International Journal of Multidisciplinary Research and Growth Evaluation.

Development and Evaluation of Mucoadhesive Buccal Patches for Controlled Release of Ondansetron

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Article Info

ISSN (online): 2582-7138
Volume: 05
Issue: 06
November-December 2024
Received: 07-09-2024
Accepted: 09-10-2024
Page No: 302-309

Abstract
Mucoadhesive buccal patches of ondansetron were prepared for the prevention and treatment of chemotherapy-induced emesis. Films of varying polymeric composition were prepared in order to facilitate initial as well as prolonged drug release that could take care of acute as well as delayed emesis. Mucoadhesive buccal patches were prepared using polymers such as ethyl cellulose and eudragit. The effect of concentration of these polymers on physical properties and drug release were studied. All the films were prepared by solvent casting method. In another part of the study, the effect of drug concentration on physical and mucoadhesive properties of patch were assessed, keeping the polymer concentration fixed. Buccal patch containing eudragit showed good mucoadhesion. The study concluded that the developed buccal films have the potential to release ondansetron required for chemotherapy induced acute and delayed emesis.

Keywords: Mucoadhesive buccal patch, ondansetron, synthetic polymers, solvent casting technique, Diffusion mechanism

Introduction
Oral route of drug delivery remains most popular route in drug delivery. Most of the dosage forms are swallowed from oral cavity. However, once swallowed enzymatic degradation and significant first pass effect may limit the bioavailability.[1] Buccal drug delivery necessitates the use of mucoadhesive polymers as a means of prolonging the residence time of the dosage form on the absorbing membrane as well as localizing drugs in a particular region. In this study a large variety of polymers in different combinations were used. The combinations of polymers were preferred because it could offer acceptable adhesion and biocompatibility properties. The selection of polymer and optimization of the formulation both from adhesion and controlled drug release point of view remain an important goal and challenge for development of a buccal dosage form.[2] Mucoadhesive dosage forms are specially designed to adhere to the mucosal surface, thus intensifying retention of the drug at the site of application, while providing a controlled rate of drug release for better therapeutic outcome [3].
An ideal patch should be flexible, elastic, and soft yet strong enough to withstand breakages due to stress from activities in the mouth. Moreover, it must also possess good mucoadhesive strength so that it is retained in the mouth for the desired duration. To prevent discomfort, swelling of the patch should not be too extensive. Recently developed mucoadhesive buccal delivery systems such as adhesive tablet, films, patches, disks, strips, ointment, gel, and creams. Tablets, films and patches appear to be the most preferred formulations [4]. Ondansetron belongs to the class of 5-HT3 antagonists which are approved by United States Food and Drug Administration (US FDA) to control chemotherapy-induced nausea and vomiting. The plasma half-life of ondansetron on oral administration has been found to be ~4 h with peak plasma level occurring within 1.5 h following oral delivery [5].

Materials
Ondansetron was obtained from Hetero labs, HYD. Eudragit and Ethyl cellulose were procured from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

Methodology

Compatibility studies of drug and polymers [6]

In the formulation of Ondansetron patch formation, API and Excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Ondansetron and the selected polymers. The pure drug and drug with excipients were scanned separately.

Formulation design [7]

Preparation of buccal patches

A series of buccal films composed of different proportions and combinations of Ethyl cellulose and Eudragit containing ondansetron (16 mg) were prepared by solvent casting technique. All patches were plasticized with similar amount of propylene glycol (100mg). Backing membrane was casted by pouring 4%w/v aqueous solution of polyvinyl alcohol (PVA) on aluminum foil in Petri dish at 42°C and left for 10 h. Weighed quantities of ethyl cellulose were suspended in 10ml of Methanol with constant stirring and small amount of water (2 ml) was added to it. This solution was mixed with Eudragit RL 100 and homogenized. Plasticizer was added to the blend and mixed. In case of drug loaded films, weighed amount of ondansetron was dissolved in propylene glycol before addition into the polymer blend. The above mix was stirred gently until a clear solution was obtained. The solution was sonicated to remove any entrapped air. The clear solution was then casted on the PVA-aluminium foil backing membrane and dried in an oven at 37°C for 16 h. The prepared films were then removed from the Petri dish and stored in vacuum desiccators.

Table 1: Formulation Design of Ondansetron Buccal patches

F. Code	Drug (mg)	Ethyl Cellulose (mg)	Eudragit RL100 (mg)	Propylene glycol (ml)	PVA
F1	16	100	-	100	4%
F2	16	200	-	100	4%
F3	16	300		100	4%
F4	16	400		100	4%
F5	16	-	100	100	4%
F6	16	-	200	100	4%
F7	16	-	300	100	4%
F8	16	-	400	100	4%

Evaluation of mucoadhesive buccal patch formulation

Physico- chemical evaluation

Physical appearance [8]

All the prepared mucoadhesive buccal patches were observed for color, clarity, flexibility, and smoothness.

Folding endurance [9]

Folding endurance folding endurance value was calculated by folding the film of suitable size at the same place and counting the number of time the film could be folded without breaking. Swelling study: Percentage of hydration and matrix erosion Film swelling properties and erosion characteristics were determined by calculating the percentage of hydration and matrix erosion of the films. Films of definite size (1 × 1 cm2) were cut and weighed (W1). Film was placed on a weighed stainless steel wire mesh. The wire mesh and the film were immersed in phosphate buffer saline (pH 6.8) for predetermined time periods (5, 10, 20, 40, 60, 90, 120 min). At these time intervals the wire mesh was withdrawn from the buffer, the films were wiped off using filter paper and weighed (W2). Percentage hydration of the films was determined using the following relation:

Thickness of the buccal patch [10]

The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

Weight uniformity [11]

The study of uniformity of drug content was done by spectrophotometric method. For this measurement a circular disc of patches of 3 cm diameter without BOPP membrane was used. The patches were initially extracted for ondansetron by dissolving in a 100 mL volumetric flask containing mixture of ethanol and Phosphate buffer (pH 6.8) (20:80) for 12 h by intermittent sonication. The solution of buccal patch was filtered by 0.45µm cellulose membrane filter and estimated for the content of drug by UV spectrophotometric measurement at 265 nm (Shimadzu 1800, Japan). The average of result was obtained from three consecutive determinations.

Disintegration time [12]

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeia disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s.

Drug content [13]

To ensure the uniformity of distribution of ondansetron in the film, a content uniformity test was done. Films (1 × 1 cm2 equivalent to 2 mg of ondansetron) were cut at three different locations and dissolved in 10 ml of phosphate buffer saline (pH 6.8) by continuous shaking on a water bath at room temperature for 8 h. The solution was filtered through Whatman filter paper and the samples were diluted suitably and analyzed using UV spectrophotometer at a λmax 265 nm against a blank (UV-1800, Double Beam spectrophotometer, SHIMADZU, Japan). A calibration curve was constructed and the drug content was estimated from the curve (2.5-20 µg/ml). The method validation was done for linearity, precision, and accuracy.

Measurement of swelling index [14]

This measurement is used to determine the extent of water uptake or the degree of hydration by the hydrophilic polymers used in the fabrication of the films. Most of the mucoadhesive polymers undergo some degree of swelling after hydration, which is necessary to initiate intimate contact of the film with the mucosal surface. The studies for determination of the Swelling Index of the films were conducted in the simulated salivary fluid of pH 6.8. The film sample (surface area: 1.75 cm^2) was weighed and placed in a preweighed stainless steel wire sieve of approximately 800 μm mesh. The mesh containing the film sample was then submerged in 15 mL of the simulated salivary medium contained in a porcelain dish. At definite time intervals, the stainless steel mesh was removed from the dish and the excess moisture was removed

by carefully wiping it off with absorbent tissue, after which it was reweighed. Increase in weight of the film was determined at each time interval until a constant weight was observed. The degree of swelling was calculated using the formula:

$$S.I = (w_t - w_0) / w_0$$

where
S.I is the Swelling Index,
w_t is the weight of film at time 't' and
w_0 is the weight of the film at time 0.

Moisture absorption studies [15]

The buccal patches were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of aluminum chloride, which maintains 76% and 86% relative humidity (RH). After 3 days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula:

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

Moisture loss studies [16]

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The moisture content (%) was determined by calculating moisture loss (%) using the formula:

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

***In-vitro* Drug release studies [17]**

The commercially available dialysis membrane (obtained from Sigma Chemicals) was employed for the study, and the *in vitro* drug release study was carried out using a Franz diffusion cell. The effective diffusion area was 1.8 cm^2. The receptor compartment (40 ml) was filled with phosphate buffer saline (PBS), pH 6.8. The patches were applied under occlusion on the dialysis membrane fitted between the donor and receptor compartments of the diffusion cell. The drug release was performed at $37 \pm 0.5°C$, at a stirring speed of 50 rpm using a magnetic stirrer. Five milliliters of the sample from receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer saline, pH 6.8. The amount of Ondansetron released into the receptor medium was quantified by using UV–visible spectrophotometer at 265 nm against a blank.

Drug release kinetics [18]

In order to predict and correlate the release behavior of Ondansetron from different patches, it is necessary to fit into a suitable mathematical model. The *in vitro* Ondansetron release data from buccal patches were evaluated kinetically using various mathematical models like zero-order, first-order, Higuchi, and Korsmeyer–Peppas model equations.

Zero-Order Kinetics

$$F = K_o t,$$

where F represents the fraction of drug released in time t, and K_o is the zero-order release constant.

First-Order Kinetics

$$\ln (1 - F) = -K_1 t,$$

where F represents the fraction of drug released in time t, and K_1 is the first-order release constant.

Higuchi Model

$$F = K_H t^{1/2},$$

where F represents the fraction of drug released in time t, and K_H is the Higuchi dissolution constant.

Koresmeyer–Peppas Model

$$F = K_p t^n,$$

where F represents the fraction of drug released in time t, K_p is the Koresmeyer–Peppas release rate constant, and n is the diffusion exponent.
The results of curve fitting into these above-mentioned mathematical models indicates the drug release behavior from these formulated buccal patches of Ondansetron. When the release rate of Ondansetron and their respective correlation coefficients were compared, it was found to follow first-order release kinetics ($R^2 = 0.9866$ to 0.9984).

Stability studies [19]

Optimized medicated films were subjected to short term stability testing. The buccal patches were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 month as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week.

Results and Discussion

FT-IR Spectrum of Ondansetron

FT-IR Spectra of Ondansetron and F8 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between drug and polymer. It also confirmed that the stability of drug during microencapsulation process.

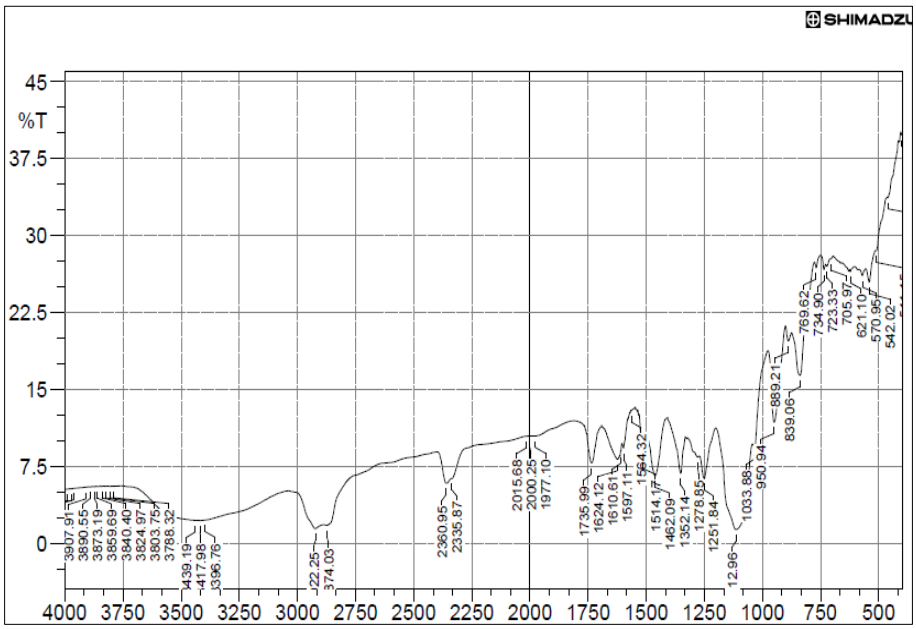

Fig 1: FT-IR Sample for Ondansetron

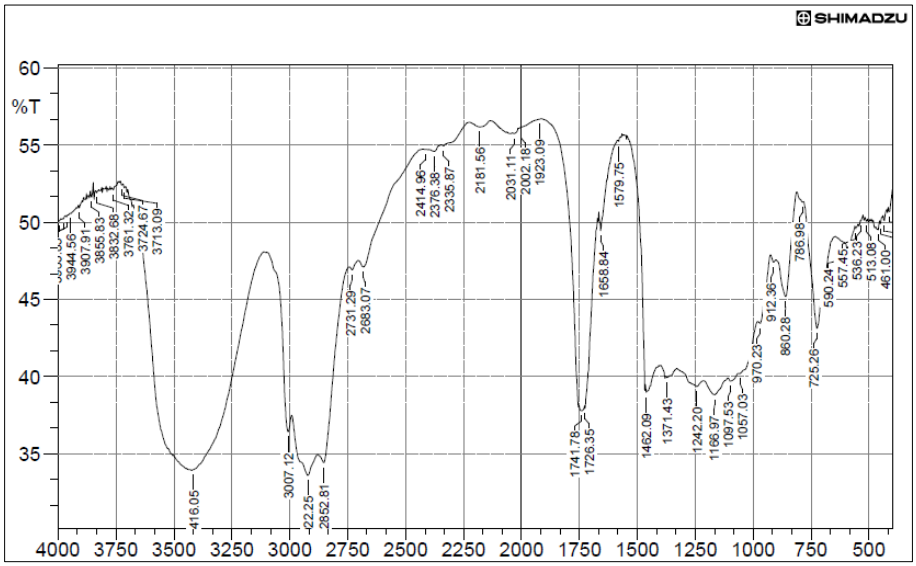

Fig 2: FT-IR Sample for physical mixture of drug and excipients

Evaluation of Buccal formulation

Physical appearance

The prepared buccal patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance

The folding endurance numbers of all the Ondansetron buccal patches are 175 – 185. The folding endurance number gives the mechanical property of the buccal patches, high folding endurance number indicate that has high mechanical property. The folding endurance number was increased with increasing the polymer content. These results indicated that the buccal patches would not break and maintain their integrity with general skin folding when applied.

Thickness of the patch

Thickness was changed from batch to batch in individual strips of medicated patch carry uniform thickness, which indicates that total medicated patch carry uniform thickness.

Weight uniformity

The weights are in the range of 152-165. The F8 formulation buccal patches showed maximum weight.

Drug content

The drug content analysis of the prepared formulations have shown that the process employed to prepare the buccal patches was capable of giving uniform drug content with minimum batch variability.

Swelling index

The swelling and hydration studies showed that the percent hydration varied from 45 to 64 between films F8 to F1, respectively.

Table 2: Physicochemical evaluation of Ondansetron buccal patches

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)	% Moisture loss	% Moisture absorption	% Swelling index
F1	160	0.84	181	77.85	8.3	9.0	45
F2	159	0.80	178	80.12	7.1	8.9	53
F3	163	0.82	182	80.22	7.5	8.8	58
F4	155	0.81	184	81.10	8.1	9.1	63
F5	163	0.89	175	80.21	8.7	8.5	60
F6	152	0.82	185	83.15	7.8	8.6	56
F7	165	0.87	178	81.20	8.3	8.8	54
F8	164	0.90	183	85.54	8.3	8.5	64

In vitro release study

Phosphate buffer pH 6.8 was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.999. The drug release profiles of Ondansetron buccal patches containing different ratios of synthetic polymer. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content.

In-vitro Dissolution Study

Table 3: *In vitro* drug release profiles of Ondansetron buccal patch (F1-F8)

Time (hr.)	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	13.68	15.93	14.50	12.31	13.26	12.35	13.90	14.63
2	26.95	28.50	27.41	26.32	28.90	27.40	27.81	25.90
3	32.94	33.96	35.46	34.25	33.41	32.14	34.82	32.90
4	42.89	45.90	46.81	45.90	44.18	43.16	45.19	44.96
5	56.98	57.94	58.90	57.33	58.90	57.80	50.49	51.28
6	72.95	73.62	75.91	70.16	72.43	73.25	75.82	74.52
7	80.38	82.15	83.46	85.46	83.21	82.16	84.28	80.34
8	91.27	93.63	94.53	93.40	94.50	95.92	93.25	96.98

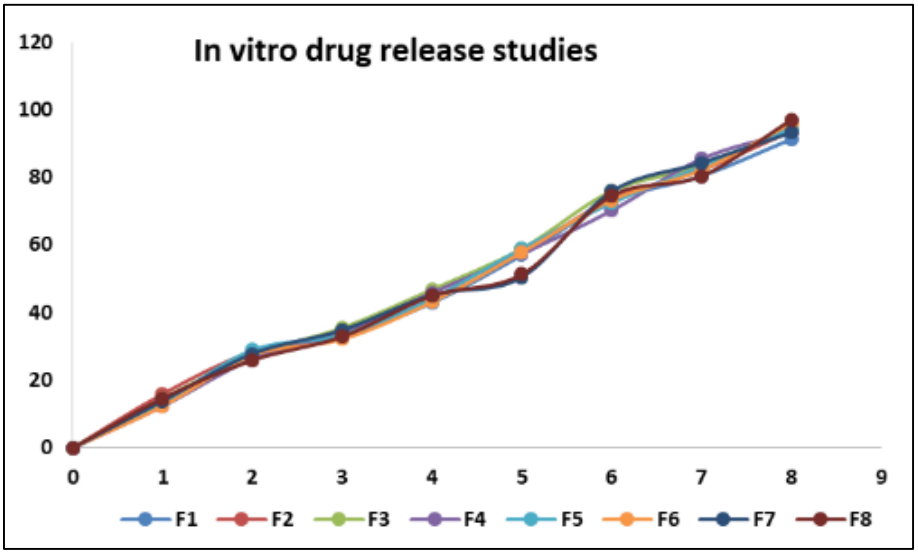

Fig 3: *In vitro* drug release studies

Kinetic modelling of drug release

All the 8 formulation of prepared buccal patches of ondansetron were subjected to *in vitro* release studies these studies were carried out using diffusion apparatus.

The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 period of time.

The results obtaining *in vitro* release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Pappas Exponential Equation)

Zero order kinetics

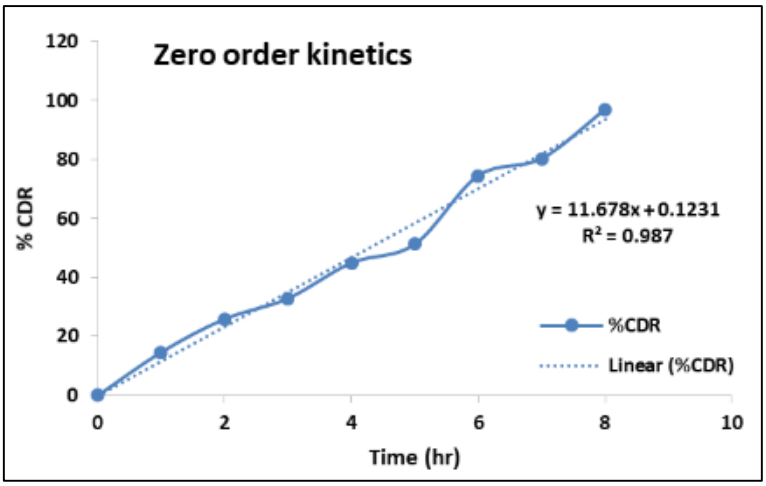

Fig 4: Zero order kinetics of optimized formulation

First order kinetics

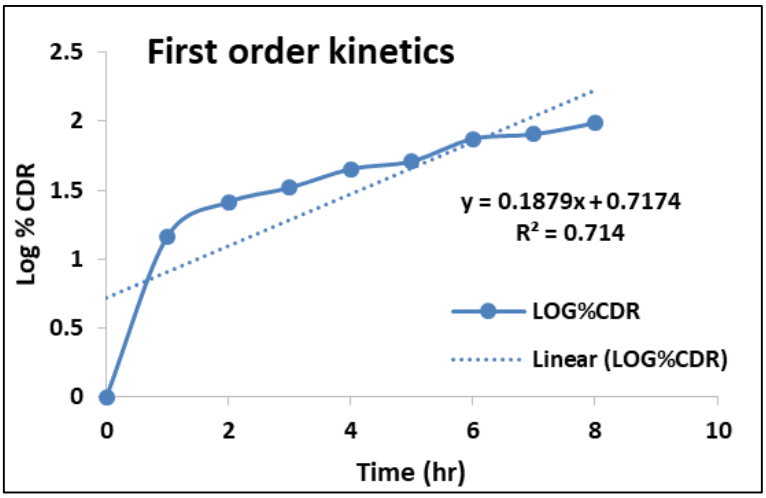

Fig 5: First order kinetics of optimized formulation

Higuchi model

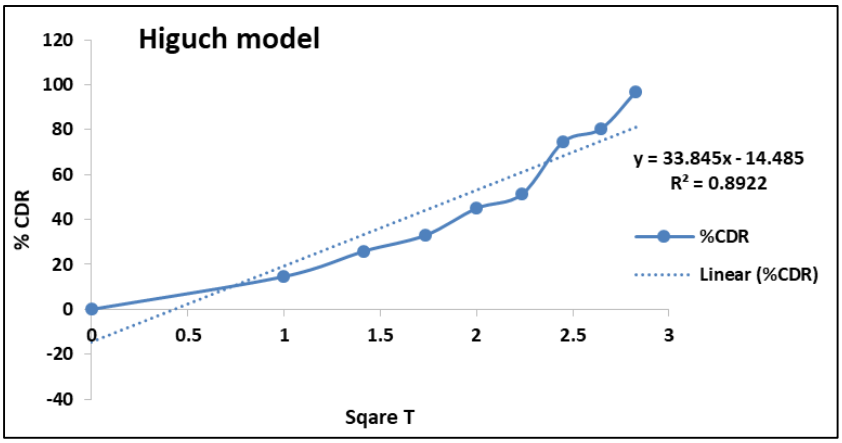

Fig 6: Higuchi model of optimized formulation

Korsmeyer peppas

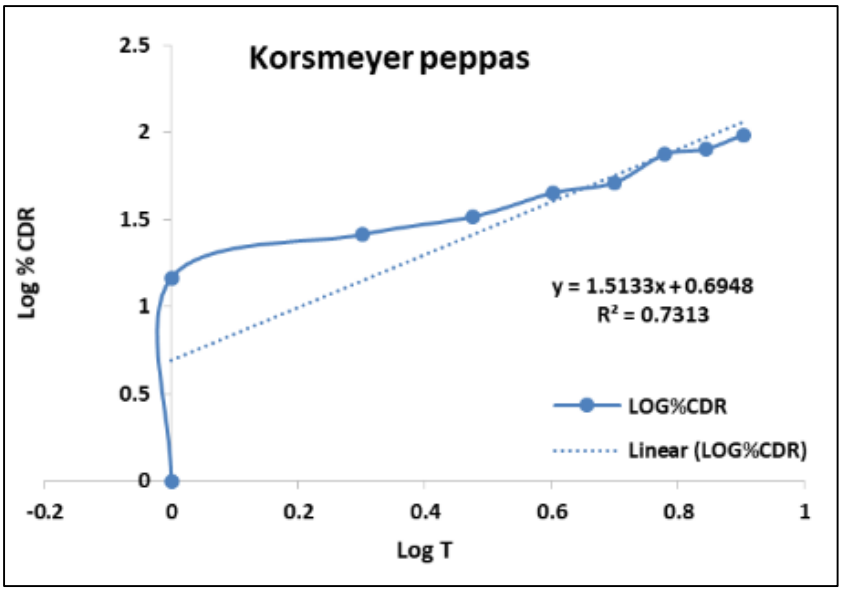

Fig 7: Korsmeyer Peppas

The kinetic values obtained for formulation F8 were shown. The values of *in vitro* release were attempted to fit into various mathematical models.

Regression values are higher with Zero order release kinetics. Therefore all the Ondansetron buccal patches follows Zero order release kinetics.

Table 4: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Time in days	Drug content (%)	Folding endurance	Physical appearance	% Cumulative drug release
0	85.54	183	No change in color	96.98
90	84.23	182	Slight yellowish color	95.60

Phosphate buffer pH 6.8 was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.996. The drug release profiles of Ondansetron buccal patches containing polymer Eudragit RL100 It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content.

Conclusion

Oral Mucoadhesive films of ondansetron prepared using ethyl cellulose and Eudragit polymers were found to be nonirritant with good mucoadhesion. These films could be effectively used to provide faster onset of action, increased bioavailability, and a prolonged drug release for ondansetron. The sustained release that films provide can provide support for delayed emesis. Further, drug release rate from the films can be regulated by increasing either the content of hydrophilic or hydrophobic polymer within the film matrix.

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