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FORMULATION DEVELOPMENT, *IN-VITRO* AND *IN-VIVO* EVALUATION OF TAPENTADOL HCL CONTROLLED RELEASE MATRIX TABLETS USING HYDROPHOBIC POLYMERS

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ABSTRACT

Tapentadol is a centrally acting synthetic analgesic, having biological half-life of 4 hours, its systemic bioavailability is 32%, is a suitable candidate for controlled release dosage form. The main aim of the present investigation was to formulate controlled release matrix tablets by using hydrophobic polymers like carnauba wax, eudragit L-100 and hydrogenated castor oil at different concentrations by using direct compression and melt granulation techniques, for an extended period of 24 hours to relieve moderate to chronic pain. Among all the formulations T-12 was selected as optimized one based on its physical parameters and *in-vitro* drug release profiles. The FTIR and DSC results of optimized formulation revealed that there is no incompatibility between drug and excipients used. For optimized formulation(T-12), the drug release mechanism was explored and explained by zero-order (r^2=0.987), first-order (r^2=0.947), Higuchi (r^2=0.967) and Korsmeyer-peppas (r^2=0.982 & n=0.855) equations, which explained the drug release follows zero-order and is fit for Higuchi equation & mechanism was anomalous diffusion i.e. diffusion and erosion. Biopharmaceutical study of the optimized (T-12) formulation in rabbit model showed 24 h prolonged drug release *in-vivo*. The results suggested that melt granulation technique, is a suitable method to formulate controlled release Tapentadol HCl and it can Perform therapeutically better than conventional immediate release dosage form.

KEY WORDS: Controlled release, Hydrogenated castor oil, hydrophobic matrix tablets, *In-vivo* drug release.

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INTRODUCTION

Tapentadol is a centrally acting analgesic believed to act through a dual mechanism as a opioid receptor agonist and an inhibitor of norepinephrine reuptake, approved for treatment of moderate to severe pain in adults 18 years and older. The short biological half-life (about 4 hr) and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hours with a maximum dosage of 600 mg/day[1]. To reduce the frequency of administration and to improve patient compliance especially for chronic pain, a controlled-release formulation of Tapentadol hydrochloride is desirable. The drug is freely soluble in water and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug. The most commonly used method of modulating the drug release is to include it in a controlled release matrix system. Controlled release is an approach by which active pharmaceutical ingredients are made available to a specified target at a rate and duration designed to accomplish an intended effect. Oral controlled release system allows a reduction in dosing frequency and control absorption rate to achieve desired plasma profiles with reduced fluctuations to an extended period of time. It overcomes many disadvantages of immediate release (IR) conventional dosage forms have to be administered several times to maintain therapeutic window. Fluctuations in plasma-drug concentrations results either ineffectiveness or toxicity[2, 3]. Drugs with high water solubility, hydrophobic polymers are suitable as matrixing agents for developing controlled-release dosage forms. Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications. Use of hydrophobic polymers like hydrogenated castor oil, eudragit L-100, carnauba wax, stearic acid will retard the drug release of such drugs with high water solubility[4].

MATERIALS AND METHODS

Tapentadol hydrochloride was a gift sample from MSN labs ltd, Hyderabad, hydrogenated castor oil, eudragit L-100, carnauba wax and stearic acid was obtained as gift sample from Aurobindo pharmaceuticals, Hyderabad. Magnesium stearate, talc, microcrystalline cellulose, dibasic calcium phosphate was obtained as gift sample from Natco Pharmaceuticals, Hyderabad, India. Other chemicals are of analytical grade.

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 dispersing them in a suitable solvent (KBr) using Fourier Transform Infrared spectrophotometer. A base line correction was made using dried potassium bromide and the spectra of the pure drug, polymer and the formulation mixture were recorded on FTIR[5]. The data was shown in Fig. 1 & 2.

Compatibility studies by FT-IR

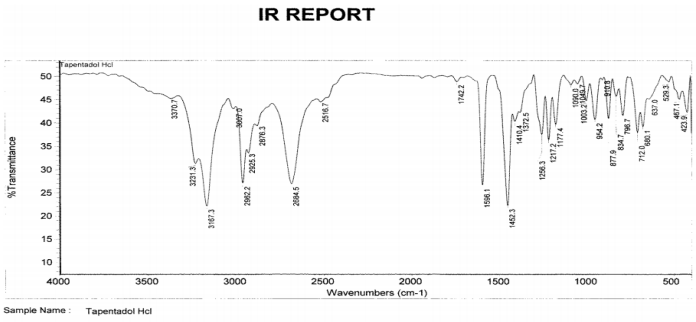

Figure - 1
Tapentadol HCl API

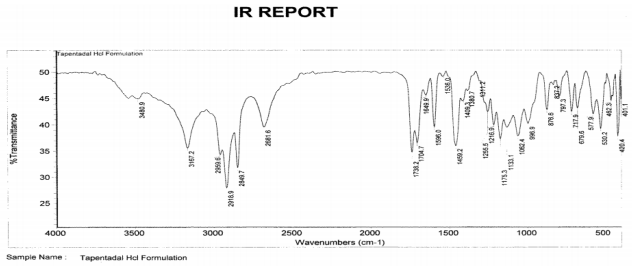

Figure - 2
Tapentadol HCl optimized formulation

Compatibility study by DSC

Differential Scanning Calorimetry (DSC) was performed on pure drug, excipients and optimized formulation. DSC measurements were done on a Shimadzu DSC-60 and samples were heated at the rate of 10^{o}C min in an aluminum cup. There is no considerable change observed in melting endotherm of drug in optimized formulation.

Micromeritic Properties of blends to be compressed

Angle of Repose tablets (Fixed Funnel Method)

The angle of repose of granules was determined by the fixed 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 granules. Powder was allowed to flow through the funnel freely onto the surface[6].

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted[7]. LBD and TBD were calculated using the following formulas.

LBD = Weight of the Powder/Volume of the packing

TBD = Weight of the powder /Tapped volume of the packing

Compressibility Index tablets

The compressibility index of the gum powder was determined by Carr's compressibility index.

Carr's Index (%) = (TBD – LBD)/TBD X 100

Preparation of matrix tablets

Direct compression method

All the ingredients weighed separately and were passed through # 40 mesh prior to mixing. Then the ingredients except drug were mixed to get a uniform polymer mixture. The drug was then mixed with the polymer mixture for a period of 30 minutes to ensure uniform mixing of the drug. These powder mixtures were lubricated with magnesium stearate and compressed using Tablet compression machine (Cadmach) to obtain tablets.

Melt granulation method

All the ingredients were weighed accurately as per the manufacturing formula. Drug and all the ingredients passed through sieve #60 mesh and collected individually. Granules were prepared by melting the polymer by heating to their melting points. Drug and diluents were gradually added to the molten mass with continuous stirring. The molten mass was allowed to cool and then was sized with a sieve #22 mesh. Prior to compression magnesium stearate and talc was mixed with each batch of granulates for 5min in polythene bag. Blended material was loaded in a hopper and compressed the powder into tablets by using compression machine (Cadmach) with standard punches[8].

Table 1
Composition of Tapentadol HCl Controlled Release tablets (T-1 to T-6) by direct compression

S.N	Ingredients (mg/tab)	T-1	T-2	T-3	T-4	T-5	T-6
1	Tapentadol HCl	116.47	116.47	116.47	116.47	116.47	116.47
2	Hydrogenated castor oil	35.0	52.5	70	-	-	-
3	Eudragit L-100	-	-	-	105	140	175
4	Microcrystalline Cellulose	183.53	166.03	148.53	113.53	78.53	43.53
5	Magnesium Stearate	10	10	10	10	10	10
6	Talc	5	5	5	5	5	5
	Total weight (mg)	350	350	350	350	350	350

Table 2
Composition of Tapentadol HCl Controlled Release tablets (T-7 to T-12) by Melt granulation method

S.N	Ingredients (mg/tab)	T-7	T-8	T-9	T-10	T-11	T-12
1	Tapentadol HCl	116.47	116.47	116.47	116.47	116.47	116.47
2	Carnauba wax	52.5	70	105	-	-	-
3	Hydrogenated Castor oil	-	-	-	70	87	105
4	Stearic acid	-	-	-	52.5	52.5	52.5
5	Dibasic calcium phosphate	113.53	148.53	113.53	96.03	78.53	61.03
6	Magnesium Stearate	10	10	10	10	10	10
7	Talc	5	5	5	5	5	5
	Total weight (mg)	350	350	350	350	350	350

Evaluation of Tablets

Weight variation

Twenty tablets were selected randomly and average weight was determined. Then individual tablets were weighed and was compared with an average weight[9].

Hardness and Friability

Hardness of the tablets is determined by Stokes Monsanto hardness tester. Friability of the tablets was checked by using Roche friabilator. This device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a height of 6 inches with each revolution. Pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed[10].

Thickness

The thickness of the tablet was measured by using digital vernier callipers, twenty tablets from each batch were randomly selected and thickness was measured.

In-vitro Dissolution studies

In-vitro dissolution test studies were carried out using USP 24 type-II dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). A 900 ml of phosphate buffer pH 6.8 used as media, thermo-stated at 37±0.5^{o}C and stirred at 75 rpm[11]. Samples were collected periodically (2, 4, 8, 12, 16, 20 & 24 hrs) and replaced with fresh dissolution medium, then the sample were analyzed using spectrophotometer at 272 nm.

Kinetic mechanism of Drug Release

Kinetic mechanism of drug release was evaluated mathematically by Zero-order, First-order, Higuchi & Korsmeyer-Peppas equations[12, 13].

In-vivo bioavailability studies

Six male rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. All efforts were made to maintain the animals under controlled environmental conditions (Temperature 25^{0}C, Relative Humidity 45% and 12 h alternate light and dark cycle] with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee (IAEC NO: P11/VCP/IAEC/2012/03/SKK/AE2/RABBITS/M 9). The rabbits were fasted overnight before administration of the formulation and pure drug. The rabbits were randomly divided into two groups each group contains three animals. The group A was received Tapentadol CR tablets, the pure drug was administered orally (Dissolved in distilled water) to group B via gastric lavage. Blood samples for pharmacokinetic analysis were obtained at different time intervals 0, 1, 2, 4, 6, 8, 12, 16, 20 and 24hrs after dosing. Blood samples were collected in heparinized tubes and were centrifuged for 10min at 3,000 rpm at room temperature. The pharmacokinetic parameters were calculated from the plasma level data obtained for the individual rabbits and presented as mean ± SD. From the data of plasma concentration, the maximum plasma concentration (C_{max}, ng/ml), the corresponding time (t_{max}, h) and other parameters were directly extracted for the two treatments in each individual animal.

RESULTS AND DISCUSSION

The presence of characteristic absorption bands of Tapentadol HCl and the formulation containing Tapentadol HCl suggest that there is no interaction takes place between the drug and excipients used in the formulation.

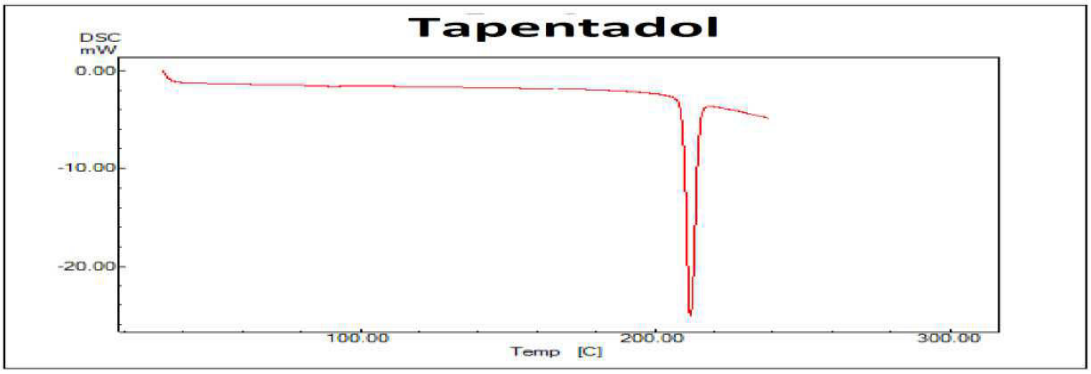

Figure - 3
DSC thermogram for Tapentadol HCl API

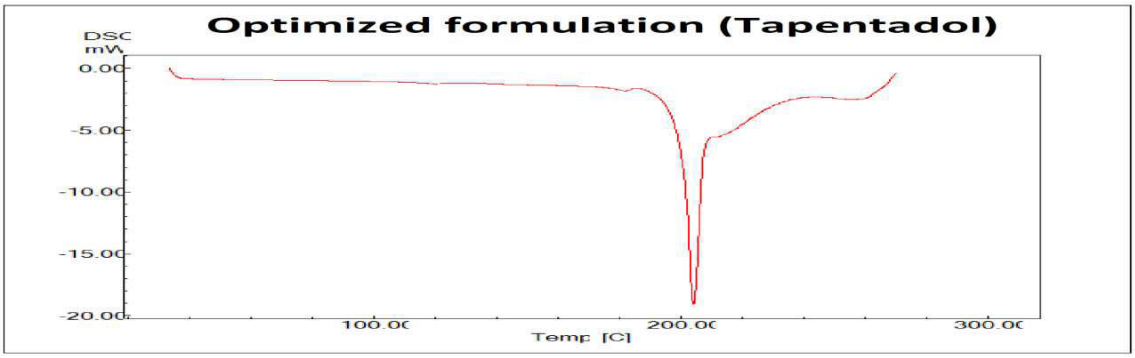

Figure 4
DSC thermogram for Tapentadol HCl Optimized formulation (T-12)

DSC thermogram revealed that there is no considerable change observed in melting endotherm of Tapentadol HCl pure drug (206.5) and drug in optimized formulation (204.5). The thermogram of pure drug Tapentadol HC was shown in Figure 3 and the thermogram of optimized formulation was shown in Figure 4 respectively. It indicates that there is no interaction takes place between drug and other excipients used in the formulation.

Micromeritic Properties of blends to be compressed

Table 3
Pre-compression characteristics of the powder blend of formulations T-1 to T-12

Formulation No.	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Compressibility index (%)	Hausner ratio	Angle of repose(°)
T-1	0.465	0.525	12.90	1.13	30.58
T-2	0.471	0.526	11.68	1.12	30.18
T-3	0.459	0.512	11.54	1.12	29.89
T-4	0.463	0.522	12.74	1.12	26.96
T-5	0.458	0.518	13.10	1.13	31.33
T-6	0.453	0.511	15.01	1.13	32.25
T-7	0.518	0.581	14.71	1.12	33.28
T-8	0.529	0.598	13.04	1.13	31.75
T-9	0.535	0.609	13.83	1.14	30.15
T-10	0.541	0.630	16.45	1.16	25.70
T-11	0.548	0.642	17.15	1.17	24.89
T-12	0.545	0.641	17.61	1.18	24.75

Powdered blend and granules of different formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index and hasner,s ratio. The results of bulk density was 0.453 to 0.548 gm/ml, tapped density was 0.511 to 0.642 gm/ml, compressibility index was 11.54 to 17.61%, hasner's ratio was 1.12 to 1.18 and angle of repose was 24.75° to 33.28°. Results were showed in Table 3.

Evaluation of Tablets

Table 4
Evaluation of Tapentadol HCl controlled release matrix tablets of formulations T-1 to T-12

Formulation	Average Weight of tablet (mg)	Thickness (mm) ± SD	Hardness (kg/cm^2) ± SD	Friability (%)	Content Uniformity (%) ± SD
T-1	353	3.08 ± 0.01	4.2 ± 0.18	0.26	99.15 ± 0.89
T-2	355	3.07 ± 0.01	4.5 ± 0.15	0.16	101.05 ± 0.55
T-3	353	3.08 ± 0.01	4.6 ± 0.19	0.13	99.75 ± 0.95
T-4	352	3.07 ± 0.01	4.3 ± 0.17	0.15	100.00 ± 1.15
T-5	353	3.08 ± 0.01	4.5 ± 0.16	0.19	100.92 ± 0.71
T-6	356	3.07 ± 0.01	4.7 ± 0.15	0.15	101.10 ± 0.63
T-7	350	3.07 ± 0.01	4.3 ± 0.16	0.22	99.35 ± 1.47
T-8	351	3.08 ± 0.01	4.5 ± 0.18	0.18	100.43 ± 0.45
T-9	350	3.07 ± 0.01	4.5 ± 0.22	0.15	99.46 ± 1.53
T-10	352	3.08 ± 0.01	4.4 ± 0.18	0.26	98.97 ± 1.28
T-11	353	3.07 ± 0.01	4.6 ± 0.19	0.18	100.03 ± 0.24
T-12	351	3.08 ± 0.01	4.8 ± 0.15	0.15	100.10 ± 0.55

The thickness of the tablets was 3.07± 0.01 mm, hardness was ranged from 4.2 to 4.8 kg/cm^2, friability was inbetween 0.13 to 0.26 %, average weight was found to be 350 to 356 mg and content uniformity was 98.97 to 101.10% and results are depicted in Table 4. The results of dissolution studies of formulationT-1 to T-12 carried out, in which formulations T-1 to T-6 released 100% drug with in 4 hours. Formulations T-7, T-8 and T-10 were released 100% the drug with in 10 hours, formulations T-9 and T-11 released 100% drug within 12 hours and formulation T-12 released 99.55% within 24 hours. Results were showed in Figure 5, 6 & 7. Dissolution profile of Tapentadol HCl controlled release tablet formulation with Marketed conventional Tablets (TYDOL 100 mg) was shown in Figure 8.

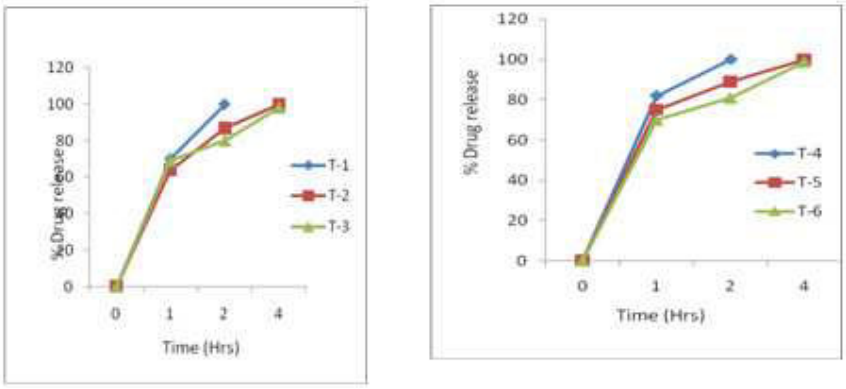

Figure - 5 & 6
Graphical representation of Comparative Dissolution profile of Tapentadol HCl Controlled Release Tablets from T-1 to T-6

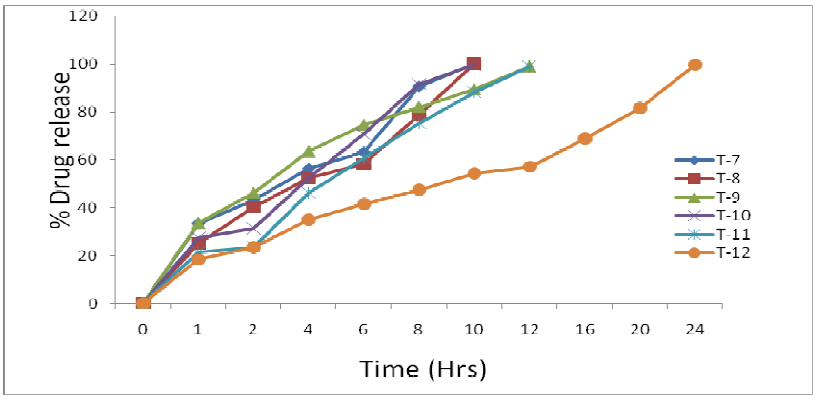

Figure - 7
Graphical representation for Comparative Dissolution profile of Tapentadol HCl Controlled Release Tablet Formulations (T-7 to T-12)

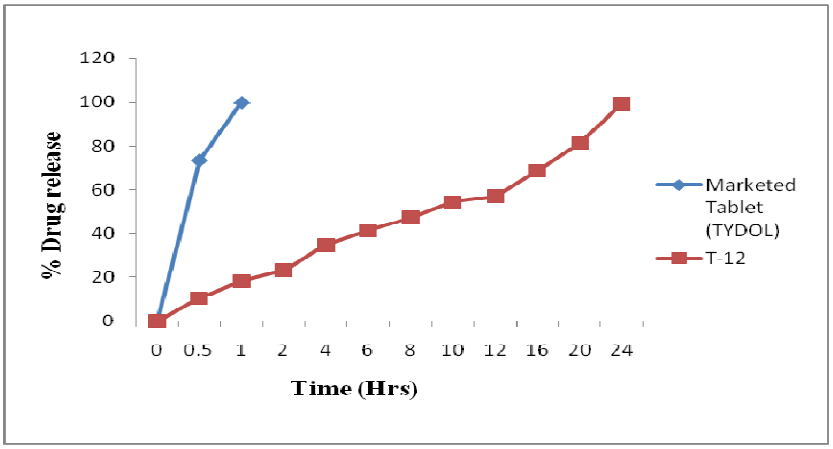

Figure - 8
Graphical representation for comparative dissolution profile of Tapentadol HCl controlled release tablet Formulation with marketed conventional tablets (TYDOL 100 mg).

To know the mechanism of drug release from the formulations, the data was plotted for zero-order, first-order, higuchi equation and korsmayer-peppas.The ptimized formulation (T-12) shown the results, zero-order (r^2=0.989), first-order (r^2=0.686), higuchi equation (r^2=0.973) and korsmayer-peppas (r^2=0.977 & n=0.568). Which explains drug release follows zero-order, *in-vitro* release profile of drug from all the formulationa could be best expressed by Higuchi's equation, as the plot showed high linearity (r^2=0.973). To coform the diffusion mechanism, the data were fit into Korsmeyer peppa's plot with linearity. 'n' value (0.568) indicates anomalous diffusion i.e, coupling of diffusion and erosion mechanisms. Results were showed in table-5.

Table 5
Kinetics of in-vitro drug release of Tapentadol HCl Controlled release Optimized (T-12) formulation

Formulation	Zero order (r^2)	First order (r^2)	Higuchi model (r^2)	Korsmayer-Peppas model		Best fit model
				r^2	"n" value	
T-12	0.989	0.686	0.973	0.977	0.568	Zero order

Table 6
Pharmacokinetic parameters of optimized Tapentadol HCl CR tablets and pure drug (Mean ± SD, n = 3).

Pharmacokinetic parameters	Tapentadol HCl CR Tablets (Optimized formulation T-12)			Tapentadol HCl pure drug(Reference)		
	Mean	±SD	CV%	Mean	±SD	CV%
C_{max} (ng/ml)	480	12.3	280.2	450	11.5	262.96
T_{max} (h)	8.0	1.3	58.56	4.0	1.6	54.9
Kel (h−1)	0.6528	0.012	330.04	0.612	0.022	309.41
$t_{1/2}$el (h)	14.2	4.125	75.32	7.1	2.254	38.19
AUC_{0-24}(ng-h/ml)	6439.92	213.22	276.50	6037.42	113.2	259.21
$AUC_{0-\infty}$(ng-h/ml)	8870.09	214.11	240.11	8315.70	118.4	225.10
$AUMC_{0-24}$(ng-h^2/ml)	72539.52	2329.42	298.44	68005.88	1589.34	279.78
$AUMC_{0-\infty}$(ng-h^2/ml)	130358.69	3429.16	281.8	122211.27	2569.33	264.18
MRT(h)	32.256	142	25.67	30.24	125	24.06

In-vivo study indicated significance difference between Tapentadol HCl pure drug and Tapentadol HCl CR tablets exhibited significant drug plasma level - time profiles. The C_{max} of the optimized formulation was found to be 480 ng/ml, where the T_{max} was 8.0 h in comparison with pure drug where C_{max} (480 ng/ml) was achieved by 4.0 h. Therefore, the present Tapentadol HCl CR tablets were considered to be potentially useful for the treatment of hypertension where improved patient compliance and convenience is expected, the results are summarized in Table 6.

SUMMARY AND CONCLUSION

The data for pre-formulation characteristics of all formulations have been found to be acceptable. All the twelve (T-1 to T-12) tablet formulations are of good quality and fulfilled the various tablets properties. Incompatibility studies all identical principle peaks were observed in all cases in FT-IR and thermograms in DSC study showed there was no chemical interaction between Tapentadol HCl and polymers (hydrogenated castor oil, eudragit L-100, carnauba wax). Dissolution of Tapentadol HCl from the optimized formulation (T-12) was released the drug over 24 hours. Release followed zero order kinetics. Data of the tablets more obeyed Higuchi, Korsmeyer-Peppas equation models. Higuchi plots were linear indicating that the drug release from these tablets was diffusion controlled. The optimized formulation (T-12) has Korsmeyer peppas “n” value was 0.568 indicating that non-fickian diffusion. The release mechanism was anomalous i.e, diffusion and erosion. *In-vivo* study indicated significance difference between Tapentadol HCl pure drug and Tapentadol HCl CR tablets exhibited significant drug plasma level - time profiles. Therefore, the present Tapentadol HCl containing CR tablets were considered to be potentially useful for the treatment of hypertension where improved patient compliance and convenience is expected.

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