Scholars Academic Journal of Pharmacy (SAJP) **ISSN 2320-4206 (Online)**
Sch. Acad. J. Pharm., 2015; 4(3): 199-207 **ISSN 2347-9531 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Research Article

Design and Development of Sustained Release Matrix Tablets of Tramadol Hydrochloride are using Gum kondagogu as a Natural polymer

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Abstract: The main objective of the present work was to develop sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and natural gums like gumkodangogu. drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of three different rate controlling material. After evaluation of physical properties of tablet, the *in vitro* release study was performed in0.1 N HCl . The effect of polymer concentration and polymer blend concentration were studied. .Dissolution data was analyzed by Korsmeyer-Peppas power law expression and modified power law expression. It was observed that matrix tablets contained polymer blend of kodangogu/HPMC were successfully sustained the release of drug upto 10 hrs. Among all the formulations, formulation F6 which contains HPMC K15M and of kodangogu release the drug which follow Zero order kinetics via, swelling, diffusion and erosion and the release profile of formulation F6 was comparable with the marketed product. Stability studies (40±2ºC/75±5%RH) for 3 months indicated that Tramadol hydrochloride was stable in the matrix tablets. The FTIR study revealed that there was no chemical interaction between drug and excipients.
Keywords: Tramadol Hydrochloride, gum of kodangogu,, microcrystalline cellulose(Avicel PH 101 ,102) , PovidineK 90 ,HPMC 1000cps ,Matrix tablets, zero-order release.

INTRODUCTION

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. Sustained release matrix tablets are drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. The Tramadol SR 100 mg tablet is a better therapeutic option, with a reduced frequency of dosing and improved patient compliance and quality of life. The main aim is to Formulate and Evaluate sustained release matrix tablets of Tramadol hydrochloride using various hydrophobic and hydrophobic polymers.[1,2] The present work is aimed at preparing and evaluating sustained-release (SR) matrix tablets of Tramadol SR 100 mg tablet using different polymers. To study the effect of nature of the polymer and drug : polymer ratio on the rate of drug release. To study the drug release kinetics.

MATERIALS AND METHODS

Preparation of matrix tablets:

Different Tramadol Hcl formulations were prepared by Wet granulations technique [3,4] (F-l to F-9). Firstly Tramadol HC1 pure drug, kondagogu & Avicel pHlOl was weighed accurately and shifted through 40# mesh. Then PVP K-90 was dissolved completely in half quantity of Isopropyl Alcohol.Wet granulation was done in Rapid Mixing Granulator (RMG). In the RMG, Tramadol Hcl pure drug, kondagogu & Avicel pHlOl the PVP K-90 solution was added slowly in 1st minute with slow speed of RMG. On 2nd minute remaining Isopropyl Alcohol was added with same speed of RMG. Then on 3rd minute the RMG operated at high speed. Then again sufficient Isopropyl Alcohol was added if necessary. Then lastly for two minutes the RMG operated on slow speed to form granules. The prepared granules were dried at 30°C for 20min in presence of dehumidifier, and then it was sifted through sieve #20.In extra granulation step the polymer Metlose 60SH & Avicel pH 102 (Diluent) was accurately weighed and shifted through 40# mesh and

mix for l0 min. In final Mixing step, in Double Cone Blender firstly dried granules of above mixture was added then lubricating agent magnesium stearate and glidant i.e. Talc was mixed for 2 minutes. Finally these granules are ready for compression. Then these granules are compressed by using 8mm punch and maintaining humidity below 50%RH. Different Tramadol HC1 formulations were prepared by Wet Granulations technique, shown in table 1

Table-1:Formulation series

Ingredients	F-l	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Tramadol	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Gum Kondagogu	150mg	150mg	125mg	100 mg	75mg	50mg	25mg	—	50mg
Avicelphlol	50mg	20mg	40mg	60mg	40mg	60mg	80mg	90mg	90mg
PvpK90	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Hpmc 10000 cps	—	50mg	50mg	50mg	50mg	50mg	50mg	50mg	—
Avicelphl02	38mg	18mg	23mg	28mg	23mg	28mg	33mg	48mg	48mg
Mg.stearate	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Talc	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
Total wt of Tablet	350mg	350mg	350mg	350mg	300mg	300mg	300mg	300mg	300mg

EVALUATION OF TABLETS:[5-12]

Thickness

The thickness of the tablets was determined using a Vernier Caliper. Five tablets from each batch were used. The results are shown in Table 2.

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 the average weight Not more than two individual weights deviate from the average weight by more than the percentage and the results are shown in Table 2.

$$\textbf{PD- } [(W_{avg}) - (W \text{ initial}) / (W_{avg})] \text{ X } 100$$

Where

PD = Percentage deviation, W_{avg}=Average weight of tablet,

$W_{initial}$ = Individual weight of table

Hardness

For each formulation, the hardness of five tablets was checked using the Mansanto hardness tester .

Friability (F):

Weighed (Win^i) and transferred into the friabilator. The friabilator was operated at 25 rpm for four mins. The tablets were weighed again (Wgnai). The percentage friability was then calculated by:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Content Uniformity Test: Drug content:

For determination of drug content three tablets from each formulation were weighed individually, crushed and diluted to 100ml with sufficient amount of 0.1N HC1. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 272 nm against blank.

Invitro dissolution studies:

The in-vitro release of Tramadol HC1 from formulated tablets was carried out for 10 hours in 0.1N HC1. The studies were performed in USP dissolution apparatus I (Electro lab, Mumbai, India) at 37 ± 0.5° C and 75 rpm speed. Samples were taken at 1, 2, 4, 6 & 10 hours and diluted to suitable concentration and analyzed for Tramadol HC1 content at 272.0 nm by using UV-visible spectrophotometer. The values are shown in Table 3 and plots for the same are shown in Figure 6.

Drug release kinetics:

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Zero-Order Kinetics:

Zero order as cumulative amount of Percentage drug released v_s time

$$\mathbf{C = K_0 t}$$

Where *KQ* is the zero-order rate constant expressed in units of concentration/time and *t* is the time in hours.

First order kinetics:

First order as log cumulative percentage of log (%) cumulative drug remaining vs time,

$$\mathbf{LogC = LogC_0 - k_t / 2.303}$$

Where *Co* is the initial concentration of drug, *k* is the first order constant, and *t* is the time.

Higuchi Model:

Higuchi's model as cumulative percentage of drug released vs square root of time

$$Q = Kt^{1/2}$$

Where *K* is the constant reflecting the design variables of the system and *t* is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmayer Peppas equations:

Korsmeyer peppas equation used to determine the mechanism of drug release form the polymer matrix of the tablet Log cumulative percentage of drug released Vs Log time, and the exponent n was calculated through the slope of the straight line.

$$Mt/M\square = Kt_n$$

RESULT AND DISCUSSION

Drug Interaction Study:

FTIR spectra of Tramadol HC1 and physical mixture of Tramadol HC1 and polymers (HPMC 10000 cps & kondagogu) were taken. Spectra are shown in figure 8 for drug & figure 7-8 for physical mixture of drug and both polymer.[13] All the characteristic peaks of pure drug were observed in the spectrum of mixture. This indicated that there was not any interaction between drug and polymer.

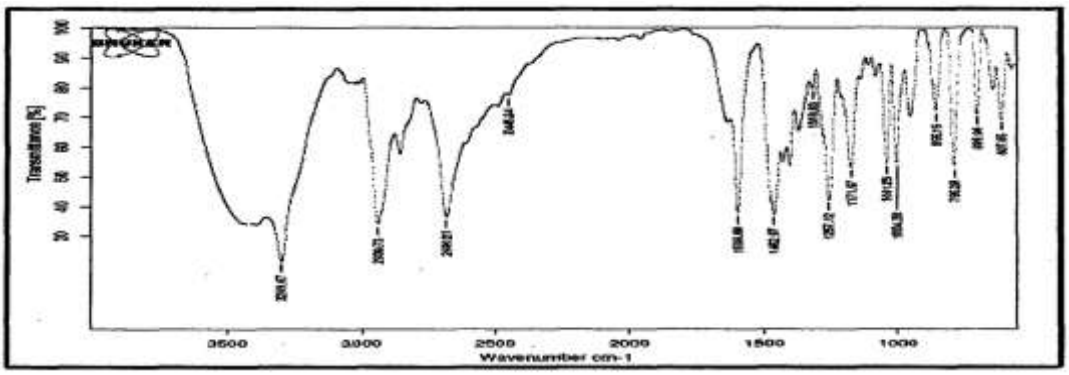

Fig-1: FTIR Spectrum of Tramadol HC1

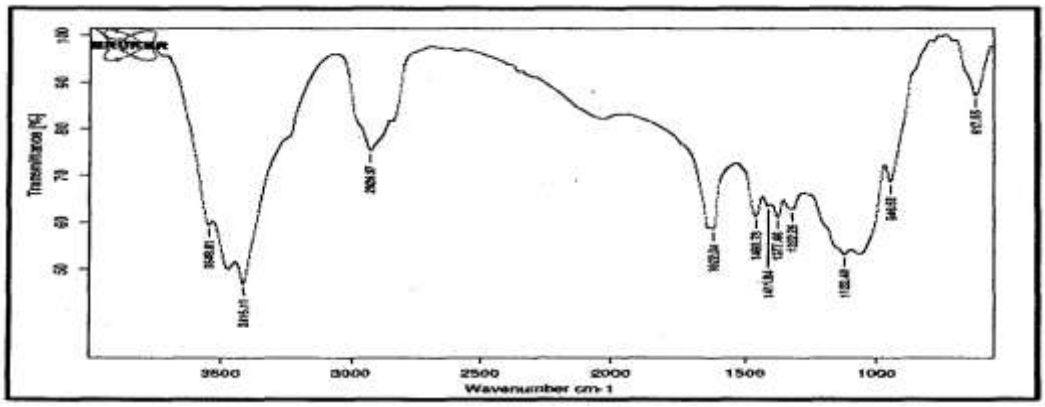

Fig-2: FTIR Spectrum of Metlose 60SH polymer sample

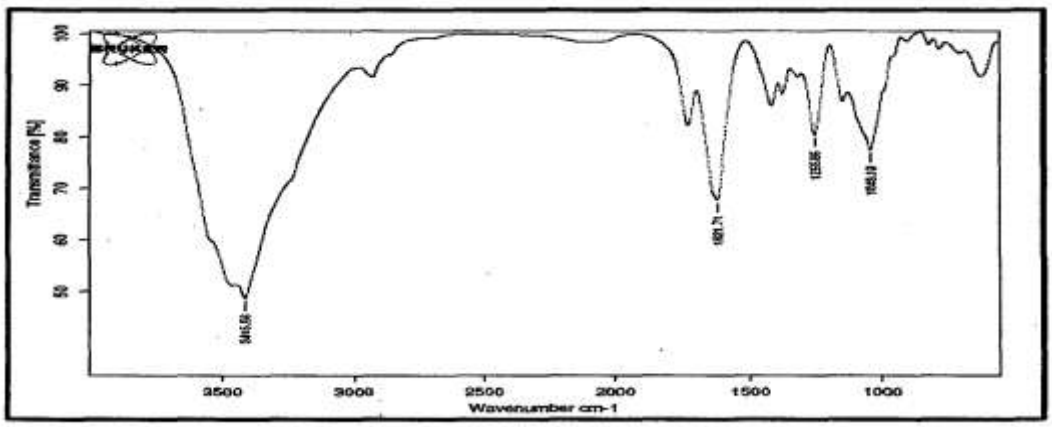

Fig-3: FTIR Spectrum of Kondagogu polymer sample

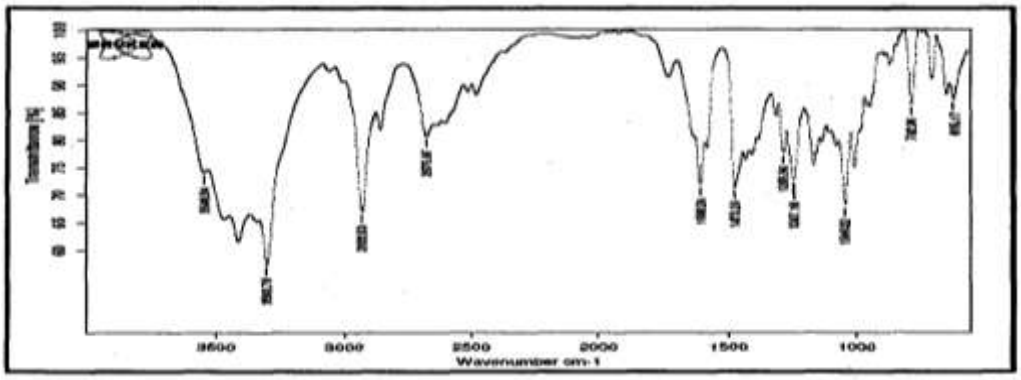

Fig-4: FTIR Spectrum of Tramadol + Metlose 60SH + Kondagogu polymer sample

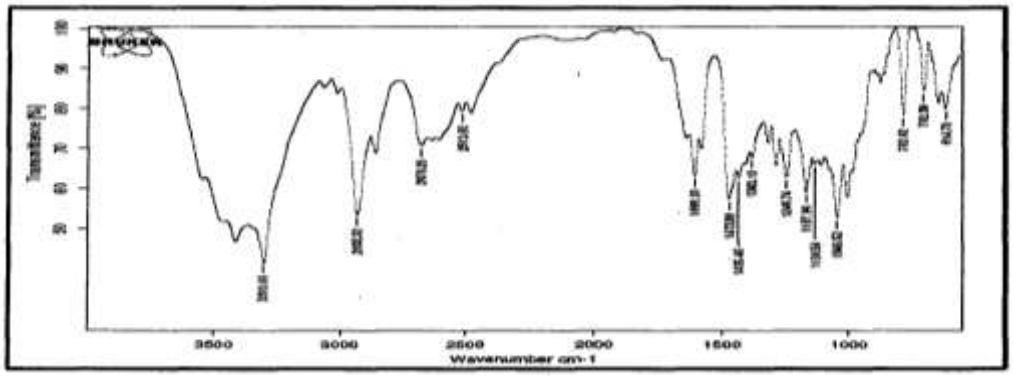

Fig-5: FTIR Spectrum of Tramadol HCl Tablets

Physical characterization of tablets of Tramadol HC1:

Tablet thickness, hardness, weight variation, friability and drug content of formulated tablets of batches from Fl to F9. All these physical parameters were found to be within acceptable limits.

Table-2: Physical characterization of tablets of Tramadol HCl(F1 to F9)

Formulation code	Hardness (k.g/cm^2)	Friability (%)	Thickness (mm)	Weight variation (mg)	Content uniformity
F-l	7.83±0.40	0.57±0.12	6.35±0.03	350.15±1.11	99.49iO.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
F-6	7.5±0.35	0.53±0.06	5.53±0.04	300.15±1.50	99.96±0.17
F-7	8.4±0.2	0.57±0.30	5.55±0.17	300.2±1.40	99.56±0.23
F-8	8.5±0.15	0.74±0.16	5.52±0.05	299.9±1.43	100.55±0.44
F-9	8.7±0.15	0.80±0.07	5.58±0.11	299.9±1.65	100.68±0.84

Effect of Polymers HPMC10000 cps (Metlose 60SH) and Gum Kondagogu on In-vitro release of Tramadol HC1:

In present study, the high viscosity grade HPMC 10000 cps as specified by USP was used as hydrophilic matrix forming agent. It forms a strong gel in aqueous media which may be useful to control the drug release of both, water soluble as well as water insoluble drugs from formulations.[14-19]The half life of Tramadol HC1 is 5.5-7 hrs. So the drug release up to 10 hrs will be able to show the pharmacological action up to 24 hrs. In attempt to prolong the drug release of drug up to 10 hrs, the release retarding agent HPMC 10000 cps and kondagogu were used.

HPMC 10000 cps is high viscosity grade polymer and results in increased hydration rate. Consequently distance required for drug to travel from tablet to dissolution medium increases. Furthermore, cross linking in the interpolymer chain increases with

increasing viscosity of polymer grade. Due to these reasons drug release was retarded by HPMC 10000 cps (Metlose 60SH).

Another polymer used Kondagogu is also release retarding polymer. It is viscosity enhancing agent. Kondagogu is granular in nature and hence useful in improving the flow properties of the granular blend of Tramadol HC1. Formulation F6 containing HPMC 10000 cps (Metlose 60SH) & kondagogu in different concentration shows the extended drug release for up to 10 hrs, among all the formulations, F6 is considered as optimized formulation because it shows similar drug release pattern with that of innovator.

In vitro drug release study

Basket method

Dissolution Data of Matrix tablets formulations of Tramadol HCL by Basket method (USP I) are reported in Table-3.

Table-3: Cumulative % drug released of formulations of Tramadol HCl tablets.

Time (Hrs)	Innovator	F-l	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0	0
1	9.84	17.96	7.5	8.12	8.9	9.21	9.68	12.34	13.43	14.21
2	20	35.31	15.93	17.5	18.59	19.21	19.84	25.62	28.9	30.31
4	38.75	60.15	30.93	35.62	36.09	37.34	38.59	50.31	55.93	58.12
6	57.34	85.15	51.093	52.65	54.53	55.46	57.03	68.59	80.78	82.96
10	98.12	100.78	81.093	83.12	85.46	92.03	97.96	99.84	100.46	100.62

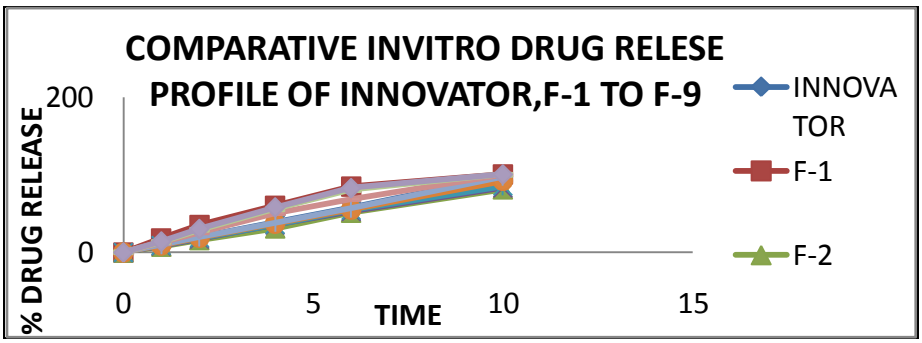

Fig-6: Dissolution profile of formulations F-l to F-9with Innovator

Table 4: Comparison of cumulative % drug released from Tramadol HC1 Matrix tablets in 0.1 N HC1 with Innovator

S.NO	TIME(Hrs)	Innovator	F-6
1	0	0	0
2	1	9.84	12.6
3	2	20	30.4
4	4	38.75	48.2
5	6	57.34	70.9
6	10	98.12	99.3

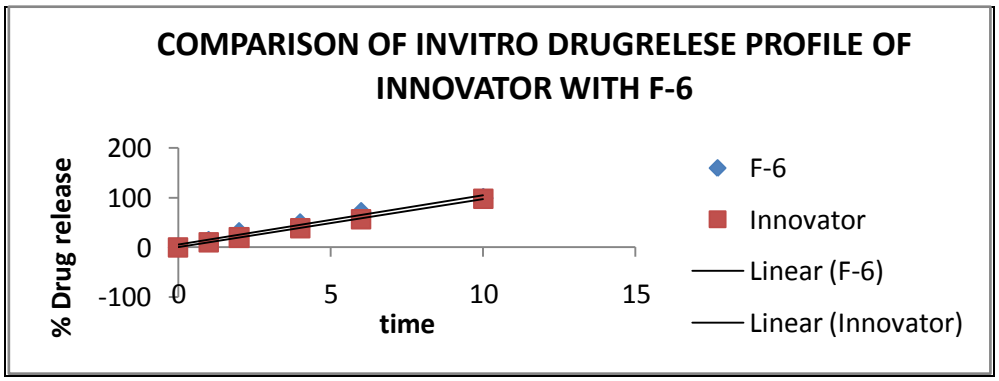

Fig-7: Dissolution profile of optimized formulations F-6 compared with Innovator in 0.l NHCL

Model-Dependent Approaches:

KINETIC MODELS:

Table-5: Zero order plot of F-6 Formulation

S.NO	TIME(hr)	% cumulative release
1	0	0
2	1	9.68
3	2	19.84
4	4	38.59
5	6	57.03
6	10	97.96

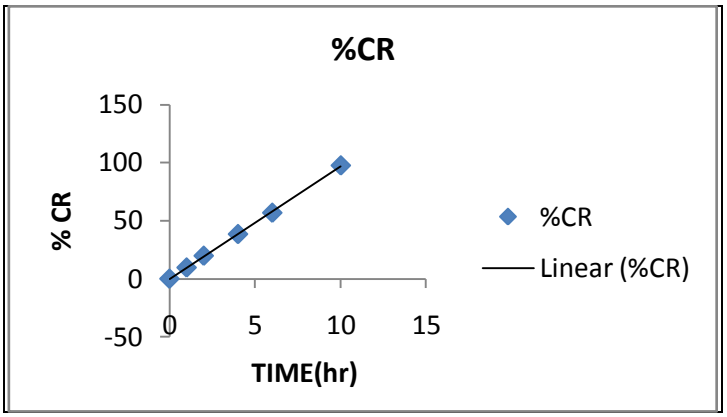

Fig-8: Zero order treatment for F-6 Formulation

Table 6: First order plot of F-6 Formulation

S.NO	TIME	LOG % CUMMULATTVE DRUG RETAINED
1	0	2
2	1	1.995
3	2	1.903
4	4	1.788
5	6	1.633
6	10	0.309

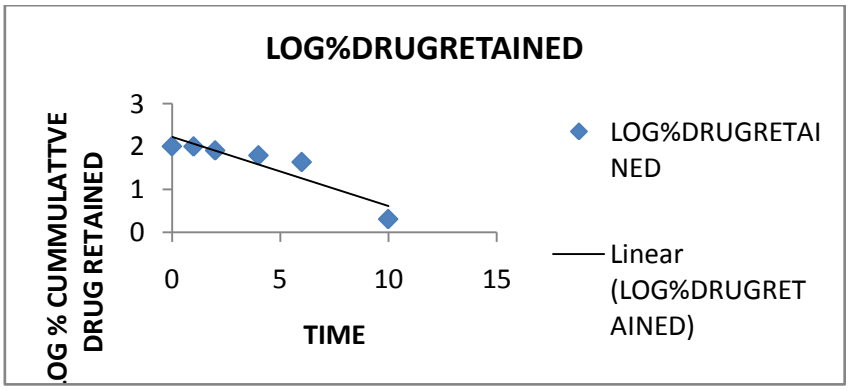

Fig- 9: First order treatment for F-6 Formulation

Table-7: Higuchi plot of F-6 Formulation

S.NO	Root T	% CR
1	1	9.68
2	1.414	19.84
3	2	38.59
4	2.449	57.03
5	3.162	97.96

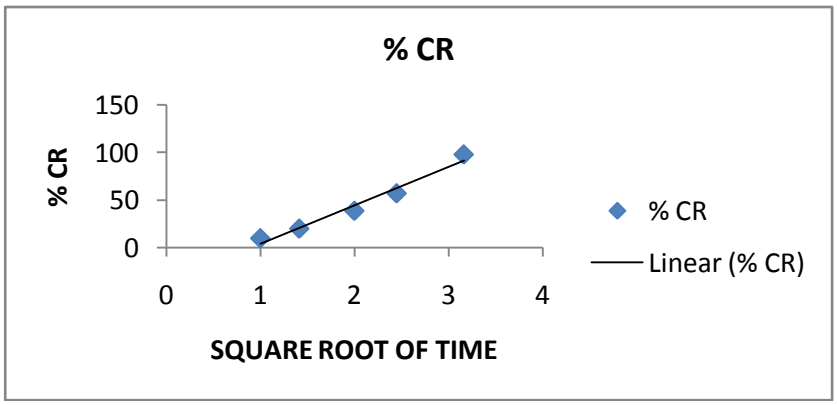

Fig-10: Higuchi treatment for F-6 Formulation

Table-8: Korsmeyer peppas plot of F-6 Formulation

S.NO	LOG TIME	LOG %CR
1	0	0.98588
2	0.301	1.29754
3	0.602	1.58648
4	0.778	1.7561
5	1	1.99105

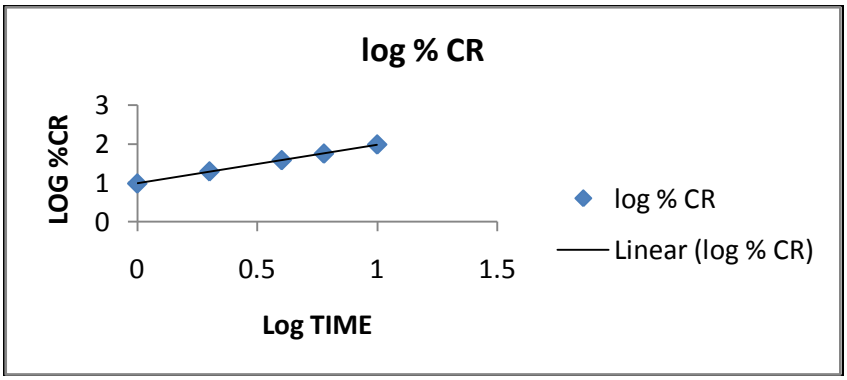

Fig-11: Kores mayer peppas treatment for F-6 Formulation

Table-9: Dissolution Kinetic Parameters

S.NO	KINETIC MODEL	R^2
1	ZERO ORDER PLOT	0.999
2	FIRST ORDER PLOT	0.837
3	HIGUCHIPLOT	0.971
4	KORSMEYAR-PEPPA'S PLOT	0.999

According to above R value, best formulation, i.e, F-6 formulation follows higuchi's model which shows that drug is released from matrix.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-6 after 3 Months. Parameters quantified at various time intervals were shown;

Table-10: Results of stability studies of optimized formulation F-6

Formulation code	Parameters	Initial	1 Month	2 Month	3 Month	Limits as per Specifications
F-6	25°C/60%RH % Release	97.96	97.86	97.66	97.56	Not less than 85%
F-6	30°C/75% RH % Release	97.96	97.84	97.59	97.59	Not less than 85%
F-6	40°C/75% RH % Release	97.96	97.88	97.78	99.62	Not less than 85%
F-6	25°C/60%RH Assay Value	99.96	99.94	99.89	99.86	Not less than 90% Not more than 110 %
F-6	30°C/75% RH Assay Value	99.96	99.95	99.87	99.83	Not less than 90 % Not more than 110 %
F-6	40°C/75% RH Assay Value	99.96	99.93	99.86	99.79	Not less than 90 % Not more than 110 %

Table-11: Stability dissolution profile of F-6 for 1st, 2nd & 3rd months with Innovator

S. NO.	TIME(hr)	Innovator	F-6(1M)	F-6(2M)	F-6(3M)
0	0	0	0	0	0
I	1	9.84	9.67	9.64	9.59
2	2	20	19.85	19.81	19.79
3	4	38.75	38.51	38.55	38.49
4	6	57.34	56.97	56.99	56.92
5	10	98.12	97.86	97.66	97.56

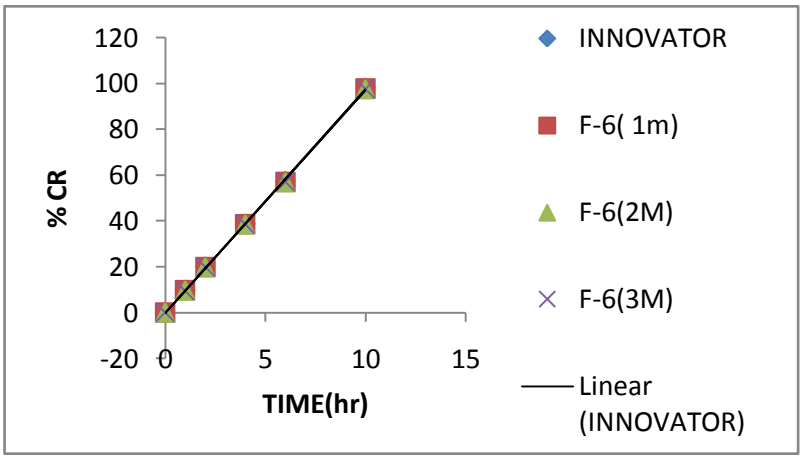

Fig-13: Dissolution profile of optimized formulations F-6 compared with Innovator of stability 1st, 2nd & 3rd months.

CONCLUSION

The present work was an aim to prepare a suitable extended release tablet of Tramadol HC1, administration of an extended release, Tramadol HC1 dosage form could reduce the dosing frequency and improve patient compliance. Extended release tablets of Tramadol Hcl were prepared using HPMC 10000 cps & kondagogu[20,21] as retardant polymers. Various evaluation parameters like thickness, hardness, friability, weight variation and drug content of the formulations were found to be satisfactory. Among all formulations prepared and evaluated F6 matches release pattern with that of Innovator release at each hour release.

ACKNOWLEDGMENTS

The authors are thankful to the principal, Staffs and management J.K.K.Nattraja College of Pharmacy for providing all facilities to carry out the remaining part of the research work.

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