TRANSDERMAL AND TOPICAL ADMINISTRATION OF VITAMINS USING BASIC PERMEATION ENHANCERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Ser. No. 12/343,000 filed on Dec. 23, 2008. U.S. Ser. No. 12/343,000 is a continuation of Ser. No. 10/860,887, filed on Jun. 3, 2004. Ser. No. 10/860,887 is a divisional of U.S. Ser. No. 10/177,436 filed on Jun. 20, 2002. U.S. Ser. No. 10/177,436 is a continuation in part of U.S. Ser. No. 09/972,008 filed on Oct. 4, 2001 and now issued as U.S. Pat. No. 6,582,724, which is a continuation in part of U.S. Ser. No. 09/738,410 filed on Dec. 14, 2000 and now issued as U.S. Pat. No. 6,586,000, which is a continuation in part of U.S. Ser. No. 09/569,889 filed on May 11, 2000 and now abandoned, which is a continuation in part of U.S. Ser. No. 09/465,098 filed on Dec. 16, 1999 and now abandoned; and is a continuation in part of U.S. Ser. No. 09/738,395 filed on Dec. 14, 2000, which is a continuation in part of U.S. Ser. No. 09/607,892 filed on Jun. 30, 2000, now abandoned, the disclosures of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] This invention relates generally to the topical and transdermal administration of pharmacologically or cosmeceutically active agents, and more particularly relates to methods and compositions for enhancing the flux of pharmacologically active agents through a body surface by treatment with a basic permeation enhancer.

BACKGROUND OF THE INVENTION

[0003] The delivery of drugs through the skin provides many advantages; primarily, such a means of delivery is a comfortable, convenient and noninvasive way of administering drugs. The variable rates of absorption and metabolism encountered in oral treatment are avoided, and other inherent inconveniences, e.g., gastrointestinal irritation and the like, are eliminated as well. Transdermal drug delivery also makes possible a high degree of control over blood concentrations of any particular drug.

[0004] Skin is a structurally complex, relatively thick membrane. Molecules moving from the environment into and through intact skin must first penetrate the stratum corneum and any material on its surface. They must then penetrate the viable epidermis, the papillary dermis, and the capillary walls into the blood stream or lymph channels. To be so absorbed, molecules must overcome a different resistance to penetration in each type of tissue. Transport across the skin membrane is thus a complex phenomenon. However, it is the cells of the stratum corneum, which present the primary barrier to absorption of topical compositions or transdermally administered drugs. The stratum corneum is a thin layer of dense, highly keratinized cells approximately 10-15 microns thick over most of the body. It is believed to be the high degree of keratinization within these cells as well as their dense packing which creates in most cases a substantially impermeable barrier to drug penetration. With many drugs, the rate of permeation through the skin is extremely low without the use of some means to enhance the permeability of the skin.

[0005] Numerous chemical agents have been studied as a means of increasing the rate at which a drug penetrates through the skin. As will be appreciated by those in the field, chemical enhancers are compounds that are administered along with the drug (or in some cases the skin may be pretreated with a chemical enhancer) in order to increase the permeability of the stratum corneum, and thereby provide for enhanced penetration of the drug through the skin. Ideally, such chemical penetration enhancers or "permeation enhancers," as the compounds are referred to herein, are compounds that are innocuous and serve merely to facilitate diffusion of the drug through the stratum corneum. The permeability of many therapeutic agents with diverse physicochemical characteristics may be enhanced using these chemical enhancement means. However, there are skin irritation and sensitization problems associated with high levels of certain enhancers.

[0006] Accordingly, although there are many chemical methods of enhancing permeation, there remains an ongoing need for a method that is highly effective in increasing the rate at which a drug permeates the skin, does not result in skin damage, irritation, sensitization, or the like, and can be used to effect transdermal delivery of even high molecular weight drugs such as peptides, proteins, and nucleic acids. It has now been discovered that basic permeation enhancers as described herein are highly effective permeation enhancers, and provide all of the aforementioned advantages relative to known permeation enhancers. Furthermore, in contrast to many conventional enhancers, transdermal administration of drugs with basic permeation enhancers, employed at the appropriate levels, does not result in systemic toxicity.

SUMMARY OF THE INVENTION

[0007] One aspect of the invention pertains to a method for enhancing the flux of a drug through a body surface, comprising: (a) administering the drug to a localized region of a human patient's body surface; and (b) administering a basic permeation enhancer to the localized region, the enhancer comprising a pharmaceutically acceptable base and being present in an amount effective to provide a pH within the range of about 8.0-13.0 at the localized region of the body surface during administration of the drug and to enhance the flux of the drug through the body surface without causing damage thereto. The pharmaceutically acceptable base can be an inorganic or an organic base.

[0008] Another aspect of the invention relates to a composition for the enhanced delivery of a drug through a body surface, comprising a formulation of: (a) a therapeutically effective amount of the drug; (b) a pharmaceutically acceptable base, in an amount effective to provide a pH within the range of about 8.0-13.0 at the body surface during administration of the drug and to enhance the flux of the drug through the body surface without causing damage thereto; and (c) a pharmaceutically acceptable carrier suitable for topical or transdermal drug administration. In one aspect of the invention the pH is about 8.0-11.5 and in another aspect, the pH is about 8.5-10.5. The formulation is typically aqueous. The pharmaceutically acceptable base can be an inorganic or an organic base.

[0009] Yet another aspect of the invention pertains to a system for the enhanced topical or transdermal administration of a drug, comprising: (a) at least one drug reservoir containing the drug and a pharmaceutically acceptable base, in an amount effective to enhance the flux of the drug through the body surface without causing damage thereto; (b) a means for maintaining the system in drug and base transmitting