World Journal of Pharmaceutical research

Volume 3, Issue 2, 2557-2568. Research Article ISSN 2277 – 7105

FORMULATION DESIGN AND EVALUATION OF FAST DISSOLVING TABLETS OF TIZANIDINE HYDROCHLORIDE BY DIRECT COMPRESSION METHOD: FOR THE EFFECTIVE TREATMENT OF MUSCLE SPASM

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Article Received on
05 January 2014
Revised on 27 January2014,
Accepted on 21 February 2014

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ABSTRACT

Objective: The purpose of this research is formulation design and evaluation of fast dissolving tablets of tizanidine hydrochloride by direct compression method.

Methods: Tizanidine hydrochloride was used as desired drug for the formulation of fast dissolving tablets. The tablets were prepared using three superdisintegrants e.g. sodium starch glycolate, crosscarmellose sodium and crospovidone. Other excipients used in this research were microcrystalline cellulose, talc, magnesium stearate and vanillin. Analytical methods such as UV- spectroscopy and DSC were used for the identification of the pure drug. Formulation blends were evaluated for pre compression parameters such as bulk density, tapped density, Carr's index Hausner's ratio and angle of repose. Direct compression method was used to prepare tablets. The prepared tablets were also evaluated for weight uniformity test, hardness, uniformity of thickness, friability test, *in-vitro* disintegration time, wetting time, water absorption ratio, drug content uniformity, *in-vitro* dissolution studies and accelerated stability studies. The release data were subjected to different models in order to evaluate their release kinetics and mechanism. **Results & discussion:** The compatibility study of the prepared tablets implies the information about no interaction between drug and polymers. Within 8 formulations, formulation TZN8 is the best and hence optimized one. **Conclusion:** After the dissolution study of prepared tizanidine hydrochloride tablets, it was concluded that the formulations TZN8 with crosscarmellose sodium and sodium starch glycolate shows better release and disintegration time than any other.

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

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. But many patients find difficult to swallow tablets and hard gelatine capsules and thus do not comply with prescription. This results in high incidence of noncompliance and ineffective therapy. Difficulty in swallowing is experienced by patient such as paediatric, geriatric, bedridden, disabled and mentally ill. To overcome these problems, scientists have developed innovative drug delivery system known as fast dissolving/disintegrating tablets (FDTs).Fast dissolving tablets are solid dosage form containing medical substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water to facilitate swallowing. Dispersion of drug (Tizanidine Hydrochloride) in saliva in oral cavity causes pre-gastric absorption of drug which dissolves and hence avoids first pass hepatic metabolism.[1, 2, 3]

Drug used & its action: Tizanidine hydrochloride (TZD HCl) 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.

Dose: It is given with a dose of 2-4 mg and maximum dose per day is 36 mg.

Pharmacokinetics: 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.

Properties: Tizanidine hydrochloride 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. [4, 5]

MATERIALS AND METHODS

Materials

The research was carried out at Nishka Labs in Hyderabad under stringent lab conditions 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: The critical parameters to formulate a fast dissolving tablet are choice of superdisintegrant and optimization of concentration of superdisintegrant. The super disintegrant like crospovidone, crosscarmellose sodium and sodium starch glycolate were used in varying concentration to formulate fast dissolving tablets. All the ingredients were passed through 16-mesh separately. Then the ingredients were weighed and mixed in the plastic container in geometrical order and compressed to form tablets of 100 mg using a 9 mm flat punch. [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.

Bulk density: Apparent bulk density was determined by placing pre-sieved bulk powder blend into a graduated cylinder via a large cylinder and measuring the volume and weight.[6]

Tapped density: It was determined by placing known mass of powder in a graduated cylinder & tapping it for fixed number of taps (around 250) until the powder bed volume reached a minimum. Using the weight of the powder in the cylinder and this volume, the tapped density was computed.[6]

Flow Properties

Carr's index (Compressibility): The simplex way of measurement of the free flow of

powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was determined by Carr's compressibility index.[7]

Hausner ratio: Hausner ratio is an indirect index of ease of powder flow. The ideal range should be 1.2-1.5. It was determined by the ratio of tapped density and bulk density.[7]

Angle of repose: It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane. The friction forces in a loose powder can be measured by the angle of repose. It is an indicative of the flow properties of the powder.[8]

2) CHRECTERIZATION BY DSC

Differential scanning calorimetric (DSC): DSC was used to assess the thermal behavior of the drug (Tizanidine) using an automatic thermal analyzer system. A single sharp characteristic endothermic peak of DSC thermogram corresponds to its melting and exothermic event is a thermal event of a material where energy is expelled by the material, i.e. crystallization. The entire sample was run at a scanning rate of 10°c/min. over a temperature range of 35-500°C. The sample was hermetically sealed in an aluminum crucible. Nitrogen gas was purged at rate of 10 ml/min. for maintaining inert atmosphere.[9]

3) POST COMPRESSION PARAMETERS OF TIZANIDINE HYDROCHLORIDE FAST DISSOLVING TABLETS

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

Weight variation: Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.[8]

Hardness: Hardness was determined by taking three tablets from each formulation, using a Monsanto Hardness Tester.[10]

Friability: The friability of a sample of 20 tablets was measured using Roche friabilator, which was rotated for 4 min at 25 rpm. After de- dusting, the total remaining mass of tablet was recorded and the percent friability was calculated. Friability below 1 % was considered acceptable.[10]

Thickness: Three tablets from each type of formulation were selected and the thickness and was determined using a screw gauge. It is expressed in mm.[11]

Water absorption ratio: A piece of tissue paper folded twice was kept in a petri dish 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 (ID 6.5cm) containing 6ml of pH 6.8 (simulated saliva fluid). A tablet was put on the paper and the time for complete wetting was measured. Three trials for each were performed[12]

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 ± 0.50 ^{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.[13]

***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°C±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.[13]

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 and it gives a straight line.[14]

First order: The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope.[14]

RESULTS AND DISCUSSION

In the present investigation, FDTs of tizanidine hydrochloride prepared by direct compression method by using superdisintegrants like crospovidone, crosscarmellose sodium and sodium starch glycolate in varying concentration. Formulations of tizanidine FDTs by direct compression method are shown in Table 1. By UV Spectrophotometer, wavelength maximum between 200-400 nm was found to be 230 nm as shown in Fig. 1. From the tizanidine hydrochloride standard stock solution (100 µg/ml), appropriate aliquots were taken into different volumetric flasks and volume was made up to 10 ml with 6.8 phosphate buffer solution so as to get drug concentration of 1.0 to 10 µg/ml and then a calibration curve was constructed as shown in Fig. 2. DSC studies: It was used to determine melting point of pure drug. An endothermic peak at 296.2^0C corresponds to melting process of drug. Although there is no interaction but difference in temperature of tizanidine hydrochloride and tizanidine physical mixture found due to different in environmental conditions. DSC thermograms of tizanidine hydrochloride and tizanidine physical mixture are presented in Fig. 3 & 4.

Bulk density and tapped density: These ranges from 0.863±0.005 to 0.893±0.015 (gm/cc) and 0.920±0.010 to 0.983±0.006 (gm/cc) respectively. Compressibility index and Hausner ratio: They range from 5.986±0.630 to 9.156±1.030 and 1.041±0.006 to 1.101±0.013 respectively. Angle of repose: It ranges from 21.890±0.820 to $28.972±0.751^0$ show blend flows freely through the hopper. The results for pre compressed parameters are shown in Table 2.

Weight variation test: It ranges from 99.87±1.640 mg to 101.51±1.332 mg as per IP specification. Hardness of tablets ranges from 4.17±0.29 to 5.17±0.289 kg/cm^2. The results indicate that the tablets are mechanically strong and are in limit. Thickness: It ranges from 1.252±0.046 to 1.481±0.050 mm; the results indicate that the tablets are suitable for packing. Friability: It is less than 0.770±0.042 % the results indicate that the percentage losses were not more than 1.0%. So the tablet complies as per IP specifications as shown in Table 3.

In-Vitro Disintegration time: Its values are between 32.57±0.51 & 81.64±1.13 seconds, the results indicate that disintegration time of tablet formulations TZN 2, TZN 4, TZN 5, TZN 6, TZN 7 and TZN 8 are within 1 minute but formulations TZN1 and TZN3 do not follow this limit. Among these formulations TZN8 shows good disintegration time 32.57 sec. Wetting time: Its values are between 73.19±0.64 & 198.53±0.61 seconds and water absorption ratio was found in between 56.40±0.656 & 86.27±1.16. Content uniformity: It was found in

between 97.230±0.961 to 99.836±0.415 %. The post compressed parameters are also shown in Table 4. Dissolution Study in 6.8 pH phosphate buffer: Formulations TZN1, TZN2, TZN3, TZN4, TZN5, TZN6, TZN7 and TZN8 have recorded zero order drug release 80.91 %, 83.39 %, 65.47%, 71.65 %, 78.45 %, 84.01 %, 98.22 %, and 98.20 % respectively at the end of 30 min, the results are shown in Fig. 5. Amount of drug remained in tablets after zero order release is obtained by first order plot. First order release plot of tizanidine hydrochloride fast dissolving tablet is shown in Fig. 6. Formulations with disintegration time and wetting time are shown in Fig. 7.

Regression analysis was performed and regression values 'R^2' were 0.626 to 0.987 for different formulations. Slope values ($0.5<n<1.0$) suggest that the release of tizanidine from fast dissolving tablets followed non-Fickian diffusion mechanism. 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.

Table 1 Formulation 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	2.5	4.5	-	-	-	-	4.5	-
Crosscarmellose Sodium	-	-	2.5	4.5	-	-	4.5	4.5
Sodium Starch Glycolate	-	-	-	-	2.5	4.5	-	4.5
Microcrystalline Cellulose	30	30	30	30	30	30	30	30
D-mannitol	56.5	54.5	56.5	54.5	56.5	54.5	50	50
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. (θ)
TZN1	0.867±0.015	0.937±0.015	7.475±0.122	1.081±0.001	26.493±0.467
TZN2	0.883±0.005	0.942±0.011	6.025±0.563	1.064±0.006	26.643±0.583
TZN3	0.883±0.011	0.920±0.010	3.986±0.630	1.041±0.006	26.746±0.910
TZN4	0.863±0.005	0.937±0.011	7.825±0.516	1.085±0.006	27.830±0.700
TZN5	0.883±0.015	0.943±0.006	6.364±1.090	1.068±0.012	28.972±0.751
TZN6	0.880±0.010	0.937±0.006	6.051±0.635	1.064±0.007	21.890±0.820
TZN7	0.893±0.015	0.983±0.006	9.156±1.030	1.101±0.013	25.887±0.650
TZN8	0.887±0.015	0.950±0.010	6.671±0.672	1.071±0.008	26.790±1.000

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	101.51±1.332	4.17±0.29	1.481±0.050	0.647±0.097
TZN2	101.14±1.440	4.83±0.764	1.456±0.049	0.713±0.127
TZN3	100.47±1.101	5.17±0.289	1.356±0.062	0.670±0.114
TZN4	100.03±1.300	4.33±0.289	1.356±0.021	0.577±0.420
TZN5	100.60±1.823	4.33±0.289	1.355±0.085	0.596±0.561
TZN6	99.87±1.640	4.67±0.289	1.252±0.046	0.770±0.042
TZN7	100.48±1.862	5.17±0.289	1.357±0.010	0.576±0.060
TZN8	100.22±1.833	5.00±0.866	1.353±0.032	0.440±0.065

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	81.64±1.13	171.53±0.75	56.40±0.65	97.230±0.961
TZN2	55.51±0.78	151.37±1.31	75.84±1.28	98.454±0.311
TZN3	72.57±1.12	198.53±0.61	73.87±1.95	99.523±0.395
TZN4	51.50±1.15	162.17±0.47	86.27±1.16	98.132±0.865
TZN5	60.17±1.45	171.63±1.01	71.41±0.91	98.973±0.384
TZN6	51.07±0.94	182.53±1.26	76.43±1.12	98.707±0.808
TZN7	35.67±0.65	74.62±0.88	71.36±1.19	99.836±0.415
TZN8	32.57±0.51	73.19±0.64	68.05±1.69	98.478±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	0.877	0.974	0.987	0.853	0.626
TZN2	0.781	0.932	0.987	0.802	0.604
TZN3	0.904	0.963	0.987	0.977	0.623
TZN4	0.910	0.972	0.980	0.963	0.718
TZN5	0.891	0.961	0.976	0.965	0.634
TZN6	0.829	0.942	0.949	0.932	0.723
TZN7	0.660	0.950	0.847	0.727	0.679
TZN8	0.918	0.960	0.955	0.953	0.982

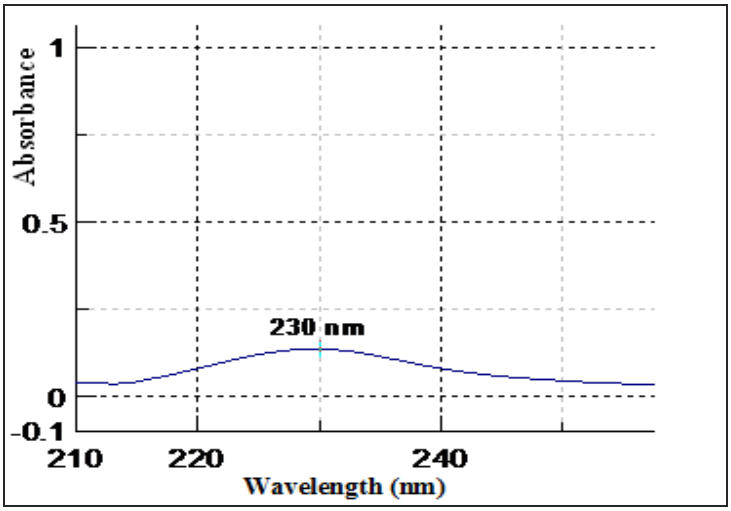

Figure 1 λ_{max} of tizanidine in pH 6.8 at 230 nm

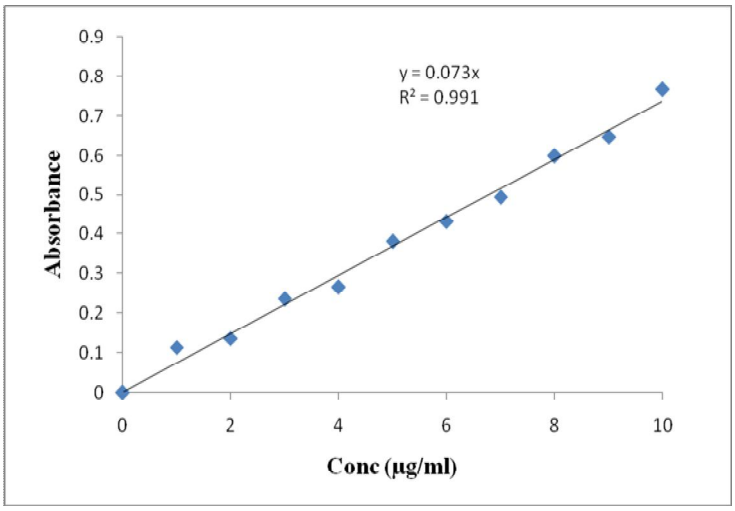

Figure 2 Calibration curve of tizanidine in pH 6.8 at 230 nm

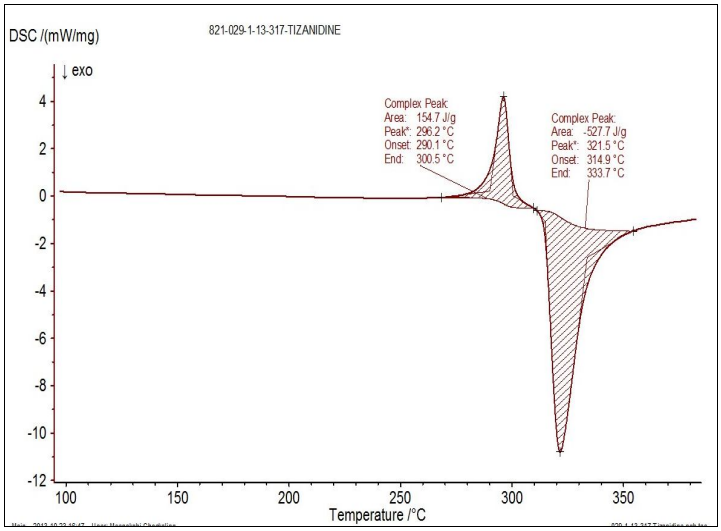

Figure 3 DSC of pure drug (Tizanidine Hydrochloride)

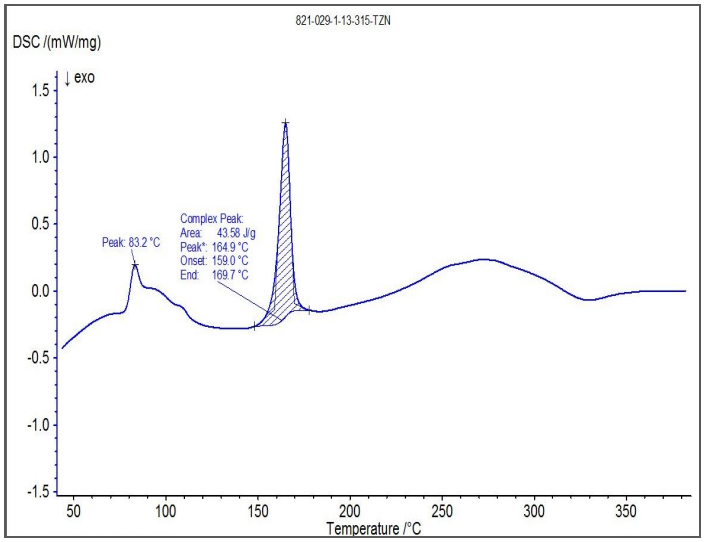

Figure 4 DSC of tizanidine physical mixture

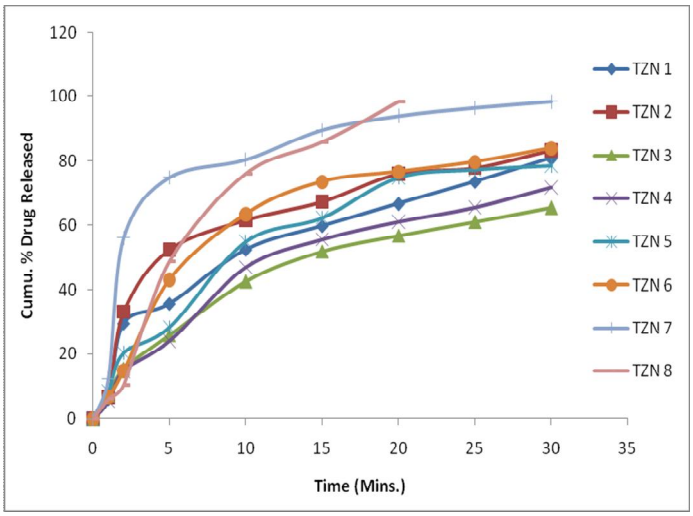

Figure 5 Zero order release plot of tizanidine hydrochloride fast dissolving tablets (TZN 1-8)

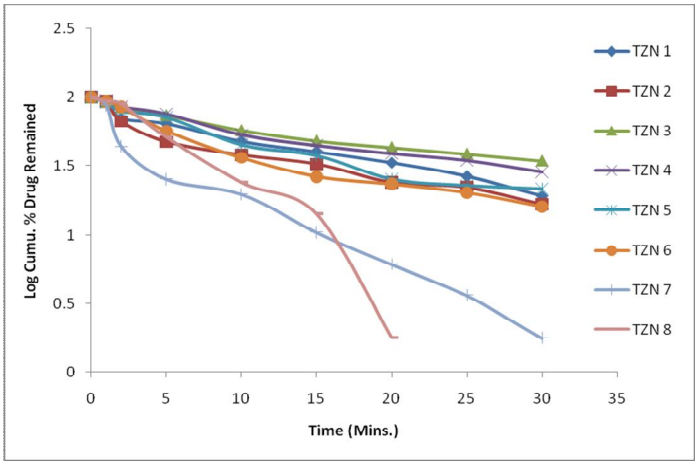

Figure 6 First order release plot of tizanidine hydrochloride fast dissolving tablets (TZN 1-8)

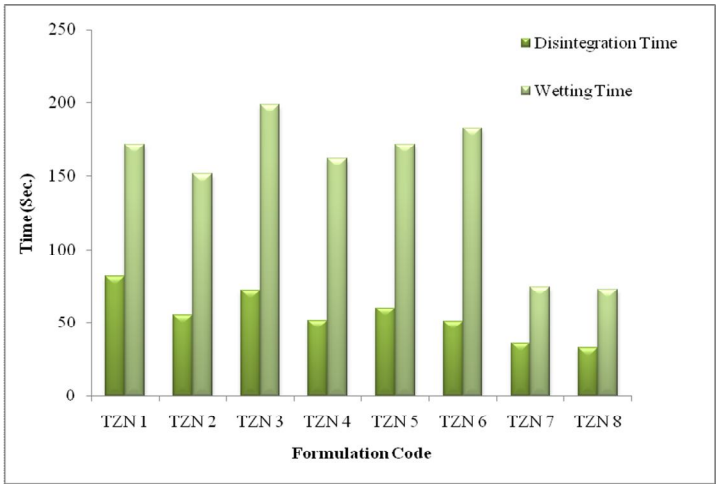

Figure 7 Disintegration and wetting time of different formulations

CONCLUSION

Fast dissolving tablets of tizanidine were successfully prepared by direct compression techniques using selected superdisintegrants for the immediate action and effective therapy. DSC 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.

ACKNOWLEDGEMENT

In the successful completion and compilation of this article, I thanks to Staff of Nishka Laboratories, Hyderabad (Mr. D. Hari Narayana and Mr. M. Nitya Swaroop Reddy) for providing me sufficient facilities, unfailing care and support during completion of this work.

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