# DEVELOPMENT AND OPTIMIZATION OF TERBINAFINE HYDROCHLORIDE FILM-FORMING GEL FOR PROLONGED TOPICAL ANTIFUNGAL DELIVERY

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## Abstract

Fungal infections of the skin, particularly superficial dermatophytoses such as tinea pedis, tinea corporis and tinea cruris, represent common dermatological disorders requiring effective topical therapy [6,8]. Terbinafine hydrochloride is a potent allylamine antifungal drug with excellent activity against dermatophytes [6,7]. Conventional topical preparations such as creams, ointments and conventional gels may be removed from the application site by washing, sweating, friction or clothing, which can reduce residence time and patient adherence [8,9]. Film-forming drug delivery systems have therefore attracted considerable interest as an approach for improving topical drug retention and providing prolonged antifungal delivery. A film-forming gel is applied as a gel-like formulation and, following evaporation of volatile components, produces a thin, flexible and adherent polymeric film on the skin. The resulting film can act as a drug reservoir and potentially provide sustained release of terbinafine hydrochloride at the site of infection [8,9,10]. Formulation variables including polymer type and concentration, solvent composition, plasticizer, penetration enhancer, drug concentration, viscosity, drying time and film mechanical properties influence drug release and skin permeation [9,10]. This review discusses the physicochemical and pharmacological properties of terbinafine hydrochloride, the rationale for film-forming topical delivery, polymers and excipients used in film-forming systems, formulation and optimization approaches, evaluation parameters, mechanisms of prolonged drug delivery, and prospects for terbinafine hydrochloride film-forming gels.

**Keywords:** Terbinafine Hydrochloride, Film-Forming Gel, Topical Drug Delivery, Antifungal Activity, Formulation Development, Formulation Optimization, Sustained Drug Release, Prolonged Drug Delivery, Skin Permeation, In Vitro Drug Release, Polymer-Based Drug Delivery, Pharmaceutical Technology.

# 1.INTRODUCTION

Topical drug delivery is an important route for the treatment of superficial dermatological disorders because it can provide drug directly at the site of action while potentially reducing systemic exposure [1,2]. Conventional creams, ointments and gels are widely used, but their performance can be affected by rubbing, washing, sweating, poor residence time and variability in the amount applied. Film-forming systems have therefore attracted attention as an alternative approach for prolonged residence on the skin. [2,3,4,5].

Superficial fungal infections are among the most common dermatological conditions worldwide. They are frequently caused by dermatophytes belonging to genera such as Trichophyton, Microsporum and Epidermophyton [6,7]. These infections commonly affect the feet, groin, trunk and nails. Topical drug delivery is attractive for superficial fungal infections because the drug can be delivered directly to infected tissue while potentially reducing systemic exposure [6,8].

Terbinafine is an allylamine antifungal agent with strong activity against dermatophytes. It inhibits fungal squalene epoxidase, interfering with ergosterol biosynthesis and causing accumulation of squalene and depletion of ergosterol [6,7]. Film-forming systems can improve residence time and may provide a local drug reservoir for prolonged delivery [8,9,10].

## Film-forming gels

A film-forming gel is a topical formulation that is applied as a liquid or semisolid and subsequently forms a thin polymeric film after evaporation of volatile components. The resulting film can improve residence time and may provide a reservoir from which the active pharmaceutical ingredient is released over an extended period [2,3,4,5]. The final performance depends on polymer selection, solvent composition, plasticizer level, drug concentration, rheological properties and drying behaviour [3,11].

## Rationale for terbinafine hydrochloride Film-Forming Gel

Terbinafine hydrochloride is a widely used allylamine antifungal drug. Its topical use makes it suitable for investigation in film-forming systems where prolonged contact with the infected skin may be advantageous [2,3,4,5]. The development objective is not simply to increase drug release, but to obtain a reproducible formulation that balances drug loading, film formation, drying time, mechanical integrity, adhesion and local drug availability [1,2,11].

After application, solvent evaporation increases polymer concentration and produces a continuous drug-containing film. The film remains in intimate contact with the skin and can provide controlled diffusion of terbinafine toward the infected tissue [9,10].

# 2.TERBINAFINE HYDROCHLORIDE

Terbinafine hydrochloride is the hydrochloride salt of terbinafine, an allylamine antifungal agent widely used for superficial fungal infections. Its antifungal activity is associated with inhibition of squalene epoxidase, an enzyme involved in ergosterol biosynthesis. Disturbance of fungal membrane sterol metabolism contributes to antifungal activity [1,6,7,12].

## Topical delivery considerations

For topical development, the formulation must maintain the drug in a suitable state for release from the dosage form and subsequent partitioning into the skin. The vehicle can influence drug solubilization, thermodynamic activity, evaporation, film structure and skin interaction. Consequently, analytical characterization should consider both the initial formulation and the properties of the dried film [1,12,13].

## Importance of formulation environment

Polymer concentration, solvent composition and plasticizer content can alter viscosity, drying rate and drug distribution. Changes in these variables may also affect the mechanical properties and permeability of the final film. A systematic development approach is therefore preferable to changing ingredients without evaluating interactions [1,12,13].

# 3. TOPICAL FILM-FORMING DRUG DELIVERY SYSTEMS

## Principle of film formation

Film-forming systems generally contain a film-forming polymer dissolved or dispersed in a vehicle together with the active ingredient and, when required, plasticizers or permeation modifiers. Following application, volatile solvent components evaporate and polymer chains associate to produce continuous film [2,3,4,5]. The film can remain on the skin and act as a matrix for drug release [3,11].

## Advantages

Potential advantages include prolonged residence, reduced frequency of application, uniform spreading, improved contact with the skin and the possibility of modifying drug release. Film-forming systems can also be designed to produce thin and cosmetically acceptable layers. However, the same properties that provide prolonged residence may slow release excessively if polymer content or film density is too high [2,3,4,5]. high potency against dermatophytes, rapid onset of antifungal action, skin retention after topical application, and suitability for incorporation into advanced topical delivery systems [7,10].

## Factors affecting film performance

Important variables include:

polymer molecular characteristics.

1. polymer concentration.
2. solvent volatility, plasticizer concentration, drug loading.
3. film thickness, drying conditions.
4. interactions between formulation components.
5. The relationship between these factors is formulation-specific and should be evaluated experimentally during development [2,3,4,5].

## Polymers Used in Film-Forming Gels

1. Hydroxypropyl cellulose can provide film-forming properties and modify viscosity and adhesion.
2. Eudragit polymers can provide persistent films and control release .
3. Polyvinylpyrrolidone and polyvinyl alcohol can contribute film formation, adhesion and flexibility.

4. Chitosan offers film-forming and bioadhesive properties [8,9].

PLGA-based systems have also been studied for prolonged terbinafine release [10]. Polymer selection should consider film strength, flexibility, adhesion, drying time, drug compatibility and release characteristics. [8,9,10].

## 4. FORMULATION COMPONENTS

### Eudragit RS PO

Eudragit RS PO is a methacrylate-based polymer used for controlled-release applications and film formation. In the supplied development frame work it is considered a benchmark film-forming polymer because it can contribute to robust films and prolonged drug release. Its concentration and compatibility with the vehicle are critical formulation variables [1,2,4,14].

### Hydroxypropyl cellulose

Hydroxypropyl cellulose (HPC) is a cellulose derivative that can contribute to film formation, viscosity and flexibility. Its use with a methacrylate polymer provides an opportunity to adjust rheology and film characteristics. The polymer ratio should therefore be treated as a critical material attribute rather than as an arbitrary excipient quantity [1,4,14].

### Solvent system

Ethanol, water, isopropanol and glycols may be considered during solvent screening depending on drug solubility, polymer compatibility, evaporation behaviour and skin tolerance. Solvent selection also influences flammability, residual solvent risk and manufacturing conditions [1,2,4,14].

### Plasticizers and modifiers

Glycerol, propylene glycol, polyethylene glycol 400 and triethyl citrate are examples of plasticizers or formulation modifiers reported for topical film systems [4,14]. Plasticizers can increase flexibility and reduce brittleness, but excessive amounts may alter drying, tackiness and drug release [14].

### Critical material attributes

Relevant material attributes include polymer grade and viscosity, drug purity and particle characteristics where applicable, solvent quality, plasticizer purity and water content [4,14]. These attributes should be controlled because variability in raw materials can translate into changes in viscosity, film formation and analytical performance [1,2,4,14].

## 5.PREFORMULATION AND COMPATIBILITY STUDIES

### Drug–excipient compatibility

Compatibility assessment is an important early activity because the drug and excipients remain in close contact during manufacturing and storage. FTIR can provide evidence of changes in characteristic functional-group bands, while DSC can be used to examine thermal behaviour. PXRD may be used when crystallinity or solid-state changes are relevant [15,16,17,18].

### Solubility and vehicle screening

The formulation vehicle should provide sufficient drug solubilization or a controlled dispersed state while maintaining polymer compatibility. Screening should consider drug concentration, polymer concentration, solvent ratio, appearance, precipitation, viscosity and drying behaviour [15,16,17,18].

### Preliminary film assessment

Simple films prepared during screening can be evaluated for transparency, uniformity, flexibility, tackiness, peeling and drying time. These observations are useful for eliminating unsuitable compositions before more resource-intensive analytical studies [15,16,17,18].

### Analytical considerations

Preformulation should also establish an analytical method capable of accurately measuring terbinafine hydrochloride in the presence of formulation excipients. A stability-indicating chromatographic method is particularly important when degradation behaviour is investigated [15,16,17,18].

## 6. FORMULATION DEVELOPMENT STRATEGY

### Quality target product profile

The target product profile can include topical route of administration, prolonged residence, acceptable drying time, suitable appearance, dose uniformity, adequate film integrity, controlled drug release and acceptable skin performance. These targets form the basis for defining critical quality attributes [19,20].

### Experimental design

A design-of-experiments approach can be used to study the influence of formulation variables and their interactions. The supplied development material describes a $3^2$ factorial strategy as a possible screening/optimization framework. Such a design can investigate two factors at three levels and can be adapted to the selected formulation variables [19,20].

### Typical optimization factors

Polymer concentration, polymer ratio, solvent composition, plasticizer level and drug loading are possible formulation factors. Responses may include viscosity, drying time, film thickness, tensile strength, elongation, drug release and skin deposition [19,20].

### Confirmation

After selection of an optimized composition, confirmatory batches should be prepared to assess reproducibility. The purpose is to demonstrate that the selected formulation lies within the intended operating region rather than representing a single successful laboratory batch [19,20].

# 7. PROCESS CHEMISTRY AND MANUFACTURING PROCESS

## General manufacturing sequence

A representative laboratory process consists of raw-material verification, preparation of the polymer phase, preparation of the drug solution or concentrate, controlled combination of phases, addition of plasticizer or modifier, final mass adjustment, deaeration and equilibration, followed by filling into suitable containers. The exact order should be established from compatibility and process studies [19,21,22,23].

## Polymer phase preparation

The polymer is introduced into the selected vehicle under controlled mixing. Adequate hydration or dissolution time is allowed where required. Mixing speed should be sufficient for uniformity without unnecessarily entraining air. Temperature should be controlled because viscosity and solvent evaporation can change with temperature [19,21,22,23].

## Drug incorporation

Terbinafine hydrochloride may be incorporated through a solution or concentrate depending on its solubility in the selected vehicle. Controlled addition helps minimize local concentration gradients and precipitation. The addition sequence should be kept consistent between development batches [19,21,22,23].

## Plasticizer addition and final adjustment

Plasticizer or permeation modifier is incorporated after establishing compatibility with the polymer system. The final batch mass or volume is adjusted using the vehicle. The formulation is then allowed to equilibrate before filling[19,21,22,23].

## Deaeration

Entrapped air can influence fill accuracy, appearance and apparent rheological behaviour. Deaeration can therefore be included as a process step when foam or bubbles are observed. Excessive vacuum or prolonged processing should be avoided if it promotes solvent loss [19,21,22,23].

## Critical process parameters

Potential CPPs include mixing speed and time, temperature, order of addition, solvent addition rate, polymer hydration time, deaeration conditions and fill weight. CPPs should be identified through risk assessment and linked to measurable CQAs [19,21,22,23].

# 8. STABILITY AND PACKAGING CONSIDERATIONS

## Stability program

Stability evaluation should monitor appearance, assay, related substances, viscosity, film performance and other relevant quality attributes over time. ICH stability principles provide a framework for selecting storage conditions and evaluation intervals [17,24,25,26].

### Packaging

The container should protect the formulation from evaporation, contamination and inappropriate exposure to light or moisture where relevant. The closure system is particularly important for a film-forming formulation because loss of volatile solvent can change viscosity and drug concentration [17,24,25,26].

### Stability-indicating analysis

Chromatographic analysis should be capable of detecting significant degradation products when stability-indicating performance is required. Stress studies can be used to challenge the analytical procedure and help establish specificity [17,24,25,26].

### Acceptance criteria

Specifications should be established from development and stability data and should reflect product performance rather than arbitrary limits. Relevant considerations include assay, related substances, physical appearance, viscosity, microbial quality where applicable and film performance [17,24,25,26].

## 9. CHALLENGES, LIMITATIONS AND FUTURE SCOPE

### Development challenges

A major challenge is achieving a balance between prolonged residence and adequate drug release. Increasing polymer concentration may improve film integrity but can slow drug liberation. Increasing plasticizer may improve flexibility but can influence tackiness and release. Solvent changes can affect both manufacturability and drying time [2,3, 20].

### Analytical challenges

Topical formulations contain polymers and excipients that may complicate sample preparation and chromatographic analysis. Extraction recovery, adsorption to laboratory materials and matrix effects should therefore be considered during method development [2,3, 20].

### Limitations of laboratory models

In-vitro release and ex-vivo permeation studies provide controlled information but do not reproduce all aspects of human skin use. Differences in skin condition, application amount, rubbing, washing and environmental exposure can influence clinical performance [2,3, 20].

### Future scope

Future development may include systematic DoE optimization, improved in-vitro–in-vivo correlation, advanced imaging or spectroscopy for film mapping, more refined skin deposition models, continuous or semi-continuous manufacturing approaches and lifecycle-based analytical control strategies [2,3, 20].

## 10, CONCLUSION

Terbinafine hydrochloride film-forming gel represents a promising topical delivery approach for improving residence and controlling drug release. Successful development requires coordinated consideration of formulation components, process chemistry, analytical technology and product performance. Eudragit RS PO and hydroxypropyl

cellulose provide a useful polymer framework for development, while solvent selection and plasticization strongly influence processing and film properties. A QbD-based approach can connect material attributes and process parameters with critical quality attributes. RP-HPLC/UPLC supported by FTIR, DSC and PXRD provides a strong analytical platform, while rheology, film mechanics, release and ex-vivo skin deposition provide complementary evidence of performance. Ultimately, the optimized product should be selected on the basis of reproducibility, stability, film quality, controlled release and meaningful local drug exposure rather than on any single response [1,2, 5,12 ,17,18].

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