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FAST DISSOLVING ORAL FILMS: A NOVEL APPROACH FOR THE DELIVERY OF IVABRADINE HYDROCHLORIDE

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Abstract: In the work undertaken, an attempt has been made to formulate and evaluate fast-dissolving oral films (FDOFs) of Ivabradine hydrochloride to have a rapid onset of action with increased bioavailability and improved patient compliance. FODFs were fabricated by solvent casting technique. Various film formers, Hydroxypropyl Methylcellulose (HPMC) of different viscosity grades, and polyhydric alcohols in various proportions and combinations were explored to optimize the composition of FDOFs. Among all polymers, a combination of HPMC E3 & E5 showed the desired film-forming capacity. The suitable plasticizer and its concentration were selected based on flexibility and tensile strength. Flexible films were obtained by using 20% w/w glycerin. Nine batches of films with the drug were prepared by varying concentrations of polymers and the resultant films were evaluated for various physicochemical properties such as weight of film, thickness, tensile strength, folding endurance, surface pH, drug content, in vitro disintegration time, and in vitro dissolution studies, all of which showed satisfactory results. Among all the formulations F4 with a combination of polymers (1:2) showed a maximum release of 96 % within 210 seconds, with a mean disintegration time of 15 seconds emerging to be the ideal formulation. The optimum film composition was also tested in vivo for film palatability in human volunteers and the results revealed that there was no bitter taste, no irritation, and a good mouth feel was observed. Furthermore, the FODFs were stable for at least 2 months when stored at 40°C and 75% relative humidity.

Keywords - Fast dissolving oral films, Ivabradine hydrochloride, Solvent casting technique, HPMC E3 & E5.

I. INTRODUCTION

For the past decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing day by day. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost-effective dosage forms (Patil et al., 2015).

Difficulty in swallowing (dysphagia) is a common problem in all age groups, especially the geriatric and pediatrics, because of physiological changes associated with these groups. Sometimes, it may be difficult to swallow conventional products due to non-availability of water (Nagaraju et al., 2013; Shetty et al., 2024). These problems led to the development of a novel type of solid oral dosage form called fast dissolving oral films that employs a hydrophilic film former in combination with suitable excipients, which allow the film to disintegrate or dissolve quickly in the mouth within a few seconds without the administration of water or chewing (Panda et al., 2012). These films have the potential to deliver the drug systemically through intragastric, sublingual, or buccal routes of administration (Patel et al., 2015).

Ivabradine hydrochloride is a novel medication used for the symptomatic management of stable angina pectoris in patients with normal sinus rhythm who have a contraindication to or intolerance of beta-blockers(Reed et al., 2024). The plasma half-life is about 2 hrs, and bioavailability is 40% as the drug undergoes hepatic first-pass metabolism. Hence in the present work, an attempt was made to prepare quick-release films of ivabradine hydrochloride to develop a dosage form for a very quick onset of action, which is beneficial in managing severe conditions of angina pectoris, aiding in the enhancement of bioavailability, and is very convenient for administration, without the problem of swallowing and without using water(Ferlak et al., 2023).

II. MATERIALS AND METHODS

2.1 Materials

Ivabradine hydrochloride was a gift from Getz Pharma Research Pvt. Ltd. (Ambernath, India). HPMC grades were received as gift samples from Colorcon Asia Pvt. Ltd. (Goa, India). PVA was purchased from S.D. Fine Chem Ltd. (Mumbai, India). Propylene glycol, PEG - 400, and Glycerine were procured from Molychem (Mumbai, India). Sucralose was received as gift samples from Gangwal Chemicals Pvt. Ltd. (Mumbai, India). All other chemicals used were of analytical grades.

2.2 Methods

2.2.1 FT-IR Studies

The compatibility of drugs and polymers was studied using Fourier Transform Infrared (FTIR) spectroscopy (Shimadzu IR affinity 1) by the KBr Disc method.

2.2.2 Preliminary Screening

a. Preliminary trial for selection of polymer

Dummy films of HPMC E3, HPMC E5, HPMC E15, and PVA were prepared by using different concentrations ranging from low to high alone and in combination and screened for their suitability as film-forming agents in the FDFs. The placebo films were prepared by solvent-casting method. First, film-forming polymers were dissolved in distilled water and allowed to stand for swelling. Plasticizer was added in a dropwise and stirred to obtain a homogenous solution. The solution was kept in a sonicator for the removal of air bubbles and then cast into the glass molds and kept at room temperature for 24 hrs to dry the films. After drying films were removed and cut into desired size i.e.2×2 cm^2, packed in aluminum foils until further use (Hirpara et al., 2014). The composition of the polymeric dispersions is reported in (Tables 3 & 4).

b. Preliminary trial for selection of plasticizer

Various plasticizers like propylene glycol, polyethylene glycol 400, and glycerine were employed at different concentrations ranging from 20 – 40% w/w of dry polymer weight (Table 5). All these placebo films of different concentrations were evaluated for different parameters like tensile strength, folding endurance, and in-vitro disintegrating time.

2.2.3 Formulation of Drug Loaded Films

Drug-loaded films were also prepared by solvent casting method (Kawale et al., 2023). A specified amount of polymers were dissolved in 6 ml water. To this polymeric solution, a suitable quantity of plasticizer was added and thoroughly mixed with the aid of a magnetic stirrer. Accurately weighed quantity of the drug was dissolved in 4 ml water. This solution-containing drug was then added to the aforementioned slightly viscous solution containing polymer and plasticizer. Both these solutions were mixed properly. Then to this solution, the remaining water-soluble ingredients were mixed i.e. sweetening agent, flavoring agent, and saliva stimulating agent. This resulting solution was then deaerated by sonication and cast into the glass mold. The glass molds were kept for drying at room temperature for 24 hrs. After drying film was removed safely from the glass mold and films of 2 x 2 cm^2 each were cut with the help of a blade. Then films were packed into aluminum packing and stored in air-tight containers or desiccators until further in-vitro tests. Films of various formulations are mentioned in Table 1.

Table: Formulation batches of fast-dissolving oral films of Ivabradine hydrochloride

Sr. No	IBH (gm)	HPMC E3 (%)	HPMC E5 (%)	Glycerine (%)	Citric Acid (mg)	Sucralose (mg)	Raspberry (ml)	D.W (ml)
F1	0.0376	1	1	20	30	40	q.s	10
F2	0.0376	2	1	20	30	40	q.s	10
F3	0.0376	3	1	20	30	40	q.s	10
F4	0.0376	1	2	20	30	40	q.s	10
F5	0.0376	2	2	20	30	40	q.s	10
F6	0.0376	3	2	20	30	40	q.s	10
F7	0.0376	1	3	20	30	40	q.s	10
F8	0.0376	2	3	20	30	40	q.s	10
F9	0.0376	3	3	20	30	40	q.s	10

IBH: Ivabradine hydrochloride; q.s: Quantity sufficient; D.W: Distilled water.

III. EVALUATION OF FDOFs

3.1 Morphological Properties

The fast-dissolving oral films were evaluated by visual observation such as the transparent or semi-transparent nature of the film, homogeneity, color, flexibility, brittleness, presence of air bubbles, and smoothness.

3.2 Weight of Film

For evaluation of film weight, three films of every formulation are taken and weighed individually on a digital balance. The average weights were calculated. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipients and API (Bhagyashri et al., n.d.).

3.3 Thickness

The thickness of the film can be measured by a micrometer screw gauge at 3 different points of the film and then the mean thickness is calculated. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of the dose in the film.

3.4 Tensile Strength

It gives an idea about to what extent the film can withstand the force or stress during processing, packaging, transport, and handling. The tensile strength was defined as the maximum load force to break the FDOF and calculated by dividing the applied load at rupture with the cross-sectional area of the film.

$$\text{Tensile Strength} = \frac{\text{Load at failure} \times 100}{\text{Film thickness} \times \text{Film width}}$$

It was measured using a peel adhesion tester (Lemi Coat Equipment) equipped with a 2 kg load cell. It consists of two load cell grips. The lower one was fixed and the upper one was movable. The film of size 2 × 2 cm^2 and free from air bubbles or physical imperfections was placed between these cell grips. The film was pulled at a rate of 10 cm min^{-1} and the force required to break the film was measured when the film broke. The whole experiment was carried out in triplicate (Rani, 2014).

3.5 Folding Endurance

This test helps to reveal the flexible properties of the films, and therefore, their ability to conform to the contours of the oral cavity after application. A brittle film may fragment soon after application or during use, which may lead to mechanical irritation and a source of discomfort to the user and also drug loss. The folding endurance is a measure of the mechanical strength and flexibility of the films that is necessary for handling. This property was determined by repeated folding of the film at the same place till the film broke. The number of times the film is folded without breaking is computed as the folding endurance value (Usha et al., 2018).

3.6 Surface pH of Film

The surface pH of FDOF was determined in order to investigate the possibility of any side effects, in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, the surface pH of the film was kept neutral. The film to be tested was placed in a petri dish and was moistened with 2 ml of distilled water and kept for a short period at room temperature and then the pH of the obtained solution was measured by pH paper. All the measurements were done in triplicate, and average values were reported.

3.7 Drug Content

The oral film of size 4 cm^2 was dissolved in 100 ml of phosphate buffer pH 6.8. The resulting solution was sonicated for 15 minutes and filtered. The filtrate was appropriately diluted and analyzed at a specified wavelength in a UV spectrophotometer. The concentration of the drug was calculated using the standard calibration curve. The average drug contents of the three films have to be taken as a final reading.

3.8 In-vitro Disintegration Time

It is the time at which the film begins to break down when brought into contact with water or saliva. Disintegration time indicates the disintegration characteristics and dissolution characteristics of the film. The disintegration time can be visually determined by dipping the Film of the desired size in a petri dish (internal diameter 5 cm) containing 10 ml of phosphate buffer pH 6.8 at 37°C. The Petri dish was swirled every 10 seconds and the time was noted when the film started to break or disintegrate. All the measurements were carried out in triplicate (Tamer et al., 2018).

3.9 In-vitro Drug Release

To mimic the natural conditions in the oral cavity the in vitro dissolution test was performed in a modified dissolution apparatus. For in vitro dissolution studies, each film was placed in a beaker containing 100 ml of phosphate buffer pH 6.8 as a dissolution medium, maintained at 37±0.5^{0}C, and the magnetic stirrer was rotated at 100 rpm. An Aliquot of 2 ml was withdrawn at different time intervals and the same amount was replaced with the fresh medium. The samples were analyzed for the drug release using a UV-VIS spectrophotometer (Mehta et al., 2014).

3.10 Consumer Acceptance Taste

A total of 10 healthy adult volunteers (six males and four females) with a mean age of 22.5 years old (22–23 years old) participated in the study after providing written informed consent. Before the study, the volunteers were briefed on the request to give the score based on the parameters, namely aftertaste, mouthfeel, ease of handling, and acceptance as presented in nature, purpose, duration and risk of the study. Prior to the study, the volunteers were required to gargle their mouth with 200 ml of distilled water. One FODF film (2×2 cm) was placed on the tongue of the volunteer. The volunteers were Table 2. The volunteers were told to spit out the test sample, followed by rinsing their mouths with 200 ml of distilled water (Liew et al., 2012).

Table 2: Parameters and score in palatability study.

PARAMETERS					
Taste	**Aftertaste**	**Mouthfeel**	**Ease of handling**	**Acceptance**	**Score**
Very bitter	Very bitter	Gritty & irritating	Very brittle	Very poor	1
Bitter	Bitter	Gritty	Brittle	Poor	2
Slightly bitter	Slightly bitter	Slightly gritty	Does not break	Acceptable	3
Slightly sweet	Slightly sweet	Smooth	Flexible & easy to handle	Good	4
Very sweet	Very sweet	Very smooth	Very easy to handle	Very good	5

3.11 Surface Morphology

The morphology and surface topography of the film were examined by scanning electron microscopy (QUANTA-200 FEI, Netherlands). Different excipients added in formulation affect the surface morphology of the film differently which affect various parameters of the film. The samples to be examined were mounted on the SEM sample stab using double-sided adhesive tape. The samples mounted were coated with gold (200 ˚A) under reduced pressure (0.001 torr) for 5min to improve the conductivity using an Ion sputtering device. The scanning electron photomicrograph of the film is taken at an excitation voltage of 20.0KV and a magnification of 5000x. The prepared film containing the drug is examined for clear and colorless surface (Kumar and Gupta, 2022).

3.12 Stability Studies

In the present study, the optimized films were subjected to short-term accelerated stability studies at $40^0C \pm 2^0C$ / 75 % RH ± 5 % RH (ICH conditions) for a period of 2 months and evaluated for different parameters like physical appearance of the film, mechanical properties, drug content, and cumulative drug release.

RESULT AND DISCUSSION

4.1 FTIR Studies

The FTIR spectra of the ivabradine hydrochloride (pure drug), and its physical mixtures are presented in Fig. 2, 3, and 4. The FTIR spectrum of ivabradine hydrochloride depicts a characteristic absorption band at 2924.21 cm^{-1} representing aliphatic C-N stretch. The absorption band around 1105.26 cm^{-1} indicated the presence of alkanes C=C stretching in the compound. The sharp absorption band at 1635.71 cm^{-1} indicated the presence of aromatic C–C bond in the structure, Aromatic C-H stretch showed a characteristic absorption band in the region of 1465 cm^{-1}. The absorption band around 3420.90 cm^{-1} indicated the presence of alkenes R-CH_2CH_3 in the compound. Peaks of the spectrum of pure drugs were compared with the peaks of the spectra of physical mixtures of drugs and polymers. The comparison of the IR spectrum revealed that there is no appreciable change in the positions of characteristic absorption bands of groups and bonds. The range of peak values was found to be the same indicating that there were no interactions of the drug with different polymers confirming the stability of the drug in the formulation.

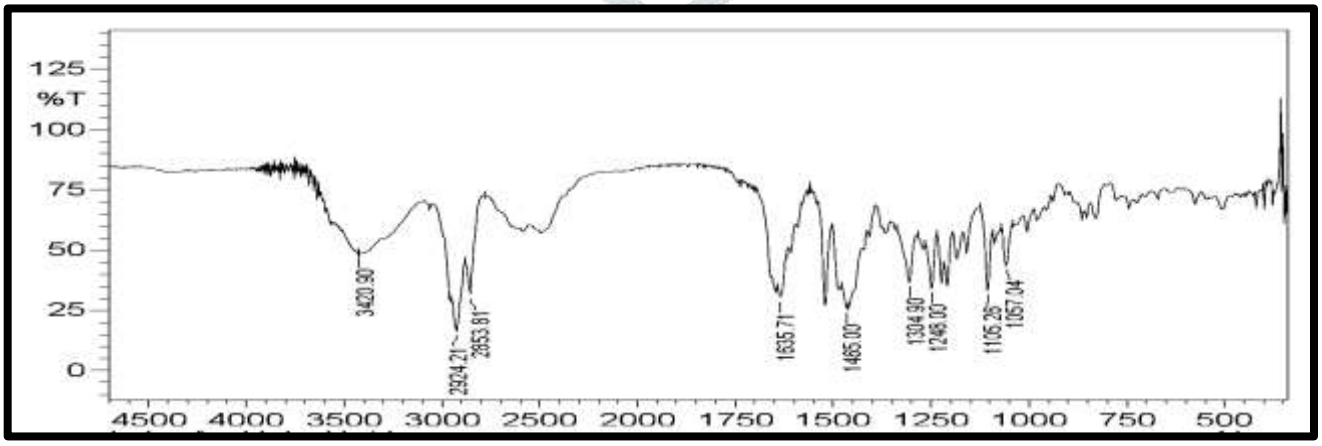

Figure 1: IR Spectrum of ivabradine hydrochloride

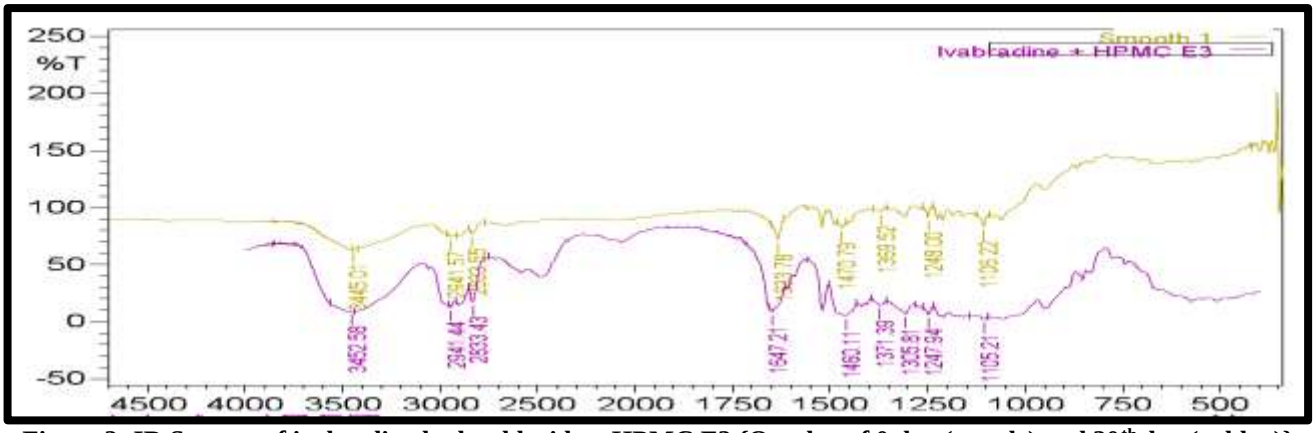

Figure 2: IR Spectra of ivabradine hydrochloride + HPMC E3 {Overlay of 0 day (purple) and 30th day (golden)}

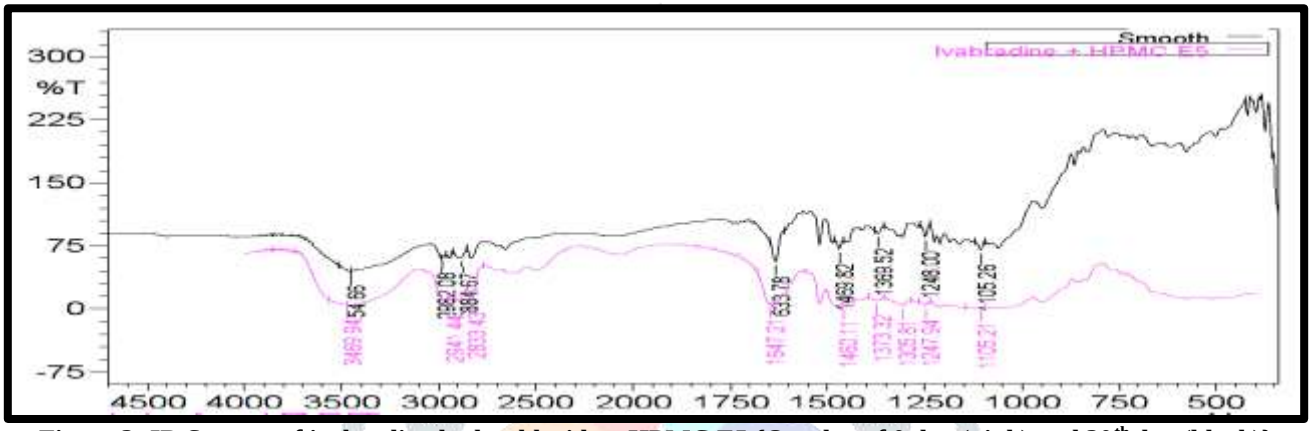

Figure 3: IR Spectra of ivabradine hydrochloride + HPMC E5 {Overlay of 0 day (pink) and 30th day (black)}

4.2 Selection of Polymer

4.2.1 Formulation Study 1

In the formulation development placebo films were first prepared using different polymers namely HPMC E3, HPMC E5, HPMC E15, and PVA. The polymer was selected based on parameters like visual appearance, film-forming ability, *in*-vitro disintegration time, and folding endurance. In formulation P1 HPMC E3 showed good film forming capacity. The film was transparent and smooth with less *in*-vitro disintegration time i.e. 10 seconds but the folding endurance was too low. Increasing the concentration to 6% increased folding endurance, but also increased in-vitro disintegration time. Film formulated using HPMC E5 at the concentration of 2% showed acceptable results for disintegration time and folding endurance. On increasing the concentration HPMC E5 failed to give good folding endurance. Films formulated using HPMC E15 at higher and lower concentrations did not give satisfactory results. Films formulated using PVA at lower concentrations were found to be sticky. 4% PVA films gave satisfactory result for disintegration time and folding endurance but failed to give a transparent film.

On the basis of the results obtained, it can be concluded that HPMC E3 provides good disintegration time but fails to give acceptable folding endurance results. Hence combinations of HPMC E3 with other polymers were considered for further studies.

Table 3: Evaluation parameters for selection of polymer

Batch Codes	Name of Polymer (Conc.)	Visual Appearance	Film Forming Ability	*In*-Vitro Disintegration Time* (Secs)	Folding Endurance* (No. of folds)
P1	HPMC E3 (2 % w/v)	Transparent, smooth	Good	10	1
P2	HPMC E5 (2 % w/v)	Transparent, smooth	Very good	29	> 100
P3	HPMC E15 (1 % w/v)	Transparent, smooth	Good	40	50

P4	PVA (1 % w/v)	Transparent, sticky	Average	3	32
P5	HPMC E3 (6 % w/v)	Transparent, smooth	Excellent	26	2
P6	HPMC E5 (6 % w/v)	Transparent, smooth	Good	180	45
P7	HPMC E15 (4 % w/v)	Transparent, smooth	Excellent	107	> 100
P8	PVA (4 % w/v)	Semitransparent, smooth	Very good	15	> 100

*values are expressed as mean (n=3)

4.2.2 Formulation Study 2

In formulation study 2, HPMC E3 was used in combination with HPMC E5, HPMC E15 and PVA.
In formulation C1 and C4, films were formulated by using combination of HPMC E3 and HPMC E5. Both the films were transparent and smooth with least disintegration time i.e 22 sec and 25 sec respectively and the folding endurance was also satisfactory.Films formulated using combination of HPMC E3 and HPMC 15 was transparent and smooth. When HPMC E15 is used in lesser concentration with that of HPMC E3, the folding endurance was comparatively less i.e 35 folds. But on increasing the concentration of HPMC E15, folding endurance were found be satisfactory. However the in-vitro disintegration time of combination HPMC E3 and HPMC E15 was comparatively greater than those obtained with combination of HPMC E3 and HPMC E5. Combination of HPMC E3 and PVA has average film forming capacity. Also the disintegration time of these films were greater than 30 seconds so combination of HPMC E3 and PVA was not selected.Based on the above finding combination of HPMC E3 and HPMC E5 were selected as the optimized film forming polymer amongst the polymers employed because very transparent visual appearance, best film forming capacity, least in-vitro disintegration time and higher folding endurance value were observed.

Table 4: Evaluation parameters for selection of combination of different polymer (C)

Batch Codes	Name of Polymer (Conc.)	Visual Appearance	Film Forming Ability	*In*-Vitro Disintegration Time* (Secs)	Folding Endurance* (No. of Folds)
C1	HPMC E3 (2 % w/v) + HPMC E5 (2 % w/v)	Transparent, smooth	Excellent	22	>100
C2	HPMC E3 (2 % w/v) + HPMC E15 (1 % w/v)	Transparent, smooth	Good	26	35
C3	HPMC E3 (2 % w/v) + PVA (2 % w/v)	Semitransparent, smooth	Average	105	>100
C4	HPMC E3 (2 % w/v) + HPMC E5 (3 % w/v)	Transparent, smooth	Very good	25	>100
C5	HPMC E3 (2 % w/v) + HPMC E15 (2 % w/v)	Transparent, smooth	Good	35	>100
C6	HPMC E3 (2 % w/v) + PVA (3 % w/v)	Semitransparent, smooth	Average	58	>100

*values are expressed as mean (n=3)

4.3 Selection of Plasticizer

4.3.1 Formulation study

The selection of plasticizer was performed based on evaluation tests like in-vitro disintegration time and mechanical properties like tensile strength and folding endurance (Bhatta et al., 2019). Film formulated using propylene glycol showed a lesser value of folding endurance as compared to films formulated using glycerine and PEG400 as a plasticizer. On comparison of mechanical properties PEG 400 formulated films showed better results than glycerine and propylene glycol. However, the in-vitro disintegration time was more than glycerine and propylene glycol-formulated films. Glycerine-containing films gave good results for tensile strength, in-vitro disintegration time, and folding endurance. At 20% and 30% w/w of dry polymer concentration of glycerine, sufficient folding endurance value (>100) was observed. The films made using 40% w/w of dry polymer concentration of glycerine were brittle in nature. On comparing 20% and 30% w/w of dry polymer concentration of glycerine for in-vitro disintegration time, 20% showed better results.

Based on the above-observed results for mechanical properties and in-vitro disintegration time, 20% w/w of dry polymer concentration of glycerine was selected.

Table 5: Evaluation parameters for selection of plasticizer (PL)

Batch Codes	Name of Plasticizer (Conc.)	Folding Endurance* (No. of Folds)	Tensile Strength* (Kg/Cm^2)	In-Vitro Disintegration Time* (Secs)
PL1	Propylene glycol (20 % w/w of dry polymer)	43	0.330	22
PL2	PEG 400 (20 % w/w of dry polymer)	>100	0.688	27
PL3	Glycerine (20 % w/w of dry polymer)	>100	0.464	17
PL4	Propylene glycol (30 % w/w of dry polymer)	99	0.430	28
PL5	PEG 400 (30 % w/w of dry polymer)	>100	0.640	36
PL6	Glycerine (30 % w/w of dry polymer)	>100	0.492	18
PL7	Propylene glycol (40 % w/w of dry polymer)	101	0.358	29
PL8	PEG 400 (40 % w/w of dry polymer)	>100	0.346	29
PL9	Glycerine (40 % w/w of dry polymer)	33	0.714	30

*values are expressed as mean (n=3)

4.4 Evaluation Parameters of Fast Dissolving Oral Films

4.4.1 Morphological properties

The physical appearance of the films was evaluated. All the films prepared with different polymer concentrations were found to be flexible, smooth, transparent, non-sticky and homogeneous except the F1 formulation batch which has average film-forming capacity and was sticky in nature.

4.4.2 Weight of film

The weight of oral strips varies from 28.667 to 70.333 mg. Formulation F1 to F3 weighed about 28.667, 40, and 49 mg respectively. For formulation, F4 to F6 values were 38, 50 and 53.333 respectively. Formulations F7 to F9 weighed about 44.667, 53.667, and 70.333 respectively. The individual weight of each of the 3 samples, of each type formulation, was found to be consistent within the formulation. Between formulations, the weight increased with the increased content of the polymers used.

4.4.3 Thickness

This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip**.** Low SD values in the film thickness measurements ensured uniformity of thickness in each formulation. Differences in the thickness of films may be due to differences in the viscosities of polymeric solutions. The thickness was gradually increased with the amount of polymers. The thickness of the oral strip varies from 0.07 to 0.117 mm.

4.4.4 Tensile strength

The effect of the concentration of polymers was observed on the tensile strength. The tensile strength of the film was found to be directly proportional to the concentration of polymer and plasticizer. Tensile strength was found to increase with the increasing content of polymer which may be due to the increase in the elasticity nature of the film-forming polymer.

The results of tensile strength from various formulations (F1 to F9) are given in Table 6. The tensile strength of all the films was in the range of 0.495 to 3.388 N/mm^2. The results suggest that all films had good mechanical strengths to withstand mechanical damage during production and application.

Table 6: Characterization of FDOFs (I)

Batch Codes	Weight (mg)	Thickness (mm)	Tensile strength (N/mm^2)	Folding Endurance (No. of folds)
F1	28.667 ± 1.247	0.07 ± 0.008	0.495	112
F2	40 ± 3.266	0.073 ± 0.005	0.730	190
F3	49 ± 4.082	0.093 ± 0.005	1.348	95
F4	38 ± 2.944	0.073 ± 0.005	1.215	187
F5	50 ± 2.449	0.1 ± 0.008	1.887	210
F6	53.333 ± 4.497	0.107 ± 0.005	2.099	60
F7	44. 667 ± 2.867	0.083 ± 0.005	1.774	196

F8	53.667 ± 3.000	0.107 ± 0.005	2.136	232
F9	70.333 ± 1.700	0.117 ± 0.005	3.388	41

4.4.5 Folding endurance

The results of folding endurance of various formulations (F1 to F9) are given in Table 6. Except F3, F6 and F9 formulations all other film formulations exhibited good folding endurance exceeding 100, indicating that they are tough and flexible. This makes the system acceptable for movement of mouth, indicating good strength and elasticity. Folding endurance test results indicated that the films would maintain integrity with buccal mucosa when applied.

The folding endurance of the oral strips varies from 41 to 232. Formula F1, F2, F4, F5, F7 and F8 showed good folding endurance. F3, F6, and F9 batches containing higher amounts of polymer (HPMC E3 and HPMC E5) scored less folding endurance as compared to earlier batches.

4.4.6 Surface pH:

The surface pH of fast-dissolving oral films was determined in order to investigate the possibility of any side effects *in vivo*. An acidic or alkaline pH of administered dosage forms can irritate the buccal mucosa. Surface pH of the prepared films was in the range of 6 to 7. It assured that there will not be any kind of irritation to the mucosal lining of the oral cavity and hence, more acceptable by the patients.

4.4.7 *In*-vitro disintegration time

The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral film. Typical disintegration time for film is 5–30 sec.

The disintegration property of the film depends on the concentration of polymer i.e as the concentration of polymer was increased, disintegration time also increased. The *in*-vitro disintegration time of films of formulation batches F1-F9 was found to be between 5 to 60 seconds as shown in Table 7. Except F9 formulation batch which shows more *in*-vitro disintegration i.e 60 sec, all other formulation batches were found to possess good *in*-vitro disintegration time. The films having less *in*-vitro disintegration time were desirable in case of fast dissolving drug delivery.

4.4.8 Drug content

According to Table 7, the drug content was found to be in the range of 95.07 to 98.90%. The drug content of formulation batch F4 was found out to be higher than the remaining formulation batches.

4.4.9 In-vitro Drug Release

The dissolution of a drug substance may depend on the drug dosage form, on the rate of disintegration and on the properties of the drug itself, such as high or low solublity, which determines the disssolution rate. In the case of oral films, the disintegration and dissolution is hardly distinguishable. If the oral film disintegrate it concurrently dissolves in a small amount of saliva which makes it difficult to mimic these natural conditions and measure with an adequate method. Different methods have been described in the literature but the standard method does not exist.

The results obtained in the *in*-vitro drug release for the formulations F1 to F9 is tabulated in Table 7.

Rapid drug dissolution was observed in F1, F2, and F4 which released 92.66%, 93.71% and 96% respectively. The % cumulative drug release of formulation batches F1, F2, and F4 was found to be more than 90% at the end of 120 sec, 240 sec, and 210 sec respectively. However, the cumulative drug release of formulation batch F4 was found to be maximum at 210 seconds.

However, the % cumulative drug release of formulation batches F3, F5, and F7 was found to be 74.2%, 82.53%, and 86.31% respectively at the end of 240 seconds.

Slow drug dissolution was observed in F6, F8 and F9 with release 67%, 63.2% and 52.55% respectively at the end of 240 seconds, as the concentration of the polymer increased, the drug release was found to be decreased. This might be due to the increase concentration of polymer, results in formation of strong matrix layer caused by more intimate contact between the particles of HPMC result in decreased in mobility of drug particles in swollen matrices, which leads to a decrease in drug release.

From all the evaluation parameters, it has been seen that the F4 formulation fulfills all the characteristics of fast-dissolving oral films, so the F4 formulation was selected as the best formulation.

Table 7: Characterization of FDOFs (II)

Batch Codes	Surface pH	In-vitro Disintegration Time (seconds)	Drug Content (%)	Dissolution Profile (%) (in 240 Secs)
F1	6 – 7	5	95.18	93.2*
F2	6 – 7	17	96.91	93.71
F3	6 – 7	21	95.61	74.2
F4	6 – 7	15	98.90	96**
F5	6 – 7	23	97.91	82.53
F6	6 – 7	26	96.55	67
F7	6 – 7	18	95.07	86.31
F8	6 – 7	25	95.89	63.2
F9	6 – 7	60	95.92	52.55

*%cumulative drug release in 120 seconds, **%cumulative drug release in 210 seconds

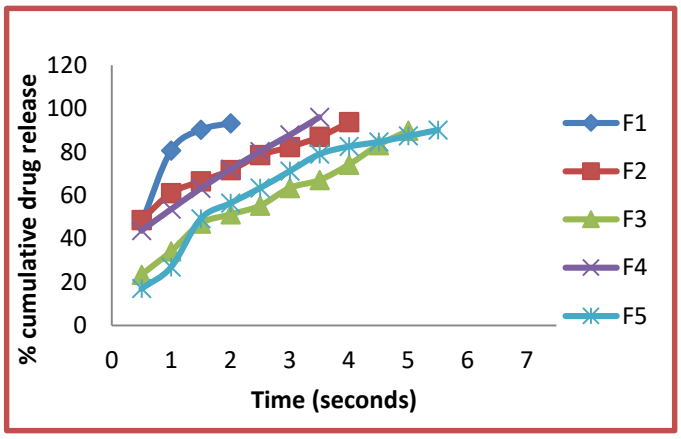

Figure 4: Comparative study of % cumulative drug release of batches F1 to F5

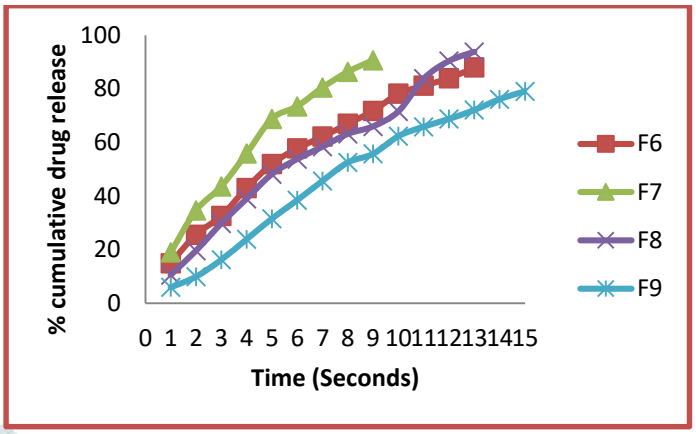

Figure 5: Comparative study of % cumulative drug release of batches F6

4.4.10 Consumer Acceptance Test

The taste masking evaluation was carried out on 10 human volunteers after carefully reading and signing the participant consent form and the following observations were obtained.

Table 8: Consumer acceptance test

Volunteers	Time (Seconds)	Final Film Formulation
1	60	5
2	60	5
3	60	5
4	60	5
5	60	5
6	60	4
7	60	5
8	60	5
9	60	5
10	60	5

The majority of the participants (9 out of 10) found the final film formulation was good (score = 5). These results confirmed that the taste of ivabradine hydrochloride was adequately masked by using sucralose as a sweetener. The volunteers have reported that the films are having good mouth feel, no bitter taste and aftertaste, no irritation, and are very easy to handle. These observations clearly demonstrate the successful formulation of fast-dissolving oral films of ivabradine hydrochloride which had good film characteristics and acceptability by the human volunteers.

4.4.11 Surface morphology

Scanning electron microscopy has been extensively employed to study the morphology of the film. The scanning electron micrographs are presented in Figure 6. The prepared film containing ivabradine hydrochloride was clear and colorless. The scanning electron photomicrograph of the film showed smooth surface with some little pores and without any scratches or transverse striations which indicates the even distribution of ivabradine hydrochloride and a uniform film.

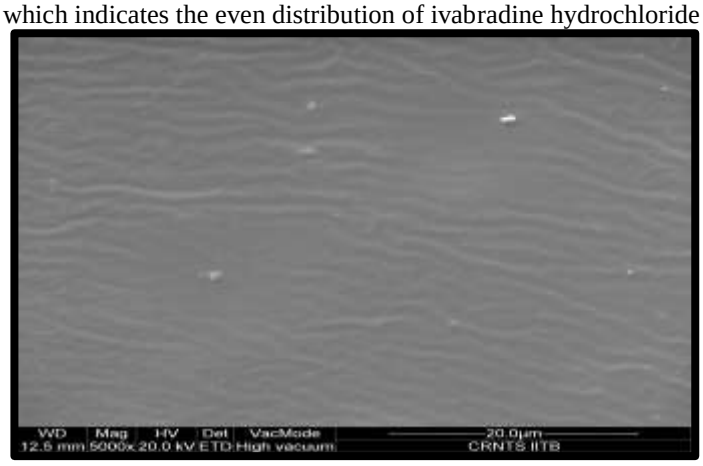

Figure 6: Scanning electron photomicrograph of ivabradine hydrochloride film at 5000x magnification

4.4.12 Stability studies

The formulation batch F4 was subjected to stability studies at 40°C ± 2°C / 75%RH ± 5% RH for 2 months. The fast-dissolving films were removed on definite intervals and subjected to different evaluation parameters as explained in Table 9. The films were found to be relatively stable.

Table 9: Evaluation performed on optimized fast-dissolving oral film at different time intervals under stability study conditions (40°C / 75%RH)

Evaluation Parameters	After 30 Days	After 60 Days
Appearance	Transparent	Transparent
Disintegration time (seconds)	16	16
Tensile strength (N/mm^2)	1.202	1.163
Drug content (%)	98.28	97.89
Cumulative drug release (%)	95.73% in 210 seconds	94.19 in 210 seconds

Stability studies of optimized formulation indicated that there are no significant changes in the film characteristics and the formulation was stable enough for the period of at least 2 months at the mentioned condition.

Figure 7: Appearance of FDOFs after removing from glass mold (F4)

IV. CONCLUSION

From this investigation, it can be concluded that ivabradine hydrochloride can be successfully formulated into fast-dissolving oral films by using solvent-casting techniques. The method of preparation was found to be simple and requires minimum excipients, thus making the product cost-effective. Various cellulose derivatives were employed for their film-forming properties of which HPMC E3 and HPMC E5 showed promising physico-chemical properties as compared to all other grades therefore, it was selected for further studies. Use of glycerine as plasticizer resulted in better films in respect to physicochemical parameter like tensile strength and folding endurance. Based on the physicochemical parameters and *in*-vitro drug release studies, formulation F4 was considered as the best formulation which exhibited a drug release of 96% at the end of 210 seconds. Stability studies results showed that optimized formulation was stable enough for the period of at least 2 months.

Finally, it can be concluded that the developed dosage form has the potential as an alternative dosage form in treating angina pectoris where a quicker onset of action for a dosage form is desirable along with the convenience of administration (Jacob et al., 2023).

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