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Design and In-Vitro Evaluation of Controlled Release Tablets of Tramodol Hydrochloride

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ABSTRACT

The aim of the present work was to design controlled release tablet of Tramadol hydrochloride for prolong release and it's *in vitro* evaluation. Controlled tablets of Tramadol hydrochloride comprised HPMC K15M, and HPMC K100M as the release retarding polymers. These tablets were prepared by direct compression method. The seven different formulations (F1-F7) were evaluated for pre- and post-compression parameters. *In vitro* dissolution studies were carried out for the optimized formulation (F7). It has found that the release of drug from the sustained release layer by 99.5% in 12 h. FT-IR studies revealed that there was no interaction between the drug and polymers used in the study. The release of Tramadol hydrochloride was found to follow a pattern of Korsmeyer-Peppas, with Quasi-Fickian diffusion. Accelerated stability studies were carried out on the prepared tablets in accordance with ICH guidelines. There were no changes observed in physicochemical properties and drug release pattern of tablets. The controlled drug release pattern was successfully achieved through the formulation of controlled tablets in this study.

Keywords: Tramadol hydrochloride, HPMC K15M, HPMC K100M, Micro crystalline cellulose, direct compression, and *In-vitro* dissolution studies etc.

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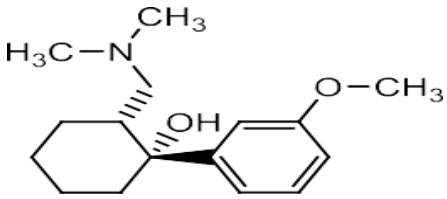
INTRODUCTION

Despite increasing research into alternative routes and methods of drug delivery the oral route remains the most popular one accounting for 70% of all forms of drug therapy. The reasons for this are readily apparent the oral route being the most convenient and acceptable one to the patients, improve compliance [1, 2]. Furthermore owing to the well-established manufacturing methods used to produce solid oral dosage forms (e.g., tablets and capsules), such dosage forms are cheaper to produce, making them the most cost-effective choice, in light of the importance of reducing overall prescribing cost for prescribers and healthcare provider. Solid dosage forms can be fabricated with the (non-immediate) modified-release technologies, which utilize polymers to alter the site or time of drug release within gastrointestinal tract [3-6]. In recent years, a growing interest has developed in designing drug delivery systems component to controlled release (CR) dosages. Tramadol hydrochloride is used as an analgesic drug, and possess short biological half-life (5-7 h). A patient should undergo frequent administration usually thrice a day which might be a risk to the patient. In order to overcome this, Tramadol hydrochloride controlled release dosage forms are formulated [7]. In the present study, Tramadol hydrochloride is proposed to be formulated as controlled tablet which comprises sustained release layer to maintain steady state concentrations of drug in the blood. The current work is to formulate and evaluate an ideal controlled release tablets of Tramadol hydrochloride profile by suing suitable methods using different polymers.



Tramadol Hydrochloride

MATERIALS AND METHOD

Tramadol hydrochloride, Micro crystalline cellulose. (Avicel pH 102), sodium carboxy methyl cellulose, were purchased from Caplin point laboratories, Puducherry (TN), India. HPMC K15, HPMC K100 from FMC biopolymer. Single pan electronic balance from Shimadzu-Corp, Japan. Vernier Calipers from Mitutoyo Corp, Japan. Hardness tester, Friability test Apparatus, Disintegration Apparatus, and Dissolution Apparatus from Electro Lab, India.

FT-IR SPECTROSCOPY

The drug and optimized formulation were characterized by IR Spectroscopy using a FT-IR 8400S (Shimadzu, Japan). The spectra were taken by KBr discs method in the range of 4000-500cm^{-1}.

Preparation and Characterization Of Tramadol HCL Controlled Release Tablets

The controlled release tablets of Tramadol hydrochloride were prepared by direct compression method. The drug and polymers were passed through a #80 sieve before their use in the formulation. The above powder blend were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min to obtain uniform distribution of the drug in formulation and subjected for pre-formulation studies.

In the present study, controlled release tablet Tramadol hydrochloride was prepared manually using single station punching machine. Accurately weighed amount of powder mix was fed manually into die cavity. The above powder blend was compressed at mild compression force using 8mm flat punches (Rimek Mini Press-1, Karnavati Engineering Ltd., Mehsana, Gujarat, India.).

Evaluation Of Granules [13, 14]

The angle of repose (θ) of the granules was determined by using funnel method. Bulk density (BD) and tapped density (TD) were calculated by formula: BD = Bulk mass/Bulk volume; TD = Bulk density = Bulk mass/Bulk volume. Compressibility index and Hausner's ratio of the granules was determined by using the formula: CI (%) = [(TD- BD/BD)]×100 and HR = TD/BD, respectively. The experiments were performed in triplicate and average value with SD were noted.

Table 1: Formulation design of Tramadol hydrochloride Controlled release Tablet

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Tramadol Hydrochloride	120	120	120	120	120	120	120
HPMC K15	2.5	7.5	12.5	***	***	***	7.5
HPMC K100M	***	***	***	2.5	7.5	12.5	7.5
Sodium carboxy methyl cellulose	25	25	25	25	25	25	25
Micro crystalline cellulose	80	75	70	80	75	70	67.5
Magnesium stearate	15	15	15	15	15	15	15
Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total weight **(mg/tab)**	250	250	250	250	250	250	250

EVALUATION OF TABLETS [15,16]

The thickness of the tablet is measured by Digital vernier calipers. 20 tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight. Tablets were evaluated for hardness using Monsanto hardness tester and friability using Roche friabilator.

***In vitro* drug release study** [17, 18]

For immediate release layer dissolution rate was studies by using USP type-I apparatus at 100 rpm using 900ml of 0.1N HCl solutions as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5^{O}C, aliquot of 5ml of dissolution medium was withdrawn at every 15 min interval the absorbance of solution was measured by UV Spectrophotometric method at 272nm and concentration of the drug was determined from standard calibration curve. The volume of the dissolution medium was adjusted to 900ml at every sampling time by replacing 5ml with same dissolution medium.

The *in vitro* release of drug from sustained layer was carried out for 12 h using basket type tablet dissolution apparatus USP type-I containing 900ml of dissolution medium maintained at 37±0.5^{O}C and speed of agitation at 100rpm. Using 900ml of pH 6.8 phosphate buffer as a dissolution medium.

Kinetic studies [19, 20]

The rate and mechanism of release of Tramadol hydrochloride from the bilayer tablets were analyzed by fitting the dissolution data into the zero- order equation:

$Q = k_o t$

Where Q is the amount of drug released at time t, and ko is the zero order release rate constant.

The first order equation:

$\ln (100-Q) = \ln 100 - k_1 t$

Where k_1 is the first order release rate constant.

The dissolution data was fitted to the Higuchi's equation:

$Q = k_2 t_{1/2}$

Where k_2 is the diffusion rate constant.

The dissolution data was also fitted to the Korsmeyer- Peppas equation, which is often used to describe the drug release behavior from polymeric systems:

$\log (M_t/M_\infty) = \log k + n \log t$

Where M_t is the amount of drug released at time t, M_∞ is the amount of drug release after infinite time, k is the release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusion exponent indicative of the mechanism of drug release.

Stability study [21, 22]

Stability study was done for the optimized formulation for a period of three months at 40±2^{O}C, 70±5% RH to provide evidence on how the quality of a drug substance varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and enables recommended storage conditions, re-test periods and shelf-lives to be established.

RESULTS AND DISCUSSION

Controlled released tablets are one of the approaches for prolong the duration action. Several attempts have been made for preparation of controlled release with variable concentrations of rate retarding polymer for adjusting release pattern according to marketed formulation and USP guidelines of Tramadol hydrochloride extended release tablet. In these formulations, tablet were formulated with the hydrophilic polymer HPMC K15M, and HPMC K100M for extended drug release.

Fig. 1 & 2 demonstrates the FT-IR spectrum of pure Tramadol hydrochloride and Optimized formulation (F7).

EVALUATION OF GRANULES

The controlled tablets were evaluated for various physical properties (Table 2). The bulk densities for the powder blend of bilayer tablets of various formulations (F1-F7) ranged between 0.301±0.01g/ml and 0.689±0.01g/ml; and tapped density ranged between 0.33±0.03g/ml and 0.804±0.06g/ml as determined by the tap densitometer. These values of bulk density indicated good packing characteristics. The Carr's index (CI) for all the formulations was ranged from 9.24±0.09 to 14.30±0.93, indicating desirable flow properties. The value of Hausner's ration was ranged from 1.09±0.00 to 1.13±0.00. The flow properties of powder blends were further analyzed by determining the angle of repose for all formulations; it ranged between 23.48 and 25.34. The values indicated satisfactory flow behavior.

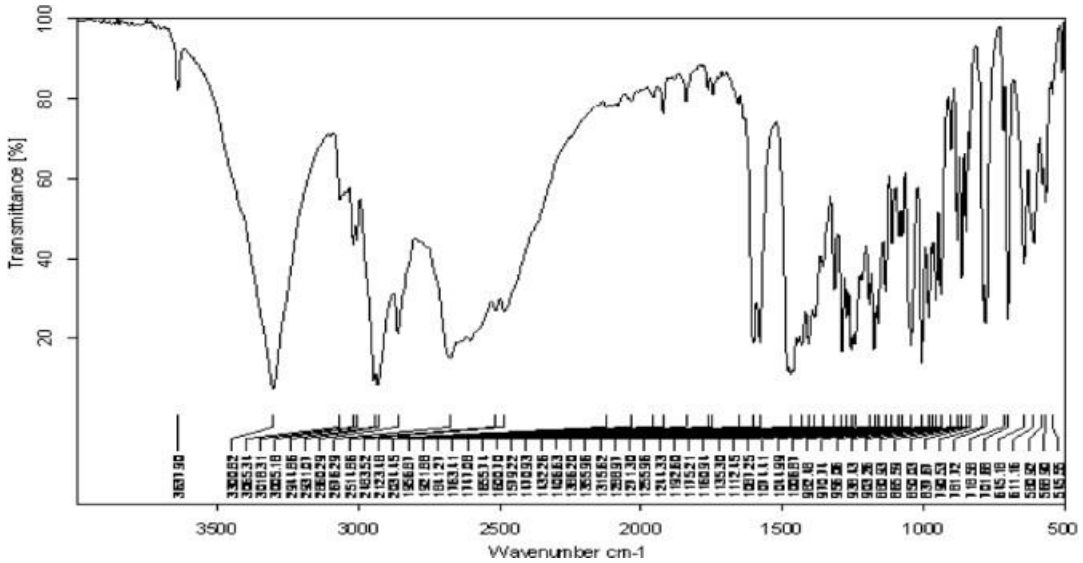


Figure 1: FT-IR Spectrum of pure Tramadol hydrochloride

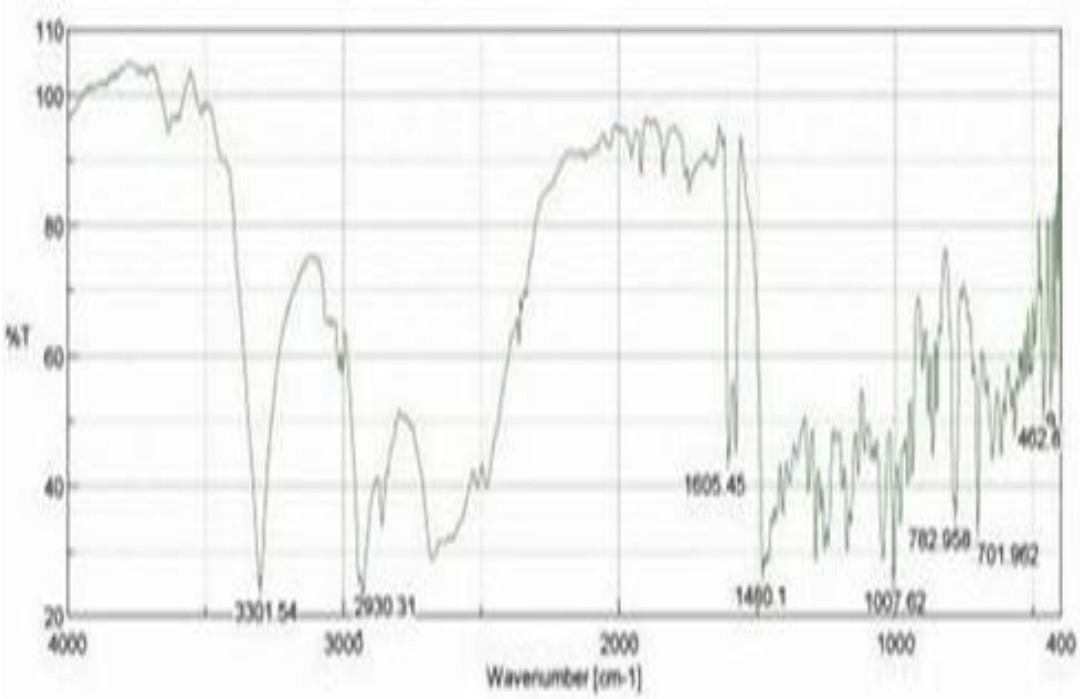


Figure 2: FT-IR spectrum of Tramadol hydrochloride controlled tablets (F7)

Table 2: Evaluation of Tramadol HCl Controlled release tablets

Formulation	Thickness (mm)	Average weight (mg)*	Hardness (kg/cm^2)	Friability (%)	Assay (%)
F1	5.01±0.02	249.1±0.94	5.12±0.01	0.52±0.04	97.20±0.05
F2	4.29±0.01	250.1±0.99	5.52±0.02	0.64±0.02	100.35±0.08
F3	4.59±0.05	249.7±0.82	4.23±0.03	0.52±0.03	98.90±0.04
F4	4.94±0.07	249.8±0.91	4.23±0.04	0.63±0.01	100.56±0.17
F5	5.03±0.01	250.6±0.96	5.01±0.05	0.64±0.02	97.30±0.02
F6	5.15±0.01	250.1±0.87	4.14±0.01	0.63±0.06	98.95±0.05
F7	4.90±0.12	250.6±0.96	4.54±0.06	0.72±0.03	99.47±0.05

*Values expressed as mean ±SD, number of trials (n) = 3

EVALUATION OF CONTROLLED RELEASE TABLETS OF TRAMODOL HYDROCHLORIDE

All the formulations (F1-F7) were produced under similar conditions to avoid processing variables. The weight variation, hardness, friability, thickness and content uniformity of all formulations were found to be within acceptable limits as per official specifications. Weight of the optimized tablet formulation (F7) was 250.6±0.96mg, hardness was 4.54±0.06kg/cm^2 and thickness was 4.90±0.12. The percentage friability of all the formulations was ranged from 0.52±0.03 to 0.72±0.03 which is less than 1% of their weight. Values of the hardness test and percent friability indicated good handling properties of the prepared bilayer tablets. The drug content (assay) uniformity in the bilayer tablets was ranged from 97.20±0.05 to 100.56±0.07%. The results were illustrated in Table 3.

Table 3 Regression coefficient values of the formulations in various kinetic models

Formulation	R^2			Korsmeyer-Peppas	
	Zero	First	Higuchi	R^2	n
F1	0.928	0.987	0.981	0.977	0.475
F2	0.945	0.980	0.986	0.979	0.421
F3	0.926	0.982	0.987	0.985	0.435
F4	0.988	0.944	0.968	0.988	0.436
F5	0.968	0.957	0.979	0.981	0.492
F6	0.989	0.949	0.974	0.994	0.451
F7	0.997	0.986	0.984	0.981	0.410

***In vitro* drug release study**

The results of *in vitro* drug release profile of controlled release tablets depicts (Fig. 3) that combination of modified polymers play important role in the retardation and optimization of the drug release and increases the retardation of drug release from the controlled release tablet. All formulations (F1-F7) the percentage drug release shown in the range of 76.52 to 99.55.

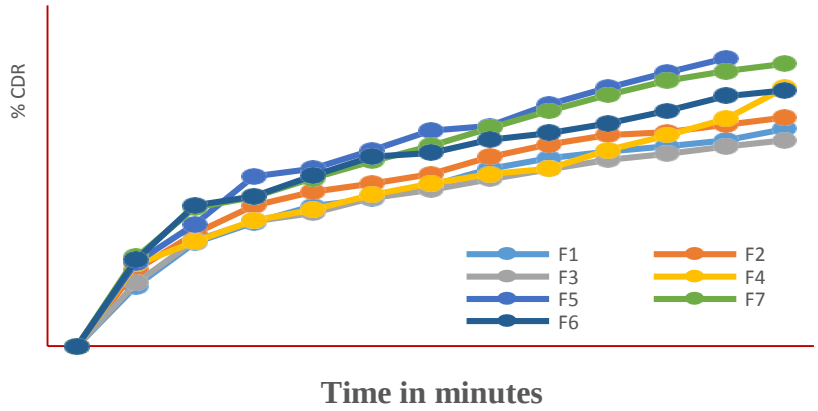


Figure 4: In vitro drug release study of Tramadol hydrochloride Controlled tablet

Kinetic studies

In order to establish the mechanism of drug release, the experimental data were fitted to zero order, first order, and Higuchi and Korsmeyer-Peppas models. The results for kinetics model fitting of the different formulations are shown in Table 4.

Table 4: Stability studies of optimized formulation (F7)

Time period	Description (color)	Friability (%)*	Hardness (kg/cm^2)*	Assay (%)
Initial	White	0.72±0.03	4.54±0.04	99.47
1^{st} month	White	0.71±0.02	4.52±0.05	98.54
2^{nd} month	White	0.71±0.04	4.50±0.06	97.58
3^{rd} month	White	0.70±0.03	4.49±0.05	98.48

*Values expressed as mean±SD, number of trials (n) =3

The coefficients of regression were in a range between 0.926 and 0.997 (Zero order), 0.944 and 0.987 (First order), 0.974 and 0.986 (Higuchi) and 0.977 and 0.988 (Peppas).

The n value for F7 was found to be 0.450, which meant that the mechanism of release for F7 was fickian diffusion and best fit model was Korsmeyer- Peppas. The n value for all formulations was in the range of 0.410 to 0.492 indicating Fickian diffusion. Overall, the release mechanisms from these bilayer systems can be explained as a result of diffusion of drug through porous matrix in which pores are created by combination hydrophilic polymers with equal portions of HPMC K15 and HPMC K100, thus more contribution of erosion to release mechanism.

Stability studies

The accelerated stability studies (Table 5) were carried out on the optimized formulation, i.e., F7. The formulation was stored at 40±2^{o}C/75±5% RH for 3 months to assess their long term stability. After stability study, tablets were subjected to various tests like hardness, thickness, friability, drug content and *in vitro* drug release study. The results indicated that, irrespective of the concentration of polymer, there were no changes observed in tablets characteristics after stability study.

STATISTICAL ANALYSIS

All the formulations were evaluated in triplicate and standard deviation was calculated. Each data point in the results is the average of three replicate tests.

CONCLUSION

The present work involves the formulation development and *in-vitro* evaluation of Controlled release tablets of Tramadol HCl for prolong drug release. Under the pre-formulation studies, drug characterizations, physicochemical evaluation results for the sustained release layer and drug-Excipients compatibility studies were carried out. All the studies showed compliance with the drug characteristics and layer passed the official limits. The controlled release tablets of Tramadol HCl of different formulations (F1–F7) were prepared. All the prepared tablets were evaluated for post compression parameters such as hardness, thickness, weight variation, drug content uniformity and *in-vitro* drug release. The optimized formulation (F7) shown desired release profile of 99.6% in 12 h. The data obtained are fitting to various kinetic models, the optimized formulation (F7) shown (r^2) value of 0.997 and the 'n' value obtained from Korsmeyer-Peppas model showed that the above formulation followed Fickian drug release mechanism. Above the stability studies confirm that there was no significant difference over a stability testing period. Finally all the above results were revealed that F7 formulation has met objective of controlled drug release, patient convenience and cost effectiveness as a twice a day dose of the drug.

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