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Development and *In Vitro* Evaluation of Mucoadhesive Buccal Tablets of Tizanidine Hydrochloride Using Natural Polymer Locust Gum

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ABSTRACT

In the present work mucoadhesive buccal tablets of Tizanidine hydrochloride (TZD HCl) were prepared by using locust gum and in combination of locust 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 0.9796 to 0.9846). 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 1.82 to 5.84 h ($t_{50\%}$), 3.13 to 7.12 h ($t_{70\%}$) and 5.83 to 6.81 h ($t_{90\%}$). The formulations TLG_1, TLG_5 and TLG_6 shows drug release 98.70%, 96.11% and 93.57% within 8 h. FTIR studies show no evidence on interaction between drug polymer.

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

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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 route [1-3]. 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 tablets [4-6], 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 muscle [11-14]. 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 understood [14]. 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 Tizanidine [15]. 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. Locust gum 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 spectroscopy [16]. IR spectrum of pure drug and polymers was seen in between 400- 4000 cm^{-1} are shown in Figure 1 and 2.

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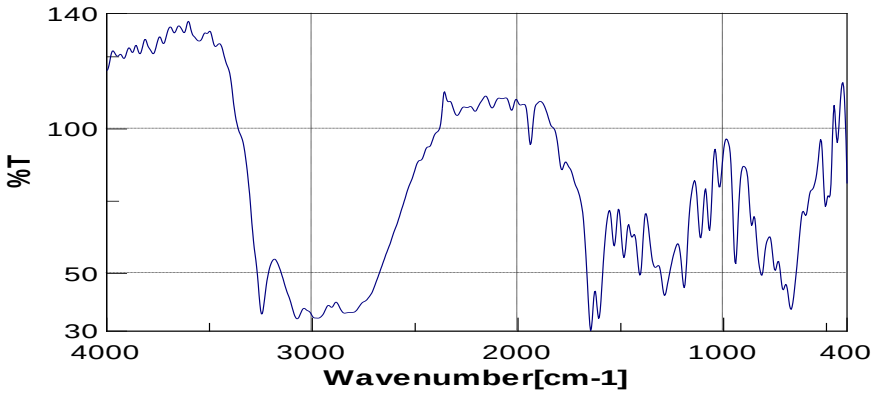

Fig. 1: IR spectrum of Tizanidine hydrochloride

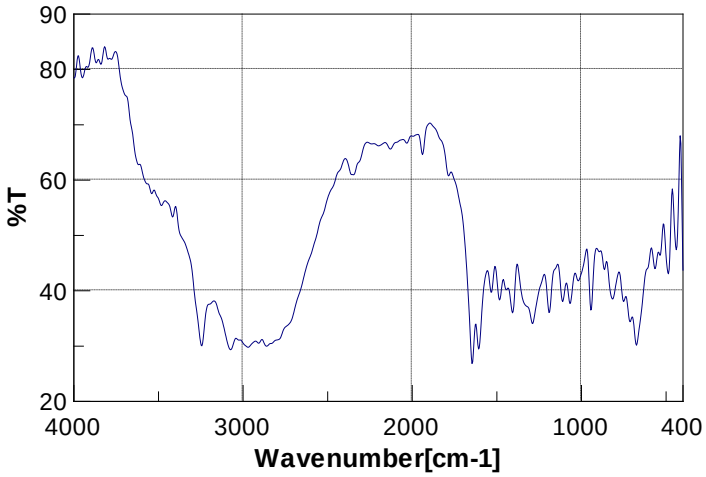

Fig. 2: IR spectrum of Tizanidine hydrochloride + Locust gum

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 locust gum and sodium aliginate 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).

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Table 1: Composition of mucoadhesive buccal tablets

Ingredients*	Formulation code						
	TLG_1	TLG_2	TLG_3	TLG_4	TLG_5	TLG_6	TLG_7
Tizanidine hydrochloride	2	2	2	2	2	2	2
Locust 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

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 result [17].

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 swell at 37 ± 1^0C for 2 h in 40 ml phosphate buffer (pH 6.8). The surface pH of swollen buccal tablets was measured using pH paper [18].

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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 $37^0C \pm 1^0C$. 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 equation [19].

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

***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 at and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37^0C. 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 ± 1^0C) 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 grams [20].

***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 ± 0.5^0C, 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), zero order (Eq 2) and Higuchi release models (Eq 3).

$$M_t/ M\infty = k_{KP}t^n \quad \text{.....1}$$

$M_t/ M\infty$ is the fraction of drug released at time't'; k_{KP} is the release rate constant; and n is the release exponent.

$$M_t = M_0 + k_0 t \quad \text{.....2}$$

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.

$$M_t = k_H t^{1/2} \quad \text{.....3}$$

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

RESULT 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 4.1kg/cm^2 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 96.11 to 98.70 %.

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 profile of different batches of tablets. The swelling indices of the tablets increased with increasing amount of locust gum and sodium alginate. The mucoadhesivity of tablets was found to be maximum in case of formulation TLG_7 i.e. 4.92gm. This may be due to fact that the combination and higher concentration of locust gum and sodium alginate. The results are give 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 regration 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^{2}' values from 0.9481 to 0.9943). 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 TLG_1, TLG_5 and TLG_6 shows drug release 98.70%, 96.11% and 93.57% 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 Locust gum.

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Table 2: Physicochemical properties of buccal tablets

Formulation code	Weight Variation of Tablet (mg) *	Hardness Kg/cm^{2} *	Thickness (mm)*	Friability (%)*	Drug Content (%)*
TLG_1	101±0.39	3.4±0.45	3.32±0.05	0.61±0.01	98.70±1.01
TLG_2	100±0.17	3.5±0.60	3.31±0.04	0.72±0.03	88.10±1.22
TLG_3	102±0.47	3.8±0.67	3.27±0.10	0.68±0.06	75.65±0.98
TLG_4	98±0.38	3.6±0.81	3.25±0.08	0.65±0.05	68.39±0.87
TLG_5	101±0.89	3.9±0.47	3.29±0.10	0.69±0.07	96.11±0.39
TLG_6	100±1.03	4.0±0.93	3.30±0.04	0.63±0.04	93.57±1.42
TLG_7	99±0.45	4.1±0.26	3.31±0.03	0.74±0.02	86.89±1.31

*Average of three determinations, values shown in parenthesis are 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*
TLG_1	5.63±0.17	31.13±1.09	4.21±0.10
TLG_2	5.89±0.10	36.28±1.23	4.74±0.12
TLG_3	6.01±0.19	42.62±1.12	4.05±0.17
TLG_4	6.17±0.15	49.71±1.96	4.67±0.08
TLG_5	6.42±0.29	40.49±1.51	4.62±0.10
TLG_6	6.20±0.12	39.37±1.43	4.28±0.15
TLG_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
TLG_1	0.9796	0.8793	0.9768	0.8662
TLG_2	0.9892	0.9763	0.9852	0.8357
TLG_3	0.9943	0.9859	0.9925	0.8486
TLG_4	0.9925	0.9517	0.994	0.9387
TLG_5	0.9049	0.9859	0.925	0.8431
TLG_6	0.9481	0.9718	0.9619	0.8989
TLG_7	0.9782	0.9846	0.9764	0.9008

Table 5: *In vitro* drug release parameters

Formulation code	$t_{50\%}$ (h)	$t_{70\%}$ (h)	$t_{90\%}$ (h)	Cumulative % drug release in 8 hrs*
TLG_1	2.76	4.09	6.03	98.70
TLG_2	3.64	5.36	--	88.10
TLG_3	4.61	7.12	--	75.65
TLG_4	5.84	--	--	68.39
TLG_5	1.82	3.13	5.83	96.11
TLG_6	2.20	3.79	6.81	93.57
TLG_7	3.00	4.86	--	86.89

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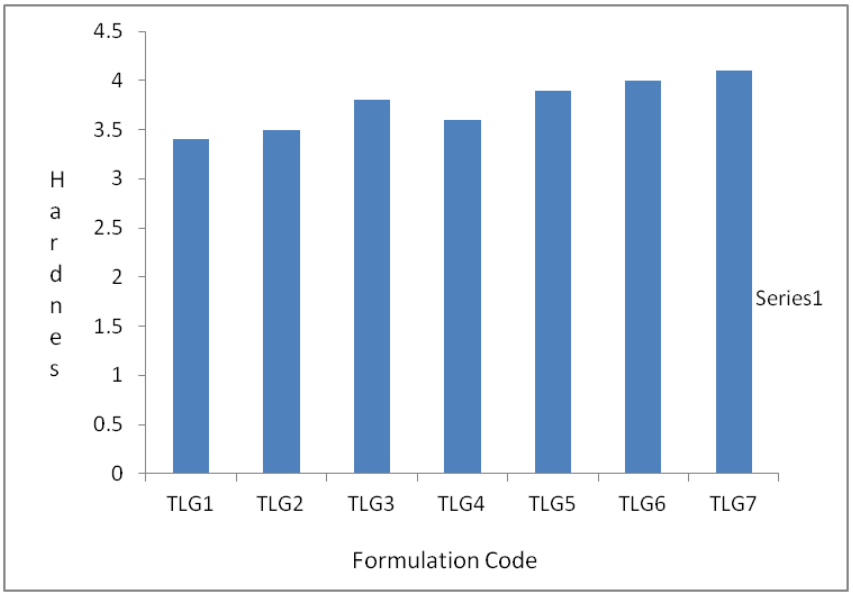

Fig.3: Comparison of hardness of different formulations of Tizanidine hydrochloride

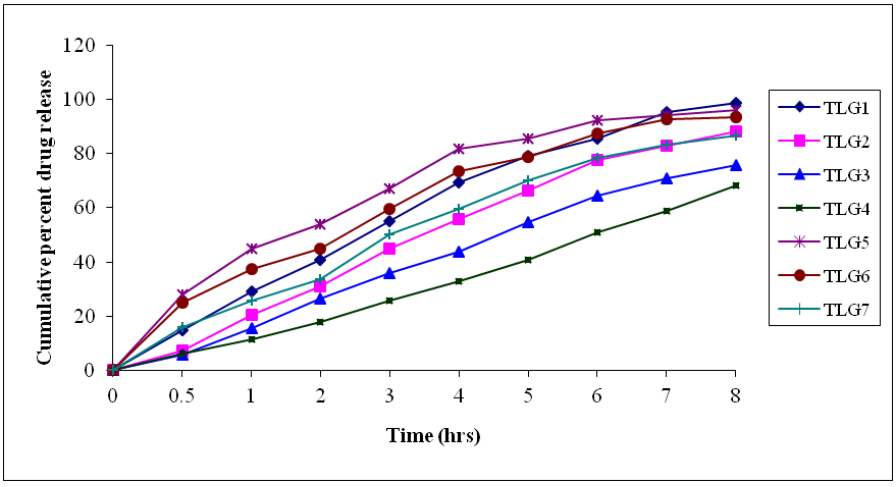

Fig.4: *In vitro* drug release profile of formulation TLG_1- TLG_7

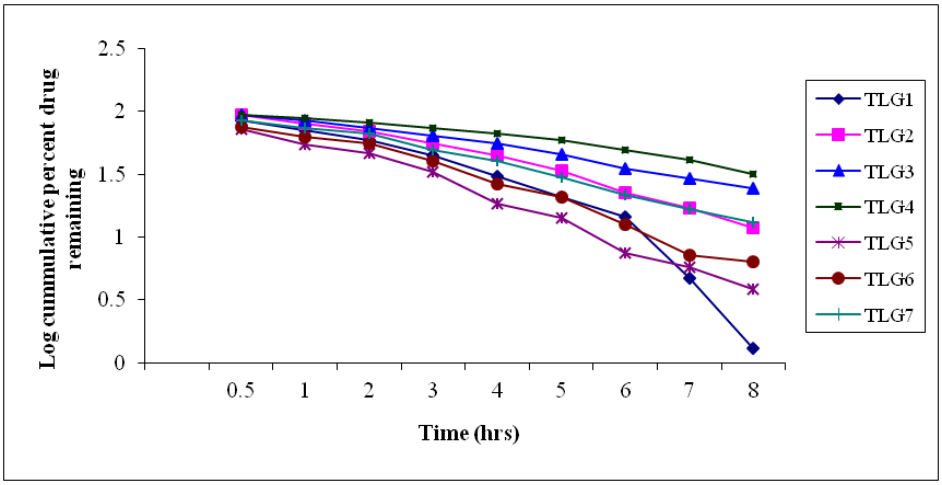

Fig. 5: Log cumulative percent drug remaining vs time plots (first order) of formulations TLG_1- TLG_7

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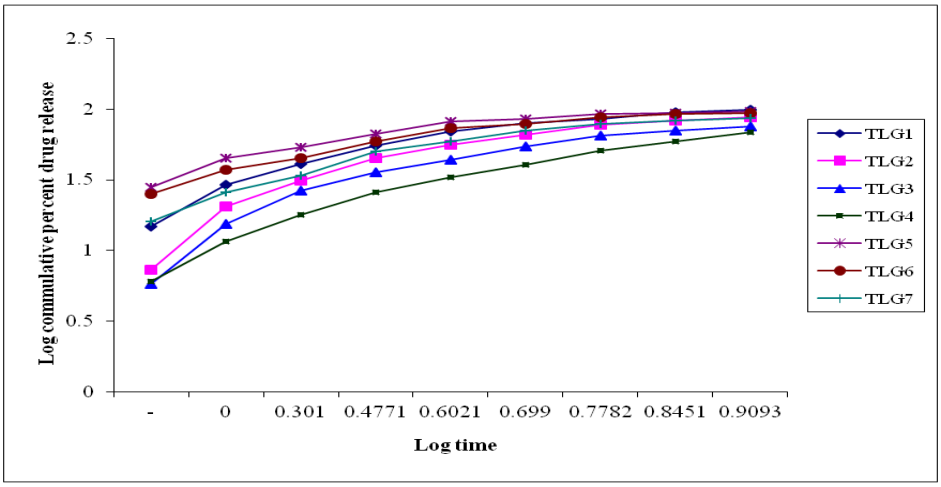

Fig. 6: log cumulative percent drug released vs log time plots (Peppas plots) of formulations TLG_1- TLG_7

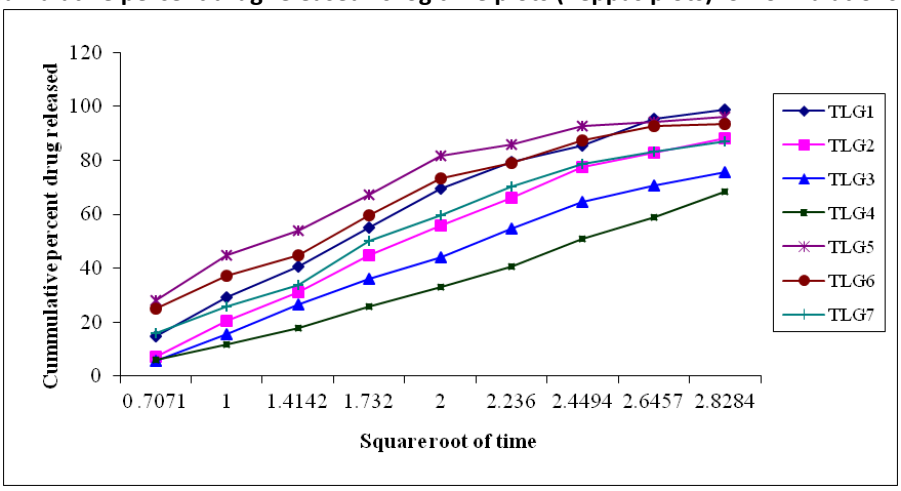

Fig. 7: Cumulative percent drug released vs square root of time plots (Higuchi plots) of formulations TLG_1- TLG_7

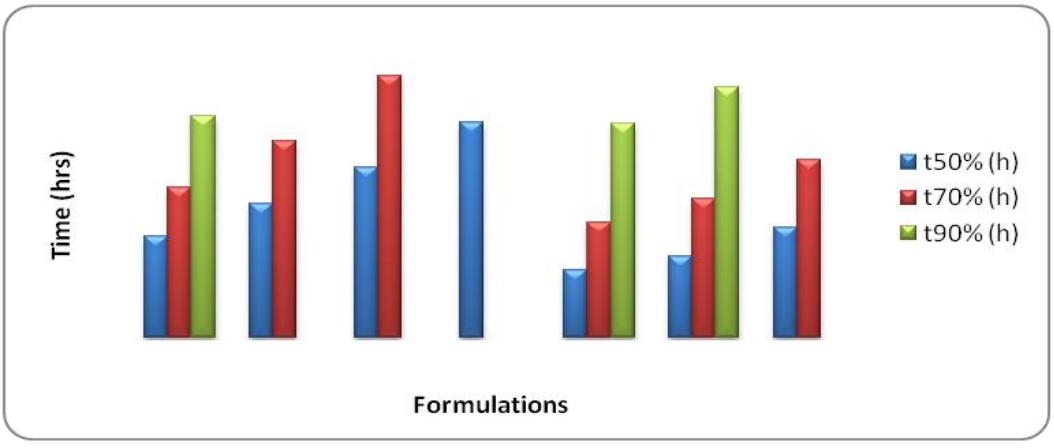

Fig. 8: Comparison of dissolution parameters ($t_{50\%}$, $t_{70\%}$ and $t_{90\%}$) of mucoadhesive tablets of Tizanidine hydrochloride.

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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 TLG1 was found to be promising, which shows an in vitro drug release of 98.70 in 8 h along with satisfactory mucoadhesion strength.

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