BORON-CONTAINING SMALL MOLECULES

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 14/537,771, filed Nov. 10, 2014, which is a continuation of U.S. patent application Ser. No. 14/201,459, filed Mar. 7, 2014, now U.S. Pat. No. 9,353,133, which is a continuation of U.S. patent application Ser. No. 13/356,488, filed Jan. 23, 2012, now U.S. Pat. No. 8,722,917, which is a continuation of U.S. patent application Ser. No. 12/629,753, filed Dec. 2, 2009, now U.S. Pat. No. 8,115,026, which is a divisional of U.S. patent application Ser. No. 11/505,591, filed Aug. 16, 2006, now U.S. Pat. No. 7,767,657, which claims the benefit of U.S. Provisional Patent Application No. 60/755,227, filed Dec. 30, 2005, and the benefit of U.S. Provisional Patent Application No. 60/746,361, filed May 3, 2006, all of which are incorporated by reference in their entirety for all purposes. U.S. patent application Ser. No. 11/505,591 is also a continuation-in-part of U.S. patent application Ser. No. 11/357,687, filed Feb. 16, 2006, now U.S. Pat. No. 7,582,621, which claims the benefit of U.S. Provisional Patent Application No. 60/654,060, filed Feb. 16, 2005, all of which are incorporated by reference in their entirety for all purposes. U.S. patent application Ser. No. 14/537,771 is also a continuation-in-part of U.S. patent application Ser. No. 13/874,329, filed Apr. 30, 2013, now U.S. Pat. No. 8,889,656, which is a continuation of U.S. patent application Ser. No. 13/224,252, filed Sep. 1, 2011, now U.S. Pat. No. 8,440,642, which is a continuation of U.S. patent application Ser. No. 12/507,010, filed Jul. 21, 2009, now U.S. Pat. No. 8,039,451, which is a continuation of U.S. patent application Ser. No. 11/357,687, filed Feb. 16, 2006, now U.S. Pat. No. 7,582,621, which claims the benefit of 60/654,060, filed Feb. 16, 2005, all of which are incorporated by reference in their entirety for all purposes.

BACKGROUND FOR THE INVENTION

Infections of the nail and hoof, known as ungual and/or periungual infections, pose serious problems in dermatology. These ungual and/or periungual can be caused by sources such as fungi, viruses, yeast, bacteria and parasites. Onychomycosis is an example of these serious ungual and/or periungual infections and is caused by at least one fungus. Current treatment for ungual and/or periungual infections generally falls into three categories: systemic administration of medicine; surgical removal of all or part of the nail or hoof followed by topical treatment of the exposed tissue; or topical application of conventional creams, lotions, gels or solutions, frequently including the use of bandages to keep these dosage forms in place on the nail or hoof. All of these approaches have major drawbacks. The following discussion is particularly directed to drawbacks associated with current treatment of ungual and/or periungual antifungal infections.

Long term systemic (oral) administration of an antifungal agent for the treatment of onychomycosis is often required to produce a therapeutic effect in the nail bed. For example, oral treatment with the antifungal compound terbinafine typically requires administration of 200 to 400 mg/day for 12 weeks before any significant therapeutic benefit is realized. Such long term, high dose systemic therapy can have significant adverse effects. For example, terbinafine has been reported to have liver toxicity effects and reduces testosterone levels in blood due to adverse effects on the testes.

Patient compliance is a problem with such long term therapies especially those which involve serious adverse effects. Moreover, this type of long term oral therapy is inconvenient in the treatment of a horse or other ruminants afflicted with fungal infections of the hoof. Accordingly, the risks associated with parenteral treatments generate significant disincentive against their use and considerable patient non-compliance.

Surgical removal of all or part of the nail followed by topical treatment also has severe drawbacks. The pain and discomfort associated with the surgery and the undesirable cosmetic appearance of the nail or nail bed represent significant problems, particularly for patients more sensitive to physical appearance. Generally, this type of treatment is not realistic for ruminants such as horses.

Topical therapy has significant problems too. Topical dosage forms such as creams, lotions, gels etc., can not keep the drug in intimate contact with the infected area for therapeutically effective periods of time. Bandages have been used to hold drug reservoirs in place in an attempt to enhance absorption of the pharmaceutical agent. However the bandages are thick, awkward, troublesome and generally lead to poor patient compliance.

Hydrophilic and hydrophobic film forming topical antifungal solutions have also been developed. These dosage forms provide improved contact between the drug and the nail. Topical formulations for fungal infection treatment have largely tried to deliver the drug to the target site (an infected nail bed) by diffusion across or through the nail.

Nail is more like hair than stratum corneum with respect to chemical composition and permeability. Nitrogen is the major component of the nail attesting to the nail's proteinaceous nature. The total lipid content of mature nail is 0.1-1.0%, while the stratum corneum lipid is about 10% w/w. The nail is 100-200 times thicker than the stratum corneum and has a very high affinity and capacity for binding and retaining antifungal drugs. Consequently little if any drug penetrates through the nail to reach the target site. Because of these reasons topical therapy for fungal infections have generally been ineffective.

Compounds known as penetration or permeation enhancers are well known in the art to produce an increase in the permeability of skin or other body membranes to a pharmacologically active agent. The increased permeability allows an increase in the rate at which the drug permeates through the skin and enters the blood stream. Penetration enhancers have been successful in overcoming the impermeability of pharmaceutical agents through the skin. However, the thin stratum corneum layer of the skin, which is about 10 to 15 cells thick and is formed naturally by cells migrating toward the skin surface from the basal layer, has been easier to penetrate than nails. Moreover, known penetration enhancers have not proven to be useful in facilitating drug migration through the nail tissue.

Antimicrobial compositions for controlling bacterial and fungal infections comprising a metal chelate of 8-hydroxyquinoline and an alkyl benzene sulfonic acid have been shown to be efficacious due to the increased ability of the oleophilic group to penetrate the lipoid layers of micro-cells. The compounds however, do not effectively increase the ability to carry the pharmaceutically active antifungal through the cornified layer or stratum corneum of the skin. U.S. Pat. No. 4,602,011, West et al., Jul. 22, 1986; U.S. Pat. No. 4,766,113, West et al., Aug. 23, 1988.

Therefore, there is a need in the art for compounds which can effectively penetrate the nail. There is also need in the