



RESEARCH ARTICLE

**Development and Evaluation of Extended Release Formulation of Tramadol
Hydrochloride Based on Osmotic Technology**

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ABSTRACT

Extended release formulation of Tramadol Hydrochloride based on osmotic technology was developed and evaluated. Target release profile was selected and different variables were optimized to achieve it. Formulation variables such as osmotic agent, plasticizer and coating thickness of semi-permeable membrane were found to markedly affect drug release. Tramadol hydrochloride release was directly proportional to the level of osmogen and plasticizer but inversely proportional to the level of coating thickness of semi-permeable membrane. Drug release from developed formulation was independent of pH and agitation intensity but dependent on osmotic pressure of release media. The optimized formulation was compared with marketed product CONTRAMAL SR and accelerated stability study was also carried out for 6 months.

KEYWORDS

Tramadol hydrochloride, extended release, osmotic pressure.

INTRODUCTION

Oral ingestion has been the most convenient and commonly used route of drug administration. In the immediate release dosage form, there is little or no control of drug release from the dosage form which often results in constantly changing, unpredictable plasma concentration.¹ Controlled release systems have been introduced to overcome the drawback associated with IR dosage form.² The majority of per-oral controlled release dosage forms fall in the category of matrix, reservoir and osmotic systems.³ Drug release from the matrix and reservoir systems is affected by pH and other hydrodynamic conditions and presence of food in the gastro-intestinal tract. Osmotic system utilizes principle of osmotic pressure which is independent of these physiological parameters.^{4,5}

Tramadol hydrochloride, a centrally acting opioid analgesic, is used in treatment of severe acute and chronic musculo-skeletal, cancer, surgical and post-operative pain. Tramadol hydrochloride has good oral bioavailability with short biological half-life, so, required to administer three to four times a day.⁶ It is absorbed from the stomach and upper part of the small intestine with bioavailability of 75%. So to improve the patient compliance and reduce dosage frequency and side effects, twice a daily dose formulation is desirable.^{7,8}

So the present study was aimed at the development and evaluation of extended release formulation of Tramadol hydrochloride based on osmotic technology.

MATERIALS AND METHODS

Tramadol hydrochloride was obtained from Win Medicare Ltd, India. Polyethylene oxide (M_r 4500000) was received from Torrent Research

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Centre, India. The following chemicals and excipients were purchased from commercial sources and were used as such: cellulose acetate, microcrystalline cellulose (Avicel PH 102), Magnesium stearate, talc, Mannitol, sodium chloride, dextrose, potassium chloride, potassium dihydrogen phosphate, sodium hydroxide (all from SD Fine Chemical, India), acetone, dibutyl phthalate (from Finar Chemicals Limited, India). CONTRAMAL SR® (Abott Healthcare Pvt Ltd, India, 100 mg sustained release tablet) was purchased from a retail pharmacy.

FORMULATION DEVELOPMENT

Before initiating formulation development, compatibility of Tramadol hydrochloride with different excipients were tested using the techniques of FT-IR (Shimadzu, Model 8400S, Japan) and DSC (Du-Pont, Model 9900, USA). Excipients used in the final formulation were found to be compatible with Tramadol hydrochloride.

Experimental Design

In this study, formulation optimization for the development of twice daily dosage forms of CPOP were conducted by a response surface box-behnken design in order to assess the optimal drug release. Three factors of interest, i.e., mannitol concentration, dibutyl phthalate concentration and level of %weight gain each at three different level were chosen and fifteen experiments are carried out with three center points. The values of the response i.e., percent cumulative drug release at 12 h, would allow the calculation of mathematical estimation model which was subsequently used to characterize the nature of the response surface. All the statistical analyses were carried out using statistical software; DESIGN EXPERT 8.0® (Statease Inc., USA).

Preparation of Core Tablets

Core tablets of Tramadol hydrochloride were prepared by direct compression method⁹ and batch size was 100 tablets. TRH was mixed with polyethylene oxide (PEO WSR 301) for 10 min. After passing this mixture through a sieve

600µm, osmotic agents (mannitol) and MCC were added in geometric dilution and mixing continued for an additional 10 min. To this mix, talc and magnesium stearate passed through 250 µm sieve, were added and mixing continued for an additional 10 min. The blend was then compressed into tablets of average mass of 400 mg using a rotary tablet punching machine (Karnavati Engineering, India) fitted with 9.5 mm round standard concave punches. The punched tablets were of $5.0 \pm 0.38 \text{ kg cm}^{-2}$ hardness on the Monsanto hardness tester (Campbell Electronics, India).¹⁰

Table 1: formula of different batches according to Box-Behnken Design

Batch number	Mannitol (mg)	Dibutyl phthalate (%)	% weight gain
F1	50	10	10
F2	100	10	10
F3	50	30	10
F4	100	30	10
F5	50	20	5
F6	100	20	5
F7	50	20	15
F8	100	20	15
F9	75	10	5
F10	75	30	5
F11	75	10	15
F12	75	30	15
F13	75	20	10
F14	75	20	10
F15	75	20	10

*Each formulation contained 100 mg Tramadol hydrochloride, 20 mg Polyethylene oxide, 4 mg Talc and 2 mg Magnesium stearate in core tablet while 3%w/v solution of Cellulose acetate in Acetone was used for coating purpose.

Coating of the Tablets

TRH core tablets were coated in a conventional laboratory coating pan (Usico India) fitted with three baffles placed at an angle of 120° having the outer diameter of 10 cm. The composition of solutions used for coating TRH tablets is given in Table 2. The coating process was done on a batch of 100 tablets; pan speed was maintained at 20 rpm and hot air inlet temperature was kept at 38–42°C. The manual coating procedure based on intermittent spraying and coating was used at a spray rate of 4–5 ml min⁻¹. Coat mass and thickness were controlled by the volume of coating solution consumed in the coating process. Coating was continued until the desired coat thickness (150 µm) was obtained on the core tablets. In all the cases, coated tablets were dried at 50°C for 10 h before further evaluation.^{11, 12}

Evaluation of Developed Formulation

Pre-compression Parameters

Bulk density and tap density of the powdered blend was determined using the USP method II and compressibility index and Hausner's ratio were calculated.¹³

Post-compression Parameters

Diameter and Thickness Measurement

Thickness and Diameter of the core and coated tablets were measured using screw gauze.

Weight Variation Test

Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.

Hardness Test

Hardness of randomly selected tablets were tested using hardness tester (Monsanto hardness tester).

Friability Test

For friability study 20 tablets are randomly selected. Dedust the tablets carefully and weigh accurately the required number of tablets. Place the tablets in the drum and rotate it 100 times. Remove the tablets, remove any loose dust from them and weigh them accurately. A maximum loss of weight not greater than 1.0 per cent is acceptable for most tablets.

In Vitro Dissolution Study

The developed formulation (n=3) of Tramadol hydrochloride was subjected to release studies using a USP dissolution apparatus type II (Electrolab TDT-06P, India) at 50 rpm. Dissolution medium used was simulated intestinal fluid (SIF) (pH 6.8, 900 ml) maintained at 37 ± 0.5°C, which was found to provide sink conditions.¹⁶ The samples were withdrawn (10 ml) at different time intervals and replaced with equivalent amounts of fresh medium. Dissolution samples, after filtration through a 0.45-mm nylon membrane filter, were analyzed using spectrophotometric method at 271 nm. After analyzing the drug content in the dissolution samples, corrections were made for volume replacement and the graph of cumulative percent of drug release vs. time was plotted.

Content Uniformity Study

For content uniformity testing, accurately weighed tablets (n=20) were dissolved in 500 ml of distilled water. The samples were sonicated for 30 min and filtered through a 0.45 µm nylon membrane filter. The filtered samples, after appropriate dilution with mobile phase, were analyzed at 271 nm using UV visible spectrophotometer (Elico SL210).¹⁸

RESULTS AND DISCUSSION

Desired Drug Release Profile

Using the different pharmacokinetic parameters of TRH, the dose needed to provide controlled delivery of TRH can be calculated by the following equation;^{18, 19}

$$D_0 = C_p T Cl_T$$

Where, D_0 is the dose, C_p is the therapeutic drug plasma level, Cl_T is total clearance and T is the dosing interval. Therapeutic range for TRH is reported to be between 0.1–0.3 mg mL⁻¹ and the desired steady state concentration of TRH for a 100 mg (four times a day) dose is 0.225 mg mL⁻¹. Taking the steady state concentration as the desired therapeutic plasma level and the dosing interval of 12 h, the following values were proposed: (i) sustaining dose 100 mg, (ii) zero-order release rate 8.1 mg h⁻¹, (iii) dosing interval 12 h. By plotting the cumulative zero-order release (%) (y) vs. time (x), the desired release profile was generated and used as the target release profile for developed formulations ($y = 9.1x$).

Effect of Formulation Variables

In the initial trial, release studies showed that more than 85 % of the drug was delivered within 6-8 h. This may be due to the high solubility of TRH or high osmotic pressure generation within the core compartment. To reduce the osmotic pressure in the core compartment, mannitol (38 atm, saturated solution) was used in place of sodium chloride and potassium chloride within the core. This approach was unsuccessful as more than 75 % drug was released within 6-8 h.²⁰

Osmotic pumps *per se* are suitable for the delivery of drugs having intermediate water solubility. It has been reported that in case of water-insoluble drugs, reasonable release rates may not be obtained using an elementary osmotic pump or controlled-porosity osmotic pump. This is because the kinetics of osmotic drug release is directly related to drug solubility within the core. Assuming a tablet core of pure drug, the fraction of drug released with zero-order kinetics is given by:²¹

$$F(z) = 1 - \frac{z}{S} \dots\dots\dots (1)$$

Where, $F(z)$ is the fraction released by zero-order kinetics, S is the drug solubility (g mL⁻¹), and ρ is the density (g mL⁻¹) of the core tablet.

According to *Eq. (1)*, highly water-soluble drugs would demonstrate a high release rate, which would be zero-order for a small percentage of

the initial drug load. Thus, the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. However, it is possible to modulate the solubility of drugs within the core, and thus extend this technology for delivery of drugs that may otherwise be poor candidates for osmotic delivery.

TRH is a basic drug with very high water solubility; pK_a value of TRH is 9.41, hence solubility is also pH independent at physiological pH. In order to get the desired release from the developed systems, PEO was added to the core formulation. After coming in contact with the surrounding fluid, swellable polymer (PEO) causes significant swelling, which creates significant internal pressure within the osmotic system leading to reduced imbibition. Also, the PEO within the core may restrict or delay the contact of solvent molecules with the drug and osmotic agent molecules, which may result in decreased osmotic pressure generation within the device and thus control the release of the drug from CPOP.

To study the effect of coat thickness of the semipermeable membrane (SPM) on drug release, core tablets of TRH were coated with the coating composition so as to get the percent weight gain of 5%, 10% and 15 % of tablet weight. Release profiles of TRH from these formulations are shown in Fig. 1. It is clearly evident that drug release decreases with the increase in coat thickness of SPM. The differences in *MDT50* between the above formulations were found to be statistically significant ($p < 0.05$).²²

To study the effect of the level of plasticizer (DBP), core formulation of TRH was coated with coating solution with different concentration of DBP, respectively. It is clearly evident that the level of plasticizer, DBP, has a direct effect on drug release. As the level of DBP increases, the membrane becomes more porous due to rapid dissolution of acidic-water soluble DBP in dissolution medium, resulting in higher drug release.²³

In vitro drug release profiles of the promising batch F10 were compared with commercial sustain release CONTRAMAL-SR®-100 mg formulations of TRH and also with the theoretically desired release profile. It is clearly evident that the developed formulations provided more controlled and prolonged drug release compared to commercial formulations of TRH. Drug release from batch F10 was found to be closest to the desired release profile. Formulation F10 was therefore selected as the optimized formulation and was further evaluated.²⁴

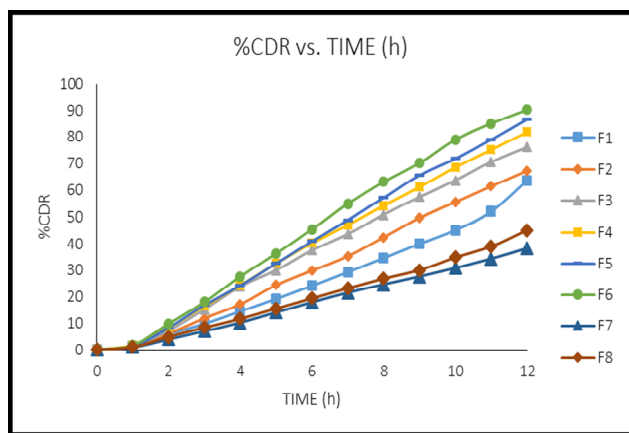


Figure 1a: In vitro Dissolution Study of Batches F1 to F8

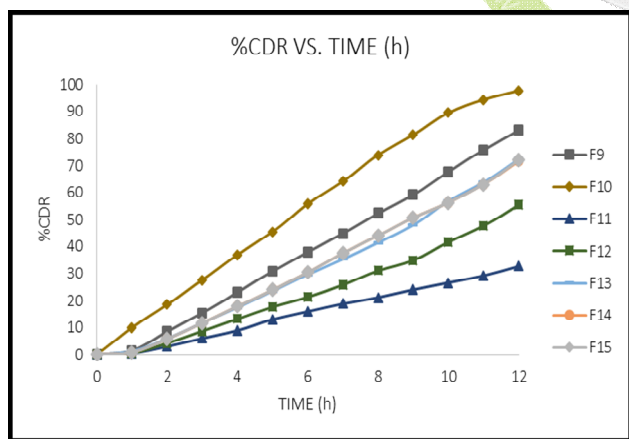


Figure 1b: In vitro Dissolution Study of Batches F9 to F15

Statistical Analysis

Box-behnken design was applied with three formulation variables at 3 different levels were used to study the effects on dependent variables. All batches of CPOP were statically (confidence

level 95 % or $P < 0.05$) evaluated with regard to %CDR using multiple regression analysis in Design Expert software (Statease inc.). A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

A second order polynomial was fitted to the experimental data;

$$Y = +71.90 + 2.49 * X_1 + 8.09 * X_2 - 23.29 * X_3 + 0.48 * X_1 * X_2 + 0.78 * X_1 * X_3 + 1.98 * X_2 * X_3 - 0.97 * X_1^2 + 1.22 * X_2^2 - 5.87 * X_3^2$$

Where, Y is the response variable (%CDR at 12 h), X_1 is osmogens mannitol, X_2 is channeling agent di-butyl phthalate and X_3 is amount of weight gain.

This equation represent the quantitative influence of membrane variables (X_2 and X_3) and their interaction on the response Y. Coefficients with more than one factor term and those with higher order terms correspond to interaction terms and quadratic relationship respectively. A positive sign denotes a synergistic effect and negative sign denotes an antagonistic effect. Results showed that mannitol and DBP have positive impact on drug release while % weight gain presented an antagonistic influence on drug release.

Model Adequacy Checking

Validation of box-behnken design was done by using check point analysis method. The tablets were formulated using the using three different composition and evaluated for %CDR at 12 h as shown in Table 2. The observed and predicted responses were critically compared. The result show the good similarity between observed response and predicted response which ensure the validation of Box-Behnken statistical model.²⁵

Formulation Optimization

The optimum formulation was selected by “trading off” response variable %CDR at 12 h and allowing the maximizing criteria of release of >85%. Upon comprehensive evaluation, the formulation with 75 mg Mannitol, 30% Di-butyl phthalate and 5% weight gain fulfilled the

optimal criteria of best % cumulative drug release of 97.85%. So, batch F10 was selected as an optimized formulation.

Table 2: Validation of Box-Behnken Design

Check Point	Independent Variables			Observed Response	Predicted Response
	X ₁	X ₂	X ₃		
1	0.5	1	-1	95.89	97.50
2	0	0.5	-1	90.46	92.41
3	0	1	0	78.01	81.21

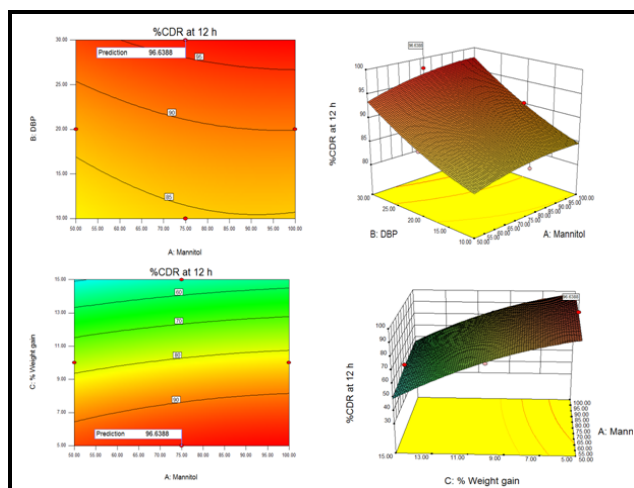


Figure 2a: Contour and 3D Surface Plot showing the Effect of Mannitol, Di-Butyl Phthalate and % Weight gain on % Drug Release

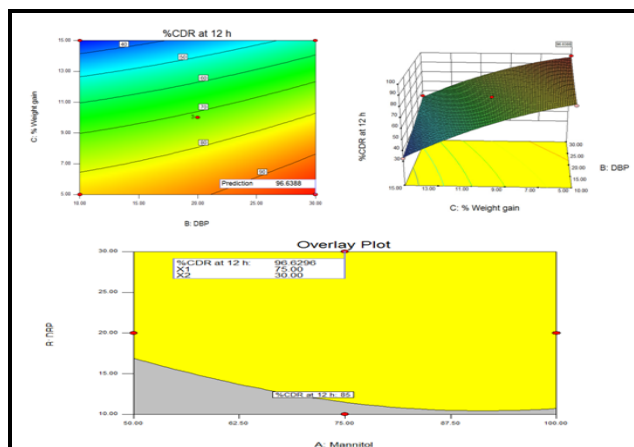


Figure 2b: Contour and 3D Surface Plot showing the Effect of Mannitol, Di-Butyl Phthalate and % Weight gain on % Drug Release

Evaluation of Optimized Formulation

The optimized batch F10 was evaluated for various pharmacopoeial and non-pharmacopoeial tests, results of which are listed in Table 3. The powder blend was fair flowing, as demonstrated by the values of the compressibility index (between 15 to 20) and Hausner's ratio (between 1.25 to 1.5). Exhausted shells, after dissolution, were visually observed for any imperfection or cracks in the coating. There were no visible cracks in the coating and it was found to be intact in all batches after 12 h of dissolution studies.

Table 3: Evaluation Parameters of Optimized Batch F10

Evaluation Parameters	Result
Diameter (mm)	9.5 ± 0.0
Thickness (mm)	4.2 ± 0.01
Hardness (kg/cm ²)	5.1 ± 0.01
Weight Variation Test (mg)	400 ± 0.22
Friability Test (%)	0.05 ± 0.01
Drug Content Test (%)	99.6 ± 0.02
% Cumulative Drug Release	97.85 ± 8.67

To study the effect of pH and to assure a reliable performance, release studies of the optimized formulation were conducted by using buffer media at three different pH (pH 1.2, pH 4.5 and pH 6.8) and compared to release data in SIF. There was not a significant difference between different pHs of release medium on TRH release compared to *in vitro* data in SIF (Fig. 3a). The *f*₁ and *f*₂ values of batch F10 were found to be 7.49 and 52.62 respectively, taking the release profile in SIF as reference.⁸

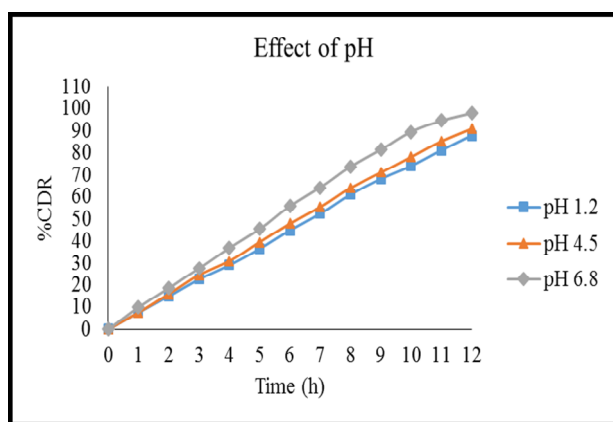


Figure 3a: Effect of pH on % Drug Release

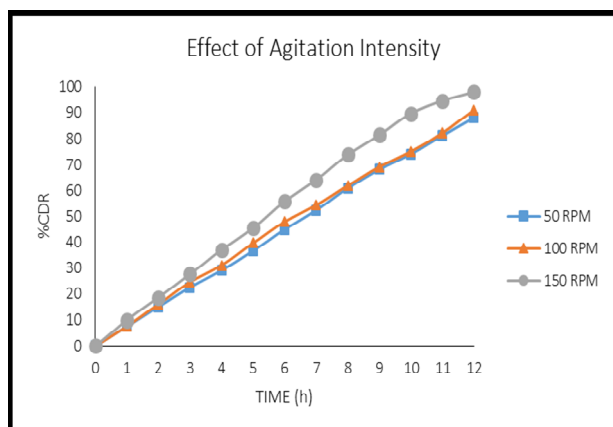


Figure 3b: Effect of Agitation Intensity on % Drug Release

To study the effect of hydrodynamic conditions on TRH release, a release study of batch F10 was carried out at three different rotational paddle speeds (50, 100, 150 rpm). There was an insignificant effect of rotational speed on TRH release from developed formulations when all the three release profiles were compared (Fig. 3b).⁸

Figure 4 shows the SEM monographs of semipermeable membrane before and after dissolution. It showed formation of pores in membrane of batch F10 after dissolution studies. This might be due to the rapid dissolution of the water soluble plasticizer (DBP) in dissolution medium. When comparison was made of the membranes containing different levels of plasticizer, it was found that the membrane that contained a higher level of plasticizer became more porous after the dissolution studies.

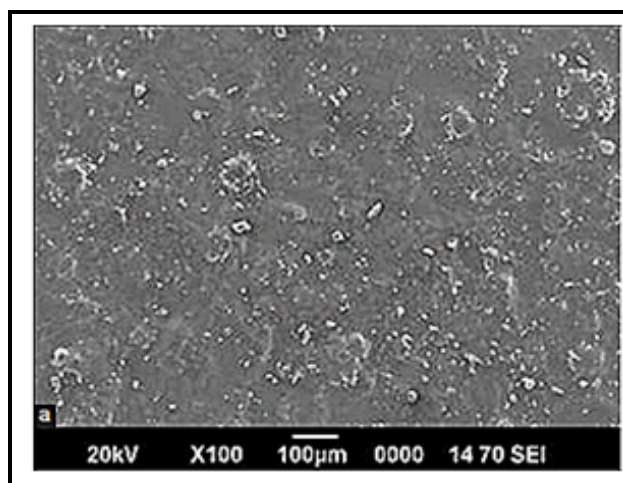


Figure 4a: SEM Study of Coating Membrane Before

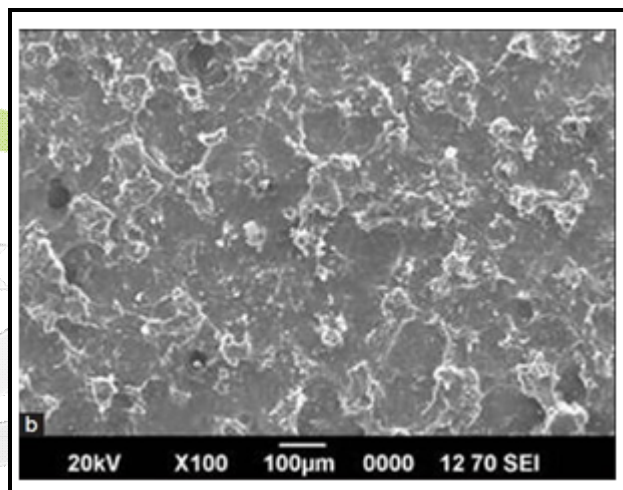


Figure 4b: SEM Study of Coating Membrane after Dissolution Study

Kinetics and Mechanism of Drug Release

Dissolution data of the optimized formulation (batch F10) was fitted to various mathematical models (zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell) in order to describe the kinetics of drug release (Table 4). Smallest value of the sum of squared residuals (SSR), Akaike information criterion (AIC) and the best goodness-of-fit test (R^2) were taken as criteria for selecting the most appropriate model. Drug release from optimized formulations fitted well into zero-order kinetics, confirming that the release from formulations is close to the desired release profile and drug load dependent.¹⁸

Table 4: Curve Fitting Analysis of Optimized Batch F10

Model	R ²	K	SSR	AIC
Zero order	0.9918	8.802	109.06	62.99
First order	0.9347	0.156	865.56	89.92
Higuchi model	0.8873	25.058	1494.17	97.02
Korsmeyer-Peppas model	0.9959	10.826	53.82	55.81
Hixson-Crowell model	0.9686	0.044	416.13	80.40

Accelerated stability study

Optimized TRH formulations were packed in strips of 0.04 mm thick aluminum foil laminated with polyvinyl chloride (PVC). Packed formulations were stored in stability chambers (Narang Scientific Work, India) maintained at 40 °C and 75 % relative humidity for 6 months. Stored formulations of optimized batch with 150-mm coat thickness were found to be stable in terms of physical properties, hardness, *in vitro* release characteristics and dissolution stability (Table 2) even after storage for 6 months. Despite statistically significant variability in the drug content, the tested formulation adhered to ICH criterion of ± 5 % drug content change from its initial value.²⁶

CONCLUSION

Controlled porosity osmotic pump tablets of Tramadol hydrochloride were developed based on osmotic technology. The effect of different formulation variables was studied to optimize the release profile. Drug release was directly proportional to concentration of osmotic agent and plasticizer, but inversely related to amount of % weight gain. Box-behnken design was

carried out for optimization purpose by using mannitol, dibutyl phthalate and % weight gain as variables. Optimized formulation was showed the zero order release which is independent of pH and agitation intensity, assuring the release to be fairly independent of pH and hydrodynamic conditions of the absorption site. Comparison of optimized formulation with sustained release marketed products showed the good similarity with marketed products and also passed the stability study.

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