Chinese Journal of Health Management
Volume 20 Issue 5, Year of Publication 2026, Page 1312-1318 | DoI-10.564220/1674-0815.2026.151

ISSN: 1674-0815

Chinese Journal of Health Management

Chinese Medical Association

Design, Formulation, and Evaluation of sublingual film containing clotrimazole as an Antimycotic.

Aniket Dhabe[1*], Dr Pratima Shinde[2], Dr. Swati Jogdand[3], Dr. Rani Divekar [4], Dr. Swati Deshmukh [5], Dr Gita Chaurasiya [6], Ms Usha Bagal [7]
CAYMET's, Siddhant College of Pharmacy, Sudumbare, Pune, 412109, Maharashtra, India.

Article Information
Received: 21-04-2026
Revised: 04-05-2026
Accepted: 18-05-2026
Published: 20-06-2026

Keywords
Clotrimazole, Sublingual film, Oral candidiasis, Solvent casting, HPMC 15 cps

ABSTRACT:

Abstract

Oral candidiasis is a common fungal infection that often requires prolonged antifungal therapy, where conventional oral formulations may exhibit poor patient compliance, delayed onset of action, and reduced bioavailability due to first-pass metabolism. The present study aimed to formulate and evaluate a clotrimazole-loaded sublingual film as a rapid and patient-friendly drug delivery system for the effective management of oral fungal infections. Sublingual films were prepared by the solvent casting method using hydroxypropyl methylcellulose (HPMC 15 cps) as the film-forming polymer, glycerol as the plasticizer, and ethanol as the solvent. Six formulations (F1–F6) were developed by varying the polymer concentration and evaluated for physicochemical properties including thickness, weight variation, folding endurance, surface pH, moisture content, drug content uniformity, and in vitro drug release. Among the prepared formulations, F3 demonstrated the most desirable characteristics, exhibiting satisfactory mechanical strength, neutral surface pH, excellent folding endurance, uniform drug distribution, and the highest cumulative drug release (61.48 ± 1.73%). The optimized formulation also showed acceptable flexibility and stability, indicating its suitability for sublingual administration. The findings suggest that clotrimazole sublingual films provide a promising alternative to conventional dosage forms by offering rapid drug release, improved patient compliance, enhanced bioavailability, and effective local antifungal therapy for the treatment of oral candidiasis.

1. INTRODUCTION:

Oral candidiasis is one of the most prevalent opportunistic fungal infections affecting the oral mucosa, primarily caused by *Candida albicans*. The condition is commonly observed in immunocompromised individuals, elderly patients, infants, denture wearers, diabetic patients, and those receiving prolonged antibiotic or corticosteroid therapy. Clinical manifestations include white pseudomembranous plaques, erythematous lesions, burning sensation, pain, dysphagia, and impaired oral function, which significantly reduce the patient's quality of life. Early and effective antifungal treatment is therefore essential to prevent disease progression and recurrence.[1]

Clotrimazole is a broad-spectrum imidazole antifungal agent widely used in the treatment of superficial fungal infections, including oral candidiasis. It exerts its antifungal activity by inhibiting the biosynthesis of ergosterol, an essential component of the fungal cell membrane, thereby increasing membrane permeability and causing cell death.[2,3]Although clotrimazole is available in various dosage forms such as lozenges, creams, ointments, mouth paints, and tablets, these conventional formulations often suffer from limitations including short residence time at the site of infection, poor patient compliance, variable drug absorption, and reduced therapeutic efficacy due to extensive first-pass metabolism following oral administration.[2-6]

The development of novel drug delivery systems has attracted considerable attention to overcome the drawbacks associated with conventional dosage forms. Among these, sublingual drug delivery has emerged as an effective alternative owing to the unique anatomical and physiological characteristics of the sublingual mucosa.[1,2] The sublingual region is highly vascularized and possesses a relatively thin epithelial membrane, enabling rapid absorption of drugs directly into the systemic circulation while bypassing gastrointestinal degradation and hepatic first-pass metabolism. Consequently, sublingual administration provides a faster onset of therapeutic action, improved bioavailability, reduced dosing frequency, and enhanced patient compliance.[3,6,8]

Sublingual films represent an advanced pharmaceutical dosage form consisting of thin, flexible polymeric strips that rapidly hydrate, disintegrate, and release the incorporated drug upon contact with saliva. These films offer several advantages, including accurate dosing, ease of administration without the need for water, portability, improved stability, and suitability for pediatric, geriatric, and dysphagic patients. Moreover, the intimate contact between the film and the sublingual mucosa facilitates efficient drug absorption and prolonged residence time, thereby improving therapeutic outcomes.[4]

Hydroxypropyl methylcellulose (HPMC) is one of the most extensively employed hydrophilic polymers in oral film formulations due to its excellent film-forming ability, biocompatibility, non-toxicity, mechanical strength, and rapid hydration characteristics. The incorporation of suitable plasticizers such as glycerol further enhances film flexibility, reduces brittleness, and improves patient acceptability.[8] The solvent casting technique remains the most widely adopted method for preparing oral films because of its simplicity, cost-effectiveness, reproducibility, and ability to produce films with uniform thickness and drug distribution.[7]

Considering the pharmacological efficacy of clotrimazole and the advantages offered by sublingual drug delivery, the development of a clotrimazole-loaded sublingual film represents a promising strategy for the management of oral candidiasis. Such a formulation has the potential to provide rapid drug release, enhanced bioavailability, improved local antifungal activity, and better patient compliance compared with conventional oral dosage forms.[9]

Therefore, the present study was undertaken to formulate and evaluate clotrimazole-loaded sublingual films using Hydroxypropyl Methylcellulose (HPMC 15 cps) as the film-forming polymer by the solvent casting technique. The prepared formulations were systematically evaluated for physicochemical characteristics, including film thickness, weight variation, folding endurance, surface pH, moisture content, drug content uniformity, and **in vitro** drug release, to identify the optimized formulation with desirable mechanical properties and drug release performance. The successful development of such a formulation may provide an effective, patient-friendly, and commercially viable alternative for the treatment of oral candidiasis and other localized fungal infections.[10-13]

2. MATERIALS AND METHODS:

2.1 Materials:

Clotrimazole was used as the active pharmaceutical ingredient (API) and was obtained from Aster Analytics, Pune, India. Hydroxypropyl methylcellulose (HPMC 15 cps) was selected as the film-forming polymer due to its excellent film-forming ability, biocompatibility, and rapid hydration properties. Glycerol was employed as a plasticizer to improve the flexibility and mechanical strength of the films, while ethanol served as the solvent for the preparation of the polymeric solution. All chemicals and reagents used in the study were of analytical reagent (AR) grade and were used without further purification.

2.2 Instruments:

The instruments used during formulation and evaluation of the sublingual films included a digital analytical balance for accurate weighing of materials, a UV–Visible spectrophotometer for drug estimation, a sonicator for removal of entrapped air bubbles, a digital Vernier caliper for thickness measurement, a pH meter for surface pH

determination, and a thermometer for monitoring temperature during preparation.

2.3 Preparation of Standard Calibration Curve of Clotrimazole:

A stock solution of clotrimazole was prepared by dissolving 10 mg of the drug in a solvent system containing methanol and 1 N hydrochloric acid. Appropriate serial dilutions were prepared to obtain working standard solutions of different concentrations. The absorbance of each solution was measured using a UV–Visible spectrophotometer in the wavelength range of 200–400 nm to determine the maximum absorption wavelength (λmax). The λmax of clotrimazole was found to be 226 nm. A calibration curve was constructed by plotting absorbance against concentration, which was subsequently used for quantitative estimation of drug content during formulation evaluation.

2.4 Formulation of Clotrimazole Sublingual Films.[12-18]

Clotrimazole sublingual films were prepared by the **solvent casting technique**. Initially, the required quantity of HPMC 15 cps was dissolved in ethanol under continuous magnetic stirring until a clear and homogeneous polymeric solution was obtained. Clotrimazole was then dispersed uniformly into the polymer solution with constant stirring. Glycerol was added as a plasticizer to improve film flexibility and prevent brittleness. The resulting solution was sonicated for approximately 18 min at 30°**C** to remove entrapped air bubbles.

The homogeneous casting solution was poured into clean glass Petri dishes and allowed to dry at room temperature for 24 h**.** After complete drying, the films were carefully peeled off and cut into uniform 2 cm × 2 cm strips. The prepared films were stored in a desiccator until further evaluation.

2.5 Composition of Formulations[18,19]

Table 1. Composition of Clotrimazole Sublingual Films

Formulation	Clotrimazole (g)	HPMC 15 cps (g)	Glycerol (mL)	Ethanol (mL)
F1	0.01	0.5	0.2	10
F2	0.01	0.6	0.2	10
F3	0.01	0.7	0.2	10
F4	0.01	0.8	0.2	10
F5	0.01	0.9	0.2	10
F6	0.01	1	0.2	10

2.6 Evaluation of Sublingual Films:[18-20]

2.6.1 Film Thickness:

Film thickness was measured at three different positions using a digital Vernier caliper with a least count of 0.01 mm. The average value and standard deviation were calculated.

2.6.2 Weight Variation:

Films of identical dimensions (2 cm × 2 cm) were randomly selected and individually weighed using a digital analytical balance. The average weight and standard deviation were calculated to assess weight uniformity.

2.6.3 Folding Endurance:

Folding endurance was determined by repeatedly folding the film at the same point until it broke. The number of folds sustained before breaking was recorded as the folding endurance value.

2.6.4 Surface Ph:

Each film was moistened with approximately 0.5 mL of distilled water and allowed to equilibrate for 30 s. The surface pH was measured by gently placing the electrode of a digital pH meter on the film surface. Measurements were performed in triplicate.

2.6.5 Moisture Content:

The prepared films were weighed initially and stored in a desiccator containing anhydrous calcium chloride for three days. The films were reweighed, and the moisture content was determined from the difference in weight.

2.6.6 Drug Content Uniformity:

Each film (2 × 2 cm) was dissolved in 100 mL of phosphate buffer (pH 6.8) under continuous stirring for 30 min. The solution was suitably diluted, and the absorbance was measured at **226 nm** using a UV–Visible spectrophotometer. Drug content was calculated using the standard calibration curve.

2.6.7 In Vitro Drug Release Study:
The in vitro drug release study was performed using a modified Franz diffusion cell. A film of known drug content was placed in the donor compartment, while phosphate buffer (pH 6.8) was used as the receptor medium. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically at **226 nm**. The cumulative percentage drug release was calculated and compared among the formulations.

2.6.8 Solubility Study:
The solubility behavior of the prepared films was evaluated in **artificial saliva (pH 6.8)** and **phosphate buffer (pH 7.0)**. The time required for complete dissolution of the films in both media was recorded.
2.6.9 Tensile Strength
The tensile strength of the prepared films was determined by measuring the maximum force required to break the film. Tensile strength was calculated by dividing the breaking force by the cross-sectional area of the film.
2.6.10 Percentage Elongation

The percentage elongation of the films was determined by measuring the increase in film length before rupture during tensile testing. The percentage elongation was calculated using the standard equation:

$$\text{Percentage Elongation} = \frac{\text{Increase in Length}}{\text{Original Length}} \times 100$$

Statistical Analysis:
All experiments were carried out in triplicate (**n = 3**), and the results were expressed as **mean ± standard deviation (SD)**. The data obtained from different formulations were compared to identify the optimized formulation exhibiting the most desirable physicochemical characteristics and drug release behavior.

3. RESULTS AND DISCUSSION:
The clotrimazole-loaded sublingual films were successfully prepared by the solvent casting technique using HPMC 15 cps as the film-forming polymer, glycerol as the plasticizer, and ethanol as the solvent. Six formulations (F1–F6) were developed by varying the concentration of HPMC. During preliminary evaluation, formulations F4–F6 exhibited excessive flexibility, increased moisture uptake, tackiness, and plasticizer migration, making them unsuitable for further investigation. Therefore, formulations F1, F2, and F3 were selected for detailed physicochemical and performance evaluation.

3.1 Physical Appearance:
The prepared sublingual films were smooth, transparent, flexible, and free from visible air bubbles or cracks. All films were easily peeled from the casting surface without damage. Formulation F3 exhibited the best appearance with optimum flexibility and mechanical integrity compared to F1 and F2.

Figure 1 F1 (0.5g)

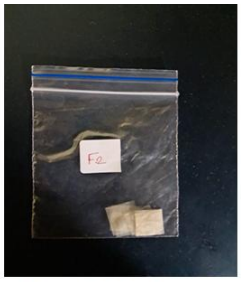

Figure 2 F2 (0.6g)

Figure 3 F3(0.7)

3.2 Film Thickness:
Film thickness is an important quality attribute influencing mechanical strength, drug loading, and release characteristics. The thickness of the prepared films ranged from **0.32 to 0.37 mm**.

Table 2. Thickness of Clotrimazole Sublingual Films

Formulation	Thickness (mm)
F1	0.32

F2	0.34
F3	0.37

The thickness increased progressively with increasing HPMC concentration. The increase in polymer content produced slightly thicker films due to higher viscosity of the casting solution. However, all formulations showed uniform thickness, indicating good casting reproducibility and uniform distribution of polymer throughout the film matrix.

3.3 Weight Variation:

Uniformity of weight indicates homogeneous distribution of the drug and polymer in the casting solution.
Table 3. Average Weight of Prepared Films

Formulation	Average Weight (g)
F1	0.03
F2	0.091
F3	0.116

All formulations demonstrated acceptable weight uniformity. The gradual increase in film weight with increasing HPMC concentration was expected because higher polymer content contributed to greater total solid content in the cast films.

3.4 Surface pH:

Surface pH is an important parameter because acidic or alkaline films may irritate the oral mucosa.
Table 4. Surface pH

Formulation	Surface pH
F1	6.67 ± 0.05
F2	6.81 ± 0.03
F3	6.93 ± 0.02

The surface pH values of all formulations were close to neutral, indicating excellent compatibility with the oral mucosal environment. Therefore, irritation or discomfort during administration is unlikely.

3.5 Solubility Study

Table 5. Solubility in Artificial Saliva (pH 6.8)

Formulation	Dissolution Time (min)
F1	7.3
F2	8.2
F3	10.15

Table 6. Solubility in Phosphate Buffer

Formulation	Dissolution Time (min)
F1	16
F2	18
F3	20

The dissolution time increased with increasing polymer concentration because thicker HPMC matrices required a longer hydration period before complete dissolution. Nevertheless, all formulations dissolved within an acceptable time suitable for sublingual administration.

3.6 Folding Endurance;

Mechanical flexibility is an essential characteristic of oral films.
Table 7. Folding Endurance

Formulation	Folding Endurance (Number of folds)
F1	200
F2	225
F3	245

The folding endurance increased with increasing HPMC concentration. Formulation F3 exhibited the highest value (245 folds), indicating superior flexibility and mechanical strength. The presence of glycerol effectively minimized brittleness while improving elasticity of the polymeric films.

3.7 Moisture Content::

Table 8. Moisture Content

Formulation	Initial Weight (g)	Final Weight (g)
F1	0.017–0.018	0.020–0.025
F2	0.02	0.024–0.025
F3	0.020–0.024	0.026–0.027

A slight increase in film weight was observed after storage, indicating moisture absorption by the hydrophilic HPMC matrix. Moisture uptake increased with increasing polymer concentration because HPMC possesses hygroscopic characteristics. However, the observed increase remained within acceptable limits and did not adversely affect film integrity.

3.8 Drug Content Uniformity:

Uniform drug distribution ensures dose accuracy in each film.

Table 9. Drug Content Uniformity

Formulation	Drug Content (g)
F1	0.0087 ± 0.01
F2	0.0088 ± 0.01
F3	0.0090 ± 0.01

All formulations exhibited satisfactory drug content uniformity, indicating efficient mixing of clotrimazole within the polymeric matrix during solvent casting. Formulation F3 showed the highest drug content and excellent uniformity, confirming the reproducibility of the preparation method.

3.9 In Vitro Drug Release:

The drug release profile is one of the most critical parameters for evaluating sublingual films.

Table 10. Cumulative Drug Release

Formulation	Drug Release (%)
F1	48.62 ± 1.54
F2	53.24 ± 1.65
F3	61.48 ± 1.73

Among all formulations, F3 exhibited the highest cumulative drug release **(**61.48 ± 1.73%). The increased polymer concentration promoted rapid hydration and swelling of the HPMC matrix, facilitating diffusion of clotrimazole into the dissolution medium. Although increasing polymer concentration generally prolongs drug release, the optimized swelling behavior of F3 resulted in greater erosion of the polymer matrix and enhanced drug diffusion. Consequently, F3 was identified as the optimized formulation for sublingual drug delivery.

DISCUSSION:

Based on the physicochemical evaluation and in vitro performance, formulation F3 demonstrated superior characteristics compared to the remaining formulations. It exhibited optimum thickness, highest folding endurance, excellent drug content uniformity, acceptable surface pH, satisfactory moisture content, and maximum cumulative drug release.

Therefore, was selected as the optimized formulation for clotrimazole sublingual film development owing to its balanced mechanical properties, uniform drug distribution, and enhanced drug release profile. These findings indicate that HPMC-based sublingual films prepared by the solvent casting method have considerable potential as an effective alternative to conventional clotrimazole dosage forms for the treatment of oral candidiasis.

CONCLUSION:

The present study successfully formulated and evaluated clotrimazole-loaded sublingual films using the solvent casting technique with Hydroxypropyl Methylcellulose (HPMC 15 cps) as the film-forming polymer and glycerol as the plasticizer. The prepared films exhibited satisfactory physicochemical characteristics, including uniform thickness, acceptable weight variation, good folding endurance, near-neutral surface pH, adequate moisture content, and uniform drug distribution, indicating the suitability of the formulation for sublingual administration.

Among the developed formulations, **F3** demonstrated the best overall performance, exhibiting excellent

mechanical strength, the highest folding endurance, satisfactory drug content uniformity, and the maximum cumulative drug release (**61.48 ± 1.73%**). The optimized formulation showed rapid hydration and effective drug release, suggesting its potential to provide faster therapeutic action and improved patient compliance compared with conventional oral dosage forms.

The findings indicate that clotrimazole sublingual films offer a promising alternative for the treatment of oral candidiasis by bypassing hepatic first-pass metabolism, improving drug bioavailability, and facilitating rapid onset of antifungal activity. Moreover, the patient-friendly nature of the sublingual film makes it particularly suitable for pediatric, geriatric, and dysphagic patients who experience difficulty swallowing conventional tablets or capsules.

Overall, the developed HPMC-based clotrimazole sublingual film represents a safe, effective, and convenient drug delivery system with significant potential for the localized treatment of oral fungal infections. Further studies involving in vivo pharmacokinetic evaluation, stability testing according to ICH guidelines, and clinical investigations are recommended to establish its therapeutic efficacy and support future commercial development.

REFERENCES

1. Almangour TA, Kaye KS, Alessa M, Aleanizy FS, Alsharidi A, Al Majid FM, et al. Efficacy of clotrimazole for the management of oral candidiasis: A meta-analysis of randomized clinical trials. J Saudi Pharm Soc. 2021;29(4):315-323. doi:10.1016/j.jsps.2021.03.003.
2. Babu NA, Anitha N. Hyposalivation and oral candidiasis: A short review. J Oral Maxillofac Pathol. 2022;26(2):144-146. doi:10.4103/jomfp.jomfp_161_22.
3. Mele A, Pullanhiyodan A, Krishnan M. Conforming film-forming systems for topical and mucosal drug delivery: Recent advances and future perspectives. Drug Deliv Transl Res. 2025.
4. Umar AK, Butarbutar M, Sriwidodo S, Wathoni N. Film-forming sprays for topical drug delivery. Drug Des Devel Ther. 2020;14:2909-2925. doi:10.2147/DDDT.S256666.
5. Bala R, Pawar P, Khanna S, Arora S. Orally dissolving strips: A new approach to oral drug delivery system. Int J Pharm Investig. 2022;12(1):1-12.
6. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: An innovative drug delivery system and dosage form. J Drug Deliv Sci Technol. 2022;72:103424.
7. Preis M. Orally disintegrating films and their technologies: Recent developments. Pharmaceutics. 2022;14(5):987.
8. Visser JC, Woerdenbag HJ, Hanff LM, Frijlink HW. Personalized medicine through orodispersible films. Pharmaceutics. 2022;14(3):531.
9. Borges AF, Silva C, Coelho JFJ, Simões S. Oral films: Current status and future perspectives. J Control Release. 2023;355:470-490.
10. Boateng JS, Pawar HV, Tetteh J. Polymeric films for pharmaceutical applications: Recent advances in oral and mucosal drug delivery. Drug Dev Ind Pharm. 2023;49(5):689-705.
11. Repka MA, McGinity JW, Zhang F, Koleng JJ, et al. Pharmaceutical applications of oral thin films: Recent advances and future opportunities. AAPS PharmSciTech. 2023;24:165.
12. Khairnar A, Jain P, More S. Advances in buccal and sublingual drug delivery systems for improved therapeutic efficacy. Int J Biol Macromol. 2024;254:127812.
13. Singh R, Sharma PK, Malviya R. Mucoadhesive oral films: Formulation strategies and pharmaceutical applications. Eur J Pharm Sci. 2024;196:106721.
14. Patel D, Patel N, Patel V. Development and evaluation of polymeric oral thin films for mucosal drug delivery. J Drug Deliv Sci Technol. 2024;89:105284.
15. Khan AB, Kingsley T, Caroline P. Sublingual drug delivery systems: Recent advances in formulation and therapeutic applications. Int J Pharm. 2024;652:123831.
16. Bhyan B, Jangra S. Recent advances in sublingual drug delivery systems for rapid therapeutic response. Pharmaceutics. 2024;16(3):421.
17. Crowley PD, Gallagher HC. Clotrimazole as a pharmaceutical: Past, present and future. J Appl Microbiol. 2022;132(6):4254-4269.
18. Kapoor D, Maheshwari R, Verma S. Advances in polymeric film formulations for oral mucosal drug delivery. Drug Deliv Transl Res. 2025.
19. Kalia V, Garg T, Goyal AK. Advances in oral thin films for systemic and local drug delivery. Pharmaceutics. 2025;17(2):188.
20. Sharma A, Verma R, Singh B. Recent trends in fast dissolving oral films: Formulation, characterization and therapeutic applications. Int J Pharm. 2025;648:124138.