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Orignal Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF TRAMADOL HYDROCHLORIDE USING NATURAL POLYMERS

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ABSTRACT

The present investigation deals with sustained release tablets. Sustained release tablets are effective in extending the duration of action of drug. In the present study sustained release tablets formulations containing Tramadol hydrochloride were prepared and studied. Designing of controlled release formulation is necessary to maintain steady state plasma concentration for longer period of time and to reduce the frequency of administration. So, an attempt was made to formulate sustained release tablets of Tramadol hydrochloride to sustain its action. Sustained release tablets were prepared using direct compression technique using varying concentrations of Delonix regia gum (DRG) and Eudragit RS100. Sustained release formulations were evaluated for FTIR, DSC, weight variation test, tablet thickness, tablet hardness, friability test, drug content uniformity, in-vitro drug release from tablets, kinetic modelling of drug dissolution profile and stability studies. The prepared sustained release tablets fulfilled all official requirements. The results of in-vitro drug release studies showed that release from sustained release tablet formulations was slow and sustained for 8 hrs. Increase in concentration of polymers showed decrease in drug release of all formulations. All formulations followed Higuchi model and release mechanism was non-fickian diffusion. From the results it was concluded that, formulations prepared using combination of DRG and Eudragit RS100 (3:2) showed better sustained release effect.

Keywords: Sustained release, Direct compression technique, Delonix regia gum, Eudragit RS 100, Tramadol hydrochloride.

INTRODUCTION

The advantage of administering a single dose of a drug that is released over an extended period of time instead of numerous doses is now a day's area of interest for formulation scientists in Pharmaceutical industry. The basic rationale of sustained drug delivery system optimizes of the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that utility is maximized, side-effects are reduced and cure of the disease is achieved. The objectives of the research work was to formulate sustained release tablets of Tramadol HCl using natural gums in combination and alone and to study the effect of concentration of polymers on in-vitro drug release [1, 2].

The goal in designing sustained release drug delivery system is to reduce frequency of dosing, to increase the effectiveness of the drug at the required site thereby minimising or eliminating side effects, providing uniform drug delivery [3].

Tramadol hydrochloride is opoid analgesics used to treat osteoarthritis and rheumatoid arthritis. It belongs to class I of biopharmaceutical classification system [4]. To study the effect of concentration of polymers on in-vitro drug release. Among the hydrophilic polymers, natural polysaccharides are preferred due to their nontoxicity, biocompatibility, biodegradability and acceptance by the regulating agencies [5]. Delonix regia belong to family Fabaceae. It is used as binding agent, sustained release agent etc [6].

MATERIALS AND METHOD

Tramadol hydrochloride was purchased from Yarrow Chem Products, Mumbai. Delonix regia seeds were collected from local area of Baramati, Eudragit RS100 was procured from Evonic industries. Other materials and solvents like Magnesium stearate, Microcrystalline cellulose, Talc, Starch, Hydrochloric acid, Potassium dihydrogen phosphate, Sodium hydroxide, Ethanol used were of analytical grades.
Tablets were punched using Tablet machine Karnavati Rimek Mini press-I, In-vitro dissolution study was performed using USP Dissolution apparatus Campbell DRS-8, UV Visible spectrophotometer shimadzu UV-1700, FTIR spectrophotometer Shimadzu 1700, Differential Scanning Calorimetry PerkinElmer 4000 was used.

METHOD

Isolation of Delonix regia gum was done using proposed method [7].
The sustained release tablets of Tramadol HCl were prepared by direct compression technique. Delonix regia gum and Eudragit RS 100 were used alone and in combination at varing concentrations as the polymers, starch was used as binder, talc as diluent, magnesium stearate as lubricant and microcrystalline cellulose as bulking agent. Each tablet weighing 300 mg was compressed by using 10 station single punch tablet compression machine (Karnavati Rimek, Mini press-I) [8].

Table no 1: Composition of Tramadol HCl Tablets

Batch	Tramadol HCl (mg)	Eudragit RS 100 (mg)	Delonix Regia Gum (mg)	Starch (mg)	Talc (mg)	Magnesium stearate (mg)	MCC (mg)	Total weight (mg)
F1	120	90	-	5	2	2	81	300
F2	120	120	-	5	2	2	51	300
F3	120	150	-	5	2	2	21	300
F4	120	-	90	5	2	2	81	300
F5	120	-	120	5	2	2	51	300
F6	120	-	150	5	2	2	21	300
F7	120	60	90	5	2	2	21	300
F8	120	90	60	5	2	2	21	300
F9	120	75	75	5	2	2	21	300

Evaluation Of Sustained Release Tablets

FT-IR Spectroscopy

Fourier transform infra-red spectroscopy of drug, polymers and physical mixtures of drug and polymers was recorded on Shimadzu FTIR spectrophotometer using KBr pellet technique. The instrument was operated under dry air purge and the scan was collected at scanning speed 2mm/sec with resolution of 4 cm^{-1} over region 4500-400 cm^{-1}. The identified peaks were compared with the principal peaks of reported FT-IR spectrum and sample was authenticated. [9, 10]

Differentiial Scanning Calorimetry (DSC)

Differential scanning calorimetry was performed for drug, polymers and physical mixtures of drug and polymers on PerkinElmer 4000 instrument. Thermogram was obtained by heating 1 mg samples in aluminum pans at heating rate 100°/min, from 30°C to 350°C, in a nitrogen atmosphere (flow rate 20mL/min). Data was analyzed, using PYRIS Version-11.1.0.0488 software, for origin to obtain onset temperature (T onset); the peak temperature (T peak) and the endset temperature (T endset) of endothermic peak. [10, 11]

Micromeritics Characteristics

The prepared formulation was evaluated for its MicromeriticsCharacterstics i.e. Angle of repose, Bulk density, Tapped density, Carr's index, and Hausner's ratio result shown in table no 2. [12]

Post compression parameters [13,14,15]

Weight Variation Test

The weight variation test was performed according to the method prescribed in USP.

Tablet Thickness

Tablet thickness was measured by using digital Vernier Calipers.

Tablet Hardness

Tablet hardness was determined by using Monsanto hardness tester.

Friability Test

The friability test for tablets was done using Roche friabilator.

Drug Content Uniformity

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. An amount equivalent to 100 mg was extracted with 100 ml pH 6.8 phosphate buffer solution and sonicated for 15 minutes. The solution was filtered through a filter paper (0.22µm pore size), properly diluted with pH 6.8 phosphate buffer solution. Absorbance of the solution was analyzed spectrophotometrically at 271 nm against suitable blank using UV-visible spectrophotometer (1700, Shimadzu, Kyoto, Japan) and drug content per tablet was calculated. [16]

In Vitro Drug Release From Tablets

In vitro dissolution study was performed using USP Dissolution Apparatus II (TDT-08L Electrolab). The dissolution test was performed using 900ml of 0.1 N HCl for first 2 hrs and PBS buffer pH 6.8 for next 6 hrs at 37±0.5°C and speed was at 50 rpm. 1 ml of the solution was withdrawn at predetermined time interval and replaced with same fresh dissolution media. The samples were filtered through Whatman filter paper No. 41. The samples were collected and diluted taking dilution factor as 10. Samples were then analyzed at 271 nm using UV spectrophotometer (Model UV 1700, Schimadzu). The % drug release was calculated and dissolution tests were performed in triplicates. [17,18]

Drug Release Kinetics

Drug release kinetics was obtained by the best curve fitting method and comparing the correlation coefficients of release data with zero order, Higuchi model and Korsemeyer-Peppas models. The in-vitro drug release profile of all tablet formulations were fitted on to various kinetic models in order to find out the mechanism of drug release. The best fit model with highest correlation coefficients was selected. [19,20]

Stability Studies

The Tramadol hydrochloride sustained release tablets were subjected to stability studies at elevated temperature 40^{o}C, Room temperature and 75% Relative Humidity for 45 days on the all formulations and result as represented in table no 5 and 6. [17,18]

RESULTS AND DISCUSSION

FT-IR Spectroscopy

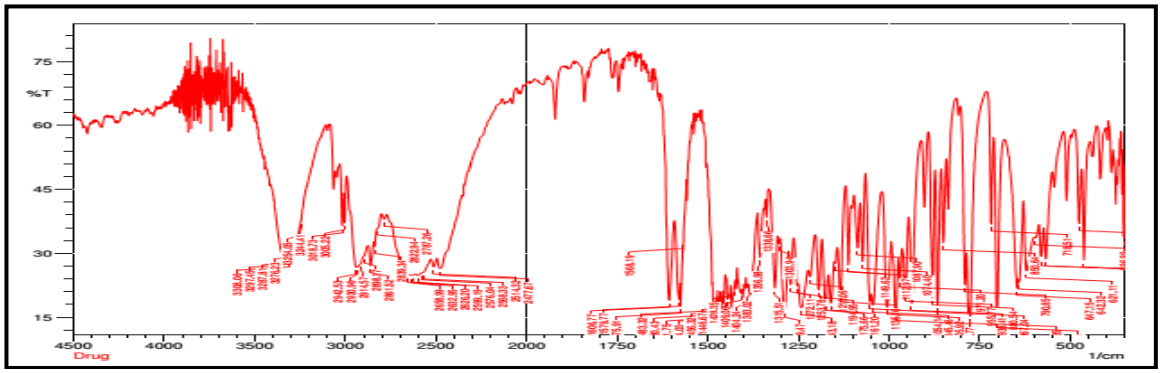

Figure 1: FTIR spectrum of Tramadol Hydrochloride

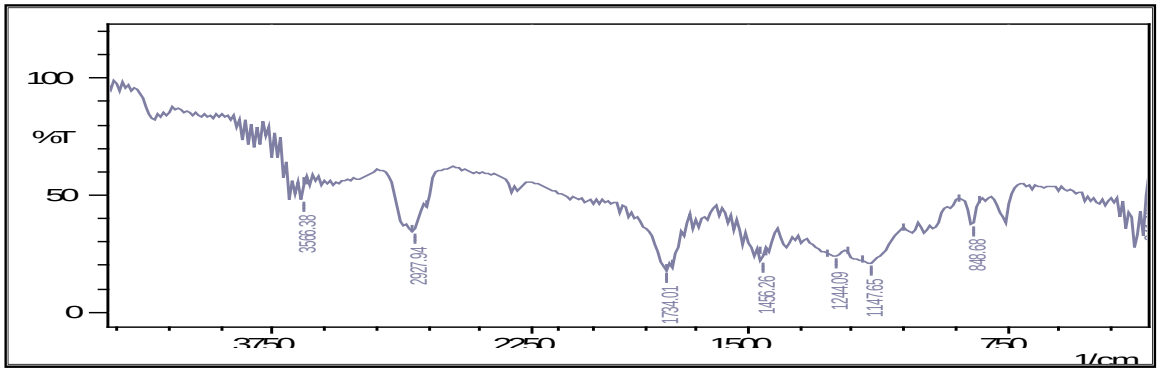

Figure 2: FTIR Spectrum of Eudragit RS100

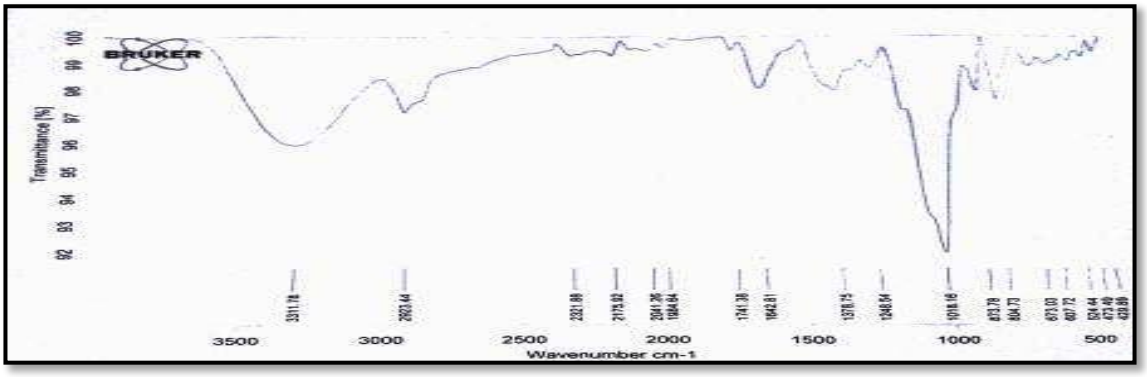

Figure 3: FTIR Spectrum of DRG

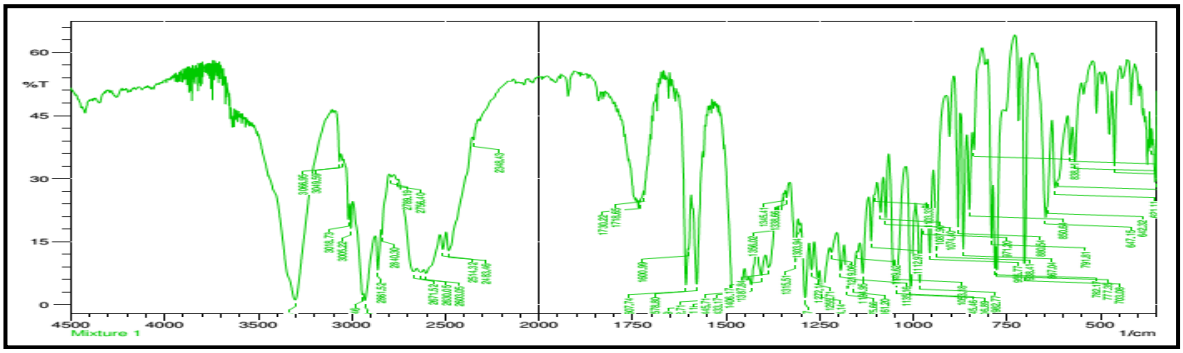

Figure 4: FTIR Spectrum of Physical Mixture of Drug and Eudragit RS 100

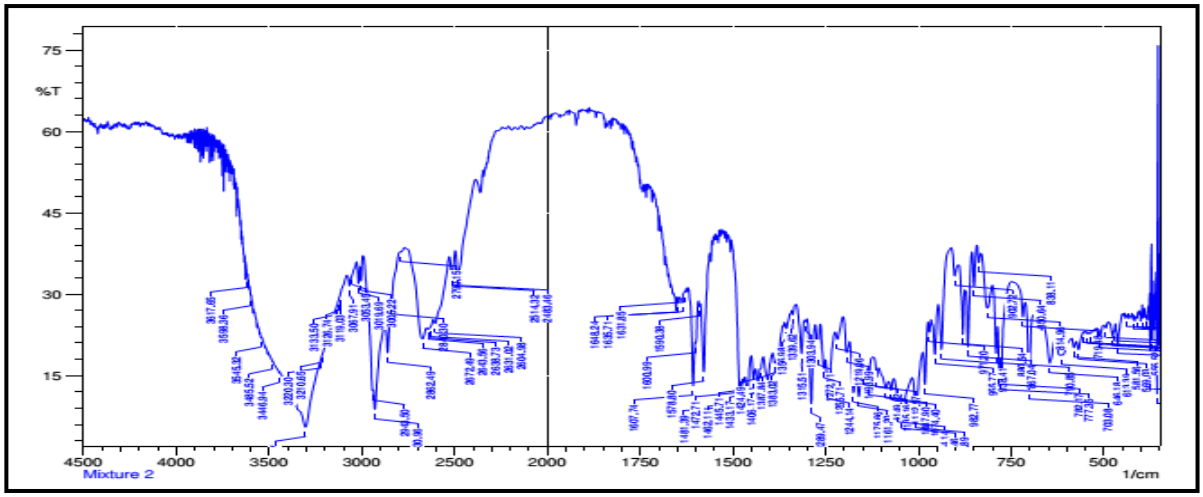

Figure 5: FTIR Spectrum of Physical Mixture of Drug and DRG

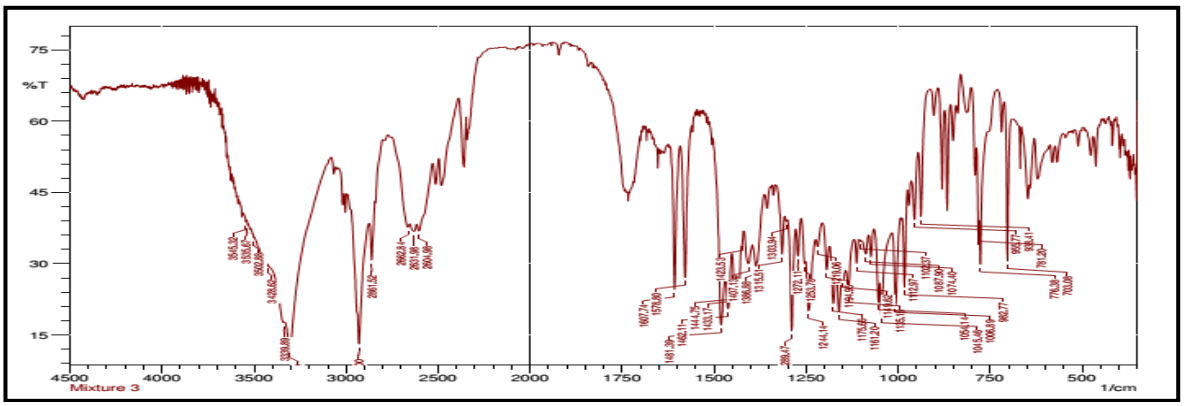

Figure 6: FTIR Spectrum of Physical Mixture of Drug, Eudragit RS100 and DRG.

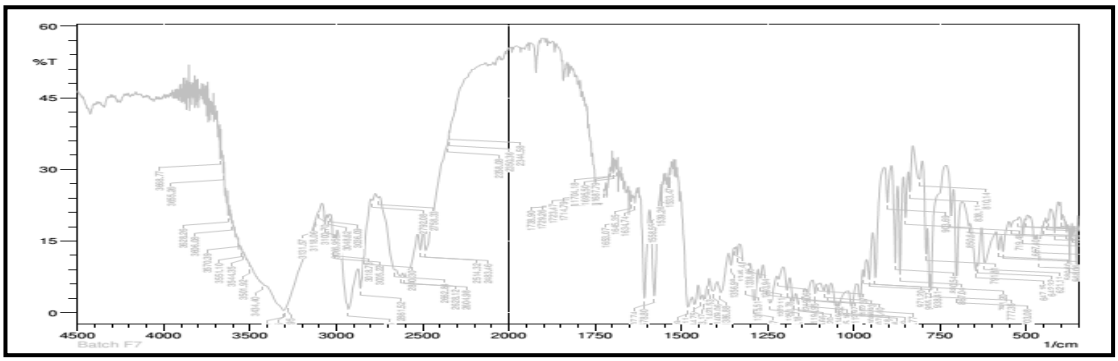

Figure 7: FTIR Spectrum of formulation F7

Differential Scanning Calorimetry

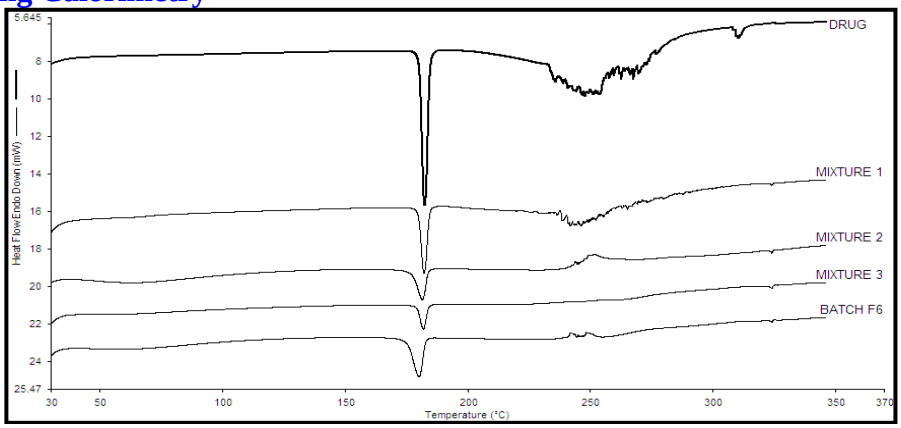

Figure 8: Mixture 1: DSC thermogram of physical mixture of drug and Eudragit RS100.

Mixture 2: DSC thermogram of physical mixture of drug and DRG.
Mixture 3: DSC thermogram of physical mixture of drug, Eudragit RS100 and DRG.
Batch F7 : DSC thermogram of formulation F7

Pre-compression Properties

Table no 2: Micromeritic properties

Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	% Compresibility Index	Angle of Repose	Hausner Ratio
F1	0.614±0.023	0.730±0.034	15.94±3.641	34.6±0.925	1.18±0.052
F2	0.601±0.04	0.730±0.034	17.65±2.808	33.98±0.525	1.21±0.041
F3	0.575±0.023	0.730±0.034	21.30±3.461	32.82±0	1.27±0.052
F4	0.540±0.023	0.659±0.025	18.03±6.065	30.47±0.735	1.22±0.09
F5	0.457±0.011	0.540±0.023	15.29±5.059	28.61±0.381	1.18±0.070
F6	0.422±0.011	0.491±0.017	14.08±4.701	27.96±0.369	1.16±0.070
F7	0.465±0.011	0.551±0.023	15.54±5.083	31.22±0.770	1.18±0.070
F8	0.519±0.011	0.659±0.028	21.18±2.941	32.83±0.840	1.26±0.045
F9	0.482±0.017	0.587±0.023	17.88±0.923	32.01±0.805	1.21±0.043

(Mean ± S.D, n=3)

Post-compression parameters

Table no 3: Evaluation of Sustained Release Tablets of Tramadol HCl

Batch	Weight Variation ± SD (gm)	Thickness± SD (mm)	Hardness± SD (kg/cm^2)	Friability ± SD (%)	Content of Uniformity ± SD (%)
F1	0.299±0.642	5.34±0.055	4±0.577	0.282±0.011	84.00±0.577
F2	0.297±0.529	5.37±0.064	5±0.577	0.395±0.028	92.00±0.525
F3	0.299±0.577	5.52±0.028	5±0.000	0.55±0.015	90.00±0.781
F4	0.298±0.503	5.05±0.050	4±0.000	0.835±0.014	94.00±0.892
F5	0.297±0.577	5.16±0.040	5±0.577	0.998±0.007	92.00±0.913
F6	0.297±0.230	5.11±0.106	4±0.577	0.608±0.110	96.00±0.523
F7	0.296±0.721	5.29±0.164	4±0.577	0.845±0.014	88.00±0.873
F8	0.298±0.642	5.35±0.083	4±0.577	0.845±0.015	92.00±0.244
F9	0.297±0.577	5.34±0.110	5±0.000	0.689±0.010	86.00±0.842

(n=3)

In-vitro drug release from tablets

A. Zero order release

Table no 4: Zero order release profile for formulations.

Time (min)	Batches								
	Percentage cumulative Drug Release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
30	13.5	15	13.5	13.5	10.5	12	10.5	10.5	10.5
60	21.02	21.02	18.02	21.02	18.01	16.51	15.01	19.51	18.01
120	30.04	25.54	27.04	27.04	28.53	27.03	24.03	28.53	25.53
180	37.57	37.57	36.07	37.57	34.56	33.06	30.06	37.57	33.06
240	45.11	45.11	43.61	42.11	40.6	39.1	34.59	42.11	36.1
300	51.16	51.16	48.15	46.66	45.15	45.14	39.13	45.15	42.14
360	57.22	55.72	52.71	54.21	49.7	49.69	42.17	48.2	46.68
420	60.28	60.28	57.27	58.77	54.25	54.25	45.22	54.26	49.74
480	66.35	64.85	61.83	63.33	58.81	57.31	49.77	58.82	52.79
R^2	**0.949**	**0.949**	**0.948**	**0.95**	**0.941**	**0.949**	**0.936**	**0.922**	**0.933**

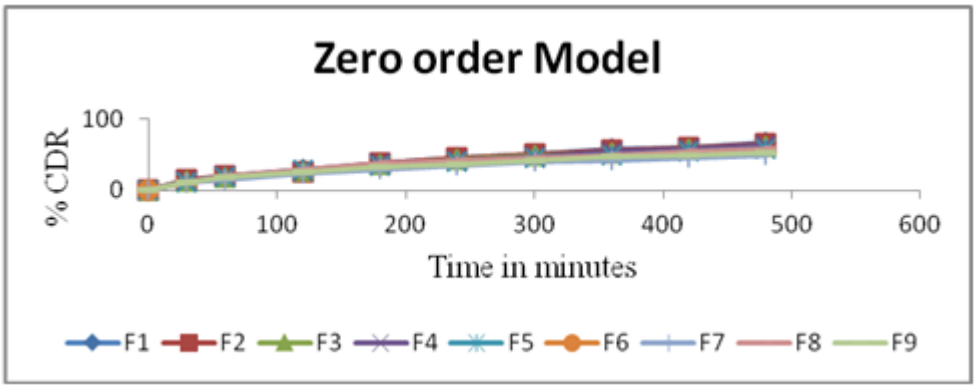

Figure 9: Graph of cumulative percent drug release vs. Time for formulations.

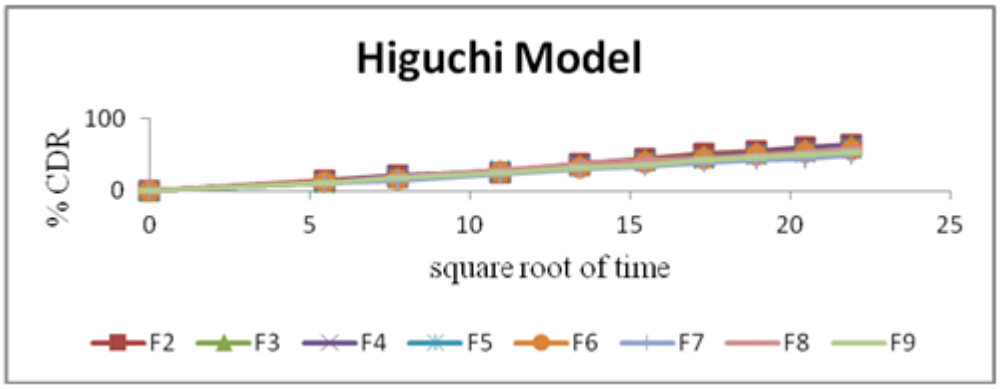

Figure 10: Graph of cumulative percent drug release vs. Square root of time for formulations.

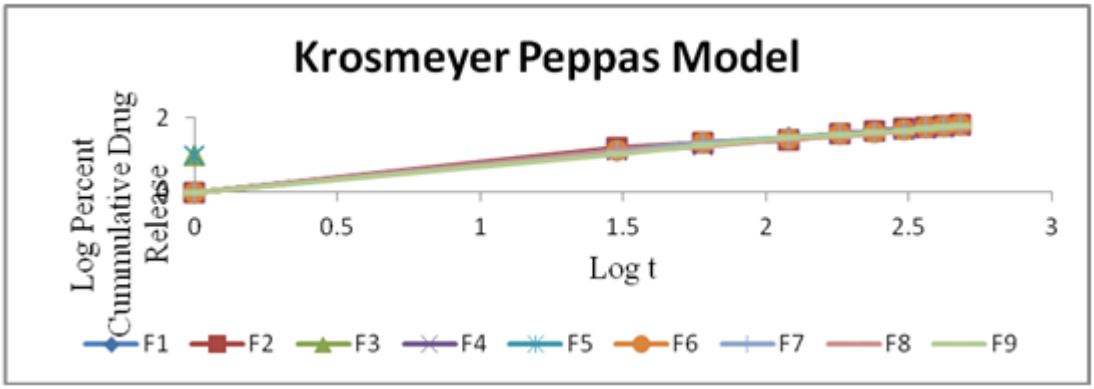

Figure 11: Graph of Log percent drug release vs. Log of time for formulations.

Kinetic model fitting for drug release

Table no 4: Model fitting data for tablet formulations

Batch	Zero order	Higuchi		Peppas Krosmeyer	
	R^2	R^2	K	R^2	n
F1	0.949	0.996	3.071	0.993	0.675
F2	0.949	0.991	3.019	0.988	0.674
F3	0.948	0.995	2.892	0.993	0.665
F4	0.95	0.994	2.908	0.991	0.664
F5	0.941	0.996	2.747	0.996	0.659
F6	0.949	0.996	2.709	0.996	0.661
F7	0.936	0.997	2.301	0.996	0.629
F8	0.922	0.993	2.719	0.993	0.659
F9	0.933	0.997	2.483	0.995	0.647

Stability Studies

It was performed for only formulation batch F7 at 40^0c and 75% RH for 45 days.

Evaluation of Tablets

Table no 5: Evaluation of various parameters of tablets after stability study

Batch No.	Weight Variation± SD	Thickness± SD (mm)	Hardness± SD (kg/cm^2)
F7	0.298±0.503	5.05±0.050	4±0.577

(n=3)

Dissolution study of formulation F7

Table no 6: Drug release from F7 formulation after stability

Time (Min)	Sq Rt. Of Time	Log T	Absorbance at 271 nm	Cum. % Drug Release	Log Percent Drug Release
0	0.000	0.000	0.000	0.00	2
30	5.48	1.48	0.019	10.50	1.951823
60	7.75	1.78	0.023	16.51	1.921626
120	10.95	2.08	0.028	24.03	1.880642
180	13.42	2.26	0.031	31.56	1.835331
240	15.49	2.38	0.032	33.09	1.82548
300	17.32	2.48	0.035	37.63	1.794987
360	18.97	2.56	0.039	43.67	1.75074
420	20.49	2.62	0.040	45.22	1.738635
480	21.91	2.68	0.043	49.77	1.700978

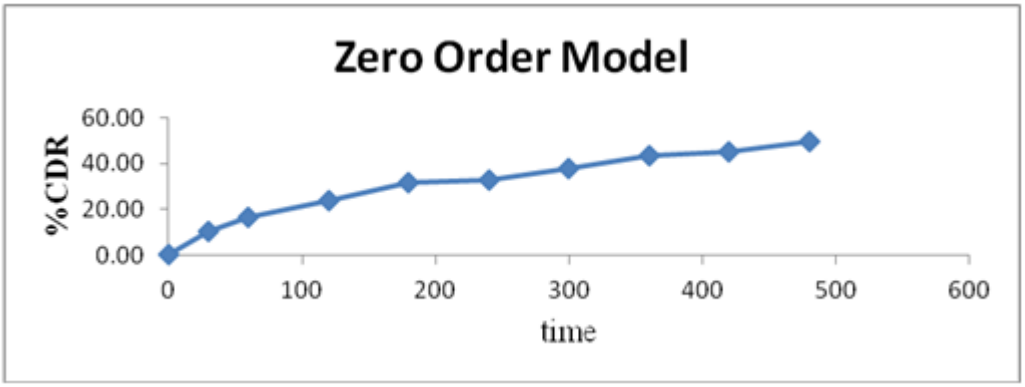

Figure 12: Graph of cumulative percent drug release vs. Time for batch F7

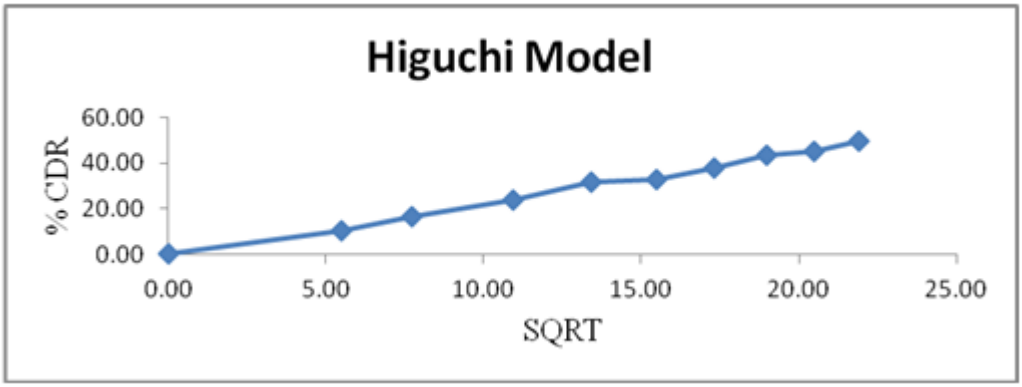

Figure 13: Graph of cumulative percent drug release vs. Square root of time for batch F7

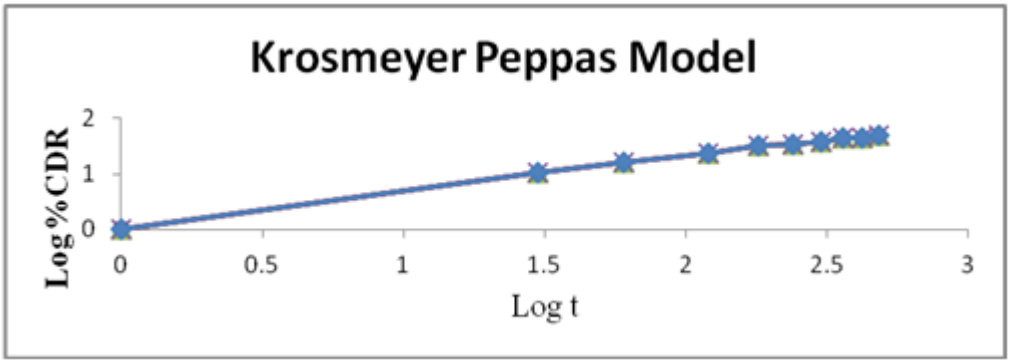

Figure 14: Graph of Log percent drug release vs. Log of time for batch F7

Table no 7: Model fitting for tablet formulation F7

Batch	Zero order	Higuchi		Peppas Krosmeyer	
	R^2	R^2	K	R^2	n
F7	0.931	0.995	2.281	0.994	0.627

DISCUSSION

FT-IR Spectroscopy

The FTIR spectrum of Tramadol Hydrochloride showed the characteristic absorption peak at 1606.77 assigned to aromatic ring stretching, peak at 2942.53 assigned to aliphatic C-H stretching, peak at 3018.73 assigned to aromatic C-H stretching, peak at 3308.06 assigned to O-H stretching which accordance with standard. The FTIR Spectrum of Eudragit RS100 showed C-N stretching due to alliphatic amine at 1147.65, C-O stretching of ester at 1244.09, -CH_3 bending of alkane at 1456.26, C=O stretching of ester at 1734.01, C-H stretching of alkane at 2927.94. FTIR of DRG showed O-H stretching at 3311.78, C-H stretching at 2923.44, C=O stretching at 1741.38, C-O stretching at 1240.54 complies with the standard range. FTIR spectra of formulations prepared by using Eudragit RS100 showed the characteristics peak of Tramadol Hydrochloride and Eudragit RS100. FTIR spectra of formulation prepared by using DRG showed the characteristics peak of Tramadol Hydrochloride and DRG. FTIR spectra of formulations prepared by using Eudragit RS100 and DRG showed the characteristics peak of Tramadol Hydrochloride, Eudragit RS100 and DRG.

Differentiial Scanning Calorimetry (DSC)

The DSC thermogram of pure drug showed a characteristics sharp endothermic peak at 182.64°c indicating amorphous nature as well as melting point of drug.

Micromeritic properties

The drug with various polymers was evaluated for the physical properties. The values of bulk density, tapped density, Carr's index, Hausner ratio and angle of repose were calculated as shown in Table no 19 and it indicates good flowability of powder.

Post-compression parameters

Weight Variation:

If the weight of tablet 300 mg, according to USP standard the weight variation limit for tablet weight between 130-324 mg is 7.50 % which is acceptable. The prepared tablets does not shows the variation within the limit.

Tablet Thickness:

The thickness of tablet was found to in the range of 5.05-5.52mm.

Tablet Hardness:

The hardness of tablets was in the range of 4-5 kg/cm^2.

Friability Test:

According to USP standard the 1% friability for tablet is acceptable. The prepared tablets showed the friability in the range of 0.282 – 0.998% which was within the limit.

Drug content uniformity:

The drug content of tablet was found to in the range of 84-96%.

In-vitro drug release from tablets

Increase in concentration of polymers showed decrease in drug release from all formulations. From the results it was concluded that, formulations prepared by using combination of DRG and Eudragit RS100 (3:2) showed better sustained effect.

Kinetic model fitting for drug release

All formulations followed Higuchi model and release mechanism was non-fickian diffusion.

Stability Studies

Drug release data after stability study for formulation F7 was fitted in Higuchi model, n value was 0.627 which showed Non-Fickian release.

CONCLUSION

DRG and Eudragit RS 100 were used in varying concentration as a sustained release polymers. Increase in concentration of polymers showed decrease in drug release from all formulations. From the results it was concluded that, formulations prepared by using combination of DRG and Eudragit RS100 (3:2) showed better sustained release effect.

ACKNOWLEDGEMENT

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