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Research Article

Formulation Development and Evaluation of Mouth Dissolving Film of Ivabradine HCL

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ABSTRACT

Oral film is the latest technology in the production of oral disintegrating dosage forms. They are thin and elegant films of edible water-soluble polymers of various sizes and shapes (such as square, rectangular or disc). The stripes can be flexible or brittle, opaque or transparent. The present investigation was undertaken to formulate Ivabradine HCL oral films. For the treatment of hypertension. F1-F3 were carried out with HPMC E15 cps, PEG 400, sodium saccharin, citric acid and flavor. The films were clear and transparent. The thickness also uniform. The flexibility also good. The films shown good mechanical properties. According to the assay result the drug was properly loaded in the film. The formulated films were more brittleness. Among all the formulations F3 shown good mechanical properties and less disintegration time of 20 seconds. All the parameters of film were found to be satisfactory. And the dissolution profile was found to be desirable and reproducible. The morphological study (SEM) of F3 shows more porous. Therefore, rapid drug release was achieved for the immediate onset of action. The stability studies were performed for about 1 month and 3 months. No significant changes were observed in the thickness, tensile strength, in-vitro disintegration and in-vitro drug release. The film (F3) samples evaluated gave maximum release within 3 minutes indicating the rapid drug release profile which entails in faster onset of action for the medicament. Therefore, the oral films have considerable advantage over the conventional dosage forms.

INTRODUCTION

Numerous illnesses and conditions have been developed for topical application. Since topical the oral route is one of the most preferred routes of drug administration as it is more convenient, cost effective, and ease of administration lead to high level of patient compliance. The oral route is problematic because of the swallowing difficulty for pediatric and geriatric patients who have fear

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of choking. Patient convenience and compliance-oriented research has resulted in bringing out safer and newer drug delivery systems. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self-administration even without water or chewing.

Recently, fast dissolving films are gaining interest as an alternative of fast dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance. As the drug is directly absorbed into systemic circulation, degradation in gastrointestinal tract and first pass effect can be avoided. These points make this formulation most popular and acceptable among paediatric and geriatric patients and patients with fear of choking. Over-the-counter films for pain management and motion sickness are commercialized in the US markets. Many companies are utilizing transdermal drug delivery technology to develop thin film formats. In the present review, recent advancements regarding fast dissolving buccal film formulation and their evaluation parameters are compiled.

MATERIALS AND METHODOLOGY

Materials

Ivabradine HCL was purchased Invochem Laboratory, HPMC E15 was from Accent microcell industries, HPMC E50 was from Symonds pvt ltd, PEG 400 was from BASF, Propylene glycol was from Spectrum chemicals and Sodium saccharin was from Aptuit laurus ltd. All other reagents used were of analytical grade.

Table 1: Composition of formulation

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ivabradine HCL (mg)	125	125	125	125	125	125	125	125	125
HPMC E12 (g)	1.0	1.25	1.5	-	-	-	1.25	-	1.25
HPMC E5 (g)	-	-	-	1.0	1.25	1.5	-	1.25	1.25
PEG 400 (g)	1.5	1.25	1.0	-	-	-	-	1.25	-
Propylene glycol (ml)	-	-	-	1.5	1.25	1.0	1.25	-	-
Citric acid (g)	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Sodium Saccharin (g)	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
Flavor (g)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Distilled water (ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

METHOD OF PREPARATION OF MDF:

Methodology

The water-soluble polymer and plasticizer are dissolved in distilled water. Stir the solution on a magnetic stirrer for 2 hours and set aside to remove all trapped air bubbles. At the same time, dissolve the excipients and drugs and fully stir for 30 minutes. After the stirring is completed, mix the two solutions. Finally, the solution is poured on a suitable petrochemical plate to form a thin film. The plate was kept in a hot air oven at 60°C for 1 hour. The dried film is gently peeled from the glass plate and cut to the required size.

Dose calculations:

Inner radius of glass plate = 7.1 cm.

Inner Area of the plate (πr2) = 2 x 7.1 x 7.1 = 100 cm2.

No. of 4 cm2 films present whole plate =100/4 =25 films.

Each films contains 5 mg of drug.

25 films contain 125 mg drug (25×5). Labelled claim= 5 mg.

Standard Graph of Ivabradine HCL

The stock solution was prepared with 50 mg Ivabradine hydrochloride in 100 ml water. Extract 10 ml from this stock solution and dilute to 100 ml with water. Prepare the calibration curve by appropriately diluting the stock solution and using different concentrations (20 µg/ml-100 µg/ml). The absorbance is measured at 234 nm.

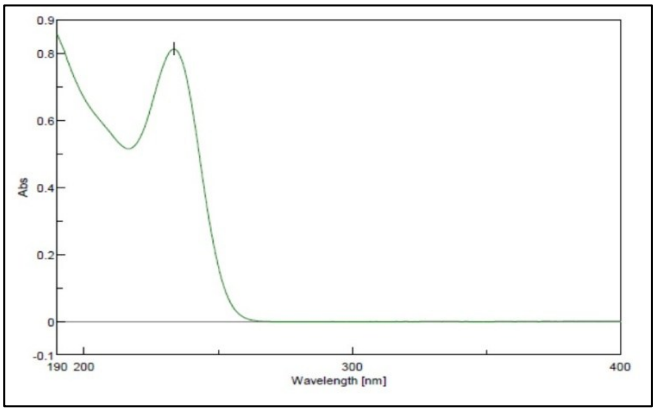

Figure 1: UV spectra of Ivabradine HCL

EVALUATION PARAMETERS

Thickness

Use a micrometer thread gauge to measure the thickness of the film. In order to obtain the uniformity of the film, the thickness was measured at 5 different places. The thickness of the film must be less than 5%.

Weight variation

Ten films were randomly selected, and their average weight was weighed. Individual films were weighed and compared with the average weight for the deviation.

Folding endurance

To determine the bending resistance, the film was cut and quickly folded in the same position until it broke. The number of times the film can be bent at the same position without breaking gives the value of the bending strength. The resistance of the film to partial folding is 100-150.

Percentage elongation

It was calculated by,

$$\% \text{ elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the formula.

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

In-vitro disintegration

Disintegrating time is defined as the time (sec) at which a film breaks when brought in contact with water or saliva.

Petri dish method

Put 2ml of distilled water into a petri dish, add a film on the water surface, and measure the time for the oral film to completely dissolve.

In-vitro dissolution

Use 900 ml 0.1N HCl as the medium and keep it at 37±0.5°C while setting the basket to 100 rpm. Cut a 4 cm2 (2 x 2 cm) film sample and place it in the basket. Take 5 ml samples every 2 minutes and replace the same amount of samples with fresh 0.1N HCl. The extracted samples were filtered and analysed using an ultraviolet spectrometer at a wavelength of 234 nm.

Drug content

The test is performed by dissolving a 4 cm2 area film in 50 ml 0.1N HCl under stirring. Filter the solution using Whatmann filter paper and dilute the filtrate to 100 ml with the same buffer in a volumetric flask. The solution was analysed using an ultraviolet spectrometer.

Assay

The test is performed by dissolving a 4 cm area film in 50 ml of pH 6.8 phosphate buffer under stirring. Filter the solution using Whatmann filter paper and dilute the filtrate to 100 ml with the same buffer in a volumetric flask. The solution was analysed using an ultraviolet spectrophotometer.

Stability studies

Stability studies are conducted according to ICH to evaluate the stability of pharmaceutical preparations. The optimized formula of F3 is sealed in polyethylene laminated aluminum

packaging. The samples were kept at 40 degrees Celsius and 75% RH for 3 months. At the end of the study period, changes in the physical appearance, color, drug content and drug release characteristics of the preparation were observed.

SEM analysis

The morphological study of the oral adhesive strips is carried out by scanning electron microscopy (SEM) at a prescribed magnification. The research involves the difference between the upper and lower surfaces of the film. It also helps determine API distribution.

RESULT AND DISCUSSION

Calibration of Ivabradine HCL

The stock solution was prepared with 50 mg Ivabradine hydrochloride in 100 ml water. Extract 10 ml from this stock solution and dilute to 100 ml with water. Prepare the calibration curve by appropriately diluting the stock solution and using different concentrations (20 µg/ml-100 µg/ml). The absorbance is measured at 234 nm. The absorbance of various concentrations measured at 234 nm. [14]

Table 2: Calibration Curve of Ivabradine HCL

Sr. No.	Conc.(ppm)	Absorbance
1	20	0.228
2	40	0.436
3	60	0.621
4	80	0.824
5	100	0.998

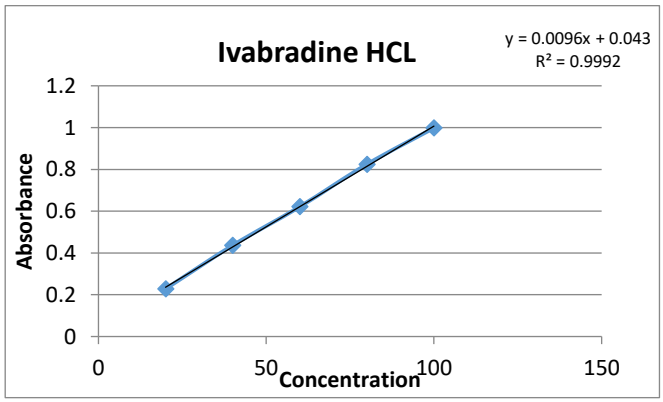

Figure 2: Calibration curve of Ivabradine HCL

Fourier Transform Infrared Spectroscopy

The FTIR spectrum of Ivabradine HCL has been shown in below figure. The major peaks observed. The spectrum shows characteristic peaks for Ivabradine HCL. [16,18]

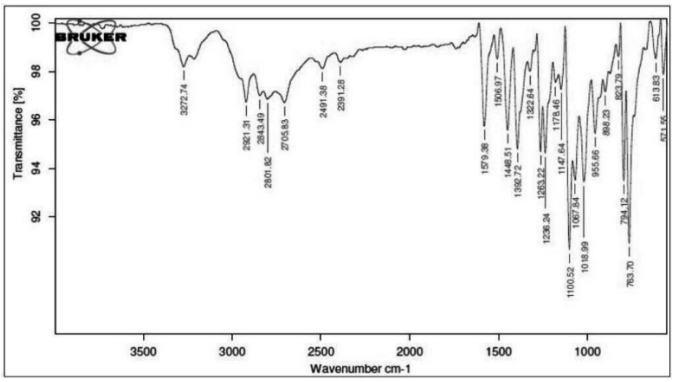

Figure 3: Representative IR spectrum of Ivabradine HCL

The absorption bands shown by Ivabradine HCL are characteristics of the groups present in its molecular structure. The presence of absorption bands corresponding to the functional groups present in the structure of Ivabradine HCL confirms the identification and purity of the Ivabradine HCL sample used in the study. [19,20]

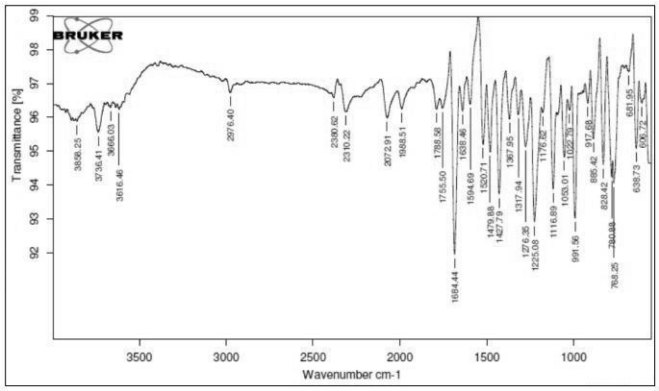

Figure 4: FTIR of Physical mixture

Table 3: Interpretation of FTIR Spectrum of physical mixture

Functional Group	Peaks	
	Pure Drug	Physical Mixture
N-H (Stretch)	Yes	Yes
C-H (Bending)	Yes	Yes
C=O (Stretch)	Yes	Yes

C=C (Stretch)	Yes	Yes
N-H (Stretch)	Yes	Yes

EVALUATION OF NANOEMULSION

Thickness

In order to obtain the uniformity of the film, the thickness was measured at 5 different places. The thickness of the film must be less than 5%.

Folding endurance

The number of times the film can be bent at the same position without breaking gives the value of the bending strength. The local folding resistance of the film is between 100-150.

Zeta Potential

According to the ICH recommendations for stability tests of different pharmaceutical formulations, zeta potential indicates the stability of the (colloidal dispersion) nanoemulsion under stress testing conditions. The zeta potential is altered by particle size; the lowest particle size in nano size, i.e., 100, exhibits -32 mV. The zeta potential implies thermodynamic instability of the dispersion.

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the formula.

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

Percentage elongation

It was calculated by

$$\text{Percentage elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

In-vitro disintegration

Petri dish method

Put 2ml of distilled water into a petri dish, add a film on the water surface, and measure the time for the oral film to completely dissolve.

Table 4: Evaluation parameters

Formulations	Thickness (mm)	Folding endurance	Tensils trength (g/cm2)	% elongation	In-vitro disintegration time(sec)
F1	0.58	9	48.41	8	25
F2	0.55	10	51.18	9	28
F3	0.59	13	62.04	11	20
F4	0.51	9	54.25	9	31
F5	0.53	11	53.68	10	35
F6	0.52	11	52.33	8	27
F7	0.55	12	56.45	7	36
F8	0.57	1	57.62	9	32
F9	0.53	9	48.63	10	35

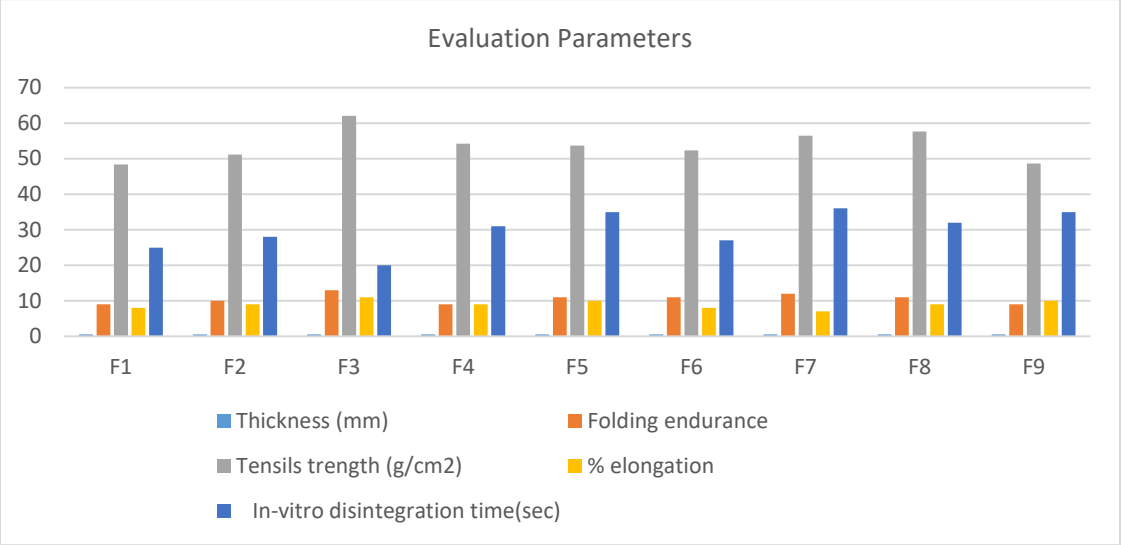

Figure 5: Bar chart of evaluation parameters

Weight variation

Ten films are randomly selected, and their average weight is weighed. Weigh a single film and compare it with the average deviation weight.

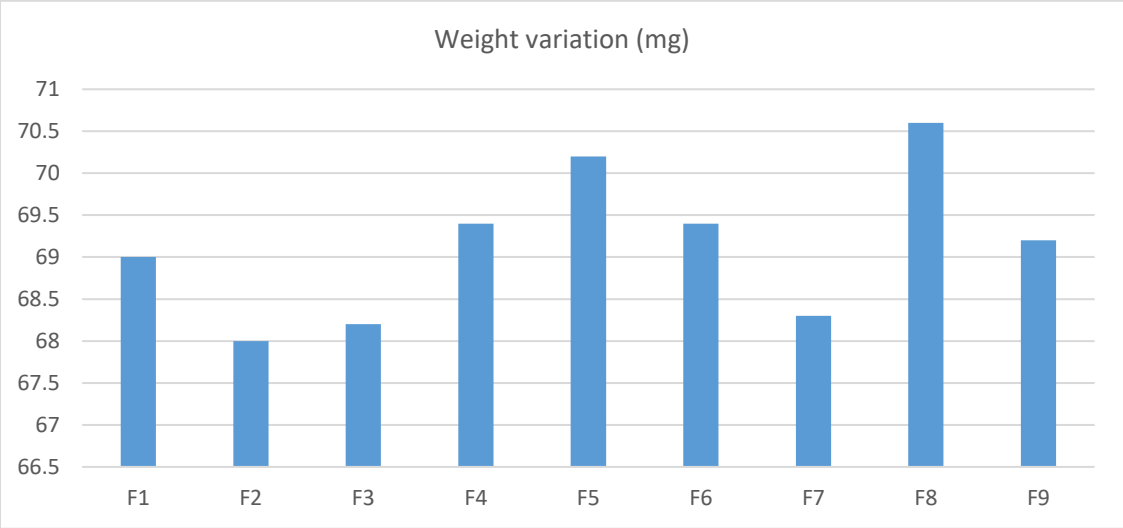

Figure 6: Bar chart of weight variation

Drug Content

The test is performed by dissolving a 4 cm2 area film in 50 ml of 0.1 N HCl under stirring. Filter the solution using Whatmann filter paper and dilute the filtrate to 100 ml with the same buffer in a volumetric flask. The solution was analyzed using an ultraviolet spectrometer.

Assay

The test is performed by dissolving a 4 cm2 area film in 50 ml pH 6.8 phosphate buffer under stirring. Filter the solution using Whatmann filter paper and dilute the filtrate to 100 ml with the same buffer in a volumetric flask. The solution was analyzed using an ultraviolet spectrophotometer.

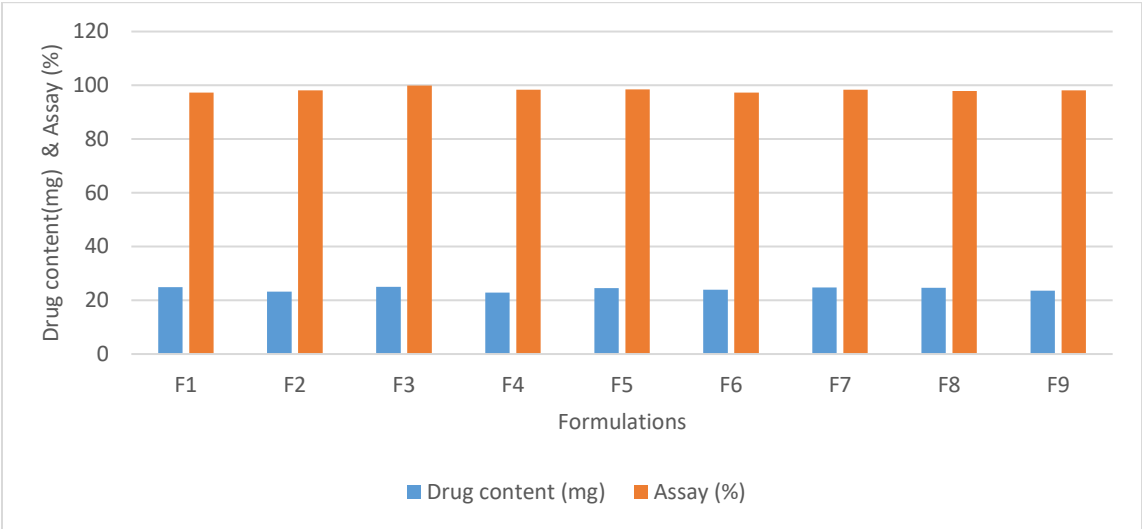

Figure 7: Bar chart of drug content and assay

In-vitro dissolution

Use 900 ml 0.1N HCl as the medium and keep it at 37±0.5°C while setting the basket to 100 rpm. Cut a 4 cm2 (2 x 2 cm) film sample and place it in the basket. Take 5 ml samples every 30 seconds and replace the same number of samples with fresh 0.1 N HCl. The extracted samples were filtered and analyzed using an ultraviolet spectrometer at a wavelength of 234 nm.

Table 5: *In-vitro* dissolution of F1-F9

Percentage drug released									
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0.5	19	21	17	23	23	21	21	17	20
1.0	32	36	37	42	41	38	38	34	36
1.5	52	58	43	58	54	57	55	58	61
2.0	71	68	78	73	72	69	69	71	70
2.5	84	86	82	81	79	84	82	82	81
3.0	93	97	99	95	94	92	97	97	96

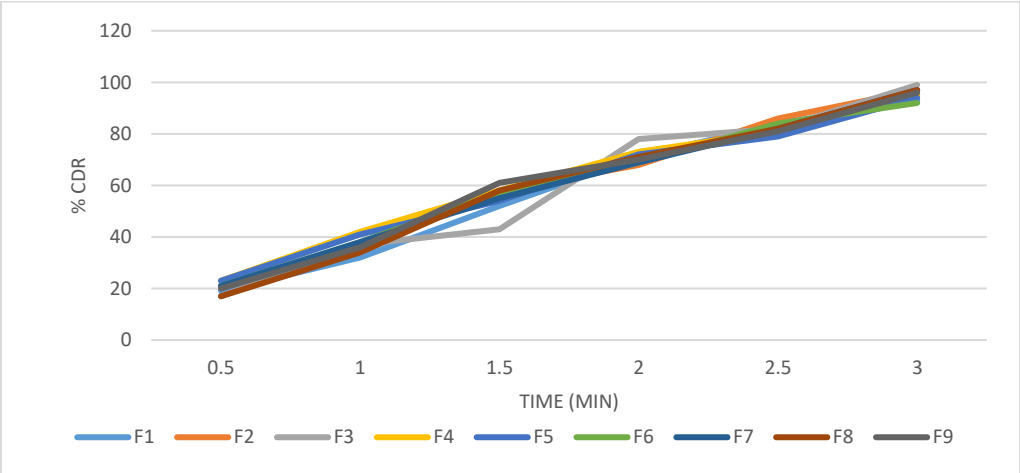

Figure 8: *In-vitro* dissolution of F1-F9

Comparison of in-vitro drug release data of marketed formulation and formulation 3

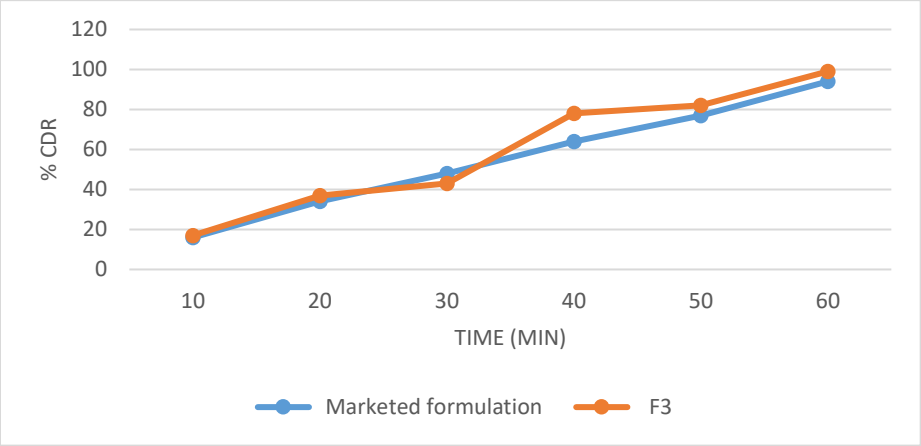

Figure 9: Comparison of in-vitro drug release data of marketed formulation and formulation 3

Stability Studies (F3)

Stability studies are conducted according to ICH to evaluate the stability of pharmaceutical preparations. The optimized formula of F3 is sealed in polyethylene laminated aluminum packaging. The samples were kept at 40 degrees Celsius and 75% RH for 3 months. At the end of the study period, changes in the physical appearance, color, drug content, and drug release characteristics of the preparation were observed.

Sem Analysis

The morphological study of the oral adhesive strips is carried out by scanning electron microscopy (SEM) at a prescribed magnification. The research involves the difference between the upper and lower surfaces of the film. It also helps determine API distribution.

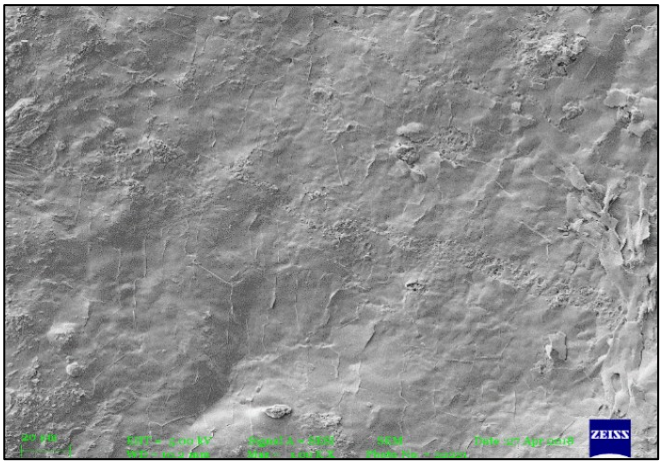

Figure 10: SEM images of F3 formulation

Table 6: Stability studies [Condition (40°C/75%RH)]

Parameters	Initial	1 month	3 months
Thickness (mm)	0.59	0.59	0.59
Folding endurance	13	13	12
Tensile strength (gm/cm^2)	54.25	54.25	53.01
in-vitro disintegration time (sec)	20	20	22
in-vitro dissolution (%)	99.26	99.26	99.06

CONCLUSION

Among all the formulations F3 shown good mechanical properties and less disintegration time of 20 seconds. All the parameters of film were found to be satisfactory. And the dissolution profile was found to be desirable and reproducible. The morphological study (SEM) of F3 shows more porous. Therefore, rapid drug release was achieved for the immediate onset of action. The stability studies were performed for

about 1 month and 3 months. No significant changes were observed in the thickness, tensile strength, in-vitro disintegration and in-vitro drug release. The film (F3) samples evaluated gave maximum release within 3 minutes indicating the rapid drug release profile which entails in faster onset of action for the medicament. Therefore, the oral films have considerable advantage over the conventional dosage forms.

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