Original Research Article
Journal der Pharmazie Forschung (**Formerly-Recent Advances in Pharmaceutical Science Research**)
Vol-2 | No-1 | 2013

Development and In-Vitro evaluation of mucoadhesive buccal tablets of Tizanidine Hydrochloride using natural polymer Locust gum

Tate SS*,Taware GV, Shinde SD, ShetePM and Gaikwad R,

Department of Pharmaceutics, SVPMS's College of Pharmacy, Malegaon, Baramati - 413116, Maharashtra, India.

Abstract

In the present work, mucoadhesive buccal tablets of Tizanidine hydrochloride 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. Thus 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 pattern of drug release ('r' values from 0.9796 to 0.9846). Higuchi and Peppas data reveals that the drug was 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 hr. FTIR studies show no evidence on interaction between drug and polymer.

Keywords: Tizanidine hydrochloride, locust gum, sodium alginate, mucoadhesive buccal tablets.

1.0 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]. Moreover, 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 gaining importance, some of the common forms of mucoadhesive buccal dosage forms are adhesive tablets [4-6], adhesive gels[7,8], adhesive patches[9,10].

Tizanidine hydrochloride (TZD HCl) 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 mucoadhesive 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.

2.0 Materials and methods

TZD HClwas 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 mixturesof drug and excipients were prepared to study thecompatibility. Drug polymer compatibility studieswere carried out using FTIR spectroscopy [16]. IRspectrum of pure drug and polymers was seen inbetween 400- 4000 $cm^{-1}$are shown in Figure-1 and 2.

Preparation of buccal tablets of TZD HClby direct compression method

Direct compression method has been employed to prepare buccal tablets of TZD HCl 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 was thoroughly mixed with mannitol on a butter paper with the help of a stainless steel spatula. Then all the ingredients except lubricant 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).

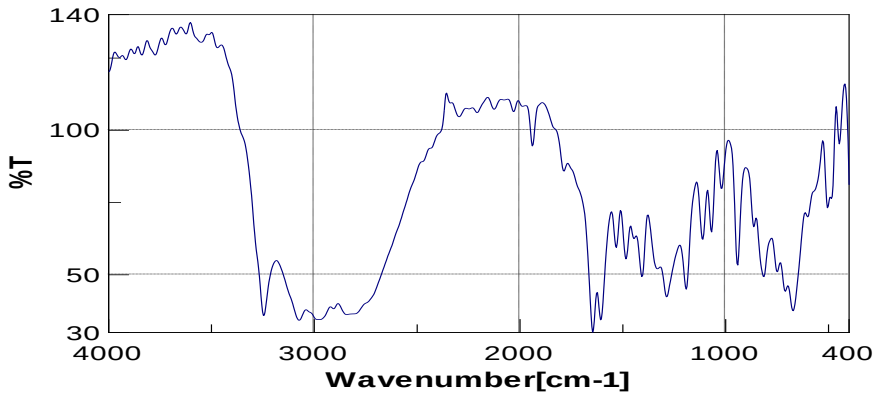

Figure-1: IR spectrum of Tizanidine hydrochloride

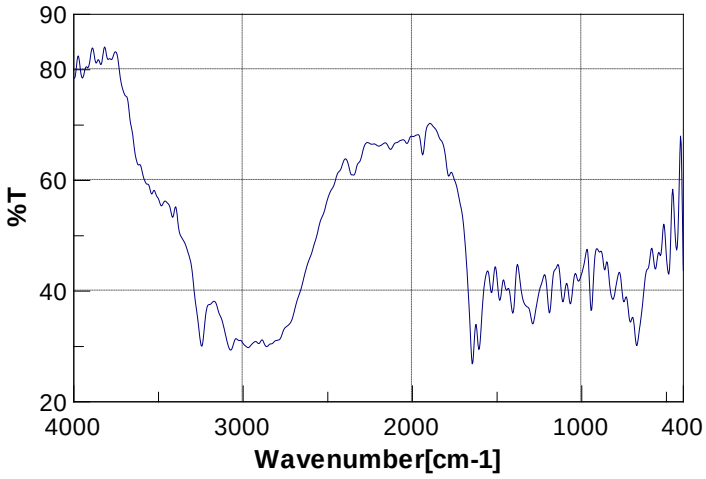

Figure-2: IR spectrum of TZD HCl+ Locust gum

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

Table-1: Composition of mucoadhesivebuccal tablets

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

Evaluation of TZD HClbuccal tablets

Ten buccal tablets of each formulation were weighed using an electronic balance

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

Weight variation test

and average weight of ten tablets and standard deviation were calculated.

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].

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 ± 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 of sample was 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 and release data were fitted to various mathematical models for describing the release mechanism from buccal tablets such as 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.

$$M_t = M_0 + k_0t \quad \text{…….2}$$

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.

$$M_t = k_Ht^{1/2} \quad \text{……..3}$$

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

3.0 Results and discussion

The FT-IR studies revealed that there was no physicochemical interaction between TZD HCland Locust gum. 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 assumed that these formulations cause no any irritation in the oral cavity. The swelling profile of different batches of tablets was also determined. 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 combination of higher concentration of locust gum and sodium alginate. The results are given in Table-3.

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

Table- 2: Physicochemical properties of buccal tablets

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

In vitro drug release data of the all the buccal tablet formulations of TZD HCl 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^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 showed drug release of 98.70%, 96.11% and 93.57% within 8 hrs are shown in Table-5 and Figure-8.

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

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

*Average of three determinations,

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-4: Kinetic data of formulations of mucoadhesive tablets

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

Table-5: *In vitro* drug release parameters

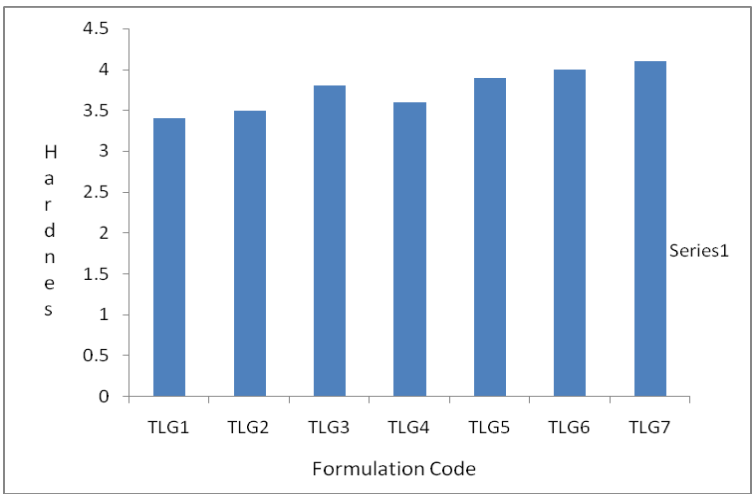

Figure-3: Comparison of hardness of different formulations of Tizanidine hydrochloride

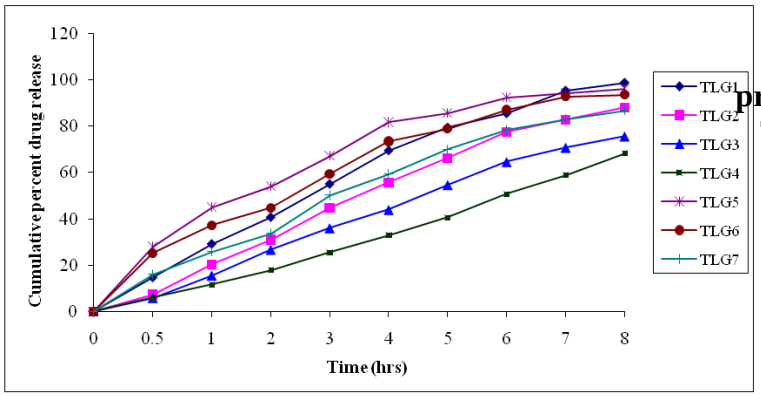

Figure-4: *In vitro* drugrelease profile of formulation TLG_1- TLG_7

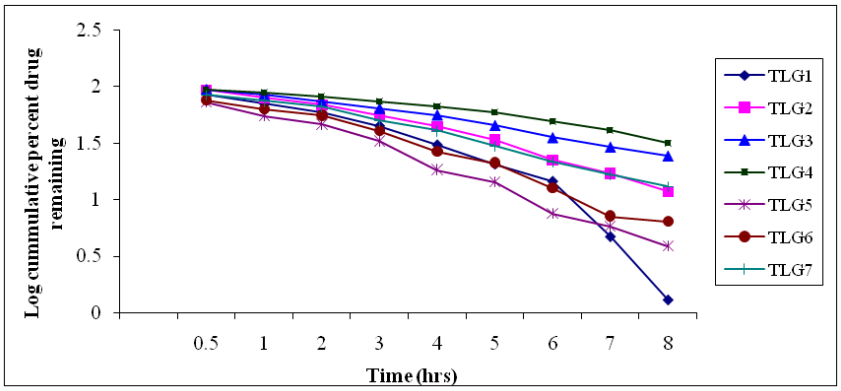

Figure-5: Log cumulative percent drug remaining vs time plots (first order) of formulationsTLG_1- TLG_7

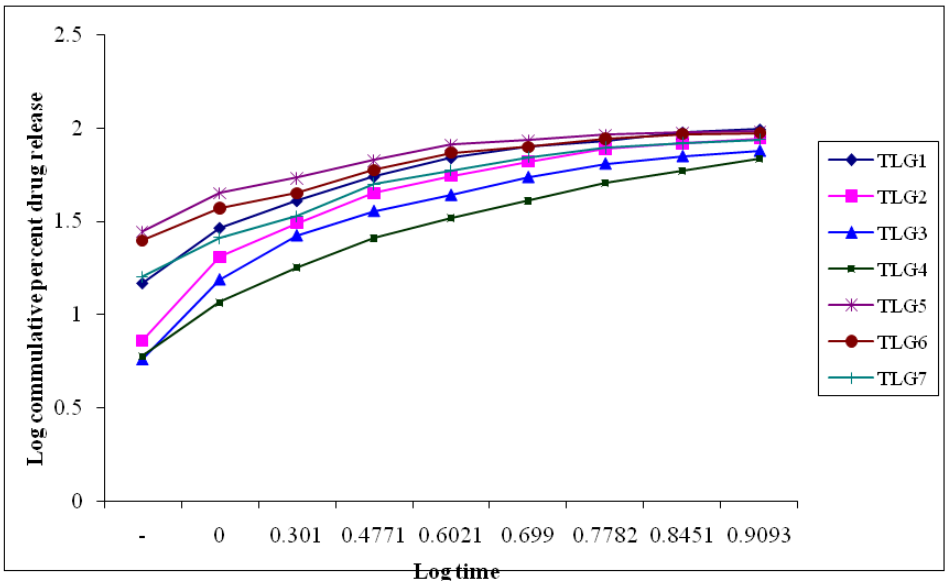

Figure-6: log cumulative percent drug released vs log time plots (Peppas plots) of formulationsTLG_1- TLG_7

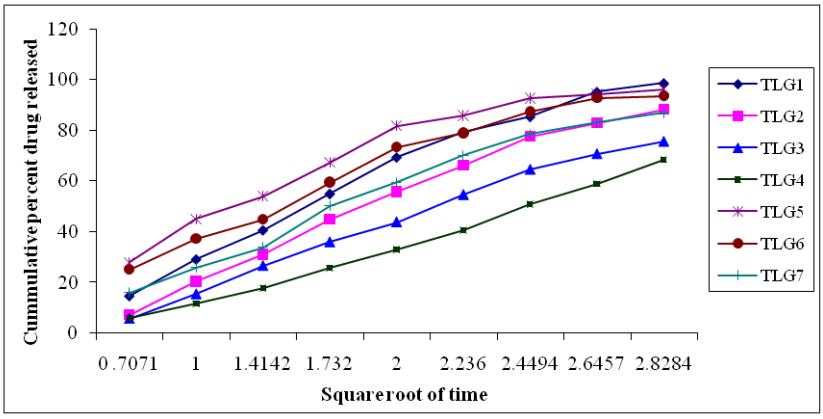

Figure-7: Cumulative percent drug released vs square root of time plots (Higuchi plots) of formulationsTLG_1- TLG_7

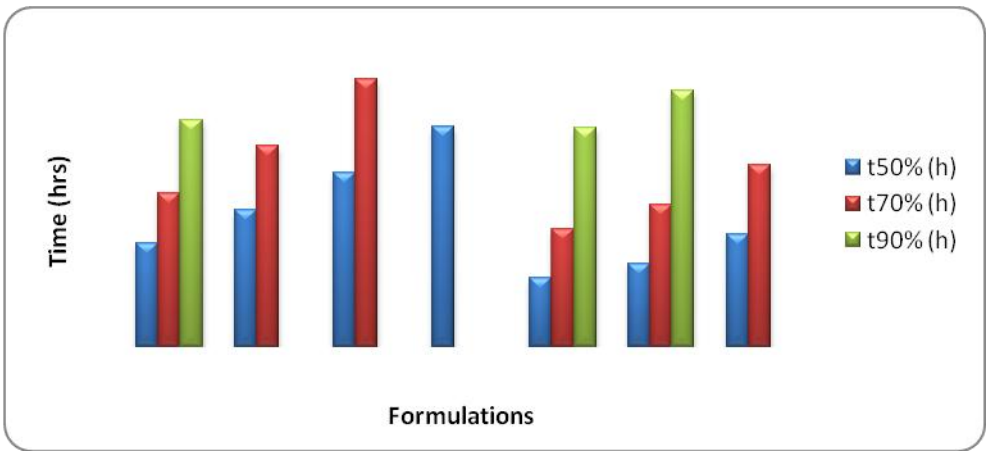

Figure-8: Comparison of dissolution parameters ($t_{50\%}$, $t_{70\%}$ and $t_{90\%}$) of mucoadhesive tablets of Tizanidine hydrochloride.

4.0 Conclusion

It can be concluded that the mucoadhesive buccal tablets of TZD HCl can be prepared by using natural polymers to control the drug release and also to avoid the first pass metabolism. The formulation TLG_1 was found to be promising, which shows an *in vitro* drug release of 98.70 in 8 h along with satisfactory mucoadhesion strength.

Acknowledgement

The authors are thankful to Sun Pharma. (Mumbai, India) for providing gift sample and also very much thankful to Dr. Kishore singh K.C. President, R.M.E.S's College of Pharmacy Gulbarga, for his valuable support and providing necessary facilities to carry out the research work.

Reference

1. Gibaldi M. The number of drugs administering buccally increasing. Clinical Pharmacology. 1985; 3: 49-56.
2. Harris D, Robinson R. Drug delivery via the mucous membranes of oral cavity. J Pharm Sci. 1992; 81: 1-10.
3. Senel S, Hincal AA. Drug penetration enhancement via buccal route; possibilities and limitations. J Control Release. 2001; 72: 133-14.
4. Davis SS, Daly PB, Kennerley JW, Frier M, Wilson CG. Design and evaluation of sustained release formulations for oral and buccal administration in controlled release Nitroglycerine in buccal and oral form. (Eds. Bussmann WD, Dries RR and Wagner W, Karger, Basle 1982; 17-25.
5. Owens TS, Dansereau RJ, Sakr A. Development and evaluation of extended release bioadhesive sodium fluoride tablets. Int J Pharm. 2005; 288: 109-122.
6. Akbari J, Nokhodchi A, Farid D, Adrangui M, SiahiShadbad MR, Saeedi M. Development and evaluation of bucoadhesive Propranolol hydrochloride tablet formulations: effect of fillers. Il Farmaco. 2004; 59:155-161.
7. Ishida M, Vambu N, Vagai R. Highly viscous gel ointment-containing carbopol for application to the oral mucosa. Chem Pharm Bull. 1983; 31: 4561-4564.
8. Packer MA, Coats JS, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Ender MT, Demets DL. Effect of Carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001; 344: 1651-1658.
9. 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.
10. Anders R, Merkle HP. Evaluation of laminated mucoadhesive patches for buccal drug delivery. Int J Pharm. 1989; 49: 231-240.
11. 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.
12. 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.
13. 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.
14. Acorda Therapeutics, Inc. Zanaflex® (Tizanidine hydrochloride) tablets and capsules prescribing information. Hawthorne: Acorda Therapeutics; 2006.
15. Moffat AC. Clark's isolation and identification of drugs. London: Pharmaceutical Press; 2006. p. 691.

16. Vamshi Vishnu Yamsani, Ramesh Gannu, Chandrasekhar Kolli, Bhanoji Rao ME, Madhusudan Rao Yamsani. Development and*in vitro* evaluation of buccoadhesivecarvediloltablets. Acta Pharm. 2007; 57:185–197.
17. Pramodkumar TM, Shivakumar HG. Novel core in cup buccoadhesive systems and films of terbutalinesulphate- development and *invitro* evaluation. Asia J Pharm Sci. 2006;1(3-4):175-87.
18. Luana P, Valeria A, Daniela R, Stefano G, Muarizio R, Paolo B. Novel muccoadhesivebuccal formulation containg metronidazole for the treatment of periodontal disease. J Control Release 2004; 95 (3): 521-33.
19. Korsmeyer, RW, Doelkar GEP, Peppas NA. Mechanisms of potassium chloride from compressed, hydrophilic, polymeric matrices: effect of entrapped air. J. Pharm. Sci 1983; 72:1189-91.
20. Lee PI. Novel zero order drug delivery via immobilized non uniformed drug distribution in glassy hydro gels. J Pharm Sci. 1984; 73:1344-7.