ORIGINAL ARTICLE

Formulation Design and *In-vitro Ex-vivo* Evaluation of Sustained Release Matrix Tablet of Tizanidine Hydrochloride by Direct Compression Method

Vamshi Vishnu Yamsani[1], Raghava Reddy[1], Syed Wajid[2], Sarah I. Bukhari[3], H. A. Mahmoud[3], Mohamed N. Al-Arifi[2]

[1]Department of Pharmaceutics, Vikas College of Pharmacy, Warangal, Andhra Pradesh, India, [2]Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, [3]Department of Pharmaceutics Female Campus, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

Abstract

Aim: This study was undertaken to formulate and evaluate the sustained release (SR) matrix tablet of tizanidine hydrochloride by direct compression technique. **Materials and Methods:** SR matrix tablets of tizanidine were formulated using polymers such as carrageenan, xanthan gum, and polyethylene oxide (PEO) as releases retardants. All the pre-compressional parameters were found to be within the standard limits. Tablets were evaluated for hardness, friability, thickness, drug content, *in-vitro* release, and stability studies. *In-vitro* drug dissolution was studied. For 12 h using USP dissolution apparatus paddle type at the speed of 50 rpm at a temperature of 37 ± 0.5°C using simulated gastric fluid (pH 1.2) and pH 6.8 phosphate buffer. **Results:** Matrix tablet with carrageenan, xanthan gum, and PEO successfully SR of tizanidine for a period of 12-h. The concentration of tizanidine was kept constant, microcrystalline cellulose-101, and lactose (1:3 ratio) used as filler. The maximum *in-vitro* release was found to be 97.8, 100.04, and 98.6 over a period of 12-h for formulations C4, X4, and P4. The data of *in-vitro* release from tablets were fitted to different kinetic models to explain the release profile. **Conclusions:** Formulations C4 and P4 were best fitted to Higuchi Fickian diffusion, whereas X4 formulation showed anomalous non-Fickian diffusion, i.e., the rate of solvent penetration and drug release are in the same range. Stability studies indicated that there was no change in the chemical and physical characteristics during the test period.

Key words: Carrageenan, matrix tablet, polyethylene oxide, tizanidine hydrochloride, xanthan gum

INTRODUCTION

Tizanidine is an agonist at α2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, tizanidine has no direct effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons.

Many new drug delivery systems have been developed to deliver drugs with relatively short duration of action or narrow therapeutic indices at a controlled rate, which will maximize the pharmacological benefits and minimize the potential side effects. Tizanidine hydrochloride (TIZH) is a relatively new treatment for spasticity associated with multiple sclerosis, stroke, spinal cord injury or disease.[1]

The benefits of administering tizanidine in a modified release formulation have been established and demonstrated by a worker in their clinical studies regarding improved spasticity and disability approximately 94% and 79%, respectively for spastic patients. Several published uncontrolled studies,

Address for correspondence:
Syed Wajid, Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. E-mail: wali@ksu.edu.sa

Received: 09-02-2016
Revised: 21-04-2016
Accepted: 05-05-2016

as well as ongoing clinical trials, have been suggested that TIZH is effective in relieving pain associated with a range of disorders such as myofascial pain, refractory pain and neuropathic pain, chronic tension-type headache, and chronic daily headache.[2-8] TIZH may also be a useful adjunct to non-steroidal anti-inflammatory drugs in the treatment of analgesic rebound headache.[9]

Many orally-administered drugs display poor bioavailability when administered as conventional dosage form, i.e., the rate and extent to which the drugs are absorbed is less than desirable. TIZH is available in the conventional dosage form. The bioavailability of the drug from a conventional dosage form is 40% due to the limitation of first pass metabolism. To compensate for this effect, a very large dose is often administered so that absorption of the therapeutically required quantity of the drug can occur. This technique may prove costly with expensive drugs, and the unabsorbed drug may also have undesirable side effect within the gastrointestinal tract. In addition, poorly absorbed drug often display large inter- and intra-subject variability in bioavailability. This problem may be overcome by modified release drug delivery system. So, sustained release (SR) matrix tablets of TIZH can increase the bioavailability of the drug. It is effectively used in the treatment of management of spasticity, indicated in muscle pain as muscle relaxant. TIZH has a biological half-life of 2.5 h, i.e., it requires three times a day dosing. The aim and objective of our current research is to formulation of SR matrix tablets to increase the bioavailability of drug.

MATERIALS AND METHODS

Materials

TIZH and carrageenan were purchased from Yarrow Chem Products, Mumbai, India. Polyethylene oxide (PEO) and Pharmatose DCL 21 were supplied as a gift sample from Dr. Reddy's Laboratories, India. Xanthan gum, microcrystalline cellulose, talc, and magnesium stearate were purchased from SD Fine-Chem Limited, Mumbai, India.

Methods

Preparation of SR tablets of TIZH by direct compression method

SR tablets were prepared by direct compression method using different polymers such as carrageenan, xanthan gum, and PEO according to the formula given in Table 1. All the ingredients including drug were weighed accurately and passed through 60# mesh sieve separately. The drug and polymer were mixed by a small portion of both each time and blend it to get a uniform mixture and kept aside. Then, all the ingredients weighed are mixed in geometrical order excluding magnesium stearate to get a uniform blend. Finally, mixture is blended with magnesium stearate and talc. Tablets were compressed of 8 mm sizes concave round punch to get tablet using compression machine. The tablets were packed in aluminum foil and stored at room temperature.

Evaluation of tablets

Thickness and diameter of tablets

Thickness and diameter test permits accurate measurement and provides information on the variation between tablets. 10 tablets were taken, and the thickness and diameter were measured using a Vernier caliper. The tablet thickness and diameter should be controlled within the ±5% variation of a standard value.[10]

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance, and the test was performed according to the official method. For tablets as per Indian Pharmacopoeia, <250 mg tablet acceptable limit of % deviation is 7.5.[11]

Hardness

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The force is measured in kilograms. The hardness was tested using Monsanto tester. Hardness factor, the average of the six determinations, was determined and reported.[12]

Drug content uniformity

All the formulations were tested for their drug content.[12]

Procedure

Five tablets were selected randomly, and average weight was calculated. Tablets were crushed in a mortar and accurately average weighed amount of tablets triturate was taken for analysis. Samples were transferred to different volumetric flasks and were diluted up to the mark using 0.1 N HCl. The content was shaken well and kept for 30 min for dissolving the drug completely. The mixtures were filtered, and appropriate dilutions were made. The drug content in each tablet was estimated at λ_{max} 319 nm against blank as a reference.

In-vitro dissolution studies

In-vitro drug release study of the samples was carried out using USP - Type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml of simulated gastric fluid (without enzyme), was placed into the dissolution flask maintaining the temperature of 37 + 0.5°C and rpm of 50. One TIZH SR tablet was placed in each basket of the dissolution apparatus. The apparatus was allowed to run for 24 h. Samples measuring 10 ml were withdrawn after every

Table 1: Composition of various tablet formulations

Formulation	Polymer	MCC	Pharmatose DCL 21	Magnesium stearate	Talc	TIZH
C1	35.00	25.78	77.35	3.00	2.00	6.87
C2	48.00	22.53	67.60	3.00	2.00	6.87
C3	61.20	19.23	57.70	3.00	2.00	6.87
C4	68.00	17.53	52.60	3.00	2.00	6.87
X1	61.20	19.23	57.70	3.00	2.00	6.87
X2	68.00	17.53	52.60	3.00	2.00	6.87
X3	81.60	14.13	42.40	3.00	2.00	6.87
X4	88.40	12.43	37.30	3.00	2.00	6.87
P1	35.00	25.78	77.35	3.00	2.00	6.87
P2	48.00	22.53	67.60	3.00	2.00	6.87
P3	61.20	19.23	57.70	3.00	2.00	6.87
P4	68.00	17.53	52.60	3.00	2.00	6.87

C1-C4: Polymer used is carrageenan, X1-X4: Polymer used is xanthan gum, P1-P4: Polymer used is PEO. TIZH: TIZH 6.87 mg equivalent to tizanidine 6 mg. All quantities in mg per tablet. Total weight 150 mg, PEO: Polyethylene oxide, TIZH: Tizanidine hydrochloride, MCC: Microcrystalline cellulose

1, 2, 3, 4, 6, 8, 10, 12 h using autosampler. First 2 h in 0.1 N HCl and then in phosphate buffer 6.8. The fresh dissolution medium (37°C) was replaced every time with the same quantity of the sample. Collected samples were analyzed at 319 nm using 0.1 N HCl and 6.8 phosphate buffer as blank. The samples were withdrawn at predetermined time points and were analyzed spectrophotometrically at 319 nm for TIZH.[13]

Stability studies

Stability of a drug is defined as the ability of a particular formulation in a specific container to remain within its physical, chemical, therapeutic, and toxicological specifications.[14]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a verity of environmental factors such as temperature, humidity, light and enable recommended storage conditions re-test periods and shelf-lives to be established. ICH specifies the length of study and storage conditions:

Long-term testing 25 ± 2°C/60% RH ± 5% for 12 months.

Accelerated testing 40 ± 2°C/75% RH ± 5% for 6 months.

Procedure

In the present study, stability studies were carried out at for a specific period up to 60 days for selected formulations in stability chamber at 40°C/ambient RH.

The selected formulations were analyzed for any change in color, hardness, and drug content and drug release studies.

RESULTS AND DISCUSSION

The current investigation deals with the optimization of SR matrix tablets of TIZH using different polymers. Polymers used were iota carrageenan, xanthan gum, and PEO. The compositions of the formulations are shown in Table 1. The concentration of TIZH was kept constant at 6.8 mg. Major aims during the formulation are to the formulation of SR matrix tablets to increase the bioavailability of drug.

The results of tablets parameters shown in Table 2. All the formulations showed uniform thickness. In a weight variation test, the pharmacopoeia limit for percentage deviation for the tablets of more than 150 mg is ±7.5%. The average percentage deviation of all the tablet formulations was found to be within the above limit, and hence, all the formulations passed the test for uniformity of weight as per the official requirements. Good uniformity in drug content was found among different batches of tablets and percentage of drug content was more than 95%. All formulations show required hardness.

In the present study, the percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable properties and complied with the in-house specifications for weight variation post compressional parameters, i.e., hardness, friability, thickness, weight variation, and drug content were within acceptable official IP limits.

Dissolution study

In-vitro drug release study for the prepared matrix tablets was conducted for period of 12-h using a USP - Type II (paddle)

apparatus at 37 ± 0.5°C and 50 rpm speed. The dissolution studies were carried out in 0.1 N HCl and phosphate buffer of pH 6.8 under sink condition. Every 1 h interval samples of 5 ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. The sample solution was analyzed at 319 nm for TIZH by an ultra violet-spectrophotometer.

The *in-vitro* drug release of different batches of TIZH with carrageenan polymer is presented in Table 3 and dissolution profile of formulation shown in (Figure 1). Batch C1, C2, and C3 shown drug release up to 4, 6, and 8 h, respectively, due to an insufficient concentration of carrageenan. Therefore, in Batch C4, much higher concentration of carrageenan was used and it shown drug release up to 12 h. Based on the above experience, it concluded that drug and polymer ratio 1:10, i.e., 68 mg of polymer show drug release up to 12 h (97.8%).

Dissolution profile of C1, C2, C3, C4 formulations

The *in-vitro* release of different batches of TIZH with xanthan gum polymer is presented in Table 3 and dissolution profile of formulation shown in (Figure 2). Batch X1, X2, and X3 shown drug release up to 4, 8, and 10 h, respectively, due

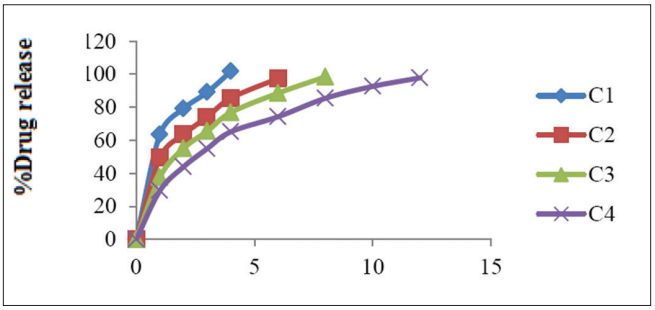

Figure 1: Dissolution profile of formulation containing carrageenan

Table 2: Evaluation of tablets

Formulation code	Hardness	Thickness	Friability	Weight variation test (%) (*n*=10)	Drug content (%)
C1	2.8±0.094	3.25±0.692	0.92	148.9±1.67	97.39
C2	3.2±0.249	3.21±0.560	0.95	147.4±2.65	96.84
C3	4.3±0.339	3.14±0.351	0.73	146.4±4.01	98.00
C4	5.5±0.156	3.21±0.543	0.61	145.9±6.62	97.90
X1	2.2±0.128	3.26±0.725	0.81	146.9±5.73	97.82
X2	3.5±0.352	3.19±0.452	0.78	148.0±2.01	97.56
X3	4.1±0.265	3.16±0.348	0.65	153.0±3.52	96.12
X4	4.1±0.350	3.22±0.569	0.72	150.3±1.99	97.48
P1	3.5±0.563	3.18±0.423	0.82	148.4±3.01	97.63
P2	4.1±0.584	3.27±0.845	0.81	153.2±4.93	96.99
P3	4.2±0.635	3.25±0.692	0.64	149.0±2.66	98.83
P4	5.0±0.265	3.27±0.832	0.66	146.1±5.30	99.45

*Each value represents as mean±SD of three determinants. SD: Standard deviation, C1-C4: Polymer used is carrageenan, X1-X4: Polymer used is xanthan gum, P1-P4: Polymer used is PEO, PEO: Polyethylene oxide

Table 3: Dissolution data of formulation containing carrageenan, xanthan gum, and PEO

Time in h	*In-vitro* drug release (*n*=3)											
	C1	C2	C3	C4	X1	X2	X3	X4	P1	P2	P3	P4
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	63.50	49.38	37.70	29.45	66.35	52.30	39.10	26.74	60.38	48.79	39.90	30.83
2	79.13	63.55	55.07	43.90	85.42	68.38	57.90	46.32	86.02	64.79	54.31	45.77
3	89.05	74.03	65.48	54.90	94.13	79.96	68.37	57.90	100.62	76.64	65.06	57.07
4	101.73	85.5	76.77	65.11	98.32	87.95	76.92	67.00	-	89.05	74.16	65.89
6	-	97.35	88.52	74.25	-	95.40	84.92	75.54	-	98.50	83.53	73.61
8	-	-	98.43	85.40	-	97.81	90.71	86.02	-	-	90.70	81.89
10	-	-	-	92.60	-	-	97.53	92.36	-	-	97.81	90.16
12	-	-	-	97.80	-	-	-	100.04	-	-	-	98.26

C1-C4: Polymer used is Carrageenan, X1-X4: Polymer used is Xanthan gum, P1-P4: Polymer used is PEO, PEO: Polyethylene oxide

to an insufficient concentration of xanthan gum. Therefore, in Batch X4, much higher concentration of xanthan gum was used, and it shown drug release up to 12 h. Based on above experience, it concluded that drug and polymer ratio 1:13, i.e., 88.4 mg of polymer show drug release up to 12 h (100.04%).

Dissolution profile of X1, X2, X3, and X4 formulations

The *in-vitro* release of different batches of TIZH with PEO polymer is presented in Table 3, and dissolution profile of formulation shown in Figure 3. Batch P1, P2, and P3 shown drug release up to 3, 6, and 10 h, respectively, due to an insufficient concentration of PEO. Therefore, in Batch P4, much higher concentration of PEO was used, and it shown drug release up to 12 h. Based on above experience, it concluded that drug and polymer ratio 1:10, i.e., 68 mg of polymer show drug release up to 12 h (98.26%).

The dissolution data were examined for models of first order, zero order, Higuchi, Korsemeyer-Peppas, and Hixon-Crowell model shown in Table 4. The derived correlation coefficient R^2 indicated good fit of Higuchi model suggesting that diffusion is the predominant mechanism limiting drug release. For formulations containing carrageenan (C4), xanthan gum (X4), PEO (P4), R^2 values of above formulations are 0.992, 0.9859, and 0.988, respectively. All the formulations gave good fit to the Higuchi model. Formulation C4 and P4 exhibited Fickian drug release, whereas X4 formulation showed anomalous non-Fickian diffusion, i.e., the rate of solvent penetration and drug release are in the same range (Figure 4). In non-Fickian model, drug diffusion from the swollen tablet. Erosion of the matrix can also influence the drug release from this polymer matrix.

Among all formulations carrageenan, xanthan gum, and PEO formulation C4 showed good release profile. The order of release profiles of polymers is C4>P4>X4. Because at 1:10 drug, polymer ratio carrageenan shown drug release up to 12 h xanthan gum shown drug release up to 8 h, and 12 h drug release of xanthan gum shown at concentration 1:13 drug, polymer ratio carrageenan was shown good hardness and retardant effect than the PEO and xanthan gum.

Release kinetic model

Stability study

Stability studies were conducted on the selected formulations of TIZH (C4, X4, P4) to assess their stability with respect to their physical appearance, drug content, and drug release characteristics after storage at 40°C/75 ± 5% RH for 3 months to assess their long-term stability. When the matrix tablets of TIZH were stored at 40°C/ambient RH for 3 months, there was no change either in physical appearance orin drug content shown in Table 5.

When the dissolution study was conducted in 0.1 N HCl and phosphate buffer (pH 6.8) asno significant difference was observed in the percentage of TIZH release from the selected

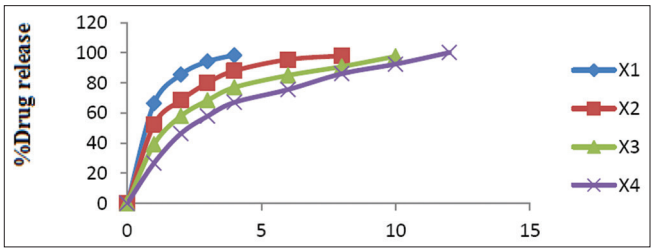

Figure 2: Dissolution profile of formulation containing xanthan gum

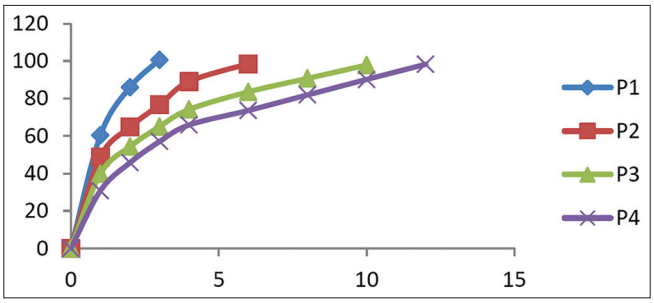

Figure 3: Dissolution profile of formulation containing Polyethylene Oxide

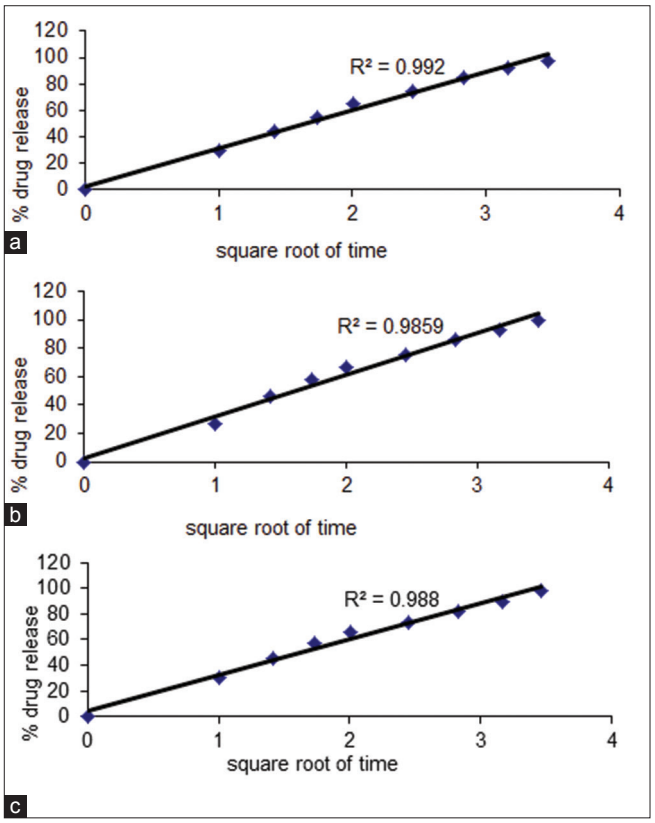

Figure 4: Higuchi plot for selected formulation (a) C4, (b) X4 and, (c) P4

Table 4: Regression analysis and correlation coefficient 'r' values of the *in-vitro* release data according to various release kinetic models

Formulation code	Zero order	Higuchi	Korsmeyer-Peppas		Hixon -Crowell
	R^2	R^2	R^2	*n*	R^2
C4	0.8680	0.9920	0.9893	0.4800	0.9890
X4	0.8566	0.9859	0.9665	0.5012	0.9001
P4	0.8524	0.9880	0.9859	0.4480	0.9690

C4: Polymer used is carrageenan, X4: Polymer used is xanthan gum, P4: Polymer used is PEO, PEO: Polyethylene oxide

Table 5: Dissolution data and drug content data for stability study of C4, X4, P4, formulations

	C4	X4	P4
Color	No change	No change	No change
Hardness	5.5±0.35	4.1±0.52	5.0±0.52
Assay	97.12	96.55	95.62
% drug release	96.52	97.98	97.25

C4: Polymer used is carrageenan, X4: Polymer used is xanthan gum, P4: Polymer used is PEO, PEO: Polyethylene oxide

formulations (C4, X4, P4) stored at 40°C/ambient RH for 3 months when compared to that released shown in Table 5 from the same formulations before storage.

CONCLUSIONS

In this study, matrix tablet of TIZH was prepared by direct compression technique using HPMC K4M, carrageenan, xanthan gum, PEO, and Metolose90SH polymers as retardant. Sustain release drug delivery was developed to overcome the first-pass metabolism and subsequent low bioavailability of the drug. The *in-vitro* studies have shown that this is a potential drug delivery system for TIZH with considerably good stability and release profile. However, future *in-vivo* studies are warranted to confirm these results *in-vivo*. Following conclusions were made.

Matrix tablet of TIZH that contained polymers such as carrageenan, xanthan gum, and PEO successfully SR of TIZH for a period of 12-h. The optimized formulations C4, X4, and P4 showed the drug release 97.8, 100.04, and 98.26, respectively, at the end of 12 h. The drug release mechanisms for formulations were best described by Higuchi's equation. The formulations followed Fickian diffusion (C4, P4) and anomalous behavior (X4). Stability studies were conducted on the selected formulations of TIZH for 3 months; there was no change either in physical appearance or in drug content and in the dissolution study at 40°C/ambient RH.

ACKNOWLEDGMENT

The authors acknowledge Dr. Reddy's laboratories, India, for providing gift samples of PEO and Pharmatose DCL 21.

REFERENCES

1. 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.
2. Hutchinson DR. Modified release tizanidine: A review. J Int Med Res 1989;17:565-73.
3. Dubin A, Gombas G, Smith HA. Retrospective Review of Tizanidine, a Centrally-Acting Alpha2-Adrenergic Agonist Muscle Relaxant, for the Treatment of Traumatically-Induced Myofascial Pain. 18th Annual General Meeting of the American Pain Society. Fort Lauderdale; 1999.
4. Hewitt D, McKenzie E. The Tolerability and Efficacy of Zanaflex (tizanidine) for Chronic Pain. 18th Annual Scientific Meeting of the American Pain Society. Fort Lauderdale; 1999.
5. Semenchuk M, Sherman S. Efficacy of Zanaflex (tizanidine) in Neuropathic Pain: An Open Label Study. 18th Annual Scientific Meeting of the American Pain Society. Fort Lauderdale; 1999.
6. Krusz JC. Tizanidine: An Effective Novel Agent for Treatment of Chronic Headaches. 18th Annual Scientific Meeting of the American Pain Society. Fort Lauderdale; 1999.
7. Freitag FG, Diamond S, Diamond M. Tizanidine HCl in the Preventive Treatment of Chronic Tension-type Headache. Worldwide Pain Conference. San Francisco; 2000.
8. Millette TJ, Laseter JT, Bosarge R. Retrospective Study of Efficacy of Zanaflex (tizanidine hydrochloride) in Patients with Chronic Daily Headache Syndrome of Cervical Myofascial Etiology, 18th Annual Scientific Meeting of the American Pain Society, Fort Lauderdale; 1999.
9. Smith TR. Low-dose Tizanidine Hydrochloride Combined with Long-Acting Nsaids for Analgesic Rebound Headache: A Retrospective Review. San Francisco: World Wide Pain Conference; 2000.
10. Aulton ME. Pharmaceutics: The Science of Dosage Form Design. 2nd ed. London: Churchill Livingstone; 1988. p. 133-5.
11. Indian Pharmacopoeia. Ministry of Health and Family Welfare. Vol. II. New Delhi: Government of India, Controller of Publications; 1996. p. 734-6.

12. Banker GS, Anderson LR. Tablets. In: Lachman L, Liberman HA, Kanig JL, editors. The Theory and Practice of Industrial Pharmacy. Mumbai, India: Varghese Publishing House; 1987. p. 293-345.
13. United States Pharmacy Convention Inc. United States Pharmacopoeia. Asian Edition. London: United States Pharmacy Convention Inc.; 2000. p. 330-1.
14. Overview of ICH Guidelines for Drug Products. Natalie Mcclure, Matrix Pharmaceutical Inc. 1997: Available from: http://www.mcclurenet.com. [Last accessed on 2006 Mar 28].

Source of Support: Nil. **Conflict of Interest:** None declared.