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RESEARCH ARTICLE

DEVELOPMENT AND *IN VITRO* EVALUATION OF FAST DISSOLVING TABLETS OF TIZANIDINE HYDROCHLORIDE BY DIRECT COMPRESSION METHOD

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ABSTRACT

In the present work, fast dissolving tablets (FDTs) have been prepared by direct compression method using tizanidine hydrochloride as a drug candidate. Tizanidine HCl is a centrally acting α-2 adrenergic agonist muscle relaxant with a slightly bitter taste having short half-life of 2.5 h. The tablets were prepared with three superdisintegrants e.g. sodium starch glycolate, crosscarmellose sodium and crospovidone. Formulations were evaluated for pre compression parameters such as bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio. The prepared tablets were also evaluated for hardness, friability, thickness, drug content, disintegration time, wetting time and in-vitro dissolution studies. The compatibility of drug with other ingredients was checked by FTIR studies. *In-vitro* release is presented by zero order and first order plot. From the point of view of maximum drug release within 20 minutes, formulation TZN8 within 8 formulations is the best and hence optimized one. From this study it was concluded that fast dissolving tablets prepared by direct compression method using different superdisintegrants enhanced dissolution which will lead to improved bioavailability and effectiveness of tizanidine hydrochloride.

Keywords: Tizanidine hydrochloride, sodium starch glycolate, crosscarmellose sodium and crospovidone

INTRODUCTION

Recent developments in the technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients. Buccal drug delivery has lately become an important route of drug administration. Various bio adhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery. The most popular solid dosage forms are being tablets and capsules. The conventional tablet seems to be most popular because of its ease of transportability and comparatively low manufacturing cost but poor patient compliance in case of pediatrics and geriatrics patients because of hand tremors and dysphasia that experienced difficulties in swallowing. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. To overcome these problems, scientists have developed innovative drug delivery system known as fast dissolving/disintegrating tablets (FDTs). These are novel types of tablets that dissolve/ disintegrate/ disperse in saliva within few seconds. The Centre for Drug Evaluation and Research (CDER), US FDA defined fast dissolving/ disintegrating tablets (FDT) as

"A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".

Drugs release from FDT get absorbed from the oral cavity, pharynx and esophagus as the saliva passes down into the stomach. Dispersion of tizanidine hydrochloride in saliva in oral cavity causes pre-gastric absorption of drug which dissolves. Any pre-gastric absorption avoids first pass hepatic metabolism which also increases bioavailability.[1, 2]

Tizanidine hydrochloride is an Imidazoline derivative which acts as agonist on centrally located α 2 receptors and this leads to myotonolytic effects on skeletal muscle. It is structurally and pharmacologically similar to Clonidine and other α-2 adrenergic agonists. It is given with a dose of 2-4 mg. About 53-66% 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 hrs. Bioavailability of Tizanidine is about 34-40% and half life is 2.5 hrs. 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 Imidazole moiety, aromatic system and the sulphur atom. This leads to lower bioavailability of Tizanidine hydrochloride. It is a white to off white, fine crystalline powder, which is odourless or with faint characteristic odour. It is slightly soluble in water and methanol, solubility in water decreases as the pH increases. Its chemical IUPAC name is 5–Chloro–4-(2–Imidazolin-2-ylamino)–2,1,3-benzothiodiazole hydrochloride.[3, 4]

MATERIALS AND METHODS

MATERIALS

The research was carried out using instruments like Friability Test Apparatus, DSC 200F3, Dissolution Test

Apparatus (8 basket), UV Spectrophotometer (Shimadzu). Tizanidine (Pure drug) and excipient polymers (Crospovidone, Crosscarmellose Sodium, Sodium Starch Glycolate, Microcrystalline Cellulose Analytical grade, Vanillin, Talc and Magnesium Stearate) were provided by Nishka labs. Mannitol, Sodium Hydroxide and Potassium Dihydrogen Ortho Phosphate were bought from SD Fine, Mumbai.

METHODS

Direct compression method: Fast dissolving tablets of tizanidine hydrochloride were prepared by direct compression method. All the ingredients were passed through sieve no. 16. Then the ingredients were weighed and mixed in the plastic container in geometrical order and compressed into tablets of 100 mg.[5]

EVALUATION

1) PRE COMPRESSION PARAMETERS OF TIZANIDINE HYDROCHLORIDE FAST DISSOLVING TABLETS

The prepared blend was analyzed for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. Determination of bulk density and tapped density:

Flow Properties

Carr's Index (Compressibility): The compressibility index is the measure of property of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It was indicated as Carr's compressibility index.[6]

Hausner Ratio: It is measurement of frictional resistance of the drug. The ideal range should be 1.2-1.5. It was determined by the ratio of tapped density and bulk density.[6]

Angle of Repose: It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane. Weighed quantity of the drug was passed through a funnel kept at a height 2 cm from the base. The powder was passed till it forms a heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated.[7]

2) DRUG -EXCIPIENTS COMPATIBLITY STUDIES

Fourier Transform Infrared Spectroscopy (FT-IR): The Fourier-transform infrared spectra of tizanidine hydrochloride and mixture of tizanidine hydrochloride with other excipients were obtained by using FTIR spectroscopy (Shimadzu, Japan). The samples were crushed with KBr to get pellets by applying pressure of 600 Kg/cm^2.[8]

3) POST COMPRESSION PARAMETERS OF TIZANIDINE HYDROCHLORIDE FAST DISSOLVING TABLETS

Evaluation parameters of tablets mention in the Pharmacopoeias need to be assessed, along with some special tests which are discussed here.

Weight Variation: Weight variation test was performed by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average one, determinations were carried out in triplicate.[9]

Hardness: The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2.[9]

Friability: Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed.[10]

Thickness: The thickness and diameter of the tablets was determined using a Vernier calliper. Three tablets from each type of formulation were used and average values were calculated. It is expressed in mm.[10]

Water Absorption Ratio: A piece of tissue paper folded twice was kept in a Petri dish (internal diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted.[11]

Wetting Time: A piece of tissue paper folded twice was placed in a small Petri dish containing 6ml pH 6.8 phosphate buffers. A tablet was placed on the paper and the time taken for complete wetting was noted.[11]

Disintegration Study: In the Disintegration time study one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffers at 37 ± 0.5^0 C and the time required for complete dispersion was determined.[12]

Drug Content: Five tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 4 mg weight and dissolved in 100 ml of 6.8 pH buffer filtered and drug content analyzed spectrophotometrically at 230 nm.[12]

***In - Vitro* Dissolution Testing:** Dissolution study is conducted for all the formulation using USP type-II apparatus. The dissolution test is per-formed using 900ml of phosphate buffer (pH 6.8) is taken as the dissolution medium at 50 rpm and 37 ±0.5°C. Ten ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples should be analyzed spectrophotometrically.[12]

KINETIC RELEASE STUDIES OF DISSOLUTION DATA

Zero Order: It describes the systems where the drug release rate is independent of its concentration of the dissolved substance. A graph is plotted between the time taken on x-axis and the cumulative % of drug release on y-axis.[13]

First Order: The data obtained are plotted as log cumulative percentage of drug remaining vs. time .[13]

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RESULTS AND DISCUSSION

Fast dissolving tablets of tizanidine hydrochloride were prepared by direct compression method by using superdisintegrants like crospovidone, crosscarmellose sodium and sodium starch glycolate in varying amount (Table 1). λ_{max} of tizanidine in pH 6.8 was found to be at 230 nm as shown in Figure 1. FT-IR studies: The FTIR spectra of the pure drug were recorded in between 4000 to 400 cm^{-1}. Characteristics peaks and chemical groups present in IR spectrum of tizanidine hydrochloride are shown in Figure 3. The FT-IR spectra of tizanidine hydrochloride revealed the presence of characteristic broad and strong peak for C=N stretching around 1644.98 cm^{-1}, stretching peak around 3089.4 cm^{-1} corresponds to the stretching vibration of C-H group and a strong band around 3245.61 cm^{-1} corresponds to N-H stretching. FTIR spectrum for tizanidine hydrochloride physical mixture is shown in Figure 4. Bulk density and tapped density: It ranges from 0.863±0.006 to 0.880±0.010 (gm/cc) and 0.923±0.006 to 0.967±0.011 (gm/cc) respectively. Compressibility index and Hausner ratio: It ranges from 4.695±0.641 to 10.686±0.466 and 1.049±0.007 to 1.120±0.006 respectively. Angle of repose: It ranges from 22.441±0.57^0 to 28.762±0.985^0, it show blend flows freely through the hopper. The results for pre compressed parameters are shown in Table 2. Weight variation test: It ranges from 99.85±1.253 to 101.71±2.531 mg as per IP specification. Hardness: It was in between 4.17±0.289 & 5.33±0.289 kg/cm^2. The results indicate that the tablets are mechanically strong and are in limit. Thickness: It ranges from 1.203±0.021 to 1.517±0.061 mm; the results indicate that the tablets are suitable for packing. Friability: It ranges from 0.553±0.223 to 0.693±0.252 %, so the results indicate that the percentage losses were not more than 1.0%. So the tablet complies as per IP specifications. *In-Vitro* Disintegration time: Its value are in between 27.46±1.12 & 59.37±0.93 seconds, the results indicate that disintegration time of tablet formulations TZN 1, TZN 2, TZN 3, TZN 4, TZN 5, TZN 6, TZN 7 and TZN 8 are within 1 minute. Wetting time: It ranges from 66.07±1.30 to 153.97±1.00 seconds and water absorption ratio: It was found in between 61.37±1.26 & 98.98±0.731. Content uniformity: It was found in between 97.47±0.681 & 99.17±0.586 %. The post compressed parameters are shown in Table 3&4. Dissolution Study in 6.8 pH phosphate buffer: Formulations TZN 1, TZN 2, TZN 3, TZN 4, TZN 5, TZN 6, TZN 7 and TZN 8 have a recorded zero order drug release 93.27 %, 94.50 %, 84.59 %, 85.85 %, 92.04 %, 94.51 %, 98.84 %, and 98.82 % respectively at the end of 30 min, the results are shown in Figure 5. First order release plot of tizanidine hydrochloride fast dissolving tablet are shown in Figures 6. Regression and slope data of release kinetics of tizanidine hydrochloride fast dissolving tablets in concern of zero order, first order, Higuchi's and Korsmeyer Peppa's are shown in table 5. Formulations with disintegration time and wetting time are shown in Figure 7.

Table 1: Formulations composition of tizanidine hydrochloride fast dissolving tablets

Ingredients (mg)	Formulation Code							
	TZN1	TZN2	TZN3	TZN4	TZN5	TZN6	TZN7	TZN8
Tizanidine HCl	4	4	4	4	4	4	4	4
Crospovidone	6.5	8.5	-	-	-	-	6.5	-
Crosscarmellose Sodium	-	-	6.5	8.5	-	-	6.5	6.5
Sodium Starch Glycolate	-	-	-	-	6.5	8.5	-	6.5
Microcrystalline Cellulose	30	30	30	30	30	30	30	30
D-mannitol	52.5	50.5	52.5	50.5	52.5	50.5	46	46
Aspartame	3	3	3	3	3	3	3	3
Vanillin	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1
Mg Stearate	2	2	2	2	2	2	2	2
Total	100	100	100	100	100	100	100	100

Table 2: Evaluation of pre-compression parameters of powder blends of formulations

Formulation Code	Bulk Density ± S.D (gm/cc)	Tapped Density ± S.D (gm/cc)	Carr's Index ±S.D	Hausner's Ratio ± S.D	Angle of Repose ± S.D (Ɵ)
TZN1	0.867±0.005	0.953±0.011	9.087±0.499	1.100±0.006	27.813±1.060
TZN2	0.880±0.010	0.950±0.010	7.365±1.021	1.079±0.011	22.441±0.570
TZN3	0.880±0.010	0.923±0.006	4.695±0.641	1.049±0.007	23.950±0.159
TZN4	0.870±0.030	0.966±0.011	9.991±1.060	1.111±0.013	27.932±0.551
TZN5	0.863±0.006	0.967±0.011	10.686±0.466	1.120±0.006	26.758±0.426
TZN6	0.867±0.006	0.937±0.006	7.828±0.592	1.085±0.007	26.754±0.813
TZN7	0.877±0.020	0.943±0.015	7.074±0.712	1.076±0.008	28.762±0.985
TZN8	0.867±0.011	0.947±0.006	8.451±1.050	1.092±0.012	27.627±0.949

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Table 3: Evaluation of post-compression parameters of tizanidine hydrochloride FDTs

Formulation Code	Avg. wt. of Tablet ±S.D (mg)	Hardness ±S.D (kg/cm^2)	Thickness ±S.D (mm)	Friability ±S.D (%)
TZN1	101.71±2.531	4.83±0.764	1.413±0.028	0.623±0.031
TZN2	100.69±1.200	4.67±0.764	1.357±0.047	0.577±0.042
TZN3	100.39±1.364	4.83±0.577	1.354±0.042	0.677±0.060
TZN4	100.50±0.947	5.33±0.289	1.343±0.042	0.571±0.065
TZN5	99.91±1.750	4.17±0.289	1.253±0.041	0.553±0.223
TZN6	100.38±1.741	4.36±0.259	1.356±0.036	0.693±0.252
TZN7	99.85±1.253	5.17±0.289	1.203±0.021	0.623±0.041
TZN8	100.48±1.58	4.67±0.764	1.517±0.061	0.670±0.129

Table 4: *In-vitro* disintegration time, wetting time, water absorption ratio and drug content of tizanidine hydrochloride FDTs

Formulation Code	*In-Vitro* Disintegration Time ±S.D (sec)	Wetting Time (sec) ±S.D	Water Absorption Ratio (%) ±S.D	Drug Content ±S.D
TZN1	32.41±0.71	123.31±1.16	73.46±1.01	98.003±0.689
TZN2	27.77±0.71	98.40±0.87	70.50±0.83	97.477±0.681
TZN3	48.23±1.35	134.77±1.44	86.27±1.16	99.052±0.445
TZN4	45.17±1.33	112.83±1.89	98.98±0.73	98.433±0.834
TZN5	59.37±0.93	153.97±1.00	82.07±1.55	99.173±0.586
TZN6	50.97±0.29	119.67±0.55	90.57±0.81	97.803±0.703
TZN7	29.51±0.56	70.55±0.76	67.21±1.68	99.017±0.608
TZN8	27.46±1.12	66.07±1.30	61.37±1.26	98.861±0.945

Table 5: Regression and slope data of release kinetics of tizanidine hydrochloride fast dissolving tablets

Formulation code	Mathematical models (release kinetics)				
	Zero order kinetics	First order kinetics	Higuchi's	Peppa's	
	r^2	r^2	r^2	r^2	n
TZN1	0.846	0.982	0.988	0.844	0.621
TZN2	0.840	0.980	0.976	0.841	0.603
TZN3	0.924	0.985	0.992	0.973	0.651
TZN4	0.919	0.988	0.991	0.974	0.640
TZN5	0.641	0.858	0.834	0.730	0.521
TZN6	0.639	0.881	0.832	0.729	0.512
TZN7	0.664	0.960	0.852	0.738	0.670
TZN8	0.911	0.959	0.962	0.956	0.835

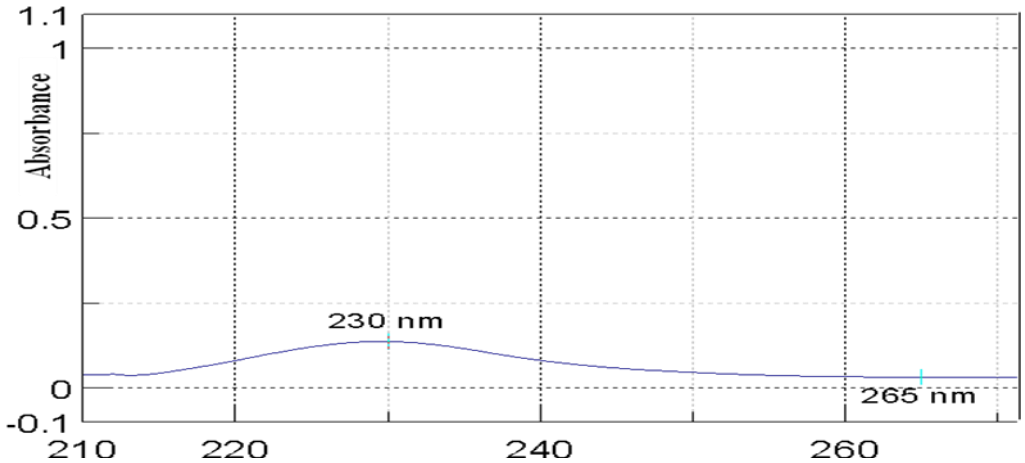

Figure 1: λ_{max} of tizanidine hydrochloride in pH 6.8 at 230nm

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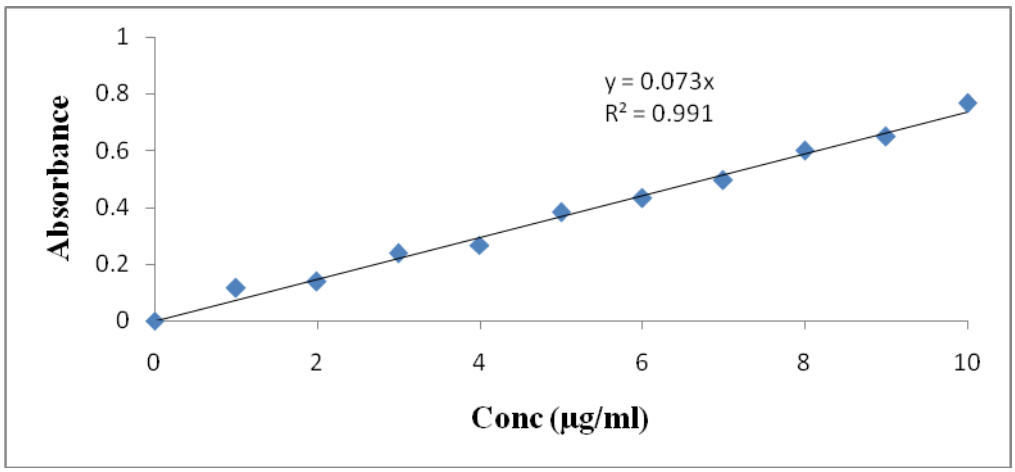

Figure 2: Calibration curve of tizanidine hydrochloride in pH 6.8 at 230nm

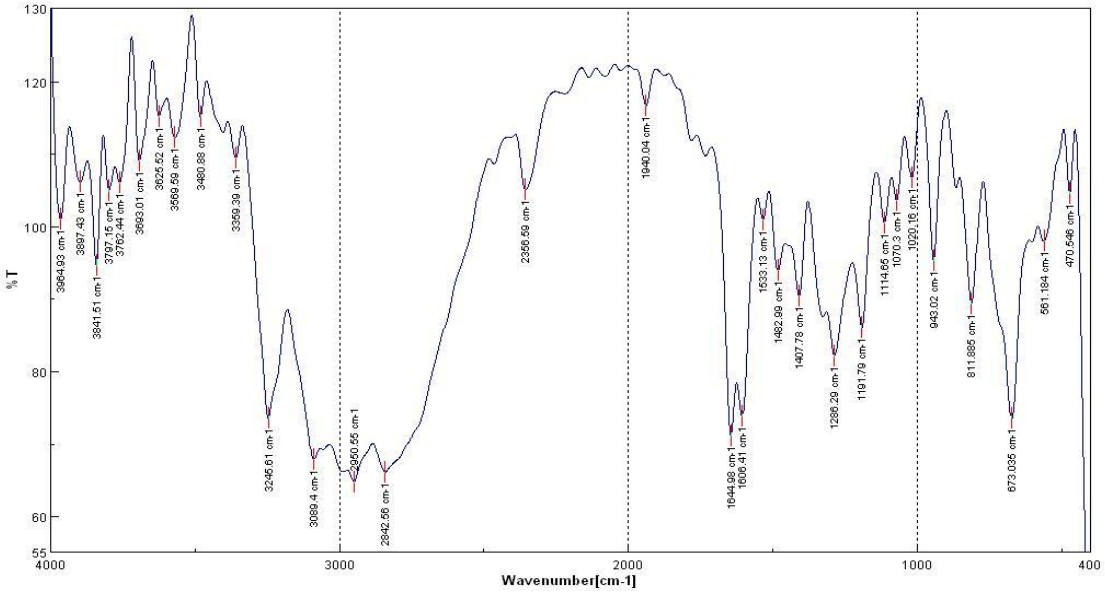

Figure 3: FT-IR spectrum of pure tizanidine hydrochloride

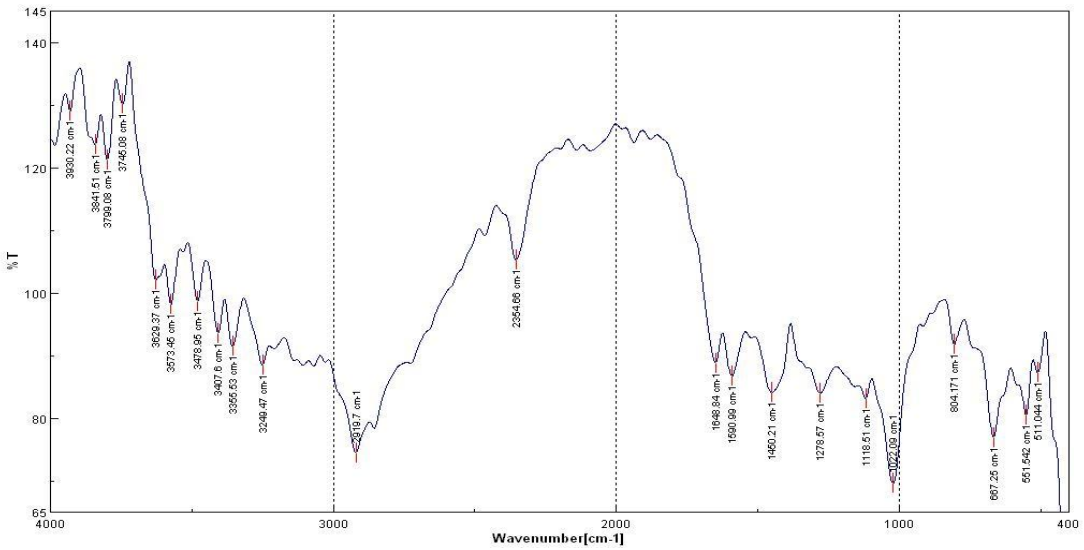

Figure 4: FT-IR spectrum of tizanidine hydrochloride physical mixture

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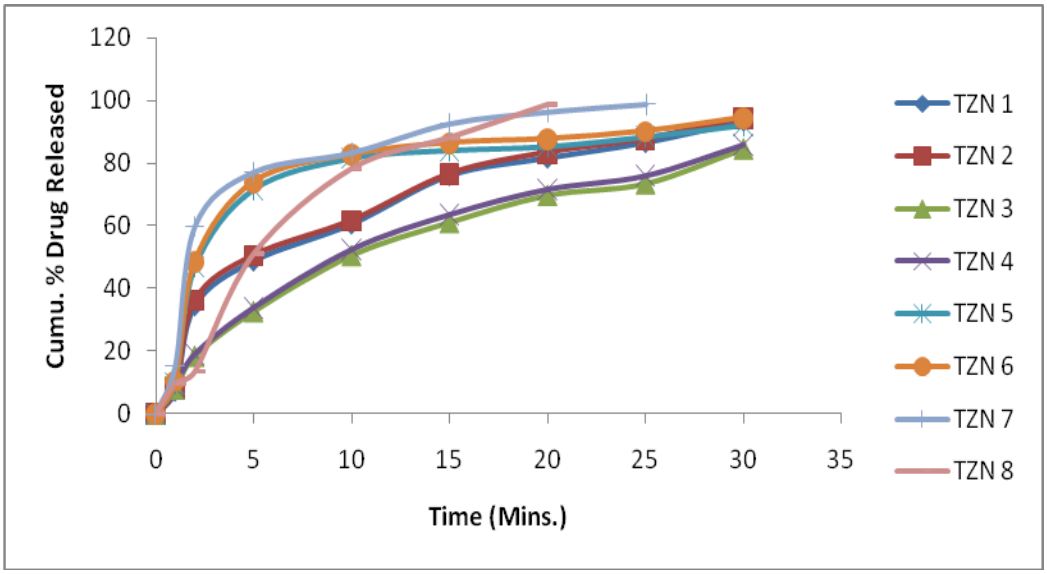

Figure 5: Zero order release plot of tizanidine hydrochloride fast dissolving tablets (TZN 1-8)

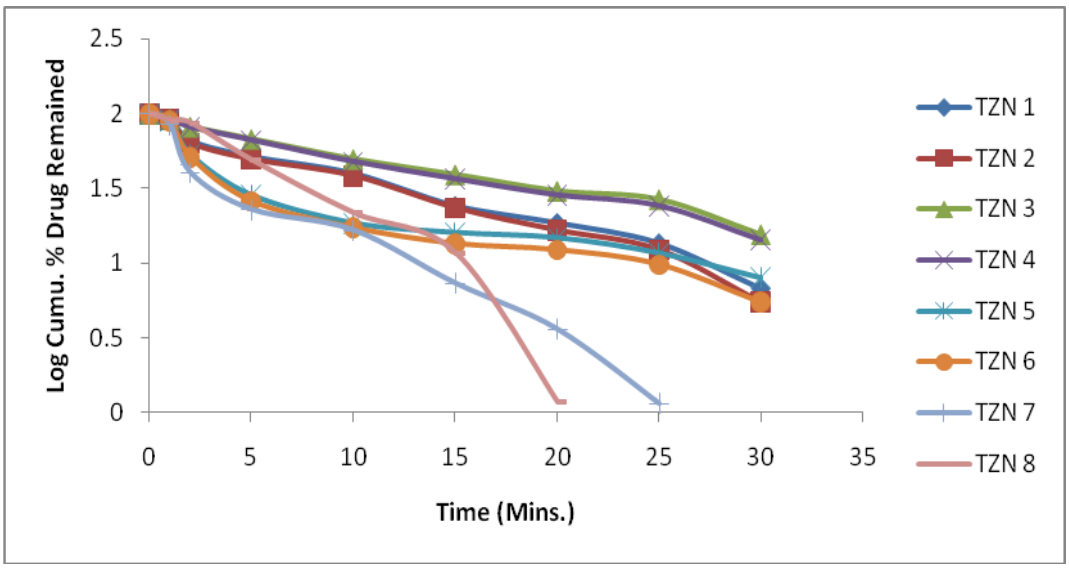

Figure 6: First order release plot of tizanidine hydrochloride fast dissolving tablets (TZN 1-8)

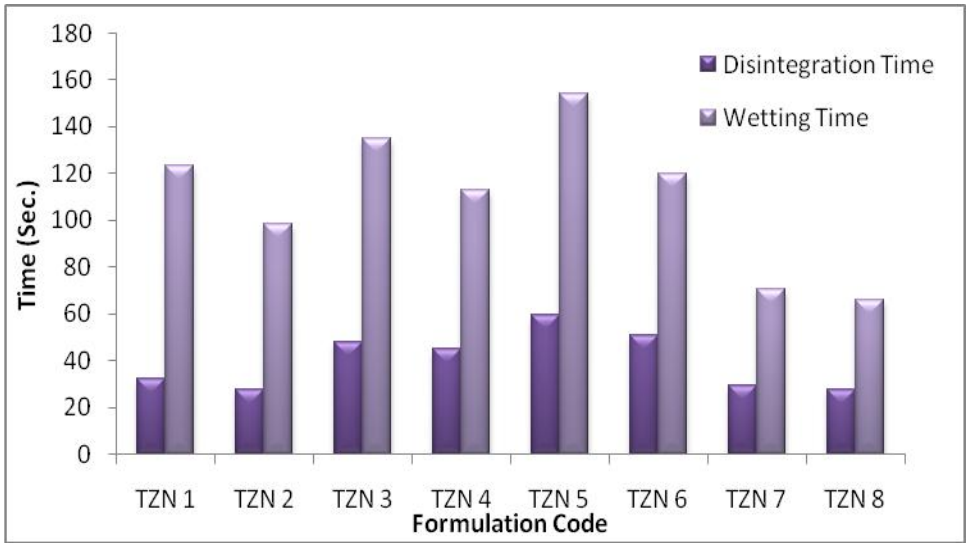

Figure 7: Disintegration and wetting time of different formulations

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CONCLUSION

Fast dissolving tablets of tizanidine were successfully prepared by direct compression techniques using selected superdisintegrants for the immediate action and effective therapy. FTIR studies revealed that there was no interaction between tizanidine hydrochloride and excipients used in tablet formulation. The prepared tablets were evaluated for various parameters like hardness, friability, drug content, *in-vitro* disintegration time, wetting time, water absorption ration and *in-vitro* dissolution. From the point of view of maximum drug release within 20 minutes, formulation TZN8 is the best and hence optimized formulation. The results concluded that fast dissolving tablets of poorly soluble drug, tizanidine hydrochloride showed enhanced dissolution, may improved bioavailability and hence better patient compliance.

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