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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF TRAMADOL HYDROCHLORIDE USING HYDROPHILIC/ HYDROPHOBIC POLYMER MATRIX SYSTEM

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Abstract:
Tramadol Hydrochloride is an opioid analgesic drug, which has a strong analgesic action. It acts as an opioid agonist through selective binding to μ-opioid receptors. It is administered when non-steroidal anti-inflammatory drugs (NSAIDs) fail to mitigate pain. It is available as three oral formulations: (i) Tramadol Hydrochloride immediate release (IR) [Tramacon®] administered three times daily; (ii) Tramadol Hydrochloride sustained-release (SR) [Tramacip SR®]. Administered twice daily, and (iii) Tramadol Hydrochloride control release (CR) [Tramazac®] administered once daily. All three formulations are bioequivalent in terms of systemic exposure to Tramadol. The objective of the present investigation is to design and evaluate sustained release dosage form of Tramadol Hydrochloride. Because of its shorter half-life and more adverse effect Tramadol was selected as the desired candidates for the formulation of sustain release preparation.
*Sustained-release tablets were prepared by direct compression method using HPMC K100M (hydrophilic polymer) and HEC (hydrophobic polymer) as matrixing agents. Total nine batches of sustained-release tablet of Tramadol Hydrochloride were formulated and evaluated with a variation in the quantities; among them, batch **F8** showed the most satisfactory drug release pattern by sustaining the release of tramadol.*
Keywords: *Sustained release Tablets, Tramadol Hydrochloride, Hydroxy propyl methyl cellulose, Hydroxy ethyl Cellulose.*

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INTRODUCTION:

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed categories of drugs worldwide in the treatment of pain and inflammation in the symptomatic treatment of rheumatoid arthritis, Osteoarthritis and spondylitis.[1,2] 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.[3,4] Patients very often miss a dose, and compliance to dosage regimen always remains a question mark.[4,5] To overcome these kinds of issues and maintain a continuous therapeutic level of drugs in the systemic circulation is a significant concern.[4,5] Tramadol Hydrochloride is a centrally acting analgesic agent having an amino cyclohexanol group on chemical structure, which has a strong analgesic action. It acts as an opioid agonist through selective binding to μ-opioid receptors, releases serotonin and inhibits the reuptake of norepinephrine. It is administered when NSAIDs fail to mitigate pain.[6-9] It is freely soluble in water and becomes an ideal candidate for formulating extended-release tablets.[8-10] The half-life ($t_{1/2}$) of Tramadol is 6 hours and so necessary for every 6 hours dosing, i.e. 3-4 times a day for maintenance of chronic pain relief. Frequent dosing of Tramadol administration may indicate reduced patient interest, chances of more adverse effects, tolerance development and fluctuation in plasma concentration, so it is desirable to prepare a sustained-release formulation of Tramadol.[11,12]

Hence, the main objective of the present study is to develop the Tramadol sustain release tablets to prolong the release time as compared to the oral immediate-release conventional drug delivery system. Sustaining the release of drug will solve problems associated with conventional multiple dosing systems, i.e. strict adherence to timely dosing, flip-flop plasma concentration and side effects associated due to systemic accumulation of the drug.

MATERIALS AND METHODS:

Materials

Table 1. Material and their sources of procurement

Materials	Source
Tramadol hydrochloride	Macleods Pharmaceuticals, Daman
Hydroxy propyl methyl cellulose K100M	Yarrow Chem products, Mumbai
Hydroxyethyl cellulose	Cosmo Chem Pvt. Ltd.
PVP K-30	Yarrow Chem products, Mumbai
Microcrystalline cellulose	Loba chemie, Thane, Mumbai
Magnesium stearate	Loba chemie, Thane, Mumbai
Talc	Cosmo Chem Pvt. Ltd.

Methods

Drug identification

By Melting point determination

The melting point denotes the temperature at which the substance has just completely melted; this is indicated by the disappearance of the solid phase and complete transparency of the melt. The melting point was determined in a capillary tube method by using electrical melting point apparatus. About 50 mg of the pure drug Tramadol HCL was ground in a clean glass mortar. The ground substance was placed in a desiccator over silica gel at room temperature and dried for about 24 hours. Then the substance was filled in a dry capillary tube (sealed at one end) of 1- mm internal diameter forming a column about 3 mm high. The melting-point apparatus was heated to a temperature 5-10ºC below the expected temperature of melting and the heating was adjusted so that the temperature in the chamber rises about 1ºC per minute. The capillary with the substance was introduced into the heated chamber and the temperature was noted in the thermometer when the sintered substance becomes completely transparent; this was considered as the melting point. The above procedure was repeated thrice to get a concordant value.

By UV spectroscopy (Determination of λ max)

Accurately weighed 100 mg of Tramadol HCL was dissolved in 100ml volumetric flask, to it 70ml distilled water were added then sonicated to dissolved and allowed to equilibrate at room temperature then volume make up to the mark. From stock solution 1 ml of pipette out and transfer in to a 10 ml volumetric flask and the volume was made up to the mark with

distilled water to prepare concentration of 100µg/ml. Sample was scanned in UV- Visible spectrophotometer in the of range 200-400nm using distilled water as blank. The maximum absorbance obtained in the graph was considered as λmax for the pure drug.

Preparation of Standard Calibration Curve of Tramadol:

Precisely weigh 10 mg of Tramadol pure drug was dissolved in 10 ml volumetric flask to 70ml distilled water added and sonicated well then volume makeup to the mark with distilled water to obtain the stock solution of 1000µg/ml. To this solution 1,2,3,4….6 ml pipette out and transferred into 100ml volumetric flask to acquired concentration series of 10 - 60µg/ml. Absorbance's of these solutions were measured at the obtained λmax using UV- Visible Spectrophotometer and standard graph was plotted.

By infra-red spectroscopy method

Accurately weighed 5mg of Tramadol were mixed with potassium bromide powered and prepared pellets by applying 10 metric ton of pressure in hydraulic press. The pellets were then scanned over a wave range of 4000 cm^{-1} to 500 cm^{-1} in FT-IR instrument (8400 S Shimadzu) to examine the compatibility.

Drug Excipient Compatibility Studies by FTIR

Drug and different excipients were taken in a 1:1 ratio. Drug and excipients were accurately weighed and mixed, and the resulting mixtures were scaled in screw glass vials and kept at 50°C for 15 days. Observations of samples were taken for observing the change in their appearance, colour and odour. The samples of pure drug and physical mixture of polymer and drug were taken and subjected to FTIR study.

Formulation of Sustain-Release Formulation:

The formulations of each sustain release tablets of Tramadol are composed of two selected polymers i.e. HEC and HPMC K100M in combination with PVP K30. The other excipients used were MCC as a diluent, Magnesium stearates as a lubricant and talc. The weight of tablet was adjusted to 300 mg and each tablet contained 75 mg of Tramadol. Total 9 batches (F1 to F 9) were prepared. All the ingredients were weighed accurately and passed through sieve 44# and mixed well in a double cone blender at 50 rpm for 15 min. Tramadol was first mixed with the polymer for 15 min to obtain uniform mixture. Then the mixture was passed through sieve 44#, Finally the mixture was blended with talc and magnesium stearate 300 mg and tablets were compressed with the help of a tablet compression machine contains 11mm flat punch. Further, these tablets were subjected to different evaluation parameters.

Evaluation of Prepared Powder Mixtures

***Bulk Density*:**

The volume of powder packing was determined on an apparatus consisting of a graduated cylinder mounted on a mechanical tapping device with a specially cut rotating cam. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Initial volume of powder was noted and the sample subjected to tapping (500, 750 or 1250 tapings) until no further reduction in volume was noted or the percentage of difference in volume was not more than 2 %. A sufficient number of taps should be employed to assure reproducibility for the material in question. The tapings should not produce particle attrition or a change in the particle size distribution of the material being tested.

$$\text{Bulk Density}\left(\frac{\text{g}}{\text{ml}}\right) = \frac{\text{Weight of sample in gm}}{\text{Volume occupied by sample in ml}}$$

***Tapped density*:**

Powder weighing 10 g was placed into 100 ml measuring cylinder. The cylinder was then subjected to a fixed number of taps (100) until the powder bed had reached the minimum. The final volume was recorded and the tap density was calculated by the following equation:

$$\text{Tapped density}\left(\frac{\text{g}}{\text{ml}}\right) = \frac{\text{Weight of sample in gm}}{\text{Volume occupied by sample in ml}}$$

***Angle of Repose*:**

The angle of repose of the powder blend was determined by using the funnel method. The accurately weighed powder was 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 powder **(Table 2)**. The diameter of the powder cone was measured and the angle of repose was calculated by using the equation

$$\text{Tan}\,\theta = \frac{\text{h}}{\text{r}}$$

Where h and r are the height of the pile and radius of the base of the pile

Table 2. Relationship between angle of repose (θ) and flow ability

Angle of Repose (θ) (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

Carr's Index:

The Compressibility index and Hausner's ratio are measures of the propensity of a powder to be compressed and the flow ability of granule. As such, they are measures of the relative importance of inter-particulate interactions. Carr's index and Hausner's ratio were calculated using following formula

$$\% \text{ Carr's Index} = \frac{\text{Tapped density-bulk density}}{\text{Tapped density}} * 100$$

$$Hausner's\ ratio = \frac{Tapped\ density}{bulk\ density}$$

Table 3. Relationship between % compressibility and flow ability

Compressibility Index (%)	Flow of Powder	Hausner Ratio
≤ 10	Excellent	1.00–1.11
11-15	Good	1.12–1.18
16-20	Fair	1.19–1.25
21-25	Passable	1.26–1.34
26-31	poor	1.35–1.45
32-37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Evaluation of Prepared Tablets:

Hardness:

The hardness of the tablet was carried out by using a Monsanto type hardness tester. The hardness of the tablet in Kg/cm^2 was measured for each batch five tablets were used.

Weight Variation Test:

Twenty tablets were selected randomly from each formulation and weighed individually to check for weight variation. Average weight was calculated and compared the individual tablet weight to the average. The US Pharmacopoeia allows a little variation in the weight of a tablet.

Table 4. Weight variation tolerance for uncoated tablets

Maximum % Deviation Allowed	Average Weight of Tablet (mg)
10%	130mg or less
7.5%	130mg to 324mg
5%	More than 324mg

Friability:
A Friability test was performed to assess the effect of friction and shocks, which may often cause the tablet to chip, cap or break. Roche Friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. A pre-weighed sample of tablets was placed in the Friabilator, which was then operated for 100 revolutions. Tablets were dusted and re-weighed. Compressed tablets should not lose more than 1% of their weight.

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,
% F - friability in percentage
W -weight of tablets after revolution
Wo- Initial weight of tablet

***Content Uniformity*:**
The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was diluted suitably, and the absorbance of the resultant solution was measured spectrophotometrically at 271nm using 0.1 N hydrochloric acid as blank. The tablet should be within 85% to 115% of the labelled claim.

Thickness:
Control of physical dimension of the tablets such as sizes and thickness, is essential consumer acceptance and to maintain tablet to tablet uniformity. The dimensional specifications were measured using Vernier callipers Six tablets from each batch were tested were calculated. The thickness of the tablet is mainly related to the tablet hardness can be used as an initial control parameter.

***In- Vitro* Drug Release studies of Formulated Tablets**
Dissolution conditions used in the study are indicated below:
Prepared 300 mg Tramadol Sustained-release tablets from optimized batch were used for *in-vitro* study to confirm the ability to provide the preferred sustained drug release. The *in-vitro* studies were performed the following parameters:
Instrument: USP dissolution tester
Apparatus: Type II Paddle
RPM: 75
Temp.: $37^0 \pm 0.5^0$C
Volume of media: 900 mL
Medium: pH 1.2 0.1 N HCl Buffer for initially 2 hrs. Followed by pH 7.4 phosphate buffer
Sampling: interval 1 Hrs.
Sampling volume: 10 mL Sample was withdrawn at different time interval as mentioned above and replaced with fresh media. Sample was analyzed for absorbance of Tramadol using UV spectroscopy at 271 nm against the same buffer used as blank. The drug release pattern of the optimized batch was observed.

Kinetics of Drug Release
To confirm the mechanism of drug release and regression coefficient (r^2), dissolution data were fitted with various models like zero order, first order, Higuchi's square root time and Korsemeyer peppas model. The *in vitro* dissolution data for the optimized formulation was compared with the marketed Sustain release product.

As per zero-order rate of drug release is independent to drug concentration. Higuchi model indicate that rate of drug release is dependent on time process. Furthermore from the peppas model n value indicate that if 'n' value between 0.1 to 0.5 than drug release follows ficks law of diffusion whereas if 'n' value 0.5 to 1 revealed that release of drug through non-fickian diffusion mechanism.

Stability Studies of Tramadol Sustain Release Tablets
The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of various environmental factors such as temperature, humidity and light, and enables recommended storage conditions, retest periods and self-lives to be established.

Mixture of drug and excipients in the ratio of 1:1 were prepared and transfer this mixture in the vial, then place rubber closure and seal it to prevent from external environment. Pure drug is also kept in another vial for solid stability study and testing was done according to ICH guidelines.

Accelerated stability studies are testing at 40 °C ± 2 °C / 75 % RH ±.5 % for a specific time period up to 1 months and long-term stability studies are testing at 25 °C ± 2 °C / 60 % RH ±5 % for a particular period of time up to 12 months.

The tablets were checked before stability studies for parameters like hardness, thickness, weight variation, friability, drug content and *in-vitro* drug release. *In-vitro* drug release was performed in 0.1 N HCl (pH-1.2) for 02 hrs and phosphate buffer (pH-6.8) and after stability studies checked weight variation, friability, drug content and *in-vitro* drug release.

Results and Discussions

Drug identification

Melting Point:

The melting point of Tramadol was found to be 182-185 °C matches with a melting point as per specification is given in certificate of analysis. This confirms the identity and purity of API.

By UV spectroscopy (Determination of λ max)

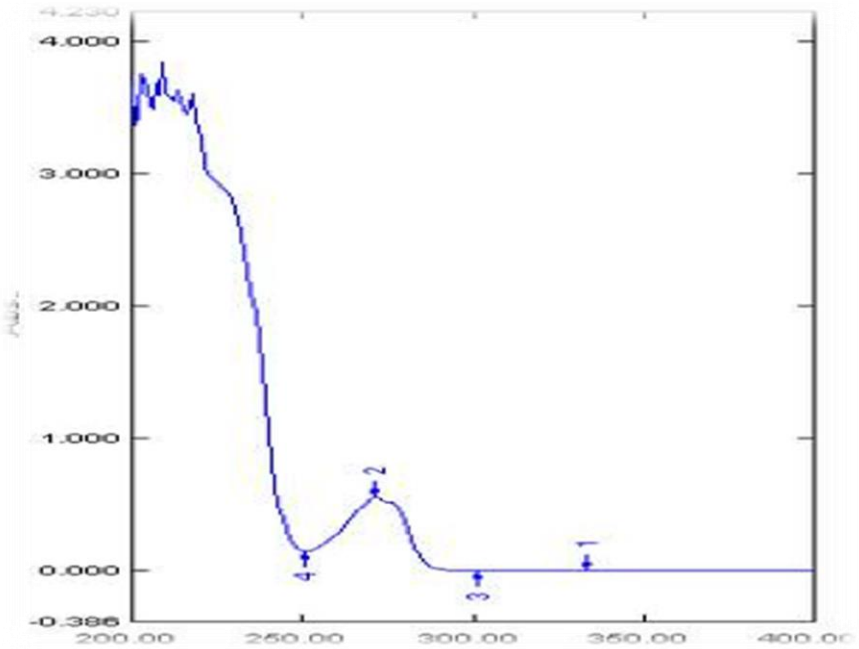

Figure 1. UV spectra of Tramadol at 10 µg/ml concentration with λ_{max} at 271 nm.

Standard Calibration Curve of Tramadol:

A calibration curve was constructed with the above working standard solutions (10 – 60 µg/ml) at 271 nm. Calibration curve was prepared by plotting concentration of Tramadol on X-axis and their respective absorbance's on Y-axis. The optical characteristics and regression data of the developed method (**Figure 2**).

Table 5. Preparation of Standard Calibration Curve of Tramadol HCL

Concentration (µg /ml)	Mean absorbance at 271.0nm
10	0.129
20	0.256
30	0.371
40	0.461
50	0.558
60	0.646

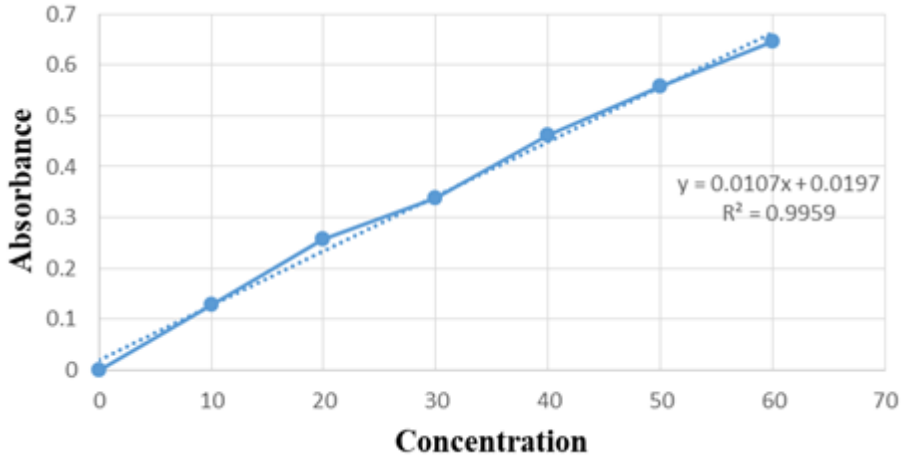

Figure 2. Standard Calibration Curve of Tramadol HCL

By infra-red spectroscopy method

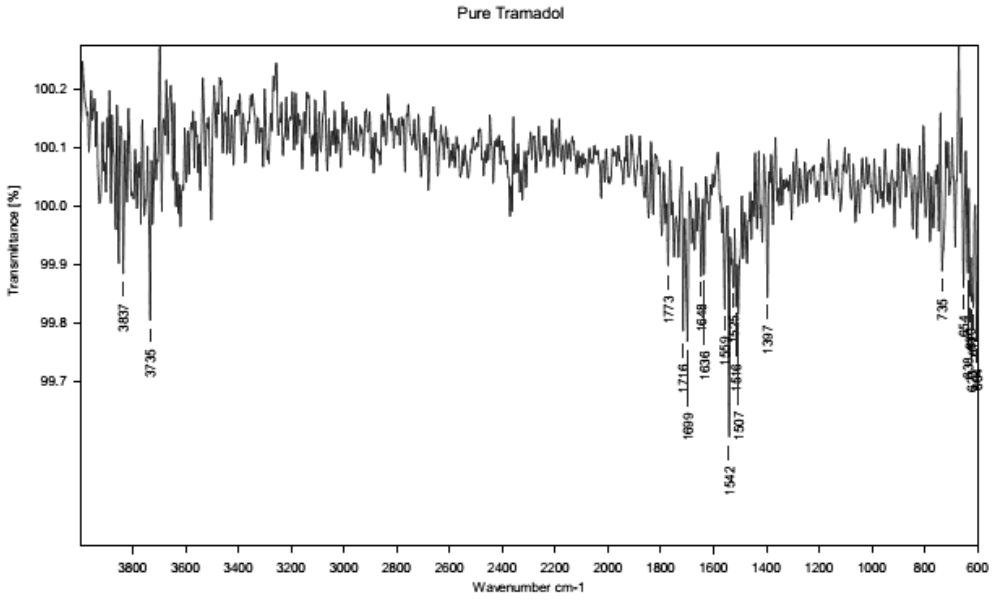

Figure 3. FTIR Spectra of Tramadol HCL

Drug Excipient Compatibility Studies by FTIR

Compatibility studies were also carried out by using FTIR spectra of pure drug, polymer, and their physical mixtures. From the results, it was found that there was no interference of the functional group as the principle peaks of the Tramadol was found to be unaltered in the drug-excipient physical mixtures, which indicates they were chemical compatible **(Figure 4-8)**.

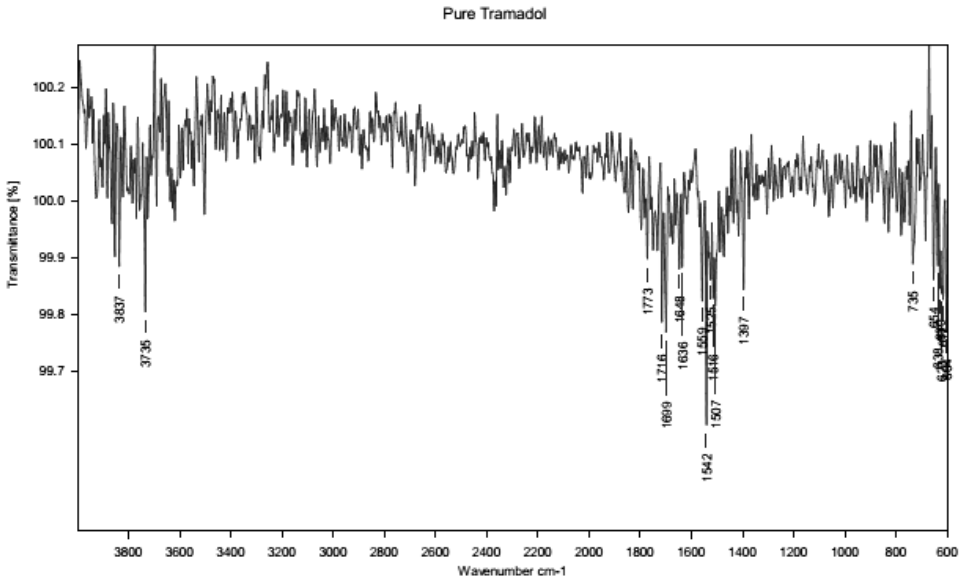

Figure 4. FTIR Spectra of Tramadol HCL

Table 6. Principle Peak and Chemical Group Present in IR Spectrum of Tramadol

Wave number (cm^{-1})	Assignment
3345	OH (Aliphatic)
3305	CH3-N-CH3(Ndialkyl)
1716	C=O (Anhydride)
1542	C=C (Alkene)
735	-C-H

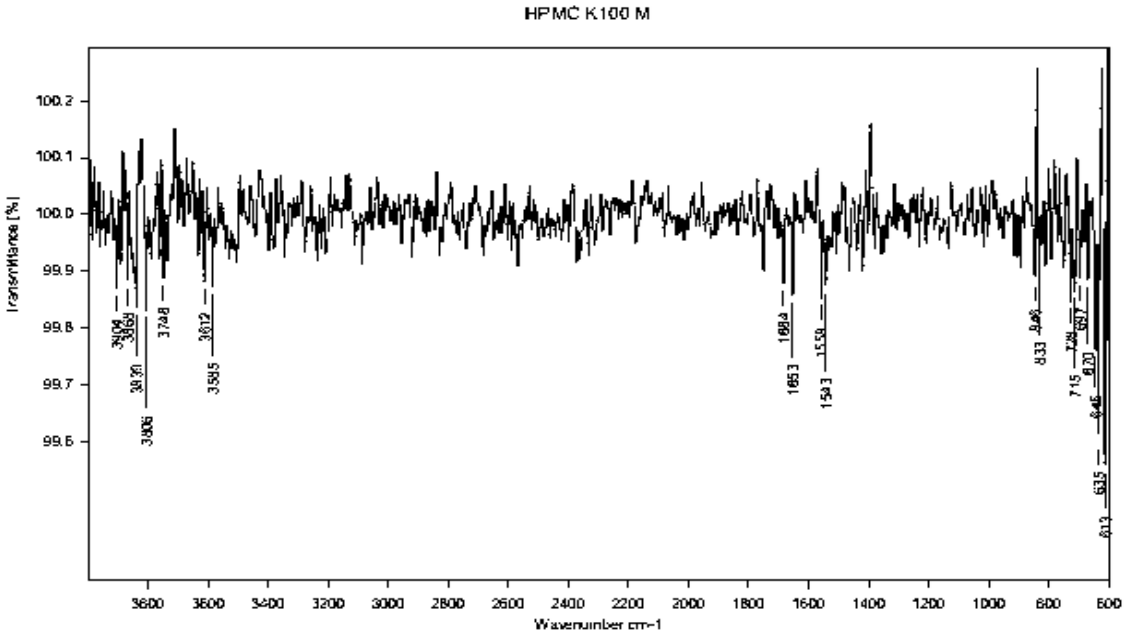

Figure 5. FTIR spectra of HPMC K100M

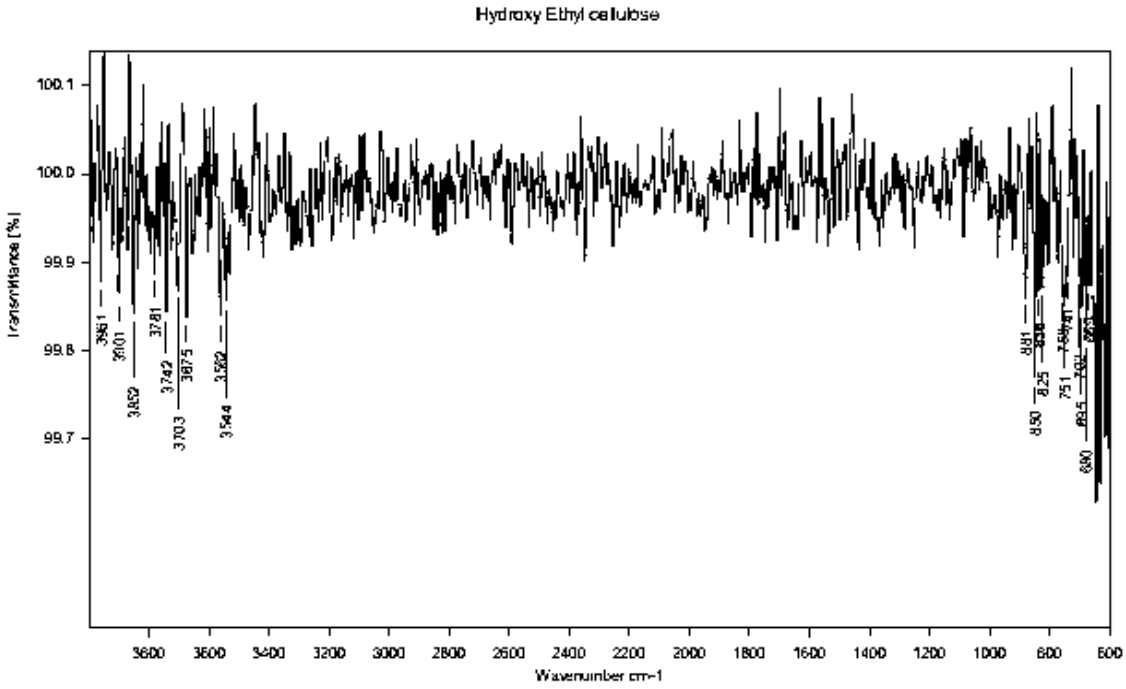

Figure 6. FTIR spectra of Hydroxy Ethyl Cellulose

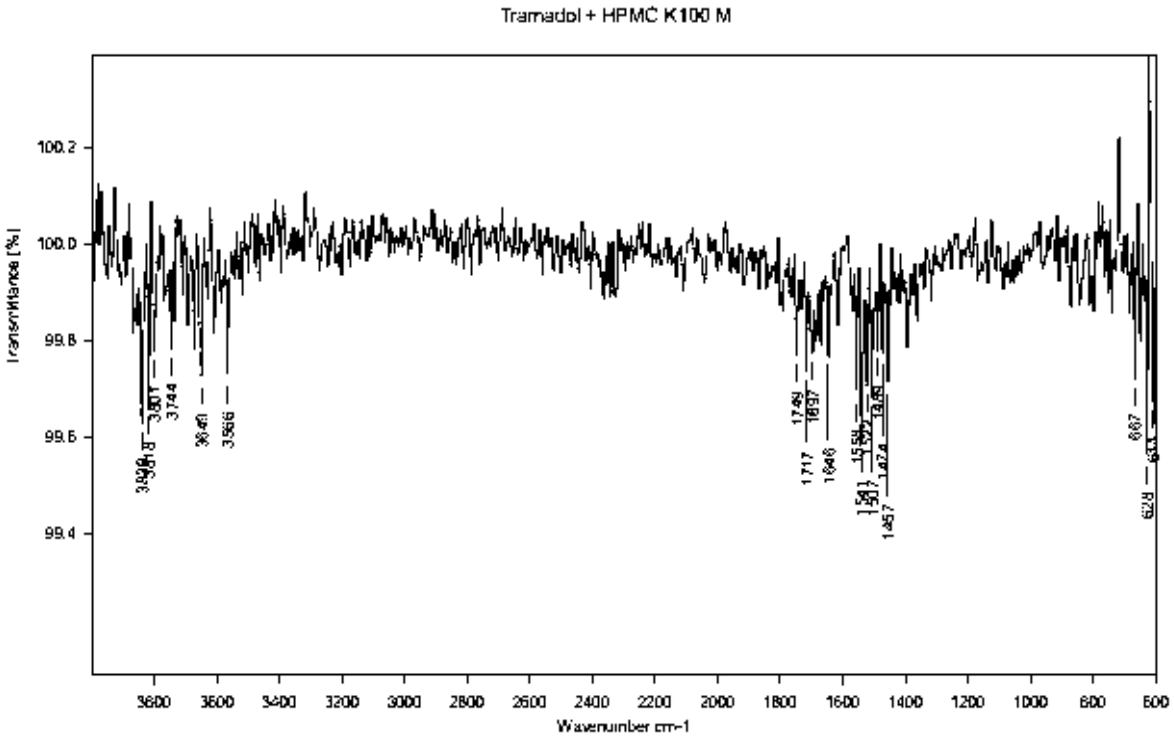

Figure 7. FTIR spectra of Tramadol + HPMC K100M

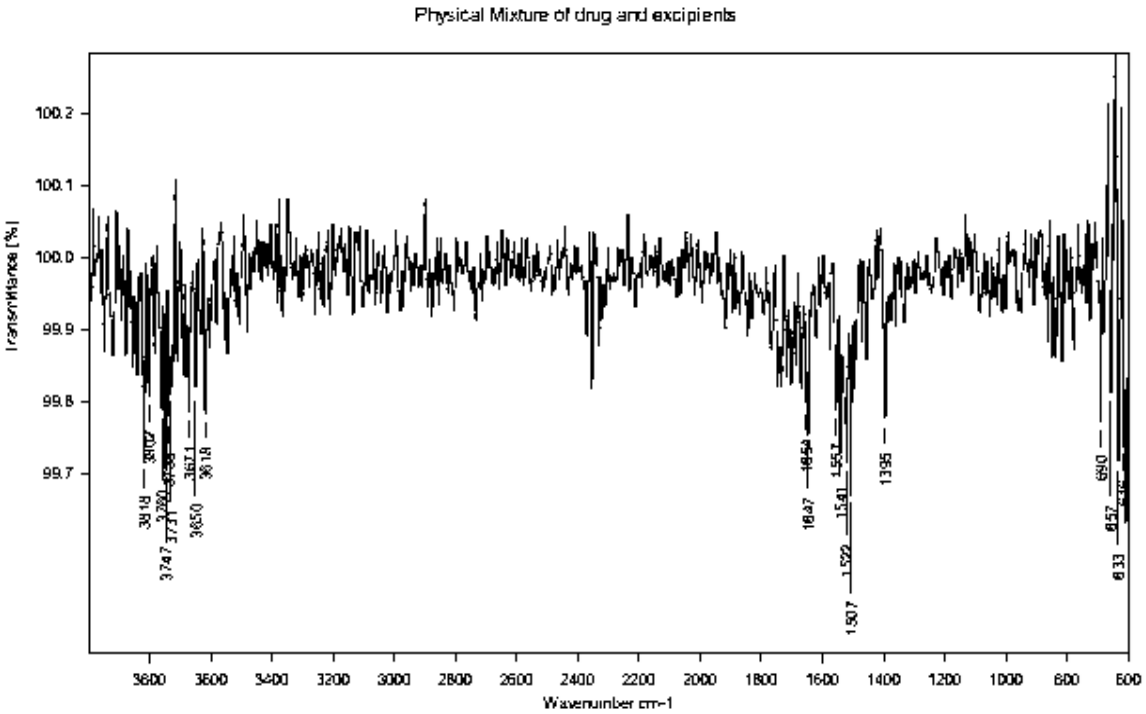

Figure 8. FTIR of Physical Mixture

Table 7. Principle Peak and Chemical Group Present in IR Spectrum of Tramadol

Wave number (cm-1)	Assignment
3550	OH (Aliphatic)
3319	CH3-N-CH3(N dialkyl)
1847	C=O(Anhydride)
1507	C=C (alkene)
690	-C-H

Formulation Design:

The present study was carried out to develop tablets of Tramadol in order to improve the therapeutic efficacy and decrease the adverse effects by minimizing the dosing frequency. In this case, nine formulations of matrix tablets were prepared using two different polymers in different concentration and combination such as Hydroxypropyl methylcellulose K100M and Hydroxy Ethyl Cellulose. These tablets were evaluated for physical parameters of appearance, hardness, friability, weight variation, and thickness, drug content, *in vitro* drug release. Optimized formulation was subjected to accelerated stability studies **(Table 8**).

Table 8. The composition, of Tramadol Sustain release tablets. (All the values are expressed in mg)

Ingredients	Formulation								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	75	75	75	75	75	75	75	75	75
HPMC K100M	45	60	75	-	-	-	45	60	75
HEC	-	-	-	45	60	75	15	30	45
Polyvinyl Pyrrolidone	30	30	30	30	30	30	30	30	30
MCC	45	30	15	45	30	15	45	30	15
Magnesium Stearate	99	99	99	99	99	99	51	69	54
Talc	6	6	6	6	6	6	6	6	6
Total weight	300	300	300	300	300	300	300	300	300

HEC- Hydroxyethyl cellulose, HPMC - Hydroxypropyl methylcellulose

Evaluation of Prepared Powder Mixtures

Table 9. Evaluation Parameters of Powder Blend

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density	0.400	0.385	0.324	0.331	0.338	0.254	0.305	**0.317**	0.302
Tapped density	0.465	0.451	0.371	0.383	0.399	0.284	0.365	**0.379**	0.348
Compressibility index	13.97	14.63	12.66	13.57	15.28	10.56	16.43	**16.35**	13.21
Hausner ratio	1.16	1.17	1.14	1.15	1.18	1.11	1.19	**1.19**	1.16
Angle of repose (Ɵ)	25.54	25.25	25.18	25.22	24.87	24.85	25.28	**26.95**	26.11

Evaluation of Prepared Tablets

Table 10. Evaluation of Sustain Release Tramadol Tablets

Parameter	Thickness ±S.D. mm n=10	Hardness ± S.D. (kg/cm^2)	Average Weight variation (n=20) mg	Drug Content (%)	Friability (% w/w)
F1	2.44±0.02	6.8 ± 0.3	101.40 ± 1.51	100.65 ±1.20	0.38 ± 0.04
F2	2.50±0.04	7.1 ± 0.5	102.63 ± 1.69	98.50 ± 1.46	0.42 ± 0.06
F3	2.55±0.03	7.2 ± 0.2	101.50 ± 1.41	97.25 ± 1.56	0.35 ± 0.02
F4	2.52±0.03	5.48 ± 0.2	100.39 ± 1.35	98.70 ± 0.92	0.45 ± 0.04
F5	2.45±0.05	5.48 ± 0.2	101.26± 1.58	99.65 ± 2.12	0.38 ± 0.08
F6	2.56±0.03	5.7 ± 0.3	102.23 ±1.60	98.80 ± 0.55	0.29 ± 0.03
F7	2.61±0.02	7.1 ± 0.5	100.41 ± 1.80	99.50 ± 0.92	0.36 ± 0.06
F8	**2.62±0.03**	**8.75 ± 0.5**	**102.47 ± 1.20**	**97.21 ± 0.83**	**0.29 ± 0.09**
F9	2.40±0.04	8.64 ± 0.2	101.51 ± 1.40	101.25 ± 1.31	0.33 ± 0.03

***In- Vitro* Drug Release studies of Formulated Tablets**

In vitro, drug release studies were carried out on dissolution test USP apparatus –II Paddle Method in 900ml of phosphate buffer pH 6.8. The release rate of the drug from the tablets decreased with an increase in polymer proportion because of an increase in gel strength as well as the formation of a gel layer with a longer diffusional path. The drug release was slower from the tablets containing HPMC and Hydroxy Ethylcellulose combination than pure HPMC and Hydroxy Ethylcellulose.

Table 11. *In-Vitro* Dissolution profile of final compressed tablet

Time (hrs.)	% CDR								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	10.40	14.80	16.62	15.19	19.21	14.65	13.41	**12.63**	07.51
2	13.11	19.46	21.54	24.30	28.32	22.87	19.23	**18.27**	11.58
3	21.23	25.66	26.52	31.68	37.47	31.92	26.52	**25.53**	19.28
4	32.52	29.12	30.46	49.32	46.27	40.13	33.12	**32.45**	28.45
5	39.21	38.32	40.33	67.52	61.17	57.44	39.65	**39.30**	38.80
6	52.62	46.25	48.56	79.98	76.52	71.01	48.91	**47.31**	40.30
7	59.83	57.11	59.36	95.17	85.25	76.46	56.11	**55.03**	57.10
8	67.47	68.55	69.55	-	93.55	81.25	64.25	**63.21**	62.25
9	76.01	77.41	79…12	-	98.12	88.15	71.24	**70.47**	69.27
10	84.95	86.68	85.32	-	-	90.12	86.43	**77.58**	75.60
11	97.81	96.97	91.16	-	-	92.25	97.13	**86.48**	85.35
12	-	-	94..31	-	-	94.57	-	**98.66**	97.30

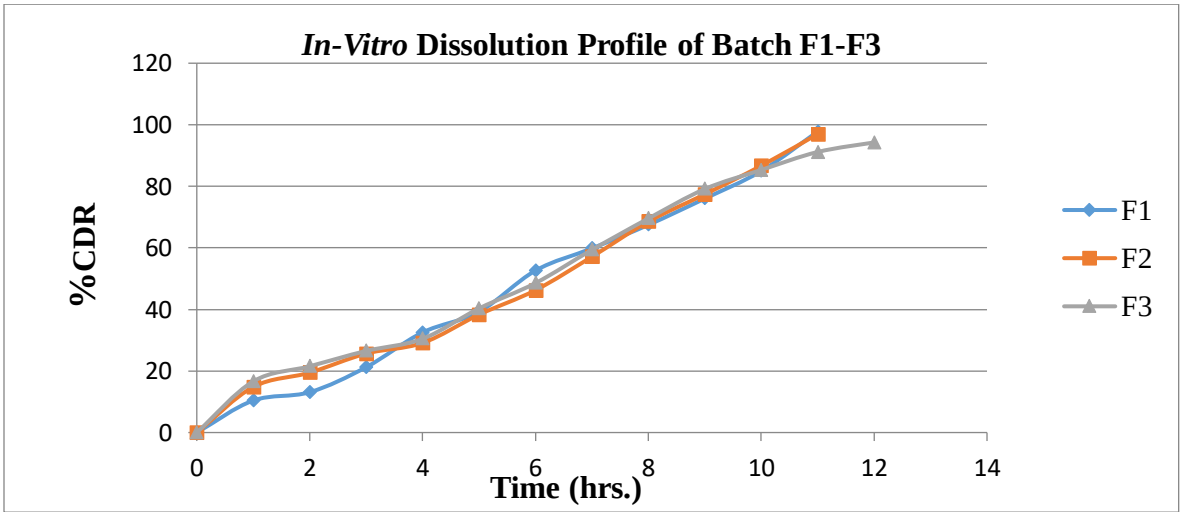

Figure 9. ***In-Vitro*** **Dissolution Profile of Batch F1-F3**

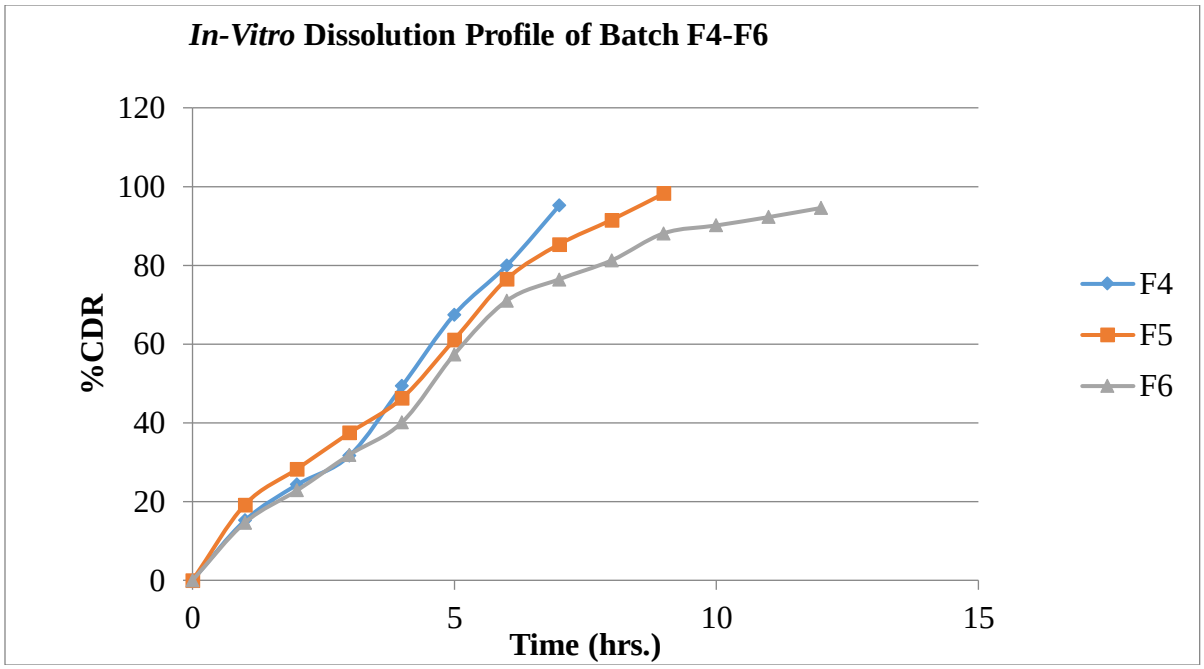

Figure 10. *In-Vitro* Dissolution Profile of Batch F4-F6

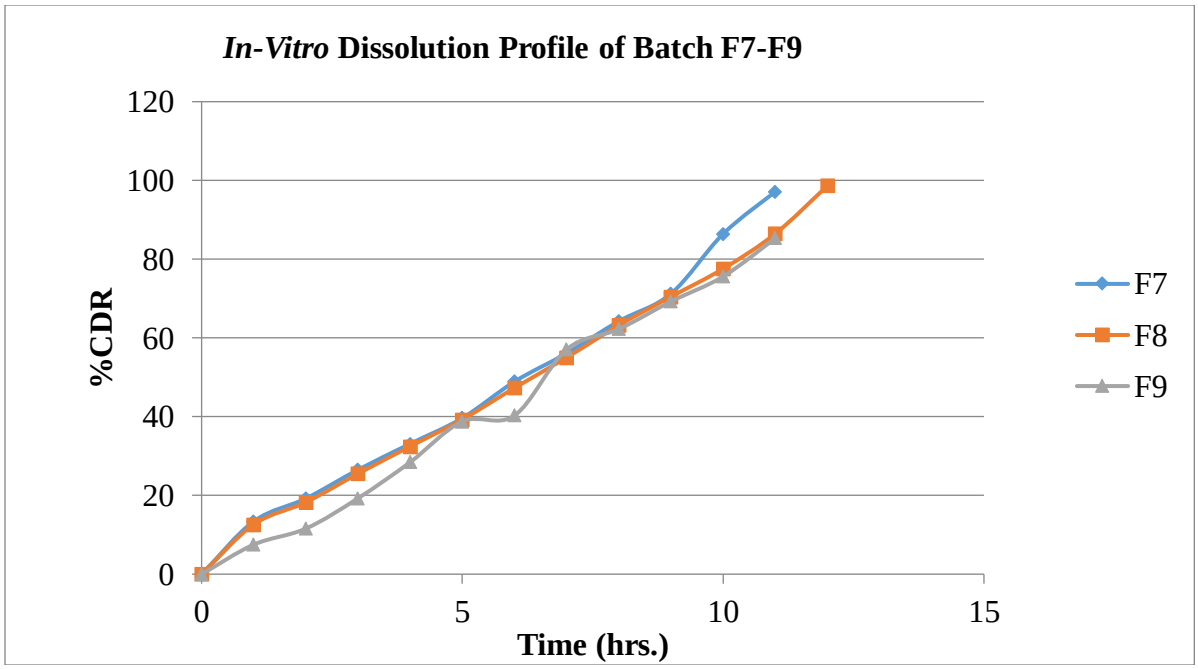

Figure 11. *In-Vitro* Dissolution Profile of Batch F7-F9

Kinetics of Drug Release

Table 12. Kinetic Data of Sustain Release Tramadol Tablets

Formulation Code	Zero order (R^2)	First order (R^2)	Matrix Model (R^2)	Korsmeyer - Peppas model (R^2)	Hixson Crowell Model (R^2)
F1	0.9952	0.8448	0.9158	0.9918	0.9255
F2	0.9979	0.7890	0.9206	0.9955	0.9064
F3	0.9897	0.8422	0.8858	0.9789	0.9174
F4	0.9952	0.9186	0.9480	0.9927	0.9664
F5	0.9950	0.8679	0.9488	0.9939	0.9471
F6	0.9950	0.8617	0.9495	0.9959	0.9458
F7	0.9962	0.7550	0.9096	0.9946	0.8929
F8	0.9991	0.8542	0.9247	0.9954	0.9422
F9	0.9990	0.7796	0.9302	0.9942	0.9203

Table 13. Estimated Values of n and k by Regression of log (M_t / M_∞) on log (t)

Formulation code	n	K	(R^2)	Best Fit Model
F1	0.8984	10.10	0.9952	Zero order
F2	0.9133	10.09	0.9969	Zero order
F3	1.0219	7.02	0.9897	Zero order
F4	0.8343	18.42	0.9952	Zero order
F5	0.8046	17.40	0.9950	Zero order
F6	0.8301	17.01	0.9959	Peppas model
F7	1.0063	8.27	0.9962	Zero order
F8	0.9454	9.10	0.9991	Zero order
F9	0.9019	10.19	0.9990	Zero order

The ‘n’ value could be used to characterize different release mechanisms as:

Table 14. nValue and Release for Korsmeyer-Peppas model

n	Mechanism
0.5	Fickian diffusion (Higuchi matrix)
0.5 < n < 1	Non-Fickian diffusion
1	Case II transport
>1	Super Case II transport

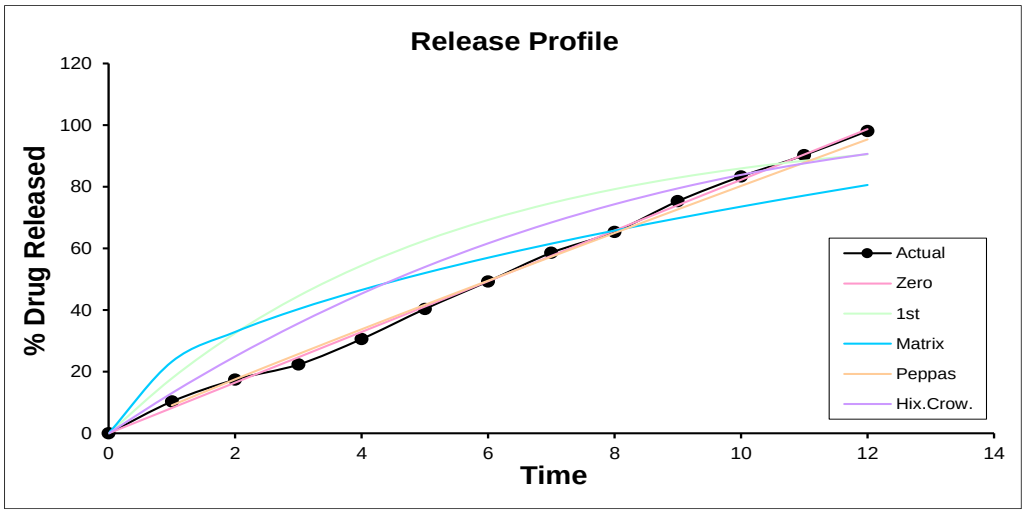

Figure 12. Zero order release kinetics of F8 formulation

Stability Studies of Tramadol Sustain Release Tablets

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of various environmental factors such as temperature, humidity, and light and enables recommended storage conditions, retest periods and self-lives to be established. Stability studies were carried out at 40 ± 2°C / 75 % RH for a specific time period up to 30 days for optimized formulation **F8**. The formulation showed good stability, and the values were within permissible limits.

Stability studies were performed, physicochemical parameter determines at the interval of 0, 15, 30 days are shown in

Table 15. It was found that the optimized tablets of batch F8 are stable even at the exaggerated condition of temperature and humidity. After the 1-month time interval, when the optimized batch **F8** was subjected for organoleptic properties, appearance, friability remains unaffected. The hardness after 1months was found to be 5.0±0.6 kg/cm^2; drug content was found to be 99.29±0.68 and 96.25±0.7 %, respectively.

Table 15. Parameters studied on F8 Formulation before and after stability study

Parameters	Drug content (%)	Hardness ± S.D. (kg/cm^2)	Friability± S.D.(%w/w)
Initial	99.50 ± 0.92	5.1 ± 0.5	0.36 ± 0.06
After 15 Days	99.27 ± 0.45	5.0 ± 0.6	0.36 ± 0.09
After one month	99.28 ± 0.42	5.0 ± 0.6	0.36 ± 0.02

Table 16. *In-Vitro* Dissolution profile of optimized batch F8

Time (hrs.)	Cumulative % Drug released		
	At initial	After 15 Days	After 1 month
0	0	0	0
1	12.63	12.75	12.84
2	18.27	18.35	18.43
3	25.53	25.59	25.66
4	32.45	32.51	32.56
5	39.30	39.35	39.43
6	47.31	47.37	47.43
7	55.03	55.08	55.16
8	63.21	63.26	63.31
9	70.47	70.54	70.60
10	77.58	77.61	77.66
11	86.48	86.54	86.62
12	98.66	98.72	98.85

The data is presented as (n = 3) mean value ± S.D.

CONCLUSION:

The present study concludes that sustained drug delivery of Tramadol can be a good way to prolong duration of action of drug by reducing the dosing frequency. The present investigation demonstrated that the use of hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained release tablets of Tramadol. Optimized formulation **F8** containing HPMC K100M and HEC optimum ratio had successfully sustained the drug release. **Table 10** showed that there were no considerable changes in thickness, hardness, drug content and sustain lag time of **F8** formulation before and after accelerated stability study. Also, **Table 11** showed that there was hardly any difference between the dissolution profile of the **F8** formulation. An accelerated stability study showed that there are no significant changes of drug delivery was observed after 15day and 30days (**Table 11)**.

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