Formulation and evaluation of sustained release matrix tablet of Tizanidine Hydrochloride by direct compression technique

Dr. Rakesh P. Patel*, Mehul H. Patel*, Bhupendra G Prajapati*, Ashok H. Baria[1]

* Department of Pharmaceutics, S. K. Patel College of Pharmaceutical Education and Research, Ganpat University, Ganpat vidyanagar, Kherva, Gujarat, India.
[1]Department of Pharmaceutics, S. J. Thakkar Pharmacy College, Gujarat Technology University, Kalawad Road, Rajkot-360005, Gujarat, India.

* For Correspondence: **Dr. Rakesh P. Patel,** Associate Professor, Head of Pharmaceutics & Pharm. Technology Department, S. K. Patel College of Pharmaceutical Education and Research, Ganpat University, Ganpat Vidyanagar, Kherva, Mehsana-Gozaria Highway, PIN-382711, City: Mehsana, State: Gujarat, India. E-mail: raka_77us@yahoo.com

ABSTRACT

Purpose: The objective of this study was to formulate and evaluate of sustained release matrix tablet of Tizanidine Hydrochloride by direct compression technique. Tizanidine hydrochloride tablets were prepared by melt direct compression technique using xanthum gum, guar gum, Glyceryl behenate, Glyceryl monostearate and Stearic acid in different proportion. Formulated sustain release tablets were evaluated for appearance, dimensions (diameter and thickness), weight variation, hardness, friability, drug content and *in-vitro* release of Tizanidine hydrochloride. Optimized batch was compared with marketed preparation. The result indicated the formulation containing Glyceryl behenate (30%) showed the release profile similar to marketed preparation with satisfactory physical properties of tablet. It is feasible to formulate sustained release tablet of Tizanidine hydrochloride with acceptable physical properties which could be amenable to replication on an industrial scale.

Keywords: Tizanidine hydrochloride, sustained release matrix tablet.

INTRODUCTION

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. Tizanidine hydrochloride (TIZH) is available in conventional dosage form. The bioavailability of the drug from a conventional dosage form is 40% due to the limitation of GI tract i.e. absorption is limited up to upper part of the GI tract. 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 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 1 to 4.3 hours i.e., it requires three-times a day dosing. The aim and objective of our current research is to formulation of sustained release matrix tablets to increase the bioavailability of drug.

MATERIALS AND METHODS

Tizanidine hydrochloride was supplied as a gift sample from Endoc Pharma, Rajkot, Gujarat, Glyceryl Behenate, Glyceryl monostearate was brought from Alembic Pharma, Baroda. Stearic Acid, Lactose, Magnesium Sterate from Wellable Pharma, Mehsana, Microcrystalline Cellulose, Talc from S.D.fine chem. Mumbai and Hydrochloric acid from Qualigen Chemicals, India and all other ingredients used were of AR Grade.

FABRICATION OF SUSTAINED RELEASE MATRIX TABLET

The melt granulation direct compression technique was followed to manufacture the TIZH tablets for all batches (Table 1) containing TIZH was added polymer on water bath was melted and then the drug which is passed from # 60 sieves was added. After cooling the material was passed from #16 sieves. Magnesium stearate and Talc were passed through # 60 sieves. Weighed amounts of melt granules as well as all other ingredients were transferred into polythene bag and blended for 10 minutes. The blend was compressed on 12-station rotary press using Round shaped punches. Punches measuring 9/32 inch were used for compression of the tablets.

EVALUATION OF TIZH SR TABLET

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, dimensions (diameter and thickness), weight variation, hardness, friability and drug content.

Appearance

The tablet should be free from cracks, depressions, pinholes etc. The color and the polish of the tablet should be uniform on whole surface. The surface of the tablets should be smooth.

Dimensions

The dimensions of the tablets are thickness and diameter. The tablets should have uniform thickness and diameter. Thickness and diameter of a tablet were measured using vernier calipers. These values were checked and used to adjust the initial stages of compression.

Uniformity of weight (Weight variation test)

This is an important in-process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (± 7.5%). The percent deviation was calculated using the following formula.

$$\%Deviation = \frac{IndividualWeight - AverageWeight}{AverageWeight} \times 100 \qquad (1)$$

Hardness test:
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.

Friability test:
Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula.

$$\%Friability = \frac{(W1 - W2)}{W1} \times 100 \qquad (2)$$

Where, W_1 = weight of the tablets before test
W_2 = weight of the tablets after test

Content uniformity
Twenty 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 minutes 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} 320 nm against blank as reference.

***In vitro* drug release study**
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 (with out enzyme), was placed into the dissolution flask maintaining the temperature of 37 $\pm$ 0.5 ^{0}C and rpm of 100. One TIZH SR tablet was placed in each basket of the dissolution apparatus. The apparatus was allowed to run for 24 hours. Samples measuring 10 ml were withdrawn after every 1, 2, 4, 6, 8, 10, 12, 14, 18, and 20 hours using auto sampler. First 2 hrs in 0.1 N HCl and then in Phosphate buffer 6.8. During sampling, samples were filtered through 10 µm filter which was in inline with auto sampler. The fresh dissolution medium (37^{o}C) was replaced every time with the same quantity of the sample. Collected samples were analyzed at 320 nm using 0.1 N HCl and 6.8 Phosphate buffer as blank. The cumulative percentage drug release was calculated.

Comparison of dissolution Profiles
Comparison of therapeutic performances of two products containing the same active substance is a critical means of assessing the possibility of alternative using between the innovator and any essentially similar product. The dissolution profile comparison may be carried out using model independent or model dependent method. A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles.

$$f_2 = 50X\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} X100\right\} \quad (3)$$

Where, R_t and T_t represent the average percent dissolved at time t for reference and test, respectively, and n is the number of time points tested. Dissolution profile was considered satisfactory if f_1 values lies below 15 (nearing zero) and f_2 value lies more than 50 (nearing 100).

RESULTS AND DISCUSSION

a) Compatibility Studies using Differential Scanning Calorimetry (DSC)

DSC curves obtained for pure TIZH and excipients are shown in Figure 1. Pure powdered TIZH showed a melting endotherm at 293.30 °C, Glyceryl Behenate showed melting endotherm at 73.02°C and the physical mixture showed melting endotherm at 73.64°C, 293.09°C. Physical mixture of all above ingredients showed their identical peaks at defined temperature range. Presence of all peaks indicates that all ingredients are compatible with drug means there is no incompatibility between the selected ingredients.

b) Formulation Development

i) Evaluation of marketed product

Marketed product was subjected to evaluation to know diameter, thickness, weight and dissolution. The values of these properties were shown in the Table 2. The dissolution profile of marketed tablet is shown in Table 3. Attempts were made to develop formulations using direct compression technique but having same dissolution profile as explained in the later sections.

ii) Manufacturing of Tizanidine hydrochloride

After getting all satisfactory physical properties of the blend, tablets were prepared. Physical as well as drug release pattern was studied for each batch. Parameters of evaluation of the batch of tablets are shown in Table 4.

The *in- vitro* release of different batches of TIZH is presented in Figure 2. Batch B1 shown drug release up to 6 hrs, due to insufficient concentration of Stearic Acid. There for in batch B2 the concentration of Stearic Acid was increased. But, batch B2 also shown drug release up to 8 hrs only. So, it concluded that still concentration of Stearic Acid is insufficient to get desire drug release. Therefore, in batch B3 much higher concentration of Stearic Acid was used and it shown drug release up to 10 hrs. Based on above experience it concluded that Stearic Acid is not suitable to get desired drug release as compared to marketed formula. That's why in further batches of polymers were tried.

Batch B4 shown drug release up to 8 hrs, due to insufficient concentration of Glyceryl Monostearate. There for in batch B5 the concentration of Glyceryl Monostearate was increased but batch B6 also shown drug release up to 10 hrs only. So, it concluded that still concentration of Glyceryl Monostearate is insufficient to get desire drug release. Therefore, in batch B6 much higher concentration of Glyceryl Monostearate was used and it shown drug release up to 12 hrs. Based on above experience it concluded that Glyceryl Monostearate is not suitable to get desired drug

release as compared to marketed formula. That's why in further batches polymer was tried.

Batch B7 shown drug release up to 8 hrs, due to insufficient concentration of Glyceryl Behenate. There for in batch 8 the concentration of Glyceryl Behenate was increased but batch B8 also shown drug release up to 10 hrs only. So, it concluded that still concentration of Glyceryl Behenate is insufficient to get desire drug release. Therefore, in batch B9 much higher concentration of Glyceryl Behenate was used and it shown drug release up to 14 hrs as compared to marketed formula. It also shown good similarity factor (82.77) when it was compared to marketed formulation drug release. But, the initial burst release was found to be slightly more than marketed formula.

Batch B10 shown drug release up to 20 hrs. Due to presence of guar gum and Xanthan gum .As in case batch B11 the combination of Xanthan gum was tried and shown drug release up to 16 hrs. Our intension is to sustain the drug release up to 14 hrs only. Therefore in batch B12 guar gum was used instead of Xanthan gum. But in this formulation also drug released was found up to 20 hrs.

So, among all 12 batches only batch B9 showed satisfactory results according to in vitro drug released when it was comparing with marketed product drug released. Therefore, batch B9 was optimized and further studies were carried out on this batch only.

iii) Reproducibility of release profiles

Batch to batch uniformity is very much essential for obtaining reproducible results. In order to verify this fact, the manufacturing procedure was confirmed by preparing one more batch of the final optimized formulation of SR tablets prepared with Glyceryl Behenate (Batch B9). The batch size was 500 tablets. Release studies were conducted as specified for *in vitro* study and similar release profiles were obtained as shown in Figure 3 for tablets of batch B9.

The f_1 and f_2 values from model independent pair wise approach were found similar in the batches of tablets. The release pattern of the graphs demonstrated that the present manufacturing procedure offers reproducible results (f_2 values 91.56 & f_1 values 1.65).

c) Comparison of TIZH release using kinetic study

The release profiles of TIZH from tablets batch B9 were processed for comparison of different orders of drug release and to understand the linear relationship, i.e., kinetic principles. The data were processed for regression analysis using MS-Excel statistical functions *In vitro* release data of time points between 1 to 14 hours were considered and treated for following kinetic principles.

As shown in Table 5, the formulation did not follow a first-order release pattern. When data was plotted according to the zero-order equation as shown in Table the formulation showed a fair linearity, with regression value of 0.907. When data was plotted according to the Higuchi's Plot as shown in Table 5, the formulation showed a fair linearity, with regression value of 0.9769.

In order to explore more precise mechanism of release of TIZH from in house developed SR tablets, the dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation) as shown in Table 5, which is often used to describe the drug release behavior from polymeric systems. When plotted according to Korsmeyers et al equation, the formulation showed $r^2 = 0.972$ and slope (n) value of 0.605. A value of $n = 0.5$ indicates case I (Fickian) diffusion or square

root of time kinetics, 0.5 <*n* <1 anomalous (non-Fickian) diffusion, *n* = 1 Case-II transport and *n* > 1 Super Case-II transport. This *n* value is 0.605 that is between 0.5 <*n* <1, hence, appears to indicate anomalous (non-Fickian) diffusion mechanism. The relative complexity of this formulation and its components may indicate that the drug release is controlled by diffusion process.

Hence, diffusion may be the mechanism for the drug release from tablets of batch B9.

CONCLUSION

On the basis of present study it was concluded that sustained release tablets of Tizanidine prolong the time for absorption as well as bioavailability and thus better patient compliance can be achieved and the sustained release formulations of TIZH developed in this investigation was found to be equivalent to commercial market product, based on *in vitro* release studies Thus the objectives envisaged in this thesis were achieved.

ACKNOWLEDGMENT

The authors wish to thank: Endoc Pharma, Rajkot, Gujarat for sparing gift sample of Tizanidine hydrochloride for research work.

REFERENCES

1. Subramanyam CVS, Thimmasetty J. Laboratory manual of physical pharmaceutics. Delhi; Vallabh Prakashan: Delhi; 2005.
2. Subrahmanyam CVS. Textbook of physical pharmaceutics. Vallabh Prakashan: Delhi; 2005.
3. Subrahmanyam CVS, Thimmasetty J, Shivanand KM, Vijayendra Swamy SM. Laboratory manual of industrial pharmacy. Delhi: Vallabh Prakashan; 2006
4. Chien, Yie W. (1992) Text Book of Novel drug delivery system. 2nd Edn. *Marcel Dekker Inc. New York.* 2.
5. Gennaro AR, (Ed.) Remington's., (2000). Pharmaceutical science. 20th Edn. *Lippincott Williams and Wilkini Publishing Co., New York*, I, 905-906.
6. Gennaro AR. (Ed.) Remington. The Science and Practice of Pharmacy. 19th Edn. 1995: Vol.-II, 1661-1662.
7. Herbert A, Lieberman and Leon Lachmman. (1982). Pharmaceutical dosage forms tablets. *Marcel Dekker Inc. New York*, III, 9-10.
8. Lachmman L, Liberman HA, Konig JL. (1991) The theory and practice of Industrial Pharmacy. 3rd Edn. *Vargheese Publishing House, Bombay*, 430.
9. Lachmman L, Liberman HA, Konig JL. (1991) The theory and practice of Industrial Pharmacy. 3rd Edn., *Vargheese Publishing House, Bombay*, 453.
10. Lisbeth Illem and Stanley S, Devis., (1987). Polymers in controlled drug delivery. 1st Edn. *Wright Publishing Co., Bristol*,3.
11. Michael E, Aulton. (1990) Pharmaceutics the science of dosage form design. 1st Edn. *ELBS Hongkong*, 316.
12. Raymond CR, Paul JS, Paul JW: Handbook of Pharmaceutical Excipients. 4th edn; New York. 2003; 72-3.

13. Robinson JR, Lee HL (Ed). (1987). Controlled drug delivery fundamentals and applications. 2nd Edn., *Marcel Dekker Inc. New York*; 395-403.
14. Robinson JR, Lee HL (Ed). (1987). Controlled Drug Delivery Fundamentals and Applications. 2nd Edn, *Marcel Dekker Inc. New York*, 374-375.
15. Williams DA., Temke TL, (2002) Foyes Principals of medicinal chemistry International student edition, 489-93.

List of Tables:

Table 1: Formulations of TIZH Tablets

Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12
TIZH*	6.87	6.87	6.87	6.87	6.87	6.87	6.87	6.87	6.87	6.87	6.87	6.87
Glyceryl -Behenate	-	-	-	-	-	-	14	28	42	28	28	28
Xanthan Gum	-	-	-	-	-	-	-	-	-	7	14	-
Guar gum	-	-	-	-	-	-	-	-	-	7	-	14
Glyceryl-monostearate	-	-	-	14	28	42	-	-	-	-	-	-
Stearic acid	14	28	42	-	-	-	-	-	-	-	-	-
MCC	40	40	40	40	40	40	40	40	40	40	40	40
Lactose	74.93	60.93	46.93	74.93	60.93	46.93	74.93	60.93	46.93	57.53	57.53	57.53
Talc	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8
Magnesium stearate	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Total weight	140	140	140	140	140	140	140	140	140	140	140	140

TIZH*= TIZH equivalent to Tizanidine 6mg
All ingredients were in milligram

Table 2: Evaluation of the marketed tablets of TIZH 6 mg

Brand Name	Shape	Diameter(mm)	Thickness(mm)	Weight of Tablet(mg)
Tizan-SR	Round	7	2.6	140

Table 3: Dissolution profile of TIZAN-SR in 0.1N HCl & in Phosphate buffer 6.8

Sampling time (hrs)	Cumulative percent drug release* AM ± SD
0	0
1	17.25±1.05
2	33.44±1.22
4	55.49±1.62
6	69.21±0.78
8	83.87±0.98
10	91.41±2.47
12	97.40±1.5
14	100.61±0.55

*Each value was an average of three determinations

Table 4: Physical Properties of TIZH Tablet

Code	Hardness (kg/cm^2)	Diameter	Friability	Thickness	Uniformity of weight (mg)	Drug content (%)
B1	5.75±0.29	7.231±0.003	0.548±0.15	2.63±0.036	140.05±0.23	98.08±1.19
B2	5.75±0.47	7.226±0.003	0.549±0.11	2.64±0.026	140.06±0.31	98.98±2.29
B3	5.67±0.35	7.179±0.045	0.40±0.04	2.643±0.02	140.02±0.20	100.44±2.06
B4	5.58±0.29	7.238±0.011	0.38±0.08	2.613±0.028	140.1±0.228	98.88±0.96
B5	5.5±0.23	7.231±0.003	0.355±0.12	2.645±0.021	140.12±0.35	98.44±0.41
B6	5.67±0.20	7.231±0.003	0.309±0.04	2.637±0.04	140.09±0.34	100.44±0.27
B7	5.75±0.24	7.231±0.003	0.356±0.072	2.604±0.029	140.07±0.27	99.88±1.92
B8	6.0±0.235	7.243±0.016	0.378±0.11	2.625±0.02	140.03±0.25	98.98±0.82
B9	6.0±0.235	7.243±0.008	0.357±0.072	2.579±0.016	140.06±0.27	100.44±0.82
B10	6.17±0.35	7.226±0.004	0.473±0.04	2.62±0.033	140.02±0.20	100.34±1.05
B11	6.17±0.35	7.159±0.043	0.428±0.02	2.65±0.021	140.38±0.28	99.56±2.33
B12	5.83±0.27	7.243±0.036	0.569±0.19	2.626±0.031	140.15±0.25	100.44±0.27

Table 5: Comparison of different orders for TIZH release

Formulation	Zero Order	First Order	Higuchi Model	Korsmeyers Equation	
	r^2	r^2	r^2	r^2	slope
B9	0.9072502	0.7725312	0.9769	0.9725	0.605

List of Figures:

Figure 1: Differential Scanning Calorimetry study of pure a) TIZH, b) Glyceryl Behenate and c) physical mixture of TIZH with Glyceryl Behenate.

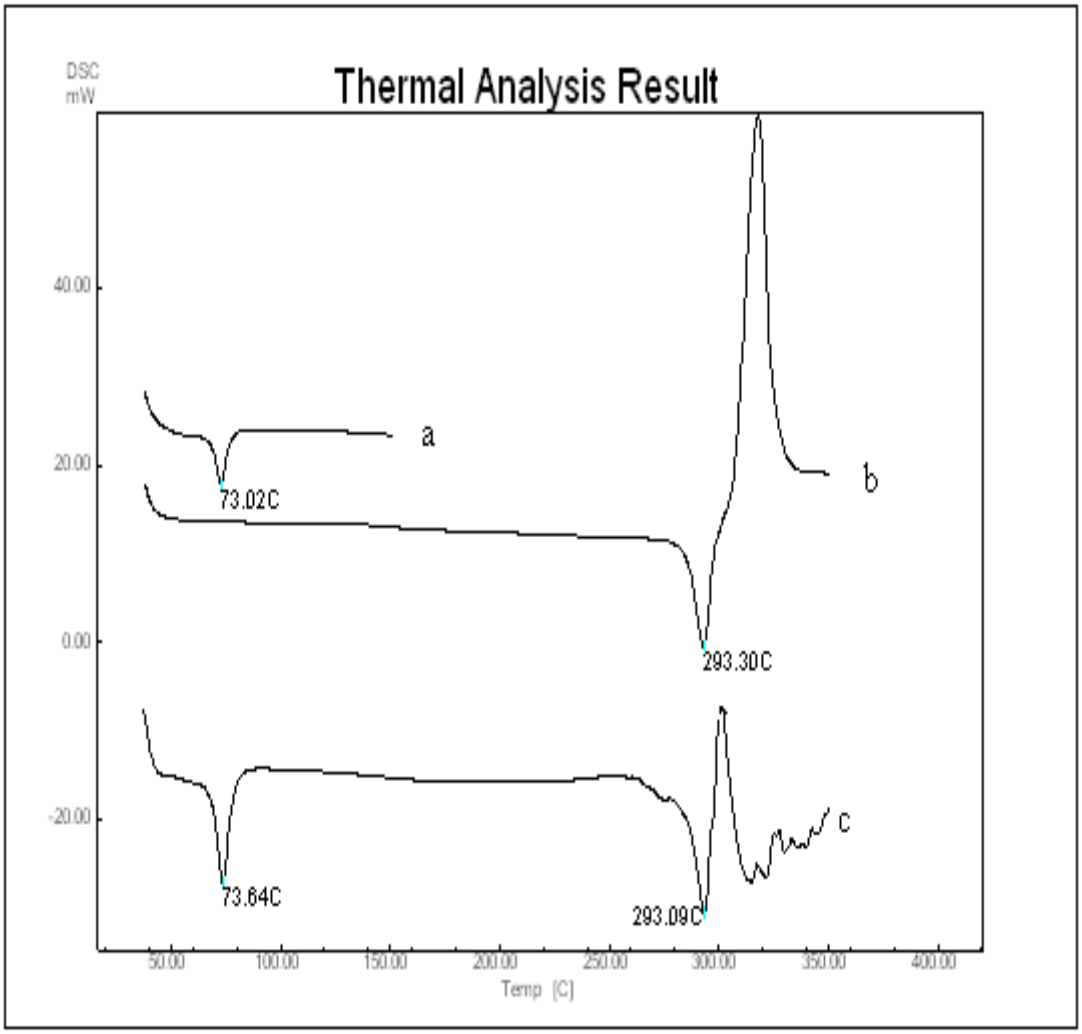

Figure 2: *In- vitro* release of different batches of TIZH

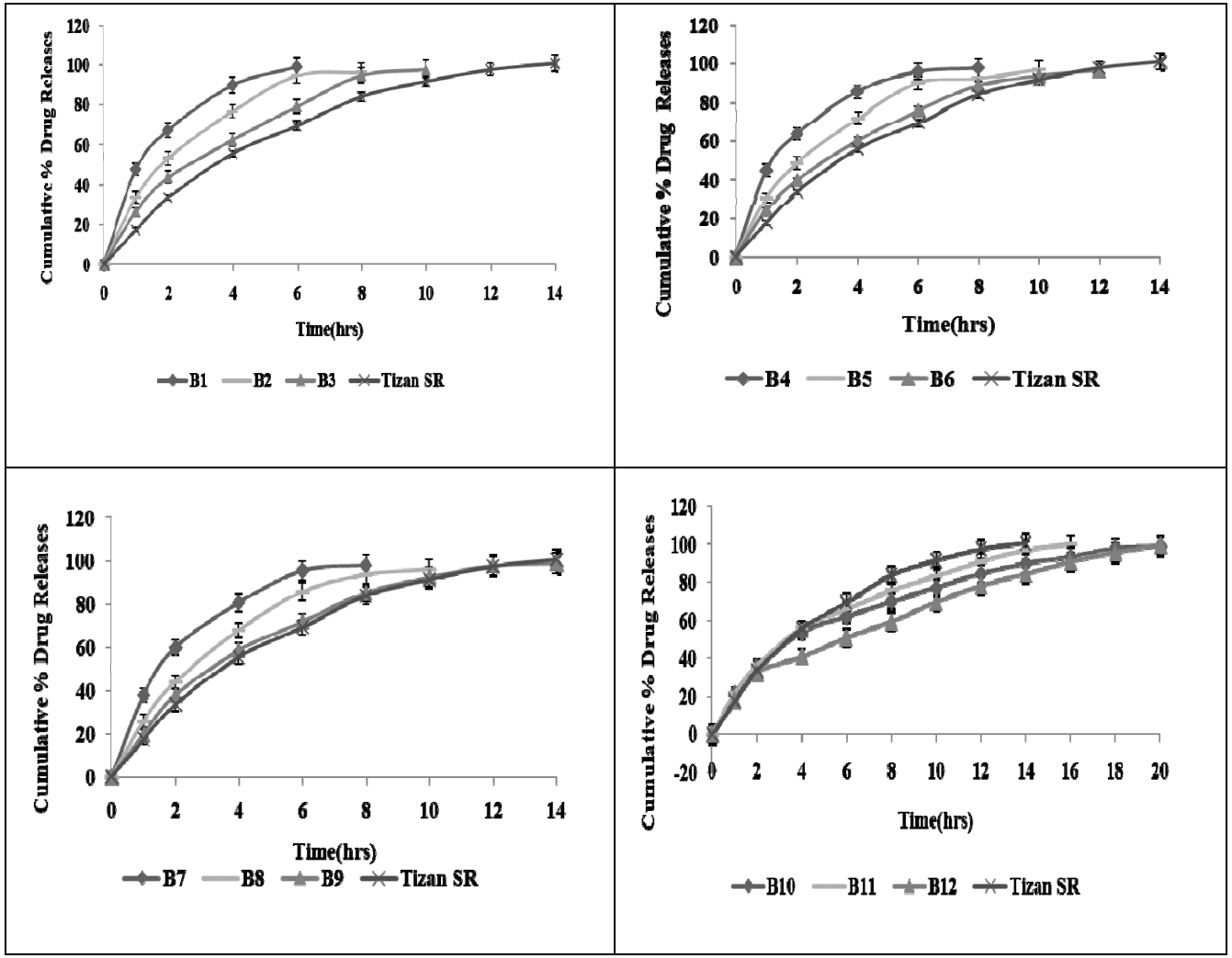

Figure 3 *In vitro* release of TIZH from tablets of batch B9 of first and second (reproducible) batches