SPECIAL EDITION SCIENCE & MEDICINE

Tolnaftate's Remarkable Transformation

Tolnaftate was synthesized in the early 1950s and is classified as a small molecule. It was first prescribed as an Rx drug for fifteen years. After millions of doses were administered, with only a statistically insignificant incidence of minor adverse reactions (pruritis and skin irritation), Tolnaftate was classified as a Category 1 GRASE (Generally Recognized As Safe and Effective) drug. As a result of its efficacy and safety, the FDA approved tolnaftate as a topical antifungal OTC in 1965. In 1972, the U.S. Food and Drug Administration (FDA) developed the OTC Review to review the safety and efficacy of OTC ingredients, doses, formulations, and labeling used in medicines available to consumers without a prescription. The FDA issued the Final Monograph for tolnaftate on September 23, 1994[1].

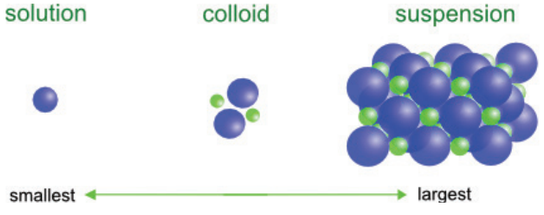
An FDA Final Monograph is a regulatory standard for ingredients in a product. Any OTC medicine that conforms to the monograph may be manufactured and sold without an individual product license. The approval of the Final Monograph made it easy for drug manufacturers to make products with tolnaftate as the only Active Pharmaceutical Ingredient (API). Pre-approval by the FDA for drugs marketed under a drug monograph is not required. The Final Monograph outlines the labeling of the product inner container and the outer packaging. It lists in precise detail the form, type, and manner by which, a drug facts box, instructions, indications, warnings, and other information are to be displayed. As long as the manufacturer abides by the precise language in the monograph, no review or further approval from the FDA is necessary. The phrase "This product is not effective on scalp or nails" is specified in the FDA monograph and MUST be displayed on all tolnaftate products. This language was required because, in 1994, tolnaftate was available only in suspension medications.

The monograph system does not relieve a manufacturer from a New Drug Application (NDA) if an inactive ingredient in their product is specifically not approved for use in human drug products. For example, combining tolnaftate with colloidal silver, DMSO, or another drug, would require an NDA. This is because the FDA has not approved: 1) colloidal silver for use in human medicine; 2) has not approved any OTC medication containing DMSO for human use; and 3) the Final Monograph specifies that "The active ingredient of the product consists of any one of the following within the specified concentration established for each ingredient"[1] making it unlawful to combine monographed antifungal drugs – like tolnaftate and undecylenic acid, for example. It's also unlawful to promote any product as "FDA Approved." The FDA does not approve products. To be clear, there has been some abuse of the monograph system.

In its original form, tolnaftate is freely soluble in chloroform, acetone, and formaldehyde. It is sparingly soluble in ether and slightly soluble in ethanol and methanol. Tolnaftate is insoluble in oil or water. For almost 40 years since its development, tolnaftate's insolubility in water and oil resulted in its use in medications that were slow acting suspensions of tolnaftate. This was in stark contrast to tolnaftate's effectiveness in vitro against a broad spectrum of organisms.

Tolnaftate is an antifungal compound which has activity against such species as Epidermophyton, Microsporum, Trichophyton, and Malassezia furfur.[2,3] Its proposed mechanism of action includes the inhibition of squalene epoxidase.[4] The use of tolnaftate to inhibit squalene epoxidase activity in Candida albicans (500 μM)[5] and in Trichophyton rubrum (IC50 = 51.5 nM) has been studied.[6] The activities of various antifungal compounds, including tolnaftate, against dermatophytes from different species, have been investigated.[7] An in vitro investigation of tolnaftate penetration into the human nail plate in the presence of N-acetyl-L-cysteine or 2-mercaptoethanol has been described.[8] The effect of tolnaftate on the biosynthesis of lipids in Aspergillus niger protoplasts has been studied.[9]

In practice, tolnaftate's broad spectrum of activity against organisms with sensitivity was clearly restricted by the lack of a vehicle to transport the drug to the site of involvement. Tolnaftate's insolubility in oil and water made penetration of the skin slow at best, and penetration of the nail practically impossible. Then, fifty years after the development of tolnaftate, everything changed with the development of Soluble Tolnaftate[10] by The Tetra Corporation. The Soluble Tolnaftate in Formula 7®, Formula 3®, and FungiFoam® has a particle size of less than 1nm. Soluble Tolnaftate is not affected by gravity – tolnaftate (solute) will not settle in the jojoba oil (solvent) making it indefinitely stable. Furthermore, in these innovative products, the tolnaftate cannot be filtered out by the skin or nail. When the product is absorbed, no tolnaftate is left behind on the surface of the treated area. By contrast, in a suspension - particles are affected by gravity and will settle out in 30 minutes to 48 hours. Suspensions leave the tolnaftate on the skin's surface and on the dorsal side of the nail. See explanation below.



Solution = .1 to 1nm Particles

In a Solution - Particles of Tolnaftate are not affected by gravity – Soluble Tolnaftate (solute) will not settle (indefinitely stable). Tyndall Effect is the scattering of light by particles in a mixture. Solutions allow light to pass through. In a solution, the solute (tolnaftate) takes on the properties of the solvent (jojoba oil) = Soluble Tolnaftate[10]. Smallest commercially filter available today is 25 nanometers.

Soluble Tolnaftate[10]

No filter available today can filter solutions. **Solutions, therefore, are not filterable and by all standards, are the optimal delivery form for Active Pharmaceutical Ingredients.**

Colloids = 1 to 1000nm Particles

In a Colloid - Particles are slightly affected by gravity. Brownian Motion states that the random erratic movement of the solvent colliding with the solute particles keeps the solute from settling. They separate slowly on standing: ranging from 60 years (for 1 nanometer particles) to 2 days (for 1 micron particles). The rate of separation is determined by particle size. Colloids are filterable if they are larger than 25 nanometers. Also, they are filterable by semi-permeable membranes found in cell walls of all living organisms.

Suspension = >1000nm Particles

In a Suspension - Particles are affected by gravity and will settle out in 30 minutes to 48 Hours. Tyndall Effect is the scattering of light by particles in a mixture. Suspensions DO NOT allow light to pass through. In a suspension, the solute DOES NOT take on the properties of the solvent. **Suspensions are filterable. Also, they are filterable by semi-permeable membranes found in cell walls of all living organisms.**

With Soluble Tolnaftate[10] the solute (tolnaftate) takes on the properties of the solvent (jojoba oil). Soluble Tolnaftate[10] is not filterable by the semi-permeable membranes found in cell walls of all living organisms. All suspensions of tolnaftate are filterable, therefore are slow to penetrate, if at all.

Today, Soluble Tolnaftate[10] is the gold standard for penetration and delivery of tolnaftate to the site of involvement. The Tetra Corporation has been the innovation leader in tolnaftate technology since 1989. We do not share our technology; we do not manufacture private label products; our process is a closely-guarded trade secret. So, if it's not a Tetra product, it's not Soluble Tolnaftate.[10]

Our newest innovation, Formula 7® - The Solution, is now available and Formula 7® - Rapid MicroGel (Patent Pending) will be launched later this year. Call Tetra today at 800-826-0479 to learn more about our doctor-dispensed products.

References:

(1) CFR Title 21, Chapter I, Subchapter D, Part 333 - TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE, Subpart C - Topical Antifungal Drug Products, Section 333.210 - Antifungal active ingredients.

(2) The Merck Index, 12th ed., Entry# 9656.

(3) Martindale The Extra Pharmacopoeia, 31st ed., Reynolds, J. E. F., ed., Royal Pharmaceutical Society (London, UK: 1996), p. 416.

(4) Barrett-Bee, K., and Dixon, G., Ergosterol biosynthesis inhibition: a target for antifungal agents. Acta Biochim. Pol., **42(4)**, 465-479 (1995).

(5) Georgopapadakou, N. H., and Bertasso, A., Effects of squalene epoxidase inhibitors on Candida albicans. Antimicrob. Agents Chemother., **36(8)**, 1779-1781 (1992).

(6) Favre, B., and Ryder, N. S., Characterization of squalene epoxidase activity from the dermatophyte Trichophyton rubrum and its inhibition by terbinafine and other antimycotic agents. Antimicrob. Agents Chemother., **40(2)**, 443-447 (1996).

(7) Favre, B., et al., Comparison of in vitro activities of 17 antifungal drugs against a panel of 20 dermatophytes by using a microdilution assay. J. Clin. Microbiol., **41(10)**, 4817-4819 (2003).

(8) Kobayashi, Y., et al., 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. Chem. Pharm. Bull. (Tokyo), **46(11)**, 1797-1802 (1998).

(9) Oh, K., et al., Effects of antimycotics on the biosynthesis of cellular macromolecules in Aspergillus niger protoplasts. Mycopathologia, **122(3)**, 135-141 (1993).

(10) The Tetra Corporation - U.S. Patent # 4,810,498 and U.S. Patent # RE 36-253