



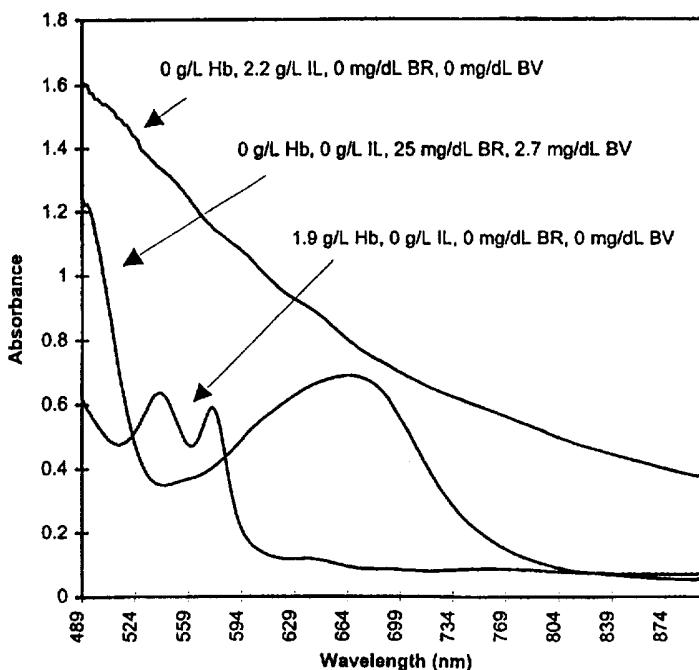
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : G01N 33/96</p>	<p>A1</p>	<p>(11) International Publication Number: WO 97/47972 (43) International Publication Date: 18 December 1997 (18.12.97)</p>
<p>(21) International Application Number: PCT/CA97/00418 (22) International Filing Date: 12 June 1997 (12.06.97) (30) Priority Data: 9612264.3 12 June 1996 (12.06.96) GB (71)(72) Applicant and Inventor: SAMSOONDAR, James [CA/CA]; 5556 Whistler Crescent, Mississauga, Ontario L4A 3R5 (CA). (74) Agent: RUDOLPH, John, R.; Gowling, Strathy & Henderson, Suite 1020, 50 Queen Street North, Kitchener, Ontario N2H 6M2 (CA).</p>		<p>(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

(54) Title: CALIBRATOR MATERIAL FOR INSTRUMENTS WHICH MEASURE INTERFERENTS IN SERUM AND PLASMA SPECIMENS

(57) Abstract

A quality control material is disclosed which is used to monitor the calibration or used for recalibration of instruments used to screen for interferents in serum or plasma specimens. In particular, the quality control material disclosed is used to monitor instrument calibrations or used for recalibration for instruments which assess the amount of hemolysis, turbidity, bilirubinemia and biliverdinemia, either separately, or any two, or any three, or all four simultaneously, in plasma or serum samples. The quality control material does not contain any blood products such as plasma lipids, bile pigments, or hemoglobin, is stable at room temperature, and is ready for use with up to four constituents.



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CALIBRATOR MATERIAL FOR INSTRUMENTS WHICH MEASURE INTERFERENTS IN SERUM AND PLASMA SPECIMENS**TECHNICAL FIELD**

This invention is in the field of spectrophotometric determinations of concentrations of substances in solution and relates to a quality control (QC) material for monitoring instrument precision on a daily basis. In particular the QC material is used to monitor instruments which are used to screen for serum or plasma specimen quantities of various interferents, by measurement of the near infrared (NIR) radiation and the adjacent visible radiation transmitted through a sample in a labelled tube, a pipette tip, or any similar material through which radiation can pass. The material can also serve as calibrators.

10 BACKGROUND OF INVENTION

Clinical laboratory tests are routinely performed on the serum or plasma of whole blood. In a routine assay, red blood cells are separated from plasma by centrifugation, or red blood cells and various plasma proteins are separated from serum by clotting prior to centrifugation. Hemoglobin (Hb), light-scattering substances like lipid particles, and bile pigments bilirubin (BR) and biliverdin (BV) are typical substances which will interfere with and affect spectrophotometric and other blood analytical measurements. Such substances are referred to as interferents, and they can be measured spectrophotometrically. The presence of such interferents affects the ability to perform tests on the serum or plasma and as such can be said to compromise specimen integrity. An apparatus or instrument used for measuring interferents in serum and plasma i.e., assess specimen integrity, is a substitute for visual inspection. The interferents may be regarded as analytes, with respect to the instrument used to measure the interferents. Because quantitative results from the determination of the concentration of such interferents are reported based on specific calibration algorithms, there is a need to monitor calibration performance daily.

Internal quality control is a process used by all clinical laboratories for monitoring instrument calibration performance, particularly precision or reproducibility. It involves testing a stable material for the analyte(s) in question on a daily basis, and establishing target values for each analyte(s). Any stable material with similar spectral characteristics at selected wavelengths as the interferences under consideration, may be used as QC material, as long as a target value for the particular analyte can be assigned to it. Also, deviation from the target values resulting in violation of some pre-established rules, e.g., Westgard's multi-rules, should indicate a need for calibration adjustment or recalibration. Usually QC materials are tested daily, and at low, medium and high levels, in order to cover the dynamic range of a given assay. For any analyte, as long as the pre-established rules are not violated, the calibration algorithm for that analyte may be considered valid.

Accuracy or agreement with the true value or actual concentration of a particular analyte is usually not the primary concern with internal QC, therefore an accurate amount of the analyte does not have to be present in the QC material. However, concentrations of the interferences can be assigned to the QC material, and their predicted and assigned values can be used to adjust the initial calibration algorithms.

When recalibration is indicated, a series of 3 to 5 QC samples with assigned analyte concentrations (may be regarded as calibrators), can be used to make calibration adjustments; recalibration is not a simple process, and adjustment of the initial calibration for biases may be preferred.

DISCLOSURE OF INVENTION

The present invention provides a material which is able to allow for monitoring the calibration of spectrophotometric instruments which are used to measure concentrations of interferences using near infrared radiation and the adjacent visible radiation, and at the same time is stable at room temperature for a considerable period of time. The material can also be used to make calibration adjustments for biases, when necessary. This is also regarded as recalibration..

In its broad aspect the invention provides a quality control material for monitoring the calibration of instruments used to screen for interferences in serum or plasma specimens. In another aspect, the invention provides a quality control material to monitor the instrument calibrations for hemolysis, turbidity, bilirubinemia and biliverdinemia, either separately, or any two, or any three, or all four simultaneously, depending on the make-up of the quality control material. The material does not contain any blood products such as plasma lipids, bile pigments, or hemoglobin, is stable at room temperature, and is ready for use with up to four constituents.

10 In a further aspect, the invention provides a material and a method for monitoring the calibration of instruments used to screen for interferences in serum or plasma specimens using the quality control material of this invention.

In yet a further aspect, the invention provides a material and a method for adjusting the calibrations for biases, by using the slope and intercept of the linear regression equation obtained by plotting the assigned values of the respective interferences on the x-axis, and the predicted values, based on the original calibration algorithms, on the y-axis. This procedure is regarded herein as recalibration.

20 In a further aspect, the invention provides a substance with an absorbance spectrum which mimics the combined presence of hemoglobin, turbidity, bilirubin, and biliverdin at selected wavelengths in the 490 to 1085 nm region, and which combination of up to four substances provides a consistent stable composition.

In a particular embodiment, the invention relates to a composition containing amaranth, titanium dioxide, and methyl orange and biliverdin dihydrochloride. This composition is preferably prepared in a phosphate buffered saline and pH adjusted to about 7.4. In an alternative embodiment of this invention a lipid emulsion of any source commercially available, e.g., Intralipid™ (IL), can be used in place of titanium dioxide, methylene blue can be used in place of biliverdin dihydrochloride, and 10 millimoles per liter sodium bicarbonate must be used instead of the phosphate buffered saline. For stability, the latter can be sterilized by autoclaving. The amaranth is used to mimic hemoglobin, the titanium dioxide or IL is used to

mimic turbidity, methyl orange is used to mimic bilirubin, and the methylene blue is used to mimic biliverdin. Other dyes may be used, for example, phenol red or basic fuchsin may be used to mimic hemoglobin; phenol red at acidic pH's or amaranth at slightly higher pH may be used to mimic bilirubin; azure, thionine, or toluidine blue O may be used in combination with amaranth, to mimic biliverdin. Also, in respect of alternatives to mimic turbidity, any substance which produces an absorbance pattern similar to the "apparent" absorbance in the region used by a calibration algorithm, may be used. One such example is copper sulfate. Turbidity causes an increase in the "apparent" absorbance. Apparent absorbance is based on the fact that transmitted light is measured and converted to absorbance units, therefore an instrument cannot distinguish true absorbance from loss of light due to scattering. In some cases, turbidity produces absorbance which is inversely proportional to wavelength. Turbidity is monitored by the slope of the absorbance curve at a single wavelength, namely, in the region greater than 800 nm.

In a preferred embodiment, the invention consists of amaranth, phenol red, copper sulfate, and toluidine blue O, in 100 millimoles per liter acetate buffer, pH 3 to 4. For low levels of BR, the amaranth can mimic both Hb and BR, making it possible to leave out phenol red. Within a given batch of QC material it is desirable to maintain a constant pH because spectral absorbance is affected by pH. Consequently, in a further aspect of the present invention, the pH of a given batch of QC material is maintained at a constant pH.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graphic representation of the absorbance spectra of three different serum specimens, with added amount of interferents as shown.

Figure 2 is a graphic representation of the absorbance spectra of three different mixtures of the quality control material, with predicted interferent concentrations as shown.

As used herein, g/L means grams per liter and mg/dL means milligrams per deciliter.

DESCRIPTION OF PREFERRED EMBODIMENTS

Instruments designed to measure Hb as a measure of hemolysis, turbidity as an equivalent IL concentration, BR and BV, may require calibration adjustment or recalibration over a period of time. As a means of monitoring the calibration of such instruments for precision or reproducibility, a material of the present invention with the following composition, namely amaranth, phenol red, copper sulfate, and toluidine blue O, in 100 millimoles per liter acetate buffer, pH 3 to 4, can be used for monitoring such calibration. The concentrations of the substances will determine the assigned or target values of the analytes.

Furthermore, so long as the combination of these four substances provides a consistent stable composition, such material may be used. However, as will be understood by those practising in the art, any of such substances can be used alone or as a combination of two or three such substances, in any combination, depending upon the situation to be monitored, so long as the combination provides a consistent stable composition.

The QC material was made by combining different amounts of stock solutions of amaranth, phenol red, copper sulfate, and toluidine blue O, dissolved in 100 millimoles per liter acetate buffer with pH values between 3 and 4; the change in pH changes the assigned values of the analytes. The concentration of a stock solution will only serve as a guide to the amount of the stock which should be added to make a lot of QC material; the assigned or target value of an analyte will be determined by averaging the predicted concentrations of the interferences, using the appropriate calibration algorithm installed in the instrument used.

Where the material is sterilized by autoclave for long term storage, target values must be assigned to lots with the same concentrations of "interferences", after sterilization; the predicted levels include any changes due to the sterilization process. As an alternative for long term storage, sodium azide may be added; in respect of an embodiment the present invention with pH around 3 to 4, the acidic pH may be sufficient to prevent microbial growth.

Different calibration algorithms may be developed for any one type of tube, pipette tip, or similar translucent material, and also algorithms may be developed for several different types of tubes combined or different translucent materials combined. The calibration algorithms installed in the instrument used to test the QC material of the present disclosure were developed for measurement in translucent pipette tips. These algorithms are as follows:

Hemolysis Algorithm

$$(g/L) \text{ Hb} = 30.14 (591\text{nm}) - 27.98 (610\text{nm})$$

where (Wnm) is the first derivative of the absorbance measurement at the wavelength specified.

Turbidity Algorithm

$$g/L \text{ IL} = 296.01 (900\text{nm}) - 0.04$$

where (Xnm) is the raw absorbance measurement at the wavelength specified.

Bilirubin Algorithm

$$\text{mg/dL BR} = 142.09 (511\text{nm}) + 89.9 (554\text{nm}) - 4.47$$

where (Ynm) is the first derivative of the absorbance measurement at the wavelength specified.

Biliverdin Algorithm

$$\text{mg/dL BV} = 160.29 (718\text{nm}) - 206.15 (781\text{nm}) + 1.42$$

where (Znm) is the first derivative of the absorbance measurement at the wavelength specified.

The calibration algorithms listed above are just examples, used to relate the spectra with their associated levels of the four analytes or interferents. The algorithms along with the absorbance measurements of respective samples are used to predict the levels of the four analytes. Sample spectra of three different serum specimens spiked with interferents, are shown in **Figure 1**, and sample spectra of three different mixtures of the QC material are shown in **Figure 2**. The predicted concentrations of the interferents in the QC samples are shown in **Figure 2**.

With respect to **Figures 1** and **2**, the serum specimens possessed varying degrees of hemolysis, turbidity, and bile pigmentation, and the QC specimens

mimicked serum or plasma specimens with different levels of interferents. Although the present description has been concerned with a QC material containing four substances, it is to be understood that the QC material can be used to monitor calibration for any one, two, three, or all four interferents
5 simultaneously.

While the invention has been particularly shown and described with reference to preferred embodiments, it will be understood by those skilled in the art that various other changes in form and detail may be made without departing from the spirit and scope of the invention.

WE CLAIM:

1. A quality control material, for use in an instrument designed to measure one or more of hemoglobin, turbidity, bilirubin, or biliverdin, wherein said instrument requires calibration or recalibration, said material comprising
5 one or more separate substances, one of each of which mimics hemoglobin, turbidity, bilirubin, and biliverdin, respectively, which substances provide a consistent, stable composition, whether said substances are used alone or in a combination of two or more of said substances.
- 10 2. The quality control material of claim 1 wherein pH is maintained at a constant value.
3. The quality control material of claim 1 wherein said substance used to mimic hemoglobin is selected from the group consisting of amaranth, phenol red and basic fuchsin.
- 15 4. The quality control material of claim 1 wherein said substance used to mimic turbidity is selected from the group consisting of titanium dioxide, copper sulfate and Intralipid™.
5. The quality control material of claim 1 wherein said substance used to
20 mimic bilirubin is selected from the group consisting of methyl orange, amaranth, and phenol red.
6. The quality control material of claim 1 wherein said substance used to mimic biliverdin is selected from the group consisting of methylene blue, azure, thionine and toluidine blue O.

- 5
7. The quality control material of claim 1 wherein said substance used to mimic hemoglobin is selected from the group consisting of amaranth, phenol red and basic fuchsin; said substance used to mimic turbidity is selected from the group consisting of titanium dioxide, copper sulfate and Intralipid™; said substance used to mimic bilirubin is selected from the group consisting of methyl orange, amaranth, and phenol red; and said substance used to mimic biliverdin is selected from the group consisting of methylene blue, azure, thionine and toluidine blue O.
- 10
8. The quality control material of claim 7 wherein pH is maintained at a constant value.
- 15
9. A quality control material, for use in an instrument designed to measure one or more of hemoglobin, turbidity, bilirubin, or biliverdin, wherein said instrument requires calibration or recalibration, said material comprising amaranth, phenol red, copper sulfate, and toluidine blue O in 100 millimoles per liter acetate buffer, and the pH of said material is 3 to 4.
- 20
10. The quality control material of claim 9 where amaranth is used to mimic both hemoglobin and bilirubin where low levels of bilirubin are involved.
- 25
11. A quality control material, for use in an instrument designed to measure one or more of hemoglobin, turbidity, bilirubin, or biliverdin, wherein said instrument requires calibration or recalibration, said material comprising amaranth, Intralipid™ and methylene blue, or azure, or thionine or toluidine blue O, and sodium bicarbonate.
12. A method of monitoring the calibration of an instrument which is designed to measure one or more of hemoglobin, turbidity, bilirubin or biliverdin said method comprising use of a quality control material, said material comprising one or more separate substances, one of each of which

mimics hemoglobin, turbidity, bilirubin, and biliverdin, respectively, which substances provide a consistent, stable composition, whether said substances are used alone or in a combination of two or more of said substances.

- 5 13. The method of claim 12 wherein pH is maintained at a constant value.
14. The method of claim 12 wherein said substance used to mimic hemoglobin is selected from the group consisting of amaranth, phenol red and basic fuchsin.
- 10 15. The method of claim 12 wherein said substance used to mimic turbidity is selected from the group consisting of titanium dioxide, copper sulfate and Intralipid™.
16. The method of claim 12 wherein said substance used to mimic bilirubin is selected from the group consisting of methyl orange, amaranth, and phenol red.
- 15 17. The method of claim 12 wherein said substance used to mimic biliverdin is selected from the group consisting of methylene blue, azure, thionine and toluidine blue O.
- 20 18. The method of claim 12 wherein said substance used to mimic hemoglobin is selected from the group consisting of amaranth, phenol red and basic fuchsin; said substance used to mimic turbidity is selected from the group consisting of titanium dioxide, copper sulfate and Intralipid™; said substance used to mimic bilirubin is selected from the group consisting of methyl orange, amaranth, and phenol red; and said substance used to mimic biliverdin is selected from the group consisting of
- 25 methylene blue, azure, thionine and toluidine blue O.

19. The method of claim 18 wherein pH is maintained at a constant value.
20. A method for monitoring the calibration of an instrument which is designed to measure one or more of hemoglobin, turbidity, bilirubin or biliverdin said method comprising use of a quality control material, said material
5 comprising amaranth, phenol red, copper sulfate, and toluidine blue O in 100 millimoles per liter acetate buffer, and the pH of said material is 3 to 4.
21. The method of claim 20 where amaranth is used to mimic both hemoglobin and bilirubin where low levels of bilirubin are involved.
22. A method for monitoring the calibration of an instrument which is designed
10 to measure one or more of hemoglobin, turbidity, bilirubin or biliverdin said method comprising use of a quality control material, said material comprising amaranth, Intralipid™ and methylene blue, or azure, or thionine or toluidine blue O, and sodium bicarbonate.
23. A method of recalibrating an instrument which is designed to measure one
15 or more of hemoglobin, turbidity, bilirubin or biliverdin said method comprising use of a quality control material, said material comprising one or more separate substances, one of each of which mimics hemoglobin, turbidity, bilirubin, and biliverdin, respectively, which substances provide a consistent, stable composition, whether said substances are used alone or
20 in a combination of two or more of said substances.
24. The method of claim 23 wherein pH is maintained at a constant value.
25. The method of claim 23 wherein said substance used to mimic hemoglobin is selected from the group consisting of amaranth, phenol red and basic fuchsin.

26. The method of claim 23 wherein said substance used to mimic turbidity is selected from the group consisting of titanium dioxide, copper sulfate and Intralipid™.
- 5 27. The method of claim 23 wherein said substance used to mimic bilirubin is selected from the group consisting of methyl orange, amaranth, and phenol red.
28. The method of claim 23 wherein said substance used to mimic biliverdin is selected from the group consisting of methylene blue, azure, thionine and toluidine blue O.
- 10 29. The method of claim 23 wherein said substance used to mimic hemoglobin is selected from the group consisting of amaranth, phenol red and basic fuchsin; said substance used to mimic turbidity is selected from the group consisting of titanium dioxide, copper sulfate and Intralipid™; said substance used to mimic bilirubin is selected from the group
15 consisting of methyl orange, amaranth, and phenol red; and said substance used to mimic biliverdin is selected from the group consisting of methylene blue, azure, thionine and toluidine blue O.
30. The method of claim 29 wherein pH is maintained at a constant value.
- 20 31. A method of recalibrating an instrument which is designed to measure one or more of hemoglobin, turbidity, bilirubin or biliverdin said method comprising use of a quality control material, said material comprising amaranth, phenol red, copper sulfate, and toluidine blue O in 100 millimoles per liter acetate buffer, and the pH of said material is 3 to 4.

32. The method of claim 31 where amaranth is used to mimic both hemoglobin and bilirubin where low levels of bilirubin are involved.
33. A method of recalibrating an instrument which is designed to measure one or more of hemoglobin, turbidity, bilirubin or biliverdin said method comprising use of a quality control material, said material comprising amaranth, Intralipid™ and methylene blue, or azure, or thionine or toluidine blue O, and sodium bicarbonate.
- 5

FIGURE 1

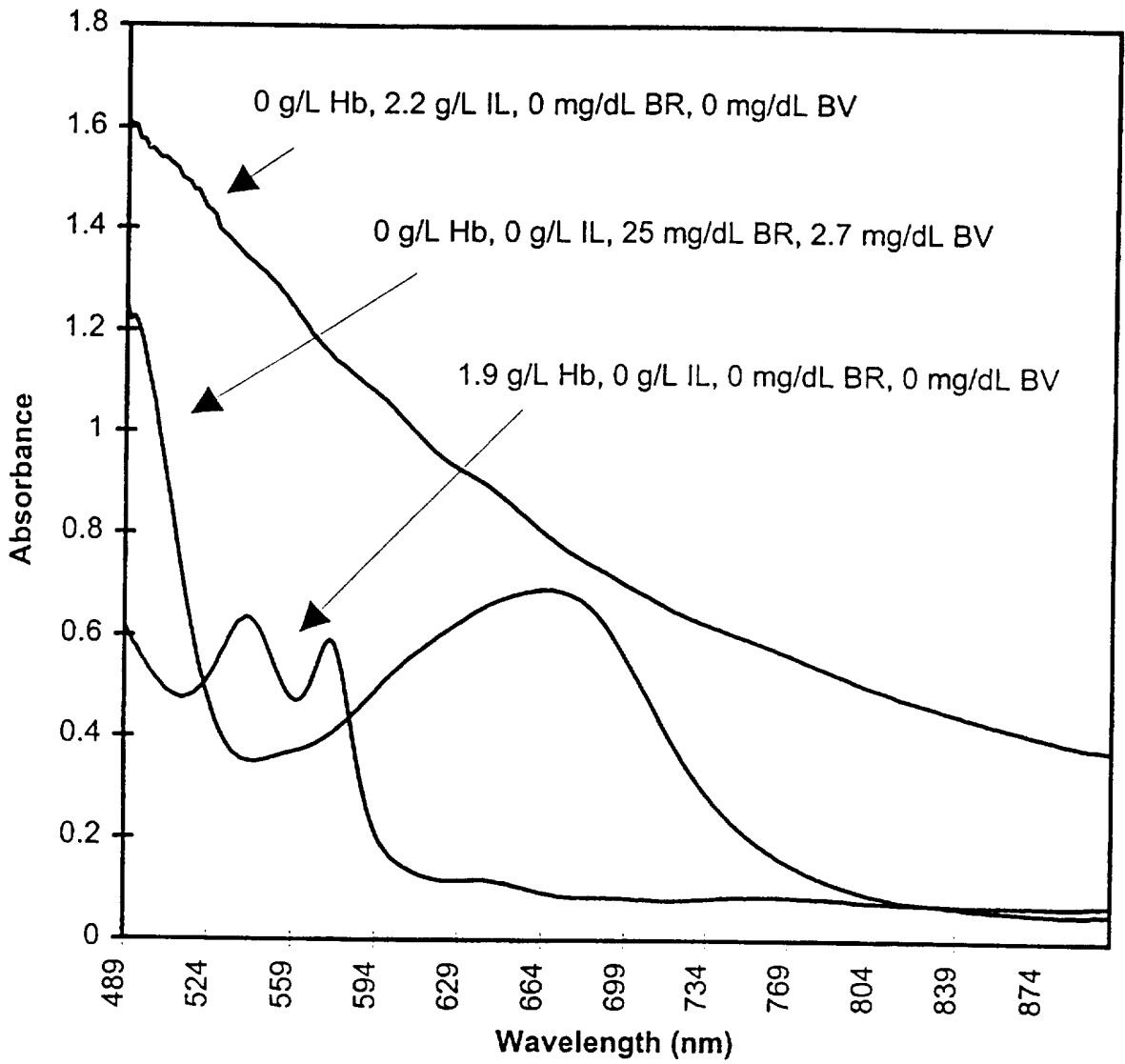
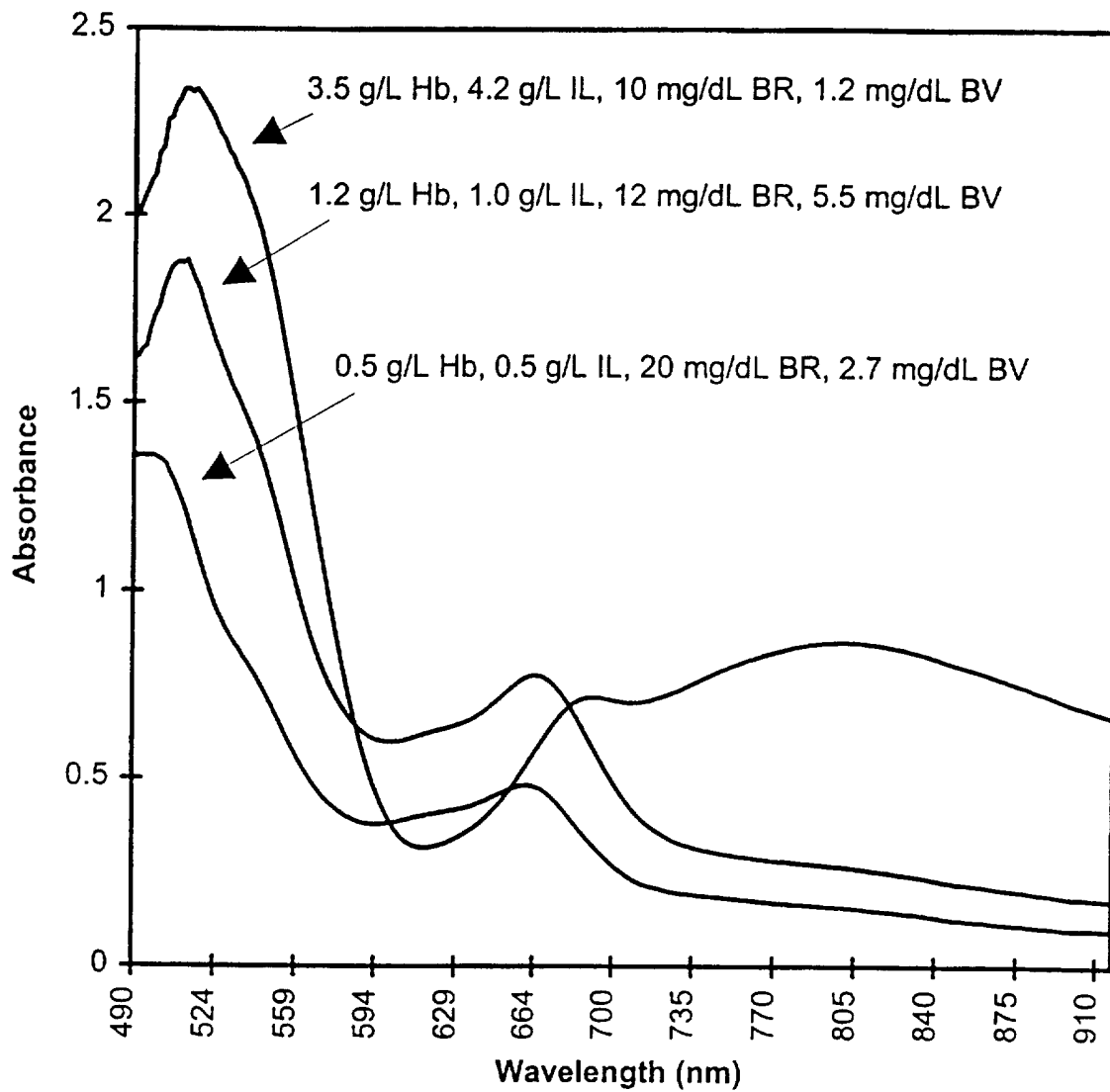


FIGURE 2



INTERNATIONAL SEARCH REPORT

In: tional Application No
PCT/CA 97/00418

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N33/96

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 132 399 A (CORNING GLASS) 30 January 1985 see abstract see page 1, line 29 - line 36 see page 3, line 1 - line 6 see page 3, line 13 - line 18 see page 4, line 18 - line 19 see page 8, line 14 - line 21 see page 9, line 1 - line 11	1, 12, 23
A	see claims 1, 2, 8, 10	2, 3, 5, 7-9, 11, 13, 14, 16, 18-22, 24, 25, 27, 29-33
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

1 October 1997

08/10/1997

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Fax: (+31-70) 340-3016

Authorized officer

Thomas, R.M.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 97/00418

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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