overlayer is sized such that it extends beyond the drug reservoir so that adhesive on the overlayer comes into contact with the body surface. The overlayer is useful because the adhesive/drug reservoir layer may lose its adhesion a few hours after application due to hydration. By incorporating an adhesive overlayer, the delivery system will remain in place for the required period of time.

[0266] Other types and configurations of transdermal drug delivery systems may also be used in conjunction with the method of the present invention, as will be appreciated by those skilled in the art of transdermal drug delivery. See, for example, Ghosh, *Transdermal and Topical Drug Delivery Systems* (Interpharm Press, 1997), particularly Chapters 2 and 8.

[0267] As with the topically applied formulations of the invention, the drug and enhancer composition contained within the drug reservoir(s) of these laminated systems may comprise a number of additional components. In some cases, the drug and enhancer may be delivered neat, i.e., in the absence of additional liquid. In most cases, however, the drug will be dissolved, dispersed or suspended in a suitable pharmaceutically acceptable vehicle, typically a solvent or gel. Other components that may be present include preservatives, stabilizers, surfactants, solubilizers, additional enhancers, and the like.

[0268] The invention accordingly provides a novel and highly effective means for increasing the flux of an active agent through the body surface (skin or mucosal tissue) of a human or animal. The base enhancers discussed herein, employed in specific amounts relative to a formulation or drug reservoir, may be used as permeation enhancers with a wide variety of drugs and drug types, including free acids, free bases, acid addition salts of basic drugs, basic addition salts of acidic drugs, nonionizable drugs, peptides and proteins. Surprisingly, the increase in permeation is not accompanied by any noticeable tissue damage, irritation, or sensitization. The invention thus represents an important advance in the field of drug delivery.

[0269] It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications will be apparent to those skilled in the art to which the invention pertains. Furthermore, the practice of the present invention will employ, unless otherwise indicated, conventional techniques of drug formulation, particularly topical and transdermal drug formulation, which are within the skill of the art. Such techniques are fully explained in the literature. See *Remington: The Science and Practice of Pharmacy,* cited supra, as well as Goodman & Gilman's *The Pharmacological Basis of Therapeutics,* 10th Ed.(2001).

[0270] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to practice the methods as well as make and use the compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. and pressure is at or near atmospheric. The following abbreviations will be used in accordance with the definitions set out below.

EXAMPLES

[0271]

ABBREVIATIONS

DI	Deionized
HPMC	Hydroxypropylmethylcellulose
HPMCP	Hydroxypropylmethylcellulose phthalate
PG	Propylene glycol
PIB	Polyisobutylene

Methods

Preparation of Round Disc Samples

[0272] Each formulation was coated onto a release liner and dried in an oven at 55° C. for two hours to remove water and other solvents. The dried drug-in-adhesive/release liner film was laminated to a backing film. The backing/drug-in-adhesive/release liner laminate was then cut into round discs with a diameter of 11/16 inch.

Measurement of Permeation of Drugs through Human Cadaver Skin

[0273] The in vitro permeation of drugs through human cadaver skin was performed using Franz-type diffusion cells with a diffusion area of 1 cm^2 . The volume of receiver solution was 8 ml. Human cadaver skin was cut to a proper size and placed on a flat surface with the stratum corneum side facing up. The release liner was peeled away from the disc laminate. The backing/drug-in-adhesive film was placed and pressed on the skin with the adhesive side facing the stratum corneum. The skin/adhesive/backing laminate was clamped between the donor and receiver chambers of the diffusion cell with the skin side facing the receiver solution.

Measurement of pH

[0274] The pH of the patches was measured using the following procedures. A 2.5 cm^2 circular patch was punched out. Ten ml purified water was pipetted into a glass vial, and a stir bar was added. The liner was removed from the patch and placed in the vial along with the patch. The vial was then placed on a stir plate and the water/patch/liner mixture was stirred for 5 minutes, at which point the liner was removed from the vial and discarded. The vial was again placed on a stir plate and stirring continued for an additional 18 hours. After 18 hours, the stir bar was removed from the vial and the pH of the solution determined using a calibrated pH meter.

Example 1

[0275] An in vitro skin permeation study was conducted using three estradiol transdermal systems, designated Est-1, Est-2, and Est-3, the compositions of which are set forth in Table 1. Round disc samples were prepared as described in