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FORMULATION DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF TRAZODONE HYDROCHLORIDE

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ABSTRACT

Formulation development is an important part of drug design and development. Bioavailability and bioequivalence are totally dependent on formulation development. Now-a-days formulation development is done by following QbD (Quality by Design).Floating drug delivery systems are the gastro retentive forms that precisely control the release rate of target drug to a specific site which facilitate an enormous impact on health care. This can be achieved by use of various polymeric substances. Trazodone Hydrochloride (TRZ), is a well-known chemical compound that is used as an antidepressant that belongs to a selective serotonin reuptake inhibitors (SARI). TRZ is used as anti-anxiety and sleep-inducing agent. The tablets of TRZ were prepared by direct compression method using gas generating agent and different polymer combinations. 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 effect on *in-vitro* drug release and floating lag time. *In vitro* drug release of floating gastro retentive tablet of TRZ shown that the formulation F9 was found to be the best formulation as it releases 97.98% TRZ in a controlled manner for an extended period of time (up to 12 hours). 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. 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.

INTRODUCTION

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 (1).

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 (2). 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 (3-6). Oral sustained drug delivery system is complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose, since the majority of drugs are absorbed in stomach or the upper part of small intestine (7, 8).

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability (9). The objective of the present research work was to provide gastro retentive formulation that will provide once daily, sustained release dosage form of TRZ.

MATERIALS AND METHODS

Trazodone HCl were obtained as pure sample from **Sun Pharmaceutical Industries Ltd.** Dewas, as gift samples along with their analytical reports. Hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M) was procured from Meditab Specialities Pvt. Ltd., Satara. PVP K30 was purchased from S.D fine chemicals, Mumbai. Sodium bicarbonate, magnesium stearate, talc were purchased from Mapromax, Life sciences Pvt. Ltd., Dehradun. Other solvents and chemicals used in the research were of LR grade. All the studies were carried in distilled water.

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 (Lab India 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.

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**.**

$$\text{Carr's index (\%)} = [(TBD - LBD)/TBD] \times 100.$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula (10-12).

Hausner's ratio = Tapped density/Bulk density.

FORMULATION DEVELOPMENT OF GASTRO RETENTIVE FLOATING TABLETS

Direct compression method

Different tablets formulations (F1-F9) 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 (13). The composition of TRZ floating tablets was shown in Table 1.

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 Study

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al* (14). 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 ± 0.5^0c 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 (37^0C) was supplanted each time with a similar amount of the sample and takes the absorbance at 246nm using spectroscopy (15-17).

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:

$$\mathbf{Q_t = Q_o + K_o\, t}$$

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_∞ < 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 (18).

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 (Lab india-3000+) in linearity range 5-25 µg/ml Fig.1.

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 0.412±0.045to 0.419±0.032 (gm/ml) and 0.501±0.012to 0.521±0.012showing that the powder has good flow properties.
The compressibility index and Hauser's ratio of all the formulations was found within limit 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.

In the present study 9 formulations with variable concentration of polymers 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 F9 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. 0.996hence indicating drug release from formulations was found to follow first order release kinetics Table 6, 7 & Fig. 3, 4.

CONCLUSION

In the present work, it can be concluded that the TRZ floating tablets can be an innovative and promising approach for the delivery of TRZ. The optimized formulation F9 contains HPMC K15, K4 and a gas generating agent. The optimized formulation F9 showed drug release of 97.98% within 12h.
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. 0.996hence indicating drug release from formulations was found to follow first order release kinetics

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Table 1 Formulation composition of Trazodone hydrochloride gastro retentive tablets

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Trazodone Hydrochloride	150	150	150	150	150	150	150	150	150
HPMC K 15	100	120	140	-	-	-	50	60	70
HPMC K 4	-	-	-	100	120	140	50	60	70
PVP K30	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	100	80	60	100	80	60	100	80	60
Total Weight	400	400	400	400	400	400	400	400	400

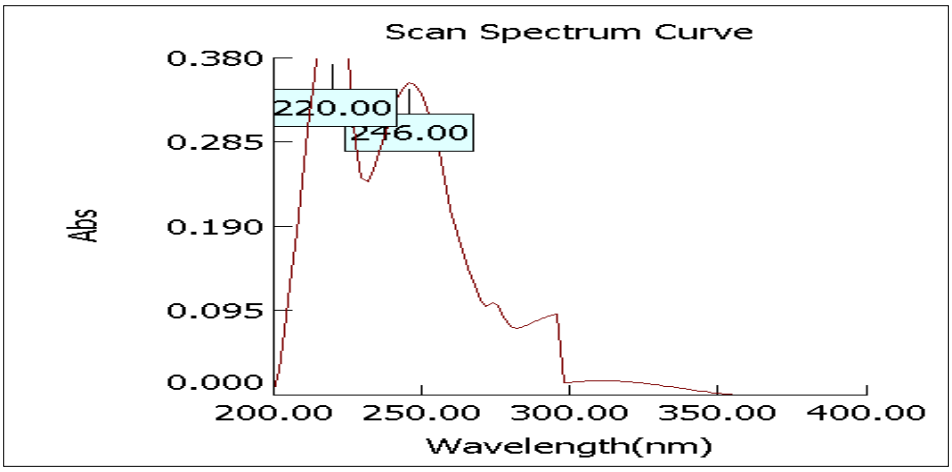

Figure 1 Determination of λ_{max} of Trazodone hydrochloride

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

Material	Angle of repose(Degree)	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
Trazodone hydrochloride					
F1	32.56±0.15	0.416±0.015	0.501±0.012	16.966±0.12	0.085±0.012
F2	32.25±0.12	0.415±0.015	0.502±0.015	17.331±0.15	0.087±0.012
F3	31.95±0.14	0.418±0.025	0.501±0.042	16.567±0.25	0.083±0.015
F4	31.25±0.12	0.416±0.012	0.512±0.014	18.750±0.23	0.096±0.021
F5	32.25±0.11	0.412±0.045	0.521±0.012	20.921±0.12	0.109±0.014
F6	32.47±0.08	0.418±0.065	0.521±0.012	19.770±0.41	0.103±0.036
F7	31.45±0.14	0.419±0.032	0.520±0.015	19.423±0.12	0.101±0.036
F8	32.15±0.15	0.417±0.012	0.510±0.025	18.235±0.25	0.094±0.012
F9	33.45±0.06	0.418±0.018	0.502±0.023	16.733±0.23	0.084±0.021

Table 3 Results of post compression properties of TRZ FGR tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3	Total floating duration (h)
F1	3.21±0.05	4.8±0.2	405±8	0.58 ± 0.10	98.98±0.12	8
F2	3.20± 0.10	4.4±0.3	410±5	0.51 ± 0.08	97.56±0.42	10
F3	3.22± 0.05	4.5±0.2	409±4	0.38 ± 0.12	98.65±0.25	>12
F4	3.22± 0.05	4.7±0.1	395±6	0.16 ± 0.04	98.98±0.32	>12
F5	3.23± 0.10	5.2±0.5	400±7	0.31 ± 0.07	99.45±0.21	>12
F6	3.25± 0.06	5.3±0.3	406±5	0.27 ± 0.05	98.78±0.14	>12
F7	3.23± 0.05	4.8±0.4	408±6	0.29 ± 0.08	98.95±0.23	>12
F8	3.15± 0.05	4.5±0.3	405±4	0.34 ± 0.12	98.98±0.21	>12
F9	3.12±0.06	4.9±0.3	405±5	0.32±0.09	98.45±0.14	>12

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

Formulation Code	Floating lag times (sec)	Total Floating Time (hrs)
F1	53	>12
F2	53	>12
F3	50	>12
F4	52	>12
F5	54	>12
F6	56	>12
F7	52	>12
F8	50	>12
F9	45	>12

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

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	48.56	45.58	40.25	38.89	36.25	33.25	28.45	26.65	23.36
1	78.89	75.56	68.98	49.98	42.25	40.56	36.45	30.35	26.69
1.5	89.98	82.23	79.78	65.58	58.98	50.56	45.58	40.56	38.78
2	96.56	95.56	88.78	78.89	75.58	70.25	65.56	61.25	45.25
3		97.25	95.56	90.12	88.98	81.25	73.32	70.25	55.56
4			97.45	95.56	95.56	90.25	88.98	83.25	68.89
6				96.98	97.45	96.45	97.89	93.56	78.58
8								96.56	89.98
12									97.98

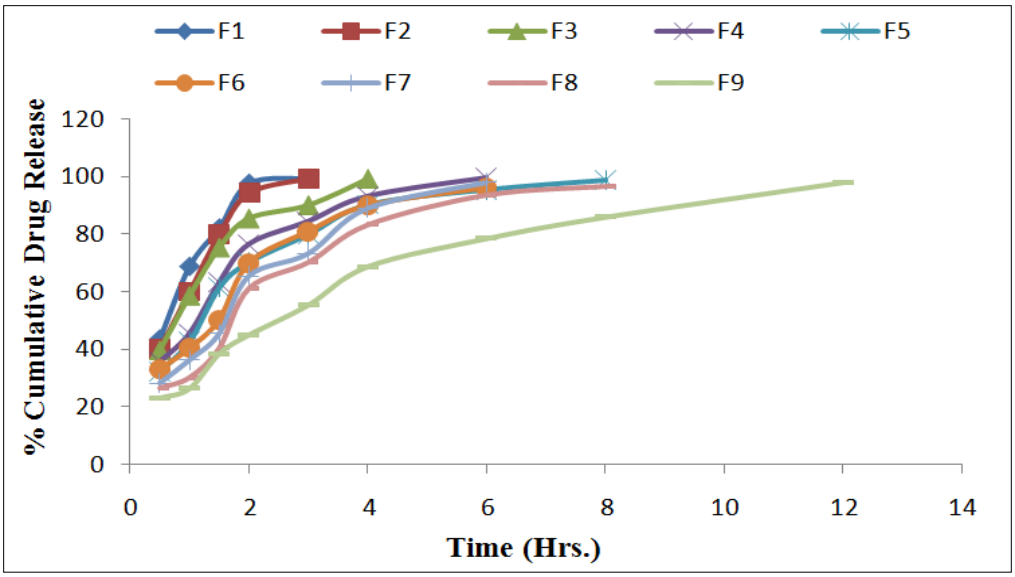

Figure 2 *In-vitro* drug release study of GRF tablets

Table 6 *In-vitro* drug release data for optimized formulation F9

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	23.36	1.368	76.64	1.884
1	1	0	26.69	1.426	73.31	1.865
1.5	1.225	0.176	38.78	1.589	61.22	1.787
2	1.414	0.301	45.25	1.656	54.75	1.738
3	1.732	0.477	55.56	1.745	44.44	1.648
4	2	0.602	68.89	1.838	31.11	1.493
6	2.449	0.778	78.58	1.895	21.42	1.331
8	2.828	0.903	85.98	1.934	14.02	1.147
12	3.464	1.079	97.98	1.991	2.02	0.305

Table 7 Regression analysis data of TRZ Floating Tablets

Batch	Zero Order	First Order
	R^2	R^2
F9	0.892	0.996

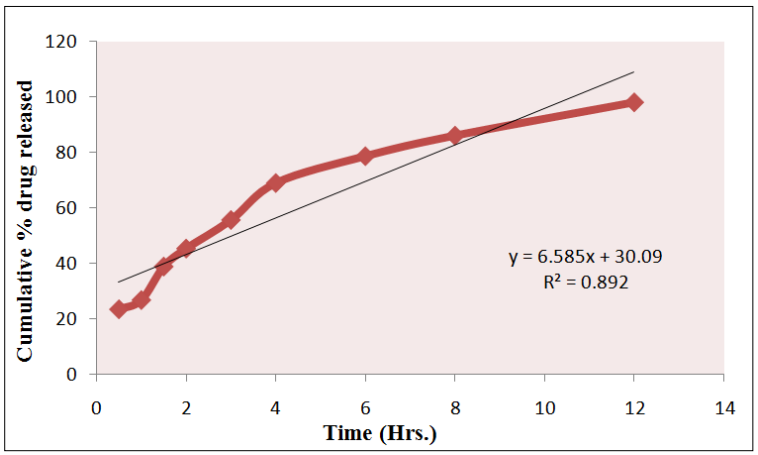

Figure 3 Zero order release Kinetics

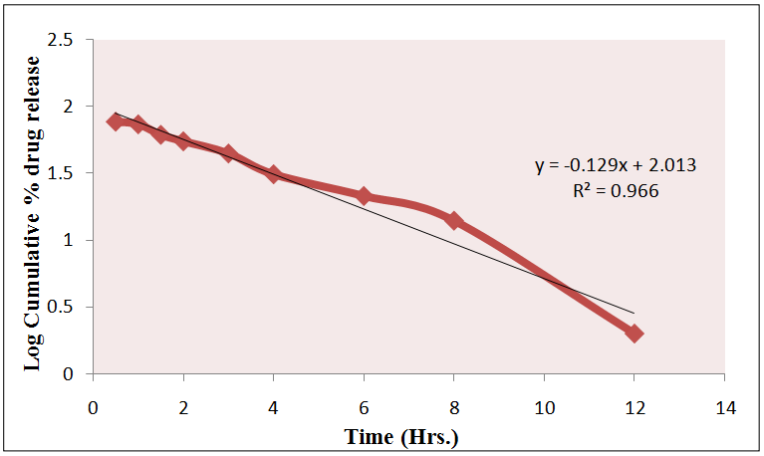

Figure 4 first order release kinetics