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(54) **ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION**

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(57) **ABSTRACT**

A composition including a surfactant and at least one alkyl glycoside and/or saccharide alkyl ester and a drug. The surfactant composition(s) when admixed with a drug is non-toxic and non-irritating, while stabilizing and increasing the bioavailability of the drug. The invention also provides compositions that enhance absorption of drugs via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route of a patient, including but not limited to insulin, glucagon and exendin-4.

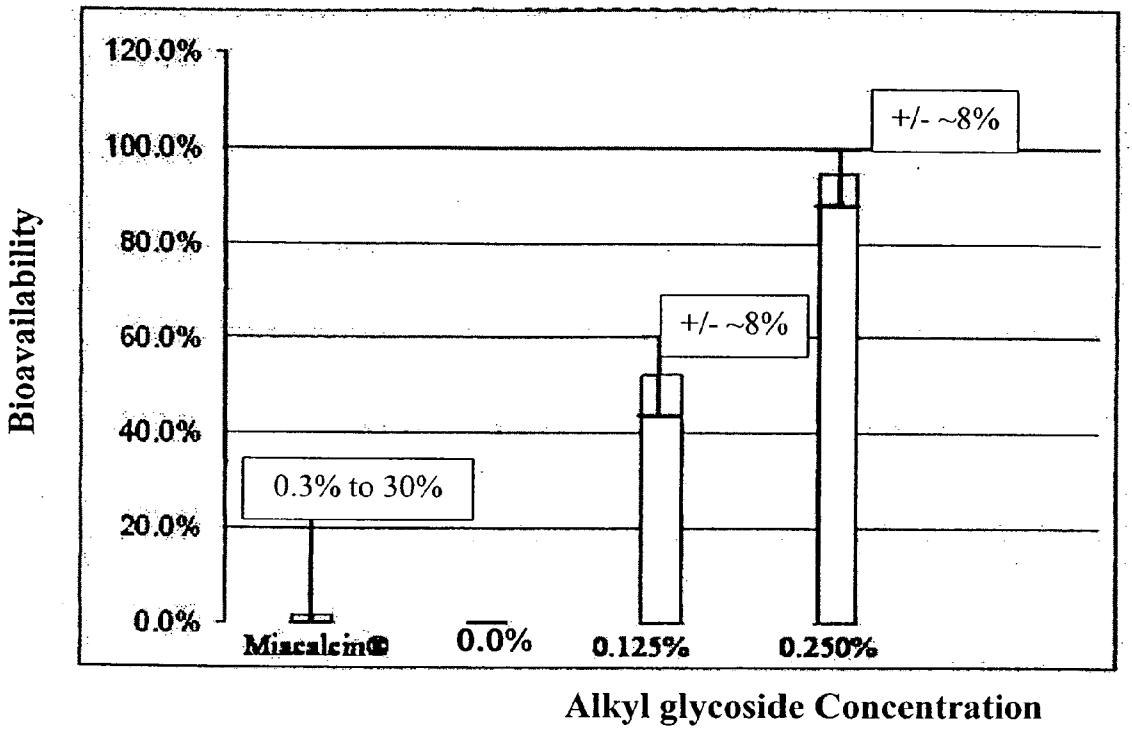

FIG. 1

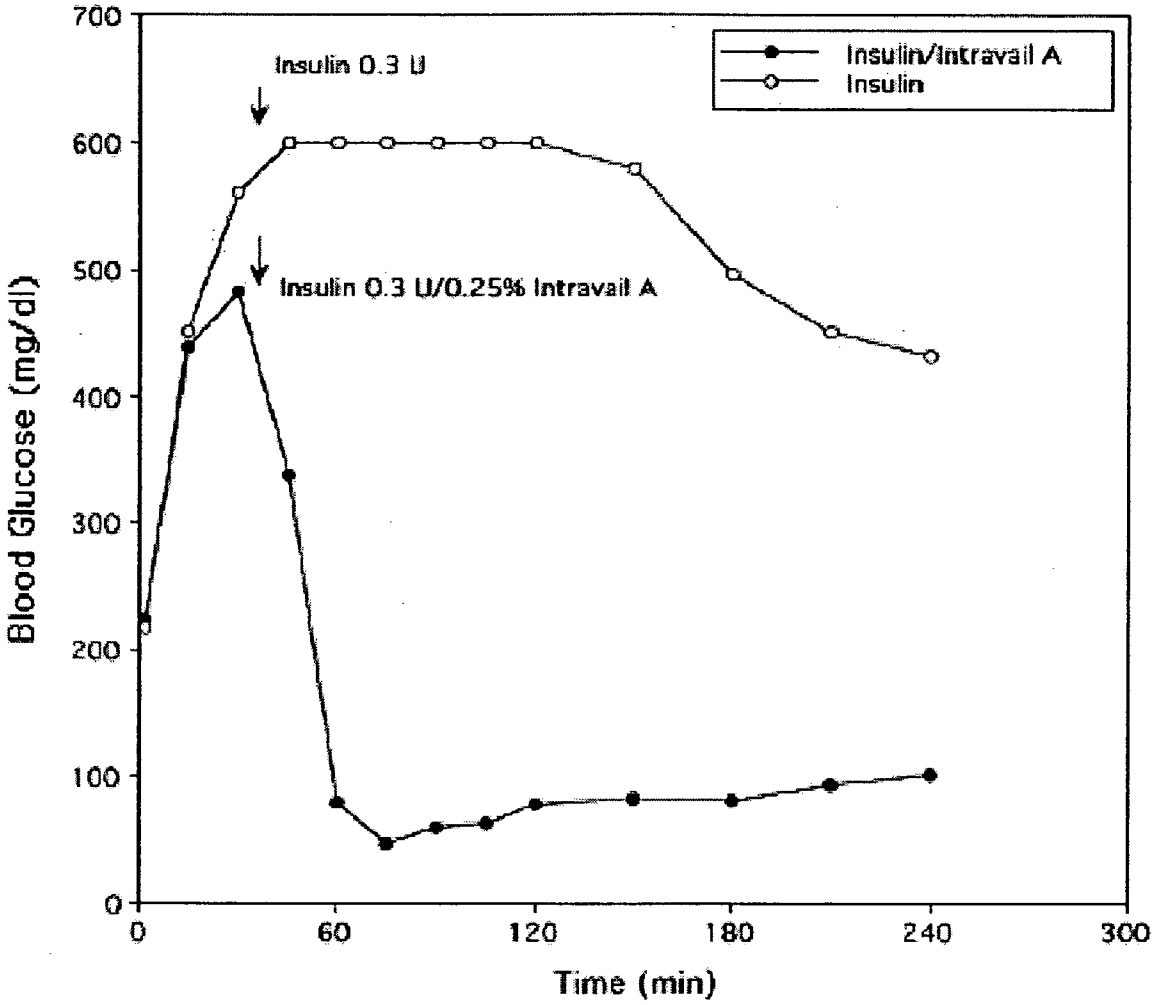

FIG. 2

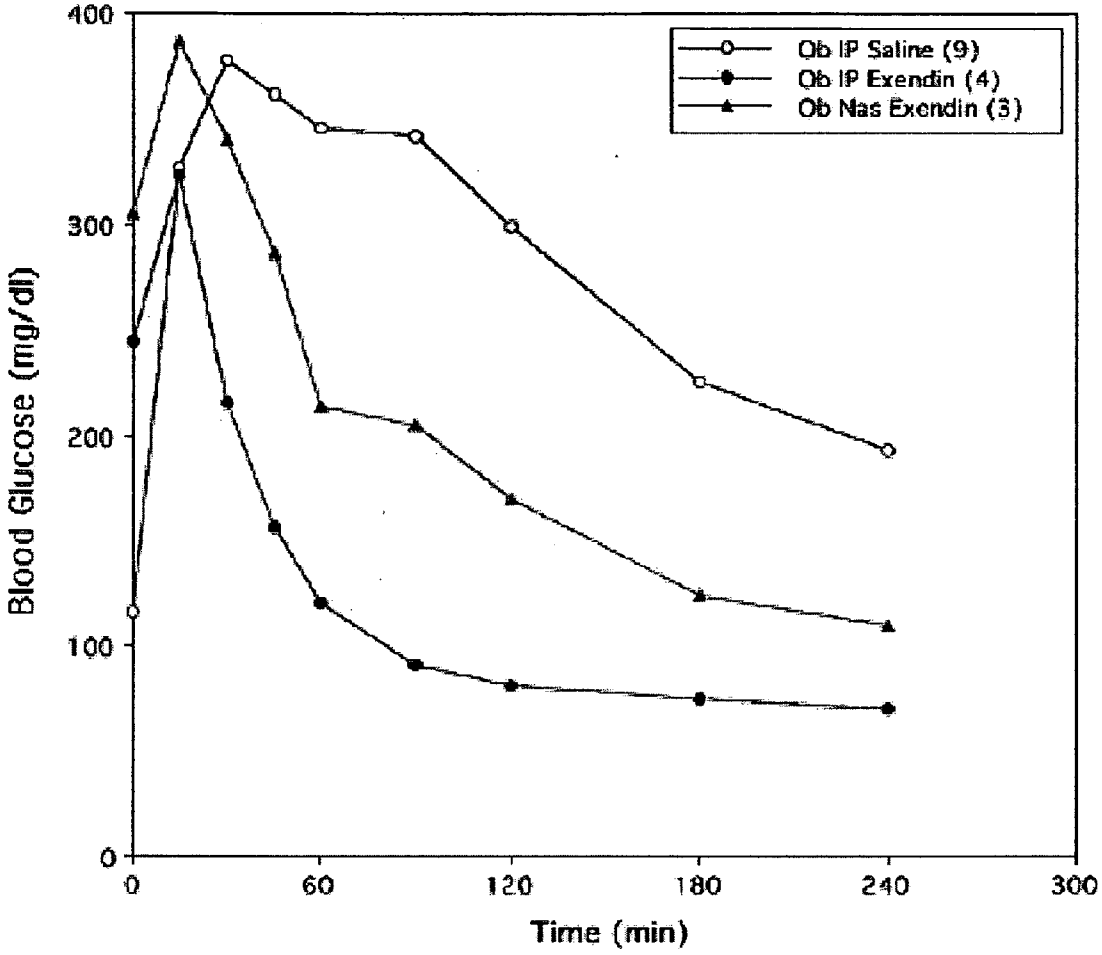

FIG. 3

ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

CROSS REFERENCE TO RELATED APPLICATION(S)

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. application Ser. No. 60/649,958 filed Feb. 3, 2005, now pending; the benefit under 35 USC § 119(e) of U.S. application Ser. No. 60/637,284 filed Dec. 17, 2004, now pending; the benefit under 35 USC § 119(e) of U.S. application Ser. No. 60/632,038 filed Nov. 30, 2004, now pending; the benefit under 35 USC § 119(e) of U.S. application Ser. No. 60/609,890 filed Sep. 14, 2004, now pending; and the benefit under 35 USC § 119(e) of U.S. application Ser. No. 60/604,296 filed Aug. 25, 2004, now pending. The disclosure of each of the prior applications is considered part of and is incorporated by reference in the disclosure of this application.

FIELD OF THE INVENTION

[0002] The invention relates generally to non-irritating, non-toxic compositions providing enhanced bioavailability and more specifically to alkyl glycoside or saccharide alkyl ester compositions for delivery of therapeutic agents to a subject.

BACKGROUND INFORMATION

[0003] Therapeutic agents are often combined with various surfactants. Yet, surfactants are frequently irritating to the skin and other tissues, including mucosal membranes such as those found in the nose, mouth, eye, vagina, rectum, esophagus, intestinal tract, and the like. Many surfactants also cause proteins to denature, thus destroying their biological activity. Another serious limitation to the development and use of such agents is the ability to deliver them safely, non-invasively, efficiently and stably to the site of action. Therefore, an ideal enhancing surfactant will stabilize the therapeutic agent, be non-toxic and non-irritable to the skin or mucosal surfaces, and enhance the passage or absorption of the therapeutic agent through various membrane barriers without damaging the structural integrity and biological function of the membrane and increase bioavailability of the agent.

SUMMARY OF THE INVENTION

[0004] The present invention is based, in part, on the development of a therapeutic composition containing a drug enhancing agent useful for increasing the absorption and bioavailability of the drug, while at the same time avoiding various adverse toxic effects of drug. In particular, the drug enhancing agents of the invention contain a non-toxic surfactant consisting of at least an alkyl glycoside and/or saccharide alkyl ester. One advantage of the therapeutic compositions of the invention is that they permit administration and delivery of the therapeutic agents with high bioavailabilities at concentrations of enhancing agents that are dramatically below their so-called "no observable adverse effect levels" (their NOAEL's). Accordingly, the present invention provides compositions, including alkyl glycosides and/or saccharide alkyl esters and a therapeutic agent (e.g. small molecule organic drug molecules, low molecular weight heparin and inhibitory RNA), methods of administering and using the compositions e.g. via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or cerebral spinal fluid (CSF) delivery route, and methods of ameliorating a disease state in a subject by administration of such compositions

[0005] In one aspect, the present invention relates to a surfactant composition having at least one alkyl glycoside and/or at least one saccharide alkyl ester, and when admixed, mixed or blended with a therapeutic agent, a drug, or biologically active compound, the surfactant stabilizes the biological activity and increases the bioavailability of the drug.

[0006] Accordingly, in one aspect, the invention provides a therapeutic composition having at least one biologically active compound and at least one surfactant, wherein the surfactant further consists of at least one alkyl glycoside and/or saccharide alkyl ester or sucrose ester and wherein the therapeutic composition stabilizes the biologically active compound for at least about 6 months, or more, and from about 4° C. to about 25° C.

[0007] The invention also provides a method of administering a therapeutic composition having a surfactant including at least one alkyl glycoside and/or saccharide alkyl ester admixed, mixed, or blended with at least one therapeutic agent, or a drug, or biologically active compound, and administered or delivered to a subject, wherein the alkyl has from about 10 to 24, 10 to 20, 10 to 16, or 10 to 14 carbon atoms, wherein the surfactant increases the stability and bioavailability of the therapeutic agent.

[0008] In yet another aspect, the invention provides a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by administering the compound via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route when admixed, mixed or blended with an absorption increasing amount of a suitable surfactant, wherein the surfactant is a nontoxic and nonionic hydrophobic alkyl joined by a linkage to a hydrophilic saccharide. Such low molecular weight compounds include but are not limited to, nicotine, interferon, PYY, GLP-1, synthetic exendin-4, parathyroid hormone, human growth hormone, or a small organic molecule.

[0009] The present invention also provides a method of treating diabetes including administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell), a blood glucose reducing amount of a therapeutic composition, for example, an incretin mimetic agent or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of incretin mimetic agent or insulin and lowering the level of blood glucose and treating diabetes in the subject.

[0010] The present invention also provides a method of treating congestive heart failure in a subject including administering to the subject in need thereof via the oral, ocular, nasal, nasolacrimal, or inhalation delivery route, a

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