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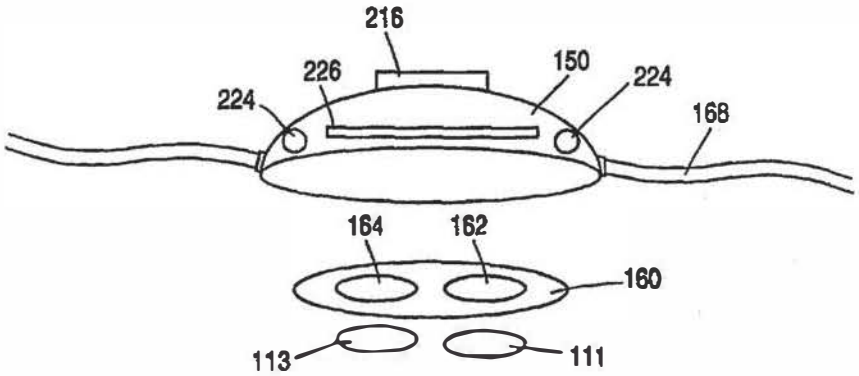

(57) Abstract

An iontophoresis apparatus for the transdermal monitoring of a target substance comprising: first and second collection reservoirs, the first collection reservoir comprising a first ionically conductive medium (111) and the second collection reservoir comprising a second ionically conductive medium (113); a first iontophoresis electrode (162) in contact with the first conductive medium (111) and a second iontophoresis electrode (164) in contact with the second conductive medium (113); a sensor for detecting the target substance contained within at least one conductive medium (111, 113); and an iontophoretic power source (224). The conductive medium (111, 113) is either an ionically conductive hydrogel or a wicking material containing an ionically conductive medium. The invention also includes a collection reservoir for use with an iontophoresis apparatus for the transdermal monitoring of a target substance, the collection reservoir comprising an ionically conductive hydrogel having a pH in the range of from about 4.0 to about 10.0 and an enzyme reactive with the target substance. The invention also includes a method for using the transdermal monitoring apparatus. In particular, the invention is a method for continuous *in vivo* monitoring of the blood glucose level of a patient comprising the following steps: (a) placing a collection reservoir on a collection site on a tissue surface of the patient; (b) applying electrical energy to the collection site to move glucose or a glucose metabolite into the collection reservoir; (c) analyzing the collection reservoir for concentration of glucose or glucose metabolite; (d) correlating the concentration determined in step (c) with blood glucose level; and (e) performing steps (a)-(d) substantially continuously.

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IONTOPHORETIC SAMPLING DEVICE AND METHOD

BACKGROUND OF THE INVENTION

This invention relates generally to the transdermal monitoring of the concentration of substances in blood and, in particular, to the use of reverse iontophoresis or electroosmosis for the continuous transdermal monitoring of blood glucose.

Many diagnostic tests are performed on humans by evaluating the amount or existence of substances in the blood. One blood substance of interest is blood glucose. Typically, blood samples are removed from a subject by either using a syringe or by pricking the skin. The amount of blood drawn, of course, depends upon the amount of blood required for testing. Thereafter, the blood sample may be prepared and specifically tested for a variety of substances using techniques well known in the art.

Over the last few years methods of determining the concentration of blood glucose or other substances without drawing blood have been developed. For example, Stanley U.S. Patent No. 5,139,023 describes a transdermal glucose monitoring apparatus that uses a permeability enhancer, such as a natural bile salt, to facilitate transdermal movement of glucose along the concentration gradient between the higher glucose concentration in the interstitial fluid and the lower glucose concentration in the receiving medium. In some embodiments, the receiving medium is the aqueous portion of a hydrogel support adhered to the subject's skin. Stanley measured the glucose concentration within the hydrogel by removing the

hydrogel from the subject's skin, placing the hydrogel in water and letting the glucose diffuse out of the hydrogel into the water. The water was then analyzed for glucose concentration.

Sembrowich U.S. Patent No. 5,036,861 describes a glucose monitor that collects the subject's sweat through a skin patch attached to the subject's wrist. Sembrowich describes the use of iontophoresis to transdermally introduce a gel into the subject's skin. The gel contains a cholinergic agent for stimulating the secretion mechanism of the eccrine sweat gland and agents that minimize or prevent loss of glucose from the sweat as it travels from the sweat gland to the skin patch. The Sembrowich device uses electrodes to measure the glucose level in the collected sweat by some unspecified method.

Schoendorfer U.S. Patent No. 5,076,273 describes a method and apparatus for determination of chemical species in body fluid. Sweat expressed from the subject's skin is collected in a patch adhered to the subject's skin. The patch concentrates the sweat in a binder layer by driving off a portion of the collected water. The collected analyte binds with a specific binding partner in the patch to present a visual indication of its presence in the patch.

Schroeder U.S. Patent No. 5,140,985 discloses a sweat-collecting device mounted on a subject. The device has an electrode-based glucose detection system that can give a qualitative indication of blood glucose concentration.

Glikfeld U.S. Patent No. 5,279,543 describes the use of iontophoresis to sample a substance through skin into a receptor chamber on the skin surface. In one embodiment, Glikfeld describes an in vitro device consisting of two gel electrodes attached to one side of

hairless mouse skin. Radiolabeled glucose is placed on the other side of the skin, and current is applied to the electrodes for a period of time. The electrodes are then analyzed for radioactivity content by conventional liquid scintillation counting. (See Glikfeld col. 7, line 51, to col. 8, line 1.) Glikfeld suggests that this sampling procedure can be combined with a specific glucose biosensor or glucose selective electrodes, but Glikfeld does not describe how that combination might be achieved. (See Glikfeld col. 9, lines 27-34.)

SUMMARY OF THE INVENTION

This invention improves on prior art transdermal monitoring methods and devices by providing an iontophoretic sampling device with an integrated sensor for monitoring the blood concentration of target substances or constituents noninvasively.

A general object of this invention is to provide a means of extracting substances in the blood through the skin using reverse iontophoresis or electroosmosis. In a preferred embodiment, one or more collection reservoirs are held in contact with the subject's skin. The reservoirs contain a conductive medium and are in turn in contact with electrodes and a means for providing electric potential or current between the collection reservoir site and another site on the subject's skin. The collection reservoirs are also in contact with a means for sensing and/or quantifying the concentration of a target substance.

This invention is particularly advantageous over drawing blood from a subject when extensive time-consuming sample preparation is required to perform a diagnostic test on whole blood. This invention is also advantageous for neonates (who have a small blood volume) and for subjects who must have frequent testing.

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