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FORMULATION AND EVALUATION OF FAST DISSOLVING BUCCAL FILM CONTANING DABIGATRAN ETEXILATE

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ABSTRACT

The main aim of this research is to improve the bio-availability of a drug Dabigatran etexilate by formulating and evaluating the fast dissolving buccal film containing Dabigatran etexilate, that helps to avoid the first pass metabolism easy compliance for patient and it is easy for administration. Dabigatran etexilate is anticoagulant that used to treat deep vein thrombosis, pulmonary embolism. Buccal films were prepared by solvent casting method by using different polymers alone and combination, Polymers like HPMC E 15, PVA, PVP K30, glycerine acts as plasticizer, saccharin acts as sweetening agent, sodium citrate acts as saliva stimulating agent, vanillin acts as flavouring agent. FTIR studies shows that there is no interaction between drug and polymer. By using calibration curve method find out the % of drug release, dissolution profile were studied by using dissolution apparatus USP type-2 by using phosphate buffer of 6.8 pH. The prepared buccal film were evaluated by folding endurance test, film thickness test, disintegration test, weight uniformity test, stability studies and *in-vitro* drug release. Among all the formulation F3 was selected as best formulation based on evaluation and *in-vitro* drug release studies.

KEYWORD: Dabigatran etexilate, HPMC E-15, PVA, PVP K30.

1. INTRODUCTION

Anticoagulants plays a crucial role in modern medicine, offering therapeutic solutions to prevent and treat thrombotic disorders, which can lead to serious health complications such as stroke, pulmonary embolism, and myocardial infarction. Among the array of anticoagulants available, Dabigatran etexilate stands out as a promising agent due to its efficacy, safety profile, and convenient administration. In recent years, innovative formulations such as fast- dissolving oral films have been developed to enhance the delivery and patient experience of Dabigatran etexilate.[1,2,3,4]

Buccal films, a dosage form administered through the buccal mucosa, have gained significant attention in pharmaceutical research and development due to their numerous advantages over conventional drug delivery systems. This innovative drug delivery system offers several benefits, including improved patient compliance, enhanced bioavailability, rapid onset of action, and reduced first-pass metabolism. Buccal films are thin, flexible polymeric matrices designed to adhere to the buccal mucosa, allowing for the controlled release of drugs into the systemic circulation.[5,6,7,8]

Dabigatran belongs to the class of direct oral anticoagulants (DOACs), which exert their therapeutic effects by specifically targeting key components of the coagulation cascade. Unlike warfarin, which acts by inhibiting vitamin K-dependent clotting factors, Dabigatran directly inhibits thrombin, a central enzyme in the coagulation process. This targeted mechanism of action confers several advantages, including predictable pharmacokinetics, a rapid onset of action, and a reduced risk of drug interactions compared to traditional anticoagulants.[1,9,10]

In conclusion, Dabigatran etexilate fast-dissolving oral films represent a promising advancement in anticoagulant therapy, offering enhanced convenience and efficacy compared to conventional dosage forms. This research work aims to provide valuable insights into the potential of Dabigatran etexilate fast-dissolving oral films in improving patient outcomes and advancing the field of anticoagulant therapy.

MATERIALS AND METHOD

MATERIALS: Dabigatran etexilate and HPMC E-15 were acquired from Yarrow Chemicals in Mumbai, PVP, PVA K-30, Disodium hydrogen orthophosphate, Potassium dihydrogen orthophosphate, Vanillin and Citric acid were acquired from SD Fine Chem Limited, while Sodium saccharin and PEG-600 were procured from Thermo Fisher Scientific India Pvt Limited.

Preparation of standard graph of Dabigatran etexilate in phosphate buffer: Serial dilution of Dabigatran etexilate was prepared (5, 10, 15, 20, 25, 30, 35 and 40µg/ml) in phosphate buffer of pH 6.8. The lambda max observed was 324 nm. Similarly the standard graph was obtained in methanol.

Determination of λ max of Dabigatran etexilate using simulated saliva buffer pH 6.8: Accurately weighed quantity of 50mg of Dabigatran etexilate was taken in 50ml volumetric flask and made up to 50ml by using Ethanol. From the above stock solution100µg/mlsolution was prepared and scanned between 200- 400nm by keeping buffer as blank in UV Visible spectrophotometer. The lambda max of Dabigatran etexilate was found to be **324nm.**

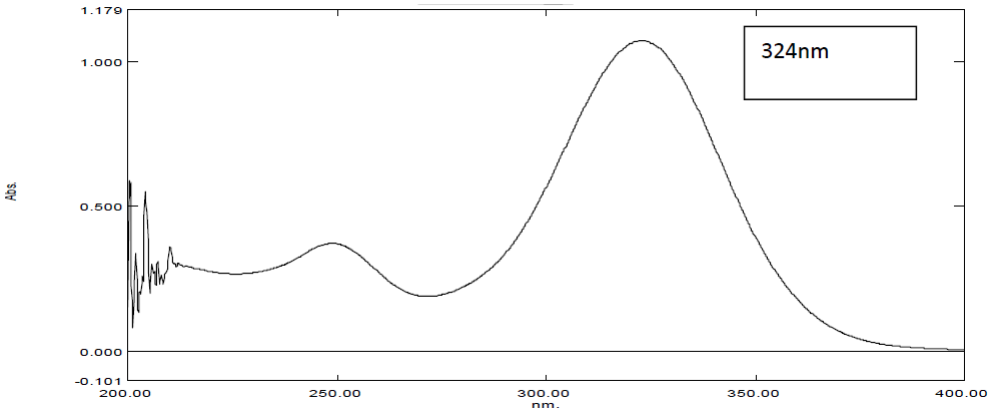

Figure No: 1. Standard graph of Dabigatran etexilate.

Preparation of Dabigatran etexilate buccal film: Buccal films shall be prepared by solvent casting method. Accurately weigh required quantity of drug and film forming polymer such as HPMC E 15, PVP K 30, PVA of various grades, PEG 600 used as plasticizers, sodium saccharin as sweetener, citric acid as saliva stimulating agent and vanilla as flavouring agent.

In beaker-A Weigh required quantity of drug and dissolve completely in 5ml of ethanol.

In beaker –B weigh required quantity of polymer dissolve in distilled water of 5 ml then pour beaker-A solution to beaker-B and keep beaker on magnetic stirrer for 10 to 15 min for stirring that mixes both solutions completely that gives clear solution Then solution dispersion shall be casted on glass mold and keep mold in hot air oven for 1 to 2 hours for temperature about 30^0 to 60^0C then remove mould from hot air oven and peel the film by using sharp blade size of 2x2 cm film.[11,12]

Table No: 1. Formulation of buccal film from F1 to F9.

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (mg)	240	240	240	240	240	240	240	240	240
HPMC E15 (mg)	250	300	350	-----	----	----	50	50	50
PVA (mg)	----	-----	-----	250	300	350	----	----	----
PVP (mg)	-----	-----	-----	-----	----	-----	200	250	300
PEG 600 (mg)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Citric acid (mg)	2	2	2	2	2	2	2	2	2
Sodium Saccharin (mg)	2	2	2	2	2	2	2	2	2
Vanillin (mg)	2	2	2	2	2	2	2	2	2
Ethanol (ml)	5	5	5	5	5	5	5	5	5
Distilled Water (ml)	5	5	5	5	5	5	5	5	5

HPMC: Hydroxy propyl methyl cellulose, PVA: Poly vinyl alcohol, PVP: Poly vinyl Pyrolidine, PEG: Poly ethylene glycol.

Evaluation study of Dabigatran etexilate fast dissolving buccal film[13,14,15,16,17]

3.1 Thickness: Utilizing a screw gauge with a minimum count of 0.01mm across multiple film spots, the thickness of all the films was measured. Three different spots on the films were analyzed for thickness, and an average was taken.

Weight uniformity: Using a Digital balance, 2x2 cm films were weighed individually, and the average weights were obtained.

Folding endurance: By repeatedly folding a 2x2 cm strip of the film in the same spot until it broke, the folding endurance of the films was determined by the number of times it can be folded in the same direction

without breaking.

Drug content uniformity: From the cast films, three separate locations were used to cut by 2x2 cm films. In a 100ml volumetric flask, each film was put, and pH 6.8 simulated saliva was added to dissolve it. The solution's absorbance was determined at lambda max 324 nm using a UV visible spectrophotometer (Shimadzu in Japan). It was decided what proportion of drugs were there.

Drug polymer interaction study: In order to understand the interaction between the drug and polymers, IR spectroscopy was one of the most effective analytical method for identifying chemicals is infrared spectroscopy. FTIR was in a thin film approach to scan the infrared spectra of formulations and pure drug Dabigatran etexilate.

In vitro drug release study: The film with 2x2 cm was placed in the 300 ml of 6.8 pH simulated saliva as dissolution medium, and temperature was maintained at 37±0.5°C. From this dissolution medium, 2ml of the sample solution was withdrawn at different time interval and absorbance was determined at 324nm using UV-visible spectrophotometer.

In vitro Disintegration studies: Disintegration was carried by using film of 2x2 cm was kept in volumetric flask which contain 50ml of phosphate buffer then shake until film break.

Stability studies: At the end based on Drug content, Disintegration, Weight variation, Film thickness, Folding endurance and *in-vitro* dissolution we selected formulation **F3** was selected as best formulation among other formulation. According to ICH guidelines stability studies were followed, F3 formulation was wrapped in aluminium foil and put in zip lock cover for a month. After 4 weeks formulation were removed and check for the drug content and in-vitro dissolution were carried out that shows there is no significant changes in result.

RESULT AND DISCUSSION

Characterization of pure drug (Dabigatran etexilate): Therefore, the first we need to do after obtaining the API is look over the characterization, which are listed in the table below.

Table No: 2: Characterization of pure drug.

Test	Result of analysis
Description	Amorphous white powder
Odour	Odourless
Solubility	Soluble in ethanol
Melting point	130°C

4.2 Standard graph of Dabigatran etexilate

Table No: 2: Standard graph of pure drug (Dabigatran etexilate).

Concentration (µg/ml)	Absorbance @324nm
0	0
5	0.134
10	0.220
15	0.289
20	0.398
25	0.512
30	0.643
35	0.737
40	0.858
45	0.95

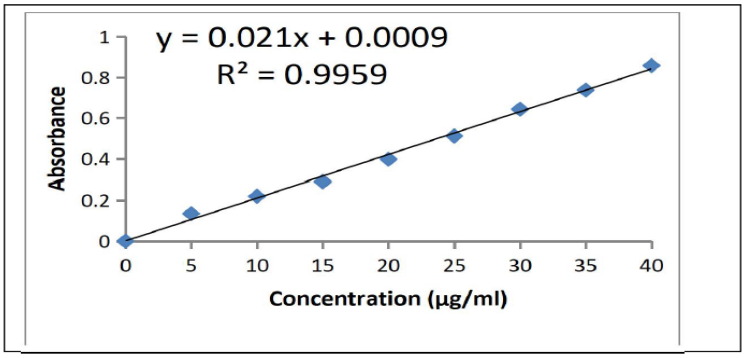

Figure No: 2. Standard graph of pure drug.

4.3 Drug polymer interaction study (FTIR studies).

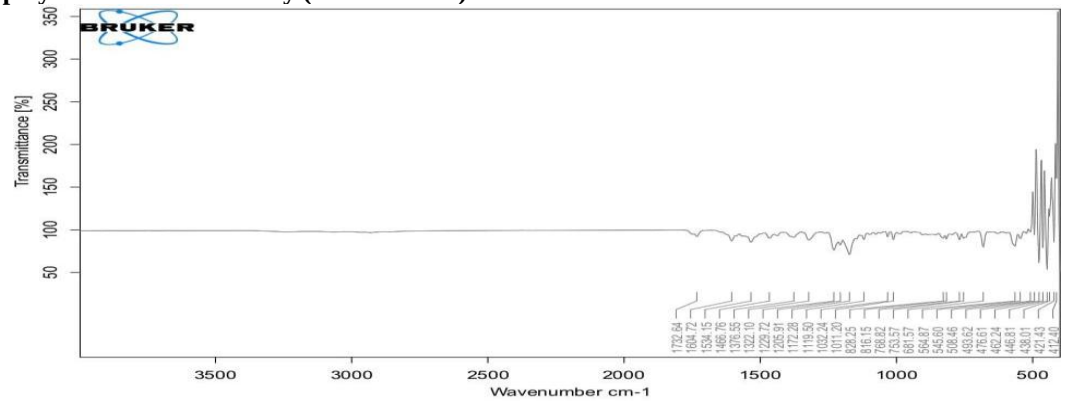

Figure No: 3. The FTIR spectrum of pure drug Dabigatran etexilate.

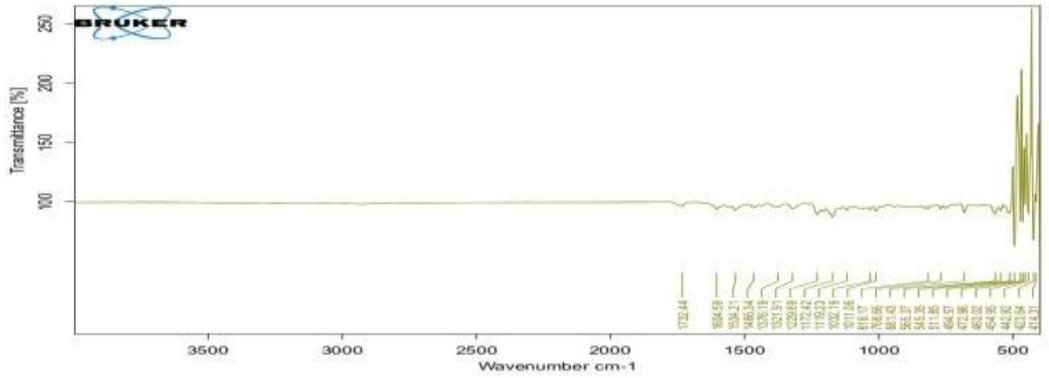

Figure No: 4. The FTIR spectrum of Drug + HPMC E15.

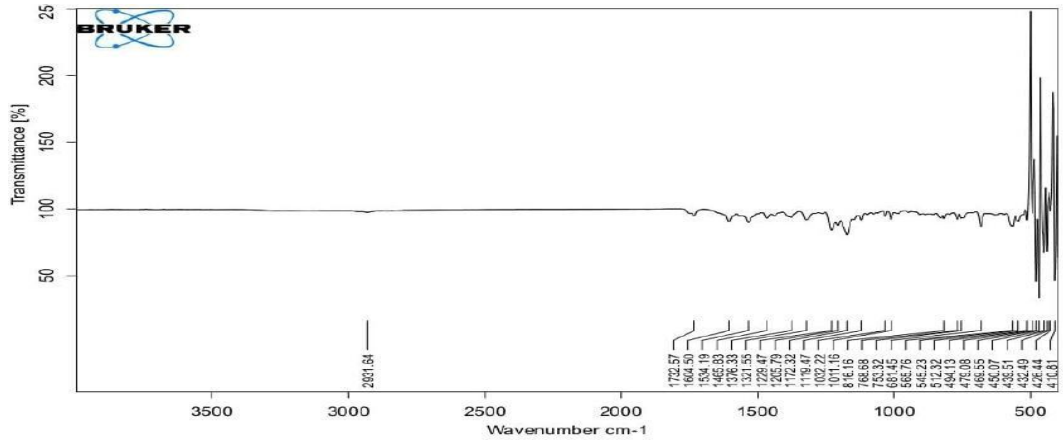

Figure No: 5. The FTIR spectrum of Drug + PVP K 30.

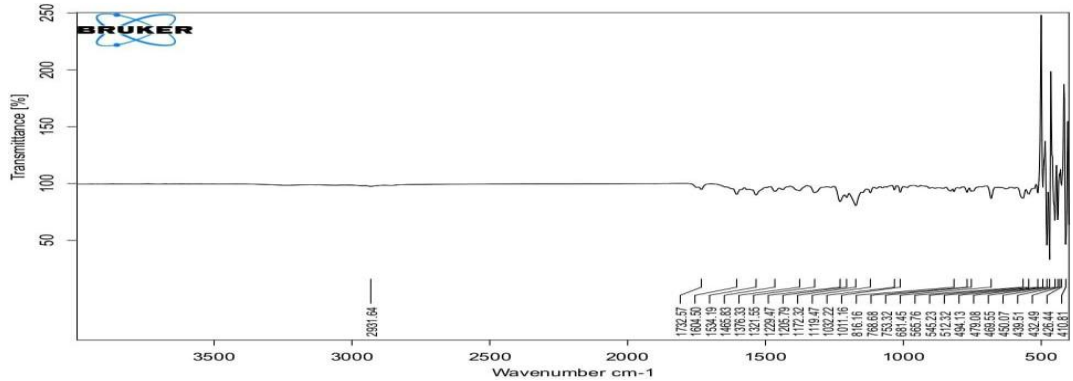

Figure No: 6. The FTIR of Drug + PVA.

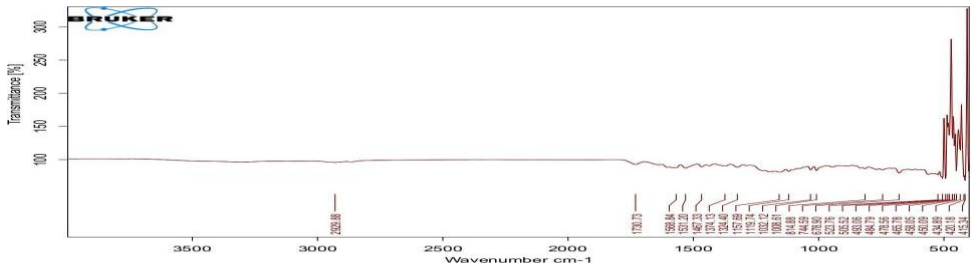

Figure No: 7. The FTIR spectrum of buccal film containing Drug and HPMC E-15 (350).

Table No: 3: FTIR studies value.

Sl no	Name of the compound	Range (cm^{-1})	Group	Observed range in the sample
		1650-1550	C=C	1534
1	Dabigatran etexilate	1550-1450	N-H	1466
		1730-1650	C=O	1732
		1150-1050	OH	1032
2	Dab: HPMC E15	1650-1550	C=C	1534
		1550-1450	N-H	1466
		1730-1650	C=O	1732
		1150-1050	OH	1032
3	Dab: PVP K-30	1650-1550	C=C	1534
		1550-1450	N-H	1465
		1730-1650	C=O	1732
		1150-1050	OH	1032
		1650-1550	C=C	1533
4	Dab: PVA	1550-1450	N-H	1466
		1730-1650	C=O	1732
		1150-1050	OH	1032
5	Dab +HPMC E- 15 (350mg)	1650-1550	C=C	1531
		1550-1450	N-H	1467
		1730-1650	C=O	1730
		1150-1050	OH	1032

All the absorption peak of Dabigatran etexilate were retained in the physical mixtures, the spectra of physical mixture did not show the shift of vibration bands of Dabigatran etexilate. It indicated that there was no any chemical interaction between the drug and excipients.

Comparative study of *in-vitro* dissolution of fast dissolving buccal film

Table No: 4: *in-vitro* dissolution of buccal film.

Time (min)	% CDR								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	21.43	32.7	27.43	20.22	25.79	27.43	18.07	20.43	22.15
4	33.86±0.50	47.05± 0.58	35.86± 0.54	33.80±0.4 8	36.65±0.61	51.07±0.34	26.3±0.46	35.22±0.22	38.43±0.63
6	42.07±0.73	57.07±0.42	42.07±0.66	46.36±0.05	55.86±0.57	63.65±0.56	33.50±0.82	36.86±0.56	49.79±0.35
8	44.51±0.22	64.26±0.08	68.16±0.58	51.57±0.11	63.43±0.58	70.72±0.43	45.82±0.49	44.72±0.73	53.25±0.42
10	53.88±0.57	71.33±0.15	96.63±0.46	60.93±0.17	70.72±0.02	89.35±0.12	51.86±0.56	55.86±0.43	60.72±0.58
12	68.18±0.65	95.86±0.63	-	77.21±0.68	88.64±0.46	94.35±0.43	59.00±0.11	60.85±0.23	67.86±0.45
14	93.77±0.39	-	-	85.07±0.61	91.50±0.49	-	67.29±0.51	70.72±0.73	83.64±0.63

Mean ± standard deviation (n=3)

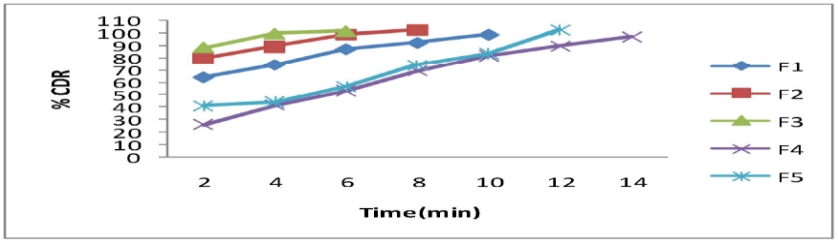

Figure No: 8. in-vitro drug release profile fromualtio F1 to F5.

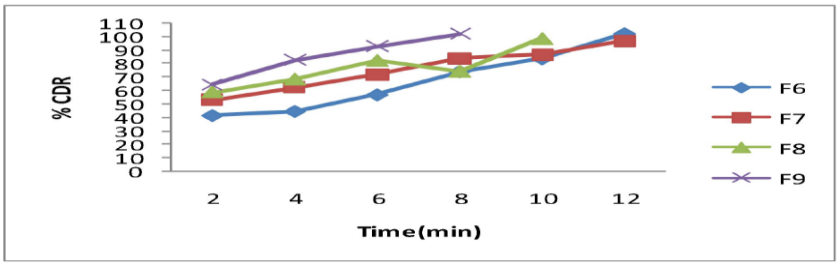

Figure No: 9. in-vitro drug release profile formulation F6 to F9.

Evaluation study

Table No: 5: Evaluation studies result of formulation F1 to F9.

Formulation	Film thickness	Weight uniformity	Folding endurance	Drug content	Disintegration time
F1	0.15±0.012	54.27±0.67	244.67±4.64	91.7±0.89	46.67±1.25
F2	0.17±0.012	56.21±0.36	221.00±2.45	95.6± 0.56	37.33±1.70
F3	0.17±0.008	57.83±0.43	224.33±2.49	96.9± 0.28	34.67±1.25
F4	0.21±0.008	51.65±0.50	244.33±2.04	93.3 ±1.19	34.00±2.16
F5	0.23±0.008	50.96±0.56	238.33±1.25	91.8± 0.06	38.67±2.62
F6	0.21±0.012	52.05±0.09	253.00±3.74	97.4± 0.51	32.67±1.70
F7	0.18±0.0050	58.06±0.21	223.67±2.49	95.8± 0.36	42.67±2.05
F8	0.20±0.0102	51.85±1.25	216.67±2.62	97.0± 0.63	47.33±1.70
F9	0.18±0.0033	58.02±0.77	230.67±1.25	94.3± 0.19	41.67±1.70

Mean ± standard deviation (n=3)

Stability studies

Table No: 6: Drug content data of stability study of formulation F3.

SL. NO	Trial no.	1st day	After 4 weeks
1	I	96.98	95.88
2	II	97.01	96.71
3	III	96.35	95.54
4	Mean	96.78±0.28	96.04±0.83

Table No: 7: In-vitro release data of stability study F3.

Time (min)	% CDR	
	ST 1 day	After 4 weeks
2	27.43±0.35	30.69±0.46
4	35.86±0.54	34.54±0.55
6	42.07±0.66	41.62±0.93
8	68.16±0.58	69.59±0.47
10	96.63±0.46	96.87±0.67

Mean ± standard deviation (n=3)

CONCLUSION

From the present research work that is "Formulation and Evaluation of fast dissolving buccal film containing Dabigatran etexilate*"* for Anti-coagulant the following point were concluded In the beginning blank polymeric strips were prepared by solvent casting technique using HPMC E15, PVP K-30, PVA, the concentration of polymer was varied and the best formulations were chosen for incorporating the drug.

The prepared films were evaluated for following parameters like physical appearance and surface texture, weight uniformity, thickness of films, folding endurance and drug content uniformity, disintegration, permeation study, drug excipients interaction studies, *in-vitro* drug release and short-term stability studies.

All the formulation showed acceptable quality control property formulation F3 having polymer concentration HPMC E15 350mg gave better drug release rate over period of 10 minutes for Dabigatran etexilate thus formulation F3 was found to be the most promising formulation on the basis of acceptable evaluation property and the *in-vitro* drug release rate. Based on the FTIR studies appear to be no possibility of interaction between the Dabigatran etexilate and polymers of other excipients used in the films.

Stability studies were conducted for the optimized formulation as per ICH guidelines for a period of 30 days which revealed that the formulation was stable. The result suggests that the developed fast release strips of Dabigatran etexilate could perform the better than conventional dosage form leading to improved efficacy

and better patient compliance.

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It is a great pleasure to utilize this unique opportunity to express my deep sense of gratitude and and offer my most sincere and humble regards to the lotus feet of his holiness Dr. Sree Siddaganga Mahaswamigalu and my Parents.

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