pyl]-N,N,N-triethylammonium (DOTMA) in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[0243] Micelles are known in the art and are comprised of surfactant molecules arranged so that their polar headgroups form an outer spherical shell, while the hydrophobic, hydrocarbon chains are oriented towards the center of the sphere, forming a core. Micelles form in an aqueous solution containing surfactant at a high enough concentration so that micelles naturally result. Surfactants useful for forming micelles include, but are not limited to, potassium laurate, sodium octane sulfonate, sodium decane sulfonate, sodium dodecane sulfonate, sodium lauryl sulfate, docusate sodium, decyltrimethylammonium bromide, dodecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, tetradecyltrimethyl-ammonium chloride, dodecylammonium chloride, polyoxyl 8 dodecyl ether, polyoxyl 12 dodecyl ether, nonoxynol 10 and nonoxynol 30. Micelle formulations can be used in conjunction with the present invention either by incorporation into the reservoir of a topical or transdermal delivery system, or into a formulation to be applied to the body surface.

[0244] Microspheres, similarly, may be incorporated into the present formulations and drug delivery systems. Like liposomes and micelles, microspheres essentially encapsulate a drug or drug-containing formulation. They are generally, although not necessarily, formed from lipids, preferably charged lipids such as phospholipids. Preparation of lipidic microspheres is well known in the art and described in the pertinent texts and literature.

[0245] Various additives, known to those skilled in the art, may be included in the topical formulations. For example, solvents, including relatively small amounts of alcohol, may be used to solubilize certain drug substances. Other optional additives include opacifiers, antioxidants, fragrance, colorant, gelling agents, thickening agents, stabilizers, surfactants and the like. Other agents may also be added, such as antimicrobial agents, to prevent spoilage upon storage, i.e., to inhibit growth of microbes such as yeasts and molds. Suitable antimicrobial agents are typically selected from the group consisting of the methyl and propyl esters of p-hydroxybenzoic acid (i.e., methyl and propyl paraben), sodium benzoate, sorbic acid, imidurea, and combinations thereof.

[0246] For those drugs having an unusually low rate of permeation through the skin or mucosal tissue, it may be desirable to include a second permeation enhancer in the formulation in addition to the inorganic or organic base enhancer, although in a preferred embodiment the base enhancer is administered without any other permeation enhancers. Any other enhancers should, like the base enhancer, minimize the possibility of skin damage, irritation, and systemic toxicity. Examples of classes of suitable secondary enhancers (or "co-enhancers") include, but are not limited to, fatty acids, both saturated and unsaturated; fatty alcohols; bile acids; nonionic surfactants, including esters of fatty acids, fatty (long-chain alkyl or alkenyl) esters of monohydric alcohols, diols, and polyols, diols and polyols that are both esterified with a fatty acid and substituted with a polyoxyalkylene, polyoxyalkylene fatty acid esters, polyoxyalkylene fatty ethers, polyoxyalkylene fatty ethers, and polyglyceryl fatty acid esters; amines; amides; N-alkylazacycloalkanones and N-alkyl-azacycloalkenones; hydrocarbon solvents; terpenes; lower alkyl esters; cyclodextrin enhancers; nitrogen-containing heterocycles; sulfoxides; and urea and its derivatives.

[0247] Specific examples of suitable co-enhancers include ethers such as diethylene glycol monoethyl ether (available commercially as Transcutol®, Gattefosse SA) and diethylene glycol monomethyl ether; surfactants such as sodium laurate, sodium lauryl sulfate, cetyltrimethylammonium bromide, benzalkonium chloride, Poloxamer (231, 182, 184), Tween (20, 40, 60, 80) and lecithin; alcohols such as ethanol, propanol, octanol, benzyl alcohol, and the like; fatty acids such as lauric acid, oleic acid and valeric acid; fatty acid esters such as isopropyl myristate, isopropyl palmitate, methylpropionate, and ethyl oleate; polyols and esters thereof such as polyethylene glycol, and polyethylene glycol monolaurate; amides and other nitrogenous compounds such as urea, dimethylacetamide, dimethylformamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, ethanolamine, diethanolamine and triethanolamine; terpenes; alkanones; and organic acids, particularly citric acid and succinic acid. Azone® and sulfoxides such as dimethylsulfoxide and decylmethylsulfoxide may also be used, but are less preferred. Percutaneous Penetration Enhancers, eds. Smith et al. (CRC Press, 1995) provides an excellent overview of the field and further information concerning possible secondary enhancers for use in conjunction with the present invention.

[0248] The formulation may also contain irritation-mitigating additives to minimize or eliminate the possibility of skin irritation or skin damage resulting from the drug, the base enhancer, or other components of the formulation. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin; and chloroquine. The irritant-mitigating additive, if present, may be incorporated into the formulation at a concentration effective to mitigate irritation or skin damage, typically representing not more than about 20 wt %, more typically not more than about 5 wt %, of the formulation.

[0249] The concentration of the active agent in the formulation will typically depend upon a variety of factors, including the disease or condition to be treated, the nature and activity of the active agent, the desired effect, possible adverse reactions, the ability and speed of the active agent to reach its intended target, and other factors within the particular knowledge of the patient and physician. Preferred formulations will typically contain on the order of about 0.5-50 wt %, preferably about 5-30 wt %, active agent.

V. Drug Delivery Systems

[0250] An alternative and preferred method involves the use of a drug delivery system, e.g., a topical or transdermal "patch," wherein the active agent is contained within a laminated structure that is to be affixed to the skin. In such a structure, the drug composition is contained in a layer, or "reservoir," underlying an upper backing layer that serves as the outer surface of the device during use. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs.

[0251] Accordingly, another embodiment of the invention is a system for the enhanced topical or transdermal administration of a drug, comprising: (a) at least one drug reservoir