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FORMULATION AND 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) of Tizanidine hydrochloride have been prepared by direct compression method. Formulations were evaluated for pre-compressional parameters such as angle of repose, % compressibility and hausner's ratio. The prepared tablets were evaluated for post-compressional parameters such as hardness, friability, thickness, *in-vitro* dispersion time, wetting time, and water absorption ratio. The prepared tablets were characterized by FTIR studies. Effect of superdisintegrants such as croscarmellose sodium, sodium starch glycolate and crospovidone on wetting time, *in-vitro* dispersion time and stability parameter has been studied. No chemical interaction between drug and excipients was confirmed by FTIR studies. From this study it was concluded that fast dissolving tablets could be prepared by direct compression method using different superdisintegrants enhanced dissolution will lead to improved bioavailability, improved effectiveness of Tizanidine hydrochloride.

Keywords: Tizanidine hydrochloride, Fast dissolving tablets, *In-vitro* evaluation, Superdisintegrants.

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INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self- administration, compactness, and ease in manufacturing. For the past one decade, there has been an enhanced demand for more patient friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost- effective dosage forms[1].

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription. This results in high incidence of noncompliance and ineffective therapy[2]. The

proper choice of superdisintegrant and its consistency of performance are of critical importance to the formulation development of fast dispersible tablets[3]. The objective of the present study is to develop fast dissolving tablets of Tizanidine HCl and to study the effect of functionality differences of superdisintegrants on the tablet properties as well as to improve the patient compliance without compromising the therapeutic efficacy.

Tizanidine hydrochloride (Fig. 1) is an imidazoline derivative, which acts as agonist on centrally located α_2 receptors and this leads to myotonolytic effects on skeletal muscle[4-7]. It is structurally and pharmacologically similar to clonidine and other α_2-adrenergic agonists[6,7]. The correct mechanism of Tizanidine in decreasing muscle tone and frequency of spasm is not clearly understood[7]. 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 2 h. Bioavailability of Tizanidine is about 34% to 40% and half-life is 2.5 h. 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 Tizanidine[8]. In order to overcome such extensive first-pass metabolism, the drug is selected as suitable candidate for fast dissolving tablets.

MATERIALS AND METHODS

Materials

Tizanidine hydrochloride was gift sample from Sun Pharma Pvt. Ltd. Mumbai, India. Croscarmellose sodium used was procured from Loba Chemicals, Mumbai. Crospovidone and Sodium starch glycolate used were procured from Merck Limited, Mumbai. All other reagents and chemicals used were of analytical grade.

Methods

Preparation of fast dissolving tablets of Tizanidine hydrochloride: Fast dissolving tablets of Tizanidine hydrochloride were prepared by direct compression. All the ingredients were passed through 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100 mg using 6 mm round flat punches on 10-station rotary tablet machine (Rimek). A batch of 50 tablets of each formulation was prepared for all the designed formulations. Different formulations compositions given in Table 1.

Evaluation of Tizanidine HCl fast dissolving tablets: The prepared tablets were evaluated for pre compressional parameters as well as hardness, thickness variation, weight variation, friability, disintegration time, wetting time, drug content and *in-vitro* dissolution studies.

Hardness: Pfizer hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers, and the handle was pressed, the force of the fracture was recorded.

Thickness: The thickness and diameter of 3 tablets were recorded during the process of compression using calipers (Mitotoyo; Japan).

Weight variation: For weight variation[9] twenty tablets were selected randomly from each formulation and weighed individually using a Shimadzu digital balance. The individual weights were compared with the average weight for the weight variation.

Friability: The friability of a sample of twenty tablets was measured using a USP type Roche friabilator. Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then dusted, reweighed and percentage weight loss (friability) was calculated.

Content Uniformity[10]: In which 10 tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 2 mg of Tizanidine HCL was extracted into distilled water and liquid was filtered by 0.22 m membrane filter disc (Millipore Corporation). The Tizanidine hydrochloride content was determined by measuring the absorbance at 320 nm (a PG instrument T_{80} model UV/VIS spectrophotometer) after appropriate dilution with distilled water. The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

Disintegration study: In the Disintegration time[11] 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.

Wetting time: In wetting time[12] study, twice-folded tissue paper was placed in a petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the

petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation:

$$R = 100 \times (w_a - w_b)/ w_b$$

Where, w_b and w_a were tablet weights before and after water absorption, respectively.

Dissolution Study: The *in-vitro* dissolution study was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution testers USP) type 2 (paddle). 900 ml of the dissolution medium phosphate buffer pH 6.8 was taken in vessel and the temperature was maintained at 37 ± 0.5^0C. The speed of the paddle was set at 50 rpm. 5 ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The samples were filtered through 0.22 µm membrane filter disc and analyzed for drug content by measuring the absorbance at 320 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates of three.

Characterization of Tizanidine HCl tablets by FTIR Studies:

The Fourier-transform infrared spectra of Tizanidine hydrochloride and mixture of Tizanidine hydrochloride with other excipients were obtained by using FTIR spectroscopy – 5300 (JASCO Japan). Samples were prepared by KBr pressed pellet technique. The scanning range was 400-1000 cm^{-1} and the resolution was 4 cm^{-1}. The spectra are shown in Fig. 6.

RESULTS AND DISCUSSIONS

The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property, were given in Table 2. The data obtained from post-compression parameters in all the formulations, friability is less than 1%, indicated that tablets had a good mechanical resistance, and were given in Table 3. Hardness of the tablets was found to be in the range of 3 to 3.5 kg/cm^2**.** Drug content was found to be in the range of 98.01 to 100.12 %, which is within acceptable limits. *In-vitro* dispersion times were found to be in the range of 22 to 67 sec. The water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water, were found to be in the range of 52 to 81 % and 26to 68 sec respectively is given in Table 4. The dissolution profiles of formulations are shown in Fig. 2 to 4. Among all the formulations TC_4 showed 50% drug release within 0.58 min and 90% of drug released within 2.53 min are shown in Fig. 5 and Table 5**.** FTIR studies revealed that there was no physico-chemical interaction between Tizanidine hydrochloride and other excipients (Fig. 6).

CONCLUSION

In present study, three types of superdisintegrants in different concentrations differed in their ability to disintegrate the model Tizanidine hydrochloride tablets. Such difference can potentially affect drug dissolution and is proposed as model formulation for disintegrants performance testing and quality control purposes. Hence, enhanced dissolution of fast dissolving tablets of Tizanidine hydrochloride will lead to improved bioavailability, improved effectiveness and hence better patient compliance.

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TABLES AND FIGURES

Table 1: Formulation of Tizanidine Hydrochloride FDTs

Ingredients(mg)	TC_1	TC_2	TC_3	TC_4	TP_1	TP_2	TP_3	TP_4	TS_1	TS_2	TS_3	TS_4
Tizanidine hydrochloride	4	4	4	4	4	4	4	4	4	4	4	4
Crosscarmellose sodium	3	6	9	12	--	--	--	--	--	--	--	--
Crospovidone	--	--	--	--	3	6	9	12	--	--	--	--
Sodium starch glcolate	--	--	--	--	--	--	--	--	3	6	9	12
Microcrystalline cellulose	30	30	30	30	30	30	30	30	30	30	30	30
Mannitol	56	53	49	47	56	53	49	47	56	53	49	47
Aspartame	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Total	100	100	100	100	100	100	100	100	100	100	100	100

Table 2: Pre-compressional parameters of Tizanidine hydrochloride FDTs

Formulation Code	Angle of repose (θ)* (± SD), n=3	Bulk density (gm/ml)* (± SD), n=3	Tapped density (gm/ml)* (± SD), n=3	Carr's index (%)* (± SD), n=3	Hausner's ratio* (± SD), n=3
TC_1	24.17±1.37	0.54±0.10	0.63±0.01	14.30±1.19	1.18±0.02
TC_2	25.45±1.44	0.52±0.03	0.62±0.01	15.19±1.31	1.10±0.05
TC_3	25.32±0.52	0.51±0.03	0.60±0.02	15.29±0.33	1.18±0.03
TC_4	25.20±0.19	0.50±0.05	0.59±0.01	15.02±0.27	1.17±0.05
TP_1	26.29±1.75	0.54±0.02	0.64±0.03	15.14±0.59	1.17±0.01
TP_2	27.11±1.33	0.53±0.10	0.62±0.04	15.12±0.25	1.17±0.07
TP_3	26.43±1.32	0.51±0.12	0.61±0.01	15.21±1.24	1.14±0.01
TP_4	26.28±1.41	0.53±0.07	0.62±0.01	15.52±0.61	1.13±0.05
TS_1	26.17±0.47	0.50±0.09	0.60±0.02	14.35±1.29	1.16±0.01
TS_2	26.52±1.11	0.51±0.01	0.60±0.01	15.41±1.46	1.17±0.01
TS_3	26.18±1.18	0.52±0.05	0.61±0.01	15.39±1.17	1.14±0.04
TS_4	27.54±1.27	0.54±0.08	0.63±0.02	15.43±1.32	1.15±0.02

* Average of three determinations

Table 3: Post-compressional parameters of Tizanidine hydrochloride FDTs

Formulation Code	Weight variation (%)* (± SD), n=3	Thickness (mm)* (± SD), n=3	Hardness (kg/cm^2)* (± SD), n=3	Friability (%)*
TC_1	101±0.49	3.31±0.23	3.2±0.15	0.59
TC_2	98±0.65	3.33±0.15	3.1±0.12	0.71
TC_3	99±1.61	3.12±0.21	3.4±0.10	0.48
TC_4	99±1.27	3.25±0.27	3.3±0.05	0.64
TP_1	101±1.21	3.26±0.16	3.2±0.16	0.62
TP_2	99±0.61	3.21±0.17	3.0±0.11	0.59
TP_3	99±0.18	3.30±0.10	3.5±0.21	0.57
TP_4	98±1.36	3.32±0.13	3.4±0.14	0.61
TS_1	99±1.17	3.40±0.11	3.1±0.10	0.38
TS_2	102±1.09	3.25±0.19	3.2±0.11	0.60
TS_3	100±0.47	3.31±0.22	3.0±0.15	0.51
TS_4	99±0.56	3.33±0.11	3.3±0.16	0.64

* Average of three determinations

Table 4: Disintegration, wetting time, water absorption ratio and drug content of Tizanidine hydrochloride FDTs

Formulation Code	*In-vitro* dispersion time (sec)* (± SD), n=3	Wetting time (sec)* (± SD), n=3	Water absorption ratio* (± SD), n=3	Drug content* (± SD), n=3
TC_1	47±1.41	51±1.15	67±1.31	99.36±0.18
TC_2	31±1.14	34±1.22	67±1.42	98.45±0.81
TC_3	25±1.35	29±1.37	73±1.26	98.01±1.11
TC_4	22±1.23	26±1.20	81±1.47	98.29±1.23
TP_1	63±1.11	67±1.13	57±1.38	100.07±1.17
TP_2	60±1.62	61±1.24	57±1.54	99.38±0.86
TP_3	58±2.59	64±1.51	62±1.28	99.52±1.43
TP_4	48±1.45	52±1.24	70±1.18	100.05±1.80
TS_1	67±1.41	76±1.17	67±1.61	99.18±0.59
TS_2	62±1.13	68±1.11	58±6.25	99.7±0.72
TS_3	51±1.57	58±1.20	64±1.56	99.44±1.19
TS_4	45±1.14	49±1.53	52±1.36	100.12±1.15

* Average of three determinations

Table 5: Release profile of fast dissolving tablets

Formulation Code	$t_{50\%}$ (min)	$t_{90\%}$ (min)
TC_1	1.56	7.52
TC_2	1.43	5.50
TC_3	1.10	3.58
TC_4	**0.58**	**2.53**
TP_1	2.55	7.59
TP_2	2.13	6.49
TP_3	1.51	5.45
TP_4	1.37	4.49
TS_1	4.10	9.15
TS_2	3.22	7.50
TS_3	2.32	6.02
TS_4	1.58	5.08

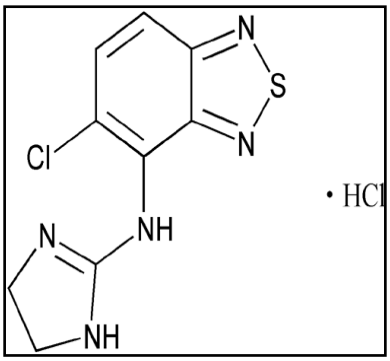

Fig. 1: Structure of Tizanidine HCl

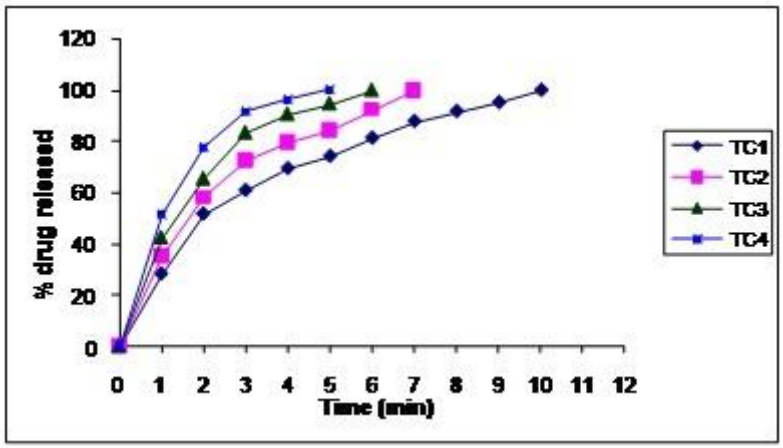

Fig.2: Dissolution profiles of formulations TC_1- TC_4

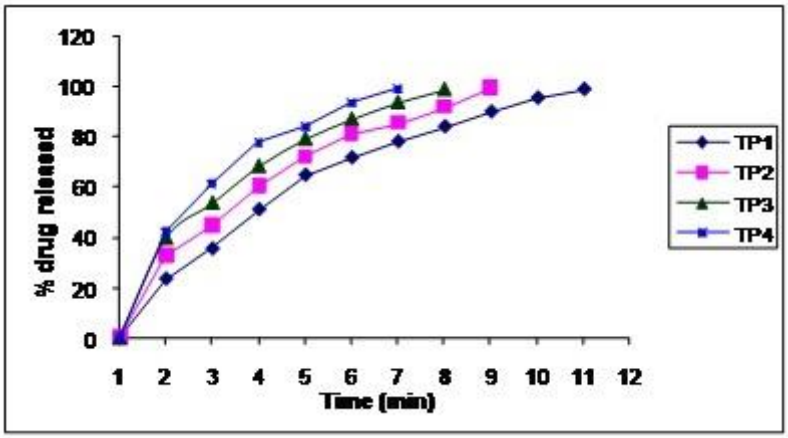

Fig.3: Dissolution profiles of formulations TP_1- TP_4

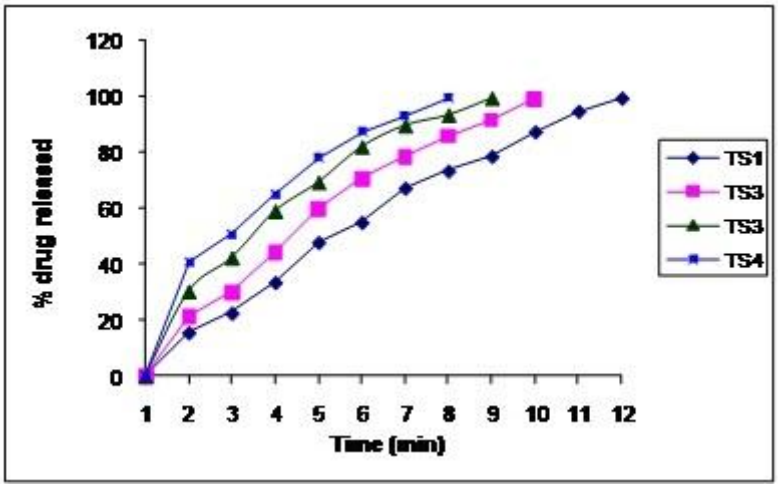

Fig.4: Dissolution profiles of formulations TS_1- TS

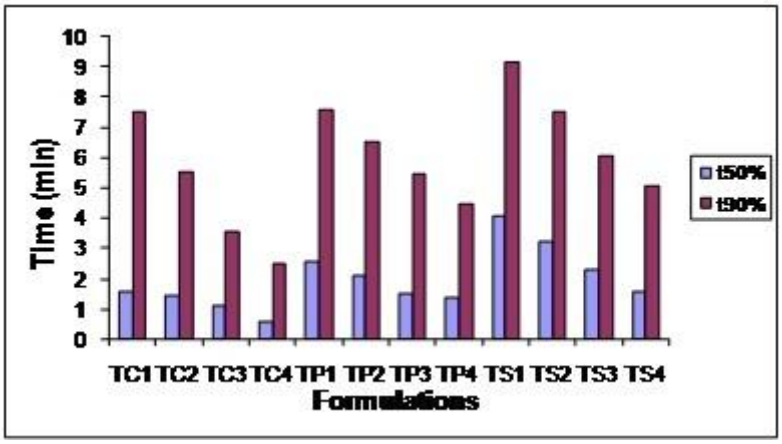

Fig. 5: Comparison of release profile ($t_{50\%}$ and $t_{90\%}$) of different tablet formulations

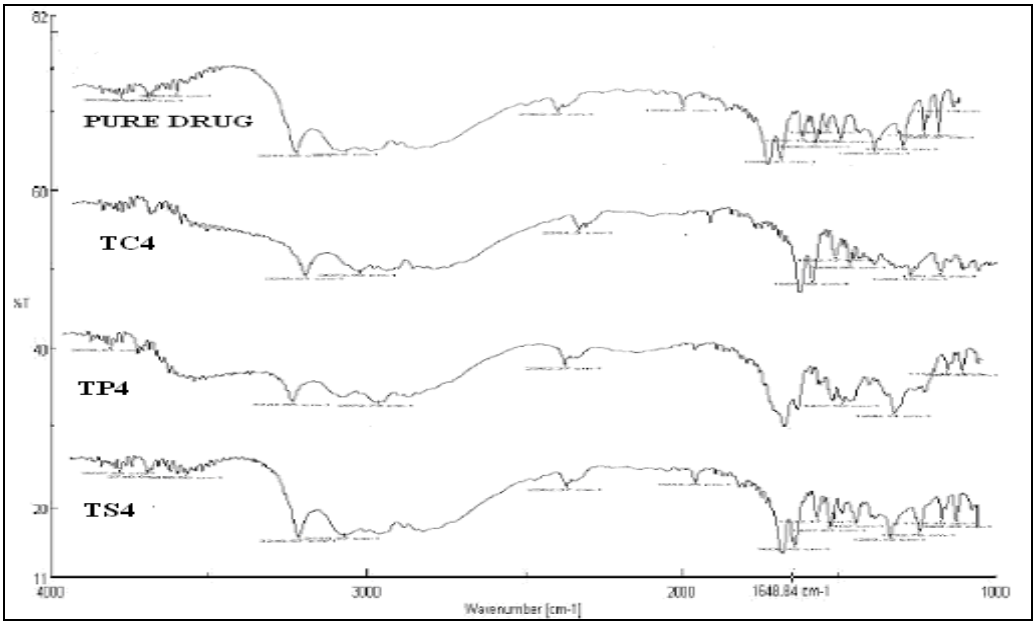

Fig. 6: IR spectrum of Tizanidine HCl, TC_4, TP_4 and TS_4