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FORMULATION DEVELOPMENT AND EVALUATION OF EXTENDED RELEASE TABLETS OF TAPENTADOL HCl

S. Maheswara Rao*, P. Prem Kumar and Manohar Babu S.

Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur,-522001, Andhra Pradesh, India.

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***Corresponding Author**
S. Maheswara Rao
Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur,-522001, Andhra Pradesh, India.

ABSTRACT

Patients experiencing acute or chronic pain require an analgesic agent that is both effective and well tolerated for management of moderate to severe pain. Therefore to overcome such pain there is need to formulate effective and stable dosage form of Tapentadol HCl with following objectives. Development and evaluation of the extended release oral tablet, which matches with innovators formulation. Performed the preformulation studies to study compatibility between drug and excipients. Evaluated the physical parameters for the prepared tablets. The marketed product was characterized for various properties of the dosage forms like assay, dissolution and other physical properties. F10 formulation found pharmaceutical equivalent to competitor product. The Final trial was packed in PVC/PVDC blister packing and kept at 40°C/75%RH±5% for 6 month and 25°C±2°C/60%RH±5% upto 24 month. Formulation found to be robust and stable.

KEYWORDS: Chronic pain, Tapentadol HCl, Dissolution Studies, pharmaceutical equivalent.

1. INTRODUCTION

In the search for safe, economical and efficient means of providing for the health and well being of mankind, modern science has produced numerous active agents through the methods of drug discovery that manipulate the biological environment around and within us. However, inability to deliver these agents to their targets at the right time and in right amounts cause some inefficiency that makes a useful drug unsuitable. This inability results in their loss,

undesirable side effects and leads to a regimen requiring repeated treatment to produce and sustain the desired effects.[1-4]

Conventional drug dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period of time. To achieve the same, a drug may be administered repetitively using a fixed dosing interval. This causes several potential problems like saw tooth kinetics characterized by large peaks and troughs in the drug concentration-time curve.[5-8]

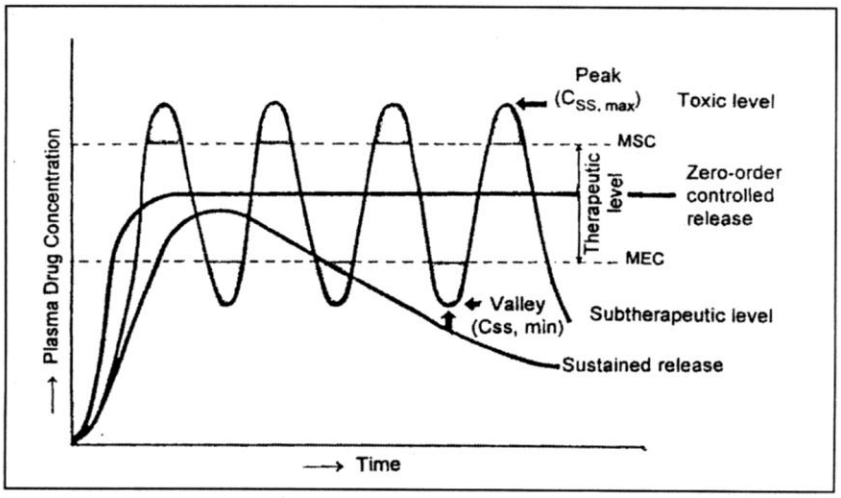

Figure No.1: Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations

1.1 EXTENDED RELEASE DRUG DELIVERY SYSTEM

The goal of drug delivery system is to provide therapeutic amount of drug at proper site in body and then maintain the desired plasma drug profile. It should deliver drug at a rate dictated by the need of the body over the period of treatment. An extended release dosage form allows at least a two-fold reduction in dosing frequency or significant increase in patient compliance or therapeutic performances as compared to a conventional release dosage form. So, the goal in designing extended or controlled release system is to reduce the frequency of dosing and /or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.[9-12]

Advantages

Extended release products offer three potential benefits as follows[13-15]:

- Sustained blood levels
- Attenuation of adverse effects
- Improved patient compliance

2. MATERIALS AND METHODS

2.1. MATERIALS USED

Table No 1: Pharmacokinetics /Pharmacodynamic properties of Tapentadol HCl.

Name of the drug	**Tapentadol HCl**
Description	White to off white crystalline powder.
Solubility	Tapentadol HCl is freely soluble in methanol. The partition coefficient is 2.87
Molecular weight	257.80
Use	Pain management.
Administration	Oral
Melting point	198-203°C
Log P	2.87
T_{max}	1.25 hr
Optical Rotation	-22° to -28°
Volume of distribution	540L
Half life	4 hours
Clearance	1530ml/min.
Protein binding	20%
pKa	9.34 & 10.45
BCS Class	Class I

Table No 2: Excipient Profile

S. No.	**Excipients**	**Brand Name**	**Functional category**
1	Microcrystalline cellulose	Avicel PH 101	Diluent
2	Hydroxypropyl methylcellulose K100M CR	Methocel K00M	Polymer
3	Carbopol 971P	Lubrizol	Polymer
4	Hydroxypropyl methylcellulose K15M Premium	Methocel K15M	Polymer
5	Ethylcellulose	Ethocel	Binder
6	Colloidal silicone dioxide	Aerosil 200	Glidant
7	Magnesium stearate	---	Lubricant
8	Opadry white	---	Film former

2.2. METHODS USED

EVALUATION OF FORMULATION[15-18]

Physical characterization of Blend

All physical tests of blend were performed like Bulk density, Tapped density, Compressibility index, Hausner's ratio and Loss on drying.

Tablet evaluation

The tablets were evaluated for the following tests.

Average weight

20 Tablets were taken randomly and weighed accurately and the average weight of the tablets from each batch was calculated.

Hardness/ Crushing strength

The term hardness indicates the ability of a tablet to withstand mechanical shocks while handling. It is generally expressed in Kg/cm^2 or in Newton (N). Hardness of a tablet was measured using hardness testers. (Erweka).

Thickness

Three samples were selected randomly and thickness was measured using "Mitutoyo" Vernier caliper.

Friability

Friability test is performed to assess the effect of friction and mechanical shocks, which may often cause tablet to chip, cap, laminate or break during packaging or transportation.

Method

Samples of 20 tablets were taken. Tablets were de-dusted prior to testing. Tablet samples were accurately weighed and were placed in the drum of friability tester (Electrolab). Drum was rotated for 100 revolutions. Tablets were deducted and reweighed.

Formula

$$\% F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Where, $W_{initial}$ – Initial weight of tablets

W_{final} – Weight of tablets after completing tests

Dissolution test

This test provides evaluation of physiological availability of drug candidate. For FDA approval and bioequivalent product, it is important to compare the dissolution profile of product with the dissolution profile of reference-listed drug. Therefore similarity factor (f_2) is recommended by various regulatory committees that demonstrated the similarity in the percent (%) dissolution of test product with reference product. Dissolution profiles are considered similar if the calculated f_2 value is between 50 and 100.

Table No 3: Dissolution Apparatus and Their Conditions

Drug Name	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)
Drug	I (Basket)	75	0.1 N HCl	900	1,2,4,6,8 and 12hrs

Assay

This method is used to analyze or quantify a substance in a sample. Assay is an analytical process to determine not only the presence of substance and the amount of substance but also the biological and pharmacological potency of a drug.

Stability study

In any rational design and evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection.

Table No 4: Time period of storage condition

Study	Storage Condition	Time Period
Long term	25°C±2°C/60%RH±5 RH	24 month
Accelerated	40°C±2°C/75%RH±5%RH	6 month

3. RESULTS

Table No 5: Different Formulation Batches of Tapentadol HCl

S. No	F1	F2	F3	F4	F5	F6	F7	F8
Tapentadol HCl	116.48	117.04	117.04	117.04	117.04	117.04	117.04	117.04
MCC 101	-	178.36	178.36	127.36	167.92	107.36	97.36	96.36
Prosolve	228.52	-	-		-		-	-
HPMC K15M	150	49.00	-		-		-	-
HPMC K100M	-	-	49.00	100.00	-	100.00	100.00	100.00

Carbopol 971P	-	-	-	-	60	-	-	-
Ethyl cellulose 10CPS	-	-	-	-	-	20.00	30.00	40.00
Aerosil 200	-	3.50	3.50	3.50	3.50	3.50	3.50	3.50
Mg.Stearate	5.0	2.10	2.10	2.10	2.10	2.10	2.10	2.10

Table No 6: Evaluation of Physical parameters all formulations

Trial	Avg. Wt. of tab (mg)	Hardness (N)	Thickness (mm)	Friability (%)
F1	500	91-96	5.2-5.3	1.04
F2	350	89-95	4.4-4.5	0.3
F3	350	80-82	4.4-4.5	0.35
F4	350	99-105	4.48-4.51	0.02
F5	350	99-104	4.64-4.66	0.25
F6	350	100-110	4.6-4.8	0.31
F7	350	110-126	4.5-4.6	0.31
F8	350	100-110	4.6-4.7	0.08
F9	350	110-120	4.6-4.7	0.12
F10	350	106-118	4.7-4.76	0.18

Table No 7: Dissolution Profile of Different Formulations

Time (hr)	%Cummulative Drug Dissolved					
	F2	F3	F4	F5	F6	INNOVATOR
1	35	34	37	28	27	30
2	47	52	55	44	38	41
4	72	75	77	64	62	68
6	89	89	91	78	78	80
8	102	97	99	88	95	93
12	103	101	103	97	96	102

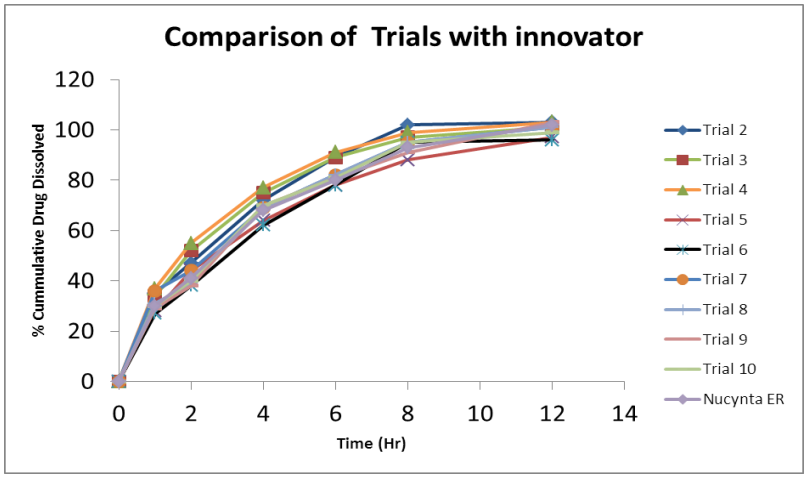

Fig.No-2: Dissolution profile of all formulations and comparison with Innovator

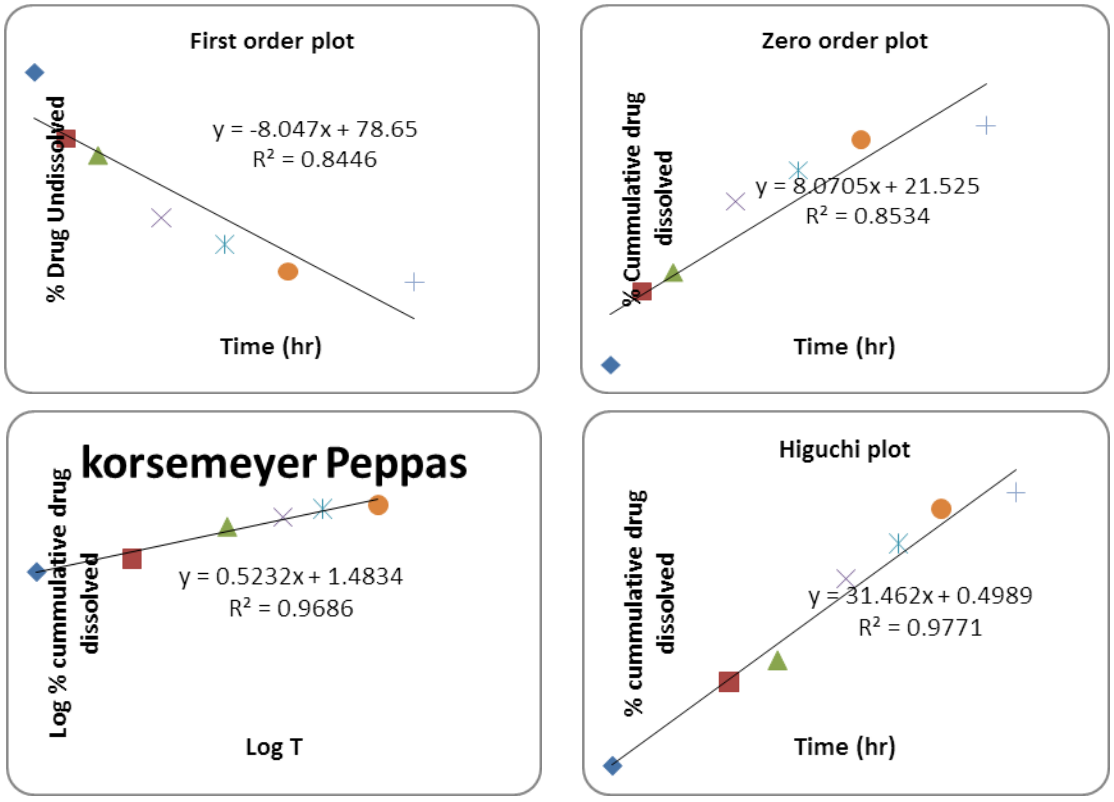

Fig.No-3: Drug Release Kinetics of Optimized formulation

Table No 8: Comparison of Dissolution Profile of Trial 10 with Innovator Product

Time (hrs)	Cumulative % Release	
	Trial 10	Nucynta ER
1	30	30
2	40	41
4	70	68
6	81	80
8	95	93
12	99	102

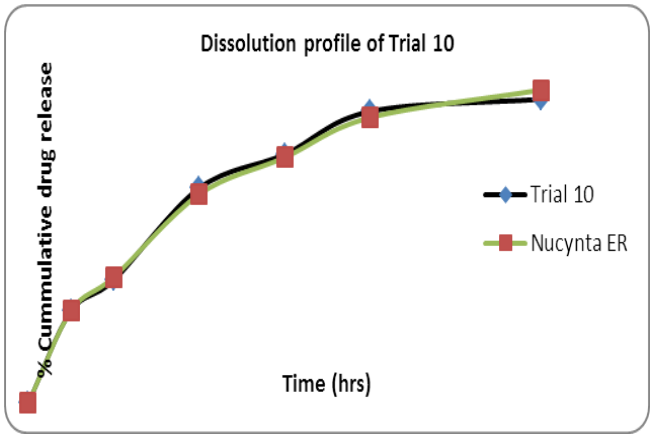

Figure No.4: Dissolution Profile of Trial 10

Table No 9: Assay evaluation of Trial batches

Trial No.	Assay Of Drug %
Trial I	-
Trial II	98.6
Trial III	98.7
Trial IV	97.2
Trial V	95.3
Trial VI	96.1
Trial VII	97.9
Trial VIII	98.4
Trial IX	98.2
Trial X	97.4

4. SUMMARY AND DISCUSSION

Table No 10: Summary and discussion

Batch No	Objective of batch	Change for previous Experiment	Observation
Trial 1	To take a trial of Extended release tablets containing Tapentadol HCl by Slugging method to match with Innovator's product.	-	Peeling and chipping problem is observed due to high friability.
Trial 2	To take a trial of Tapentadol HCl tablets containing by Slugging method to match with Innovator's product.	Diluent is changed.	Chipping and peeling problems were solved, but dissolution results found non satisfactory.
Trial 3	To take a trial of Tapentadol HCl tablets by using HPMC K100M CR to obtain dissolution profile matching with innovator.	Rate controlling polymer is changed to HPMC K100M CR	Dissolution studies found faster.
Trial 4	To take a trial by increasing the concentration of HPMC K100M CR to improve dissolution profile to match with innovator.	Concentration of rate controlling polymer is increased to 100mg/tab	Sealing concentration of HPMC is attained but there is no control over drug release rate.

Trial 5	To take a trial by replacing HPMC K100M CR with Carbopol 971P to control the rate of dissolution.	Rate controlling polymer is changed to Carbopol 971P	Rate of drug release found much faster than previous formulations
Trail 6	To take a trial of Extended release tablets of Tapentadol HCl by non-aqueous granulation technique by using ethyl cellulose (binder) & HPMC K100M CR as a rate controlling polymer.	Ethyl cellulose is used as a binder in the concentration of 20mg/tab.	Weight variation problem is observed due to high content of fines.
Trail 7	To take a trial of Extended release tablets of Tapentadol HCl by non-aqueous granulation technique by increasing the concentration of ethyl cellulose to 30mg/tab to decrease the quantity of fines.	Concentration of binder is increased to 30mg/tab.	Weight variation problem is overcome, but dissolution profile is on lower side.
Trail 8	To take a trial batch of Extended release tablets. Containing Tapentadol HCl by increasing the concentration of binder to 40mg per tab.	Concentration of binder is increased to 40mg/tab.	Dissolution profile is matching with the innovator product.
Trail 9	To take a trial of Tapentadol ER tablets as reproducible trial of trial 8 by wet granulation method and to evaluate different packaging materials on stability.	Trial batch is taken and evaluated for different packing materials.	Tablets packed in Alu/Alu founds stable.
Trail 10	To take a scale-up trial of Tapentadol HCl by wet granulation method (scale up trial).	Taken as a Scale up trial.	All physical and chemical parameters found stable and reproducible.

5. CONCLUSION

It is imperative to summarize the findings of the dissertation entitled "Formulation Development and Evaluation of Extended Release Tablets of Tapentadol HCl". Prior to the development of dosage form, all the fundamental physical and chemical properties of the drug molecule are evaluated and the results were found satisfactory. This information will dictate the subsequent events and possible approaches in formulation development viz. selection of suitable process, selection of the correct technical grade of excipients. Preformulation studies were carried out and it was concluded from the observations that the drug was compatible with the studied excipients.

The marketed product was characterized for various properties of the dosage forms like assay, dissolution and other physical properties. Wockhardt formulation found pharmaceutical equivalent to competitor product.

The Final trial was packed in PVC/PVDC blister packing and kept at 40°C/75%RH±5% for 6 month and 25°C±2°C/60%RH±5% upto 24 month. Formulation found to be robust and stable.

6. FUTURE SCOPE

This research project has a wide future scope with respect to delivery of drug for the treatment of acute pains.

Following are the certain future scopes for the above study:

1. Pilot-Bioequivalence study of the final formulation.
2. To be launched commercially for domestic market.
3. Development of the formulation in different strengths with the same API

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