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Corresponding Author:

***R. S. Pentewar,**
Channabasweshwar Pharmacy College,
Kava Road, Latur.
Maharashtra,
India-413512

*Email Id-rohitbharti1990@gmail.com

Formulation and In-Vitro Evaluation of Modified Release Delivery of Trazodone Hydrochloride Tablets

R. S. Pentewar[1], Rohit Udhav Bharti[1], Kiran Suryawanshi[2], R.V. Sugave

ABSTRACT

The objective behind this study was to formulate and evaluate Modified release tablet of Trazodone hydrochloride by using different hydrophilic and hydrophobic polymers by Wet granulation technology and to study the effect of different concentrations of polymers on release rate from tablet. Tablets were prepared using carnauba wax as extra fine powder (8.5-28%), hydroxypropyl methylcellulose (HPMC) (2-14.5%), and polyvinyl pyrollidone (PVP K-30) (8.5-30%) as release retardant polymers. The FTIR and DSC analysis does not show any interaction of drug with Excipients. The formulation was optimized on the basis of acceptable pre and post compressional parameters and *in-vitro* drug release. The resulting formulations produced monolithic tablets with optimum hardness, consistent weight uniformity and low friability. The results of dissolution studies indicated that Batch F8 exhibited drug release of 99% at the end of 12h to provide sufficient concentration for achieving satisfactory therapeutic value for extended period of time. The drug release from Batch F8 formulation was sustained up to 12 h. Fitting *in-vitro* drug release data from optimized matrix formulation to first order followed by Korsmeyer's-Peppas indicated that diffusion could be mechanism of drug release.

Key-words: Trazodone HCl, Carnauba wax, Wet Granulation, Modified Release (MR).

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[1]*Channabasweshwar Pharmacy College, Kava Road, Latur.(M.S.) India;*
[2]*Department of Formulation Development, V-Ensure Pharma tech. Pvt. Ltd. NaviMumbai, (M.S.) India;*

INTRODUCTION[1, 2, 3]

As the development and marketing of new drug entities is very complicated as well as very expensive, so there is constant development of formulation design, which aim to tailor drug delivery where rate of release is dependent on delivery device rather than physiological condition.

These are the dosage form which releases the drug over an extended period of time to obtain a prolonged therapeutic effect. USP used the term to describe a formulation that does not release active substance immediately after oral dosing and that also allow a reduction in dosing frequency. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and / or targeting the delivery of drug to a tissue. Trazodone is known antidepressant drug which is also described as having some usefulness in the treatment of acute phase of cerebral stroke.

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. Solubility of Trazodone is pH dependent and has a pKa of 6.74 in water. As a result, Trazodone is highly soluble in acid media (as found in stomach and upper intestine) i.e. when below its pKa. In contrast, when above its pKa, its solubility is very low, for example, in the neutral and basic conditions of the lower intestines. Such insolubility obviously has an effect on its dissolution and, therefore, on the availability of the drug for absorption in the lower intestine. These features would be expected to hinder the development of long acting (for example greater than 8 hours) forms of Trazodone, which require substantially uniform absorption along the length f the gastrointestinal tract, in particular, absorption during passage through both the upper and lower intestinal tracts.

Frequent dosing with immediate release Trazodone may results in fluctuations in drug release and which may crosses the therapeutic range and which, therefore, can be associated with higher risks of dose related adverse effects. As a result, there is a need for a once a day (OAD) formulation of Trazodone which can maintains stable, effective concentrations over 12 hours that is pH-independent in its release profile so that Trazodone may be uniformly absorbed along the upper and lower gastrointestinal tract, thereby reducing the frequency and severity of side effects such as drowsiness during the day.

MATERIAL AND METHODS

Trazodone HCl is procured from Piramal Healthcare Pvt. Ltd. Mumbai. Carnauba wax (extra fine Powder) and sucrose procured from signet Pharma agencies, Mumbai. HPMC procured from colorcon Asia Pvt. Ltd. Mumbai. PVP K-30 and PVP K-90 is procured from BASF, Germany. Dichloromethane (DCM) and Isopropyl alcohol (IPA) is from Merck. Magnesium Stearate from Ferro Corps, USA. All reagents and chemicals used were of research/analytical grade.

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Formulation of Trazodone HCl Modified release Tablet

Process flow diagram

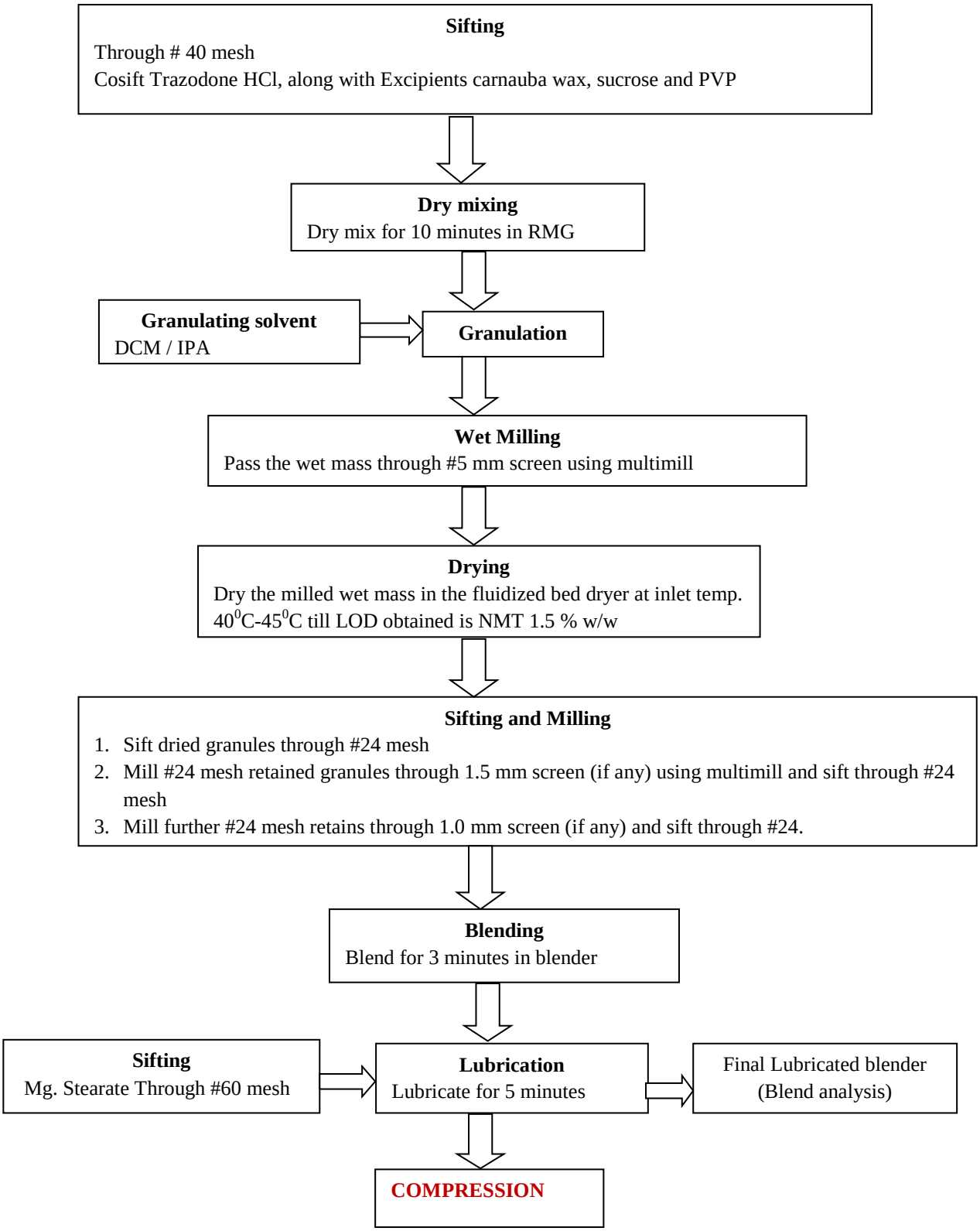


Table no. 1: Composition of All Batches (quantity in mg/tablet)

Batch No.	F1	F2	F3	F4	F5	F6	F7	F8
INTRAGRANULAR								
TZD HCL	150.49	150.49	150.49	150.49	150.49	150.49	150.49	150.49
CarnaubaWax	24	60	50	50	24	50	--	80
PVP K30	83.51	30	40	24	24	24	--	30
Sucrose	24	41.50	41	59.51	83.51	59.51	83.5	21.51
GRANULATING FLUID								
Purified water(ml)	---	240	320	25	15	---	QS.	---
IPA (ml)	75	---	---	25	35	150	---	---
MDC (ml)	25	---	---	---	---	---	----	QS.
EXTRAGRANULAR								
Mg. Stearate	5.55	4.8	3.24	6	6	4	6.0	6
MethocelE4M	---	---	---	---	---	---	6.0	---
MethocelK100	---	---	---	---	---	---	42	---

EVALUATION

Pre-compression parameters	Post-compression parameters
Loss on drying.	Physical appearance.
Density analysis.	Hardness test.
Compressibility Index and Hauser's ratio.	Thickness.
Sieve analysis.	Friability test.
Angle of Repose.	Weight variation.
	Uniformity of drug content.
	Dissolution studies.

Table no. 2: Precompressional parameters of MR formulation of different batches

Formulation	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility index (%)	Angle of Repose(°)	Hausner's ratio (HR)
F1	0.555 ±0.001	0.642 ±0.002	13.28 ±0.21	27.45 ±0.65	1.15 ±0.02
F2	0.570 ±0.001	0.654 ±0.003	12.84 ±0.25	27.40 ±0.70	1.14 ±0.03
F3	0.695 ±0.002	0.793 ±0.002	15.17 ±0.54	28.59 ±0.84	1.17 ±0.01
F4	0.615 ±0.003	0.725 ±0.001	12.19 ±0.84	28.01 ±0.99	1.13 ±0.02
F5	0.720 ±0.010	0.820 ±0.001	13.28 ±0.21	29.59 ±0.62	1.18 ±0.04
F6	0.585 ±0.001	0.695 ±0.002	15.82 ±0.45	29.48 ±1.01	1.17 ±0.03
F7	0.665 ±0.010	0.781 ±0.001	14.85 ±0.65	29.10 ±1.20	1.15 ±0.05
F8	0.695 ±0.002	0.793 ±0.002	12.35 ±0.24	27.00 ±0.78	1.14 ±0.01

Table no. 3: Physical Characterization of Tablets

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (N)	Friability (%)	Disintegration (min)	Assay (%)
F1	289-290	4.39-4.42	69.1-68.6	0.12	38	100.1
F2	291-296	4.51-4.57	62-67	0.11	100	99.9
F3	289-295	4.26-4.30	62.1-69.1	0.11	78	99.1
F4	287-296	4.09-4.19	68-78	0.09	70	99.5
F5	289-291	4.21-4.31	75-80	0.16	59	96.8
F6	289-292	4.26-4.29	76-80	0.11	57	100.3
F7	289-291	4.08-4.10	68-78	0.08	42	98.8
F8	287-290	4.21-4.28	72-82	0.12	95	100.3

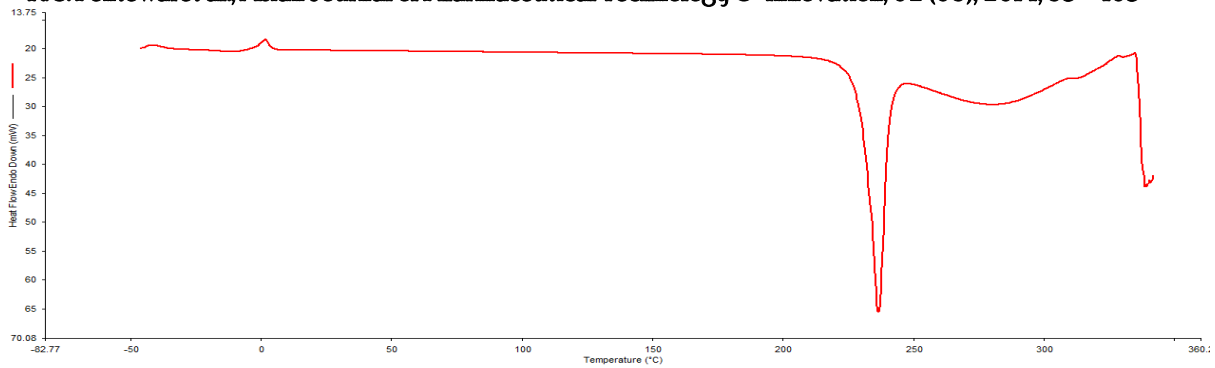


Figure No. 1: DSC of Trazodone hydrochloride (API)

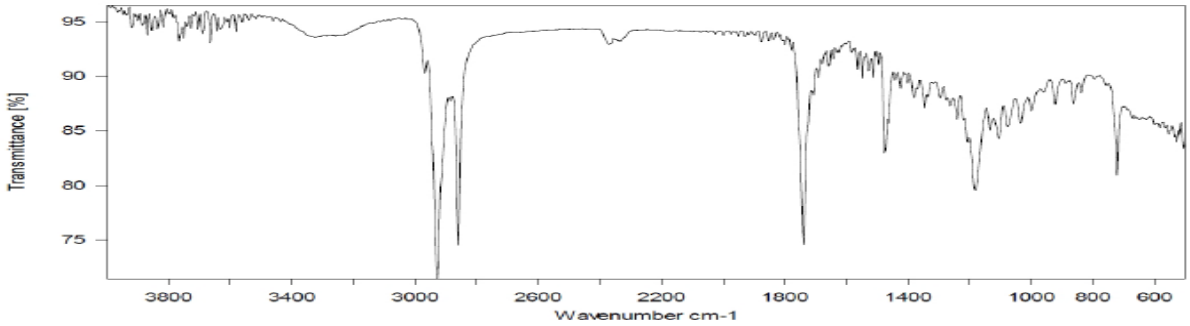


Figure No. 2: FTIR spectrum of Carnauba wax (extra fine powder)

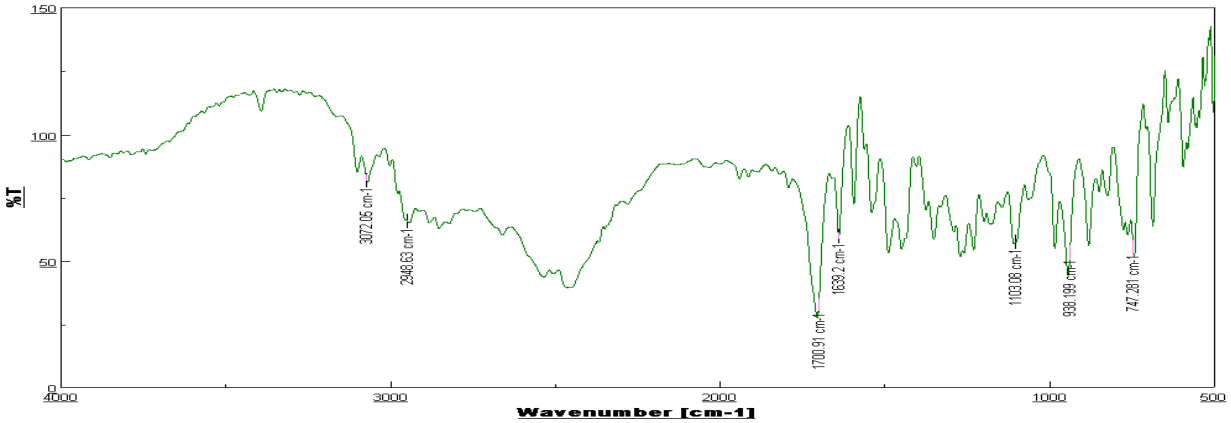


Figure No. 3: FTIR spectrum of Trazodone HCl formulation

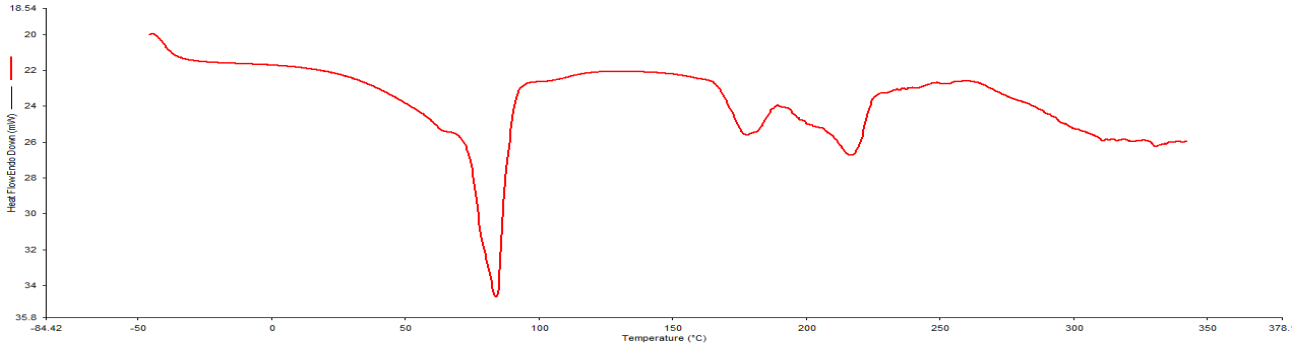


Figure No. 4: DSC spectrum of Trazodone HCl formulation

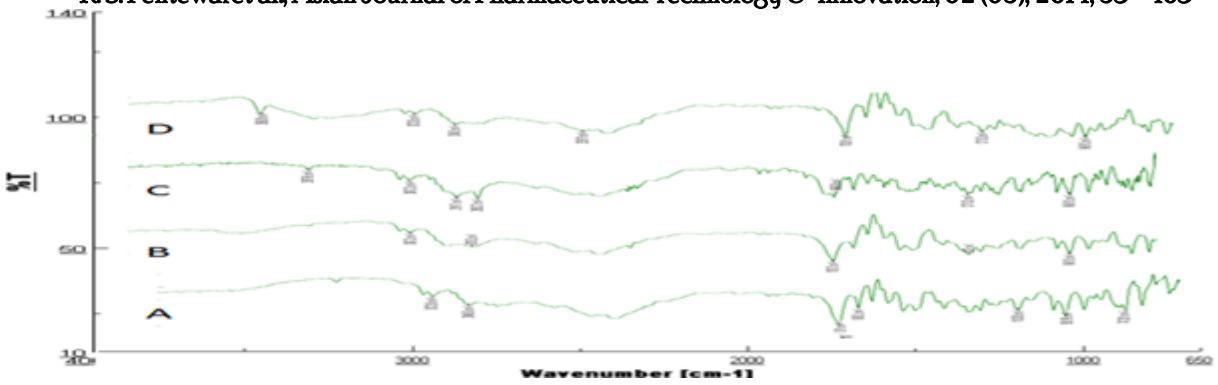


Figure No. 5: Compatibility study by the FT-IR spectrum of API and excipients

(In above FT-IR spectrum, graph A for API, B for API+PVP K30, C for API+ Carnauba Wax and D for AIP+ Sucrose.)

Table No. 4: FTIR Interpretation of Trazodone HCl

Sr. No.	Frequency (cm^{-1})	Attributed to
1	600-800	C-Cl
2	1670-1820	C=O
3	1080-1360	C-N
4	1639	C=N
5	1715	Ph-CH
6	2850-3000	HC-CH

Table no. 5: In-vitro drug Release Profile

Time (hr.)	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0
1	44	49	46	52	53	19	43
2	64	66	66	69	74	28	63
4	78	78	79	80	83	37	81
6	89	86	87	91	90	44	90
8	92	93	87	93	98	59	95
10	95	97	91	95	94	73	98
12	95	102	93	95	94	96	99

COMPARATIVE STUDY OF ALL BATCHES

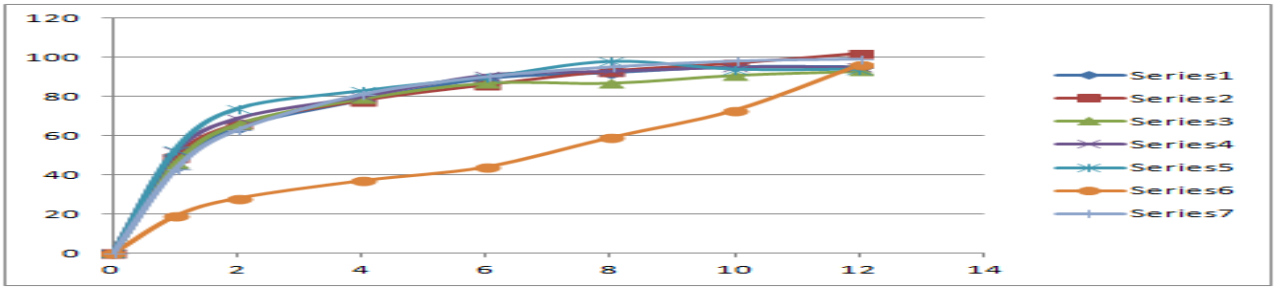


Figure No. 6: Comparative Drug Release Profile for All batches

RESULTS AND DISSCUSSION

Drug Excipients Compatibility studies by using DSC

The Drug and Excipients Compatibility study was done by using DSC method. Results are shown in Figure 1 and Figure 4.

Drug-Excipients Compatibility studies by using FTIR

FTIR Interpretation of Trazodone HCl in the Drug excipients study is shown in Figure 3 and Figure 5 and their interpretation given in Table no. 4.

Characterization of Granules

The blend prepared in all Batches for Precompressional granules were evaluated for their flow properties; the results for Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio and Angle of Repose, were shown in Table no. 2.

Characterization of Tablets

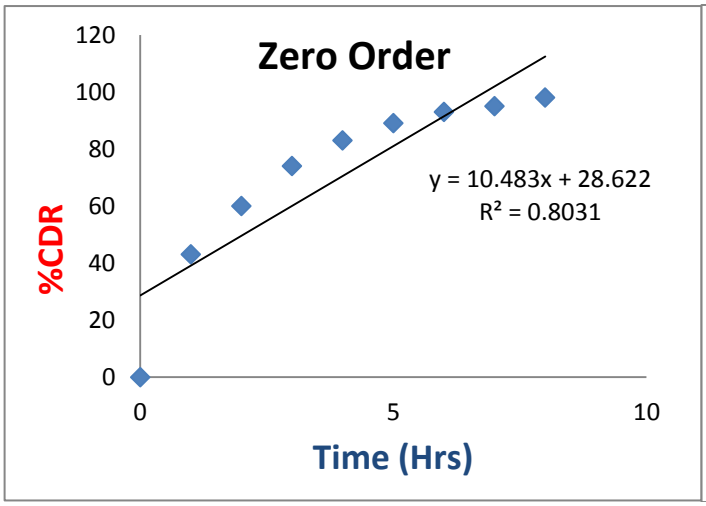
Tablets were formulated by Wet Granulation Technique By using RMG and tests such as Weight Variation, Thickness, Hardness, Friability, Disintegration and Drug Content were carried out and Results were shown in Table no. 3.

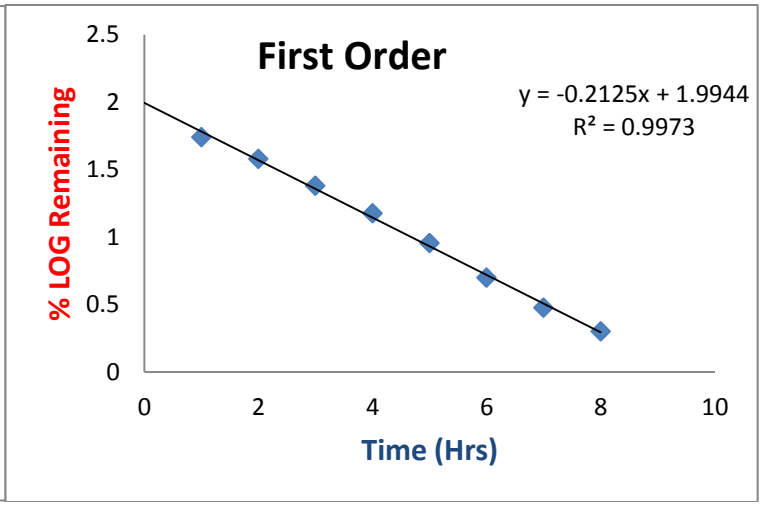
***In-vitro* Drug Release Profile for Formulation**

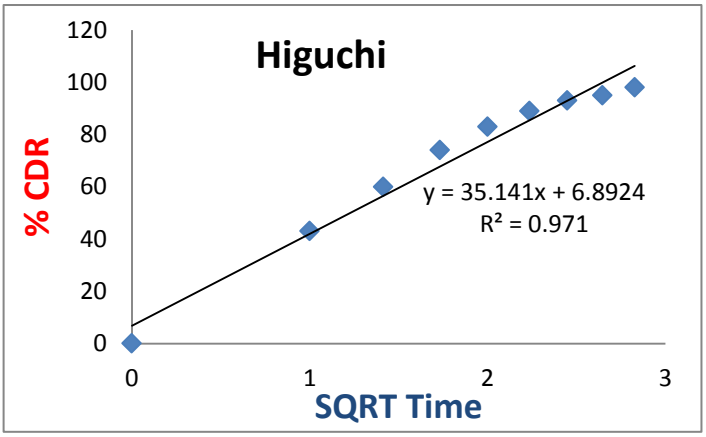
The *In-vitro* drug release studies for the prepared formulations from F2 to F8 were conducted for a period of 12 hours using an Electrolab TDT O8L Dissolution Tester USP Type –II apparatus (rotating paddle) set at 50 rpm and a temperature of 37± 0.5°C. Formulation was placed in the 900ml of the medium. Aliquots of dissolution media containing 10ml samples were withdrawn at specific time intervals and replaced same dissolution media maintained at same temperature was replaced after each withdrawal. The samples were analyzed by HPLC equipped with UV-VIS detector at 256nm using water as blank. The raw dissolution data was analyzed for calculating the amount of drug released and percentage cumulative drug released at different time intervals. Results were shown in Table no. 5.

Evaluation of Drug Release Kinetics

The optimized formulation (F8) was evaluated for drug release kinetics using Zero order, First order, Higuchi, Korsmeyer-Peppas model and R^2 values of the formulations were tabulated in the Table no. 6.







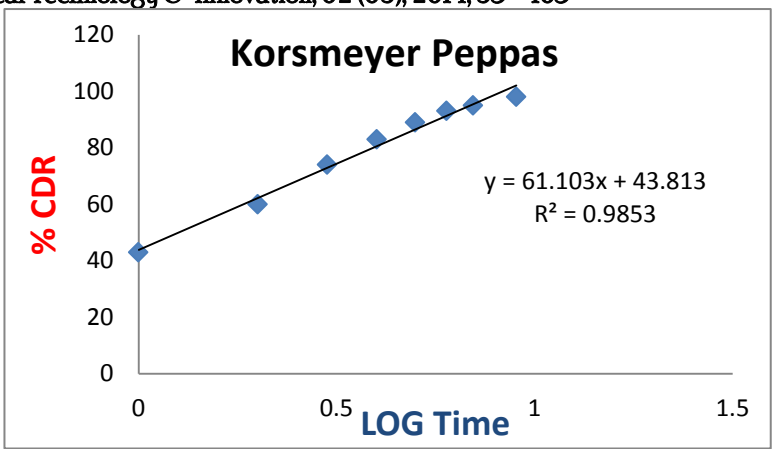


Table no. 6: Evaluation of drug release kinetics

Batch No.	R^2 values (correlation coefficient)			
	Zero order	First order	Higuchi	Korsmeyer-Peppas
F8	0.803	0.997	0.971	0.985

Comparison study: Dissolution Comparison Reference 150mg vs. Test 150mg

Product Details	Trittico AC 150	Trazodone HCl MR 150mg
Batch No.	874	F8

Medium: Release Media (0.01M HCl)

Agitation: 50 RPM, Apparatus: Paddle (USP-II), Volume: 900 ml

Table No.9: Dissolution Comparison Reference 150mg vs. Test 150mg

Sr. No.	Time Points (Min.)	% Dissolution Reference (874)	% DissolutionTest (F8)
1	0	0	0
2	30	33	32
3	45	41	39
4	60	47	45
5	90	57	55
6	120	64	62
7	180	75	75
8	240	83	85
9	300	89	91
10	360	92	96
11	480	98	99
12	600	98	99
13	720	98	99
10	**F2 Value**	**84.72**	

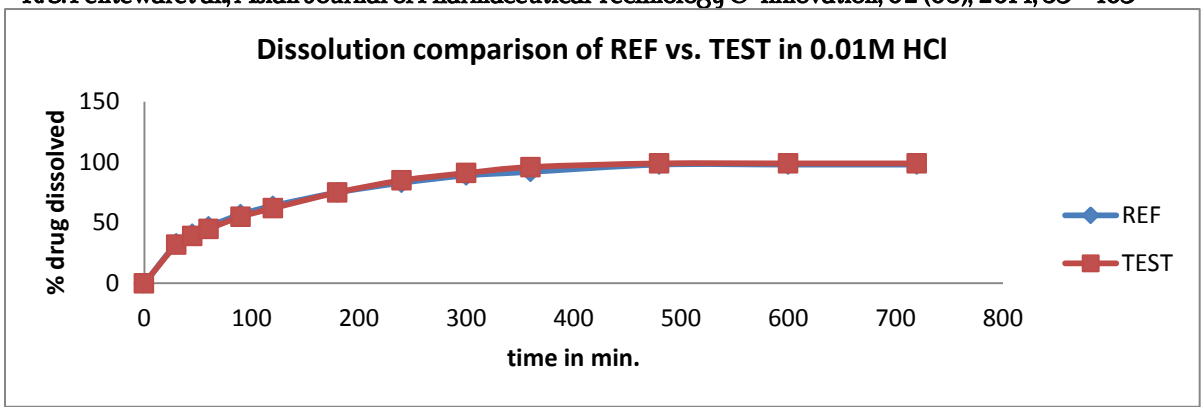


Figure 7: Dissolution comparison by graphical presentation (REF vs. TEST) in 0.01M HCl

Table No. 10: Change over Dissolution media profile comparison (in vitro fed and fasting condition)

Sr. No.	Time Points (Min.)	% Dissolution REF 874	% Dissolution TEST F8
1	60 (0.01N HCl)	48	45
2	120 (0.01N HCl)	64	62
3	180 (at 6.8 pH)	64	63
4	240	66	66
5	360	69	71
6	480	72	74
7	600	74	77
8	720	75	79
10	**F2 value**	**80.10**	

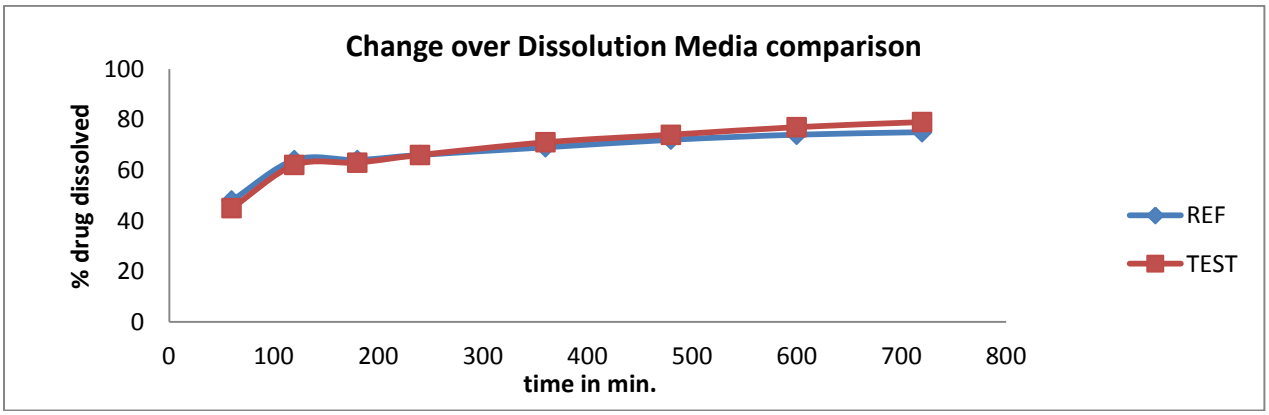


Figure 8: Change over Dissolution comparison by graphical presentation (REF vs. TEST)

DISCUSSION

In the present study an attempt has been made to prepare Modified release tablet of Trazodone HCl using Carnauba wax (extra fine powder), Different grades of HPMC & Different concentrations of PVP K-30 as release retardant polymer by Wet Granulation technique using RMG. Different concentrations of carnauba wax such as 8.5-28.0%, PVP K-30 about 8.5-30.0% and HPMC (Methocel K4M 2% &Methocel K100M 14.5%) were used as release retardant polymers. In all formulations of Trazodone HCl was 52.8% w/w.

Drug Excipients Compatibility Study

Drug remained intact in physical mixture containing polymers. So, it was concluded that there was no major interaction occurred between drug and excipients used in the formulation.(Figure 5)

Physical characterization of Granules prepared by Wet Granulation

The Granules prepared by Wet Granulation technique using RMG evaluated for characterization such as Bulk Density, Tapped Density, Cars Index, Hausner's Ratio and Disintegration. The results are shown in Table no. 2, all granules shows good flow property.

Physical characterization of Tablets prepared by Wet Granulation

The Modified release tablet containing Trazodone HCl 150mg prepared by Wet granulation evaluated for characterization such as Hardness, Friability, Weight variation and content Uniformity, the results are shown in table no. 3. All tablets show sufficient Physical parameters. Friability of all the batches from F1 To F8 was less than 1%. Hardness in the range of 60-80 N and drug content in the range of 95-105%.

Because of very low Disintegration time of Batch F1 about 38 min. this batch F1 is not included in dissolution study.

Dissolution Study

From the Dissolution study (Table no. 5) and comparative graph (Figure 6) it was concluded that increase in concentration of Carnauba wax (extra fine powder) shows decrease in drug release from tablet. Batch F8 shows 99% drug release at 12h in comparison with batch F2 & F3 which shows 95 & 97% release at 10h respectively. Batch F4 shows 93% drug release; batch F6 which release drug about 98% at 8h. Batch F7 release only 73% at 10h. As among all batches, batch F8 shows 99% cumulative drug release at the end of 12hours.

Drug Release Kinetic Studies

In-vitro Drug release data of all the formulations were fitted to various kinetic models like Zero order, First order, Higuchi, Korsmeyer-Peppas and Pass First order model and among the all formulations, F8 shows highest R^2 value (0.997) as well as Korsmeyer-Peppas model having R^2 value (0.985) among other models.

CONCLUSION

In the present study an attempt has been made to Formulate and evaluate Modified release tablet of Trazodone HCl using different polymers like Carnauba wax as extra fine Powder, different grades of HPMC & PVP K-30 as release retardant polymer. FTIR study shows compatibility between drug and excipients. Pre-compression study shows good flow property of granules prepared by Wet granulation. Among all batches Batch F8 shows 99% drug release at 12h and change over dissolution study shows F2 value (similarity factor) 80.10 in comparison with reference Trittico AC 150 Tablet. *In-vitro* drug release data of optimized formulation (Batch F8) pass First order Model as it has highest R^2 value (0.997) as well as Korsmeyer-Peppas model having R^2 value (0.985) among other models. Trazodone HCl MR Tablet successfully prepared and evaluated.

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