

Eplerenone sublingual dissolving film: preparation and evaluation

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ABSTRACT: Eplerenone is a medication used to manage hypertension and chronic heart failure by inhibiting aldosterone receptors. This study's objective is to prepare sublingual dissolving films containing Eplerenone, to enhance patient adherence, avoid first-pass metabolism, and minimize the need for repeated dosing. To achieve this goal, eight different formulations were prepared using a solvent-casting method. The study examined how various formulation factors influenced the physical and mechanical characteristics of the films, as well as their drug-release behavior. Notably, the results showed that the Eplerenone oral film, which included a combination of hydroxypropyl methylcellulose (HPMC E5) and polyvinyl alcohol (PVA), exhibited the fastest disintegration time, dissolving within just 27 seconds. Furthermore, formula F3, containing 25 mg of HPMC E5, 25 mg of PVA, and 30% glycerin, demonstrated a remarkable drug release rate of 72.4% within a 2-minute period with satisfactory mechanical properties. To summarize, this investigation successfully developed sublingual dissolving films for Eplerenone to improve patient adherence and decrease the necessity for frequent dosing. These films disintegrate rapidly and provide effective drug release, offering a patient-friendly alternative for managing conditions such as hypertension and chronic heart failure.

KEYWORDS: Eplerenone; hydroxypropyl methylcellulose (HPMC E5); polyvinyl alcohol (PVA); sublingual dissolving film, solvent casting method.

1. INTRODUCTION

In the past few decades, development and imagination have become essential competencies for making progress in developing novel dosage forms. But every dosage form has shown some drawbacks like pain of the parenteral dosage form and choking of tablets and capsules [1]. Drug delivery through the oral cavity offers many advantages, The oral mucosa is conveniently and easily accessible and therefore allows uncomplicated application of dosage form, furthermore the oral mucosa is hurt against local stress or any damage and shows fast cellular recovery after such incident [2].

Sublingual dissolving films are the most flexible solid dose forms currently available. These dosage forms are advantageous for patients with diarrhea, sudden episodes of allergic reactions, pediatric, geriatrics, coughing, or being bedridden or emetic. They are also advantageous for people with an active lifestyle [3]. These films are made of thin oral strips made of hydrophilic polymers that quickly dissolve and disintegrate when inserted in the mouth, releasing the medication and making it accessible for oro-mucosal absorption without chewing or consuming water [4]. Due to the high vascularity and permeability of this area, which allows for quick absorption and action of the included medication, fast-dissolving films can be utilized via a sublingual route for systemic drug delivery [5].

Eplerenone (EPL), an aldosterone receptor antagonist, is used to treat high blood pressure and chronic heart failure [6]. EPL is categorized As a BCS class II medication with poor oral bioavailability (about 69%) caused by its low solubility and limited absorption through the gastrointestinal (GI) barrier contributes to its poor therapeutic efficacy [7]. EPL (Figure-1) with a molecular weight of 414.49 g/mol, exists as a crystalline powder and exhibits low solubility (very slightly soluble) in water, with a solubility of less than (1 mg/mL). Additionally, it has a high octanol/water partition coefficient, specifically a (log Kow value of 7.1 at pH 7) [8].

The present study is undertaken to prepare Eplerenone oral dissolving films, to improve patient compliance, reduce the frequency of administration, and obtain greater therapeutic efficacy.

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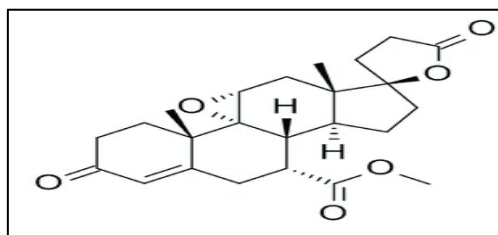


Figure 1. Chemical structure of Eplerenone [9]

2. RESULTS and DISCUSSION

2.1. Determination of Melting point

Using the capillary tube technique, the melting point of EPL was observed to be 242 °C, which is an indication of purity. This result agrees with the reference.

2.2. Determination of λ_{\max}

By using UV- spectroscopy (200- 400 nm), the λ -max of EPL in phosphate buffers (6.8), the λ_{\max} (Figure 2) was found 245 nm as reported. The λ_{\max} was selected to construct the calibration curve and complete the other characterization [10].

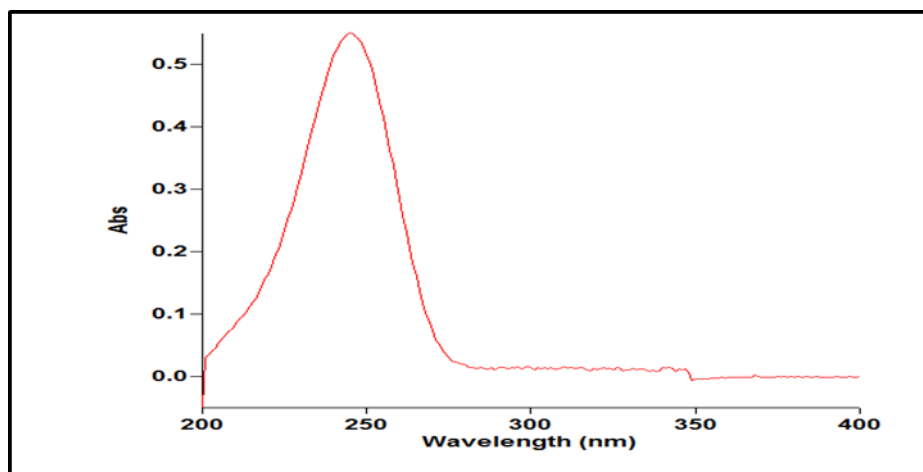


Figure 2. UV spectrum of EPL in phosphate buffer pH 6.8

2.3. Construction of calibration curves

Figure 3 show EPL calibration curves constructed in phosphate buffer (pH 6.8). Prior to any analysis, calibration curves were prepared. curve was produced by plotting diluting concentrations in $\mu\text{g}/\text{ml}$ against their corresponding absorbance using Microsoft Excel, which resulted in a straight line, suggesting that all the curves match Beer Lambert's law.

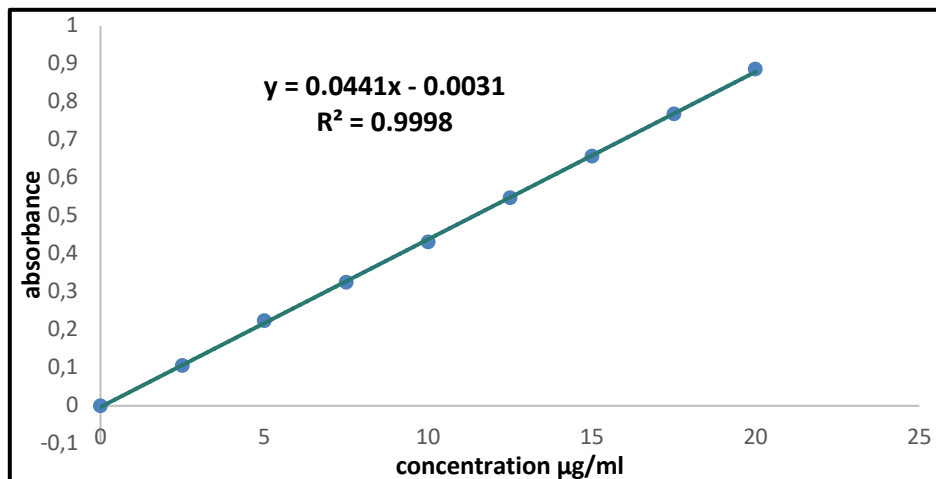


Figure 3. Calibration curve of EPL in phosphate buffer pH 6.8

2.4. Evaluation of sublingual dissolving film

2.4.1. Visual appearance

Table 1 depicts that A total of 8 films were prepared with different types of polymers to find successful films. Only three of the formulated films were successful, F1, F2, and F3.

Table 1. Properties of the prepared films.

Formulas	Film appearance	Peelability and brittleness
F1	Clear, transparent, and smooth surface	Peelable, not brittle, and flexible
F2	Clear, transparent, and smooth surface	Peelable, not brittle, and flexible
F3	Clear, transparent, and smooth surface	Peelable, not brittle, and flexible
F4	Clear, transparent, and smooth surface	Peelable and brittle
F5	Clear, transparent, and rough surface	Sticky
F6	Clear, transparent, and rough surface	Sticky
F7	Clear, transparent with rough surface	Sticky cannot be removed
F8	Opaque film with smooth surface	Easily peelable but brittle

2.4.2. Weight uniformity

As shown in table 2 the films prepared with EPL exhibited an average weight range of (98.6±2.1, 97.4±1.9, and 96.9±1.32 mg) to F1, F2, and F3 respectively. The method employed for preparation demonstrated excellent reproducibility and uniformity in film weight, as evidenced by very low standard deviation (SD) values. These results confirm the accuracy of the administered dose and the consistent weight distribution of films.

2.4.3. Thickness Measurements

The average thickness of the oral films ranged from 0.042±0.013 to 0.17±0.015 mm, indicating the high precision and reliability of the formulation method used. The very low ± SD values further validate the accuracy and applicability of the method in achieving uniform thickness across the films.

2.4.4. Folding endurance

The folding endurance of the EPL oral film was determined to be within the range of more than 300 times for all three formulas (F1, F2, and F3).

2.4.5. Drug Content

The films prepared in this study demonstrated practicality and exhibited an acceptable drug content within the range of (98.31±2.1 to 99±1.9), as presented in Table 2. These results complied with the specified content uniformity limit, typically ranging from 85% to 115%. The low SD values indicated the effectiveness and reproducibility of the solvent casting method employed for the EPL film preparation.

2.4.6. Surface pH measurement

The pH values of the oral films, closely resembled the pH of the oral mucosa, ranging from 6.83±0.01 to 6.9±0.04. This pH compatibility indicates that the films are well-suited for oral administration without causing any mucosal irritation. Thus, these oral films can be considered safe and suitable for use in the oral cavity.

2.4.7. In-vitro disintegration time (DT)

The in vitro disintegration time for EPL film (F1) was determined to be 40±2.44 sec, while the (F2) 35±2.9 sec, and (F3) 27±2.1sec. F3 oral film demonstrated the shortest in vitro disintegration time, indicating superior disintegration properties compared to other films.

Table 2. Physicochemical properties of the successful prepared sublingual films of Eplerenone

Formula code	Film weight	Thickness (mm)	Folding endurance	Drug content 4cm ²	Surface pH	In vitro DT (sec)
F1	98.6±2.1mg	0.17±0.015	>300	98.31±2.1	6.9±0.04	40±2.44
F2	97.4±1.9mg	0.042±0.013	>300	99±1.9	6.87±0.1	35±2.9
F3	96.9±1.32	0.082±0.009	>300	98.6±1.32	6.83±0.01	27±2.1

2.4.8. In-vitro dissolution study of oral film

F3 Formulation showed that the drug was rapidly released 77.5% within 2 minutes and Formulation F2 released 66.7% within 2 minutes as shown in Figure 4 and this is due to improving wettability, promoting rapid disintegration, and ensuring uniform drug dispersion. On other hand, F1 Formula has low release which is 11.45% within 2 minutes this is because HPMC E5 has an extensive swelling character, which produces a thick gel barrier for drug diffusion [11].

2.4.9. Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy was employed to study the infrared spectra of raw Eplerenone, soluplus, HPMC E5, PVA, mannitol, crospovidone, glycerin, physical mixture, and the EPL film presented in Figure (5). The analysis was conducted using a KBr disc, as depicted in the corresponding figure. The spectra of EPL exhibited distinct absorption bands corresponding to its main functional groups. These included a C-H stretching band at 2970.38 cm⁻¹, an anhydride O-C-O stretching band at 1778.37 cm⁻¹, a C-O ester stretching band at 1724.36 cm⁻¹, and a C-O stretching band at 1654.92 cm⁻¹ [8, 12]. The characteristic peaks of EPL were retained in both the physical mixture and the EPL film. Additionally, a broad peak was observed between 3250 cm⁻¹ and 3650 cm⁻¹ of O-H stretching groups, indicating the presence of hydrogen bonding interactions between water molecules or between water and other functional groups in the formulation [13], confirming the successful production of sublingual dissolving film and the absence of any chemical interactions between the formulation's ingredients.

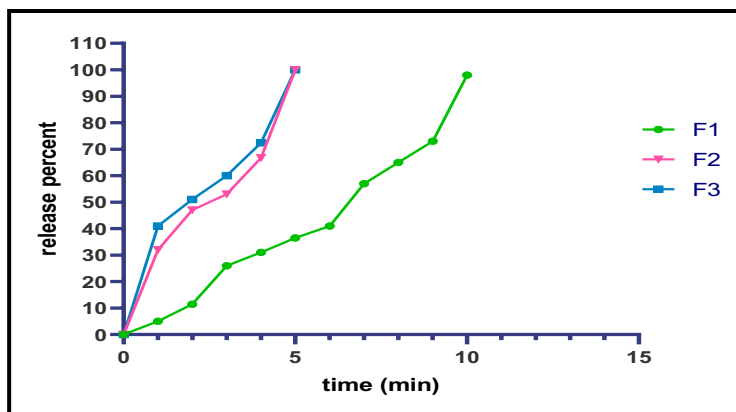


Figure 4. In-vitro dissolution profile of sublingual dissolving film of Eplerenone in phosphate buffer 6.8.

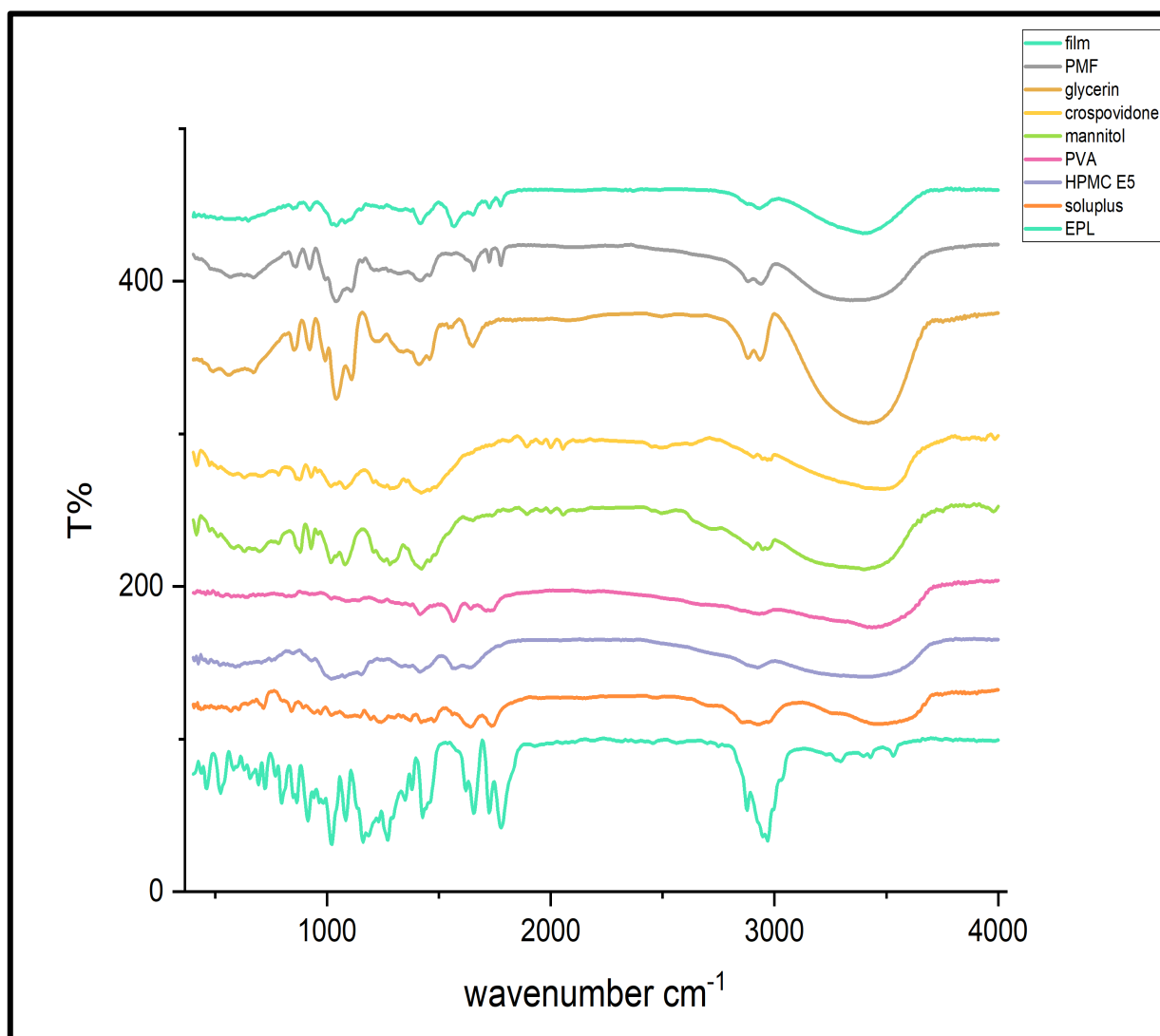


Figure 5. FTIR of Eplerenone, soluplus, PVA, HPMC E5, mannitol, crospovidone, glycerin, physical mixture (PMF), and optimize film formula F3.

3. CONCLUSION

On the basis of the results obtained; a combination of hydroxy propylmethyl cellulose and polyvinyl alcohol (25mg HPMC E5:25mg PVA) showed the fastest disintegration time. In addition, acceptable physicochemical properties and dissolution behavior were achieved.

4. MATERIALS AND METHODS

4.1. Materials

Eplerenone was purchased from Zhejiang Shenzhou pharmaceutical co., LTD, china, Poly(vinyl alcohol) PVA from BASF SE, Germany, Disodium hydrogen phosphate(Na_2HPO_4), and Potassium dihydrogen phosphate (KH_2PO_4) was provided by Thomas Baker, India, Methanol Panreac Quimica SLU, C, Spain, Hydroxy propyl methyl cellulose (HPMC E5 and E 15) from Baoji, China., pullulan Hyperchemical comp. China, Glycerol from Fluka Chemi AG, Switzerland, Mannitol from HOPKIN&WILLIMS LTD, England, and Crospovidone from alpha chemika, India

4.2. Method

4.2.1. Characterization of Eplerenone

Determination of Melting point

The melting point of Eplerenone powder was measured by using capillary tube method. The tube, closed from one end, dipped in the drug powder and placed inside the melting point apparatus and the temperature was increased gradually. The temperature at which the powder was converted to liquid was recorded as the melting point [14].

Determination of λ_{max}

10 milligrams of Eplerenone were dissolved in 100 ml phosphate buffer (pH 6.8), to prepare 0.1 mg/ml stock solution. from this stock solution, a dilute solution was prepared and scanned by UV spectrophotometer at 200–400 nm to determine the wavelength of maximum absorbance (λ_{max}) of Eplerenone.

4.2.2. Construction of calibration curves

Calibration curves of Eplerenone phosphate buffer (pH 6.8) were constructed by preparing suitable dilutions of the drug from 0.1mg/ml stock solution to get concentration of 2.5, 5, 7.5, 10, 12.5, 15, 17.5 and 20 $\mu\text{g}/\text{ml}$. The prepared samples were analyzed spectrophotometrically at λ_{max} . The absorbances obtained were recorded and plotted against concentrations to obtain a calibration curve.

4.2.3. Preparation of sublingual dissolving film

The solvent casting technique was used to produce sublingual films of Eplerenone that were previously prepared as crystal nanosuspension with a composition of soloplus at 0.05%, utilizing the HPMC E5 and HPMC E15, PVP k90, pullulan, and combination of HPMC E5 with polyvinyl alcohol (PVA). The composition of sublingual dissolving film formulation of Eplerenone were illustrated in Table 3. The procedure for forming a homogenous polymer solution involved adding 350 mg of polymer gradually while dissolving it in water. This process was stirred on a magnetic stirrer at 500rpm for around 60 minutes. The polymeric solution was then given a plasticizer addition of 30% w/w glycerin, which was stirred continuously for 60 minutes. The remaining excipients, including mannitol as a cooling agent and crospovidone as a super disintegrant agent, were dissolved in 2 mL of hot water and added to the polymeric solution. Equivalent to 175 mg of EPL was then added to the polymeric solution with constant stirring for a further hour and set aside to remove the trapped air bubbles [15].

The final homogeneous dispersion was cast onto a Petri-dish (6 cm) devoid of air bubbles and allowed to dry for three days at room temperature. After drying, the film was cut to the proper size of 2*2 cm² before being carefully removed from the petri dish using a sharp blade. A dose of EPL equal to 25 mg was present in each film. It was then wrapped in aluminum foil and sealed for later analysis [5].

4.2.4. Evaluation of sublingual dissolving film

Visual appearance

The visual evaluation assessed surface texture, uniformity, and cleanliness of physical appearance [16, 17].

Weight uniformity

Ten different films were weighed, and average weights were determined. The weighted average and the accepted film weight shouldn't vary too much from one another [18].

Thickness Measurements

A typical Vernier caliper was used to measure it. Five places were used to measure six films, and the average thickness was calculated [19].

Table 3. Composition of sublingual dissolving film formulation of Eplerenone

Ingredients (mg)	Formula code							
	F1	F2	F3	F4	F5	F6	F7	F8
Eplerenone	25	25	25	25	25	25	25	25
PVA		15	25		40			
HPMC E5	50	35	25			40		
HPMC E 15				50				
CMC					10	10		
PVP k90							50	
Pullulan								50
Glycerin	15	15	15	15	15	15	15	15
Crosspovidone	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mannitol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Folding endurance (FE)

Film was manually folded repeatedly at a predetermined location until it broke or cracked, at which point average values were calculated and reported. FE of greater than 300 provides an excellent indication of the formulation's flexibility and durability [20, 21].

Drug Content

Three films were each placed in a 100 ml solution of phosphate buffer (pH 6.8) and stirred for 30 minutes. The amount of EPL was calculated spectrophotometrically [22].

Surface pH measurement

Given that the mucosal membrane of the oral cavity may become irritated by sharp acidic or basic pH, it is crucial to look at the possibility of adverse effects while employing the films in-vivo. Three films were allowed to dissolve in 2 ml of deionized water individually in order to assess the pH value. The pH of the resulting solution was then measured using a pH meter [23].

In-vitro disintegration time (DT)

By adding 10 ml of distilled water to a tiny petri-dish, shaking one film on the water, and then recording the disintegration time as the film started to break or disintegrate, the disintegration time was estimated in this way. The disintegration period of the film component is typically 5 to 30 seconds, and it varies depending on the formulation's composition [24].

In-vitro dissolution study of oral film

Using the USP dissolution apparatus type II (paddle type), a film with a diameter of 2x2 cm² was positioned at the bottom of 900 mL of phosphate buffer pH 6.8 (dissolving media) at 37 C° and spun at 50 rpm. A 5 mL sample was taken and replaced with the same volume of phosphate buffer pH 6.8 at regular intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, and 30 minutes) to maintain sink condition. The material was then filtered at 0.45 mm and subjected to a UV-spectrophotometer analysis at its λ_{max} . Every reading was done in triplicate [25, 26].

Fourier transform infrared spectroscopy (FTIR)

Using an FTIR spectrometer (FTIR-8300 Shimadzu, Japan), the drug was ground with potassium bromide (KBr), pressed into a thin disc using a specific process, and scanned at the waves number between 4000-400 cm⁻¹ to record the FTIR spectra of the selected formula's EPL film in comparison to its corresponding physical mixture (1:1) and the individual solid components. The FTIR analysis aimed to

identify any potential interactions or complexation between Eplerenone and the excipients employed in the formulation [27, 28].

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