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Design and evaluation of controlled release buccal tablet of tizanidine hydrochloride using natural polymer guar gum

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ABSTRACT

Tizanidine is an alpha-2-adrenergic agonist and act by increasing the pre-synaptic inhibition of spinal motor neurons. Natural polymers have gained profound importance as lead compounds for delivery of drugs in treatment of various infections. The aim of this study was to formulate Tizanidine hydrochloride into a buccoadhesive tablet, using natural polymers in order to enhance its bioavailability. In the present study four formulations (F14-F17) were prepared by using natural polymer guar gum and some additives such as aspatanase, lactose and magnesium state. Among all the formulations F17 formulation containing guar gum as a quantity of 50 mg as optimized formulation having 86.78 % in 11 hrs showing sustained release based on invitro drug release, swelling and bioadhesive strength.

Key words: Mucoadhesive, Tizanidine hydrochloride, Guar gum, Buccal Tablets.

INTRODUCTION

The antispasmodic agent is primarily indicated to accompany rest, physical therapy and other measures for the relief of discomfort associated with acute, painful disorders of skeletal muscles [1]. Musculoskeletal disorders include lower back pain, neck pain, tension headaches and myofascial pain. Anti-spasticity medications, such as tizanidine act centrally on the spinal cord or brain stem and inhibit neuronal transmission [2, 3]. Tizanidine is an alpha-2-adrenergic agonist and it is believed to act by increasing the pre-synaptic inhibition of spinal motor neurons [5,8].

Oromucosal preparations are widely used to administrate drugs to the oral cavity or to the throat to obtain both a local and systemic effect. Indeed, the oral mucosa is easily accessible and highly vascularized by a relative fast blood flow (2.4 mL/min/cm2), allowing a direct access to the systemic circulation by-passing the liver firstpass effect with consequent high bioavailability and acceptability by the patient. Moreover, as being characterized by a rapid cellular turnover, the oral mucosa is less susceptible to damage or irritation potentially related to drugs or excipients used to design the dosage forms [4, 6]. On the other hand, the main disadvantages are related to the low permeability of the mucosal membrane and short permanence time of conventional dosage forms due to mechanical stresses and swallowing. To overcome these limitations, mucoadhesive dosage forms have gained interest [7, 9].

The aim of this study was to formulate Tizanidine hydrochloride into a buccoadhesive tablet, in order to enhance its bioavailability. In an attempt to control Tizanidine hydrochloride release, we prepared with varying concentration of guar gum. In the present study the effect of natural gum in formulation. It is also focused on the selection of bioadhesive polymers and its activity in various combinations and ratios, mucoadhesive component in buccal tablets, following their application to the buccal mucosa. The release characteristics of Tizanidine hydrochloride were compared with oral formulation

MATERIALS AND METHODS

Tizanidine hydrochloride and guar gum were purchased from Balaji drugs Gujrath, Microcrystalline sulphate, Magnesium stearate, lactose, Aspartame and ethyl cellulose were purchaised from loba chemie Mumbai. India

EVALUATION OF GUM

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

METHOD OF PREPARATION OF BILAYERED BUCCAL TABLET

Preparation of mucoadhesive layer[10,12,]

The mucoadhesive layer containing Tizanidine hydrochloride (2 mg) was prepared by using 20, 30, 40 and 50 mg of guar 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 tablets can be changed dramatically by the amount of backing material and those changes could alter the drug release profile

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 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 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 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 320 nm.

Hardness and friability testing [10-12]

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 hydrochloride and its physical mixtures (1:1) with guar 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 4000cm^{-1}

Bioadhesion study [10-12, 14]

***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, 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, U.K)equipped with a 5g load cell was employed to determine the bioadhesion using rabbit intestinal mucosa as the model tissue. The intestinal mucosa was stored

frozen in a simulated saliva solution and thawed to room temperature before used. The rabbit intestinal 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 rabbit intestinal mucosa on the Perspex support at the cross sectional end to provide cushioning effect. The rabbit intestinal 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 rabbit intestinal 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 instrument. These two Perspex support were aligned to ensure that the tablet would coming to direct contact with the exposed surface of rabbit intestinal when the upper tablet support was lowered on measurements were conducted at a room temperature of 25^0c and a relative humidity of 52-60%

During measurements, 200µlof stimulated saliva solution was evenly spread on the surface of tissues. The upper Perspex support was lowered at sapped 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 [10-13]

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 (pH6.8) in an incubator at 37^0C. 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 [13, 14]

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 [11-15]

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 hydrochloride buccal tablet

Release of Tizanidine HYDROCHLORIDE from buccal tablets was studied in phosphate buffer of 6.8 pH (400 ml) using a USP XXI/XXII dissolution rate apparatus, with a paddle rotating at a rate of 75 rpm and at 37^0c

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. Aspartame used as a sweetener in formulation. Lactose was incorporated to formulation as filler-binder. Magnesium stearate used as an anti-adherent agent and as a lubricant purpose.

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 148.2 and 151.6 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 with in control.

Table 1.1: Composition of mucoadhesive layer of buccal tablets of Tizanidine hydrochloride with Guar gum Drug-excipent compatibility study

Formulation	Tizanidine hydrochloride (mg)	Guar gum (mg)	Microcrystalline cellulose (mg)	Lactose	Aspartame	Magnesium sterate (mg)
F 1	2	0	141	6	1	1
F 14	2	20	121	6	1	1
F 15	2	30	111	6	1	1
F16	2	40	101	6	1	1
F17	2	50	91	6	1	1

The physicochemical compatibility between drug and polymers was recognized by FTIR analysis. IR spectral analysis of Tizanidine hydrochloride showed the peaks at wave numbers of 1604 (N-H bending), 1644, 1649(C=C Stretching), 2849, 2954(CH_2 Asymmetric stretching), 3029, 3075, 3245 (Associated N-H stretching), confirming the purity of drug with standard respectively. The polymer shows broad spectrum at range of 3200-3500 which shows the presence of number of OH group.

In the physical mixture of Tizanidine hydrochloride with Guar gum shows the peaks at 1604 (N-H bending), 1644, 1649(C=C Stretching), 2849, 2954(CH_2 Asymmetric stretching), 3029, 3075, 3245 (Associated N-H stretching). The mixture also shows broad spectrum at the range of 3200-3500. Apart from that there was additional peaks were absorbed in the spectra indicating no chemical interaction in Tizanidine hydrochloride and polymer mixtures. The obtained FTIR spectra were shown in the figure1.1.

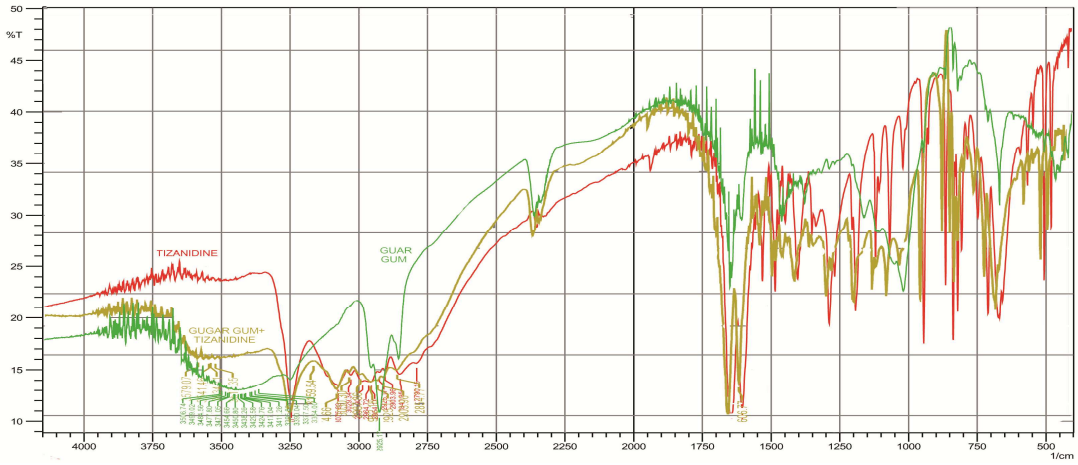

Fig. 1.1: The IR spectra of tizanidine hydrochloride, guar gum and physical mixture of tizanidine hydrochloride and guar gum

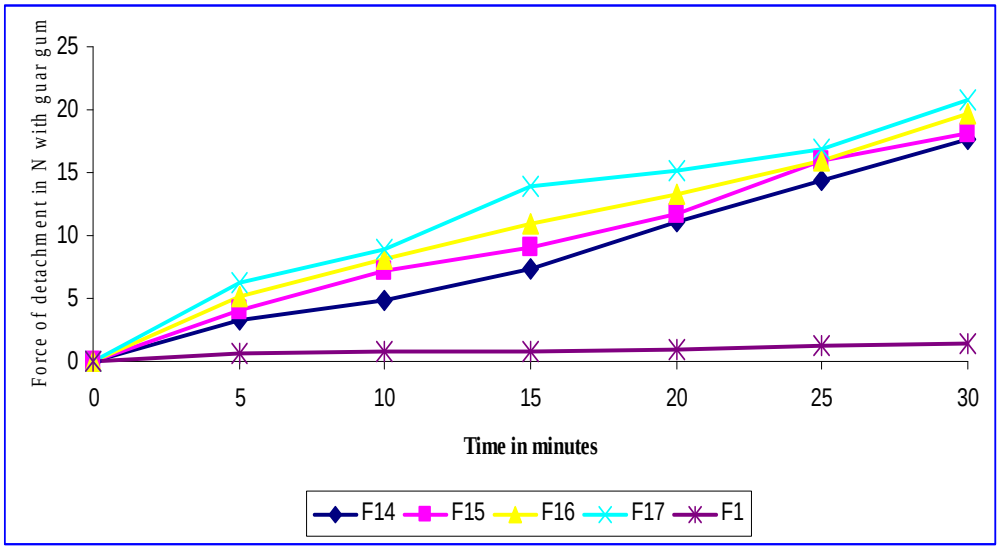

Fig. 1.2: The force of detachment from rabbit intestine for directly compressed Tizanidine hydrochloride buccal tablets containing 20, 30, 40 and 50 mg of Gugar gum. All data points represent the mean value ± standard deviation of three experiments

Bioadhesion study

The profile showing the mean value of Guar gum, following their application to excised rabbits intestinal mucosa is shown in Fig.1.2. 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 grater for formulation containing 50 mg of Guar gum. In the present study, the amount of guar gum incorporated into the buccal tablets was observed to be a critical factor in defining the resulting bioadhesive strength. The bioadhesive bond strength increases with increase in guar gum with the mucosal layer. It was also assume that the buccal formulation contain guar gum considered satisfactory adhere to mucosal layer up to a time of 12 hours.

Swelling index

The swelling index for the various formulations is shown in Fig1.3. These profiles indicate the uptake of water into the tablet matrix producing an increase in weight. The swelling studies for all nine formulations were performed and it was observed that as the polymer concentration increased, there was a marked increase in the swelling index up to some extent.

Formulations F14, F15, F16 and F17 containing Guar gum showed faster water uptake increased with increase in time to become fully hydrated. Higher concentration of Guar 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. The adhesion occurs shortly after swelling but the bond formed is not very strong. The adhesion increases with the degree of hydration till the point of disentanglement at the polymer tissue surface, which leads to abrupt drop in adhesive strength due to over hydration.

These results suggest that formulation containing 50 mg of Guar gum is suitable concentration for hydrophilic swellable matrix in order to achieve controlled drug release.

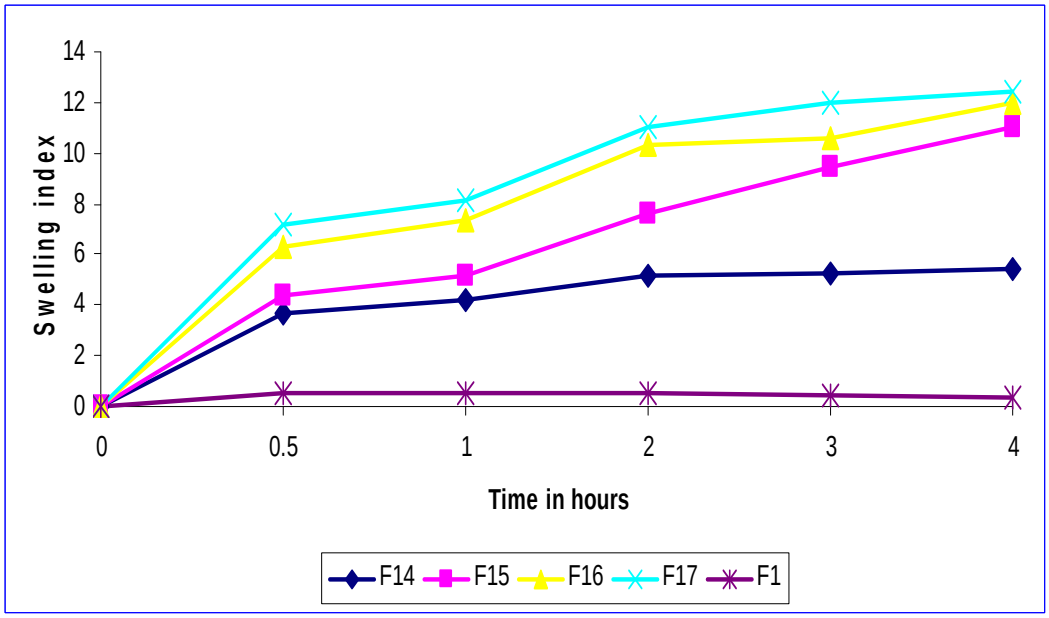

Fig. 1.3: Swelling index of Tizanidine hydrochloride buccal tablets using Guar gum

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 Table1.2. 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 hydrochloride buccal tablets containing Guar gum

Drug + Polymer	Formulation	Surface pH
Tizanidine hydrochloride + Gugar gum	F1	7.1
	F14	6.2
	F15	6.3
	F16	6.5
	F17	6.7

Drug release characteristics

The drug release profiles from the prepared Tizanidine hydrochloride buccal tablet s containing various concentration of Guar gum are shown in and Fig. 1.4.

Among all the four formulations, F17 was found to be highest percentage drug release. During the study, it was observed that the tablets were initially swell and no erodible over the period of 10 hrs. It was concluded that by increasing the concentration of guar gum in the formulation, the drug release rate from the tablets was found to be decreased. This may be due to increased hydration (or) swelling characteristics of polymers with increased concentrations.

From the overall data, it was found that the formulation F17 showed the maximum percentage of drug release, i.e. 86.78% at the end of 11 hrs .Sustained release of Tizanidine hydrochloride was obtained from F14, F15, F16 and F17 with almost 111.71, 96.03, 87.65 and 86.78 in 11^{th} hour respectively

Increase in concentration of Guar gum decreased the release of Tizanidine hydrochloride in a controlled manner.

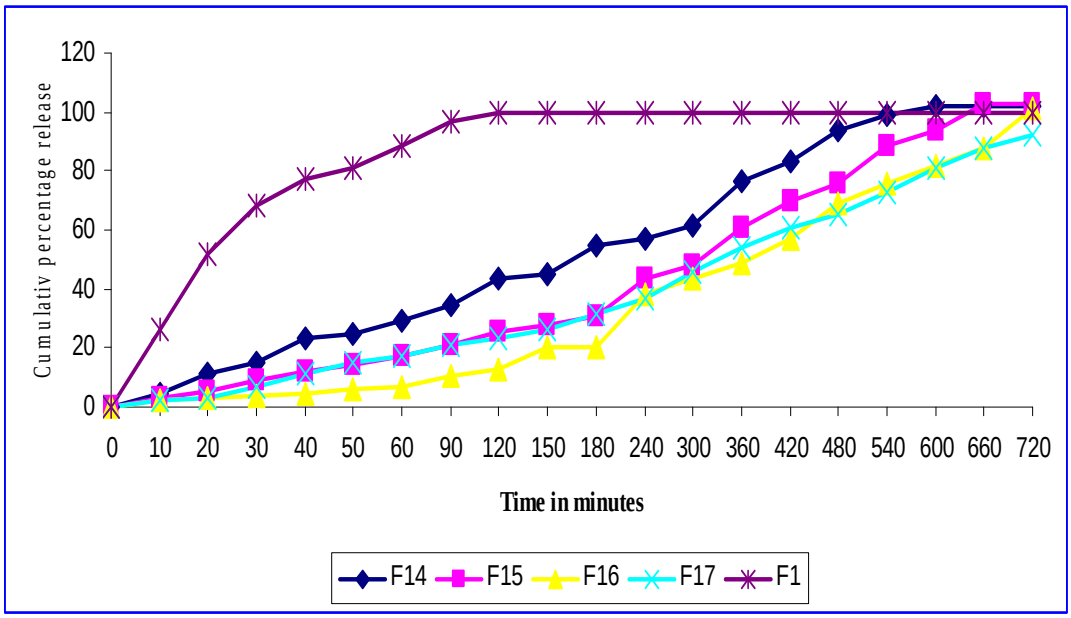

Fig: 1.4: Cumulative percentage release of Tizanidine hydrochloride buccal tablets containing 20, 30, 40 and 50 mg of Guar gum in phosphate buffer pH 6.8

Drug release kinetics

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

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

Where $M_t/M\infty$ 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∞ vs log (t) of different formulations are shown in Table 6.6.

Data analysis

The data obtained from dissolution kinetic studies were analyzed using PCP DissoV2.08 software.

Dissolution profile for guar gum demonstrates a diffusion release of Tizanidine hydrochloride from formulation containing 20, 30 and 40 mg of guar gum and swelling and chain relaxation mechanism for formulation contains 50 mg of guar gum. All the formulation follow non- fickain releases kinetics involving a combination of both diffusion and chain relaxation mechanism

$T_{50\%}$ release

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

Table 1.3: Time (H) for 50% Tizanidine hydrochloride release from the prepared buccal tablet

Drug + polymer	Formulation code	$T_{50\%}$
Tizanidine hydrochloride + Guar gum	F14	1.2
	F15	1.1
	F16	1.04
	F17	0.96
	F1	-

CONCLUSION

The controlled release of tizanidine hydrochloride was obtained using guar gum. Tizanidine hydrochloride buccal tablets were prepared by direct compression method. Four formulations (F14-F17) were prepared by using natural polymer guar gum and some additives such as aspatanase, lactose and magnesium sterate. Among all the formulations F17 formulation containing guar gum as a quantity of 50 mg as optimized formulation having 86.78 % in 11 hrs showing sustained release based on invitro drug release, swelling and bioadhesive strength.

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