Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF TRAMADOL HYDROCHLORIDE AND STUDY IT'S RELEASE (DISSOLUTION) KINETICS

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ABSTRACT

The objective of this work was to develop sustained release tablets of highly water soluble Tramadol HCl using polymers (HPMC K100M, HPMC K15M, Sodium Carboxy Methyl Cellulose, Polyethyleneoxide-N-80) as cost effective, non toxic easily available and suitable hydrophilic matrix system. Tramadol is a centrally acting analgesic drug. Due to high frequency of drug administration (4–6 hourly), small dose (50–100 mg) and short biological half-life (6 h) rationally call for the development of its sustained release. Highly soluble and permeable, this drug can be safely regarded as a BCS class I therapeutic agent. In order to optimize the various parameters 9 different formulations of SR layer were prepared and compressed separately. Sustained release tablet of Tramadol HCl (dose 100mg) were produced by wet granulation method. The drug release studies were performed using USP apparatus type I using pH 1.2 buffer and pH 6.8 phosphate buffer as dissolution medium. The best fit release kinetics was achieved with the zero order plot followed by the Zero order, First order, Hixon Crowel, Higuchi and Korsmyer and Peppas equation. The data obtained proved that the formulations are useful for a sustained release of Tramadol HCl due to the percentage released after 24 hr. is nearly to 100%. The drug release was dependent on the type and concentration of the polymer.

Keywords: Tramadol Hydrochloride, Sustained Release, Dissolution kinetics, HPMC, Matrix Tablet

INTRODUCTION

Tramadol, a synthetic opioid of the aminocyclohexanol group, is a centrally acting analgesic with weak opioid agonist properties.²⁰ The chemical name for tramadol hydrochloride is (±)cis – 2 - [(dimethylamino) methyl] – 1 - (3 methoxyphenyl) cyclohexanol hydrochloride. Tramadol hydrochloride was first introduced into clinical practice in the last seventies as a strong analgesic of opioid profile acting on receptors. Tramadol hydrochloride has been proved to be effective in both experimental and clinical pain without causing serious cardiovascular or respiratory side effects⁶. The half-life of the drug is about 5.5 hours and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hours 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 hydrochloride is desirable.¹⁰

The most commonly used method of modulating the drug release is to include it in a matrix system. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.² The drug release for extended duration, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. Sustained release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half-life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance¹. Matrix type sustained delivery systems are popular because of their ease of manufacture. It excludes complex production procedure such as coating and pelletization during manufacturing and drug release from the dosage form is controlled mainly by the type and proportion of the polymers used in the preparation. Hydrophilic polymer matrix is widely used for

formulating a sustained release dosage form. Hydrophilic polymer matrix system are widely used for designing oral sustained release delivery systems because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance³. The hydrophilic polymer selected for the present study was HPMC K- 100 forms transparent tough and flexible films from aqueous solution. Polymer matrix systems have the advantages of prolonging drug release and reducing adverse effects in patients^{12,13}. An attempt has been made in the present study to achieve suitable Tramadol hydrochloride therapeutic profile by formulating sustained release tablets using various viscosity grades of HPMC.

MATERIALS AND METHODS

All the materials used in the formulations, evaluations and other experiments are listed below. The chemicals used were of laboratory reagent grade.⁷

List of materials used with supplier

Tramadol hydrochloride was a gift sample from Glenmark Pharmaceuticals, Sinnar, Nashik. Hydroxy Propyl methyl cellulose K100M, Hydroxy Propyl methyl cellulose K15M, Sodium carboxy methyl cellulose, Polyethyleneoxide-N-80, PVP K 30, Microcrystalline cellulose (AvicelPh 101), Magnesium Stearate was obtained as laboratory sample from Merck. Millipore water was used where ever required.

Preformulation Solubility

The solubility of Tramadol hydrochloride is determined by adding excess amount of drug in the solvent at room temperature and kept for 24 h with occasional shaking. Equilibrium solubility was

determined by taking supernatant and analyzing it on Shimadzu UV 2501, double beam spectrophotometer. Solubility values are shown in table.^{5,9}

UV spectroscopy

1 Determination of λ max of TH by UV spectroscopy method

A. In pH 1.2 phosphate buffer

1. Scanning of TH: The absorption maximum of the standard solution was scanned between 200 to 400 nm regions.

2. Calibration curve of TH: Accurately weighed 100 mg of the drug was dissolved in little quantity of pH 1.2 phosphate buffer and volume was then adjusted to 100 ml with the same. The prepared standard solution has the concentration 1 mg / ml. From the standard solution, various concentration prepared & Absorbances of these solutions were measured against pH 1.2 phosphate buffer as blank at 271nm using Shimadzu 1800 spectrophotometer.^{8,9}

B. In pH 6.8 phosphate buffer

1. Scanning of TH: The absorption maximum of the standard solution was scanned between 200 to 400 nm regions.

2. Calibration curve of TH: Accurately weighed 100 mg of the drug was dissolved in little quantity of pH 6.8 phosphate buffer and volume was then adjusted to 100 ml with the same. The prepared standard solution has the concentration 1 mg / ml. From the standard solution, various concentration prepared & Absorbance's of these solutions were measured against pH 6.8 phosphate buffer as blank at 271nm using Shimadzu 1800 spectrophotometer.^{8,9}

Composition of matrix tablet

Table 1: Formula

Ingredient (mg)/ tablet	F1	F2	F3	F4	F5	F6	F7	F8	F8
Tramadol HCl	100	100	100	100	100	100	100	100	100
HPMC K-15M	100	125	100	100	-	-	-	-	-
HPMC K100M	-	-	-	-	100	125	100	100	-
SCMC	-	-	50	-	-	-	50	--	75
PEO N-80	-	-	-	50	50	-	-	50	75
PVP K-30	6	6	6	6	6	6	6	6	6
MCC	87.5	62.5	37.5	37.5	87.5	62.5	37.5	37.5	37.5
Mg. stearate	4	4	4	4	4	4	4	4	4
Colloidal silica	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total (mg)	300	300	300	300	300	300	300	300	300

Evaluation of tablets^{3,4,9}

1 Weight variation:

2 Hardness and Friability:

Hardness of the tablets is determined by Erweka hardness tester. Friability of ten tablets was checked by using Roche friabilator.

3 Thickness:

The thickness of the tablet was measured by using digital vernier callipers.

Drug and polymer compatibility studies

Compatibility study by FT-IR

This can be confirmed by carrying out with infrared light absorption scanning spectroscopy (IR) studies. Infrared spectra of pure drug, polymer and physical mixture of formulations in ratio 1:1 were recorded by using **Attenuated Total Reflectance (ATR)**. After the crystal area has been cleaned and the background collected, the solid material is placed onto small crystal area. The pressure arm positioned over crystal area. Force is applied to the sample, pushing it onto the diamond surface.¹¹

Micromeritic Properties of blends to be compressed^{3,5}

1 Angle of repose

2 Apparent bulk density

3 Tapped Density

4 Carr's Index

5 Hausner ratio

Preparation of matrix tablets

Weight accurately Drug with other polymer, lactose and microcrystalline cellulose, pass through 40 no. sieves and mix it properly for 3 to 5 minutes in a steel tub. Prepare binder solution by dispersing PVP K30 in isopropyl alcohol. Granulation of above mixture is done by prepared binder solution by kneading up to granulation end point is obtained (Dough mass). Pass the dough mass through 12 mess and keep it in a tray dryer for drying and finally keep the loss on drying (LOD) up to 2-3 %. Remove the dried granules from oven and pass through 20 mess sieve to get optimum size granules. Lubrication is done by using Magnesium stearate and talc previously passed through 60 mess sieve of the granules for 3 to 4 min. in a steel tub and then in polybag. Compression is done by using 16 station single rotary CADMACH machine by using 9.1 mm standard concave circular punch.^{3,5,18,19}

In-vitro Dissolution studies

In-vitro dissolution test studies were carried out using USP 24 type-II dissolution test apparatus (Electrolab TDT-08L, Mumbai, India). A 900 ml of phosphate buffer pH 1.2 for first two hour and pH6.8 used as media, thermo-stated at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. Samples were collected periodically (1, 4, 8, 12, 16, 18, 20 & 24 hrs) and replaced with fresh dissolution medium, then the sample were analyzed using spectrophotometer at 272nm.^{8,9}

Kinetic mechanism of Drug Release

Kinetic mechanism of drug release was evaluated mathematically by Zero-order, First order, Hixon-crowell, Higuchi & Korsmeyer-Peppas Equations.^{8,18}

RESULTS AND DISCUSSION

Preformulation

- The melting point of Tramadol hydrochloride was found to be in the range of 183° to 185°C.
- Tramadol hydrochloride is highly soluble in polar solvents with pKa 9.41. Its solubility is pH independent (shown into table no 2).
- Wavelength of maximum absorbance (λ_{max}) of tramadol hydrochloride was found to be 270.60 nm and 272 nm in pH1.2

buffer & pH 6.8 buffer respectively. The spectra in different media are given in Figure 2 and 4.

- The FTIR spectra are shown in figure 5 and interpretation of FT-IR spectra are given in table 5.

Table 2: Solubility data of tramadol hydrochloride

Solvent	Solubility in mg/ml
Distilled water	>500
0.1 N HCL	>500

The preformulation study of drug was carried out by conducting various physicochemical tests including description, solubility, melting point and pH determination, spectral analysis such as UV spectrum and IR spectrum for pure TH. From preformulation studies, it was found that the sample of TH is pure.

Table 3: Concentration and Absorbance values for tramadol hydrochloride in pH 1.2 buffer (λ_{max} -270.6 nm)

Concentration ($\mu\text{g/ml}$)	Absorbance	Extinction coefficient	Average
20	0.135	0.00675	
40	0.301	0.007525	
60	0.386	0.006433	
80	0.552	0.0069	0.006876
100	0.69	0.0069	
120	0.798	0.00665	
140	0.964	0.006886	
160	1.094	0.006838	
180	1.273	0.007072	
200	1.362	0.00681

Figure 1: Calibration curve in pH 1.2 buffer (270.6 nm)

Figure 2: UV spectra of tramadol hydrochloride showing its calibration in pH 1.2 bufer (270.6nm)

Table 4: Concentration and Absorbance values for tramadol hydrochloride in pH 6.8 buffer (λ max-272 nm)

Concentration ($\mu\text{g/ml}$)	Absorbance	Extinction coefficient	Average
20	0.141	0.00705	
40	0.301	0.007525	
60	0.437	0.007283	
80	0.602	0.007525	0.007429
100	0.751	0.00751	
120	0.907	0.007558	
140	1.057	0.00755

Figure 3: Calibration curve in pH 6.8 buffer (272 nm)

Figure 4: UV spectra of tramadol hydrochloride showing its calibration in pH 6.8 buffer (272 nm)

Figure 5: FTIR spectrum of tramadol hydrochloride

Table 5: Interpretation of FTIR spectrum of drug

Principal peaks (cm^{-1})	Peak observed (cm^{-1})	Interpretation
1284	1288.36	C-O stretching
1601,1575	1608.52,1577.66	C=C stretching (aromatic)
1042	1045.35	C-O stretching (alcohol)
1238	1242.07	C-N stretching
702	702.04	C-H bending
3300	3305.76	O-H stretching

Figure 6: FTIR Spectra of Tramadol Hydrochloride

Figure 7: Tramadol Hydrochloride + PEO N-80

Figure 8: Tramadol hydrochloride+ HPMC K15M

Figure 9: Tramadol hydrochloride + HPMC K100M

Figure 10: Tramadol Hydrochloride + SCMC

Interpretation of FTIR spectrums

The major IR peaks observed in TH were 3500 (N-H stretching vibration, ter. amine), 1325 (C N stretching vibration), 2786 (C-H stretching, alkyl) and 3652 (OH stretching, alcoholic).

The major IR peaks observed in matrices were 1736 (C=O stretching, carbonyl gp), 1623 (C=C stretching) of HPMC& 2730 (C-H stretching), 3402 (N-H stretching vibration, ter. amine), 1298 (C-N stretching vibration) of TH.

The major IR peaks observed in matrices were 1737 (C=O stretching, carbonyl gp), 1625 (C=C stretching) of SCMC and 2780 (C-H stretching), 3392 (N-H stretching vibration, ter. amine), 1295 (C-N stretching vibration) of TH.

The major IR peaks observed in PEO N-80 were 1731 (C=O stretching, carbonyl group) and 1630 (C=C stretching). From IR spectroscopic study, it was found that there was no evidence of interaction between drug and polymers as shown into figure 6-10

Figure 11: Thermogram of Tramadol HCl

***In vitro* drug release study of Contamal SR tablets (marketed formulation)**

Table 6: Cumulative % drug released profile of marketed formulations Contramal SR

Time (Hrs)	Cumulative % release (mean $\pm$ S.D.)						
	Formulation code						Avg $\pm$ S.D
	T ₁	T ₂	T ₃	T ₄	T ₅	T ₆	
1	21.64	22.87	23.92	22.78	26.82	21.02	23.17 $\pm$ 2.05
4	38.88	40.49	42.77	39.83	38.98	40.49	40.24 $\pm$ 1.42
8	52.11	58.91	57.47	54.79	58.93	58.35	56.76 $\pm$ 2.75
12	69.41	69.96	68.64	64.03	70.45	70.98	68.91 $\pm$ 2.53
16	80.64	79.71	76.84	78.74	81.57	84.31	80.30 $\pm$ 2.55
18	85.24	87.43	85.53	85.38	83.66	85.51	85.46 $\pm$ 1.20
20	91.61	88.20	89.48	90.04	88.58	87.83	89.30 $\pm$ 3.73
22	96.90	96.73	96.18	96.52	96.39	96.20	96.49 $\pm$ 0.29
24	100.66	100.37	99.01	99.84	99.81	99.97	99.95 $\pm$ 0.56

Figure 12: Average % cumulative drug release of six marketed formulations Contramal SR

Evaluation of powder blend

Table 7: Evaluation of powder blend

Formulation	Bulk density (mg/ml)	Tapped density (mg/ml)	Carr's index	Hausner's ratio	Angle of repose
F ₁	0.265	0.340	22.058	1.283	43.53
F ₂	0.280	0.355	21.126	1.267	37.49
F ₃	0.250	0.322	22.360	1.288	46.81
F ₄	0.193	0.311	37.940	1.611	35.23
F ₅	0.343	0.427	19.672	1.244	38.12
F ₆	0.355	0.450	21.111	1.267	38.11
F ₇	0.302	0.410	26.341	1.357	39.10
F ₈	0.323	0.448	27.901	1.387	44.30
F ₉	0.357	0.468	23.710	1.310	43.15

Various micrometrics properties of the granules from each batch are summarized in table 7. The granules of various formulations containing drug and meltable binders were evaluated for the angle of repose, Loose Bulk Density (LBD), Tapped Bulk Density (TBD), void volume, and total porosity. These In Process Quality control (IPQC) parameters were evaluated for the flow properties and the compressibility of granules.

The angle of repose for all formulations fell within the range of 16-20 indicating excellent flow.

The values for LBD and TBD were found to be in the range of 0.57 to 0.74 g/cm³ and 0.62 to 0.80 g/cm³ indicating good packing capacity.

Tablets of each formulation type (MG1 to MG9) were evaluated for parameters such as weight variation, drug content, thickness, diameter, hardness and friability given in table 8. Tablets with acceptable physical properties were obtained in all formulations studied.

Evaluation of matrix tablets

Weight variation

The % deviation in weights of tablets was $\pm 5\%$ for formulations F2, F3, F5, F6, F7, F8, and F9 while $\pm 7.5\%$ for formulations MG1 and MG3 which is within the range according to IP. This shows uniform die fill during tablet compression.

Drug content

The tablets were analyzed for potency. The drug content uniformity was in range of 95 to 100% showing uniform distribution of drug in matrix.

Thickness

As there was no much variation in thickness of tablets in each formulation, it shows that granules and powder blends were consistent in particle size and uniform behavior during compression process.

Hardness

The hardness of tablet was measured on Erweka hardness tester. The hardness was in range of 75-80N.

Friability

Friability was found to be 0.68 ± 0.03 to $0.92 \pm 0.03\%$. As friability was below 1 %tablets in each formulation can withstand the mechanical shocks. All the parameters were run 3 times (n=3).

In-vitro drug release study of TH matrix tablets

The in-vitro drug release characteristics were studied in 900 ml of pH 1.2 was used for 2 h followed by 22 h study in pH 6.8 phosphate buffer using USP type II dissolution apparatus. The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in predetermined manner.⁹

Table 8: Cumulative % drug released profile of formulation of tramadol hydrochloride containing

Time (Hrs)	Cumulative % drug release						
	Formulation code						
	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉
1	8.445	11.651	15.226	15.103	12.760	20.897	10.541
4	35.862	44.387	43.913	37.748	23.927	43.945	30.572
8	40.376	51.414	49.582	46.218	54.758	52.449	48.372
12	58.352	68.341	72.293	60.528	61.102	68.149	52.215
16	68.784	76.485	73.308	64.313	69.576	74.195	61.625
18	89.380	90.836	86.039	78.597	73.163	90.876	73.059
20	98.501	101.319	96.618	87.657	85.522	95.318	87.760
22	103.84	-	100.104	100.09	99.920	97.316	93.541
24	-	-	-	-	99.723	99.679	95.392

Figure 13: Comparison of % cumulative drug release profile of F₃, F₄ & F₅ with that of the marketed tablet Contramal SR.

Figure 14: Comparison of % cumulative drug release profile of F₆, F₇, F₈ & F₉ with that of the marketed tablet Contramal SR.

Table 9: Data treatment of dissolution results of Contramal SR and various formulations

Formulation	Zero order (R ²)	First order (R ²)	Higuchi model (R ²)	Hixson Crowell (R ²)	Kores meyer Peppas	
					(R ²)	N
Contramal SR	0.943	0.915	0.999	0.918	0.996	0.461
F ₃	0.975	0.723	0.943	0.735	0.971	0.907
F ₄	0.951	0.917	0.974	0.714	0.966	0.508
F ₅	0.957	0.831	0.979	0.807	0.976	0.581
F ₆	0.958	0.914	0.963	0.698	0.978	0.567
F ₇	0.959	0.351	0.961	0.785	0.973	0.657
F ₈	0.949	0.880	0.993	0.878	0.985	0.489
F ₉	0.971	0.844	0.947	0.917	0.983	0.668

Kinetic treatment

Higher levels of HPMC K100M and SCMC retarded the release more than that required. Formulations F₃, F₆, F₇, F₉, showed higher R² values when subjected to Kores meyer peppas treatment with varying n values. As shown into table 10.

Release exponent (n) of formulations F₃, F₆, F₇, F₉ is greater than 0.5 so the mechanism is Fickian diffusion.

Table 10: F1 (difference factor) and F2 (similarity factor) of all the formulations with respect to the Contramal SR

Formulation	F1 (difference factor)	F2 (similarity factor)
F ₃	27.79	18.52
F ₄	37.35	12.11
F ₅	21.96	19.19
F ₆	24.59	18.86
F ₇	26.02	18.69
F ₈	4.71	65.18
F ₉	13.80	42.98

Comparison of % cumulative drug release profile of the formulations with that of the marketed formulation Contramal SR

Formulations F₈ were found to be closest to that of the marketed formulation with a F2 value greater than 50 which indicates that the difference between the % releases at each time point is less than 10%.

CONCLUSION

From preformulation studies, it was found that the sample of Tramadol hydrochloride is pure and suitable drug candidate for formulation of hydrophilic matrix tablets. From compatibility studies we can concluded that there was no evidence of interaction between drug and polymers. HPMC K100M, HPMC K15M, Sodium carboxy methyl cellulose, polyethylene oxide these polymers are suitable for

preparation of matrices of highly water soluble drug. The pre-compression studies of Tramadol hydrochloride granules shows that parameters like bulk density, tapped density, angle of repose complies the standards of Indian pharmacopoeia. The post-compression studies of Tramadol hydrochloride granules also shows that friability, hardness, weight variation test complies the standards of Indian pharmacopoeia and the wet granulation method is suitable for preparation of Tramadol hydrochloride matrices. From the % cumulative release study we can concluded that formulation F₈ is found to be best and optimized formulation.

It was found that matrix tablet with combination of HPMC K15 & Polyethylene oxide N-80 effectively retarded the release of drug. Matrix tablet of Tramadol hydrochloride prepared by wet granulation technique shows the drug release for prolonged duration than

marketed Sustained release preparation of Tramadol hydrochloride (Contamal SR).

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