



DEVELOPMENT AND *IN-VITRO* EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF TIZANIDINE HYDROCHLORIDE USING NATURAL POLYMER XANTHAN GUM

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ABSTRACT

In the present work mucoadhesive buccal tablets of Tizanidine hydrochloride (TZD HCl) were prepared by using xanthan gum and in combination of xanthan gum with sodium alginate as mucoadhesive polymers. Seven formulations were developed with varying concentrations of polymers. The prepared tablets were evaluated for the weight variation, thickness, hardness, friability, surface pH, swelling index, mucoadhesive strength and *in vitro* drug release. All the formulations displayed zero order release kinetics (r' values from 0.9770 to 0.9944). Higuchi and Peppas data reveals that the drug released by non-Fickian diffusion mechanism. The *in vitro* release parameter values ($t_{50\%}$, $t_{70\%}$, and $t_{90\%}$) displayed by the various formulations range from 1.84 to 5.86 h ($t_{50\%}$), 3.13 to 7.12 h ($t_{70\%}$) and 5.83 to 6.81 h ($t_{90\%}$). The formulations TXG₁, TXG₅ and TXG₆ shows drug release 98.80%, 97.08% and 94.66% within 8 h. FTIR studies show no evidence on interaction between drug polymer.

Keywords: Tizanidine hydrochloride, Xanthan gum, Sodium alginate, Mucoadhesive, Buccal tablets.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism, drug degradation in harsh gastro intestinal environment can be circumvented by administering a drug via buccal route¹⁻³. More over buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing. Therefore mucoadhesive dosage forms were suggested for oral drug delivery which include adhesive tablets⁴⁻⁶, adhesive gels^{7,8}, adhesive patches.^{9,10}

Tizanidine hydrochloride is an imidazoline derivative, which acts as agonist on centrally located α_2 receptors and this leads to myotonolytic effects on skeletal muscle¹¹⁻¹⁴. It is structurally and pharmacologically similar to clonidine and other α_2 -adrenergic agonists^{13,14}. The correct mechanism of tizanidine in decreasing muscle tone and frequency of spasm is not clearly understood¹⁴. About 53% to 66% of the dose administered is being absorbed through the gastrointestinal tract after oral administration and the peak plasma concentration is reached within 1 to 2 h. Bioavailability of Tizanidine is about 34% to 40% and half-life is 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 (approximately 95% of a dose), leading to the oxidation of the imidazoline moiety, aromatic system, and the sulfur atom. This leads to lower bioavailability of Tizanidine¹⁵. In order to overcome such extensive first-pass metabolism, the drug is selected as suitable candidate for bioadhesive buccal drug delivery.

The aim of the present study was to develop a new mucoadhesive sustained-release tablets for buccal drug delivery of Tizanidine hydrochloride.

MATERIALS AND METHODS

Tizanidine hydrochloride was gift sample from Sun Pharma Pvt. Ltd. Mumbai. Xanthan and sodium alginate were procured from Lucid group Mumbai. All other reagents and chemicals used were of analytical grade.

Fourier transform infrared (FTIR) spectroscopy

Compatibility studies were carried out to know the possible interactions between TZD HCl and excipients used in the formulation. Physical mixtures of drug and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using FTIR spectroscopy¹⁶. IR spectrum of pure drug and polymers was seen in between 400- 4000 cm^{-1} are shown in Figure 1 and 2.

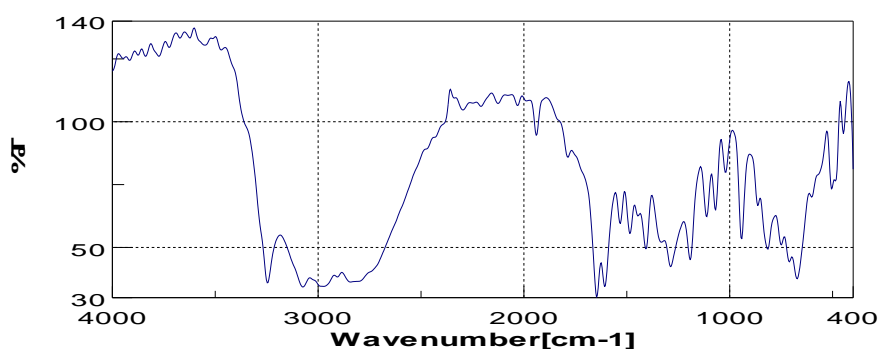
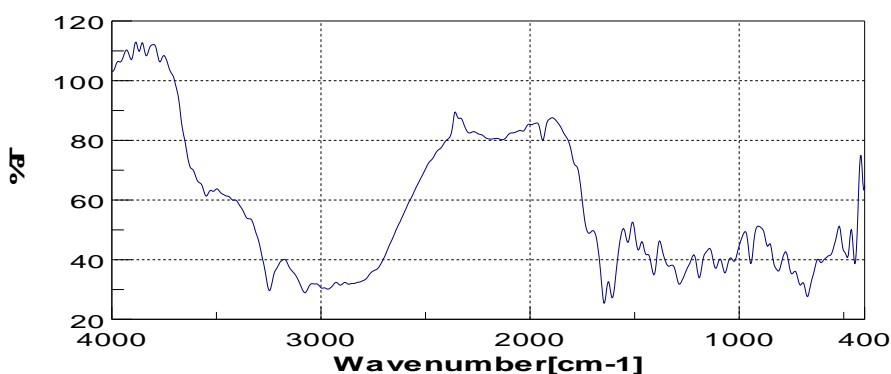
Preparation of buccal tablets of Tizanidine hydrochloride by direct compression method Direct compression method has been employed to prepare buccal tablets of Tizanidine hydrochloride using xanthan gum and sodium alginate as polymers. All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula (Table 1). The drug is thoroughly mixed with mannitol on a butter paper with the help of a stainless steel spatula. Then all the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min and compressed in to tablets of 100 mg using 6 mm round flat punches on 10-station rotary tablet machine (Rimek).



Table 1: Composition of mucoadhesive buccal tablets

Ingredients*	Formulation code						
	TXG ₁	TXG ₂	TXG ₃	TXG ₄	TXG ₅	TXG ₆	TXG ₇
Tizanidine hydrochloride	2	2	2	2	2	2	2
Xanthan Gum	45	47	49	51	43	41	45
Sodium Alginate	-	-	-	-	2	4	6
PVP K30	5	5	5	5	5	5	5
Mannitol	42	40	38	36	42	42	36
PEG 6000	2	2	2	2	2	2	2
Aspartame	2	2	2	2	2	2	2
Magnesium Stearate	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1
Total Wt (mg)	100	100	100	100	100	100	100

*Weight expected as mg per tablets; PVP- Poly vinyl pyrrolidone, PEG- Poly ethylene glycol

**Figure 1:** IR spectrum of Tizanidine hydrochloride**Figure 2:** IR spectrum of Tizanidine hydrochloride + Xanthan gum

Evaluation of Tizanidine hydrochloride buccal tablets

Weight variation test

Ten buccal tablets of each formulation were weighed using an electronic balance and average weight of ten tablets and standard deviation were calculated.

Tablet thickness

Thickness of each formulation was measured using vernier calipers. Ten buccal tablets from each batch were used and average values were calculated.

Drug content uniformity

Ten buccal tablets from each formulation were crushed and mixed separately. From the mixture 4 mg of

Tizanidine equivalent of mixture was extracted in 100 ml of methanol. Amount of drug present in extract was determined using UV spectrophotometer at 320 nm. This procedure was repeated thrice to get accuracy in the result¹⁷.

Surface pH

The surface pH of the buccal tablets was determined in order to predict the possible irritant effects of the formulation on the buccal mucosa. The buccal tablets were allowed to swell at $37 \pm 1^\circ\text{C}$ for 2 h in 40 ml phosphate buffer (pH 6.8). The surface pH of swollen buccal tablets was measured using pH paper¹⁸.



Swelling study

Three buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$. At regular 1 h time intervals until 6 h, the tablet was removed from the petri dish and excess surface water was removed carefully with filter paper. The swollen tablet was then reweighed (W2) and the swelling index (SI) was calculated using the formula given in equation¹⁹.

$$\text{Swelling Index} = [(W2-W1)/ W1] \times 100$$

Ex Vivo mucoadhesive strength

A modified balance method was used for determining the *ex vivo* mucoadhesive strength. Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. The mucosal membrane was separated by removing underlying and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37°C . The sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8, at $37 \pm 1^{\circ}\text{C}$) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper. The two sides of the balance were made equal before the study, by keeping a 5 gm weight on the right-hand pan. A weight of 5 gm was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 min contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams²⁰.

In vitro Dissolution Studies

The United States Pharmacopeia (USP) XXIII rotating paddle method was used to study the drug release from the tablets. The dissolution medium consists of 500 ml of phosphate buffer pH 6.8. The release was performed at $37 \pm 0.5^{\circ}\text{C}$, with a rotation speed of 50 rpm. The buccal tablet was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Five ml sample were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometer at 320 nm. Kinetic analysis of TZD HCl *in vitro* release data Release data were fitted to various mathematical models for describing the release mechanism from buccal tablets; Korsmeyer-Peppas (Eq 1)²¹, zero order (Eq 2)²² and Higuchi release models (Eq 3)²³.

$$M_t / M_{\infty} = k_{kp} t^n \dots\dots\dots 1$$

M_t / M_{∞} is the fraction of drug released at time 't'; k_{kp} is the release rate constant; and n is the release exponent.

$$M_t = M_0 + k_0 t \dots\dots\dots 2$$

M_t is the amount drug released at time 't'; M_0 the concentration of drug in the solution at t=0; k_0 the zero-order release constant.

$$M_t = k_{Ht}^{1/2} \dots\dots\dots 3$$

M_t is the amount of drug release at time 't'; and k_H is the Higuchi release constants.

RESULTS AND DISCUSSION

It could be observed that all the prepared tablets fulfill the IP requirements for physicochemical properties and results are given in Table 2. The hardness of prepared buccal tablets was found to be in the range of 3.4 to 4.1 kg/cm² and shown in Figure 3. The thickness and weight variation were found to be uniform as indicated by the low values of standard deviation. The thickness and weight of the prepared buccal tablet were found to be in the range of 3.25 to 3.32 mm and 98 to 102 mg respectively. Friability values of all tablets were less than 1 % indicate good mechanical strength to with stand the rigorous of handling and transportation. The average drug content of the buccal tablets was found to be within the range of 97.21 to 99.46 %.

The surface pH of all the formulations was found to be in the range of 5.63 to 6.91. Hence it is assume that these formulations cause no any irritation in the oral cavity. The swelling indices of the tablets increased with increasing amount of xanthan gum and sodium alginate. The mucoadhesivity of tablets was found to be maximum in case of formulation TXG₇, i.e. 4.92 gm. This may be due to fact that the combination and higher concentration of xanthan gum and sodium alginate. The results are given in Table 3.

In vitro drug release data of the all the buccal tablet formulations of Tizanidine hydrochloride was subjected to goodness-of-fit test by linear regression analysis according to zero order, first order kinetics and according to Higuchi's and Korsmeyer-Peppas equations to assertion mechanism of drug release are shown in Table 4 and in Figures 4 to 7. It is evident that all the formulations displayed zero order release kinetics ('r' values from 0.9770 to 0.9944). Higuchi and Peppas data reveals that the drug released by Non-Fickian diffusion mechanism. The *in vitro* release parameter values ($t_{50\%}$, $t_{70\%}$, and $t_{90\%}$) displayed by the various formulations range from 1.84 to 5.86 h ($t_{50\%}$), 3.13 to 7.12 h ($t_{70\%}$) and 5.83 to 6.81 h ($t_{90\%}$). The formulations TXG₁, TXG₅ and TXG₆ shows drug release 98.80%, 97.08% and 94.66% within 8 hrs are shown in Table 5 and Figure 8. The FTIR studies revealed that there was no physicochemical interaction between Tizanidine hydrochloride and Xanthan gum.



Table 2: Physicochemical properties of buccal tablets

Formulation code	Weight Variation of Tablet (mg) *	Hardness Kg/cm ² *	Thickness (mm)*	Friability (%)*	Drug Content (%)*
TXG ₁	101±0.39	3.4±0.45	3.32±0.05	0.61±0.01	98.36±1.01
TXG ₂	100±0.17	3.5±0.60	3.31±0.04	0.72±0.03	99.29±1.22
TXG ₃	102±0.47	3.8±0.67	3.27±0.10	0.68±0.06	99.46±0.98
TXG ₄	98±0.38	3.6±0.81	3.25±0.08	0.65±0.05	97.21±0.87
TXG ₅	101±0.89	3.9±0.47	3.29±0.10	0.69±0.07	98.17±0.39
TXG ₆	100±1.03	4.0±0.93	3.30±0.04	0.63±0.04	99.23±1.42
TXG ₇	99±0.45	4.1±0.26	3.31±0.03	0.74±0.02	99.45±1.31

*Average of three determinations, values shown in parenthesis is standard deviations.

Table 3: Result of Surface pH, Swelling index and Mucoadhesive strength of all formulations

Formulation code	Surface pH*	Swelling Index after 8 hr*	Mucoadhesive Strength*
TXG ₁	5.63±0.17	31.13±1.09	4.21±0.10
TXG ₂	5.89±0.10	36.28±1.23	4.74±0.12
TXG ₃	6.01±0.19	42.62±1.12	4.05±0.17
TXG ₄	6.17±0.15	49.71±1.96	4.67±0.08
TXG ₅	6.42±0.29	40.49±1.51	4.62±0.10
TXG ₆	6.20±0.12	39.37±1.43	4.28±0.15
TXG ₇	6.91±0.35	50.21±1.33	4.92±0.11

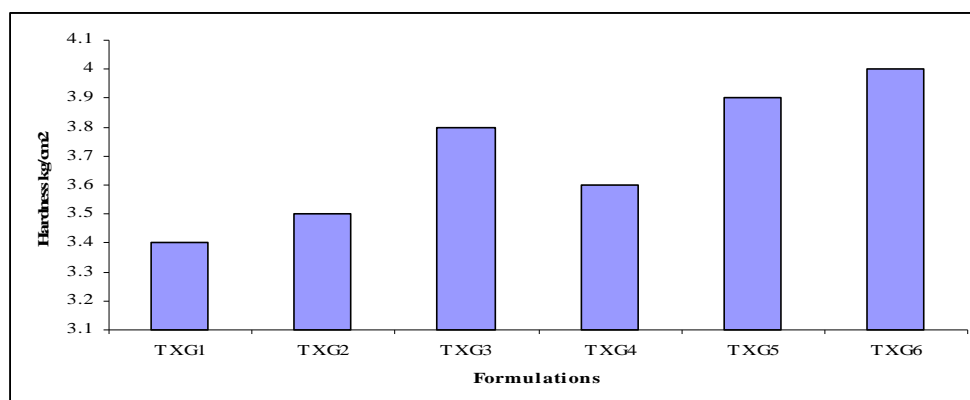
*Average of three determinations

Table 4: Kinetic data of formulations of mucoadhesive tablets

Formulation Code	R ² Zero Order	R ² First Order	R ² Higuchi equation	R ² Peppas equation
TXG ₁	0.9802	0.8968	0.9768	0.8875
TXG ₂	0.9923	0.9618	0.9894	0.8630
TXG ₃	0.9944	0.9882	0.9926	0.8764
TXG ₄	0.9848	0.9474	0.9850	0.9681
TXG ₅	0.9099	0.9836	0.9321	0.8536
TXG ₆	0.9483	0.9727	0.9647	0.8957
TXG ₇	0.9770	0.9834	0.9748	0.9051

Table 5: *In vitro* drug release parameters

Formulation code	t _{50%} (h)	t _{70%} (h)	t _{90%} (h)	Cumulative % drug release in 8 hrs*
TXG ₁	2.77	4.09	6.03	98.80
TXG ₂	3.66	5.36	--	89.74
TXG ₃	4.65	7.12	--	74.15
TXG ₄	5.86	--	--	67.37
TXG ₅	1.84	3.13	5.83	97.08
TXG ₆	2.21	3.79	6.81	94.66
TXG ₇	3.00	4.86	--	87.84

**Figure 3:** Comparison of hardness of different formulations of Tizanidine hydrochloride

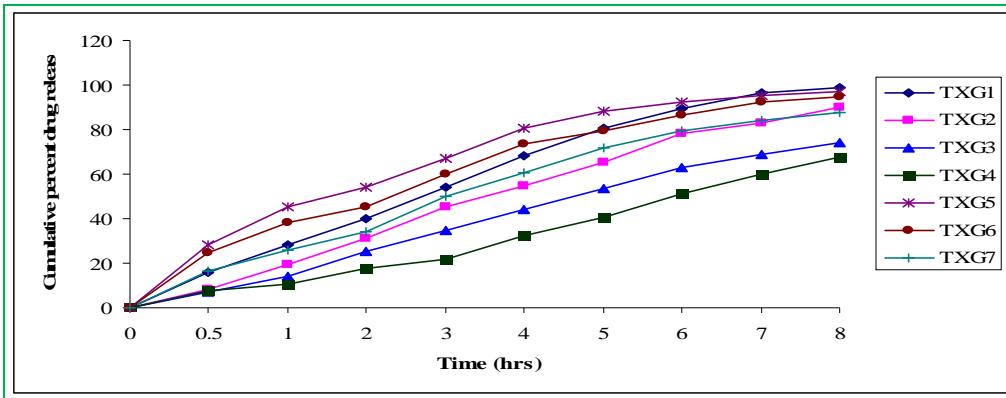


Figure 4: *In vitro* drug release profile of formulation TXG₁- TXG₇

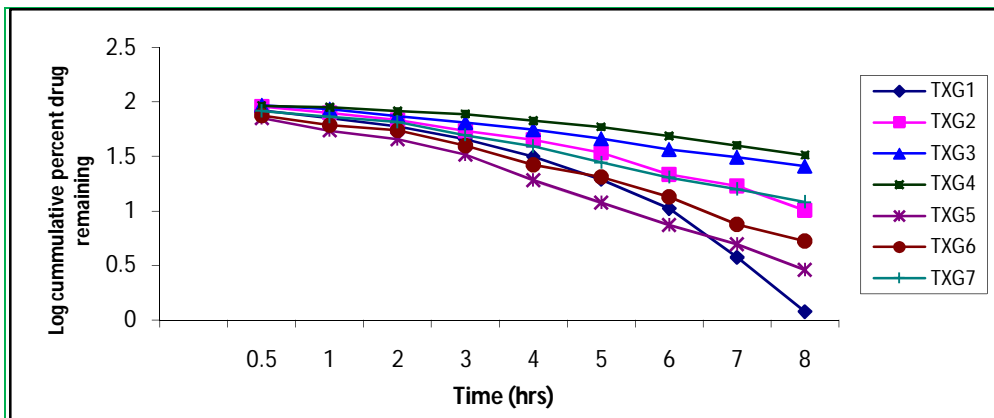


Figure 5: Log cumulative percent drug remaining vs time plots (first order) of formulations TXG₁- TXG₇

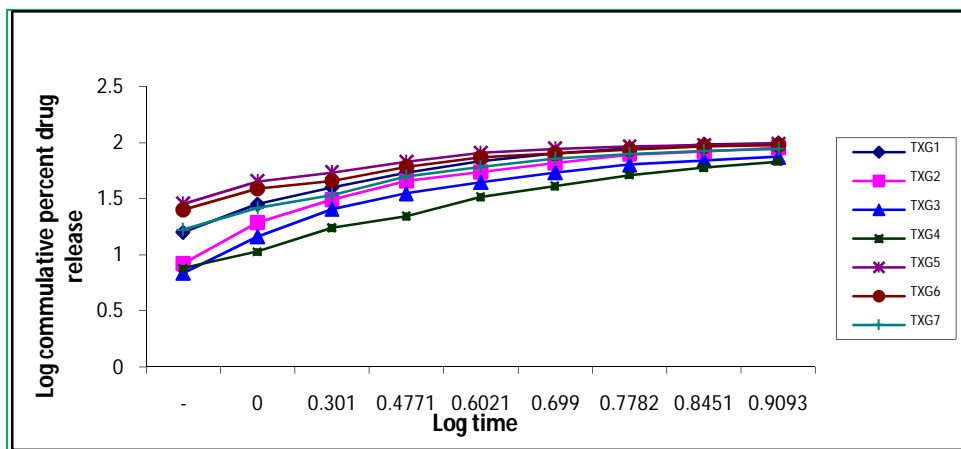


Figure 6: log cumulative percent drug released vs log time plots (Peppas plots) of formulations TXG₁- TXG₇

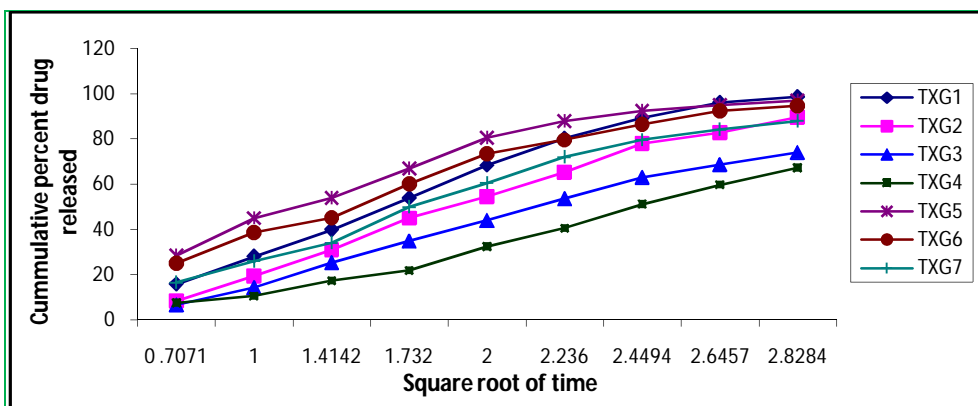


Figure 7: Cumulative percent drug released vs square root of time plots (Higuchi plots) of formulations TXG₁- TXG₇

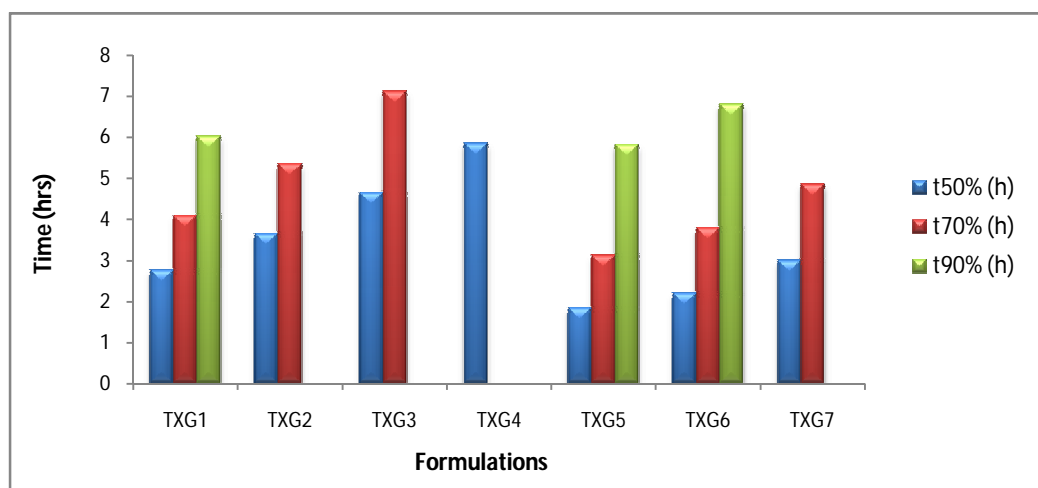


Figure 8: Comparison of dissolution parameters ($t_{50\%}$, $t_{70\%}$ and $t_{90\%}$) of mucoadhesive tablets of Tizanidine hydrochloride.

CONCLUSION

It can be concluded that the mucoadhesive buccal tablets of Tizanidine hydrochloride can be prepared by using natural polymers to control the drug release and also to avoid the first pass metabolism. The formulation TXG₁ was found to be promising, which shows an *in vitro* drug release of 98.80 in 8 h along with satisfactory mucoadhesion strength.

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REFERENCES

- Gibaldi M. The number of drugs administered buccally increasing, *Clinical Pharmacology*. 1985; 3: 49-56.
- Harris D and Robinson R. Drug delivery via the mucous membranes of oral cavity, *J Pharm Sci*. 1992; 81: 1-10.
- Senel S and Hincal AA. Drug penetration enhancement via buccal route; possibilities and limitations, *J Control Release*. 2001; 72: 133-14.
- Davis SS, Daly PB, Kennerley JW, Frier M and Wilson CG. Design and evaluation of sustained release formulations for oral and buccal administration in controlled release Nitroglycerine in buccal and oral form, (Eds. Busmann WD, Dries RR and Wagner W, Karger, Basle 1982; 17-25.
- Owens TS, Dansereau RJ and Sakr A. Development and evaluation of extended release bioadhesive sodium fluoride tablets, *Int J Pharm*. 2005; 288: 109-122.
- Akbari J, Nokhodchi A, Farid D, Adrangui M, Siahshadbad MR and Saeedi M. Development and evaluation of bucoadhesive Propranolol hydrochloride tablet formulations: effect of fillers, *Farmaco*. 2004; 59:155-161.
- Ishida M, Vambu N and Vagai R, Highly viscous gel ointment-containing carbopol for application to the oral mucosa, *Chem Pharm Bull*. 1983; 31: 4561-4564.
- Packer MA, Coats JS, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Ender MT and Demets DL. Effect of Carvedilol on survival in severe chronic heart failure, *N Engl J Med*. 2001; 344: 1651-1658.
- Guo JH. Bioadhesive Polymer buccal patches for buprenorphine controlled delivery formulation, *in vitro* adhesion and release properties, *Drug Dev Ind Pharm*. 1994; 20: 2809-2821.
- Anders R and Merkle HP. Evaluation of laminated mucoadhesive patches for buccal drug delivery. *Int J Pharm*. 1989; 49: 231-240.
- Nance PW, Bugaresti J, Shellenberger K, the North American Tizanidine study group. Efficacy and safety of tizanidine in the treatment of spasticity in patients with spinal cord injury. *Neurology* 1994; 44:S44-51.
- United Kingdom Tizanidine Trial Group. A double blind, placebo-controlled trial of tizanidine in the treatment of spasticity caused by multiple sclerosis. *Neurology* 1994; 44:S70-8.
- 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; 53:435-52.
- Acorda Therapeutics, Inc.. Zanaflex® (tizanidine hydrochloride) tablets and capsules prescribing information. Hawthorne: Acorda Therapeutics; 2006.
- Moffat AC. Clark's isolation and identification of drugs. London: Pharmaceutical Press; 2006. p. 691.
- Vamshi Vishnu Yamsani, Ramesh Gannu, Chandrasekhar Kolli, M. E. Bhanoji Rao, Madhusudan Rao Yamsani. Development and *in vitro* evaluation of bucoadhesive carvedilol tablets. *Acta Pharm*. 2007;57:185-197.
- T.M. Pramod kumar, H.G. Shivakumar. Novel core in cup bucoadhesive systems and films of terbutaline sulphate- development and *in vitro* evaluation. *Asia J Pharm Sci*, 2006;1(3-4):175-87.
- Luana P, Valeria A, Daniela R, Stefano G, Muarizio R, Paolo B. Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease. *J Control Release* 2004; 95 (3): 521-33.



19. Korsmeyer, R.W., Doelkar, G.E.P., Peppas, N.A. Mechanisms of potassium chloride from compressed, hydrophilic, polymeric matrices: effect of entrapped air. J. Pharm. Sci 1983; 72:1189-91.
20. Lee, P.I. Novel zero order drug delivery via immobilized non uniformed drug distribution in glassy hydro gels. J. Pharm. Sci. 1984; 73:1344-7.
21. Higuchi T. Mechanism of sustained action mechanism: theoretical analysis of rate of release of solid drug dispersed in solid matrices. 1963; 52:1145-9.

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