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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM LOADED WITH AMBRISENTAN FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION (PAH) AS A NOVEL DRUG DELIVERY SYSTEM

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Keywords:

Ambrisentan, Fast dissolving oral film, Dispersion time, and dissolution rate, Physicochemical interaction

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ABSTRACT: Ambrisentan is an endothelin receptor antagonist for rapid administration during early disease progression to provide therapeutic benefit. This study aimed to develop Ambrisentan as a fast-dissolving oral film (FDOF) and evaluate the physicochemical and performance characteristics of the formulated films. The FDOFs were prepared using film-forming polymers, including hydroxypropyl methylcellulose (HPMC E6 LV) and 2-hydroxypropyl β-cyclodextrin (HPβCD), with xanthan gum and propylene glycol 400 at varying concentrations. Eleven formulations were developed and evaluated for parameters including film color, thickness, brittleness, peelability, transparency, surface smoothness, tackiness, film-forming capacity, content uniformity, dispersion time, and dissolution behaviour. The optimized formulation (F9) showed excellent film properties, with content uniformity of 99.6 ± 0.8%, dispersion time of 15 ± 2 s, and dissolution rate of 98.2 ± 1.08% within 12 min. Fourier transform infrared spectroscopy revealed no physicochemical interaction between Ambrisentan and polymers. Differential scanning calorimetry showed no significant changes in the melting endotherm of the pure drug and optimized formulation, indicating drug-excipient compatibility. Comparative dissolution studies demonstrated that formulation F9 exhibited superior dissolution performance compared with the marketed oral tablet of Ambrisentan.

INTRODUCTION: Although oral administration remains the most preferred route for drug delivery due to its convenience and patient acceptance, swallowing conventional tablets can be difficult for paediatric, geriatric, and dysphagic patients, as well as for individuals without immediate access to water, such as travellers [1, 2]. These limitations often lead to poor medication adherence and compromised therapeutic outcomes. To overcome these challenges, fast-dissolving oral dosage forms have been developed as an innovative drug delivery approach, offering rapid disintegration, ease of administration, and improved patient compliance.

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Oral thin films, in particular, have emerged as a promising alternative due to their ability to dissolve quickly in the oral cavity without the need for water, thereby enhancing convenience and adherence in special patient populations [3, 4]. Pulmonary hypertension (PH) is a progressive and life-threatening disorder that significantly impairs

exercise capacity and quality of life, particularly in advanced stages of the disease. It is characterized by elevated pulmonary arterial pressure resulting from structural and functional changes in the pulmonary vasculature, including vasoconstriction, inflammation, and vascular remodelling [5, 6]. pH is hemodynamically defined by a mean pulmonary artery pressure (mPAP) greater than 20 mmHg at rest. A distinct subgroup of PH, pulmonary arterial hypertension (PAH), is diagnosed based on additional criteria, including a pulmonary artery wedge pressure ≤15 mmHg and a pulmonary vascular resistance index (PVRi) greater than 3 Wood units, in the absence of other causes such as lung or left heart disease [7, 8]. Although PAH is rare in children, its reported incidence ranges from 2 to 16 cases per million children, highlighting the severity and clinical importance of early diagnosis and management [9]. Endothelin (ET) is a potent vasoconstrictor peptide primarily produced by vascular endothelial cells and plays a key role in vascular tone regulation and smooth muscle cell proliferation [10, 11]. Elevated endothelin levels have been observed in the blood and lungs of patients with PAH, indicating its significant contribution to disease progression [12-14]. Ambrisentan is an orally active endothelin type-A (ETA) receptor antagonist commonly used in the management of PAH1 [5, 16]. The present study aimed to evaluate the effectiveness of eleven fast-dissolving oral film (FDOF) formulations of Ambrisentan for the treatment of pulmonary arterial hypertension.

MATERIALS AND METHODS:

Materials: Ambrisentan was purchased from MSN Laboratories, Hyderabad, India. The film-forming polymer, hydroxypropyl methylcellulose (HPMC E6 LV), was procured from Colorcon Asia Pvt. Ltd., Goa, India. The solubilizing agent, 2-hydroxypropyl β-cyclodextrin (HPβCD), was obtained from CycloLab India Pvt. Ltd., India.

Xanthan gum, used as a stabilizing agent, was purchased from CP Kelco India Pvt. Ltd., India, while sodium saccharin, used as a sweetening agent, was obtained from NutraSweet India Pvt. Ltd., India. Vanillin flavor was procured from Firmenich India Pvt. Ltd., India. All other chemicals and reagents used in the study were of analytical grade and procured from approved Indian suppliers.

Preformulation Studies: Preformulation studies were conducted to evaluate the physicochemical properties of the active pharmaceutical ingredient (API) and excipients to ensure suitability for formulation development. These studies included solubility analysis of Ambrisentan in different pH buffer solutions, evaluation of flow properties, and drug–excipient compatibility studies. Primary physical evaluation of the fast-dissolving oral films (FDOFs) was performed by visual inspection to assess parameters such as film colour, thickness, brittleness, peelability, transparency, surface smoothness, tackiness, and film-forming capacity. Peelability was assessed based on the ease or difficulty of removing the film from the release liner without damage. Transparency was evaluated by placing the film against an illuminated background and visually inspecting it for the presence of any opacity or non-uniformity. Film-forming capacity was defined as the ability of the polymer to form a uniform, continuous, and defect-free film.

Calibration Curve of Ambrisentan: A calibration curve for Ambrisentan was constructed using standard solutions prepared in pH 7.2 acetate buffer. Solutions with concentrations of 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 30 µg/ml were prepared, and their absorbance values were measured at 262 nm using a UV–visible spectrophotometer (Shimadzu UV-1800) as given in **Table 1** and **Fig. 1.**

Method of Validation: The UV–visible spectrophotometric method developed for the estimation of Ambrisentan was validated in accordance with the International Council for Harmonisation (ICH) guidelines with respect to linearity, accuracy, precision, specificity, limit of detection (LOD), and limit of quantification (LOQ) and result as in **Table 4.**

Linearity: Linearity was evaluated by analysing standard solutions of Ambrisentan in the concentration range of 1–30 µg/mL prepared in pH 7.2 acetate buffer. The absorbance was measured at 262nm, and a calibration curve was constructed by plotting absorbance versus concentration. The method exhibited good linearity over the studied range with a regression equation of $y = 0.041x + 0.012$ and a correlation coefficient ($R^2 = 0.998$).

Accuracy: The accuracy of the method was assessed by recovery studies using the standard addition method at three concentration levels (80%, 100%, and 120% of the nominal concentration). Known amounts of Ambrisentan were added to pre-analyzed samples and analyzed in triplicate. The percentage recovery was found to be in the range of 98.2%–101.6%**,** indicating good accuracy of the method.

Precision: Precision was evaluated in terms of intra-day and inter-day precision. Intra-day precision was determined by analyzing three different concentrations of Ambrisentan three times on the same day, while inter-day precision was assessed by analyzing the same concentrations on three consecutive days. The percentage relative standard deviation (%RSD) for both intra-day and inter-day precision was found to be less than 2%, confirming the precision of the method.

Specificity: Specificity was assessed by analyzing blank, placebo, and sample solutions to detect any potential interference at 262 nm. No interference from excipients or solvents was observed, confirming that the method was specific for Ambrisentan.

Limit of Detection (LOD) and Limit of Quantification (LOQ): The LOD and LOQ were calculated based on the standard deviation of the response (σ) and the slope (S) of the calibration curve using the following equations:

$$LOD = 3.3\sigma / S$$

$$LOQ = 10\sigma / S$$

Based on these calculations, the LOD and LOQ were found to be 0.21 µg/mL and 0.64 µg/mL, respectively, demonstrating that the developed method is sufficiently sensitive for the quantitative estimation of Ambrisentan. The calibration curve was generated by plotting absorbance versus concentration, as illustrated in **Table 1** and **Fig. 1.**

TABLE 1: CALIBRATION DATA OF AMBRISENTAN SHOWING THE RELATIONSHIP BETWEEN CONCENTRATION AND ABSORBANCE

Concentration (µg/mL)	Absorbance
0	0
5	0.119
10	0.234
15	0.345
20	0.458
25	0.575
30	0.694

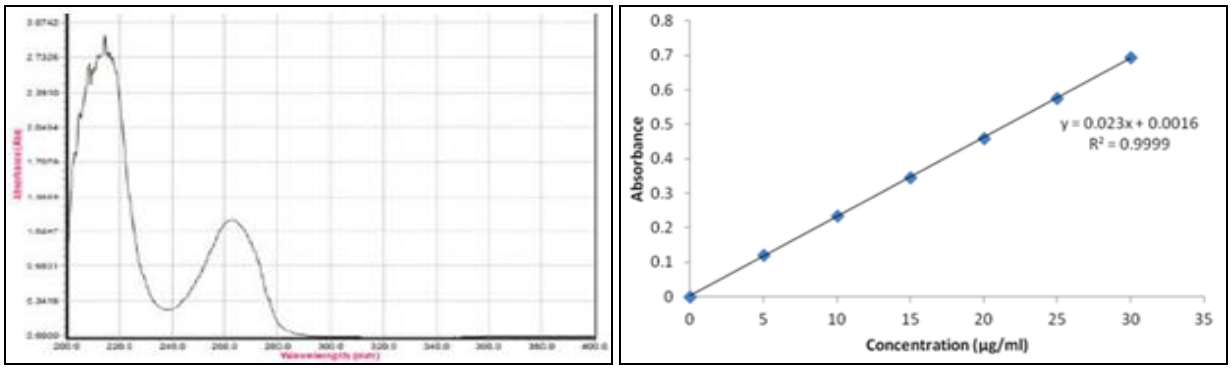

FIG. 1: ABSORBANCE MAXIMA AND CALIBRATION CURVE OF AMBRISENTAN

pH Dependent Solubility Studies: An accurately measured 100 mL of solvent was taken in a stoppered conical flask, and the drug was added incrementally with gentle mixing until saturation was achieved. The mixture was sonicated briefly to confirm saturation, followed by the addition of excess drug if required. The suspension was sonicated for 30 minutes, allowed to equilibrate, and then filtered. The filtrate was analyzed for drug content, and solubility was expressed as mg/mL. The study was conducted in different pH media to evaluate pH-dependent solubility as in **Fig. 3.**

Angle of Repose: Accurately weighed drug powder (10 g) was allowed to flow through a funnel of fixed height above a flat surface, and the height and radius of the formed powder cone were measured. The angle of repose (θ) was calculated using the following equation:

$$\tan \theta = h / r$$

The experiment was performed in triplicate and the mean value was recorded.

Bulk Density: Bulk density was determined in Bulk density apparatus and was calculated using the formula:

Bulk density = Mass of powder / Bulk volume

The flow characteristics of Ambrisentan powder were interpreted based on angle of repose, Carr's index, and Hausner's ratio. Lower values of angle of repose (< 30°), Carr's index (< 15%), and Hausner's ratio (< 1.25) indicate good flow properties mentioned in **Table 3.**

Preparation of Ambrisentan Fast-Dissolving Oral Films: Fast-dissolving oral films (FDOFs) of Ambrisentan containing 10 mg drug per 4 cm² were prepared by the solvent casting method. A fixed batch size of 100 mL of film-forming solution was maintained for all formulations. Hypromellose (HPMC E6 LV) was used as the film-forming polymer, xanthan gum as a film stabilizer, and propylene glycol as a plasticizer. The polymer was dispersed in purified water and allowed to hydrate for 24 h to obtain a homogeneous solution. Xanthan gum was added gradually under controlled stirring, followed by the addition of propylene glycol. Ambrisentan was complexed separately with hydroxypropyl β-cyclodextrin (HPβCD) and incorporated into the polymeric dispersion. Sodium saccharin, vanillin, FD&C Red, and ethanol were dissolved in purified water and added with continuous stirring to ensure uniform drug distribution. A fixed volume (20 mL) of the final solution was poured into a 9 cm diameter petri dish and dried in a hot air oven at 45 °C for 6 h. The dried films were cooled, carefully peeled, and cut into 4 cm² strips, each containing 10 mg of Ambrisentan. The films were wrapped in aluminum foil and stored in polyethylene pouches until further evaluation. The prototype formulation was developed using hypromellose E6 LV as the primary polymer, and formulation optimization was carried out by varying polymer, solubilizer, and plasticizer concentrations. The prepared FDOFs **Table 2** and **Fig. 2** were subsequently evaluated for physicochemical, mechanical, and performance parameters to identify the optimized formulation.

TABLE 2: COMPOSITION OF VARIOUS TRIAL BATCHES OF FDOF USING HPMC E6LV FOR AMBRISENTAN

S. no.	Ingredients (in mg)	Formulation Codes										
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	Ambrisentan (API)	159.0	159.0	159.0	159.0	159.0	159.0	159.0	159.0	159.0	159.0	159.0
2	HPMC E6 LV (polymer)	300.0	310.0	320.0	330.0	340.0	350.0	360.0	370.0	380.0	390.0	400.0
3	HPBCD (complexing agent)	270.0	260.0	250.0	240.0	230.0	220.0	210.0	200.0	190.0	180.0	170.0
4	Propylene glycol 400 (Plasticier)	80.0	80.0	100.0	100.0	100.0	100.0	140.0	100.0	140.0	120.0	120.0
5	Xanthan gum (film integrity)	10.0	10.0	10.0	8.0	8.0	8.0	10.0	10.0	10.0	8.0	8.0
6	Sodium Sachharin	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
7	Ethanol (Cosolvent)	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
8	Purified Water	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
9	Vanilla flavor	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
10	FD&C Red	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

"q.s." denotes quantity sufficient to make up the total volume of the solution to 20 mL, which is required to obtain a uniform casting solution. This volume yields films cast in a 9 cm diameter Petri dish (63.64 cm²), from which individual 4 cm² films containing 10 mg of drug per dose of 6 films are obtained.

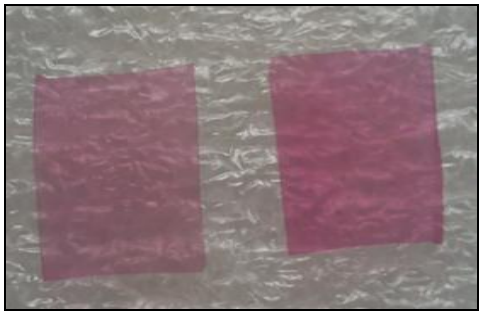

FIG. 2: AMBRISENTAN FDOF PIECES OF 4CM^2

Evaluation of Prepared Ambrisentan Fast-Dissolving Oral Films:

Characterization of Fast-Dissolving Oral Films: The prepared fast-dissolving oral films (FDOFs) were subjected to primary physical evaluation by visual inspection to assess parameters such as film color, thickness, brittleness, peelability, transparency, surface smoothness, tackiness, and

film-forming capacity, as described by Kulkarni *et al.* (2011) [15] as in **Table 5.**

***In-vitro* Quality Control Tests:** The dried films, with a total surface area of 63.64 cm², were cut into uniform square pieces of 4 cm² (2 cm × 2 cm**)**, each representing a single dosage unit. The prepared FDOFs were evaluated for the following quality control parameters.

Uniformity of Weight: The uniformity of weight test was performed to assess batch-to-batch consistency, following the methods described by Dinge *et al.* (2008) and Devi *et al.* (2003) [17, 18]. Ten films (n=10) were randomly selected from each formulation batch and weighed individually using a digital balance with a precision of 1 mg. The mean weight and standard deviation were calculated.

Thickness: The thickness of the FDOFs, a critical parameter influencing dispersion time and drug release, was measured using a digital Vernier calliper with a precision of 0.010 mm (10 µm). Measurements were taken at different locations (centre and corner) on each film, and the average thickness was determined (n=3). Ideally, FDOFs are expected to have a thickness of up to 100 µm, as reported by Raju *et al.* (2011) and Choudary *et al.* (2011) [19, 20].

Folding Endurance: Folding endurance was assessed to determine the mechanical strength and flexibility of the films. Each FDOF was repeatedly folded at the same position until breakage occurred. The number of folds the film endured without breaking was recorded as the folding endurance, following the method described by Shinde *et al.* (2008) [21].

Folding Endurance (FE) = Number of folds required to break the film

Surface pH Study: The surface pH of the fast dissolving oral films (FDOFs) was measured to evaluate the potential for irritation to the oral mucosa. Adrop (0.5 mL) of distilled water was placed on the surface of the film and allowed to hydrate and equilibrate for 30 s at room temperature. After equilibration, the electrode of a calibrated digital pH meter was gently placed in contact with the moistened film surface without damaging the film. The surface pH was measured for three films from each formulation (n = 3), and the mean value was calculated, following the method described by Raju *et al.* (2011) and Choudary *et al.* (2011) [18, 19].

Dispersion Time: Dispersion time was determined to evaluate the rapid disintegration behaviour of the FDOFs. Each film was placed in a Petri dish containing 10 mL of simulated saliva fluid (pH 6.8) maintained at 37 ± 0.5°C. The time required for the film to completely disperse without leaving visible residues was recorded as the dispersion time. The test was performed in triplicate, and the results were expressed as mean ± SD.

Drug Content Uniformity: Drug content uniformity was evaluated to ensure uniform distribution of Ambrisentan within the fast-dissolving oral films (FDOFs). Individual films of 4 cm² area were placed in 100 mL of pH 7.2 acetate buffer and stirred continuously for 30 min to ensure complete drug extraction. The resulting solution was filtered through Whatman filter paper No. 1, and 1 mL of the filtrate was diluted to 10 mL (1:10 dilution) with the same buffer. The diluted solution was analysed using a validated UV–visible spectrophotometric method at 262 nm. Drug content was calculated using the calibration curve, and the results were expressed as percentage drug content (mean ± SD, n = 3).

***In-vitro* Dissolution Studies:** *In-vitro* dissolution studies were performed to evaluate the drug release behaviour of the FDOFs using a USP dissolution apparatus type II (paddle method). The dissolution medium consisted of 900 mL of pH 6.8 phosphate buffer, maintained at 37 ± 0.5°C, with a paddle rotation speed of 50 rpm. Each film (4 cm²) was placed in the dissolution medium, and samples were withdrawn at predetermined time intervals (2, 4, 6, 8, 10, and 12 min). An equal volume of fresh dissolution medium was added to maintain sink conditions. The withdrawn samples were filtered, suitably diluted and analyzed spectrophotometrically at 262 nm. The cumulative percentage of drug released was calculated and plotted against time as in **Table 6.**

Fourier Transform Infrared Spectroscopy (FTIR): This was performed to evaluate the compatibility between Ambrisentan and the

excipients used in the fast-dissolving oral film formulation, following the method of Kai Bin Liew *et al.* (2011). FTIR analysis was carried out using a Shimadzu IR Affinity-1 spectrophotometer. Spectra of pure Ambrisentan, individual excipients, and the optimized formulation were recorded using the potassium bromide (KBr) pellet method. Approximately 2–3 mg of sample was mixed with 100 mg of dry KBr, finely triturated, and compressed into transparent pellets under hydraulic pressure. The spectra were scanned over the range of 4000–400 cm^{-1} at a resolution of 4 cm^{-1} with 32 scans per sample to identify characteristic functional groups and to detect any possible drug–excipient interactions as in **Fig. 5.**

Differential Scanning Calorimetry (DSC): Differential scanning calorimetry was performed to evaluate the thermal behavior and compatibility of Ambrisentan with excipients, following the method of Doaa Ahmed El-Setouhy *et al.* (2010). DSC analysis was carried out using a Shimadzu DSC-60 instrument (TA-60 software, Japan). Samples of pure Ambrisentan, individual excipients, and the optimized formulation (F9) (5–8 mg) were sealed in aluminium pans, with an empty pan used as reference. The samples were heated from 30 to 300 °C at a rate of 10 °C/min under a nitrogen purge (40 mL/min) to maintain an inert atmosphere and to detect any thermal interactionsas in **Fig. 6** and **Table 7.**

Stability Studies of Optimized FDOF (F9): Stability of a formulation means, the quality and efficacy of a formulation to remain unchanged of its physical parameters, chemical parameters, organoleptic characteristics and toxic levels as per the method mentioned in Yellanki SK *et. al*., (2011) [16]. The purpose of stability testing is to provide evidence of how the quality and safety of a API or a formulation varies with time under the influence of a various of environmental factors such as heat, relative humidity and light. Stability studies were executed for 6 months period at two different conditions.

1) 40°C/75%RH- Accelerated conditions as per regulatory guidelines.

2) 25°C/60%RH- Long term conditions as per regulatory guidelines.

Optimized formulation (F9) was preferred for stability studies on the basis of satisfactory drug release pattern. Samples were wrapped in butter paper and packed in Alu – Alu pouches. Then loaded in Stability chamber in accelerated conditions for 6 months according to regulatory ICH guidelines. The results are mentioned in **Table 9, 10** and **11.**

Comparison of Final Optimized Formulation with Marketed Formulation: It has been concluded that, from the above data F9 was noticeable optimum for the formulation of Ambrisentan FDOFs. Thus, Drug release pattern of F9 formulation was noticeable to be comparable with the Innovator product VOLIBRIS (10 mg). Based on above data of **Table 8** and **Fig. 5**, F9 formulation shows rapid release in comparison with Innovator product (Volibris 10 mg) due to its fast-dissolving characteristics as in **Table 12.**

RESULTS AND DISCUSSIONS: The pH-dependent solubility study of Ambrisentan showed a gradual increase in solubility with an increase in pH. The drug exhibited very low solubility in acidic medium (0.005 mg/mL at pH 1.21), which increased progressively in acetate and phosphate buffer systems. Maximum solubility was observed at pH 7.25 (0.035 mg/mL). This behaviour indicates the pH-dependent ionization characteristics of Ambrisentan. The bar diagram **Fig. 3** illustrates the pH-dependent solubility of Ambrisentan in various dissolution media. The drug exhibited the lowest solubility in 0.1 N HCl (pH 1.21) and water (pH 5.75). A progressive increase in solubility was observed with increasing pH, with maximum solubility recorded in acetate buffer pH 7.25. This confirms the pH-dependent solubility behaviour of Ambrisentan.

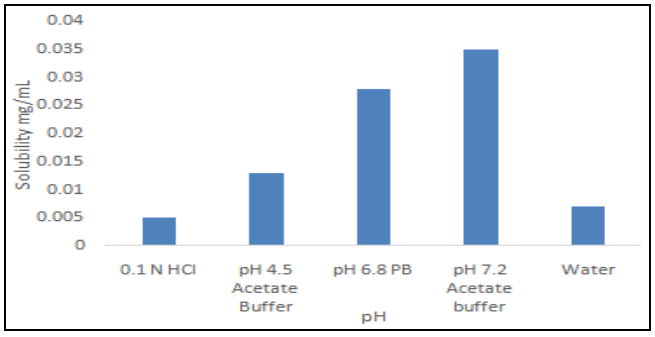

FIG 3: PH DEPENDENT SOLUBILITY STUDIES OF AMBRISENTAN

The flow properties of Ambrisentan powder were evaluated using angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio. The angle of repose was found to be 32.4°, indicating fair flow characteristics. The Carr's index (14.6%) and Hausner's ratio (1.17) further confirmed acceptable flow behaviour of the drug powder, suggesting its suitability for further formulation development.

TABLE 3: FLOW PROPERTIES OF AMBRISENTAN

S. no.	Parameter	Value
1	Angle of repose (°)	32.4 ± 0.6
2	Bulk density (g/cm³)	0.41 ± 0.02
3	Tapped density (g/cm³)	0.48 ± 0.01
4	Carr's Compressibility Index (%)	14.6 ± 0.5
5	Hausner's ratio	1.17 ± 0.02

The developed UV–visible spectrophotometric method for estimation of Ambrisentan was validated as per ICH guidelines. The method showed excellent linearity in the concentration range of 1–30 µg/mL with a correlation coefficient of 0.998 (y = 0.041x + 0.012). Accuracy studies using the standard addition method showed percentage recoveries of 98.2–101.6%. Precision studies demonstrated good repeatability, with intra-day and inter-day %RSD values below 2%.

The method was found to be specific, with no interference from excipients or solvents at 262 nm. The LOD and LOQ were 0.21 µg/mL and 0.64 µg/mL, respectively, indicating adequate sensitivity. Overall, the method is simple, accurate, precise, and suitable for routine analysis of Ambrisentan in fast-dissolving oral film formulations.

TABLE 4: VALIDATION OF UV METHOD FOR AMBRISENTAN

Validation Parameter	Results	Acceptance Criteria
Detection Wavelength	262 nm	—
Linearity Range	1–30 µg/mL	Correlation coefficient ≥ 0.99
Regression Equation	y = 0.041x + 0.012	—
Correlation Coefficient (R^2)	0.998	≥ 0.99
Accuracy (% Recovery)	98.2–101.6%	98–102%
Precision (Intra-day, %RSD)	< 2%	≤ 2%
Precision (Inter-day, %RSD)	< 2%	≤ 2%
Specificity	No interference observed	No interference at λmax
Limit of Detection (LOD)	0.21 µg/mL	As low as possible
Limit of Quantification (LOQ)	0.64 µg/mL	As low as possible
Analytical Method	UV–Visible Spectrophotometry	—
Solvent / Buffer	pH 7.2 acetate buffer	—

Physical and Mechanical Evaluation of Fast Dissolving Oral Films: The prepared fast dissolving oral film formulations (F1–F11) were evaluated for thickness, weight uniformity, folding endurance, surface pH, content uniformity, and in vitro disintegration time. The results are summarized in **Table 5.**

Thickness: The thickness of the films ranged from 69 ± 1 µm to 85 ± 1 µm, indicating uniform film formation across all formulations. Minor variations in thickness may be attributed to differences in polymer concentration and casting conditions. The relatively narrow thickness range confirms good control over the solvent casting process.

Uniformity of Weight: All formulations exhibited acceptable weight uniformity, with values ranging from 51.85 ± 4% to 56.12 ± 3% (w/w). The low standard deviation values indicate uniform distribution of the casting solution and reproducibility of the formulation process.

Folding Endurance: Folding endurance values varied significantly among the formulations, ranging from 51 ± 2 to 103 ± 2 folds. Formulations F9, F10, and F11 showed the highest folding endurance (>100), indicating excellent mechanical strength and flexibility. The improved folding endurance may be attributed to optimal polymer–plasticizer interaction, which enhances film elasticity and resistance to breakage.

Surface pH: The surface pH of all formulations ranged between 5.38 ± 0.2 and 5.97 ± 0.2, which is close to the physiological pH of saliva. This suggests that the films are unlikely to cause irritation or discomfort to the oral mucosa, making

them suitable for buccal or sublingual administration.

Content Uniformity / Assay: The drug content of all formulations was found to be within acceptable limits, ranging from 90.2 ± 0.7% to 99.6 ± 0.8%, indicating uniform distribution of Ambrisentan within the films. Formulations F9 and F10 showed the highest drug content (>99%), demonstrating efficient drug incorporation and minimal drug loss during formulation.

In-vitro **Disintegration Time:** The *in-vitro* disintegration time of the films ranged from 15 ± 2 to 34 ± 2 seconds, confirming the fast-dissolving nature of the prepared films. Among all formulations, F9 exhibited the shortest disintegration time (15 ± 2 seconds), which may be attributed to its optimal polymer composition and improved wettability.

Optimized Formulation: Based on the collective evaluation of mechanical strength, surface pH, content uniformity, and rapid disintegration, formulation F9 was identified as the optimized formulation. It demonstrated superior folding endurance, highest drug content, and the fastest disintegration time, making it suitable for fast dissolving oral film delivery of Ambrisentan.

TABLE 5: EVALUATION OF AMBRISENTAN LOADED FDOF

Formulation codes	Thickness (µm)	Uniformity of weight (mg) (n=10)	Folding Endurance (count of foldings) (n=3)	Surface pH	Content Uniformity/ assay (%)	*In-vitro* DT (sec)
F1	71±1	51.85± 4	51±2	5.84±0.1	90.3±0.14	30±2
F2	69±1	52.12± 5	57±2	5.64±0.1	92.6±0.45	34±2
F3	81±3	54.27± 3	59±1	5.54±0.4	90.2±0.7	29±2
F4	84±1	53.82± 3	52±4	5.38±0.2	94.6±0.15	24±2
F5	84±1	53.13± 4	60±1	5.59±0.1	94.3±0.6	28±2
F6	85±1	52.89± 3	62±2	5.59±0.5	95.4±1.2	29±2
F7	77±1	55.73± 4	53±2	5.47±0.4	91.3±0.3	25±2
F8	83±0	53.71± 3	61±2	5.83±0.1	92.5±1.9	19±2
F9	82±2	56.12± 3	102±2	5.97±0.2	99.6±0.8	15±2
F10	81±2	54.96± 3	103±2	5.91±0.2	99.4±0.8	24±2
F11	75±2	54.36± 2	100±2	5.58±0.1	93.5±0.5	26±2

In-vitro **Drug Release Studies:** The *in-vitro* dissolution profiles of the prepared fast dissolving oral films (FDOFs) were evaluated over 12 min. No drug release was observed at 0 min, indicating uniform film integrity and absence of surface drug. All formulations exhibited rapid and progressive drug release with time. Initial release of 10–45% was observed within 1–2 min, attributed to quick hydration and swelling of hydrophilic polymers. At 4–6 min, drug release increased to 30–70%, indicating efficient matrix erosion and diffusion. Several formulations achieved more than 80–90% release within 8–10 min. The optimized formulation (F9) showed nearly complete drug release (≈96–98%) within 10–12 min, demonstrating superior dissolution performance. Overall, the rapid dissolution behavior confirms the suitability of the developed FDOFs for fast oral delivery of Ambrisentan as depicted in **Table 6** and **Fig. 4.**

TABLE 6: *IN-VITRO* DISSOLUTION STUDIES OF AMBRISENTAN LOADED FDOF

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	0	0	0	0	0	0
1	10.0±1.40	15.3±1.03	16.5±1.46	26.6±1.60	23.8±1.01	28.8±1.70	22.4±1.21	13.3±2.34	25.4±1.24	18.3±1.37	20.2±1.16
2	19.2±1.30	32.3±1.24	25.4±1.24	33.5±1.10	32.6±1.37	41.9±1.50	31.3±1.25	24.3±1.25	45.5±1.25	23.5±1.28	30.5±1.35
4	26.4±1.10	41.4±1.73	31.3±1.35	45.6±1.10	36.3±1.50	54.5±1.08	36.1±1.35	30.3±1.25	54.5±1.35	32.8±1.54	44.8±1.64
6	37.7±1.32	48.5±1.35	52.5±1.56	48.6±1.14	40.8±1.25	66.3±1.42	42.3±1.56	43.3±1.23	72.4±1.36	46.6±1.85	52.3±1.75
8	46.3±1.34	63.3±1.46	67.5±1.14	60.3±1.36	71.4±1.65	77.5±1.15	51.3±1.40	51.3±1.20	89.3±1.30	61.3±1.55	64.5±1.26

10	57.5±1.35	69.8±1.24	74.6±1.21	82.3±1.35	86.6±1.34	90.3±1.37	66.2±1.12	69.2±1.12	96.8±1.38	71.3±1.53	76.5±1.45
12	57.3±1.75	75.4±1.45	81.2±1.00	89.2±1.27	90.1±1.38	91.1±1.42	74.2±1.25	80.2±1.34	98.2±1.08	83.1±1.33	79.8±1.05

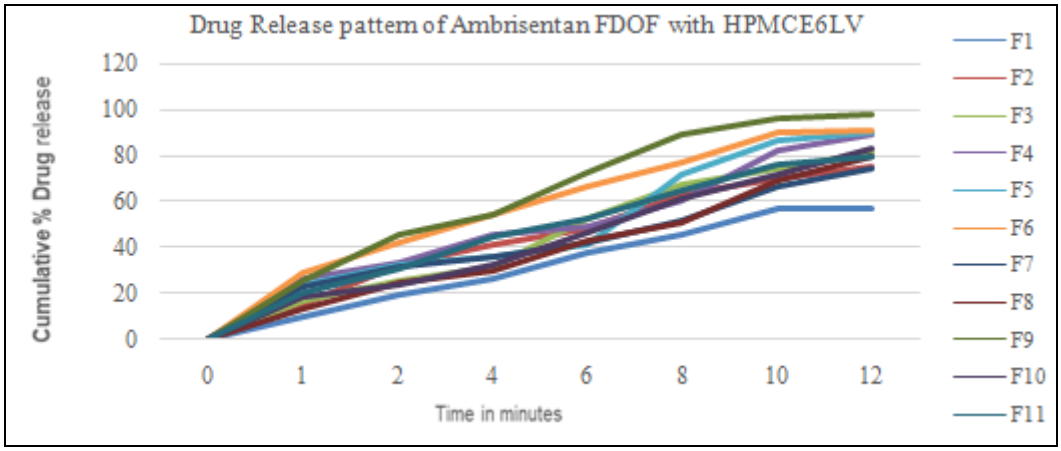

FIG. 4: DRUG RELEASE PATTERN OF AMBRISENTAN LOADED FDOF

The FTIR spectrum of pure Ambrisentan showed characteristic absorption bands at 1281 cm^{-1} corresponding to C–N stretching, 3659 cm^{-1} due to O–H stretching, 1629 cm^{-1} attributed to heterocyclic C=C stretching, and 3329 cm^{-1} due to N–H bending vibrations. The FTIR spectrum of Ambrisentan-loaded films exhibited characteristic peaks at 1289 cm^{-1} (C–N stretching), 3651 cm^{-1} (O–H stretching), 1623 cm^{-1} (heterocyclic C=C stretching), and 3346 cm^{-1} (N–H bending), corresponding closely to those of the pure drug. Minor shifts in peak positions were observed, which may be attributed to physical interactions or hydrogen bonding; however, no disappearance or formation of new peaks was detected. The retention of all characteristic absorption bands of Ambrisentan in the formulated films indicates the absence of significant chemical interaction between the drug and inactive ingredients, confirming their compatibility.

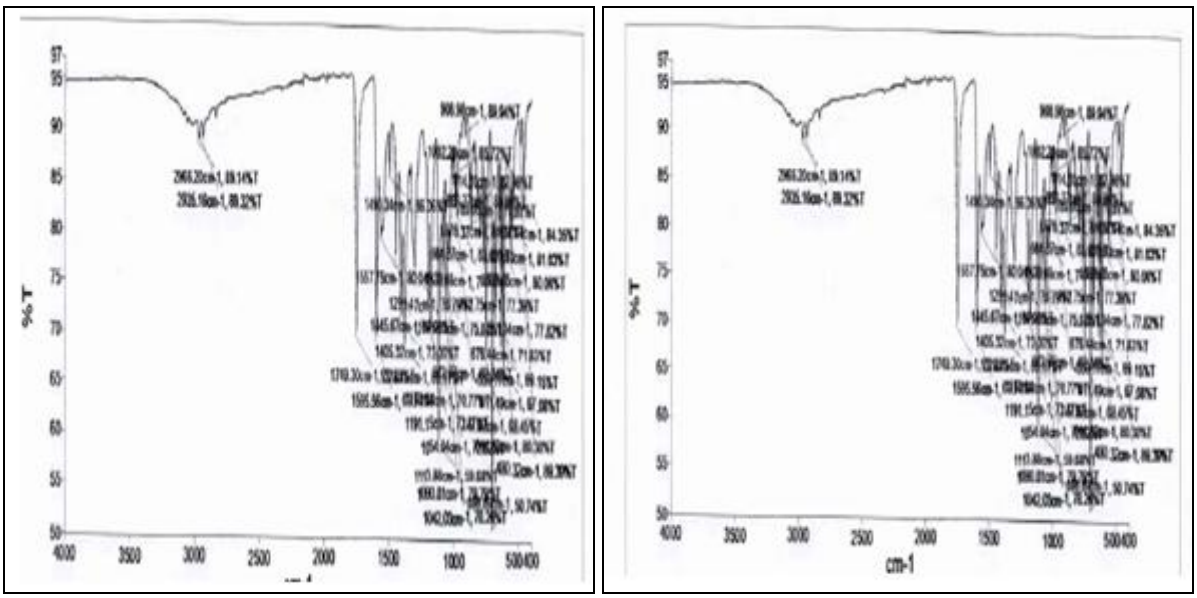

FIG. 5: COMPARATIVE FTIR SPECTROSCOPY OF AMBRISENTAN PURE DRUG AND FDOF

The DSC thermogram of pure Ambrisentan exhibited a sharp endothermic peak (T_p) corresponding to its melting point, with an associated enthalpy change (ΔH), confirming its crystalline nature. The thermo grams of the optimized formulation showed the presence of the characteristic drug peak with slight shifting and/or reduced peak intensity, which may be attributed to

drug dispersion within the polymeric matrix or partial amorphization. No disappearance of the characteristic melting peak or formation of new peaks was observed, indicating the absence of significant drug–excipient interaction and confirming the thermal compatibility of Ambrisentan with the excipients used.

TABLE 7: MELTING POINTS FROM DSC DATA FOR AMBRISENTAN AND EXCIPIENTS AND FDOF

Ingredients	Melting point (°C)
Ambrisentan	171.6
Xanthan gum	130
HPMC E6	172
Optimized formulation	171.47

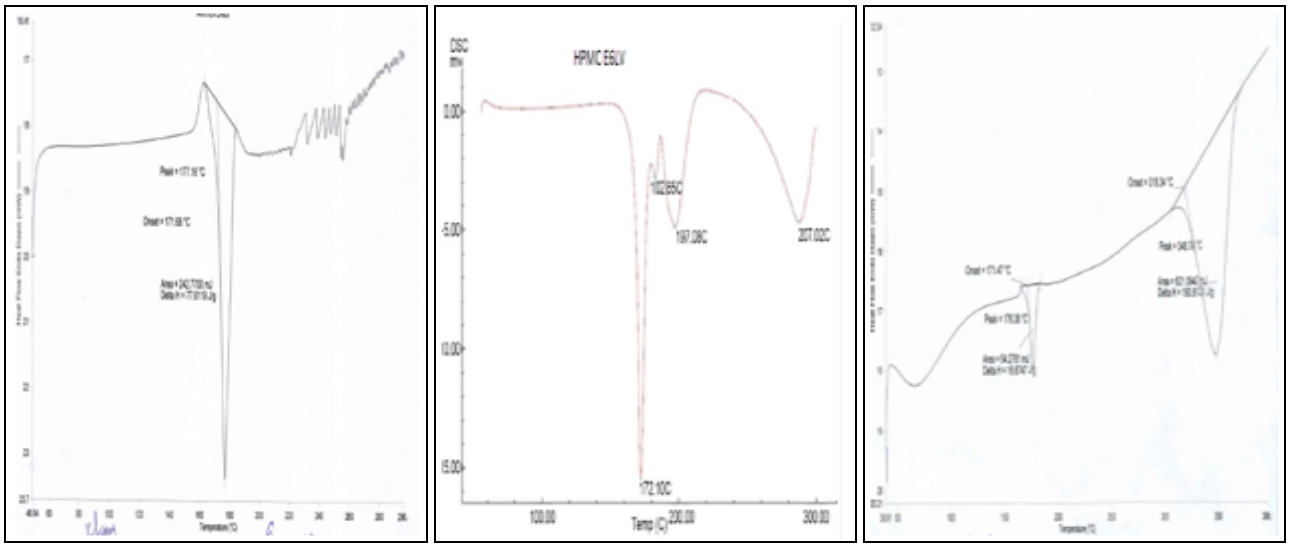

FIG. 6: COMPARATIVE DSC THERMOGRAMS OF AMBRISENTAN, HPMCE6LV AND FDOF

Stability Studies of Optimized FDOF (F9): The stability of the optimized fast dissolving oral film formulation (F9) was evaluated as per ICH guidelines under accelerated (40 ± 2 °C / 75 ± 5 % RH) and long-term (25 ± 2 °C / 60 ± 5 % RH) storage conditions for six months. Samples were analyzed at 0, 1, 3, and 6 months for physical appearance, tackiness, drug content, and *in-vitro* drug release. Under accelerated conditions, F9 maintained a clear, uniform, and non-tacky appearance, with no signs of discoloration or deformation. Drug content decreased slightly from 99.2 ± 0.6 % to 97.5 ± 0.9 %, and drug release from 98.5 ± 1.1 % to 96.6 ± 1.6 %, both remaining within acceptable limits. Similar results were observed under long-term storage, with minimal changes in drug content (99.2 ± 0.6 % to 98.2 ± 0.7 %) and drug release (98.5 ± 1.1 % to 97.6 ± 1.4 %). Overall, the results confirm that formulation F9 is physically and chemically stable under both storage conditions and suitable for long-term storage.

TABLE 8: STABILITY STUDY DESIGN FOR OPTIMIZED FDOF (F9)

Stability Condition	Temperature	Relative Humidity	Duration	Sampling Intervals
Accelerated	40°C ± 2°C	75% ± 5% RH	6 months	0, 1, 3, 6 months
Long-term	25°C ± 2°C	60% ± 5% RH	6 months	0, 1, 3, 6 months

TABLE 9: STABILITY EVALUATION PARAMETERS FOR OPTIMIZED FORMULATION (F9)

Parameter	Specification / Observation
Physical appearance	No discoloration, cracking, or deformation
Tackiness	Non-tacky
Folding endurance	No significant change
Disintegration time	Within acceptable limits
Drug content (%)	95–105%
In-vitro drug release	No significant change

TABLE 10: ACCELERATED STABILITY STUDY RESULTS OF OPTIMIZED FDOF (F9)

Time (Months)	Physical Appearance	Tackiness	Drug Content (%)	*In-vitro* Drug Release (%)
0	Clear, uniform	Non-tacky	99.2 ± 0.6	98.5 ± 1.1
1	No change	Non-tacky	98.8 ± 0.7	97.9 ± 1.3

3	No change	Non-tacky	98.1 ± 0.8	97.2 ± 1.5
6	No change	Non-tacky	97.5 ± 0.9	96.6 ± 1.6

(40°C ± 2°C / 75% ± 5% RH)

TABLE 11: LONG-TERM STABILITY STUDY RESULTS OF OPTIMIZED FDOF (F9)

Time (Months)	Physical Appearance	Tackiness	Drug Content (%)	*In-vitro* Drug Release (%)
0	Clear, uniform	Non-tacky	99.2 ± 0.6	98.5 ± 1.1
1	No change	Non-tacky	99.0 ± 0.5	98.2 ± 1.2
3	No change	Non-tacky	98.6 ± 0.6	97.9 ± 1.3
6	No change	Non-tacky	98.2 ± 0.7	97.6 ± 1.4

(25°C ± 2°C / 60% ± 5% RH) Values are expressed as mean ± SD (n = 3). No statistically significant changes were observed during the stability study period.

Comparison of *In-vitro* Drug Release Pattern of Optimized Formulation with Marketed Formulation: The *in-vitro* dissolution profiles of the optimized fast-dissolving oral film formulation (F9) and the marketed tablet (Volibris® 10 mg) are presented in **Table 12** and **Fig. 7.** Formulation F9 exhibited a rapid and significantly higher drug release compared to the marketed formulation at all sampling time points. Within the first minute, F9 released 25.4 ± 1.24% of Ambrisentan, whereas Volibris released only 12.56 ± 1.26%, indicating a markedly faster initial dissolution rate. At 2 minutes, the drug release from F9 reached 45.5 ± 1.25%, nearly double that of the reference tablet (19.40 ± 2.20%). A rapid and continuous increase in drug release was observed for F9, achieving 72.4 ± 1.36% release within 6 minutes and more than 96% within 10 minutes, whereas Volibris released only 60.29 ± 1.94% at the same time point. Complete drug release (98.2 ± 1.08%) was achieved by F9 within 12 minutes, demonstrating its fast-dissolving behavior. In contrast, the marketed tablet released only 69.92 ± 1.50% of the drug at 12 minutes, indicating a comparatively slower dissolution profile. The significantly enhanced dissolution performance of F9 can be attributed to its thin film structure, high surface area, and optimized polymeric composition, which facilitate rapid hydration, disintegration, and drug diffusion. These findings clearly demonstrate the superiority of the fast-dissolving oral film over the conventional tablet and support its potential for faster onset of action and improved bioavailability in the treatment of pulmonary arterial hypertension.

TABLE 12: COMPARATIVE DRUG RELEASE STUDY OF F(9) WITH MARKETED FORMULATION

Time (min)	0	1	2	4	6	8	10	12
F 9	0	25.4±1.24	45.5±1.25	54.5±1.35	72.4±1.36	89.3±1.30	96.8±1.38	98.2±1.08
Volubris (10 mg)	0	12.56 ±1.26	19.40 ±2.20	26.50 ±1.4	37.45 ±1.35	53.05 ±1.5	60.29 ±1.94	69.92 ±1.5

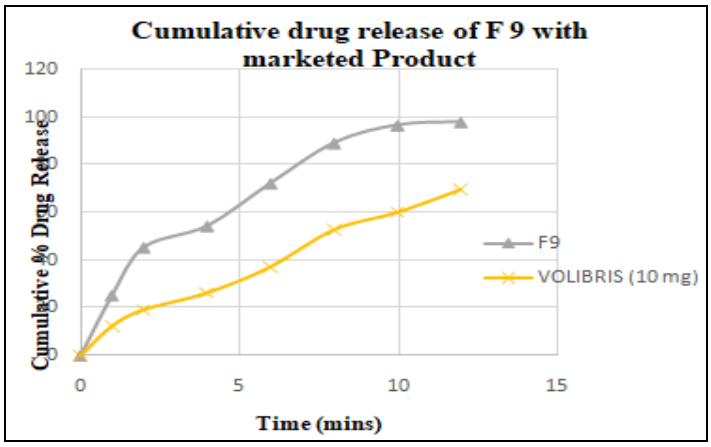

FIG. 7: RELEASE PATTERN OF FDOF F(9) WITH MARKETED FORMULATION

CONCLUSION: Fast-dissolving oral formulations have gained significant attention as an effective drug delivery approach for conditions requiring rapid therapeutic action, such as pulmonary arterial hypertension (PAH). These systems are particularly beneficial for special patient populations, including

geriatric and pediatric patients, due to their ease of administration and improved compliance. In the present study, eleven formulations were developed and evaluated, among which Formulation 9 (F9) exhibited optimal fast-dissolving properties and superior drug release performance. The results indicate that fast-dissolving oral films offer a promising and patient-friendly delivery platform with strong potential for future clinical application.

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