JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH

Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLET OF TRAMADOL HYDROCHLORIDE

Umesh Pant*, Dr. G. Gnanarajan and Prof.(Dr.) Preeti Kothiyal
Shri Guru Ram Rai Institute of Technology & Science,Division of Pharmaceutical Sciences Patel Nagar, Dehradun, Uttarakhand.
Corresponding Author Email: Umeshpant91@gmail.com

ABSTRACT

The present examination manages detailing of Tramadol hydrochloride Sustained release tables. Tramadol is a water dissolvable medication and is endorsed for three to four time multi day. Along these lines it is fundamental for the medication to build up a Sustained release dose frame with lessened danger of medication organization, reaction and patient consistence. The medication excipients similarity think about was done by Fourier Transform Infrared spectroscopy (FTIR) which uncovers no collaboration amongst tranquilize and excipients. Add up to are six batch were defined. Six detailing were set up by utilizing every polymer like Hydroxy propyl methyl cellulose (HPMC K4M) and MCCP. In the wake of settling the proportion of medication and polymer for control the arrival of medication up to wanted time. After the assessment of physical properties of tablet, the in vitro discharge think about was performed in 0.1 N HCL pH 1.2 for 8 hrs. The disintegration ponders it was obvious that the detailing (F3) indicated best and wanted medication discharge design i.e., 98.76 % in 8 hrs.

Key words: Hydroxy propyl methyl cellulose, Tramadol hydrochloride, Microcrystalline cellulose, kinetic study , stability studies.

INTRODUCTION

Sustained release dosage form is defined as "Any medication or dose shape change that drags out the restorative action of the medication". This conveyance framework is progressively being utilized as a part of the treatment of intense and ceaseless sicknesses as they keep up the centralization of medication in plasma over the base viable focus to and beneath the base poisonous level for an

expanded timeframe. Supported discharge, maintained activity, delayed activity controlled discharge, expanded activity, coordinated discharge, terminal and store measurements shapes are terms used to distinguish sedate conveyance framework that are intended to accomplish or drawn out helpful impact by persistently discharging prescription over a broadened timeframe after organization of a solitary dosage.[1-5]

Tramadol Hydrochloride is an opiod analgesic drug which draws attention in the treatment of osteoarthritis. It is a centrally acting drug and blocks the transmission of pain signals sent by nerves to the brain. It is freely soluble in water and hence becomes an ideal candidate for formulating extended release tablets. It is white or almost white crystalline powder in nature. Tramadol is a non-steroidal anti-inflammatory drug. It is used primarily to treat mild-severe pain, (both acute and chronic). Tramadol chemical name is (+) -trans-2-(Dimethyl amino methyl)-1-(m-methoxyphenyl) cyclohexanol. It is a synthetic pad of the amino cyclohexanol group, is a centrally acting analgesic with weak opoid agonist properties. It has two different mechanisms like first it binds to the μ-opioid receptor and Second, it inhibits the reuptake of serotonin and norepinephrine.[6-11]

Long term treatment with managed discharge Tramadol once every day is by and large safe in patients with osteoarthritis or obstinate low back torment and is very much endured. It can possibly give patients expanded control over the administration of their torment, less intrusions in rest, and enhanced consistence. The half-existence of a medication is around 5.5 hrs and the standard oral dose regimen is 50 to 100 mg each 4 to 6 hrs with a greatest measurements of 400 mg/day. To diminish the recurrence of organization and to enhance tolerant consistence, a supported discharge plan of Tramadol is produced. Managed discharge tablets touch base to crest focuses after 4.9 hrs and have a bioavailability of 87% to 95% gauge with capsules.[12-16]

MATERIAL AND METHOD

Materials:

Tramadol hydrochloride was obtained as Vaikunth Chemical pvt.ltd(Ahmedabad). Polyvinylpyrrolidone K30 (PVPK30), Hydroxypropyle methylcellulose (HPMC K_4M), MCCP (Dow chemical Ltd., Chennai), were selection as a dispersion base. Isopropyl alcohol was selected as a good solvent, (Fine chemical Ltd., Mumbai). All other solvent and reagents were of analytical grade.

Method:

Sustained release tablet of Tramadol hydrochloride was manufactured by wet granulation technique. Tramadol HCL, H.P.M.C., M.C.C.P, is passed through sieve no. #40. Mix well the ingredients together in RMG for 10 min. PVPK 30 dissolve in IPA of sufficient amount for the preparation of binder solution to form granules. After addition of binder solution, RMG is again operated for 3 min. For proper mixing wet granules mass is then passed through sieve no.#10. The granul was dried at 50- 55^{0}C for 2 hrs. dried granules were lubricated with aerosol, magnesium stearate and talc for 5 min. Tablet were manufactured using a tablet compression machine and the compressed tablet were coated (sustained released film coating).

Table 1: Composition of tablet formulation

Material	F1	F2	F3	F4	F5	F6
Tramadol hydrochloride	100	100	100	100	100	100
M.C.C.(Avicel 102)	150	145	140	135	130	125
H.P.M.C. K4M	60	65	70	75	80	85
P.V.P. K30	9	9	9	9	9	9
Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
Talcum powder	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2

Table 2: Composition of tablet coating

H.P.M.C. E-15	3	3	3	3	3	3
Titanium Dioxide	1	1	1	1	1	1
Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
Methylene chloride	q.s	q.s	q.s	q.s	q.s	q.s
Purified Talcum	1	1	1	1	1	1

PREFORMULATION STUDIES[17-19]

Preformulatin testing is the first step in the rationale development of dosage form of a drug. It can defined as an investigation of physical and chemical properties of drug substances, alone and when in combined with expients. The overall objectives of the preformulation testing is to generate information useful to the formulation in development stable and bioavilability dosage form which can be mass produced.

The goals of preformulation studies are:

i. To establish the necessary physiochemical characteristics of a new drug subsrances.
ii. To determine its kinetic release rate profile.
iii. To establish it's compatibility with different excipients.

Here, the following parameters were selected for the preformulation studies for the pure drug.

Identification tests

Organoleptic characteristics

The colour, odour, and taste of the drug were characterized and recorded.

Solubility analysis

Preformulation solubility analysis was done to select suitable solvent system to dissolve the drug as well as various excipients used for formulation and also to test drug solubility in the dissolution medium, which was to be used.

Melting point determination

Melting point of Tramadol hydrochloride was determination by capillary method. Fine powder of Tramadol HCL was filled in capillary tube (previously sealed at one end). The capillary tube inserted in sample holder of melting point apparatus and a thermometer was also placed in the apparatus. The temperature at which powder melted was noticed.

Infra red spectroscopy

The IR absorption spectrum of Tramadol hydrochloride was determined by Fourier Transform Spectrophotometer using KBr dispersion method. The IR spectrum of the obtained sample of drug was compared with the standerd IR spectra of the pure drug.

Compatibility studies of Tramadol hydrochloride and polymers

The FTIR spectroscopy study was carried out separately to confirm the identity of the drugs and the physical mixture of polymers used for the preparation of sustained released tablet. This study was carried out to detect any changes in chemical constitution of drugs after combining it with excipients. The FT-IR was preformed for drug and physical mixture of drug and polymer.

The IR spectra of drug with polymer were compared with the standard IR spectrum of the pure drug. In the technique 1mg of sample and 100 mg of potassium bromide was finely ground using mortar and pestle. A small amount of mixture was kept in the sample holder and scanned form 4000 cm^{-1} to 400 cm^{-1} in Shimadzu FT-IR spectrophotometer.

Bulk density:[20-21]The granular powder weighing 50 gram is placed in 250 ml measuring cylinder. Volume occupied by the powder was noted without disturbing the cylinder and bulk density was calculated by the following equation.

ρb = M / V

Where, ρb = bulk density,

M = weight of powder,

V = volume powder.

Tapped density: Weigh 50 gram of granular powder and placedin a 250 ml measuring cylinder. The cylinderwas then subjected for the fixed number oftaps (100) until the powder bed has reachedthe minimum. The final volume was recordedand the tap density is calculated by followingequation.

ρt = M / Vt

Where, M = Mass of the Powder ,

Vt = Tapped volume of the powder.

Angle of repose: For determining angle of repose a funnel was mounted on a stand at a fixed height and a fix weighed quantity of each blend was poured through the funnel. The height and the base diameter of the pile was noted and angle of repose was calculated as:

Angle of repose = $\tan^{-1}$ (H/ r)

H = height of the pile (cm),

r = radius of heap (plane surface occupied by the powder)

Table 3: Angle of repose

Sr.NO.	Angel of repose	Type of flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Compressibility index: The simplest method of measurement of freeflow of powder is compressibility, anindication of the ease with which a materialcan be induced to flow is given bycompressibility index which is calculated asfollows.

% compressibility (I) = ρt – ρb / ρt × 100

Where, ρt = Tapped density ,

ρb = Bulk density.

The value below 15% indicates a powder which usually gives rise to excellent flow properties, whereas above 25% indicate poor flow ability.

Hausner's ratio (H): This is an indirect index of ease of powderflow. Lower Hausner's ratio **(<1.25)** indicates better flow properties than higher ones **(>1.25).**

It is calculated by the following formula.

Hausner's ratio = ρt / ρb

Where, ρb = Bulk density, ρt = Tapped density

Table 4: Flow Properties Corresponding to Compressibility Index and Hausner's Ratio

Flow character	Compressibility index (%)	Hausner's ratio
Excellent	<10	1.00-1.11
Good	11-15	1.12-1.18
Fair	16-20	1.19-1.25
Passable	21-25	1.26-1.34
Poor	26-31	1.35-1.45
Very poor	32-37	1.46-1.59
Very, very poor	>38	>1.60

EVALUATION OF SUSTAINED RELEASED TABLET

General appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot- to- lot uniformity and tablet- to- tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Size & Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micrometer or by other device. Tablet thickness should be controlled within a ±5% variation of standard value.

Organoleptic properties:

Colour distribution must be uniform with no mottling. For visual colour comparison compare the colour of sample against standard colour.

Weight Variation: Weight variation was calculated as per method descried in Indian Pharmacopoeia (I.P. 2007). 20 tablets were weighed individually and the average weight was calculated. The requirements are met if the weights of not more than 2 tablets differ by more than the percentage listed in Table and no tablets differ in weight by more than double that percentage.

Table 5 : Weight Variations Allowed as per I.P. 2007

Average weight of tablet (mg)	Percentage difference allowed
80 mg or less	±10
More than 80 mg but less that 250 mg	±7.5
250 mg or more	±5

Tablet hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester or Pfizer hardness tester. It is expressed in Kg/cm^2. 5 tablets were chosen randomly and tested for hardness.

Friability: Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 20 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes. The tablets were dedusted and weighed again. The percentage of weight loss was calculated again .

The percentage of weight loss was calculated using the formula.

% Friability = [(W1-W2)100]/W1

Where, W1= Weight of tablet before test (Initial Weight)

W2 = Weight of tablet after test (Final Weight).

Thickness: 20 tablet were taken randomly for this purpose, the tablet thickness were determined individually with the aid of a vernier caliper.

Content uniformity: In this test, 30 Tablets are randomly selected for the sample and at least 10 of them are assayed individually.

Nine of the 10 tablet must contain not less than 85% and more then 115% of the label drug content. The 10 tablet may not less than 75% or more than 125% of the labelled content. If these condition were not met. The tablet remaining form the 30 must be assayed individually, and none may fall outside of the 85% to 115% range. In evaluation a particular lot of tablet, several sample of tablet should be taken form various part of production run to satisfy statistical procedure.

Dissolution test (In-vitro dissolution study):

The release rate of Tramadol Hydrochloride SR tablet was determined using USP XXIV dissolution testing apparatus II (Paddle method). The in vitro release study was performed in 0.1 N HCL (pH

1.2) for 8 hrs. At every interval 10 ml of the solution was withdrawn form the dissolution apparatus at 1,2,4,6 and 8 hrs and sample were replaced with fresh dissolution medium to maintain the constant volume. The sample were filtered through a filter(0.45µ) and absorbance of these solution was measured at 270 nm Shimadzu 1700 in UV-Visible Spectrophotometer.

Study of Release Rate Kinetics from Dissolution Rate[22]

Various models were studied for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

Zero–order release kinetics were studied and release rate data were fitted to the following equation,

F = Ko t

Where, 'F' is the drug release at time't', and 'Ko' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics

The release rate data are fitted to the following equation,

Log (100-F) = kt

A plot of log cumulative percent of drug remaining to be released vs. time was plotted to study first order release.

Higuchi release model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

F = K t 1/2

Where, 'K' is the Higuchi constant.

In Higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$Mt/ M\infty = K\ en$

Where, $Mt/ M\infty$ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1,and for supercase II transport, n > 1. In this model, a plot of log ($Mt/ M\infty$) versus log (time) is linear.

STABLITY STUDIES[23]

The stability studies were as per the ICH guideline by keeping for optimized Sustained released tablet (F3) at $40^0C \pm 2^0C$ with 75±5% RH for 3 month in stability chamber and tablets were with drown at every month and tested for herdness, thickness, colour change, drug content and in –vitro drug release.

RESULT AND DISCUSSION

Table 6: Organoleptic properties

S.NO.	Properties	Result
1	Description	Solid (Crystalline powder)
2	Taste	Bitter
3	Odour	Odourless
4	Colour	White

Solubility analysis

Table 7: Result of solubility analysis of Tramadol Hydrochloride

S.NO.	Solvent	Solubility
1	Water	Freely Soluble
2	Methanol	Freely Soluble
3	Acetone	Very Slightly Soluble
4	0.1 N HCL	Soluble

Melting point determination:

Melting point of Tramadol hydrochloride was determined by capillary method. The melting point of Tramadol hydrochloride was found to be in the range of 180 ^{0}C -182^{0}C.The reported melting point is about 180^{0}C.

Table 8:

TEST	LIMITS	RESULT
Description	A white and almost white crystalline powder	A white crystalline powder
Solubility	Freely Soluble in water and methanol	Complies
Melting point	180^{0}C - 182^{0}C	180^{0}C
Identification	By I.R.	Complies
Water for K.F.R.	> 0.5%w/w	0.3519%
Sulphated ash residue	> 0.1% w/w	0.06% w/w
Assy (Anhydrous basis)	99.0% to 101.0%	99.52%

Drug – Polymer interaction study by FT-IR Spectrophotometer:

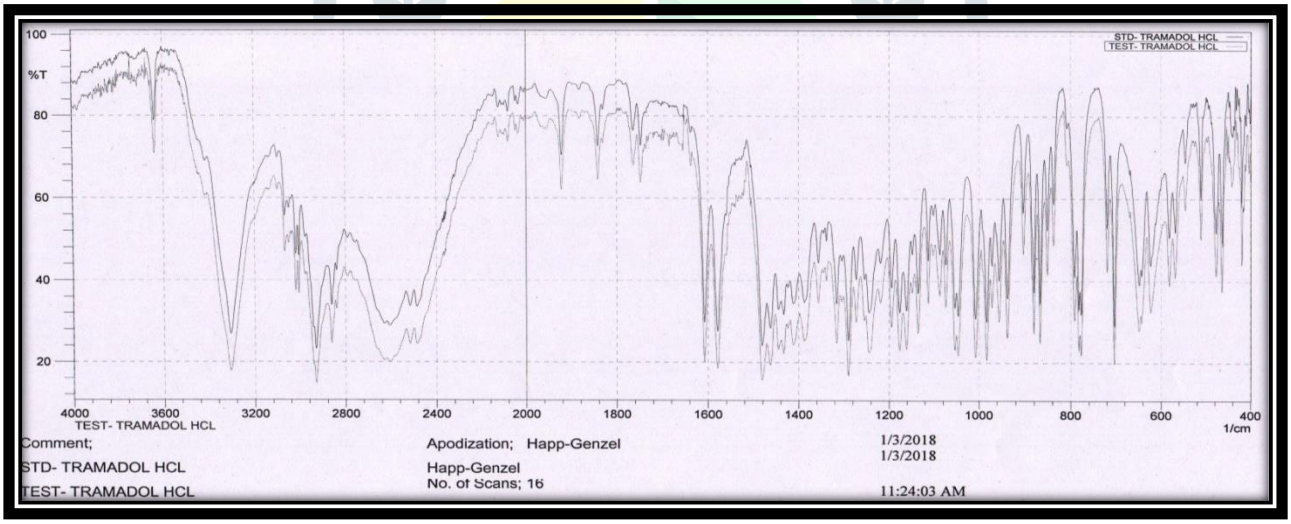

Figure 1: IR spectrum of Tramadol Hydrochloride

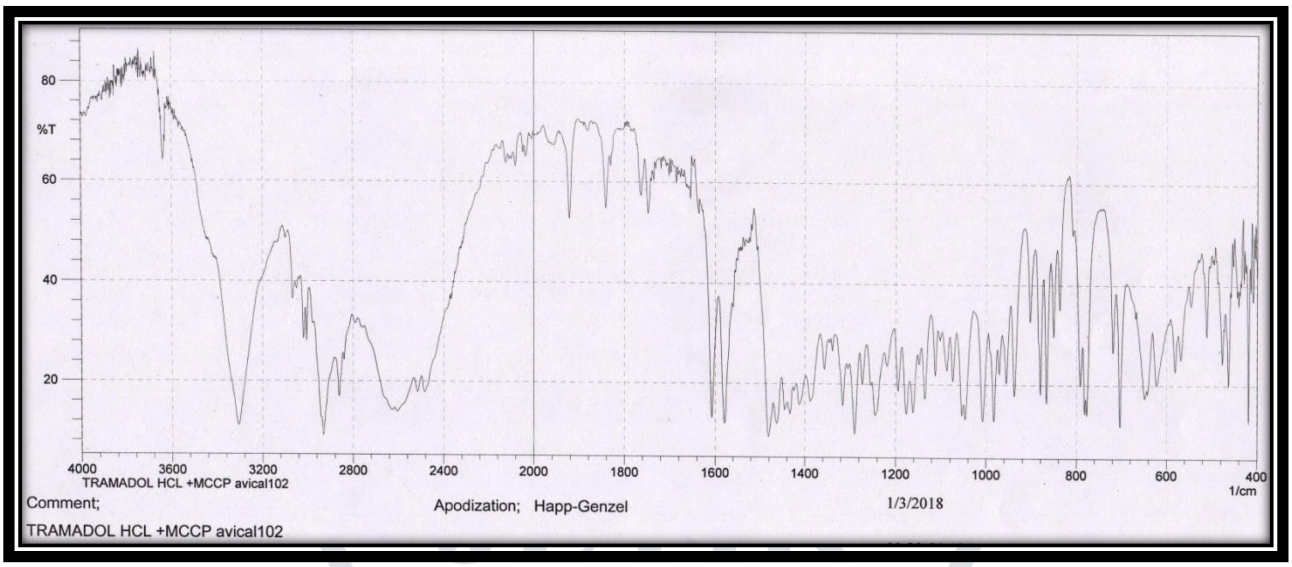

Figure 2: IR Spectrum of Tramadol HCL + MCCP 102

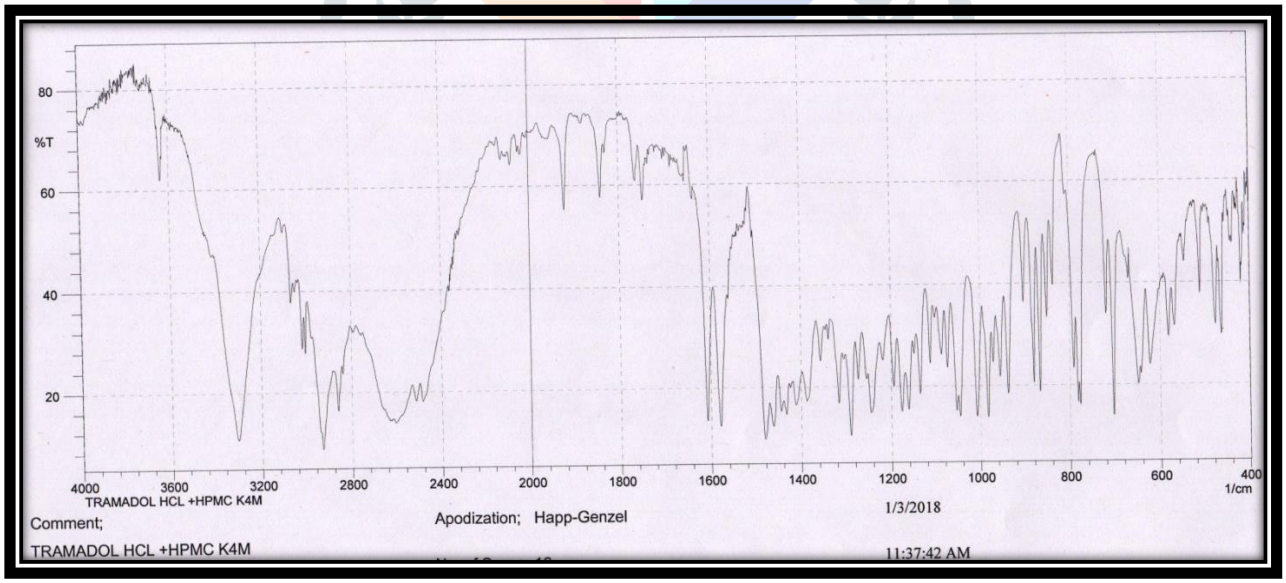

Figure 3: IR Spectrum of Tramadol HCL+ HPMC K4M

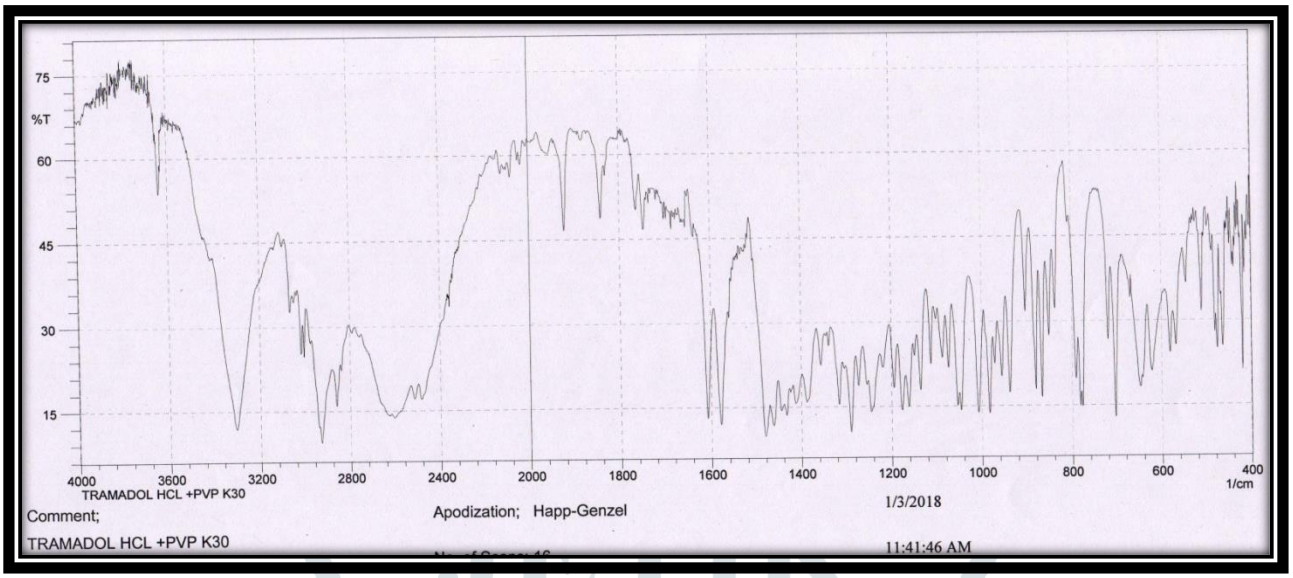

Figure 4: IR Spectrum of Tramadol HCL+ PVP K30

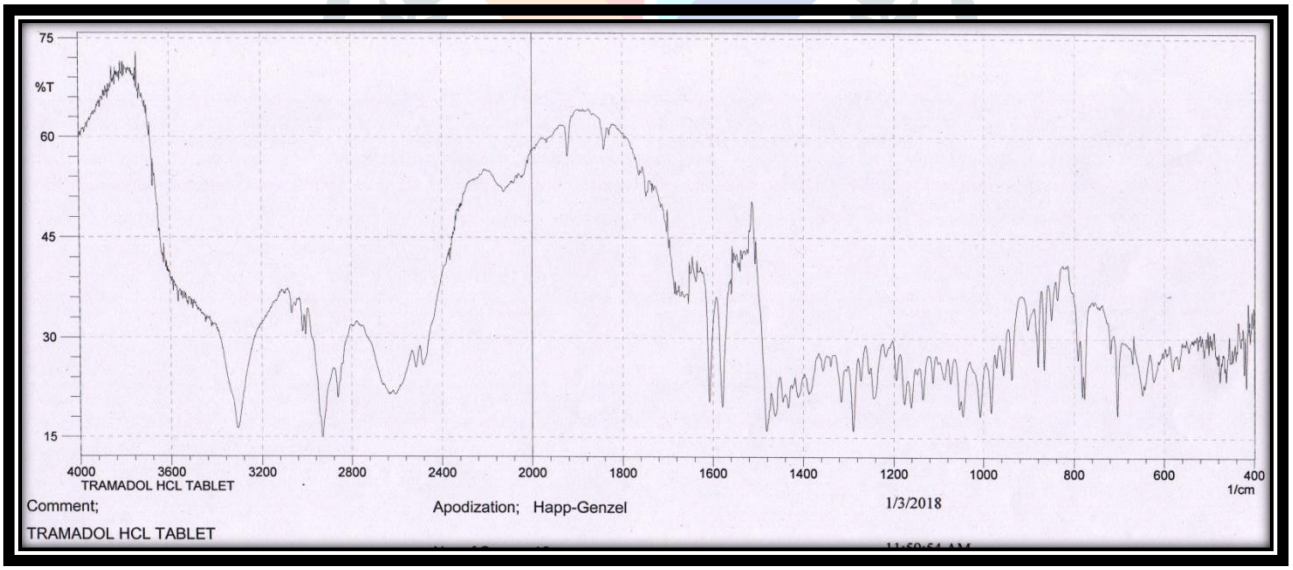

Figure 5: IR Spectrum of Tramadol HCL Tablet

ANALYTICAL METHODS DEVELOPMENT FOR TRAMADOL HYDROCHLORIDE BY UV- SPECTROPHOTOMETRY

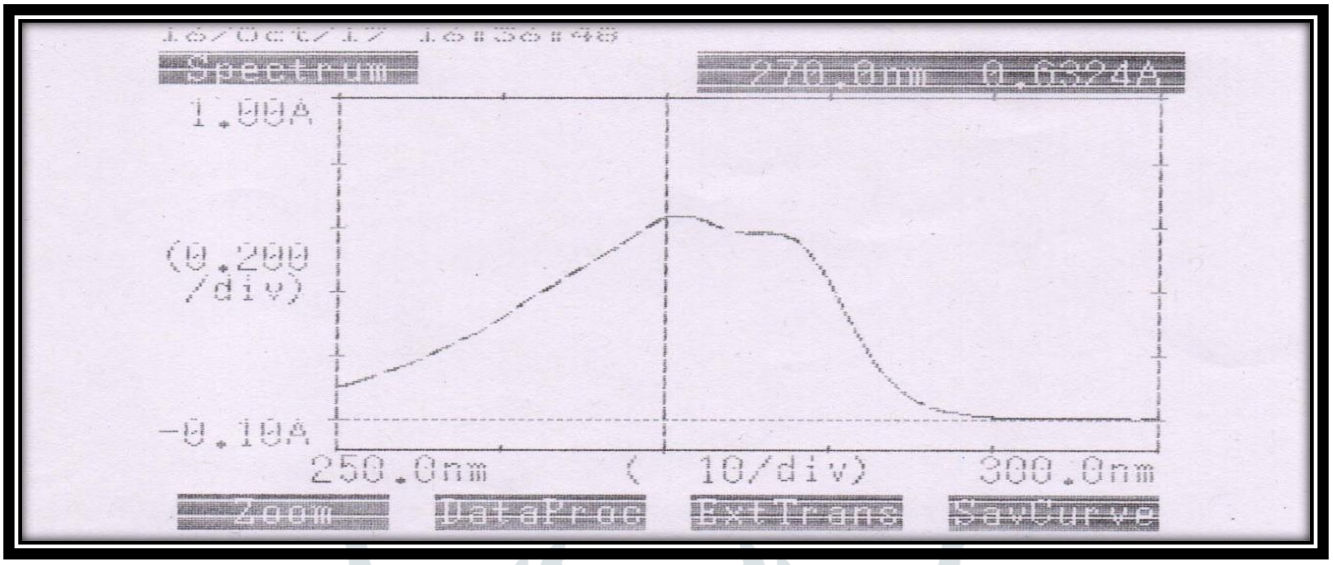

Figure 6: UV Spectrum of Tramadol Hydrochloride

Table 9: Wavelength of maximum absorption (λ_{max}) in Methanol

S.NO.	Name of drug	Solvent	λ_{max}
1	Tramadol HCL	Methanol	270

Table 10: Data for calibration curve of Tramadol Hydrochloride

S NO.	Conc.(µg/ml)	Absorbance (λ_{max}-270nm)
1	0	0
2	10	0.1621
3	20	0.2749
4	30	0.3991
5	40	0.5180
6	50	0.6421
7	60	0.7523
8	70	0.8652
9	80	0.9721

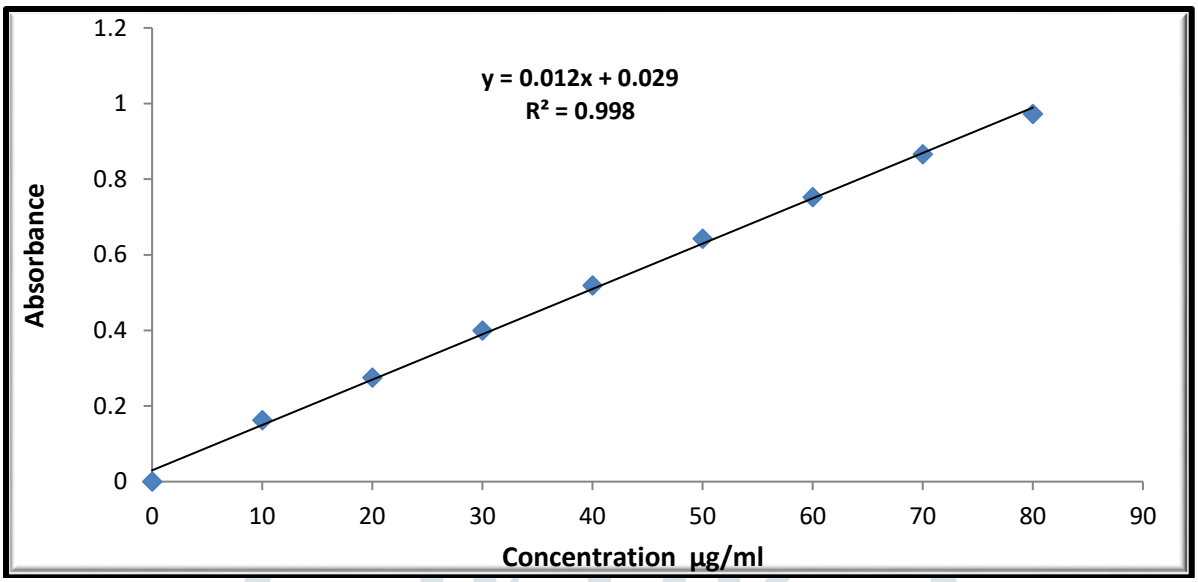

Figure 7:Standard curve of Tramadol HCL

Table 11: Result of Pre- formulation parameters of granules

Formulations	Parameters				
	Angle of repose	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio (%)
F1	27.47	0.362	0.435	16.78	1.20
F2	28.81	0.357	0.442	19.23	1.25
F3	27.92	0.370	0.454	18.50	1.23
F4	30.5	0.368	0.463	20.52	1.26
F5	28.37	0.379	0.439	13.67	1.16
F6	29.25	0.362	0.450	19.56	1.24

Table 12: Evaluation of Tramadol HCl uncoated tablet:

Formulations	Individual Weight	Hardness (kg/cm2)	Thickness (mm)	Friability (%)
F1	321.0	5.5	4.29	0.28%
F2	322.5	5.0	4.32	0.19%
F3	323.9	4.5	4.35	0.23%
F4	323.0	6.0	4.30	0.28%
F5	321.3	5.5	4.28	0.13%
F6	324.7	5.0	4.25	0.22%

Table 13: Evaluation of Tramadol HCl coated tablet:

Formulations	Individual Weight	Hardness (kg/cm2)	Thickness (mm)
F1	329.9	7.5	4.44
F2	331.4	7.0	4.47
F3	334.3	7.5	4.50
F4	333.0	8.0	4.45
F5	330.3	7.0	4.43
F6	334.8	6.5	4.40

Table 14: In- Vitro release profile of formulation F1-F6 of Tramadol HCL

Time(hrs)	Cumulative % drug release						
	F1	F2	F3	F4	F5	F6	Marketed formulation
1	18.01	20.26	22.29	21.54	15.25	16.59	18.39
2	36.57	43.36	44.71	44.45	32.67	36.27	39.59
4	48.86	59.15	61.03	60.28	47.04	47.58	57.43
6	63.18	82.63	84.11	83.30	65.25	65.26	78.12
8	79.70	98.28	98.76	98.56	86.49	80.40	95.18

Table 15: Release Kinetic Result of Formulation

Formulation	Zero order	Higuchi plot	Korsmayer peppas plot
	R^2	R^2	R^2
F1	0.957	0.980	0.977
F2	0.965	0.975	0.975
F3	0.959	0.981	0.980
F4	0.961	0.979	0.975
F5	0.984	0.955	0.983
F6	0.963	0.974	0.965

Table 16: Stability studies of optimized formulation (F3) at 40^0C ±2^0C (75±5% RH)

Parameter	Initial	After 1 month	After 2 month	After 3 month
Individual weight	334.3	333.9	334.1	334.5
Hardness	7.5	7.0	7.5	7.0
Thickness	4.50	4.51	4.48	4.53
Colour change	Off white	No change	No change	No change
Drug content	99.65	99.62	99.59	99.49

Table 17: Dissolution profile of optimized batch F3 kept for Stability studies

Time (hrs)	Cumulative % drug release	
	Initial	After 3 month
1	22.29	22.15
2	44.71	44.55
4	61.03	60.86
6	84.11	83.99
8	98.76	98.58

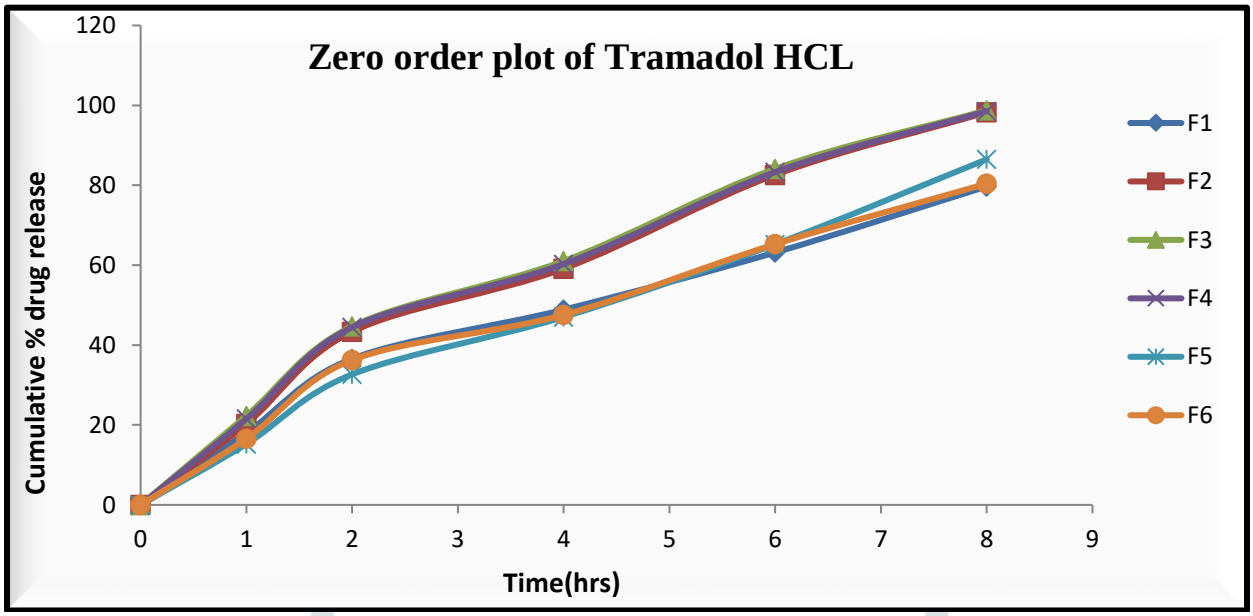

Figure 8: Zero order plot of Tramadol HCL

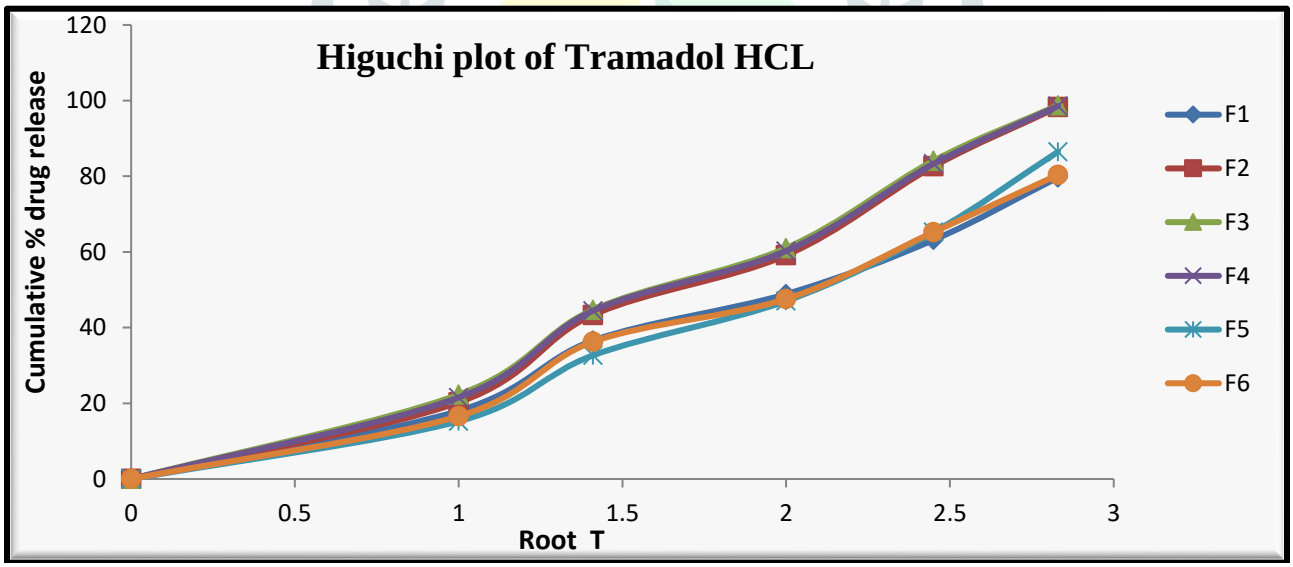

Figure 9: Higuchi plot of Tramadol HCL

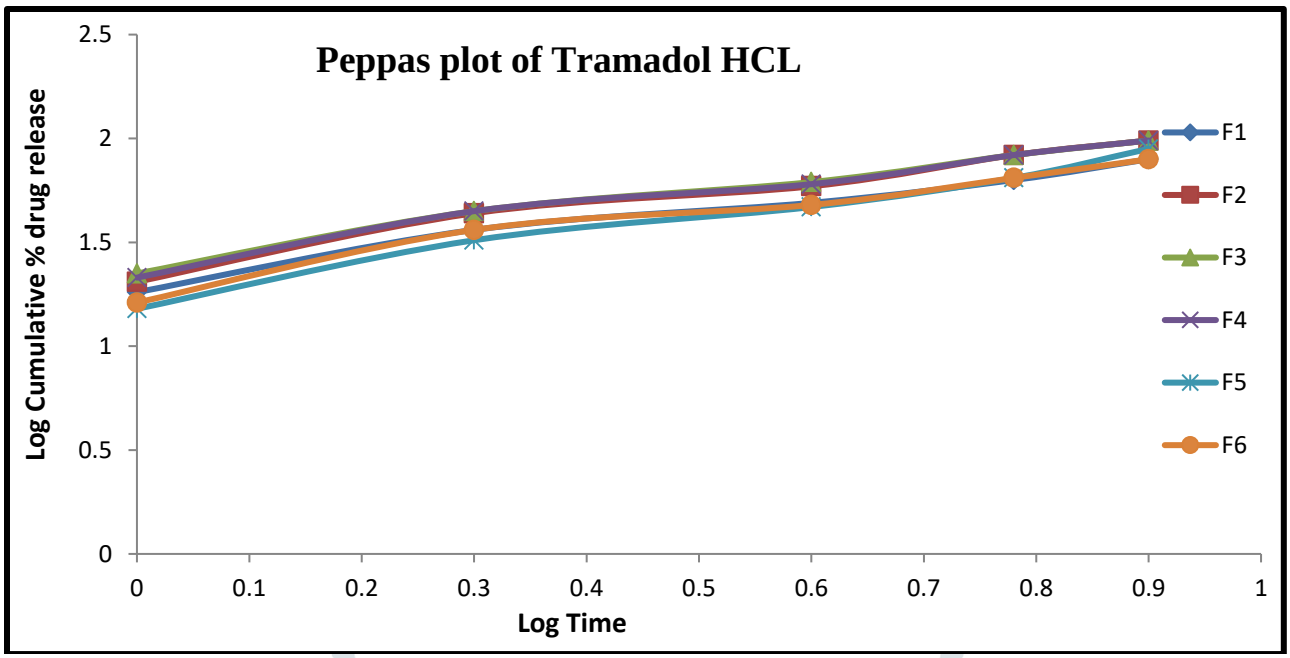

Figure 10: Peppas plot of Tramadol HCL

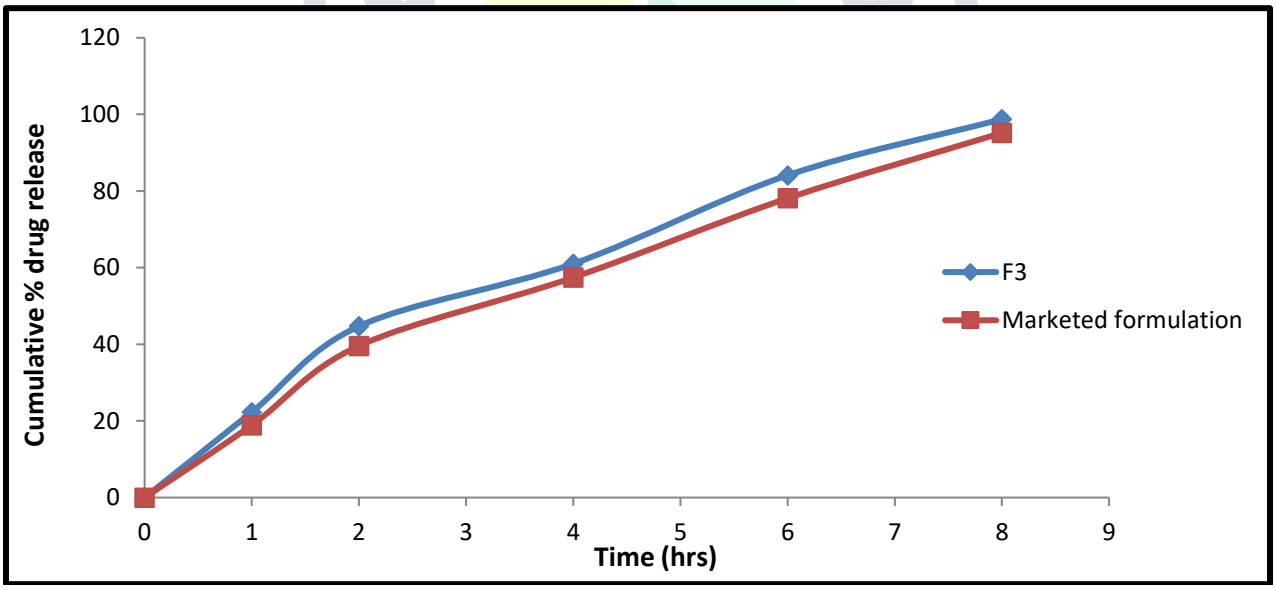

Figure 11: Comparison of In-vitro drug release of Marketed formulation and Optimized Formulation F3

DISCUSSION

The sustained release tablet of Tramadol Hydrochloride were prepared by wet granulation method, They were evaluated for weight variation, drug content, friability, hardness, and thickness for all batches (F1 to F6). No significant difference was observed in the weight of individual tablets from the average weight. Tablet weights of all batches were found within recommended pharmacopoeia limits. The data of uniformity of content indicated that tablets of all batches had drug content within pharmacopoeia limits. The hardness of tablets of all batches is in acceptable limits(NLT 4 kg/cm^2)(table 13). All the formulation showed % friability less than 1% (table 12) that indicates ability of tablets to withstand shocks, which may encounter. No significant difference was observed in the thickness of individual tablet from the average weight. In Kinetic assessment the data was plotted according to Zero order shows (table 15) R2 (0.957 to 0.963) suggested the rate of drug released was followed zero order for HPMC K4M batches. The data was fitted with Higuchi with (table 15) R2 (0.980 to 0.974) indicating the mechanism was diffusion controlled. To known the preciously whether the Fickian and non- Fickian. Release mechanism, the data was fitted to Korsmeyer's Peppas equation. All formulation compared with the marketed product for drug release pattern, which showed that formulation F3 performed similar to the marketed product therapeutically. Based on the evaluation result the formulation F3 containing HPMC K4M was selected as best formulation.

The results of stability study after three monthare given in Table 16 & 17. The stability study was selected formulation of F3 was performed as per ICH guidelines. Stability study is carried out for 3 month at 40^0C, 75% RH. The tablets were tested for release during the stability period and confirmed that result were found within the limit.

CONCLUSION

Drug released of optimized formulation F3 formulated with HPMC K4M as the polymer has extended the Tramadol hydrochloride release up to 8 hrs. excipients used in the formulation reduced the cost, which are available at lower price in market. As the excipients used are mostly available and cheaper at cost. The study includes development of the robust and product, which complies with the marketed product.

REFERENCE:

[1] Misal1*Ravikumar, Waghmare1Atish, Aqueel1 Shaikh, et al. Matrix tablet: A Promising Technique for Controlled drug delivery, Indo American Journal of Pharmaceutical Research2013; 3(4): 3791-3805

[2] Deore K Rakesh1*, Kuncha Kavita and Theetha G Tamizhmani. Preparation and evaluation of sustained release matrix tablets of tramadol hydrochloride using Glyceryl Palmitostearate,Tropical journal of pharmaceutical research 2010; 9(3):275-2818

[3] Mamdouh Ghorab, Elsayed Khafagy, Marima Kamel and Shadeed Gad*.Formulation,Charaterization and Comparative in-vitro in-vivo evaluation of Sustained release theophylline tablets, International Journal of Pharmacy and Pharmaceutical Sciences,2012; 4(3):721-728

[4] Rao Raghavendra N. G., Raj Prasanna Richard K., Nayak Sanjeev. Review on Matrix Tablet as Sustained Release, International Journal of Pharmaceutical Research & Allied Sciences, 2013; 2(3):1-1717

[5] Wani Shivadas Manish. Controlled Released System - A Review,2008

[6] Rossi S. Australian medicines handbook. The Australian medicines handbook unit trust. 2013; 978-0-9805790-9-3.

[7] Grond S and Sablotzki A. Clinical pharmacology of tramadol. Clinical Pharmaco. 2004; 43(13):879–923.

[8] . Carville S, Arendt N and Bliddal H. Eular evidence based recommendations for the management of fibromyalgia syndrome. Annal Rheum Disease. 2008;67:536–41.

[9] Gary S F, Ralph B, Sherin EG, James R and Iain BM. Cartilage, bone and heritable tissue disorders. Textbook of Rheumatology by Kelleys. Library of Congress cataloging, China. 2012; 9th Edi:1056.

[10] . Tiwari S, Murthy K and Raveendra P. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS Pharm Scien Tech. 2003;4(3):1-6.

[11] Leppert W. Tramadol as an analgesic for mild to moderate pain. Pharmacological Reports. 2009;61(6):978–92.

[12] **.** Reynolds JEF, Eds., In; Martindale; The Extra Pharmacopoeia, 29th Edn., The Royal Pharmaceutical Society of Great Britain, London, 1993, 295.

[13] McNaman JO, Hardman JG, Limbird LE, Molinoff PB and Ruddon RW. Eds., The Pharmacological Basis of Therapeutics: 9th Edn. Mc Graw-Hill, New York, 1996, 46.

[14] Clark's Analysis of Drugs and Poisons, London; Pharmaceutical Press. Electronic version, 2006.

[15] **.** Indian Pharmacopoeia Ministry of Health and Family Welfare.. Delhi: Controller of publications; 1996.

[16] Tiwari SB, Krishna Murthy T, Raveendra Pai M, Mehta PR, Chowdary PB. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS Pharm Sci Tech 2003; 4 (3) article 31.

[17] Banker, G.S. and Anderson, N.R. 1990. The theory and practice of Industrial Pharmacy: tablet, Lachman, (3rd ed) Varghese Publishing House, Bombay, pp.293-303.

[18] Gennaro, A.R. 1990. Remington: the science and practice of pharmacy, Lippincott Williams & wilkins, Philadelphia, vol. 1, pp.700-719.

[19] Banker and Rhodes C.T. , Modern pharmaceutics, Marcel Dekker, New York, PP. 239-261.

[20] Nagar Priyanka et al., Orally disintegrating tablets : formulation, Preparation techniques and evaluation, Journal of Applied Pharmaceutical Science, 2011, Vol 1, pp. 5-8.

[21] ZachariahMarkose et al., Formulation and evaluation of dispersible tablets of Amoxicillin trihydrate and Dicloxacillin sodium, International research journal of pharmacy, 2012, Vol 3, pp. 112-113

[22] Korsmeyer. RW; Gurny. R; Doelker, EM and Buri. P "Mechanism of solute release from porous hydrophilic polymers",International Journal of Pharmaceutics 15 (4): 1983, 25-35.

[23] Liberman, H.A., Pharmaceutical Dosage Form; Tablets, 2 edn., vol.1, 201–213.