Research Article

FABRICATION AND EVALUATION OF FAST DISSOLVING TABLETS OF TIZANIDINE HYDROCHLORIDE BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Tizanidine hydrochloride (TZD HCL) which is used in the present study is an imidazoline derivatives, which acts as agonist on centrally located α 2 receptors and this leads to myotonolytic effects on skeletal muscle. TZD HCl fast dissolving tablets have been prepared by solid dispersion technique. The prepared tablets were 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 all the formulations the hardness test indicates good mechanical strength. Friability of all formulations was less than 1%, which indicates that the tablets had a good mechanical resistance. Thickness of the tablets range from 3.40 to 3.48 mm. Drug content was found to be high 99% and uniform in all the formulations. The weight variation results revealed that average percentage deviation was less then ± 7.5 %, which provides good uniformity in all formulations. Tablets prepared with PVP solid dispersion were showed disintegration time between the ranges of 38-60 sec and drug release showed between the ranges of 7-9 min. However tablets prepared with PVA solid dispersions were showed the disintegration time in 40-65 sec and the drug release showed in the range of 8-10 min. Among all the formulations TP 3 showed 50% drug release within 1.04 min and 90% of drug released within 5.02 min. FTIR results revealed that there was no interaction between dug and other excipients. The stability study was conducted as per ICH guideline and all the formulations were found to be stable. The results concluded that fast dissolving tablets of poorly soluble drug, TZD HCl showed enhanced dissolution, may lead to improved bioavailability and hence better patient compliance.

Keywords: Fast dissolving tablets, tizanidine hydrochloride, croscarmellose sodium, solid dispersion.

INTRODUCTION

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. 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 sulfur atom. This leads to lower bioavailability of TZD HCl [1-6].

Hence improvement of its water solubility and dissolution is of the therapeutic importance[7-8]. The enhancement of the solubility of poorly water soluble drug is one of the major current challenges to pharmaceutical scientists. Several techniques have been developed over the years to enhance the dissolution of drug such as micronization, inclusion, complexation and salt formation. Among other techniques, solid dispersion is the most simple and precise method for enhancing solubility and dissolution rate of any poorly soluble drug. In solid dispersion the particle size is reduced from crystalline to microcrystalline or molecular state[9] which enhance the solubility. There is widespread interest in solid dispersion since they offers a means of facilitating the dissolution and thereby bioavailability of poorly soluble drug when combined with freely soluble carriers.[10]

Thus increase in dissolution rate is achieved by a combination of effects. The most significant of which is reduction of particle size to an extent that cannot be readily achieved by conventional combination approaches. Other contributing factors include increased wettability of the materials, reduced aggregation and agglomeration and lightly increase in solubility of the drug owing to the presence of water soluble carriers[11-12].

In the present study, fast dissolving tablets of TZD HCL were prepared by using solid dispersion technique. The solid dispersions were prepared by solvent evaporation method using polyvinyl pyrrolidone (PVP) and polyvinyl Alcohol (PVA) as carriers at different ratios.

MATERIALS AND METHODS

Tizanidine hydrochloride was obtained in a gift sample from Blue-Cross PVT LTD. Nashik (India). Croscarmellose sodium (CCS) obtained as gift sample from Maruti Chemicals Ahmedabad (India) Aspartame from Aan Pharma Rakanpur (India). Microcrystalline cellulose, talc, magnesium stearate and lactose were purchased from SD Fine chemical Mumbai.

Preparation of SD of TZD HCL: SD of TZD HCL was prepared by solvent evaporation method. Drug was weighed and taken in china dish, dissolved in methanol and then carrier was added (PVP, PVA in the ratio of 1:1, 1:2, 1:4). The solvent was evaporated at room temperature and dried in hot air oven at 50^0C for 4 hrs. The resultant mass was passed through sieve no. 60 and stored in desiccator.

Drug content of SD: 8 mg of 1:1 SD, 12mg of 1:2 SD and 20mg of 1:4 SD were weighed and transferred to 250ml of volumetric flask. Dissolved in phosphate buffer pH 6.6 and the volume were made up with the same. An aliquot of the filtrate was diluted and analyzed spectrophotometrically (UV-1700, Shimadzu Corporation, Japan) at 228 nm.

Preparation of tablets containing SD of TZD HCL: The SD equivalent to 4mg of drug was taken. Then mixed with directly compressible diluent and superdisintegrant in a plastic container. Magnesium stearate, talc, aerosol were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend.

Evaluation of TZD HCL Tablets: The prepared tablets were evaluated for hardness, thickness, friability, disintegration time, wetting time, drug content, *in-vitro* dissolution studies and stability studies. Pfizer hardness tester is used for the determination of hardness of tablets. Tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture was recorded. The thickness of tablets was recorded during the process of compression using calipers (Mitotoyo, Japan). The friability of tablets was determined using Roche friabilator (Cambel Electronics Mumbai, India). Two tablets were accurately weighed and placed in the friabilator and operated for 100 revolutions. The tablets were de-dusted and reweighed. Percentage friability was calculated using the following formula.

$$F= (1-W_0 /W) X 100$$

Where,

Wo is the weight of tablets before the test and W is weight of the tablet after the test. Six tablets were tested from each formulation. In the disintegration time study tablet was put into 100ml distilled water at 37 ± 2 ^{0}. Time required for complete dispersion of the tablet was measured with the help of digital tablet disintegration test apparatus. In wetting time study a piece of tissue paper folded twice was placed in a small petri dish (internal diameter = 6.5cm) containing 5ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. For the determination of drug content, tablets were weighed individually, pulverized and diluted to 250ml with sufficient amount of phosphate buffer pH 6.6. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically (UV- 1700 Shimadzu Corporation, Japan) at 228nm.

The *in-vitro* dissolution study was carried out in the USP dissolution test apparatus (Electrolab TDT-08 L Dissolution tester USP) type 2 (Paddle). 900ml of the dissolution medium (Phosphate buffer pH 6.6) was taken in vessel and the temperature was maintained at 37 ± 0.5^{0}C. The speed of the paddle was set at 50rpm. 5ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The sample withdrawn was filtered and diluted with phosphate buffer pH 6.6 prior to analysis in the UV spectrophotometer (UV- 1700 Shimadzu Corporation, Japan) at 228nm. The stability study of the tablets was carried out according to ICH guidelines at 40 ± 2^{0}C/75 ± 5 % RH for three months by storing the samples in stability chamber (Lab Care, Mumbai).

RESULTS AND DISCUSSION

The values of pre-compression parameters were within the prescribed limits and indicated free flowing properties **(Table 2).** The data obtained from post compression parameters such as hardness, friability, thickness, drug content, wetting time and *in-vitro* disintegration. In all the formulations, hardness test indicated good mechanical strengths, friability is less than 1% indicated that tablets had a good mechanical resistance. Thickness of the tablets range from 3.40 to 3.48 mm. The results of hardness, friability and thickness were given in **Table 3.** Drug content was found to be high 99% and uniform in all the formulations. The disintegration time was found between the ranges of 38 to 60 sec in the case of tablets prepared by using PVP as carrier. The disintegration time was found in the range of 40 to 65 sec in case of tablets prepared by PVA carrier **(Table 4).** The percent of drug release showed between the ranges of 7-10 min, among all the formulations TP3 showed 99% drug release within the 7 min**.** The dissolution of TZD HCL from the tablets is shown in **Fig 1**. *In-vitro* dissolution studies on the promising formulation TP 3 and TA 3 were carried out in Phosphate buffer pH 6.6, and the various dissolution parameter values viz., percent drug dissolved in 2 min, 4 min, 6 min, 8 min and 30 min (D_2, D_4 D_6, D_8, and D_{10}), $t_{50\%}$, and $t_{90\%}$ are shown in **Table 5**. The formulation TP 4 50 % of drug released in 1.04 min, and 90 % of drug released in 5.02 min. The dissolution rate of tablets prepared with SD with PVP in the ratio 1:1, 1:2, 1:4 and with PVA in the ratio 1:1, 1:2, 1:4 increased significantly ($P<0.05$). This may be due to the use of croscarmellose sodium, which causes swelling to 4-8 folds in sec[13] and due to particle size reduction and improved wettability[14]. In addition to micronization, conversion of drug to amorphous form during the preparation might have also contributed to the increased dissolution rate absorbed with the SD[15]. The stability study for all the formulations were carried according to ICH guidelines by storing the tablets in a stability chamber (Lab Care, Mumbai) at 40^0 ± 2^0 C/ 75 ± 5% RH for three months. There was no significant change in *in-vitro* dispersion time, wetting time and drug content of the formulations **(Table 6)**.

Table 1: Formula used in the preparation of TZD tablets using PVP and PVA SD.

Formulation Code	Amount of PVP SD equivalent to 4mg of TZD HCL	Amount of PVA SD equivalent to 4mg of TZD HCL	Lactose	Aspartame	CCS	MCC
TP1	8.5	-	109. 35	2	6	20
TP2	12.24	-	105.26	2	6	20
TP3	20.50	-	95	2	6	20
TA1	-	8.80	108.7	2	6	20
TA2	-	12.35	105.15	2	6	20
TA3	-	20.30	94.7	2	6	20

All the formulations contain 1.5mg of magnesium stearate, talc and aerosil.
*** CCS = Croscarmellose Sodium, MCC = Microcrystalline Cellulose.*

Table 2: Pre-compressional Parameters

Formulation	Angle Of Repose (Θ) (±SD), n=6	Compressibility (%) (±SD), n=6	Hausner Ratio (±SD), n=6
TP1	22.40 (0.79)	22.70 (0.90)	1.33(0.07)
TP2	23.70 (1.55)	25.65 (1.30)	1.40 (0.08)
TP3	22.12 (0.65)	19.66 (2.20)	1.20 (0.06)
TA1	24.38 (0.50)	23.80 (0.70)	1.39 (0.05)
TA2	22.65 (0.45)	24.52 (0.35)	1.25 (0.00)
TA3	23.60 (0.70)	20.00 (2.10)	1.22 (0.04)

Table 3: Post-compressional Parameters of tablets

Formulation	Hardness (kg/cm^2) (±SD), n=6	Friability (%) (±SD), n=6	Thickness (±SD), n=6
TP1	3.59 (0.30)	0.25 (0.05)	3.42 (0.044)
TP2	3.55 (0.40)	0.33 (0.07)	3.46 (0.049)
TP3	3.00 (0.20)	0.29. (0.08)	3.48 (0.043)
TA1	3.60 (0.10)	0.28 (0.06)	3.44 (0.055)
TA2	3.08 (0.30)	0.24 (0.05)	3.40 (0.052)
TA3	3.20 (0.40)	0.37 (0.08)	3.41 (0.042)

Table 4: Disintegration, wetting time and drug content of tablets

Formulation	Disintegration time (sec) (±SD), n=6	Wetting time (sec) (±SD), n=6	Drug content (%) (±SD), n=6
TP1	60 (1.00)	128 (2.70)	100.00 (0.50)
TP2	48 (2.20)	111 (1.60)	98.40 (0.90)
TP3	38(1.20)	96 (0.50)	99.60 (0.40)
TA1	65 (2.20)	134 (3.30)	101.00 (0.60)
TA2	59 (1.50)	122 (2.10)	99.50 (0.20)
TA3	40 (2.50)	101 (1.50)	98.10 (1.00)

Table 5: *In- vitro* Dissolution parameters of different TZD HCl fast dissolving tablet formulations.

Formulation Code	Parameters						
	D_2	D_4	D_6	D_8	D_{10}	$T_{50\%}$	$T_{90\%}$
TP 3	61.41	81.19	97.88	100	--	1.04 min	5.02 min
TA 3	52.75	74.80	89.02	96.02	99.73	1.89 min	6.93 min

TP 3 and TA 3 are promising fast dissolving tablet formulation, D_2 is percent drug released in 2 min, D_4 is percent drug release in 4 min, D_6 is percent drug release in 6 min, D_8 is percent drug release in 8 min, D_{10} is percent drug release in 10 min, $t_{50\%}$ is time for 50 % drug dissolution, $t_{90\%}$ is time for 90% drug dissolution.

Table 6: Results of Stability Study

Formulation	Disintegration time (sec) (±SD), n=6	Wetting time (sec) (±SD), n=6	Drug content (%) (±SD), n=6
TP1	61 (1.30)	130 (3.50)	99.50(0.60)
TP2	48(1.22)	110 (2.20)	98.30 (0.70)
TP3	39(1.25)	97 (2.30)	99.30 (0.40)
TA1	65 (2.50)	135(2.37)	99.00(0.30)
TA2	60 (1.50)	120(2.50)	99.10(0.40)
TA3	40 (0.90)	100(3.50)	98.00(1.50)

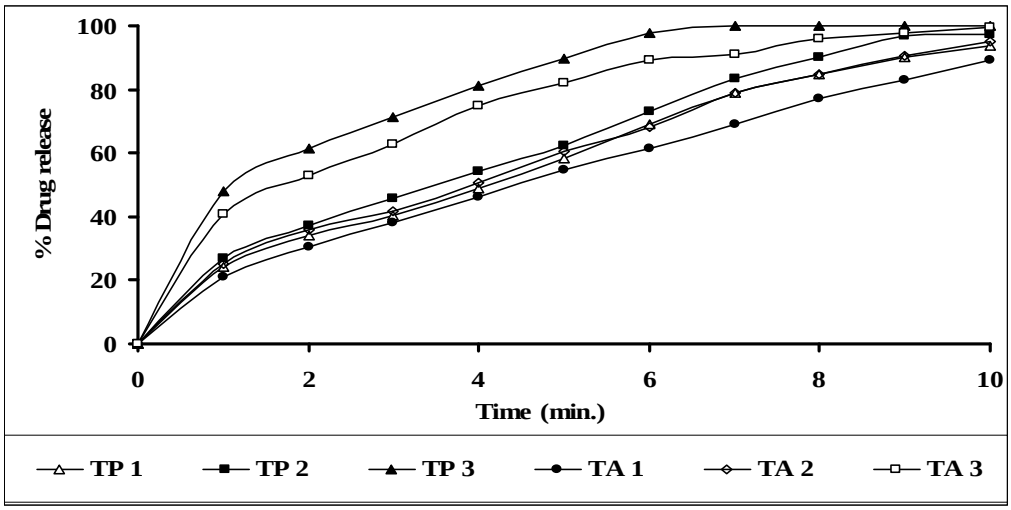

Figure 1: Dissolution Profile of TZD HCL tablets using PVP and PVA SD.

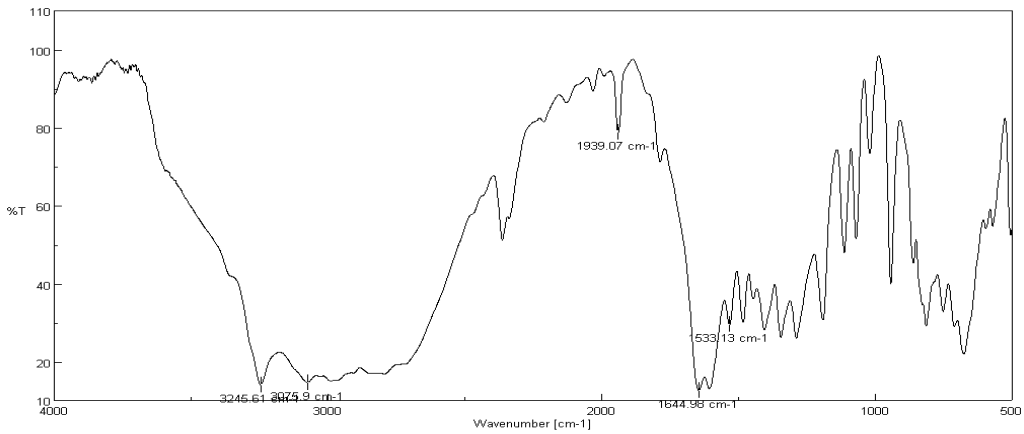

Figure 2: IR Spectrum of pure TZD.

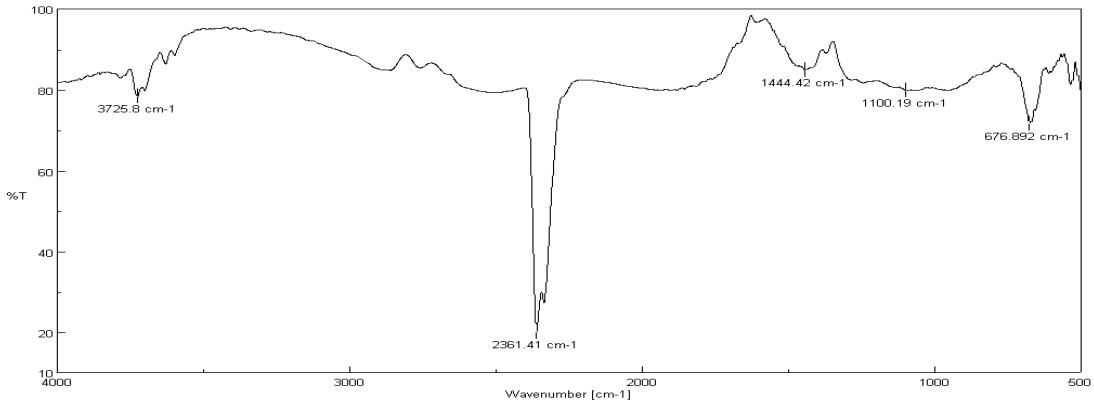

Figure 3: IR Spectra of PVA.

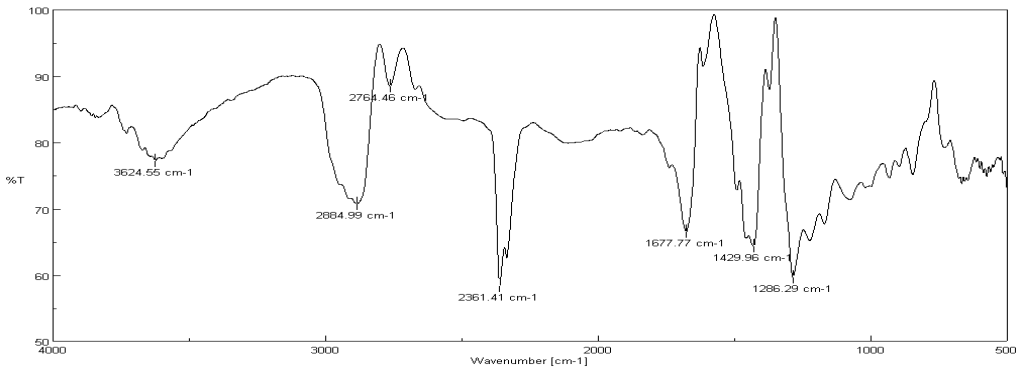

Figure 4: IR Spectra of PVP.

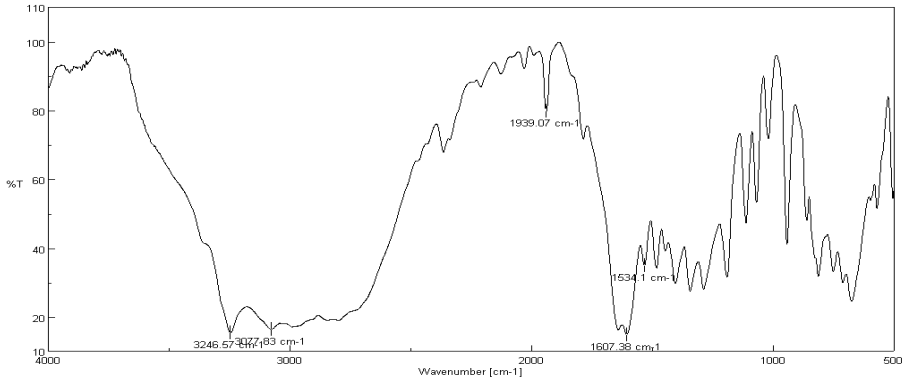

Figure 5: IR Spectra of PVA + TZD.

Drug-Carrier Interaction study by FTIR:

The Fourier transform infrared spectroscopy studies were carried out for pure drug along with polymers. The results are summarized as follows.

IR Spectra	Peak of functional groups [wave length (cm^{-1})]		
	C=N Stretch	C-H Stretch	Amide NH Stretch
Tizanidine HCl (pure)	1644.98 cm^{-1}	3075.9 cm^{-1}	3245.61 cm^{-1}
Tizanidine + PVA polymer	1607.38 cm^{-1}	3077.89 cm^{-1}	3246.57 cm^{-1}
Tizanidine + PVP polymer	1607.38 cm^{-1}	3077.83 cm^{-1}	3246.57 cm^{-1}

The above peaks can be considered as characteristic peaks of TZD. These peaks were not affected and prominently observed in IR spectra of TZD along with polymers. This indicates there is no interaction between TZD and polymers **(Fig 2-5).**

CONCLUSION

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. Bioavailability of Tizanidine is about 34% to 40% and half life is 2.5 hrs. The results concluded that fast dissolving tablets of poorly soluble drug, TZD HCl showed enhanced dissolution, may improved bioavailability and hence better patient compliance.

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