for the purpose of increasing the intimacy and duration of contact of drug with the absorbing membrane. Mainly synthetic polymers are in use for this purpose. Probably the biodegradability of the synthetic polymers are questionable, In the present work mucoadhesive buccal tablets of Tizanidine hydrochloride (TZD HCL) were prepared by using locust bean gum that have better mucoadhesive property than synthetic polymer. The *in-vitro* adhesive and mucoadhesive strength and swelling property of mucoadhesive material locust bean gum were evaluated by Share Stress and Park and Robinson methods. Buccal formulations of tizanidine HCL tablets were prepared using locust bean gum and thickness, hardness, friability, weight variation and assay of tablets were tested. The *in-vitro* drug release study of tizanidine HCL exhibited extended drug release profile for tablets prepared. Higuchi and Peppas data reveals that the drug released by non-Fickian diffusion mechanism. The present study shows that formulation containing 50% locust bean gum have greater mucoadhesive property than all other formulation.

Keywords: Mucoadhesive, Tizanidine HCL, and tablets. bioadhesive

INTRODUCTION

Tizanidine HCL is an agonist Fat α_2 -adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, tizanidine has no direct effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons. Absolute oral bioavailability of tizanidine is approximately 40% (CV = 24%), due to extensive first-pass hepatic metabolism. Tizanidine is extensively distributed throughout the body with a mean steady state volume of distribution of 2.4 L/kg (CV = 21%) following intravenous administration in healthy adult volunteers. Tizanidine is approximately 30% bound to plasma proteins. Tizanidine has linear pharmacokinetics over a dose of 1 to 20 mg. Tizanidine has a half-life of approximately 2.5 hours (CV=33%).^{1,2,3}

Buccal drug delivery has been considered as an alternative to oral dosing for subjected to degradation in the G I tract or to hepatic first pass metabolism. Buccal drug delivery offers a safer mode of drug utilization in case of toxicity. Since natural polymers are found in abundance, safe, nontoxic, the present study was undertaken by using such natural polymers^{5,6}

The aim of the present study was to design buccoadhesive tablets to release the drug unidirectionally in buccal cavity for extended period of time in order to avoid first-pass metabolism for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance. Evaluate natural polymer Locust been gum in the concentration 20, 30, 40 and 50 mg as a mucoadhesive component in buccal tablets, following their

application to the buccal mucosa. The release characteristics of Tizanidine HCL were compared with oral formulation

MATERIALS AND METHOD

Tizanidine HCL purchased from balaji drugs gujrath, Locust been gum Fluka, Japan. Microcrystalline sulphate, magnesium stearate, lactose, Aspartame and ethyl cellulose were purchased from loba chemie Mumbai, India

Evaluation of Gum

Organoleptic evaluation, physical evaluation, determination of ash value and microbial count of tamarind seed gum were performed according to Indian pharmacopeia.

PREPARATION OF BILAYERED BUCCAL TABLET

Preparation of mucoadhesive layer^{4,5,8,9}

The mucoadhesive layer containing tizanidine HCL (7.5mg) was prepared by using 20, 30,40 and 50 mg of badam gum. Various components of each formulation were weighed, mixed and passed through the mesh (250 micron) to ensure complete mixing. The average weight of about 150mg were separately weighed and compressed using a 13 mm diameter of a die on an infrared hydraulic pellet press using a force of 8 tons for 60 seconds. The placebo tablets were also prepared in the same manner. The prepared mucoadhesive layers were 13.32 mm in diameter and 1.10 mm in thickness.

Formulation of backing layer to the mucoadhesive layer

The backing layer was made up of ethyl cellulose. The solution was prepared by dissolving 5% ethyl cellulose in chloroform. The prepared solution was sprayed onto 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,

avoids loss of drug due to washout of saliva and swelling profile of buccal disc can be changed dramatically by the amount of backing material and those changes could alter the drug release profile

Table. 1.1: Composition of mucoadhesive layer of buccal tablets of Tizanidine HCL with Locust bean gum

Formulation	Tizanidine HCL (mg)	Locust bean gum (mg)	Microcrystalline cellulose (mg)	Lactose	Aspartame	Magnesium stearate (mg)
F 1	2	0	141	6	1	1
F 6	2	20	121	6	1	1
F 7	2	30	111	6	1	1
F8	2	40	101	6	1	1
F9	2	50	91	6	1	1

EVALUATION OF BUCCAL TABLETS

All the formulated dosage forms of Tizanidine HCL buccal tablets have been subjected to the following quality control test.

Uniformity of weight and medicament content^{11,12}

Test for uniformity of weight of tablets was done according to I.P. ten tablets from each batch were evaluated for uniformity in tablet weight. Ten tablet from each batch were powdered individually and a quality equivalent to 7.5 mg of Tizanidine HCL was accurately weighed and transfer to a volumetric flask containing 50 ml of phosphate buffer (pH 6.8), sonicated for 30 minutes, and stirred continuously for 8 hours on a magnetic stirrer the volume was made unto 100ml with phosphate buffer pH6.8 and the absorbance were measured in a UV spectrophotometer at 276 nm.

Hardness and friability testing^{11,12}

Hardness and friability of each ten randomly ,selected tablets of each formulation using Erweka hardness tester (TBH30) and the Erweka friabilitor (GmbH,Germany) respectively.

Infrared (IR) absorption spectroscopy

To investigate any possible interactions between the drug and the polymers, the IR spectra of pure drug Tizanidine HCL and its physical mixtures (1:1) with badam gum were carried out using FT R--8400S(CE),SHIMADZU spectrophotometer. The samples were prepared as KBr disks compressed under a pressure of 6 ton/nm². The wavelength selected ranged between 400 and 4000cm⁻¹.The data are shown in fig.1.1-1.3

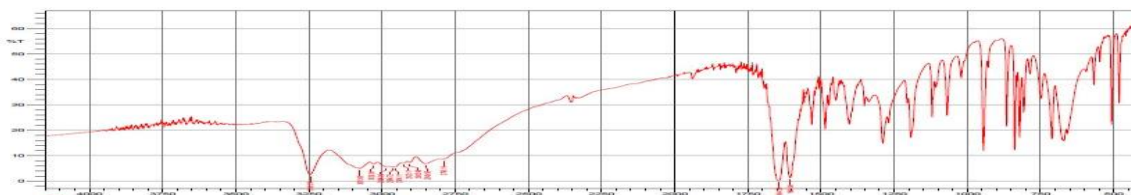


Fig: 1.1: IR spectrum of Tizanidine HCL



Fig: 1.1: IR spectrum of Locust bean gum

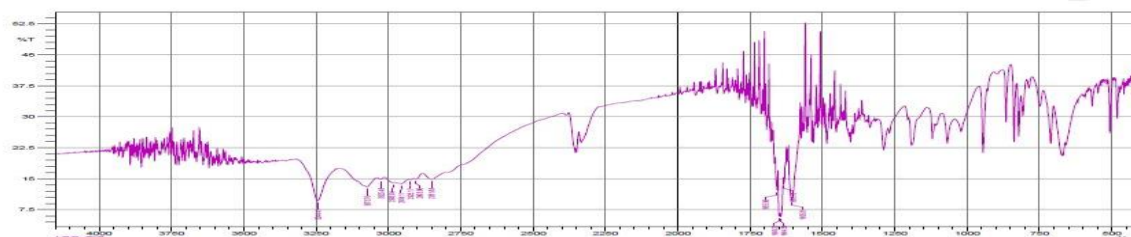


Fig: 1.1: IR spectrum of Tizanidine HCL+ Locust bean gum

Bioadhesion study^{11,12}

In vitro bioadhesion study

Satisfactory bio adhesion is essential for successful application of a buccal bioadhesive drug delivery system. It implied the strength of attachment of the dosage form to biological tissue. Several techniques for in vitro determination of bioadhesion have been reported, which include tensile testing shear stress testing, adhesion weight method, fluorescent probe method, flow channel techniques and colloidal gold staining method. In our study the polymers evaluated using TA.XT2 texture analyzer equipment rabbit buccal mucosa as a model tissue under simulated buccal condition

Bioadhesion measurement

A TA.XT2 texture (stable Mirosystem, Haslemere, Surrey, U.K.) equipped with a 5g 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 and thawed to room temperature before used. The pig buccal mucosa was mounted on to a cylindrical Perspex support of 2cm diameter and 2cm length and secured with a string. A foam type 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 aluminium 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 positioned at the bottom of the measuring system and held in place by a clamp. The 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 instrument. These two Perspex support 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. On measurements were conducted at a room temperature of 25°C and a relative humidity of 52-60%

During measurements, 200µl of stimulated saliva solution was evenly spread on the surface of tissues. The upper Perspex support was lowered at a speed of 1mm/sec until contact was made with the tissue and the contact force of .5N was applied. At various contact times 5, 10, 15, 20, 25 and 30 min. The detachment force in 'N' was measured.

SWELLING STUDY^{14,15,17}

The 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 plastic vessel containing 4 ml of isotonic buffer (pH 6.8) in an incubator at 37°C. At time intervals 0.5, 1, 2, 3 and 4 hrs excess water was carefully removed and the swollen tablets were weighed (W_2). The swelling index was determined from formula

$$\text{Swelling index} = \frac{\text{Swelling index } (W_2 - W_1)}{\text{Initial weight } (W_1)}$$

SURFACE pH OF THE TABLET^{19,20}

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 1.0 ml of demineralised water (pH 6.8) for 2 hrs. A combined glass pH electrode was brought in contact of the swollen tablet and the pH measured after 1 min equilibrium.

INVITRO DRUG RELEASE STUDIES

Dissolution studies^{12,14,19,21}

It has been reported that the normal pH of 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 the 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 without any movement (since the tablet should release the drug from a fixed area in the buccal region).

Tizanidine HCL buccal tablet

Release of Tizanidine HCL from buccal tablets was studied in phosphate buffer of 6.8 pH (900ml) using a USP XXI/XXII dissolution rate apparatus, with a paddle rotating at a rate of 75 rpm and at 37°C

RESULTS AND DISCUSSION

Evaluation of tablet

Table 1.1 shows the composition of buccal tablets. The microcrystalline cellulose added in the formulation as direct compression adjuvant.

Tablet hardness 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 150.6 mg and the assay content of Tizanidine HCL varied between 98.8 and 99.7%

Thus all the parameters of the compressed tablets were practically within control.

Bioadhesion study

The profile showing the mean value of locust bean Gum, following their application to excised rabbits intestinal mucosa is shown in Fig. 1.4. It can be noted that the mean values of force of detachment increased with time and reached a plateau at later time points. The mean values of force of detachment were greater for formulation containing 50 mg of locust bean Gum and the bioadhesive strength increased with increase in concentration of locust bean Gum

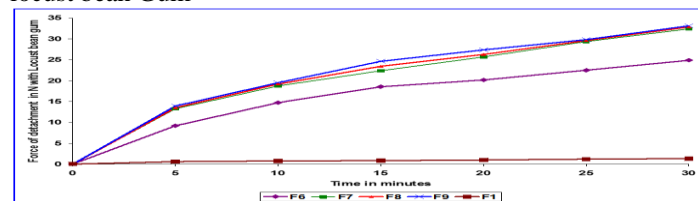


Fig. 1.4 : The force of detachment from rabbit intestine for directly compressed Tizanidine HCL buccal tablets containing 20, 30, 40 and 50 mg of locust bean gum. All data points represent the mean value ± standard deviation of three experiments

Swelling index

The swelling index for the various formulations is shown in Fig 1.5. These profiles indicate the uptake of water into the tablet matrix producing an increase in weight.

Formulations F6, F7, F8 and F9 containing Locust Bean Gum showed faster water uptake increased with increase in time to become fully hydrated. Higher concentration of locust bean gum displays a greater hydration capacity. The capacity of the formulation to take up water is an important intrinsic parameter of polymeric system in consideration of release of drug on mucosal surface.

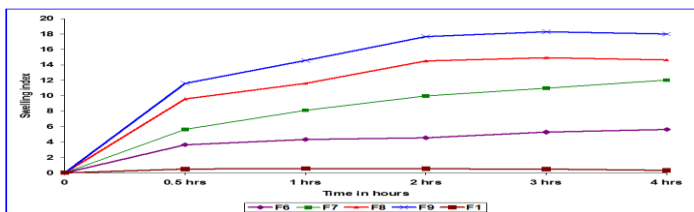


Fig. 1.5: Swelling index of Tizanidine HCL buccal tablets using Locust bean gum

Surface pH

An acidic or alkaline pH may cause irritation to buccal mucosa. The surface pH of tablet was determined in order to investigate the possibility of any side effects in vivo. The surface pH of the tablet has been given in Table 1.2. 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.

Table .1.2 :Surface pH of Tizanidine HCL buccal tablets containing Locust Bean Gum

Drug + Polymer	Formulation	Surface pH
Tizanidine HCL + Locust bean gum	F 1	7.1
	F 6	6.4
	F 7	6.2
	F8	6.5
	F9	6.6

Drug release characteristics

The drug release profiles from the prepared Tizanidine HCL buccal tablets containing various concentration of locust bean gum are shown in Fig. 1.6

Sustained release of Tizanidine HCL was obtained from F6, F7, F8 and F9 and with almost 102.88, 95.87, 96.09 and 90.64 in 13th hour respectively.

Increase in concentration of locust bean gum decreased the release of Tizanidine HCL.

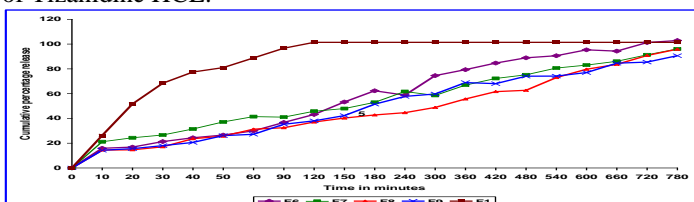


Fig. 1.6 Cumulative percentage release of Tizanidine HCL buccal tablets containing 20, 30, 40 and 50 mg of Locust bean Gum in phosphate buffer pH 6.8

Drug release kinetics

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

$$\frac{Mt}{M\infty} = Kt^n$$

Where Mt/M is fractional drug released at time t , k is the kinetic constant incorporating structural and geometric characteristic of drug/polymer system (device) and n is diffusional exponent that characterizes the mechanisms of drug release. For non-Fickian release, the n value falls between 0.5 and 1 ($0.5 < n < 1.0$), whereas in the case of Fickian diffusion, $n=0.5$, for zero order release (case II transport) $n=1$ and for super case II transport, $n > 1$. The values of n as estimated bilinear regression of $\log Mt/M$ vs $\log (t)$ of different formulations are shown in Table 1.3

Table . 1.3: Kinetic release constants (K) and diffusion exponents (n) after fitting the release data to simple power law ($\log M_t/m_a$ Vs $\log t$)

Drug+polymer	Formulation code	n value	K value	Release characteristics
Tizanidine HCL + Locust bean gum	F6	0.50	3.72	fickain
	F7	0.50	7.98	fickain
	F8	0.50	3.72	fickain
	F9	0.51	3.95	non-fickain
	F1	0.34	9.33	

n_2 = the diffusion exponent 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-fickain (anomalous) release and $n > 1$ for super case II transport

Data analysis

The data obtained from dissolution kinetic studies were analyzed using PCP Disso V2.08 software.

Dissolution profile for Locust bean gum in Fig 1.3 demonstrates a diffusion release of Tizanidine HCL from formulation containing 20, 30 and 40 mg of locust bean and swelling and erosion mechanism for formulation contains 50 mg of locust bean gum

T_{50%} release

The time for 50% ($T_{50\%}$) release of Tizanidine HCL from the prepared buccal tablets were estimated by linear regression of $\log MT/M_a$ vs $\log (t)$ of different formulations are shown in table 1.4. The results were clearly indicated increasing the half life ($T_{50\%}$) of Tizanidine HCL release from the prepared tablets by increasing the concentration of locust bean gum.

Table .1.4 : Time (H) For 50% Tizanidine HCL release from the prepared buccal tablet

Drug + polymer	Formulation code	T _{50%}
Tizanidine HCL+ Locust bean gum	F6	4.45
	F7	4.47
	F8	4.84
	F9	4.9

CONCLUSION

Increase in concentration of locust bean gum increases in the bioadhesive strength and swelling ratio in the 50 mg of locust bean gum. Cumulative percentage release decreases with increase in concentration of tamarind seed gum. The formulations F6, F7 and F8 shows fickain diffusion mechanism. And formulation F9 shows non fickain mechanism. Fickain release kinetics involving diffusion mechanism and non-Fickian release kinetics involving a combination of both diffusion and chain relaxation mechanism

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