WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 8, 1641-1654. Research Article ISSN 2277– 7105

DEVELOPMENT AND *IN-VITRO* EVALUATION OF TRAMADOL HCL SUSTAINED RELEASE TABLETS

[1]Amrapali Jadhav and [2]*Sachin Tukaram Thorat

[1]Ass. Professor, Govt. College of Pharmacy, Aurangabad.

[2]Head R & D, Melwa Pharma, Colombo, Srilanka.

Article Received on
16 June 2020,

Revised on 06 July 2020,
Accepted on 26 July 2020,

DOI: 10.20959/wjpr20208-18178

***Corresponding Author**
Sachin Tukaram Thorat
Head R & D, Melwa Pharma,
Colombo, Srilanka.

ABSTRACT

Drug delivery has metamorphosed from the concept of pill to molecular medicine pharmacodynamic principles in design of drug delivery system has lead to improve therapeutic efficacy. Drug research has evolved and matured through several phases beginning. Tablets and capsules are the major oral preparations before the introduction of advances, controlled drug delivery systems. However, last two decades the drug delivery technology has been developed rapidly and many novel oral drug delivery systems have been invented.

KEYWORD: Introduction, Method, Formulation study, equipment results.

INTRODUCTION

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables, as drug carriers.

This type of drug delivery system is known to provide a prompt release of drug or immediate release product. Such immediate release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects.

However, after absorption of drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetics profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity.

Before this point is reached another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore, maintain plasma drug concentrations, beyond what is typically seen using immediate release dose.

METHODS

A. Preformulation studies[60]

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. 1. Organoleptic properties:[60]

Color

A small quantity of Tramadol Hcl powder was taken on butter paper and viewed in well-illuminated place.

Taste and odors

Very less quantity of Tramadol Hcl was used to get taste with the help of tongue as well as smelled to get the order.

2. Physical characteristics

Loss on drying

This is employed in IP, EP and USP. Although the loss in weight, in the samples so tested, principally is due to water, small amount of other volatile materials will a contribute to the weight loss. The moisture balance combines both the drying process and weight recording, it is suitable where large numbers of samples are handled and where a continuous record of loss in weight with time is required.

Procedure

Placed about 1 gm of Tramadol Hcl in the plate of digital moisture balance instrument. Set the temperature 105 °C and run the instrument up to constant weight. Finally read out the percentage loss on drying automatically.

3. Flow properties[62]

Procedure

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of sample powder is filled in

funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction. The height of the heap was measured by using scale. The values of angle of repose are calculated by using the following formula:

tan □□ = h/r, □□ = tan $^{-1}$ h/r

Where, h- height of the heap

r- Radius of the heap

For most pharmaceutical powders, the angle of repose values range form 25° to 45°, with lower values indicating better flow characteristics. If values of angle of repose,

1) < 25° : Excellent flow

2) 25-35°: very good flow

3) 35-40°: good flow

4) > 40° : Poor flow

4. Bulk density[62]

Bulk density is defined as the mass of powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particles become more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease.

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Procedure

A known quantity of powder was poured into the measuring cylinder carefully level the powder with out compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula m/Vo.

Tapped density: [62-b]

Tapped Density = $\frac{m}{Vf}$

Generally replicate determinations are desirable for the determination of this property.

Measurement of Powder Compressibility

The compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. These differences are reflected in the compressibility Index and the Hausner Ratio Calculated by the formula:

Compressibility index: = $100 \frac{(V_0 - Vf)}{V_0}$

Hausner Ratio: = $\frac{V_0}{Vf}$

5. Melting point[63]

It is one of the parameters to judge the purity of crude drugs. In case of pure chemicals or phytochemicals, melting points are very sharp and constant.

Procedure

A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

6. Assay of Tramadol Hcl

Assay or percentage of purity of Tramadol Hcl is done by Potentiometric titration.

7. FT-IR spectrophotometer[68]

To identified drug Tramadol Hcl IR spectrophtometric analysis was carried out by Kbr disc method, and recorded the spectrum in the range of 4000 cm^{-1} and 450cm^{-1}. See (Fig.-----)

TRAIL 1st

(BATCH F1)

AIM: - To formulate Tramadol Hcl SR Tablet 100 mg using HPMC (K15M) as Sustained Release polymer.

OBJECTIVES: - Trial planned with the use of HPMC (K15M) as a Sustained Release Polymer.

Batch size: - 200 tablets.

MANUFACTURING FORMULA

Sr. No.	Ingredients	Speci-	Qty/Tablet	Qty/ Batch
		fication	(mg)	All Wt. in (gm)
1	Tramadol Hcl	B.P.	100	20
2	HPMC(K15M)	I.P	160	32
6	Magnesium Stearate	I.P	5	1
5	colloidal silicon dioxide	I.P	5	1

METHOD OF PREPARATION

1) DRY MIXING:-Weigh Following ingredients & pass through the respective Sieve nos.

Tramadol Hcl- 30 #

HPMC - 60 #

and then transfer this mixture to the polybag. Mix for 5 Min.

2) LUBRICATION:-To the above step-I blend, add geometrically colloidal silicon dioxide and magnesium stearate which were passed through sieve 60 #, shake well in Polybag

3) COMPRESSION:- The granules were compressed by using 10.3MM round standard concave punch plain on both side with Avg. Wt. of 270 mg/tablet.

*** PRE COMPRESSION PARAMETERS**

Given in Table no.

***CORE TABLET EVALUATION**

Description- White coloured round shaped, uncoated tablet.

Given in Table no.

***DISSOLUTION**

Given in Table no.

REMARK

Problem of capping was observed while compression .hence decided to discard the batch.

CONCLUSION

It is decided, the next trial will be taken with Avicel PH-102 -- 20mg/ Tab. By reducing the quantity of HPMC. HPMC Will be 140 mg /Tab.

TRAIL 2st

(BATCH F2)

AIM: - To formulate Tramadol HclSR Tablet 100 mg using HPMC (K15M) as Sustained release polymer. & Avicel PH-102 to avoid capping

OBJECTIVES: - Trial planned with the use of HPMC (K15M) as a Sustained Release Polymer. & Avicel PH-102 to avoid capping

Batch size: - 200 tablets.

MANUFACTURING FORMULA

Sr. No.	Ingredients	Specification	Qty/Tablet mg	Qty/ Batch gm
1	Tramadol Hcl	B.P.	100	20
2	HPMC(K15M)	I.P	140	28
3	Magnesium Stearate	I.P	5	1
4	Avicel PH-102	I.P.	20	4
5	colloidal silicon dioxide	I.P	5	1

METHOD OF PREPARATION

1) DRY MIXING:-Weigh Following ingredients & pass through the respective Sieve nos.

Tramadol Hcl- 30 #

HPMC - 60 #

Avicel PH-102 - 60 #

and then transfer this mixture to the polybag. Mix for 5 Min.

2) LUBRICATION:-To the above step-I blend, add geometrically colloidal silicon dioxide and magnesium stearate which were passed through sieve 60 #, shake well in Polybag

Granules ready for compression

3) COMPRESSION:-Then the granules were compressed by using 10.3MM round standard concave punch plain on both side with Avg. Wt. of 270 mg/tablet.

*** PRE COMPRESSION PARAMETERS**

Given in Table no.

***CORE TABLET EVALUATION**

Description- White coloured round shaped, uncoated tablet.

Given in Table no.

***DISSOLUTION**

Given in Table no.

REMARK

The dissolution profile of this batch was not matched with standard (market) sample.

Within 30 min the release was 50 %which was not in limit.

CONCLUSION

It is decided, the next trial will be taken with HPMC-K-100M By replacing HPMC-K-15M. to control the release profile.

TRAIL 3

(BATCH F3)

AIM: - To formulate Tramadol Hcl SR Tablet 100 mg using HPMC (K100M) as Sustained release polymer.

OBJECTIVES: - Trial planned with the use of HPMC (K100M) as a Sustained Release Polymer. & Avicel PH-102 to avoid capping

Batch size: - 200 tablets.

MANUFACTURING FORMULA

Sr. No.	Ingredients	Specification	Qty/Tablet mg	Qty/ Batch gm
1	Tramadol Hcl	B.P.	100	20
2	HPMC(K100M)	I.P	140	28
3	Magnesium Stearate	I.P	5	1
4	Avicel PH-102	I.P.	20	4
5	colloidal silicon dioxide	I.P	5	1

METHOD OF PREPARATION

1) DRY MIXING:-Weigh Following ingredients & pass through the respective Sieve nos.

Tramadol Hcl- 30 #

HPMC - 60 #

Avicel PH-102 - 60 #

and then transfer this mixture to the polybag. Mix for 5 Min.

2) LUBRICATION:-To the above step-I blend, add geometrically colloidal silicon dioxide and magnesium stearate which were passed through sieve 60 #, shake well in Polybag Granules ready for compression.

3) COMPRESSION:-Then the granules were compressed by using 10.3MM round standard concave punch plain on both side with Avg. Wt. of 270 mg/tablet.

*** PRE COMPRESSION PARAMETERS**

Given in Table no.

***CORE TABLET EVALUATION**

Description- White coloured round shaped, uncoated tablet.

Given in Table no.

***DISSOLUTION**

Given in Table no.

REMARK

The dissolution profile of this batch was not matched with standard (market) sample.

Within 30 min the release was 40% and 50% within 2 hours, which was not in limit.

CONCLUSION

It is decided, the next trial will be taken with HPMC-K-100M and HPMC-K-15M. to control the release profile.

DISCUSSION

STANDARD CALIBRATION CURVE

Standard calibration curve of Tramadol Hcl was drawn by plotting absorbance v/s concentration. The absorbance values are tabulated in Table no.1. Standard calibration curve of Tramadol Hcl in the Beer's range between 10-100 µg/ml is shown in figure-1.

Table-1: Calibration curve of Tramadol Hcl in water at λ max 270 nm.

Sr. No	Concentration (µg/ml)	Absorbance*
1	Blank	0.000
2	10	0.06
3	20	0.122
4	30	0.184
5	40	0.228
6	50	0.3

* Each reading is an average of 3 determinations

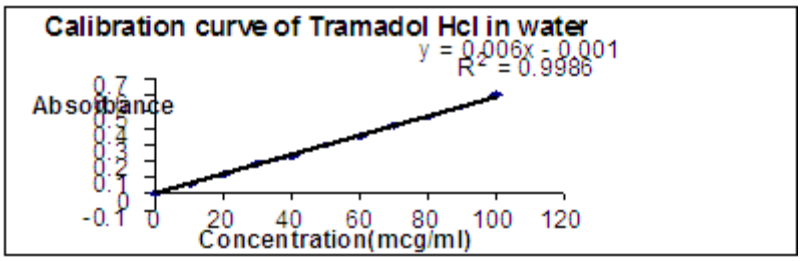

Figure-1: Standard calibration curve for Tramadol Hcl in water at λ max 270 nm.

The linear regression analysis for standard curve in water

The linear regression analysis was done on absorbance data points. The results are as follows:

The Slope = 0.006

The intercept = 0

The correlation coefficient = 0.998

RESULT AND DISCUSSION

A. PRE FORMULATION STUDIES

1. Organoleptic properties of API

These tests were performed as per procedure given in material and method part. The results are illustrated in following table.

Table No.:08

Test	Specification	Observations
Color	White powder	White powder
Taste	Bitter	Bitter
Odor	Odorless	Odorless

The result of table indicates the drug Tramadol Hcl complies with specifications.

2. Physical characteristics of API

Water Content by K F R Method

This test was done as per procedure stated in material and method section. The result illustrated in following table.

Table No.:09

Test	Specification	Observations
Water content By KFR	NMT 50 %	0.25 %

The result of table indicates the drug Tramadol Hcl complies with specifications.

Angle of repose

It was determined as per procedure given in material and method part. The results are illustrated in following tables.

Table No.:10

S. No	Material	Angle of repose	Average angle of repose
1.	Tramadol Hcl	a) 56.0° b) 55.0° c) 56.0°	55.66°

Powder compressibility

It was determined as per procedure given in material and method part. The results are illustrated in table.

Materials	Compressibility index	Hausner ratio
Tramadol Hydrochloride	10 %	1.111

Melting point

It was determined as per procedure given in material and method part. The results are illustrated in following table.

Determination of Melting Point

S. No	Material	Melting point
1.	Tramadol Hydrochloride	183°C

3. Solution Properties Of API

Solubility

Freely soluble in water and in Methanol, Very slightly soluble in acetone.

S. No	Buffer	Result
1	pH 2.0 (0.1 N Hcl)	Soluble
2	Phosphate Buffer (6.8)	Soluble
3	Water	Freely Soluble
4	Methanol	Freely Soluble
5	Phosphate Buffer (6.8)	Soluble
6	Acetone	Very slightly soluble

5. ASSAY OF TRAMADOL HCL (BY POTENTIOMETRIC TITRATION METHOD)

Method	Specification(BP)	Percentage found
Potentiometrically	99 to 101 %	99.34%

The results of Table indicates that, are complies with as per limit.

Drug release profile

Table-: *In vitro* drug release profile of Tramadol Hcl from Marketed Formulation.

Time (hrs)	√T	Log T	Abs*	Conc. (µg/ml)	Drug Release (mg)	Drug Release (%)	CDR (mg)	CDR (%)	Log % CDR
30 min	0.545	0	0.193	32.16	28.94	28.94	28.94	28.94	1.461
1.0	1.414	0.301	0.252	42.00	37.8	37.8	37.8	37.8	1.577
2.0	1.732	0.477	0.315	52.5	47.25	47.25	47.25	47.25	1.674
4.0	2	0.602	0.431	71.83	64.64	64.64	64.64	64.64	1.810
6.0	2.449	0.778	0.501	83.50	75.15	75.15	75.15	75.15	1.875
8.0	2.828	0.903	0.550	91.66	82.49	82.49	82.49	82.49	1.916
10.0	3.162	1	0.597	99.50	89.55	89.55	89.55	89.55	1.952
12.0	3.464	1.079	0.634	105.66	95.09	95.09	95.09	95.09	1.978

* Each reading is an average of 3 determinations

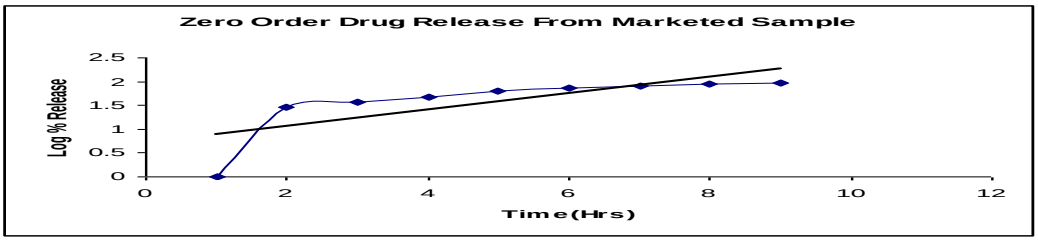

Figure-7: Zero order drug release from Market sample.

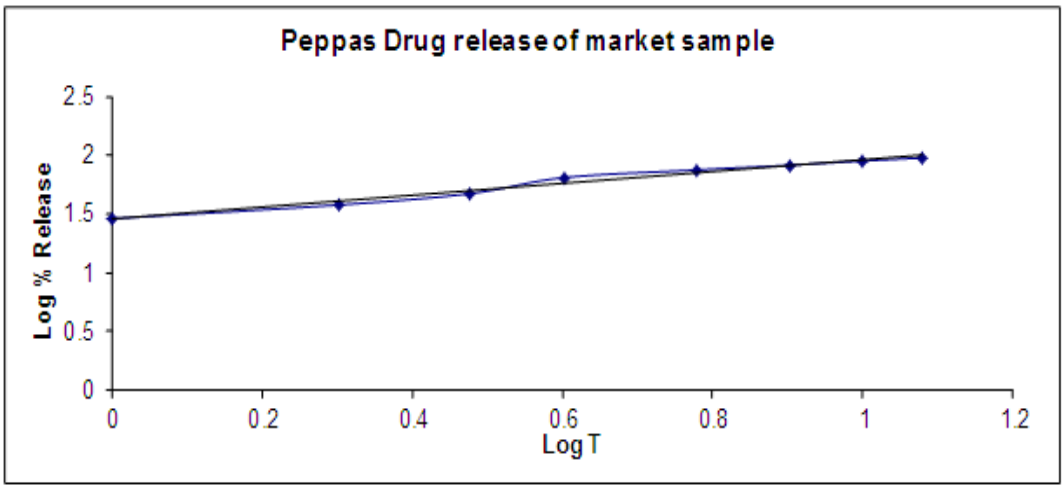

Figure-8: Peppas Drug release from Marketed Sample.

	Peppas Equation			Zero order Equation		
	Slope	Rate constant (K) mg. hr^{-1}	Regression coefficient (R^2)	Slope	Rate constant (K) mg. hr^{-1}	Regression coefficient (R^2)
F4	0.480	1.45	0.951	0.168	0.753	0.553
F 5	0.546	1.40	0.976	0.167	0.724	0.566
F6	0.582	1.39	0.967	0.177	0.685	0.606

SUMMARY

In present work, attempts have been made to formulate sustained release matrix tablets of Tramadol Hydrochloride, by using hydrophilic polymer HPMC, Tramadol Hydrochloride which is preferably used for treatment of severe to moderate pain. Matrix tablets were prepared by direct compression technique.

Tramadol hydrochloride meets all the ideal characteristics to formulate in the form of sustained release drug delivery system Under preformulation study, the organoleptic properties were complied with the pharmacopeal specification.

Physical properties such as bulk density and tapped density were more in case of granules ready for compression than that of Tramadol Hydrochloride. Melting point determinations were given the information about purity of the drug powder.

Water content of drug was within the BP limit and the result of angle of repose of drug powder showed the poor flow properties than blend ready for compression. Assay of Tramadol Hydrochloride was carried out by potentiotometric titration method and was found to be 99.34%.

The physical compatibility evaluation was performed in visual basic. The study implies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description.

All the formulations were evaluated on the basis of Pharmacopoeial specification. Shape of the tablets was round plain concave, hardness, thickness, weight variation, dissolution test were carried out.

Infra Red spectrum of Tramadol Hydrochloride matches with the standard spectrum as well in tablet there are no any additional peak formation.

Differential Scanning Colorimetry thermo gram of the tablet shows decrease in melting point of drug, which may be due to fusion.

Stability studies of the selected formulated tablets were carried out by keeping the tablets at 40°C $\pm$ 2°C/ 75 $\pm$ 5 % RH and 30°C $\pm$ 2°C/ 65 $\pm$ 5 % RH (stability chamber) for 3 months. All the parameters were within the limit after 3 months.

The release rate of Tramadol Hydrochloride from matrix tablets followed first order kinetics, which was obtained by plotting, a graph of log % drug remained Vs time.

The mechanism of drug release form matrix tablets was combination of swelling diffusion and erosion in all cases.

CONCLUSION

In the present study attempts were made to formulate 100 mg sustained release tablet of Tramadol Hydrochloride which can provide effective drug release for 12 hours.

Sustained release matrix tablets Tramadol Hydrochloride were prepared by Direct compression method. *In-vitro* study showed batch No 2,3,4 for 100 mg label claimed were well suited to be sustained release formulation.

Batch No. 2 was found to obey first order drug release, governed by diffusion through swollen matrix and erosion of the matrix, showing anomalous diffusion or non fickian transport.

Infra Red spectrum and Differential Scanning Colorimetry thermo gram of the tablet reveals that there is no interaction of the polymer and tablet matrix with the Tramadol Hydrochloride.

Further, *in- vivo* and continuation of stability studies are recommended.

REFERENCES

1. Vyas, S.P., and Khar, R.K. Controlled drug Delivery and advances (1st ed.). Vallabh Prakashan., Delhi, 155-195.
2. Yie. W. Chien, “Novel drug delivery system", 2nd edition, 1.
3. Ashok V. Bhosale, Rahul V. Takawale, sanjay D. Sawamy, “oral noval drug delivery system “The Easterm pharmalist”, September 2000, 41-43.
4. Loyd V. Allen, Jr, Nchols G. Popovich, Howard C. Ansel, Ansel’s “pharmaceutical dosage forms and Drug Delivery System” 8th edition, 260-275.
5. Thomas wai-Yip lee, joseph R. Robinson, controlled-release drug delivery system’s, chapter-47, Remington “The Science and Practice of Pharmacy”, 20th edition, vol-1, 903.
6. N.K. Jain, “Advances in controlled and Novel Drug Delivery”, CBS publications, 268-269.

7. Gul Majed khan, "past and present status of controlled release matrixes"; Asia network for scientific in permeation ISSN 1608-8689, 2001; 1(5): 350-350.
8. Heather J Tangeman, `Extended-Release Metoprolol Succinate in Chronic Heart Failure. The Annals of Pharmacotherapy, 37(5): 701-710. www. Theannals.com/cgi/content/abstract/37/5/701
9. Hamed M. Abdou, "Dissolution characteristics of controlled Release systems", chapter - 12 "Dissolution Bioavailability and bioequivalence," 215-218.
10. Leon Lachman, Herbert A. Liberman, Joseph L. Kanig, "The Theory and Practice of Industries Pharmacy", 3rd edition.
    a) Chapter 14, in sustained Release Dosage forms, 430 – 456.
    b.) Chapter 11 in tablets, 296-303.
11. James swarbrick and James C: Boylan, "Encyclopedia of Pharmaceutical technology", (vol 14); 304-307.
12. H. Popli and S.N.Sharma, "Trend in oral sustained release formulation– 1", The Eastern Pharmacist, August 1989, 99.
13. Thomas Wai- Yip, Lee, Joseph R.Robinson, "Controlled–release drug delivery system", chapter -3, method to achieve sustained drug delivery, Vol -6, 132.