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DEVLOMENT OF MUCOADHESIVE BUCCAL FILM OF ZOLMITRIPTAN FOR RAPID MIGRAINE

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Abstract:

The present study focuses on the development and evaluation of a Zolmitriptan buccal film to enhance bioavailability, ensure sustained therapeutic effect, and improve patient compliance. Buccal films were prepared using mucoadhesive polymers via the solvent casting method, incorporating suitable plasticizers to achieve flexibility and uniformity. Formulations were evaluated for physical characteristics, including thickness, weight uniformity, and drug content, all of which met pharmacopeial standards. In vitro drug release studies demonstrated sustained release over 8 hours, with the optimized formulation (F4) achieving approximately 97.85% cumulative release. Stability studies under various temperature and humidity conditions (25°C/60% RH, 30°C/75% RH, 40°C/75% RH) revealed no significant changes in physical properties or drug release over 90 days, highlighting the formulation's robustness. Overall, the developed Zolmitriptan buccal film demonstrates a safe, stable, and patient-friendly platform for sustained drug delivery, offering potential advantages over conventional oral dosage forms in pain management and opioid therapy.

Keywords: *Zolmitriptan, FTIR Studies, Solvent evaporation method, Polymers, In vitro drug release studies*

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INTRODUCTION:

The oral cavity has two common regions for drug delivery such as sublingual mucosa (area beneath the tongue) and buccal mucosa (inner lining of cheeks). Selecting one over the other is mainly based on anatomical and permeability properties of the various oral mucosal sites, desired residence time, and desired effects of the drug. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs and is convenient, accessible and generally well accepted. On the other hand, the buccal region of oral cavity is an attractive target for administration of drug of choice.Other than the common advantages of novel drug delivery systems, buccal mucosa has several specific advantages like, faster and richer blood flow (2.4 mL / min / cm2) than other parts of oral region. The thickness of the buccal mucosa is 500 - 800 ɜm and is rough textured. Moreover, the permeability of the buccal mucosa is 4 - 400 times greater than that of the skin. The mucus network of buccal mucosa carries a negative charge, which may play role in mucoadhesion. Buccal drug delivery offers direct access to the systemic circulation through the external jugular vein, which bypass the drugs from the hepatic first-pass metabolism, leading to higher bioavailability.

Buccal mucosa, like skin, has the primary function of protecting fundamental structures from foreign agents. The oral mucosa is anatomically is divided into 1. Epithelium 2. Basement membrane and connective tissue Epithelium. An undulating cellar film that isolates the stratified squamous epithelium of the buccal mucosa from the basic connective tissue. Keratinocytes in this delineated squamous epithelium change in size, shape and content as they relocate from the basal to the shallow areas, where the cells are shed. As a defensive layer for the tissues under, the epithelium is ordered into two kinds: (a) non-keratinized epithelium found in the mucosal covering of the delicate sense of taste, the floor of the mouth, ventral surface of the tongue, alveolar mucosa, vestibule, lips and cheeks. (b) Keratinized epithelium is found in the hard sense of taste and non-adaptable districts of the oral cavity. while moving towards the surface, epithelial cells that begin from basal cells develop, change shape, and fill in size. Basement membrane and connective tissue. The basement film is a ceaseless layer of extracellular materials that isolates the epithelium's basal layer from the connective tissues. While connective tissue and basement membrane are supposed to have even less impact on the dissemination of most pharmacologically significant compounds, they may limit the development of specific macromolecules and complexes.

MECHANISM OF MUCOADHESION

There are many chemical bonds responsible for the mucoadhesion. Ionic (where two oppositely charged ions attract each other via electrostatic interactions to form a strong bond) and covalent (where electrons are shared, in pairs, between the bonded atoms in order to fill the orbital in both) bonds are the stronger bonds which help the formulation to adhere to the mucosa. The weaker bonds involved in mucoadhesion are hydrogen bonds, Van-derWaals bonds and other hydrophobic bonds. The mechanism by which a mucoadhesive bond is formed will depend on the nature of the mucous membrane and mucoadhesive material, the type of formulation, the attachment process and the subsequent environment of the bond. It is understood that a single mechanism for mucoadhesion cannot be proposed for all the different occasions when adhesion occurs. But, an understanding of these mechanisms in each instance will assist the development of new, enhanced drug delivery systems.

MATERIALS:

Zolmitriptan was procured from Synpharma Research Labs, Hyd, HPMC, Propylene glycol, Aspartame and DMSO were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY:

Drug- excipient compatibility study

FTIR Spectral Studies FTIR spectra of pure drug, polymers and their physical mixtures (stored at 40 ± 2 ºC / 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 Zolmitriptan buccal Films

F.no	Ingredients (mg)					
	Zolmitriptan (mg)	**HPMC k15M (mg)**	**Aspartame(mg)**	**PEG - 400**(ml)	**DMSO** (ml)	**Water**
F1	25	25	2	1	0.1	Q.S
F2	25	50	2	1	0.1	Q.S
F3	25	75	2	1	0.1	Q.S
F4	25	100	2	1	0.1	Q.S

Preparation of buccal films by solvent casting method

Preparation of Polymer Solution

Accurately weighed quantity of polymers was taken and dissolved in a small quantity of distilled water. The solution was stirred continuously using a magnetic stirrer until a clear and homogeneous polymer solution was obtained.

Drug Solution Preparation

Accurately weighed Zolmitriptan was dissolved in a small quantity of water to ensure complete dissolution of the drug.

Addition of Plasticizer

PEG-400 was added to the polymer solution and mixed thoroughly. PEG-400 acts as a plasticizer to improve flexibility and prevent brittleness of the film**.**

Addition of Sweetening Agent

Aspartame was added to the polymer mixture and stirred well to mask the bitter taste of the drug**.**

Mixing of Drug and Polymer Solution

The prepared drug solution was slowly added to the polymer solution with continuous stirring to obtain a uniform and bubble-free film forming solution**.**

Casting of Film

The final solution was poured carefully into a clean glass Petri dish or casting plate and spread uniformly to form a thin layer.

Drying

The films were allowed to dry at room temperature or in a hot air oven at about 40°C for 24 hours to allow complete evaporation of the solvent.

Cutting and Storage

The dried films were carefully removed from the Petri dish and cut into uniform pieces (2 × 2 cm) containing the required dose of drug. The prepared films were stored in a desiccator until further evaluation**.**

Evaluation of mucoadhesive buccal film formulation:

Physico- chemical evaluation:

Physical appearance:

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

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 (1,2,3,4,5,6,7 and 8hrs.). 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 film:

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:
The study of uniformity of drug content was done by spectrophotometric method. For this measurement a circular disc of films of 3 cm diameter without BOPP membrane was used. The films were initially extracted for Zolmitriptan 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 film was filtered by 0.45µm cellulose membrane filter and estimated for the content of drug by UV spectrophotometric measurement at 223 nm (Shimadzu 1800, Japan). The average of result was obtained from three consecutive determinations.

Drug content:
To ensure the uniformity of distribution of Buprenorphine in the film, a content uniformity test was done. Films (1 × 1 cm2 equivalent to 2 mg of Buprenorphine) 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 282 nm against a blank (UV-1800, Double Beam spectrophotometer,Lab India).

Measurement of swelling index :
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:
The buccal films 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:
The buccal films were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the films 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:
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 (10 ml) was filled with phosphate buffer saline (PBS), pH 6.8. The films 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 ± 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 Zolmitriptan released into the receptor medium was quantified by using UV–visible spectrophotometer at 223 nm against a blank.

Stability studies:
Optimized medicated films were subjected to short term stability testing. The buccal films 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 month.

RESULTS AND DISCUSSION:

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

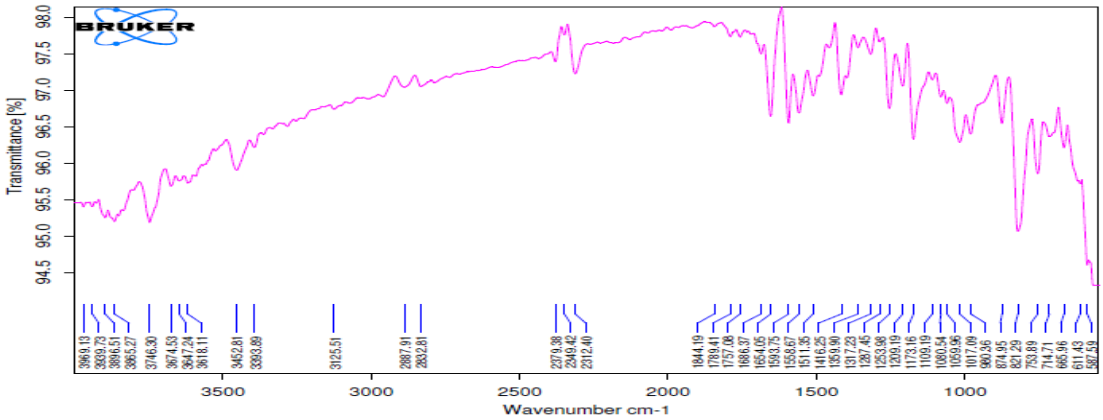


Fig-1: FT-IR Sample for Zolmitriptan

Table-2: Characteristic Peaks and frequency of Zolmitriptan

S. No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	N–H stretching	3500-3000	3452.81
2	C=O stretching	3000-2500	2887.91
3	C=C stretching	2000-1500	1844.19
4	C–N stretching	1500-1000	1253.98

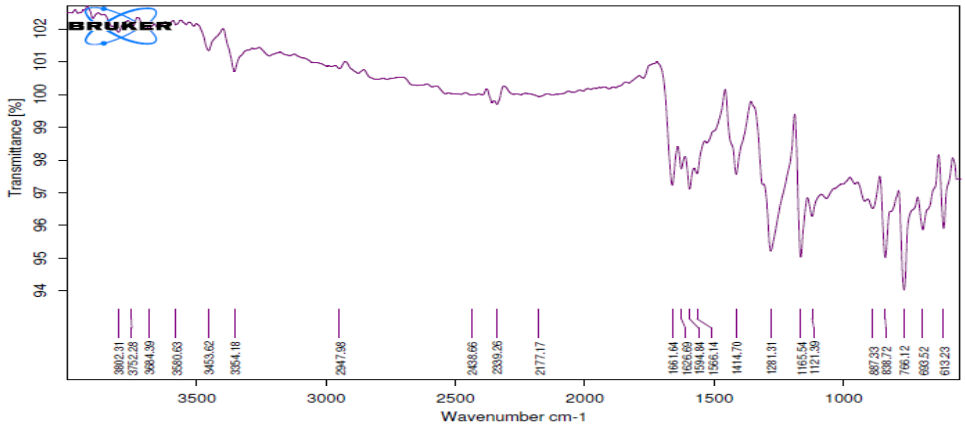


Fig-2: FT-IR Sample for physical mixture of drug and excipients

Table-3: Characteristic Peaks and frequency of physical mixture of drug and excipients

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	N–H stretching	3500-3000	3453.62
2	C=O stretching	3000-2500	2947.98
3	C=C stretching	2000-1500	1661.64
4	C–N stretching	1500-1000	1281.31

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.

Thickness (mm)
Range observed: 0.21 – 0.32 mm
Thickness increased from F1 → F4 due to increased HPMC concentration
Indicates uniform film casting
All films are within acceptable range (0.2–0.4 mm)

Weight Variation (mg)
Range: 52 – 65 mg
Increase due to higher polymer content
The variations remained within reasonable range, confirming uniform film casting and drug loading.

Drug Content Uniformity (%)
Range: 96.2% – 99.1%
All formulations comply with pharmacopeial limits (95–105%)
Shows uniform drug distribution
F4 showed highest uniformity

Folding Endurance
Range: 210 – 310 folds
Indicates good mechanical strength and flexibility
Increase due to higher polymer concentration + PEG-400 plasticizer
F4 shows best flexibility → suitable for handling

% Moisture Loss
Range: 2.9% – 3.8%
Low moisture loss indicates good stability
Decreases with increase in polymer (better water retention)

% Moisture Absorption
Range: 5.6% – 7.5%
Increased with polymer concentration
Indicates hydrophilic nature of HPMC
Important for mucoadhesion

Swelling Index (%)
Range : 66% – 84%
Higher swelling in F4 due to higher HPMC
Swelling is essential for:
Mucoadhesion
Drug diffusion
Excess swelling may lead to erosion, but F4 is optimal

Table -4: Physicochemical evaluation data of Zolmitriptan Buccal Films

F. code	F1	F2	F3	F4
Thickness (mm)	0.21	0.24	0.28	0.32
Weight variation (mg)	52	56	60	65
Drug content Uniformity	96.2	97.5	98.3	99.1
Folding endurance	210	245	280	310
% Moisture loss	3.8	3.5	3.2	2.9
%Moisture absorption	5.6	6.2	6.8	7.5
Swelling index (%)	56	65	72	84

Drug release studies

Table-5: In vitro release data of film F5 to F4

Time (hrs.)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	24.58	25.69	25.94	28.98
2	35.69	35.60	36.82	38.42
3	42.20	40.22	44.58	45.98
4	55.36	53.16	55.25	56.47
5	63.49	63.98	68.19	69.25
6	75.82	72.54	75.36	76.82
7	85.63	83.26	85.15	86.15
8	92.52	93.26	96.39	97.85

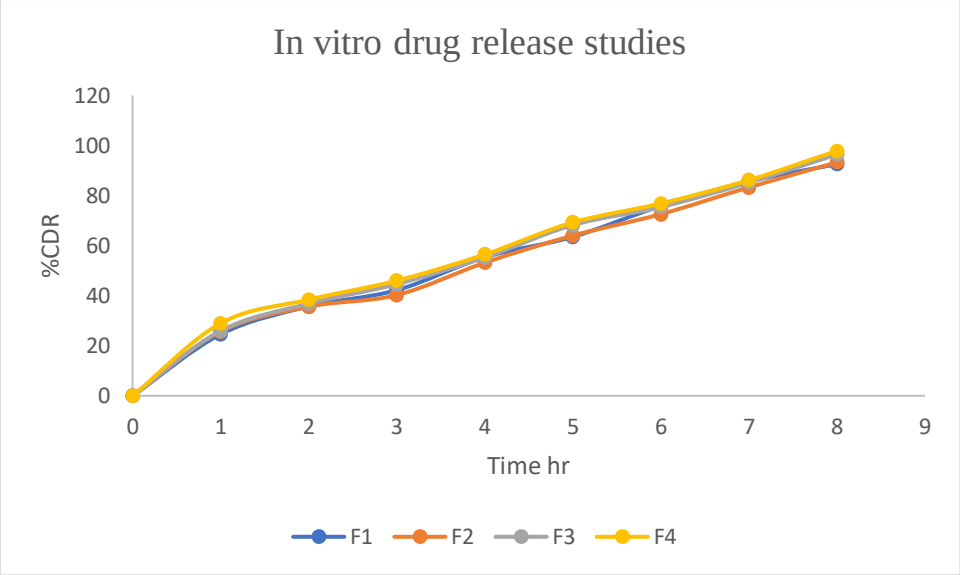


Fig-3: In vitro drug release of (F1- F4) formulation

All formulations achieved controlled release with >90% drug release within 8 hrs, suitable for sustained drug delivery.
Among them, F4 provided the most rapid and complete release (97.85%)

Stability studies:

Optimized formulations F4 was selected for accelerated stability studies as per ICH guidelines. The films were observed for color, appearance and flexibility for a period of three months. % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

Table-6: Stability studies of optimized formulations

S.NO	Time in days	Physical changes	Mean % drug release		
			Zolmitiptan		
			25^0C/60%	30^0C/75%	40^0C/75%
1	01	No Change	97.85	97.85	97.85
2	30	No Change	97.28	97.36	97.67
3.	60	No Change	96.21	96.01	96.50
4.	90	No Change	95.62	95.02	95.52

The formulation maintains physical integrity and >95% drug release under all tested conditions for 90 days. This indicates good chemical and physical stability, making it suitable for commercial development and patient use.

SUMMARY AND CONCLUSION:

The present study successfully developed and evaluated mucoadhesive buccal films of Zolmitriptan with the objective of achieving controlled drug release, improving bioavailability, and enhancing patient compliance. The buccal films were prepared using suitable polymers to regulate drug release, while plasticizers and other excipients were incorporated to provide adequate flexibility, uniformity, and mucoadhesive properties. All formulations exhibited smooth surface characteristics, satisfactory flexibility, uniform thickness, acceptable weight variation, and drug content within pharmacopeial limits, ensuring dose uniformity and formulation quality. The moisture absorption properties were found to be suitable for buccal application, indicating good compatibility with the buccal mucosa and minimal risk of irritation. In vitro drug release studies demonstrated sustained release of Zolmitriptan over a period of 8 hours, with formulation F4 showing the highest cumulative drug release of approximately 97.85%, making it the optimized formulation. Stability

studies conducted for 90 days under ICH storage conditions (25 ± 2°C/60 ± 5% RH, 30 ± 2°C/75 ± 5% RH, and 40 ± 2°C/75 ± 5% RH) revealed no significant changes in the physical appearance or drug release profile, with drug release remaining above 95%, confirming the excellent stability of the optimized formulation. Overall, the developed mucoadhesive buccal films of Zolmitriptan demonstrated controlled and predictable drug delivery, satisfactory physicochemical characteristics, excellent stability, and the potential to improve therapeutic efficacy and patient compliance compared with conventional oral dosage forms.

CONCLUSION:

The study successfully developed a controlled-release Zolmitriptan buccal film with the following key outcomes:Sustained Drug Release: Achieved nearly complete drug release (~98%) over 8 hours.Physical and Chemical Stability: Films remained stable with no changes in appearance or drug release under various storage conditions.Patient Compliance: Thin, flexible, and mucoadhesive films offer easy administration, especially for patients with swallowing difficulties.The optimized Zolmitriptan buccal film is a promising alternative to conventional oral formulations, capable of providing controlled drug delivery, improved bioavailability, and enhanced patient adherence. This formulation can potentially reduce dosing frequency and improve therapeutic efficacy in pain management and opioid dependence therapy.

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