International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE **V-1, I-2, 2012**

Box-Behnken Design for Optimization of Formulation Variables of Tramadol HCl Sustained Release Matrix Tablet

Gandhi CK*, Mehta TJ, Patel MR, Patel KR, Patel NM
Shri B. M. Shah College of Pharmaceutical Education & Research, College Campus, Dhansura Road, Modasa, Dist: Sabarkantha, 383315, Gujarat, India
Manuscript No: IJPRS/V1/I2/00062, Received On: 02/05/2012, Accepted On: 15/05/2012

ABSTRACT

The objective of this work was to develop sustained release tablets (Once in a day) of highly water soluble Tramadol HCl using hydrophilic polymers (HPMC K100M, HPMC K15M, HPMC K 4M) as cost effective, non toxic easily available and suitable hydrophilic matrix system. Sustained release tablet of Tramadol HCl (dose 200mg) were produced by wet granulation method by PVP K30 5% solution. After the evaluation of physical characteristics of granules & tablets, The dissolution test was performed in 0.1 N HCl for 2 hr and remaining 22 hr performed in 6.8 pH buffer solution. We concluded that T1-T15 batches of Box-behnken design passed the pre-compressional and post-compressional parameters and increasing the polymer concentration, decreasing the drug release. Higher viscosity grade HPMC K100M is more drug retarding agent as compare to HPMC K15M & HPMC K4M. In combination of HPMC K4M, HPMC K15M & HPMC K100M, T7 batch having drug releasing up to 24 hrs as compare to others. Kinetics treatment of the box-behken design batches, concluded that zero order R^2 value is near to 0.999 as compared to the first order R^2 value. So, all batches follow the Zero order release mechanism. From the korsmeyer-peppas model, concluded that drug release mechanism is diffusion with dissolution or anomalous diffusion (Non-fickian). From the statastical analysis full model and reduced model was analyzed and got the significant effect of X_3 polymer as compared to X_1 & X_2. X_3 having more negative value than the X_1 & X_2 so concluded that the X_3 polymer is effective to retardation of the drug release. T1-T15 batches are compared with marketed product (Tramazac OD tab.). T7 batch had more 73.58 similarity factor (f_2) when Marketed formulation taken as a reference. So T7 batch is optimized batch. The optimized batch is passed the accelerated stability studies, No significant change in the dissolution profile.

KEYWORDS

Box-Behnken Design, Hydroxypropylmethylcellulose, PVP *K*-30, Sustained Release, Tramadol HCl, Wet Granulation.

INTRODUCTION

Hydrophilic matrices containing swellable polymers are referred to as hydrogel matrices, swellable sustained release system or hydrophilic matrix tablets. A number of polymers have been investigated to develop in-situ gel forming systems due to ability of these hydrogels to release an entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and cross linking.[1,2,3] Hydroxypropylmethylcellulose (HPMC) is the polymer most widely used as the gel forming agent in the formulation of sustained release dosage form. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from these dosage form are controlled by the hydration of HPMC which forms a gel barrier through which

***Address for Correspondence:**
Gandhi Chintankumar Krishnajivanbhai
Shri B. M. Shah College of Pharmaceutical Education & Research, College Campus, Dhansura Road, Modasa, Dist: Sabarkantha, 383315, Gujarat, India.
E-Mail Id: chintan.gandhi1987@yahoo.co.in

the drug diffuses.[4,5] The adjustment of the polymer concentration, the viscosity grade and the addition of different types and levels of excipients. The HPMC matrix can modify the drug release rate.[6]

Tramadol is used in the treatment of osteoarthritis when non-steroidal anti-inflamatory drug (NSAIDS), acetaminophen, or cox-2 inhibitors alone produce inadequate pain relief.[7] Tramadol HCl is a "Class-I" drug according to Biopharmaceutics Classification System (BCS), possessing both high solubility and high permeability absorption characteristics. Tramadol HCl is rapidly and completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 2 hours after oral dosing and its elimination half-life ranges from 5.5-7 hrs.[8] and requires dosing every 6 hours in order to maintain optimal relief of chronic pain.[9,10] Consequently once daily extended release tablets have been formulated. Long term treatment with sustained release Tramadol once daily is generally safe in patients with osteoarthritis or refractory low back pain and is well tolerated.[11,12] It has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep and improved compliance.[13]

Tramadol HCl has a short elimination half-life and rapidly absorbed in gastrointestinal tract. If it is formulated by conventional tablets, it will require multiple daily administrations (2-3 times daily) which ultimately results into inconveniency to the patients and possibility of reduced compliance with prescribed therapy. Also fluctuation in plasma drug concentration leads to exaggerated side effects, this all limitations can be minimized by adopting extended release formulation.

MATERIALS AND METHODS

MATERIALS

Tramadol HCl were procured from Lincoln Pharmaceutical Ltd. Ahmedabad, HPMC K100M, HPMC K15M, HPMC K4M, Lactose were procured from Colorcon Asia Pvt Ltd. Goa, PVP *K*-30 were procured from Oxford Chemicals, Magnesium Stearate, Talc were procured from ACME Chemicals, Tri-Sodium Ortho Phosphate was purchased from S.D.Fine Chem Pvt Ltd.

INTERFERENCE STUDY

This study has been done to check whether there is any compatibility related problems are associated with drug and excipients used for the formulation of tablet. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive and easy to administer and safe. If the excipients are new and not been used in formulations containing the active substance, the compatibility studies are of paramount importance. The IR spectral analysis of a drug and other excipients were taken using Press pellet technique (using KBr). The IR spectra's were determined by using 8400 S Shimadzu FT-IR. All the spectra were recorded in the range of 4000-400 cm^{-1}.

FORMULATION OF SR TRAMADOL HCL MATRIX TABLET

Weight accurately (Digital Weighing Balance, AUX 220 Shimadzu Corp.) Drug with HPMC K100M, HPMC K15M, HPMC K4M, and lactose pass through 40# sieve and mix it properly for 3-5 minutes in a China dish. Prepare 5% binder solution by dispersing PVP *K*-30 in Ethanol. Granulation of above mixture is done by prepared binder solution by kneading up to granulation end point is obtained (Dough mass). Pass the dough mass through 40# sieve and keep it in a Hot air oven (Labtronic Ltd) for drying for 10 min at 55^0C and finally keep the loss on drying (LOD) up to 2-3 %. Remove the dried granules from oven and pass through 20# sieve to get optimum size granules. Lubrication is done by using Magnesium stearate and talc previously passed through 60# sieve of the granules for 3-4 min. In a china dish and then in polybag. Compression is done by using 6 station punching rotary compression machine (Ratnakar Pharma Machinary) by using 12 mm standard concave circular punch.

PRE-COMPRESSION PARAMETERS[14]

Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (Vo) was measured. Then graduated cylinder was closed with lid, set into the ETD 1020 Tap density tester (USP). The density apparatus was set for 500 taps and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density and tapped density were calculated using the following formulas;

Bulk density = W/Vo.....(1)

Tapped density = W/Vf.....(2)

Where,

Vo = Initial Volume

Vf = Final Volume

Compressibility Index

The Compressibility index and Hausner's ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interaction, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner's Ratio.

Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x100]/TD.....(3)

Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material.

Hausner's Ratio = TD / BD.....(4)

Table 1: Effect of Carr's Index and Hausner's ratio on Flow Property

Carr's Index (%)	Flow Character	Hausner's Ratio
< 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Angle of Repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\theta = \tan^{-1} h/r$.....(5)

Where,

h = Height of pile

r = Radius of the base of the pile

θ = Angle of repose

Table 2: Effect of Angle of Repose (θ) on Flow Property

Angle of Repose (θ)	Type of Flow
< 20	Excellent
20-30	Good
30-34	Passable
>35	Very poor

POST-COMPRESSION PARAMETERS[14]

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in Table 3 Percentage deviation allowed under weight variation.

Table 3: Percentage Deviation Allowed Under Weight Variation Test

Average weight of tablet (X mg)	Percentage deviation (%)
X< 80 mg	10
80 < X < 250 mg	7.5
X > 250 mg	5

Friability

Twenty tables were weighed and placed in the EF-2 Electorlab Friabilator (USP) and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula.

% F = {1- (Wt/W)} x 100.....(6)

Where,

%F= Friability in percentage

W = Initial weight of tablet

Wt = Weight of tablet after revolution

Hardness

Hardness was measured using Monsanto hardness tester. For each batch ten tablets were tested.

Dimension

Twenty tables were randomly selected from each batch and there thickness and diameter was measured by using Calibrated digital vernier calipers.

Determination of Drug Content

The Tramadol HCl matrix tablets were tested for their drug content. 20 tablets were finely powdered; 400 mg of the powder was accurately weighed & transferred to a 50 ml volumetric flask. Then the volume was made up with 0.1 N HCl & shaken for 10 min to ensure complete solubility of drug. The mixture was centrifuged & 10 ml of supernatant liquid was diluted 20 times with 0.1 N HCl & after centrifugation the absorbance was determined 1800 UV-Visible spectrophotometer (1800 Shimadzu Corp.) at 271 nm.

BOX-BEHNKEN DESIGN

Box-Behnken design is one experimental design for optimization purpose & quadratic response surface approach. It is specifically selected because it requires fewer experimental runs, require less time, cost effective technique & do not have axial points. It requires minimum 3 factors & 3 levels. If 3 factors & 3 levels are there, Minimum 15 runs are occurred in this design. In table 5 coded value & actual value are described.

Polynomial equation:

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_{12}X_1X_2 + \beta_{13}X_1X_3 + \beta_{23}X_2X_3 + \beta_{123}X_1X_2X_3 + \beta_{11}X_1^2 + \beta_{22}X_2^2 + \beta_{33}X_3^2 \ldots\ldots\ldots (7)$$

Table 4: BBD Formulation of Batch T1-T15

Batch No.	Ingredients (Quantity in mg)									
	Drug	**HPMC K4M**	**HPMC K15M**	**HPMC K100M**	**Lact-ose**	**Mg. Stearate**	**Talc**	**PVP K30**	**Ethanol**	**Total Weight**
T1	200	40	40	70	130	8	12	5%	Qs	500
T2	200	100	40	70	70	8	12	5%	Qs	500
T3	200	40	100	70	70	8	12	5%	Qs	500
T4	200	100	100	70	10	8	12	5%	Qs	500
T5	200	40	70	40	130	8	12	5%	Qs	500
T6	200	100	70	40	70	8	12	5%	Qs	500
T7	200	40	70	100	70	8	12	5%	Qs	500
T8	200	100	70	100	10	8	12	5%	Qs	500
T9	200	70	40	40	130	8	12	5%	Qs	500
T10	200	70	100	40	70	8	12	5%	Qs	500
T11	200	70	40	100	70	8	12	5%	Qs	500
T12	200	70	100	100	10	8	12	5%	Qs	500
T13	200	70	70	70	70	8	12	5%	Qs	500
T14	200	70	70	70	70	8	12	5%	Qs	500
T15	200	70	70	70	70	8	12	5%	Qs	500

Table 5: Box-Behnken Design Layout

Factors		**Levels**		
		-1	**0**	**1**
X1	HPMC K4M	40 mg	70 mg	100 mg
X2	HPMC K15M	40 mg	70 mg	100 mg
X3	HPMC K100M	40 mg	70 mg	100 mg

IN-VITRO DISSOLUTION STUDY[15]

The dissolution study was carried out first 2 hr in 0.1N HCl and another 22 hr in 6.8 pH buffer solution using USP II dissolution test apparatus (TDT-08L Electrolab Ltd.) employing paddle stirrer. In this study one tablet containing 200 mg of tramadol was placed inside the 900 ml dissolution medium and speed of paddle was set at 75 rpm. Samples were (10ml) withdrawn at a particular time interval and same volume of fresh medium was replaced.

The sample were analyzed for drug content against 0.1N HCl for first 2 hr and for another 22 hr 6.8 pH buffer solution as a blank at λmax 271 nm . The percentage drug release was plotted against time to determine the release profile.

KINETICS TREATMENT ON DRUG RELEASE

Different mathematical models may be applied for describing the kinetics of the drug release process from the formulation matrix; the most suited being the one which best fits the experimental results. The kinetics of Tramadol HCl release from tablets was determined by finding the best fit of the dissolution data (drug release Vs time) to distinct models: Zero order [eq.8], first-order [eq.9], Higuchi [eq. 10], and Korsmeyer-peppas model [eq. 11].

$$Q_t = k_0 t \text{……(8)}$$

$$Q_t = Q_\infty (1\text{-}e^{-k1t}) \text{….(9)}$$

$$Q_t = k_H t^{1/2} \text{…….(10)}$$

$$Q_t/Q_\infty = k_{KP} t^n \text{…….(11)}$$

Where,

k_0 = Zero order rate constant expressed as concentration/time & t is the time.

k_1 = First order constant.

k_H = Constant reflecting the design variables of the system.

Q_t = Amount of drug released in time t.

Q_0 = Initial amount of drug in tablet.

Qt/Q_∞ = Fraction of drug release.

k_{KP} = Release rate constant.

n = Diffusional release exponent indicative of the drug release mechanism.

T = Dissolution time.

ACCELERATED STABILITY STUDY

The batch T7 was selected as an optimum batch and the stability study was carried out at accelerated condition at 45°C and 75 ± 5% RH condition for a period of three month.

Method

Ten tablets were individually wrapped using aluminum foil and packed in ambered color screw cap bottle and put at above specified condition in incubator for three months. After three month tables were evaluated for *in-vitro* drug release.

Observation

The results of stability study after three month are given through the plot of cumulative % drug release v/s Time (hr) depicted as Figure 9.

RESULTS & DISCUSSION

INTERFERENCE STUDY

FT-IR Spectroscopy

Overlapping of IR spectra indicate no significant difference in characteristic peak at wave numbers of the drug in presence of the excipient given in figure 1 & table 6.

Interpretation of FT-IR Spectrum

Table 6: Interpretation of IR-Spectrum of Tramadol HCl & Formulation

Functional Group	Frequency	
	Pure Drug	Formulation
O-H Stretching	3651 Cm^{-1}	3652 Cm^{-1}
N-H Stretching	3492 Cm^{-1}	3486 Cm^{-1}
C-H stretching due to –OCH_3	2905 Cm^{-1}	2928 Cm^{-1}
C-N Stretching	1311 Cm^{-1}	1311 Cm^{-1}
C-O-C Group	1048 Cm^{-1}	1048 Cm^{-1}
Substituted Benzene ring	783 Cm^{-1}	783 Cm^{-1}

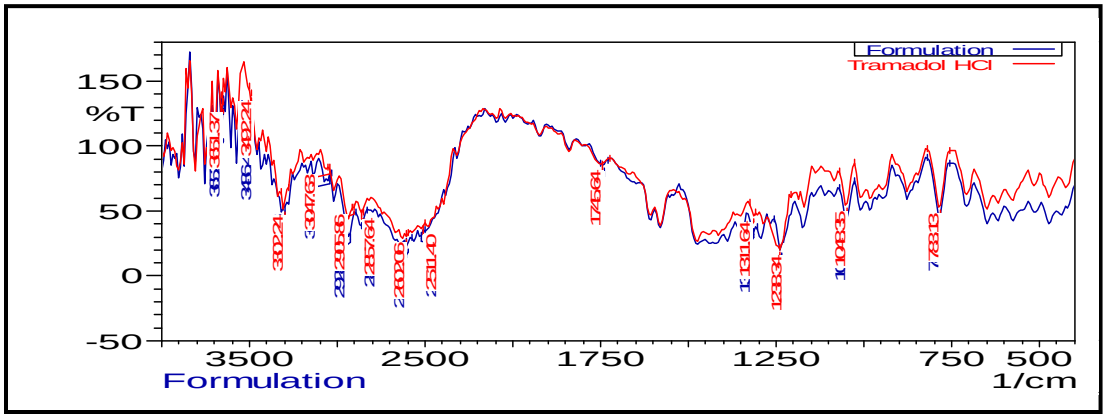

Figure 1: IR-Spectrum of Tramadol HCl & Formulation

EVALUATION OF TRAMADOL HCL MATRIX TABLETS

PRECOMPRESSION EVALUATION PARAMETERS

Various micromeritics properties of the granules summarized in table 7.

Table 7: Precompression Evaluation of formulated Tramadol HCl Granules

Batch Code	Bulk Density	Tapped Density	Carr's Index	Hausner Ratio	Angle of Repose (θ)
T1	0.442 ±. 0.024	0.506 ± 0.014	12.65 ± 0.015	1.14 ± 0.014	27^0 ± 3
T2	0.486 ± 0.018	0.556 ± 0.026	12.59 ± 0.022	1.14 ± 0.016	30^0 ± 2
T3	0.529 ± 0.016	0.593 ± 0.021	10.79 ± 0.021	1.12 ± 0.014	27^0 ± 3
T4	0.512 ± 0.019	0.574 ± 0.025	10.80 ± 0.019	1.12 ± 0.018	29^0 ± 2
T5	0.544 ± 0.022	0.601 ± 0.022	9.48 ± 0.014	1.10 ± 0.019	28^0 ± 2
T6	0.539 ± 0.017	0.586 ± 0.021	10.02 ± 0.016	1.09 ± 0.021	26^0 ± 3
T7	0.499 ± 0.018	0.564 ± 0.016	8.52 ± 0.024	1.13 ± 0.022	27^0 ± 3
T8	0.523 ± 0.018	0.599 ± 0.022	12.14 ± 0.021	1.11 ± 0.012	23^0 ± 2
T9	0.534 ± 0.016	0.588 ± 0.021	9.18 ± 0.021	1.10 ± 0.017	28^0 ± 3
T10	0.522 ± 0.017	0.586 ± 0.024	10.92 ± 0.021	1.12 ± 0.022	29^0 ± 2
T11	0.513 ± 0.013	0.578 ± 0.027	11.25 ± 0.021	1.12 ± 0.021	28^0 ± 1
T12	0.534 ± 0.017	0.566 ± 0.022	5.65 ± 0.021	1.05 ± 0.033	26^0 ± 2
T13	0.529 ± 0.014	0.589 ± 0.029	10.19 ± 0.021	1.11 ± 0.019	25^0 ± 3
T14	0.524 ± 0.012	0.586 ± 0.019	10.58 ± 0.021	1.11 ± 0.021	26^0 ± 2
T15	0.526 ± 0.013	0.589 ± 0.024	10.70 ± 0.021	1.12 ± 0.022	26^0 ± 3

POST-COMPRESSION EVALUATION PARAMETERS

Table 8: Evaluation of Tablets T1-T15

Batch Code	Weight variation (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
T1	500 ± 0.97	12.00 ± 0.03	2.34 ± 0.05	6.50 ± 0.50	0.62	101.65
T2	500 ± 0.68	12.01 ± 0.03	2.32 ± 0.03	6.60 ± 0.50	0.62	98.22
T3	500 ± 0.05	12.01 ± 0.02	2.33 ± 0.04	6.40 ± 0.30	0.42	103.99
T4	500 ± 0.01	12.02 ± 0.04	2.32 ± 0.03	6.50 ± 0.40	0.49	99.55
T5	500 ± 0.84	12.04 ± 0.03	2.31 ± 0.04	6.30 ± 0.50	0.65	96.98
T6	500 ± 0.36	12.00 ± 0.03	2.34 ± 0.04	6.50 ± 0.50	0.53	96.42
T7	500 ± 0.14	12.09 ± 0.02	2.32 ± 0.03	6.60 ± 0.30	0.44	100.15
T8	500 ± 0.15	11.93 ± 0.02	2.33 ± 0.07	6.40 ± 0.50	0.53	96.89
T9	500 ± 0.56	12.02 ± 0.02	2.35 ± 0.06	6.60 ± 0.80	0.54	98.34
T10	500 ± 0.65	12.04 ± 0.01	2.37 ± 0.04	6.40 ± 0.70	0.45	95.67
T11	500 ± 0.78	12.01 ± 0.03	2.32 ± 0.07	6.80 ± 0.20	0.57	98.97
T12	500 ± 0.23	11.98 ± 0.05	2.38 ± 0.04	6.20 ± 0.30	0.67	99.78
T13	500 ± 0.69	11.98 ± 0.02	2.33 ± 0.05	6.80 ± 0.90	0.59	99.67
T14	500 ± 0.79	12.02 ± 0.06	2.35 ± 0.03	6.70 ± 0.40	0.61	99.78
T15	500 ± 0.88	11.99 ± 0.05	2.33 ± 0.05	6.70 ± 0.60	0.62	99.88

Tablets of each formulation were evaluated for parameters such as thickness, diameter, weight variation, hardness, friability and drug content in given table 8.

IN-VITRO DRUG RELEASE STUDIES

In-Vitro Drug Release Data of Tramadol HCl Matrix Tablets

Table 9: Dissolution Profiles of Batch T1-T15

Batch Code	Time (Hr) (Cumulative Percentage Drug Release)						
	1	4	8	12	16	20	24
T1	24.47	40.51	61.84	80.27	95.39	-	-
T2	23.46	38.79	60.94	78.96	93.83	-	-
T3	26.53	39.20	54.51	71.44	86.61	100.63	-
T4	18.17	29.31	44.06	57.49	71.27	82.60	90.75
T5	18.84	41.94	67.28	83.88	100.36	-	-
T6	18.28	32.31	55.75	71.59	86.77	101.03	-
T7	19.84	30.03	40.71	59.98	75.91	88.89	99.77
T8	18.89	30.82	45.36	61.77	70.49	78.70	84.69
T9	20.51	43.61	68.41	85.15	99.39	-	-
T10	20.01	31.31	49.78	66.05	81.80	94.98	-
T11	20.34	27.06	41.29	60.30	76.24	92.12	-
T12	17.89	29.37	44.82	55.74	62.65	69.11	80.61
T13	19.84	32.94	48.06	64.22	78.02	83.95	91.80
T14	19.79	33.39	47.98	64.50	78.01	84.78	91.59
T15	19.84	32.94	48.06	64.09	78.26	84.36	91.84

Comparative Dissolution Profile

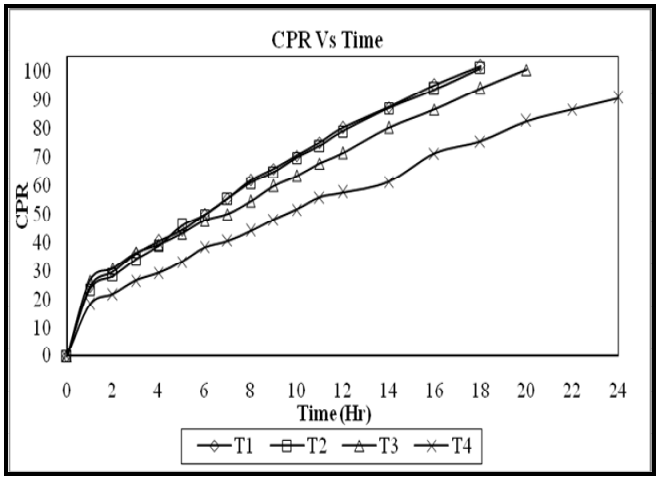

Figure 2: *In-Vitro* Dissolution Profile for T1, T2, T3 & T4

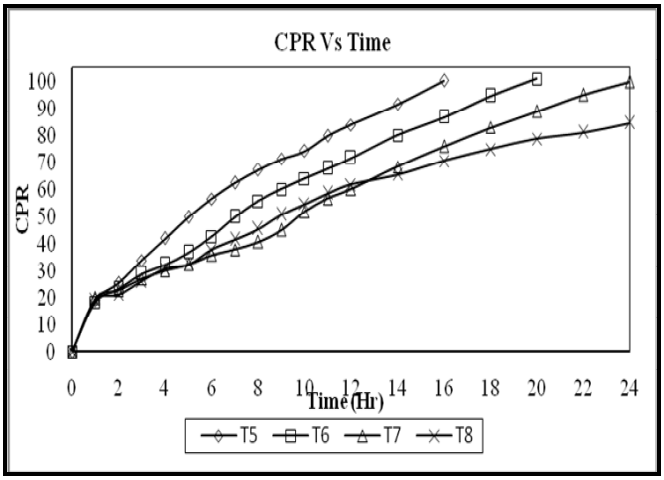

Figure 3: *In-Vitro* Dissolution Profile for T5, T6, T7 & T8

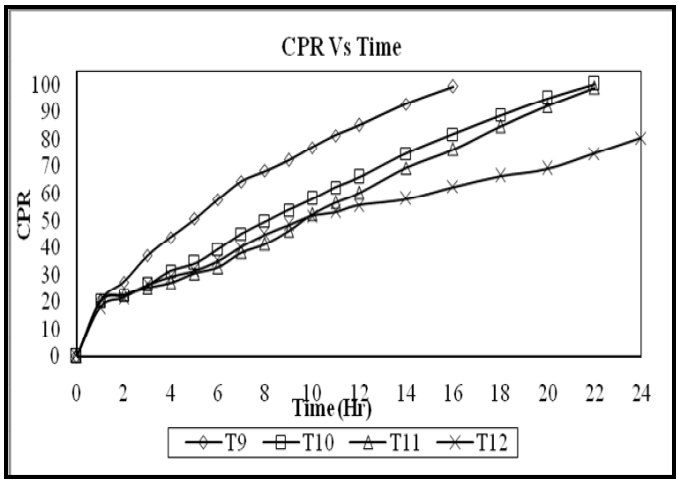

Figure 4: *In-Vitro* Dissolution Profile for T9, T10, T11 & T12

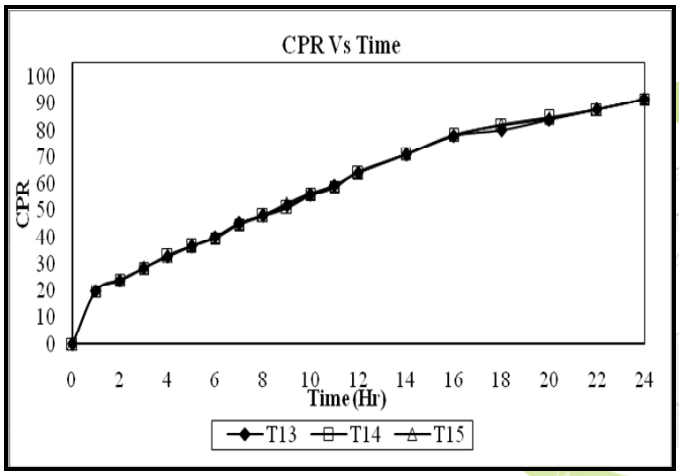

Figure 5: *In-Vitro* Dissolution Profile for T13, T14 & T15

From *In-vitro* dissolution study, In T1-T3 batch drug release up to 20 hr because its having below the optimum level of polymer weight but in batch T4 its having above the optimum level so its release up to 30 hr. Among these remaining batches, T7 batch having optimum level of the polymer so its release up to 24 hr.

DRUG RELEASE KINETICS OF TRAMADOL HCL MATRIX TABLETS

In Box-Behnken design, Independent variables are X_1 (HPMC K4M), X_2 (HPMC K15M) & X_3 (HPMC K100M), Dependent variables are Q_8 (Percentage drug release after 8 hr), Q_{12} (Percentage drug release after 12 hr) & Q_{16} (Percentage drug release after 16 hr). Results of dependent variables are given in table 10.

Table 10: Results of Dependent variables for Box-Behnken Design Batches

Batch Code	Percentage Drug Release		
	Q8	Q12	Q16
T1	61.84	80.27	95.39
T2	60.94	78.96	93.83
T3	54.51	71.44	86.61
T4	44.06	57.49	71.27
T5	67.28	83.88	100.36
T6	55.75	71.59	86.77
T7	40.71	59.98	75.91
T8	45.36	61.77	70.49
T9	68.41	85.15	99.39
T10	49.78	66.05	81.80
T11	41.29	60.30	76.24
T12	44.82	55.74	62.65
T13	48.06	64.22	78.02
T14	47.98	64.50	78.01
T15	48.06	64.09	78.26

To know the mechanism of drug release from these formulations the data were treated according to first-order (log cumulative percentage of drug remaining vs time), Higuchi's (Cumulative percentage drug released vs squared root of time & Korsmeyer and peppas (log cumulative percentage drug released vs time) pattern. The results of kinetics treatment applied to dissolution profiles of tablet of each batch were shown in table 11 & table

12. All the formulation follows the zero order pattern as compare to first order. Zero order Correlation co-efficient value is nearest to 0.999 as compare to first-order correlation co-efficient value. Here zero order values are between 0.983-0.999 and first order values are between 0.930-0.984. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factor of diffusion.

Diffusion is related to transport of drug from the dosage matrix into the *in-vitro* study fluid depending on the concentration. As gradient varies, the drug is released and the distance for diffusion increases. In our experiments, the *in-vitro* release profiles of drug from all the formulation could be expressed by Higuchi's equation as the plot showed linearity (R^2 = 0.971-0.999). To confirm the diffusion mechanism, the data were fit into the korsmeyer & peppas equation, formulation T7 showed linearity (R^2 = 0.971) with comaparatively slope (n) value of 0.563.The n value of Korsmeyer & to first-order correlation co-efficient value. Here zero order values are between 0.983-0.999 and first order values are between 0.930-0.984. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factor of diffusion. Diffusion is related to transport of drug from the dosage matrix into the *in-vitro* study fluid depending on the concentration. As gradient varies, the drug is released, and the distance for diffusion increases. In our experiments, the *in-vitro* release profiles of drug from all the formulation could be expressed by Higuchi's equation as the plot peppas equation is between 0.5-0.85 of all formulation T1-T15. So diffusion is coupled with dissolution may be the mechanism of the drug release from all the formulation T1-T15. This n value, however, appears to indicate a coupling of diffusion & dissolution mechanism so called anomalous diffusion or non-fickian diffusion. Hence diffusion is coupled with dissolution may be the mechanism of the drug release from T7.

STATASTICAL ANALYSIS

Surface response plot to depict the polymer (X_1), polymer (X_2) & polymer (X_3) on Q_8, Q_{12} & Q_{16}.

Full Model & Reduced Model for Q_8:-

Full Model:- $Q_8 = 51.6 - 1.72\ X_1 - 4.39\ X_2 - 8.63\ X_3 - 3.50\ X_{12} + 4.04\ X_{13} + 5.54X_{23} + 2.23\ X_{11} + 2.10\ X_{22} - 0.98\ X_{33}$…….(12)

Reduced Model:- $Q_8 = 51.9 - 4.91\ X_2 - 8.63\ X_3$…….(13)

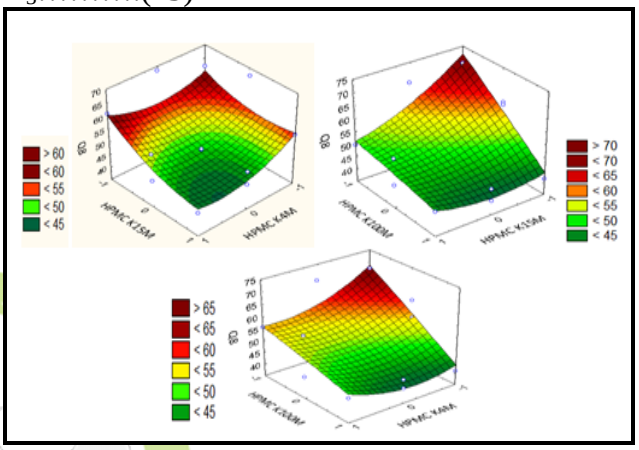

Figure 6: Response Surface Plot for Q_8

Full Model & Reduced Model for Q_{12}

Full Model

$Q_{12} = 68.4 - 2.63\ X_1 - 6.46\ X_2 - 8.61\ X_3 - 4.34\ X_{12} + 3.52\ X_{13} + 3.64\ X_{23} + 2.37\ X_{11} + 1.14\ X_{22} - 0.90\ X_{33}$…….(14)

Reduced Model

$Q_{12} = 68.4 - 6.74\ X_2 - 8.61\ X_3$…….(15)

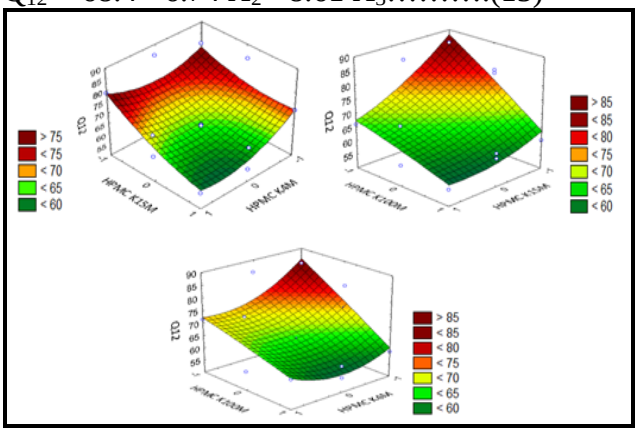

Figure 7: Response Surface Plot for Q_{12}

Table 11: Kinetics Treatment of Dissolution Profile of Batch T1-T8

	T1	T2	T3	T4	T5	T6	T7	T8
Zero Order Model								
B	4.663	4.664	3.935	3.204	5.378	4.447	3.669	2.985
A	22.058	21.193	23.622	17.663	19.750	16.487	14.761	20.103
R^2	0.997	0.997	0.999	0.997	0.987	0.995	0.997	0.983
First Order Model								
B	0.035	0.036	0.029	0.028	0.044	0.037	0.030	0.027
A	1.455	1.440	1.474	1.368	1.403	1.370	1.356	1.384
R^2	0.966	0.962	0.978	0.958	0.930	0.952	0.977	0.936
Higuchi Model								
B	25.013	25.061	21.966	19.621	27.828	25.087	22.154	18.579
A	-7.523	-8.517	-3.216	-8.429	-12.287	-14.592	-14.150	-5.126
R^2	0.992	0.993	0.986	0.992	0.998	0.993	0.979	0.994
Korsmeyer and Peppas Model								
n	0.525	0.540	0.469	0.545	0.626	0.611	0.563	0.533
k	0.209	0.200	0.221	0.150	0.178	0.154	0.148	0.155
R^2	0.988	0.990	0.980	0.989	0.998	0.991	0.971	0.989
B = Slope, A = Intercept, R^2 = Square of Correlation co-efficient, n = diffusion exponent								

Table 12: Kinetics Treatment of Dissolution Profile of Batch T9-T15

	T9	T10	T11	T12	T13	T14	T15
Zero Order Model							
B	5.272	4.019	3.963	2.621	3.226	3.246	3.244
A	22.041	16.120	12.278	20.218	21.078	20.908	21.084
R^2	0.986	0.997	0.997	0.985	0.989	0.989	0.988
First Order Model							
B	0.041	0.033	0.034	0.025	0.027	0.027	0.027
A	1.434	1.369	1.321	1.375	1.414	1.413	1.414
R^2	0.930	0.963	0.984	0.936	0.945	0.947	0.945
Higuchi Model							
B	27.343	23.548	22.813	16.297	19.971	20.074	20.091
A	-9.532	-13.968	-16.187	-1.888	-5.856	-6.129	-6.026
R^2	0.999	0.989	0.971	0.995	0.995	0.994	0.995
Korsmeyer and Peppas Model							
n	0.595	0.584	0.573	0.501221	0.529	0.529	0.531
k	0.194	0.152	0.143	0.155816	0.167	0.167	0.167
R^2	0.998	0.982	0.958	0.992126	0.992	0.990	0.991
B = Slope, A = Intercept, R^2 = Square of Correlation co-efficient, n = diffusion exponent							

Full Model & Reduced Model for Q_{16}

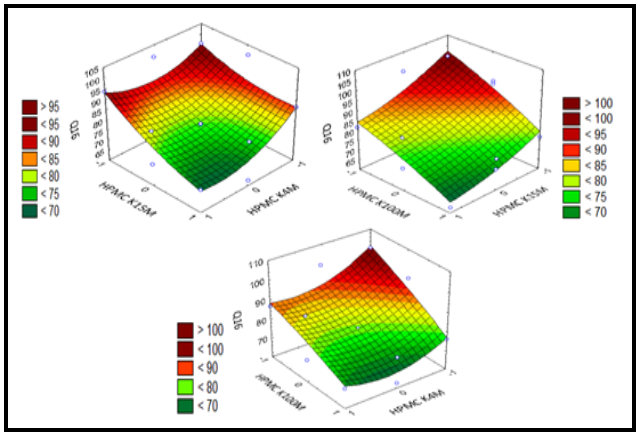

Figure 8: Response Surface Plot for Q_{16}

Full Model

$Q_{16} = 83.0 - 4.75\ X_1 - 7.75\ X_2 - 10.4\ X_3 - 2.92\ X_{12} + 2.04\ X_{13} + 1.00\ X_{23} - 1.06\ X_{11} + 0.26\ X_{22} - 1.41\ X_{33}$…….(16)

Reduced Model

$Q_{16} = 82.3 - 7.81\ X2 - 10.4\ X3$…….(17)

Full Model can be reduced by ommited factor having no significant p value. If p value is more than 0.05, this factor were omitted for making reduced model, this indicate no significant change in the reduced model. In present investigation HPMC K4M (X_1), HPMC K15M (X_2) and HPMC K100M (X_3) were having negative value. More negative value indicate the drug release retardation was more. In these equation X_3 value had more negative value as compared to X_1 and X_2. So HPMC K100M was more drug retarding polymer.

COMPARISON OF T1-T15 FORMULATIONS WITH MARKETED FORMULATION

In Present Investigation, test formulation & reference formulation are compared with each other. Marketed formulation is taken as a reference & other formulation T1-T15 is taken as a test. Marketed product is Tramazac OD Tablet from Cadila HealthCare. Similarity factor (f_2) & Dissimilarity factor (f_1) are found. T7 Formulation had high similarity or near to 100 (f_2 = 73.58) as compared to others formulation. The Similarity factor is described in Table 14. T7 batch is similar to marketed product Tramazac OD tablet. So T7 batch is the optimized batch. Comparative dissolution profile of T7 formulation & Marketed formulation (Tramazac OD tablet) is given in figure 9.

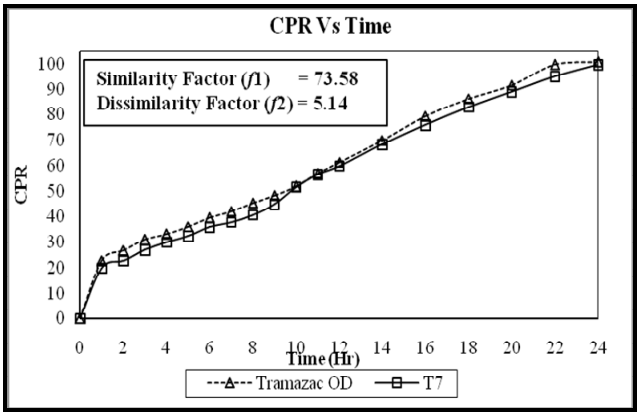

Figure 9: Comparative Dissolution Profile of T7 batch & Marketed Product

Table 14: Comparison of Box-Behken Design Batches with Marketed Formulation

Batch Code	Similarity Factor (f_2)	Dissimilarity factor (f_1)
T1	44.49	19.7
T2	45.69	18.22
T3	54.73	12.79
T4	59.73	8.77
T5	39.52	23.06
T6	55.92	9.02
T7	73.58	5.14
T8	55.08	8.59
T9	38.31	24.69
T10	70.74	2.59
T11	70.64	4.84
T12	46.26	15.23
T13	65.92	2.35
T14	66.78	2.27
T15	66.26	2

Table 13: Calculation for Testing the Model in Portions

For Q8							
	DF	**SS**	**MS**	**F**	**R^2**	**$F_{Cal.}$**	**$F_{Crit.}$ DF = (7,5)**
Regression FM	9	1057.72	117.52	6.19	0.918	2.02	4.87
RM	2	788.88	394.44	13.01	0.684		
Error FM	5	94.83	18.96	-	-		
RM	12	363.66	30.30	-	-		
For Q12							
	DF	**SS**	**MS**	**F**	**R^2**	**$F_{Cal.}$**	**$F_{Crit.}$ DF = (7,5)**
Regression FM	9	1190.50	132.27	5.60	0.910	1.41	4.87
RM	2	957.01	478.50	16.33	0.731		
Error FM	5	118.03	23.60	-	-		
RM	12	351.53	29.29	-	-		
For Q16							
	DF	**SS**	**MS**	**F**	**R^2**	**$F_{Cal.}$**	**$F_{Crit.}$ DF = (7,5)**
Regression FM	9	1587.11	176.34	5.80	0.913	1.11	4.87
RM	2	1350.14	675.07	20.83	0.776		
Error FM	5	151.87	30.37	-	-		
RM	12	388.84	32.40	-	-		
DF: Degree of Freedom, SS: Sum of Squares, MS: Mean of Squares, F: Fischer's ratio, R^2: Regression Co-efficient, FM: Full Model, RM: Reduced Model							

ACCELERATED STABILITY STUDY

Figure 10 shows the effect of accelerated storage conditions on dissolution profile. Similarity factor (f_2) is 81.53 after accelerated stability study. It is evident from the stability testing results that there was no significant change in the dissolution profile of optimized batch.

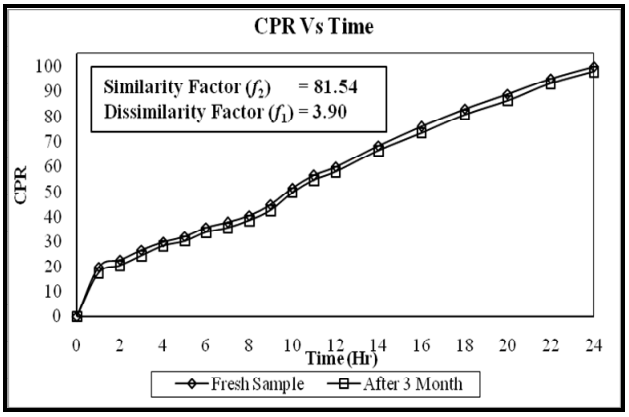

Figure 10: Comparative Dissolution Profile after accelerated stability study

CONCLUSION

From the results and discussion, we concluded that

- From Preformulation studies, it was found that the sample of Tramadol HCl is pure & suitable drug candidate for formulation of Hydrophilic matrix tablets.
- From Interference studies, it was concluded that there was no evidence of interaction between drug & polymers and these polymers are suitable for preparation of matrices of highly water soluble drug i.e. Tramadol HCl.
- From Pre-Compression studies, it was concluded that all the parameters passes the standards & the granules are suitable for preparation of Tramadol HCl matrices.
- From Post-Compression studies, it was concluded that all the parameters passes the standards and wet granulation method was suitable for preparation of Tramadol HCl matrices.
- From the *In-Vitro* release study, it was concluded that the concentration of HPMC K4M, HPMC K15M & HPMC K100M is increased, the drug release rate was decreased.
- It was found that matrix tablet with combination of HPMC K4M, HPMC K15M & HPMC K100M most effectively retarded the drug release as compared to individuals..
- HPMC K4M, HPMC K15M & HPMC K100M having low, medium & high viscosity respectively. So HPMC K100M polymer was more release retarding as compare to others.
- From the Statastical analysis, we got the effect of combination of two independent variables on drug release after 8 hr, 12 hr, 16 hr by response surface methodology Box-Behnken design..
- From the drug release kinetics, n value of Korsmeyer peppas equation was between 0.5-0.85. So BBD batches T1-T15 were drug released through dissolution with diffusion. All the BBD Batches were follow the non-fickian drug release mechanism.
- Comparison of similarity and dissimilarity factor, Box-behnken design batches T1-T15 to marketed formulation. T7 batch having more similarity 73.58 as compared to others. So T7 batch was optimized batch.
- From the accelerated stability studies, the optimized batch and optimized 3 months storage condition batch was compared with dissolution profile. And concluded that the no significant change in physico-chemical parametrs & *in-vitro* dissolution profile of the matrix tablet.

REFERENCES

1. Krowczynsky L, Extended-Release dosage Form, CRS press Boca Raton. FL, 1987.
2. Chien Y, Novel Drug Delivery System, 2nd Edn, New York, Mercel Dekker, 1992.
3. Kumar R, Kumar M, N.Polymeric., Controlled Drug-Delivery Systems perespective issues and opportunities, Drug Dev. Ind.Pharm., 2001, 27, 1-30.
4. Sung K, Nixon P, Skoung J, Ju T, Gao P, Topp E, Patel M, “Effect of Formulation variables on Drug and Polymer Release from HPMC-Base Matrix Tablets”, Int. pharm., 1996, 142, 53-60.
5. Siepmann J, Kranj H, Bodmeier R, HPMC matrices for controlled drug delivery: A new model combinig Diffusion, swelling and dissolution mechanisms and predicting the Release kinetics. Pharm Res., 1999, 16, 1748-1756.
6. Ford J, Mitchell K, Rowe P, Armstrong D, Elliot P and Hogan J, “Drug Release from Hydroxy Propyl Methyl Cellulose Matrices: Effect of the temperature”, Int. J. Pharm., 1991, 71, 95-104.
7. Fttman R, Hochberg M, Moskowitz R and Schnitzer T, Recommondation For the medical management of osteoarthritis of Rheum., 2000, 43, 1905-1915.
8. Grounds F, Sablotzki A, Clinical pharmacology of Tramadol. Clin Pharmacokinetics., 2004, 43, 879-923.
9. Medical Economics staff, Physicians Desk Reference, Grennwood village, co: Thomson Micromededex. 2003.

10. Rubber M, Hoffman S, Junge K, Mombergeo H, Kuhn D, Analgesic efficacy and tolerability of Tramadol 100 mg sustained release capsules in patients with moderate to severe chronic low back pain. Clin Drug. Invest., 1999, 17, 415-423.
11. Malonne H, Coffiner M, Fontaine D, *et.al*., Long term tolerability of Tramadol LP a new once daily formulation in patients with osteoarthritis or low back pain., J. Clin. Pharm. Ther., 2003, 30, 113-120.
12. Malone H, Coffiner M, Sonet B, Sereno A, Vander Bist F., Efficicacy and tolerability of sustained release Tramadol in the treatment of symptomatic osteoarthritis of the hip or knee. A multi center randomized double blind, placebo-controlled study., Clin. Ther., 2004, 26, 1774-1782.
13. Babule N, Noveck R, Chipman H, Roth S, Gana T, Albert K, Efficicacy and safety of extended-release once daily Tramadol in chronic pain. A randomized 12-week clinical trial in osteoarthritis of the knee, Joint pain symptom manage., 2004, 28, 59-71.
14. Lachman L, Liberman HA and Kanig J, The Theory and Practice of Industrial Pharmacy, 3rd Edn, Vargheses publishing House Bombay, 443-453, 171.
15. Jaleh V, "Use of Hydrophilic Natural Gums in Formulation of sustained – release matrix Tablet of Tramodol Hydrochloride", AAPS Pharm Sci Tech., 2006, 7(1), 24.