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Formulation Development and Evaluation of Gastroretentive Floating Tablets of Trazodone Hydrochloride Using Natural Polymer

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ABSTRACT

Trazodone Hydrochloride (TRZ) is a well-known chemical compound that is used as an antidepressant that belongs to selective serotonin reuptake inhibitors (SARI). TRZ is used as anti-anxiety and sleep-inducing agent. The objective of the present investigation was formulation and evaluation of gastroretentive floating tablets of TRZ for prolongation of gastric residence time with a view to deliver the drug at the sustained and controlled manner in the gastrointestinal tract. The tablets of TRZ were prepared by direct compression method using gas generating agent and different polymer combinations such as hydroxy propyl methylcellulose and xanthan gum, guar gum. The prepared tablets of TRZ were evaluated for hardness, thickness, friability, weight variation, drug content uniformity, buoyancy lag time, total floating time, swelling index, *in-vitro* dissolution study, etc. All the compositions were resulted in adequate Pharmacopoeial limits. The varying concentration of gas generating agent and polymers was found to affect on *in-vitro* drug release and floating lag time. *In vitro* drug release of floating gastro retentive tablet of TRZ shown that the formulation F7 was found to be the best formulation as it releases 98.89±0.32% TRZ in a controlled manner for an extended period of time (up to 12 hrs). The release data was fitted to various mathematical models such as higuchi, korsmeyer-peppas, first order and zero order to evaluate the kinetics and mechanism of the drug release. The Optimized formulation (F7) showed no significant change in physical appearance, drug content, floating lag time, *in vitro* dissolution studies after 75%±5% RH at 40±20C relative humidity for 6 months. Prepared floating tablets of TRZ may prove to be a potential candidate for safe and effective controlled drug delivery over an extended period of time for gastro retentive drug delivery system.

Keywords: Trazodone Hydrochloride, Serotonin reuptake inhibitors, Gastro retentive, Floating tablet, Total floating time.

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INTRODUCTION

Rapid gastrointestinal transit could result in incomplete drug release from the dosage form above the absorption zone leading to diminished efficacy of the administered dose. These considerate have led to the development of a controlled or sustained delivery system. The main purpose for developing these systems was to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for long time. Gastroretentive drug delivery is an approach to prolong gastric retention time, thereby targeting site- specific drug release in the upper GIT for local and systemic effect. Therefore, different approaches have been proposed to retain the dosage form in the stomach. These include bioadhesive systems, swelling and expanding systems and floating systems. Floating drug delivery or hydrodynamically balanced systems have a sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period [1-4]. 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 [5]. 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 [6]. 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 non selective serotonin receptor agonist which might outweigh the benefits of TRZ [7-10]. A majority of the investigations on natural excipients in drug delivery systems have centered on proteins and polysaccharides due to their ability to produce a wide range of materials and properties according to molecular structural alterations. In recent years, plant gums and mucilages have evoked tremendous interest due to their diverse pharmaceutical applications such as diluents, binders, disintegrants in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels and bases in suppository, thus making them attractive substitutes for costly semisynthetic and synthetic excipients. India, due to its geographical and environmental positioning, has traditionally been a good source for such products among the Asian countries [11]. With an aim to improve the absorption and oral bioavailability we took an attempt to formulate floating drug delivery systems using TRZ as the drug candidate employing methocel of various grades like K4, K15 and natural polymers like guar gum, xanthan gum.

MATERIALS AND METHODS

Materials

Trazodone HCl were obtained as pure sample from Sun Pharmaceutical Industries Ltd. Dewas, as gift samples along with their analytical reports. HPMC K15, K4 was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Xanthan gum, guar Gum, polyvinyl pyrrolidone K 30, lactose and talc were purchased from SD Fine Chem. Limited, Mumbai. Magnesium stearate, sodium bicarbonate and citric acid were purchased from Loba Chemie Pvt. Ltd, Mumbai. All other chemical 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.

Methods

Determination of absorption maxima

A solution of containing the concentration 10µg/ ml was prepared in 0.1N HCl. UV spectrum was taken using Double beam UV/VIS spectrophotometer (Labindia-3000+). The solution was scanned in the range of 200-400nm.

Preparation calibration curve

10mg of drug was accurately weighed and dissolved in 10ml 0.1N HCl in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100µg/ml) sub stock solution (2), then final concentrations were prepared 5-25µg/ml with 0.1N HCl. The absorbance of standard solution was determined using UV/ VIS spectrophotometer (Labindia 3000+) at 246.0 nm. Linearity of standard curve was assessed from the square of correlation coefficient (r^2) which determined by least-square linear regression analysis.

Fourier transform infrared (FTIR) spectroscopy

The physical properties of the physical assortment were comparing with those of TRZ pure drug. Samples was assorted comprehensively through 100mg potassium bromide IR powder as well as compacted under vacuum at a pressure of concerning 12 psi for 3 minutes. The ensuing disc was mounted in an appropriate holder in Brukers Alpha IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Pre compression evaluation

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, tapped density, carr's index and hausner's ratio.

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation.

$$\theta = \tan\text{-}1(h/r)$$

Where, h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula [12-14].

Hausner's ratio = Tapped density/Bulk density.

Formulation development of tablets

Direct compression method

Different tablets formulations (F1-F8) were prepared by direct compression technique. All powders were passed through 40 meshes. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as glidant. Lactose was used as diluents. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests [15]. The composition of TRZ floating tablets was shown in Table 1.

Table 1 Formulation composition of trazodone hydrochloride gastro retentive tablets

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Trazodone hydrochloride	10	10	10	10	10	10	10	10
HPMC K 15	90	120	-	-	-	-	-	-
HPMC K 4	-	-	90	120	-	-		-
Xanthan gum	-	-	-	-	90	120	45	60
Guar gum	-	-	-	-	-	-	45	60
PVP K30	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	30	30	30	30
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Lactose	110	80	110	80	110	70	100	70
Total Weight	250	250	250	250	250	250	250	250

Evaluation of tablets

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape were evaluated. Appearance was judged visually.

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab).Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was 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 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 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 analyzed for drug content by UV spectrophotometer at a λmax of 246 nm using of 0.1 N HCl as blank.

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al* [16]. The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time necessary for the tablet to increase to the outside and float was determined as floating lag time. The experiments were conducted in triplicate. Total floating times were measured during *in vitro* dissolution studies.

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 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 10 hours using 10ml pipette. The new disintegration medium (37^{0}C) was supplanted each time with a similar amount of the sample and takes the absorbance at 246nm using spectroscopy [17-19].

Mathematical treatment of *in-vitro* release data: The quantitative analysis of the qualities got in dissolution/release tests is simpler when mathematical formulas that express the dissolution comes about as an element of a portion of the measurement frames attributes are utilized.

Zero-order kinetics: The pharmaceutical dosage frames following this profile release a similar measure of medication by unit of time and it is the ideal method of medication release keeping in mind the end goal to accomplish a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$Q_t = Q_o + K_o t$$

where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution (most times, Q_o=0) and K_o is the zero order release constant.

First-order kinetics: The following relation expresses this model:

$$\log Q_t = \log Q_o + \frac{K_1 t}{2.303}$$

where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution and K_1 is the zero order release constant.

Along these lines a graphic of the decimal logarithm of the released measure of drug versus time will be linear. The pharmaceutical dosage shapes following this dissolution profile, for example, those containing water-solvent drugs in permeable frameworks, discharge drug in a way that is corresponding to the measure of drug staying in its inside, in

such way, that the measure of drug released by unit of time reduce.

Higuchi model: Higuchi built up a few theoretical models to ponder the arrival of water-solvent and low dissolvable medications in semi-strong or potentially strong grids. Mathematical expressions were acquired for sedate particles scattered in a uniform grid acting as the diffusion media. The simplified Higuchi model is expressed as:

$$Q = K_H.t^{1/2}$$

Where Q is the amount of drug released in time t and K_H is the Higuchi dissolution constant. Higuchi model describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be utilized to portray the drug dissolution from a few kinds of modified release pharmaceutical dosage structures, for example, transdermal systems and matrix tablets with water-dissolvable drugs.

Korsmeyer-Peppas model: Korsmeyer *et al.* used a simple empirical equation to describe general solute release behaviour from controlled release polymer matrices:

$$\frac{M_t}{M_\infty} = a\,t^n$$

where M_t/M_∞ is fraction of drug released, a is kinetic constant, t is release time and n is the diffusional exponent for drug release. 'n' is the slope value of log M_t/M_∞ versus log time curve. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. Peppas used this n value in order to characterize different release mechanisms, concluding for values for a slab, of n =0.5 for fickian diffusion and higher values of n, between 0.5 and 1.0, or n =1.0, for mass transfer following a non-fickian model. In case of a cylinder n =0.45 instead of 0.5, and 0.89 instead of 1.0. This equation can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent n the portion of the release curve where $M_t/M_\infty < 0.6$ should only be used. To use this equation it is also necessary that release occurs in a one-dimensional way and that the system width-thickness or length-thickness relation be at least 10. A modified form of this equation was developed to accommodate the lag time (l) in the beginning of the drug release from the pharmaceutical dosage form:

$$\frac{M_{t-l}}{M_\infty} = a\,(t-l)^n$$

When there is the possibility of a burst effect, b, this equation becomes:

$$\frac{M_t}{M_\infty} = at^n + b$$

In the absence of lag time or burst effect, l and b value would be zero and only at^n is used. This mathematical model, also known as *Power Law*, has been used very frequently to describe release from several different pharmaceutical modified release dosage forms [20].

Stability studies

The optimized formulation of TRZ were packed in strips of 0.04 mm thick aluminum foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40 ^{0}C and 75% RH for 6 months. The samples were withdrawn periodically and evaluated for their floating lag time, content uniformity and for in vitro drug release.

RESULTS AND DISCUSSION

Solubility of TRZ was freely soluble in methanol and ethanol, slightly soluble in 0.1N NaOH, soluble in water, 0.1N HCL and 6.8 pH phosphate buffers. The melting point of TRZ was 223-226ºC and λ_{max} of TRZ was found to be 246.0 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25 µg/ml.

Tablet powder blend was subjected to various pre-compression parameters Table 2. The angle of repose values indicates that the powder blend has good flow properties. The bulk density and tapped density of all the formulations was found to be in the range of 0.489to 0.498 (gm/ml) and 0.608 to 0.615 showing that the powder has good flow properties. The compressibility index and Hauser's ratio of all the formulations was found to be ranging between 18.586 to 20.488 and 1.228 to1.258 which show that the powder has good flow properties. TRZ tablet quality control tests such as weight variation, hardness and friability, thickness, drug content and drug release studies in different media were performed on the compression tablet. All the parameters such as weight variation, hardness, friability, thickness and drug content were found to be within limits Table 3.

Table 2 Result of pre-compression properties of TRZ FGR tablets

F. Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausner's ratio
Trazodone hydrochloride				
F1	0.498	0.612	18.627	1.229
F2	0.495	0.608	18.586	1.228
F3	0.497	0.615	19.187	1.237
F4	0.495	0.613	19.250	1.238
F5	0.489	0.615	20.488	1.258
F6	0.492	0.612	19.608	1.244
F7	0.496	0.615	19.350	1.240
F8	0.498	0.614	18.893	1.233

Table 3 Results of post compression properties of TRZ GRF tablets

F. code	Thickness* (mm)	Hardness* (kg/cm2)	Weight variation* (mg)	Friability* (%)	Drug content* (%)
F1	2.85±0.12	5.1±0.2	255±2	0.895±0.012	98.98±0.12
F2	2.86±0.25	5.2±0.3	249±3	0.856±0.015	98.45±0.25
F3	2.84±0.32	5.1±0.1	256±4	0.985±0.016	98.65±0.23
F4	2.86±0.14	5.1±0.2	257±6	0.965±0.014	99.02±0.41
F5	2.89±0.25	5.3±0.2	259±5	0.845±0.015	98.65±0.21
F6	2.83±0.23	5.4±0.3	252±7	0.865±0.023	99.06±0.45
F7	2.81±0.32	5.4±0.1	249±8	0.745±0.032	98.85±0.52
F8	2.83±0.45	5.2±0.3	248±9	0.658±0.041	99.12±0.41

In the present study 8 formulations with variable concentration of polymers (HPMC K4, K 15 guar gum and xanthan gum) were prepared by direct compression method and evaluated for physicochemical properties. The results of buoyancy lag time, total floating time and *in vitro* drug release was given in Table 4, 5 & Fig.2. The results indicated that optimizes formulation F7 on immersion in 0.1N HCl at 37±0.5^{0}C tablets immediately and remain buoyant up to 12hr without disintegration. These 2 factors are essential for tablets to acquire density< 1, so that it remains buoyant on the gastric fluids. The *in vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, higuchi's and korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of first order was maximum i.e. 0.974 hence indicating drug release from formulations was found to follow first order release kinetics Table 6, 7 & Fig. 3, 4.

Table 4 Results of *in-vitro* buoyancy study of TRZ

F. Code	Floating lag times (sec)	Total floating time (hrs)
F1	36	MT 12
F2	45	MT 12
F3	40	MT 12
F4	36	MT 12
F5	32	MT 12
F6	36	MT 12
F7	35	MT 12
F8	39	MT 12

Table 5 *In-vitro* drug release study of GRF tablets

Time	% Cumulative Drug Release*							
(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	30.25±0.25	29.98±0.32	27.78±0.14	25.65±0.23	32.25±0.23	33.12±0.32	22.32±0.36	20.12±0.25
1	45.56±0.32	40.56±0.41	39.98±0.25	36.65±0.25	40.23±0.32	39.98±0.12	36.65±0.32	30.45±0.32
1.5	56.65±0.45	53.65±0.23	50.23±0.32	48.89±0.32	59.98±0.12	60.23±0.25	45.65±0.14	41.32±0.41
2	89.98±0.65	73.32±0.44	69.98±0.33	65.52±0.14	66.45±0.41	65.45±0.41	55.65±0.25	50.23±0.32
3	98.89±0.52	85.56±0.33	79.98±0.41	73.32±0.52	80.23±0.25	78.85±0.23	66.65±0.36	56.65±0.52
4	-	99.12±0.25	86.65±0.45	82.23±0.32	98.89±0.23	89.98±0.32	75.56±0.65	63.32±0.12
6	-	-	98.45±0.65	90.45±0.41	-	96.65±0.65	83.32±0.41	78.89±0.12
8	-	-	-	98.85±0.25	-	-	91.15±0.23	85.56±0.23
12	-	-	-	-	-	-	98.89±0.32	89.98±0.32

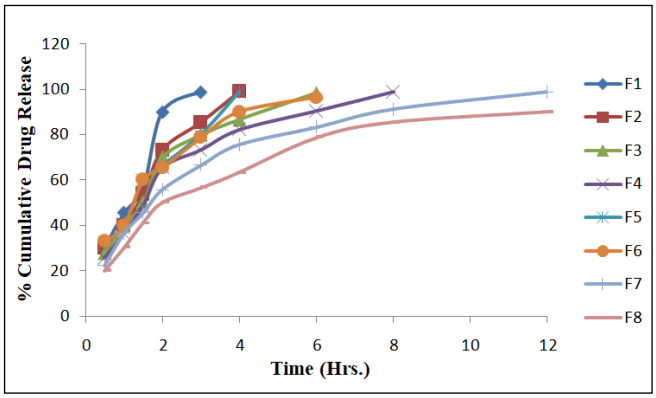

Fig.2 *In-vitro* drug release study of GRF tablets

Table 6 *In-vitro* drug release data for optimized formulation F7

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	22.32±0.36	1.368	76.64	1.884
1	1.000	0.000	36.65±0.32	1.426	73.31	1.865
1.5	1.225	0.176	45.65±0.14	1.589	61.22	1.787
2	1.414	0.301	55.65±0.25	1.656	54.75	1.738
3	1.732	0.477	66.65±0.36	1.745	44.44	1.648
4	2.000	0.602	75.56±0.65	1.838	31.11	1.493
6	2.449	0.778	83.32±0.41	1.895	21.42	1.331
8	2.828	0.903	91.15±0.23	1.954	10.02	1.001
12	3.464	1.079	98.89±0.32	1.995	1.11	0.045

Table 7 Regression analysis data of TRZ floating tablets

Batch	Zero Order	First Order
	R^2	R^2
F7	0.820	0.974

CONCLUSION

Trazodone Hydrochloride floating tablets were successfully formulated by floating technique. The optimized formulation (F7) was selected on the basis of *in vitro* buoyancy and *in vitro* drug release. The addition of gel forming agent and gas generating agent was essential to achieve *in vitro* buoyancy. The results of the *in vitro* drug release and *in vitro* buoyancy study showed that the optimized formulation (F7) sustained the drug release (98.89) up to 12 hrs and remained buoyant for >12 hrs. Optimized formulation (F7) does not show any significant change in physical appearance, floating properties and drug release after storage at 40°C/75% RH and stable for 6 months.

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