Research Article

Formulation and Evaluation of Stable Extended Release Tablets of Tapentadol Hydrochloride

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ABSTRACT

Modified release matrix tablets of Tapentadol hydrochloride were prepared with HPMC K100 M as retarding polymer by wet granulation method. The granules were evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and Hausners ratio. The tablets were subjected to weight variation, hardness, friability and drug content test. Invitro release studies revealed that Tapentadol formulation with high proportion of HPMC K100M was able to control the drug release for 12 hours. Fitting the invitro drug release data to kinetic analysis, optimized formulations followed the mechanism of diffusion. All the formulations were stored at 40°C and 75%RH and subjected to stability studies up to 6 months. It showed that all the formulations are physically and chemically stable.

Keywords: Tapentadol Hydrochloride, HPMC, Wet granulation.

INTRODUCTION

Tapentadol is a centrally acting analgesic with a low affinity for opioid receptors. Tapentadol is a synthetic codeine analogue that is a weak mu-opioid receptor agonist. Part of its analgesic effect is produced by inhibition of uptake of nor epinephrine and 5-hydroxytryptamine. In the treatment of mild-to-moderate pain, Tapentadol is as effective as morphine or meperidine. The half life of the drug is about 4 hours and the approximate equi-analgesic dose is 50-250 mg twice a day.

Tapentadol is available in market as immediate release tablet for the treatment of acute pain. Hence for the treatment of chronic and moderate pain a modified release formulation was prepared. Tapentadol hydrochloride is freely soluble in water; hence release retarding polymers such as Hydroxy propyl methyl cellulose plays an important role in controlling the release of Tapentadol from the formulation.[1-3]

Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in designing a sustained release system.[4] The present study aims to develop sustained release matrix tablets using hydrophilic matrix materials, such as HPMC K 15 and HPMC- K 100 along with drug in varying proportions by wet granulation method. For sustained release systems, the oral route of drug administration has received the most attention as it is natural, uncomplicated, convenient and safer route.[5]

Matrix tablets were prepared by either wet granulation or direct compression method. Currently available sustained matrix tablets are generally prepared by wet granulation method. The aim of the present work was to prepare sustained release matrix tablets of Tapentadol and to study the effect of in-vitro release characteristics, kinetics of the prepared formulations and stability studies.

MATERIALS AND METHODS

Materials

Tapentadol hydrochloride was procured from MSN labs Hyd, HPMC K4M, HPMC K15M and HPMC K100M were provided as a gift sample by colorcon. Povidone sample was procured from ISP technologies. Other chemicals were purchased from Pure Chem. Laboratories, Pune and of analytical grade.

Methods

Tapentadol hydrochloride tablets were prepared by wet granulation method. The ingredients were passed through 40 mesh sieve and weighed accurately as per the manufacturing formula. Povidone was dissolved in water used as binder. The binder solution was added to the contents and wet dough mass was obtained by using rapid mixing granulator. Wet mass was dried in fluid bed granulator, where temperature is maintained at 60^0C in which dried granules was passed through 20 mesh sieve. Finally, milled granules were passed through 20 mesh sieve. Remaining quantity of HPMC K4M or HPMC K15M or HPMC K100M, colloidal silicon dioxide was mixed with the above prepared blend and final lubrication was done with magnesium stearate. All the batches were compressed on 8 station tablet compression machine (Cadmach, India).

Table 1: Composition of modified release tablets of Tapentadol

Composition	F1	F2	F3	F4	F5	F6	F7	F8
	Mg/tablet							
Tapentadol HCL	291.20	291.20	291.20	291.20	291.20	291.20	291.20	291.20
MCC	153.8	153.8	153.8	98.80	108.80	93.80	78.80	58.80
Povidone	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Purified Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
HPMC K 4 M	125.00	-	-	-	-	-	-	-
HPMC K 15 M	-	125.00	-	-	-	-	-	-
HPMC K 100 M	-	-	125.00	180.00	170.00	170.00	170.00	170.00
Croscarmellose Sodium	-	-	-	-	-	15.00	30.00	30.00
Co-povidone	-	-	-	-	-	-	-	20.00
Colloidal SiO2	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00
Magnesium Stearate	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
Tablet weight	600.00	600.00	600.00	600.00	600.00	600.00	600.00	600.00

Evaluation of powder blend

The powder blend used for preparation of tablets was evaluated for angle of repose, and compressibility index [6].

Angle of repose

10 gm of powder was passed through funnel and the pile was formed. The height and weight of the pile was measured and the angle of repose was calculated by using the formula:-

Angle of repose (θ) = tan-1 (height /radius) ..... (1)

The angle of repose less than 300 usually indicate a free-flowing material and more than 400 suggests a poorly flowing material.[7]

Carr's compressibility index

The Carr's compressibility index was calculated by calculating the tapped and bulk density using 100 ml measuring cylinder. Compressibility is calculated by the formula.

Carr's compressibility index = (TBDLBD)/ TBD X100 .... (2)

Where, TBD is tapped bulk density and LBD is loose bulk density. A Carr's index greater than 25 is considered to be an indication of poor flowability and below 15, of excellent flowability.[8]

Evaluation of tablets

All the formulations were evaluated for various parameters such as hardness, friability, weight variation, % drug content, buoyancy lag time, swelling index, in-vitro drug release, release experiments, IR spectroscopy and optimized formulation were evaluated for in-vivo study.

Hardness

Hardness of tablets was determined using Monsanto hardness tester.

Friability

A sample of pre weighted 20 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 mins. The tablets were then dusted and reweighed. Percent friability (%F) was calculated as follows,

% F= (loss in weight / initial weight) x 100 ..... (3)

Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable. [7, 8]

Thickness:

Thickness of all tablets was measured using a vernier calliper.

Weight variation

The weight of 20 tablets was taken on electronic balance and the weight variation was calculated.

The weight variation tolerance allowed for tablet weighing 324 mg and more is 5% I.P.[9].

Drug content

Ten milligrams of the tablet powder was added to 10 ml of 0.1N HCL and drug solution was filtered through Whatman paper. The sample was analyzed for drug content by UV spectrophotometer (Varian Cary 100) at 272 nm after suitable dilutions.

***In Vitro* Dissolution Studies**

The release rate of Tapentadol HCl from modified release tablets was determined using United States Pharmacopeia (USP) dissolution testing apparatus 2 (paddle method). The dissolution test was performed using 900 mL of 0.1N HCl, at 37 ± 0.5°C and 75 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µ membrane

filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 272 nm using double beam UV spectroscopy.

Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to zero order, first-order, matrix, Hixon- Crowell, Korsemeyer and Peppas to ascertain the kinetic modeling of drug release. The kinetic modeling was found out by employing the PCP disso v3 software.[10, 11]

Infrared (IR) spectroscopy

The drug excipient compatibility and the drug polymer interaction were detected by the IR spectroscopic studies. The polymer- polymer compatibility is also found out by the IR spectroscopic studies.

RESULTS AND DISCUSSION

Evaluation of powder blend

Angle of repose

Angle of repose of all the powder blends was obtained within the range of 20-30^0. This indicates that all the powder blends shows good flow property.

Carr's compressibility index

The compressibility index of all the powder blends was obtained below 10. The compressibility index indicates the good flowability of the powder blend.

Evaluation of tablets

Infrared (IR) spectroscopic study of the formulation

Figure 1 and 2 shows the Infrared spectroscopic scan of Tapentadol hydrochloride mixed with KBr. The IR scan shows prominent peaks for the various active groups such as 3554 cm^{-1} corresponding to the N-H stretch in the tertiary amino group, 1457 cm^{-1} corresponding the C-O stretch between phenolic C and O group.

IR Spectroscopic study of drug, polymer and formulations

The formulations containing the polymers showed all the prominent peaks of Tapentadol HCl with no change in the intensity of the peaks. This indicates that there is no interaction between the excipient and drug that can affect the efficacy of drug.

In Vitro Dissolution Studies

The drug release patterns from all the formulations are shown in figure 3. The percent drug release after 12 hours is as shown in table 3.

The drug release profile of formulations F1- F8 indicates that as the concentration of polymers increases, the drug release decreases. From the comparison of release profile of all the batches, it was observed that the formulations containing HPMC K4M (F1) and HPMC K15M (F2) shows more drug release. Formulations containing HPMC K100M shows retardation compare than HPMC lower grades. Formulation F4 shows more retardation and show less drug release at the end of 12 hrs. In order to increase drug release at end point croscarmellose sodium was added and it shows prominent results. In formulation F8 co povidone was added to match the innovator.

Kinetic Modeling of Drug Release

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the in-vitro drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix and Korsmeyer Peppa's model. The values were compiled in table 4. The formulation shows Fickian diffusion mechanism of drug release.

Stability study

There was no significant difference in physical nature, % drug content and amount of Tapentadol hydrochloride released from F8 after storing for 6 months at normal conditions and for 3 month at 40°C temperature 75 % relative humidity.

Table 2: Evaluation results of formulations F1-F8

Batch No	Blend Parameters					Physical Parameters of Tablets		
	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner ratio	Compressibility Index	Hardness (N)	Friability (%)	Average weight (mg)
F1	21.5	0.483	0.543	1.12	11.04	120 ± 4	Nil	601.0 ± 1.52
F2	22.5	0.453	0.553	1.22	18.08	115 ± 2	Nil	600.8 ± 1.42
F3	29.8	0.432	0.587	1.35	26.40	120 ± 3	Nil	601.0 ± 1.35
F4	24.3	0.442	0.572	1.29	22.72	125 ± 4	Nil	600.5 ± 1.25
F5	22.8	0.412	0.528	1.28	21.96	125 ± 3	Nil	601.0 ± 1.92
F6	21.2	0.437	0.534	1.22	18.16	128 ± 5	Nil	600.6 ± 1.12
F7	21.3	0.467	0.566	1.21	17.49	130 ± 5	Nil	601.2 ± 1.42
F8	21.8	0.489	0.559	1.14	12.52	130 ± 5	Nil	600.4 ± 1.74

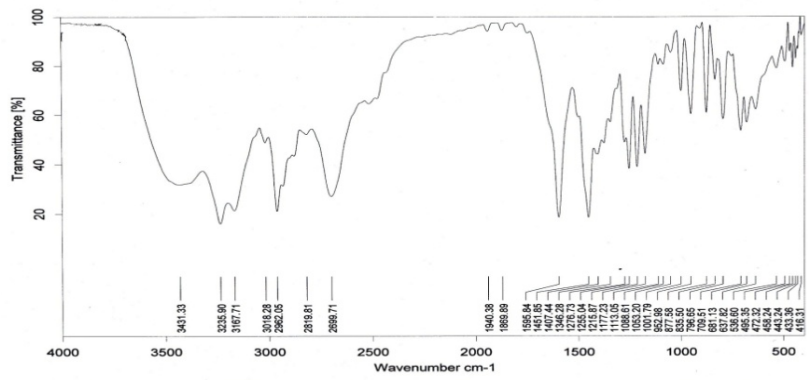


Figure 1: IR Spectra of Tapentadol Hydrochloride

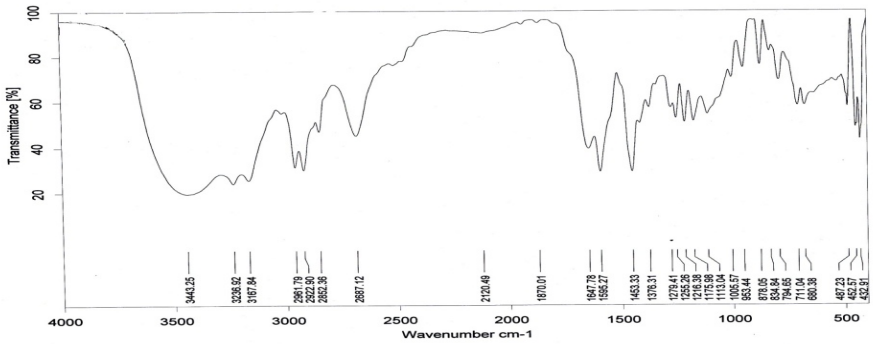


Figure 2: IR Spectra of Tapentadol Hydrochloride formulation

Table 3: *In vitro* drug release of formulations F1- F8.

Formulation	% Drug Release						
	0.5 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12hrs
F1	50.4	67.8	76.4	84.3	92.8	97.2	99.2
F2	39.7	48.9	57.4	68.1	79.5	92.1	99.4
F3	24.5	37.9	49.8	59.9	67.3	82.4	93.4
F4	8.2	19.4	30.4	41.8	52.7	64.5	73.4
F5	13.5	30.1	51.2	63.2	73.2	74.0	81.4
F6	13.2	31.6	48.6	65.7	75.0	85.0	88.7
F7	13.5	32.3	52.0	66.0	75.5	79.2	90.2
F8	13.6	35.5	54.6	68.7	79.9	89.5	95.2
Innovator	13.2	34.5	55.2	69.4	81.0	91.7	97.2

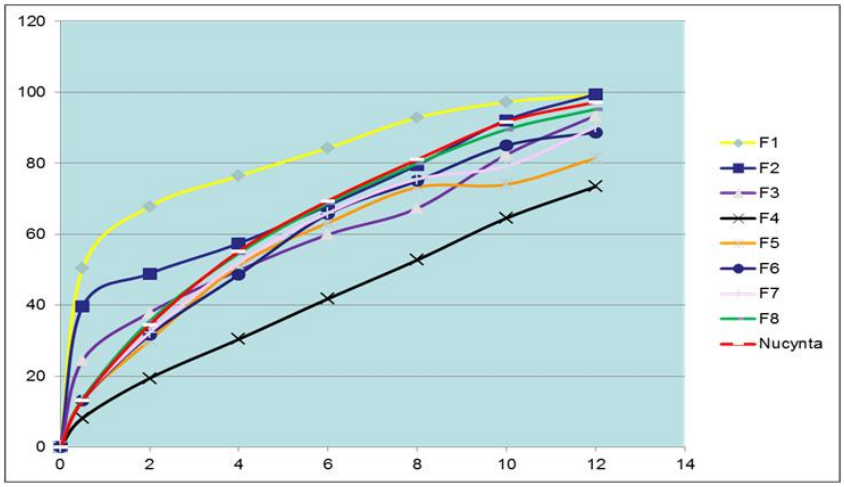
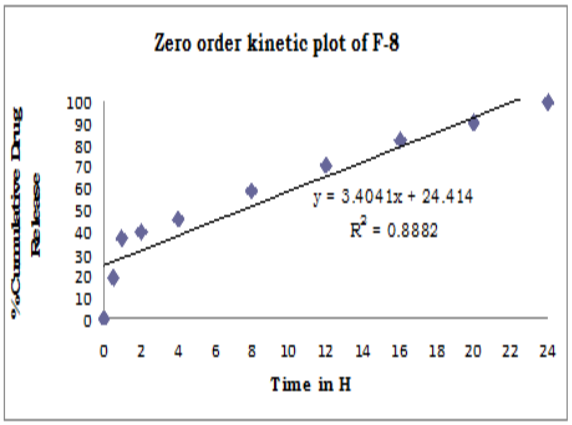
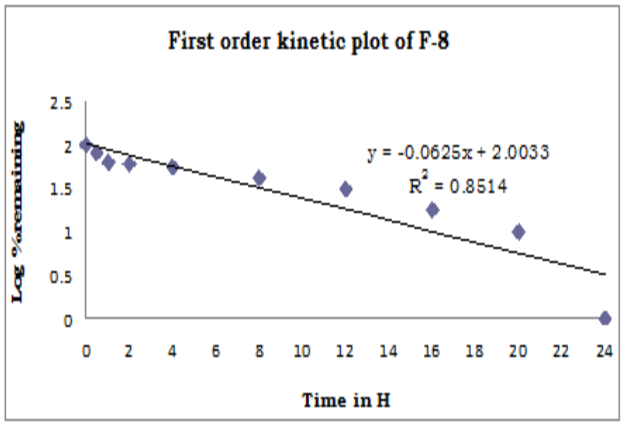


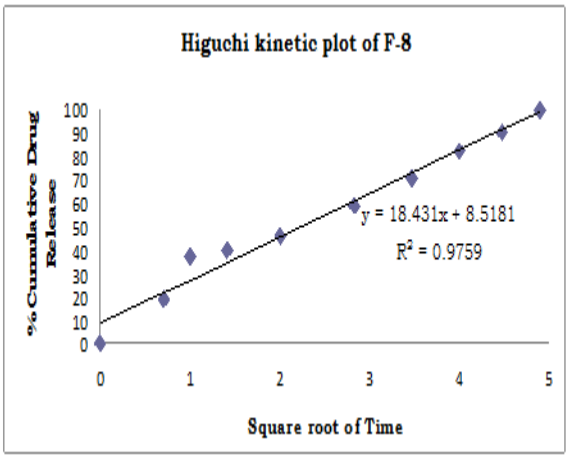
Figure 3: Dissolution graph of F1 – F8 trials

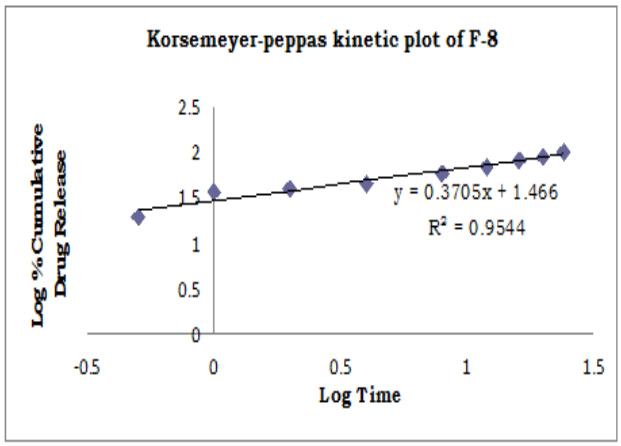
Table 4: Release kinetics of formulation F8

Formulation code	Mathematical models				
	Zero order	First order	Higuchi's model	Korsmeyer Peppa's model	
	R^2	R^2	R^2	R^2	N
F-8	**0.888**	0.851	0.976	0.954	0.370









CONCLUSION

The results of experimental studies of Tapentadol matrix tablets proved that the granules of Tapentadol showed good flow properties, tablet evaluation tests are within the acceptable limits. IR spectral analysis proved that there was no drug- polymer interaction, the kinetic studies revealed that all the formulations followed fickinian diffusion drug release and stability studies revealed that all the formulations were found to be stable after storing at 40°C and 75 % RH for 6 months.

The results of the above study clearly indicated that Tapentadol can be formulated as controlled release tablets using HPMC K 100M as retarding polymer combination with croscarmellose sodium and copovidone by wet granulation method, which will provide continuous release of drug at a predetermined rate and for a predetermined time.

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