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FORMULATION AND EVALUATION OF SUSTAINED-RELEASE TABLET OF TRAZODONE HYDROCHLORIDE

S. Kadam Vaishali * and G. R. Shendarkar

CRPS, Nanded College of Pharmacy, Nanded - 431605, Maharashtra, India.

Keywords:

Trazodone hydrochloride, Wet granulation, Eudragit RS 100, Eudragit RL100, Sustained release

Correspondence to Author:
S. Kadam Vaishali

CRPS, Nanded College of Pharmacy, Nanded - 431605, Maharashtra, India.

E-mail: kjvaishali@gmail.com

ABSTRACT: The main objective of this study was to formulate a Sustained release tablet by wet granulation method. A sustained release tablet of trazadone hydrochloride was prepared by using synthetic polymer. The prepared tablets were evaluated for their diameter, thickness, drug content, Hardness, friability, weight variation. The thickness and diameter of the tablet range from 5.43±0.288 to 5.76±0.05 and 09.68±0.577 to 10.04±0.04, respectively. Drug content was studied, and its ranges from 92.03 to 98.60%. Hardness was studied; its ranges 5.5 to 6.5 kg/cm^2, Friability ranges 0.71 to 0.95%, Weight variation ranges between 434±1.49 to 460±1.23. FTIR and DSC analysis does not show any interaction of drug with Excipient. The formulation was optimized on the basis of acceptable pre and post-compression parameters. The results of dissolution studies indicated that Batch F4 containing eudragit RL 100 exhibited drug release of 88.06% at the end of 12 h to provide sufficient concentration for achieving satisfactory therapeutic value for an extended period of time. Optimized batch best fitted to Higuchi model. The n value indicates a non-fickinan or anomalous diffusion pattern. This means that both the diffusion and erosion mechanisms were prevalent. By the above results, it can be concluded that the above-prepared tablet of trazadone hydrochloride could be able to extend the drug release by avoiding problems such as dose dumping, more gastric residence time and improve patient compliance.

INTRODUCTION: The oral route is the oldest and convenient route for the administration of therapeutic agents because of low cost of therapy, and ease of administration leads to a higher level of patient compliance [1]. The goal of an extended-release dosage form is to maintain therapeutic drug levels in plasma for an extended period of time [2, 3].

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The primary benefits of a sustained release dosage form in comparison with conventional dosage form maintain uniform drug plasma concentration over an extended period of time and hence the uniform therapeutic effect is achieved [4].

Trazodone is serotonin-2 receptor antagonist that also decreases extracellular gamma-amino-butyric acid (GABA) levels in the cerebral cortex. Through the blockade of 5-hydroxytryptamine 2A receptors. Trazodone, therefore a psychoactive compound with sedative and anti-depressant properties [5, 6]. Poly acrylates and polymethacrylate, glassy substances, are commonly referred to by the trade name eudragit.

The commonly used eudragit for the preparation of controlled release formulations are eudragit RL, eudragit RS. Eudragit RL and eudragit RS, are ammoniomethacrylate copolymers. The ammonium groups are present as salts and are mainly responsible for the independent pH permeability of the polymers [7].

There is a challenge to the pharmaceutical technologist for developing oral controlled-release tablets for highly water-soluble drugs with a constant release rate. If water-soluble-containing drugs not formulated properly, then most of these drugs may readily release the drug at a faster rate and are likely to produce toxic concentrations when administered orally [8].

Trazodone hydrochloride is an antidepressant chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. Trazadone is used primarily in the treatment of mental depression or depression/anxiety disorders. As the conventional doses release the Trazodone hydrochloride in just minutes and therefore the therapeutic concentration are maintained for a short period of time generating a need for administration of another dose.

Therefore an attempt was made to maintain the therapeutic concentration for a longer period of time. This was achieved by developing a sustained release drug delivery system. These sustained-release tablets are mainly prepared for the release of the drug for a longer period of time *i.e.,* 12 h, and utilizing the drug to full extent, avoiding unnecessary frequency of dosing.

The sustained or controlled release formulation provides a plasma concentration of Trazodone for at least 12 h that was effective in treating one or more of the symptoms of depression. In the sustained release, formulation provides an effective amount of Trazodone for treating disorders, for example, improving sleep architecture. Trazadone HCl having a Biological half-life 3-6 h due to the need of frequent dosing for depression patients. Hence attempt had been made to formulate sustained release of Trazadone HCl.

MATERIALS: Trazadone hydrochloride was received as a gift sample FDC Pvt. Ltd., Aurangabad (Maharashtra), Eudragit RS100 and Eudragit RL100 were gifted from Vikram Thermo India Ltd. Gujrat, Ahmadabad. Other excipients as PVP K30, Magnesium stearate, Lactose, Talc gifted from Nanded College of pharmacy Nanded.

METHODS:

Drug Excipients Compatibility Study: Compatibility study was carried for pure Trazodone hydrochloride and a combination of Trazadone HCL with excipients. The FT-IR spectra for pure drug and polymer were recorded using the potassium bromide disk method. Samples were prepared in a potassium bromide disk by means of a hydrostatic press. Spectral measurements were obtained by powder diffuse reflectance on an FT-IR spectrophotometer (Shimadzu, 8033) in the wavenumber region 400-4000 cm^{-1}

Differential Scanning Calorimetry (DSC): Thermal analysis was carried out using a differential scanning calorimeter (SHIMADZU DSC 60 PLUS). Tests of conditions: Temperature range: 30 °C to 300 °C, Heating/Cooling rate: 5°C / min., Gas: Nitrogen; Flow rate: 100 ml. / min.

Determination of Absorption Maxima: [9] 10 µg/ml solutions were taken to determine absorption maxima. Initially, blank buffer solution was kept and scanned in the region of 200 – 400 nm. Then the sample was kept for analysis and scanned in the same region. Absorption maxima were found to be 246.40 nm. Hence all further analysis was carried out at 246.40nm in pH 1.2 buffer and 6.8 pH phosphate buffer.

Preparation of Standard Calibration Curve: The solution of different 5 µg/ml – 40 µg/ml concentrations of Trazadone hydrochloride was prepared in pH 1.2 phosphate buffer and 6.8 phosphate buffer. The absorbance of these samples was noted shown at 246.40 nm by using a double beam UV - spectrophotometer. The graph of absorbance *v/s* concentration in µg/ml was plotted. The R^2 value of this graph was calculated to see the linearity of the absorbance against concentration.

Preparation of Sustained Release Tablet of Trazadone Hydrochloride: [10] All ingredients formulation shown in **Table 1** were passed through a # 80 sieve and weighed. Mix drug with lactose. Then add talc; after this, add synthetic polymer RS 100. Mix well and Evaluate blend for flow

properties. The lubricated formulation was compressed by a direct compression technology using Karnavati multi punch tablet machine having 12 mm punch and die to obtain the tablet. The same procedure was repeated by using synthetic polymer-polymer RL 100.

Formulation of Trazadone HCl Tablet:

TABLE 1: COMPOSITION OF ALL BATCHES (QUANTITY IN MG / TABLET)

Batch	Trazodone HCl	RS 100	RL 100	PVP K30	Lactose	Mag. Stearate	Water	Talc
F1	150	75	----	30	175	10	Q.S.	10
F2	150	112.5	----	30	137.5	10	Q.S.	10
F3	150	150	----	30	100	10	Q.S.	10
F4	150	------	75	30	175	10	Q.S.	10
F5	150	-----	112.5	30	137.5	10	Q.S.	10
F6	150	-----	150	30	100	10	Q.S.	10

*Total Weight of Tablet = 450mg

Evaluation Parameter of Sustained Release Tablet of Trazodone Hydrochloride:

Post Compression Parameter: [11, 12, 13]

Physical Appearance: The general appearance of tablets, its visual identity, and overall elegance is essential for consumer acceptance.

Hardness Test: The hardness of the tablet of each formulation was checked by using Monsanto Hardness tester in terms of kg/cm^2.

Friability Test: [16] This test performed to evaluate the ability of tablets to withdrawal abrasion in packaging, handling, and transporting. Initial weights of 10 tablets were taken, and these are placed in the friabilator, rotating at 25 rpm for 4 min. The difference in the weight is noted and expressed. It should be perfectly below 1.0%.

$$\% \text{ Friability} = [(W_1-W_2)/W_1] \times 100$$

Where, W_1= weight of tablets before test, W_2 = weight of tablets after test.

Weight Variation: [14] 20 tablets were taken and weighed individually on a digital weighing balance. Average weight was calculated and the individual tablet weight was compared to the average. The tablet pass the U.S.P. test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Average weight = weight of 20 tablets / 20

***In-vitro* Drug Release Study:** [15, 17] The *in-vitro* drug release studies for the prepared formulation were conducted for a period of 12 hrs using an EDT 08LX dissolution tester USP Type - II apparatus (rotating paddle) set at 50 rpm and a temperature of 37± 0.5°C formulations was placed in the 900ml of the medium. For first 2 h tablet was placed in a 1.2 pH medium, which was replaced with 6.8pH phosphate buffer for the remaining 10 h. At specified intervals, 5ml samples were withdrawn from the dissolution medium and replaced with a fresh medium to keep the volume constant. The absorbance of the sample solution was analyzed at 246.40 nm for the presence of the model drug using a UV-visible spectrophotometer.

RESULTS AND DISCUSSION: Absorption maxima were found to be 246.40 nm, given in figure number one. Hence all further analysis was carried out at 246.40 nm in pH 1.2 buffer and 6.8 pH phosphate buffers.

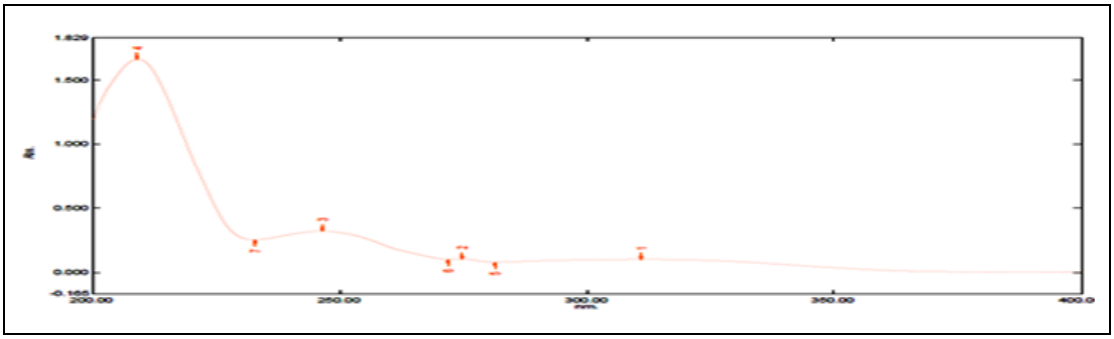

FIG. 1: UV SPECTRA (λ_{max}) OF TRAZADONE HCL DRUG

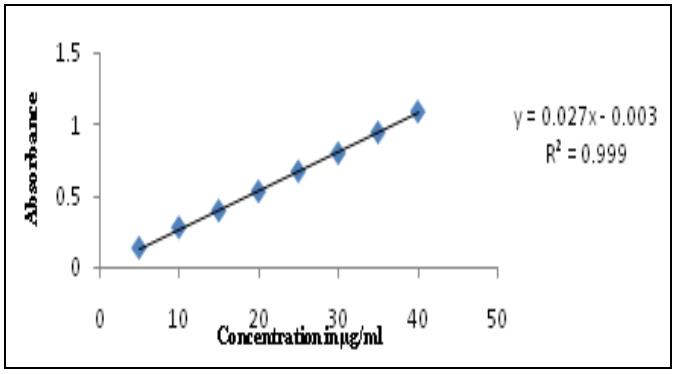

FIG. 2: LINEARITY CURVE OF TRAZODONE HCl IN pH 6.8

Drug Excipients Compatibility Study by Using FTIR: In the present study, FTIR data of the drug and excipients was compared with the standard spectrum of pure Trazodone hydrochloride was shown in the figure. The characteristics peak associated with specific functional group and bonds of the molecular and their presence/absence in the polymer carrier formulation were noted. The IR spectra showed that there was no significant evidence for interaction between the drug and excipients.

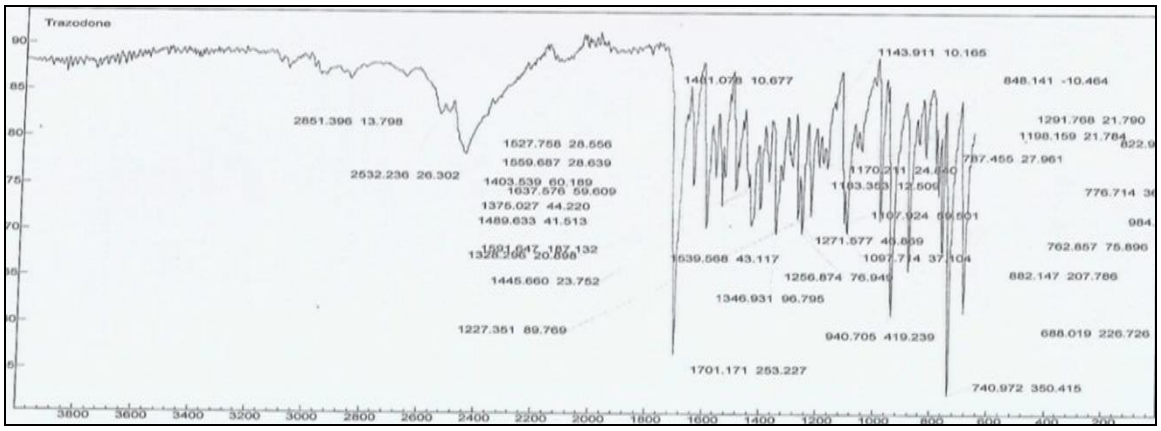

FIG. 3: FTIR SPECTRUM OF PURE DRUG TRAZODONE HCL

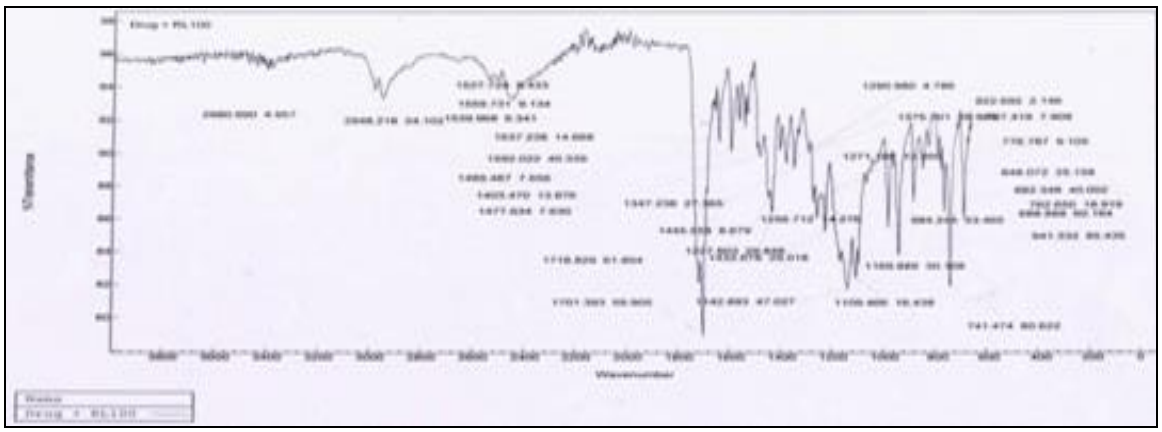

FIG. 4: FTIR SPECTRUM OF TRAZODONE HCL WITH EUDRAGIT RL 100

FIG. 5: FTIR SPECTRUM OF TRAZODONE HCL WITH EUDRAGIT RS 100

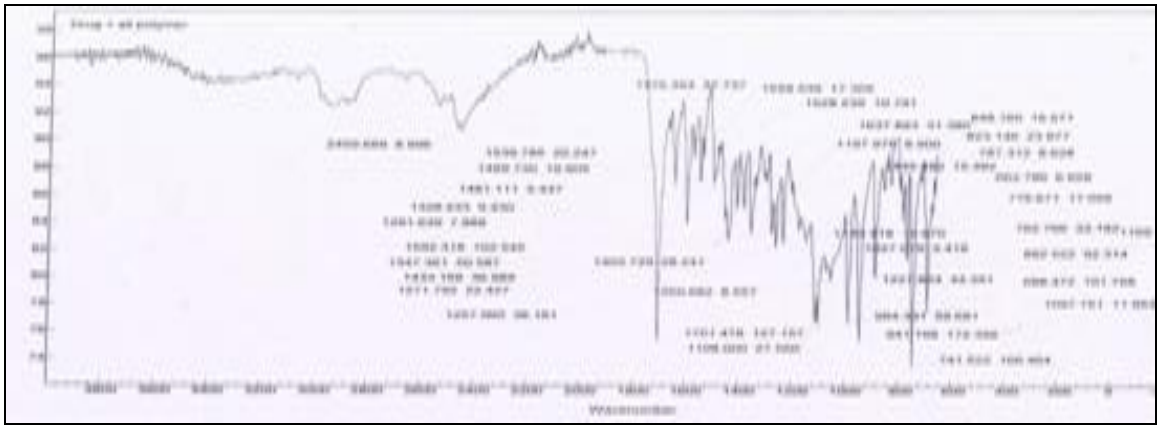

FIG. 6: FTIR SPECTRUM OF TRAZODONE HCL WITH ALL POLYMERS

TABLE 2: FTIR INTERPRETATION OF TRAZODONE HCL AND FORMULATION

S. no.	Functional Group	Range	Peak	Intensity
1	C-Cl	600-800	688	Strong
2	C=O	1670-1820	1701	Strong
3	C-N	1080-1360	1108	Strong
4	C=N	1639	1637	Medium
5	Ph-Ch	1715	1592	Low
6	Hc-Ch	2850-3000	2851	Strong

Differential Scanning Calorimetry: DSC Thermo grams of pure Trazodone Hydrochloride, blend of polymer with the drug were determined. Pure Trazadone HCl showed a sharp peak at 228.44 °C, correspondings to its melting point. There was no appreciable change in the melting endotherms of the physical mixture compared to that of pure drug Trazodone hydrochloride. The absence of any new endothermic peak or disappearance or shift of endothermic peak confirms that there was no interaction, and hence polymers were compatible with the drug.

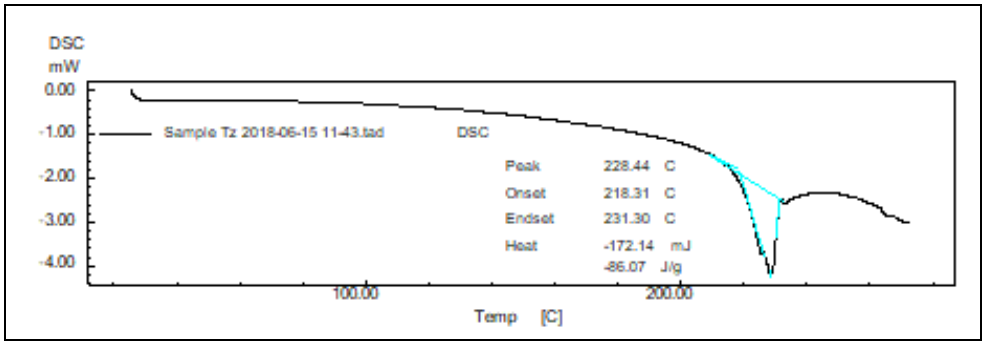

FIG. 7: DSC SPECTRUM OF PURE DRUG TRAZADONE HCL

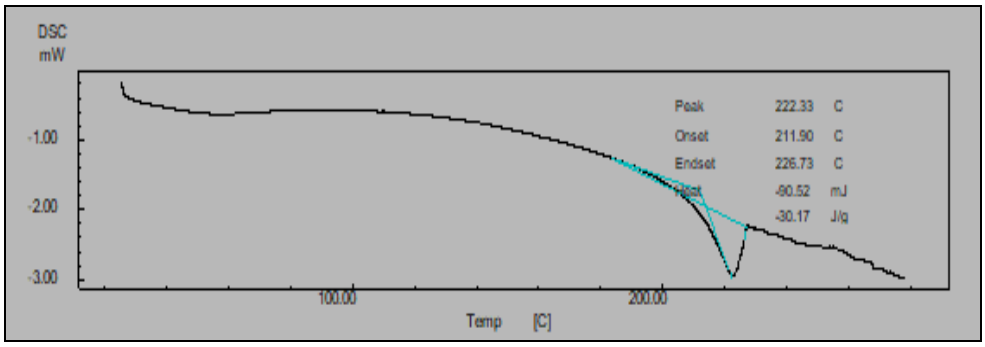

FIG. 8: DSC SPECTRUM OF OPTIMIZED BATCH F4

Pre-compression Parameter: As the result of the evaluation test given in table, the granules of all formulations were evaluated for LBD & TBD. The values of LBD & TBD ranged from 0.505 ± 0.15 to 0.578 ± 0.12 and 0.520±0.18 to 0.622±0.13 respectively. Values obtained for Compressibility index for all formulations range between 6.37% to 12.37 % indicating that granules had required flow property. Hauser's ratio was determined from the ratio of tapped density to poured density, and it was

found in the range of 1.06 to 1.14, which means the granules were free-flowing. Values of the angle of repose for all formulations were found to be in the range from 14.37 °C to 18.55 °C. This indicates good flow property of granules for compression.

TABLE 3: PRE-COMPRESSION PARAMETERS

Batch	Bulk Density (gm/cm^3)	Tap Density (gm/cm^3)	Carr's Index	Hausner's Ratio	Angle of repose
F1	0.512±0.09	0.575±0.15	10.95±0.12	1.12±0.09	14.37±0.580
F2	0.530±0.10	0.598±0.12	11.37±0.11	1.12±0.16	18.55±0.488
F3	0.570±0.07	0.616±0.14	7.46±0.18	1.08±0.10	16.90±0.290
F4	0.578±0.12	0.620±0.18	6.77±0.09	1.07±0.09	16.51±0.438
F5	0.505±0.15	0.565±0.15	12.37±0.14	1.14±0.07	16.56±0.494
F6	0.540±0.12	0.622±0.13	6.37±0.13	1.06±0.14	17.52±0.427

All the values represent mean ± Standard deviation (n=3)

Post Compression Parameters: The prepared sustained release tablets were evaluated for; tablets' mean thickness was almost uniform in all the ten formulations. The diameter & thickness of the tablet range between 09.68mm to 10.04mm & 5.43mm to 5.73mm respectively. The measured hardness of tablets of each batch ranged between 5.5 to 6.5 kg/cm^2. This ensures good handling characteristics of all batches. The values of the friability test were calculated. The % friability was found to range between 0.71 to 0.95%, which was less than 1% in all the formulation, ensuring that the tablets were mechanically stable. The percentage weight variation for all formulations were all the tablets passed the weight variation test as the % weight variation was within the Pharmacopoeia limits of ± 5 % of the weight. The weights of all the tablets were found to be uniform, with a low standard deviation value. Weight variation range between 438 to 459 mg.

TABLE 4: POST COMPRESSION PARAMETER

Batch	Diameter (mm) (n=3)	Thickness (mm) (n=3)	Hardness Kg/cm^2 (n=3)	Drug Content (%)	Friability (%) (n=10)	Weight Variation (n=20)
F1	09.68±0.577	5.43±0.288	5.5	92.03±0.09	0.71	441±1.29
F2	10.02±0.00	5.43±0.288	6.0	96.42±1.09	0.95	438±1.37
F3	10.04±0.04	5.63±0.05	6.5	98.60±1.08	0.83	440±1.33
F4	10.02±0.00	5.66±0.11	6.0	94.89±0.09	0.71	459±1.22
F5	10.02±0.00	5.73±0.05	6.0	98.01±1.03	0.76	450±1.21
F6	10.04±0.04	5.63±0.05	6.5	97.08±1.05	0.76	441±1.19

TABLE 5: PERCENT DRUG RELEASE OF BATCH F1 TO F6

Time (h)	1	2	4	6	8	10	12
F1	15.67±0.020	33.72±0.02	45±0.00	50.64±0.011	56.93±0.05	65.37±0.54	77.23±0.009
F2	21.46±0.321	28.83±0.05	37.56±0.487	43.59±.0516	48.12±0.01	57.48±0.00	74.02±0.009
F3	8.26±0.009	20.62±0.009	27.71±0.005	35.75±1.01	50.11±0.005	61.43±1.148	71.2±1
F4	11.34±0.0057	34.41±0.0057	49.95±0.046	54.60±0.115	59.12±0.025	67.72±0.02	88.06±0.03
F5	22.4±0.17	25.19±2.33	41.12±0.02	43.47±0.009	46.75±0.043	51.82±0.02	78.75±0.55
F6	8.31±0.005	11.65±0.402	20.15±0.00	36.06±0.005	41.37±0.02	48.64±0.02	68.25±2.29
F7	6.001±0.009	10.12±0.010	30.96±0.05	43.4±0.34	68.2±0.26	70.47±0.41	73.59±0.005
F8	11.92±0.009	24.23±0.07	27.59±0.02	51.1±0.14	68.34±0.48	70.07±0.09	74.44±0.03
F9	6.30±0.73	18.71±0.65	45.16±6.11	55.34±0.02	69.16±0.03	76.19±0.025	78.21±0.009

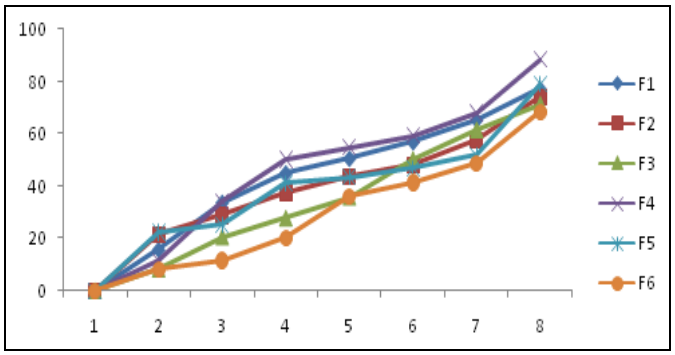

FIG. 9: COMPARATIVE *IN-VITRO* RELEASE GRAPH FOR FORMULATION F1 – F6 BATCH

Release Kinetics of Best Optimized Batch:

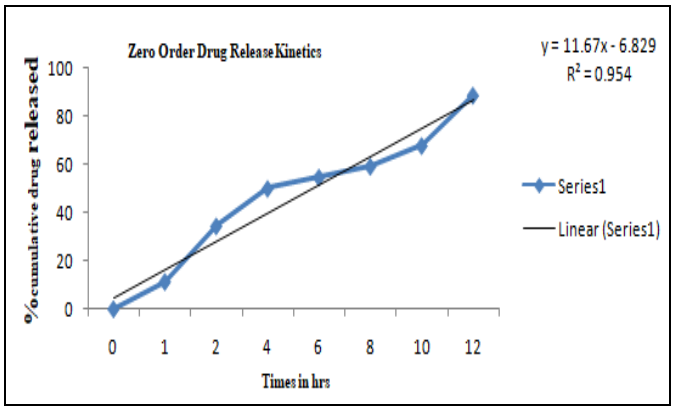

FIG. 10: ZERO ORDER RELEASE OF BATCH F4

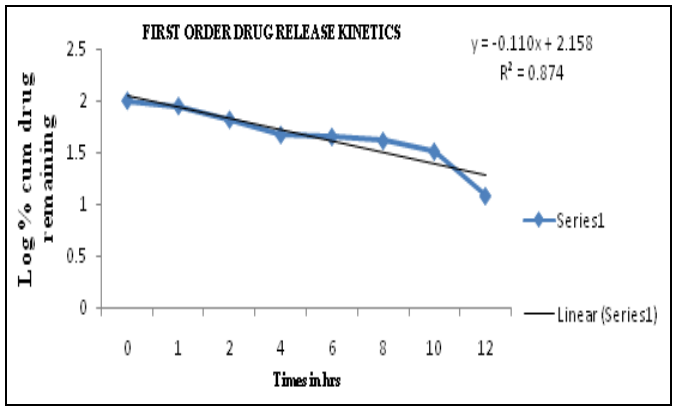

FIG. 11: FIRST ORDER KINETIC MODEL OF BATCH F4

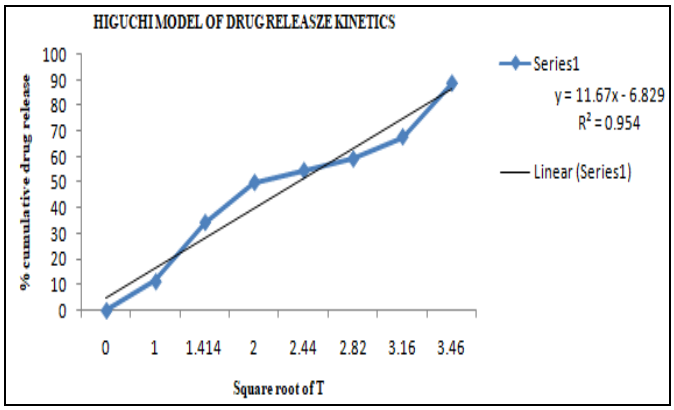

FIG. 12: HIGUCHI MODEL OF BATCH F4

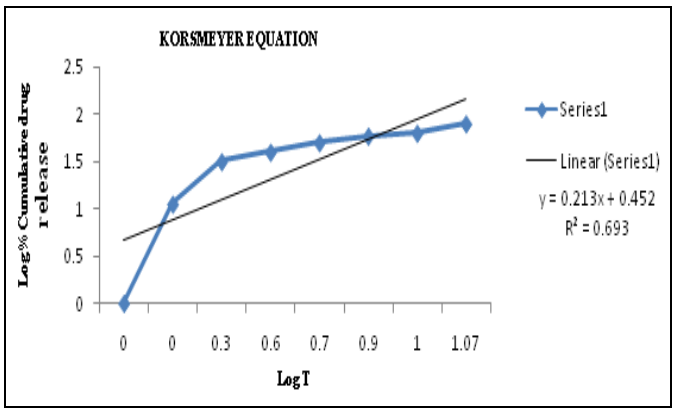

FIG. 13: KORSMEYER – PEPPAS EQUATION BATCH F4

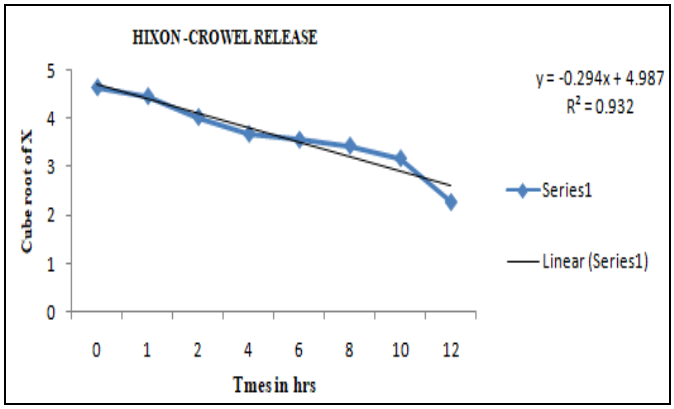

FIG. 14: HIXON CROWEL RELEASE OF BATCH F4

Eudragit RL100 and Eudragit RS100 are insoluble in aqueous media, but they are permeable, and both have pH-independent release profiles. The permeability of Eudragit RS100 and RL100 in aqueous media was due to the presence of quaternary ammonium groups in their structure; Eudragit RL 100 has a greater proportion of these groups and such as is more permeable than Eudragit RS100. Eudragit RL100 reduced the drug release due to the reduction in the penetration of solvent molecules into the system. The rate of release was controlled by the permeability of the matrix structure. The dissolution rate was studied using 900 ml of 0.1N Hydrochloride (pH 1.2) for the first 2 hrs followed by phosphate buffer (pH 6.8) for the remaining hours under sink condition using USP dissolution apparatus type II. The results reveal that batch F1, F2, F3, F4, F5 and F6, showed drug release as 75.22% for 11 h 74.02% for 12 hrs, 71.20% for 12 hrs, 88.06% for 12hrs, 78.75 for 12 hrs, 68.25 for 12 hrs. *In-vitro* release study results revealed that the release of the drug was retarded with the proportional increase of the polymer concentration.

Large concentrations of hydrophilic polymers swell in the presence of water. These polymers form porous structures on the surface of the tablet matrix and form a strong viscous gel layer, which slows down the water diffusion. The phenomenon of swelling resulted in slow drug release. Batch R1 was considered as optimized batch comparative all formulated batches depending on drug release. All the formulations showed the initial burst in release rate. This may be due to the drug release from the surface and the time needed for the formation of an active gel layer capable of controlling water penetration and drug diffusion. *In – vitro* drug release data of optimized formulation (Batch F4) pass zero-order Model as it had highest r^2 value (0.954) as well as Higuchi model having r^2 value (0.954) among other models which indicated the release mechanism govern by diffusion from the matrix. In the present study diffusion value of the exponent was 0.890; therefore release of the formulations was mainly by Anomalous (non-Fickian) transport.

CONCLUSION: An attempt has been made to Formulate and evaluate sustained release tablets of Trazadone HCl using different polymers like Eudragit RS 100 and Eudragits RL 100. FTIR and DSC studies showed compatibility between drugs and excipients. Among all batches, Batch F4 showed 88.06% drug release at 12 hr containing polymer Eudragit RL 100. *In-vitro* drug release data of optimized formulation F4 pass zero order as well as Higuchi model having r^2 value (0.954) among other models. The diffusion value of the exponent was found to be 0.890, respectively. Therefore the release of the formulations was mainly by Anomalous (non-Fickian) transport. The n value indicates a non-fickian or anomalous diffusion pattern. This means that both the diffusion and erosion mechanisms were prevalent. Hence we concluded that once-daily sustained-release tablet of Trazodone hydrochloride having a satisfactory sustained release profile which may provide increased therapeutic efficacy.

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CONFLICTS OF INTEREST: None

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