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# Mucoadhessive Bilayered Buccal Tablets of Tizanidine Hydrochloride

**K.Shivanand[1]*, S.A.Raju[2], B.Jaykar[3]**

[1]Acharya & B.M.Reddy College of Pharmacy, Bangalore,India

[2]H.K.E'S College of Pharmacy, Gulbarga,India

[3]Vinayaka Mission's College of Pharmacy, Salem,India

*Corres.author: shivanand@acharya.ac.in*

**Abstract:** The aim of this work was the design mucoadhesive bilayered buccal tablets of Tizanidine Hydrochloride (TZD HCl), using mucoadhesive polymers Carbopol 934(CP), HPMC K4M, HPMC K15M and Sodium carboxymethylcellulose along with ethyl cellulose as an impermeable backing layer. Preformulation studies of TZD HCl like compatibility studies with polymers, using FTIR and DSC were carried out. The bilayered buccal tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, mucoadhesive time, swelling index, *in vitro* drug release and *ex vivo* permeation. FTIR and DSC found to be compatible with selected polymers. Bilayered buccal tablets containing CP and HPMC K4M in the ratio 1:1 (BT1) had the maximum percentage of *in vitro* drug release in 6 hours. The swelling index of the tablets increased with increasing amounts of CP. The optimized formulation (BT1) follows non-Fickian release mechanism.

**Key-words:** Tizanidine Hydrochloride (TZD HCl), Bilayered buccal tablets, Carbopol 934(CP), HPMC K4M, HPMC K15M, Sodium carboxymethylcellulose.

## Introduction

The interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs impaired by the narrow absorption window in the gastrointestinal tract. Drug delivery via the buccal route using bioadhesive dosage forms offers such a novel route of drug administration. This route has been used successfully for the systemic delivery of number of drug candidates. Problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover, buccal drug delivery offers a safe and easy method of drug utilization, because drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity. It is an alternative route to administer drugs to patients who are unable to be dosed orally. Therefore, adhesive mucosal dosage forms are suggested for buccal delivery, including adhesive tablets, adhesive gels, and adhesive patches.[1]

During the past decade, bioadhesive polymers have received considerable attention for platforms of buccal controlled delivery because of their ability to localize the dosage form in specific regions to enhance drug bioavailability. Bioadhesive polymers can not only cause the adhesion effects but can also control the release rate of the drug. From a technological point of view, an ideal buccal dosage form must have 3 properties. It must maintain its position in the mouth for a few hours; release the drug in a controlled fashion, and provide the drug release in a unidirectional way toward the mucosa. In regard to the first requirement, strong adhesive contact to the mucosa is established by using mucoadhesive polymers as excipients. If the mucoadhesive excipients are able to control drug release, the second requirement can also be achieved. The third objective can be fulfilled by preparing a system having uniform adhesiveness and impermeable backing layer.[1]

Tizanidine hydrochloride is an imidazoline derivative, which acts as agonist on centrally located α2 receptors and this leads to myotonolytic effects on skeletal muscle. It is structurally and pharmacologically similar to clonidine and other α2-adrenergic agonists. The correct mechanism of TZD HCl in decreasing muscle tone and frequency of spasmis not clearly understood. 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 2h. Bioavailability of TZD HCl is about 34% to 40% and half- life is 2.5h. 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 TZD HCl. In order to overcome such extensive first-pass metabolism, the drug is selected as suitable candidate for bioadhesive buccal drug delivery[2].

**Materials and Methods**

Tizanidine HCL (TZD HCl) was gift sample from Lincoln Pharmaceutical Ahmedabad. HPMC K4M and HPMCK15M were supplied from Colorcon. Sodium CMC and Carbopol 934 obtained from Loba Chemie, Mumbai. Aspartame was obtained from Strides Arco Labs, Bangalore. Lactose, magnesium stereate and ethyl cellulose obtained from Loba Chemie Mumbai.

**Fourier transform infrared (FT-IR) 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 FT-IR spectroscopy[3]. IR spectrum of pure drug and polymers was seen in between 600- 4000 $cm^{-1}$.

**Differential scanning calorimetry (DSC)**

To study the compatibility pure drug, physical mixtures of drug and excipients the DSC studies were carried out. The analysis were performed under nitrogen (nitrogen flow rate 50 ml/min) in order to eliminate oxidative and pyrolytic effects at a standard heating rate of 10 ºC/min over a temperature range of 50 ºC – 400 ºC using a Universal V4 5A TA instruments[4].

**Preparation of bilayered buccal tablets**

Bilayer buccal tablets of TZD HCl were prepared by a direct compression procedure involving 2 steps. Various batches were prepared by varying the ratio of CP, HPMC K4M, HPMC 15M and Sodium CMC. The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug with CP, polymer, lactose and magnesium strearate in a glass mortar for 15 minutes (Table 1). The mixture (121 mg) was then compressed using an 8 mm diameter die in a single-stroke multistation tablet machine (Karnavati mini press, India). The upper punch was raised and the backing layer of EC was placed on the above compact; the 2 layers were then compressed into a mucoadhesive bilayer tablet. Each tablet weighed ~141 mg.

**Weight variation**

Ten bilayer buccal tablets of each formulation were weighed using an electronic balance and average weight of ten tablets and standard deviation were calculated.

**Thickness**

Thickness of each formulation was measured using vernier calipers. Ten bilayer buccal tablets from each batch were used and average values were calculated.

**Content uniformity**

Ten bilayer 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[3].

**Surface pH**

The surface pH of the bilayer buccal tablets was determined in order to predict the possible irritant effects of the formulation on the buccal mucosa. The bilayer buccal tablets were allowed swell at 37 ± 1°C for 2 h in 40 ml phosphate buffer (pH 6.8). The surface pH of swollen Bilayer buccal tablets was measured using pH paper[4].

**Swelling study**

Three bilayer 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°C ± 1°C. 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) were calculated using the formula given in equation[5].

Swelling Index = [(W2-W1) W1] × 100……1

***Ex Vivo* bioadhesive 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°C. 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°C) so that it just touched the mucosal surface. The bilayer 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 g weight on the right-hand pan. A weight of 5 g 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[6].

***Ex Vivo* Mucoadhesion Time**

The *ex vivo* mucoadhesion time was performed after application of the buccal tablet on freshly cut sheep buccal mucosa. The fresh sheep buccal mucosa was tied on the glass slide and a bilayer buccal tablet core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 sec. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8 and was kept at 37 ± 1°C. After 2 min, a 50 rpm stirring rate was applied to simulate the buccal cavity environment and tablet adhesion was monitored for 12 h. The time for the tablet to detach from the sheep buccal mucosa was recorded as the mucoadhesion time[6].

***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°C, with a rotation speed of 50 rpm. The backing layer of bilayer 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[7].

**Kinetic analysis of TZD HCl *in vitro* release data**

Release data were fitted to various mathematical models for describing the release mechanism from bilayered buccal tablets; Korsmeyer-Peppa (Eq 1)[8], zero order (Eq 2)[9] and Higuchi release models (Eq 3)[10].

$M_t/ M\infty = k_{KP}t^n$ ……..2

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

$M_t = M_0 + k_0t$ …….3

$M_t$ 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.

$M_t = k_Ht^{1/2}$……4

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

***In Vitro* Diffusion Studies**

The *in vitro* buccal drug permeation study of TZD HCl through the sheep buccal mucosa was performed using type glass diffusion cell at 37°C ± 0.2°C. Fresh sheep buccal mucosa was mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and the compartments clamped together. The donor compartment was filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment (55 ml capacity) was filled with phosphate buffer pH 7.4 and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. One ml sample was withdrawn at predetermined time intervals and analyzed for drug content using an UV spectrophotometer at 320 nm[1].

## Results and Discussion

The main aim of this work was to prepare bilayered buccal tablets of TZD HCl to release the drug at mucosal site in unidirectional pattern for extended period of time without wash out drug by saliva. Carbopol 934, HPMC K4M, HPMC K15M and Sodium CMC were selected as buccoadhessive polymers on the basis of their matrix forming properties and mucoadhesiveness while ethyl cellulose, being hydrophobic, as backing material. Ethyl cellulose has recently been reported to be an excellent backing material, given its low water permeability and moderate flexibility.

**Drug polymer compatibility studies using FTIR**

All the characteristic IR peaks related to pure drug, TZD HCl were also appear in the IR spectrum of mixture of Drug-Polymer, so there was no any chemical incompatibility between drug, polymer and excipients (Fig 1).

**Drug polymer compatibility studies using DSC**

In order to investigate the possible physical interaction between drug and excipients, DSC studies were carried out. The drug exhibited a sharp melting endotherm at 289.9°C which is the melting point of the drug. Similarly the thermograms of the physical mixture of TZD HCl with polymers under study exhibited endothermic peak in the vicinity of its melting point range indicating absence of any drug polymer interactions (Fig 2).

**Preparation of bilayered buccal tablets of TZD HCl**

Bilayered buccal tablets of TZD HCl were formulated using direct compression technique, which involved compressing the tablets in two layers. The backing layer was composed of ethyl cellulose to achieve unidirectional drug release and the bioadhesive sustained release layer consisted of mucoadhesive polymers mixed with TZD HCl. The formulations with various polymers alone and in different combinations were prepared. The various combinations used were Carbopol 934 with HPMC K4M, Carbopol 934 with HPMC K15M, sodium CMC with HPMC K4M, and sodium CMC with HPMC K15M (Table 1).

**Weight variation and thickness**

The maximum average weight of the tablets was found to be 137 ± 1.18 mg. As none of the formulation shows a deviation (I.P. limit, ± 7.5%) for any of the tablets tested, the prepared formulations comply with the weight variation test (Table 2).

The average thickness from all the formulations was found to be 3.01 mm. Thickness of the tablet will affect side flow of the drug from the formulation, so it should be as small as possible (Table 2).

**Hardness and Friability**

Hardness bilayered buccal tablets ranged from 5.4 to 5.2 kg/ $cm^2$ (Table 2). Friability of bilayered buccal tablets was found to be within the limits of conventional oral tablets stated in the Indian Pharmacopoeia (1996).

**Surface pH**

The surface pH of bilayered buccal tablets was found to be in between 6 to 7, which was within 7±1.5 units of the neutral pH, and hence these buccal tablets should not cause any irritation in the buccal cavity (Table 2).

**Swelling Studies**

The bioadhesion and drug release profile are dependent upon swelling behavior of the buccal tablets. Swelling index was calculated with respect to time. Swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration. The swelling indices of the tablets with Carbopol 934 increased with increasing amounts of Carbopol 934. Maximum swelling was seen with the formulation containing sodium CMC and CP, the values increased with increasing amounts of sodium CMC and Carbopol 934.

***Ex Vivo* bioadhesive strength**

The bioadhesive strength of the tablets was found to be a function of nature and concentration of polymer.

The tablets with the HPMC K4M and CP have bioadhesive strength in between the 12.3 g to 20.5 g. The tablets with the HPMC K15M and CP have bioadhesive strength 11.2 g to 19.6 g. The tablets with the Sodium CMC and CP have bioadhesive strength in between the 13.5 g to 22.5 g.

The bioadhesive strength exhibited by the HPMC K4M and Na CMC tablets can be considered satisfactory for maintaining them in the oral cavity (Table 2).

**Mucoadhesion Time**

The mucoadhesive time on sheep buccal mucosa ranged from 6 to 12 h. The effect of CP was more significant than the effect of HPMC K4M, HPMC K15M and Sodium CMC. The increase in concentration of CP in series from formulation BT1 to BT12, showed a gradual rise in mucoadhesion time, while HPMC K4M, HPMC K15M and Sodium CMC where also a good mucoadhesive polymers, showed a decrease in mucoadhesion time (Table 2).

**Content uniformity:**

The maximum % drug content from all the formulations was found to be 100.85 ± 0.75. The minimum % drug content from all the formulation was found to be 98.95 ± 0.68 (Table.2).

***In vitro* dissolution studies:**

Release of drug from the bilayered buccal tablets varied according to the type and ratio of matrix-forming polymer. Carbopol 934P has excellent mucoadhesive, gelling properties and also helps in sustaining effect.

The *in vitro* drug release profile of tablets containing CP with HPMC K4M show cumulative percent drug release for formulation BT1 to BT4 were ranging from 20.44% to 18.65% during first hour. Also at the end of 6 h, the cumulative percent drug releases were found to vary from 78.38% to 58.91%. On physical examination of tablets during dissolution study, it was found that tablets were initially swell and slowly eroded over the period of time (Fig.3).

The *in vitro* drug release profile of bilayered buccal tablets containing CP with HPMC K15M show cumulative percent drug release for formulation BT5 to BT8 were ranging from 22.49 to 21.21 during first hour. Also at the end of 6 h the cumulative percent drug release was found to vary from 65.04 % to 50.43%. On physical examination of tablets during dissolution study, it was found that tablets were initially swell and slowly eroded over the period of time (Fig.4).

Formulations BT9 to BT12 (Sodium CMC) showed a higher percentage of drug release compared to other groups. The *in vitro* drug release profile of bilayered buccal tablets containing CP with Sodium CMC show cumulative percent drug release for formulation BT9 to BT12 were ranging from 24.28% to 18.91% during first hour. Also at the end of 6 h the cumulative percent drug release was found to vary from 90.47% to 80.14%. On physical examination of

tablets during dissolution study, it was found that tablets were initially and slowly eroded over the period of time (Fig 5).

Carbopol 934 is more hydrophilic than HPMC: it can swell rapidly; therefore decrease of CP content delays the drug release. Drug release rate was increased with increasing amount of hydrophilic polymer.

**Release mechanism**

For non-Fickian release, the value of n falls between 0.5 and 1.0, while in case of Fickian diffusion, n=0.5; for zero order release (case II transport), n=1; and for supercase II transport, n is greater than 1. Observation of all the $R^2$ values indicated the maximum for Higuchi, Peppas. The n value of formulation BT1 was 0.741 and it also had the R2 (0.992).

**Permeation study of bilayered tablets of TZD HCl across biological barriers**

The selected formulations (BT1, BT5, and BT9) were further taken for permeation study across biological barrier (isolated porcine buccal mucosa). Formulation BT1 containing HPMC K4M with CP sustained the drug upto 24 h with a flux 8.4 x $10^{-2}$ ± 0.0004 mg.cm$^2$/min and permeability coefficient of 2.10 x $10^{-2}$ ± 0.00003. Formulation BT5 containing HPMC K15M with CP sustained the drug upto 24 h with a flux 8.14 x $10^{-2}$ ± 0.0005 mg.cm$^2$ /min and permeability coefficient of 2.03 x $10^{-2}$ ± 0.00005. Formulation BT9 containing HPMC K4M with CP sustained the drug upto 24 h with a flux 9.66 x $10^{-2}$ ± 0.0009 mg.cm$^2$ /min and permeability coefficient of 2.41 x $10^{-2}$ ± 0.00004 (Fig 6).

**Table 1: Formulation details of bilayered buccal tablets of Tizanidine HCl**

| Formulation code | TZD HCl (mg) | HPMC K4M | HPMC K15M | Sodium CMC | Carbopol 934P | Aspartame | Lactose | Magnesium stearate | Ethyl cellulose |
|---|---|---|---|---|---|---|---|---|---|
| **BT1** | 4 | 54 | | | 54 | 1 | 6 | 2 | 20 |
| **BT2** | 4 | 65 | | | 43 | 1 | 6 | 2 | 20 |
| **BT3** | 4 | 72 | | | 36 | 1 | 6 | 2 | 20 |
| **BT4** | 4 | 81 | | | 27 | 1 | 6 | 2 | 20 |
| **BT5** | 4 | | 54 | | 54 | 1 | 6 | 2 | 20 |
| **BT6** | 4 | | 65 | | 43 | 1 | 6 | 2 | 20 |
| **BT7** | 4 | | 72 | | 36 | 1 | 6 | 2 | 20 |
| **BT8** | 4 | | 81 | | 27 | 1 | 6 | 2 | 20 |
| **BT9** | 4 | | | 54 | 54 | 1 | 6 | 2 | 20 |
| **BT10** | 4 | | | 65 | 43 | 1 | 6 | 2 | 20 |
| **BT11** | 4 | | | 72 | 36 | 1 | 6 | 2 | 20 |
| **BT12** | 4 | | | 81 | 27 | 1 | 6 | 2 | 20 |

**Table 2. Physiochemical Properties of Bilayered Buccal Tablets of TZD HCl**

| Formulation code | Average Weight of tablet (mg ± SD) | Thickness in mm | Drug content (%) | Surface pH | Ex Vivo mucoadhesion time (h) | Mucoadhesion Strength (g) |
|---|---|---|---|---|---|---|
| **BT1** | 140 ± 1.34 | 3.03 | 95.52 ± 0.70 | 7 | 12.0 ± 1.0 | 20.5 ± 1.5 |
| **BT2** | 141 ± 1.16 | 3.02 | 97.99 ± 0.70 | 6 | 11.5 ± 0.7 | 18.7 ± 2.2 |
| **BT3** | 142 ± 1.33 | 3.00 | 95.83 ± 0.92 | 7 | 10.5 ± 0.8 | 15.0 ± 1.3 |
| **BT4** | 139 ± 1.46 | 3.01 | 96.45 ± 0.96 | 6 | 10 .0± 0.5 | 12.3 ± 1.5 |
| **BT5** | 140 ± 1.22 | 3.02 | 96.91 ± 1.41 | 7 | 11.0 ± 1.2 | 19.6 ± 1.3 |
| **BT6** | 143 ± 1.18 | 3.00 | 97.37 ± 0.70 | 6 | 10.5 ± 0.5 | 17.3 ± 1.1 |
| **BT7** | 140 ± 1.42 | 2.99 | 99.69 ± 0.96 | 6 | 10.0 ± 0.7 | 14.0 ± 1.2 |
| **BT8** | 141 ± 1.18 | 2.98 | 97.68 ± 1.06 | 7 | 09.0 ± 0.9 | 11.2 ± 1.6 |
| **BT9** | 144 ± 1.72 | 3.03 | 95.52 ± 1.16 | 6 | 11.0 ± 0.5 | 22.5 ± 1.4 |
| **BT10** | 140 ± 1.11 | 3.03 | 95.52 ± 0.70 | 7 | 09.2 ± 0.4 | 19.4 ± 1.3 |
| **BT11** | 139 ± 1.08 | 3.01 | 94.59 ± 0.70 | 6 | 07.5 ± 0.6 | 17.4 ± 1.6 |
| **BT12** | 137 ± 1.38 | 3.02 | 99.69 ± 0.96 | 6 | 06.0 ± 0.5 | 13.5 ± 1.3 |

**Table 3: Drug release kinetic studies from buccal tablet of TZD HCl**

| Formulation Code | ZERO ORDER | | HIGUCHI | | PEPPAS | | |
|---|---|---|---|---|---|---|---|
| | $K_0$ | $R^2$ | $K_H$ | $R^2$ | $K_P$ | $R^2$ | n value |
| **BT1** | 12.28 | 0.987 | 31.06 | 0.955 | 17.783 | 0.992 | 0.741 |
| **BT2** | 10.61 | 0.964 | 27.56 | 0.984 | 19.998 | 0.991 | 0.613 |
| **BT3** | 09.68 | 0.960 | 25.00 | 0.969 | 14.550 | 0.969 | 0.757 |
| **BT4** | 09.18 | 0.932 | 24.32 | 0.989 | 17.906 | 0.982 | 0.622 |
| **BT5** | 09.94 | 0.967 | 25.47 | 0.961 | 18.663 | 0.951 | 0.593 |
| **BT6** | 08.99 | 0.960 | 23.40 | 0.983 | 17.378 | 0.989 | 0.599 |
| **BT7** | 08.75 | 0.954 | 22.59 | 0.962 | 17.258 | 0.936 | 0.572 |
| **BT8** | 07.58 | 0.925 | 20.19 | 0.994 | 18.281 | 0.979 | 0.491 |
| **BT9** | 14.60 | 0.990 | 36.76 | 0.949 | 20.417 | 0.983 | 0.754 |
| **BT10** | 13.81 | 0.989 | 34.40 | 0.929 | 17.701 | 0.969 | 0.791 |
| **BT11** | 13.71 | 0.991 | 33.94 | 0.919 | 15.922 | 0.968 | 0.845 |
| **BT12** | 12.81 | 0.982 | 31.45 | 0.891 | 14.997 | 0.950 | 0.822 |

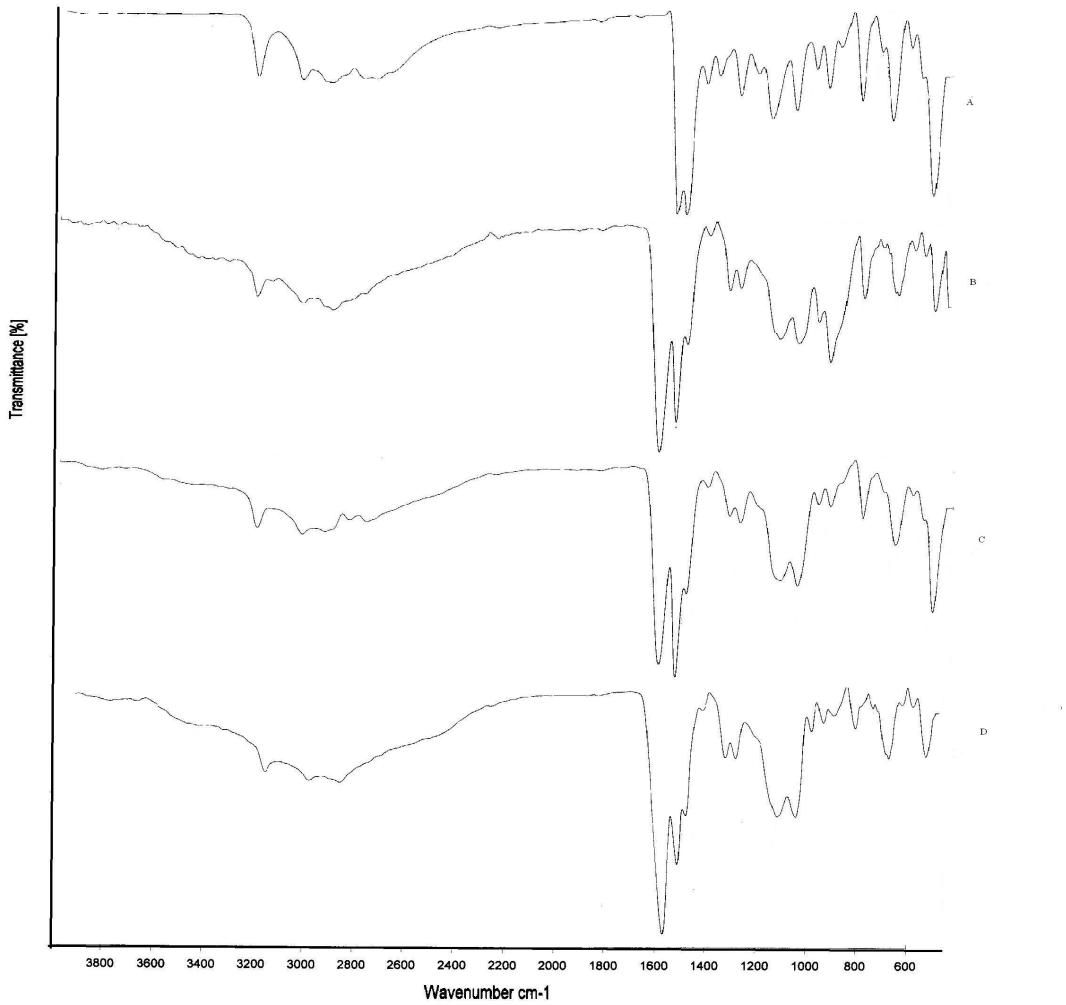


**Figure 1: FTIR Spectra of Tizanidine hydrochloride (TZD HCl)**
**A. Tizanidine hydrochloride pure, B. Tizanidine hydrochloride + HPMCK4M + Carbopol 394, C. Tizanidine hydrochloride + HPMCK15M + Carbopol 394, D. Tizanidine hydrochloride + Sodium CMC + Carbopol 394.**

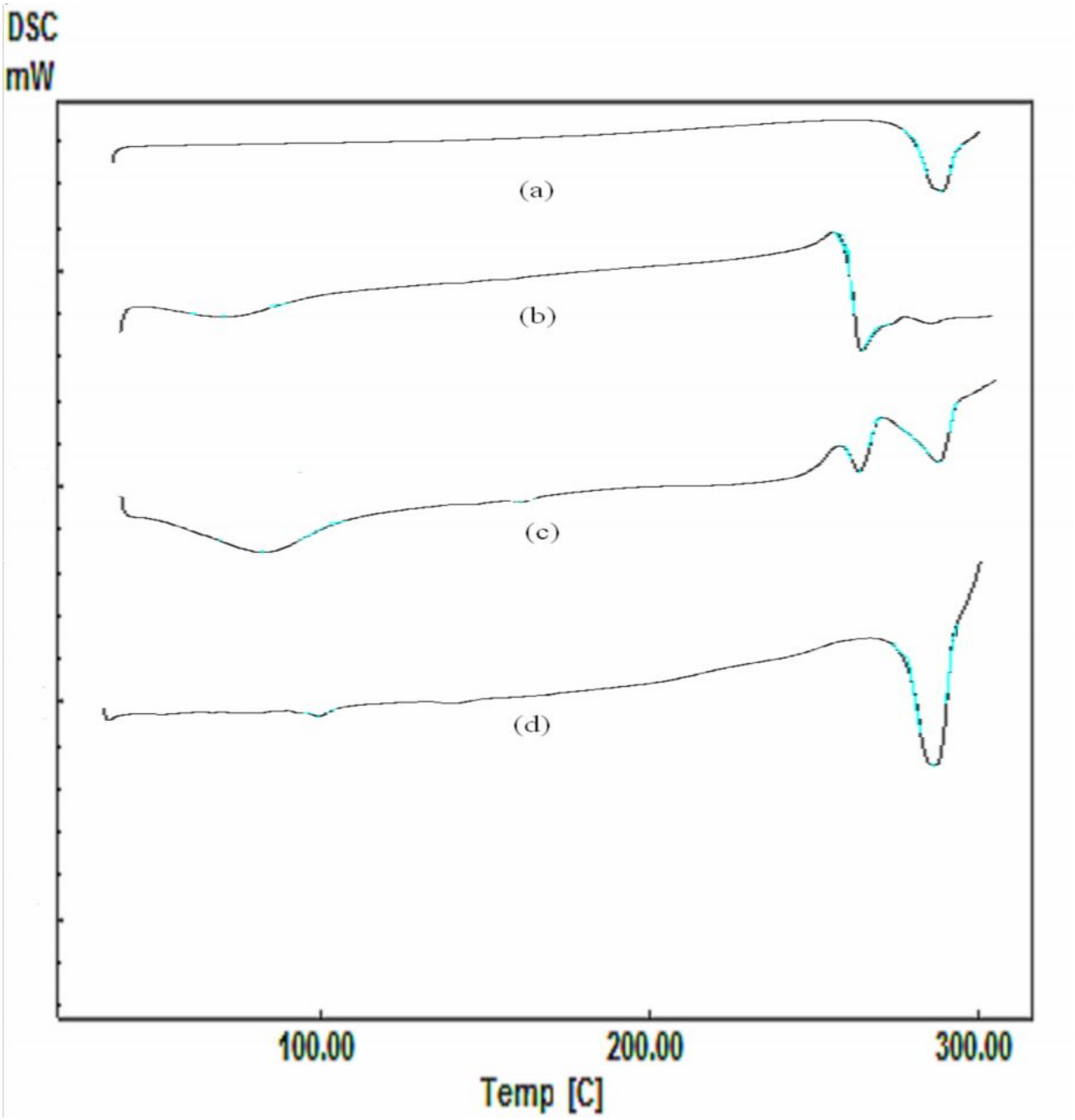


**Figure 2: DSC Thermograms of Tizanidine hydrochloride (TZD HCl)**
**(a) Tizanidine hydrochloride pure, (b) Tizanidine hydrochloride + HPMCK4M + Carbopol 394, (c) Tizanidine hydrochloride + HPMCK15M + Carbopol 394, (d) Tizanidine hydrochloride + Sodium CMC + Carbopol 394.**

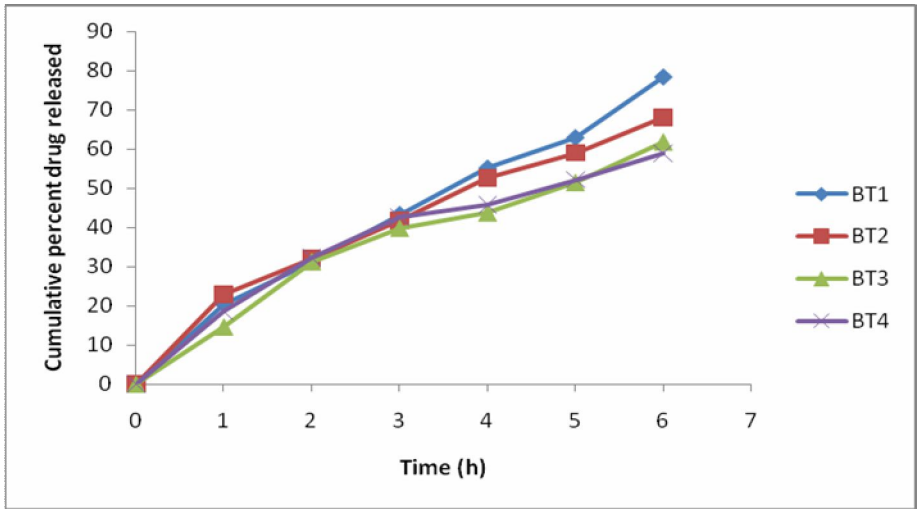


**Fig 3: Cumulative drug released from BT1 to BT4.**

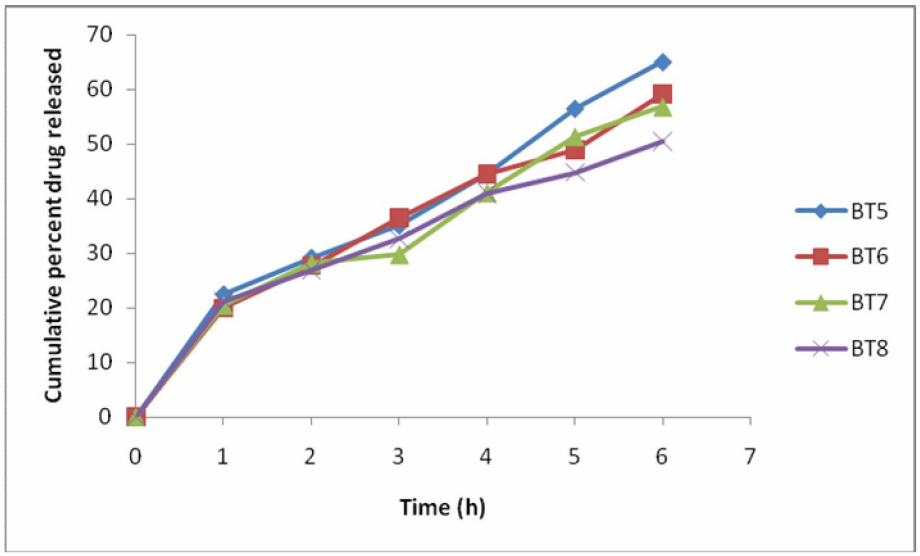


**Fig 4: Cumulative drug released from BT5 to BT8.**

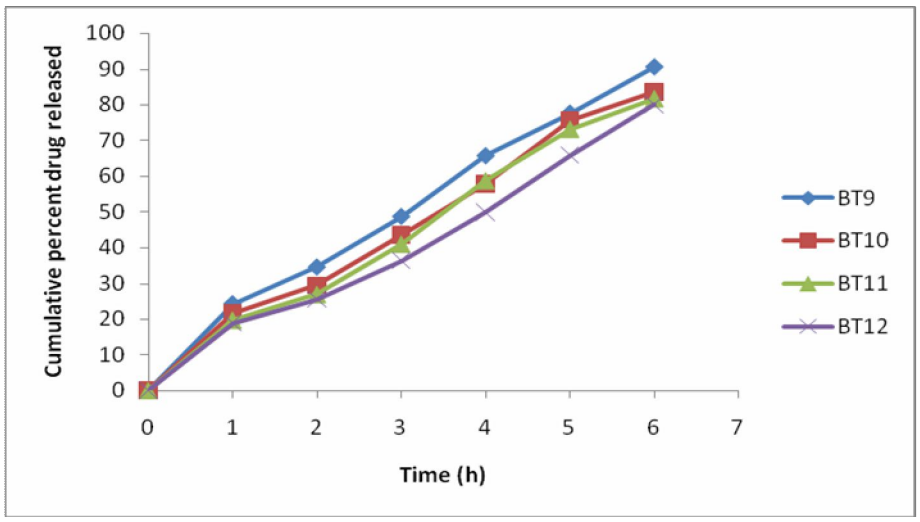


**Fig 5: Cumulative drug released from BT9to BT12.**

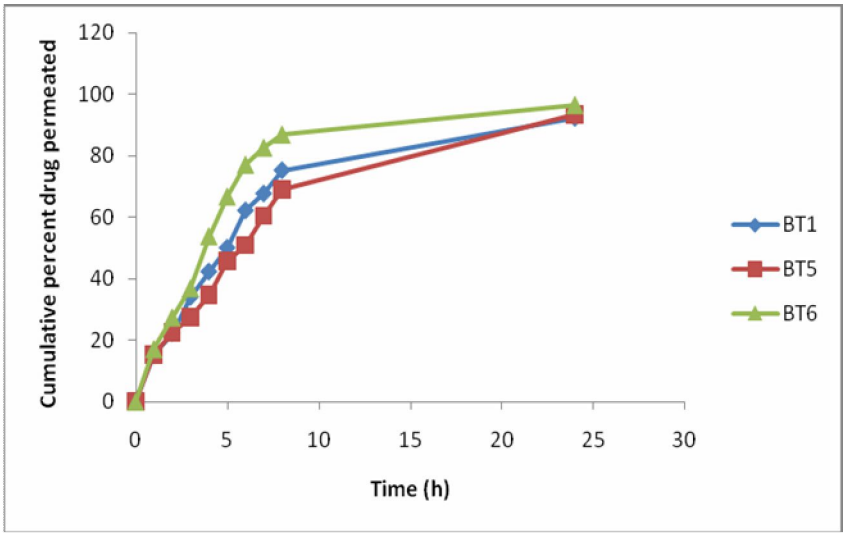


**Fig 6: Cumulative percent drug permeated from BT1, BT5 and BT9**

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