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DEVELOPMENT AND IN VITRO EVALUATION OF TRAMADOL HYDROCHLORIDE BUCCAL FILM

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Abstract:

The present study was aimed at the formulation and evaluation of Tramadol hydrochloride buccal films for sustained drug delivery using different polymers by solvent casting technique. Buccal drug delivery systems offer several advantages, including improved bioavailability, avoidance of first-pass metabolism, prolonged drug release, and enhanced patient compliance. Preformulation studies such as organoleptic evaluation, solubility studies, melting point determination, UV spectrophotometric analysis, and FTIR compatibility studies were carried out to characterise the drug and evaluate its compatibility with excipients. Buccal films were prepared using Ethyl cellulose and HPMC K15M as film-forming polymers, PEG as plasticizer, Aspartame as a sweetening agent, and DMSO as a permeation enhancer. The prepared films were evaluated for various physicochemical parameters, including thickness, weight variation, folding endurance, drug content uniformity, moisture absorption, moisture loss, swelling index, and surface appearance. All formulations showed satisfactory physicochemical characteristics with good flexibility and uniformity. In vitro drug release studies were performed using a Franz diffusion cell apparatus in phosphate buffer pH 6.8 for 8 hours. Among all formulations, formulation F8 exhibited the highest cumulative drug release of 99.4% and showed satisfactory mechanical and physicochemical properties. Drug release kinetic studies revealed that the optimised formulation followed Higuchi diffusion kinetics, indicating diffusion-controlled drug release mechanism. Accelerated stability studies conducted for 90 days under different storage conditions showed no significant changes in physical appearance or drug release profile, confirming good stability of the optimised formulation. The study concluded that Tramadol hydrochloride buccal films prepared by solvent casting method can be considered a promising approach for sustained buccal drug delivery with improved therapeutic efficacy and patient compliance.

Keywords: *Tramadol hydrochloride, Ethyl cellulose, HPMC K15M, Buccal films, Solvent casting technique, In vitro drug release studies.*

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INTRODUCTION:

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic widely used for the management of moderate to severe pain. It acts through dual mechanisms by binding to μ-opioid receptors and inhibiting the reuptake of norepinephrine and serotonin.[1] Buccal drug delivery systems have gained considerable attention as an alternative route for systemic drug administration. The buccal mucosa is highly vascularized and allows direct absorption of drugs into the systemic circulation, thereby bypassing hepatic first-pass metabolism.[2] Buccal films provide several advantages such as ease of administration, rapid onset of action, improved patient compliance, prolonged residence time, and ease of termination of therapy when required.[3] In the present study, Ethyl cellulose and HPMC K15M were selected as film-forming polymers due to their excellent film-forming ability and controlled release characteristics.[4] The solvent casting method is one of the most widely employed techniques for the preparation of buccal films because of its simplicity, uniformity, and reproducibility.[5] Prepared films can be evaluated for various physicochemical and mechanical parameters such as thickness, weight variation, folding endurance, drug content, swelling index, moisture uptake, and in vitro drug release behaviour.[6] Therefore, the present research work was undertaken to develop and evaluate buccal films of Tramadol hydrochloride using different polymers with the objective of achieving sustained drug release, improved bioavailability, enhanced patient compliance, and better therapeutic effectiveness.[7] The prepared films were characterised by physicochemical evaluation, in vitro release studies, release kinetics, and stability studies to identify the optimised formulation suitable for buccal drug delivery.[8]

MATERIALS AND METHODS:

MATERIALS

Tramadol hydrochloride was procured from Hetero Labs, HYD. Ethyl cellulose and HPMC K15M were obtained from AR Chemicals, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METODOLOGY

Drug- excipient compatibility study[9]

FTIR Spectral Studies FTIR spectra of pure drug, polymers and their physical mixtures (stored at 40 ± 2 °C / 75% ± 5% RH for 2 months) were recorded. The samples were prepared by potassium bromide disc method and scanned for 49 absorbance (Yukinao et al 1997; Mario and Mira 2004; James 2005; John and Wyka 2005).drug and excipients.

Formulation Development

Table-1: Formulation Design of Tramadol hydrochloride buccal Films

F.no	Ingredients (mg)					
	Drug (mg)	Ethyl cellulose (mg)	HPMC k15M (mg)	Aspartame(mg)	PEG (ml)	DMSO (ml)
F1	50	50	-	5	1	1
F2	50	100	-	5	1	1
F3	50	150	-	5	1	1
F4	50	200	-	5	1	1
F5	50	-	50	5	1	1
F6	50	-	100	5	1	1
F7	50	-	150	5	1	1
F8	50	-	200	5	1	1

Preparation of buccal films by solvent casting method

The solvent casting method is widely used for the preparation of buccal films. A flat bottom glass Petri plate with the diameter of 10 cm was selected for preparing buccal films. A polymeric solution was prepared using solvent solution. To this solution drug solution was added. To this solution, PEG,

Aspartame was added. Polymeric solution was mixed under constant stirring for 45 mins. Both permeation enhancers (DMSO) were added to the above solution while mixing. The resulting solution was cast into Petri plate and kept in an oven at 55 °C for 24 hr[10].

Characterization of Buccal formulation

Physico- chemical evaluation[11,12,13]

Physical appearance:

All the formulated Tramadol hydrochloride films were observed for color, clarity, flexibility, and smoothness.

Folding endurance:

Buccal films folding endurance was estimated by frequently double over at the same place till it broke. The number of times the films could be folded at the same place without breaking is the folding endurance. This was restate on all the films for three times and the mean values plus standard deviation was calculated.

Thickness of the films:

The thickness of each films was measured by using screw gauze. Buccal films thickness was estimated at various sites on each film and the average thickness of the buccal film was capture as the thickness of the film.

Weight uniformity:

The formulated buccal films are to be dried at 60^0C for 6 hours before trial. A identify the area of 4.52 cm^2 of films is to be cut in different parts of the film and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content:

The medicated film (2 cm diameter), without backing membrane was allowed to dissolve in 10 mL of simulated saliva solution (pH 6.8) for 2 – 3 h under occasional shaking. The resultant solution was filtered through 0.45 µm filter paper and after suitable dilution, the amount of drug present in the film was determined spectrophotometrically at 275 nm (Shimadzu 1800, Japan).

Swelling behavior

The initial diameter of the original film (2 cm diameter), without backing membrane was determined. Then the sample was allowed to swell on the surface of an agar plate (prepared as described under measurement of surface pH section) kept in an incubator maintained at 37 ± 1 °C. Measurement of the diameter of the swollen film was carried out at predetermined time intervals for 90 min.

Moisture absorption studies:

The buccal films were weighed exactly and placed in a desiccator containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies:

Three films were weighed separately and kept in a desiccator contains calcium chloride at 37^0C for 24 hours. Then the last weight was noted when there was no further change in the weight of the film. The percentage of moisture loss was calculated using the following formula.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

***In vitro* release study:**

The release rate of the drug was determined by using Franz diffusion cell apparatus temperature maintained at 37 ± 0.5 ^{0}C and stirred at a rate of 200 rpm. Sink conditions was maintained all over the study. The vessel containing 10ml of phosphate buffer pH 6.8 phosphate buffer solution. Aliquots of 1ml of samples were withdrawn at various time meanwhile and then analyzed using a UV Spectrophotometer.

% release rate of drug was determined using the following formula.

$$\text{Perentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug in the films

Da = The amount of drug released

Conditions:

Medium: Phosphate buffer pH 7.4 phosphate buffer

RPM: 200

Temperature: 37 ± 0.5^0C

Time intervals: 1, 2, 3, 4, 5, 6, 7, 8 hours.

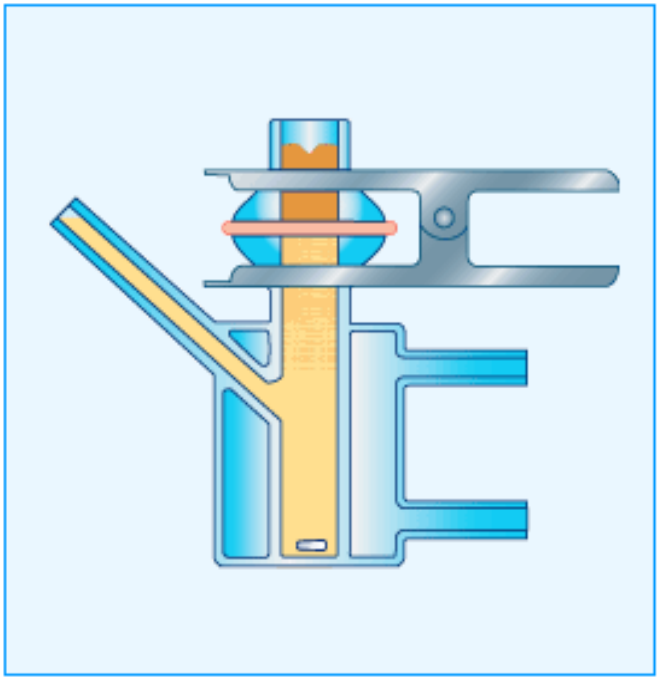

Fig-1: Franz diffusion cell apparatus

Drug release kinetics

In order to describe the Drug release kinetics from individual formulations, the corresponding dissolution data were fitted in various kinetic dissolution models:

Zero order, first order, and Higuchi respectively.

$$Qt = Q0 + K0\ t \text{……..} (3)$$

where, Qt is the amount of drug released at time t; Q0 the amount of drug in the solution at t = 0, (usually, Q0 = 0) and K0 the zero order release constant.

$$\log Qt = \log Q\alpha + (K1/2.303)\ t \text{…….} (4)$$

Qα being the total amount of drug in the matrix and K1 the first order kinetic constant.

$$Qt = KH.\ t\ ½ \text{…….} (5)$$

where,

KH is the Higuchi rate constant.

Further, to better characterise the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Korsmeyer and Peppas.

$$Q\ (t-l)\ /Q\alpha = KK\ (t-l)n \text{……} (6)$$

where, Qt corresponds to the amount of drug released in time t, *l* is the lag time (*l* = 2 hours), Qα is the total amount of drug that must be released at infinite time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the release exponent indicating the type of drug release mechanism. To the determination of the exponent n, the points in the release curves where Q (t-*l*)/Qα>0.6, were only used. If n approaches to 0.5, the release mechanism can be Fickian. If n approaches to 1, the release mechanism can be zero order and on the other hand if 0.5<n<1, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ‘‘best model’’ was the one with the highest coefficient of determination (r^2).

Stability studies:

Selected films were subjected to accelerated stability testing by wrapping them in aluminium foil and packing them in glass vials. These films were kept in an incubator maintained at 37 ± 0.5 oC and 75 ± 5% RH for 6 months. The film was stable only up to 37 ºC while conducting the stability studies. When the films were kept at 40 ºC, the films become pliable and showed instability. Changes in the appearance, residence time, in vitro drug release and drug content of the stored films were investigated after 3 months. The data presented were the mean of three determinations.

RESULTS AND DISCUSSION:

Compatibility studies of drug and polymers:

All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Tramadol hydrochloride and polymer. It also confirmed that the stability of drug during encapsulation process.

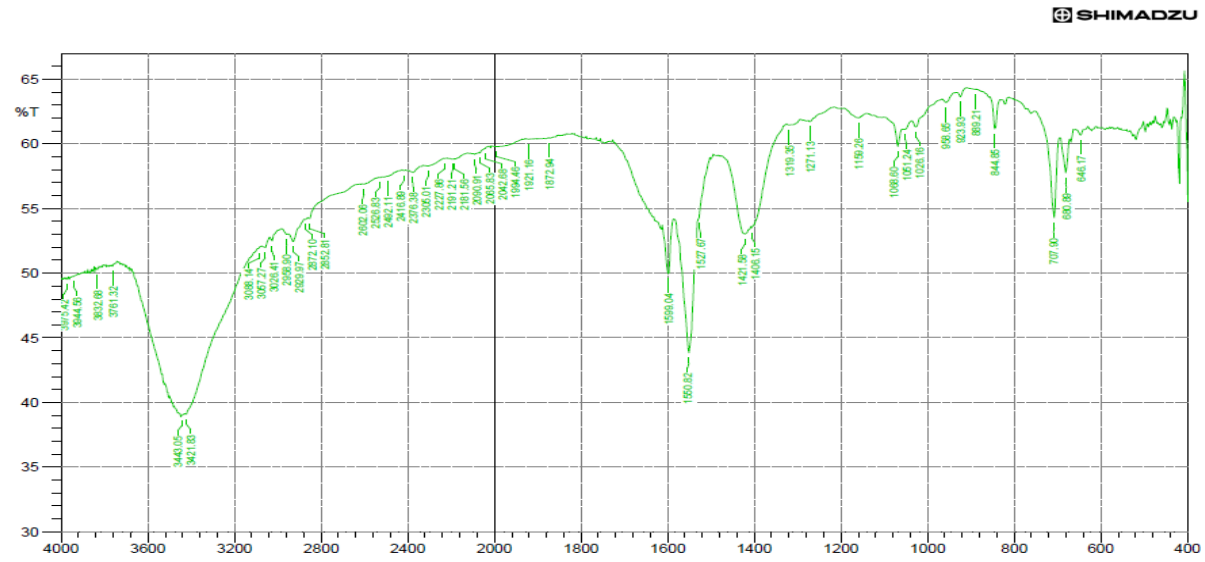

Fig-2: FT-IR Sample for Tramadol hydrochloride

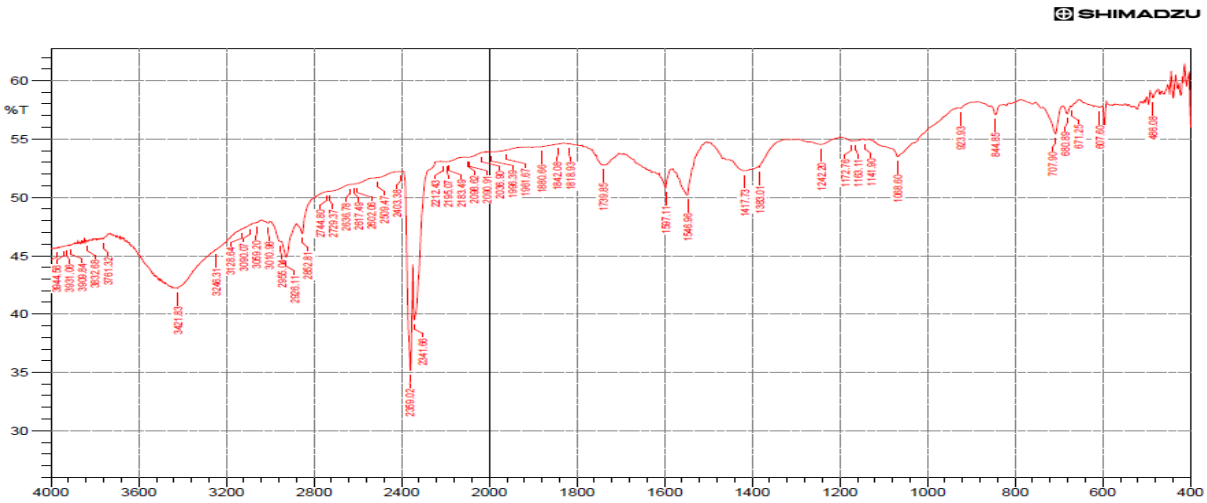

Fig-3: FT-IR Sample for physical mixture of drug and excipients

Physical appearance and surface texture of buccal films

These parameters were checked simply with visual inspection of films and by feel or touch. The observation reveals that the films are having smooth surface and they are elegant in appearance.

Weight uniformity of buccal films:

The weight of the films was determined using digital balance and the average weight of all films

Thickness of buccal films:

The thickness of the films was measured using screw gauge and the average thickness of all films.

Folding endurance of buccal films:

The folding endurance gives the idea of flexible nature of films. The folding endurance was measured manually, films were folded repeatedly till it broke, and it was considered as the end point. The folding endurance was found optimum and the films exhibited good physical and mechanical properties and the average folding endurance of all films.

Drug content uniformity of buccal films:

Tramadol hydrochloride buccal films prepared with various polymers were subjected to the valuation for uniform dispersion of drug throughout the patch. In each case three films were used and the average drug content was calculated.

% Moisture loss:

The Moisture content in the buccal films ranged from 2.92 to 4.10 %. The moisture content in the formulations was found to be increased by increase in the concentration of polymers.

% Moisture absorption:

The Moisture absorption in the buccal films ranged from 5.22 to 8.63 %.

Swelling index:

The swelling index in the buccal films ranged from 42.6 to 80.3 %.

Table -2: Physicochemical evaluation data of Tramadol hydrochloride Buccal Films

F. code	F1	F2	F3	F4	F5	F6	F7	F8
Thickness (mm)	0.18	0.20	0.24	0.26	0.19	0.23	0.27	0.32
Weight variation (mg)	108	155	200	246	112	160	208	258
Drug content Uniformity	96.12	97.25	96.15	97.91	94.63	96.75	97.58	98.69
Folding endurance	215	227	240	255	269	279	292	305
% Moisture loss	3.85	3.49	3.15	2.92	4.10	3.90	3.56	3.30
% Moisture absorption	5.22	5.64	7.12	6.39	7.89	8.48	9.30	8.63
Swelling index (%)	42.6	48.8	55.6	59.8	67.8	79.9	73.5	80.3

Drug release studies

Table-3: *In vitro* release data of film F_1 to F_8

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
1	24.56	22.6	21.5	24.5	23.6	21.9	20.9	25.5
2	34.8	35.9	29.8	30.8	32.2	33.1	34.9	36.4
3	53.6	52.8	41.5	46.7	45.9	49.5	50.1	51.8
4	68.7	65.9	62.9	63.5	65.1	66.3	65.2	64.5
5	75.6	74.5	70.5	73.5	72.2	70.1	74.9	75.6
6	80.2	76.9	79.8	80.8	81.9	80.5	82.3	83.2
7	89.5	85.6	92.2	89.9	92.5	90.3	93.5	95.8
8	96.8	98.6	94.5	95.6	96.7	97.2	98.4	99.4

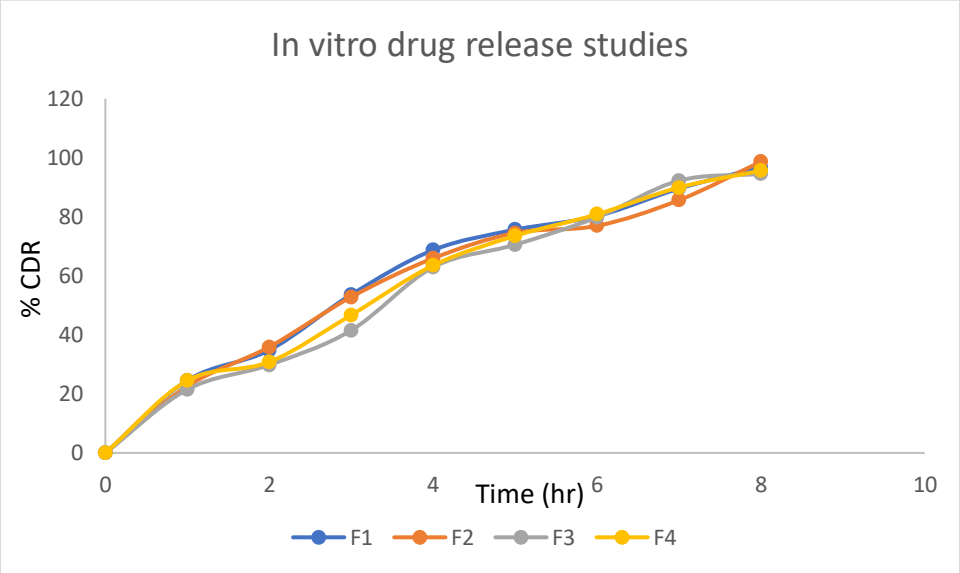

Fig-4: In vitro drug release of (F1- F4) formulation

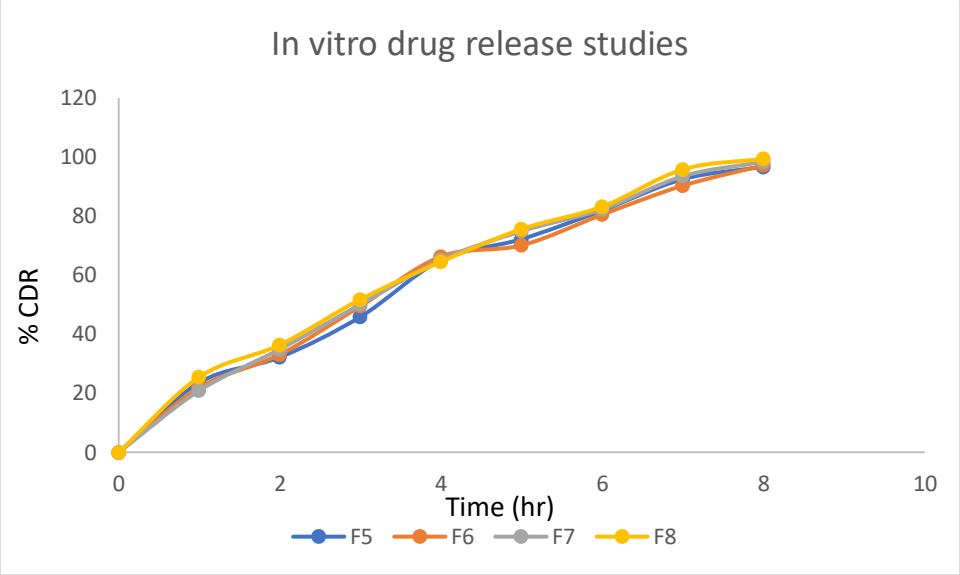

Fig-5: In vitro drug release of (F5- F8) formulation

Drug release kinetics:

All the formulation of prepared Tramadol hydrochloride buccal films was subjected to in vitro release studies these studies were carried out using Franz diffusion cell apparatus.

The dissolution medium consisted of 10 ml of Standard buffer pH 6.8 period of time.

Zero order kinetics

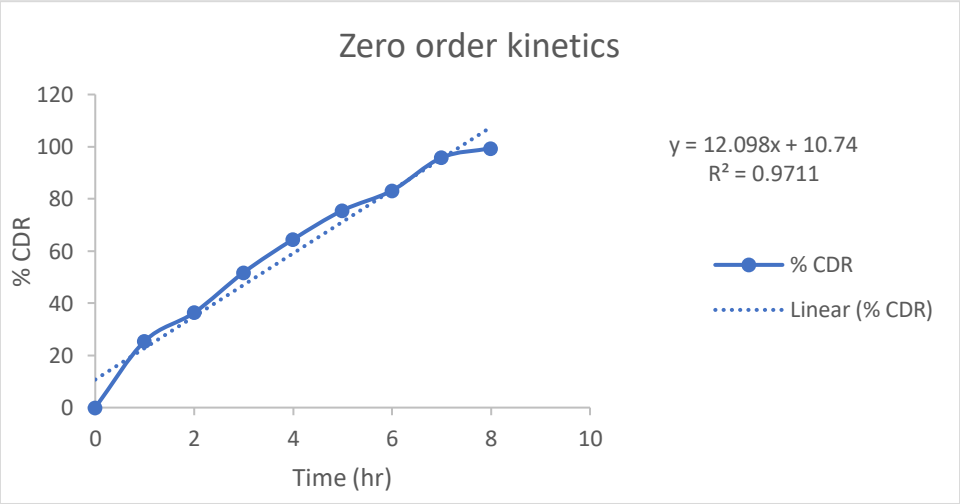

Fig-6: Zero order kinetics of Optimized formulation

First order kinetics

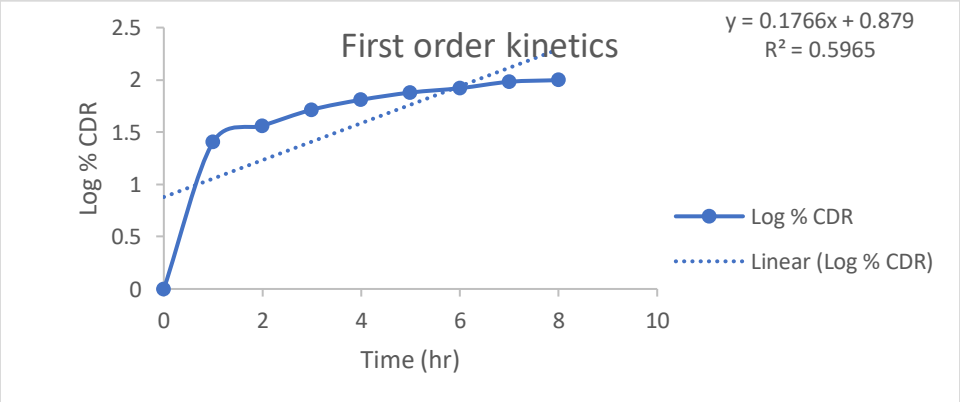

Fig-7: First order kinetics of Optimized formulation

Higuchi model

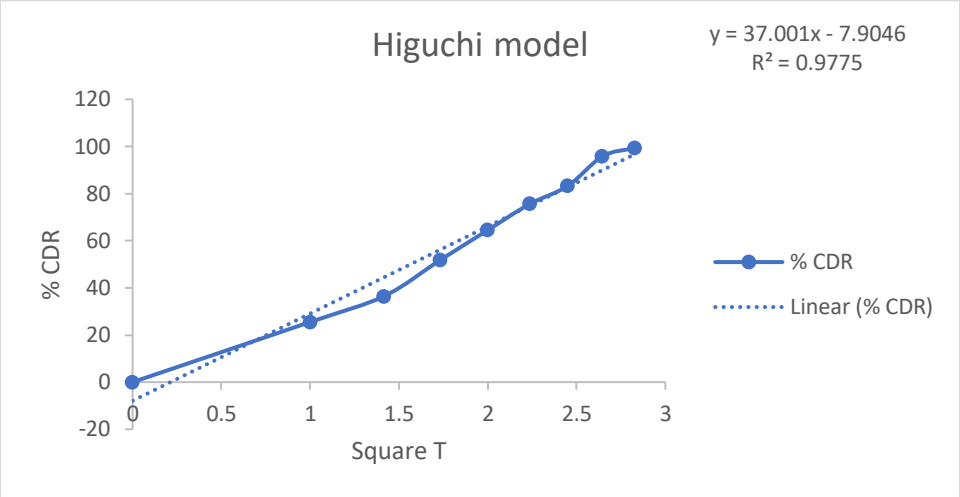

Fig-8: Higuchi model of Optimised formulation

Korsmeyer peppas

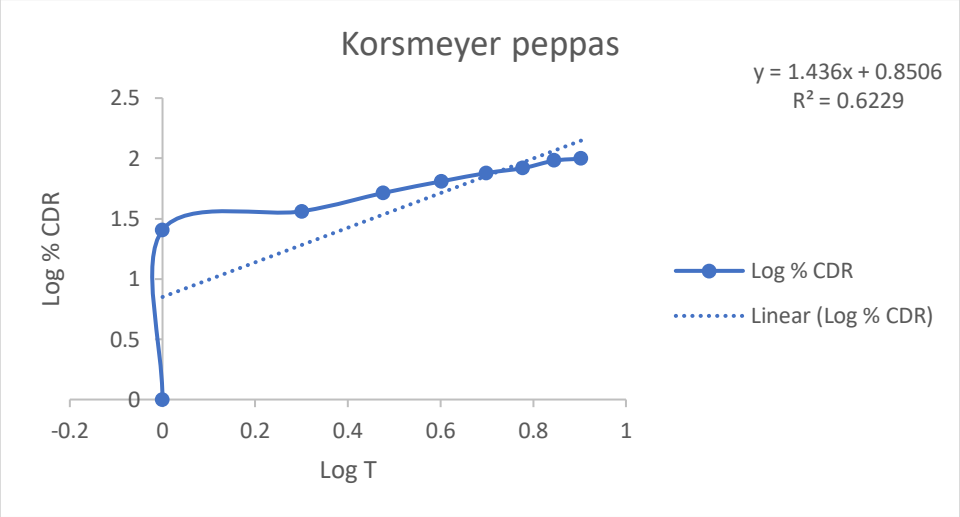

Fig-9: Korsmeyer peppas of Optimised formulation

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix, Peppas were respectively. Regression values are higher with Zero order release kinetics. Therefore, all the Tramadol hydrochloride buccal films Zero order release kinetics.
The table indicates that r^2 values are higher for Higuchi's model compared for all the formulation. Hence Tramadol hydrochloride release from all the buccal films followed diffusion rate-controlled mechanism.

Stability studies:

Table-4: Stability studies of optimized formulations

S.NO	Time in days	Physical changes	Mean % drug release		
			Tramadol hydrochloride		
			25^0C/60%	30^0C/75%	40^0C/75%
1	01	No Change	99.4	99.4	99.4
2	30	No Change	98.5	98.9	98.1
3.	60	No Change	97.5	97.3	97.4
4.	90	No Change	96.9	96.5	96.2

The stability studies of the optimized buccal film formulation of Tramadol hydrochloride were carried out for a period of 90 days under different storage conditions such as 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH. The formulation was evaluated for physical appearance and percentage drug release at predetermined intervals. The results indicated that there were no significant physical changes in the formulation throughout the study period under all storage conditions. The films remained smooth, uniform, and flexible without any signs of discoloration, brittleness, or microbial growth, indicating good physical stability of the formulation. The percentage drug release showed only a slight decrease during storage. Initially, the optimized formulation exhibited 99.4% drug release, which gradually decreased to 96.9%, 96.5%, and 96.2% after 90 days at 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH respectively. The reduction in drug release at elevated temperature and humidity conditions may be attributed to minor changes in the polymer matrix and moisture absorption during storage. However, the decrease in drug release was minimal and remained within acceptable limits, demonstrating that the formulation retained its drug release characteristics even after storage. Among the tested conditions, the formulation stored at 25°C/60% RH showed comparatively better stability, whereas slightly higher reduction was observed at 40°C/75% RH due to accelerated conditions. Overall, the stability study confirms that the optimized Tramadol hydrochloride buccal film formulation possesses good stability and can maintain its physical integrity and drug release performance over the storage period.

CONCLUSION:

The present investigation successfully developed and evaluated Tramadol hydrochloride buccal films using the solvent casting method. The prepared formulations exhibited satisfactory physicochemical characteristics, good flexibility, uniform drug distribution, and sustained drug release properties. Among all formulations, formulation F8 containing HPMC K15M showed the best performance with maximum drug release of 99.4% over 8 hours, excellent folding endurance, acceptable moisture uptake, and good swelling behavior. Drug release kinetics indicated that the formulation followed Higuchi diffusion mechanism, confirming controlled drug release from the polymeric matrix. FTIR studies confirmed the compatibility between drug and excipients, while stability studies demonstrated that the optimized formulation remained stable under various storage conditions without significant changes in physical appearance or drug release profile. Therefore, it can be concluded that the developed Tramadol hydrochloride buccal film formulation is a promising drug delivery system for sustained buccal administration and may improve therapeutic effectiveness, patient compliance, and bioavailability compared to conventional dosage forms.

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