

What Published Studies Tell Us Regarding Nanoparticles, N-acetyl-L-cysteine, Urea and Tea Tree Oil

[Chem Pharm Bull \(Tokyo\)](#). 1998 Nov;46(11):1797-802.

Enhancing effect of N-acetyl-L-cysteine or 2-mercaptoethanol on the in vitro permeation of 5-fluorouracil or tolnaftate through the human nail plate.

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Abstract

The enhancing effects of various vehicles on the in vitro permeation of a hydrophilic model drug, 5-fluorouracil (5-FU), or a lipophilic model drug, tolnaftate (TN), through human nail plates were investigated using a modified side-by-side diffusion cell. Tip pieces from the 5th finger-nail, clipped from healthy volunteers, were used in this permeation study. The swelling and softening properties of the nail pieces were also measured in each vehicle. The weights and stresses of the nail pieces were dramatically changed after immersion in aqueous solvents containing N-acetyl-L-cysteine (AC) or 2-mercaptoethanol (ME). However, no significant change in the physicochemical properties of the nail pieces was found in the lipophilic vehicles. Thus, the water content in the nail plates absorbed from vehicles may relate to their physicochemical properties. Although keratin-softening agents and new skin permeation enhancers did not significantly promote 5-FU permeation compared with water alone, the flux from solvent systems containing AC or ME was substantially higher. In addition, TN permeation from solvents containing AC or ME could be measured, whereas that from other solvents was undetectable. When the AC concentration was increased, the 5-FU permeation and the nail weight increased, and the stress of each nail piece decreased. It is concluded from these experimental results that AC and ME may be useful as enhancers for increasing drug permeation through the human nail plate.

PMID: 9845958

[Ann Dermatol](#). 2015 Aug;27(4):450-1. doi: 10.5021/ad.2015.27.4.450. Epub 2015 Jul 29.

Effects of Topical N- Acetylcysteine on Skin Hydration / Transepidermal Water Loss in Healthy Volunteers and Atopic Dermatitis Patients.

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Nanoparticles and nanofibers for topical drug delivery

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Abstract

This review provides the first comprehensive overview of the use of both nanoparticles and nanofibers for topical drug delivery. Researchers have explored the use of nanotechnology, specifically nanoparticles and nanofibers, as drug delivery systems for topical and transdermal applications. This approach employs increased drug concentration in the carrier, in order to increase drug flux into and through the skin. Both nanoparticles and nanofibers can be used to deliver hydrophobic and hydrophilic drugs and are capable of controlled release for a prolonged period of time. The examples presented provide significant evidence that this area of research has —and will continue to have — a profound impact on both clinical outcomes and the development of new products.

Melaleuca alternifolia (Tea Tree) oil: a review of antimicrobial and other medicinal properties.

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Abstract

Complementary and alternative medicines such as tea tree (melaleuca) oil have become increasingly popular in recent decades. This essential oil has been used for almost 100 years in Australia but is now available worldwide both as neat oil and as an active component in an array of products. The primary uses of tea tree oil have historically capitalized on the antiseptic and anti-inflammatory actions of the oil.

This review summarizes recent developments in our understanding of the antimicrobial and anti-inflammatory activities of the oil and its components, as well as clinical efficacy. Specific mechanisms of antimicrobial and anti-inflammatory action are reviewed, and the toxicity of the oil is briefly discussed.



Solid Lipid Nanoparticles and Nanostructured Lipid Carriers of Tolnaftate: Design, Optimization and In-Vitro Evaluation

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ABSTRACT

Objective: The target of our work is the preparation of tolnaftate (TOL) loaded solid lipid nanoparticles (SLNs) as well as nanostructured lipid carriers (NLCs).

Methods: The high shear homogenization method was chosen for the preparation of nanoparticles. The nanoparticle dispersions were prepared using Compritol 888ATO, Tefose 63, Miglyol® 812, Poloxamer188, and Tween80. Particle size (PS), zeta potential (ZP), polydispersity index (PDI), drug entrapment efficiency (EE) and in vitro release study were determined. Differential Scanning Calorimetry (DSC) analysis and morphological transmission electron microscopy (TEM) examination were conducted. A stability study for 3 months was performed.

Results: The results revealed that NLC and SLN dispersions had spherical shapes with an average size between 41.10 ± 1.92 nm and 98.85 ± 1.01 nm. High entrapment efficiency was obtained with negatively charged zeta potential with PDI value ranging from 0.251 ± 0.012 to 0.759 ± 0.028 . The release profiles of all formulations were characterized by a sustained release behavior over 24 h and the release rates increased as the amount of liquid lipid in lipid core increased. Tolnaftate loaded NLC showed more stability than its corresponding SLN.

Conclusion: It can be fulfilled from this work that NLCs may represent a promising carrier for tolnaftate delivery offering both sustained release and stability.

[Trop Med Int Health](#). 1999 Apr;4(4):284-7.

Treatment of toenail onychomycosis with 2% butenafine and 5% Melaleuca alternifolia (tea tree) oil in cream.

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Abstract

The prevalence of onychomycosis, a superficial fungal infection that destroys the entire nail unit, is rising, with no satisfactory cure. The objective of this randomized, double-blind, placebo-controlled study was to examine the clinical efficacy and tolerability of 2% butenafine hydrochloride and 5% Melaleuca alternifolia oil incorporated in a cream to manage toenail onychomycosis in a cohort. Sixty outpatients (39 M, 21 F) aged 18-80 years (mean 29.6) with 6-36 months duration of disease were randomized to two groups (40 and 20), active and placebo. After 16 weeks, 80% of patients using medicated cream were cured, as opposed to none in the placebo group. Four patients in the active treatment group experienced subjective mild inflammation without



discontinuing treatment. During follow-up, no relapse occurred in cured patients and no improvement was seen in medication-resistant and placebo participants.

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Cream formulation impact on topical administration of engineered colloidal nanoparticles.

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Abstract

In order to minimize the impact of systemic toxicity of drugs in the treatment of local acute and chronic inflammatory reactions, the achievement of reliable and efficient delivery of therapeutics in/through the skin is highly recommended. While the use of nanoparticles is now an established practice for drug intravenous targeted delivery, their transdermal penetration is still poorly understood and this important administration route remains almost unexplored. In the present study, we have synthesized magnetic (iron oxide) nanoparticles (MNP) coated with an amphiphilic polymer, developed a water-in-oil emulsion formulation for their topical administration and compared the skin penetration routes with the same nanoparticles deposited as a colloidal suspension. Transmission and scanning electron microscopies provided ultrastructural evidence that the amphiphilic nanoparticles (PMNP) cream formulation allowed the efficient penetration through all the skin layers with a controllable kinetics compared to suspension formulation. In addition to the preferential follicular pathway, also the intracellular and intercellular routes were involved. PMNP that crossed all skin layers were quantified by inductively coupled plasma mass spectrometry. The obtained data suggests that combining PMNP amphiphilic character with cream formulation improves the intradermal penetration of nanoparticles. While PMNP administration in living mice via aqueous suspension resulted in preferential nanoparticle capture by phagocytes and migration to draining lymph nodes, cream formulation favored uptake by all the analyzed dermis cell types, including hematopoietic and non-hematopoietic. Unlike aqueous suspension, cream formulation also favored the maintenance of nanoparticles in the dermal architecture avoiding their dispersion and migration to draining lymph nodes via afferent lymphatics.

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Influence of penetration enhancers and molecular weight in antifungals permeation through bovine hoof membranes and prediction of efficacy in human nails.

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Abstract

This work aimed to evaluate the effect of different substances on the permeation of geraniol through bovine hoof membranes. Different penetration enhancers were able to increase the permeability up to 25 times compared to control. It was demonstrated that acetylcysteine in association with ascorbic acid increased the permeation, even in acid formulations. In addition, some antifungal drugs were incorporated into a gel formulation of HPMC containing acetylcysteine 5% and ascorbic acid 0.2% and then the permeation coefficient through bovine hoof membranes was evaluated. The relationship between permeability and molecular weight was established for fluconazole, miconazole, terbinafine, butenafine, geraniol and Nerol. Geraniol and Nerol, the antifungals with lower molecular weight, had the better permeability results. Permeability coefficients for nail plates were estimated and geraniol demonstrated similar or even better efficacy index values against *T. rubrum*, *T. mentagrophytes* and *M. canis* compared with terbinafine and miconazole.

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Topical N-acetylcysteine improves wound healing comparable to dexpanthenol: an experimental study.

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Abstract

In this study, we aimed to compare the effects of dexpanthenol and N-acetylcysteine on wound healing. The wound healing process is a multifaceted sequence of activities associated with tissue restoration process. A number of investigations and clinical studies have been performed to determine new approaches for the improvement of wound healing. A total of 30 rats were divided into 3 equal groups. A linear 2-cm incision was made in the rats' skin. No treatment was administered in the first (control) group. Dexpanthenol cream was administered to the rats in the second group and 3% N-acetylcysteine cream was administered to the rats in the third group. The wound areas of all of the rats were measured on certain days. On the 21st day, all wounds were excised and histologically evaluated. The epithelialization and granulation rates between the groups were revealed to be similar in microscopic evaluations. Although the fibrosis was remarkable in the control group as compared with the other groups, it was similar in N-acetylcysteine and dexpanthenol groups.



Angiogenesis rate was remarkable in the N-acetylcysteine group compared with the others. In multiple-comparison analysis, Dexpanthenol and N-acetylcysteine groups had similar results in terms of wound healing rates ($P < 0.05$), which were both higher than in the control group ($P > 0.05$). The efficacy of N-acetylcysteine in wound healing is comparable to dexpanthenol, and both substances can be used to improve wound healing.

PMID: 25583306 PMID: [PMC4400934](#) DOI: [10.9738/INTSURG-D-14-00227.1](#)

[J Pharm Sci.](#) 2008 Dec;97(12):5186-97. doi: 10.1002/jps.21368.

Mechanistic study of electroosmotic transport across hydrated nail plates: effects of pH and ionic strength.

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Abstract

The objective of this study was to investigate the effects of pH and ionic strength on electroosmotic transport in transungual iontophoresis. Transungual iontophoretic transport of model neutral permeants mannitol (MA) and urea (UR) across fully hydrated human nail plates in phosphate-buffered saline of different pH and ionic strengths were investigated in vitro. Two protocols were involved in the transport experiments with each protocol divided into stages including passive and iontophoresis transport at 0.1 and/or 0.3 mA. Nail plate electrical resistance and water uptake of nail clippings were measured at various pH and ionic strengths. In the pH study, electroosmosis enhanced the anodal transport of MA at pH 9 and cathodal transport at pH 3. The Peclet numbers of MA were more than two times higher than those of UR under these conditions. No significant electroosmosis enhancement was observed for MA and UR at pH 5. In the ionic strength study, a decrease in solution ionic strength from 0.7 to 0.04 M enhanced electroosmotic transport. Nail electrical resistance increased with decreasing the ionic strength of the equilibrating solution, but reached a plateau when the ionic strength was less than approximately 0.07 M. Solution pH and ionic strength had no significant effect on nail hydration. Under the studied pH and ionic strength conditions, the effects of electroosmosis were small compared to the direct-field effects in transungual iontophoretic transport of small to moderate size permeants.

PMID: 18386836 PMID: [PMC2614830](#) DOI: [10.1002/jps.21368](#)

[Dermatol Online J.](#) 2013 Nov 15;19(11):20392.

Urea: a comprehensive review of the clinical literature.

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Abstract

INTRODUCTION:

Urea is an organic compound that has been used clinically for dermatological diseases for more than a century. Urea is a potent emollient and keratolytic agent, making urea an effective monotherapy for



conditions associated with dry and scaly skin. A systematic review of the literature is needed to provide clinicians with evidence-based applications of urea in the treatment of dermatological diseases.

METHODS:

A PubMed search was conducted using the term "urea" combined with "skin," "ichthyosis," "psoriasis," "xerosis," "emollient," "onychomycosis," "dermatitis," and "avulsion." A total of 81 publications met inclusion criteria and were evaluated. Treatment indication(s), test agents, number of subjects, treatment protocols, results, and side effects were recorded.

RESULTS:

Effective treatment with urea has been reported for the following conditions: ichthyosis, xerosis, atopic dermatitis/eczema, contact dermatitis, radiation induced dermatitis, psoriasis/seborrheic dermatitis, onychomycosis, tinea pedis, keratosis, pruritus, and dystrophic nails. Furthermore, urea has been used with other medications as a penetration enhancing agent. Mild irritation is the most common adverse event, proving urea to be a safe and tolerable topical drug without systemic toxicity.

DISCUSSION/CONCLUSION:

Urea is a safe, effective dermatologic therapy with wide-ranging clinical utility and minimal, non-systemic side effects. In order to optimize patient care, dermatologists should be well informed with regards to urea's indications and efficacy.

PMID: 24314769

[Mycopathologia](#). 2013 Apr;175(3-4):281-6. doi: 10.1007/s11046-013-9622-7. Epub 2013 Feb 8.

Antifungal activity of nanocapsule suspensions containing tea tree oil on the growth of *Trichophyton rubrum*.

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Abstract

The aim of this study was to evaluate, for the first time, the antifungal efficacy of nanocapsules and nanoemulsions containing *Melaleuca alternifolia* essential oil (tea tree oil) in an onychomycosis model. The antifungal activity of nanostructured formulations was evaluated against *Trichophyton rubrum* in two different in vitro models of dermatophyte nail infection. First, nail powder was infected with *T. rubrum* in a 96-well plate and then treated with the formulations. After 7 and 14 days, cell viability was verified. The plate counts for the samples were 2.37, 1.45 and 1.0 log CFU mL⁽⁻¹⁾ (emulsion, nanoemulsion containing tea tree oil and nanocapsules containing tea tree oil, respectively). A second model employed nails fragments which were infected with the microorganism and treated with the formulations. The diameter of fungal colony was measured. The areas obtained were 2.88 ± 2.08 mm⁽²⁾, 14.59 ± 2.01 mm⁽²⁾, 40.98 ± 2.76 mm⁽²⁾ and 38.72 ± 1.22 mm⁽²⁾ for the nanocapsules containing tea tree oil, nanoemulsion containing tea tree oil, emulsion and



untreated nail, respectively. Nail infection models demonstrated the ability of the formulations to reduce *T. rubrum* growth, with the inclusion of oil in nanocapsules being most efficient.

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Microb Pathog. 2017 Dec;113:432-437. doi: [10.1016/j.micpath.2017.11.005](https://doi.org/10.1016/j.micpath.2017.11.005). Epub 2017 Nov 21.

Antimicrobial activity of *Melaleuca alternifolia* nanoparticles in polymicrobial biofilm in situ.

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Abstract

Microbial biofilms represent a challenge in the treatment of infections, due to the low efficacy of the antimicrobials. This study evaluated the antimicrobial effect of nanoparticles of *Melaleuca alternifolia* (TTO) in dental biofilm. Thirty-eight volunteers used an oral device in situ including four bovine enamel specimens for 07 days. From the fifth day four solutions were applied randomly for each specimen: Physiological Saline Solution (0.85% NaCl) (C+), Chlorhexidine 0.12% (CHX), *M. alternifolia* oil 0.3% (TTO), and a nanoparticle solution of 0.3% *M. alternifolia* oil (NPTTO). The nanoparticles of TTO were characterized for pH, IPD, medium size, zeta potential and Transmission Electron Microscopy. Antimicrobial activity was evaluated by viable microorganisms count and the structure of the biofilm by atomic force microscopy. The NPTTO presented pH 6.4, particle diameter of 197.9 ± 1 nm, polydispersion index of 0.242 ± 0.005 , zeta potential of -7.12 mV and $\pm 0:27$ spherical shape. The C+ resulted in 100% of bacterial vitality, while CHX, TTO and NPTTO showed 34.2%, 51.4% and 25.8%, respectively. The AFM images showed biofilms with an average roughness of 350 nm for C+, 275 nm for CHX, 500 nm for TTO and 100 nm for NPTTO. The NPTTO demonstrated excellent antimicrobial activity in the biofilm formed in situ and will possibly be used in future for the treatment/prevention of oral biofilms.

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Role of antibiofilm-antimicrobial agents in controlling device-related infections

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Abstract

Objectives: To assess the effects of N-acetylcysteine (NAC) on organism viability in planktonic and biofilm phases, biofilm thickness, and extracellular polysaccharide content.

Methods: We performed time-kill curves and broth macrodilution assays of bacterial and fungal clinical isolates with varying concentrations of NAC. We also created in vitro bacterial biofilms, incubated them with NAC or control, and then stained with propidium iodide and FITC-labeled concanavalin A. We measured biofilm thickness, number of non-viable cells, and fluorescent intensity as a marker of extracellular matrix via a confocal laser scanning microscope. All experiments were conducted in triplicate. Tested organisms included methicillin-sensitive and -resistant *Staphylococcus aureus* (MSSA, MRSA), *S. epidermidis*, vancomycin-resistant *Enterococcus faecalis* (VRE), *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Candida albicans* and *C. krusei*.

Results: NAC 80 mg/ml was uniformly bactericidal (>99.9% reduction) against all tested bacteria with no recoverable organisms after 30 minutes of incubation, but was fungistatic against candida species.

Minimum inhibitory and bactericidal concentrations of NAC ranged from 5-10 mg/ml. Biofilm thickness was significantly decreased in NAC-treated biofilms for all organisms except VRE. The number of non-viable cells in NAC-treated Gram-positive biofilms was increased ($p < 0.05$ for MRSA and VRE). NAC-treated Gram-negative biofilms had scant cellularity and lacked complex 3-dimensional structures that were characteristic of controls. Fluorescent intensity was similar in the experimental and control arms.

Conclusions: NAC is bactericidal against clinically relevant and drug-resistant bacteria and also leads to biofilm disruption. NAC has the potential for use as a novel agent for prevention or treatment of biofilm-related infections.

