ORIGINAL ARTICLE

IN-VITRO STUDIES OF TIZANIDINE CONTROLLED-RELEASE MICROCAPSULAR MATRICES

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ABSTRACT

Oral microencapsulated controlled release preparations of tizanidine (TIZ) were tried. The designed system is able to maintain plasma concentration without the need of frequent dosing and reduce side effects unlike in case of conventional dosage form. Microcapsules were prepared by modified solvent evaporation technique using different proportions of cellulose acetate. The microcapsules (TIZ1, TIZ2 and TIZ3) were compressed in to tablets (T-TIZ1, T-TIZ2 and T-TIZ3) for oral delivery. The prepared microcapsules were white, free flowing and spherical in shape with the particle size varying from 175.92± 9.82 to 194.94±14.28 µm. The t60% of TIZ release from microcapsules was found to be 2.39±0.6, 3.39±0.6 and 4.55±0.8 h respectively for formulation TIZ1, TIZ2 and TIZ3 while their tablets i.e., T-TIZ1, T-TIZ2, T-TIZ3 and marketed SR were in 5.28±1.5, 6.86±0.6, 8.25 ±0.6 and 3.75±1.20 h respectively indicating more extension of time in tablet than microcapsules. The mechanism of drug release from tizanidine microcapsules and their tablets were studied by using Higuchi and Korsmeyer-Peppas models. The r-value for TIZ1, TIZ2 and TIZ3 indicates diffusion controlled with first order kinetic. The value of exponent coefficient (n) for T-TIZ1, T-TIZ2 and T-TIZ3 were found to be 0.844, 0.901 and 0.914 indicating anamolous, case-II and case-II transport release mechanism respectively.

Keywords: Tizanidine, cellulose acetate, microencapsulation, oral controlled tablet.

INTRODUCTION

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 is a relatively new treatment for spasticity associated with multiple sclerosis, stroke, spinal cord injury, or disease (Wagstaff and Bryson, 1997). The benefits of administering tizanidine in a modified release formulation have been established and demonstrated by worker (Hutchinson DR, 1990) in their clinical studies regarding improved spasticity and disability approximately 94% and 79% respectively for spastic patients. Several published uncontrolled studies, as well as ongoing clinical trials has been suggested that tizanidine is effective in relieving pain associated with a range of disorders such as myofascial pain (Dubin *et al*., 1999), refractory pain (Hewitt and McKenzie, 1999) and neuropathic pain (Semenchuk and Sherman, 1999), chronic tension-type headache and chronic daily headache (Krusz, 1999; Freitag, 2000 and Millette, 2000). Tizanidine may also be a useful adjunct to NSAIDs in the treatment of analgesic rebound headache (Smith, 2000).

In the present study, microcapsule based oral controlled release matrices were designed for TIZ by varying the proportion of cellulose acetate as the retardant material by a modified emulsion solvent evaporation method. There are variety of sustained release formulation of tizanidine are available in the market e.g., Tizan-SR and Tizan etc. In these brands tizanidine is sustained by only matrix system. Therapy with conventional tizanidine tablets is effective in the relief of spasticity, but it has a short half-life (2-4h). Physical characteristics, micromeritics and in-vitro release studies were carried out to evaluate the release characteristics of TIZ from these microcapsules. Further, the microcapsules were tabletted to control the release profile, which may give one of the efficient means of drug delivery with improved patient compliance.

MATERIALS AND METHODS

Materials

Tizanidine (Gift sample from Ranbaxy Labs. Dewas (India), cellulose acetate (Zeim Laboratries Nagpur (M.H.)) and all other chemicals and reagents used were of analytical grade supplied by S.D. Fine Chem. Ltd.

Bulk drug tizanidine were characterized by various tests of identification and analyzed by an UV spectrophotometric method (UV-1700-Shimadzu Japan) at 318.5 nm in methanol. The IR spectrum obtained (FTIR-8400 S Shimadzu (Japan) was compared with that of the standard. The effects of various formulation excipients (e.g. cellulose acetate and petroleum ether) on the stability and analysis of TIZ were also studied by the UV spectrophotometric method.

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Preparation of microcapsules and its tablets

A modified solvent evaporation with modifications (Abd EI-Hameed and Kellaway, 1997; Chowdhary and Ramesh, 1995; Sajeev *et al*., 2002; Saravanan, 2003 and Saraf *et al*., 2006) method was employed to formulate TIZ microcapsules using different ratios of CA and TIZ (1:1(TIZ1), 2:1(TIZ2) and 3:1 (TIZ3)). CA was dissolved completely in acetone (10 ml) in a glass vessel, and pulverized TIZ was dispersed in the solution of CA in acetone with vigorous stirring. The mixture was stirred at 150 rpm at room temperature for 15min. The resultant solution was intermittently sprayed using a spray gun (0.5mm nozzle size, 60 psi pressure) into liquid paraffin (previously heated up to 60°C), stirred at 800 rpm over a period of 10min. The mixture was kept in a stirring condition at a constant temperature of 60°C for 10min until the solvent was removed completely. The microcapsule were collected by decantation and washed with petroleum ether to remove adhering liquid paraffin. The product was then dried to obtained discreet microcapsules. Controlled release non-disintegrating tablets of TIZ microcapsules (T-TIZ1, T- TIZ 2, and T- TIZ 3) were prepared by direct compression of different microcapsules of TIZ (1:1(TIZ1), 2:1(TIZ2) and 3:1 (TIZ3) separately. Each microcapsules of varying polymer: drug ratio was made in triplicate.

Each tablet contained microcapsules equivalent to 6mg of TIZ. The microcapsules were blended with dummy microcapsules (final wt. of tablet100mg) of respective ratio, 1% talc and 0.5% magnesium stearate and compressed on a single station hand operated tablet machine (Cadmach, Ahmedabad, India). Three batches of tablets were prepared for each formulation.

Physical characterization of the microcapsules and its tablets

The prepared microcapsules were studied for appearance and size distribution by using optical microscopy. The drug content of TIZ in each batch of microcapsules was determined by dissolving an accurately weighed quantity of CA microcapsule (equivalent to 6 mg tizanidine) was extracted in 20ml of pH 6.8 alkaline phosphate buffer solution and coating polymeric material is separate out through the 0.45µm Whatman filter paper. The polymer was washed three times (7 ml each time) with pH 6.8 alkaline phosphate buffer and all filtrates were added and assayed spectrophotometrically (UV-1700-Shimadzu Japan) after suitable dilution at 318.5nm. The concentration of drug in filtrate was determined from the calibration curve of tizanidine by using equation (A=0.0545*Conc.+0.111, R^2=0.999) in alkaline phosphate buffer pH 6.8 and encapsulation efficiency for microcapsules was calculated. Each determination was made in triplicate.

Drug content was determined in each batch of tablets. For each batch, 20 tablets were weighed and finely ground. Aliquot amount of this powder (equivalent 6 mg of TIZ) was accurately weighed, suitably dissolved in methanol and filtered through the 0.45µm (Whatman) filter paper. The filtrate was assayed spectrophotometrically similar to microcapsules. Each determination was made in triplicate.

Other physical parameters of the tablets, like weight variation, hardness, friability and thickness, were determined as per official procedures.

Release rate studies

The USP method II or paddle dissolution test was used with a pH 6.8 alkaline phosphate buffer as the release medium The stirring speed was 100 rpm and the temperature of the release medium was kept at 37±0.5°C. An equivalent amount of microcapsules containing 6mg of TIZ or microcapsule-based tablets containing 6 mg of TIZ were placed in the dissolution basket. Then, samples (5ml) were withdrawn at programmed intervals and replaced by fresh buffer preheated at 37±0.5°C). The samples were filtered through Whatman filter (0.45µm) and assayed spectrophotometrically at 318.5 nm after suitable dilution. The amount of TIZ was calculated from the calibration curve. Cumulative percentage of drug released was calculated and the mean of six tablets from three different batches was used in data analysis.

RESULTS AND DISCUSSION

Supplied TIZ passed the tests of identification and analysis as per supplier's specification. The formulation additives, in the concentrations used, did not affect the stability and UV absorbancy and IR spectra profile of TIZ.

The microcapsules were white, free flowing and spherical in shape observed under the projection microscope (Quasmo, India). The mean particle size varied between 175.92±9.82 to 194.94±14.28 µm for different formulations of TIZ-EC microcapsules (table 1). The entrapment efficiency of the microcapsule was variable in different ratio of drug and polymer. Data of average diameter and entrapment efficiency of CA microcapsules were compared statistically using unpaired t-test and one-way analysis of variance (ANOVA) at a significant level $P \leq 0.05$.

Physical appearance, hardness, friability, weight variation and drug content uniformity of different tablet formulations were found to be satisfactory under pharmacopoeial standards of tablet evaluation (table 2). Tablet hardness varied between 5.0±0.9 to 5.5±0.8 kg/cm^2 and friability was less than 0.5%(w/w). The manufactured tablets showed low weight variation and a high degree of drug content uniformity. This could be attributed to uniform coating or the spherical nature of the microcapsules, leading to good flow and uniform mixing.

Table 1: Physical characteristics of the microcapsules

S. No.	Characteristics	Formulations		
		TIZ1	TIZ2	TIZ3
1.	Components	TIZ: CA (1:1)	TIZ: CA (1:2)	TIZ: CA (1:3)
2.	Particle size[a] (Mean diameter in μm)	175.92±9.82	188.69±13.78	194.94±14.28
3.	Entrapment efficiency[b] (%)	66.58±2.8	83.32±5.7	77.84±4.7

[a] Average of hundred microcapsules ± SD - [b] Average of three batches± SD

Table 2: Physical properties of tablets of TIZ microcapsules

S. No.	Characteristics	Formulations		
		T-TIZ1	T-TIZ2	T-TIZ3
1.	Drug content (mg/tab)[a]	5.9±0.23	5.92±0.3	6.2±0.4
2.	Weight variation (%)[b]	±3.1	±2.4	±2.7
3.	Hardness (Kg/cm^2)[c]	5.0±0.9	5.5±0.4	5.5±0.8
4.	Friability (%)	<0.5	<0.4	<0.4

[a] Mean of triplicate with SD, [b] ± max % variation from the mean, [c] Mean of 20 tablets with SD

Table 3: *In- vitro* release parameters of TIZ released from microcapsules and tablets

S. No.	Formulations[a]	Time for 25% release ($t_{25\%}$), hours	Time for 50% release ($t_{50\%}$), hours	Time for 60% release ($t_{60\%}$), hours	Time for 90% release ($t_{90\%}$), hours
1.	TIZ1	0.747±0.4	1.81±0.5	2.39±0.6	6.02±0.3
2.	TIZ2	1.061±0.2	2.57±0.6	3.39±0.6	8.56±0.9
3.	TIZ3	1.42±0.7	3.44±0.6	4.55±0.8	11.81±0.3
4.	T-TIZ1	1.69±0.8	4.25±0.9	5.28±1.5	8.35±1.2
5.	T-TIZ2	1.71±0.7	5.40±1.4	6.86±0.6	11.22±0.7
6.	T-TIZ3	2.41±0.7	6.58±0.9	8.25±0.6	13.25±0.6
7.	SR tab.6 mg	0.940±0.5	2.26±1.32	3.758±1.20	7.5±1.12

[a] Average of triplicate observations of three batches with standard deviations

Table 4: Release rate parameters of tablets of TIZ microcapsules

S. No.	Parameters	Formulations			
		SR.Tab.6mg	T-TIZ1	T-TIZ2	T-TIZ3
1.	K[a]	10.643	9.7636	6.8776	5.995
2.	($t_{60\%}$)[b]	3.758±1.20	5.280±1.5	6.86±0.6	8.25±0.6
3.	r[c]	0.9705	0.9376	0.8802	0.8884
4.	Release Mechanism	-	Anomalous transport	Case-II transport	Case-II transport

[a] Release rate constant, [b] Time for 60%of the drug release in hours, [c] Correlation coefficients

Release rate studies

In-vitro release study of the CA microcapsules (fig. 1) showed that the time for 90% (*t*90) TIZ release was extended to 6.02±0.3, 8.56±0.5 and 11.81±0.3 h for TIZ1, TIZ2 and TIZ3 respectively (table 3). The results indicate that increasing the proportion of CA decreased the release rate (figure 2), which may be attributed to the slower rate of diffusion of dissolution medium into the microcapsules due to increased thickness of the coat. The extent of surface pores decreased with decreasing core: coat ratio. The CA-based microcapsules did not fragment but enlarged in size, leading to increases in size of the pores as well tabletting the microcapsules resulted in prolonged release (table 3). As the intention was to make non-disintegrating tablets, the

hardness in all the designed formulation was kept above 5.0 kg/cm^2 to prevent disintegration during the drug release study. The t90% release was extended from 8.35 to 11.22 h by increasing the core: coat ratio from 1:1 to 1:2. Further increase in the ratio to 1:3 (T-TIZ3) significantly controlled the release, up to 13.25h. The predicated duration of TIZ release from this formulation was beyond 16 h. The plot between cumulative percentage of TIZ released and time gave a linear relationship (fig. 3), suggesting zero-order release kinetics of TIZ from the CA microcapsule-based tablets. The most probable mechanism of TIZ release from the CA matrix appeared to be by diffusion of TIZ from the insoluble porous matrices into the dissolution medium due to swelling of the CA matrix. Throughout the duration of release, very marginal erosion of the matrix base was observed.

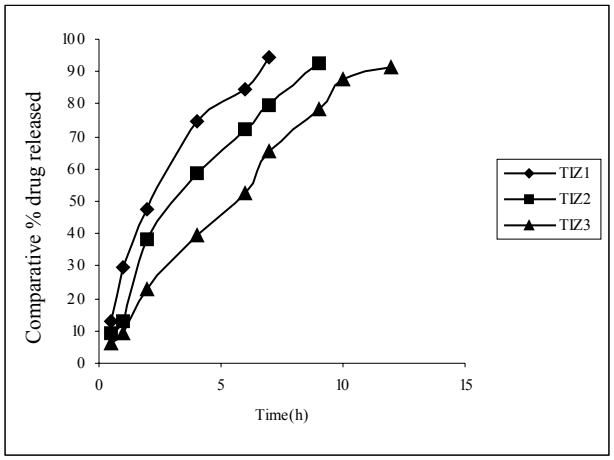

Fig. 1: Release profile of tizanidine microcapsules.

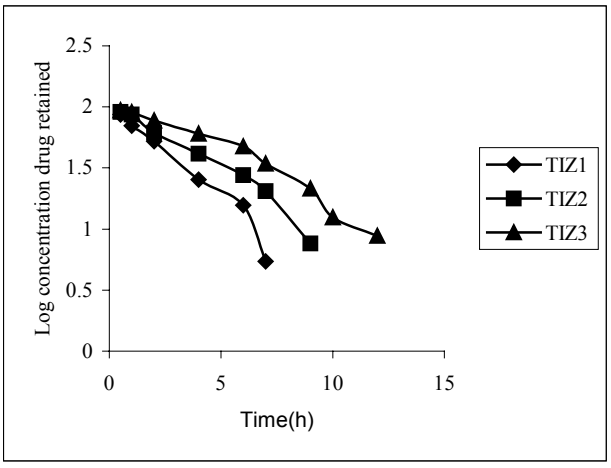

Fig. 2: Plots of Log concentration of tizanidine retained versus time from microcapsules.

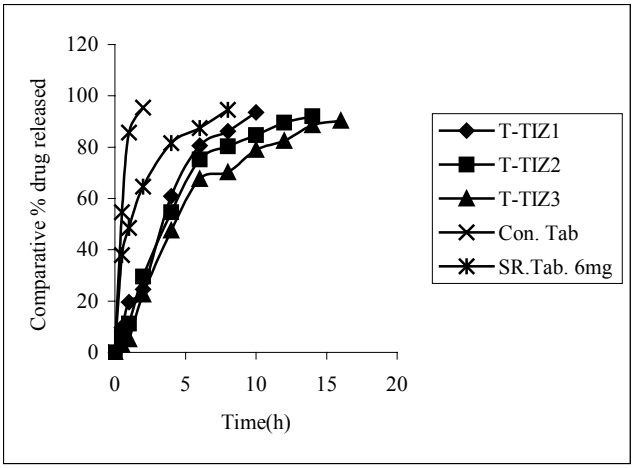

Fig. 3: Release profile of tizanidine, conventional and SR marketed tablets.

The release mechanism and the release rate constants (%h^{-1}) for TIZ release from tablet formulations were further elucidated by the power equation (Ritger and Peppas, 1987). This was done by fitting the dissolution data after 1 h to those values less than or equal to 90% release in the following equation:

$$Mt/ M\infty = K\ t^n$$

Where Mt/M∞ is fraction of drug released at any time *t*, *K* is the release rate constant incorporating the structural and geometric characteristics of the tablets, and *n* is the diffusional exponent, indicative of the release mechanism. The values of *K*, *n*, *t*60 (time required for 60% of drug release) and *r* (correlation coefficient), as obtained from the dissolution data for different formulations, are given in table 4.

For these tablets, the values of *n* ranged from 0.874 to 0.913, indicating a release mechanism anamolous to case-II transport with an increase in *n*-value as the core: coat ratio decreases. The release rate of TIZ from T-TIZ3 was slowest (K = 5.995% h$^{-0.913}$; *t*60 = 15.24 h) and fastest from T-TIZ1 (K = 9.7636% h$^{-0.874}$; *t*60 =5.28 h). The release kinetics of T-TIZ formulation was compared with marketed SR tablet and conventional tablet, and found that T-TIZ formulation have slow release than marketed SR tablet (K_1= 10.643% h$^{-0.9705}$) as required for tizanidine SR formulation while conventional tablet releases

CONCLUSION

Tizanidine release matrices were prepared successfully utilizing cellulose acetate as a retardant material. From the technological point of view, microencapsulation and then direct compression method enables the preparation of these

matrices. The physical properties described in table 2 for matrix tablets were found to be optimal for the manufacturing process. The release rate of tizanidine from microcapsules and their matrices were largely depends on the polymer concentration. As concentration of drug: polymer increases from 1:1 to 1:3, the release rate of TIZ was found to be decreased and release mechanism was shifted from anamolous to case-II transport with an increase in n- value. The study established that tablets made of CA microcapsules could be a good approach for controlled release zero order oral formulation of tizanidine.

ACKNOWLEDGEMENT

The authors gratefully acknowledge Ranbaxy Lab. Ltd., Dewas (M.P) and Zeim Lab, Nagpur (M.H) for the supply of tizanidine and cellulose acetate.

The authors wish to thank Head, Department of Geology, M.L. Sukhadia University, Udaipur (Raj.) for providing SEM facility.

The authors also wish to thank Head, National Medical Library, New Delhi for providing library facility for literature survey.

REFERENCES

Abd EI, Hameed MD and Kellaway IW (1997). Preparation and *in-vitro* characterization of mucoadhesive polymeric microspheres as intra-nasal delivery systems. *Eur. J. Pharm. Biopharm*., **44**: 53-60.

Chowdhary KPR and Ramesh KVRNS (1995). Microencapsulation of Solid Dispersions of Nifedipine-Novel approach for controlling drug Release. *Indian Drug*, **32**(10): 477.

Dubin A, Gombas G and Smith HA (1999). 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 October. Fort Lauderdale.

Freitag FG, Diamond S and Diamond M (2000). Tizanidine HCl in the preventive treatment of chronic tension-type headache. Worldwide Pain Conference July, San Francisco.

Hewitt D and McKenzie E (1999). The tolerability and efficacy of Zanaflex (tizanidine) for chronic pain. 18th Annual Scientific Meeting of the American Pain Society October. Fort Lauderdale.

Hutchinson DR (1990). Modified release tizanidine: a review. *J. Int. Med. Res.,* **18**(1):

Krusz JC (1999). Tizanidine: an effective novel agent for treatment of chronic headaches. 18th Annual Scientific Meeting of the American Pain Society October, Fort Lauderdale.

Millette TJ, Laseter JT and Bosarge R (1999). 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 October. Fort Lauderdale

Ritger PL and Peppas NA (1987). A simple equation for the description of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *Journal of Controlled Release,* **5**: 23-26.

Sajeev C, Vinay G, Archna R and Saha RN (2002). Oral controlled release formulation of diclofenac sodium by microencapsulation with ethyl cellulose. *J. Micro-encapsul.,* **19**(6): 753-60.

Saraf S, Dashora K and Saraf S (2006). Effect of Processing Variables on Micro Particulate System of Aceclofenac. *Pak. J. Pharm, Sci.*, **19**(2): 6-10.

Saravanan M, Bhaskar G, Srinivasa Rao and Dhanaraj U (2003). Ibuprofen-loaded ethyl cellulose/polystyrene microspheres: an approach to get prolonged drug release with reduced burst effect and low ethylcellulose content. *J. Microencapsulation*, **20**(3): 289-302.

Semenchuk M and Sherman S (1999). Efficacy of Zanaflex (tizanidine hydrochloride) in neuropathic pain: an open label study. 18th Annual Scientific Meeting of the American Pain Society October, Fort Lauderdale.

Smith TR (2000). Low-dose tizanidine combined with long-acting NSAIDs for analgesic rebound headache: a retrospective review. Worldwide Pain Conference July, San Francisco.

Wagstaff AJ and Bryson HM (1997). Tizanidine A. review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. *Drugs*, **53**(3): 435-452.

Received: 29-03-2006 – Accepted 09-06-2006