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Formulation Development and Evaluation of Sublingual Film of Antimigraine Drug

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ABSTRACT

The aim of formulation of fast dissolving sublingual film of Zolmitriptan was to provide quicker onset of action in short duration of time and in addition to providing immediate action after administration of dosage form. The pre-formulation study was carried out by FTIR with the pure drug (Zolmitriptan) and formulation mixture (Zolmitriptan -HPMC K4M and Zolmitriptan Pectin). It was observed that disintegration time varies from 19 to 30 sec for all the formulations. Weight variation varies from 49.33 mg to 66.66 mg. All the formulations were evaluated for folding endurance, surface pH, Tensile Strength, thickness and weight variation. It was also observed that HPMC K4M & Pectin was able to modulate the Zolmitriptan release as a lower amount of HPMC K4M as well as Pectin resulted in the release of drug a faster rate.

INTRODUCTION

Fast dissolving films are also called as sublingual films, melt in mouth films, Orodispersible films, rapid melts, porous films, quick-dissolving, etc. Fast dissolving films are those when put under tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva. The faster the drug into solution, the quicker the absorption and onset of clinical effect. [1, 2]. Some drugs are absorbed from the mouth, pharynx, and esophagus as the saliva passes down into the stomach. In such cases, the bioavailability of the drug is significantly greater than those observed from conventional tablets dosage form. The advantage of fast dissolving dosage forms is increasingly being recognized in both, industry and academics. Their growing importance was underlined recently when European pharmacopeia adopted the term "Orodispersible films" as a film that to be placed under the tongue where it disperses rapidly before swallowing [3, 4] more ever, the amount of drug that is subjected to the first-pass metabolism is reduced as compared to a standard tablet. The technologies used for manufacturing fast-dissolving films are solvent casting method, hot-melt extrusion, semisolid casting, solid dispersion extrusion, rolling. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. These people eventually will experience deterioration of their physiological and physical abilities. [5, 6]. The total daily dose of Zolmitriptan is 2.5 mg (e.g., 2.5 mg once a day depending on meal patterns), hence it required frequent dosing. Sublingual Film of Zolmitriptan was prepared for fast immediate release; improve the bioavailability of drug and patient compliance.

MATERIALS AND METHODS

Zolmitriptan was obtained as a gift sample from Dr.Reddy Lab. Hyderabad, India. The HPMC K4M & PEG400 was purchased from Oxford Laboratory, Mumbai, India. All other materials used in analytical grades.

Preparation of Fast Dissolving Sublingual Films. Weight accurate amount of polymer and socked in respective solvents for overnight. Zolmitriptan was dissolved in the required quantity of solvent. Mix the solution and add PEG 400 as a plasticizer. Heat the solution and keep standing for half an hour to get the proper viscosity. (Stir the solution continuously while heating). Sonicate the solution for 15 mins to remove the air bubbles. Then keep the solution overnight and next day casting procedure was carried out. Next day, lubricate the Petri dish with the help of castor oil. Pour the solution in Petri dish and keep it overnight for

proper drying. After complete drying of film, the film was removed with the help of a cutter. Wrap the film with aluminum foil and store in normal room temperature. [7]

Table No.1-Formulation for Fast Dissolving Sublingual Film of Zolmitriptan.

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Zolmitriptan (mg)	80	80	80	80	80	80	80	80	80
2	HPMC K4M (gm)	1.5	1.5	1.5	1.8	1.9	2.0	2.1	2.1	2.1
3	PEG 400 (ml)	1	1	1	1	1	1	1	1	1
4	Ethanol (ml)	30	25	20	30	25	20	30	25	20
5	Water (ml)	20	25	30	20	30	20	25	20	30

Table No.2-Formulation for Fast Dissolving Sublingual Film of Zolmitriptan

Sr. No.	Ingredients	F10	F11	F12	F13	F14	F15	F16	F17	F18
1	Zolmitriptan (mg)	80	80	80	80	80	80	80	80	80
2	Pectin (gm)	1.5	1.5	1.5	1.8	1.9	2.0	2.1	2.1	2.1
3	PEG400 (ml)	1	1	1	1	1	1	1	1	1
4	Ethanol (ml)	30	25	20	30	25	20	30	25	20
5	Water (ml)	20	25	30	20	30	20	25	20	30

Evaluation Parameter of Fast Dissolving Sublingual Film

Thickness:

The thickness of the film was measured using digital vernier caliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the film and the average was taken and Standard Deviation was calculated. [8]

Weight variation:

Four centimeter square (2 X 2 cm) of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated. [9]

Folding Endurance:

Folding endurance was determined by repeated folding of the film at the same place until the strip breaks. The number of times the film is folded without breaking was computed as the folding endurance value. [10]

Tensile Strength: [11]

Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area (MPa).

$$\textbf{Tensile strength} = \frac{\textbf{Force at break (N)}}{\textbf{Initial cross-section area (mm}^2\textbf{)}}$$

Percentage Elongation: [12]

For the determination of percentage elongation of the film formulations, the distance between the tensile grips of the tensile strength testing film was measured before and after the fracture of the film. Then the percentage elongation of the films was computed with the help of the formula given below:-

$$\textbf{\% E = Df – D0/D0 × 100}$$

Where: - % E = Percentage elongation

D0 = Distance between the tensile grips before the fracture of the film.

Df = Distance between the tensile grips after the fracture of the film

$$\textbf{\% Elongation} = \frac{\textbf{Increasing in length of strip}}{\textbf{The initial length of the strip}} \times 100$$

Surface pH:

It was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. The oral film was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film.

The procedure was performed in triplicate and average with standard deviation was reported. [13]

Disintegration Time:

In-vitro disintegration time was determined visually in a Petri dish containing 25 ml of pH 7.2 artificial saliva with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates. [14]

Drug Content:

Drug content determination of the film was carried out by dissolving the film of 4 cm^2 in 100 ml of pH 7.2 artificial saliva using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at λmax of 237 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation were recorded. [15]

In-vitro Dissolution:

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 900 ml of pH 7.2 artificial saliva maintained at 37°C at 50 rpm. 10 ml aliquots of samples were taken at various time intervals which were replaced with the same volume of fresh pH 7.2 artificial saliva maintained at 37°C. Zolmitriptan in the samples was then determined spectrophotometrically at λmax of 237 nm. The results were expressed as the mean of three determinations. [16, 17]

Infrared spectroscopy:

Zolmitriptan was identified and confirmed by using an FT-IR spectrometer-80 (Shimadzu Corporation, Japan). The samples were weighed out and mixed thoroughly with potassium bromide. This mixture was transferred to an agate mortar and powder. The resulting powder was mixed thoroughly and compressed to clear disc using Space Pellet Press, under the force of 10 tons of pressure for 5 min under a vacuum. The bands (cm-1) have been assigned.

Differential scanning Calorimetry (DSC) study of the pure drug:

The melting point of the drug was determined by using DSC. Thermogram for Zolmitriptan was obtained using DSC (Mettler Toledo, Switzerland). The drug was sealed in perforated aluminum pans and heated at a constant rate of 80C/min over the starting temperature ranges

of 350C. A sample consisting of the pure drug (Zolmitriptan), polymer (HPMC K4M) and a sample of the mixture (Zolmitriptan + HPMC K4M) (Zolmitriptan + Pectin)were analyzed for differential scanning calorimetry (DSC) at Department of Pharmaceutics. Differential scanning calorimetry curves were obtained by differential scanning calorimeter (DCS 60, TA 60WS and Mettler DSC 1Star System Zurich, Switzerland.) at a heating rate of 50 C/min.

Stability Study:

Stability study was carried out at room conditions. Each piece of the films of the formulation was packed in butter paper followed by aluminum foil and plastic tape. After 4 weeks, the films were evaluated for the physical appearance, surface pH, drug content and in vitro drug release. In in-vitro % drug release studies, dissolution at 10 minutes compared with respective formulation batch. [18]

RESULTS AND DISCUSSION

The pre-formulation study was performed by Infrared Spectroscopy and found that there was no interaction between Zolmitriptan and excipients (Figure 1-4)**.**

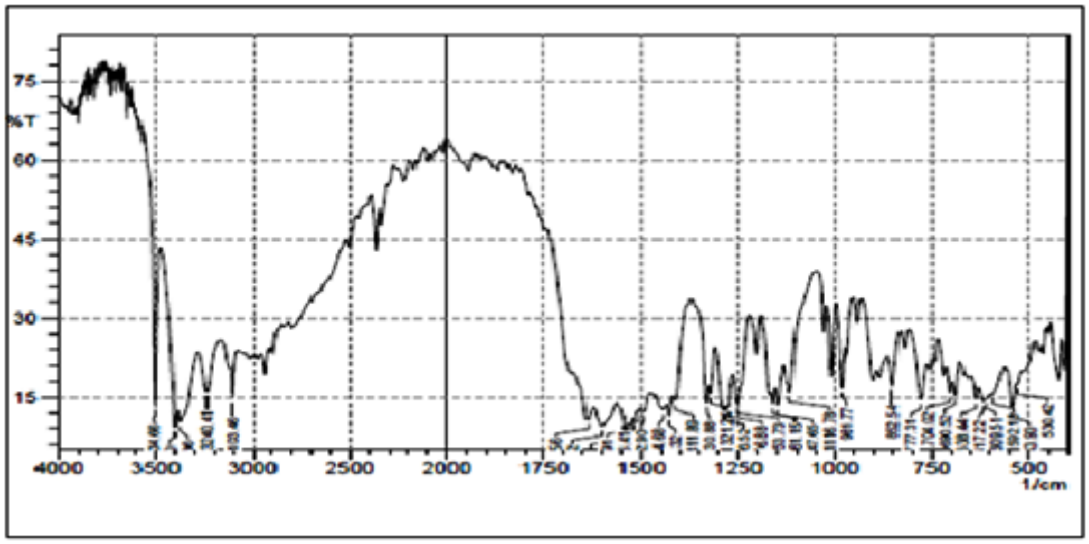

Figure No.1-FT-IR spectra of Pure Drug Zolmitriptan.

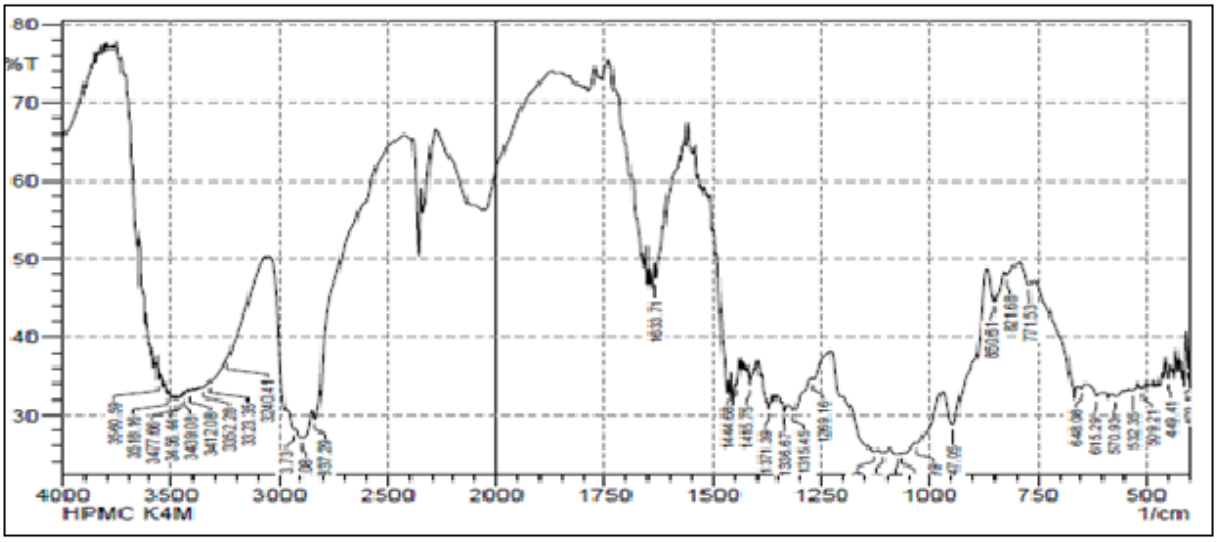

Figure No. 2-FT-IR spectra of HPMC K4M.

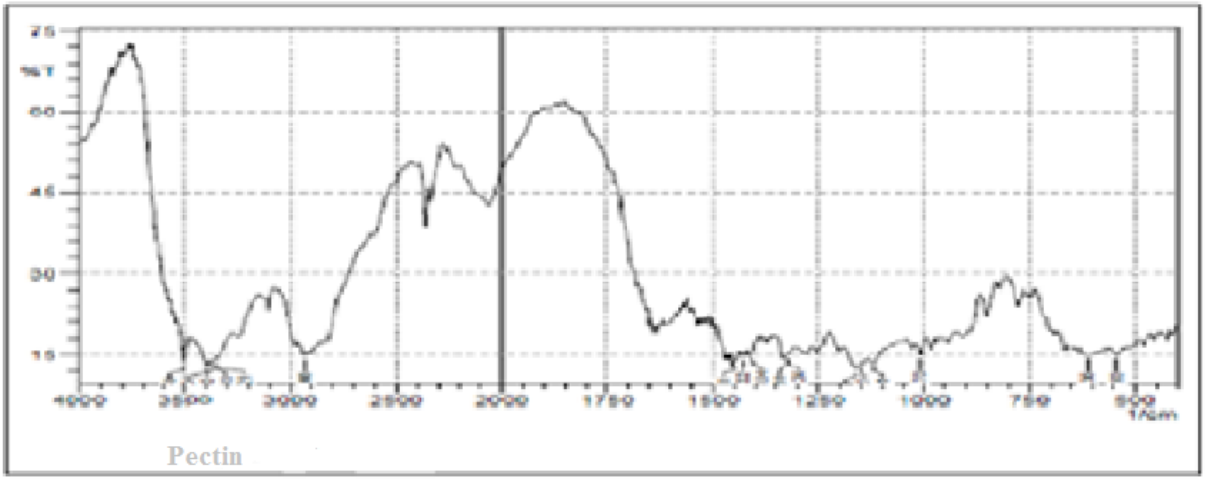

Figure No.3-FT-IR spectra of Pectin.

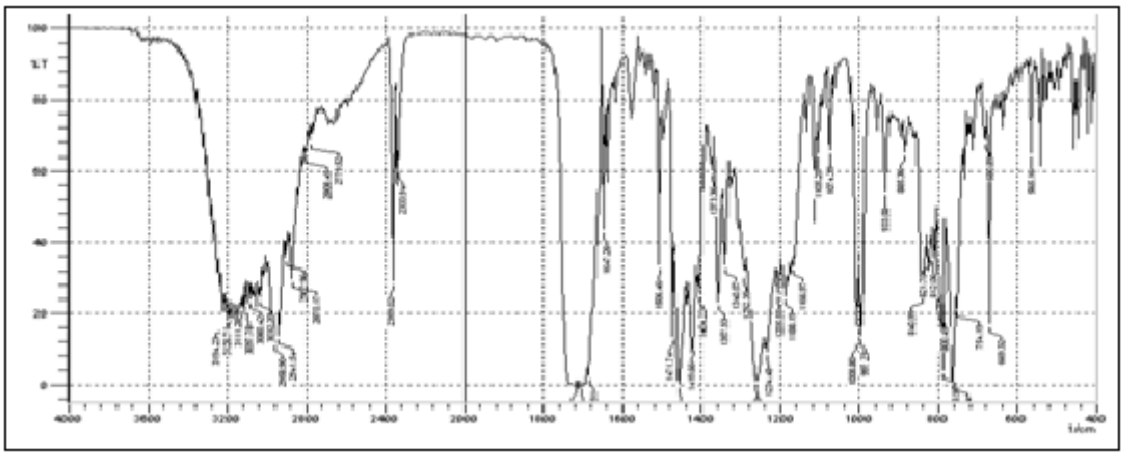

Figure No.4- FT-IR spectra of Optimized Batch F9.

Thickness:

As all the formulations contain different amount of polymers, hence the thickness was gradual increases with the number of polymers. All the film formulations were found to have a thickness in the range of 0.05mm to 0.15 mm. The result was shown in table no.3.

Weight Variation:

Three films each of 4cm2 were cut at three different places from the casted film and weight variation was determined. Weight variation varies from 49.33 mg to 66.66 mg. Results were shown in table no.3.

Surface pH:-

The surface pH of the films was ranging from 6.67 to 6.93. Since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity. Results were shown in table no.3.

Table No.3-Evaluation Parameter of Sublingual Film Batch F1 to F18.

Formulation Code	Thickness (mm)	Weight (mg)/4cm2	Surface pH
F1	0.053±0.0057	49.33±0.472	6.86±0.057
F2	0.066±0.0000	51.33±0.472	6.90±0.100
F3	0.0880.0057	53.33±0.472	6.96±0.057
F4	0.093±0.0057	55.33±0.472	7.06±0.057
F5	0.100±0.0057	58.00±0.472	7.00±0.100
F6	0.113±0.0057	60.33+0.472	7.10±0.100
F7	0.126±0.0057	62.33±0.472	7.03±0.152
F8	0.140±0.0000	64.66±0.472	7.06±0.057
F9	0.150±0.0000	66.66±0.472	7.16±0.057
F10	0.146±0.0000	65.30±0.472	7.04±0.057
F11	0.148±0.0000	64.18±0.472	7.02±0.150
F12	0.148±0.0050	65.96±0.472	7.14±0.057
F13	0.142±0.0057	62.40±0.472	6.98±0.057
F14	0.137±0.0000	60.33±0.472	6.94±0.100
F15	0.129±0.0057	59.72±0.472	6.90±0.100
F16	0.117±0.0057	57.80±0.472	6.88±0.057
F17	0.100±0.0057	56.82±0.472	6.86±0.057
F18	0.90±0.0000	52.00±0.472	6.80±0.057

n=6±SD.

Disintegration Time:

It was observed that disintegration time varies from 19 to 30 sec for all the formulations. Disintegration time of Fast Dissolving Film containing HPMC K4M as polymer was affected by the thickness of the film. Disintegration time of the films was found to increase with the increase in the amount of the polymer. Results were shown in table no.4.

Folding Endurance:

Folding endurance of film was increased with the increase in the concentration of polymer. The number of time the film fold until it broke is reported. The maximum folding endurance occurred in F9 & F12 Batch. Results were shown in table no.4.

Table No.4-Evaluation Parameter of Sublingual Film Batch F1 to F18.

Formulation Code	Disintegration Time in sec.	Folding Endurance
F1	19.00±1.73	201±3.60
F2	18.33±1.54	212±2.08
F3	17.66±0.57	220±5.00
F4	22.33±0.57	229±7.50
F5	23.66±0.57	241±9.07
F6	25.33±0.57	249±6.55
F7	27.66±0.57	264±8.38
F8	29.00±0.00	273±2.88
F9	30.00±0.00	278±1.52
F10	28.73±0.00	276±1.52
F11	28.86±0.00	232±7.50
F12	29.68±0.00	279±1.52
F13	25.48±0.57	260±8.32
F14	23.73±0.57	255±6.55
F15	22.69±0.57	247±6.52
F16	17.82±0.00	238±7.50
F17	18.76±0.00	220±5.00
F18	18.64±0.00	238±7.49

n=6±SD.

Tensile Strength:

The tensile strength was found to increase with the concentration of HPMC K4M. Formulation F9 was found the maximum of 53.95 mg. The result was shown in table no.5.

Elongation:

The percentage elongation of all the batches ranges from 5-20 mm elongation. It increased upon polymer as shown by the formulations. Formulation F9 F12 had highest percentage elongation. Results were shown in table no.5.

Drug Content:

The prepared film formulations were assayed for drug content. It was observed that all the formulations were satisfactory showing drug content as per labeled amount. Results were shown in table no.5.

Table No.5-Evaluation Parameter of Sublingual Film Batch F1 to F18.

Formulation Code	Tensile Strength (mg) with S.D.	Elongation (mm) with S.D.	Drug Content (%) with S.D.
F1	51.83±0.015	5.33±0.57	92.13±0.32
F2	51.53±0.011	5.66±0.57	94.30±0.10
F3	52.92±0.025	6.66±0.57	93.63±0.35
F4	52.72±0.037	8.33±0.57	93.53±0.23
F5	53.52±0.025	10.00±0.00	93.40±0.45
F6	53.02±0.068	10.66±0.57	93.16±0.28
F7	53.22±0.026	13.00±0.00	94.60±0.30
F8	53.59±0.136	13.66±0.57	94.33±0.28
F9	53.95±0.050	14.66±0.57	95.11±0.90
F10	53.02±0.015	14.29±0.57	94.86±0.78
F11	52.68±0.021	13.56±0.00	94.47±0.31
F12	53.92±0.025	14.80±0.57	94.98±0.23
F13	52.47±0.011	11.98±0.57	93.76±0.24
F14	52.26±0.026	10.47±0.57	93.27±0.21
F15	51.87±0.015	9.04±0.00	93.04±0.20
F16	51.68±0.014	8.35±0.57	92.32±0.18
F17	51.48±0.011	6.40±0.00	92.57±0.18
F18	51.18±0.09	6.37±0.57	92.20±0.14

n=6±SD.

Dissolution Study:

Rapid dissolution of all the film preparations was observed by the dissolution test, in which approximately 90% of Zolmitriptan within 10 min. The formulations F1 to F18 showed

approximately 95 to 99% drug release within 10 minutes. It was also observed that HPMC K4M & Pectin was able to modulate the Zolmitriptan release as a lower amount of HPMC K4M as well as Pectin resulted in the release of drug a faster rate. Results were shown in figure no.5.

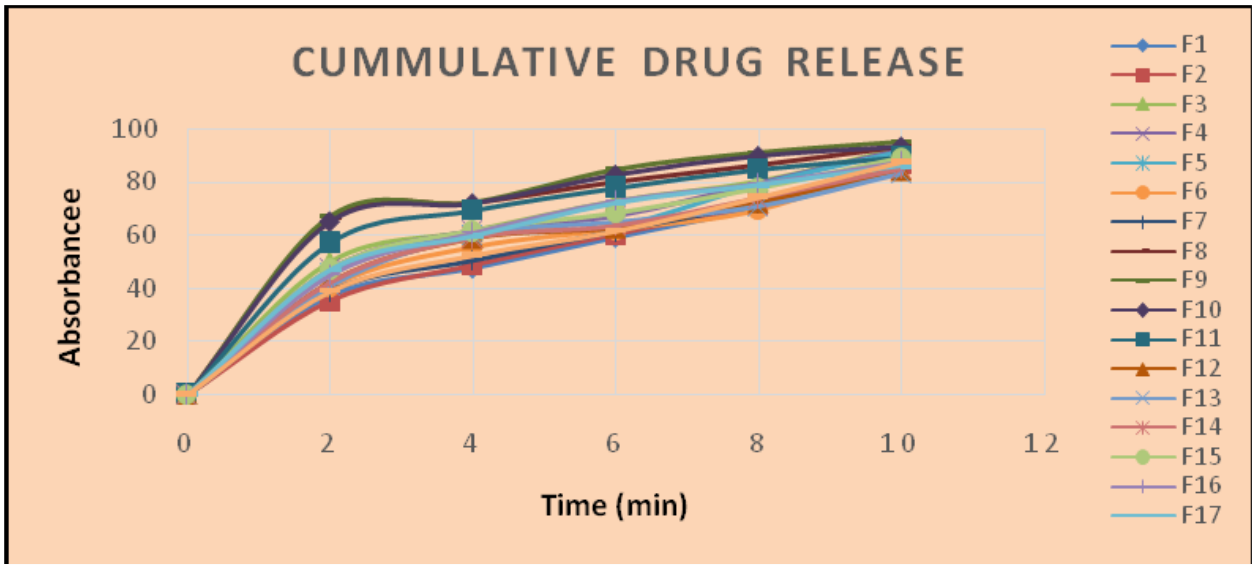

Figure No. 5-In-vitro Dissolution Profile of Formulation Batch F1 to F18.

Differential Scanning Calorimetry (DSC) Study

The preformulation study was performed by Differential Scanning Calorimetric (DSC) and found that there was no interaction between Zolmitriptan and excipients. By the Differential Scanning Calorimetry conclude that Zolmitriptan gives a peek at 143.460C which has its Melting point peak which is correlated with formulation Melting point peak. So, there was no interaction between Drug and Polymers. HPMC K4M gives a peek at 271.330C so, 271.330C is Melting point of HPMC K4M.

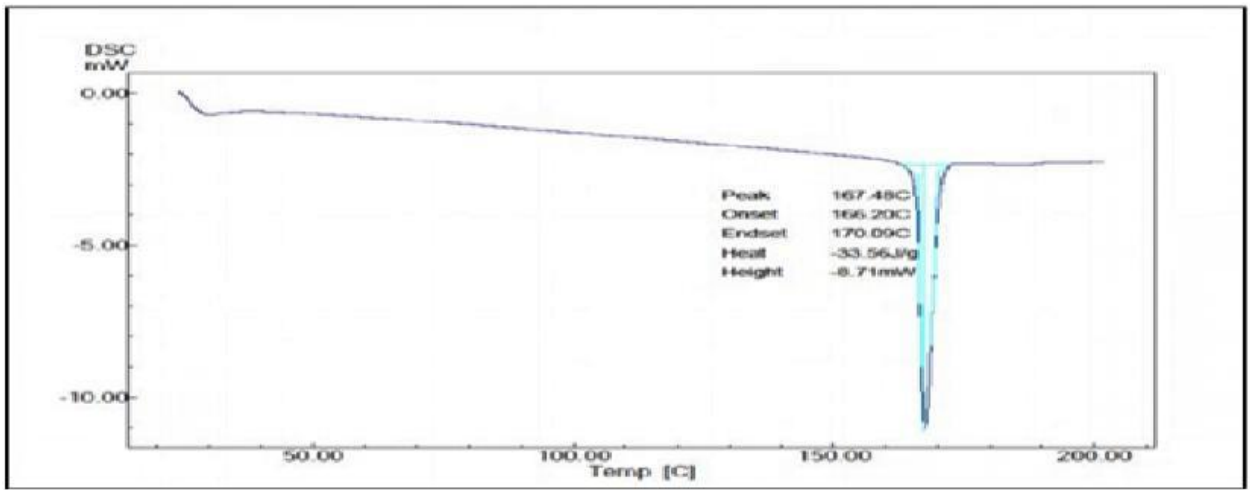

Figure No.6-DSC study of Risperidone (Pure Drug).

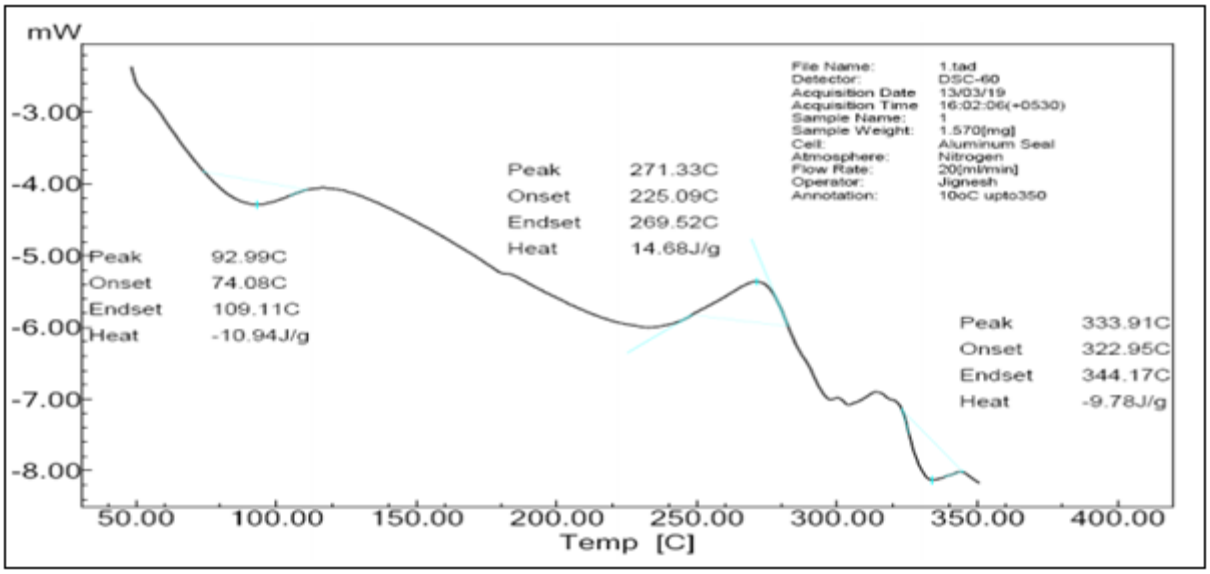

Figure No.7-DSC study of Polymer (HPMC K4M).

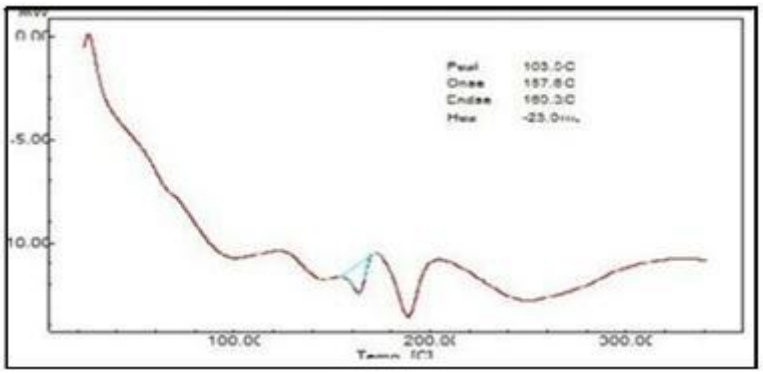

Figure No. 8-DSC study of Polymer Pectin.

Stability Study:

The stability study of the formulation F1 and F18 was carried out at normal room conditions for one month. The films do not show any change in appearance and flexibility. The drug content and surface pH was found almost constant for up to one month. Dissolution time of the films after the stability study was also not found to be affected. Results were shown in table no.6 & table no.7.

In Vitro Dissolution Study:

Result of dissolution study of the films after the stability study was also not found to be affected Results was shown in table no.6 & 7.

Table No.6-Evaluation of optimized batch F9 during stability studies.

Stability condition Observation:

Accelerated Condition (40±20C and 75±5%RH)

Sampling time	Folding endurance	In-vitro DT (seconds)	Visual appearance	Drug Content	Surface pH	% CDR
Initial (0day)	278	30	Clear homogeneous	95.11	7.16	95.11
After 10 days	279	32	film	95.02	7.15	95.08
After 20 days	278	35	Slightly hazy film	94.97	7.15	94.97
After 30 days	280	37	Slight recrystalization	94.95	7.14	94.95

Table No. 7-Evaluation of optimized batch F12 during stability studies.

Stability condition Observation:

Accelerated Condition (40±2ºC and 75±5%RH)

Sampling time	Folding endurance	In-vitro DT (seconds)	Visual appearance	Drug Content	Surface pH	% CDR
Initial (0day)	279	29	Clear homogeneous	94.98	7.14	94.57
After 10 days	275	30	film	94.95	7.12	94.49
After 20 days	276	32	Slightly hazy film	94.92	7.12	94.41
After 30 days	281	35	Slight recrystalization	94.90	7.10	94.38

Optimized formulation F9 & F12 at 40ºC± 2 oC, 75% RH ± 5 % was found to be stable up to 30 days. There was no significant change in drug content, visual appearance i.e. change in color. All Formulations stored at elevated temperature showed a slight change in pH and *in-vitro* residence time, other parameters were found to be unchanged.

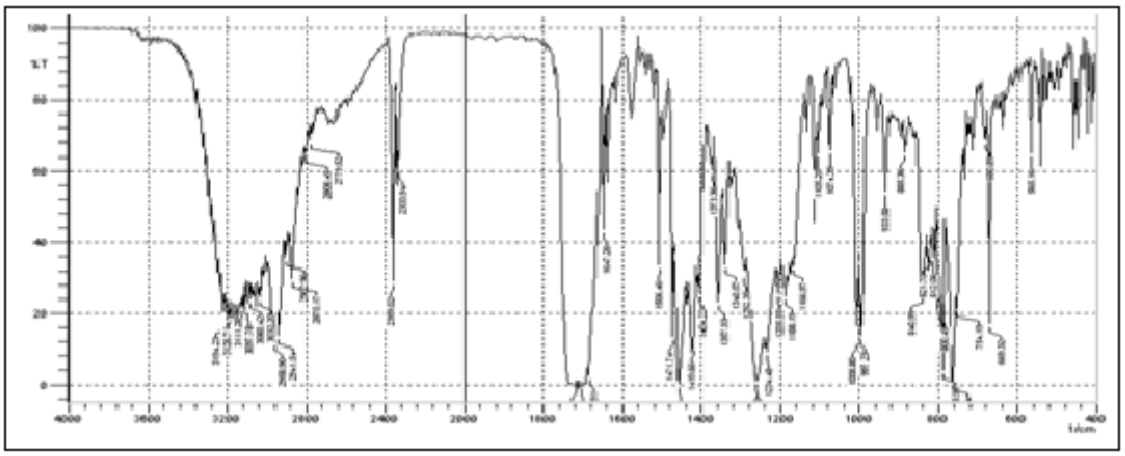

Figure No. 9- FT-IR spectra of Optimized Batch F9.

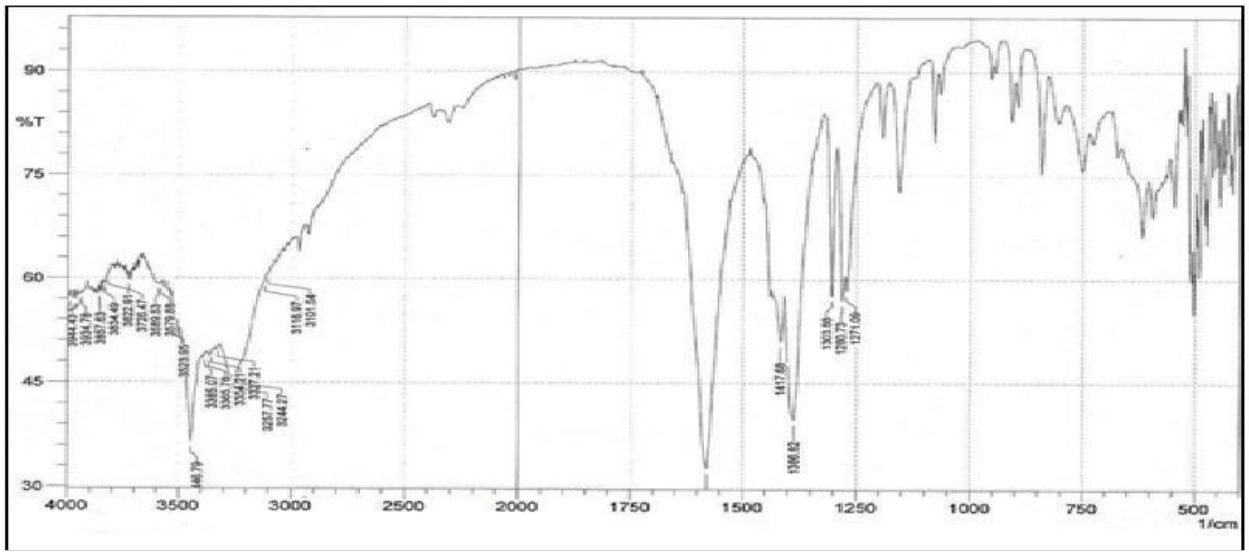

Figure No. 10- FT-IR spectra of Optimized Batch F12.

CONCLUSION

The fast disintegrating sublingual dosage form of Zolmitriptan offers a fast release of drug beneath the tongue and it reaches the systemic circulation directly with improved patient compliance particularly for those who have difficulty in swallowing. From the above results, we can conclude that 3% of HPMC K4M gives an immediate release of drug as compared to another formulation batch. Zolmitriptan is used in the treatment of Antimigraine. The quick onset of action is desirable in the acute treatment of these disorders. From the present investigation, it can be concluded that fast-dissolving sublingual film formulation can be a potential novel drug dosage form for pediatrics, geriatrics and also for the general population.

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