WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 11, 1972-1987. Research Article ISSN 2277–7105

DEVELOPMENT OF FAST-DISSOLVING SUBLINGUAL FILMS OF METOPROLOL SUCCINATE: A NOVEL APPROACH FOR HYPERTENSION MANAGEMENT

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Article Received on
20 April 2025,

Revised on 10 May 2025,
Accepted on 30 May 2025

DOI: 10.20959/wjpr202511-37043

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1. ABSTRACT

The present study aims to develop and evaluate fast-dissolving sublingual films of metoprolol succinate to enhance its onset of action and improve patient compliance in the management of hypertension. Metoprolol succinate, a selective β1-blocker, undergoes extensive first-pass metabolism, which significantly reduces its oral bioavailability. To overcome this limitation, sublingual films were formulated using the solvent casting method. Hydroxypropyl methylcellulose (HPMC E15) was selected as the film-forming polymer, while propylene glycol served as the plasticizer. Other excipients like citric acid, sucrose, peppermint oil and distilled water were optimized to enhance the films mechanical properties, taste and patient acceptability. A series of trial batches were prepared and evaluate based on parameter like film thickness, folding endurance, surface pH, Weight Variation. The results confirmed that the films were uniform, flexible, smooth and compatible with the physiological pH of saliva, indicating their suitability for sublingual administration of metoprolol succinate.

2. KEYWORDS: Metoprolol succinate, Sublingual film, Solvent casting, Fast dissolving film.

3. INTRODUCTION

3.1 Importance of fast drug delivery systems

Rapid drug delivery systems have gained importance in modern healthcare, particularly for managing acute conditions like heart attacks, asthma attacks, seizures, and hypertensive

crises. In such emergencies, conventional dosage forms such as tablets or syrups may delay therapeutic action due to the time required for gastrointestinal absorption and first-pass metabolism.

To overcome these limitations, fast-dissolving systems have been developed to deliver drugs more efficiently. These formulations bypass the gastrointestinal tract, allowing the drug to enter systemic circulation rapidly and provide quicker relief. Among these, the sublingual route is especially effective due to the rich blood supply under the tongue, enabling faster absorption and onset of action.

Sublingual drug delivery also avoids degradation by stomach acid and liver enzymes, enhancing the drug's bioavailability. This approach can reduce the required dose, minimize side effects, and improve the overall therapeutic response.

Moreover, fast-dissolving sublingual films are particularly beneficial for patients who have difficulty swallowing, such as children, the elderly, and those with neurological disorders. By improving both convenience and compliance, these systems play a crucial role in patient-centered therapy, especially in time-sensitive medical conditions.

3.2 Structural features of oral mucosa

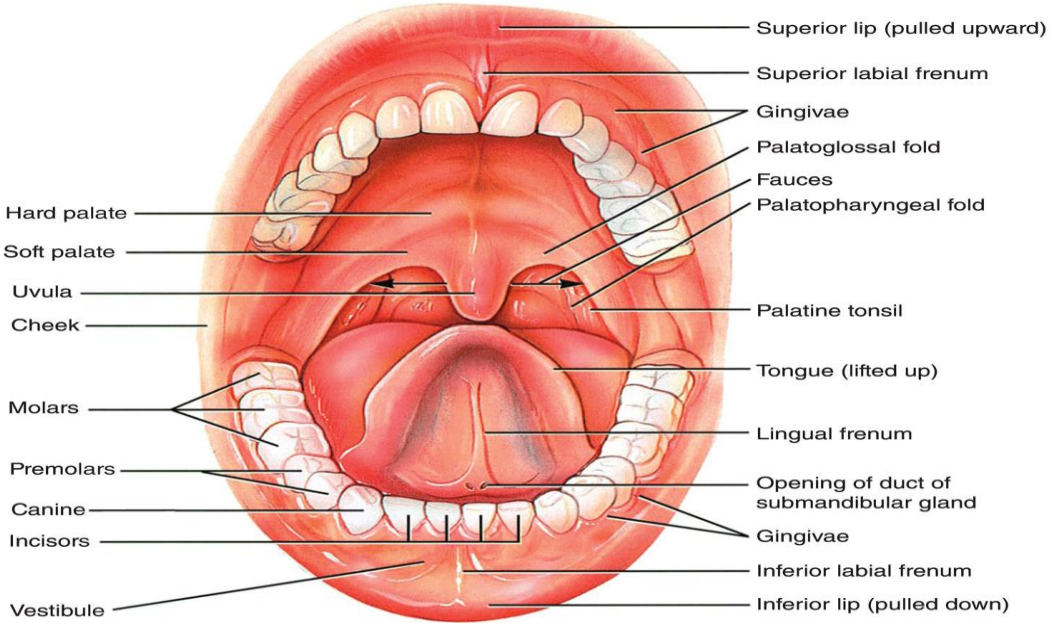
a. Oral cavity

The oral cavity, the initial part of the digestive system, plays a crucial role in ingestion, mastication, taste, and the early absorption of drugs. It is divided into two regions: the vestibule, located between the cheeks and teeth, and the oral cavity proper, extending from the teeth to the oropharynx. Key structures include the lips, cheeks, tongue, teeth, hard and soft palates, and salivary glands.

The inner surface is lined with oral mucosa composed of stratified squamous epithelium. Regions such as the floor of the mouth and the underside of the tongue have thin mucosal layers and are richly vascularized, making them ideal for rapid drug absorption.

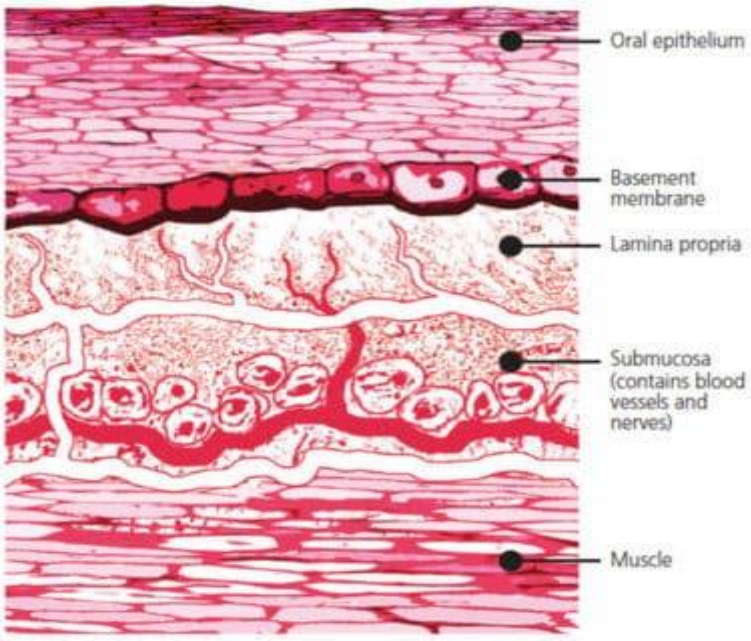
Physically, the oral cavity is a moist, hollow space bounded externally by the lips and cheeks, superiorly by the hard and soft palate, and inferiorly by the floor of the mouth and tongue. It is supported by the maxilla and mandible bones. The oral mucosa varies regionally: areas exposed to mechanical stress, such as the gums and hard palate, are covered by keratinized epithelium for protection, while softer regions like the cheeks, floor of the mouth, and ventral

tongue are lined with non-keratinized epithelium, facilitating flexibility and drug permeation. Numerous minor salivary glands dispersed throughout maintain moisture via continuous saliva secretion, supporting various oral functions.



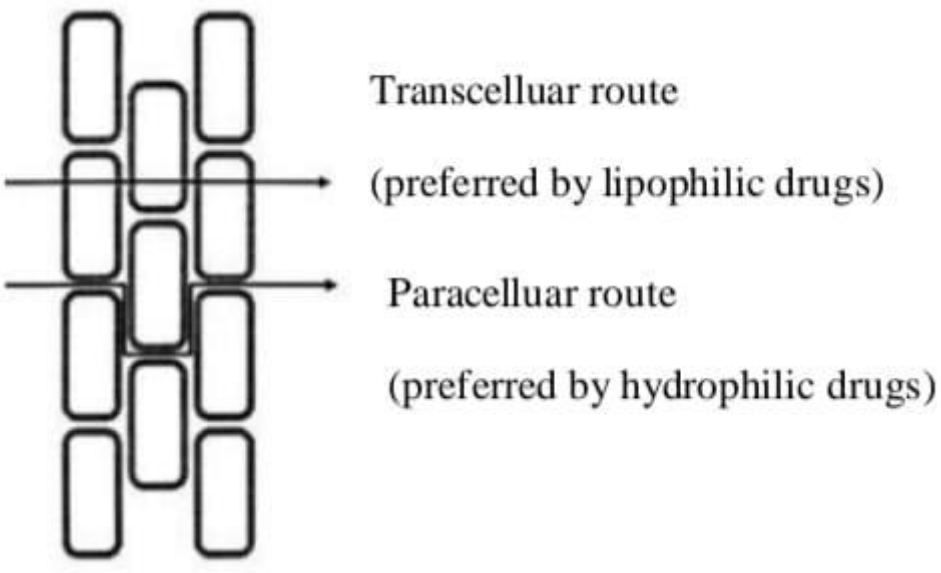
b. Structure of oral mucosa

The oral mucosa, lining the interior of the mouth, is primarily composed of three layers: stratified squamous epithelium, basement membrane, and connective tissue. Areas such as the floor of the mouth and the underside of the tongue feature thinner, non-keratinized epithelium, which enhances permeability and facilitates drug absorption.



c. Absorption pathway

Drug absorption through the oral mucosa is vital for rapid drug delivery systems such as sublingual films. The oral mucosa offers a large surface area, abundant blood supply, and a permeable membrane that facilitates direct drug entry into systemic circulation. This pathway bypasses hepatic first-pass metabolism, leading to a faster onset of therapeutic effect.



d. Release mechanism

The release mechanism of sublingual films is both simple and effective. Upon placement beneath the tongue, the film rapidly interacts with saliva, absorbs moisture, and begins to dissolve within seconds. This dissolution releases the drug into the oral cavity, from where it is absorbed through the highly vascularized sublingual mucosa.

Due to the thin epithelial layer and rich blood supply, drug molecules quickly diffuse into the bloodstream, bypassing the gastrointestinal tract and hepatic first-pass metabolism. This ensures that the drug reaches systemic circulation in its active form, leading to a faster onset of action and improved therapeutic efficacy.

e. Advantages of sublingual films

- Rapid onset of action
- Bypass of first-pass metabolism
- No need for water during administration
- Improved patient compliance
- Ideal for pediatric, geriatric and dysphagic patients

f. Ideal properties of a sublingual film

- Should disintegrate within seconds to a few minutes
- Must possess sufficient mechanical strength to handle
- Should be non-irritating and compatible with oral tissues
- Must ensure uniform drug content and stability throughout shelf life

4. AIM AND OBJECTIVE

Aim

To develop and evaluate a fast-dissolving sublingual film formulation of metoprolol succinate to provide rapid therapeutic action in hypertensive conditions.

Objectives

- To formulate sublingual films of metoprolol succinate using appropriate film-forming polymers.
- To assess the physical characteristics of the prepared films.
- To evaluate surface pH to ensure compatibility with sublingual mucosa.

5. Literature Review

Kumar et al., (2020) developed and characterized sublingual films of metoprolol succinate using Hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA) as film-forming polymers. The films showed rapid disintegration and good mechanical strength. In vitro drug release studies indicated over 90% drug release within 5 minutes, suggesting potential for rapid onset of action.

Singh and Sharma (2019) investigated fast-dissolving sublingual films of atenolol, a beta-blocker similar to metoprolol. They used pullulan as a film-former and evaluated film properties such as thickness, tensile strength, and disintegration time. The optimized films demonstrated improved bioavailability compared to oral tablets, confirming sublingual films as a promising alternative for cardiovascular drugs.

Patel et al., (2021) prepared buccal films of propranolol hydrochloride using solvent casting method. The films exhibited uniform drug distribution, satisfactory tensile strength, and rapid disintegration within 30 seconds. Stability studies confirmed the films retained drug content and mechanical properties under accelerated conditions.

Gupta and Kumar (2022) studied the effect of plasticizers and polymers on the physicochemical properties of sublingual films of metoprolol succinate. Using a factorial design approach, they optimized formulation parameters to achieve films with good flexibility, rapid dissolution, and acceptable taste masking. The films demonstrated enhanced bioavailability in in vivo studies.

Sharma et al., (2023) developed novel sublingual films of metoprolol succinate incorporating natural polymers such as sodium alginate and gelatin. The films showed promising mechanical properties, rapid disintegration, and efficient drug release. In vitro permeability studies confirmed enhanced mucosal absorption, supporting their use for fast-acting antihypertensive therapy.

6. Experimental design

6.1 Materials

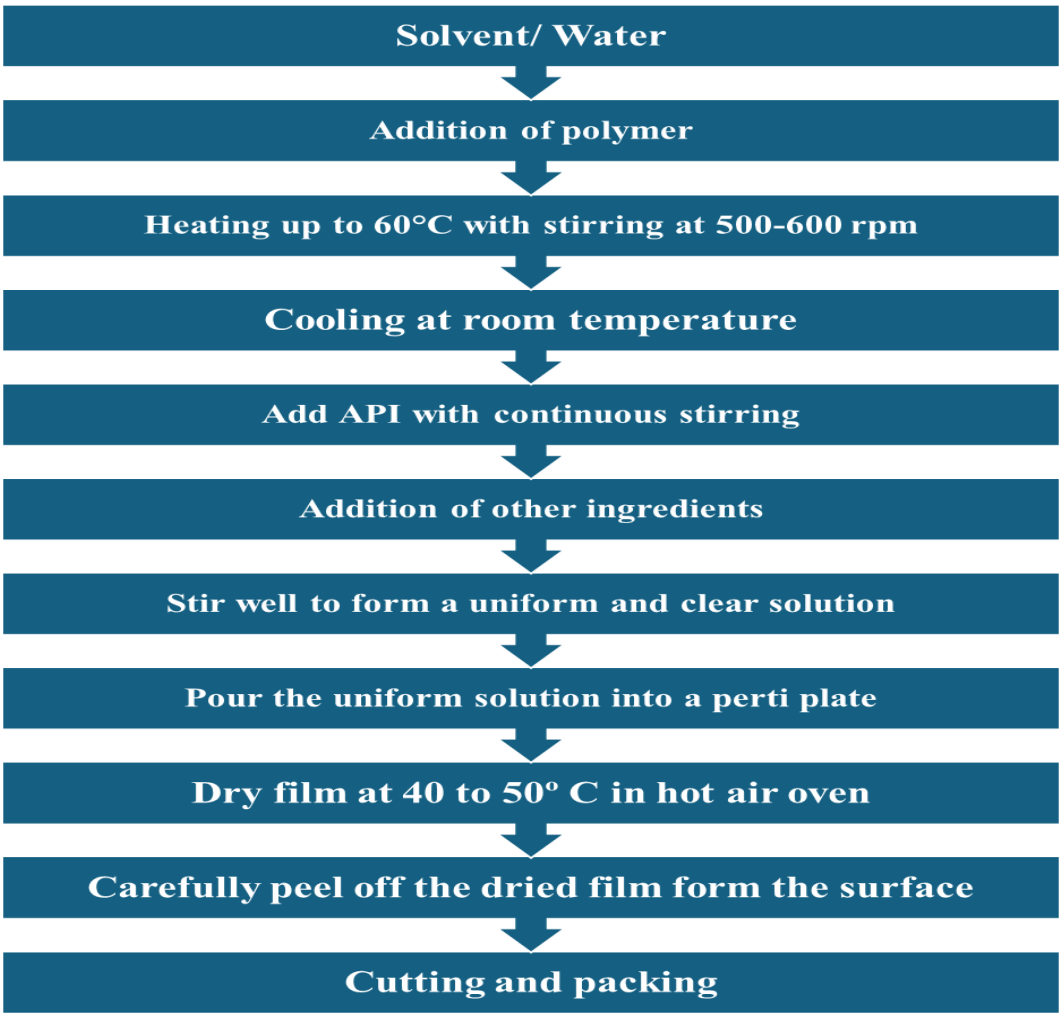
Sr. No.	Materials
1	Metoprolol succinate
2	HPMC E15
3	Propylene glycol
4	Citric acid
5	Peppermint oil
6	Sucrose

6.2 Equipment used

Sr. No.	Equipment
1	Digital Weighing Balance
2	Magnetic Stirrer
3	Hot Air Oven

7. Method of prepapration

Prepared by solvent casting method



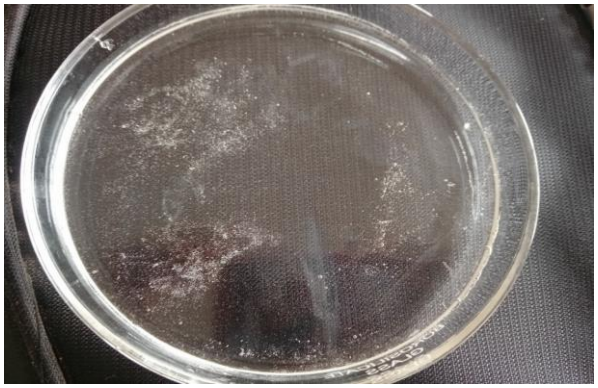
8. Trial formulations

Trial formulation

I. F1

Table no. 6: Trial formulation 1.

Sr. No.	Ingredient	Quantity
1	Metoprolol Succinate	50 mg
2	HPMC E15	900 mg
3	Propylene Glycol	150 mg
4	Citric Acid	80 mg
5	Sucrose	100 mg
6	Peppermint Oil	2 ml
7	Distilled Water	20 ml

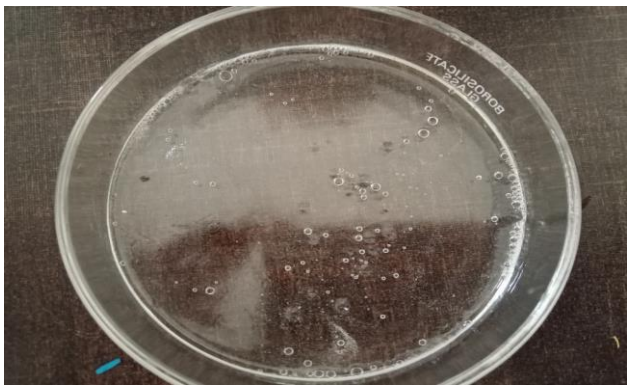


Justification: Improper dispersion or incomplete solubility of HPMC E15 in the solvent led to white patches.

II. F2

Table no. 7: Trial formulation 2.

Sr. No.	Ingredient	Quantity
1	Metoprolol Succinate	50 mg
2	HPMC E15	850 mg
3	Propylene Glycol	200 mg
4	Citric Acid	90 mg
5	Sucrose	110 mg
6	Peppermint Oil	2 ml
7	Distilled Water	15 ml



Justification: Reduce polymer and higher plasticizer increased film flexibility but trapped air during casting, causing visible bubbles.

III. F3

Table no. 8: Trial formulation 3.

Sr. No.	Ingredient	Quantity
1	Metoprolol Succinate	50 mg
2	HPMC E15	1200 mg

3	Propylene Glycol	100 mg
4	Citric Acid	110 mg
5	Sucrose	130 mg
6	Peppermint Oil	2 ml
7	Distilled Water	15 ml

Justification: Plasticizer was too low, and film dried excessively fast, sticking hard to the surface and tearing during removal.

IV. F4

Table no. 9: Trial formulation 4.

Sr. No.	Ingredient	Quantity
1	Metoprolol Succinate	50 mg
2	HPMC E15	750 mg
3	Propylene Glycol	200 mg
4	Citric Acid	120 mg
5	Sucrose	135 mg
6	Peppermint Oil	2 ml
7	Distilled Water	15 ml

Justification: Lower polymer caused weak matrix; although plasticizer was optimum, the film retained moisture and stayed gel-like even after drying.

V. F5 Optimized formula

Table no. 10: Optimized formulation.

Sr. No.	Ingredient	Quantity
1	Metoprolol Succinate	50 mg
2	HPMC E15	1000 mg
3	Propylene Glycol	200 mg
4	Citric Acid	120 mg
5	Sucrose	135 mg
6	Peppermint Oil	2 ml
7	Distilled Water	15 ml

Justification: This final formula was successful because the film was smooth, easy to peel and dried properly.

9. Evaluation

Organoleptic evaluation

1. Appearance

The prepared sublingual film was smooth, uniform, and free from visible imperfections such as air bubbles or cracks. It exhibited a clear and consistent surface throughout.

2. Texture

On gentle touch, the film was soft, flexible, and non-sticky. It was easily foldable without cracking, indicating good plasticity and film-forming properties.

3. Odour

The film had a mild, pleasant peppermint-like odour due to the added flavouring agent, with no detectable odour of the drug or other excipients.

4. Transparency

The film showed moderate transparency, allowing partial passage of light. This semi-transparent nature is desirable for aesthetic acceptability and confirms uniformity in formulation.

Physical test

- **Organoleptic evaluation**

I. **Appearance:** The prepared sublingual film was observed to be smooth, uniform and free from any visible imperfection such as air bubbles and cracks. It exhibited a clear and consistent surface throughout.

II. **Texture:** On gentle touch, the film exhibited a soft flexible and non-sticky texture. It was easily foldable without cracking, indicating good plasticity and film-forming properties.

III. **Odour:** The film possessed a mild, pleasant peppermint- like odour due to the added flavouring agent, with no detectable odour of the drug or other excipients.

IV. **Transparency:** The film showed moderate transparency. It allowed partial passage of light, indicting semi-transparent nature, which is desirable for aesthetic acceptability and confirming uniformity in formulation.

- **Physical characteristics**

I. **Thickness**

- **IP Standard value:** 0.05-0.4 mm
- **Procedure:** Measured using vernier caliper at 3 different points; average was noted.
- **Calculation details:** Avg. thickness= (0.11+0.12+0.13)mm /3 = 0.12mm
- **Experimental result:** 0.12 mm

II. **Folding endurance**

- **IP Standard value:** There is no specific IP limit for folding endurance, but generally, a value above 200 folds is considered acceptable, indicating good flexibility and mechanical strength.
- **Procedure:** The film was repeatedly folded at the same place manually until broke. The number of folds required to break the film was recorded. The test was repeated for three films, and the average was calculated.
- **Calculation details:** Reading 1: 245 folds

Reading 2: 255 folds

Reading 3: 250 folds

Average folds= (245+255+250)/3= 250 folds.

- **Experimental result:** Avg. 250 folds

III. Surface pH

- **IP Standard value:** The surface pH of sublingual films should be in the range of 6.5 to 7.5 to avoid irritation to the oral mucosa and ensure patient comfort.
- **Procedure:** A film was placed in 5ml of distilled water for 1min to allow swelling. The surface pH was then measured by pH paper.
- **Calculation details:** Avg. pH= (6.5+6.6+6.7)/3= 6.6 pH
- **Experimental result:** Avg. pH 6.6

IV. Weight variation

- **IP Standard value:** The weight variation of sublingual films should not deviated by more than ±5% from the average weight of the batch.
- **Procedure:** Three films were randomly selected and weighted individually using an analytical balance. The average weigh was calculated and the percentage deviation from the average weight was determined to assess uniformity.
- **Calculation details:** Avg. weight= (44.8+45.6+45.2) /3 = 45.2 mg

% Deviation Calculation:

i. Film 1: [(44.8 - 45.2) / 45.2]* 100 = 0.88%

ii. Film 2: [(45.6 - 45.2) / 45.2]* 100 = 0.88%

iii. Film 3: [(45.2 – 45.2) / 45.2]* 100 = 0%

- **Experimental result:** Avg. weight= 45.2 mg

Avg. deviation= 0.59%

RESULT AND DISCUSSION

The development of the metoprolol succinate sublingual film involved the preparation and evaluation of several trial batches. Each batch was carefully assessed based on parameters such as physical appearance, ease of peeling, drying time, and overall film integrity. After iterative adjustments, the fifth formulation was identified as the optimized batch due to its superior characteristics.

This optimized formulation incorporated Hydroxypropyl Methylcellulose (HPMC E15) as the primary film-forming polymer, propylene glycol as a plasticizer, citric acid to stimulate

salivation, sucrose as a sweetening agent, peppermint oil for flavour, and purified water as the solvent. The resulting film demonstrated the following desirable features:

- Consistent thickness and smooth texture
- Absence of surface defects such as cracks or bubbles
- Easy removal from the casting surface
- Adequate folding endurance indicating good flexibility

These findings indicate the successful formulation of a stable and efficient sublingual film of metoprolol succinate prepared via the solvent casting technique.

CONCLUSION

This study successfully formulated and evaluated a sublingual film of Metoprolol Succinate designed to provide rapid onset of action and enhanced patient compliance. Through multiple trial batches, an optimized formulation was developed using Hydroxypropyl Methylcellulose (HPMC E5) as the film-forming polymer and propylene glycol as the plasticizer, prepared by the solvent casting method.

The final film demonstrated favourable physicochemical characteristics such as uniform thickness, good folding endurance, and effective drug release. By bypassing first-pass metabolism, the formulation enables faster therapeutic effects, highlighting its potential as a convenient and efficient alternative to conventional oral dosage forms of Metoprolol Succinate.

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