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Formulation and Characterization of Sublingual Films of Almotriptan Malate

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ABSTRACT

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The present study focused on the development of a sublingual film of Almotriptan malate using hydrophilic polymers to achieve rapid drug release and enhance patient compliance. Sublingual films were prepared by the solvent casting method using Sodium Alginate as the primary film-forming polymer along and Plantago ovata as natural superdisintegrant with suitable excipients. The prepared films were evaluated for physicochemical properties including thickness, weight variation, folding endurance, disintegration time, drug content and in vitro drug release study. The optimized formulation (F9), containing 300 mg of Sodium Alginate and 9 mg of Plantago ovata, demonstrated rapid in vitro disintegration time 13 ± 1.15 seconds and achieved 99.46% cumulative drug release within 15 minutes. Stability study of optimized batch was conducted for one month indicated that the optimized formulation remained stable, with no significant changes in its physical characteristics, drug content and drug release profile. Overall, the developed sublingual film of Almotriptan malate represents a promising and patient-friendly dosage form for effective and rapid management of migraine.

INTRODUCTION:

Headache disorders, characterized by recurrent headache, are among the most common disorders of the nervous system. Headache itself is a painful and disabling feature of a small number of primary headache disorders, namely migraine, tension-type headache, and cluster headache. Amongst these, the migraine headache is ubiquitous, prevailing, disabling and essentially treatable, but still under-estimated and under-treated. Migraine is a common chronic headache disorder characterized by recurrent attacks lasting 4–72 hours, of a pulsating quality, moderate or severe intensity aggravated by routine physical activity and associated with nausea, vomiting, photophobia or phonophobia.

It has been termed the seventh disabler due to its considerable impact on the quality of life (QOL) of patient. It is the most frequent cause of headache in children and adolescents.[1]

The study of migraine in the pediatric population is critical because of its burden on children and their families and the diagnostic and therapeutic difficulties determined by varying phenotype and possible differential diagnosis.

Most common trigger factors were emotional stress (79%), sleep disturbance (64%) and dietary factors (44%). Sleep and stress were significant trigger factors in patients with migraine with aura, whereas

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environmental factors were important trigger factors in patients with migraine without aura. Trigger factors are frequent in migraine patients, and avoidance of such factors may result in a better control of the disorder.[2]

Almotriptan malate, a type of medication known as triptans, is commonly prescribed for the treatment of acute migraine headaches in both adults and teenagers. It falls under the BCS class III category, characterized by its high solubility and low permeability. Its primary metabolic pathway involves monoamine oxidase-A, with additional involvement from cytochrome P450 (CYP) enzymes such as CYP3A4 and CYP2D6.

Furthermore, swallowing conventional dosage forms can be challenging, especially for pediatric and geriatric patients. During migraine attacks, patients often find it difficult to swallow medication due to the severity of pain, which can sometimes lead to vomiting and nausea.

Sublingual films provide a convenient solution for such patients as they eliminate the need for swallowing. Administering films can be an effective alternative for pediatric, geriatric, and other patients who struggle with conventional dosage forms during migraine episodes.[3-6]

MATERIALS AND METHODS:

MATERIALS:

Almotriptan malate is used as the active pharmaceutical ingredient in the formulation which was procured from Zydus Healthcare, Ahmedabad, Gujarat, India. While sodium alginate, Propylene glycol (PG), Citric acid, Tween 80 and Aspartame were purchased from chemdyes corporation Rajkot, Gujarat, India.

METHOD:

Formulation of Almotriptan malate Sublingual Film by Solvent Casting method:

The sublingual film was prepared by dissolving the polymers and plasticizer in a suitable solvent, while the drug was dissolved separately in another solvent. Both solutions were then mixed well with continuous stirring to obtain a uniform mixture. The mixture was poured into a glass Petri dish and left to dry at room temperature for 24 hours. After drying, the formed film was carefully removed and stored in a desiccator for further use.[7-9] Composition is mentioned in table 1.

Table1: Formulation of Sublingual Film

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Almotriptan malate (mg)	51.82	51.82	51.82	51.82	51.82	51.82	51.82	51.82	51.82
Sodium Alginate (mg)	200	250	300	200	250	300	200	250	300
Plantago Ovata (mg)	3	3	3	6	6	6	9	9	9
Aspartame (%w/v)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
PG (ml)	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Tween 80 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Citric acid (mg)	4	4	4	4	4	4	4	4	4
Distilled Water (ml)	10	10	10	10	10	10	10	10	10

PREFORMULATION STUDIES

Determination of Melting point of Almotriptan malate: The melting point of Almotriptan malate was determined using a melting point apparatus.

Estimation of Almotriptan malate by UV-Visible Spectrophotometry:

Preparation of standard stock solution in phosphate buffer at pH 6.8: A standard stock solution of Almotriptan malate was prepared by dissolving 10 milligrams of the drug in 100 milliliters of phosphate buffer at pH 6.8. Resulted in 100 parts per million (ppm) as final Stock solution.

Determination of λ_{max} of Almotriptan malate in phosphate buffer at pH 6.8: For determination of λ_{max}, stock solution was scanned between 200–800 nm against phosphate buffer (pH 6.8) as a blank in the UV-Visible spectrophotometer.

Preparation of working solutions: Working solutions with concentrations of 5, 10, 15, 20, and 25 parts per million (ppm) were prepared by pipetting out 0.5, 1, 1.5, 2.0, and 2.5 milliliters, respectively, from the stock solution of 100 ppm. Each portion was then diluted up to a 10milliliter volumetric flask. The absorbance of these working solutions was measured in triplicate at the wavelength of maximum absorption (λ_{max}) at 227 nanometers against phosphate buffer at pH 6.8, serving as a blank.

Evaluation Parameters of Sublingual Film [10-18]

Physical Appearance: Formulated batches were analyzed for Stickiness, Surface appearance and

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Film clarity.

Weight variation: Ten films were chosen randomly and weighed using an analytical balance to ascertain the average weight of each film. Consistency in weight is desirable for films, indicating that they contain the correct proportions of excipients and active pharmaceutical ingredient (API). This ensures uniformity in dosage and efficacy.

Thickness of Films: Using a micrometer screw gauge, the thickness of the film was measured at five distinct locations, and an average of these measurements was computed. This step is crucial to ensure uniformity in film thickness, as it directly impacts the accuracy of the dosage within the film.

Folding Endurance: The folding endurance of the film was assessed by repetitively folding the film at the same location until it ruptured. The folding endurance value corresponds to the number of times the film could be folded without breaking.

In-vitro **Disintegration Time**: A film was positioned on a stainless steel wire-mesh within a petri dish containing 10 milliliters of phosphate buffer at pH 6.8. The duration taken for the film to rupture was recorded, with an average of three readings being considered for accuracy.

% Moisture Uptake: The films were cut into the desired size and left exposed to room temperature conditions for a period of one week. Subsequently, the moisture uptake was determined by calculating the difference between the final weight and the initial weight of the films. The percentage of moisture uptake was then computed based on this difference.

$$\%\ \textbf{Moisture uptake} = \frac{\textbf{Final weight} - \textbf{Initial weight}}{\textbf{Initial weight}} \times 100$$

Drug Content: The Film was dissolved in 10ml of Phosphate buffer pH 6.8 and it was then filtered. Drug content was estimated using double beam UV Visible Spectrophotometer at 227 nm and then concentration was calculated from calibration curve.

In vitro **dissolution study**: In vitro dissolution test was conducted utilizing a USP type II Dissolution apparatus. The apparatus was filled with 500 milliliters of phosphate buffer solution adjusted to pH 6.8 and kept at a constant temperature of 37 ± 5 degrees Celsius while being agitated at 50 revolutions per minute (rpm). The film sample was positioned on a watch glass, covered with nylon wire mesh, and securely clamped. This assembly was then carefully inserted into the dissolution flask. At various intervals, 5 milliliter aliquots were withdrawn and replaced with an equivalent volume of fresh buffer solution to maintain sink conditions. These withdrawn samples were subsequently analyzed at a wavelength of 227 nanometers using a UV-Visible Spectrophotometer.

Stability Study: The optimized batch was enveloped in aluminum foil and placed inside a Stability Chamber in accordance with ICH Guidelines. It remained there for duration of one month, maintained at 40˚C ± 2˚C and 75% ± 5% relative humidity. Upon completion of the one-month period, the film was removed from the chamber and subjected to evaluation for all pertinent parameters.

RESULTS AND DISCUSSION:

Melting point of Almotriptan malate

Melting point determination is a commonly employed technique to identify drugs, performed using a melting point apparatus. The melting point of Almotriptan malate was determined to fall within the range of 160 - 163 °C

The reported melting point of Almotriptan malate is 162 °C, which closely aligns with the observed melting point in this study. (Table 2)

Table2: Melting point of Almotriptan malate

Sr. No.	Reported Melting Point	Observed Melting point
1.	162 °C	160 - 162 °C
2.		161 - 163 °C
3.		160 - 162 °C

Estimation of drug by UV overlay spectra

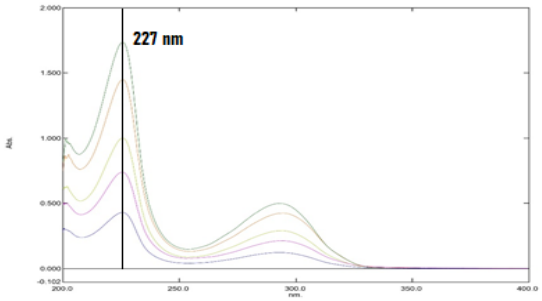

Figure 1. Almotriptan malate UV overlay spectra

Overlay spectra of the drug were acquired by scanning solutions of various concentrations, including 5, 10, 15, 20, and 25 ppm, revealing maximum absorption at 227 nm. Given that the reported λmax is 227 nm, it can be inferred that the analyzed drug is Almotriptan malate. As mentioned in Figure 1, 2 and table 3.

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Table 3: Absorbance of different concentration of Almotriptan malate in phosphate buffer at pH 6.8

Sr.No.	Concentration(ppm)	Absorbance			Mean Absorbance± S.D.
		I	II	III	
1	5	0.432	0.434	0.432	0.432 ± 0.001
2	10	0.739	0.741	0.738	0.739 ± 0.001
3	15	1.002	1.005	1.002	1.003 ± 0.001
4	20	1.444	1.442	1.442	1.442 ± 0.001
5	25	1.739	1.734	1.735	1.73 ± 0.002

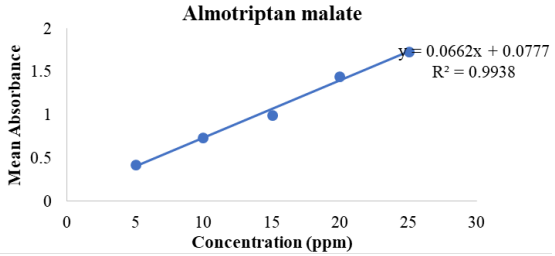

Figure 2. Almotriptan malate Calibration curve

Post formulation parameters:

Physical appearance: From physical appearance parameters it was seen that all batches were Nonsticky in nature, smooth and transparent in appearance. As mentioned in table 4.

Table 4: Physical Appearance of Sublingual films

Batch	Stickiness	Surface Appearance	Film Clarity
F1	NonSticky	Smooth	Transparent
F2	NonSticky	Smooth	Transparent
F3	NonSticky	Smooth	Transparent
F4	NonSticky	Smooth	Transparent
F5	NonSticky	Smooth	Transparent
F6	NonSticky	Smooth	Transparent
F7	NonSticky	Smooth	Transparent
F8	NonSticky	Smooth	Transparent
F9	NonSticky	Smooth	Transparent

Thickness of film: The thickness of the film was measured using a micrometer screw gauge, revealing that the thickness ranged from 0.122 ± 0.001 mm to 0.143 ± 0.005 mm.

Weight variation: Weight variation tests conducted on all prepared films indicated a range of weight from 29.8 ± 1.32 mg to 61.2 ± 1.32 mg.

Folding endurance: The folding endurance values of the prepared films ranged from 106 ± 2.52 folds to 142 ± 2.65 folds. It was observed that as the polymer concentration increased in the formulations, the folding endurance values also increased. (Table 5).

Table 5: Weight variation, Thickness, Folding endurance of Sublingual films

Batch	Thickness (mm ± S.D.) (n=3)	Weight variation (mg ± S.D.) (n=3)	Folding Endurance (mean ± SD) (n=3)
F1	0.122 ± 0.001	29.8 ± 1.32	106 ± 2.52
F2	0.127 ± 0.004	35.4 ± 1.17	121 ± 3.51
F3	0.129 ± 0.005	42.5 ± 3.47	138 ± 3.21
F4	0.127 ± 0.009	36.9 ± 1.29	127 ± 2.08
F5	0.131 ± 0.008	43.4 ± 1.51	136 ± 2.15
F6	0.134 ± 0.009	50.2 ± 1.75	138 ± 3.21
F7	0.129 ± 0.004	45.6 ± 0.97	122 ± 2.08
F8	0.135 ± 0.009	53.2 ± 1.62	134 ± 2.52
F9	0.143 ± 0.005	61.2 ± 1.32	142 ± 2.65

% Moisture uptake: The percentage moisture uptake values of the prepared films ranged from 2.07 ± 0.74% to 4.64 ± 2.46%.

***In vitro* Disintegration test:** The disintegration time ranged from 13 ± 1.15 seconds to 45 ± 2 seconds. Batch F9 exhibited the lowest disintegration time, measuring 13 ± 1.15 seconds.

Drug Content: The drug content of all formulations fell within the range of 97.26% to 99.62%. Therefore, all films exhibited drug content within acceptable limits. (Table 6)

Table 6: Percentage moisture uptake, Disintegration time, Drug Content Data

Batch code	Percentage moisture uptake (% ± S.D.) (n=3)	Disintegration time (sec ± S.D.) (n=6)	Drug Content (%)
F1	3.14 ± 2.29	45 ± 2.08	97.81
F2	3.99 ± 4.48	34 ± 1.53	98.26
F3	2.59 ± 2.33	25 ± 1.53	97.63
F4	4.64 ± 2.46	44 ± 2.08	99.59
F5	3.45 ± 2.29	36 ± 1.73	99.18
F6	3.24 ± 2.12	31 ± 2.08	98.52
F7	2.07 ± 0.74	24 ± 2.52	97.26
F8	2.89 ± 1.19	19 ± 1.73	98.45
F9	2.78 ± 0.81	13 ± 1.15	99.62

***In vitro* Drug Release data:** Batch F1, F2 and F3 showed drug release of 98.07 %, 98.91 % and 98.81% at 21, 21 and 18 minutes respectively. Batches F4, F5 and F6 showed drug release of 99.18 %, 96.31 % and 99.25 % at 21, 18 and 18 minutes respectively. Whereas batches F7 to F9 showed drug release of 97.19 %, 97.44 % and 99.46 % of drug release in 18, 15 and 15 minutes respectively. Thus from the above results it was concluded that the drug release of batch F9 was faster in only 15 mins as compared to all other batches. (Figure 3, 4 and 5)

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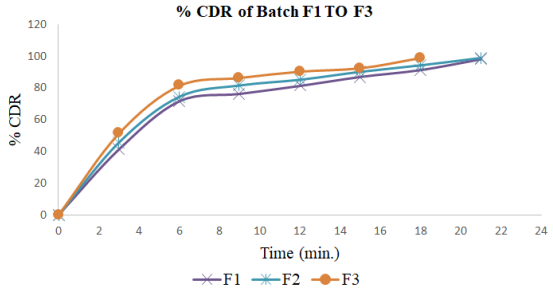

Figure 3: *In Vitro* Drug Release profile of batch F1 to F3

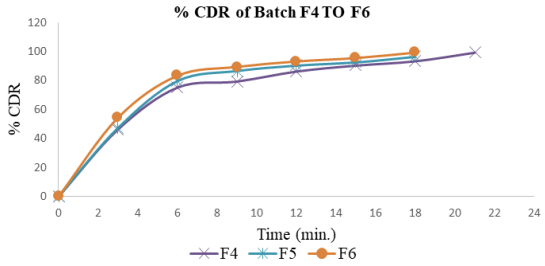

Figure 4: *In Vitro* Drug Release profile of batch F4 to F6

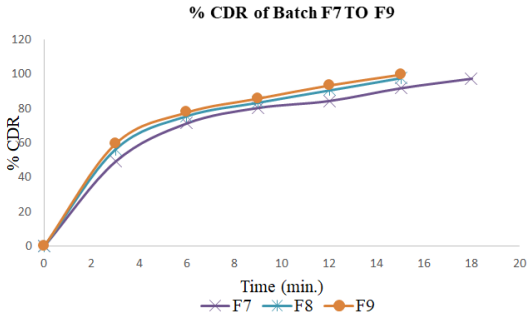

Figure 5: *In Vitro* Drug Release profile of batch F7 to F9

Stability Study: The optimized film underwent one month of stability testing and was determined to be stable in terms of Physical Appearance, Thickness, weight variation, Folding Endurance, % Moisture Uptake, drug content, *in vitro* disintegration time, and *in vitro* drug release study. Comparison study between the result of optimized batch and after time period of stability is graphically illustrated in Figure 6 and tabulated in Table 7 and 8.

Table 7: Result of stability study

Sr. No.	Evaluation parameter	Results of optimized batch F9	Result after 1 month
1.	Physical Appearance	Non Sticky Smooth Transparent	Non Sticky Smooth Transparent
2.	Thickness	0.143 ± 0.005 mm	0.139 ± 0.008 mm
3.	Weight Variation	61.2 ± 0.94 mg	61.3 ± 0.92 mg
4.	Folding Endurance	142 ± 2.65	139 ± 2.89
5.	% Moisture Uptake	2.78 ± 0.81	1.17 ± 0.42
6.	*In Vitro* Disintegration Time	13 ± 1.2	16 ± 1.2
7.	Drug Content	99.62	99.15

Table 8: *In Vitro* Drug Release study of Stability batch

Time (Min.)	*In Vitro* Dissolution time	
	Optimized Batch F9	After 1 Month (%)
0	0	0
3	59.36	55.12
6	77.56	71.45
9	85.64	82.92
12	93.25	91.04
15	99.46	98.69

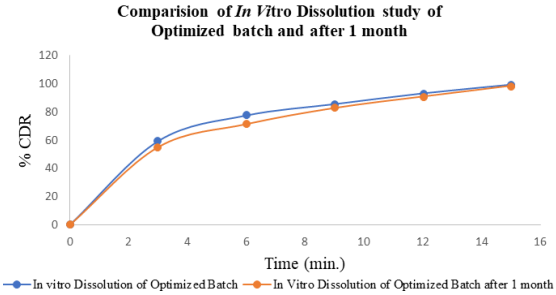

Figure 6: Comparison of *In Vitro* Drug Release study of Optimized batch and Stability batch

CONCLUSION:

The present research successfully developed and evaluated sublingual films of Almotriptan malate using the solvent casting method with different concentration hydrophilic polymer Sodium Alginate. Preformulation studies confirmed the identity and purity of Almotriptan malate. All formulated films (F1–F9) showed good physical appearance, being non-sticky, smooth, and transparent. In vitro drug release studies revealed rapid and efficient drug release, with the optimized formulation F9 (containing 300 mg Sodium Alginate and 9 mg Plantago ovata as natural superdisintegrant) showing the fastest disintegration time (13 ± 1.15 seconds) and highest cumulative drug release of 99.46% within 15 minutes. Stability studies of formulation F9 for one month indicated no significant changes in physical appearance, drug content, disintegration time and drug release profile, confirming good stability. Overall, the study concludes that Sodium Alginate is an effective film-forming polymer and the optimized sublingual film of Almotriptan malate is a promising, patient-friendly dosage form for rapid migraine management.

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CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest.

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