Original Research Article

Formulation and Evaluation of Mouth Dissolving Tablets of Tramadol Hydrochloride

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Abstract

Purpose: To prepare, and evaluate in vitro and in vivo tramadol hydrochloride mouth dissolving tablets (MDT).

Methods: Tramadol HCl MDT were prepared by direct compression using Pharmaburst as co-processed excipient and compared with a reference product (Rybix ODT, 50 mg). Physicochemical parameters including hardness, friability, weight variation, disintegration time and dissolution studies were determined for all the formulations. In-vivo studies were performed for the optimized formulation (F13), using as reference, a commercial product (Trambax IR, 50 mg), by a two-way crossover design under fasting conditions on eight healthy adult human subjects. Drug-plasma concentrations obtained from the bioequivalence study for test and reference products were analyzed in each subject by high performance liquid chromatography (HPLC), and basic pharmacokinetic parameters, including C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{\frac{1}{2}}$ and λ_z, were calculated.

Results: The tablet formulation prepared with Pharmaburst (F13) showed good flow properties, low disintegration time (15 s) and improved drug release (99 % at 30 min) compared with those of the reference product (88 % at 30 min) and passed 6 months accelerated stability test. Bioequivalence of the test product with that of the reference product under fasting conditions was established by computing 90 % confidence interval for the In-transformed pharmacokinetic parameters of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for tramadol. The 90 % confidence intervals for C_{max} were 99.70 - 114.31, for AUC_{0-t} 97.31 - 108.87 and for $AUC_{0-\infty}$ 97.17 - 109.75. This confidence interval, in each case, was within bioequivalence criteria limit

Conclusion: A suitable preparation of tramadol HCl MDT that is bioequivalent with a reference commercial product under fasting condition can be obtained when Pharmaburst is used as a disintegrant.

Keywords: Bioequivalence, dissolution, Mouth dissolving tablets, Pharmaburst, Tramadol hydrochloride, Disintegration time

INTRODUCTION

The oral route is the most preferred route for administration of therapeutic agents because of ease of administration, accurate dose, self medication and patient compliance. In this regard, tablets and capsules are most preferred dosage forms for oral route. But these dosage forms are difficult to administer to children and geriatrics. Hence, MDT are favoured for its ease of administration and improvement in therapeutic efficacy of dosage form [1-3].

Mouth dissolving tablets (MDT) disintegrate and/or dissolve in the mouth (in saliva) within a few seconds without any need to administer it with liquid. They are also called fast dissolving, oro-dispersible, orally disintegrating and fast melting tablets. MDT combines the advantages of both conventional and liquid formulations [4,5].

Tramadol hydrochloride is used to treat moderate to severe pain and it comes under the category of centrally acting analgesics. In India, the drug is available as a conventional tablet, so there is need to develop the mouth dissolving tablets to allow the administration of dosage form with out need of water which is particularly important for pediatrics and geriatrics.

Tramadol hydrochloride Oro dispersible tablets are currently available in USA and Europe and there is no marketed product in India. Therefore, the present work focused on mouth dissolving tablets due to the increasing proportion of the aged in the population and also because of the need to develop appropriate dosage form for the elderly.

EXPERIMENTAL

Materials

Tramadol hydrochloride was received as a gift from Jubilant life sciences, Noida and other excipients used in this work was obtained as gifts from BASF, India.

Preparation of mouth dissolving tablets

Initially, four batches of tramadol HCl mouth dissolving tablets were formulated by direct compression method and four additional batches were formulated by wet granulation method with the same composition as that of the reference product (Rybix ODT, Shionogi Inc, USA).
Tramadol hydrochloride, mannitol, crospovidone, copovidone, ethyl cellulose and pharmaburst were individually sifted through 420 μm aperture sieve size and neotame, tutti frutti flavor, silicon dioxide, colloidal anhydrous silica and

magnesium stearate was sifted through 250μm aperture sieve size and collected separately in a polyethylene bag.

Tramadol hydrochloride, mannitol, crospovidone, copovidone, and ethyl cellulose were placed in a (Bectochem Pvt Ltd) and mixed thoroughly for 10 min; sifted silicon dioxide and magnesium stearate were added to the blend and mixed for 5 min. The final blend was compressed into tablets by using a rotary compression machine (KMP-D-8, KAMBERT).

Wet granulation method was used with water as granulating fluid. Initially, the active ingredient and mannitol were dry-mixed and added to the binder solution (water and crospovidone) to obtain a wet mass. Then wet mass was sieved and the produced granules were dried and blended with crospovidone and ethylene cellulose in blender for 10 min. The sifted silicon dioxide and magnesium stearate were added and mixed for 5 min.in the blender. The lubricated blend was compressed into tablets by using rotary compression machine. The composition of the formulations is given in Table 1.

Furthermore, three more batches were prepared by direct compression method with pharmaburst as a co-processed excipient system, colloidal anhydrous silica as glidant and magnesium stearate as lubricant in different concentrations. Initially added sifted Tramadol hydrochloride and pharmaburst into the blender and blended for 10 minutes and then added sifted colloidal anhydrous silica and magnesium stearate to blender and lubricated for 5 minutes and compressed into tablets. Next two more batches were formulated as that of F11 with different concentrations of flavor and sweetener to optimize the organoleptic characteristics. For these two batches the process is same as that of above process; flavor and sweetener was included along with tramadol hydrochloride and Pharmaburst at initial blending step. The composition is given in Table 2.

Table 1: Composition of tramadol mouth dissolving tablets (MDT)

Ingredient	Content (mg/tablet)							
	F1	F2	F3	F4	F5	F6	F7	F8
Tramadol HCl	50	50	50	50	50	50	50	50
Mannitol	88.75	84.25	81.25	78.25	88.75	84.25	81.25	78.25
Crospovidone	3.0	4.5	6.0	7.5	3.0	4.5	6.0	7.5
Copovidone	3.0	3.75	3.75	3.75	3.0	3.75	3.75	3.75
Water	---	---	---	---	q.s.	q.s.	q.s.	q.s.
Ethyl cellulose	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Silicon dioxide	0.75	1.5	1.5	1.5	0.75	1.5	1.5	1.5
Magnesium stearate	3.0	4.5	6.0	7.5	3.0	4.5	6.0	7.5

Table 2: Composition details of F9-F13 by direct compression method

Composition	Unit formula (mg/tablet)				
	F9	F10	F11	F12	F13
Tramadol Hydrochloride	50	50	50	50	50
Pharmaburst	97	95.5	94	92.35	91.45
Neotame	---	---	---	1.5	2.25
Tutti frutti flavor	---	---	---	0.15	0.3
Colloidal anhydrous silica	---	---	1.5	1.5	1.5
Magnesium stearate	3.0	4.5	4.5	4.5	4.5
Total tablet weight	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**

Evaluation of Blend

The blend parameters like bulk density, tapped density and compressibility index was performed for all batches according to methods described previously by some authors [6].

Physicochemical characterization of compressed tablets

The physical parameters like hardness, friability, weight variation and disintegration time was performed for all batches of the tablets [7-8]. Other tests including assay, dispersion time and water absorption ratio were performed on the optimized formulation (F13) to evaluate dispersion time and water absorption capacity of the MDTs [9,10].

In-vitro drug release studies

The study was conducted with six tablets for each formulation using USP type I dissolution apparatus and 900 ml of 0.1N HCl as dissolution medium at a basket rotating speed of 75 rpm. Aliquots of 5 ml were withdrawn at selected time intervals through auto sampler and filtered through 0.45 μ filter and the same volume of dissolution medium was used to replenish dissolution medium in order to maintain sink conditions. The absorbance of aliquots was measured at 215 nm using a UV-spectrophotometer after appropriate dilutions. Comparative *in-vitro* dissolution study was conducted for optimized test formulation with reference product (Trambax, 50 mg immediate release tablet, Ranbaxy Pharmaceuticals, India).

Flavor and sweetener optimization

The batches F12 and F13 were formulated with tutti frutti as flavor and neotame as taste masking agent in different concentrations. Formulations were given to five human healthy adult volunteers and evaluated the taste and flavor [11].

Assay of drug

Drug content was measured for optimized formulation F13 by HPLC method at 271 nm using C_{18} 250 mm × 4.6 mm, 5µm column with an injection volume of 20μl at a flow rate of 1.0 ml/min [12].

Stability studies

As per ICH guidelines, accelerated stability studies were conducted for optimized formulation F13 for a period of six months. The tablets were withdrawn from stability chamber after 1st, 2nd, 3rd, 6th months and analyzed for friability, assay, dissolution, disintegration time and dispersion time [13].

In-vivo bioequivalence studies

Before commencing the study, the protocol (no. 355-03/SRPH/WGL/IHEC/2012) of the study was approved by the institutional ethical committee. The study was conducted as per the ICH harmonized tripartite guideline, namely, Guidelines for Good Clinical Practice (E6) [14]. The study was conducted on eight healthy adult male human subjects at SR College of Pharmacy, affiliated to Kakatiya University, Warangal, India. The subjects were selected based on a defined inclusion/exclusion criteria, medical history and physical examination.

Inclusion and exclusion criteria

Subjects enrolled in the study had a body mass index between 18.5 to 30.0 kg/m^2, body weight not < 50 kg. Other vital parameters were blood pressure (BP) within the range of 100 - 139 mmHg systolic and 60 – 89 mmHg diastolic; pulse rate 60 – 100/min and oral temperature between 36.55^{0}C-37.2^{0}C.

Subjects excluded from the study include those having a history of smoking, drinking, tuberculosis, diabetes mellitus, renal, cardiac, hepatic, metabolic, neurological and hematological systems.

Study design

Open label, single dose, randomized, two treatment, two period, two sequence, two-way crossover study under fasting conditions with a washout period of seven days.

Collection of blood samples

Twenty blood samples were collected from each subject at various intervals ranging from 0.0 (pre-dosing) to 24 h. After dosing, the collected blood samples were transferred to heparin sodium tubes, centrifuged, plasma was separated and stored in a deep freezer pending analysis.

Analysis of tramadol hydrochloride

The plasma samples were analyzed by validated HPLC method using empowers chromatography software. Chromatographic separation was done by using Chromolith [TM] Performance RP-18e 50mm×4.6mm column protected by a Chromolith [TM] Guard Cartridge RP-18e 5mm×4.6 mm. And phosphoric acid was used for adjustment of pH to 2.5 for methanol: water mixture (13:87 v/v) [15].

Pharmacokinetic and statistical analysis

For each subject after every time interval the Tramadol hydrochloride plasma concentrations and time data were analyzed by using non-compartmental model of WinNonlin software version 5.3 and calculated basic pharmacokinetic parameters like C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and also calculated formulation means of tramadol hydrochloride and 90% confidence interval. The statistical significant differences between groups were defined as *p* < 0.05.

RESULTS

Physical Characterization of Powder blend before compression

The various physical characterization of powder blend like bulk density, tapped density and compressibility index were performed and the results of the same were given in the Table 3.

Evaluation of Physical parameters of tablets

The various physical parameters of tablets like hardness, friability, weight variation and disintegration time were performed and the results of the same were given in the Table 4

The other parameters for optimized formulation (F13) like assay, water absorption ratio and

dispersion time were performed and the results of the same were given in the Table 5.

Table 3: Physical characteristics of powder blend

Batch	Parameter		
	Bulk density (g/cm^{-3})	Tapped density (g/cm^{-3})	Carr's index (%)
TM 01	0.66	1.00	34
TM 02	0.68	1.02	33
TM 03	0.66	0.90	27
TM 04	0.66	0.89	26
TM 05	0.71	0.95	25
TM 06	0.72	0.94	23
TM 07	0.74	0.93	20
TM 08	0.74	0.92	20
TM 09	0.72	0.88	18
TM 10	0.72	0.86	17
TM 11	0.70	0.80	13
TM 12	0.70	0.78	10
TM 13	0.70	0.78	10

Table 5: Parameters for optimized formulation (F13)

Parameter	Value
Drug content (%)	99.7±0.7
Water absorption ratio (%)	103.2±0.6
Dispersion yime (s)	10.0±0.2

In-vitro drug release

The *in-vitro* drug release studies were performed for all batches of tablets but initial batches i.e. F1-F8 did not met the targeted release profile. But next batches i.e. F9-F11 were found to be satisfactory and drug release data was shown in Figure 1
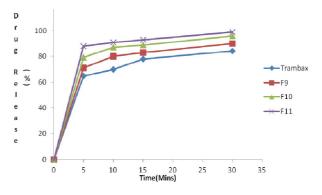

Figure 1: Comparative dissolution profiles of tramadol MDTs

Stability studies

The accelerated stability study was conducted for optimized formulation F13 for a period of 6 months and the results revealed that there was no noticeable change observed in dissolution, assay, friability, disintegration time and

Table 4: Some physical parameters of tablets (mean ± SD)

Batch	Hardness (kg/cm^2)	Friability (%)	Mean weight (mg)	Disintegration time (s)
TM 01	4.59±0.7	0.11±0.03	148.2±1.15	104±1.85
TM 02	4.49±0.9	0.12±0.02	147.9±1.64	95±2.12
TM 03	4.18±0.6	0.11±0.04	150.5±1.86	84±2.15
TM 04	4.28±1.4	0.13±0.06	149.1±1.22	78±2.52
TM 05	4.79±0.5	0.10±0.05	148.6±1.26	98±1.85
TM 06	4.28±1.1	0.11±0.02	146.2±2.24	87±1.26
TM 07	4.08±0.8	0.12±0.05	148.5±1.95	75±1.65
TM 08	4.18±0.7	0.16±0.03	148.2±2.16	60±1.18
TM 09	4.08±0.8	0.10±0.08	147.3±2.12	45±1.24
TM 10	4.38±0.8	0.13±0.09	148.2±1.24	28±1.02
TM 11	4.18±0.8	0.12±0.06	147.9±1.28	15±0.68
TM 12	4.28±0.9	0.11±0.06	148.5±1.08	16±0.89
TM 13	4.18±0.8	0.12±0.08	148.6±1.15	15±0.62

Table 6: Stability data for optimized formulation (mean ± SD)

Parameter	Time (month)				
	Initial	1st	2nd	3rd	6th
Dissolution					
5 min	85	84	85	83	85
10 min	90	89	91	89	89
15 min	95	95	96	94	96
30 min	99	99	99	98	99
Drug content (%)	99.7	99.7	99.6	99.8	99.8
Friability (%)	0.12±0.08	0.10±0.04	0.18±0.06	0.15±0.05	0.19±0.08
Disintegration time (min)	15±0.62	13±0.09	16±0.95	17±0.49	14±0.14
Dispersion time (min)	10±0.24	11.8±0.33	11.5±0.31	11±0.15	12.1±0.18

Table 7: Descriptive statistics of test MDT and reference products

Parameter	Mean ± SD (Un – transformed)	
	Test MDT	Reference
C_{max} (ng/ml)	171.466 ± 30.254	162.665 ± 25.165
AUC_{0-t} (mg.h/ml)	1488.098 ± 242.101	1450.378 ± 257.422
$AUC_{0-\infty}$ (ng.h/ml)	1629.404 ± 296.234	1581.535 ± 307.192
AUC_%Extrap_obs (%)	8.287 ± 3.429	7.925 ± 3.373
Tmax (h)	1.844 ± 0.516	2.219 ±0.619
t ½ (h)	6.653 ± 1.272	6.385 ± 1.145
λ_z (h)	0.107 ± 0.018	0.111 ± 0.018

Table 8: 90% confidence intervals for tramadol hydrochloride

Parameter	Ratio [A/B]%	90% Confidence interval*		Power
		Lower	Upper	
C_{max} (ng/ml)	106.76	99.70	114.31	100.00
AUC_{0-t} (ng.h/ml)	102.93	97.31	108.87	100.00
$AUC_{0-\infty}$ (ng.h/ml)	103.27	97.17	109.75	100.00

* Calculated for in-transformed data

In-vivo bioequivalence

In-vivo studies were performed and results of descriptive statistics of test and reference product was shown in Table 7 and 90 % confidence interval of Tramadol hydrochloride was shown in Table 8, and mean plasma concentration vs. time profile of tramadol hydrochloride was shown in Figure 2.

DISCUSSION

All batches of blend (F1-F13) were evaluated for blend parameters and confirmed that lubricated blend was very much useful for compression and the results were found to be satisfactory. Also all batches of tablets were evaluated for physical parameters like hardness, friability, average weight and disintegration time. The results of all

parameters were found to be within the acceptable Pharmacopoeial limit. Other parameters like assay, dispersion time and water absorption ratio were performed for optimized formulation (F13) and results were found to be satisfactory.
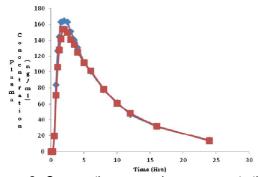

Figure 2: Comparative mean plasma concentrations vs. time profiles. ***Note:*** ■ = reference; ♦ = test product

In-vitro drug release studies for initial batches i.e. F1-F4 were showed very slow rate of drug release and dissimilar with reference product drug release at all time intervals. No improvement of drug release was observed for further batches i.e. F5-F8 even though the method of preparation of tablets was changed. The preceded batches of tablets were showed deviations in drug release, so next batches were formulated by changing the composition of the drug product with pharmaburst. The batch F9 showed better drug release than the preceded batches and met the reference product's drug release profile at all time intervals but did not met the targeted release profile (80% of drug should release with in 5 minutes). The F10 batch showed improved drug release than F9 batch and meeting the drug release of reference product at all time intervals but did not met the targeted release profile. F11 batch showed to improve the drug release than the reference product and also met the targeted drug release as per the dissolution concern and confirmed that F11 batch was the optimized formulation. Next batches were formulated with same composition as that of F11 to optimize the organoleptic characteristics. The formulation prepared with 1.5% of neotame and 0.2% of tutti frutti flavor i.e. F13 batch was showed very good taste and flavor than other formulations and was confirmed as optimized formulation in concern of disintegration time, dispersion time, dissolution and organoleptics.

Six months accelerated stability study was conducted for optimized formulation F13 and observed that all parameters were found to be within the limit and the drug was stable for a period of 6 months at accelerated condition with out any noticeable change and confirmed that F13 batch was the optimized formulation. Then *in-vivo* studies were conducted for optimized formulation F13 with reference product under fasting condition. In each subject, drug and plasma concentrations were analyzed by HPLC and the pharmacokinetic parameters like C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and means of test and reference product were observed. The descriptive statistics and 90% confidence interval of Tramadol hydrochloride was calculated and found that test formulation is bioequivalent with reference product.

CONCLUSION

Tablets prepared with Pharmaburst as co-processed excipient is the most suitable disintegrant for the preparation of mouth dissolving tablets. The optimized test formulation showed superior drug release to reference product and also demonstrated good stability over a period of 6 months. It was bioequivalent with the reference product used in the study.

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