Research Article

FORMULATION AND EVALUATION OF STABLE MODIFIED RELEASE TABLETS OF TRAMADOL HYDROCHLORIDE WITH BI-PHASIC RELEASE MODEL

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ABSTRACT

A stable once daily modified release tablet of Tramadol hydrochloride was developed as bi-phasic release model using a simple manufacturing technology, which involves first preparing the extended release core tablets and then coating these tablets with immediate release coating. The extended release core tablets were prepared by using different controlled release polymers viz Kollidon SR, xanthan gum and polyethylene oxide by direct compression technique. Physical parameters and *in-vitro* drug release studies were evaluated to finalize the composition and compared with reference product i.e. RYZOLT and found that test product was similar with reference product. Further, stability studies were conducted under accelerated conditions for the finalized composition and evaluated for all quality parameters. From the studies it was concluded that composition containing Polyethylene oxide is well controlled drug release as well as most stable under accelerated conditions and meeting predetermined specifications of Assay and Dissolution.

Keywords: Direct compression, Extended release core, Immediate release coating, Polyethylene oxide, Tramadol hydrochloride.

INTRODUCTION

Tramadol (figure 1) is a centrally acting analgesic and is readily soluble in water and ethanol and has a pKa of 9.41. It has approved in various countries for the management of moderate to moderately severe pain. It is well absorbed orally with an absolute bioavailability of 75% and having a volume of distribution of approximately 2.7L/kg. It is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. One metabolite, M1, is pharmacologically active in animal models. It has plasma half-life of 5.5 hours.[1] Tramadol hydrochloride is available as immediate release tablets under brand name of ULTRAM in USA. Due to very less half-life these tablets required to be taken every 4-6 hours up to 400 mg/day.[2] Tramadol HCl is indicated for chronic pain and it should require therapy round the clock. During night time also the patient needs to take the tablet every 4-6 hours to relive from pain. So it is difficult to take the tablets every 4 hours to the patient, as the patient is already suffering from pain and taking tablets during night is again problem for the patient.[2-5]

In end of 2008 US FDA approved tramadol hydrochloride extended release tablets under brand name of Ryzolt® of Purdue Pharma. RYZOLT® is extended-release dosage form comprising immediate-release compression coat over an extended-release core. In the extended-release core it contains Contrmid® as release controlling polymer. Contramid® is patented (US Patent no. 6,607,748) technology of Labopharm, which contains cross-linked, high amylose starch. Ryzolt® technology was protected by United States Patent No. 7,988,998. Ryzolt® tablets produces mean plasma concentration of at least 100 ng/mL within 2 hours of administration and continues to provide a mean plasma concentration of at least 100 ng/mL for at least 22 hours after administration on administration of 200 mg tablets.

Ryzolt® tablet uses the patented technology of polymer as well as process of compression coating which is tedious and costly. The present authors developed simple cost-effective matrix core tablets using polymers other than Contramid® followed by immediate release coating on the core to attain similar *in-vitro* dissolution profile of Ryzolt® tablets and also studied stability of developed tablets.

The main aim of the present investigation is to develop a Bi-phasic modified release (immediate release followed by extended release) Tramadol HCl tablets with various hydrophilic polymers such as Kollidon SR, Xanthan gum and Polyethylene oxide in different concentrations. Immediate release portion of drug will serve as loading dose and extended release portion of drug will serve as maintenance dose. Thus, the developed formulation will provide the rapid and long action.

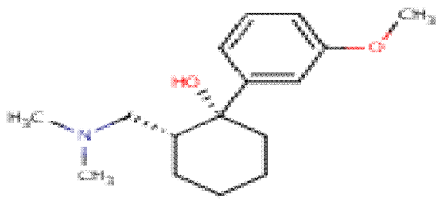

Figure 1: Chemical structure of Tramadol

Kollidon SR is derived from polyvinyl acetate dispersion and is an excipient for drug delivery matrices and possesses good controlled release properties. Due to excellent flow properties and dry binding activity of Kollidon SR, it is effectively used for development and production of sustained release tablets.[6]

Xanthan gum is a natural polymer and is soluble in both hot and cold water, but insoluble in most of the inorganic solvents. Even at low concentrations of xanthan gum solution shows high degree of viscosity in comparison with other polysaccharide solutions.[7]

Polyethylene oxide is a water soluble hydrophilic polymer and is extensively used in modified release formulations to modify the drug release and is available in different molecular weights. Once the tablets exposed to liquid, polyethylene oxide starts to hydrate and swell, then it forms a gel layer around the tablet. The gel layer further regulates the penetration of liquid into the matrix and diffusion of drug molecules from the dosage form. Due to the formation of gel layer, the rate of water intake slows down and the drug release decreases and prolongs.[8]

MATERIALS AND METHODS

Tramadol hydrochloride was obtained as gift sample from jubilant life sciences, Hyderabad, India. Kollidon SR and Povidone K90F were purchased from BASF, Germany. Xanthan gum was provided by CP kelco, India. Polyethylene oxide was provided by Dow chemicals, Mumbai. Micro crystalline cellulose was provided by Reliance cellulose products limited. Stearic acid was provided by Taurus chemicals limited, Secunderabad. Colloidal silicon dioxide was provided by Cabot sanmor ltd, USA. Opadry was provided by Colorcon Asia private ltd, India. Water was filtered through Millipore 0.22µm filter before used.

Design of Modified release Tramadol HCl tablets

Manufacturing of extended release core tablets

The present work was developed simple technology for once daily extended release tablets preparation, which consists of an extended release core and immediate release coating layer on the extended release core tablets. The extended release core contains 80% of drug & the immediate release coating layer contains 20% of drug. Initially the extended release core tablets were prepared by direct compression method. Various trails were prepared using 3 different types of polymers in various concentration ranges.

F01 & F02 are prepared using Kollidon SR as controlled release polymer in the ratio of drug: polymer 1:1 & 1:2. F03 & F04 are prepared using Xanthan gum as controlled release polymer in the ratio of drug: polymer 1:1 & 1:2. F05, F06, F07 & F08 are prepared using Polyethylene oxide as controlled release polymer in the ratio of drug: polymer 1:1, 1:2, 1:2.5 & 1:2.5. The formulation details of all the trails were in table 01.

Preparation of Modified release tablets: The process is same for all the trails except the polymer change.

i) Sifted and collected separately Tramadol hydrochloride, controlled release polymer (Kollidon SR / Xanthan gum / Polyethylene oxide), Povidone K90F, Stearic acid, Micro crystalline cellulose through # 40 mesh and colloidal silicon dioxide through #60mesh.

ii) Loaded sifted, Tramadol hydrochloride, controlling release polymer, Microcrystalline cellulose and Povidone K90 F in a blender, blended for 15 minutes. Then added sifted Stearic acid and Colloidal silicon dioxide, lubricated for 5 minutes.

iii) The lubricated blend was compressed into round tablets using Rotary compression machine.

Table 1: The formulation details of extended release tablets

Batch No →	**F01**	**F02**	**F03**	**F04**	**F05**	**F06**	**F07**	**F08**
Composition ↓	**Unit formula (mg/tablet)**							
Core tablets								
Tramadol hydrochloride	160	160	160	160	160	160	160	160
Kollidon SR	160	320	0	0	0	0	0	0
Xanthan gum	0	0	160	320	0	0	0	0
Polyethylene oxide	0	0	0	0	160	320	400	400
Microcrystalline cellulose	50	50	50	50	50	50	50	50
Povidone K 90F	30	30	30	30	30	30	30	30
Stearic acid	5	5	5	5	5	5	5	5
Colloidal silicon dioxide	3	3	3	3	3	3	3	3
Core tablet weight	**408**	**568**	**408**	**568**	**408**	**568**	**648**	**648**
Immediate release Coating								
Tramadol hydrochloride							40	40
Opadry							25	25
Water							qs	qs
Total tablet weight							**713**	**713**

Application of outer immediate release coating

Immediate release coating solution was prepared by dissolving Tramadol hydrochloride and Opadry pink in purified water, mixed well to form a uniform dispersion. Extended release core tablets were then coated with above prepared coating solution using manual coating pan. Coating was continued up to till target weight was achieved and finally dried the tablets for 15minutes in same coating pan.

Evaluation of formulation

Physicochemical characterization for blend and tablets

The lubricated blend was evaluated for physical parameters such as Bulk density, Tapped density and Compressibility index/Carr's index. During compression the tablets were evaluated for physical parameters such as Hardness, Friability and Weight variation.

In-vitro drug release studies

The compressed tablets were evaluated for drug release studies using USP apparatus type I. The dissolution media 0.1N HCl with volume of 900ml and rotation speed of 75

rpm was used. The dissolution media was maintained at 37°C ±0.5°C till completion of the dissolution. Aliquots of 10ml were collected at specified intervals and were analyzed using UV spectrophotometer at 215nm.

Drug release kinetics

The *in-vitro* drug release data were fit into different equations and kinetic models to explain the release kinetics of Tramadol HCl modified release tablets. The zero order kinetics describes the systems drug release rate was independent of its concentration.[9] The first-order kinetics describes the systems drug release rate was concentration-dependent.[10] Higuchi's describes the drug release from insoluble matrix as a square root of time-dependent process based on Fickian diffusion.[11] The Hixson–Crowell cube root law describes the release from systems where there is a change in the surface area and diameter of particles or tablets.[12]

Assay method

For the determination of Tramadol Hydrochloride in the prepared formulation, RP-HPLC method at 271 nm using C18: 250 mm × 4.6 mm, 5µm column at Flow rate of 1.0 ml / minute was employed. Mobile phase was prepared using mixture of Trifluoroacetic acid, Acetonitrile and water in the ratio of 10:300:690 (v/v/v). Separately injected equal volumes of about 20 µl of diluent as blank, six replicate injections of standard preparation and test preparation into HPLC.

Stability studies

To evaluate the formulated product in shelf life, the optimized formulation F08 trial was packed into PVC/Al blisters and charged in stability chamber at accelerated conditions 40°C/75% RH. The samples were withdrawn at 1st, 2nd, 3rd and 6th month after incubation and analyzed for Appearance, Assay and dissolution (Q1E Evaluation of stability data, 2004).[13]

RESULTS AND DISCUSSION

Evaluation of formulation parameters

Blend parameters evaluation

The lubricated blends of all the trails F01- F08 were evaluated for blend parameters and the results (provided in table no 2) confirm that all the blends having very good flow properties. The blends are very much useful for direct compression process.

Core tablets evaluation

All the trials of prepared tablets were evaluated for physical parameters such as Hardness, Friability and Average weight. The hardness of the tablets for all the trials found satisfactory. The tablets from all the trials showed very good friability with less than 0.3% which is well within wide accepted range of Pharmacopoeias limit (1.0%). Average weight of the tablets was found within acceptable limit of 5% for all the trails. The results of the compressed tablets were given in table no 2.

Table 2: Physical parameters of Blend and Compressed tablets

Batch No	Lubricated blend parameters			Compressed tablet parameters		
	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hardness (N)	Friability (%)	Average weight (mg)
F01	0.65±0.04	0.72±0.02	10±0.96	120±2.56	0.28±0.03	406±2.8
F02	0.65±0.03	0.78±0.04	17±1.11	125±2.31	0.20±0.01	567±1.4
F03	0.62±0.02	0.69±0.03	10±0.52	122±1.10	0.21±0.02	410±3.2
F04	0.62±0.04	0.72±0.05	14±0.94	126±2.24	0.19±0.01	569±3.0
F05	0.58±0.05	0.69±0.03	16±0.84	130±2.45	0.22±0.03	408±2.3
F06	0.61±0.04	0.72±0.03	15±0.69	132±2.14	0.18±0.02	566±1.9
F07	0.62±0.02	0.71±0.05	13±0.82	130±2.35	0.15±0.04	650±1.8
F08	0.60±0.03	0.69±0.04	13±1.15	135±2.23	0.16±0.01	649±1.5

Data presented as Mean ± SD.

Table 3: *In-vitro* drug release studies for trials F01-F06 extended release core tablets

Time (h)	% Cumulative Drug Release							
	Target Profile*	F01	F02	F03	F04	F05	F06	F07
2	6	96 ± 1.35	85 ± 1.56	65 ± 1.25	57 ± 1.10	41±0.52	24±0.95	7±0.49
4	15	98 ± 1.62	99 ± 1.31	85 ± 1.13	77 ± 0.89	58±0.95	42±0.84	17±0.34
8	33	100 ± 1.53	100 ± 1.12	98 ± 0.84	95 ± 0.62	65±0.91	55±0.79	34±0.38
12	50	101 ± 1.12	100 ± 1.62	100 ± 1.49	100 ± 1.23	71±0.63	62±0.63	53±0.39
16	66	98 ± 1.24	101 ± 1.49	99 ± 1.24	100 ± 1.24	98±1.20	85±0.62	69±0.43
20	83	100 ± 1.51	99 ± 1.32	100 ± 0.94	101 ± 1.02	99±1.08	90±0.34	85±0.49
24	100	101 ± 1.34	99 ± 1.38	99 ± 0.85	98 ± 0.85	99±0.61	101±0.60	100±0.21

Data presented as Mean ± SD; * Target profile for exteneded release core was derived after subtracting 20% at each time point from the reference product release profile.

In-vitro drug release studies

All the trials of prepared tablets were evaluated for drug release studies and observed that release profile is greatly influenced by percentage of drug polymer concentration. The results of *in-vitro* drug release studies reveals that the concentration of polymer increases, it retards the drug release. This means that the drug release from the tablets is indirectly proportional to the polymer concentration. Trials F01-F02 were formulated with Kollidon SR as a controlled release polymer, drug release was observed faster and within 2 hours almost 85% of the drug was released. The trials F03-F04 were prepared with Xanthan gum as a controlled release polymer; also did not able to control the drug release more 12 hours and around 55% of drug was released in 2 hours even with highest quantity of xanthan gum studied. The trial F05 was prepared with 1:1 ratio of Polyethylene oxide was shown good control of drug release up to 20 hours. Then trial F06 was prepared with 1:2 ratio of Polyethylene oxide, shown good control of drug release up to 24 hours, however the drug release is faster compared to the target profile. The trial F07 was prepared with increasing concentration of Polyethylene oxide in the ratio of 1:2.5 to further control the drug release. Dissolution profile of F07 core trial reveals that drug release is controlled and meeting with target profile of extended release core tablets. The *in-vitro* drug release data of trials F01-F06 was given in Table 03.

Then F07 tablets were coated with immediate release coating dispersion and evaluated for drug release. One more repetition batch (F08) was also prepared with same composition as that of F07 and evaluated for drug release studies. From the dissolution data of F07 coated and F08 coated it was found that the data is reproducible and meeting with reference product release profile. The *in-vitro* dissolution data of trials F07-F08 were given in table no 4.

Table 4: *In-vitro* drug release studies for trials F07-F08

Time (h)	% Cumulative Drug Release		
	Reference Product (RYZOLT, B. No: 115210PR1)	F07 Coated	F08 Coated
1	17	17±0.61	17±0.62
2	25	24±0.34	23±0.46
4	32	33±0.65	32±0.52
8	46	45±0.55	45±0.38
12	59	61±0.43	60±0.45
16	73	73±0.46	72±0.65
20	86	87±0.35	88±0.78
24	100	99±0.48	99±0.62

The optimized formulation (F08) was compared with reference formulation i.e. RYZOLT and calculated similarity factor f_2 and found to be more than 50 (83.6). The *in-vitro* dissolution data of test and reference formulations were given in Table 05 and the graph of the same was shown in Figure 02.

Table 5: Comparative dissolution data for Test and Reference products

Time (h)	Optimized Test Product (B. No: F08)	Reference Product (RYZOLT, B. No: 115210PR1)
1	17	17
2	23	25
4	32	32
8	45	46
12	60	59
16	72	73
20	88	86
24	99	100

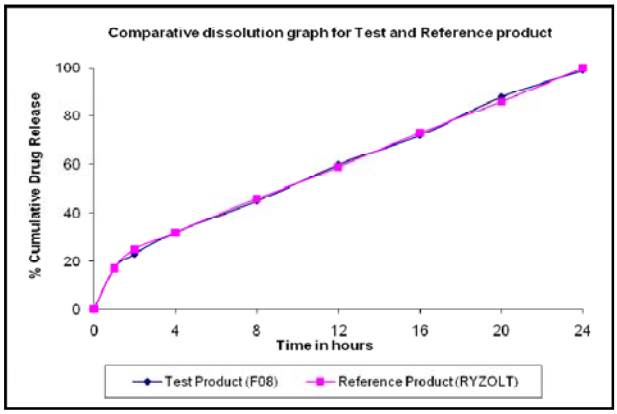

Figure 2: Comparative dissolution graph for Test and Reference products

Drug release kinetics

Release kinetics for optimized formulation F08 was calculated and the observed Regression coefficients (R^2) were presented in table 6. From the observed data it was found that drug release rate is concentration independent and drug releases from matrix as a square root of time process. The release exponent for Tramadol HCl was obtained is 0.538. So, it follows Non-Fickian diffusion mechanism, which means that drug transport mechanism associated with stresses and state transition in hydrophilic glassy polymers. The R^2 value of Hixon-crowell cube root plot indicates that drug release changes from tablets when surface area and diameter of particles changes.

Table 6: Mathematical models for optimized formulation (F08)

Formulation code	Zero order	First order	Higuchi's model	Peppa's model		Hixon-Crowell
	R^2	R^2	R^2	R^2	N	R^2
F08	0.978	0.841	0.988	0.969	0.538	0.959

Table 7: Stability data for optimized formulation (F08)

Test	Specification	Results				
		Initial	1st month	2nd month	3rd month	6th month
Appearance	Pink colored tablets	Pink colored tablets	Pink colored tablets	Pink colored tablets	Pink colored tablets	Pink colored tablets
Assay (%)	95-105	99.8	99.5	99.7	100.2	99.9
Dissolution	f2 more than 50	83.64*	81.63**	85.75**	85.75**	80.29**
* Initial release profile was compared with reference product (RYZOLT). ** Stability release profile was compared with initial release profile.						

Stability results

The samples were withdrawn at 1st, 2nd, 3rd and 6th month after incubation and analyzed for Appearance, Assay and Dissolution. From the stability results it revealed that the appearance remains same and there is no change in assay values. The dissolution studies were carried out and Similarity factor (f2) was calculated against the initial release profile, it was found more than 50 for all the periods. Overall from the six months stability results it concluded that the product was stable for a period of six months at accelerated conditions. The results of the same are presented in table 7 and the graph of drug release studies under stability conditions were shown in figure 3.

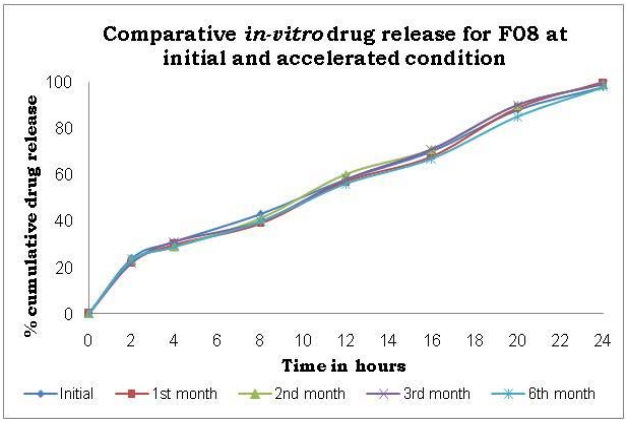

Figure 3: Dissolution graph of Tramadol modified release tablets in stability

CONCLUSION

From the above results it was concluded that the use of this simple technology achieves expected bi-phasic release of Tramadol HCl. The drug release of final composition was compared with reference product i.e. RYZOLT, found to be similar as that of Reference product and stability results confirmed that the composition was more stable at accelerated conditions.

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