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Development and *in-vitro* characterization of sustained release tramadol hydrochloride by film coating technique

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ABSTRACT

Tramadol Hydrochloride is a centrally acting analgesic. Tramadol acts as a μ-opioid receptor agonist, serotonin-nor epinephrine reuptake inhibitor (SNRI), NMDA receptor antagonist, 5-HT_2C receptor antagonist, nicotinic acetylcholine receptor antagonist and M1 and M3 muscarinic acetylcholine receptor antagonist. The main objective of the present work was to develop sustained release film coated tablets of water soluble Tramadol hydrochloride by wet granulation. Various polymers and the combination of polymers were used for controlling the release of drug up to desired time. Sustaining the release of drug from the dosage form was useful for achieving controlled plasma level of the drug as well as improving bioavailability. The precompression parameters were evaluated for flow properties. After evaluation of post compression parameters of tablet, the in vitro release study was performed in 0.1N HCl pH 1.2 for 16 hrs. Among all formulations (F1-F10), formulation F5 was identified to be the best as it showed 99.39% drug release and sustained action for 16 hrs. The optimized formulation (F5) was kept at stability studies according to ICH guidelines for 3 months, which showed that the formulation was stable. FTIR studies showed no unacceptable extra peaks which confirm the absence of chemical interaction between the drug and polymers.

Key words: Tramadol Hydrochloride, Ethylcellulose N20, HPMC E5, PEG, Wet granulation, Conventional Coating Pan, SR Tablets.

INTRODUCTION

Analgesics are drugs which provide symptomatic relief from painful conditions. These drugs are very often consumed by patients suffering from acute and chronic pains. However these drugs are not consumed by patients as per prescription advice. Patients very often miss a dose and compliance to dosage regimen always remains a question mark. To overcome these kinds of issues and also to maintain a continuous therapeutic level of drugs in systemic circulation, Sustained release tablets come in handy as a solution. A sustained-release dosage form is defined as “any drug or dosage form modification that prolongs the therapeutic activity of the drug” [1]. The primary objectives of sustained drug delivery are to ensure safety and enhancement of efficacy of drug with improved patient compliance. This delivery system is increasingly being used in the treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above the minimum effective concentration and below the minimum toxic level for an extended period of time. Thus, sustained drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects [2]. Tramadol, a synthetic opoid of the aminocyclohexanol group, is a centrally acting analgesic with weak opoid agonist properties. Tramadol has been proved to be effective in both experimental and clinical pair without causing serious side effects. The half-life of a drug is about 5.5 hrs and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hrs 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 developed. Long term treatment with sustained-release Tramadol is generally safe in patients with osteoarthritis or refractory low back pain and is well tolerated. It has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep, and improved compliance.

An attempt was made in this study to prepare and evaluate Sustained release tablets of Tramadol Hydrochloride by employing HPMC E5, Ethyl Cellulose N20, Ethylcellulose 7 premium, Polyethylene glycol as rate retarding polymers in various combinations and proportions.

MATERIALS AND METHODS

Materials:

Materials used in the experiment were Tramadol HCl (Bal Pharma, Hyderabad), Hydroxypropyl Methylcellulose E5 (Colorcon Asia, Goa), Ethylcellulose N20 (Ming Tai Chemical co. Ltd., Taiwan), Ethylcellulose 7 premium (Colorcon Asia, Goa), Polyethylene glycol (FMC Bio polymer,India), Polyvinylpyrrolidone K-30 (International Fine Chemicals, India), Micro crystalline cellulose (S.D. Fine Chem Ltd,India), Lactose (S.D. Fine Chem Ltd,India), Isopropyl Alcohol (Luzenac Pharma,India), Dichloro methylene (Merck Pvt. Ltd,India), Talc (Rankem, India), Hydrochloric acid (Merck Pvt. Ltd,India), Magnesium stearate(S.D. Fine Chem Ltd,India).

Compatibility studies:

Method: The drug-excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR). Drug and excipients in 1:1 ratios were mixed and stored in glass vials at 50^0C for 30 days. The samples were analyzed for compatibility by IR studies in the methods described.

Fourier Transform Infrared Spectroscopy (FT-IR)

Fourier-transform infrared (FTIR) spectroscopy was performed on each of the samples to determine the structure of the organic compounds and to identify the presence of specific functional groups within a sample. Furthermore, drug-polymer **1:1** interactions were examined using the resulting spectra. Spectra are obtained by passing infrared radiation through a sample and determining what fraction of incident radiation is absorbed at a particular energy. The energy of a peak in the spectrum corresponds to the frequency of vibration of part of the sample compound. 3-5 mg of composite sample was added to approximately 100 mg of KBr. The mixture was then ground to a fine powder using a mortar and pestle, and transparent discs were formed using a pellet press. The discs were then placed in the FTIR spectroscopy apparatus, and spectra were collected. The range of the collected spectra was 4000-500cm^{-1}.

Method of Preparation of SR Tablets of Tramadol HCl:

Tramadol SR tablets were prepared by wet granulation method [3]. Weigh accurately all the ingredients as shown in **Table.1** and pass drug and excipients through #40 sieve and then transferred into RMG (Rapid mixer granulator), mix it for 10 min. Add previously prepared binder solution (PVP K30+ Purified water) slowly to granulator containing mixture with appropriate speed of impellor and chopper to obtained granules. Dry the granules at room temperature till the solvent was evaporated. Dry the semi-dried granules at 45ºC till the required LOD are achieved. Magnesium stearate passes and talc was added finally. Compression was done by using 16 station tablet compression machine of 9.5mm punches [4]. The obtained tablets were coated with sustained release polymers.

Coating Procedure:

Preparation of coating solution:

Isopropyl Alcohol (IPA) filtered through 200 nylon mesh cloth and collected in a container.IPA and Dichloro methylene were added to HPMC E5, Ethyl cellulose N 20, Ethyl cellulose 7 premiums and polyethylene glycol separately and mixed well through sonicator for 15min[5].

Coating process:

Load the core tablets into the coating pan and proceed for coating with set the process parameters as mentioned in below table. Coating process is continued to achieve desired mass build up. After completion of spraying dry the tablets in pan for required time.

Film Coating Process Parameters

S.NO	PROCESS PARAMETERS	RANGE
1.	Inlet temperature	52-56^{0}C
2.	Product temperature	30-40^{0}C
3.	Exhaust temperature	43-46
4.	Pan RPM	11
5.	Atomization	2.0
6.	Spray speed(rpm)	4-6

Table.1 Formulation of Tramadol HCl tablets

INGREDIENTS (Mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Tramadol HCl	100	100	100	100	100	100	100	100	100	100
Microcrystalline cellulose PH101	60	70	80	90	100	110	120	130	140	150
Lactose	115	105	95	85	75	65	55	45	35	25
PVP K 30	15	15	15	15	15	15	15	15	15	15
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
COATING										
HPMC E 5	30	__	__	__	15	15	15	__	__	__
Ethyl cellulose N 20	__	30	__	__	15	__	__	15	15	__
Ethyl cellulose 7 premium	__	__	30	__	__	15	__	15	__	15
Polyethylene glycol	__	__	__	30	__	__	15	__	15	15
Dichloro Methylene	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight	330	330	330	330	330	330	330	330	330	330

EVALUATION OF SR TABLETS OF TRAMADOL HCL:

Pre Compression Studies [6, 7]**:**

Angle of repose:

The angle of repose of powders was determined by the funnel method. Accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was calculated by using the given formula and the results were tabulated in Table.4.

$$\tan\theta = \frac{h}{r}$$

Where,

h = height of the powder cone

r = radius of the powder cone

Bulk density and tapped density:

A quantity of 4gms of powder from each formula was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was tapped continuously until no further change in volume was observed. Then bulk density (BD) and tapped density (TD) were calculated by using the given formula and the results were tabulated in Table.4.

$$BD = \frac{\text{Weight of the powder}}{\text{Initial volume}}$$

$$TD = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

Carr's index:

The Compressibility of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which it is packed.The formula for carr's Index is given below and the results were tabulated in Table.4.

$$\text{Carr's index } (\%) = \frac{TD - BD}{TD} \times 100$$

Hausner's ratio:

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by using the given formula and the results were tabulated in Table.4.

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

Post Compression Studies [8, 9]**:**

Thickness:

Tablet thickness can be measured using digital vernier calipers. 3 tablets were taken and their thickness was measured and the average thickness for each tablet was calculated. The results were tabulated in Table.5 & 6.

Hardness:
It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using monsanto hardness tester. An average of three observations is reported. The results were tabulated in Table.5 & 6.

Friability test:
Friability of the tablets was determined using Roche friability. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Conventional tablets that lose less than 1% of their weight are acceptable. The results were tabulated in Table.5 & 6.

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight variation:
The weight variation test is done by weighing 10 tablets individually, calculating average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.The results were tabulated in Table.5 & 6.

$$\%\ \text{Weight variation} = \frac{\text{Average weight} - \text{Initial weight}}{\text{Average weight}} \times 100$$

Drug content
Five tablets were taken and powdered; the powder equivalent to 10 mg of tramadol was dissolved in 100 ml of 0.1 M HCl of p^H 1.2, filtered, diluted suitably to 10mcg/ml concentration and analyzed at 271 nm using UV-Visible spectrophotometer. The results were tabulated in Table.7.

***In vitro* dissolution studies** [10, 11]**:**
In vitro dissolution studies of tramadol HCl tablets were conducted with the USP type II apparatus. The dissolution studies were performed using 900 ml of 0.1 M HCl of p^H 1.2 as dissolution medium at 37±0.5°C with 75 rpm speed. A tablet of each formulation containing 100 mg of drug was added into the dissolution medium. The sample of 10 ml aliquots were withdrawn at regular intervals and filtered. The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The filtered solutions were diluted and analyzed for their drug release by using UV spectrophotometer at wavelength of 271 nm. Percentage of drug dissolved was calculated by plotting time on X- axis against percent cumulative drug release on Y-axis.The results were tabulated in Table.8 and Figure.7.

Drug release kinetics of the selected formulation [12]**:**
The release kinetics and curve fitting was studied using an MS- Excel based software program.

STABILITY STUDIES [13, 14]**:**
Stability studies of pharmaceutical products were done as per ICH guide lines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. Selected formulations were stored at different storage conditions at elevated temperatures such as 25oC± 20C / 60% ± 5% RH, 300C ± 20C / 65% ±5% RH and 400C ± 20 / 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of 30 days and checked for physical changes, hardness, friability, and Percent cumulative drug release

RESULTS AND DISCUSSION

Table.2 Preformulation Study of Active Pharmaceutical Ingredient

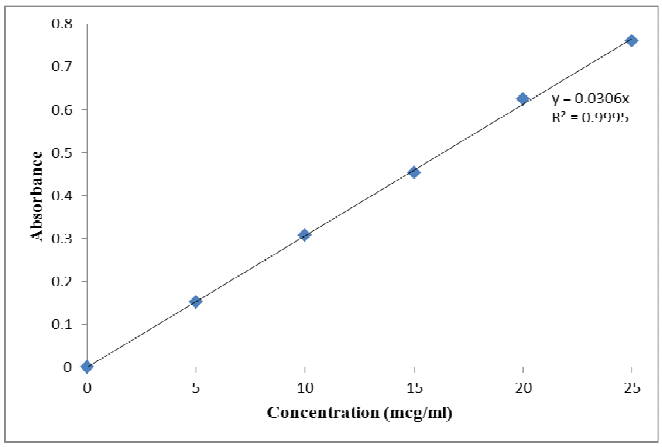
S.No	Characteristics	Results
1	Physical appearance	A white (or) almost white powder, odorless.
2	Solubility	Sparingly soluble in water and soluble in Methanol, practically soluble in Methylene chloride.
3	Bulk density	0.72gm/ml
4	Tap density	0.84gm/ml
5	Compressibility index	14.28%
6	Melting point	180-184^{0}C
7	Molecular weight	299.84.

Calibration Curve of Tramadol HCl

Table.3 Standard curve data of Tramadol HCl using 0.1 M HCl of pH 1.2

Concentration (mcg/ml)	Absorbance
5	0.152
10	0.308
15	0.453
20	0.624
25	0.760

Figure.1 Standard curve of Tramadol HCl in 0.1 M HCl of pH 1.2



Compatibility Studies

Figure.2 FTIR spectrum of Tramadol HCl

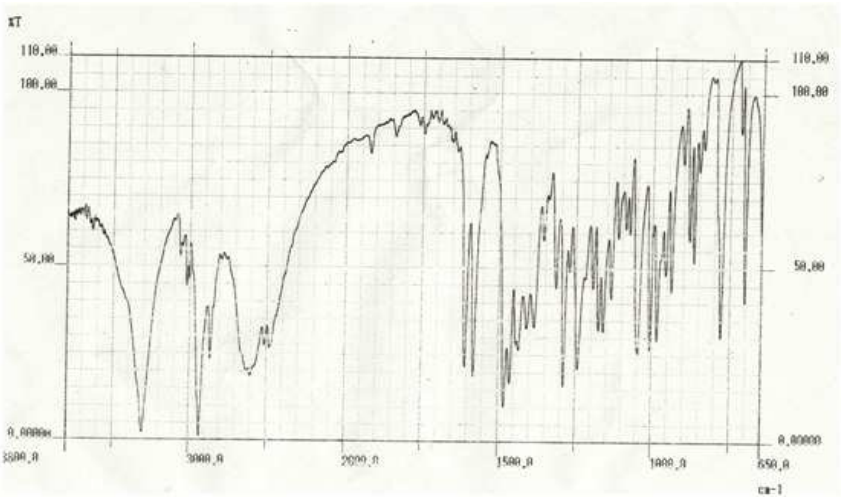


Figure.3 FTIR spectrum of Tramadol HCl + EC N20

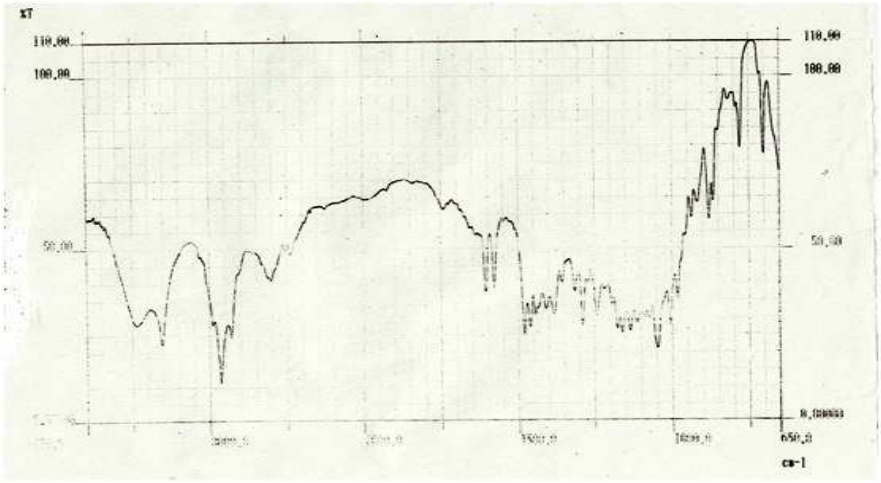


Figure.4 FTIR spectrum of Tramadol HCl + PEG

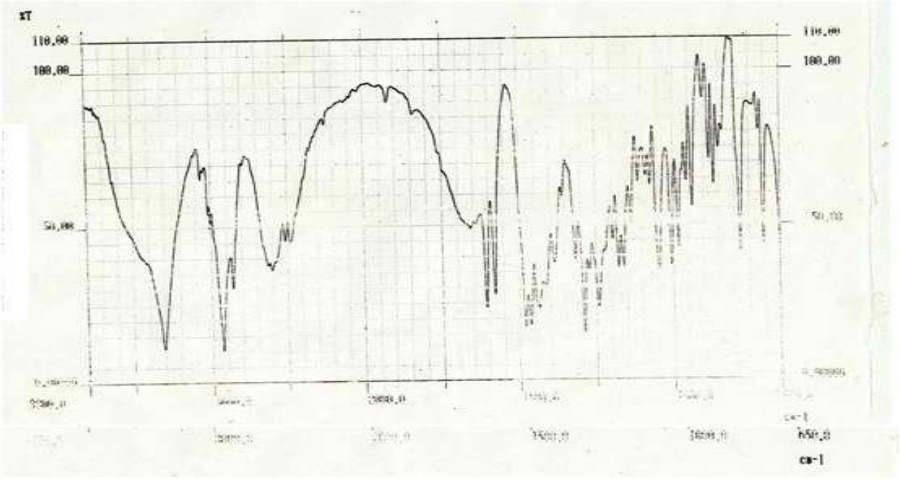


Figure.5 FTIR spectrum of Tramadol HCl + HPMC E5

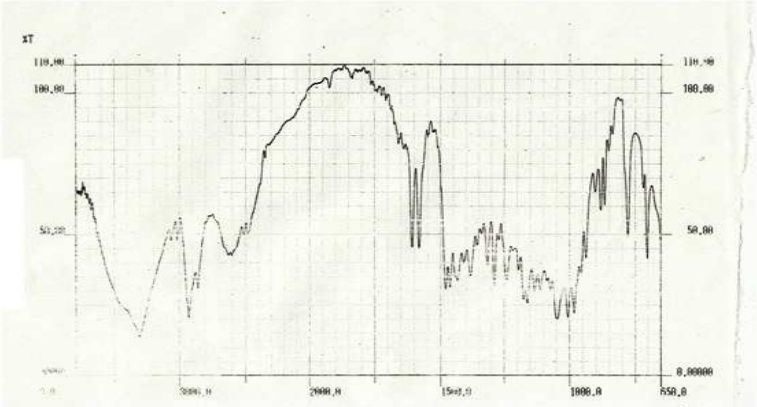
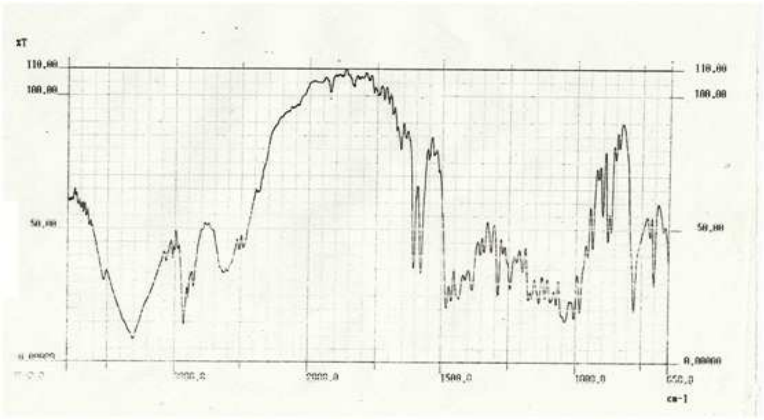


Figure.6 FTIR spectrum of Tramadol HCl + EC 7 Premium



There is no much sifting of principal peaks in physical mixtures when compared to pure drug Tramadol HCl .FTIR spectra revealed that there was no interaction between the drug and the polymers used for the formulation of sustained release tablets.

Precompression Studies

Table.4 Physical parameters of powder blend

S.No	Formulation code	Angle of Repose (θ)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Hausner's ratio
1	F1	29.51	0.71	0.84	15.47	1.181
2	F2	27.41	0.74	0.86	14.28	1.176
3	F3	27.32	0.73	0.85	14.11	1.196
4	F4	26.93	0.71	0.82	13.41	1.216
5	F5	28.14	0.72	0.85	15.29	1.193
6	F6	25.85	0.75	0.85	11.76	1.197
7	F7	26.06	0.79	0.87	16.47	1.216
8	F8	27.40	0.76	0.90	17.77	1.186
9	F9	28.68	0.74	0.87	16.01	1.193
10	F10	27.97	0.79	0.83	16.25	1.211

The bulk density of all formulations, powder blend containing excipients was found to be in the range of 0.71 to 0.79 gm/ml, whereas the tapped density was observed between 0.82 to 0.90 gm/ml. From the values of bulk density and tapped density the values for compressibility index and hausner's ratio were calculated. The values for compressibility index were found between 11.76to 17.77 %. The values for hausner's ratio were found in between 1.176 to1.216. All these values are within the specified limit which indicates good flow properties. Angle of repose was found to be less than 30 which indicate good flow of powder. Overall these values indicate good flow properties of powder blend, uniform die fill and better compression ability.

Post Compression Studies

Table.5 Physical parameters of Tramadol HCl uncoated tablets

Formulation code	Weight(mg)± SD (n = 20)	Thickness (mm)± SD (n=10)	Hardness (kg/cm^2) ± SD (n=5)	% Friability
F1	300.12± 0.52	4.32± 0.54	5.9± 0.13	0.328
F2	302.24± 0.84	4.25± 0.78	5.6± 0.80	0.341
F3	303.64± 0.23	4.19± 0.15	5.2± 0.60	0.874
F4	300.82± 0.08	4.11± 0.17	4.9± 0.31	0.354
F5	296.77± 0.07	4.06± 0.64	4.6± 0.14	0.541
F6	297.85± 1.02	4.01± 0.73	4.3± 0.09	0.120
F7	299.64± 0.23	3.94± 0.15	4.1± 0.60	0.874
F8	301.82± 0.08	3.77± 0.17	3.9± 0.31	0.354
F9	303.77± 0.07	3.46± 0.64	3.7± 0.14	0.541
F10	307.85± 1.02	3.29± 0.73	3.5± 0.09	0.120

The weight of tablets of all formulations was found to be in range of 296.77 to 307.85.Hardness test for all formulations was carried out and observations obtained were in the range of 3.5 to 5.9 kg/cm^2. Hardness for all formulations was observed to be proper, which signify that crushing strength of all formulations was maintained

after direct compression. The thickness of all formulations was found to be in the range of 3.29 to 4.32 mm. Friability test was conducted for all formulations, % friability was found to be in the range of 0.120 to 0.874. Friability test for all formulations indicated that % friability was less than 1%, which showed the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation.

Table.6 Physical parameters of Tramadol HCl coated tablets

Formulation code	Weight(mg)± SD (n = 20)	Thickness (mm)± SD (n=10)	Hardness (kg/cm^2) ± SD (n=5)	% Friability
F1	330.12± 0.52	5.32± 0.54	6.5± 0.13	0.318
F2	332.24± 0.84	5.35± 0.78	6.1± 0.80	0.321
F3	333.64± 0.23	5.43± 0.15	5.8± 0.60	0.834
F4	330.82± 0.08	5.39± 0.17	5.3± 0.31	0.345
F5	326.77± 0.07	5.26± 0.64	5.0± 0.14	0.511
F6	329.85± 1.02	5.32± 0.73	4.8± 0.09	0.220
F7	329.64± 0.23	5.41± 0.15	5.3± 0.60	0.814
F8	331.82± 0.08	5.29± 0.17	4.8± 0.31	0.364
F9	333.77± 0.07	5.46± 0.64	5.1± 0.14	0.501
F10	337.85± 1.02	5.31± 0.73	4.5± 0.09	0.217

The weight of tablets of all formulations was found to be in range of 326.77 to 337.85.Hardness test for all formulations was carried out and observations obtained were in the range of 4.5 to 6.5 kg/cm^2. Hardness for all formulations was observed to be proper, which signify that crushing strength of all formulations was maintained after direct compression. The thickness of all formulations was found to be in the range of 5.26 to 5.46 mm. Friability test was conducted for all formulations, % friability was found to be in the range of 0.217 to 0.834. Friability test for all formulations indicated that % friability was less than 1%, which showed the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation.

Drug Content

Table.7 Drug content of all formulations

S.No	Formulation code	Drug content
1	F1	97.05
2	F2	95.05
3	F3	95.59
4	F4	94.99
5	F5	99.12
6	F6	93.45
7	F7	92.12
8	F8	94.38
9	F9	94.45
10	F10	96.98

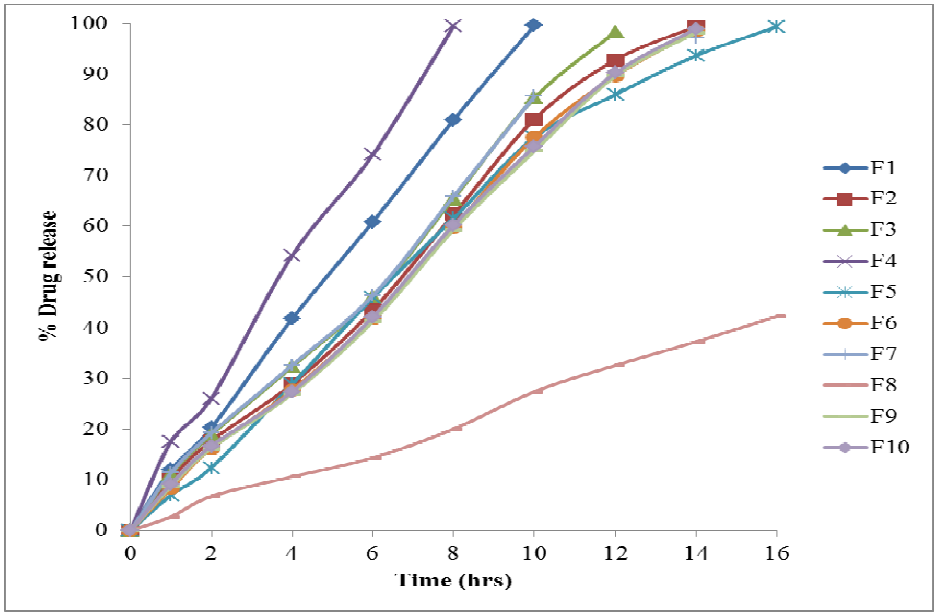
Drug content of all formulations was observed between 92.12 to 97.05%. Drug content for all formulations showed uniformity which indicated that there was uniform flow and uniform distribution of drug.

Dissolution of Tramadol HCl Film Coated Tablets

Table.8 Dissolution data of Tramadol HCl film coated tablets

S. No.	Time (hrs)	% Cumulative drug release									
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
1	1	11.93	10.17	11.05	17.51	6.94	8.26	11.34	2.68	8.70	9.14
2	2	20.23	17.70	18.89	26.02	12.36	16.22	19.19	6.72	16.22	16.67
3	4	41.75	28.87	32.28	54.21	28.82	27.68	32.58	10.59	26.94	27.39
4	6	60.87	43.50	46.04	74.14	45.95	41.85	46.34	14.34	41.26	42.15
5	8	80.99	62.34	65.49	99.50	61.56	59.80	65.94	20.03	59.35	60.25
6	10	99.63	81.14	85.33		77.54	77.55	85.64	27.38	74.88	75.78
7	12		92.80	98.27		85.94	89.63	97.02	32.54	89.61	9220.
8	14		99.38			93.65	98.51		37.22	98.19	98.95
9	16					99.39			42.24		

Figure.7 Dissolution profile of Tramadol HCl film coated tablets



After 16th hour the percentage drug release from the F5 formulation was 99.39%.The Tramadol HCl from formulations with Ethylcellulose7 is comparatively lower than the one with Ethyl cellulose N20, due to the fact that EC N20 is more viscous and release retarding capacity is more when compared to EC 7.

Drug Release Kinetics

Table.9 Correlation coefficient (r) & rate constant (k) values of Tramadol HCl film coated tablets

Kinetic model		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
First order	r	0.977	0.983	0.978	0.991	0.968	0.969	0.977	0.949	0.929	0.939
	k	0.376	0.276	0.308	0.578	0.242	0.248	0.309	0.239	0.239	0.288
Hixon-crowell	r	0.997	0.997	0.996	0.994	0.998	1	0.996	0.997	0.999	0.999
	k	0.330	0.244	0.270	0.456	0.217	0.230	0.270	0.053	0.225	0.234
Zero order	r	0.999	0.998	0.999	0.998	0.999	0.999	0.999	0.998	0.999	0.999
	k	10.291	8.85	9.445	13.182	7.852	8.11	9.595	3.36	8.11	8.335
Higuchi	r	0.991	0.998	0.990	0.999	0.986	0.974	0.991	0.965	0.981	0.983
	k	32.40	29.013	29.640	34.986	28.268	28.514	29.672	10.356	28.208	28.404
Peppas	r	0.998	0.999	1	0.993	0.998	0.998	1	0.996	0.998	0.998
	k	0.937	0.904	0.893	0.858	1.073	0.963	0.884	1.080	0.941	0.926
DE 30		41.19	31	33.4	52.15	29.38	29.4	33.72	10.57	29.07	29.6
DE 90		43.41	54.09	50.1	36.87	51.23	51.99	50.35	18.69	51.36	52
T 50		4.84	6.53	6.13	3.70	6.59	6.78	6.09	0.00	6.85	6.75
T 90		9.02	11.52	10.6868	7.20	13.05	12.08	10.65	0.00	12.09	11.97

Tramadol hydrochloride tablets were prepared by wet granulation method. *In-vitro* dissolution studies were conducted for Tramadol HCl film coated tablets for 16 hrs.The results were shown in Table No.18 and Figure No.12. Out of 10 formulations F5 containing HPMC E5 and Ethyl cellulose N 20 in 1:1 ratio as a film former showed sustained action for 16 hrs.

The dissolution parameters such as dissolution efficiency (DE) at 30 and 90 percent were increased proportionately. Half-life of drug *i.e.*, T_{50} was found to be 4.84, 6.53, 6.13, 3.70, 6.59, 6.78, 6.09, 6.85 and 6.75 hrs for F1, F2, F3, F4, F5, F6, F7, F9 and F10 formulations respectively. Shelf-life of the drug *i.e.*, T_{90} was found to be 9.02, 11.52, 10.68, 7.20, 13.05, 12.08, 10.65, 12.09 and 11.97 hrs for F1, F2, F3, F4, F5, F6, F7, F9 and F10 formulations respectively. The drug releases data of Tramadol HCl film coated tablets have treated with different kinetic models are shown in Table No.19. The drug release patterns of Tramadol HCl film coated tablets had followed the zero order kinetic model predominantly followed by surface erosion. This release patterns are evident with the correlation coefficient 'r' values which are nearer to 1. F5 is considered as optimized this may be it contains both hydrophilic and hydrophobic nature excipients as film former.

Drug Release Kinetics for Optimized Formulation (F5)

Table.10 Data for representing different kinetic models

Zero order		First order		Higuchi		Peppas		Hixson-Crowell	
Time	%cumulative drug release	Time	Log % drug remaining	Square root of time	% cumulative drug release	Log time	Log %cumulative drug release	Time	Cube root of % drug remaining
1	6.94	1	1.968	1	6.94	0	0.841	1	4.531
2	12.36	2	1.942	1.414	12.36	0.301	1.092	2	4.441
4	28.82	4	1.852	2	28.82	0.602	1.459	4	4.144
6	45.95	6	1.732	2.449	45.95	0.778	1.662	6	3.78
8	61.56	8	1.584	2.828	61.56	0.903	1.789	8	3.374
10	77.54	10	1.351	3.162	77.54	1	1.889	10	2.821
12	85.94	12	1.147	3.464	85.94	1.079	1.934	12	2.413
14	93.65	14	0.802	3.741	93.65	1.146	1.971	14	1.851

Figure.8 Zero order plot for optimized formulation (F5)

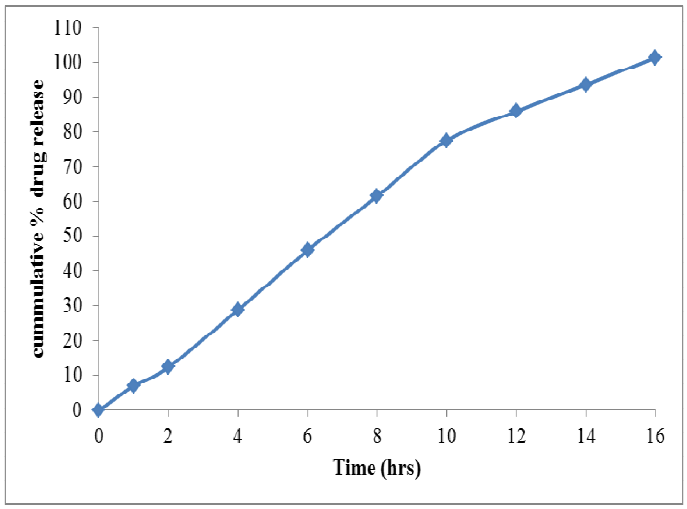


Figure.9 First order plot for optimized formulation (F5)

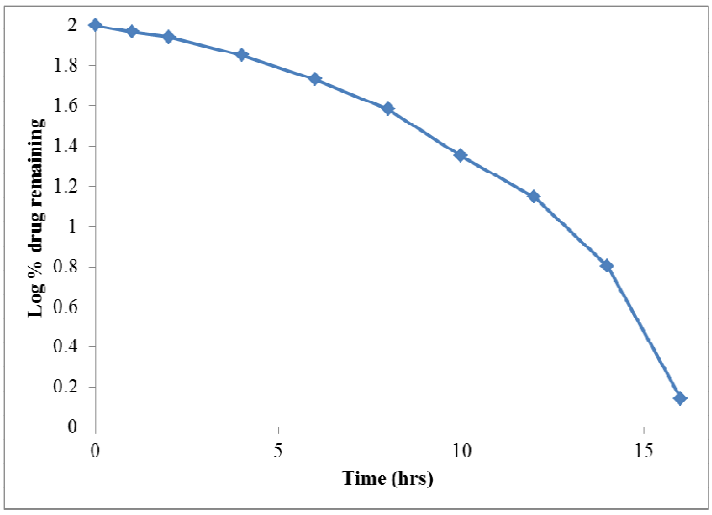


Figure.10 Higuchi plot for optimized formulation (F5)

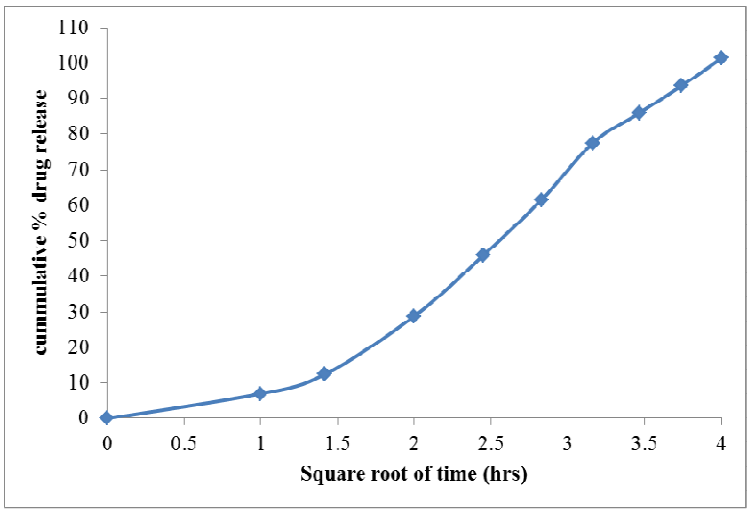


Figure.11 Peppas plot for optimized formulation (F5)

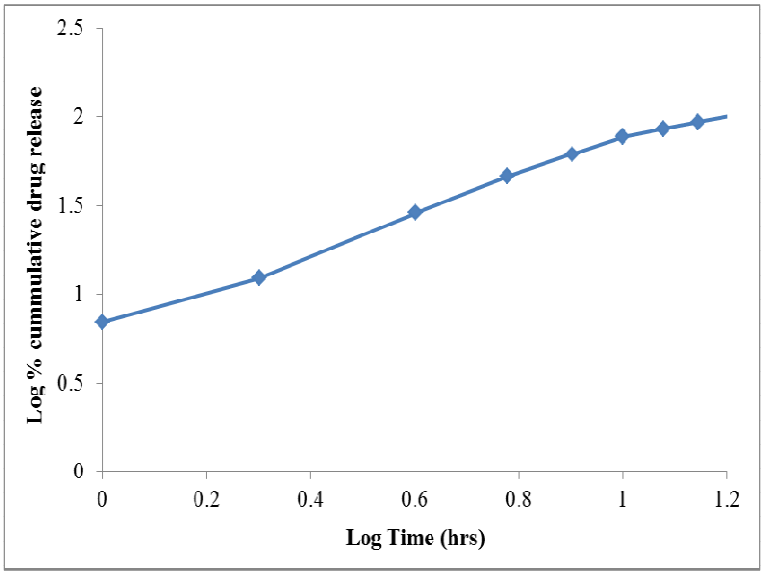
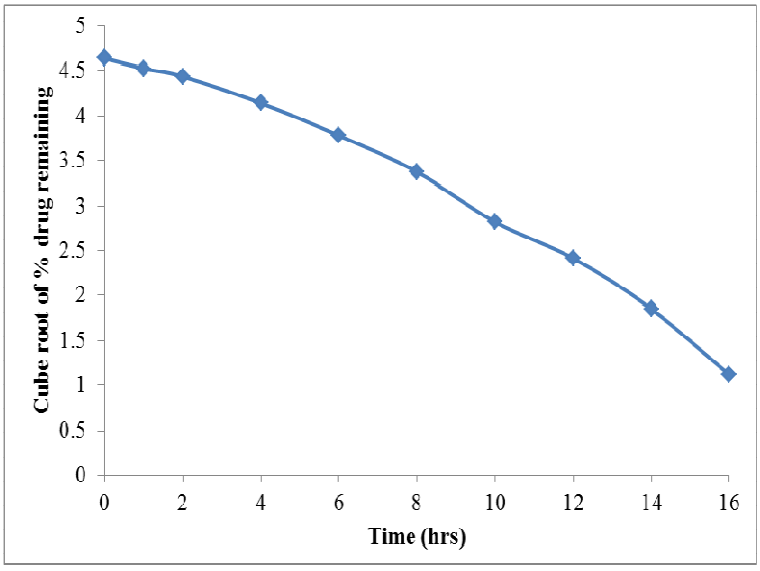


Figure.12 Hixson-crowell plot for optimized formulation (F5)

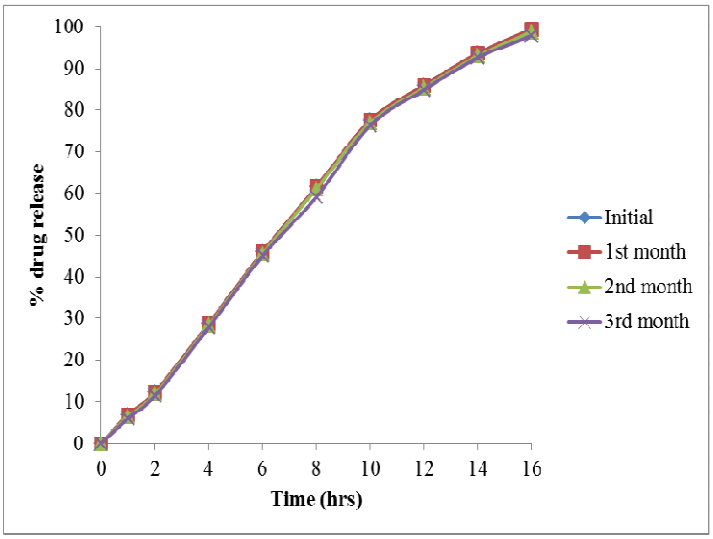


Stability Studies

Table.11 *In-vitro* dissolution data of optimized formulation (F5)

S. No.	Time (hrs)	Percent cumulative drug release			
		Initial	1st month	2nd month	3rd month
1	1	6.94	6.94	6.50	6.06
2	2	12.36	12.36	11.91	11.47
3	4	28.82	28.82	28.37	27.92
4	6	45.95	45.95	45.50	45.05
5	8	61.56	61.56	61.11	59.18
6	10	77.54	77.54	76.94	76.33
7	12	85.94	85.94	85.33	84.87
8	14	93.65	93.65	93.05	92.59
9	16	99.39	99.39	98.78	97.87

Figure.13 *In-vitro* dissolution profile of optimized formulation (F5)



The optimized F5 formulation is evaluated for *In-vitro* drug release studies after keeping the tablets at accelerated stability conditions (40^0C/75%RH) for 3 months. It is evaluated initially, 1 month and 3 months. *In-vitro* drug release studies were performed in 0.1 M HCl of pH 1.2 by using USP dissolution test apparatus-Type II, Rotating Paddle method. The results indicated that there was no significant change in *In-vitro* drug release studies. The data for *in-vitro* release profile was shown in Table.11and Figure.13.

CONCLUSION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain acts as a warning signal against disturbances either in the body or in the external environment of an individual. Pain arising from the skin and from the deep structure like muscles, bone and joints is also termed as somatic pain. This is generally caused by inflammatory reaction in the tissues. Tramadol acts as a μ-opioid receptor agonist, serotonin-nor epinephrine reuptake inhibitor (SNRI), NMDA receptor antagonist, 5-HT_{2C} receptor antagonist, $(\alpha 7)_5$nicotinic acetylcholine receptor antagonist and M_1 and M_3muscarinic acetylcholine receptor antagonist.

The present work aimed at developing sustained release tablets of Tramadol HCl by wet granulation method. FTIR studies showed no unacceptable extra peaks which confirm the absence of chemical interaction between the drug and polymers. Angle of repose, Carr's index and hausner's ratio values for all the formulations were within the range which indicates that tablets prepared were satisfactory for further studies. The percentage drug content of Tramadol was determined by extraction with methanol and analyzed by using UV-visible spectrophotometer at 271nm.After 16th hour the percentage drug release from the F5 formulation was 99.39%.The Tramadol HCl from formulations with Ethylcellulose7 is comparatively lower than the one with Ethyl cellulose N20, due to the fact that EC N20 is more viscous and release retarding capacity is more when compared to EC 7. Formulation F5 was identified to be the best as it showed sustained action for 16 hrs. The release mechanism was explored and explained with different kinetic equations, which indicates that tablets followed erosion mechanism for drug release.

The optimized formulation (F5) was kept at stability studies according to ICH guidelines for 3 months, which showed that the formulation was stable.

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REFERENCES

[1] Chien. Novel Drug Delivery Systems, Marcel Dekker, New York, **1992**, 2,307-315.
[2] YW. Chein. Controlled and modulated release drug delivery system, Encyclopedia of Pharmaceutical Technology, **1990**, 281 – 313.
[3] L. Lachman, HA. Lieberman, JL. Kanig, "The Theory and practice of Industrial pharmacy", Mumbai: Verghese publication house; **1987**,3,331-361.
[4] GM. Jantez, JR. Robinson, Sustained- and Controlled- release drug delivery systems, editors. Modern pharmaceutics., In: GS Banker, CT Rhodes, New York: Marcel Dekker Inc; **1996**, 3,115.
[5] H. Popli., SN. Sharma., *The Eastern Pharmacist* **1989**, 32,99-103.
[6] NG. Raghavendra Rao., et al. Gandhi sagar., *Ind.J.Pharm.Sci.*, 1, **2009**, 60-70.
[7] D. Indrajeet., H et al. Avinash, *Drug.Discov. Ther*, 3, **2009**, 176-180.
[8] SK. Singh, S. Singh, et al. Seth NR, *Int.J.Pharm.Tec.Resch*, 1, **2009**, 885-891.
[9] TarunParashar, Soniya, Vishal Singh, Gaurav Singh, Satyanand Tyagi, Chirag Patel, Anil Gupta, *International Journal of Research and Development in Pharmacy and Life Sciences*, **2013**,2,2,262-269.
[10] Corrigan, Owen and Healy Marie Anne, Surfactants in Pharmaceutical of Pharmaceutical Technology", edited by James SwarbrickInforma healthcare Inc., **2003,**3,3590.
[11] Priya.P, Sivabalan.M, Balaji.M, Rajashree.S, Muthu Dhanabakiam.H. *IJPBS*, **2013**, 3,310-326
[12] Pramod Kumar, Sanjay Singh, Brahmeshwar Mishra, *Acta Pharm.*, **2009**,59,15–30.
[13] B.Selvaraj, P.Malarvizhiand P.Shanmugapandiyan, *International Journal of Pharmacy and Pharmaceutical Sciences*, **2013**,5,966-971.
[14] Harish Gopinath, G Syam Prasad, ChAnjaneyulu, Syed Peer Basha, *Journal of Chemical and Pharmaceutical sciences*, **2012**,5,98-104.
[15] R. Gendle, B. Kaushik, S. Verma, R. Patel, S.K.Singh, K.P. Namdeo, *International Journal of ChemTech Research*, **2010**,2,1,4-10.