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Formulation And Evaluation of Mouth Dissolving Film of Almotriptan Malate

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Abstract:
The present study was aimed to formulate and evaluate mouth dissolving films of almotriptan malate using polymers HPMC E-15, HPMC E-4 and Gelatin as the film forming agents. Formulation batches were formulated using 32 full factorial designs. The fast dissolving oral films were designed using optimal design and numerical optimization technique was applied to find out the best formulation. PEG 400 was incorporated as plasticizer to improve flexibility of films. Aspartame as sweetner. Sodium starch glycolate used as a disintegrant. An attempt was made to prepare mouth dissolving films of almotriptan with the purpose of developing a dosage form for quick onset of action. The films were prepared by solvent casting method. The FTIR studies revealed that there is no physicochemical interaction between excipients and drug. They were evaluated for physicochemical characterization such as uniformity of weight, thickness, folding endurance, uniformity of drug content, surface pH, percentage elongation and tensile strength all of which showed satisfactory results. The formulations were also subjected for in vitro disintergration and in vitro drug release. Melt in mouth films of almotriptan containing single polymer HPMC E-15 showed best results, in terms of tensile strength (1.76 ± 0.11), percentage elongation (36.63 ± 0.288%), folding endurance (>300), in-vitro disintegration time (26.01 ± 0.11sec.), surface pH (6.20 ± 0.001 pH), thickness (0.096 ± 0.011mm) and percentage content uniformity (97.23 ± 0.091). Satisfactory dissolution profile was obtained with maximum release of 96% of drug within 120 sec. The stability studies showed that there was no appreciable change in parameters when stored at three different temperatures.

Keywords: Almotriptan Malate, Solvent Casting method, mouth dissolving film, HPMC E-15, Migraine

INTRODUCTION

Fast-dissolving buccal film drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. They are usually used for pharmaceutical and nutraceutical products. It is the newest drug delivery technology that provides a very convenient means of taking medications and supplements. A fast-dissolving buccal film drug delivery system, in most cases, is a film containing active ingredient that dissolves or disintegrates in the saliva remarkably fast, within a few seconds without the need for water or chewing. Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredients then swallowed by the patient's saliva along with the soluble and insoluble excipients[1].

The rapidly dissolving dosage forms were introduced in 1970's as an alternative to the conventional tablet and capsule which require swallowing of the dosage form[2]. This type of technology offer a convenient way of dosing medication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population [3,4].

Migraine headache is thought to be caused by widened blood vessel exerting pressure on the brain. In migraine, patients experience one or more short lived attacks of intense headache, usually at the same time every day and often at night and are usually of sufficient severity to disturb or prevent daily activities. Almotriptan is a serotonin (5-HT1) receptor agonist “triptan”. It mainly acts by narrowing the blood vessel in the brain and thereby reducing pressure and pain in the brain. Almotriptan relieves nausea, vomiting, photophobia (light hypersensitivity) and phonophobia (sound hypersensitivity) associated with migraine attacks pain. Thus for an anti- migraine drug like almotriptan, a quick

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release dosage form will be very suitable, so that at times of severe attacks the film can be conveniently consumed by the patient without the help of water, for an immediate action. Formulation and availability of such type of dosage form will prove to be very useful and convinent for the population whose work efficiency is significantly hampered due to frequent migraine attacks. Also, since the drug starts getting absorbed from the oral cavity itself, the bioavailability may be expected to increase. Hence, it was thought worthwhile to formulate quick release film type of dosage form for Almotriptan Malate.

The objective of this study was to develop oral drug delivery system in the form of fast dissolving film which overcomes first pass metabolism and the drug achieve to specific site for greater therapeutic action. Another objective of the study is to improve health standard of life of people suffering from migraine for years.

MATERIAL AND METHODS

Material:

All the material used i.e. Almotriptan malate is from Mylan Pharmaceuticals, Nashik, India and others like HPMC E-15, PEG 400, Aspartame, Sodium starch glycolate are from research lab., Mumbai, India.

Compatibility study of drug: Fourier Transform Infra-red (FTIR) analysis:

Infra-red spectroscopic analysis was performed by Fourier Transform Infrared Spedctrophotometer IR Affinity (Shimadzu), with a resolution of 8 cm-1, in the range of 4000-500 cm-1, using KBr pellets.

Compatibility study of drug with polymer: Fourier Transform Infra-red (FTIR) analysis:

Infra-red spectroscopic analysis was performed by Fourier Transform Infrared Spedctrophotometer IR Affinity (Shimadzu), with a resolution of 8 cm-1, in the range of 4000-500 cm-1, using KBr pellets.

Preparation of Mouth Dissolving Film by Solvent Casting Method:

In this solvent casting method, firstly water soluble polymers were dissolved in water. Then the drug along with other excipients were dissolved in the same solution and then mixed and stirred it for 2 to 2.5 hours on magnetic stirrer. Then sonicate this solution for 1 hour for removing all bubbles and finally casted in to the Petri plate and then dried it at 50°C for 24 hours. Then removed the film from petridish carefully, checked for any imperfections and then cut into the required size to deliver the equivalent dose per strip. Then the samples are stored in desiccator at RH until further analysis[5].

PREPARATION OF MOUTH DISSOLVING FILM OF ALMOTRIPTAN MALATE BY USING 3^2 FULL FACTORIAL DESIGN:

Optimization using 3^2 full factorial design:

In general, the procedure consists of preparing a series of formulations, varying the concentrations of the formulation ingredients in some systematic manner [6].

A 3^2 randomized full factorial design was applied in the present study. In the design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. These are usually referred to as low, intermediate and high levels. These levels are numerically expressed as 0, 1 and 2 or -1, 0 and +1. A study, in which there are two factors with 3 levels, is called a 3^2 factorial design. The concentration of HPMC E15 and concentration of PEG 400 were used as independent variables. The disintegration time and folding endurance of the film were used as dependent variables.

Table 1. Layout of 3^2 Full Factorial design

Variable	F1	F2	F3	F4	F5	F6	F7	F8	F9
X_1	-1	-1	-1	0	0	0	1	1	1
X_2	-1	0	1	-1	0	1	-1	0	1

Table 2. Coded value for (PEG 400) and (HPMC E15) concentration

Coded level	-1	0	1
X_1 (PEG 400)	110	155	200
X_2 (HPMC E15)	150	275	400

Evaluation of formulations [7-14]**:**

Weight variation:

For weight variation three films of every formulation were taken weighed individually on digital balance then average weight was calculated.

Tensile strength:

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Strip thickness x Strip width}} \text{ x } 100$$

Percentage Elongation:

$$\% \text{ Elongation} = \frac{\text{Increase in length of strip}}{\text{Initial length of strip}} \text{ x } 100$$

Folding endurance:

Folding endurance is determined by repeated folding of the films at the same place till the strip breaks. The number of times the fast dissolving film is folded without breaking is computed as the folding endurance value.

In-vitro disintegration time:

In vitro disintegration time is determined visually in USP disintegration test apparatus. The disintegration time is the time when the film starts to break or disintegrates when brought inh contact with water, is less than 1 minute for the fast dissolving film. So here A1 –A5 batches were found to be in the optimum range.

In-vitro dissolution studies:

The in vitro dissolution study is carried out in simulated saliva solution pH 6.4 phosphate buffer using USP basket apparatus at 37±0.5°C. Samples are withdrawn at regular time interval of 1-6 minutes of all the nine batches from F1 – F9 and same amount is replaced by solvent and then it is analyzed by using UV-Visible spectrophotometer at 227.5nm.

Content uniformity:

The uniformity of dosage units of the oral film preparation was tested in which the content of Almotriptan malate, was determined by UV-spectrophotometric method at 227.5 wavelength nm. The acceptance value (AV) of the preparation is less than 1-2 % w/w, the contents of major component in the preparation should be within a range between 98.0% and 101.0%.

Thickness:

The thickness of the patch was measured using digital Vernier Calliper with a least count of 0.01 mm. The thickness was measured at different strategic points of the film and average was taken and SD was calculated.

Surface pH:

The film to be tested was placed in a petridish and was

Table 3. Formulation of Fast Dissolving Film of Almotriptan Malate

Formulation code	Drug (mg)	PEG 400 (mg)	HPMCE15 (mg)	SSG (mg)	Aspartame (mg)
F1	58.5	110	150	1	7
F2	58.5	110	275	1	7
F3	58.5	110	400	1	7
F4	58.5	155	150	1	7
F5	58.5	155	275	1	7
F6	58.5	155	400	1	7
F7	58.5	200	150	1	7
F8	58.5	200	275	1	7
F9	58.5	200	400	1	7

moistened with 1 ml of distilled water and kept for 1 h. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and kept for 1 min to allow equilibrium condition.

RESULTS AND DISCUSSION

Fourier transforms infrared spectroscopy (FT-IR) analysis

To study the compatibility of drugs with excipients IR spectra of drug in combination with excipients in 1:10 ratio was studied. The IR spectrum shown in Fig. 12 indicates that there was no physicochemical interaction in between the drug and the used excipients. The results of the preformulation study suggest that all the studied excipients were compatible with Almotriptan Malate.

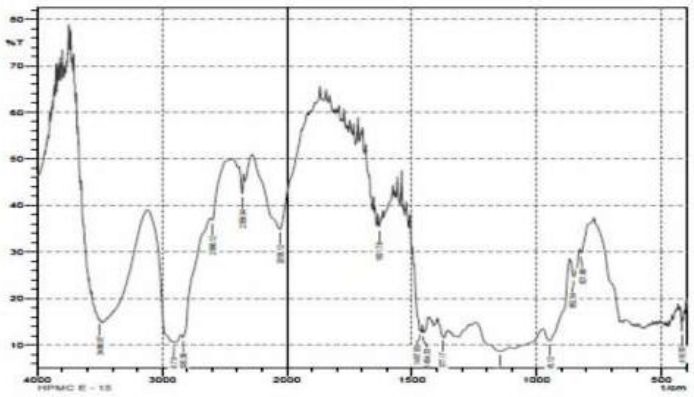

Fig. 1: FTIR Spectrum of pure Almotriptan Malate

Table 4. Interpretation Of FTIR Spectrum

Sample	Obtained Peak values (cm-1)	Actual Wave number (cm-1)	Bond	Characteristic functional groups
Almotriptan Malate	3327	3500-3300	N-H stretch	Amines
	3045	3130-3030	N-H stretch	Amino acids
	2970	3030-2950	C-H stretch	Alkanes
	1119	2775-2720	C=O stretch	carboxylate
	1479	1600-1450	C=C stretch	Aromatics
	1089	1150-1050	C-O stretch	Esters
	1014	1300-1000	C-N stretch	Alkyl, Aryl
HPMC E- 15	3498	3500-3300	O-H stretch	Phenols
	2906	3030-2900	C-H stretch	Alkane
	2598	3000-2500	O-H	Carboxylic acid
	1157	1280-1020	C-N stretch	Aliphatic tertiary
PEG 400	3446	3500-3300	O-H stretch	Alcohol
	2870	2950-2850	C-H stretch	Alkanes
	1105	1150-1050	C-O stretch	Ether
Almotriptan Malte + HPMC E-15 +PEG 400	3331	3500-3300	N-H stretch	Amines
	1458	1600-1450	C=C stretch	Aromatics
	2970	3030-2900	C-H stretch	Alkane
	1139	1200-1025	C-N stretch	Alkyl
	3308	3500-3300	O-H strech	Alchol

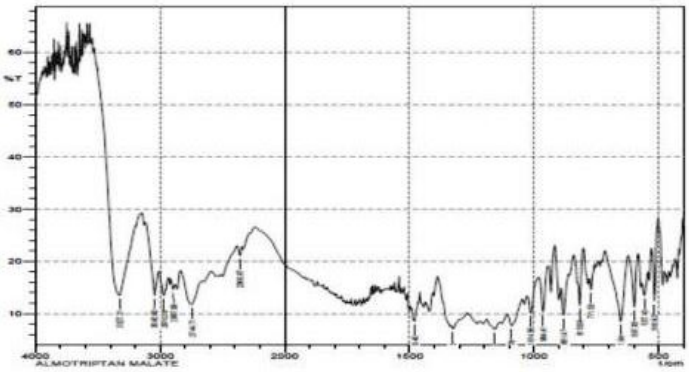

Fig. 2: FTIR Spectrum of HPMC E-15

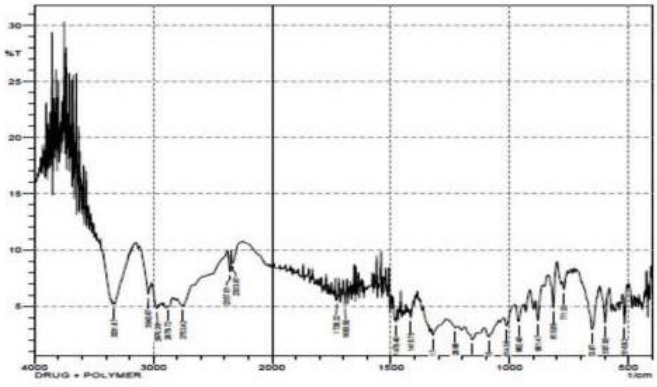

Fig.3: FTIR Spectrum of PEG 400

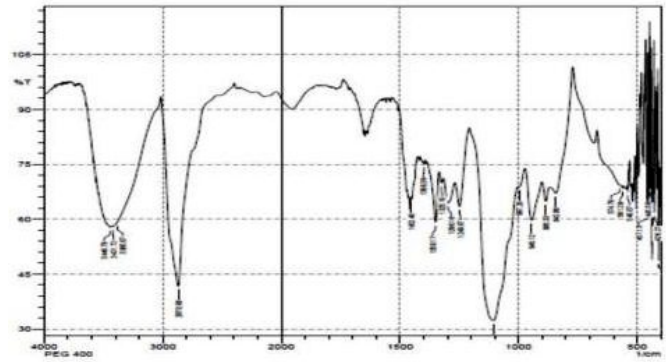

Fig. 4- FTIR Spectrum of Almotriptan Malate +HPMC E15 +PEG 400

Interpretation:

The above FTIR spectrums showed the peaks of major functional groups of polymers. These peaks are nearly unchanged as compared to spectrum of mixture of drug along with polymers.

The IR spectra of Almotriptan Malate exhibited principal peaks at wavenumbers 3327, 3045, 2970, 2897, 2744 cm-1 Table no. 10 gives the interpretation some of the peaks obtained in the IR spectra along with their corresponding functional groups IR results shows the presence of above groups in the IR spectra of drug which conformed that the drug molecule was Almotriptan malate.

In the IR spectra of mixture of drug with polymer the principal peaks of drug was obtained at wave numbers 3331, 1458, 2970,1139, 3308 cm-1. o, from the above spectrum it can be concluded that there is no interaction between drug, and polymers used in the formulation.

Physical appearance

It was observed that films prepared with HPMC E4 as polymer and PEG 400 as plasticizer were found to be opaque and in some cases brittle (fig:14) so HPMC E4 was eliminated for further study. A4 was found to be more flexible, transparent and clear.

Folding endurance

Folding endurance of A4 and A5 batches were found to be 312 and 351 respectively, which favors formation of fexible film.

Disintegration time

The typical disintegration time, which is defined as the time at which the film begins to break when brought in contact with water, is less than 1 minute for the fast dissolving film. So here A1 – A5 batches were found to be in the optimum range.

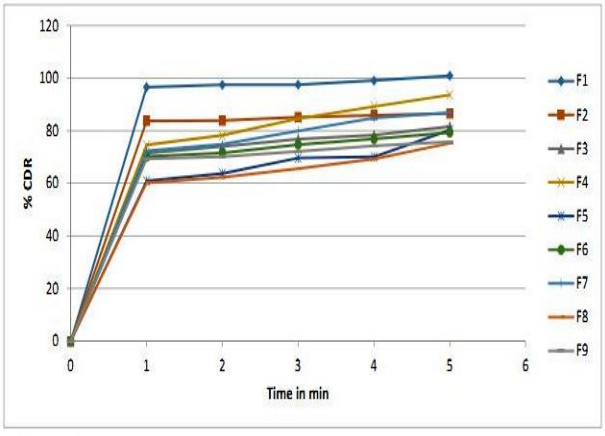

Fig.5 : In-vitro Drug release study

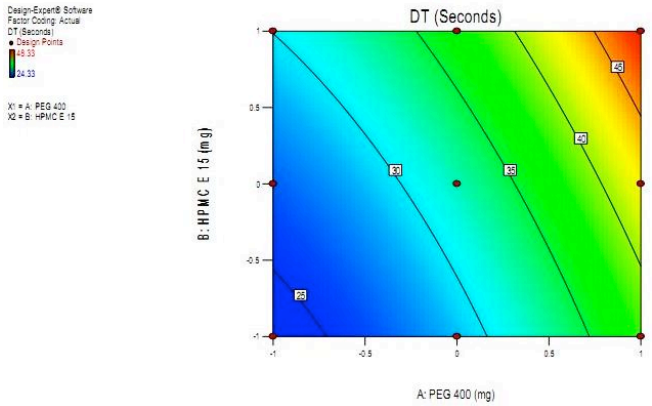

Fig.6: Contour plot shows the effect of PEG 400 (A) and HPMC E-15 (B) on the disintegration time.

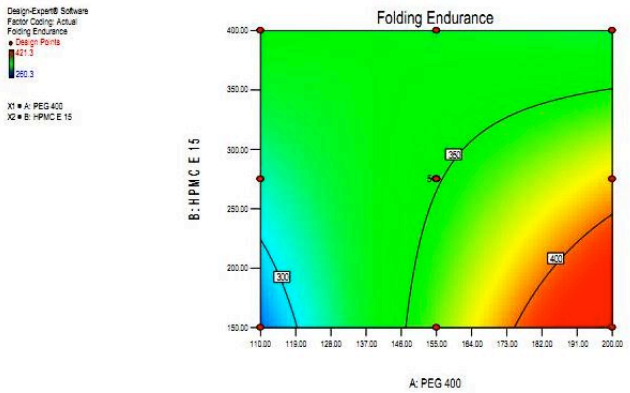

Fig.8: Contour plot shows the effect of PEG 400 (A) and HPMC E-15 (B) on the Folding Endurance.

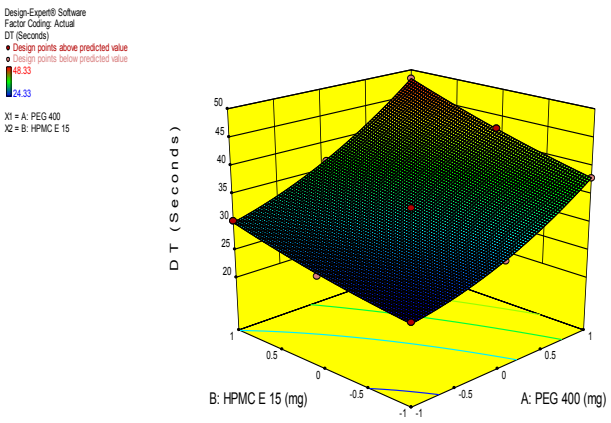

Fig.7: 3D Contour plot shows the effect of PEG 400 (A) and HPMC E-15 (B) on the disintegration time.

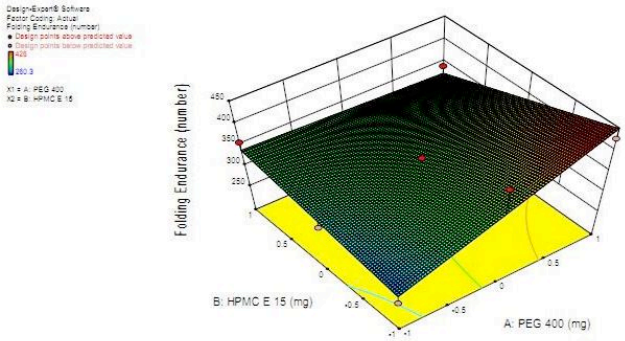

Fig.9: 3D Contour plot shows the effect of PEG 400 (A) and HPMC E-15 (B) on the Folding Endurance.

Table 5. Physical appearance

Batch code	HPMC E15(mg)	HPMC E4 (mg)	PEG 400 (mg)	Water (ml)	Physical appearance	Peel ability
A1	100	*	50	10	Transparent	Easily peelable
A2	150	*	80	10	Transparent	Easily peelable
A3	200	*	110	10	Transparent	Easily peelable
A4	300	*	155	10	Transparent	Easily peelable
A5	400	*	200	10	Transparent	Easily peelable
A6	*	100	50	10	opaque	Easily peelable
A7	*	150	80	10	opaque	Easily peelable
A8	*	200	110	10	opaque	Easily peelable
A9	*	300	155	10	opaque	Easily peelable
A10	*	400	200	10	opaque	Easily peelable

The effect of other exicipent for composition of fast mouth dissolving film (Batches F1 – F9)

Sweetening agent: Aspartame was added as sweeting agent in all drug loaded F1 to F9 formulation. Sucrose was added in trial batches. Sucrose containing trial batch was found to be bitter in taste.

Superdisintegrant: Sodium starch glycolate was added as superdisintegrant in all drug loaded 9 optimized batches.

Flavoring agent: Strawberry was used as a flavoring agent. In all 9 formulation

Table 6. Folding endurance

Batch code	HPMC E15 (mg)	HPMC E4 (mg)	PEG 400 (mg)	Water (ml)	Folding endurance
A1	100	*	50	10	156
A2	150	*	80	10	221
A3	200	*	110	10	267
A4	300	*	155	10	312
A5	400	*	200	10	351
A6	*	100	50	10	49
A7	*	150	80	10	83
A8	*	200	110	10	115
A9	*	300	155	10	134
A10	*	400	200	10	197

In-vitro Drug release study:

In-vitro dissolution study shows maximum release i.e. 100.91% for F1 formulation this could be attributed to concentration of HPMC E- 15 and lower concentration of PEG 400 in the formulation. In-vitro drug release data is shown in Table 10.

Optimization

Statistics was applied to the results obtained from general factorial design in which two independent variables varied namely PEG 400 (X1) and HPMC E-15 (X2) and their effect is recorded on dependent variable namely Disintegration time and Folding endurance.Evaluation and interpretation of research findings are almost important and the p-value serves a valuable purpose in these findings. Table 22 and 23 shows ANOVA for the dependent variable disintegration time and folding endurance. The values of X1 and X2 were found to be significant at $p < 0.05$, hence confirmed the significant effect of both the variables on the selected responses. Variable caused significant change in the responses. From this data optimum concentration of PEG 400, 110 mg and HPMC E-15 275 mg was found.

Table 7. Disintegration time

Batch code	HPMC E15 (mg)	HPMC E4 (mg)	PEG 400 (mg)	Water (ml)	Disintegration time
A1	100	*	50	10	21 sec
A2	150	*	80	10	25 sec
A3	200	*	110	10	29 sec
A4	300	*	155	10	35 sec
A5	400	*	200	10	43 sec
A6	*	100	50	10	>1 min
A7	*	150	80	10	>1 min
A8	*	200	110	10	>1 min
A9	*	300	155	10	>1 min
A10	*	400	200	10	>1 min

Equation for disintegration time

Folding Endurance = 32.25 +8.05*A +4.06*B +1.08*AB +2.29*A^2 +0.61*B^2 eq….1

The Model F-value of 488.32 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant. In this case A, B, AB are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Table 8. Evaluation of fast dissolving film

Batch Codes	Uniformity of weight (mg) Mean ± SD	Disintegration time(sec) Mean ± SD	Folding endurance Mean ± SD	Tensile strength (kg/mm^2) Mean ± SD
F1	36.65 ± 1.515	24.33 ±1.52	260.3± 27	1.8992 ± 0.03892
F2	35.72 ± 1.506	26.0 ± 2	282.0 ± 16	1.7629 ± 0.1198
F3	42.56 ± 1.631	30.33±1.52	356.6±30	1.9802 ± 0.0909
F4	33.66 ± 0.862	28.66±2.58	421.3 ±16	1.4248 ± 0.2565
F5	37.33 ± 1.26	32.66±2.06	356.0±5	1.4658 ± 0.31312
F6	44.00 ±0.577	36.66 ±2.52	311.6 ±13	0.9109 ± 0.1329
F7	40.05 ± 1.000	38.0 ±2.64	419.0± 10	1.3180± 0.1591
F8	43.26 ± 0.661	42.66 ±2.08	363.0± 10	1.3367± 0.3109
F9	44.21 ±0.577	48.33 ± 2.51	340.3 ±13	1.0986± 0.2365

Table 9. Evaluation of fast dissolving film

Batch Codes	Surface pH	Thickness (mm)	% Elongation	Uniformity of drug conten
F1	5.74 ±0.23	0.096 ±0.004	27.32 ± 1.565	92.3566±1.020
F2	6.20 ±0.05	0.096±0.1154	36.63 ± 0.650	97.23±0.974953
F3	6.16 ±0.22	0.1166±0.020	46.53 ± 0.665	95.623±2.058
F4	5.95 ±0.13	0.0933±0.057	25.63 ± 0.710	90.85±1.3157
F5	6.31 ±0.167	0.1033±0.015	28.76 ± 0.780	94.366±2.077
F6	6.44 ±0.077	0.12±0.01	38.76 ± 0.795	91.453±2.228
F7	6.15 ±0.047	0.1±0.01	24.19 ± 1.250	90.69±1.9030
F8	6.49 ±0.399	0.116±0.015	27.28 ± 0.635	94.84±1.212
F9	6.73 ±0.105	0.1233±0.020	35.36 ± 0.685	92.35±0.819

Data is expressed as Mean ± SD.

From the equation 1 it was concluded that PEG 400 (factor A) and HPMC E-15 (factor B) having individual as well as combined effect on the Folding endurance. According to the obtained results, the developed models are statistically accurate and can be used for further analysis.

Counter plot

The following counter plot shows that the when the concentration of PEG 400 and HPMC E -15 kept minimum, the formulation shows minimum disintegration time and disintegration time increases with increase in concentration of both polymer.

Table 10. In-vitro Drug release study

Time in Min	Cumulative drug release (%) ±SD								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	96.57 ±0.9452	83.71 ±0.4618	71.43 ±0.3987	74.56 ±0.3129	60.92 ±0.6124	70.15 ±0.5839	72.32 ±0.241	60.15 ±0.512	69.25 ±0.4623
2	97.43 ±0.8532	83.84 ±0.4525	74.01 ±0.7835	78.23 ±0.356	63.74 ±0.4365	71.56 ±0.4629	74.89 ±0.3286	62.26 ±0.468	70.12 ±0.152
3	97.48 ±0.7256	85.15 ±0.3863	76.81 ±0.9230	84.62 ±0.7122	69.66 ±0.4184	74.70 ±0.3412	79.92 ±0.756	65.57 ±0.2984	72.16 ±0.297
4	99.05 ±0.6298	85.82 ±0.2987	78.37 ±0.4523	89.25 ±0.4378	70.07 ±0.3985	76.87 ±0.491	84.91 ±0.267	69.25 ±0.7623	74.24 ±0.2854
5	100.91 ±0.5421	86.58 ±0.5154	81.57 ±0.4234	93.65 ±0.5314	80.25 ±0.4981	79.27 ±0.4715	86.82 ±0.484	75.27 ±0.3984	75.79 ±0.328

Therefore both polymers as has effect on disintegration time.

Perturbation

Figure 16 shows the relationship between the disintegration time on one side and PEG 400(A) and HPMC E-15(B) on the other side. The disintegration time is found to be more responsive to the HPMC E-15 concentration than to PEG 400. In other words, increasing the HPMCE-15 would result in a drastic enhancement in the disintegration time of formulation.

Equation for folding endurance

Folding Endurance = 348.78+ 37.23*A- 15.35*B- 43.75*A*B eq….2

The Model F-value of 7.38 implies the model is significant. There is only a 0.085% chance that an F-value this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant. In this case A, B, AB are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

From the equation 2 it was concluded that PEG 400 (factor A) and HPMC E-15 (factor B) having individual as well as combined effect on the Folding endurance. According to the obtained results, the developed models are statistically accurate and can be used for further analysis.

Counter plot

The following counter plot of PEG 400 (A) and HPMC E-15 (B) shows that the when the concentration of PEG 400 and HPMC E -15 kept minimum, the formulation shows minimum folding endurance and folding endurance increases with increase in concentration .therefore both polymers as has effect on folding endurance.

Perturbation

Figure 16 shows the relationship between the folding endurance on one side and PEG 400(A) and HPMC E-15(B) on the other side. The folding endurance is found to be more responsive to the PEG 400 concentration than to HPMC E-15. In other words, increasing the PEG 400 would result in a drastic enhancement in the folding endurance of formulation.

Table11. Stability studies: Accelerated stability study

Sr. No	Observations	Before Accelerated Stability Testing	After Accelerated Stability Testing		
			30 days	60 days	90 days
1	Drug content	97.23%	97.12%	97.07%	97.01%
2	Visual appearance (Colour changes)	Light yellow	Light yellow	Light yellow	Light yellow
3	pH	6.2	6.2	6.5	6.7
4	Disintegration time	26 Sec	28 Sec	29 Sec	30Sec

Stability studies:

Accelerated stability study

Formulation F2 at 40oC temperature is found to be stable upto 3 months. There is no significant change in drug content, visual appearance i.e. change in colour and disintegration time.

All films stored at elevated temperature showed slight change in pH, other parameters are found to be unchanged. There is slight change in pH.

CONCLUSION

Almotriptan Malate is selected as a drug candidate for the development of Mouth dissolving films, because of low molecular weight, lipophilicity, considerable first pass metabolism in liver and excellent absorption properties. Preliminary investigation of drug was carried out with different parameters, drug determines the sharp melting point at 171-1730C, determination of solubility shows that drug was soluble in water and phosphate buffer 6.8. Compatibility of drug with polymers was confirmed by FT- IR study. Finally it is concluded that the drug release from the mouth dissolving Film was increased by using the increased concentration of superdisintegrant thus assisting in faster disintegration in the buccal cavity. The fast-dissolving film of almotriptan malate obtained by the solvent casting method showed acceptable mechanical characteristics and satisfactory % drug release. The prepared film was transparent with smooth surface without any interactions between drug and polymer. The high % drug release of the film in simulated saliva indicated that it could be helpful for the treatment of acute migraine where quick bioavailability of the drug is desired.

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