



FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF TRAMADOL HYDROCHLORIDE

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ABSTRACT

The main objective of the present work was to develop sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and natural gums like Karaya gum (KG) and Carrageenan (CG). Varying ratios of drug and polymer like 1:1 and 1:2 were selected for the study. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of three different rate controlling material. After evaluation of physical properties of tablet, the *in vitro* release study was performed in 0.1 N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. Different ratios like 80:20, 60:40, 50:50, 40:60 and 20:80 were taken. Dissolution data was analyzed by Korsmeyer-Peppas power law expression and modified power law expression. It was observed that matrix tablets contained polymer blend of HPMC/CG were successfully sustained the release of drug upto 12 hrs. Among all the formulations, formulation F16 which contains 20% HPMC K15M and 80% of CG release the drug which follow Zero order kinetics via, swelling, diffusion and erosion and the release profile of formulation F16 was comparable with the marketed product. Stability studies (40±2°C/75±5%RH) for 3 months indicated that Tramadol hydrochloride was stable in the matrix tablets. The DSC and FTIR study revealed that there was no chemical interaction between drug and excipients.

Keywords: Tramadol Hydrochloride, Carrageenan Gum, Karaya gum, HPMC K 15 M, Matrix tablets, zero-order release.

INTRODUCTION

Tramadol is a non-steroidal anti-inflammatory drug, which is used in the treatment of osteoarthritis when NSAIDs like acetaminophen, or COX-2 inhibitors alone produce inadequate pain relief. After oral administration, tramadol is rapidly and almost completely absorbed. Sustained-release tablets reach to peak concentrations after 4.9 hrs and have a bioavailability of 87% to 95% compared with capsules. The mean elimination half-life is ~6 hrs and requires dosing every 6 hrs in order to maintain optimal relief of chronic pain. Consequently, once-daily extended-release tablets have been formulated. Long term treatment with sustained-release tramadol once daily is

generally safe in patients with osteoarthritis or refractory low back pain and is well tolerated. It has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep, and improved compliance¹⁻³. Tramadol, a synthetic opoid of the aminocyclohexanol group, is a centrally acting analgesic with weak opoid agonist properties. Tramadol has been proved to be effective in both experimental and clinical pair without causing serious side effects. The half-life of a drug is about 5.5 hrs and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hrs 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 is developed⁵. The main objective of the present work was to develop sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and natural gums like Karaya gum (KG) and Carrageenan (CG). Varying ratios of drug and polymer like 1:1 and 1:2 were selected for the study. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of three different rate controlling material. The matrix tablets were prepared and evaluated for different physiochemical parameters such as appearance, weight variation, thickness, hardness, friability, drug content and *in vitro* release. The marketed product was evaluated for the said physiochemical parameters and the *in vitro* release of tramadol from the developed formulation was compared with the marketed one. The marketed product is available as tablet containing tramadol hydrochloride 100 mg.

MATERIALS AND METHODS

Materials: Tramadol hydrochloride was procured as gift sample from Rantus pharmaceutical private Ltd. KG and CG were obtained as gift samples from M/s H.B. Gum Industries Pvt Ltd, Kalol, and Gujarat. HPMC K15M was purchased from M/s S.D. fine chemicals Mumbai. All other solvents and reagents were of analytical grade.

Methods

Formulation of matrix tablets

Matrix tablet containing 100mg of tramadol hydrochloride were prepared by wet

granulation technique. The composition of each tablet is shown in table 1. All the components were screened and then thoroughly mixed in a bottle using tumbling method for a period of 15 mins. The powder mix was granulated with 5% w/w alcoholic solution of povidone. The wet mass was passed through # 16 and the granules were dried at 50°C for 2 hrs in a hot air oven. The dried granules were passed through # 20 and lubricated with magnesium stearate by further blending for 3 mins and finally talc was added to the blend. Compression was done on 10 station Rimek tablet compression machine (M/s Karnawati Engg. Ltd. Ahemadabad) using 8 mm punches.

Evaluation of tablets

The prepared tablets were evaluated for weight variation, hardness, thickness, friability, drug content, and stability studies. Pfizer hardness⁴ tester was used for the determination of the hardness. In weight variation test twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight. The tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture was recorded. In this work, for each formulation the hardness of 6 tablets was evaluated. The crown-to-crown thicknesses of ten tablets from each batch were determined using vernier calipers. The Friability⁴ of the tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed

sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = (1 - W_0 / W) \times 100$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test. For determination of drug content at least three tablets from each formulation were weighed individually, pulverized, and diluted to 250ml with sufficient amount of phosphate buffer pH 6.8. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 271nm.

In vitro drug release studies for the prepared matrix tablets were conducted for a period of 12 hrs using a 8 station USP TDT-08L (Electro lab, Mumbai.) apparatus at $37 \pm 0.5^\circ\text{C}$ and at 100 rpm speed, the *in vitro* release study was performed in 0.1 N HCL pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 271 nm for tramadol hydrochloride by a UV-Visible spectrophotometer. The amount of drug present in the samples was calculated.

Stability Studies

The stability study of the tablets F7 (H8K2), F16 (H2C8) and F17 (K8C2) were carried out according to ICH guidelines at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH for three months by storing the samples in (Lab-care, Mumbai) stability chamber.

FTIR Studies

IR spectra for tramadol HCl and formulation F16 (H₂C₈) tablets were recorded in a Fourier

transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA.) with KBr pellets.

DSC Studies

DSC scans of about 5mg; using an automatic thermal analyzer system performed accurately weighed tramadol hydrochloride and tablet containing the same amount of drug. (DSC 60, Shimadzu, Japan) Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of $10^\circ\text{C}/\text{min}$ from $50\text{--}300^\circ\text{C}$.

RESULTS AND DISCUSSION

Precompressional parameters of granules shows (Table 2), angle of repose (25.32 to 31.30), % compressibility (14.69 to 16.98%), and Hausner's ratio (1.11 to 1.26) are in the range given in official standards.

Table 3 shows postcompressional parameters i. e. hardness (5.06 to 6.76 kg/cm²), friability (0.32 to 0.89%), weight variation (1.22 to 2.76) and thickness (4.23 to 5.56 mm). Drug content was (98.97 to 100.16%) within the acceptable official limits.

Dissolution study of all the formulations was carried out using 0.1 N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 upto 12 hrs. Formulations F1 to F3 were prepared by using ratio of drug and polymer as 1:1. Figure 1 shows the release profile of formulations F1 to F3. Among those formulations, formulation prepared with CG shown faster drug release within 6 hrs than formulations prepared with other polymers and formulations with KG and HPMC K 15 M shown drug release in 8 hrs. With all three formulations, an initial burst release of the

drug followed by a steady-state release was observed. The initial burst release can be accounted for the high concentration of highly soluble Tramadol hydrochloride at the surface that dissolves immediately. Figure 2 shows the release profile of formulations F4 to F6. These formulations were prepared by using ratio of drug and polymer as 1:2. With all three formulations, an initial burst release of the drug followed by a steady-state release was observed. Formulation F4 which is prepared with HPMC K15M has showed 88.87% release in 12 hrs and the formulation F5 which is prepared with KG shows 82.96% in 12 hrs whereas formulation F6 which is prepared with CG shows 98.07% release in 12 hrs. From the release study it was found that the polymer concentration in formulation F4 to F6 was sufficient to sustain the drug release up to 12 hrs. Among these six formulations, formulations with HPMC K15M alone show higher initial burst release due to hydration rate of this synthetic polymer relates to its hydroxy propyl substitutes percentage⁶. HPMC K15M contains the greatest amount of these groups and produces strongly viscous gel that plays an important role in drug release especially at the beginning of the release profile. Figure 3 shows the release profile of formulations F7 to F11. These formulations were prepared with polymer blend of HPMC K15M and KG. Different ratios like 80:20, 60:40, 50:50, 40:60 and 20:80 were taken. From the release study it is observed that, from the formulations drug release will be controlled up to 12 hrs. In these formulations as the concentration of HPMC K15M increased, the release rate is decreased from 88.66% to 81.06%. Figure 4 shows the release profile

of formulations F12 to F16. These formulations were prepared with polymer blend of HPMC K15M and CG. Different ratios like 80:20, 60:40, 50:50, 40:60 and 20:80 were taken. From the release study it is observed that, from the formulations drug release will be controlled upto 12 hrs. In these formulations as the concentration of HPMC K15M increased, the release rate is decreased. This is possibly due to slower erosion of HPMC and may be due to the increased viscosity of CG, which might have helped to keep the hydrated gel intact thus, releasing the drug for 12 hrs⁷. Among these formulations F16 (H₂C₈) contain the ratio of 20:80 of HPMC: CG showed 99.20% release in 12 hrs, which is comparable with the marketed product. Figure 5 shows the release profile of formulations F17 to F21. These formulations were prepared with polymer blend of KG and CG. Different ratios like 80:20, 60:40, 50:50, 40:60 and 20:80 were taken. From the release study it is observed that, from the formulations drug release will be controlled up to 12 hrs. In these formulations, as the concentration of KG increased, the release rate is decreased from 96.63% to 82.42%. It is mainly due to high swelling rate of KG⁸. Figure 6 shows the release profile of formulations of F22 to F24. These formulations were prepared by mixture of three polymers. Among these three formulations, the formulation, which is having high concentration of CG, show faster drug release than other formulations. From the release study it is clearly seen that there is no any synergism effect between them as there are other formulations with two polymers or even one that showed.

Kinetics and mechanism of drug release

Kinetic results shown in table 4 reveals that all formulations follows zero-order kinetics as correlation coefficient (r^2) values are higher than that of first-order release kinetics. The calculated n values from power law equation for drug release profiles were between 0.5119-0.7523 with a correlation coefficient (r^2) values >0.93 , suggest that drug release mechanism from matrix tablets followed non-Fickian (anomalous) transport mechanism.

Stability Studies

The stability study of the optimized tablets [F7 (H8K2), F16 (H2C8) and F17 (K8C2)] were carried out according to ICH guidelines at $40\pm 2^\circ\text{C}/75\pm 5\%$ RH for three months by storing the samples in (Lab-care, Mumbai) stability chamber. The results from stability studies are shown in table 5.

FTIR Study

Figure 7 shows the IR spectra of tramadol hydrochloride (**A₁**) and formulation F16 (**H₂C₈**) (**A₄**). IR spectrum of tramadol hydrochloride (Figure 8 **A₁**) shows a broad peak at 3304 cm^{-1} may be due to hydrogen bonding, 3048 cm^{-1} may be due to aromatic C-H stretching, 2926 cm^{-1} may be due to C-H stretching of $-\text{OCH}_3$, 2512 , 2602 , 2860 cm^{-1} maybe due to C-H stretching of $-\text{CH}_2$ and $-\text{CH}_3$ groups. 1606 , 1578 cm^{-1} may be due to C=C ring stretching. 1288 , 1301 cm^{-1} $-\text{C-H}$ bending of symmetric and asymmetric of $-\text{CH}_2$ and $-\text{CH}_3$ groups. 1045 cm^{-1} may be due to $-\text{C-O-C}$ group. 781 cm^{-1} may be due to substituted benzene ring. The IR spectrum of the best formulation obtained during the present work showed, the characteristic absorption bands at 3300 , 3064 , 2926 , 2512 , 2602 , 2860 , 1606 , 1578 , 1288 cm^{-1} and 1045 , 781 cm^{-1} . In addition to this, the IR spectrum of the best formulation also shown the major characteristic absorption bands of the polymers CG and HPMC K 15M with negligible difference of absorption band values.

From the results, it is clear that, there is no appreciable change in the positions of the characteristic bands of the drug along with the IR spectrum of the best formulation derived during the present investigation. Since there is no change in the nature and position of the bands in the formulation, it can be concluded that the drug maintains its identity without going any chemical interaction with the polymers used.

DSC study

Figure 8 shows the DSC thermographs of pure drug (**A₁**) and formulation F16 (**H₂C₈**) (**A₄**). Thermographs obtained by DSC studies, revealed that the melting point of pure drug is 185°C and that of the drug in the formulation is 183°C as there is no much difference in the melting point of the drug in the thermographs of drug and that of in the formulation. It may be concluded that, the drug is in the same pure state even in the formulation without interacting with the polymers.

CONCLUSION

The formulations prepared with drug: polymer ratio 1:1 show 100% drug release in 6 to 8 hrs and formulations prepared with drug: polymer ratio 1:2 could retard the drug release upto desired time period. The tablets containing polymer blend of HPMC K 15 M and KG retard the drug release because both are swellable polymer. The tablets containing polymer blend of HPMC K 15 M and CG retard the drug release. From the release study it is observed that as we increase the concentration of HPMC, the release of drug is decreased. This is possibly due to slower erosion of HPMC and may be due to the increased viscosity of CG which might have helped to keep the hydrated gel intact thus releasing the drug for 12 hrs. Among these formulations **F16 (H₂C₈)** contain the ratio of 20:80 of HPMC: CG showed 99.20% release in 12 hrs and the release profile follows zero order kinetics which is comparable with the

marketed product. Tablets prepared with polymer blend of KG and CG also retard the drug release up to 12 hrs. From the release study it is observed that as we increase the concentration of KG, the release of drug is decreased due to higher swelling rate of KG which is observed from the data of swelling study. In the later part, formulation prepared with triple mixture, but data shows no synergistic effect. From the Korsmeyer-

peppas study, the n value of the formulations show that the release profile obeys non-fickian diffusion which shows that drug is released via, swelling, diffusion and erosion mechanism. Stability studies, FTIR, and DSC indicated that drug was stable in the tablets. In conclusion, KG, CG and HPMC K 15 M can be used as rate controlling polymers by appropriate selection of the level of polymers in the matrix.

Table 1: Composition of 400 mg Tramadol HCL matrix tablet. (Weight in mg)

Formulation	Code	Tramadol HCl	Karaya gum	HPMC K 15 M	Carrageenan
F1	K1	100	100	-	-
F2	H1	100	-	100	-
F3	C1	100	-	-	100
F4	K2	100	200	-	-
F5	H2	100	-	200	-
F6	C2	100	-	-	200
F7	H8K2	100	40	160	-
F8	H6K4	100	80	120	-
F9	H5K5	100	100	100	-
F10	H4K6	100	120	80	-
F11	H2K8	100	160	40	-
F12	H8C2	100	-	160	40
F13	H6C4	100	-	120	80
F14	H5C5	100	-	100	100
F15	H4C6	100	-	80	120
F16	H2C8	100	-	40	160
F17	K8C2	100	160	-	40
F18	K6C4	100	120	-	80
F19	K5C5	100	100	-	100
F20	K4C6	100	80	-	120
F21	K2C8	100	40	-	160
F22	K6H2C2	100	120	40	40
F23	H6K2C2	100	40	120	40
F24	C6K2H2	100	40	40	120

† All of the formulations have,
1% w/w magnesium stearate
1% w/w talc

‡ 5% w/w polyvinyl pyrrolidone,
* Wet granulation

Table 2: Precompressional parameters of all granules.

Formulation	Code	Angle of repose, (θ) (\pm SD), n=3	% Compressibility (\pm SD), n=3	Hausner's ratio, (\pm SD), n=3
F1	K1	25.32(0.71)	16.83(0.42)	1.22(0.00)
F2	H1	26.78(0.72)	14.73(0.72)	1.24(0.01)
F3	C1	28.14(0.73)	16.32(0.14)	1.17(0.11)
F4	K2	29.12(0.81)	15.99(0.38)	1.17(0.02)
F5	H2	30.10(0.11)	15.56(0.36)	1.19(0.02)
F6	C2	30.82(0.21)	16.98(0.33)	1.15(0.02)
F7	H8K2	30.81(0.22)	14.69(0.32)	1.26(0.02)
F8	H6K4	29.58(0.81)	15.22(0.37)	1.26(0.02)
F9	H5K5	29.12(0.17)	16.69(0.3)	1.19(0.02)
F10	H4K6	30.18(0.29)	16.37(0.35)	1.18(0.02)
F11	H2K8	31.25(0.23)	15.49(0.33)	1.13(0.02)
F12	H8C2	30.18(0.22)	15.61(0.32)	1.18(0.02)
F13	H6C4	30.12(0.18)	15.42(0.33)	1.12(0.02)
F14	H5C5	29.87(0.23)	14.73(0.35)	1.12(0.01)
F15	H4C6	25.99(0.18)	15.99(0.33)	1.19(0.03)
F16	H2C8	26.17(0.16)	16.02(0.36)	1.12(0.02)
F17	K8C2	30.32(0.13)	15.32(0.33)	1.13(0.01)
F18	K6C4	29.15(0.81)	15.36(0.34)	1.12(0.02)
F19	K5C5	31.30(0.82)	16.39(0.33)	1.13(0.03)
F20	K4C6	29.22(0.18)	16.88(0.12)	1.12(0.02)
F21	K2C8	30.23(0.16)	15.88(0.13)	1.11(0.00)
F22	K6H2C2	29.34(0.12)	16.36(0.35)	1.17(0.03)
F23	H6K2C2	26.11(0.32)	15.99(0.14)	1.16(0.02)
F24	C6K2H2	27.34(0.33)	15.50(0.32)	1.18(0.04)

Table 3: Postcompressional parameters of all formulations.

Formulation	Hardness Test (Kg/cm ²) (\pm SD), n=6	Friability (%), (\pm SD), n=10	Weight variation (%), n=20	Thickness (mm), (\pm SD), n=10	Drug content (%), (\pm SD), n=3
F1	6.22(0.01)	0.32(0.01)	1.93	4.23(0.02)	98.97(0.65)
F2	5.72(0.36)	0.76(0.01)	1.22	4.36(0.02)	99.12(1.30)
F3	6.02(0.01)	0.82(0.01)	1.71	4.35(0.02)	99.14(0.65)
F4	5.24(0.35)	0.49(0.01)	2.13	4.28(0.02)	99.58(0.65)
F5	6.52(0.36)	0.39(0.01)	1.98	4.25(0.02)	99.73(0.65)
F6	6.29(0.36)	0.59(0.01)	2.39	4.32(0.02)	99.45(0.65)
F7	6.53(0.36)	0.66(0.01)	2.45	4.43(0.02)	99.26(0.65)
F8	5.55(0.35)	0.42(0.01)	2.19	4.35(0.02)	98.98(0.65)
F9	6.76(0.36)	0.59(0.01)	1.83	4.45(0.02)	99.89(0.65)
F10	6.23(0.35)	0.65(0.01)	2.36	4.36(0.02)	100.16(0.65)
F11	6.67(0.34)	0.73(0.01)	2.59	4.46(0.02)	99.6(0.65)
F12	5.06(0.33)	0.79(0.01)	2.76	4.39(0.02)	99.43(0.65)
F13	5.12(0.32)	0.73(0.01)	1.89	4.36(0.02)	99.46(0.60)
F14	5.52(0.33)	0.83(0.01)	2.79	4.46(0.02)	99.42(0.60)
F15	5.59(0.36)	0.89(0.01)	2.73	4.56(0.02)	99.45(0.62)
F16	6.53(0.36)	0.72(0.01)	2.74	4.43(0.02)	98.99(0.60)
F17	6.52(0.32)	0.36(0.01)	1.71	4.23(0.02)	99.92(0.62)
F18	6.23(0.3.3)	0.45(0.01)	1.98	4.35(0.02)	98.92(0.63)
F19	6.29(0.36)	0.75(0.01)	1.22	4.43(0.02)	99.42(0.60)
F20	5.88(0.33)	0.66(0.01)	2.15	4.35(0.02)	99.68(0.61)
F21	5.55(0.32)	0.45(0.01)	1.98	4.32(0.02)	98.97(0.65)
F22	6.52(0.36)	0.59(0.01)	1.76	4.29(0.02)	98.99(0.65)
F23	6.50(0.32)	0.68(0.01)	1.71	4.45(0.02)	100.12(0.64)
F24	6.35(0.22)	0.66(0.01)	2.52	4.42(0.02)	99.98(0.64)
Marketed	5.92(0.36)	0.45(0.01)	2.53	4.43(0.02)	99.96(0.62)

Table 4: Kinetic parameters of all formulations.

Formula	First- order(r²)	Zero-order(r²)	Kors.-Peppas (n)	Kors.-Peppas (r²)
K1	0.8204	0.9628	0.5623	0.9557
H1	0.8978	0.9069	0.5337	0.9840
C1	0.9028	0.9613	0.5915	0.9352
K2	0.9651	0.9884	0.5911	0.9847
H2	0.8923	0.9247	0.5655	0.9879
C2	0.9101	0.9749	0.5740	0.9830
H8K2	0.8721	0.9680	0.5551	0.9730
H6K4	0.9023	0.9677	0.5753	0.9631
H5K5	0.9055	0.9868	0.5640	0.9871
H4K6	0.9103	0.9904	0.5530	0.9780
H2K8	0.9225	0.9864	0.5563	0.9788
H8C2	0.9123	0.9670	0.5119	0.9861
H6C4	0.9056	0.9870	0.5588	0.9751
H5C5	0.8823	0.9372	0.5693	0.9870
H4C6	0.8204	0.9587	0.5795	0.9723
H2C8	0.8524	0.9221	0.5681	0.9736
K8C2	0.8956	0.9363	0.6213	0.9795
K6C4	0.9023	0.9889	0.5983	0.9658
K5C5	0.8921	0.9106	0.5532	0.9725
K4C6	0.8756	0.9366	0.5026	0.9373
K2C8	0.8923	0.9887	0.7523	0.9880
K6H2C2	0.9258	0.9523	0.7089	0.9989
H6K2C2	0.9155	0.9661	0.5689	0.9956
C6K2H2	0.9656	0.9870	0.5462	0.9876

Table 5: Stability studies data

Formulation	Duration of period	Drug content (%), n=3, (±SD)	Hardness Test, (Kg/cm²) (±SD), n=6	Friability (%), (±SD), n=10
	One month	98.89 (0.83)	6.22 (0.01)	0.32 (0.01)
F7 (H8K2)	Two month	98.20 (0.83)	6.20 (0.01)	0.35 (0.01)
	Three month	98.02 (0.83)	6.20 (0.01)	0.38 (0.01)
	One month	99.32 (0.80)	5.72 (0.01)	0.76 (0.01)
F16 (H2C8)	Two month	98.96 (0.80)	5.69 (0.01)	0.78 (0.01)
	Three month	98.10 (0.80)	5.69 (0.01)	0.80 (0.01)
	One month	99.92 (0.81)	6.32 (0.36)	0.55 (0.01)
F17 (K8C2)	Two month	99.10 (0.81)	6.30 (0.36)	0.58 (0.01)
	Three month	98.45 (0.81)	6.30 (0.36)	0.60 (0.01)

Fig. 1: Comparative release profile of formulation F1 to F3.

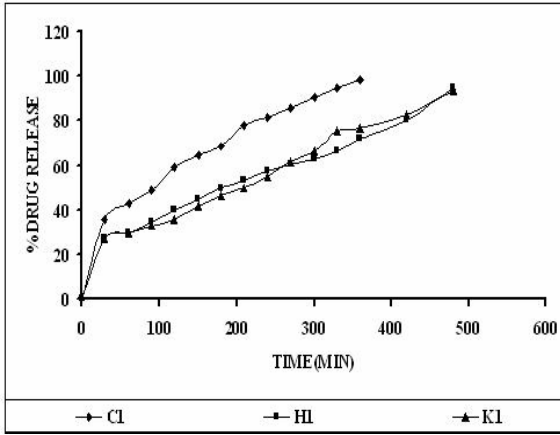


Fig. 4: Comparative release profile of formulation F12 to F16 and marketed Formulation.

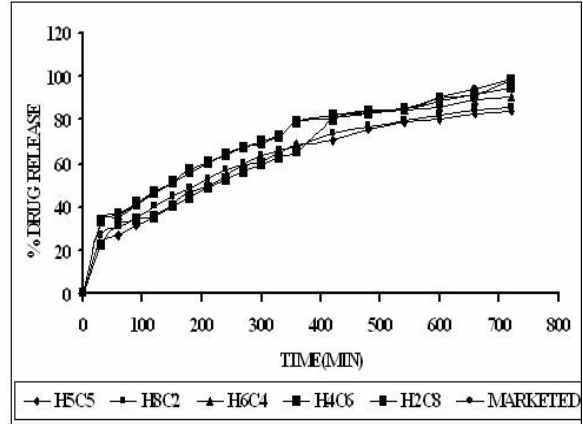


Fig. 2: Comparative release profile of formulation F4 to F6.

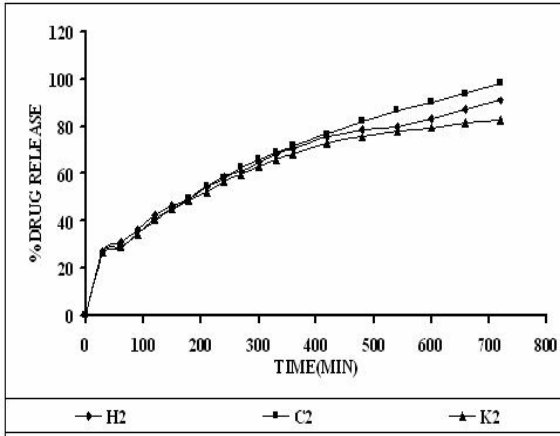


Fig. 5: Comparative release profile of formulation F17 to F21.

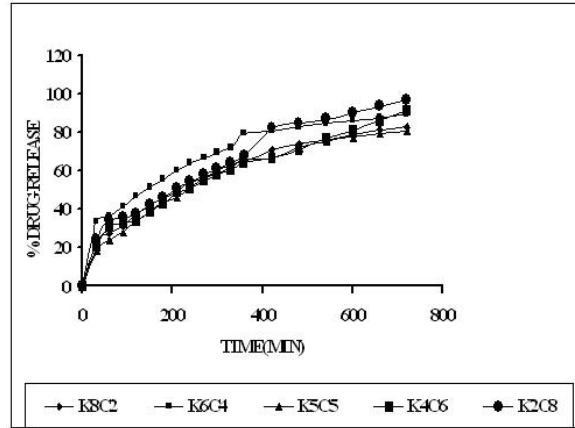


Fig. 3: Comparative release profile of formulation F7 to F11.

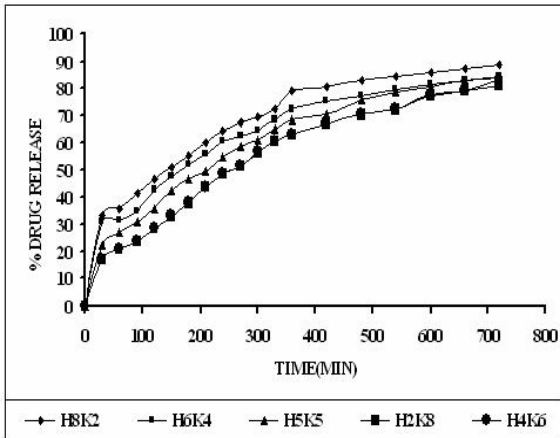
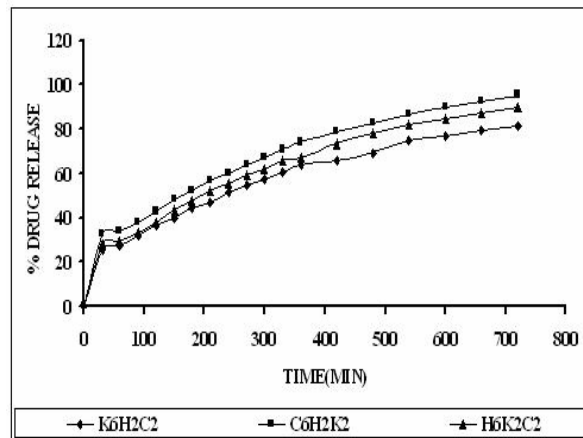


Fig. 6: Comparative release profile of formulation F22 to F24.



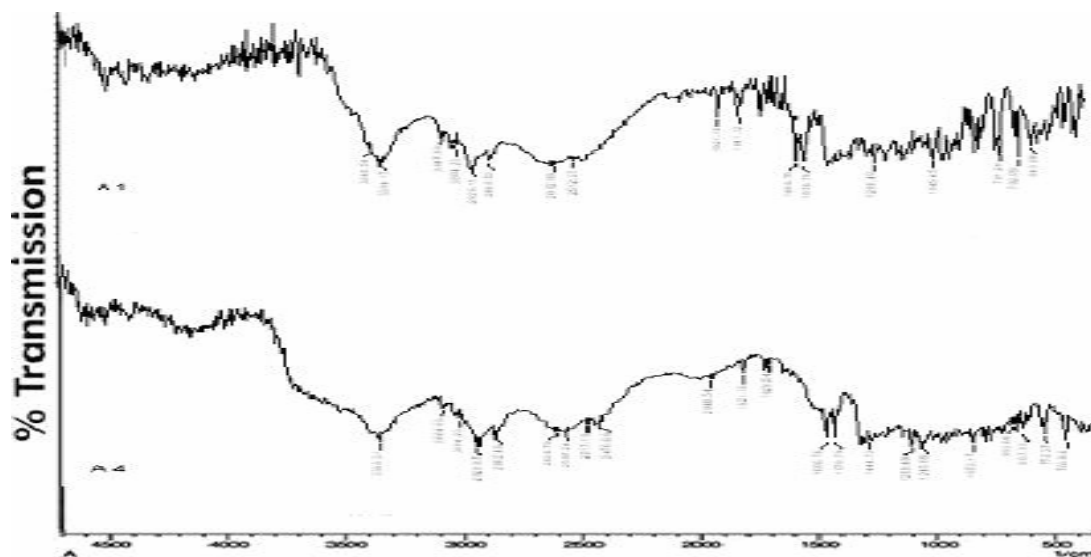


Fig.7: IR spectrum of Tramadol HCL (A₁), IR spectrum of Formulation F16 (H₂C₈)(A₄).

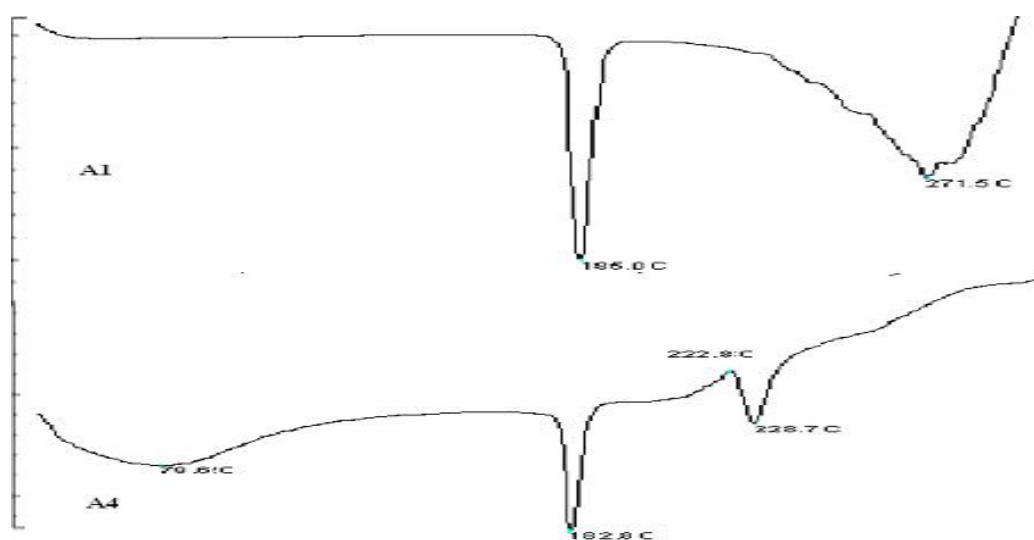


Fig. 8: (A₁): DSC Thermogram of Tramadol HCL (A₁), DSC thermogram of Formulation F16 (H₂C₈)(A₄).

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