ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 8, Issue 6, 2015

ISSN - 0974-2441

Research Article

EVALUATION OF A NOVEL, NATURAL LOCUST BEAN GUM AS A SUSTAINED RELEASE AND MUCOADHESIVE COMPONENT OF TIZANIDINE HYDROCHLORIDE BUCCAL TABLETS

HARIKRISHNAN V[1]*, MADHUSUDHAN S[2], SANTHIAGU A[3]

[1]Department of Pharmaceutics, National College of Pharmacy, Kerala, India. [2]Department of Pharmacy, Annamalai University, Chidambaram, Tamil Nadu, India. [3]Department of Biotechnology, School of Biotechnology, NIT Calicut, Kerala, India.
Email: harik84pharma@gmail.com

Received: 03 July 2015, Revised and Accepted: 08 September 2015

ABSTRACT

Mucoadhesive polymers that bind to the gastric mucins or epithelial cell surface are useful in drug delivery for the purpose of increasing the intimacy and duration of contact of the drug with the absorbing membrane. Mainly synthetic polymers are in use for this purpose. Probably the biodegradability of the synthetic polymers is questionable. In the present work mucoadhesive buccal tablets of tizanidine hydrochloride were prepared using locust bean gum that has 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 hydrochloride 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 hydrochloride exhibited extended drug release profile for tablets prepared. Higuchi and Peppas data reveal 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. Increase in concentration of locust bean gum increases in the bioadhesive strength and swelling ratio in the 50 mg of locust bean gum.

Keywords: Mucoadhesive, Tizanidine hydrochloride, Tablets, Locust bean gum.

INTRODUCTION

Tizanidine hydrochloride is an agonist Fat α2-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%) the following intravenous administration in healthy adult volunteers. Tizanidine is approximately 30% bound to plasma proteins. Tizanidine has linear pharmacokinetics over a dose of 1-20 mg. Tizanidine has a half-life of approximately 2.5 hrs [1-3].

Buccal drug delivery has been considered as an alternative to oral dosing for subjected to degradation in the gastrointestinal tract or to hepatic the 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, non-toxic, this 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 an extended period of time in order to avoid the first-pass metabolism for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance. This study evaluates natural polymer locust bean 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 hydrochloride were compared with oral formulation.

MATERIALS

Tizanidine hydrochloride purchased from Balaji drugs Gujarat, locust bean gum fluka, Japan. microcrystalline sulfate, magnesium sterate, lactose, aspartame, and ethyl cellulose were purchased from Loba Chemie, Mumbai. Maharashtra, India.

Evaluation of gum

Organoleptic evaluation, physical evaluation, determination of ash value, and microbial count of locust bean gum were performed according to Indian Pharmacopeia 2010.

METHODS

Preparation of mucoadhesive layer [4,5,8,9,16]

The mucoadhesive layer containing tizanidine hydrochloride (2 mg) 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 µ) to ensure complete mixing. The average weight of about 150 mg were separately weighed and compressed using a 13 mm diameter of a die on an infrared (IR) 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).

Evaluation of buccal tablets

All the formulated dosage forms of tizanidine hydrochloride 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 IP 2010. 10 tablets from each batch were evaluated for uniformity in tablet weight. 10 tablets from each batch were powdered individually and a quality equivalent to 2 mg of tizanidine hydrochloride 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 hrs on a magnetic stirrer the volume was made unto 100 ml with phosphate buffer pH 6.8 and the absorbance were measured in a UV spectrophotometer at 276 nm.

Hardness and friability testing [10-12]

Hardness and friability of each 10 randomly, selected tablets of each formulation using Erweka hardness tester (TBH30) and the Erweka friabilitor (GmbH, Germany) respectively.

IR absorption spectroscopy

To investigate any possible interactions between the drug and the polymers, the IR spectra of pure drug tizanidine hydrochloride and its physical mixtures (1:1) with locust bean 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/nm^2. The wavelength selected ranged between 400 and 4000/cm.

Bioadhesion study [10-12,18]

In vitro bioadhesion study

Satisfactory bioadhesion 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, fluresent prob method, flow channel techniques, and colloidal gold staining method. In our study, the polymers evaluated using TA.XT2 texture analyzer equipment rabbit intestinal mucosa as a model tissue under simulates buccal condition.

Bioadhesion measurement

A TA.XT2 texture (Stable Mirosystem, Haslemere, Surrey, UK) equipped with a 5 g load cell was employed to determine the bioadhesion using buccal intestinal mucosa as the model tissue. The mucosa was stored frozen in a simulated saliva solution and thawed to room temperature before used. The rabbit intestinal was mounted onto a cylindrical Perspex support of 2 cm diameter and 2 cm length and secured with string. A foam type was placed underneath the porcine mucosa on the Perspex support at the cross-sectional end to provide cushioning effect. The intestinal mucosa was further secured by placing an aluminum cap over the Perspex support. A circular hole of 17 mm 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 the 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 the instrument. These two Perspex support were aligned to ensure that the tablet would coming to direct contact with the exposed surface of 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, 200 µl of stimulated saliva solution was evenly spread on the surface of tissues. The upper Perspex support was lowered at sapped of 1 mm/second until contact was made with the tissue and the contact force of 0.5 N was applied. At various contact times 5, 10, 15, 20, 25, and 30 minutes. The detachment force in 'N' was measured.

Swelling study [13-15,17]

The swelling index of the tablet was evaluated for six tablets of each formulation. These were weighed and placed separately in a pre-weighed basket made of stainless steel mesh. The total weight was recorded (W_2). This basket was placed in a 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 demineralized 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 minute equilibrium.

***In vitro* 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. Hence, 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). The release of tizanidine hydrochloride from buccal tablets was studied in phosphate buffer of 6.8 pH (900 ml) using a USP XXI/XXII dissolution rate apparatus, with a paddle rotating at a rate of 75 rpm and at 37°C.

RESULTS

Evaluation of tablet

Table 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/cm^2 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 hydrochloride 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. It can be noted that the mean values of force of detachment increased with time and reached a plateau at later time points.

Swelling index

The swelling index for the various formulations is shown in Fig. 2. 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.

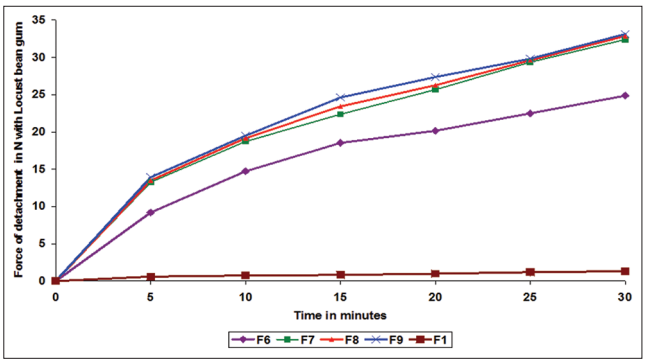

Fig. 1: The force of detachment from rabbit intestine for directly compressed tizanidine hydrochloride buccal tablets containing 20, 30, 40, and 50 mg of locust been gum. All data points represent the mean value±standard deviation of three experiments

Table 1: Composition of mucoadhesive layer of buccal tablets of tizanidine hydrochloride with locust bean gum

Formulation	Tizanidine hydrochloride (mg)	Locust bean gum (mg)	Microcrystalline cellulose (mg)	Lactose (mg)	Aspartame (mg)	Magnesium sterate (mg)
F1	2	0	141	6	1	1
F6	2	20	121	6	1	1
F7	2	30	111	6	1	1
F8	2	40	101	6	1	1
F9	2	50	91	6	1	1

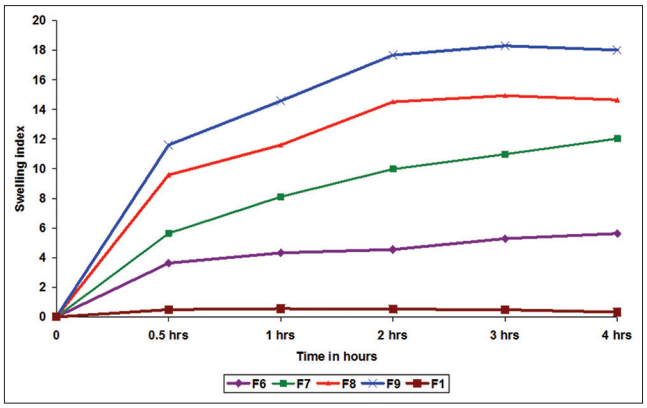

Fig. 2: Swelling index of tizanidine hydrochloride buccal tablets using locust bean gum. All data points represent the mean value±standard deviation of three experiments

Surface pH

An acidic or alkaline pH may cause irritation to buccal mucosa. The surface pH of the tablet was determined to investigate the possibility of any side effects *in vivo*. The surface pH of the tablet has been given in Table 2. The surface pH of all the formulation was found to be within the pH range of 5-7 and hence these formulations do not produce any irritation in the buccal cavity.

Drug release characteristics

The drug release profiles from the prepared tizanidine hydrochloride buccal tablets containing a various concentration of locust bean gum are shown in Fig. 3.

Drug release kinetics[7]

To examine the release mechanism of tizanidine hydrochloride from the prepared bioadhesive tablets, the results were analyzed according to the following equation:

$$\frac{Mt}{M\infty}=Ktn$$

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 expectorant 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 versus log (t) of different formulations are shown in Table 3.

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. 3 demonstrates a dissolution release of tizanidine hydrochloride 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.

Table 2: Surface pH of tizanidine hydrochloride buccal tablets containing locust bean gum

Drug+polymer	Formulation	Surface pH
Tizanidine hydrochloride+ locust bean gum	F1	7.1
	F6	6.4
	F7	6.2
	F8	6.5
	F9	6.6

Table 3: Kinetic release constants (K) and diffusion exponents (n) after fitting the release data to simple power law (logMt/mα vs. Logt)

Drug+polymer	Formulation code	n value	K value	Release characteristics
Tizanidine hydrochloride+ 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	

$T_{50\%}$ release

The time for 50% ($T_{50\%}$) release of Tizanidine hydrochloride from the prepared buccal tablets was estimated by linear regression of log MT/Mα versus log (t) of different formulations are shown in Table 4. The results were clearly indicated increasing the half-life ($T_{50\%}$) of tizanidine hydrochloride release from the prepared tablets by increasing the concentration of locust bean gum.

DISCUSSION

The purity of drug sample was identified by scanning the drug sample on IR spectrophotometer. The peaks of the IR spectra of drug sample were found to be similar with the standard IR spectra of pure tizanidine hydrochloride as reported. Fig. 4 shows the IR spectra of tizanidine hydrochloride. The IR spectra of the mixture of drug and polymer indicated no incompatibility between drug and polymers. Hence, locutbean gums were chosen as polymers for further investigations. The spectrum of drug shows absorption bands at 1604/cm N-H amide bending, 3029/cm aromatic C-H stretching, 2954/cm aliphatic C-H stretching for confirming incompatibility of tizanine hydrochloride with mixture of polymer. The double layered structure design was expected to provide drug delivery in an unidirectional fashion to the mucosa and to avoid loss of drug due to wash out by saliva, release drug immediately to produce a prompt pharmacological action and remain in the oral cavity and provide a sustained release of enough drug over an extended period of time.

The mean values of force of detachment were grater for the formulation containing 50 mg of locust bean gum and the bioadhesive strength increased with increase in the concentration of locust bean gum. A 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 the release of the drug on mucosal surface. Sustained release of tizanidine hydrochloride was obtained from F6, F7, F8, and F9 and with almost 102.88, 95.87, 96.09, and 90.64 in 13th hrs, respectively.

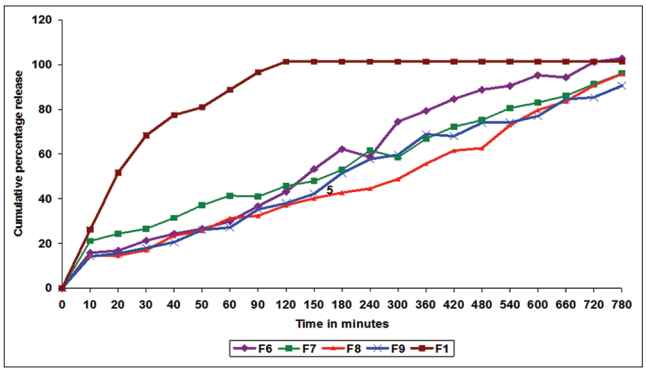

Fig. 3: Cumulative percentage release of tizanidine hydrochloride buccal tablets containing 20, 30, 40, and 50 mg of locust bean gum in phosphate buffer pH 6.8. All data points represent the mean value±standard deviation of three experiments

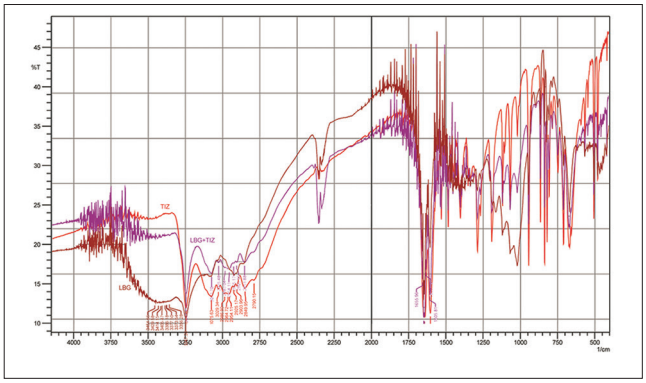

Fig. 4: Fourier transform infrared spectra of tizanidine hydrochloride, locut bean gum and its mixture drug

Table 4: Time (H) for 50% tizanidine hydrochloride release from the prepared buccal tablet

Drug+polymer	Formation code	T_{50}%
Tizanidine hydrochloride+ locust bean gum	F6	4.45
	F7	4.47
	F8	4. 84
	F9	4.9
	F1	

The increase in the 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 the concentration of locust bean gum. The formulations F6, F7, and F8 show Fickain diffusion mechanism. Moreover, 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.

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 the concentration of locust bean gum. The formulations F6, F7, and F8 show Fickain diffusion mechanism. Moreover, 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.

REFERENCES

1. Nance PW, Bugaresti J, Shellenberger K, Sheremata W, Martinez-Arizala A. Efficacy and safety of tizanidine in the treatment of spasticity in patients with spinal cord injury. North American Tizanidine Study Group. Neurology 1994;44 11 Suppl 9:S44-51.
2. Wagstaff AJ, Bryson HM. Tizanidine. A review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. Drugs 1997;53(3):435-52.
3. Moffat AC. Clark's Isolation and Identification of Drugs. London: Pharmaceutical Press; 2006. p. 691.
4. Mumtaz AM, Ching HS. Design of a dissolution apparatus suitable for *in situ* release study of triamcinolone acetonide from bioadhesive buccal tablets. Int J Pharm 1995;121:129-39.
5. Bottenberg P, Cleymaet R, de Muynck C, Remon JP, Coomans D, Michotte Y, *et al.* Development and testing of bioadhesive, fluoride-containing slow-release tablets for oral use. J Pharm Pharmacol 1991;43(7):457-64.
6. Cafaggi S, Leardi R, Parodi B, Caviglioli G, Russo E, Bignardi G. Preparation and evaluation of a chitosan salt-poloxamer 407 based matrix for buccal drug delivery. J Control Release 2005;102(1):159-69.
7. Duchene D, Touchard F, Peppas NA. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Dev Ind Pharm 1988;14:283.
8. El-Samaligy MS, Yahia SA, Basalious EB. Formulation and evaluation of diclofenac sodium buccoadhesive discs. Int J Pharm 2004;286(1-2):27-39.
9. Mohammed FA, Khede H. Preparation and *in vitro*/*in vivo* evaluation of the buccal bioadhesive propertis of slow - Release tablets containing Miconazole Nitrate. Drug Dev Ind Pharm 2003;29:321-37.
10. Finn A, Collins J, Voyksner R, Lindley C. Bioavailability and metabolism of prochlorperazine administered via the buccal and oral delivery route. J Clin Pharmacol 2005;45(12):1383-90.
11. Nakhat PD, Kondawar AA, Babla IB, Rathi LG, Yeole PG. Studies on buccoadhesive tablets of terbutaline sulphate. Indian J Pharm Sci 2007;69(4):505-10.
12. Park K, Robinson JR. Bioadhesive polymers as platforms for oral – Controlled drug delivery: Method to study bioadhesion. Int J Pharm 1984;19:107-27.
13. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001;13(2):123-33.
14. Peppas NA, Korsmeyer RW. Hydrogels in Medicine and Pharmacy: Properties and Application. Vol. 1. Boca Raton: CRC; 1986. p. 103-9.
15. Pramod Kumar TM, Shivakumar SG. Novel core in cup buccoadhesive systems and films of terbutaline sulphate – Development and *in vitro* evaluation. AJPS 2006;1:175-87.
16. Chanda R, Mahapatro SK, Roy A, Bahadur S. Development of oral mucoadhesive tablets of terbutaline sulphate using some natural materials extracted from *Albelmoschus esculeatus* and *Tamarindus indica*. Res J Pharm Technol 2008;11:46-52.
17. Save T, Shah MU, Ghamande AR, Venkitachalam P. Comparative study of buccoadhesive formulation and sublingual capsule of nifedipine. J Pharm Pharmacol 1994;46:192-5.
18. Chen WG, Chi Hwang GC. Adhesive and *in vitro* release characteristics of propranolol bioadhesive disc system. Int J Pharm 1992;82:61-6.
19. Yamazaki N, Monma Y, Tanabe T. Effect of propranolol and atenolol on rat kidney. Nippon Yakurigaku Zasshi 1983;81(5):33-9.
20. Vijayaraghavan C, Vasanthakumar S, Ramakrishnan K. An *in vitro* and *in vivo* evaluation of locust bean gum and chitosan combination as a carrier for buccal drug delivery. Pharmazie 2008;63(5):112-4.
21. Degim T, Eglen B, Ocak O. A sustained release dosage form of acyclovir for buccal application: An experimental study in dogs. J Drug Target 2006;14(1):35-44.