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INFLUENCE OF XANTHUM, GUAR AND ACACIA GUM ON RELEASE OF EXTENDED RELEASE TABLET OF TRAZADONE HYDROCHLORIDE

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ABSTRACT

The objective of this work was to formulate extended release tablets of highly water-soluble Trazadone Hydrochloride using natural gums xanthum, guar and acacia gum as cost effective, nontoxic, easily available and suitable hydrophilic matrix systems by direct compression method and to study the effect of different concentration of polymers like xanthum gun, guar gum, and acacia on release rate from tablet. FTIR analysis does not show any interaction of drug with Excipients. Formulation was optimized on the basis of acceptable pre and post compressional parameters. The results of dissolution studies indicated that Batch F6 exhibited drug release of 93% at the end of 12h to provide sufficient concentration for achieving satisfactory therapeutic value for extended period of time. The drug release from Batch F6 formulation was sustained up to 12 h. Fitting *in-vitro* drug release data from optimized matrix formulation to zero order followed by Higuchi model indicated that diffusion could be mechanism of drug release. The n value indicates a non-fickian or anomalous diffusion pattern. This means that both the diffusion and erosion mechanisms were prevalent.

Keywords: Trazodone hydrochloride, direct compression, xanthum gum, guar gum, acacia, extended release.

INTRODUCTION

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance. [(1)] Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and historically too, oral drug administration has been the predominant route for drug delivery. [(2)(3)] Hydrophyllic matrixes containing swallable polymers are called as swellable controlled release system or hydrophilic matrix tablets.

A number of polymers have been investigated to develop in situ-gel-forming system, due to the ability of these matrices to release an entrapped drug in aqueous medium and to regulate release of such drug by control of swelling and cross-linking. [(4)(5)] 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. [(6)(7)(8)] Hydrophilic polymers are becoming very popular in formulating oral controlled-release tablets. As the dissolution medium or biological fluid penetrates the dosage form, the polymer material swells and drug molecules begin to move out of the system by diffusion.

There is challenge to the pharmaceutical technologist for developing oral controlled-release tablets for highly water-soluble drugs with constant release rate. If water soluble containing drugs if not formulated properly then most of these drugs, may be readily release the drug at a faster rate and are likely to produce toxic concentrations when administered orally.[9]

MATERIAL AND METHOD

Materials: Trazodone hydrochloride was received as a gift sample from Teva pharmaceutical ltd. Goa. Xanthum gum, guar gum, acacia, microcrystalline cellulose and magnesium starate were gifted from Glenmark pharmaceutical privet. Goa.

Method:

Drug excipients compatibility study: Compatibility study was carried for pure trazodone hydrochloride and combination of trazodone HCl with excipients Fourier transfer infra-red (FTIR) spectroscopic (shimadzu, Japan) studies were carried out by approximately diluting the sample with dried potassium bromide (1:1 and acquiring infrared (IR) spectrum in the range of 400 to 4000$cm^{-1.}$

Determination of absorption maxima[10]

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 sample was kept for analysis and scanned in the same region. Absorption maxima were found to be 246.40nm. Hence all further analysis was carried out at 246.40 nm in pH 1.2 buffer and 6.8pH phosphate buffer.

Preparation of Standard Calibration Curve

The solution of different 5ug/ml- 40ug /ml concentrations of trazodone 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 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.

Formulation of Extended release tablet of Trazodone hydrochloride by direct compression

Method: Various formulation batches of trazodone hydrochloride extended release tablets were prepared using different polymers at 20, 40, 60 concentration of total weight of tablet matrix respectively all ingredients accepts magnesium stearate were blended in glass mortar uniformly. Then this above mixture pass through sieve #60. and to the above mixture add magnesium stearate and wait for 10-15 minutes finally compressed in 12 mm circular punches with tablet weight of 450

POST COMPRESSION PARAMETERS [11]

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

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

Thickness: Thickness was measured using Vernier caliper. It was determined by checking ten tablets from each formulation

Friability Test: This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 10 tablets is taken and these are placed in the Friabrilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably below 1.0%.

% Friability = $[(W_1-W_2)/W_1]$ X 100

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

Weight variation [12]

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 that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

Swelling characteristics of tablet: The extent of swelling was measured in term of percent weight gain by the tablets. The swelling behavior of formulation was studied. One tablet from each formulation was kept in petri dish containing pH 1.2 buffer for 12 hours. At the end of each hour tablet was withdrawn soaked with tissue paper and weighed. Then after every hours. Swelling index of tablet was calculated using formula:

$$S.I. = \{(Mt - Mo) / Mo\} \times 100.$$

Where,

SI- Swelling index

Mt- Weight of tablet at time‘t’

Mo- Weight of tablet at time ‘o’ in mg.

***In vitro* drug release study**[13]

The *in vitro* drug release mechanism of 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 100 rpm and a temperature of 37± 0.5°C formulation was placed in the 900ml of the medium. For first 2 hr tablet was placed in 1.2pH medium which was replaced with 6.8pH phosphate buffer for remaining 10 hours. At specified intervals 5ml samples were withdrawn from the dissolution medium and replaced with fresh medium to keep the volume constant. The absorbance of the sample solution was analyzed at 246.40 nm for

the presence of model drug, using a UV-visible spectrophotometer.

RESULT 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 pH1.2 buffer and 6.8 pH phosphate buffers.[10]

Drug Excipients Compatibility Studies by using FTIR: In the present study FTIR data of the drug and excipients was compared with standard spectrum of pure Trazodone hydrochloride was shown in figure 4,5,6,7. The characteristic 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.

Pre compression parameters: As the result of evaluation test given in table number three, the powder blends of all formulations were evaluated for LBD & TBD. The values of LBD & TBD ranged from 0.578±0.12 to 0.505±0.15 and 0.650±0.06 to 0.565 ± 0.15 respectively.

The values obtained for Compressibility index for all formulations were calculated in Compressibility index value ranges between 12.93% to 06.37% indicating that the powder blend have the required flow property.

Post compression parameters: Hauser's ratio is determined from the ratio of tapped density to poured density, and it was found in the range of 1.15 to 1.06 that means the powder is free flowing.

The values obtained for angle of repose for all formulations were calculated and the values were found to be in the range from 29°.94' to 23°.21'. This indicates good flow property of the powder blend for direct compression.

Trazodone hydrochloride is an antidepressant is used primarily in the treatment of mental depression or depression/anxiety disorders. Conventional tablet of trazodone hydrochloride requires frequent dosing hence attempt had been made for formulation of extended release trazodone of hydrochloride to maintain the therapeutic concentration for longer period of time. These extended release tablets mainly prepared for release of the drug for longer period of time i.e., 12 hours and utilizing the drug to full extent avoiding unnecessary frequency of dosing. For the formulation of extended release tablet Xanthum gum, guar gum, acacia gum was used as matrix forming agents. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. The prepared controlled release tablets were evaluated for hardness in between 5.5 to 6.5, Weight variation (434 to 460), thickness (6.00 to 6.04), friability (0.72 to 0.82), drug content uniformity (92.03 to 98.60%), the swelling of tablet occurred due to the formation of the matrix layer by the gum around the tablet, enabling it to sustain release of drugs. As the swelling continues, the swollen matrix retains more water until the shear forces in the dissolution medium disentangle the individual polymer chains from the matrix. *In-vitro* dissolution study showed that polymer containing ghur gum extended the drug release up to 10 hours and does not having matrix integrity, while polymer containing xanthum gum extended the drug release up to 12 hrs and having matrix integrity. And polymer containing acacia gum release the drug upto 10 hrs, It was observed that Formulations F6 containing xanthum gum extended the drug release up to 12 hrs. having matrix integrity and hence were subjected for four different kinetic models viz. Zero order, First order, Higuchi matrix and Peppas model equations. F6 batch formulations best fit in to the zero order model and Higuchi model. In the present study diffusion value of exponent is 0.890 respectively therefore release of the formulations was mainly by Anomalous (non-Fickian) transport.

CONCLUSION

In the present study an attempt has been made to Formulate and evaluate extended release tablet of Trazadone HCl using different polymers like xanthum gum, guar gum and acacia. FTIR study shows compatibility between drug and excipients. Among all batches Batch F6 shows 93% drug release at 12h. In-vitro drug release data of optimized formulation (Batch F6) pass zero order as well as Higuchi model having r2 value (0.982) among other models. Diffusion value of exponent was found 0.890 respectively therefore 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 extended release tablet of Trazadone hydrochloride having satisfactory extended release profile which may provide an increased therapeutic efficacy.

Table no 1 Formulation of extended release tablet

Batches	Trazodone HCl	Guar gum	Xanthum gum	Acacia	MCC	Mag. Sterate	Talc
F1	100	80	----	----	260	5	5
F2	100	160	----	----	180	5	5
F3	100	240	-----	----	70	5	5
F4	100	----	80	----	260	5	5
F5	100	----	160	----	180	5	5
F6	100	----	240	----	100	5	5
F7	100	----	----	80	260	5	5
F8	100	----	----	160	180	5	5
F9	100	----	----	240	70	5	5

Total tablet - 450 mg

Table 2- Calibration data of Trazodone HCl in pH 1.2

Concentration(µg/ml)	Absorbance(nm)
5	0.131
10	0.255
15	0.401
20	0.507
25	0.661
30	0.793
35	0.936
40	1.059

Table no 3- Calibration data of Trazodone HCl in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance(nm)
5	0.231
10	0.374
15	0.563
20	0.768
25	0.963
30	1.123

Table 4: 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	26.28±0.12
F2	0.530±0.10	0.598±0.12	11.37±0.11	1.12±0.16	26.97±0.10
F3	0.570±0.07	0.616±0.14	7.46±0.18	1.08±0.10	27.33±0.15
F4	0.578±0.12	0.620±0.18	6.77±0.09	1.07±0.09	29.94±0.22
F5	0.505±0.15	0.565±0.15	12.37±0.14	1.14±0.07	24.92±0.19

F6	0.540±0.12	0.622±0.13	6.37±0.13	1.06±0.14	23.21±0.16
F7	0.517±0.03	0.589±0.09	10.30±0.09	1.15±0.12	26.12±0.17
F8	0.521±0.06	0.598±0.07	12.93±0.16	1.13±0.09	24.24±0.16
F9	0.545±0.05	0.650±0.06	10.62±0.09	1.09±0.19	25.22±0.21

Table 5: Post compression parameters

Batches	Diameter (mm)n=3	Thickness (mm) n=3	Hardness (Kg/cm^2) n=3	Drug content (%)	Friability(%) n=10	Weight Variation (mg) n=20
F1	09.03 ±0.014	6.04 ±0.012	5.5	92.03±0.09	0.82	441±1.29
F2	09.03 ±0.026	6.04 ±0.009	6.0	96.42±1.09	0.75	438±1.37
F3	09.02 ±0.040	6.01 ±0.002	6.5	98.60±1.08	0.72	440±1.33
F4	09.03 ±0.036	6.03 ±0.005	6.0	94.89±0.09	0.80	459±1.22
F5	09.01 ±0.014	6.02 ±0.009	6.0	98.01±1.03	0.82	450±1.21
F6	09.02 ±0.023	6.02 ±0.008	6.5	97.08±1.05	0.78	441±1.19
F7	09.01 ±0.019	6.04 ±0.003	5.5	95.82±1.03	0.74	460±1.23
F8	09.03 ±0.023	6.00 ±0.010	6.5	96.80±0.08	0.79	434±1.49
F9	09.02 ±0.024	6.04 ±0.011	6.5	98.09±1.05	0.82	445±1.19

Table 6 Swelling Study of Batch F1 to F9

Time/ Batch	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr
F1	0.49	0.56	0.76	0.89	1.47	1.68	2.12
F2	0.48	0.84	1.02	1.32	1.73	1.88	2.45
F3	0.57	1.02	1.08	1.35	1.62	1.96	2.48
F4	0.56	1.13	1.34	1.51	1.75	1.92	2.16
F5	0.68	1.22	1.48	1.75	1.98	2.35	2.59
F6	0.59	1.47	1.64	1.82	2.25	2.45	2.71
F7	0.48	0.84	0.97	1.09	1.22	1.75	1.75
F8	0.78	0.77	0.91	1.13	1.32	1.65	1.65
F9	0.80	0.96	1.35	1.72	2.02	1.17	1.17

Table 7: Percent drug release of batch F1 to F9

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	5.33 ±1.52	5.00 ±1.00	5.66 ±0.57	6.66 ±1.52	4.66 ±0.57	4.00 ±1.00	8.66 ±1.15	6.00 ±1.73	5.66 ±0.57
1	19.00 ±1.00	15.66 ±0.57	10.66 ±1.15	15.33 ±0.57	11.00 ±1.73	15.33 ±0.57	19.33 ±0.57	16.33 ±1.52	18.33 ±1.15
2	35.33 ±1.52	24.33 ±1.52	23.00 ±1.73	24.00 ±1.73	29.00 ±1.00	20.33 ±1.52	34.33 ±1.52	35.00 ±1.00	38.33 ±0.57
4	55.00 ±1.73	43.33 ±1.15	39.33 ±1.52	39.33 ±1.52	43.66 ±1.52	33.00 ±1.00	59.00 ±1.00	44.33 ±0.57	55.33 ±1.52
6	68.00 ±1.00	58.33 ±1.52	64.00 ±1.00	53.33 ±1.15	57.33 ±1.15	54.66 ±1.15	72.00 ±1.73	58.66 ±1.15	73.00 ±1.00
8	84.33	77.33	77.66	82.00	73.66	64.33	81.66	82.00	91.66

	±1.15	±0.57	±0.57	±1.00	±0.57	±1.52	±1.52	±1.15	±0.57
10	96.66 ±1.52	92.66 ±1.15	86.33 ±1.52	97.33 ±0.57	88.33 ±1.52	84.00 ±1.00	106.33 ±1.52	101.66 ±1.52	102.33 ±0.57
12	---	---	----	---	---	97.66 ±0.57	---	---	---

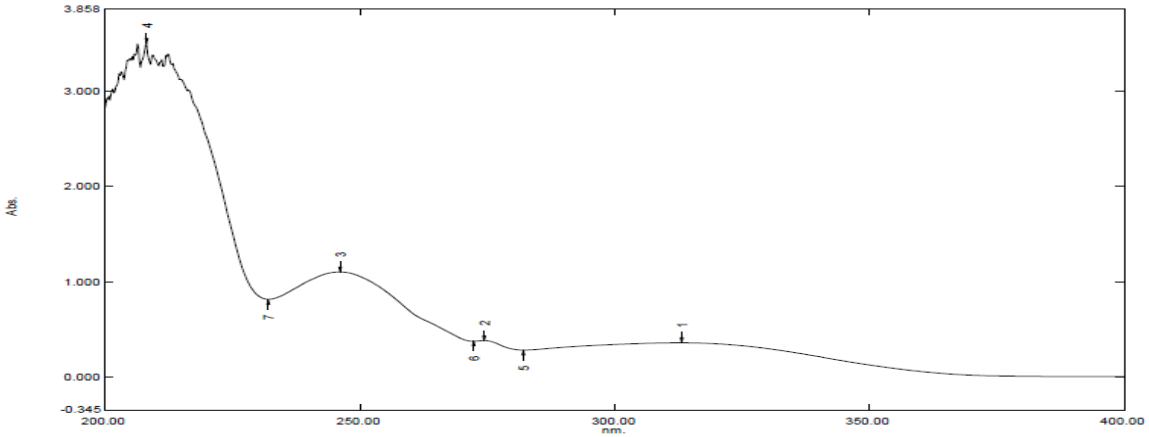

Figure 1: UV Spectra (λ_{max}) of Trazodone HCl Drug

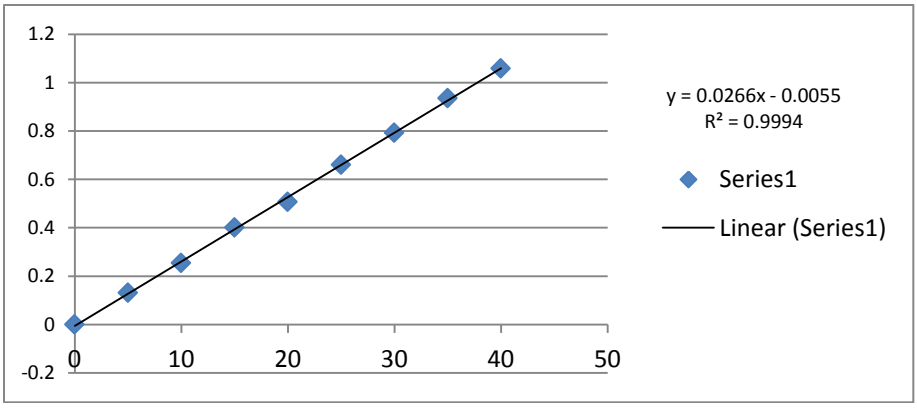

Fig no. 2 linearity curve of Trazodone HCl in pH1.2

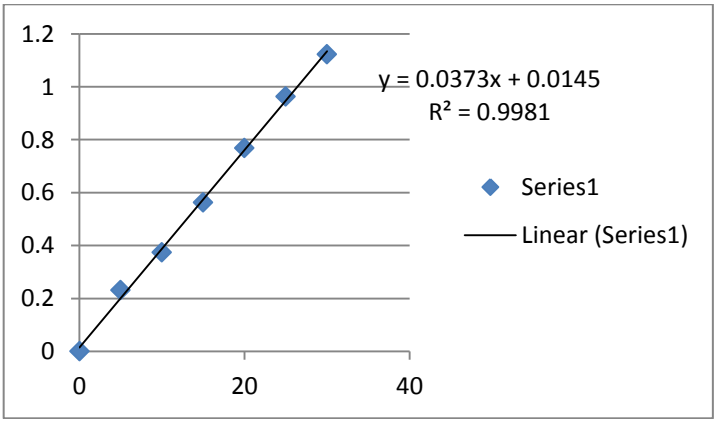

Fig no 3 Linearity curve of Trazodone HCl IN Phosphte buffer 6.8

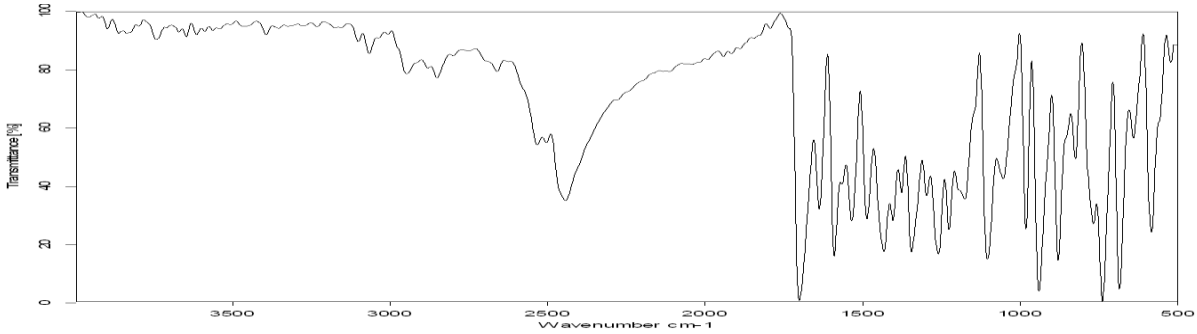

Figure 4: FTIR Spectrum of Drug Trazodone HCl

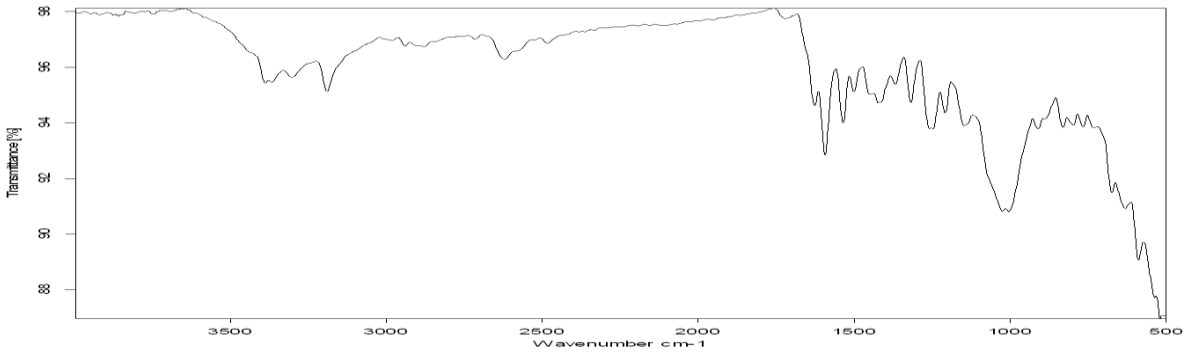

Figure 5: FTIR Spectrum of Trazodone HCl with Xanthum gum

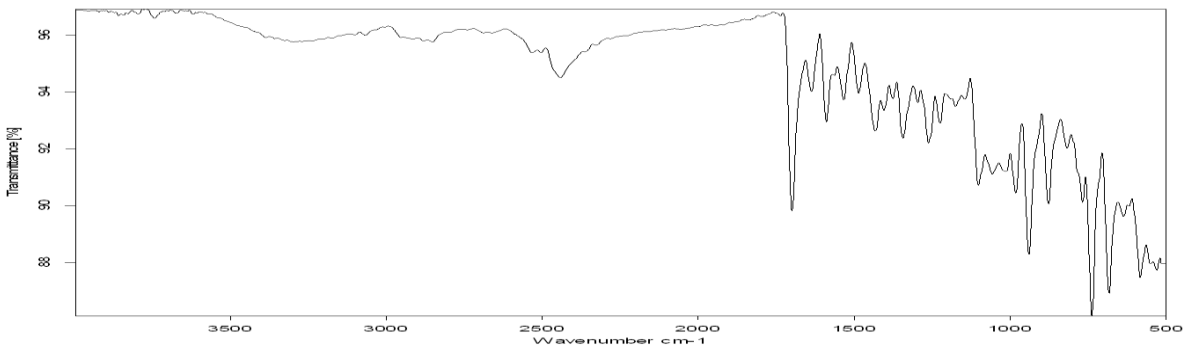

Figure 6: FTIR Spectrum of Trazodone HCl with Guar gum

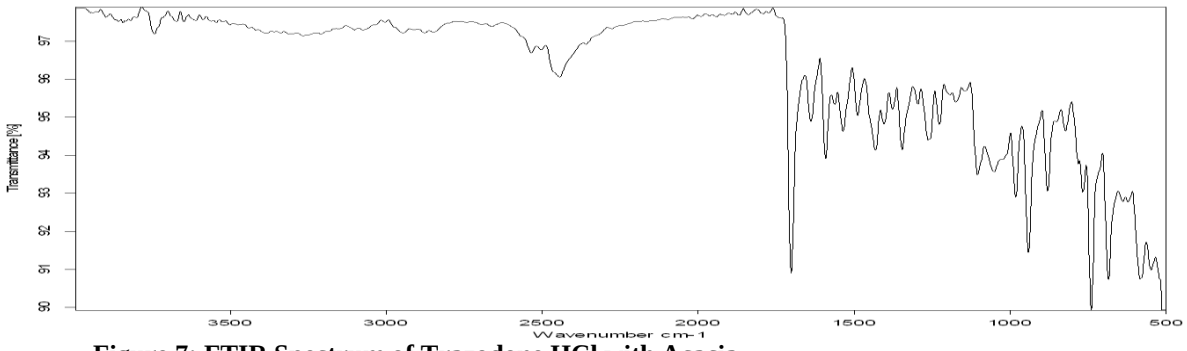

Figure 7: FTIR Spectrum of Trazodone HCl with Acacia

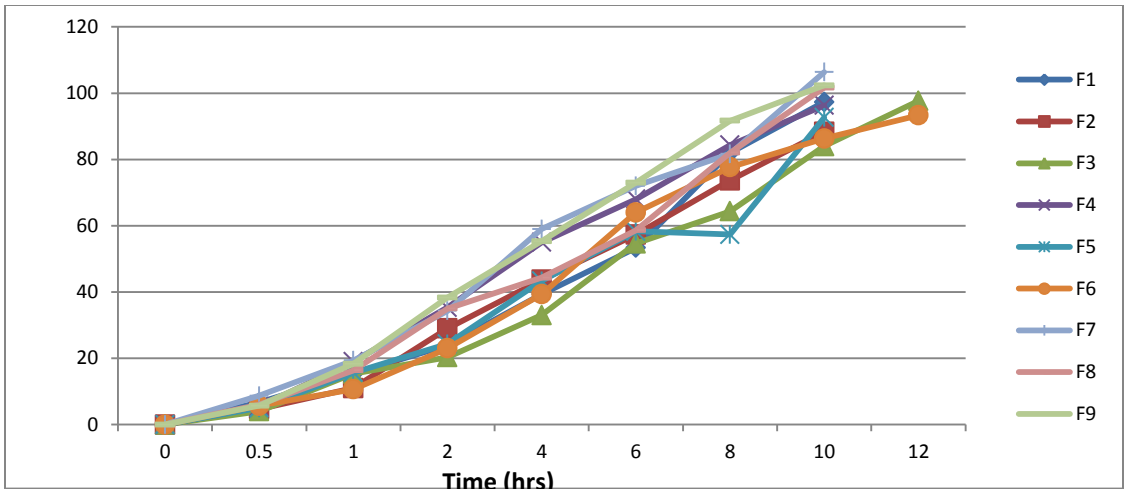

Figure 8: Comparative in-vitro release graph for formulation F1-F9 batches

Release kinetics of best optimized batch

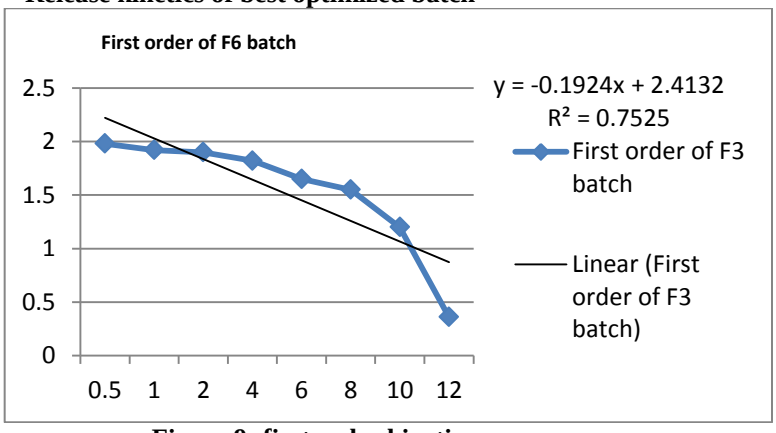

Figure 9- first order kinetics

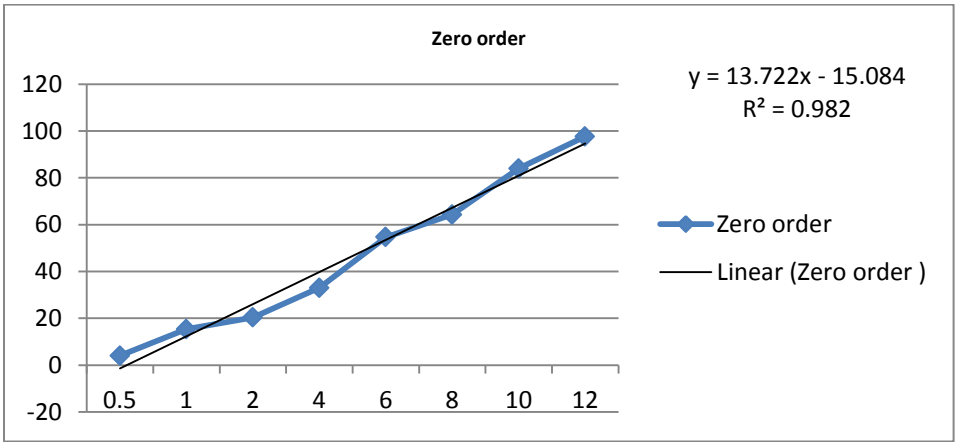

Figure 10 Zero order kinetic

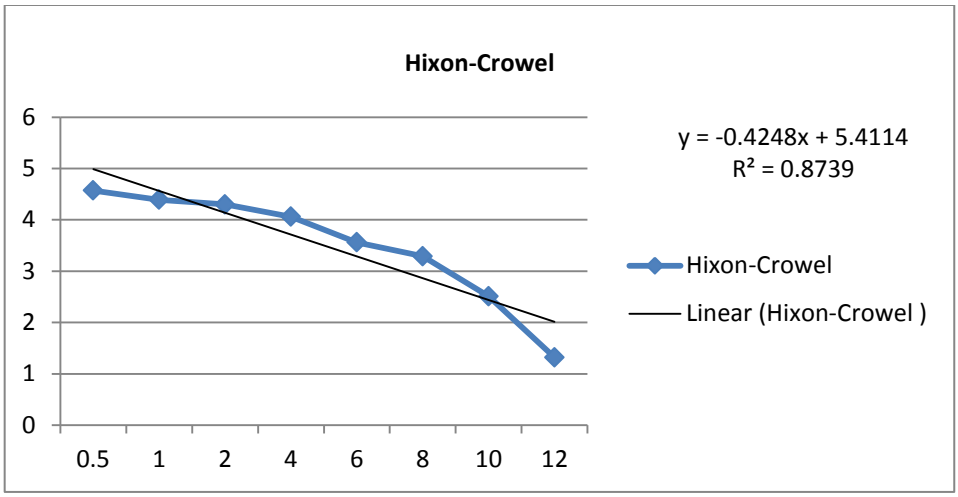

Figure 11- Hixon Crowel kinetic release

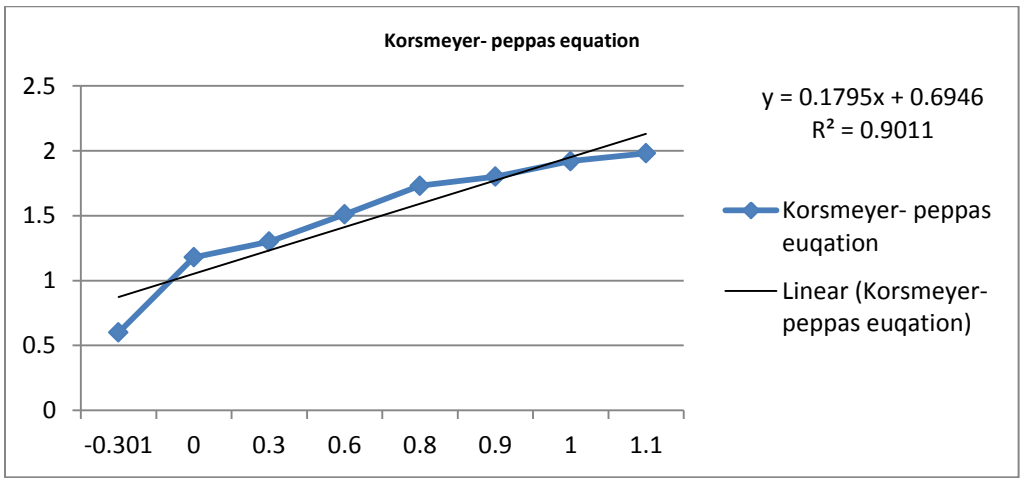

Figure 12- Korsmeyer – peppas kinetic release

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