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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF MATRIX TABLET TRAZODONE HYDROCHLORIDE USING NATURAL POLYMER

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ABSTRACT

Increased complications and costs of marketing of innovative drugs focused greater attention to the development of sustained release (SR) or controlled release (CR) drug delivery systems. Trazodone Hydrochloride (TRZ) is a well-known chemical compound that is used as an antidepressant that belongs to a selective serotonin reuptake inhibitor (SARI). The objective of present work was to develop and evaluated oral sustained release matrix tablet of TRZ. Pre-compression parameters were evaluated. The tablets were evaluated for post-compression parameters such as thickness, hardness, average weight, friability and In vitro release studies. No interactions were observed between TRZ and excipients from the Fourier transform infrared spectroscopy. The present research work was successful in improving the efficacy TRZ oral therapy as the drug release was extended for 12 hours thus reducing dosing frequency thereby improving patient compliance. The study also revealed the applicability of HPMC K-15, Gaur gum and PVP K30 as rate-controlling polymers in matrix tablets. The hydrophilic matrix of HPMC alone cannot control the release TRZ effective for 12 h while when combined with guar gum, may slow down the release of the drug and therefore, can be successfully employed for the formulation of matrix tablets SR. It may be concluded from the study that; the optimized formulation F-8 was shown maximum drug release 99.12 % in 12 h of dissolution. The release kinetic data of formulation F-8 shown first order release kinetics ($R2$ = 0.980).

KEYWORDS: Trazodone Hydrochloride, Pre/post-compression parameters, Direct compression, HPMC, Gaur gum.

INTRODUCTION

The conventional dosage forms such as tablets and capsules are the major oral preparations and have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance in last two decades [1]. Sustained release dosage forms are the formulations which release the therapeutically active agents for longer period of time at expected rate after its single dose administration [2]. When highly water-soluble drugs are prepared as oral sustained release dosage form cause problems like they may be released more rapidly and result in toxicity if not prepared in appropriate fashion [3]. Many methods are there to formulate oral sustained release dosage form among which matrix system is most appropriate due to consistency, validation, scale up and cost effective [4]. Microcrystalline cellulose and PVP were used as diluents and binder respectively. Oral CR systems present a variety of benefits above conventional dosage forms that include decrease in dosage rate, patient ease, minimum toxicity and improved patient compliance [5]. On the other hand, more constant level of drug in the blood constant flow with minimum peak-valley is reached, achieve greater efficacy. TRZ is chemically 2-{3-[4-(3-chlorophenyl) piperazin-1-yl] propyl}-2H, 3H-[1, 2, 4] triazolo[4,3-a]pyridin-3-one. It is a serotonin antagonist and reuptake inhibitor (SARI), which is a second-generation antidepressant compound belonging to the class of phenyl piperazine. It acts as a serotonin agonist at high doses and low doses. The drug showing antidepressant activity is due to the blockage of serotonin reuptake by inhibiting serotonin reuptake pump at the presynaptic neuronal membrane. TRZ shows its therapeutic actions through 5-HT_2A receptors. TRZ also induces anti-anxiety and sleep-inducing effects [6]. It does not have similar properties to selective serotonin reuptake inhibitors (SSRIs) since its inhibitory effect on serotonin reuptake and 5-HT_2C receptors are relatively weak [7]. The result of α-adrenergic action blocking and modest histamine blockade at H receptor due to sedative effect of TRZ. It weakly blocks presynaptic α_2-adrenergic receptors and strongly inhibits postsynaptic α_1 receptors. TRZ does not show any action on the reuptake of norepinephrine or dopamine within the CNS. It has fewer anticholinergic side effects than most of the tricyclic antidepressants such as dry mouth, constipation and tachycardia. TRZ metabolizes to its primary m-chlorophenyl piperazine (mCPP) which is a nonselective serotonin receptor agonist which might outweigh the benefits of TRZ [8-11]. Hence, in the present study, an attempt has been made to develop sustained release matrix tablets of TRZ using the synthetic polymers like HPMC K-15 and natural polymers like Gaur gum and fixed to retard the drug release up to 12 h.

MATERIALS AND METHODS

Trazodone HCl were obtained as pure sample from Sun Pharmaceutical Industries Ltd. Dewas, as gift samples along with their analytical reports. HPMC K15M was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Guar Gum, Polyvinyl Pyrrolidone K 30, Lactose and Talc were purchased from SD Fine Chem. Limited, Mumbai. Magnesium stearate was purchased from Loba Chemie Pvt. Ltd, Mumbai. All other

chemicals were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Preformulation studies

Standardization of TRZ by UV-Visible spectrophotometry

Preparation of stock solution: Stock solution 100µg/ml TRZ was prepared in 0.1 N HCl solutions. This solution was suitably diluted with 0.1 N HCl to obtain a concentration of 10µg/ml. The resultant solution was scanned in the range of 200-400 nm using UV double beam spectrophotometer (Lab India UV-3000+).

Standard calibration of vildagliptin in 0.1 N HCl: 100 mg of TRZ was accurately weighed and dissolved in100 ml of 0.1 N HCl to obtain a concentration of 1000µg/ml. From the above 10 ml was withdrawn and diluted to 100 ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5, 1, 1.5, 2, and 2.5 ml were diluted in 10 ml volumetric flask with phosphate buffer to give concentrations in the range of 5-25µg/ml, respectively, absorbance was measured at 256 nm.

Drug-excipient compatibility study

FTIR spectra of pure drugs, polymers used, and blends were recorded on KBr disk method using Brukers Alpha Spectrophotometer with IR solution software to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with potassium bromide in a glass mortar with pestle and compressed into disks in a hydraulic press (Techno search Instruments, India). FTIR spectra of all the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolutions.

Preparation of matrix tablets

A total of 9 formulations were prepared by direct compression technique in keeping with the formulas given Table 1. Sustained release matrix tablets of TRZ were prepared by combining HPMC K15M, PVP K30 and guar gum as matrix forming materials, whereas lactose as a directly compressible dilutant and talc as an anti-adherent. All ingredients used were passed through 80 # sieve, weighed and blended. The powders were prepared by direct compression technique and evaluated for its flow properties. The powdered mixture was compressed by using eight mm concave faced punches using in an eight-station compression machine (Shakti Pharmatech. Pvt. Ltd, Gujarat). The composition of formulation was given in table 1.

Table 1. Various formulations of TRZ matrix tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
TRZ	50	50	50	50	50	50	50	50	50
HPMC K-15	40	60	80	-	-	-	20	30	40
Gaur Gum	-	-	-	40	60	80	20	30	40
PVP K30	15	15	15	15	15	15	15	15	15
Talc	10	10	10	10	10	10	10	10	10
Lactose	110	90	70	110	90	70	110	90	70
Total Weight	225	225	225	225	225	225	225	225	225

Evaluation of TRZ SR matrix tablets

Evaluation of granules

Angle of repose

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend were measured. The angle of repose was calculated using the following formula [12].

$$\tan \Theta = h/r$$

Where, "h" is the height of the heap and "r" is the radius of the heap of granules.

Bulk Density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The BD of powder blends was determined using the following formula [13].

Bulk density = Total weight of powder/Total volume of powder

Tapped bulk density (TBD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of powder blends were determined using the following formula [14].

TBD = Total weight of powder/Total volume of tapped powder

Carr's compressibility index

The Carr's compressibility index was calculated from bulk density (BD) and tapped density of the blend. A quantity of 2 g of blend from each formulation, filled into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25 ± 2/min to measure the tapped volume of the blend. The BD and tapped density were calculated by using the bulk volume and tapped volume.

Carr's compressibility index was calculated using the following formula [15, 16].

Carr's compressibility index (%) = [(Tapped density-Bulk density) ×100]/Tapped density

Evaluation of Matrix Tablets

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper [17].

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness

and average of six values was noted along with standard deviations.

Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, de dusted and reweighed. The friability was calculated as the percentage weight loss.

% friability was calculated as follows

$$\% \text{ Friability} = (W1 - W2) \times 100/W1$$

Where W1 = Initial weight of the 10 tablets, W2 = Final weight of the 10 tablets after testing.

Friability values below 0.5-1% are generally acceptable [17].

Weight Variation Test

To study weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ_{max} of 246 nm using of 0.1 N HCl as blank.

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask maintaining the temperature of 37±0.5^{0}c and rpm of 75. One TRZ tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 12hours. Sample measuring 5ml were pulled back after time intervals up to 12 hours using 5ml pipette. The new disintegration medium (37^{0}C) was supplanted each time with a similar amount of the sample and takes the absorbance at 246.0 nm using spectroscopy.

Kinetic Analysis of Dissolution Data

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero-order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$$C = K0\ t \quad (1)$$

Where, K0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{LogC} = \text{LogC0} - K1\ t / 2.303 \quad (2)$$

Where, C0 is the initial concentration of drug and K1 is first order constant.

$$Q = KHt1/2 \quad (3)$$

Where, KH is the constant reflecting the design variables of the system.

$$Q01/3 - Qt1/3 = KHC\ t \quad (4)$$

Where, Qt is the amount of drug remained in time t, Q0 is the initial amount of the drug in tablet and KHC is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data - Cumulative % drug release vs. time (Zero order kinetic model); Log cumulative of % drug remaining vs. time (First order kinetic model); Cumulative % drug release vs. square root of time (Higuchi model); And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law) [18].

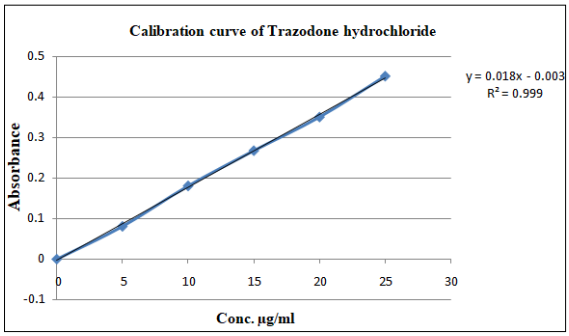

Fig. 1: Calibration curve of TRZ at 246 nm

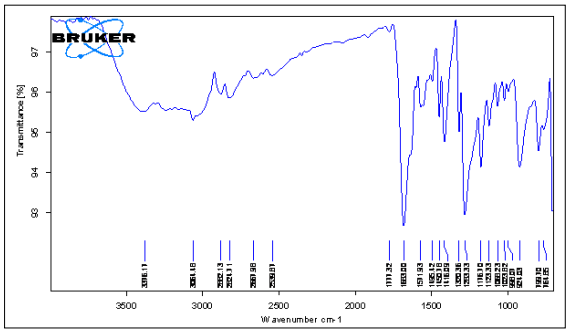

Fig. 2: FT-IR Spectrum of Pure Drug (TRZ)

Table 2: Result of pre-compression properties of TRZ matrix tablets

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's index	Hauser's ratio
F1	0.458	0.523	12.428	1.142
F2	0.465	0.526	11.597	1.131
F3	0.458	0.539	15.028	1.177
F4	0.456	0.537	15.084	1.178
F5	0.451	0.542	16.790	1.202
F6	0.462	0.533	13.321	1.154
F7	0.471	0.542	13.100	1.151
F8	0.465	0.523	11.090	1.125
F9	0.478	0.541	11.645	1.132

Table 3: Results of post compression properties of TRZ matrix tablets

F. Code	Thickness (mm)	Hardness (kg/cm^2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3
F1	3.12	4.6	Pass	0.852	97.95
F2	3.15	4.7	Pass	0.865	99.89
F3	3.32	4.9	Pass	0.898	98.75
F4	3.14	4.8	Pass	0.856	98.65
F5	3.16	4.5	Pass	0.845	98.98
F6	3.14	4.7	Pass	0.832	99.15
F7	3.18	4.6	Pass	0.854	98.78
F8	3.19	4.8	Pass	0.865	99.12
F9	3.18	4.7	Pass	0.854	98.98

Table 4: In-vitro drug release study of TRZ matrix tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	38.98	35.65	33.36	32.23	30.25	30.25	25.56	22.23	18.89
1	48.89	40.25	39.98	38.98	35.56	33.36	31.45	29.98	26.65
1.5	69.98	63.36	55.65	53.32	51.12	48.98	42.23	40.12	32.25
2	93.36	89.98	69.98	63.36	62.32	55.65	51.25	50.23	43.12
3	98.98	95.65	78.89	79.98	76.65	69.98	68.89	65.56	51.25
4		98.45	89.98	91.25	93.69	79.95	75.65	73.32	60.25
6			98.78	98.89	98.98	88.89	82.23	85.56	69.98
8						98.42	97.89	92.23	73.25
12								99.12	79.98

Table 5: In-vitro drug release data for optimized formulation F8

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	22.23	1.347	77.77	1.891
1	1.000	0.000	29.98	1.477	70.02	1.845
1.5	1.225	0.176	40.12	1.603	59.88	1.777
2	1.414	0.301	50.23	1.701	49.77	1.697
3	1.732	0.477	65.56	1.817	34.44	1.537
4	2.000	0.602	73.32	1.865	26.68	1.426
6	2.449	0.778	85.56	1.932	14.44	1.160
8	2.828	0.903	92.23	1.965	7.77	0.890
12	3.464	1.079	99.12	1.996	0.88	-0.056

Table 6: Regression analysis data of TRZ

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	R^2
F8	0.832	0.980	0.945	0.968

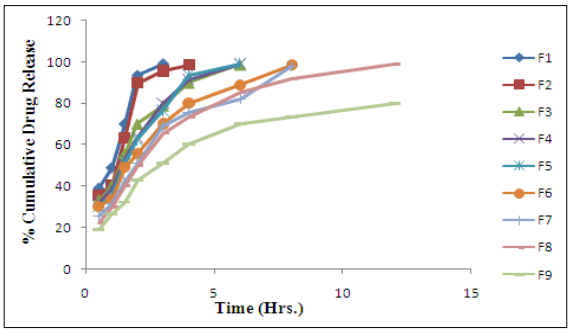

Fig. 3: In-vitro drug release study of matrix tablets

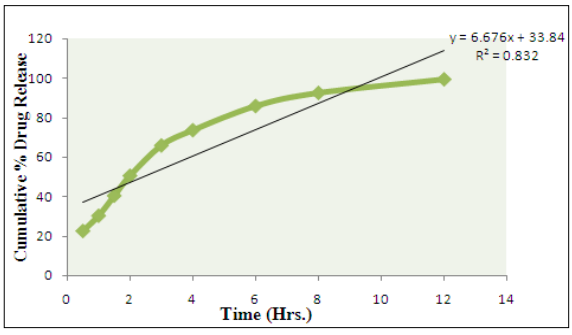

Fig. 4: Zero order release Kinetics

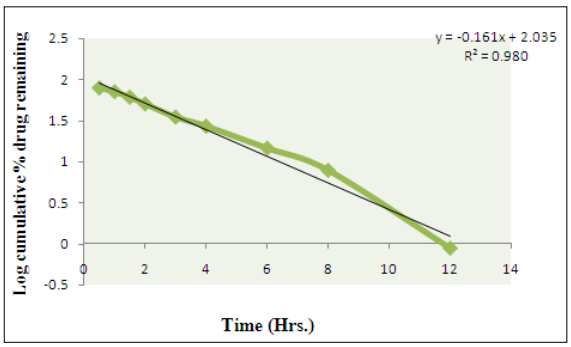

Fig. 5: First order release kinetics

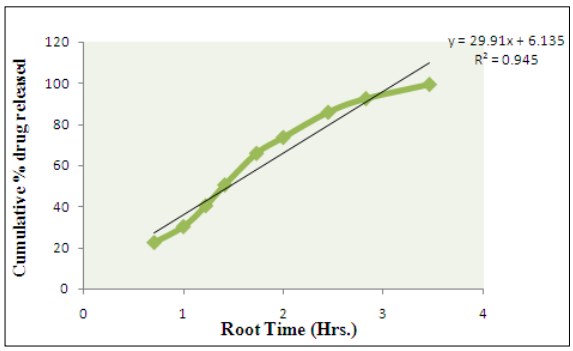

Fig. 6: Higuchi release Kinetics

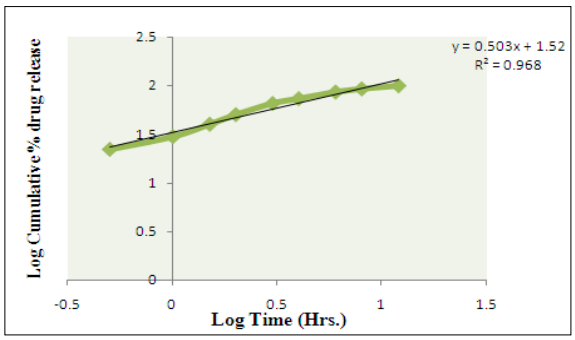

Fig. 7: Korsmeyer-Peppas release Kinetics

RESULT AND DISCUSSION

According to experiment TRZ was freely soluble in methyl alcohol and ethyl alcohol and it is slightly soluble in 0.1N NaOH, 0.1N HCL and 6.8 pH phosphate buffers. The melting point of TRZ was calculated 223-226ºC. λ_{max} of TRZ was 246.0 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25 µg/ml Fig.1. Identification of TRZ was performed by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification Fig.2.

Tablet powder blend was subjected to various pre-compression parameters (Table 2). Value of angle of repose was indicates that the powder blend has good flow properties. The bulk density of all the formulations of TRZ was found to be in the range of 0.451 to 0.478 (gm/ml) according to this range, powder has good flow properties. The tapped density of all the formulations was calculated from range of 0.523 to 0.542 which show that good flow properties. The compressibility index of all the formulations was found to be ranging between 11.090 to 16.790 which show that the powder has good flow properties. All the formulations have shown the Hauser's ratio ranging between 1.131 to 1.202 indicating the powder has good flow properties.

The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight. The hardness of the tablets ranged from 4.5 to 4.9kg/cm^2 and the friability values were less than 0.9% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 3.12 to 3.32mm. All the formulations satisfied the content of the drug as they contained 97 to 99 % of TRZ and good uniformity in drug content was observed. Thus, all the physical attributes of the prepared tablets were found be practically within control.

The tablets were evaluated for in vitro dissolution studies in 0.1N HCl for 12 hours. The results of in-vitro drug release revealed that the TRZ was released in a controlled manner from all the formulations where formulation F8 showed maximum drug release i.e. 99.12% at the end of 12th hour. The results of release studies of formulations F1 to F9 are shown in Table 4 and Figure 3.

The optimized formulation F8 was subjected to goodwill of fit test by linear regression analysis according to zero order, Higuchi's, first order kinetic equation, and Korsmeyer's models in order to determine the mechanism of drug release in vitro drug release study. When regression coefficient values of were compared, it was perceiving that 'r' values of first order was maximum i.e. 0.980 hence indicating the drug release from formulations was found to follow first order release kinetics Table 5, 6 & Fig. 4-7.

CONCLUSION

The present research work was successful in improving the efficacy of TRZ oral therapy as the drug release was extended for 12 hours thus reducing dosing frequency thereby improving patient compliance. The sustained release matrix tablets of TRZ were prepared by direct compression method. FTIR spectra indicated the absence of probable chemical interaction between the drug and polymers. TRZ SR matrix tablets were formulated with natural and synthetic polymer. Among 9 formulations, F8 is optimized based on the cumulative % drug release is 99.12 in 12 hrs. The in vitro drug release data was plotted for various kinetic models. The R^2 value for optimized formulation F8 for first order was found to be 0.980.

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