Research Article
Journal of Pharmaceutical Research & Education

ISSN: 2456-4508

JPRE

Journal homepage: http://www.gyanvihar.org/researchjournals/

Design, Development and In-vitro evaluation of Natural Gum Based Matrix Tablet of Tramadol Hydrochloride

Dr. Santosh Kumar Singh* and Dhara Singh
Pharmaceutics Divison, Gyan Vihar School of Pharmacy, SGVU, Jaipur

Abstract;
The purpose of this research was to develop and optimize a sustained release matrix tablet of freely soluble drug, tramadol hydrochloride using natural gums (Gum copal and Gum Dammar) as cost effective, non toxic easily available matrixing polymers. Sustained release tablet of Tramadol HCl (dose 100mg) were produced by wet granulation method. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, and in-vitro dissolution profile and found satisfactory. A 3^2 full factorial design was used for optimization by taking the Gum copal (X1) and Gum Dammar (X2) as an independent variables. Tramadol hydrochloride is a centrally acting analgesic available throughout the world. Its dual opioid and non-opioid mechanisms of action, favourable efficacy and safety clinical profiles and non-controlled regulatory status in most markets contribute to its widespread use. A drawback of the immediate-release formulation of tramadol four-times-a-day dosing due to its short elimination half life 5.5 hr and thus it is necessary for the drug to develop a sustained dosage form with reduced risk of drug administration, side effects and improved patient compliance. The formulations were found to have good preformulation characteristics. FTIR spectroscopy indicated the absence of any significant chemical interaction within drug and excipients.

Key word: Tramadol hydrochloride, Sustained Release Matrix, Gum Copal, Gum Dammar, 3^2 full factorial design.

Introduction;
Sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Economy and greater patient compliance are other advantages. Sustained release dosage forms would be the most applicable one for drugs having low therapeutic indices and short elimination half-lives (George *et al.*,1987)[20]. Tramadol Hydrochloride, a synthetic opioid and non-opioid of the aminocyclohexanol group, is a centrally acting analgesic with weak opioid agonist

properties. The half-life of the drug is about 5.5 hours and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hours with a maximum dosage of 400 mg/day. To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of tramadol is desirable. Tramadol HCL is a white or almost white, crystalline powder, freely soluble in water and in methanol, very slightly soluble in acetone. It is a centrally-acting analgesic1-7, used for treating moderate to moderately severe pain. The drug has a wide range of applications, including treatment for restless leg syndrome, acid reflux, and fiber myosis.

Materials and method:

Materials:

Tramadol hydrochloride was obtained as gift sample from Shakti Bioscience (Mumbai, India). Gum Copal and Gum Dammar obtained from AV Oversease (New Delhi,India), HPMC 15cps, Dicalcium Phosphate, Magnesium srearate were collected from CDH lab. All other chemicals and reagents used were of high analytical grade.

Method;

Drug Analysis; Tramadol hydrochloride was analysed by UV- spectrophotometer (SHIMBADZU Japan model-1800) at 272nm. Calibration curve was prepared in phosphate buffer of pH 7.4 in concentration ranges from10-30 mcg/ml. Correlation coefficients were found to be (r^2=0.9980) in all cases and no interference of additives used in formulation was observed.

Preparation of matrix tablet:

The matrix tablet containing Tramadol Hydrochloride 100 mg were prepared by wet granulation method. The composition of tablet is shown in table 2. The powders were blended and granulated with isopropyl alcohol which is used as granulating agent. The wet mass was passed through sieve no.22# and the wet granules were dried at 50 °C for 2 h. The dried granules were lubricated with magnesium stearate. The lubricated granules were compressed with a single station tablet machine.

Tbale 1; Formulation variable and levels;

Batch code	**Variable levels in coded form**	
	X1(mg)	X2(mg)
F1	-1	-1
F2	0	-1
F3	+1	-1

F4	-1	0
F5	0	0
F6	+1	0
F7	-1	+1
F8	0	+1
F9	+1	+1

Low (-1) = 25

Medium (0) = 37.5

High (1) = 50

Table2: the full factorial design layout of films containing Tramadol hydrochloride;

Formulation code	**Drug (mg)**	**Gum Copal**	**Gum Dammar**	**HPMC 15cps**	**Dicalcium phosphate (mg)**	**Magnesium stearate (mg)**
F_1	100	25	25	30	65	5
F_2	100	37.5	25	30	52.5	5
F_3	100	50	25	30	40	5
F_4	100	25	37.5	30	52.5	5
F_5	100	37.5	37.5	30	40	5
F_6	100	50	37.5	30	27.5	5
F_7	100	25	50	30	40	5
F_8	100	37.5	50	30	27.5	5

F_9	100	50	50	30	15	5

Where**, X_1** indicates Gum Copal and **X_2** Gum Dammar.

Evaluation of granules;

The flow properties of granules were determined by different parameters like angle of repose (Ɵ) of granules was determined by the funnel method. Angle of repose was calculated by using the equation, TanƟ = (h/r), where h and r are the height and radius of the pile respectively. Both bulk density (BD) and Tapped density (TD) were determined and calculated by using following equation, BD = weight of granules/ bulk volume , TD = weight of granules/ tapped volume. The compressibility index of the granules was determined by Carr's index using the equation, Carr's index = [(TD-BD) X 100)]/TD. All values were found to be satisfactory (**table 3**).

Evaluation of tablets;

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.

Friability;

Twenty tables were weighed and placed in the Electorlab friabilator and apparatus was rotated at 25 rpm for 4 minutes. The percentage friability was measured using the formula,

$$\% F = \{ 1- (Wt/W)\} \times 100 \quad \text{.....(1)}$$

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 batches 10 tablets were tested.

Dimension; Twenty tables were randomly selected from each batch and there thickness and diameter were measured by using digital vernier callipers.

Drug Content of Tramadol HCL;

Accurately weigh of 100 mg of Tramadol HCl reference Standard into a 100.0 ml volumetric flask, dissolve in methanol and dilute to volume. Accurately weigh an amount of tablet powder, equal to 100mg of Tramadol HCl, into a 100.0 ml volumetric flask, and add methanol to volume. Stirr during one night to allow the tramadol to dissolve. Centrifuge and inject (20 µl) the clear solution and % drug content of the filtrate was recoded at λmax of 272 nm with help of UV spectrophotometer. [7]

In-vitro dissolution study;

In vitro drug release studies for the prepared matrix tablets were conducted for a period of 10 hrs using a 6 station USP TDL-06L (Electro lab, Mumbai.) apparatus at 37±0.5oC and at 50 rpm speed, the in vitro release study was performed in 0.1 N HCL pH 1.2 for 2 hrs and in phosphate buffer pH 7.4 up to 10 hrs. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 272 nm for tramadol hydrochloride by a UV-Visible spectrophotometer. The amount of drug present in the samples was calculated. Commercial sustained release (CSR) tablet: CONTRAMAL® was purchased from the market and was evaluated for *in vitro* release characteristics following the above procedure.

Optimization of variables using full factorial Design

A 3^2 randomized full factorial design was used in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The amount of Gum Copal (X1) and Gum Dammar (X2) were chosen as independent variables in 3^2 full factorial designs. The formulation layout for the factorial design batches (F1-F9) is shown in Table 1. The prepared formulations were evaluated for drug content, drug release and hardness were selected as dependent variables. In addition the individual dependent variables (Drug content, drug release and hardness) were calculated with help of Design Expert 8.0.6.1 trial software and applied to approximate surface response, contour plots and correlation between actual and predicted values. The general model as shown below was generated,

$$Y = b_0+b_1x_1+b_2x_2+b_3x_1x_2+b_4x_1^2+b_5x_2^2+b_7x_1x2^2 \quad \text{.....(2)}$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of all 9 batches. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms ($X_1.X_2$) show how the response changes when two factors are simultaneously changed. The polynomial terms ($X1^2$and$X2^2$) are included to investigate nonlinearity. [0]

Compatibility study;

Fourier Transform Infrared Spectroscopy;

Drug polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for pure drug and physical mixture of polymers with API using JASCOFT/IR-4200, JASCO. The samples were prepared as KBr discs. The scanning range was 400-4000 cm^{-1} and resolution was 2 cm^{-1}.

Thermal analysis;

Differential scanning calorimeter (DSC) was carried out using DSC-60, SHIMADZU. The sample were hermetically sealed in aluminium pans and heated over the temperature range 25^{o}C to 300^{o}C with heating rate of 10^{o}C/min.

X-ray diffraction studies;

The crystallinity of tramadol hydrochloride was studied by X-ray diffractometry, before and after tablet formulation. The instrument was set up with the tube voltage of 40 kV, current 30 mA and scanning rate of 5^0/min, over a range of 8-60^0 diffraction angle (2Ɵ) range.

Kinetic Study

Different kinetic equations [zero order (Eq.3), first order (Eq.4) and Higuchi's equation (Eq.5)] were applied to interpret the release rate of drug from the matrix system. Coefficient of correlation (r) value was used for the selection of most appropriate model.

$Mt = M0 + k0t$ …… (3)

$In\ Mt = In\ M0 + k1t$ …….…….... (4)

$Mt = M0 + kHt1/2$ …….…….... (5)

Where Mt is cumulative amount of drug released at any time, t, and M0 is dose of drug incorporated in delivery system. K0, k1 and kH are rate constants for zero order, first order and Higuchi models respectively. The dissolution data were also fitted according to the well known exponential Korsmeyer-Peppas equation which is often used to describe drug release behaviour from the polymeric systems. [12]

$$Mt/M\infty = Kt^n \quad .....(6)$$

Mt/M∞ is the fraction of drug release at time t, and K is the kinetic constant, n is the release exponent indicating the mechanism of drug release, K was a constant which incorporates the properties of the macromolecular polymeric system and drug and n was the diffusional exponent, which characterized the drug transport mechanism (Agarwal and Mishra., 1999). When, $n < 0.5$ indicates fickian diffusion, when $n \geq 0.500$ to 0.890 indicates non-fickian or anomalous diffusion, when n=0.890 case II transparent, $n > 0.89$ indicates super case II transport.[6]

Comparison of dissolution profiles for selection of optimum batch

The similarity factor (f2) given by SUPAC guidelines for a modified release dosage form was used as a basis to compare dissolution profiles. The dissolution profiles are considered to be similar when f2 is between 50 and 100. The dissolution profile of products were compared using a f2 which is calculated from following formula,

$$f2= 50\bullet\log \{[1+(1/n)\Sigma t=1n (Rt – Tt)2] -0.5 \bullet 100\}\ldots\ldots\ldots\ldots\ldots\ldots(7)$$

Where *n* is the number of time points, R is the dissolution value of the reference at time t, and T is the dissolution value of the test at time t. [16]

Result and discussion;

The matrix tablet containing Tramadol hydrochloride were designed with the objective of sustained release drug delivery for improving bioavailability and patient

compliance by reducing multiple dosing and hence reduces side effect. The hydrophobic natural gums i.e. Gum copal and gum dammar were selected for preparation of sustained release matrix tablet. The prepared tablets were found to be good without any tablet defects i.e. sticking, chipping, capping to be satisfactory.

Optimization of different formulations:

The Model F-value of 873.97 implies the model is significant**.** There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. In this case A, B, B^2 are significant model terms. The "Pred R-Squared" of 0.9917 is in reasonable agreement with the "Adj R-Squared" of 0.9982. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable and ratio of 84.706 indicates an adequate signal. Final models in terms of coded factors for drug content was aas follow,table

$$\text{Drug release} = +80.28-1.94X_1-4.84X_2+0.30X_1X_2-0.37X_1^2+1.39X_2^2$$

The calculated R-sqeared, Adj R-squared, Pred R-squared and Adeq Precision value for dug content were 0.9993, 0.9982, 0.9917 and 84.706 respectevely. The Model F-value of 873.97 implies the model is significant. As regards the effect of gum oncentration, decrease in drug release rate was observed when gum copal and gum dammar content in the matrix was incrased. This may be due to the higher concentration of gums in tablet might have produce dense matrix around the drug paricles, which providing more barriers for them to scape and dissolve. Further, these dense matrix, specially when it hydrophic in nature, may be expected to favour less penitration of dissolution medium in the tablets. This may also be the auxiliary reason for obtaining slow drug release profile through gum copal and gum dammar matrix tablets.

Table 3; Response 1-Drug release; Analysis of vairance (ANOVA) for selected factorial model

Source	**Sume of square**	**Df**	**Mean square**	**F value**	**p-value Prob>f**	
Model	167.15	5	33.43	873.97	<0.0001	
A-Gum Copal	22.27	1	22.27	582.27	0.0002	**significant**
B-Gum dammar	140.36	1	140.36	3669.27	<0.0001	

AB	0.37	1	0.37	9.57	0.0537	
A^2	0.27	1	0.27	7.03	0.0536	
B^2	3.88	1	3.88	101.51	0.0021	
Residual	0.11	3	0.038			
Core total	167.26	8				

Fig 1; surface response plot for drug release;

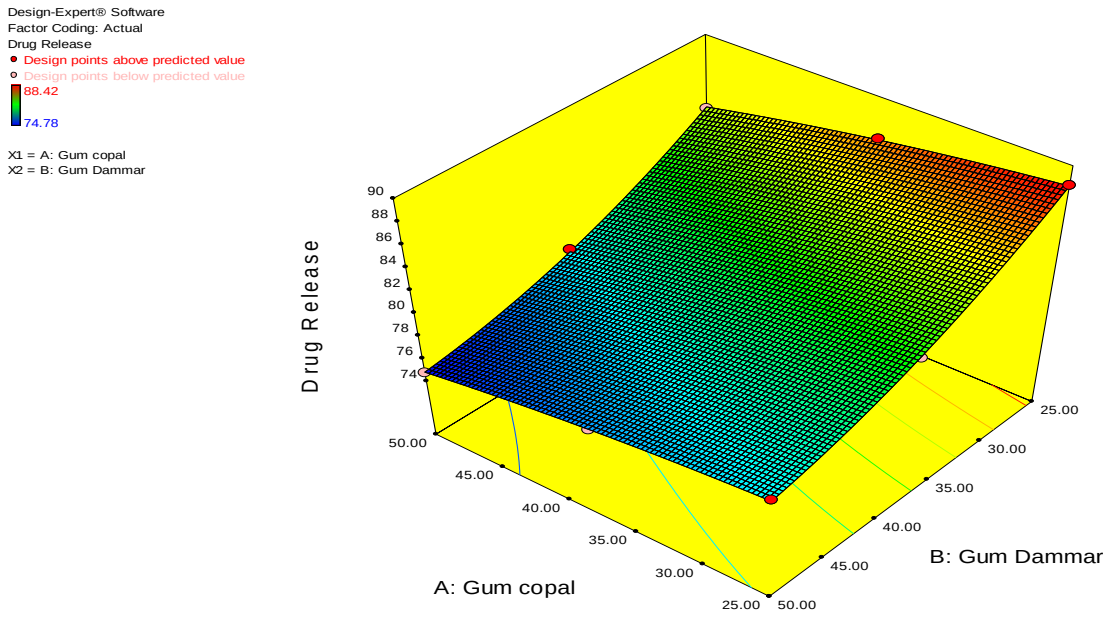


Fig2 ; corrrlation between the actual value and predicted value;

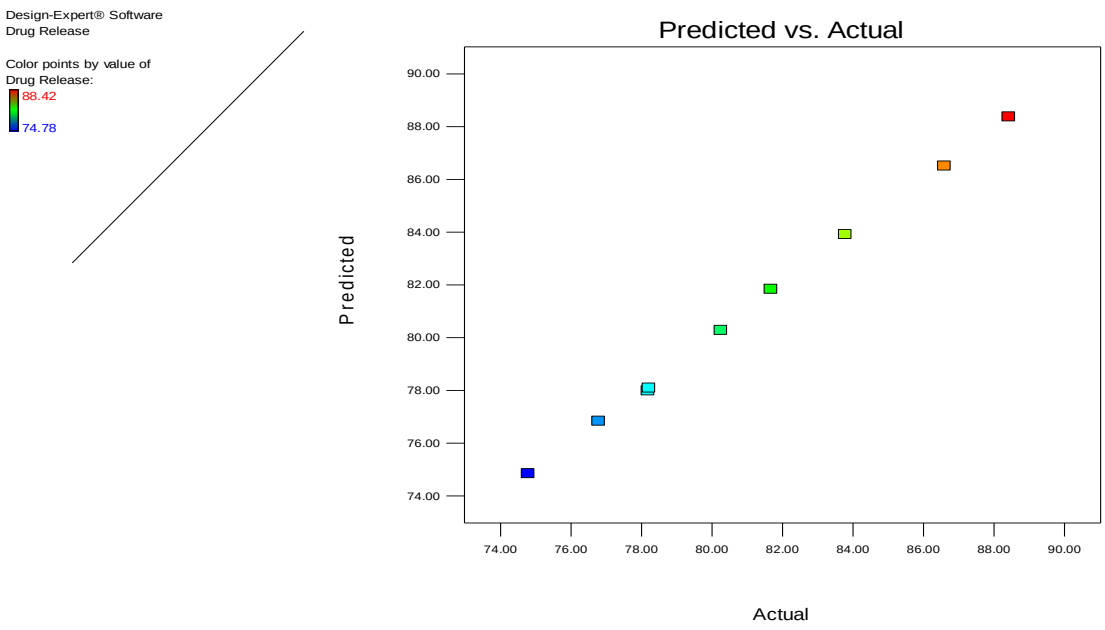
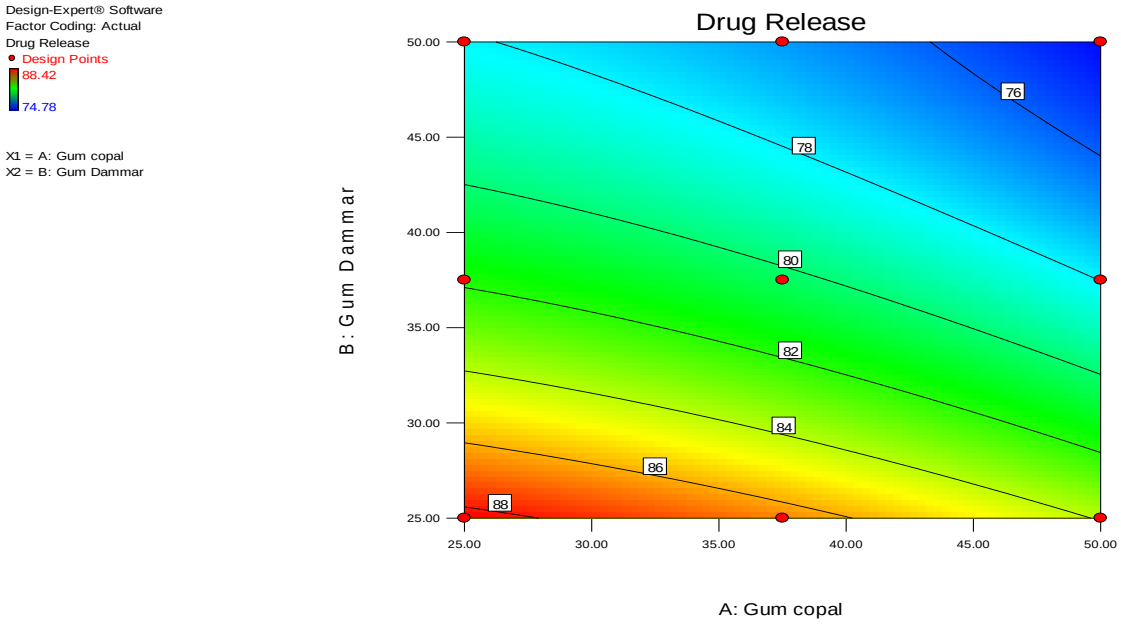


Fig3 .contour plot between Gum Copal and Gum Dammar for drug content;



The Model F-value of 229.92 implies the model is significant. There is only a 0.04% chance that a "Model F-Value" this large could occur due to noise. In this case A, B, AB, A^2 are significant model terms. The "Pred R-Squared" of 0.9804 is in reasonable agreement with the "Adj R-Squared" of 0.9931. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable and ratio of 45.496 indicates an

adequate signal. Final models in terms of coded factors for drug content was as follow.[table 4]

$$\text{Hardness} = +4.74+0.35X_1+0.62X_2-0.12X_1X_2+0.13X_1^2+0.065X_2^2$$

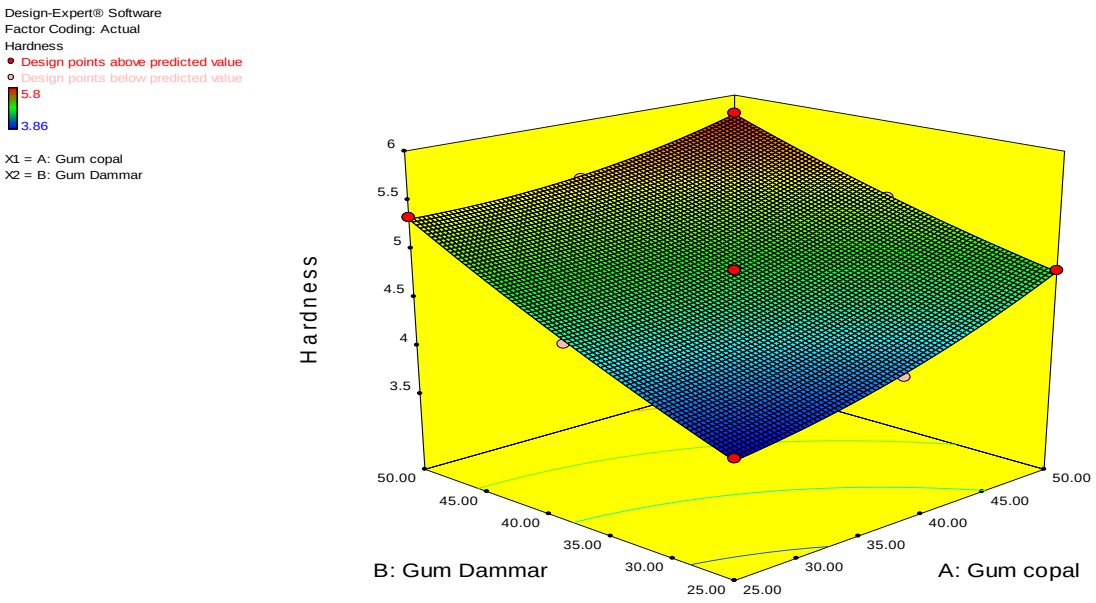
The calculated R-sqeared, Adj R-squared, Pred R-squared and Adeq Precision value for dug content were 0.9974, 0.9931, 0.9804 and 45.496 respectevely. The prepared tablet evaluated for hardness the result shwon in table 7. The hardness of formulation F1 was found 3.86 kg/cm^2 which is due to lesser concentration of gums there for there is low cohesiveness between the polymers. But in case of formulation F9 the hardnes was found 5.80 kg/cm^2. This may be due to the higher concentration of both gums i.e. gum copal and gum dammar. The contour plot for hardness reflect that the gum copal is more effective than gum dammar due to slightly difference in their molecular weight (150 and 180).[21]

Table4; Response 11-Hardness; Analysis of vairance (ANOVA) for selected factorial model

Source	**Sume of square**	**Df**	**Mean square**	**F value**	**p-value Prob>f**	
Model	3.17	5	0.63	229.92	0.0004	
A-Gum Copal	0.75	1	0.75	271.84	0.0005	**significant**
B-Gum dammar	2.32	1	2.32	841.51	<0.0001	
AB	0.058	1	0.058	20.90	0.0196	

A^2	0.034	1	0.034	12.27	0.0394	
B^2	8.45	1	8.45	3.07	0.1782	
Residual	8.457	3	2.756			
Core total	3.18	8				

Fig4; surface response plot for Hardness;



Fig;5 corrrlation between the actual value and predicted value;

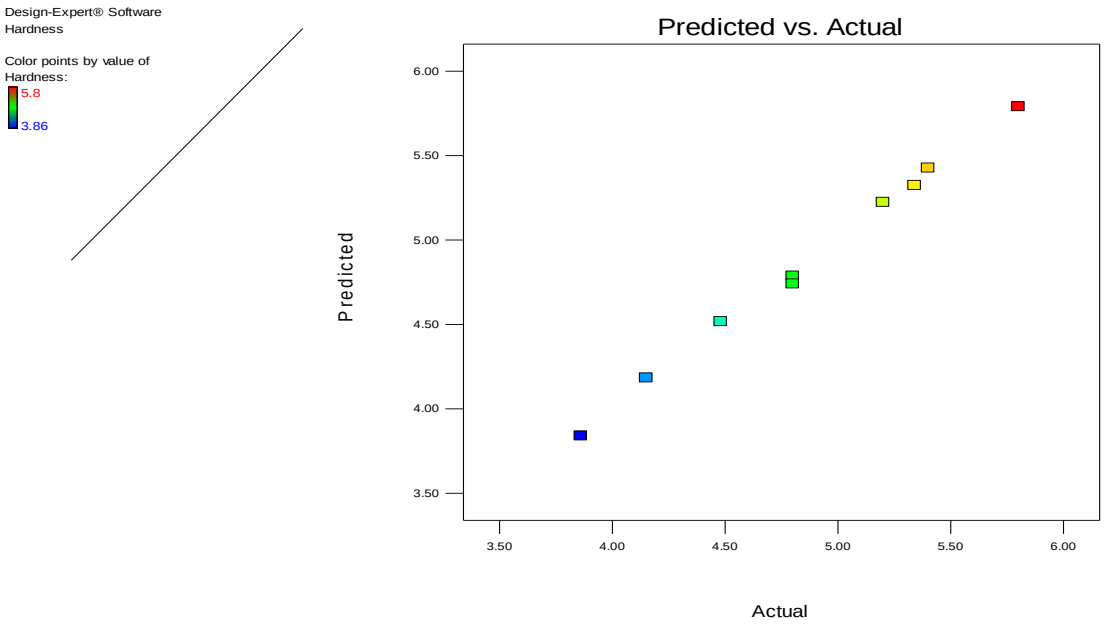
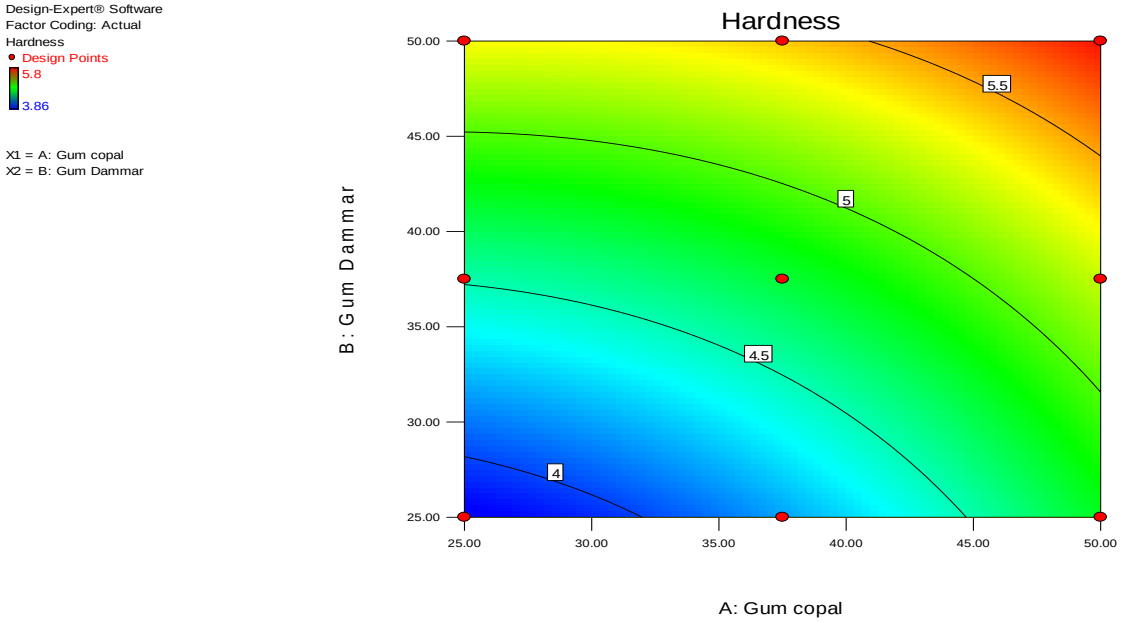


Fig6.contour plot between Gum Copal and Gum Dammar for Hardness;



FTIR Spectroscopy; The IR spectra of pure drug tramadol hydrochloride and optimized product have been showed in (fig10 a and b) respectively. The major peaks observed in the spectra for tablet formulation were OH-stretching at 3650-3700 cm^{-1} , C-H stretching at 3400-3000 cm^{-1} (methoxy group), C-H stretching at 3000-2900cm^{-1} (methyl group), C=ring stretch at 1500-1600 cm^{-1}, C-N stretch at 1300-1250 cm^{-1},C-O-C asymmetric stretch at 1190-1160 cm^{-1}, C-H bend at 790-750 cm^{-1}, C==C bend at 700-690 cm^{-1}, which are characteristics of tramadol hydrochloride. When this is compared to IR spectra of physical mixture, it was nonobious interaction between drug and the polymers.

Table 5; characteristics peaks for IR spectra

Characteristics Peak	**Functional**	**Peak (cm^{-1})**

	Groups	
C-N stretching	C-N group	1300-1250 cm^{-1}
C-H stretching	0CH_3 group	3400-3000cm^{-1}
C-H Stretching	CH_3 group	3000-2900 cm^{-1}
C=C bending	C=C in six member ring	700-690 cm^{-1}
=C-H out of plane bending	C=C aromatic group	790-750 cm^{-1}
C=ring stretching	C=ring	1500-1600 cm^{-1}
O-H stretching vibration, inter-molecular hydrogen bonding	Bonded with –OH	3650-3700 cm^{-1}

Fig 7;Ir spectra of , (a)-pure drug Tramadol hydrochloride, (b)- physical mixture

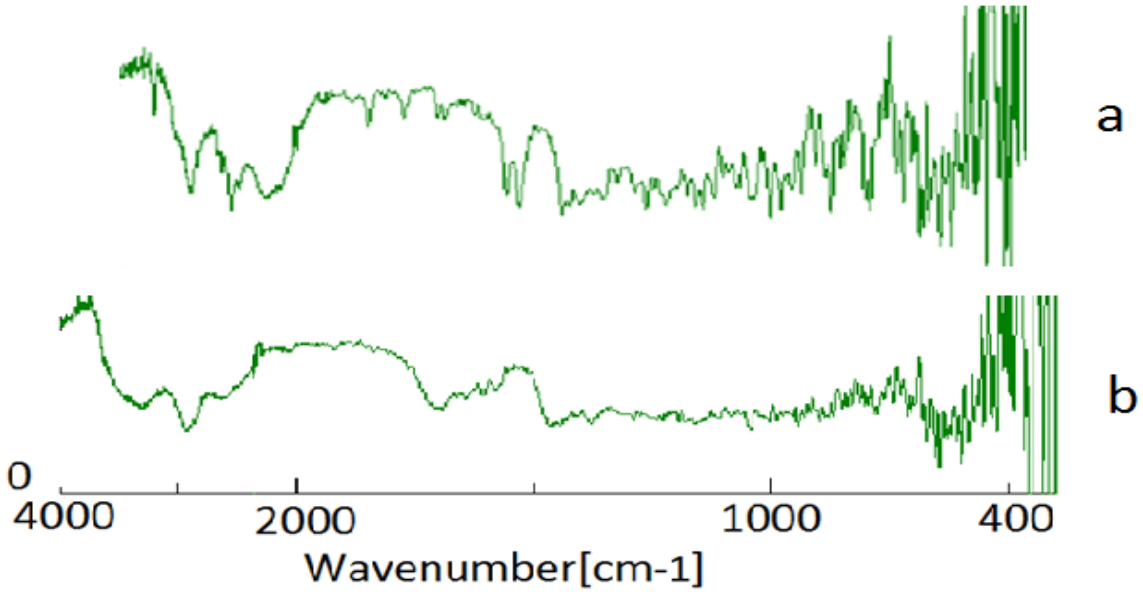
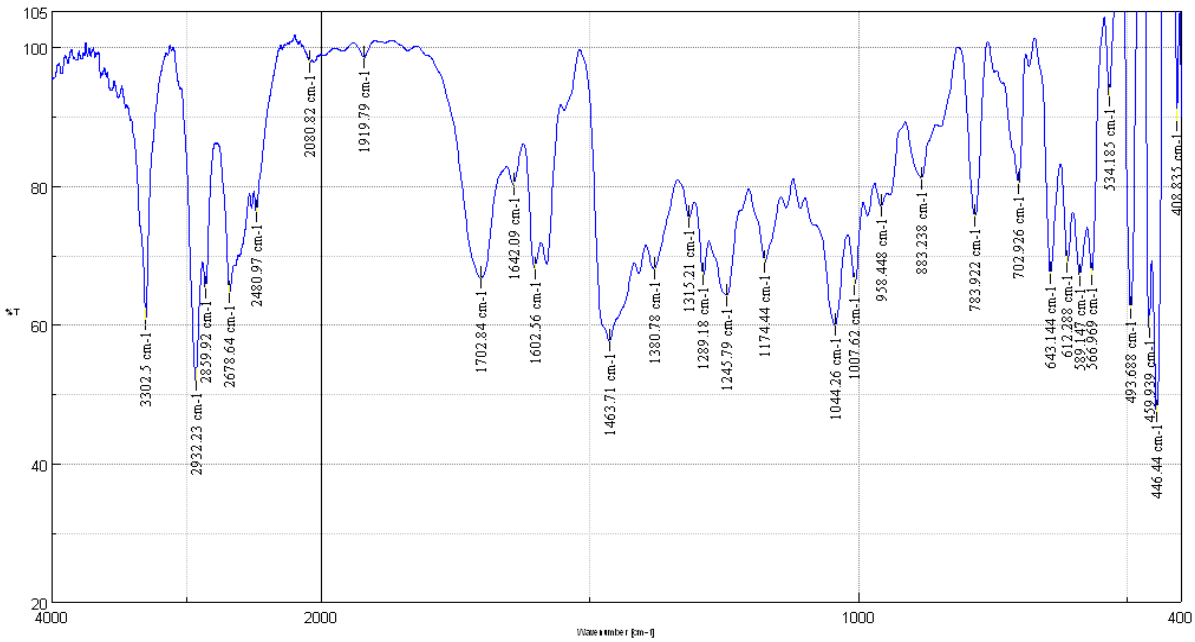


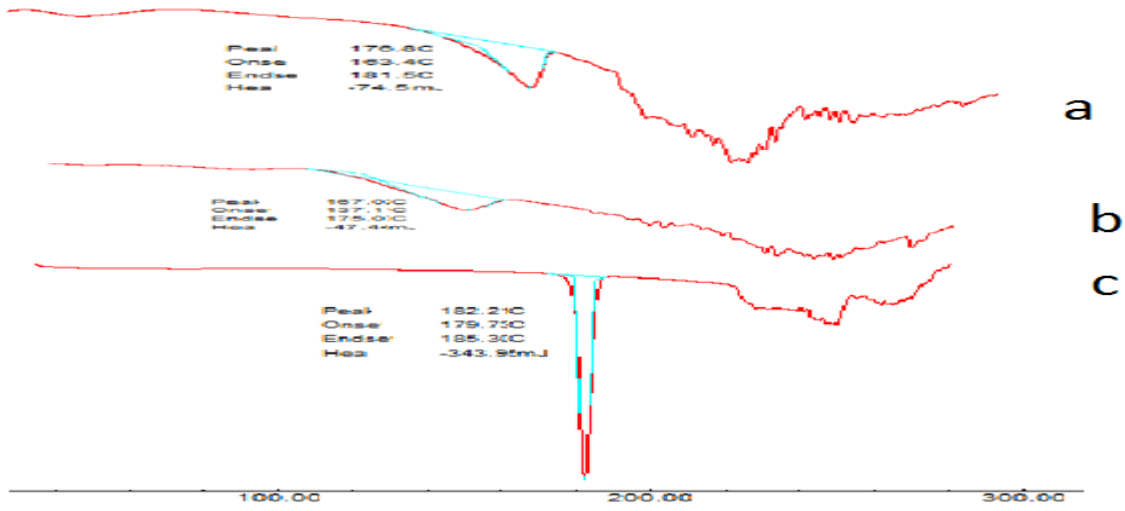
Fig8 ; IR spectra of optimized product F9



Differential Scanning Calorimetry;

In order to confirm the physical state of the pure drug, DSC of the drug alone, physical mixture of drug and the optimized product. The DSC trace of drug showed a sharp endothermic peak at 182.21°C, its melting point. The physical mixture of drug and polymers showed the endothermic peak at 176.8°C as the individual component, indicating that there was no interaction between the drug and the polymer in the solid state.

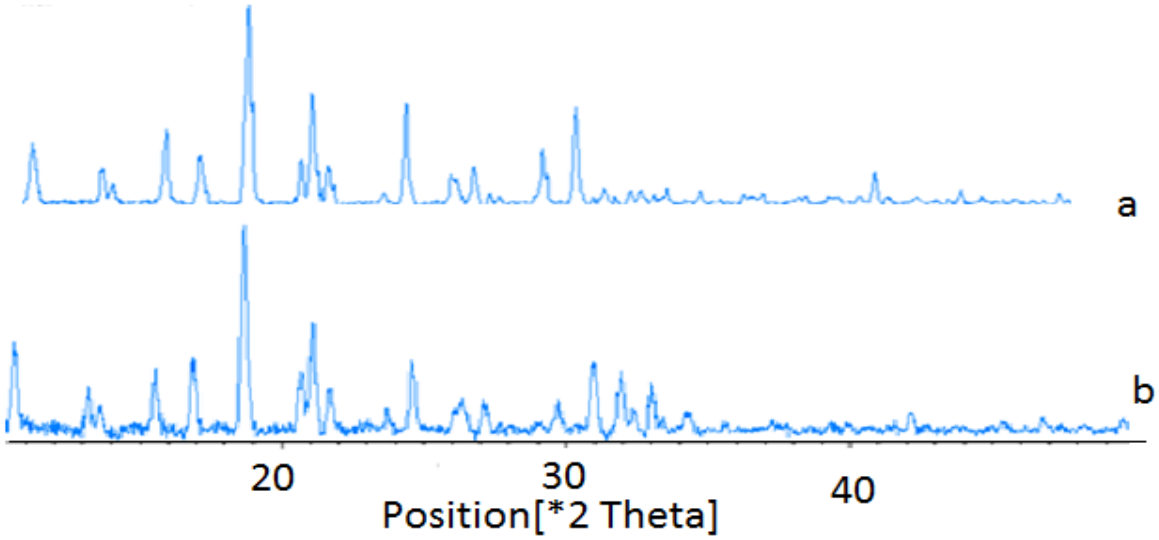
Fig 9; DSC (a)-physical mixture,(b)- optimized product, (c)- Tramadol hydrochloride



X-Ray Diffractogram;

The X-ray diffractograms of Tramadol HCl confirmed its crystalline nature (fig…), as evidenced from the number of sharp and intense peaks which are absent in case of amorphous drugs. The pure Tramadol Hydrochloride exhibited the diffraction at 2Ɵ values of 10.67^0, 13.68^0,18.78^0, 21.67^0, 24.69^0, 26.39^0, 29.75^0, 31.02^0, 42.18^0. The X-ray diffractogram of tramadol hydrochloride confirm its crystalline nature, as evidenced from the appearance of number of sharp and intense peaks. However, finally the diffraction pattern of optimized product represents complete appearance of sharp and intense peaks which indicates that the drug till in its crystaline nature and there is no inhibitory effect of selected polymers on the crystallization of drug, which indicate there is no changes in the molecular mobility of drugs and hence confirms its crystalline nature.

Fig10; **x-ray diffractrogram of (a)-Tramadol hydrochloride, (b)-optimized product F9**



Evaluation of granules;

The physical mixture for matrix tablets were characterized with respect to angle of repose, bulk

density, tapped density and Carr's index (table 6). Angle of repose were found between 25 ^{o} -31^o and Carr's index values were found between 12-18 % for the powder of all the batches indicating excellent to poor flowability and compressibility. Hausner's ratio was found to be between 1.14 to1.23 for all the batches indicating that passable to poor flow properties.

Table6; Pre-compression evaluation matrix tablets of Tramadol Hydrochloride

formulation	Angle of repose (^{o})	Bulk Density(gm/ml)	Tapped Density(gm/ml)	Carr's Index(%)	Hausner's ratio

F1	25.79±0.15	0.241±0.010	0.285±0.05	17.52±0.07	1.22±0.03
F2	31.27±0.46	0.322±0.010	0.374±0.07	12.56±0.52	1.14±0.01
F3	26.91±0.33	0.283±0.00	0.352±0.08	18.05±0.71	1.21±0.02
F4	27.51±0.04	0.294±0.00	0.366±0.06	18.37±0.35	1.22±0.01
F5	25.36±0.18	0.296±0.00	0.362±0.01	15.14±0.25	1.19±0.03
F6	26.59±0.04	0.278±0.00	0.331±0.00	15.17±0.05	1.16±0.07
F7	29.11±0.13	0.292±0.00	0.344±0.09	16.43±0.25	1.17±0.05
F8	26.99±0.11	0.285±0.01	0.347±0.06	16.92±0.12	1.21±0.03
F9	28.41±0.16	0.289±0.00	0.338±0.06	16.09±0.03	1.23±0.04

Drug Content and Physical Properties;

Prepared tablets were evaluated for parametric tests (Table7). The drug content in various formulations was varied between 97.83±0.67 to 102.1±0.88%. The Maximum thickness and hardness of prepared tablets were found between 3.51± 0.019mm and 5.80kg/cm^2 respectively. Friability of prepared tablets ranges between 0.466± 0.016 to 0.913±0.020.

Table 7: Characterization of prepared tramadol hydrochloride matrix tablet (100mg):

Formulation	**Wt variation (mg)**	**Hardness (kg/cm2)**	**Friability (%)**	**Thickness (mm)**	**Drug content (%)**
F1	5.753±0.32	3.86±0.030	0.746±0.015	3.313±0.030	100.4±0.50
F2	6.323±0.09	4.15±0.025	0.663±0.015	3.320±0.095	102.1±0.88
F3	5.880±0.21	4.80±0.050	0.786±0.030	3.493±0.025	101.1±0.90
F4	5.873±0.08	4.50±0.015	0.913±0.020	3.396±0.020	98.67±0.46
F5	6.963±0.13	4.80±0.015	0.676±0.015	3.370±0.020	99.48±0.42
F6	5.530±0.25	5.20±0.026	0.760±0.030	3.363±0.025	97.83±0.67
F7	5.130±0.18	5.340±0.019	0.666±0.013	3.510±0.019	100.7±0.52
F8	4.540±0.27	5.40±0.026	0.566±0.015	3.510±0.029	99.94±0.57

F9	5.296±0.13	5.80±0.025	0.466±0.016	3.486±0.030	98.78±0.38

Invitro Drug release study;

The drug release data are shown in (table 8 and fig 11) drug release from the tablets prepared by wet granulation were found 88.42%, 80.25%, 78.21%, 76.78% and 74.78% for F1, F5, F7, F8 and F9 respectively after 10 hr. Different combinations of natural gums (copal and dammar) with HPMC and as triple mixture of these polymers were used to provide matrix tablets for sustained release of water-soluble tramadol HCl. In the different formulation it was observed even the concentration of using gums were low (F1), the release of drug have shown about 88.42 % after 10 hr. But as the ratio of the gums varies results were varied accordingly. The formulation F9 contained maximum concentration of both natural gum which reflect the more effective release retardant (74.78%) as compare to others one.

Fig11; In vitro dissolution profile of prepared formulations (F1-F6)

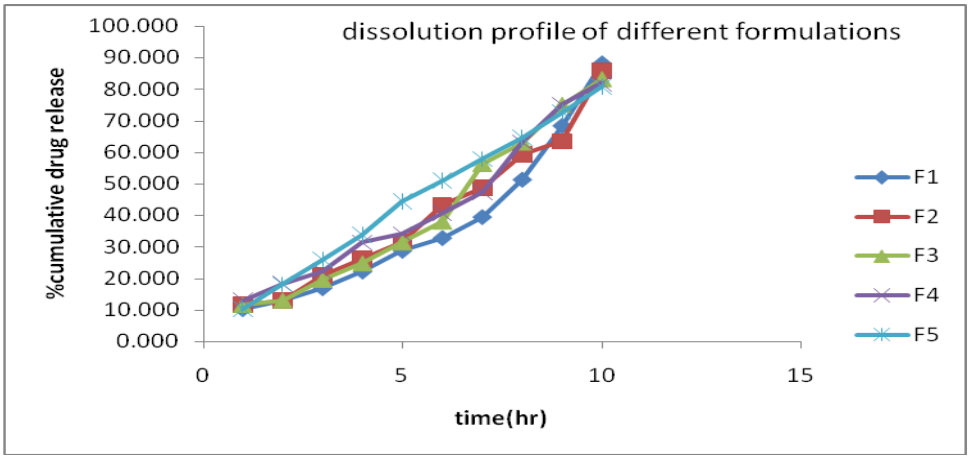


Fig12; In vitro dissolution profile of prepared formulations (F7-F9, Mkt)

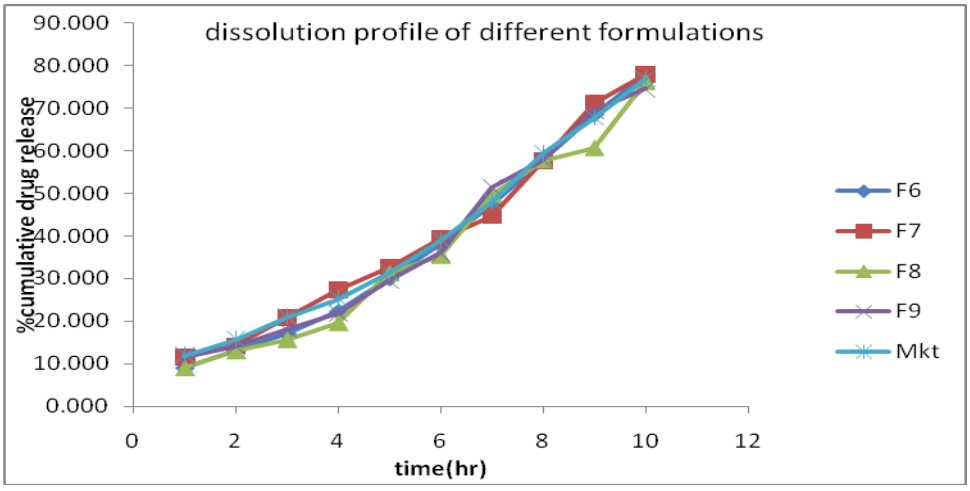


Table 8: Regression coefficient of different formulations

Formulation	Cumulative% drug relase (after 10hr)	Kinetic release model for dissolution data				
		Zero order (R^2)	First order (R^2)	Higuchi plot (R^2)	Hixon crowell (R^2)	Korsmeyer peppas (R^2)
F_1	88.42	0.964	0.847	0.815	0.778	0.910
F_2	86.59	0.960	0.891	0.897	0.919	0.941
F_3	83.78	0.965	0.884	0.898	0.921	0.927
F_4	81.67	0.963	0.869	0.900	0.933	0.949
F_5	80.25	0.998	0.960	0.983	0.987	0.991
F_6	78.18	0.974	0.897	0.909	0.930	0.956
F_7	78.21	0.969	0.888	0.906	0.917	0.952
F_8	76.78	0.967	0.951	0.905	0.928	0.940
F_9	74.78	0.963	0.910	0.895	0.932	0.917

Drug release kinetics;

In order to investigate the drug release kinetics, data were fitted to models (Sankar *et al*., 2001) representing zero-order and Korsemayer-Peppas model. The data were analysed by the regression coefficient method and regression coefficient value (r2–value) of all batches were shown in Table 9 and 10. On analysing regression coefficient values of all batches, it was found that all Batches followed zero order and Korsemayer-Peppas model. The values of *n* were in the range of 0.359 to 0.556 (i.e. more than 0.5, table 9) indicating Non-Fickian release (diffusion controlled), which indicated drug release to occur through diffusion and relaxation.[20]

Table 9: Kinetic Treatment for dissolution data:

Release Model	Parameter	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Zero order	Slope(b)	8.550	7.832	8.479	7.767	7.818	7.859	7.510	7.550	7.566
	Intercept(a)	-5.280	-2.756	-5.019	-0.011	3.021	-5.155	-1.524	-4.662	-3.171

	R^2	**0.964**	**0.960**	**0.965**	**0.963**	**0.998**	**0.974**	**0.969**	**0.967**	**0.963**
First order	Slope(b)	-0.058	-0.062	-0.077	-0.071	-0.070	-0.064	-0.063	-0.053	-0.061
	Intercept(a)	2.096	2.087	2.137	2.104	2.075	2.108	2.091	2.076	2.091
	R^2	**0.847**	**0.891**	**0.884**	**0.869**	**0.960**	**0.897**	**0.888**	**0.951**	**0.910**
Higuchi plot	Slope(b)	32.38	32.35	34.96	32.09	33.15	32.44	31.04	31.21	31.17
	Intercept(a)	-35.63	-32.37	-36.92	-29.38	-28.47	-34.83	-29.97	-33.27	-31.60
	R^2	**0.815**	**0.897**	**0.898**	**0.900**	**0.983**	**0.909**	**0.906**	**0.905**	**0.895**
Hixon-crowell	Slope(b)	-0.200	-0.179	-0.210	-0.202	-0.191	-0.183	-0.18	-0.171	-0.175
	Intercept(a)	4.976	4.835	4.937	4.841	4.755	4.892	4.836	4.862	4.846
	R^2	**0.778**	**0.919**	**0.921**	**0.933**	**0.987**	**0.930**	**0.917**	**0.928**	**0.932**
Korsme-yer peppas	Slope(b)	0.918	0.897	0.936	0.819	0.930	0.980	0.866	0.970	0.881
	Intercept(a)	0.873	0.935	0.914	1.094	0.992	0.843	0.956	0.835	0.924
	R^2	**0.910**	**0.941**	**0.927**	**0.949**	**0.991**	**0.956**	**0.952**	**0.940**	**0.917**
	N	**0.503**	**0.459**	**0.477**	**0.483**	**0.359**	**0.498**	**0.502**	**0.497**	**0.556**

Conclusion:

It can be concluded from above study that, the matrix tablets containing tramadol hydrochloride using different ratio of hydrophobic natural gums (gum copal and gum dammar) were prepared by wet granulation method were found to be good without any tablet defects i.e. sticking, chipping, capping. Natural gums (gum copal and gum dammar) were used in the as 10%, 15% and 20% (w/w) of total tablet weight with the combination of HPMC 15cps. Both gums with 20% concentration retarded the tramadol hydrochloride release beyond 10 hr. Gum copal was found more effective than gum dammar at low concentration (10%) with combination of HPMC 15cps in sustaining the drug release rates. The prepared formulations were followed the zero order release kinetics. Gum copal and gum dammar was not effective separately with combination of HPMC 15cps. Formulation (F9) containing both gums (gum copal and gum dammar 0f 20% w/w) with HPMC 15cps shows greater release retarded batch.

References:

1) Basu SK, Kunchu K and Mani RupeshKuar. Evaluation of Ionotropic Cross-Linked Chitosan/Gelatin B Microspheres of Tramadol Hydrochloride. *AAPSPharmsci.Tech*. 2011;12: 28-34
2) kodam D,Veerareddy PR, Garrepali S. Formulation and evaluation of Tramadol Hydrochloride sustained matrix tablets. *Der Pharmacia Lettre*,2011 3(3): 245-249
3) Phani Kr. G.K, Battu G, Lova R, Kotha N.S. Studies on the Applicability of Tamarind Seed Polymer for the Design of Sustained Release Matrix Tablets for Tramadol HCl. *Journal of pharmacyResearch*,2011 4(3): 703-705
4) Sudha BS, Sridhar BK And Srinatha A. Modulation of Tramadol Release from a Hydrophobic Matrix: Implications of Formulations and Processing Variables. *AAPSPharmSciTech* 2010; 11(1): 433-440
5) Singh SK, Bothara SB, Singh S, Patel R and Dodia R. Formulation and Evaluation of Mucoadhesive Tablet: Influence of Some Hydrophilic Polymers on the Release Rate and *In Vitro* Evaluation. *IJPSN*; 2010;3(3): 1111-1121
6) Verma MM, Bhavani GLD, Raju DB. Development and *In Vitro* Evaluation of Tramadol Hydrochloride Oral Controlled Release Matrix Tablets.*IJPR*; 2010: 2(2): 30-34

7) Gendle R, Kaushik B, Verma S, Patel R, Singh SK, Namdeo KP. Formulation and evaluation of sustained release matrix tablet of tramadol hcl. *IJCRGG*; 2010:2(1): 04-10
8) Murthy KVR, Nyamathulla S, Parveen DT, Subramanyam GSV and Ganapaty S. Preparation and evaluation of twice daily matrix tablets of tramadol hcl using ispagula husk powder .*IJPT*;2010:2(4): 969-976
9) Gharge D and Panduranga D. Simultaneous Estimation of Tramadol Hydrochloride and Paracetamol by UV Spectrophotometric Method from Tablet Formulation. *IJPRIF*;2010:2(2): 1119-1123
10) Kavitha K, Deore RK and Tamizhmani TG. Preparation and Evaluation of Sustained Release Matrix Tablets of Tramadol Hydrochloride Using Compritol 888 ATO by Melt Granulation Technique. *RJPBCS*;1(3): 431-440
11) Shekar BS, KIran RS, Babu BN. Design and evaluation of sustained release monolithic matrix tablets of tramadol hydrochloride. *IJPI's Journal of Pharmaceutics and cosmetology*, 2010: 1(1): 1-11
12) Deore RK, Kunchu K and Theetha G. Preparation and Evaluation of Sustained Release Matrix Tablets of Tramadol Hydrochloride Using Glyceryl Palmitostearate. *Trop J PharmRes*, 2010:9(3): 275-281
13) Madgulkar AR, Bhalekar MR, Padalkar RR. Formulation Design and Optimization of Novel Taste Masked Mouth-Dissolving Tablets of Tramadol Having Adequate Mechanical Strength. *AAPS PharmSciTech*;2009:10(2): 574-581
14) Ammar HO,Ghorab M, El-Nahhas SA and Kamel R. Polymeric Matrix System for Prolonged Delivery of Tramadol Hydrochloride, Part I: Physicochemical Evaluation. *AAPS PharmSciTech*, 2009; 10(1): 7-20
15) Gonjari ID,, Hosmani AH, Karmarkar AB, Kadam SB, GodgeAS, Khade TS. Microspheres of tramadol hydrochloride compressed along with a loading dose: A modified approach for sustaining release. *Drug Discov Ther*.2009;3(4): 176-180
16) Gonjari ID, Karmarkar AB, Hoshmani AH. Evaluation of Invitro Dissolution Profile Comparison Methods of Sutained Release tramadol Hydrochloride Liquisolid Compact Formulations with Marketed sustained Release tablets. *DJNB*,2009;4(4): 651-661

17) Raghavendra rao NG, Sagar G, Patel T. Formulation and Evaluatiion of Sustained Release Matrix Tablets of Tramadol Hydrochloride.IJPPS,2009;1(1): 60-70

18) Amir MN, and Ahmad M. Development of Tramadol Microparticles by Non-solvent Addition Method and their In Vitro Characterization. *Iranian Polymer journal*, 2009; 18(12): 937-946

19) Varshosaz J, Tavakoli N, and Kheirolahi F. Use of Hydrophilic Natural Gums in Formulation of Sustained-release Matrix Tablets of Tramadol Hydrochloride. *AAPS PharmSciTech*, 2006;7(1): E1-E7

20) Mishra B, Bakde BV, singh PN and Kumar P. Development and In-vitro Evaluation of Oral Sustained Release Formulation of Tramadol Hydrochloride. *Acta Pharmaceutica Sciencia*,2006; 48: 153-166

21) Tiwari SB, Murthy TK, Pai MR, Mehta PR and Chowdary PB. Controlled Release formulation of Tramadol Hydrochloride Using Hydro-philic and Hydrophobic Matrix System. *AAPS PharmSciTech*, 2003; 4(3): 1-6