EXHIBIT 1016:

U.S. PAT. NO. 6,733,655 TO DAVIES. ("THE '655 PATENT")

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Davies et al.

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(54) **MEASUREMENT OF SUBSTANCES IN LIQUIDS**

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(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(52) **U.S. Cl.** **205/775**; 205/777.5

(58) **Field of Search** 204/401, 403, 204/416, 424, 403.01, 403.1, 403.11, 403.12, 403.14; 205/775, 777.5

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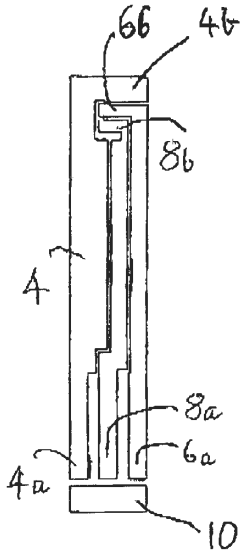
(57) **ABSTRACT**

In a method of measuring the concentration of a substance such as glucose in a sample liquid such as blood or interstitial fluid, a measuring device is provided having a working sensor part (**6***b*), a second working sensor part (**8***b*) and a reference sensor part (**4***b*). The sample liquid is applied to the measuring device and an electric current proportional to the concentration of the substance in the sample liquid is measured at each sensor part (**6***b*, **8***b*). The electric currents are compared to establish the difference. If the difference is greater than a predetermined threshold, an error indication is given. A disposable test strip with two working sensors (**6***b*, **8***b*) is also disclosed.

3 Claims, 2 Drawing Sheets



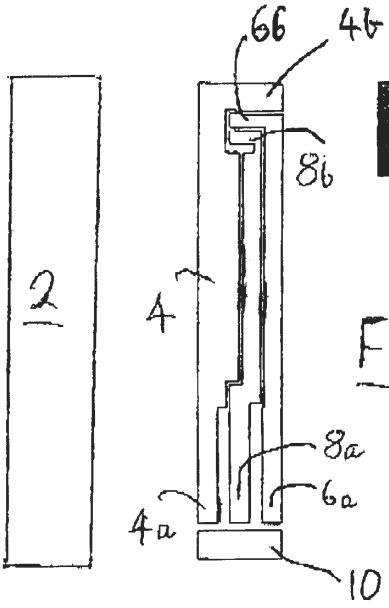
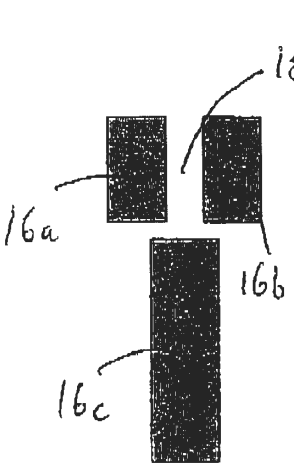
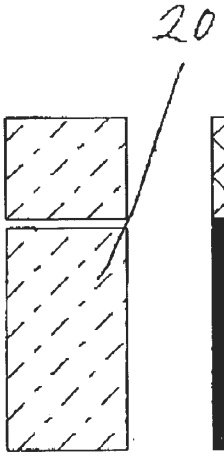


Fig 1 Fig 2 Fig 3 Fig 4





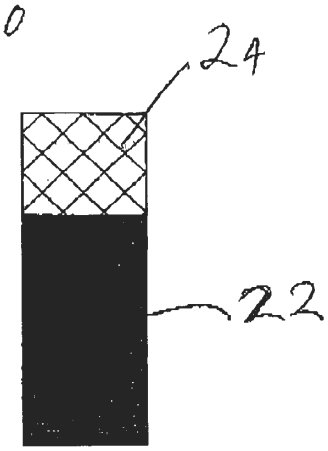


Fig 5 Fig 6 Fig 7

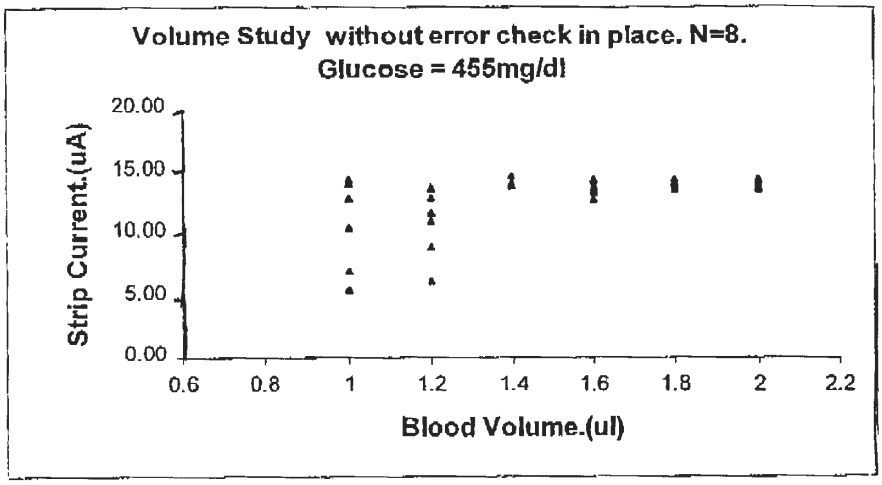


Fig 8

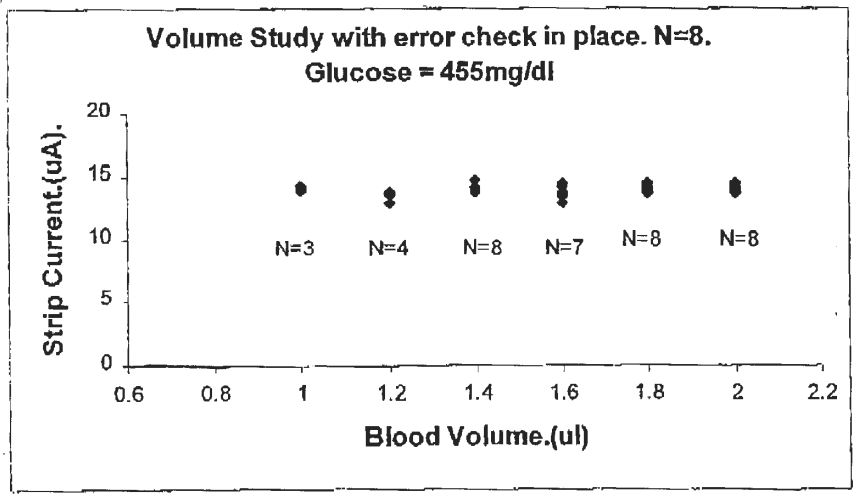


Fig 9

MEASUREMENT OF SUBSTANCES IN LIQUIDS

This invention relates to apparatus for measuring the concentration of a substance in a liquid and particularly, but not exclusively, to apparatus for measuring the concentration of glucose in blood.

Devices for measuring blood glucose levels are invaluable for diabetics, especially devices that may be used by the sufferers themselves since they may then monitor their own glucose levels and take an appropriate dose of insulin. Correspondingly therefore the accuracy of such devices is very important since an inaccurate reading could lead to the wrong level of insulin being administered which could be very harmful.

It is also the case that in all practical blood glucose measuring systems at least part of the device, i.e. that part which comes into contact with the sample blood, is disposable. This means that it is particularly important that the cost particularly of any disposable parts can be minimised as a user will generally need large numbers of them regularly.

Known glucose measuring devices now favour an electrochemical measurement method over old colorimetric methods. The general principle is that an electric current is measured between two sensor parts called the working and reference sensor parts respectively. The working sensor part comprises an electrode onto which is laid a layer of enzyme reagent which comprises an enzyme and an electron mediator compound. When a potential is applied across the sensor parts a current is generated by the transfer of electrons from the substance being measured (the enzyme substrate), via the enzyme and to the surface of the electrode. The current generated is proportional to both the area of the sensor part and also the concentration of glucose in the test sample. Since the area of the working sensor part is supposedly known, the electric current should be proportional to the glucose concentration.

It has been recognised in the art that inaccurate results are obtained if the working sensor part is not fully covered with blood since then its effective area is reduced. Various ways of dealing with this problem have been proposed, two of which are disclosed in U.S. Pat. No. 5,628,890 and U.S. Pat. No. 5,582,697. Both of these methods rely on a unidirectional flow of blood across the surface of the test strip and both initiate the test measurement by detecting the presence of the sample liquid at an electrode or sensor part located downstream of the working sensor part.

The problem of insufficient sample liquid being present and thus the working sensor part not being completely covered may of course be reduced by reducing the size of the working sensor part. However a small area for the working sensor part tends to give a greater variability in calibrated results.

The present inventors have realised that as well as incomplete coverage of the working sensor part, inaccurate results can also arise from occasional defects in the production of the test strips for such devices and also from accidental damage to the working sensor part e.g by a user. As far as the inventors are aware, the only practical way to deal with this problem so far has been to ensure that the printing process used to produce the test strips is as accurate as possible and to rely on adequate quality control.

It is an object of the present invention at least partially to alleviate the above-mentioned disadvantages and when viewed from a first aspect the invention provides a method of measuring the concentration of a substance in a sample liquid comprising the steps of:

providing a measuring device having a first working sensor part, a second working sensor part and a reference sensor part;

applying the sample liquid to said measuring device;

measuring an electric current at each sensor part proportional to the concentration of said substance in the sample liquid;

comparing the electric current from each of the working sensor parts to establish a difference parameter; and

giving an indication of an error if said difference parameter is greater than a predetermined threshold.

Thus it will be seen that in accordance with the invention the substance-concentration-dependent current is effectively measured twice and the two measurements compared so that each can be used as a check for the other.

The invention is considered to be particularly beneficial in the context of electrochemical assays in which the substance whose concentration it is desired to check, e.g. glucose in blood, reacts with an element of on the working sensor parts, e.g. an enzyme reagent, to generate charge carriers and thereby give rise to the electric current proportional to the concentration of the substance in the liquid.

Furthermore the measuring device used in this method is novel and inventive in its own right and thus from a second aspect the present invention provides a device for measuring the concentration of a substance in a sample liquid, said device comprising:

a reference sensor part,

a first working sensor part for generating charge carriers in proportion to the concentration of said substance in the sample liquid; and

a second working sensor part also for generating charge carriers in proportion to the concentration of said substance in the sample liquid.

Thus it will be seen that in accordance with the invention the measuring device compares the current passed by two working sensor parts as a result of their generation of charge carriers and gives an error indication if the two currents are too dissimilar—i.e. the current at one sensor part differs too greatly from what would be expected from considering the current at the other. Not only can this method detect when one of the sensor parts has not been properly covered with sample liquid, but it can also detect if there is a manufacturing defect in either sensor part or if either has been damaged after manufacture, since even with complete coverage of the working sensor parts, an anomalous current will arise at the affected sensor part in such circumstances.

In accordance with the invention the only type of defect or damage which would not necessarily be recognised is one which affected both of the working sensor parts to the same degree. However, this is logically less likely than a defect affecting a single working sensor part and is thus an improvement over the prior art. In practice such a likelihood is considered to be negligible. In any event the invention is not limited to providing just two working sensor parts and the skilled person could therefore choose to provide three or more working sensor parts to further reduce the probability that they are all affected by an identical defect.

Looking at the invention another way, it provides an arrangement whereby for a given total area of working sensor part and thus a given minimum sample volume, detection of inadequate fill and of defects or damage to the working sensor part can be provided by separating the area of the working sensor part into two.

Some or all of the sensor parts may be provided as part of an integrated device. Preferably however at least the working sensor parts are provided on a removable test

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