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Development and in Vitro Evaluation of Tizanidine hydrochloride Buccal Tablet using Tamarind Seed Gum

Harikrishnan.V[a *], Madhusudhan.S[b], Santhiagu. A [c].

[a] *Assistant professor, National college of pharmacy, Calicut, Kerala, 673602,India*
[b] *Assistant Professor, Department of Pharmacy, Annamalai Univeristy, Annamalai Nagar, Tamilnadu - 608002.India*
[c] *Associate Professor, School of Biotechnology,NIT Calicut, Kerala-673601,India*

Abstract

An endeavor has been made to create buccoadhesive bilayered tablets comprising of drug containing bioadhesive layer and drug free backing layer to release the drug for extended period of time with reduction in dosing recurrence. Tablets of Tizanidine hydrochloride were prepared by direct compression method using bioadhesive polymer tamarind seed gum with backing layer of ethyl cellulose. The physical characteristics, swelling index, surface pH, in vitro bioadhesion strength, and in vitro release of formulated tablets were shown to be obsessed with characteristics and composition of bioadhesive materials used. The modified in vitro assembly was used to measure and compare the bioadhesive strength of tablets with fresh intestinal mucosa of rabbits as a model tissue. The maximum bioadhesive strength was observed in tablets formulated with 50% tamarind seed gum and strength decreases with decrease in its content. The tablets were evaluated for in vitro release in pH 6.8 phosphate buffer. In order to determine the mode of release, the data was subjected to Korsmeyer and Peppas model. All the formulations followed non-Fickian release mechanism. Tamarind seed gum could be used to design viable and stable buccoadhesive tablets of Tizanidine hydrochloride.

Keywords: Buccoadhesive tablet, Tizanidine hydrochloride, Swelling index, Bioadhesion, *In vitro* release, *In vivo* release

1. INTRODUCTION

The anti-spasticity agent is used to reduce a spasm that impairs the function or daily living activities, such as in multiple sclerosis (MS) and spinal cord injuries [1]. 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. Musculoskeletal disorders include lower back pain, neck pain, tension headaches and myofascial pain [2].

Tizanidine is well absorbed on oral administration and has been noted to attain maximum plasma concentration (Cmax) within 2.5-4 h. Bioavailability of tizanidine is about 21-40 % and half-life is 2-2.5 h. The drug is widely distributed throughout the body and 30 % of drug binds to plasma proteins. It undergoes rapid and extensive first-pass metabolism in the liver (about 95 % of the dose), with $T_{1/2}$ of 2-3 h [3, 4].

Mucoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. While the subject of mucoadhesion is not new, there has been increased interest in recent years in using mucoadhesive polymers for drug delivery. Substantial effort has recently been focused on placing a drug or a formulation in a particular region of the body for extended periods of time. This is needed not only for targeting of drugs but also to better control of systemic drug delivery [4-6]. Drugs that are absorbed through the mucosal lining of tissues can enter directly into the blood stream and not be inactivated by enzymatic degradation in the gastrointestinal tract. Several polymeric bioadhesive drug delivery systems have been fabricated and studied in the past. Different types of bioadhesive synthetic polymers such as acrylicbased hygrogels i.e. synthetic polymers such as carbopol 934, carbopol 937 and hydroxypropylmethylcellulose are also used to prepare oral mucoadhesive tablets [7 - 9].

The aim of present study was to evaluate the natural polymer tamarind seed gum in the concentration of 20,30,40 and 50 as a mucoadhesive component in buccal tablets, following their application to buccal mucosa and their influence in mucoadhesion and drug release.

2. MATERIALS AND METHODS

2.1. Materials

Tizanidine hydrochloride and tamarind seed gum purchased from Balaji drugs Gujrath, Microcrystalline sulphate, magnesium street, lactose, Aspartame and ethyl cellulose were purchaised from loba chemie Mumbai. India.

2.2. Evaluation of Gum

Organoleptic evaluation, physical evaluation, determination of ash value and microbial count of tamarind seed gum were performed according to Indian pharmacopoeia 2010.

2.3. Method of Preparation of Bilayered Buccal Tablet

The mucoadhesive layer containing Tizanidine hydrochloride (2 mg) was prepared by using 20, 30, 40 and 50 mg of Tamarind seed 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.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 [4, 8, 15 - 17].

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.

2.4. **Evaluation of Buccal Tablets**

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

2.5. Uniformity of weight and medicament content

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.

2.6. Hardness and friability testing

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

2.7. **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 tamarind gum were carried out using FT R--8400S(CE),SHIMADZU spectrophotometer. The samples were prepared as KBr disks compressed under a pressure 6 ton/nm^2. The wavelength selected ranged between 400 and 4000cm-1

2.8. *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.A TA.XT2 texture equipped with a 5g load cell was employed to determine the bioadhesion using rabbit intestinal mucosa as the model tissue. The rabbit 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 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 mucosa when the upper tablet support was lowered on measurements were conducted at a room temperature of 25^{0}c 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 [5, 10, 18].

2.9. Swelling Study

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^{0}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 [11, 12].

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

2.10. **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 1.0 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 [5, 8].

2.11. ***In vitro* Drug Release Studies**

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).Release of Tizanidine hydrochloride from buccal tablets was studied in phosphate buffer of 6.8 pH (400ml) using a USP XXI/XXII dissolution rate apparatus, with a paddle rotating at a rate of 75 rpm and at 37^{0}c [13, 14].

2.12. Stability Study in Human Saliva

The stability study of buccoadhesive tablets was performed in natural human saliva. Samples of human saliva were collected from 10 humans (ages 18-40 years) and filtered. The tablets were placed in separate petridishes containing 5 ml of human saliva and put in a temperature controlled oven at 37°C ± 0.2°C for 6 h. At regular time intervals tablets were examined for morphology and physical stability [21].

2.13. Stability studies as per ICH

The formulation F5 was selected and the stability studies were carried out at accelerated condition of 40±2 0C, 75±5% RH conditions, stored in desiccators, the tablets were packed in aluminium foil and kept in above said condition for period of three months. The tablets were analyzed periodically for their physical appearance, swelling index, drug content, buccoadhesive strength and in-vitro drug release [17, 21].

Table: 1.Composition of mucoadhesive layer of buccal tablets of Tizanidine hydrochloride with Tamarind Seed Gum

Formulation	Tizanidine hydrochloride (mg)	Tamarind Seed Gum (mg)	Microcrystalline cellulose (mg)	Lactose (mg)	Aspartame (mg)	Magnesium sterate (mg)
F 1	2	0	141	6	1	1
F 2	2	20	121	6	1	1
F 3	2	30	111	6	1	1
F4	2	40	101	6	1	1
F5	2	50	91	6	1	1

Table .2: Surface pH of Tizanidine hydrochloride buccal tablets containing Tamarind seed gum

Drug + Polymer	Formulation	Surface pH
Tizanidine hydrochloride + Tamarind seed gum	F1	7.1±0.01
	F 2	6.8±0.02
	F 3	6.3±0.01
	F4	6.1±0.01
	F5	5.9±0.01

Table. 3: Kinetic release constants (K) and diffusion exponents (n) after fitting the release data to simple power law ($\log M_t/m_\alpha$ Vs Log_t)

Drug + polymer	Formulation code	n value	K value	Release characteristics
Tizanidine hydrochloride + Tamarind Seed Gum	F2	0.72	1.1436	non- fickain
	F3	0.74	1.0773	non- fickain
	F4	0.72	1.1436	non- fickain
	F5	0.71	1.1667	non- fickain
	F1	0.34	9.3335	-

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

Table 4: Stability studies of optimized formulation

Parameters	1st month	2nd month	3rd month
Physical appearance	No Change	No Change	No Change
Swelling index (4hrs)	4.11±0.16	3.98±0.06	3.93±0.12
Drug content	99.15±41	98.93±32	99.10±23
Buccoadhesive Strength(30 min)	12.3±0.36	11.74±0.36	12.12±0.36
In-vitro drug release	88.04±0.14	88.724±0.01	87.96±0.31

3. RESULTS AND DISCUSSION

The current work was undertaken to design bilayered Mucoadhesive buccal tablets of Tizanidine hydrochloride by direct compression method using natural polymers tamarind gum to perform the *in-vitro* and *in-vivo* evaluation of the formulation. The aim was to confirm the two layers of the bilayered tablet functioned independently such that the Mucoadhesive layer of the tablet which was designed to adhere to the buccal mucosa posses good bioadhesive strength and Controlled release layer controls the drug release uni¬directionally. Table 1 shows the composition of buccal tablets. The microcrystalline cellulose added in the formulation as direct compression adjuvant, since Tamarind Seed Gum does not produce sufficient hardness, Lactose was incorporated to formulation as filler-binder. Magnesium stearate used as an anti-adherent agent and as a lubricant purpose.

3.1. Evaluation of Tablets

Tablet hardness varied between 4.7and 5.0kg/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 hydrochloride varied between 98.8 and 99.7%. Thus all the parameters of the compressed tablets were practically with in control.

3.2. Drug Polymer Interaction

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 2849, 2903 (C-H stretching), 1604, 1644 (N-H bending), 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 tamarind shows the peaks at 1645 (N-H bending) as finger print region of Tizanidine hydrochloride. It also shows peaks at 2849 (C-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 Fig. 1

3.3. Bioadhesion Study

The profile showing the mean value of Tamarind Seed Gum, following their application to excised rabbits intestinal mucosa is shown in Fig. 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 Tamarind Seed Gum and the bioadhesive strength increased with increase in concentration of Tamarind Seed Gum.

The mucoadhesive strength tests were carried out for all formulations and it was found that there was gradual increase in the mucoadhesive strength with the increase in the concentrations of mucoadhesive polymer and the formulation F5 shown maximum mucoadhesive strength (11.3± 0.36) at 30 minute. According to the reported works materials having highest rate of hydration rate possess the highest mucoadhesive strength. It has been proposed that mucoadhesion occurs in three stages. The first stage involves the formation of an intimate contact between the mucoadhesive and mucous. Secondly, the mucoadhesive macromolecules swell and interpenetrate the mucus macromolecules, becoming physically entangled. Thirdly, these molecules interact with each other via secondary, non-covalent bonds such as hydrogen bonds.

3.4. Swelling index

The swelling index for the various formulations is shown in Fig.3. These profiles indicate the uptake of water into the tablet matrix producing an increase in weight.Formulations F2, F3, F4 and F5 containing Tamarind Seed Gum showed faster water uptake increased with increase in time to become fully hydrated. Higher concentration of Tamarind Seed 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. Formulations F5 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 suggest that formulation F5 containing 50 mg of Tamarind Seed Gum is suitable concentration for hydrophilic swellable matrix in order to achieve controlled drug release.

3.5. 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. The surface pH of the formulations ranged from 5.7 to 6.8 indicating that no irritation is expected from these polymers when applied to the buccal mucosa.

3.6. Drug release characteristics

The drug release profiles from the prepared Tizanidine hydrochloride buccal tablets containing various concentration of Tamarind Seed Gum are shown in Fig. 4.Sustained release of Tizanidine hydrochloride was obtained from F2, F3, F4 and F5 and with almost 99.42, 97.25, 94.12 and 87.04 in 9^{th} hour respectively. In addition to mucoadhesivity, controlled drug release was also a prerequisite for the formulation. The formulations were subjected to in vitro dissolution testing to study their drug release profile. The UV–Vis spectra were obtained in pH6.8 at 320 nm wave number. To evaluate the drug release, the sink condition was maintained. The dissolution profile is a useful tool in formulation development and can show differences in the dissolution caused by factors related to the drug, excipients, and manufacturing process. According to the results the designed formulation F5 has displayed more than 87.04±0.54drug release in 9 h.

3.7. 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 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 [20]. The values of n as estimated bilinear regression of log Mt/M vs log (t) of different formulations are shown in Table 1.3. The data obtained from dissolution kinetic studies were analyzed using PCP Disso V2.08 software. Dissolution profile for Tamarind Seed Gum formulations demonstrate a slow release of Tizanidine hydrochloride from all the formulations of Tamarind Seed Gum demonstrate a slower Tizanidine hydrochloride release due to the combination of swelling and erosion in the matrix. The obtained N value for formulation F2, F3, F4 and F5 n was 0.72, 0.74, 0.72 and 0.71 respectively. These indicate the non-fickian release kinetics, involving a combination of both diffusion and chain relaxation mechanism.

3.10. Stability study in human saliva

The prepared formulation was placed in natural human saliva containing petridish and these were checked

regularly for the appearance, colour, shape and physical stability. The results were indicating there is no change in the tablet physical properties.

3.8. Stability studies as per ICH

The stability of the formulation at accelerated conditions shows satisfactory results in physical appearance, swelling index, drug content, buccoadhesive strength and in-vitro drug release. Differences were considered statistically significant at $p<0.05$ and the data were presented in table 4. Accelerated stability studies were performed at a temperature of 40 ± 20°C/75 ± 5% RH over a period of three months (90 days) on the promising buccal tablets of Tizanidine HCL which were Shows there were no changes in the colour, integrity and no significant changes in the drug release

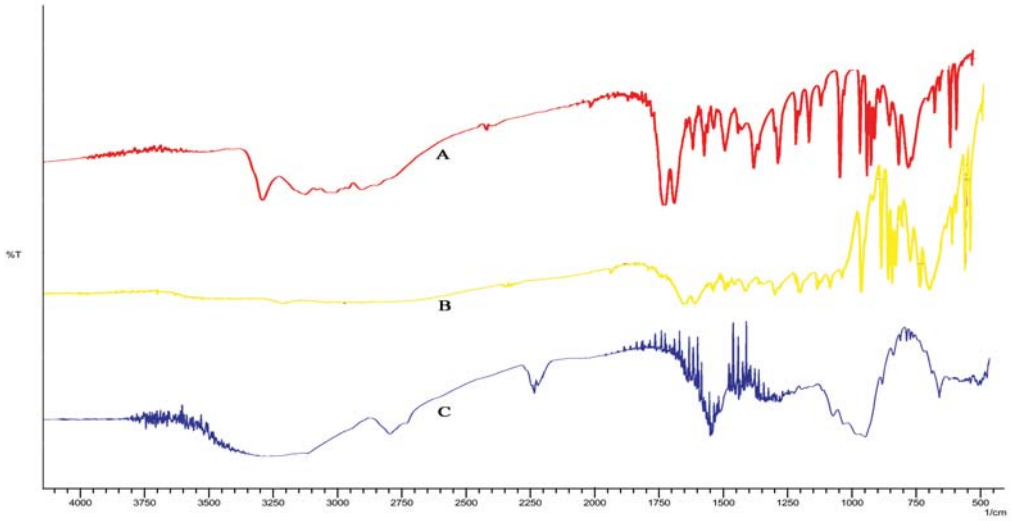

Fig. 1: Fourier transform Infrared spectra of Tizanidine hydrochloride, Tamarind seed gum and its mixture drug

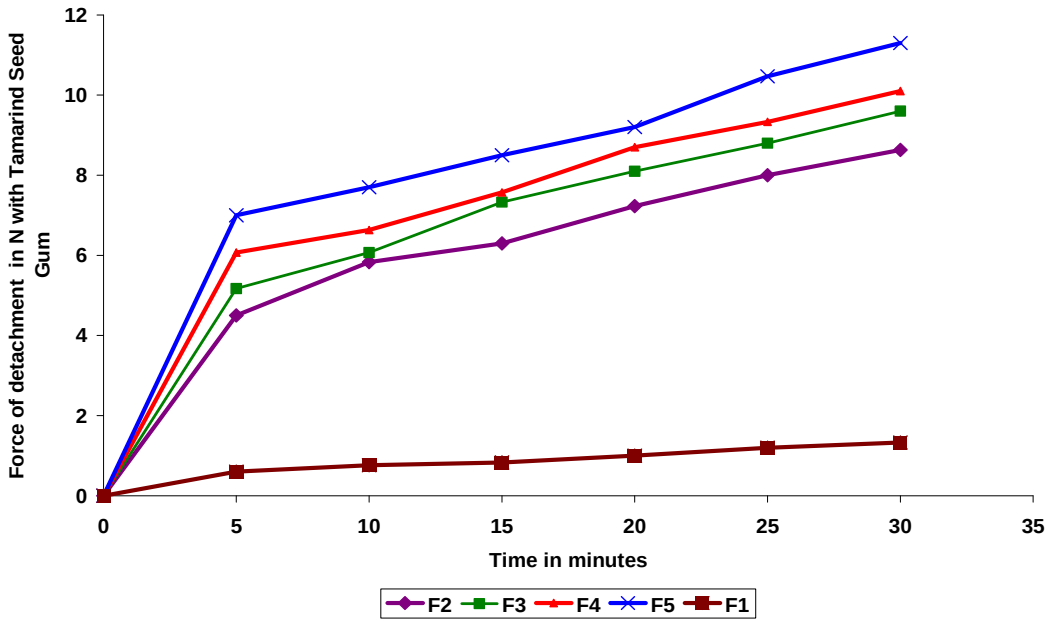

Fig. 2: The force of detachment from rabbit intestine for directly compressed Tizanidine hydrochloride buccal tablets containing 20, 30, 40 and 50 mg of Tamarind seed gum. All data points represent the mean value ± standard deviation of three experiments

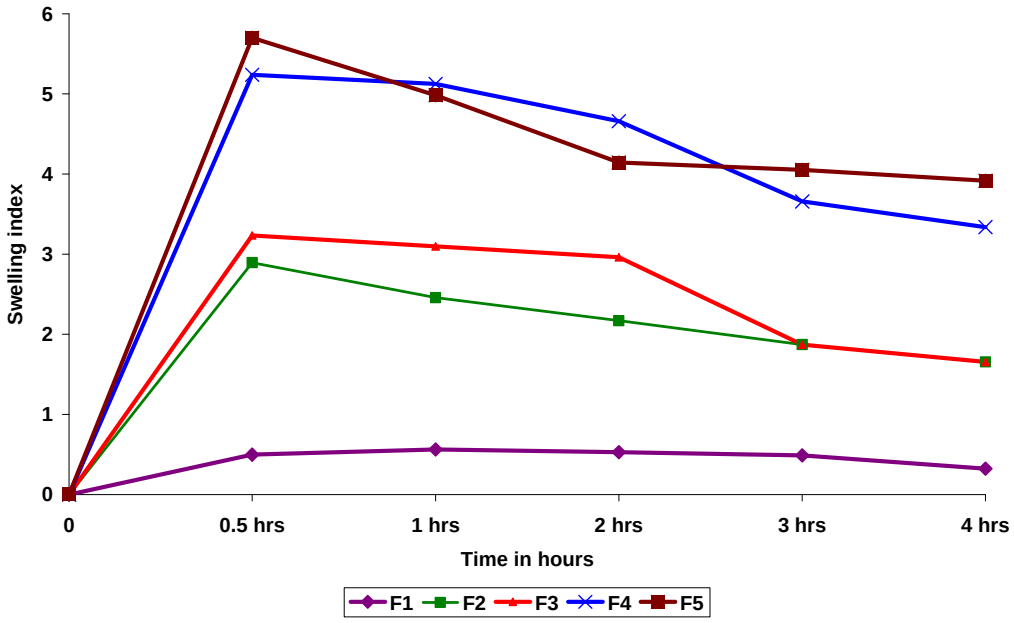

Fig. 3: Swelling index of Tizanidine hydrochloride buccal tablets using tamarind seed gum

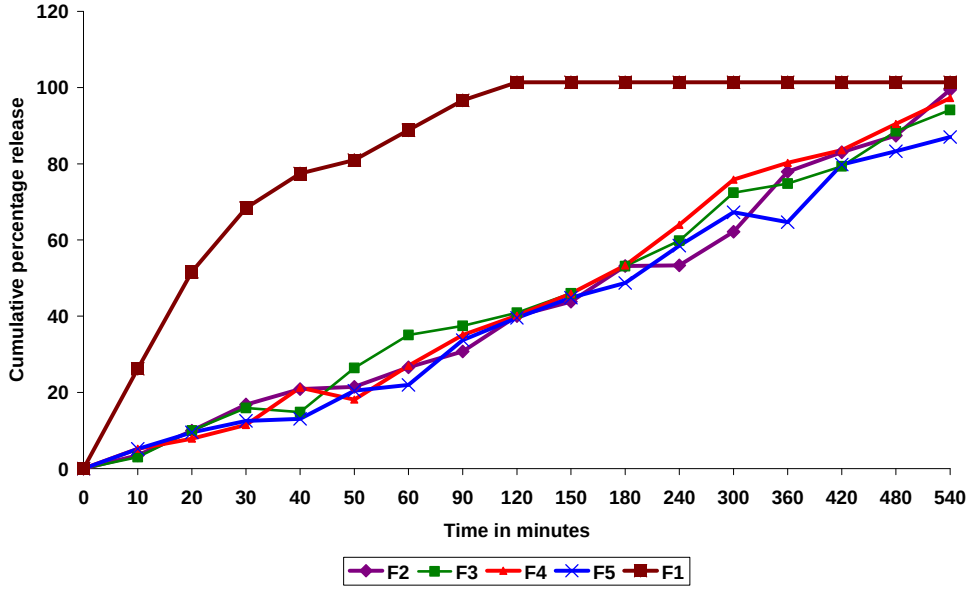

Fig. 4: Cumulative percentage release of Tizanidine hydrochloride buccal tablets containing 20, 30, 40 and 50 mg of Tamarind Seed Gum in phosphate buffer pH 6.8

4. CONCLUSION

Increase in concentration of tamarind seed gum increases in the bioadhesive strength and swelling ratio in the 50 mg of tamarind seed gum. Cumulative percentage release decreases with increase in concentration of tamarind seed gum. All formulations indicate non-Fickian release kinetics involving a combination of both diffusion and chain relaxation mechanism these results introduce buccoadhesive tablets as promising patient-friendly systems for controlled delivery of highly metabolized drugs with short elimination half-lives. As a result, dose reduction and minimizing frequency of administration could be achieved, enhancing patient compliance.

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