Formulation, Development and Characterization of Ondansetron Hcl Buccal Film by Using Natural Polymer

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***Abstract*—The study aimed to develop oral dissolving films of ondansetron HCl to enhance therapeutic efficacy and improve patient compliance by addressing the limitations of conventional and parenteral formulations. Ondansetron HCl, an antiemetic, is widely used for managing chemotherapy and radiotherapy-induced vomiting, as well as postoperative and drug-induced nausea. Oral dissolving films were fabricated via the solvent casting method using varying proportions of Pectin, Xanthum gum, Sodium alginate and Acacia as polymeric bases. The films underwent evaluation for physicochemical properties, drug release, and disintegration. The optimized formulation, F4, demonstrated superior drug release (71.17% in 7 minutes), uniform thickness, high folding endurance (>300), and a buccal cavity-compatible surface pH. The release profile followed the trend F4 > F2 > F5 > F1 > F6 > F3 > F7 > F8, with F3 also exhibiting the highest drug content and the shortest disintegration time. These findings indicate that films with higher Acacia concentrations out performed rapid release of drug, making them a promising option for rapid and effective delivery of ondansetron HCl.**

***Index Terms*—Ondansetron HCl, Antiemetic, Acacia, Solvent Casting.**

I. INTRODUCTION

Fast-dissolving oral films have gained significant attention as an innovative drug delivery system due to their ease of administration and rapid onset of action. These films are administered via the buccal route, enabling the drug to bypass gastrointestinal degradation and the first-pass effect by being absorbed directly into the systemic circulation. The buccal mucosa is highly permeable due to its thin membrane and rich blood supply, which facilitates quick drug absorption and immediate bioavailability, resulting in faster therapeutic effects. This method is particularly advantageous for patients with dysphagia or difficulty swallowing, as it eliminates the need to swallow a traditional tablet, thereby improving patient compliance. [1]

Incorporating mucoadhesive polymers into the formulation are highly soluble n water, allowing fast dissolving films containing acacia to disintegrate quickly when exposed to saliva. This ensures that the drug is released rapidly and providing a fast onset of action whch improving drug absorption. Ondansetron, a 5-HT_3 receptor antagonist widely used to manage chemotherapy-induced nausea and vomiting, is a prime candidate for this delivery system. The drug exhibits limited oral bioavailability (approximately 60–70%) due to extensive first-pass metabolism and has a relatively short half-life of 3–5 hours. Research indicates that ondansetron hydrochloride is efficiently absorbed through the sublingual or buccal mucosa, making it suitable for delivery via this route. [2]

This study aims to enhance the therapeutic efficacy of ondansetron HCl by developing fast-dissolving buccal films, leveraging the advantages of rapid absorption and bypassing hepatic metabolism for improved bioavailability and patient outcomes. [3]

II. MATERIAL AND METHODS

MATERIALS:

Ondansetron HCl was obtained from Yarrow Chem Laboratory, Mumbai. Polymers and other excipients such as Pectin was obtained from Molychem, Thane; Xanthum gum, Sodium alginate were obtained from Research Lab, Mumbai; Acacia Arabica, PEG 400, Citric acid, Crosspovidone, Fructose were obtained from Loba Chemie, Mumbai.

PREFORMULATION STUDIES:

A. Organoleptic Properties of drug

The sample of Ondansetron HCl was analysed for its nature, color and taste.

B. Melting Point

The melting point was determined by using Melting Point apparatus mehod. Three capillaries were sealed from one end and filled with drug and then inserted in melting point apparatus. The point at which drug starts melting was noted and average of three readin was calculated as melting point.

C. Solubility Determination

The solubility of Ondansetron HCl was checked in different solvents like water, methanol, ethanol, buffer solution pH 6.8 etc. [5]

D. Determination of λ_{max}

A solution of Ondansetron HCl containing 10 µg/ml was prepared in ethanol and absorbance was taken using Shimadzu (UV-1900) Uv spectrophotometer. The solution was scanned in the range of 200-400nm. [6]

Preparation of drug solutions of Ondansetron HCl:

Primary stock solution: 10mg of Ondansetron HCl dissolved in 10 ml of ethanol and sonicated for 5 min.

Secondary stock solution: 1 ml from primary solution diluted to 10 ml of ethanol

Sample Solution

Aliquots were prepared from the secondary stock solution by pipetting 0.5, 1.0, 1.5, 2.0, 2.5 were pipette into 10 ml volumetric flasks and make up the volume with ethanol to get concentration 5, 10, 15, 20, 25 µg/ml respectively. The absorbance of prepared drug solutions was measured at 248nm using UV-spectrophotometer against an appropriate blank solution. The obtained absorbance values were plotted against the concentration of ondansetron HCl and calibration curve was developed. [8]

COMPATIBILITY STUDY OF DRUG WITH EXCIPIENT:

A. Fourier Transform Infra-Red (FTIR) Spectroscopy

IR spectral studies lie more in the qualitative identification of substances either in pure form or in combination with polymers and excipients acts as tool in establishment of chemical interartion. Since, I.R. is related to covalent bonds, the spectra can provide detailed information about structure of molecular compounds. In order to establish this point, comparisons were made between the spectrum of the substances and the pure compound. The above discussion imply that infrared data is helpful to confirm the identity of drug and to detect the interaction of the drug with the carriers.

For the study of interaction of drug with excipients the samples of pure drug (Ondansetron HCl), Physical mixture (Pure drug, Pectin, Acacia, Sodium alginate, Xanthum gum) were analysed on FTIR (BRUKER). [1]

B. DSC Spectra

Foe the compatibility of drug with excipients and in formulation, samples of drug pure drug (Ondansetron HCl), Physical mixture (Pure drug, Pectin, Acacia, Sodium alginate, Xanthum gum) were recorded in a DSC analyser model DSC 60 at a heating rate of 20^0C/ min from 0 to 300^0C in a nitrogen atmosphere. [2]

III. METHODS

Preparation of buccal film

The oral dissolving films containing Ondansetron HCl were prepared by solvent casting method. The required amount of polymer (Pectin, Acacia, Sodium alginate, Xanthum gum) were weighed and dispersed in 25 ml of casting solvent (25ml of water) by continuous stirring. To this solution, Citric acid, Crosspovidone and Fructose was added. This solution was stirred until all he materials gets completely dissolved. Later, PEG 400 was added to the polymer solution while stirring. Drug (Ondansetron HCl) was added to this polymeric solution and then stirred until homogeneous. The solutions were then left at room temperature to remove air bubbles. After the disappearing of air bubbles, the solution was poured into the petridish. The mixture was then kept at oven at 64^0C temperature for 6 hrs. After drying, the film was removed from the petridish careful and cut according to the size of 2cm x 2cm. Dried Films were packed in aluminium foil and stored in a desiccator for further evaluation. [3]

Table 1: Formulation design of buccal film

Sr. No	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
1.	Ondansetron HCl	60.79	60.79	60.79	60.79	60.79	60.79	60.79	60.79
2.	Pectin	100	300	_	_	_	150	150	300
3.	Xanthum gum	50	_	_	_	_	_	_	50
4.	Sodium alginate	100	_	300	_	150	_	150	_
5.	Acacia	100	_	_	300	150	150	_	_
6	PEG 400	400	400	400	400	400	400	400	400
7	Citric acid	45	45	45	45	45	45	45	45
8	Crosspovidone	60	60	60	60	60	60	60	60
9	Fructose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

IV. EVALUATION PARAMETER OF BUCCAL FILM

1. Appearance: Visual inspection of buccal film was assessed by feel or contact. [9]

2. Weight Variation: Weight of buccal film was weighed by calibrated weighing balance. Individual weight 2x2cm^2 of each film were calculated. Average weight was calculated and analyzed weight of film. [11]

3. Thickness: A calibrated digital Vernier calliper is used to determine the thickness of buccal film. The thickness of film was measured at five different points the average of thickness of all film was calculated. [12]

4. Folding Endurance: Folding endurance of the film was determined by repeatedly folding the small film of size (2x2cm^2) at the same place till it breaks. The number of times the film can be folded at the similar place without breaking give the value of folding endurance. The three-reading average and standard deviation of all films was calculated. [13]

5. Percentage moisture loss: Films of dimension 2x2 cm^2 were weighed and accurately placed in the desiccator containing fuse anhydrous calcium chloride at room temperature for 72hr. After that it is removed and weighed then average percentage moisture loss was calculated by below formula. [13]

Percentage Moisture Loss = (Initial weight – film weight)/ Initial weight x 100

6. Surface pH: For determining the surface pH of mucoadhesive buccal film, three buccal films of each formulation were allowed to swell for 15 min at room temperature in the contact of 1 ml distilled water (pH 6.6 ±0.5), and the pH was determined by bringing the electrode in contact of buccal film surface and allowing equilibrate for 1 min. The surface pH was recorded using pH meter. [14]

7. Swelling Index: The initial weight of the film was determined using a digital balance (W0). Then the films are allowed to swell on the surface of petri plate and kept in an incubator maintained at 37 °C. Weight of the swollen film was determined (Wt) at predetermined time intervals for 5 min. The percentage of swelling (% S) was calculated using the following equation. [15]

$$\% S = (W_t - W_o) \times 100 / W_o$$

Were,

W_t is the weight of swollen film after time t,

W_0 is the initial weight of film at t=0.

8. Tensile strength: Buccal film of size 2×2 cm² was placed between the clamp of the Apparatus and clip through which the weighing pan was attached above the ground level in the air. For the measurement of tensile strength of the film weights were added to the pan till the film gets breaks. [17]

9. Mucoadhesive strength: Determined by an analytical balance. Mucoadhesive buccal patch is placed on the glass slide by placing a drop of water on buccal mucosa of goat on the one side of analytical balance another end weighing pan was attached. Weight was slowly added to the pan until mucosa get detached from patch. Weight required to detach the patch from the mucosa is measured as mucoadhesive strength. [6]

Force of bioadhesion (N) =Mucoadhesive strength x 9.81/1000

Bond strength (N/mm^2) =Force of adhesion (N)/Surface area of buccal mucosa (mm^2)

10. Drug Content Uniformity: Film of dimension 2×2 cm^2 was added in 100 ml of phosphate buffer pH 6.8, stirred continuously for 30min. additionally, this solution was filtered, suitably dilution, and analyzed at 248 nm using a UV spectrophotometer. The average and standard deviation of drug content for three patches was taken as final reading. [5]

11. *In-vitro* disintegration time: It is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The time at which film started to break or disintegrate is recorded as the in vitro disintegration time. [1]

12. In-vitro drug release: An in vitro dissolution study was carried out using USP type II apparatus (Basket type apparatus). PBS of pH 6.8 buffer (500 mL) is used as a dissolution medium at 50 rpm speed and 37 ± 0.5^0C temperature. At specific time intervals, 1 ml samples were withdrawn and replaced with the equal quantity of fresh dissolution medium. Buccal films were filtered through 0.45µm Whatman filter paper, and analyzed spectrophotometrically at λ_{max} of 248nm using UV-visible spectroscopy active pharmaceutical ingredient. [9]

Conditions:

Medium: Phosphate buffer pH 6.8

RPM: 50

Temperature: 37 ± 0.5^0C

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

Drug release mechanisms:

The release kinetic was evaluated based on four mathematical models: zero order, first order, Higuchi, and Korsmeyer–Peppas.

In the zero-order release model, the drug release rate is independent of concentration. Dosage forms following this model are ideal systems.

$$Q_t = Q_0 + (K_0 \times t) \text{ ……Equation No. 1}$$

In this case, Q_0 is the initial amount of drug released, Q_t is the cumulative amount of drug released at time t, and K_0 is the zero-order release model constant.

In the first-order release model, the release rate depends directly on the amount of remaining drug in the film. Therefore, the release rate decreases over time due to the reduction of the remaining drug.

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 \times t /2.303\text{……. Equation No. 2}$$

In this case, K_1 is the first-order release model constant.

The Higuchi release model is developed for matrix-based drug delivery systems following diffusion-controlled release.

$$Q_t = KH \times t_{1/2}\text{……. Equation No.3}$$

In this case, KH is the Higuchi release model constant.Korsmeyer

It described the dependence of drug release with different polymeric carriers. To derive the primary release mechanism, only the first 60% of drug-released data were fitted to the Korsmeyer–Peppas equation.

$$\text{Log } (Q_t/Q_\infty) = \log K_p + (n \times \text{Log } t) \text{ ……. Equation No. 4}$$

In this case, Q_∞ is the total amount of drug released, K_P is the Korsmeyer–Peppas release model constant, and n is the release model exponent, which depends on the mass transfer mechanism of the drug.

For the case of buccal film drug delivery systems, n = 0.5 corresponds to a First order mechanism, 0.5<n corresponds to an anomalous transport mechanism, and n = 1 refers to a polymer swelling mechanism. [19]

13. *Ex-vivo* diffusion study: For in vitro release study, goat buccal mucosa membrane is used as a barrier membrane with Phosphate buffer (pH 6.8) as a medium. Drug release from film is evaluated by Franz diffusion cell. Buccal mucosa membrane is mounted between the donor and receptors compartments. The film is placed on the mucosal membrane. The diffusion cell is placed in simulated saliva maintained at 37±5°C. The receptor compartment is filled with 50 ml phosphate buffer (pH 6.8) and hydrodynamics is maintained by stirring with a magnetic bead at 50 rpm. 1 ml sample is withdrawn and replaced with 1 ml fresh medium to maintain the sink condition. The samples are analyzed by U.V. spectrophotometer at specific wavelength. [9]

V. RESULTS AND DISCUSSION

a) Organoleptic properties of Ondansetron HCl

The sample of Ondansetron HCl was analyzed for its organoleptic properties, Solubility and the melting point which was determined by using Melting point Apparatus. The results are shown in Table 2, Table 3 & Table 4 respectively.

Table 2: Description of drug

Description	Observed	Standard
Colour	White to off white colour	White
Odour	Odourless	Odourless
Taste	bitter	Intensely Bitter

b) Melting Point Determination

Table 3: Melting point

Drug Name	Observed	Standard
Ondansetron HCl	185±0.17^{0}C	182^{0}C-195^{0}C

c) Solubility study:

Table 4: Solubility Study

Sr.No	Medium	Qualitative Solubility
1.	Water	Sparingly Soluble
2.	Methanol	Soluble
3.	Ethanol	Soluble
4.	HCl	Freely soluble
5.	Buffer Sol 6.8	Sparingly Soluble

d) Determination of of λ_{max} of Ondansetron HCl

Calibration curve of Ondansetron:

The results of Calibration curve of Ondansetron HCl in ethanol shown below in Table 5. The absorption maxima of Ondansetron HCl were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer using concentration range of 5-25 µg /ml ondansetron hydrochloride in ethanol. Ondansetron HCl presented maximum absorbance at 248nm. shown in Fig No.2.

Table 5: Calibration curve of ondansetron hydrochloride

Sr. No.	Concentration (µg/ml)	Absorbance (AU) (Mean± SD)
1.	5	0.1552 ±0.016
2.	10	0.3445 ±0.012
3.	15	0.5298 ±0.019
4.	20	0.7877 ±0.014
5.	25	0.9758 ±0.007

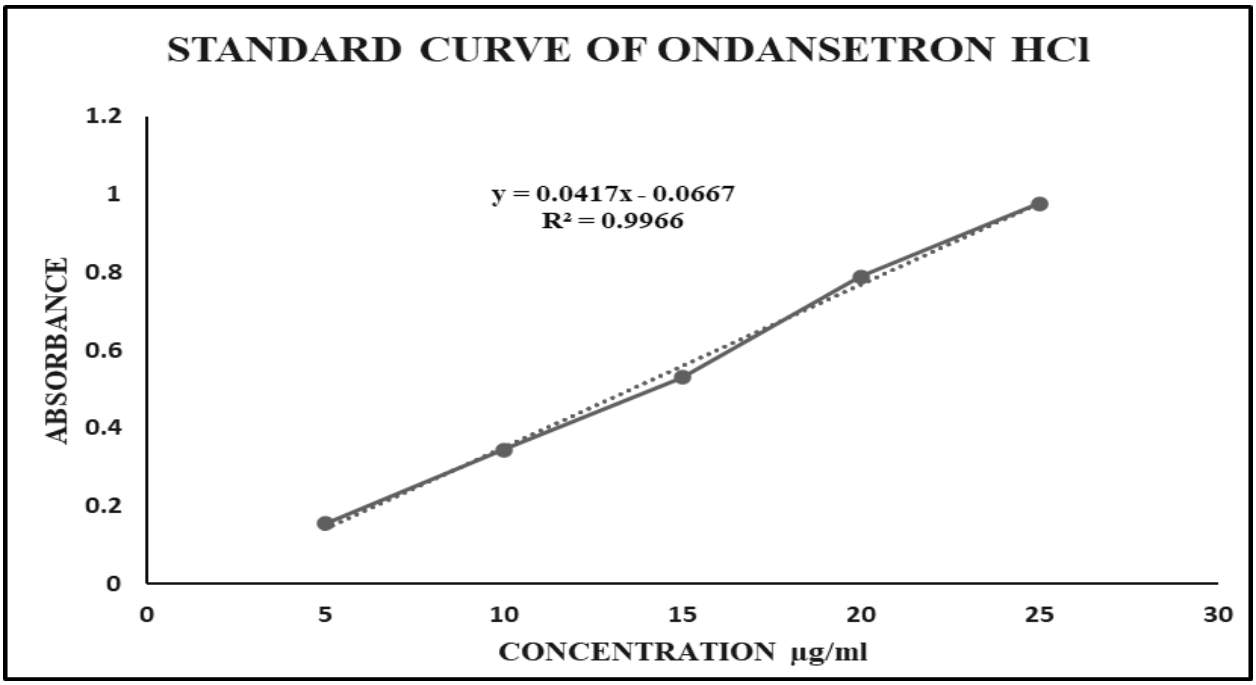

Fig No.1: Calibration curve of Ondansetron HCl

Wavelength range: 200-400nm

Scan speed: Medium

Model: Simadzu UV-1900

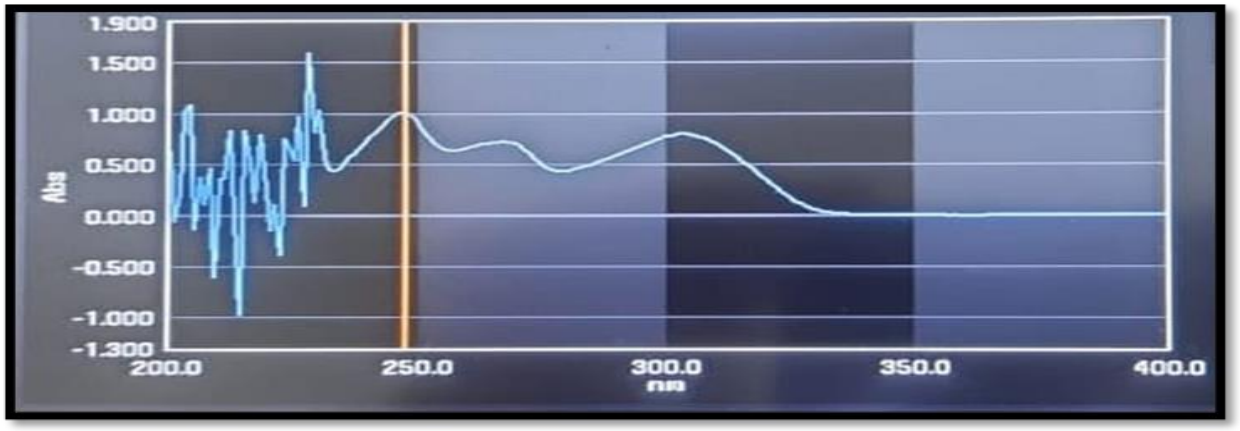

Fig No.2: Observed Ondansetron HCl wavelength Maxima

e) COMPATIBILITY STUDY OF DRUG WITH EXCIPIENT

A. Fourier Transform Infra-Red Spectroscopy (FTIR):

The drug-polymer interactions were examined by Fourier Transformation Infra-Red Spectroscopy (FTIR) studies. FTIR analysis of pure drug Ondansetron HCl is shown in Fig No. 3 and for mixture physical mixture are shown in Fig No.4 Respectively. The FTIR spectrum of pure drug Ondansetron HCl was characterized by peaks at 665.01 cm^{-1} (-CH stretch), 1325.50 cm^{-1} (CN stretch), 1697.63 cm^{-1} (C=O Streching), 3420.45 cm^{-1} (NH stretch), 1280.47 cm^{-1} (OH stretch), 2722.84 cm^{-1} (CH stretch). Physical mixture showed peaks at 665.25 cm^{-1} (-CH stretch), 1327.58 cm^{-1} (CN Streching), 1729.58 cm-1 (C=O Steching), 3412.02 cm^{-1} (NH stretch), 1279.72cm^{-1} (OH stretch) and 2724.21 cm^{-1} (CH stretch).

Careful examination of IR spectrum of pure drug Ondansetron HCl and physical mixture it could be concluded that no physical interaction existing between pure drug Ondansetron HCl and physical mixture with no new peak, indicting an absence of any chemical interaction between them.

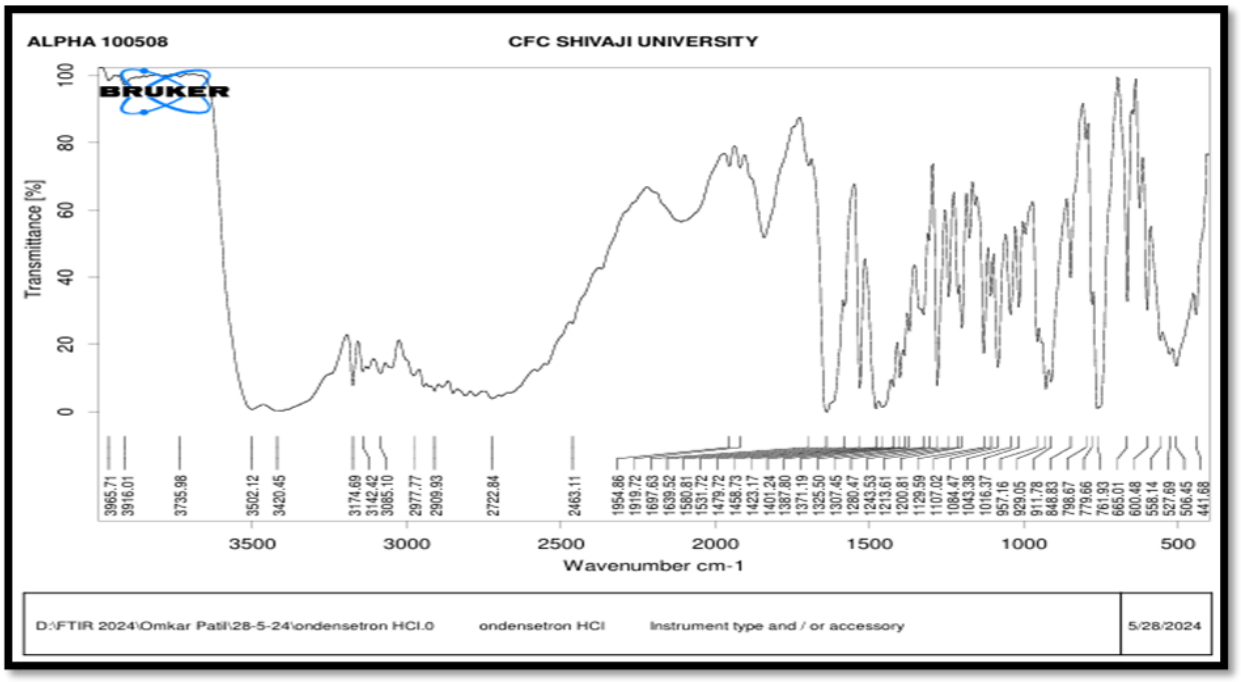

Fig No.3: IR Spectrum of pure drug Ondansetron HCl

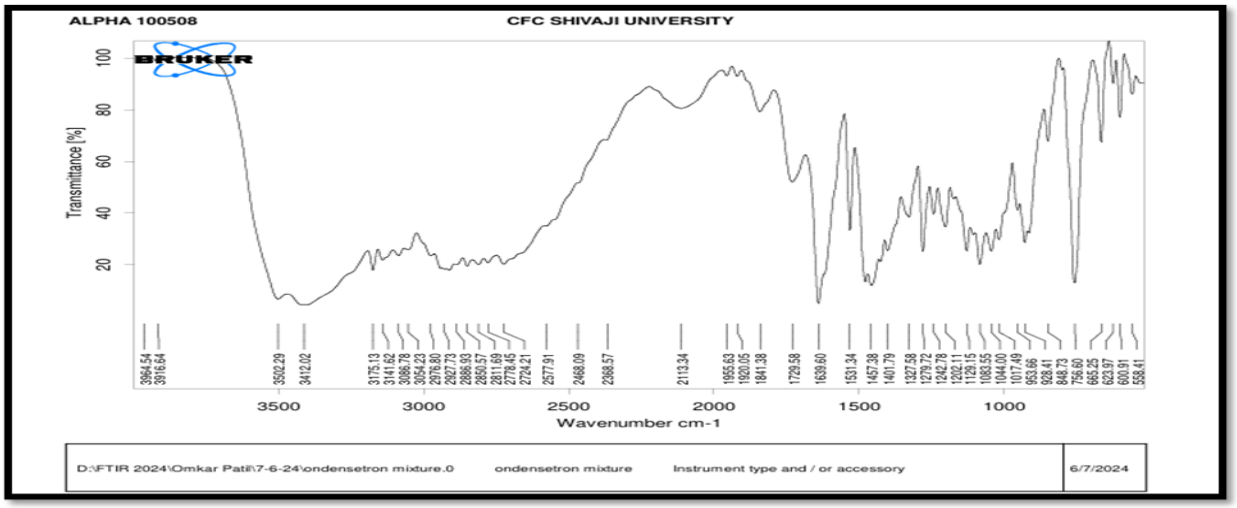

Fig No.4: IR Spectra of Ondansetron HCl + Polymer mixture

B. Differential Scanning Calorimetry (DSC):

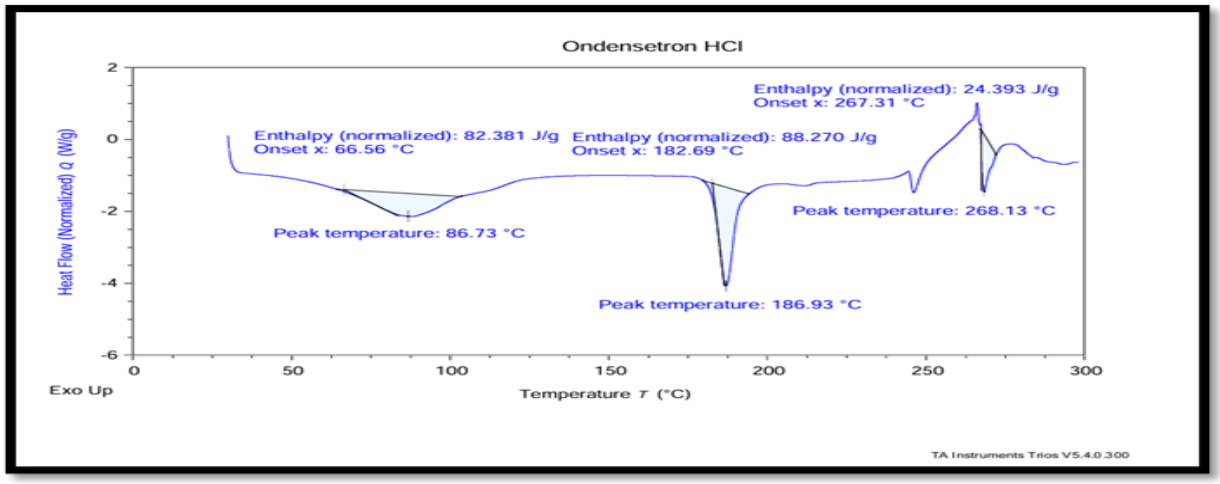

Fig No.5: DSC of pure Ondansetron HCl

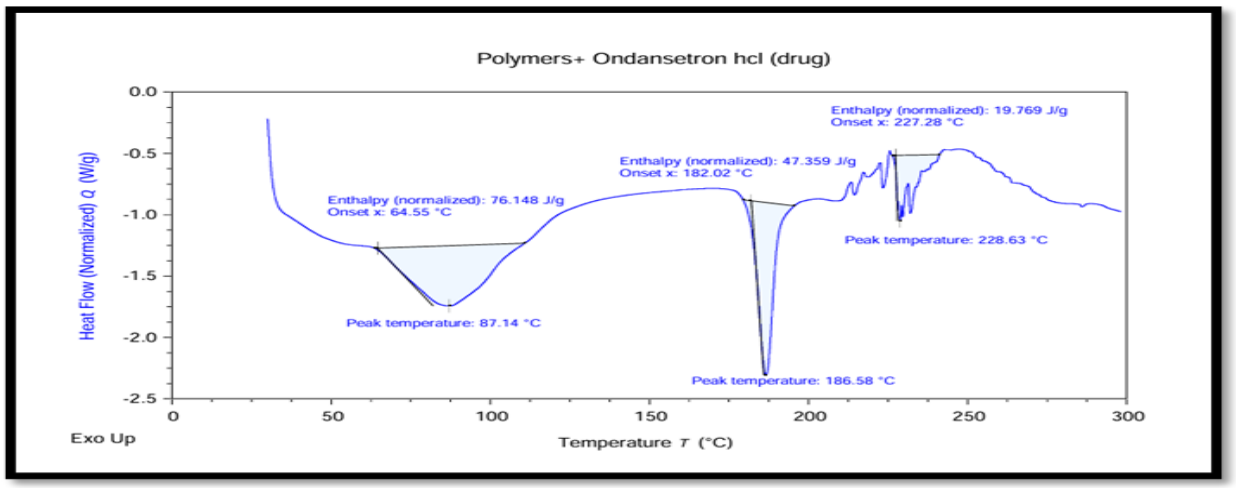

Fig No.6: DSC of Ondansetron HCl + Polymer mixture

The absence of interaction was confirmed with the help of DSC. The confirmation of stability of drug in the prepared formulations was done by DSC thermogram of pure drug and physical mixture and comparing that with of pure drug.

The DSC analysis of the drug was performed. The melting point of Ondansetron HCl was determined, exhibiting a sharp endothermic peak at 186.93^{0}C (Reported value: 182^{0}C-195^{0}C) within the reported range & melting point of drug with mixture was exhibiting a sharp endothermic peak at 186.58^{0}C which confirms the melting point and thereby the purity of drugs.

VI. EVALUATION PARAMETERS OF FORMULATED BUCCAL FILM:

1. Appearnce

The physical appearance and flexibility were noted visually, for all the films from F1 to F8 were white in colour, smooth, and elegant in appearance.

Table 6: Appearance of patch (F1 toF8)

Description	Observed
Colour	White to off-white
Odour	Odourless
Texture	smooth
Appearance	Elegant

2. Weight variation: The weight of buccal film was determined using digital weighing balance and the average weight of all films (F1 to F8) was found to be in the range of 60-78 mg. From the result, it was observed that the weight of films increases with the increased in the polymer concentration ratio. The drug-loaded buccal film was found to be uniform.

3. Thickness of film: Thickness of all mouth dissolving films was measured with digital Vernier caliper. The average thickness of all the films ranges from 0.181±0.06 mm to 0.242±0.19 mm and results were given in Table 7. The optimized film has thickness of 0.224±0.04 mm. A result of thickness measurement showed that as the concentration of polymer increases, thickness of mouth dissolving film also increases. Dimension of the films is 4cm^2. The measured thickness of F1-F8 film was approximately less than 1 mm which implies their usefulness for buccal application with least discomfort to the patients.

4. Folding endurance: Folding endurance gives an indication of brittleness of the film. It was shown that as the concentration of polymer increases, folding endurance of mouth dissolving film increases. The folding endurance value of the prepared films ranged from 89±2 to 108±2 and results were given in Table 7. The optimized film (F4) has folding endurance value of 104±3, which was desirable.

5. Surface pH: The surface-pH was noted by pH meter near the surface of mucoadhesive buccal film and allowed for equilibration and the surface-pH of all films was found to be in the range of 6.2±0.123 to 7.5±0.128 pH, which was close to the neutral pH, which indicated that films may have less potential to irritate the sublingual mucosa, and hence, more acceptable by the patients.

6. Swelling Index: Swelling index of all formulations was evaluated. The swelling index values of the films ranges from 13.65±1.06 to 24.73±1.29. This may be due to water absorption capacity of polymers used. The formulation F1 due to lower hydrophilicity or crosslink density, restricting water absorption. In F4, acacia have higher swelling index because of increased hydrophilic groups or lower crosslinking, allowing it to absorb more water and swell more.

7. Percent moisture loss: The percent moisture loss of all formulations from F1 to F8 was estimated. The average % moisture loss was found in the range of 1.29±0.01% to 2.51±0.01%. The acceptable limit for percent moisture loss ranges from 1% to 10%. The film made with acacia, pectin, sodium alginate and xanthum gum is influenced by their water retention properties. Acacia and xanthum gums are hydrophilic and form a gel like structure, helping to retain moisture and reduce water loss. Pectin and sodium alginate also have strong water absorbing abilities, forming films that maintain hydration. The combined hydrophilic nature of these polymers minimizes moisture loss by creating a hydrated matrix. All formulation shows moisture loss within limits that is evidence for the stability of the film against microbial growth.

8. Tensile strength: Tensile strength of prepared buccal films varies from 4.09±0.32 to 9.72±0.05 N/mm² revealing that the films had good mechanical strength and flexibility. Tensile strength of buccal films increases with the increase in the polymeric concentration. This range ensures that the film is strong enough to handle manipulation without tearing but flexible enough to conform to buccal mucosa

comfortably. Formulation F4 showed the good tensile strength i.e 8.49±0.64 N/mm^2.

9. Mucoadhesive Strength: The mucoadhesive values ranged from 5.3±0.17 to 8.7±0.02. Formulation F4 has showed moderate mucoadhesive properties, its natural gum composition suports film flexibility and adhesion to a lesser extent than alginate or pectin. Xanthum gum contributed to the viscosity of the formulation, providing moderate adhesion by forming stable gel network. This ensuring that the film stays in place while maintaining comfort during use. Pectin and sodium alginate form strong hydrogen bond with mucin, leading to higher mucoadhesive strength, also sodium alginate forms a gel-like structure upon hydration, enhancing adhesion. Thus, F1 shows the highest mucoadhesive strength value, as the attached buccal films can make the removal difficult from buccal cavity, which may cause discomfort to patient.

10. Drug content: The percent of drug content for all the formulations F1 to F8 was obtained in the range of 76.78±0.22 to 81.57±0.10 given in the Table 8. The results indicate that the drug is distributed uniformly in all film formulations and will deliver the dose of drug accurately. The drug content across all formulation falls within the acceptable range, indicating uniform drug distribution in the film. F4 (80.405%) and F5 (81.16%) shows highest drug content, suggesting optimal incorporation of active pharmaceutical ingredients in this formulation. F1 (76.785%) and F8 (77.83%) have the lowest drug content, which may indicate polymer drug interaction or mixing efficiency during the (76.785%) and F8 (77.83%) have the lowest drug which may indicate polymer drug interaction or mixing efficiency during the preparation process.

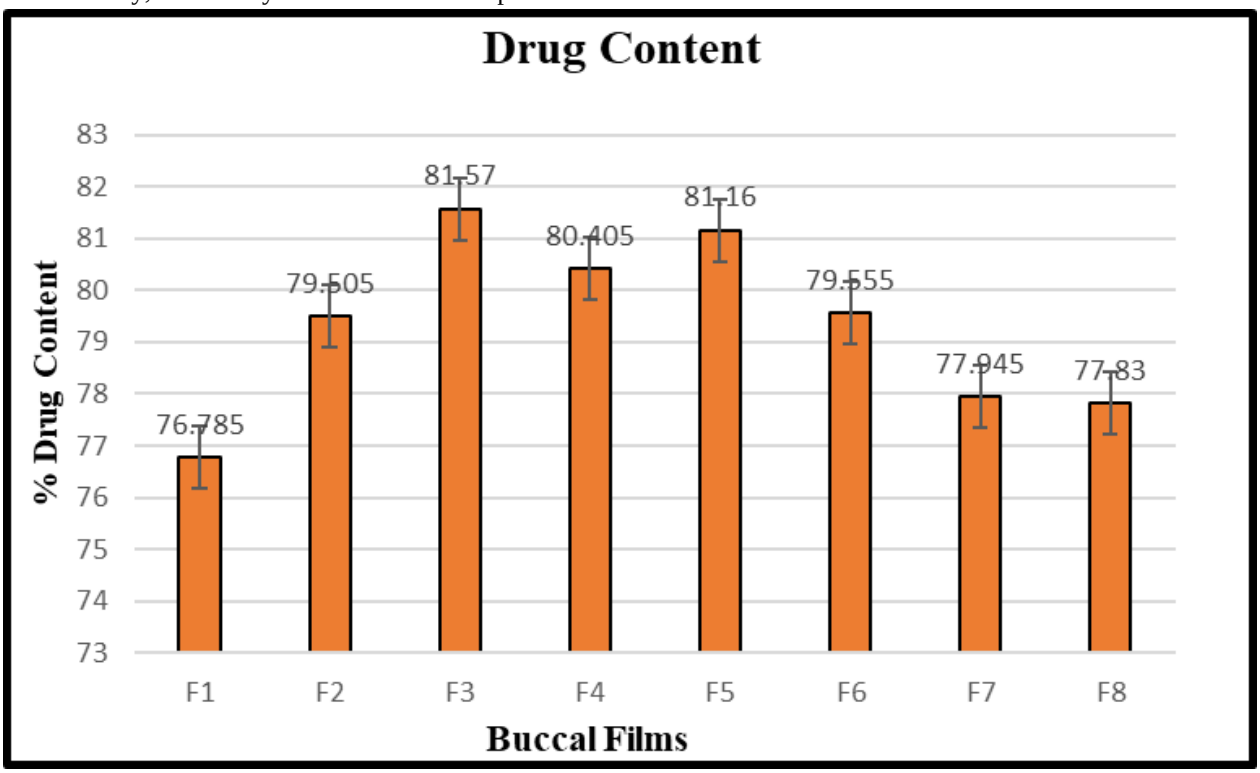

Fig No.7: Graphical representation showing drug content

11. Disintegration time: The disintegrating time of all the formulations was ranges from 43±0.5 to 86±0.7 Sec and results were given in Table 8. The disintegration time of optimized formulation (F4) was found to be 43±0.5sec, which was very less and desirable for faster onset of action.

(7 & 8).

Evaluation of Weight variation, Thickness, Folding Endurance, Percent moisture loss, Surface pH, Tensile strength, Disintegration time, and Drug content uniformity is shown in following Tables

Table 7: Evaluation parameters-1

F. Code	Weight Variation (mg)	Thickness (mm)	Folding Endurance (count)	Surface pH	Swelling Index
F1	74.40±0.63	0.243±0.19	106±1	7.2±0.121	13.65±1.06
F2	60.30±0.54	0.181±0.06	89±2	6.2±0.123	17.39±0.33
F3	68.26±0.89	0.192±0.01	93±3	6.7±0.130	20.93±0.97
F4	69.94±0.23	0.224±0.04	104±3	6.9±0.145	24.73±1.29
F5	67.71±0.62	0.197±0.05	102±2	6.4±0.116	22.51±0.53
F6	67.58±0.83	0.234±0.07	105±1	7.2±0.125	18.56±0.04
F7	69.09±0.66	0.229±0.02	99±2	6.3±0.152	17.95±0.86
F8	78.32±0.57	0.239±0.07	108±2	7.5±0.128	21.07±0.31

Table 8: Evaluation parameters-2

F. code	Percent moisture loss (%)	Tensile Strength N/mm²	Mucoadhesive Strength	Drug Content (%)	Disintegration Time (Sec)
F1	1.38±0.01	7.36±0.91	8.7±0.02	76.785±0.22	48±0.4
F2	2.42±0.13	5.02±0.16	7.4±0.12	79.505±0.14	45±0.2
F3	2.51±0.01	4.09±0.32	7.9±0.86	81.57±0.10	49±0.8
F4	1.35±0.07	8.49±0.64	5.4±0.35	80.405±0.12	43±0.5
F5	1.29±0.01	5.07±0.73	6.8±0.25	81.16±0.28	58±0.4
F6	1.37±0.08	3.82±0.29	6.9±0.12	79.555±0.51	69±0.2
F7	1.49±0.01	7.06±0.61	5.3±0.17	77.945±0.69	72±0.2
F8	1.13±0.05	9.72±0.05	6.8±0.70	77.83±0.35	86±0.7

12. *In-Vitro* Drug Release:

Drug release from F1 to F8 was found to be ranges of 51.558±0.2% to 71.175±0.02%.

The cumulative % drug release for the MDF formulations F1 to F8 are tabulated in Table 17 and shown in Fig No.8.

Films was carried out using a dissolution apparatus USP Type II Buffer (pH 6.8) was used as the dissolution medium.

The formulation F4 was selected as an optimized formulation based on these in vitro release studies which showed high percentage of drug release within a short period 71.17±0.02% in 7 min.

F1 formulation drug release start at 11.34% at 1min. and reaches 63.57% at 7 mins. Although F1 shows a fast release, it has a lower overall percentage release at 7 mins, compared to F4, making it less efficient for rapid drug delivery.

F2 formulation release start at 12.73% at 1 min and reaches 64.54% at 7 mins. F2 shows slightly higher release than F1 but is still less than F4 by the 7 mins.

F3 starts at 9.12% at 1 min and reaches 57.93% at 7 mins. F3 exhibits slower release compared to other batches, particularly F4, making it less suitable for rapid release requirements.

F4 formulation starts at 14.98% at 1 min and reaches 71.17% at 7 mins. F4 demonstrates the highest overall drug release (71.17%) at the 7 mins, making it the best candidate for rapid drug release. The initial burst release at 1 min is also higher than other batches, supporting its rapid release capability.

F5 starts at 9.17% at 1 min and reaches 64.32% at 7 mins, while the release at 7 mins is fairly high, but the initial release is slower.

F6 starts at 8.77% at 1 min and reaches 58.92% at 7 mins. F6 is one of the slowest in terms of initial drug release, which makes it less suitable for rapid release formulation.

F7 formulation starts at 8.86% at 1 min and reaches 59.91% at 7 mins. Similar to F6, the overall release at 7 mins is much lower compared to F4, and the initial burst is also slower.

F8 starts at 8.81% at 1 min and reaches 51.55% at 7 mins. It has slowest release among all batches, making it the least suitable for rapid drug release purposes.

Therefore, F4 was selected as the optimized batch because it achieved the highest percentage drug release at 7 mins (71.17%), which is need for the rapid drug release from buccal film. Other formulations either exhibited slower release profiles or had lower overall drug release, making them less effective for this specific goal.

The selected optimized formulation F4 was used further for the evaluation of *ex-vivo* permeation studies through goat buccal mucosa.

Table 9: % CDR of formulation (F1-F80

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
1 min	11.34±3.12	12.73±1.21	9.12±2.95	14.98±2.69	9.17±1.49	8.776±2.31	8.86±2.53	8.81±3.07
2 min	15.77±3.47	16.83±3.11	10.19±3.44	19.30±3.34	13.30±2.11	10.359±1.37	13.09±4.38	13.59±1.20
3 min	26.05±4.91	28.95±4.52	16.76±4.11	26.88±3.91	21.76±3.47	15.623±1.48	19.76±2.51	20.59±3.62
4 min	32.49±1.19	32.58±2.37	32.87±4.57	42.64±3.91	31.52±3.21	29.352±3.40	20.91±1.19	31.47±5.18
5 min	42.84±3.14	42.60±1.64	41.77±2.75	51.48±2.64	39.23±3.52	37.577±2.85	31.18±3.14	34.12±2.94
6 min	54.68±4.38	55.25±1.79	50.92±1.60	64.50±2.93	52.67±2.56	54.688±4.02	40.21±1.27	41.73±3.15
7min	63.57±2.53	64.54±3.60	57.9±3.46	71.17±2.36	64.32±3.51	58.225±3.18	55.91±1.60	51.55±2.20

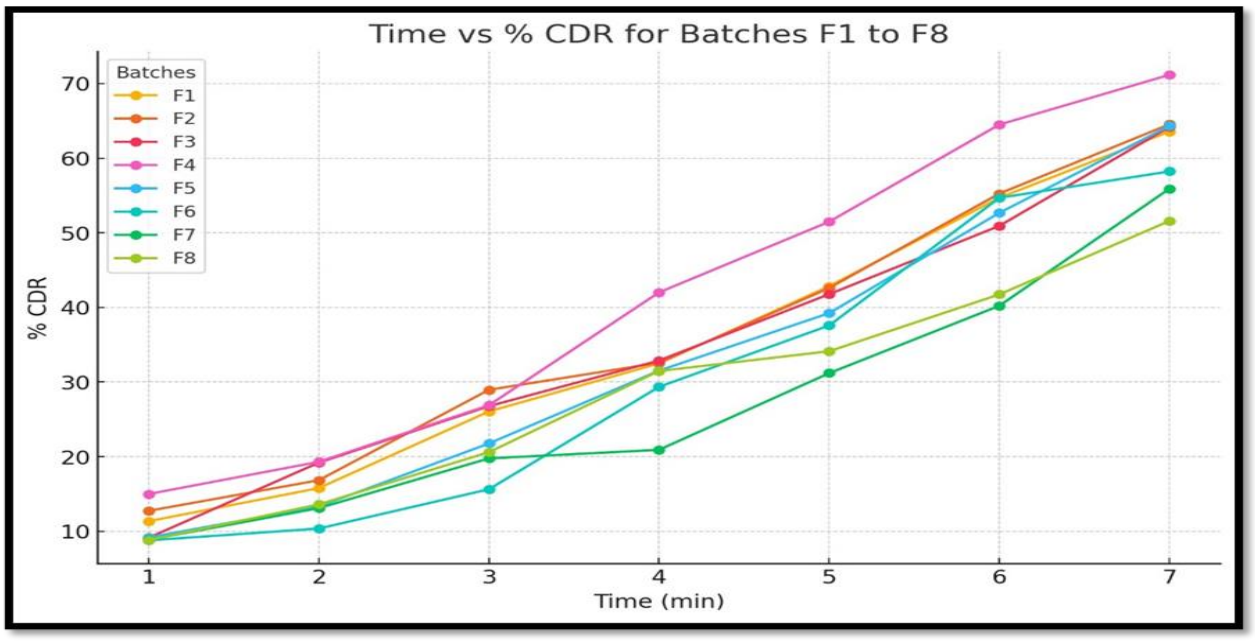

Fig No.8: *In-vitro* drug release study

13. *Ex-vivo* permeation studies: The formulation F4 was selected as optimum for the ex-vivo permeation studies due to adequate in-vitro drug release, and mucoadhesive studies. The result of drug permeation from the mucoadhesive buccal film containing drug release of Ondansetron HCl through the goat buccal mucosa reveals that drug was released from formulation and permeated through the goat buccal membrane and hence can feasibly be permeated through the human buccal membrane. The result indicated that the drug permeation was fast of 68.59±1.41% of Ondansetron HCl permeate through the buccal membrane from the optimized formulation in 7mins. The cumulative percentage amount of Ondansetron HCl that had penetrated through the buccal epithelium from the buccal film was shown in the Fig No.9 & Table 10.

Table 10: % *Ex-vivo* drug release

Time (min)	1 min	2 min	3 min	4 min	5 min	6 min	7 min
Optimized batch of (F4)	11.39±1.18	17.26±2.69	24.81±1.22	39.74±3.27	48.36±2.41	59.03±1.41	68.59±1.41

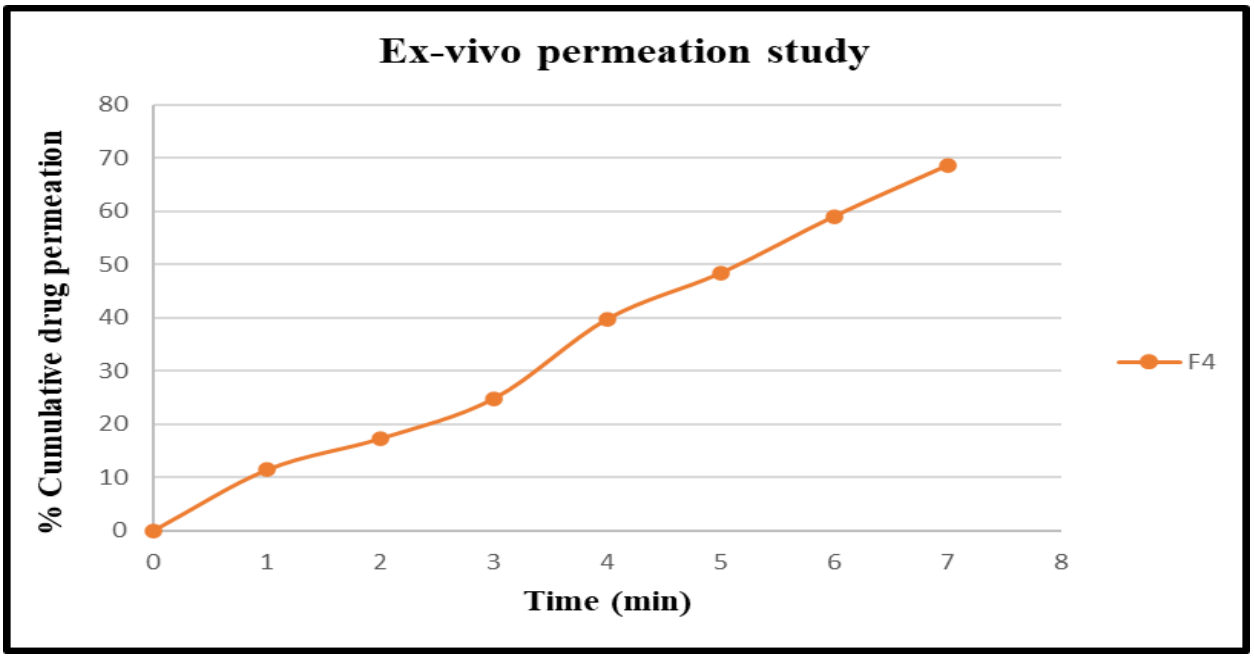

Fig No.9*: Ex-vivo* permeation of optimized buccal film

Kinetics of Drug Release:

Table 11, provides the value of the coefficient of regression for various models with optimized formulations. While this model fits the data very well, zero-order kinetics are more suitable for controlled or sustained-release formulations, not fast-dissolving systems. A fast-dissolving film should release most of its drug content quickly, which is not characteristic of zero-order kinetics. This model is a better fit for fast-dissolving systems.

The fast initial release is desirable, as the drug should dissolve rapidly in the buccal cavity, followed by complete absorption. However, the lower R^2 compared to zero-order suggests it may not be the dominant model. The Higuchi model typically applies to matrix-based systems, where drug release is governed by diffusion. While the fit is weaker (R^2= 0.8995), this model might still partially describe drug release, especially if the film has a porous structure or a polymeric matrix influencing diffusion.

Given the high R^2, this model suggests a mixed release mechanism, potentially involving both diffusion and erosion. This fits well with fast-dissolving buccal films, where both dissolution and rapid diffusion into the buccal mucosa occur.

The Korsmeyer-Peppas model (R^2 = 0.9517) and the First-order model (R^2 = 0.9591) provide the most relevant descriptions for a fast-dissolving buccal film. These models suggest that drug release is rapid and potentially driven by both diffusion and dissolution.

While the Zero-order model provides the best fit (R^2 = 0.9892), it is more suited to controlled-release formulations, which is not ideal for a fast-dissolving buccal film.

The First-order model is more appropriate in describing the rapid initial release, which is key for fast-dissolving systems.

Thus, the fast-dissolving buccal film formulation likely follows a combination of first-order kinetics and the Korsmeyer-Peppas model, ensuring a rapid onset of action with efficient drug release.

Table 11: Kinetic Parameters of ondansetron buccal film

Kinetic model	R^2 Value	Equation	Diffusion mechanism
Zero order	0.9892	y=10.21x+0.56	N/A
First order	0.9591	Y= -0.18x+4.69	Fickian diffusion
Higuchi Model	0.8995	Y=27.42x+9.90	Ficks Law
Korsmeyer-peppas model	0.9517	Y=0.86x+1.10	Fickian, anomalous transport

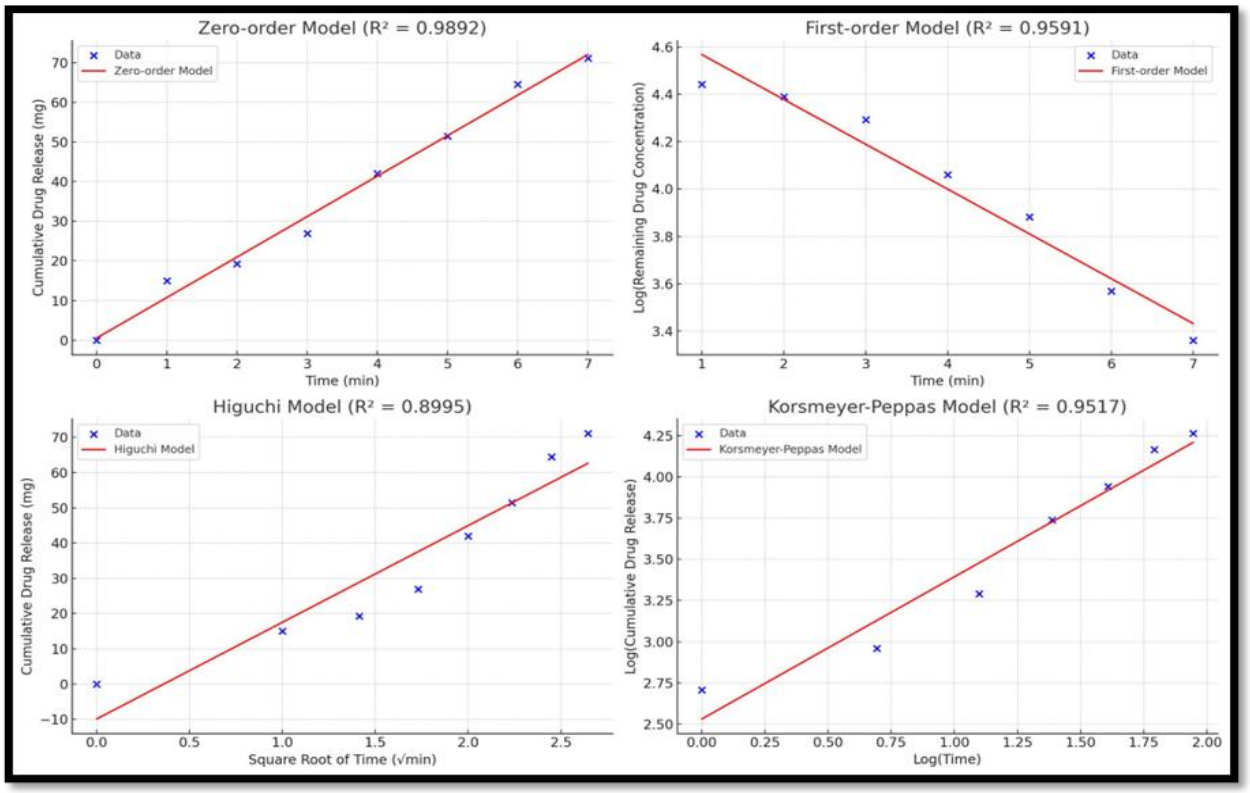

Fig No.42: Kinetic models of zero order, first order, higuchi model, kormeyer-peppas model

VII. CONCLUSION

The buccal films of Ondansetron HCl is rational in all the aspects of mouth dissolving dosage form. DSC studies show compatibility drug with the polymers. Optimized formulation passed entire evaluation tests. This formulation also stable at accelerated conditions. The mouth melting buccal films was found superior in palatability and patient convenience. Hence it is more

suitable for paediatrics and elderly patients due to is convenience.

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