International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.5, No.2, pp 492-500, April-June 2013

Development And Invitro Characterization Of Tramadol Hydrochloride Sustained Release Tablets

B.Selvaraj[1], P.Malarvizhi[1] and P.Shanmugapandiyan[2]*[*]

[1]Prist University, Thanjavur - 613403, Tamilnadu, India.
[2]Mohamed Sathak A.J College of Pharmacy, Sholinganallur, Chennai- 600119, Tamilnadu, India.

***Corres.author: shanmugapandiyan@gmail.com**
Phone.No: 044-24502572,Fax.No: 044-24502573
Mobile.No: 09952923477

Abstract: Tablets are the most preferred formulations with wide acceptance of around 50 – 60% when compared to other dosage forms. Ease of administration, manufacturing, storage and transport makes it to the number one level. Among tablets, sustained or extended or prolonged release tablets provide advantages such as once/twice daily administration, continuous delivery of drug into systemic circulation and benefits to patients for compliance. In this study, an attempt was made to prepare and characterize novel sustained release tablets of freely water soluble drug Tramadol Hydrochloride using a polymeric matrix system. The matrix system adopted in this study had Hydroxy Propyl Cellulose and Hydroxy Propyl Methyl Cellulose K 100 as rate retarding polymers individually as well as in combinations and direct compressible diluents such as Di Calcium Phosphate. The process employed direct compression technique to make it as one of the cost effective affordable and reliable method for the preparation. Tramadol Hydrochloride is an opiod analgesic which works by mimicking the action of naturally occurring pain reducing chemicals called endorphins. It blocks the transmission of pain signals sent by the nerves to the brain. Tramadol Hydrochloride is fairly a strong pain killer used in the management of moderate to severe pain. Various formulations with different proportions of Drug: Polymer were tried to optimize the process and release of the drug. The pre-compression parameters were characterized for flow properties, compressibility index and other physical properties. All the formulations exhibited good physical properties. The rate retarding effects of polymers were studied by *invitro* dissolution studies which indicated that the higher level of polymer Hydroxy Propyl Cellulose in the formulation retarded the release of Tramadol Hydrochloride. The release rates of the polymer Hydroxy Propyl Cellulose were studied using zero order, first order, higuchi, korsmeyer peppas, and hixson crowell plots. Hixson crowell and Korsmeyer peppas plots were the best fit for the formulation containing Hydroxy Propyl Cellulose at higher concentration. Drug/Polymer compatibility was confirmed through IR spectral studies and DSC studies. XRD studies were also done to study the crystallinity of the drug. Stability studies of the tablets were performed at accelerated conditions for six months and there was no significant change in the release pattern, drug content and other physical properties. It is evident from this study that sustained release tablets of Tramadol Hydrochoride could offer a 12 hour release using Hydroxy Propyl Cellulose matrix system.

Keywords: Matrix System, Sustained Release, Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose K 100, Tramadol Hydrochloride

Introduction

Tramadol Hydrochloride is a synthetic analgesic used to treat moderate to moderately severe pain[1]. It is a centrally acting drug with wide range of applications, including treatment of arthritis. Tramadol is a very weak opioid receptor agonist which induces serotonin release and inhibits the uptake of nor epinephrine[2,3]. Tramadol HCl is white or almost white crystalline powder freely soluble in water and methanol.

Orally administered dosage forms enjoy more preference over other dosage forms among the patients due to ease of administration, storage, transport etc. However they suffer from certain disadvantages such as repeated administration, patient compliance etc. To overcome these issues, sustained release tablets come in hand to support compliance coupled with therapeutic advantage to patients. An attempt was made to develop sustained release matrix tablets of Tramadol HCl using Hydroxy propyl cellulose and Hydroxypropyl methyl cellulose K100 as rate retarding polymers[4].

Experimental

Materials and Methods

Tramadol Hydrochloride was obtained from M/s. Stedman Pharmaceuticals Pvt Ltd, Chennai as gift sample. Excipients[5] Dicalcium phosphate, Hydroxy propyl cellulose, Hydroxypropyl methyl cellulose K100, Magnesium stearate, Colloidal silicon dioxide of Pharmacopoeial grades were obtained as gift samples from M/s Safetab Life sciences, Puducherry. Other materials, reagents and solvents used were of an analytical grade.

Preparation of Tablets

Pre formulation studies were carried out for designing the experiments which involved thorough literature search, compatibility studies, evaluation of granules, factorial design etc. The study was designed in such a way that it involved few excipients and minimum process methods.

Matrix tablets[6] were prepared using direction compression method by simple admixing of raw materials. Tramadol with other excipients Dicalcium Phosphate, Magnesium Stearate, Colloidal silicon including rate retarding polymers (Hydroxy propyl cellulose and Hydroxypropyl methyl cellulose K100 individually as well as in combinations.) were admixed thoroughly after sieving through 60# mesh and the blend directly compressed. The blend exhibited good flow properties(Table – 1). The various formulations employed in the present study are tabulated in Table – 2.

Direct compression is a dry process which eliminates moisture, complex granulation stages and there by provide better product stability with energy and resources conservation. 3^2 Factorial design was involved in the Design Of Experimet (DOE) as there were three levels of polymer concentration and two variable polymers(Table -3). The tablets were compressed by using 9mm standard circular concave punches in a 16 station rotary compression machine. The compressed tablets exhibited good physical properties.

Evaluation of Matrix Tablets

Tablets were evaluated for weight variation, hardness, friability, thickness, dissolution, drug content and stability(Table – 4). Twenty tablets were weighed collectively and individual weight was compared with average weight to access weight variation of tablets. The strength of the tablets i.e. Hardness and friability were tested using hardness tester friabilator. Digital vernier was used to determine the thickness and diameter of tablet.

Dissolution studies[7] were performed by using USP Type I basket apparatus in two different mediums 0.1N HCl and pH 6.8 Phosphate buffer at 37ºC ± 0.5 ºC with 100 rpm to evaluate the rate of dissolution. However 0.1 N HCl medium was taken into consideration as there was no significant difference in the results among both the mediums and also since acidic medium forms the starting GI condition. Aliquots were withdrawn for upto 12 hours and sink conditions maintained by replenishing the media. Samples were tested for their absorbance at 270 nm to evaluate the rate of drug release. Marketed sample was also used to compare the dissolution profile with the test samples(Table – 5, Fig – 1).

Drug content of the tablets were evaluated by HPLC method using Hypersil BDS C18 column, Acetonitrile/Triflour acetic acid as mobile phase (295 ml acetonitrile: 705 ml, 0.2 % v / v Trifluor acetic acid) with a flow rate of 1.0 ml/min and UV detector to measure the absorbance at 270nm. Compatibility studies for F3 were performed by using FT-IR and DSC to compare the spectra, melting point of pure drug, polymer and tablet (Fig – 2,3,4,5). XRD studies were also performed to study the crystallinity of the drug (Fig – 6,7,8).

Accelerated stability studies of the test samples F3 were performed for 6 months at 40ºC±2ºC & 75% RH±5%RH and evaluated for physico chemical properties (Table –6). Release rate studies for F3 were performed by applying zero order, first order[8], higuchi, hixson-crowell and kores-meyar peppas equation.

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
1	Angle of Repose	25.2	24.8	25.2	24.6	24.8	25.0	23.8	24.2	25.4
2	Bulk Density	0.60	0.56	0.51	0.62	0.60	0.52	0.66	0.60	0.54
3	Tapped Density	0.68	0.64	0.58	0.70	0.67	0.60	0.74	0.68	0.62
4	Compressibility Index	11.76	12.50	12.06	11.42	10.44	13.33	10.81	11.76	12.90
5	Hausner's Ratio	1.13	1.14	1.13	1.13	1.11	1.15	1.12	1.13	1.14

Table – 2 Formulations

S.No	Ingredients (mg)	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
1	Tramadol HCl	100	100	100	100	100	100	100	100	100
2	Dicalcium Phosphate	134	104	74	134	104	74	134	104	74
3	Hydroxy Propyl Cellulose	60	90	120	-	-	-	30	45	60
4	HydroxyPropyl Methyl Cellulose K 100	-	-	-	60	90	120	30	45	60
5	Colloidal Silicondioxide	3	3	3	3	3	3	3	3	3
6	Magnesium Stearate	3	3	3	3	3	3	3	3	3
Total (mg)		300	300	300	300	300	300	300	300	300

Table – 3 Design of Experiment

Polymer	Ratio		
	1:0	1:0	1:1
	HPC	HPMC K 100	HPC : HPMC K 100
P 1 –20 %	F 1	F 4	F 7
P 2 –30 %	F 2	F 5	F 8
P 3 – 40%	F 3	F 6	F 9

Table – 4 Evaluation of Tablets

S.No	Parameters	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
1	Weight Variation %	±3.2	±3.4	±2.9	±4.6	±3.8	±4.5	±4.5	±4.7	±4.1
2	Thickness in mm	4.22 ±0.04	4.31 ±0.05	4.30 ±0.03	4.21 ±0.05	4.20 ±0.03	4.30 ±0.02	4.40 ±0.04	4.41 ±0.02	4.40 ±0.03
3	Diameter in mm	9.05 ±0.01	9.10 ±0.02	9.02 ±0.01	9.11 ±0.01	9.03 ±0.02	9.06 ±0.03	9.12 ±0.02	9.10 ±0.03	9.01 ±0.03
4	Friability %	0.66 ±0.15	0.58 ±0.14	0.61 ±0.12	0.71 ±0.13	0.75 ±0.12	0.77 ±0.15	0.65 ±0.22	0.69 ±0.20	0.70 ±0.21
4	Hardness in kg/cm^3	11.5 ±0.5	10.4 ±0.6	10.5 ±0.5	11.0 ±0.4	10.5 ± 0.3	10.8 ±0.6	10.6 ±0.4	10.2 ±0.3	11.0 ±0.2
5	Assay (Drug Content)	99.41 ±0.51	99.70 ±0.88	99.07 ±0.12	99.77 ±0.14	99.98 ±0.22	100.28 ±0.80	100.08 ±0.51	99.48 ±0.36	99.87 ±0.28

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	Market Product
1	36.12	35.06	33.14	48.08	42.22	35.42	40.33	41.19	37.42	30.54
2	52.24	50.02	48.90	64.78	59.14	50.11	54.26	55.28	49.44	45.68
4	74.47	71.65	64.56	88.66	78.37	70.54	75.88	76.96	73.17	70.51
6	86.08	82.52	75.24	98.97	89.15	82.52	88.46	89.90	87.72	83.92
8	95.49	91.94	82.76	-	95.82	89.30	96.10	96.86	96.02	96.14
10	-	95.23	90.12	-	-	96.04	-	-	-	-
12	-	-	96.18	-	-	-	-	-	-	-

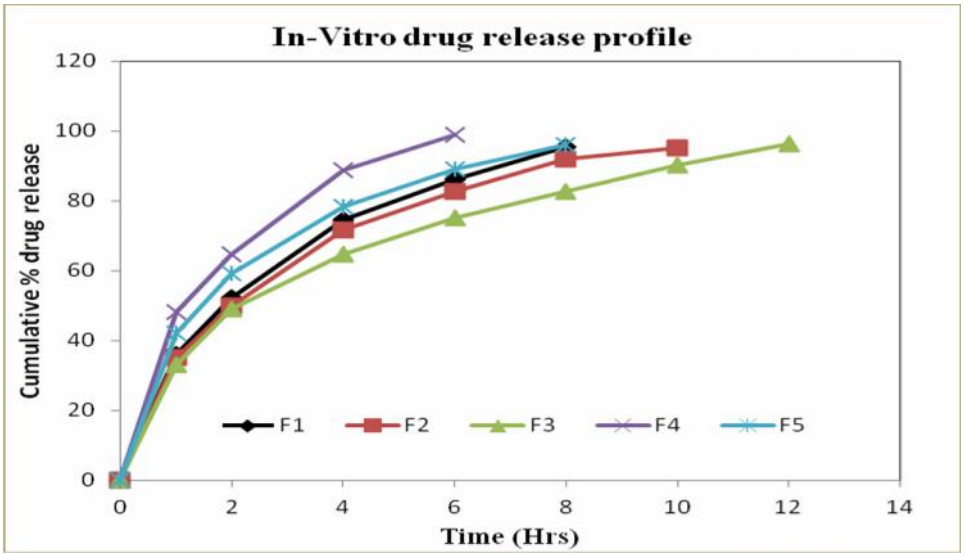

Fig - 1.a Dissolution Profile

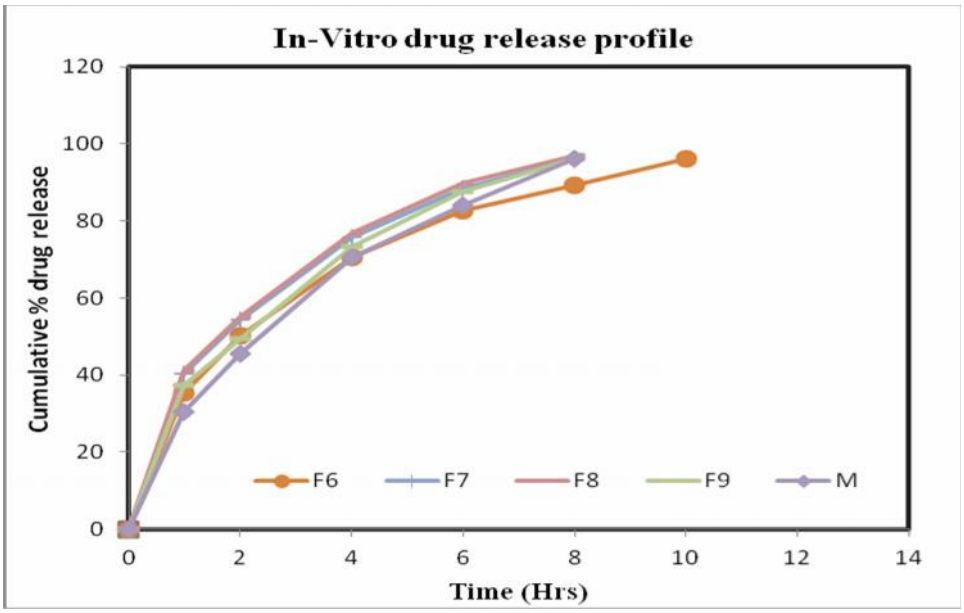

Fig - 1.b Dissolution Profile

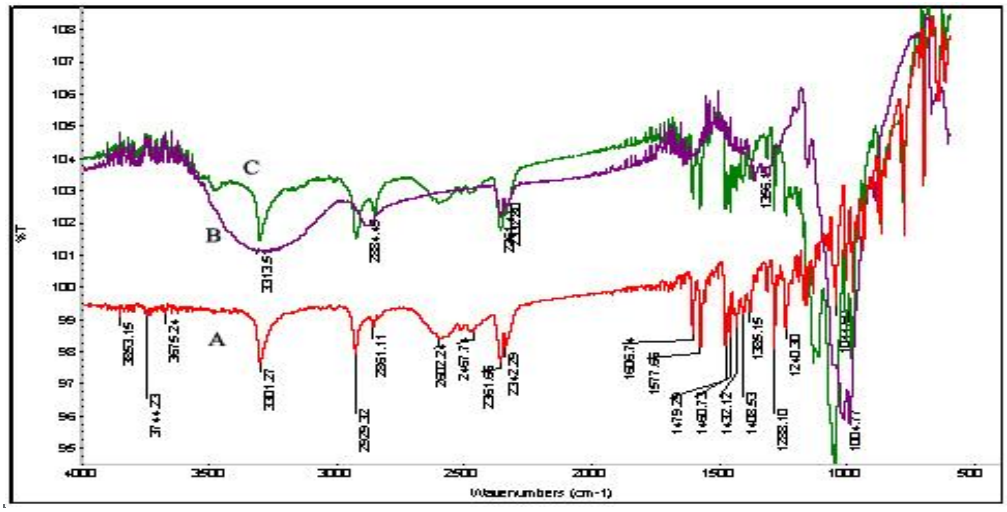

Fig – 2 FT-IR Spectrum
A (Red)– Pure Drug, B (Purple)– Polymer, C(Green) – Tablet, F3

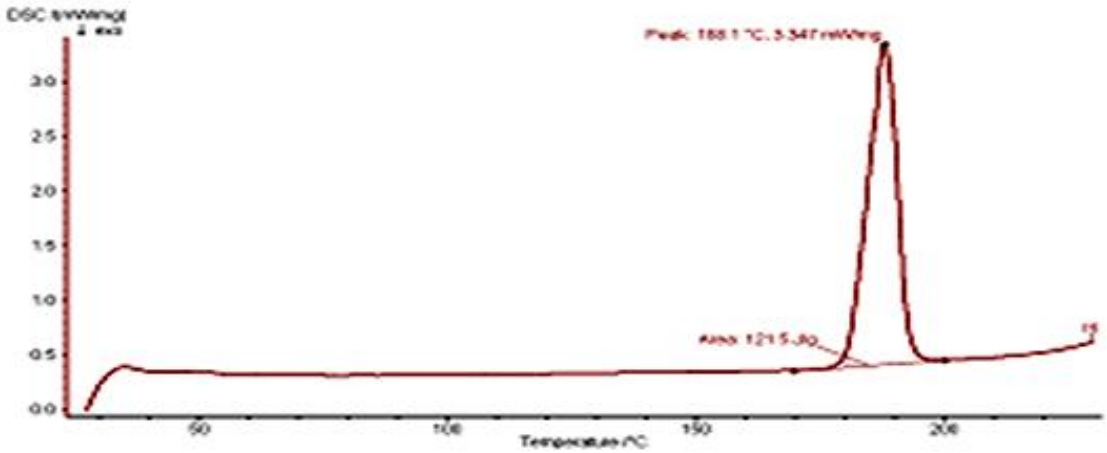

Fig – 3 DSC Spectrum – Pure Drug

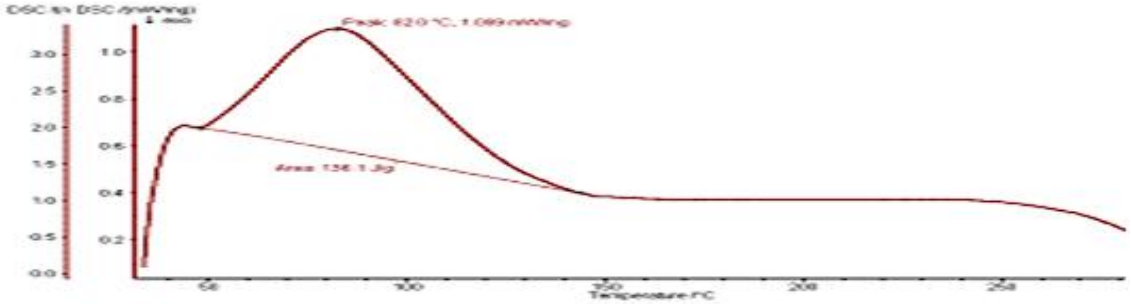

Fig – 4 DSC Spectrum – Polymer

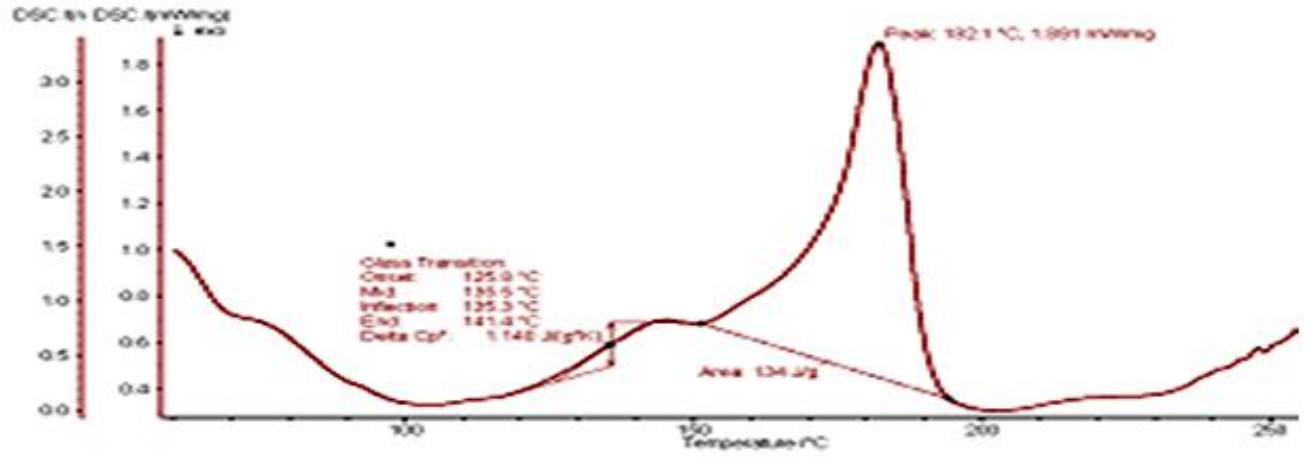

Fig – 5 DSC Spectrum – Tablet, F3

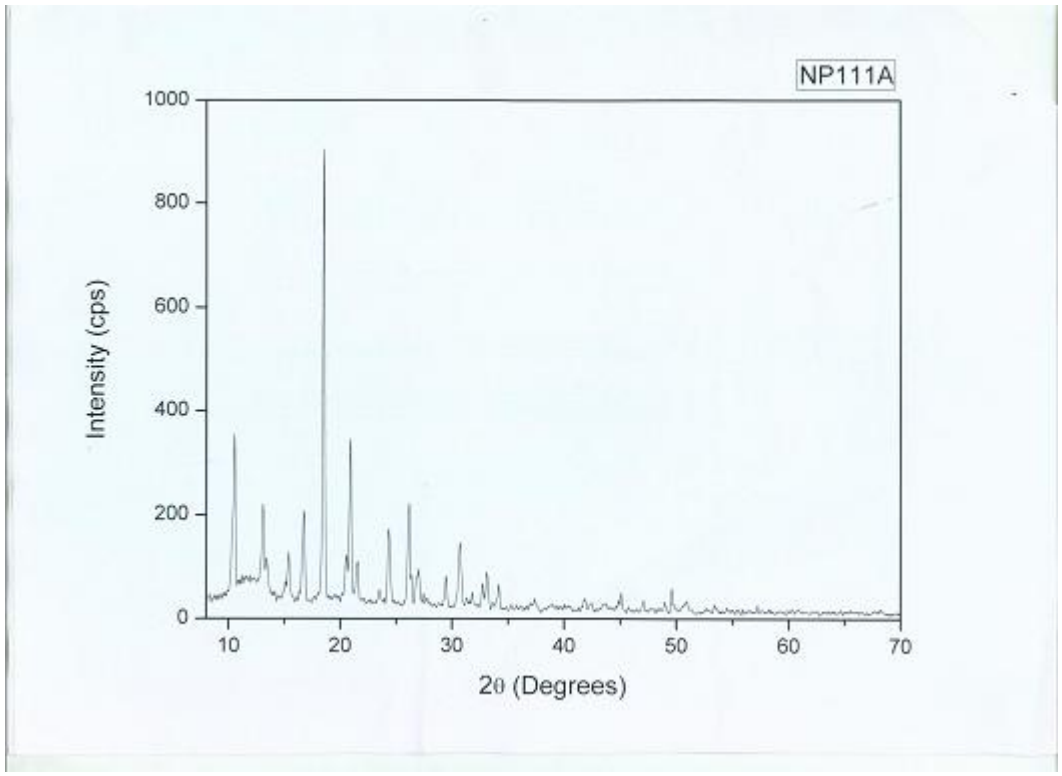

Fig – 6 XRD Spectrum – Pure Drug

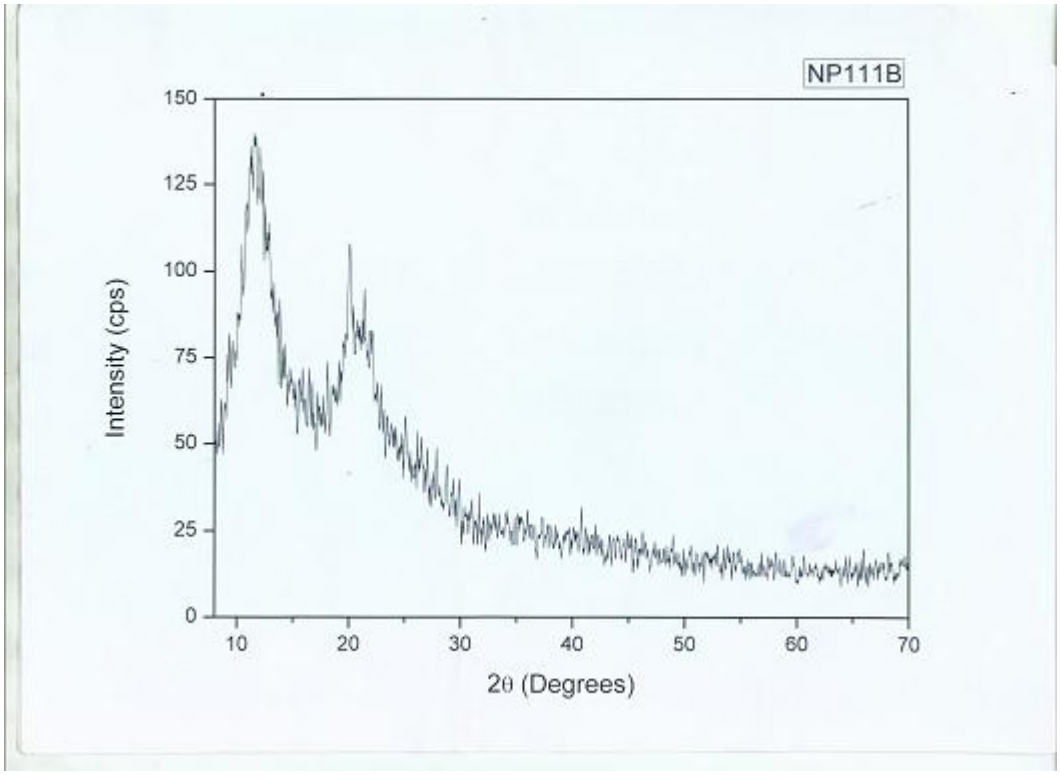

Fig – 7 XRD Spectrum – Polymer

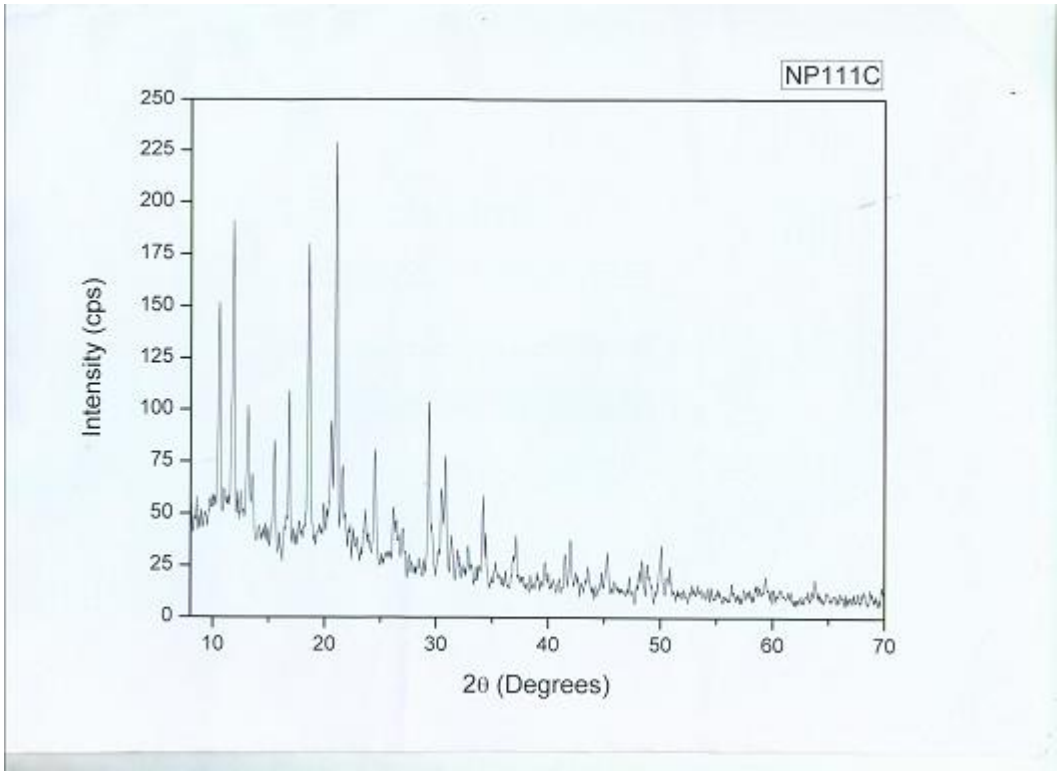

Fig – 8 XRD Spectrum – Tablet, F 3

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	10.5	4.30	9.02	0.61	99.07
1	40	75	10.6	4.31	9.06	0.72	101.88
3	40	75	10.6	4.22	9.11	0.74	98.94
6	40	75	10.5	4.19	9.05	0.69	99.12

Results And Discussion

Nine formulations of Tramadol Hydrochloride 100 mg sustained release tablets were arrived using Hydroxy Propyl Cellulose and Hydroxypropyl Methyl Cellulose K100 as rate retarding polymers. Hydroxy Propyl Cellulose and Hydroxypropyl Methyl Cellulose K100 were used at various concentrations (20%, 30% & 40%) individually and also in combinations (10%+10%, 15%+15%, & 20%+20%). All the formulations exhibited good flow properties[9] and compressibility index. The bulk density, tapped density, angle of repose, compressibility index and hausner's ratio of the blend were in the range of 0.51 - 0.66, 0.58 – 0.74, 23.8 – 25.40, 10.81 – 13.33 and 1.11 – 1.15 respectively.

The weight variation of the tablets was within acceptable limits and ranged within ± 5%. The tablets possessed very good friability and were <1% with a hardness ranging from 10.2 kg/cm^3 to 11.5 kg/cm^3. The thickness and diameter of the tablets was within 4.2mm to 4.41mm and 9.01 to 9.11 mm indicating very minimal variation. Drug content was found to be in the range of 99.07% to 100.28% indicating a very good blend of the tablet.

The results of dissolution studies indicated that all the formulations were independent of pH conditions and gave the same release pattern. All the formulations retarded the release of drug from matrix tablets for long hours. Formulation F3 containing Hydroxy propyl cellulose at 40% concenttration gave a release for upto 12 hours when compared to F2 at 30% concentration and F1 at 20% concentration which gave upto 10 hours & 8 hours respectively.

Compositions containing Hydroxypropyl Methyl Cellulose K100 were comparable to Hydroxy Propyl Cellulose containing formulations. However the period of release for Hydroxypropyl Methyl Cellulose K100 formulations were upto 10 hrs, 8 hrs and 6 hrs for F6, F5, & F4 respectively. Combinations of Hydroxy Propyl Cellulose & Hydroxypropyl Methyl Cellulose K100 also delivered almost similar to stand alone polymer formulations. F7, F8 & F9 gave a release for upto 8 hrs.

Marketed product gave a release for upto 8 hrs under similar conditions. Dissolution studies indicated formulation F3 containing Hydroxy propyl cellulose at 40% is a better formula for maximum period of release. Release rate studies indicate that F3 followed Hixson Crowell and Korsmeyer Peppas equations with a regression value of 0.9928 and 0.9914 respectively. Higuchi, First order and Zero order plots gave regression values of 0.9889, 0.9643 and 0.9372 respectively.

Formulation F3 was subjected to FT-IR studies and the results indicated that there was no incompatibility between the drug Tramadol HCl and polymer Hydroxy propyl cellulose. The IR Spectrum[10,11] of pure drug - Tramadol HCl, polymer - Hydroxy propyl cellulose and tablet F3 were taken and investigated for any additional peaks. Prominent sharp peaks at 3301, 2861 of pure drug - Tramadol HCl and sharp peaks at 3313, 2884 of tablet F3 were visible in the spectrum. This clearly proves that there is no incompatibility. It is evident that only slight shift in some of the functional groups of the drug - Tramadol HCl took place with overlapping and broadening. No prominent new peaks were detected in the FT-IR spectra of tablet F3 indicating no interaction between the drug - Tramadol HCl and polymer Hydroxy propyl cellulose.

DSC studies was conducted to evaluate the melting behavior of pure drug Tramadol HCl, polymer-Hydroxy Propyl Cellulose and tablet F3. DSC of pure drug Tramadol HCl showed an endothermic peak at 188.1 ºC which is an indication of its melting point. Similarly an endothermic peak at 182.1 ºC was observed in the DSC spectrum of tablet F3 indicating the chemical stability of Tramadol HCl in the formulation.

XRD studies were performed to identify the crystallographic properties of drug Tramadol HCl, polymer Hydroxy propyl cellulose and tablet F3. Tramadol HCl showed characteristic intense peaks between 2 θ of 10º and 30º due to the crystalline nature. However the intensity of peaks is reduced in the spectrum of tablet F3. This is due to the reduced crystallinity of drug when it is mixed with polymer matrix.

The stability studies performed on F3 for a period of 3 months at accelerated conditions gave satisfactory results on physico chemical properties. These results indicated that the F3 is a stable composition.

Conclusion

The overall evaluation of formulations F1 to F9 indicate that F 3containing Hydroxy propyl cellulose at 40% is a suitable composition for producing sustained release matrix tablets of Tramadol Hcl (100 mg) where an action of upto 12 hours is desired. The Hixson Crowell and Higuchi equation best defines the release pattern indicating both dissolution and diffusion. Korsmeyer Peppas equation indicated the fickian diffusion with an' n' value of 0.41.

Formulations of Hydroxypropyl methyl cellulose K100 F4, F5, F6 are also good in retarding the release rate of drug for an extended period. The present study indicates that proportion of polymers is directly influential in retarding the release of drug. Higher concentration of polymers yield much more extended period of release. The release rates are not modified by the pH conditions (1.2 & 6.8) in all the formulations.

References

1. Bernard R Rubin, DO, Osteoarthritis, Journal American Osteopathic Association, 2001, 101(4), 2s-5s.
2. Flaminia Coluzzi , Consalvo Mattio, Chronic non cancer pain: Focus on once daily Tramadol formulations, Journal of Therapeutics and Clinical Risk Management, 2007, 3(5), 819-829.
3. Tramadol in acute and chronic non malignant pain, ACC Review, December 2005, 24, 11-12. (http://www.acc.co.nz)
4. Gentle.R., Kaushik.B., Verma.S., Patel.R., Singh.S.K and Namdeo.K.P., Formulation and evaluation of sustained release matrix tablet of Tramadol Hydrochloride, International Journal of ChemTech Research, 2010, 2(1), 4-10.
5. Raymond C Rowe, Paul J Sheskey, Marian E Quinn, Handbook of Pharmaceutical Excipients, 6th Edition, 2009, 317-321. (http://www.pharmapress.com)
6. D.M. Brahmankar, Sunil.B.Jaiswal, Textbook of BioPharmaceutics and Pharmacokinetics, Vallabh prakashan, Newdelhi, 1995, 215-219.
7. Raghavendra Rao N.G, Gandhi Sagar, Patel Tarun, Formulation and evaluation of sustained release matrix tablet of Tramadol Hydrochloride, International Journal of Pharmacy and Pharmaceutical Sciences, 2009, 1(1), 60-70.
8. Leon Lachman, Herbert A Liberman, Joseph L Kanig, The Theory and Practice of Industrial Pharmacy, 3rd Edition, Lea & Febiger, 1986, 66-95.
9. Deepthi Kodam, Prabhakar Reddy Veera Reddy, Saritha Garrepalli, Formulation and evaluation of Tramadol Hydrochloride sustained matrix tablets, Scholars Research Library, Der Pharmacio Letter, 2011, 3(3), 245-249.
10. S.Ravisankar, Text Book of Pharmaceutical Analysis, 4th Edition, Rx Publication, Tirunelveli, 2010, 5.6.
11. R.M.Silverstein, G.Clayton Bassler and Terence C.Morrill, Spectrometric identification of organic compounds, 5th Edition, John Wiley & sons, 1991, 100-131.

*****