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FORMULATION AND EVALUATION OF TRAMADOL HCL SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

The present work was an aim to prepare a suitable extended release tablet of Tramadol HCL, which could reduce the dosing frequency and improve patient compliance. Extended release tablets were prepared using HPMC10000cps & Acacia as retardant polymers. Various evaluation parameters were evaluated and the results were found to be satisfactory. On comparing equation of line and regression coefficient (R2) innovator, the formulation **F4** shows similarity of results with innovator. Hence **F4** was considered as formulation extending 98.96% of drug was released at the end of 10hrs. The stability studies were carried out for a period of 3 monthsas per ICH guidelines and were in acceptable limits.

KEYWORDS: Tramadol Hydrochloride, Hydroxypropyl methylcellulose, Matrix tablets.

INTRODUCTION

Tramadol HCl (TmH) is a centrally acting analgesic havingboth opioid and nonopioid effects. TmH acts as opiate agonist, through selective binding to the μ-opioid receptor,and weak inhibition of norepinephrine and serotonin uptake.It is administered when non-steroidal anti-inflammatorydrugs fail to mitigate pain. It is readily absorbed after oraladministration.Its bioavailability is 68-72 %. It has a plasma elimination half-lifeof 4 - 6 h with a usual dosage regimen of 50-100 mg andmaximum dose 400 mg (50 mg 4 times a day). Therefore, toreduce frequency of administration and improve patientcompliance, a controlled release matrix dosage formulationof tramadol HCl is desirable. Long term treatment with sustained release tramadol Hcl once daily is generally safe in patients with osteoarthritis or refractory low back

pain and is well tolerated.[1,2] It has a potential to provide patients increased control over the management of their pain,fewer interruptions in sleep and improved compliance.[3]

Sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period. The sustained plasma drug levels provide by sustained release products often times eliminates the need for night dosing, which benefits not only the patients but the care given as well. The basic rationale of a sustained drug delivery system is to optimize the Biopharmaceutic, Pharmacokinetic and Pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route.[4]

MATERIALS AND METHODS

Tramadol hydrochloride was obtained as gift sample from Wanbury Limited India.Acacia obtained from Nanhang industries Co. Lmtd, china.

MCC(Avicel pH 101,102 grades) obtained from FMC Ireland .Hypromellose obtained from Shin ETSU,Japan. Magnesiumstearate obtained from Ferro,USA.Talc and other chemicals and reagents used were of high analytical grades.

PREPARATION OF MATRIX TABLETS

Different Tramadol Hcl formulations were prepared by melt granulation technique (F1-F5).Firstly pure drug and acacia were blended, then avicel pH 101was added,blended and mixed well,then add PVPK 90 to the above mixture and this blend is melted and 2ml of isopropyl alcohol was added to above mixture. This is cooled to room temperature and is passed through 40# mesh to obtain granules. These granules were semidried in air dryer without giving temperature for about 20 mins. These were subsequently passed through 12# and 16# mesh. In extra granulation step polymers HPMC E 10 M premium and Avicel pH102 were added.Magnesium stearate and talc were also added .then these granules are compressed using punch size of length 19.7 mm and 7.3 mm width maintaining humidity below 50%RH. (Table.1)

PREFORMULATION STUDIES

1 Preformulation study

1.1 Color, odor, taste and appearance

The drug sample was evaluated for its color and odor .the results are shown in (Table 2).

1.2 Melting point determination

Melting point of the drug sample was determined by capillary method by using melting point apparatus. The reported and observed Mp is shown in (Table 3).

1.3 Determination of solubility

The solubility of the Tramadol Hclwas determined by adding excess amount of drug in the solvent and equilibrium solubility was determined by taking supernatant and analyzing it on shimadzu UV 2501 PC, double beam spectrophotometer.

1.4 Fourier Transformation Infra-red (FTIR) analysis

FTIR spectra of the drug and polymer were obtained on Alpha Brooker FTIR. The spectra was scanned over the wave number range 4200 to 500 cm-1.The peaks were shown in Fig1,2&3.

1.5 Particle Size

The average diameter and particle size distribution (PSD) of drug sample was analysed by Malvern Mastersizer instrument based on laser diffraction method.

1.6 Bulk density,Tapped density,% Compressibility index &hausner ratio

1.6.1 Apparent Bulk Density

The bulk density was determined by transferring the accurately weighed sample of powder to the graduated cylinder. The initial volume and weight was noted. Ratio of weight of the sample was calculated using the following formula

Density = Mass/ volume.

1.6.2 Tapped Density

Weighed powder sample was transferred to a graduated cylinder and was placed on the tapped density apparatus, was operated for fixed number of taps (500). The tapped density was determined by the following formula.

Density = Mass/Tapped volume.

3) Percentage Compressibility

Based on the apparent bulk density and the percentage compressibility of bulk drug was determined by the following formula.

% Compressibility = tapped bulk density-Initial bulk density*100/ tapped bulk density.

4) Hausner's Ratio: It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.

Hausner ratio =Tapped density/poured density

G.Moisturecontent: A 5 gms of pure tramadol Hcl was transferred into an aluminium plate of moisture analyzer and moisture was determined at 105^0C.The moisture content was determined using Electrolab analyzer. All results are shown in Table 4.

I.Drug to polymer compatibility study: The IR spectrum of physical mixtures of tramadol & individual polymers (metalose,ethyl cellulose&acacia)were recorded using Alpha BrookerFTIR(Tokyo,Japan) using pellet technique. All these results are shown in figure 1,2& 3.

EVALUATION OF TABLETS

- **Thickness:** Thickness of the tablets was determined using a vernier caliper. Five tablets from each batch were used. The results are shown in Table 5.
- **Weight variation:** To study weight variation,20 tablets of each formulation were weighed using an electronic balance, average weights was calculated, individual tablet weights were compared with average weight not more than two individual tablets deviate from the average weight by more than the percentage And the result are shown in table 5.

  % Deviation=Average weight –individual weight *100 / Average weight
- **Hardness:** Foreachformulation twenty tablets were selected randomly and weighed. Tablets were then placed in Roche friabilator which was rotated at a speed of 25 rpm for 4 mins. Tablets were then weighed and friability values are determined and are replaced in Table 5.
- **Content Uniformity Test:**Tramadol hydrochloride tablets were determined by powdering 10 tablets in each batch. Powder equivalent to 500 mg of Tramadol Hcl was dissolved in 450 ml of 10 %Acetonitrile while stirring in suitable homogenizer at 4000rpm for 5 mins and stock for 2 mins. Repeat the same procedure for further 2 mins, wash the beaker and stirrer and transfer the washing and the sample solutions into 500ml

volumetric flask. Sonicate the sample with intermittent vigorous shaking for 10 mins. Then soak for 1 hr and makeup the volume to mark. Centrifuge and collect the sample with 0.45m nylon filter paper.Record the chromatograms. Resolution between peaks due to Tramadol related compounds and Tramadol is not less than 1.5. The tailoring factor is not less than 0.8 and not more than 2. The relative Standard deviation for six replicate injections of standard solution is not more than 1.5%and NTM 10% for Tramadol related compounds.

- **Dissolution studies:** The in-vitro release of Tramadol Hcl from formulated tablts was carried out for 10 hrs in 6.8 pH phosphate buffer. The studies were performed in USP dissolution apparatus II at 37±0.5^{0}C and 100 rpm speed. Samples were taken at 1,3,5,7 &10 hrsand diluted to suitable concentration and analyzed for Tramadol Hcl content at 223nmby using UV-visible spectrophotometer.The values are shown in Table 6 and plots for the same are shown in figure 5.
- **Dissolution in Multimedia:**The optimized batch is evaluated for multimedia dissolution study. The pH4.5 phosphate buffer and 0.1 N Hcl are used as dissolution medium. Then the drug release is compared with innovator drug release respectively. The values are shown in Table7 and plots for same are given in figure 7.

RESULTS AND DISCUSSION

- **Drug release kinetics:** Dissolution data was fitted in Zero order, first order and Higuchi equations.
- **Stability studies:** The optimized formulation F4 and innovator sample are also kept for stability at room temperature for 2 months. The results were shown in table 8.

Table 1: Ingredients used in formulationof tramadol Hcl sustained release matrix tablets.

Ingredients	F-1	F-2	F-3	F-4	F-5
Tramadol HCl	100mg	100mg	100mg	100mg	100mg
Acacia	100mg	100mg	75mg	80mg	-
AvicepH101	30	30	30	50	100
Cetyl alcohol	-	25mg	50mg	50mg	-
PEG 4000	25mg	-	-	-	-
Hpmc10,000cps	50mg	50mg	50mg	50mg	50mg
Avicel ph102	20mg	20mg	20mg	45mg	80mg
Mg.stearate	5mg	5mg	5mg	5mg	5mg
Talc	2mg	2mg	2mg	2mg	2mg
Total wt of Tablet	297mg	332mg	332mg	382mg	337mg

Table 2: Results of identification tests of drug and polymer

S.No	Parameter	Drug
1	Color	White or colorless
2	Odor	Odorless
3	Appearance	Crystalline powder
4	Taste	Tasteless

Table 3: Melting Point of drug

Reported Melting Point	Observed Melting point
180-1810C	180-1810C

Determination of Solubility

The drug was found to be freely soluble in water and in ethanol,very slightly soluble in acetone.

Fourier Transformation Infra-red (FTIR) analysis

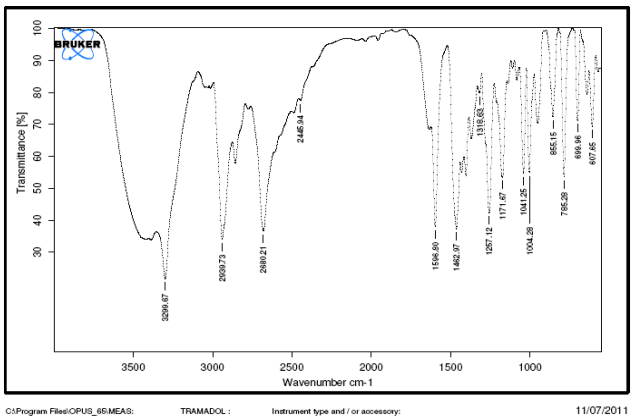

Figure1: FTIR spectrum of Tramadol Hcl

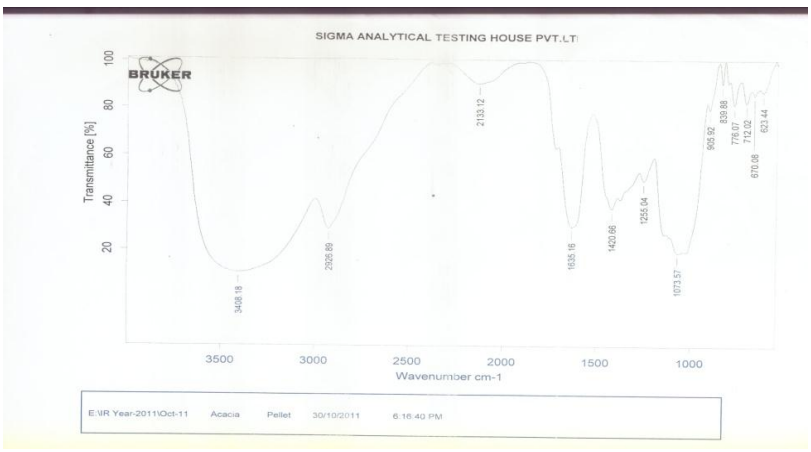

Figure 2: FTIR spectrum of Acacia

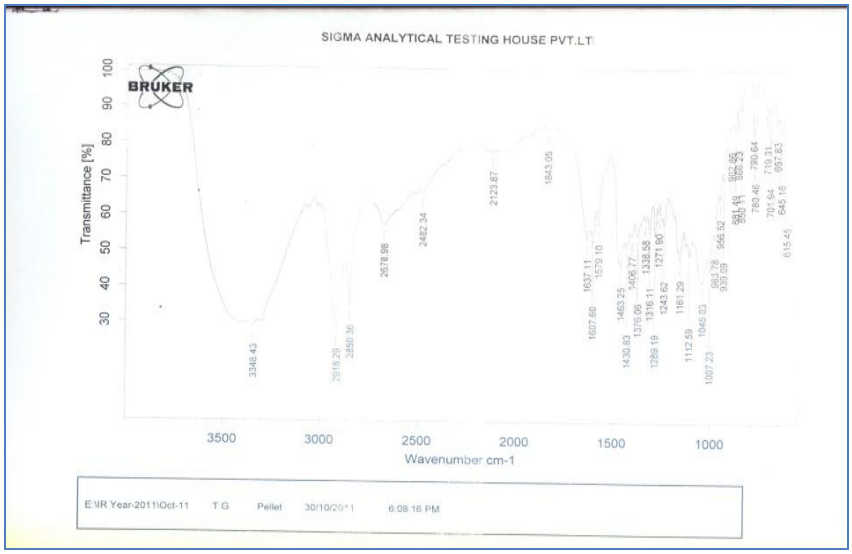

Figure 3 FTIR spectrum of Tramadol Hcl tablets

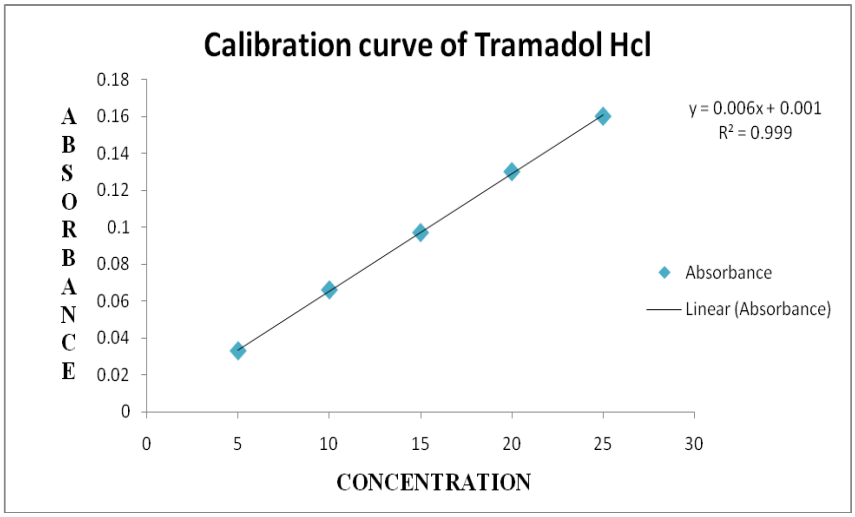

Figure 4: standard graph of Tramadol Hcl

Table 3: Standard graph of Tramadol Hcl in 0.1NHcl

Concentration	Absorbance	Equation of line and regression
5µg/ml	0.033	Y = 0.006X + 0.001 R^2 = 0.999
10 µg/ml	0.066	
15 µg/ml	0.097	
20 µg/ml	0.13	
25 µg/ml	0.16	

Table 4: Evaluation of Blend

Batch No	Bulk Density	Tapped Density	Compresibility (%)	Hausner Ratio	Angle Of Repose (°)
F1	0.55	0.652	15.64	1.23	38.86
F2	0.535	0.681	21.4	1.27	42.92

F3	0.55	0.652	15.64	1.23	38.86
F4	0.543	0.627	13.39	1.15	41.86
F5	0.539	0.635	15.11	1.17	39.09

Table 5: Evaluation of formulated tablets

Formulation Code	Hardness (Kg/Cm^2)	Friability (%)	Thickness (Mm)	Weight Variation(mg)	Content Uniformity
F-1	7.83±0.40	0.57±0.12	6.35±0.03	350.15±1.11	99.49±0.18
F-2	7.73±0.20	0.54±0.09	6.34±0.03	350.18±1.54	99.64±0.23
F-3	7.83±0.40	0.57±0.12	6.35±0.03	350.15±1.11	99.49±0.18
F-4	8.33±0.20	0.60±0.15	6.35±0.03	350.02±1.34	99.50±0.24
F-5	7.4±0.2	0.42±0.17	5.55±0.04	299.9±1.52	99.78±0.17

Table 6: Cumulative % drug release of formulated Tramadol Hcl Tablets

TIME(Hrs)	*Innovator*	F-1	F-2	F-3	F-4	F-5
0	0	0	0	0	0	0
1	9.84	39	35	39.37	38	39.46
2	20	58	58.78	57.81	58.12	58.28
4	38.75	78	79.4	75.93	77.81	81.4
6	57.34	91	91.56	90.25	90.1	93.75
10	98.12	102	101	100	98.9	102.23

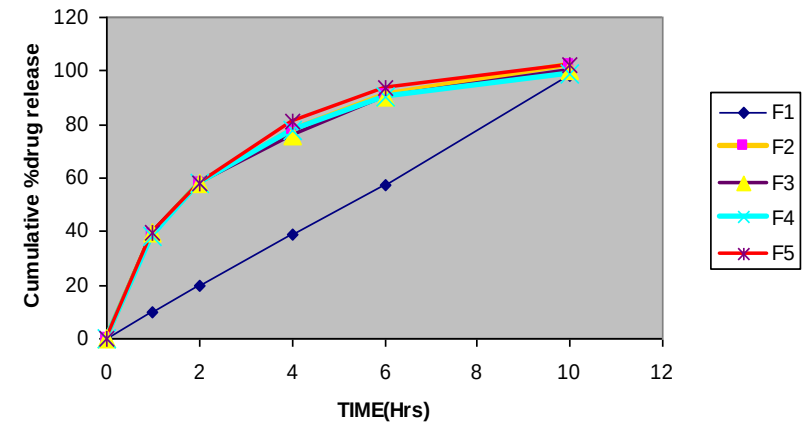

Figure 5: Comparative *Invitro* drug release profiles of different formulations F1-F5

Table7: Comparision of cumulative %drug release from Tramadol Hcl matrix tablet in 0.1 N Hcl with innovator

S.NO	TIME(Hrs)	Innovator	F-4
1	0	0	0
2	1	9.84	38
3	2	20	58.12
4	4	38.75	77.81
5	6	57.34	90.1
6	10	98.12	98.9

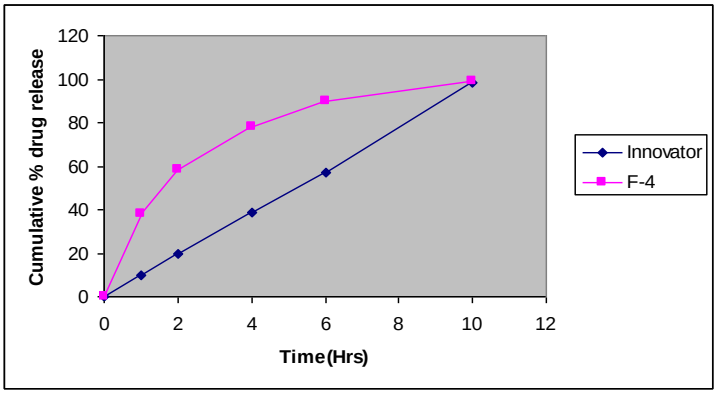

Figure 7: Comparative *Invitro* drug release profiles of different formulations F1-F5

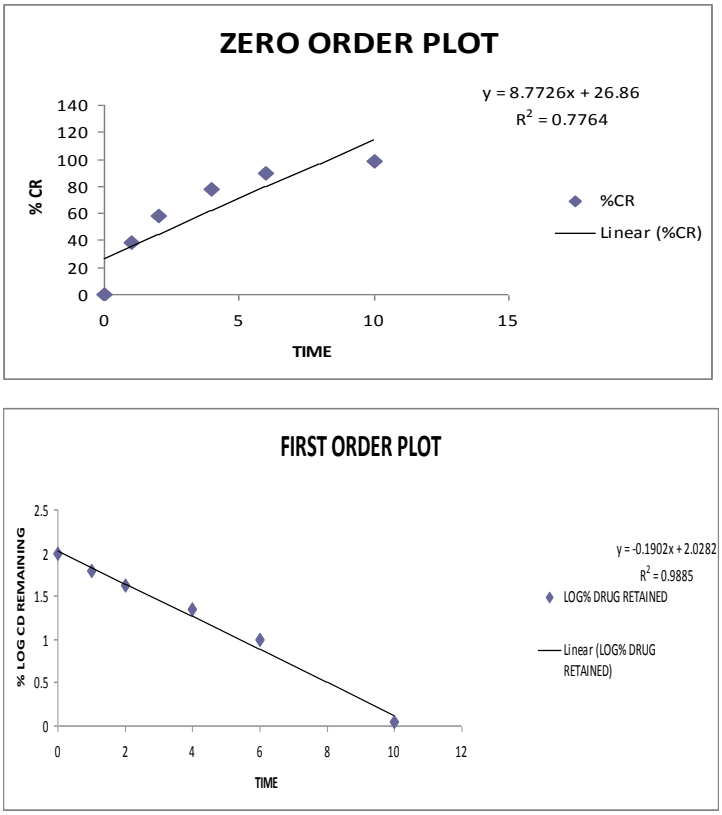

Figure 8: Kinetic models

Table 8: Results of stability studies of optimized formulation F-4

Formulation code	Parameters	Initial	1 Month	2 Month	3 Month	Limits as per Specifications
F-4	25^0C/60%RH % Release	97.96	97.86	97.66	97.56	Not less than 85 %
F-4	30^0C/75% RH % Release	97.96	97.84	97.59	97.59	Not less than 85 %
F-4	40^0C/75% RH % Release	97.96	97.88	97.78	99.62	Not less than 85 %
F-4	25^0C/60% RH Assay Value	99.96	99.94	99.89	99.86	Not less than 90 % Not more than 110 %

F-4	30^0C/75% RH Assay Value	99.96	99.95	99.87	99.83	Not less than 90 % Not more than 110 %
F-4	40^0C/75% RH Assay Value	99.96	99.93	99.86	99.79	Not less than 90 % Not more than 110 %

All the formulations were evaluated for weight variation,hardness, thickness, friability and % drug content. The weightof the formulation varied from 299.9±1.52to 350.18±1.54mg. Thickness of the formulation varied from 5.55±0.04 to6.35±0.03 mm. Hardness of the tablet varied from 7.4±0.2to 8.33±0.22(kg/cm2) and drug content was found to bebetween 99.49± 0.18 to 99.78 ± 0.17(Table 5).

All formulations showed uniform thickness. The average percentage deviation of all parameters was found within thelimit. The friability for all formulations were found below 1%indicating good abrasion resistance characteristics of tablets. All formulations showed acceptable physicochemicalproperties and specifications for weight variation, thickness, hardness, friability and drug content. Percentage drug releaseof all the formulations in 0.1 N hydrochloric acid was studiedfor the 10 hours. Formulation F4showed maximum releaseover aperiod of 10hrs and % drug release was found to be 98.96±0.24%.

DISCUSSION

The results indicated that dissolution rate of tramadolhydrochloride was highest in formulation containing acacia (80mg), and HPMC 1000 cps(50mg). From the dissolution study it was clear that F4 had fast dissolution rate as compared to other formulations.So formulation F4 was found to be optimum controlled release matrix tablet.

CONCLUSION

- Tramadol hydrochloride sustained release matrix tablets were prepared successfully using Acacia and HPMC as a release retarding Polymers.
- Sustainability in the drug release is possibly due to slower erosion of HPMC and may be due to the higher viscosity of Acacia which might have helped to keep the hydrated gel intact thus releasing the drug for 10 hrs.
- Among these formulations F4 showed 98.96% release in 10 hrs and the release profile follows zero order kinetics which is comparable with the marketed product.

- From the Korsmeyer peppas study, the n value of the formulations show that the release profile obeys non-fickian diffusion which shows that drug is released via, swelling, diffusion and erosion mechanism.
- The Stability studies and FTIR indicated that drug was stable in the tablets. In conclusion, Acacia and HPMC 10,000 cps can be used as rate controlling polymers by appropriate selection of the level of polymers in the matrix.

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