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RESEARCH ARTICLE

FORMULATION AND DEVELOPMENT OF TRAMADOL HYDROCHLORIDE EXTENDED RELEASE TABLETS

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ABSTRACT

Objective Extended release tablets are considered as a boon to patients suffering from pain as they provide continuous availability of drugs in systemic circulation. Tramadol Hydrochloride is a water soluble opiod analgesic drug which acts centrally by blocking the pain signals sent by the nerves to brain. It is widely accepted as a drug for the treatment of osteoarthritis.

Design An attempt was made to prepare Tramadol Hydrochloride extended release matrix tablets by employing various polymers Hydroxy propyl cellulose, Ethyl cellulose, Hydroxy propyl methyl cellulose K100 and Chitosan in combinations to retard the release rates. Direct compression technique was adopted for preparing matrix tablets. Dicalcium phosphate, Magnesium stearate, Colloidal silicon dioxide were used as excipients along with rate retarding polymers.

Intervention Precompression and post compression parameters like flow properties, compressibility index, hausner's ratio, weight variation, hardness, thickness, content uniformity etc., were evaluated by appropriate methods. *Invitro* dissolution studies were performed to study the rate retarding effects of polymers.

Result Formulations containing Hydroxy propyl cellulose and Ethyl cellulose at higher concentration gave very good dissolution profile leading to extended release. Other formulations with various combinations and proportions also retarded the release rate to various levels.

Conclusion it is evident that combination of Hydroxy propyl cellulose and Ethy cellulose are suitable polymers for preparing extended release Tramadol Hydrochloride matrix tablets. Also other polymer combinations indicated a promising solution to prepare extended release matrix tablets.

Key words Tramadol Hydrochloride, Matrix, Polymer, Extended release, Hydroxy propyl cellulose, Ethyl cellulose, Hydroxy propyl methyl cellulose K100, Chitosan.

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, extended release tablets come in handy as a solution.

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[1]. It is white or almost white crystalline powder in nature.

An attempt was made in this study to prepare and evaluate extended release matrix tablets of Tramadol Hydrochloride by employing Hydroxy propyl cellulose, Ethyl Cellulose, Hydroxy propyl methyl cellulose K100 and Chitosan as rate retarding polymers in various combinations and proportions.

MATERIALS AND METHODS

M/s. Stedman Pharmaceuticals Pvt Ltd., Chennai provided Tramadol Hydrochloride BP as gift sample for this study. M/s. Safetab Life Science, Pondicherry was kind enough to provide required quantities of polymers / excipients including Hydroxy propyl cellulose, Ethyl Cellulose, Hydroxy propyl methyl cellulose K100, Di calcium phosphate, Colloidal silicon dioxide and Magnesium Stearate. Chitosan (Chitopharm M) was a gift sample from M/s Cognis. All other materials, reagents and solvents used in this study were of analytical grade.

Preparation of Extended Release Matrix Tablets

The drug, Tramadol Hydrochloride and excipients were subjected to preformulation studies for characterization. All the raw materials comprising Tramadol Hydrochloride, rate retarding polymers in various combinations & proportions and excipients including Dicalcium phosphate, Magnesium stearate and Colloidal silicon dioxide were passed through sieve No 30 and thoroughly mixed to form a uniform matrix blend. This mixed blend was compressed directly in a 16 station rotary tableting machine using 9 mm circular standard concave punches. As the process involved dry method of direct compression, the demerits of wet granulation were totally eliminated leading to energy saving. The experiment was designed in such a way that all

formulations were with three levels of polymer concentration[2].

Tablets Evaluation

The prepared tablets were subjected to weight variation, hardness, friability, thickness, diameter, drug content, dissolution and stability studies. Twenty tablets were collectively and individually weighed in a digital balance and compared with the average weight of the tablet. Hardness tester was employed to evaluate the hardness and friabilator was used to study the friability nature of the tablet. The thickness and diameter of the tablets were evaluated by using digital vernier. Release rates of the tablets were evaluated by *Invitro* dissolution studies using USP Type I basket apparatus in 0.1 N HCl at 37° C ± 0.5° C with 100 rpm. Samples were drawn for upto 10 hours and sink conditions were appropriately maintained. Samples drawn were analysed for absorbance using UV Spectrophotometer at 270 nm to study the percentage drug release at a period of time. Similarly marketed product was also subjected to *Invitro* dissolution studies to compare the release profile with test formulations.

Drug content was estimated by RP-HPLC method using Hypersil BDS C18 column. 295ml Acetonitrile and 705 ml of 0.02% v/v Trifluoroacetic acid was used as mobile phase with a flow rate of 1.0 ml/min. UV detector was used to measure the absorbance at 270 nm.

Drug- Polymer Compatibility was studied by using FT-IR and the spectra of pure drug, polymers & tablets were compared. The test formulation F3 was subjected to accelerated stability studies for 6 months at 40° C ± 2° C 75% RH ± 5% RH and evaluated for physical and chemical properties. Zero order, First order, Higuchi, Hixson- Crowell and Korsmeyer – Peppas equations were applied to test formulation F3 for performing release rate studies[3].

RESULTS AND DISCUSSION

Twelve formulations of extended release matrix tablets of Tramadol Hydrochloride 100 mg were prepared using Hydroxy propyl cellulose, Ethyl cellulose, Hydroxy propyl methyl cellulose K100 and chitosan as rate retarding polymers in various combinations and proportions (Table 2). The total ratio of polymer combination was maintained at 1:1 with 20%, 30% and 40% concentrations (Table 3). All the formulations exhibited satisfactory physico-chemical properties. The bulk density, tapped density, angle of repose, compressibility index and hausner's ratio of the blend were in the range of 0.54 – 0.72, 0.63 – 0.82, 22.2- 25.6, 12.20 – 16.66 and 1.14 -1.20 respectively (Table 1).

Table 1: Evaluation of blend

S. No	Parameters	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
1	Angle of Repose	24.6	24.8	25.2	22.2	23.2	23.4	24.8	25.4	25.6	23.2	23.6	24.2
2	Bulk Density	0.54	0.56	0.54	0.66	0.68	0.70	0.56	0.58	0.60	0.68	0.70	0.72
3	Tapped Density	0.63	0.66	0.64	0.78	0.80	0.82	0.66	0.68	0.72	0.78	0.80	0.82
4	Compressibility Index	14.28	15.15	15.63	15.38	15.00	14.63	15.15	14.70	16.66	12.82	12.50	12.20
5	Hausner's Ratio	1.16	1.18	1.19	1.18	1.18	1.17	1.18	1.17	1.20	1.15	1.14	1.14

Table 2: Formulations

S.N	Ingredients (mg)	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
1	Tramadol HCl	100	100	100	100	100	100	100	100	100	100	100	100
2	Dicalcium Phosphate	134	104	74	134	104	74	134	104	74	134	104	74
3	Hydroxy Propyl Cellulose	30	45	60	30	45	60	-	-	-	-	-	-
4	HydroxyPropyl Methyl Cellulose K 100	-	-	-	-	-	-	30	45	60	30	45	60
5	Ethyl Cellulose	30	45	60	--	-	-	30	45	60	-	-	-
6	Chitosan	-	-	-	30	45	60	-	-	-	30	45	60
7	Colloidal Silicondioxide	3	3	3	3	3	3	3	3	3	3	3	3
8	Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Total (mg)		300	300	300	300	300	300	300	300	300	300	300	300

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The weight variation of the tablets was within acceptable limits of ± 5%. The friability tests for formulations were satisfactory with values less than 1%. The tablets possessed good hardness in the range between 4.22 to 8.60 kg/cm^3. The thickness and diameter of the tablets were within 4.14 mm to 4.45 mm and 9.01 mm to 9.03 mm indicating very less variation. Assay of the tablets were found to be in the range of 97.88 to 99.04% indicating good uniformity of drug content (Table 4).

Table 3: Design of Experiment

Polymer	Ratio			
	1:1	1:1	1:1	1:1
	HPC : EC	HPC : Chitosan	HPMC K 100 : EC	HPMC K 100 : Chitosan
P 1 –20 %	F 1	F 4	F 7	F 10
P 2 –30 %	F 2	F 5	F 8	F 11
P 3 – 40%	F 3	F 6	F 9	F 12

Table 4: Evaluation of Tablets

S.N	Parameters	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
1	Weight Variation %	±2.0	±2.2	±1.8	±3.8	±4.4	±4.6	±3.4	±3.6	±3.5	±4.7	±4.5	±4.4
2	Thickness in mm	4.14 ±0.03	4.22 ±0.04	4.18 ±0.02	4.30 ±0.04	4.32 ±0.04	4.40 ±0.02	4.20 ±0.03	4.26 ±0.03	4.22 ±0.04	4.45 ±0.02	4.41 ±0.02	4.37 ±0.02
3	Diameter in mm	9.01 ±0.02	9.02 ±0.01	9.01 ±0.01	9.03 ±0.01	9.02 ±0.01	9.01 ±0.02	9.01 ±0.01	9.01 ±0.02	9.02 ±0.02	9.03 ±0.03	9.03 ±0.02	9.02 ±0.01
4	Friability %	0.68 ±0.13	0.62 ±0.12	0.72 ±0.12	0.80 ±0.10	0.78 ±0.12	0.82 ±0.14	0.58 ±0.18	0.60 ±0.22	0.68 ±0.16	0.76 ±0.14	0.74 ±0.18	0.80 ±0.16
4	Hardness in kg/cm^3	8.24 ±0.6	8.40 ±0.4	8.60 ±0.5	5.48 ±0.4	5.10 ± 0.6	4.80 ±0.4	7.10 ±0.2	6.88 ±0.3	6.52 ±0.2	4.22 ±0.4	4.60 ±0.2	4.52 ±0.3
5	Assay (Drug Content)	98.72 ±0.66	99.04 ±0.26	99.12 ±0.18	97.98 ±0.10	98.14 ±0.28	98.28 ±0.60	99.06 ±0.58	98.77 ±0.44	98.90 ±0.22	97.88 ±0.18	98.04 ±0.34	98.14 ±0.30

Dissolution studies indicated that all the formulations retarded drug release at various levels. Formulation F3 containing Hydroxy propyl cellulose[4-6] and Ethyl cellulose[7-9] at 40% concentration in the ratio of 1:1 gave a release for upto 10 hours (Table 5).

Table 5: Dissolution Profile

Sampling Time in hours	Percentage Drug Released												
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12	Market Product
1	50.18	37.90	33.16	57.69	53.08	36.11	58.74	51.12	38.45	59.14	57.90	51.38	30.54
2	67.80	54.17	48.94	80.34	65.18	55.42	82.50	66.40	56.80	81.72	80.12	66.85	45.68
4	86.15	77.12	68.07	97.92	85.05	78.81	97.54	86.55	76.15	96.12	95.48	86.57	70.51
6	95.92	89.28	80.52	-	96.42	90.16	-	95.98	88.82	-	-	96.10	83.92
8	-	96.06	90.04	-	-	96.38	-	-	97.44	-	-	-	96.14
10	-	-	95.88	-	-	-	-	-	-	-	-	-	-

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Formulations F2 containing Hydroxy propyl cellulose + Ethyl cellulose[10,11] at 30% concentration, F6 containing Hydroxy propyl cellulose + Chitosan[12-14] at 40% concentration and F9 containing Hydroxy propyl methyl cellulose K100[15] + Ethyl cellulose at 40% concentration gave a release for upto 8 hours and was comparable with marketed product which also gave a similar release for upto 8 hours.

Formulations F1 containing Hydroxy propyl cellulose + Ethyl cellulose at 20% concentration, F5 containing Hydroxy propyl cellulose + Chitosan at 30% concentration, F8 containing Hydroxy propyl methyl cellulose K100 + Ethyl cellulose at 30% concentration and F12 containing Hydroxy propyl methyl cellulose K 100 + Chitosan at 40% concentration gave a release for upto 6 hours.

Formulations F4 containing Hydroxy propyl cellulose + Chitosan at 20% concentration, F7 containing Hydroxy propyl methyl cellulose K100 + Ethyl cellulose at 20% concentration, F10 containing Hydroxy propyl methyl cellulose K100 + Chitosan at 20% concentration and F11 containing Hydroxy propyl methyl cellulose K100 + Chitosan at 30% concentration retarded the release for only upto 4 hours (Fig 1A ad 1 B).

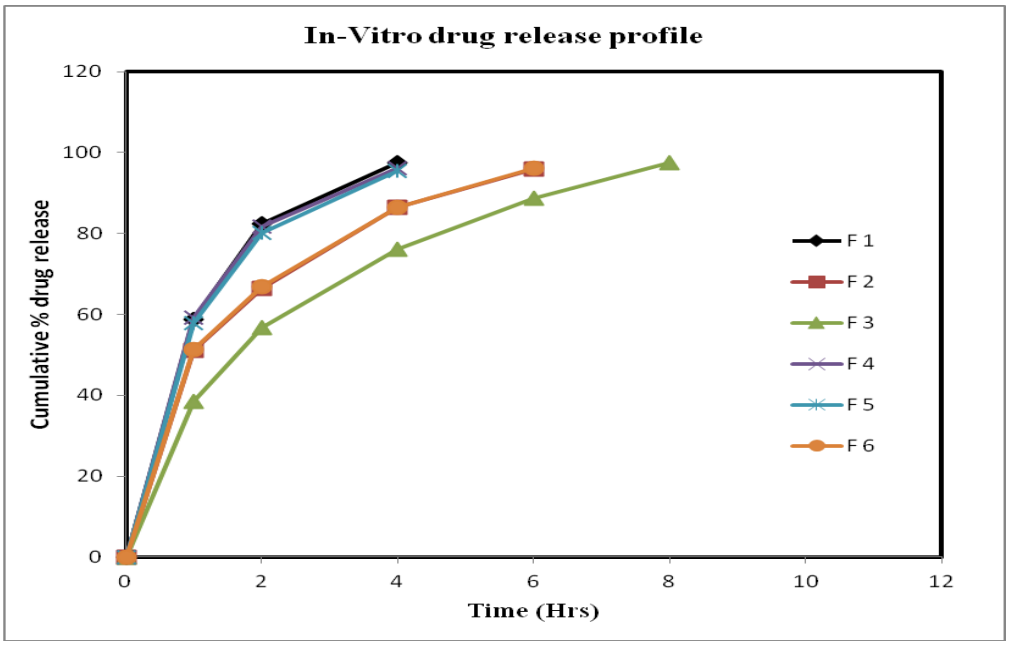

Figure 1A: Dissolution Profile

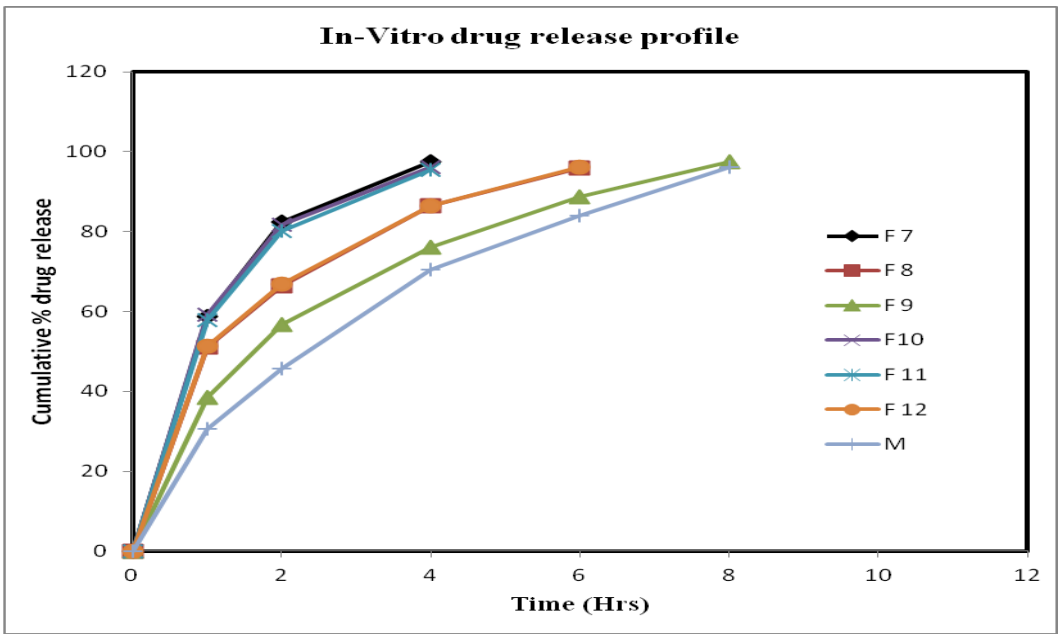

Figure 1B: Dissolution Profile

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Dissolution studies of the formulations indicated F3 as a better composition when compared to other formulations as it gave a maximum release for upto 10 hours. Release rate studies indicated that F3 followed Hixson crowell, Korsmeyer - Peppas and Higuchi equations with regression values of 0.9988, 0.9928 and 0.989 respectively. The First order and zero order plots gave regression values of 0.986 and 0.9398 respectively.

FT-IR studies performed on formulation F-3 indicated that there was no incompatibility between the drug Tramadol Hydrochloride and polymers Hydroxy propyl cellulose and Ethyl cellulose. The IR spectrum of Pure Drug, Polymers - Hydroxy propyl cellulose & Ethyl cellulose and Tablet F3 were taken and investigated for any additional peaks. Characteristic prominent peaks at 1606, 1578 of pure drug – Tramadol Hydrochloride and peaks at 1604, 1579 of tablet F3 containing were visible in the spectrum. This clearly indicated that there is no incompatibility between drug and polymers (Fig 2).

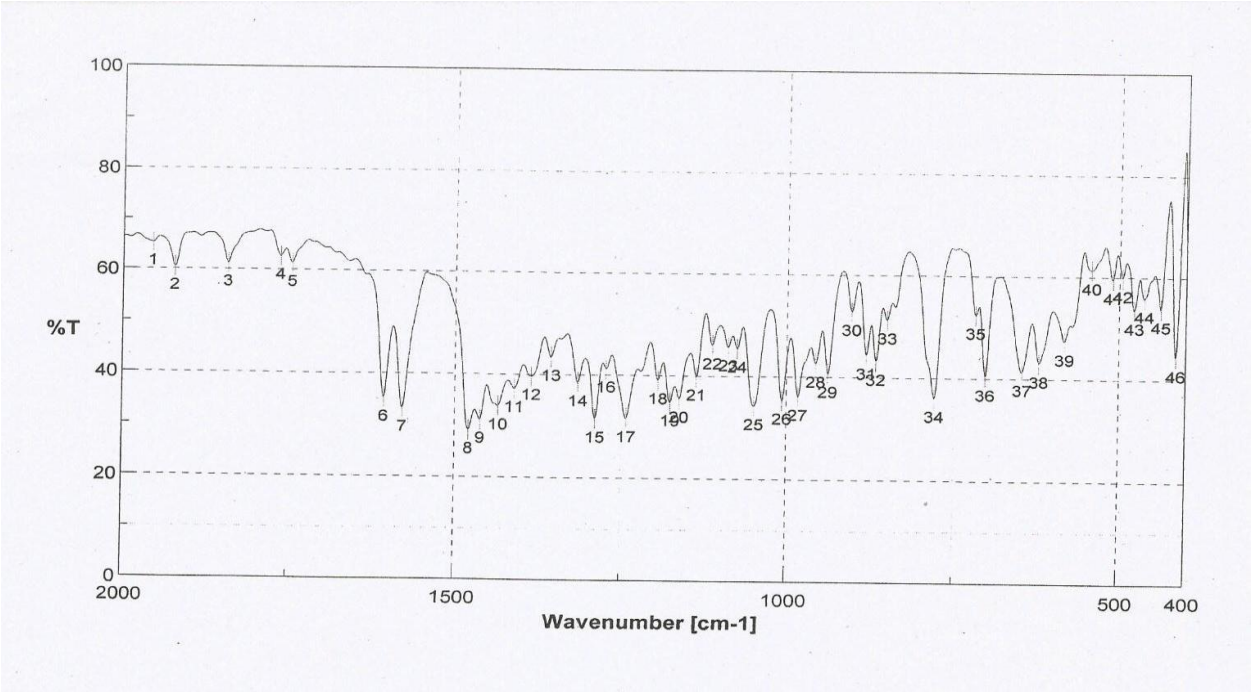

Figure 2A: FT-IR Spectrum of Pure Drug

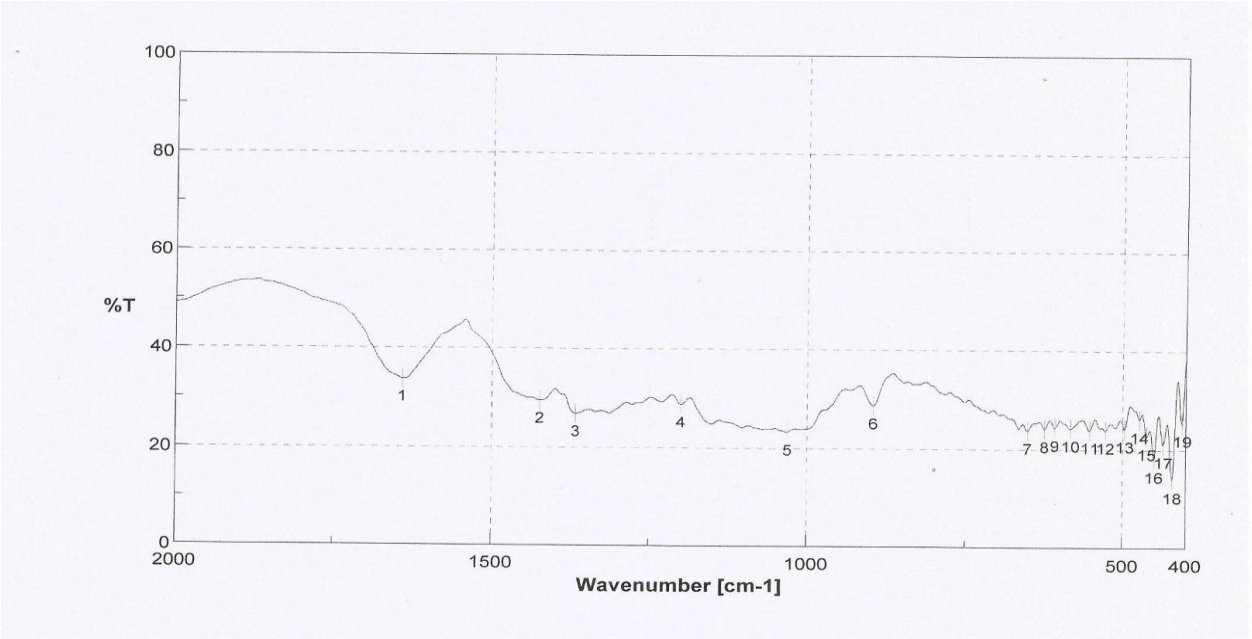

Figure 2B: FT-IR Spectrum of Polymer (HPC)

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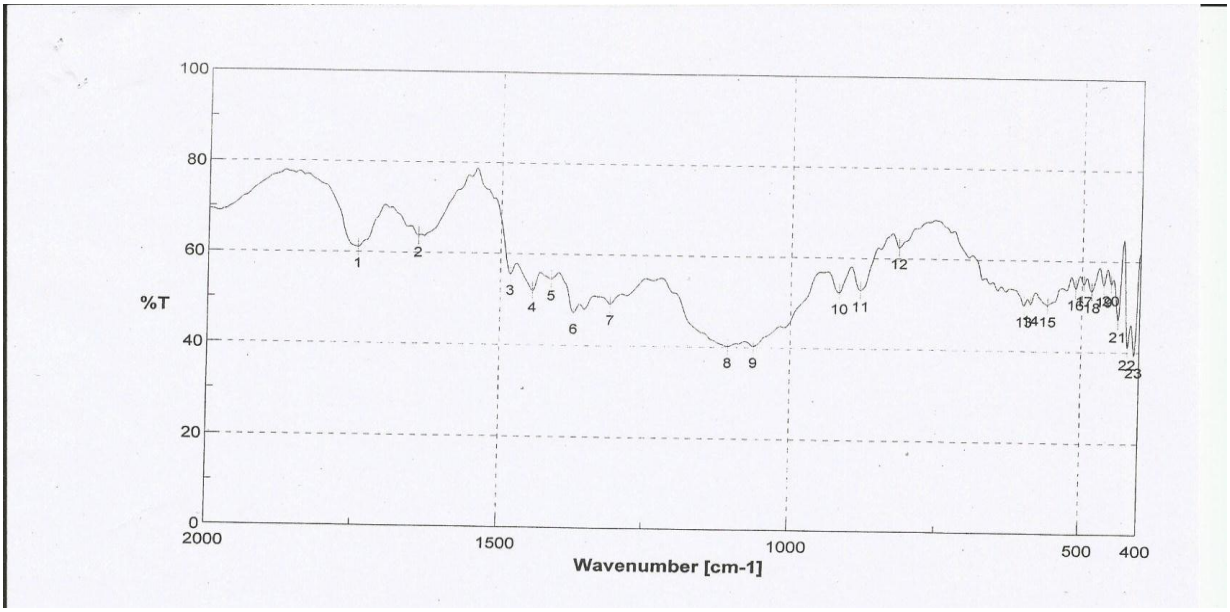

Figure 2C: FT-IR Spectrum of Polymer (EC)

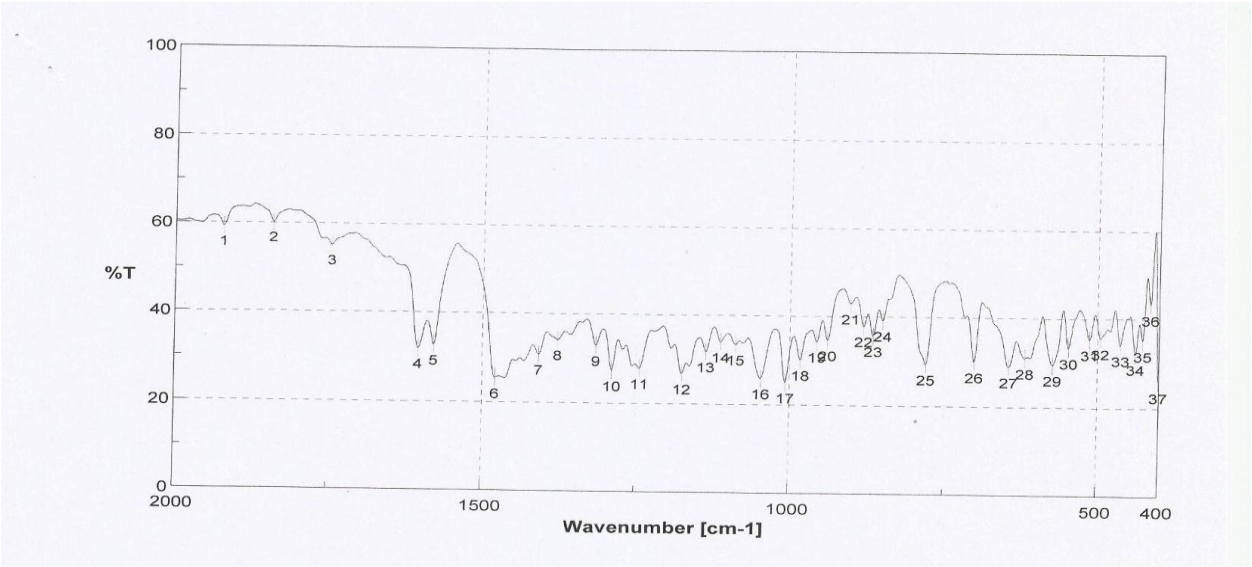

Figure 2D: FT-IR Spectrum of F 3 Tablet

Accelerated stability studies performed on tablet F3 for a period of 6 months gave satisfactory results on physical and chemical properties indicating a stable formulation[16] (Table 6).

Table 6: Stability Studies of F3

No. of Months	Temperature in ° C ± 2 ° C	Relative Humidity in % ± 5 %	Hardness in kg/cm^3	Thickness mm	Diameter mm	Friability %	Assay in %
Initial	40	75	8.60	4.17	9.01	0.72	99.12
1	40	75	8.50	4.17	9.02	0.74	99.88
3	40	75	8.40	4.17	9.01	0.78	98.94
6	40	75	8.50	4.18	9.01	0.74	98.12

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CONCLUSION

The evaluation of formulations F1 to F12 indicate that F3 containing Hydroxy propyl cellulose and Ethyl cellulose at 40% concentration in the ratio of 1:1 is a suitable composition for preparing extended release matrix tablets of Tramadol Hydrochloride (100 mg) when long action is desired. Higuchi and Hixson crowell equation best defines the release pattern indicating dissolution and diffusion as the mechanisms. Korsmeyer – Peppas equation indicated the anomalous diffusion with an 'n' value of 0.46. Other formulations also retarded the drug release to various levels based on their proportions and concentration. The present study indicates that the polymers are directly proportional in retarding the drug release.

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