

# The Screening of Permeation Enhancers for Trans-Nail Delivery of Terbinafine Hydrochloride

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## Abstract

In this project, several permeation enhancers were screened to improve the penetration of terbinafine hydrochloride into the nail plate. Human nail plate clippings were used to perform the screening studies. As the results of high throughput screening, tween 80, tween 60, tween 40 and tween 20 showed the ability to improve the penetration of terbinafine into the nail clippings ~2.5, 2, 3 and 2.5-fold more compared to control. The amount of terbinafine penetrated in the nail clippings in case of PEG-35 castor oil and PEG-40 castor oil was ~2.5 and 2.5-fold more compared to control. Glycerol, sodium lauryl sulfate and span 80 enhanced the penetration of terbinafine into the nail clippings by ~2, 4.5 and 2.5-fold more compared to control. Transcutol, TPGS, propylene glycol, isopropyl myristate, octyldodecanol, decyl oleate and oleyl oleate were not able to improve the penetration of terbinafine in the nail clippings compare to control. Screening studies concluded that sodium lauryl sulfate was found to be potential permeation enhancer which improved the penetration of terbinafine significantly.

**Keywords:** Terbinafine hydrochloride; Permeation enhancers; Drug delivery

## Introduction

Systemic treatment of nail diseases is not completely successful due to poor blood circulation in the nail apparatus [1]. Nowadays, topical therapy is mostly prepared due to its advantages such as non-invasiveness, targeted action, less side effects, cost effectiveness and patient's compliance [2]. However, nail delivery of drugs is limited due to poor permeability of nail plate. Nail plate is consisted of three layers which are dorsal, intermediate and ventral. Dorsal layer of the nail plate is considered to be the main barrier for the nail drug delivery [3]. Terbinafine is a broad spectrum antifungal drug which is used for the treatment of onychomycosis [3]. Several active techniques such as iontophoresis, ultrasound and microneedles have previously been investigated to improve the nail delivery of terbinafine hydrochloride [4-6]. However, these techniques are not patient compliance and the medical personnel is required to perform the technique. Chemical permeation enhancers are mostly preferred in the formulations to improve the permeation of drugs into the nails due to their cost effectiveness and patient compliance [3,7]. Permeation enhancers are chemicals which improve the penetration of drug using various mechanism such as break the disulfide bond of the keratin and improve the water holding capacity of the nail plate [3]. In this project, several permeation enhancers were screened to find out the potential permeation enhancer to improve the penetration of terbinafine hydrochloride into the nail plate [1]. Screening studies were performed using human nail clippings.

## Material and Method

### Materials

Terbinafine was purchased from by VWR International (Coimbatore, India). The surfactants and humectants were gifted by BASF Corporation (Florham Park, NJ). The solvents (analytical grade) were purchased from BD Scientific (Bhopal, India).

### Methods

**Formulations:** Twenty-one permeation enhancers were tested in a high throughput screening campaign. A testing formulation was

composed of 5% w/w permeation enhancer and 95% w/w ethanol. Ethanol in the testing formulation was used as a solvent. The list of permeation enhancers is mentioned in the Table 1 and Figure 1.

**High throughput screening procedure:** Human nail plate clipping (area 0.07 cm<sup>2</sup>) was used to perform the high throughput screening study. Before starting an experiment, each nail clipping was cleaned and washed with phosphate buffer saline (PBS) and then pat dried with

Permeation enhancers	The total amount of terbinafine (µg/mg)
Control	0.10 ± 0.03
Tween 80	0.26 ± 0.09
Glycerol	0.20 ± 0.07
Transcutol	0.18 ± 0.02
PEG-35 castor oil	0.25 ± 0.04
PEG-40 castor oil	0.25 ± 0.05
Sodium lauryl sulfate	0.45 ± 0.06
Tween 40	0.30 ± 0.03
Tween 20	0.25 ± 0.05
TPGS	0.14 ± 0.02
Tween 60	0.23 ± 0.03
Propylene glycol	0.12 ± 0.02
Span 80	0.25 ± 0.05
Isopropyl myristate	0.08 ± 0.05
Octyl dodecanol	0.08 ± 0.01
Decyl oleate	0.08 ± 0.02
Oleyl oleate	0.10 ± 0.03

Table 1: The total amount of terbinafine extracted from the nail clippings.

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Received June 26, 2018; Accepted July 18, 2018; Published July 28, 2018

**Citation:** Kushwaha AS (2018) The Screening of Permeation Enhancers for Trans-Nail Delivery of Terbinafine Hydrochloride. J Bioequiv Availab 10: 75-77. 381. doi: 10.4172/0975-0851.1000381

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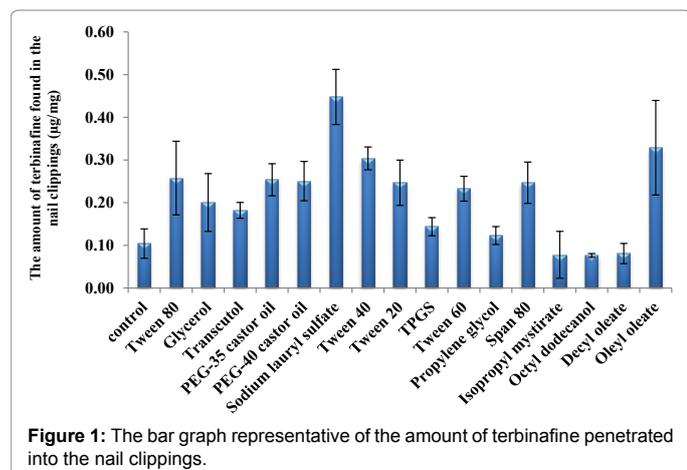


Figure 1: The bar graph representative of the amount of terbinafine penetrated into the nail clippings.

Kimwipes<sup>®</sup>. Nail clipping was placed dipped in a testing formulation once and placed in a 5 ml glass vial. Glass vial was kept at room temperature. After 24 h, each nail clipping was washed 5 times with a 3 ml of 50% ethanol solution in water. Each nail clipping was pat dried with Kimwipes<sup>®</sup>. The amount of terbinafine is penetrated in the nail plate after 24 h was quantified using HPLC method [1,2,8].

**Extraction of terbinafine from nail clipping:** Before starting a terbinafine extraction procedure, the weight of each nail clipping was recorded and then each clipping was placed in a 5 ml glass vial which was filled with a 3 ml of DMSO to extract the terbinafine. Nail clipping in DMSO was shook for around 24 h. 1 ml of extraction sample was collected and then filtered to using 0.45 µm syringe filter. Extraction was analyzed using HPLC method [1,2,8].

**Analytical method:** The amount of terbinafine was quantified using Shimadzu Prominence-i 2030C plus HPLC (high-performance liquid chromatography) which was consisted of quaternary pump, auto sampler and UV-VIS Detector. The mobile phase was prepared by mixing aqueous phase and acetonitrile in a 60:40 proportion. The pH of the mobile was adjusted at pH 2 using 0.096M triethyl amine, 0.183M orthophosphoric acid. Terbinafine was eluted at a flow rate of 1.0 ml/min at 224 nm. The HPLC method was validated from 1 µg/ml of terbinafine to 10 µg/ml [9,10].

**Statistical analysis:** Statistical analysis of the data of high throughput screening studies was performed using ANOVA test. The p value less than 0.05 was considered statistical significant.

## Result and Discussion

Nail plate consists of three layers which are dorsal, intermediate and ventral layer. Dorsal layer is the outer most layer which is considered to be the main barrier for the drug delivery [3]. Ventral layer is directly attached to the nail bed and it is more hydrated than dorsal layer. Topical nail delivery of drugs is mostly preferred for the treatment of nail diseases due to the direct application of drug on the site of infection. In recent years, many active (Iontophoresis, electroporation, and ultrasound) and passive (chemical penetration enhancers) techniques have been explored to improve the trans-ungual permeation the terbinafine [3,6,11]. Murthy et al., screened several permeation enhancers to improve the permeation of terbinafine across the nail [8]. Nair et al., also investigated the iontophoresis technique to improve the permeation of terbinafine [5]. Kushwaha et al. reported to deliver terbinafine hydrochloride from hyponychium region to the

nail apparatus. In this project, we investigated some new permeations enhancers to enhance the penetration of terbinafine into the nail plate [12,13].

In topical formulations, permeation enhancers are chosen at the first-place due lower cost of treatment and patient compliance. Permeation enhancer are chemicals which improve the permeation of drugs into and across the nail plate using several mechanisms. Kushwaha et al. reported that some permeation enhancers break the disulfide bond of the keratin proteins and some improve the water holding capacity of nail plate to enhance the permeation of drugs into and across the nail plate [1,13]. In this project, vitamin ETPGS is used as a non-ionic surfactant. It is well known for its emulsifying and solubilizing the poor water-soluble drugs [14,15]. Kolliphor<sup>™</sup> RH 40 (PEG-40 castor oil) and Kolliphor<sup>™</sup> EL (PEG -35 castor oil) are commonly used as non-ionic solubilizer and emulsifier [15,16]. Tweens (Tween 20, 40, 60 and 80) and spans are non-ionic surfactant and used to as solubilizer and emulsifier [15]. Oleyl oleate, decyl oleate and octyldodecanol are used as the skin-Conditioning agent and permeation enhancers for skin delivery of drugs [17]. Isopropyl myristate is used as solvent and permeation enhancer for skin delivery of drugs [18]. Glycerol and propylene glycol are commonly used as moisturizing agent and solvents [15]. Transcutol is a very effective permeation enhancer and solvent for skin delivery of drugs. Sodium lauryl sulfate is a ionic surfactant, normally used in the shampoos and gels [2,15].

As a result of screening study, tween 80, tween 60, tween 40 and tween 20 improved the penetration of terbinafine ~2.5, 2, 3 and 2.5-fold more compared to control. The amount of terbinafine extracted from nail clippings in case of PEG-35 castor oil and PEG-40 castor oil was ~2.5 and 2.5-fold more compared to control. Glycerol, sodium lauryl sulfate and span 80 enhanced the penetration of terbinafine into the nail clippings by ~2, 4.5 and 2.5-fold more compared to control. Transcutol, TPGS, propylene glycol, isopropyl myristate, octyldodecanol, decyl oleate and oleyl oleate were not found to be effective to improve the penetration of terbinafine compare to control.

## Conclusion

Sodium lauryl sulfate was found to be potential permeation enhancer which improved the penetration of terbinafine significantly. Sodium lauryl sulfate can be a good candidate to be investigated to improve the permeation of terbinafine in the nail apparatus for the treatment of onychomycosis.

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