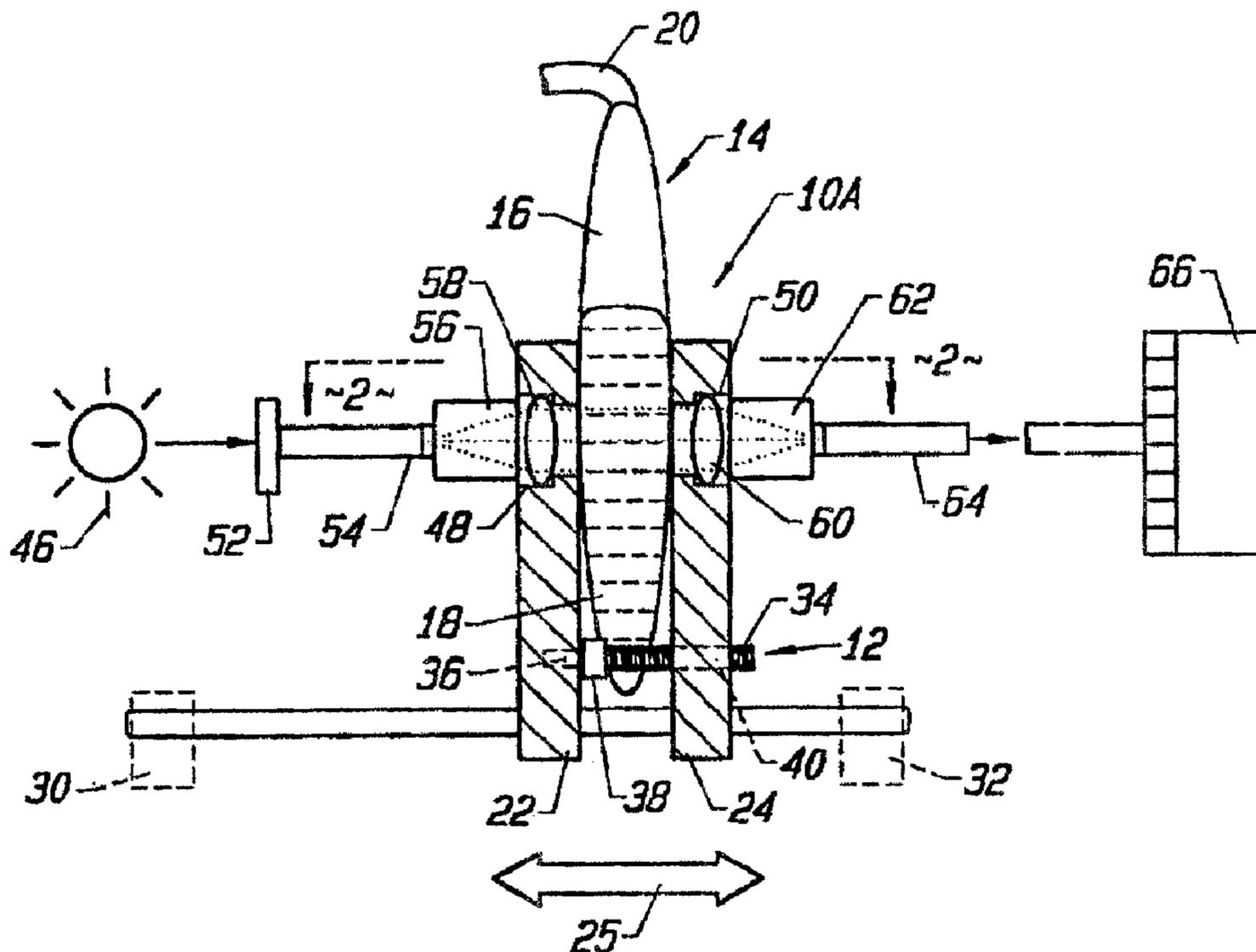




(22) Date de dépôt/Filing Date: 1995/09/27  
 (41) Mise à la disp. pub./Open to Public Insp.: 1996/04/04  
 (45) Date de délivrance/Issue Date: 2005/11/22  
 (30) Priorité/Priority: 1994/10/03 (08/317,114) US

(51) Cl.Int.<sup>7</sup>/Int.Cl.<sup>7</sup> G01N 21/47, G01N 21/90, G01N 21/84,  
G01N 21/17, G01N 21/01  
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(54) Titre : APPAREIL PERMETTANT DE MESURER LE LIQUIDE CONTENU DANS UN SACHET TRANSPARENT ET  
METHODE CONNEXE  
 (54) Title: APPARATUS AND METHOD FOR MEASURING COMPONENTS IN A BAG



(57) Abrégé/Abstract:

An apparatus for measuring components in a liquid medium, in particular parenteral nutrients, within a flexible transparent bag. A spacer is utilized to fix or determine the optical path across the bag chamber and includes a passage for electromagnetic radiation of selected wavelengths. The source of electromagnetic radiation is capable of sending radiation into the bag chamber and to detector means which analyzes the radiation passed through or reflected from the components in the bag chamber.



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**ABSTRACT OF THE DISCLOSURE**

An apparatus for measuring components in a liquid medium, in particular parenteral nutrients, within a flexible transparent bag. A spacer is  
5 utilized to fix or determine the optical path across the bag chamber and includes a passage for electromagnetic radiation of selected wavelengths. The source of electromagnetic radiation is capable of sending radiation into the bag chamber and to detector  
10 means which analyzes the radiation passed through or reflected from the components in the bag chamber.

S P E C I F I C A T I O NTITLE**"APPARATUS AND METHOD FOR  
MEASURING COMPONENTS IN A BAG"**

5

BACKGROUND OF THE INVENTION

The present invention relates to a novel and useful apparatus and method for non-invasively analyzing liquid medium components in a bag.

10

Liquid compounds are often placed in bags for various purposes. For example, the use of total parenteral nutrients (TPN) which are eventually the source of intravenous feeding are stored in transparent or translucent flexible bags. TPN compounds are commonly mixed in pharmacies using commercially available compounders which accept three or more TPN compounds and automatically mix these compounds into an appropriate container such as an intravenous (I.V. bag). Intravenous use of the bags usually takes place at a later time in a hospital or medical facility. Typical compounds include 70% dextrose injection U.S.P., 10% Travasol (amino acid) injection, Intralipid 20% fat I.V. emulsion, sterile water, and many others.

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Presently, methods such as color coding are relied upon to avoid making errors during the compounding or mixing process. Different tubes feeding the I.V. bag possess connectors of different colors which correspond to the colors of the specific mixing positions on the compounder. For example, setting a red indicator on a compounder for 100 milliliters would deliver 100 milliliters from a starting bottle connected to the tubing line which possesses red connectors. However, there is no

assurance that the correct compound was initially connected to the red tubing line. Consequently, an incorrect connection of the tubing between bottles of dextrose solution and water, for example, may have dire consequences, such as death for patients with sugar intolerance.

5 Many of the TPN compounds are clear liquids. That is to say, water, amino acid injection, dextrose injection, and electrolytes are clear liquids precluding visual distinction among them. Furthermore, it is preferable to perform identification of TPN components non-invasively and rapidly to minimize potential contamination and to minimize analysis time by personnel.

10 An article entitled "Near Infrared Multi-Component Analysis of Parenteral Products Using The InfraAlyzer 400" by John J. rose 71-78, dated March-April 1892. examined meglumine and meglumine diatrizoate in 30% diatrizoate meglumine injections solutions using diffuse reflectance in the near infrared region. The best combinations of three or four wavelength filters from nineteen (19) available  
15 wavelength filters were selected using multiple regression statistical methods. The specific wavelengths were not identified.

An article entitled "The Spectrophotometric Absorbance of Intralipid" by Cane *et al.*, pp. 53-55, dated 1980. develops calibrations for Intralipid in water in concentrations from 2.5 to 40 mg/ml at six (6) visible wavelengths between 505 and  
20 626.6 nanometers. Intralipid interferes with spectrophotometric analysis of oxyhemoglobin, carboxyhemoglobin, and total hemoglobin.

A writing entitled, "Simple Methods For The Quantitative Determination of Procaine Hydrochloride In Parenteral Products" by Das Gupta *et al.*, pp. 408-410, dated July 1969. presents calibrations in the ultraviolet region of  
25 spectrophotometry. Specifically, the Das Gupta reference obtained calibrations at 228 nanometers for buffered solutions of procaine hydrochloride in the 0-20 microgram/ml concentration range.

An article entitled "Nondestructive NIR and NIT Determination Of Protein, Fat, And Water In Plastic Wrapped, Homogenized Meat" by Tomas Isaksson  
30 *et al.*, pp. 1685-1694, dated 1992. describes NIR measurements of proteins by diffuse reflectance in meat samples with and without plastic coatings. Samples were placed in a rubber cup prior to covering the meat sample with plastic laminant.

United States patents 4,800,279 and 5,002,397 describe methods and devices for visible and near-infrared evaluation of physical properties of samples.

United States patent 4,872,868 shows an analyzer for collection bags which provides an envelope that permits the insertion of reagent's test strips and the  
5 like.

United States patents 3,857,485 and 3,924,128 teach a method of analyzing sample containers by liquid scintillation spectrometry which utilizes light transmission sealing means to prevent entry of ambient light or the escape of light from the photomultiplier tube detection devices.

10 United States patent 5,239,860 describes a sensor for continuously measuring alcohol and gasoline fuel mixtures in a clear Teflon™ tube using a predetermined optical path and electromagnetic radiation at a pair of wavelengths which are generated by rapidly switching currents through a light-source. Thermopile detectors are used to detect an increase in temperature due to light transmitted through  
15 the flowing gasoline/alcohol mixture.

An apparatus and method for identifying solutions in a translucent transparent or semi-transparent plastic bag, such as parenteral nutrients, non-invasively, qualitatively and quantitatively would be a notable advance in the chemical analysis field.

20

### SUMMARY OF THE INVENTION

In accordance with the present invention a novel and useful apparatus and method for identifying parenteral nutrients is herein provided.

25 Accordingly, in one aspect of the present invention there is provided an apparatus for measuring a component in a liquid medium within the chamber of a flexible translucent container formed by a wall portion, comprising:

a. spacer means for sequentially determining a plurality of optical paths across the container wall portion and chamber, and the bag wall portion alone,  
30 said spacer means including a passage for electromagnetic radiation; and

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b. a source of electromagnetic radiation capable of directing electromagnetic radiation through said passage, through the wall portion of the container, and along any of said determined optical paths, said source of electromagnetic radiation being capable of interaction with a component in the bag chamber and the wall portion of the bag; and

c. detector means for analyzing said electromagnetic radiation after interaction with the components in the bag chamber and the wall portion of the bag.

According to another aspect of the present invention there is provided a method of analyzing components in a liquid medium within the chamber of a flexible bag comprising the steps of:

a. placing the bag in spacer means for determining the optical path across the bag chamber, said spacer means including a passage for electromagnetic radiation;

b. directing electromagnetic radiation from a source of electromagnetic radiation to the components in said bag chamber for interaction therewith; and

c. analyzing said electromagnetic radiation with detector means after interaction of said electromagnetic radiation with the components in the bag chamber.

According to yet another aspect of the present invention there is provided an apparatus for detecting light scattering components in a liquid medium within the chamber of a flexible translucent bag formed by a wall portion, comprising:

a. a fence element, said fence element including a passage for electromagnetic radiation to the wall portion of the bag;

b. a source of electromagnetic radiation capable of directing electromagnetic radiation through said fence element passage, said source of

- 4a -

electromagnetic radiation being capable of interaction with a component in the bag chamber and the wall portion of the bag; and

5 c. detector means for analyzing said electromagnetic radiation after interaction with the components in the bag chamber and the wall portion of the bag, said detector means receiving said electromagnetic radiation, after interaction with a component in the bag chamber, through said fence passage.

According to still yet another aspect of the present invention there is provided an apparatus for non-invasively identifying components in a liquid medium within an interior of a flexible bag, the apparatus comprising:

10 a source of electromagnetic radiation capable of directing electromagnetic radiation into the interior of the flexible bag, the source of electromagnetic radiation capable of interaction with the components in the flexible bag interior and the flexible bag;

15 optical detector means located outside the flexible bag receiving the electromagnetic radiation after interaction with the components in the flexible bag interior and the wall portion of the flexible bag and providing a signal indicative thereof; and

means for analyzing the signal to identify the components of the liquid medium in the flexible bag.

20 The apparatus of the present invention employs spacer means for supporting a flexible transparent or translucent bag and for determining the optical path across the bag chamber. The spacer means includes a passage for electromagnetic radiation. The spacer means may take the form of a pair of rigid elements or fences and a mechanism for shortening or lengthening the distance  
25 between the rigid fences. The rigid fences may support the bag against vertical movement and also be capable of exerting compressive force on the bag to a precisely determined dimension between the rigid fences. Such dimension would correspond to a particular optical path, which may include the bag wall alone or the bag wall and the bag filled with components in a liquid medium.

30 A source of electromagnetic radiation directs electromagnetic radiation through the spacer passage and to the wall portion of the bag. The

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source of electromagnetic radiation may produce coherent light, ultraviolet radiation, x-rays, infrared radiation, broad band radiation e.g., a tungsten source, and the like.

5                    Detector means is also employed in the present invention for analyzing the electromagnetic radiation passed through the spacer passage and along a determined optical path which is through a dimension of the bag chamber. In certain cases the optical path  
10 may pass completely across the bag such that the detector is receiving light which has been transmitted through the bag. In other cases, the detector may be placed on the same side of the bag as the source of electromagnetic radiation and receive light which has  
15 interacted with the contents of the bag by diffuse reflectance. Further, the detector may receive light by diffuse reflectance and/or by diffuse transfectance, i.e., where light passes through the bag and then is reflected back through the bag by a  
20 diffuse reflector or mirror located on the opposite side of the bag relative to the detector. It has been found that near-infrared radiation is particularly useful in detecting parenteral nutrients in a flexible I.V. bag. In addition, specific wavelengths, rather  
25 than a continuum of wavelengths, may be used as the radiation sought for analysis to enable the use of simpler and less expensive instrumentation comprised of several discrete detectors, each covered by a narrow wavelength filter. Fiber optics may also be  
30 utilized to carry light to and from the I.V. bag. Mathematical models may be employed to quantitatively and qualitatively detect components within the I.V. bag accurately and quickly.

Another adaption of the device of the present invention produces a self referencing device with respect to the intensity. Specifically, transmittance measurements may be taken of the bag  
5 alone, squeezed to eliminate a chamber and to expel the liquid components, and along a determined optical path of the bag filled with certain components. Absorbance for a sample may be accurately determined under the Beer's Law relationship. Chemical  
10 concentration can be directly related to an absorbance difference obtained from a spectral measurement using two different path lengths. This technique minimizes or eliminates common spectroscopic measurement problems due to contamination, changes in the  
15 spectroscopic windows holding the sample, instrument problems due to temperature changes on internal optical elements, the source of electromagnetic radiation, and the like.

It may be apparent that a novel and useful  
20 apparatus for analyzing components in a liquid medium has been described.

It is therefore an object of the present invention to provide an apparatus and method for analyzing liquid components in a flexible transparent  
25 or translucent container or without invading the integrity of the bag.

Another object of the present invention is to provide a method and apparatus for analyzing components in a liquid medium within a flexible  
30 transparent or translucent container to prevent misuse of such components in treating patients in a medical facility.

A further object of the present invention is to provide a method and apparatus for analyzing components in a liquid medium found in a transparent or translucent plastic container which is accurate and may include qualitative as well as quantitative measurements of the components therein.

A further object of the present invention is to provide a method and apparatus for analyzing components in a liquid medium found in a transparent or translucent flexible bag where such components are parenteral or enteral nutrients typically used for intravenous feeding.

A further object of the present invention is to provide a method and apparatus for analyzing components in a liquid medium found in a translucent flexible bag which is capable of detecting light from a source after interaction with the bag alone and after interaction with the bag and the components in the bag.

Another object of the present invention is to provide a method and apparatus for analyzing components in a liquid medium within a flexible bag employing either transmittance or diffuse reflectance techniques.

According to one aspect of the invention, there is provided an apparatus for measuring a component in a liquid medium within the chamber of a flexible translucent container formed by a wall portion comprising: spacer means for sequentially determining a plurality of optical paths across the container wall portion and chamber, and the bag wall portion alone the spacer means including a passage for electromagnetic radiation; and a source of electromagnetic radiation capable of directing electromagnetic radiation through the spacer means passage, through the wall portion of the container, and along any of the determined optical paths,

**A**

the source of electromagnetic radiation being capable of interaction with a component in the bag chamber and the wall portion of the bag; and detector means for analyzing  
5 the electromagnetic radiation after interaction with the components in the bag chamber and the wall portion of the bag.

According to another aspect of the invention, there is provided a method of analyzing components in a  
10 liquid medium within the chamber of a flexible bag comprising the steps of: placing the bag in spacer means for determining the optical path across the bag chamber, the spacer means including a passage for electromagnetic radiation; directing electromagnetic radiation from a  
15 source of electromagnetic radiation to the components in the bag chamber for interaction therewith; and analyzing the electromagnetic radiation with detector means after interaction of the electromagnetic radiation with the components in the bag chamber.

20 According to a further aspect of the invention, there is provided a method of analyzing components in a liquid medium within the chamber of a flexible bag in which the components are parenteral and enteral nutrients.

25 According to yet a further aspect of the invention, there is provided an apparatus for detecting light scattering components in a liquid medium within the chamber of a flexible translucent bag formed by a wall portion comprising: a fence element, the fence element  
30 including a passage for electromagnetic radiation to the wall portion of the bag; a source of electromagnetic radiation capable of directing electromagnetic radiation through the fence element passage, the source of electromagnetic radiation being capable of interaction



with a component in the bag chamber and the wall portion  
of the bag; and detector means for analyzing the  
electromagnetic radiation after interaction with the  
5 components in the bag chamber and the wall portion of the  
bag, the detector means receiving the electromagnetic  
radiation, after interaction with a component in the bag  
chamber, through the fence passage.

According to yet another aspect of the  
10 invention, there is provided an apparatus for non-  
invasively identifying components in a liquid medium  
within an interior of a flexible gas, the apparatus  
comprising: a source of electromagnetic radiation capable  
of directing electromagnetic radiation into the interior  
15 of the bag, the source of electromagnetic radiation  
capable of interaction with the components in the bag  
chamber and the bag; optical detector means located  
outside the bag receiving the electromagnetic radiation  
after interaction with the components in the bag chamber  
20 and the wall portion of the bag and providing a signal  
indicative thereof; and means for analyzing the signal to  
identify the components of the liquid medium in the bag.

The invention possesses other objects and  
advantages especially as concerns particular  
25 characteristics and features thereof which will become  
apparent as the specification continues.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a sectional view of a first  
embodiment of the apparatus of the present invention.



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FIG. 2 is a sectional view of the apparatus of Fig. 1 taken along line 2-2 of Fig. 1.

FIG. 2A is a sectional view taken along line 2A-2A of Fig. 2.

5 FIG. 2B is a sectional view of an I.V. bag collapsed by the apparatus of the present invention.

FIG. 3 is a side sectional view of another embodiment of the apparatus of the present invention.

10 FIG. 4 is a graphical representation with experimental results described in Example 1.

FIG. 5 is a graphical representation of the experimental results described in Example 2.

FIG. 6 is a graphical representation of experimental results described in Example 3.

15 FIG. 7 is a graphical representation of an experimental result described in Example 4.

FIG. 8 is a graphical representation of PCA plot of scores described in Example 5.

20 FIGS. 9 and 10 are graphical representations depicting predictions using PLS analysis described in Example 4.

FIG. 11 is a graphical representation of a PLS model utilizing data found in Example 4.

25 FIGS. 12, 13, and 14, are graphical representations of MLR methods applied to the data shown in Table 2 of Example 4.

FIG. 15 is a graphical representation of a step wise MLR program utilizing the data of Table 1 of Example 4.

30 For a better understanding of the invention reference is made to the following detailed description of the preferred embodiments which should be referenced to the herein before described drawings.

**DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

Various aspects of the present invention will evolve from the following detailed description of the preferred embodiments thereof which should be taken in  
5 conjunction with the herein before described drawings.

The invention as a whole is depicted in the drawings by reference character 10. The apparatus 10 is shown in the drawings as including multiple embodiments, denoted by the addition of an upper case letter. Referring to Fig. 1, apparatus 10A is depicted in which spacer means 12 is provided to hold a flexible  
10 transparent or semi transparent bag 14 in place. The term "translucent" is used herein to indicate a transparent, semi-transparent, or non- opaque bag. Bag 14 includes a chamber 16 which is capable of holding components in a liquid medium 18. Liquid medium including such components 18 are passed through tube 20, shown partially in Fig. 1, which is ultimately clamped or sealed when the bag 14 is filled. Bag 14 may  
15 take the form of a plastic intravenous bag (I.V. bag) formed of polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), and like materials. However, other containers may be employed herein. The liquid medium and components 18 found within bag 14 may consist of mixtures of parenteral or enteral nutrients which may be intravenously fed to a patient. For example, such nutrients may include sterile water, 70% dextrose  
20 injection U.S.P., 10% Travasol™ (amino acid) Aminosyn or FreeAmine injection, Intralipia™ 20% fat I.V. emulsion, potassium chloride, and the like, individually or in various combinations.

Spacer means 12 includes a pair of elements 22 and 24 which are shown in Figs. 1 and 2 as a pair of solid fences placed in opposition to one another. Fences 22 and 24 are slidably supported by rods 26 and 28 which are supported to a surface by stands 30 and 32, depicted in phantom on Figs. 1 and 2. Rods 26 and 28 serve as a guide for fences 22 and 24. A threaded screw 34 is fixed to fence 22 through a boss 36. Knurled wheel and bearing unit 38 is capable of turning relative to boss 36. The turning of wheel 38 also rotates threaded connect screw 34 which threadably engages a threaded bore 40 through fence 24. Thus, fence 22 is stationary relative to rods 26 and 28 while fence 24 is moveable thereto, manually or by motor means, such as a solenoid, directional arrow 25. Unit 38 serves to measure or to stop the relative movement of fences 22 and 24, to determine the optical path through bag 14 or sequentially determine a plurality of optical paths through bag 14. It should be noted that fences 22 and 24 may be hingedly attached to one another to determine the distance therebetween, like a clamshell.

With reference to Fig. 2A, it may be observed that such optical path (O.P.) of components 18 within bag 14 may be easily adjusted by the movement of fence 24 relative to fence 22. The O.P. may vary between 1.0 millimeter to 15 millimeters in many cases. In certain instances, an empty bag 14 may be compressed by fences 22 and 24 such that walls 42 and 44 touch one another, Fig. 2B, eliminating chamber 16. This configuration is useful in obtaining a reference value for the bag without medium 18 in chamber 16. Inner surfaces 42 and 44 of fences 22 and 24, respectively

also provide sufficient friction to prevent the  
slippage of bag 14 downwardly between fences 22 and  
24. Of course, other structures may be employed to  
prevent the slippage of bag 14 within spacer means 12  
5 such as a floor, or suspension device pulling upwardly  
on bag 14 while bag 14 is within spacer means 12, and  
the like.

Apparatus 10 further possesses a source of  
electromagnetic radiation 46. Source 46 may take the  
10 form of laser light, infrared radiation, ultraviolet  
radiation, visible radiation, or any other  
electromagnetic radiation found in the spectrum.  
Light 46 is passed to bag chamber 16 through passage  
48 in fence 22 and from chamber 16 of bag 14 through  
15 passage 50 of fence 24. Electromagnetic radiation  
from source 46 may be filtered by filter 52 and led to  
passage way 48 by optical fiber or fiber bundle 54.  
Fitting 56 directs radiation from fiber optical bundle  
54 to collimating lens 58. Parallel rays of  
20 electromagnetic radiation are then passed through bag  
14 and liquid medium 18 containing various components  
to converging lens 60. Fitting 62 directs the  
electromagnetic radiation through optical fiber or  
fiber optic bundle 64 to a detector 66 for analysis.  
25 Detector means 66 in its broadest sense may take the  
form of any suitable spectrophotometer, single or  
multiple detectors, or sources being appropriately  
filtered for the wavelength of interest, in  
combination with a computer employing an appropriate  
30 software program such as Gram 386, available from  
Galactic Industries, Inc. of Salem NH.

With reference to Fig. 3, embodiment 10B of  
the present invention is depicted. Apparatus 10B

possesses a pair of opposing elements or fences 68 and 70. As in embodiment 10A, guide 72 may take the form of a pair of rods supported by stands on a surface a hinged clamshell configuration or the like. Fence 68 is fixed to guide 72 while fence 70 is moved and the distance between fences 68 and 70 is set by threaded screws 74, in the same manner as threaded screw 34 found in embodiment 10A. Fence 68 includes a diffuse reflector 76 on one side of bag 14 containing liquid medium 18 having various components therewithin. Of course, diffuse reflector may be formed integrally with bag 14. Diffuse reflector 76 may take the form of a white ceramic disk or other suitable reflector. Light from source 46, not shown, passes through outer fiber or fiber bundle 78, from bag 14 containing a liquid medium having various components 18, and through fiber optic bundle 80, which is formed concentrically with fiber optic bundle 78. Analysis of the components within bag chamber 16 takes place by interaction of the electromagnetic radiation from fiber optic bundle 78 by diffuse reflectance, by diffuse transfectance, in conjunction with diffuse reflector 76, or a combination of both. The latter is especially useful where liquid medium is murky to an uncertain degree. Such diffuse reflectance measurements may be obtained simply by pressing an I.V. bag filled with light scattering material against fence 70 without the use of fence 68. Again, fiber optic bundles 78 and 80 may be angularly disposed with respect to each other i.e., 30 degrees, to minimize specular components of electromagnetic radiation reflected from bag 14.

The general operation of embodiments 10A and 10B takes place by supporting bag 14 within spacer means 12, which may include elements 22 and 24 of embodiment 10A, or fences 68 and 70 of embodiment 10B. Spacer means 12 is then adjusted to solely determine the desired optical path within bag 14 or to sequentially determine the optical path through a plurality of bags such as bag 14. In general, where liquid medium 18 is not perfectly clear, as in the case of lipids, the optical path would be short. For murky light scattering liquids, it is unlikely that radiation will reach the far side of bag 14 and be reflected back from diffuse reflector or mirror 76. In such a case, the space between fences 68 and 70 is not critical. The converse is true with clear liquid medium 18. Electromagnetic radiation from source 46 is then directed through passages 48 and 50 of elements 22 and 24, or simply directed through passage 82 of fence 70 of embodiment 10B. After interaction with the components in a liquid medium 18, electromagnetic radiation is passed from bag 14 to detector 66 for analysis by a suitable software program in conjunction with a personal computer. Where bag 14 is collapsed by fences 22 and 24, electromagnetic radiation may be passed through bag 14 to obtain a reference reading for use with spectral analyses of liquid in bag 14.

This spectroscopic method and apparatus of the present invention is capable of identifying and measuring many components in a liquid medium 18. Colorless materials, such as parenteral nutrients have distinctive spectral characteristics in regions outside the visible electromagnetic spectrum (400-

700nm). In particular, infrared (3000-25,000nm) regions of the electromagnetic spectrum produces distinctive spectral features arising from specific molecular structures that are characteristics of the compounds. Such features derive from molecular vibrations of bonded atoms such as oxygen-hydrogen, carbon-hydrogen, nitrogen-hydrogen, and oxygen-carbon. Different types of carbon-hydrogen bonds can be distinguished, such as those arising from terminal C-H groups or CH<sub>3</sub> groups, i.e., fundamental molecular vibrations. Similar features occur at multiples of these fundamental frequencies (i.e., shorter wavelengths) and, hence, commonly occurred in the near-infrared. These are referred to as vibrational overtones such as the first and second overtones of carbon-hydrogen near 1700 and 1100 nm, respectively. Several different fundamental vibrations can combine to form a vibrational absorption at shorter wavelengths called a combination mode, ie., such as oxygen and hydrogen in molecular water near 1900nm. Therefore, many regions of the electromagnetic spectrum may be used to obtain useful spectral data.

While in the foregoing, embodiments of the present invention have been set forth in considerable detail for the purposes of making a complete disclosure of the invention, it may be apparent to those of skill in the art that numerous changes may be made in such detail without departing from the spirit and principles of the invention. Further description of the invention is contained in the following examples.

The following examples are described in detail herein for the purpose of illustration of the

present invention, but are not deemed to limit the scope of the invention herein.

**EXAMPLE 1**

5           The near infrared spectra of several  
parental nutrient compounds, i.e., water, 70% dextrose  
injection USP and 10% Travasol amino acid injection  
was measured individually or in various combinations  
to illustrate spectral characteristics. Such  
10        compounds formed an optically clear solution, which  
was placed in a fused quartz cuvette having an optical  
path of one (1) millimeter. The spectral data were  
acquired with a germanium detector found in a  
spectrophotometer, Model 200, manufactured by Guided  
15        Wave, Inc. of El Dorado Hills, California. Two (2)  
one meter long, 500 micron core diameter, silica-clad  
low-OH optical fibers and collimating lenses were  
connected to the spectrophotometer. Collimating  
lenses were placed between one end of each fiber and  
20        the cuvette. One fiber transmitted light from the  
tungsten light source inside the spectrophotometer  
through collimating lens and cuvette. The second  
collimating lens received light passing through the  
cuvette and focused the light into the second fiber,  
25        which transmitted the light back to the monochromator  
and detector in the spectrophotometer. The absorbance  
characteristics obtained are charted in Fig. 4. Water  
reaches a maximum absorbance between 1400 and 1500  
nanometers. The remaining components produce  
30        additional changes on the long wavelength side of the  
main water peak in the 1500-1800 nanometer region in  
Fig. 4.

EXAMPLE 2

5 A polyvinyl chloride bag used for intravenous feeding (IV bag) was filled with sterile water, 70% dextrose injection, USP, and 10% Travasol amino acid injection, which are typical parenteral nutrients. These components formed an optically clear solution. Utilizing the apparatus shown in Fig. 1, spectral data were attained with a germanium detector found in a spectrophotometer distributed by Guided Wave, Inc. under the designation model 200. A pair of one meter long, 500 micron core diameter, silica-clad low-OH optical fiber and collimating lenses were employed with the subject detector. The IV bag was compressed to an optical path of 15 millimeters. 10 Distinguishing characteristics were uncovered in the compounds within the I.V. bag in the 800 to 1100 nanometer region of an electromagnetic source of radiation. Reference analysis was also performed on an empty I.V. bag. Fig. 5 represents the results of this analysis. 15 20

EXAMPLE 3

25 The parenteral compounds of Examples 1 and 2 were placed in an I.V. bag with the addition of a common 20% Intralipid intravenous fat emulsion (I.V. fat emulsion). The final mixture of nutrients included fat compounds occupying less than 50% of the volume of the I.V. bag mixture. Fig. 6 shows that, in spite of the light scattering characteristics of the milky solution found in the IV bag containing the fat compounds, transmission may still be performed through 1-2 millimeters of an optical path of the bag. In other words, the bag shown in Fig. 6 represents a squeezing of the bag to a smaller optical path, (1.5 to 2 millimeters) than the optical path represented in 30

Fig. 5. It is estimated that 95% of the light passed through the bag in this Example was scattered and lost through the first millimeter of the optical path. Various mixtures of 70% dextrose injection USP, 20% Intralipid I.V. fat emulsion, 10% Travasol, and water are employed and are identified on Fig. 6. The absorbance characteristics are clearly identifiable for each mixture in which changes in the intensity of the water peak near 1450 nm, effects due to amino acids and dextrose in the 1500-1700 nm region, and contribution from lipid near 1200 nm are identifiable. As will be shown from diffuse reflectance spectral data hereinafter in Example 4, these features can be used to perform quantitative analysis of the mixtures in the bag.

#### EXAMPLE 4

The apparatus shown in Fig. 3 was employed to conduct diffuse reflectant/transmittance measurements through I.V. bags constructed of polyvinyl chloride (PVC) filled with mixtures of parenteral nutrients. The mixtures were composed of 20% Intralipid I.V. fat emulsion, 10% Travasol (amino acid injection solution), 70% dextrose injection solution, and sterile water. Nutrients were measured volumetrically with a graduated cylinder mixed, and placed in one (1) liter PVC I.V. bags. The device depicted in Fig. 3 was set to provide an optical path, excluding the thickness of the I.V. bag material, of about 15 millimeters through the solution in the filled I.V. bag. The set screw spacer means 12, Fig. 1, was employed to compress the bag to this particular optical path setting. Since these mixtures all contained lipid and hence, scattered light suitable

for diffuse reflectance measurements, the space set  
for the optical path was not critical to the  
measurement. A spectrophotometer was employed,  
similar to the spectrophotometer utilized in Example 1  
5 using an InGaAs detector. The source of light was a  
tungsten lamp. The light was delivered through a 6 mm  
dia hole in a white Spectralon block available from  
Labsphere, Inc., North Sutton, NH from a 20 watt  
tungsten source. This block was attached to the  
10 stationary fence 70 in Fig. 3. A bundle of 10  
individual fibers of the type described in Example 1  
were cemented into a small metal fitting and inserted  
through the Spectralon block at 30 degrees to the hole  
containing the tungsten light source. The end of the  
15 fiber bundle fitting was coincident with the end of  
the block in contact with the IV bag. Near infrared  
spectra were collected between 1100 and 1650  
nanometers. Fig. 7 depicts the results obtained where  
the various mixtures used were clearly recognizable,  
20 with the exception of the 75:25 Travasol and lipid  
mixture, which, generally, is only slightly different  
from the 75:25 water and lipid mixture.

The spectral differences shown in Fig. 7 can  
be quantified with the commonly used method of  
25 Principal Component Analysis (PCA). PCA is  
essentially a pattern recognition procedure that can  
assign one number to the entire spectrum employed in  
the analysis. PCA is accomplished by analyzing all  
spectral data of all samples in determining the linear  
30 combination of data that explains the largest  
variation of spectral information. A different linear  
combination is next determined that shows the next  
largest variation in the spectral data. The linear

combinations are determined in this way. Each linear combination is referred to as a FACTOR which provides co-efficient that multiply the data at each wavelength. The product of this multiplication is summed to determine one number which is referred to as a SCORE. Thus, by plotting SCORES from FACTOR I against those from FACTOR II, samples can be distinguished or identified. In mathematical terms, FACTORS are a set of orthogonal eigenvectors whose lengths represent the percentage of variation in spectral data. SCORES are obtained by multiplying the elements of each eigenvector, referred to as a LOADING (each of which is a co-efficient for the spectral data at a specific wavelength) times the absorbance at that wavelength, and summing the results. Essentially, each sample is projected on each eigenvector and the distance from the origin i.e., the intersection of all eigenvectors is thus measured. Other mathematical methods exist for the purposes of identification of data, including the computation of direction cosines, factor analysis, and cluster analysis. Referring to Fig. 8, a PCA plot is illustrated using SCORES from the first two FACTORS of the diffuse reflectance data from the samples presented in Fig. 7. Table 1 herein represents the volume fraction of the nutrients employed in the preparation of Fig. 8:

TABLE I

	<u>SAMPLE</u>	<u>10% TRAVASOL</u>	<u>STERILE WATER</u>	<u>70% DEXTROSE</u>	<u>20% INTRALIPID</u>
	1			0.50	0.50
5	2	0.50			0.50
	3		0.50		0.50
	4			0.85	0.15
	5	0.85			0.15
	6		0.85		0.15
10	7			0.75	0.25
	8			0.75	0.25
	9	0.75			0.25
	10	0.75			0.25
	11		0.75		0.25
15	12		0.75		0.25
	13	0.25	0.25	0.25	0.25
	14	0.25	0.25	0.25	0.25

These two factors account for 97% of the spectral variation among all of the samples, each identified by a sample number with a circle around the same. The 70% dextrose injection USP, water, and 10% Travasol amino acid injection components are clearly distinguished by the solid lines of Fig. 8. The 20% intralipid fat emulsion content is also clearly shown by the three dashed lines representing 15%, 25%, and 50% intralipid. The solid Travasol and water lines lie closer to one another, but are significantly spaced from the dextrose line in Fig. 8. Such a relationship corresponds to spectral data in which water and Travasol are more similar to each other than dextrose. Repeated measurements on the same IV bag showed reasonable reproducibility, i.e., samples 7 and 8 and samples 11 and 12 of Fig. 8.

Partial-Least Squares (PLS) method was also employed in the diffuse reflectance method for the samples shown in Fig. 8. The results of this method are shown in Figs. 9-10 of the present invention.

Partial-Least Squares (PLS) multivariate procedure is commonly used to determine chemical or physical property information from spectral data. Computer programs such as UNSCRAMBLER are available from Camo  
5 of Norway. SPECTRACALC, and GRAMS/386 are available from Galactic Industries, Inc., of Salem, New Hampshire. Pirouette is available from Infometrics of Redmond, Washington. GRAMS/386 was used in the present analysis with a personal computer. PLS  
10 incorporates the benefits of PCA and attempts to provide a model of the data with as few a number of FACTORS as is needed. A six FACTOR PLS model of the diffuse reflectance data of Table I represents a strong indication that mixtures in IV bags can be  
15 analyzed non-invasively. Figs. 9 and 10 show predictions of 70% dextrose injection and 20% intralipid IV fat emulsion.

PLS analysis of the one millimeter optical path using transmission through cuvettes, shown in  
20 Fig. 4 for samples without fat emulsion, also produced excellent quantitative results. The prediction for 70% dextrose injection USP in the mixture from a five FACTOR PLS model as presented in Fig. 11. The standard error of calibration for the sample set was  
25 5%. The PLS, model in Fig. 11 utilized all spectral information from all samples as seen in Fig. 4.

Since it is often desirable to use a simple system comprising only a few wave lengths for quantitative analysis, a multi linear Regression  
30 Method (MLR) can also be used to predict physical properties of liquids and solids and analyze mixtures from near infrared spectra. MLR was performed on the one millimeter transmission spectra shown in Fig. 4.

The result in calibration are presented in Figs. 12, 13, and 14, for 70% dextrose injection USP, sterile water, and 10% Travasol amino acid injection, respectively. The data were generated by employing 2, 3, and 5 wavelengths between 1100 and 1800 nanometers, respectively. This data are shown in Table 2 as follows:

**TABLE II**

	<u>70% DEXTROSE</u>			<u>WATER</u>		<u>10% TRAVASOL</u>	
	<u>SAMPLE</u>	<u>ACT.</u>	<u>PRED.</u>	<u>ACT.</u>	<u>PRED.</u>	<u>ACT.</u>	<u>PRED.</u>
10	1	0.000	0.007	0.000	0.014	1.000	1.003
	2	0.000	-0.005	1.000	0.977	0.000	0.072
	3	1.000	0.986	0.000	-0.041	0.000	-0.061
	4	0.000	0.008	0.500	0.468	0.500	0.475
15	5	0.500	0.522	0.500	0.517	0.000	-0.063
	6	0.500	0.489	0.000	0.038	0.500	0.524
	7	0.333	0.344	0.333	0.310	0.333	0.307
	8	0.667	0.681	0.166	0.128	0.166	0.241
	9	0.166	0.156	0.166	0.198	0.667	0.675
20	10	0.166	0.162	0.667	0.653	0.167	0.149
	11	0.700	0.697	0.300	0.306	0.000	0.052
	12	0.250	0.240	0.500	0.488	0.250	0.219
	13	0.300	0.308	0.700	0.747	0.000	0.057
	14	0.400	0.399	0.200	0.209	0.400	0.352
25	15	0.000	-0.007	0.300	0.320	0.700	0.683

	<u>Wavelength</u>		<u>Waveln.</u>		<u>Waveln.</u>	
	<u>nm</u>	<u>Coeff.</u>	<u>Waveln.</u>	<u>Coeff.</u>	<u>Waveln.</u>	<u>Coeff.</u>
	1566	16.21	1528	3.5355	1533	-51.3572
30	1716	-5.3741	1716	-104.7859	1778	56.0781
	Offset	-4.9432	1744	98.6863	1287	194.9018
	Mult. R	0.99378	Offset	-3.4804	1193	-668.3302
	SEC	0.0347	Mult. R	0.99521	1194	455.3483
			SEC	0.0306	Offset	9.8891
35					Mult.R	0.98888
					SEC	0.0548

As may be observed, wavelengths of 1566 and 1716 nanometers were employed for dextrose. The wavelengths employed for water and Travasol are also indicated on Table 2. The indication is that a simpler and less expensive system having several

discrete detectors, each covered by a narrow wavelength filter or a device having means to switch between several discrete wavelengths, could be built to quantitatively predict the composition of mixtures as these shown in Fig. 4.

A stepwise multiple linear regression program was also used to determine a small set of wavelengths which could be used to predict the intralipid and 70% dextrose mixture in IV bags filled with the samples identified in Table II, analyzed by the embodiment of 10A of Fig. 1 (transmittance). The optical path was set to a distance of approximately 1.6 mm. Actual versus predicted values were plotted as shown on Fig. 15. It should be noted that a perfect calibration would plot on the diagonal line found in Fig. 15. Three (3) and five (5) wavelengths were used to produce excellent fits with standard errors of prediction of 2.1 and 3.7% for the 20% intralipid component and the 70% dextrose component in the mixture, respectively. The three (3) wavelengths used for the 20% intralipid were 1606, 1536, and 1532 nanometers which are listed in decreasing order of importance. Similarly, the five (5) lengths employed for the 70% dextrose were 1414, 1610, 1212, 1424, and 1200 nanometers, also listed in order of importance. Each mathematical solution also included a constant term.

## WHAT IS CLAIMED IS:

1. An apparatus for measuring a component in a liquid medium within the chamber of a flexible translucent container formed by a wall portion, comprising:
  - a. spacer means for sequentially determining a plurality of optical paths  
5 across the container wall portion and chamber, and the bag wall portion alone~ said spacer means including a passage for electromagnetic radiation; and
  - b. a source of electromagnetic radiation capable of directing electromagnetic radiation through said passage, through the wall portion of the container, and along any of said determined optical paths, said source of  
10 electromagnetic radiation being capable of interaction with a component in the bag chamber and the wall portion of the bag; and
  - c. detector means for analyzing said electromagnetic radiation after interaction with the components in the bag chamber and the wall portion of the bag.
- 15 2. The apparatus of claim 1 in which said spacer means includes a pair of elements placed in opposition to one another, at least one of said elements including a passage for electromagnetic radiation to the wall portion of the bag.
3. The apparatus of claim 2 wherein said apparatus additionally comprises  
20 adjustment means for establishing the distance between said pair of elements.
4. The apparatus of claim 3 in which said adjustment means includes a threaded member spanning said pair of elements, said threaded member threadingly engaging one of said elements to effect movement of said one of said elements thereby, and a  
25 guide for confining movement of said one of said elements to a predefined direction.
5. The apparatus of claim 4 in which said guide includes a pair of elongated elements extending between said pair of elements.

6. The apparatus of claim 1 which additionally includes a fiber optic conduit for transporting electromagnetic radiation from said source of electromagnetic radiation to said spacer means passage.
- 5 7. The apparatus of claim 1 which additionally includes a fiber optical conduit for transporting electromagnetic radiation from said spacer means to said detector means.
8. The apparatus of claim 2 which additionally comprises a reflector located at  
10 one of said pair of elements, said reflector being located to reflect electromagnetic radiation, passed through the chamber of the flexible translucent bag back through the chamber of the flexible translucent bag.
9. The apparatus of claim 1 in which said source of electromagnetic radiation  
15 emanates electromagnetic radiation in the near-infrared region of the electromagnetic spectrum.
10. The apparatus of claim 1 which additionally includes at least one wavelength  
20 filter placed between said source of electromagnetic radiation and said detector means.
11. The apparatus of claim 10 which additionally includes a lens placed between said source of electromagnetic radiation and said detector means.
- 25 12. A method of analyzing components in a liquid medium within the chamber of a flexible bag comprising the steps of:
- a. placing the bag in spacer means for determining the optical path across the bag chamber, said spacer means including a passage for electromagnetic radiation;

b. directing electromagnetic radiation from a source of electromagnetic radiation to the components in said bag chamber for interaction therewith; and

c. analyzing said electromagnetic radiation with detector means after interaction of said electromagnetic radiation with the components in the bag chamber.

5

13. The method of claim 12 in which said step of analyzing said electromagnetic radiation further includes the step of analyzing electromagnetic radiation transmitted through said components in the bag chamber.

10 14. The method of claim 12 in which said step of analyzing said electromagnetic radiation further includes the step of analyzing electromagnetic radiation reflected from said components in the flexible bag.

15 15. The method of claim 12 in which said step of analyzing said electromagnetic radiation further includes the step of analyzing electromagnetic radiation transmitted through and reflected back through components in the bag chamber.

16. The method of claim 12 wherein electromagnetic radiation is passed through the flexible bag alone in order to obtain a reference spectrum.

20

17. The method of claim 16 which further comprises the step of expelling the liquid medium from the flexible bag prior to said step of passing electromagnetic radiation through the flexible bag alone.

25 18. The method of claim 16 in which said optical path is a first optical path and said method further comprises the steps of d) placing the bag in said spacer means for determining a second optical path across the bag chamber; .e) directing electromagnetic radiation to the components in said chamber for interaction therewith; and f) analyzing said electromagnetic radiation with said detector means after  
30 interaction of said electromagnetic radiation with the components in the bag chamber.

19. The method of analyzing components in a liquid medium within the chamber of a flexible bag according to claim 12 wherein said components are parenteral and enteral nutrients.

5

20. An apparatus for detecting light scattering components in a liquid medium within the chamber of a flexible translucent bag formed by a wall portion, comprising:

a. a fence element, said fence element including a passage for electromagnetic radiation to the wall portion of the bag;

10 b. a source of electromagnetic radiation capable of directing electromagnetic radiation through said fence element passage, said source of electromagnetic radiation being capable of interaction with a component in the bag chamber and the wall portion of the bag; and

15 c. detector means for analyzing said electromagnetic radiation after interaction with the components in the bag chamber and the wall portion of the bag, said detector means receiving said electromagnetic radiation, after interaction with a component in the bag chamber, through said fence passage.

21. An apparatus for non-invasively identifying components in a liquid medium within an interior of a flexible bag, the apparatus comprising:

20 a source of electromagnetic radiation capable of directing electromagnetic radiation into the interior of the flexible bag, the source of electromagnetic radiation capable of interaction with the components in the flexible bag interior and the flexible bag;

25 optical detector means located outside the flexible bag receiving the electromagnetic radiation after interaction with the components in the flexible bag interior and the wall portion of the flexible bag and providing a signal indicative thereof; and

30 means for analyzing the signal to identify the components of the liquid medium in the flexible bag.

FIG. 1

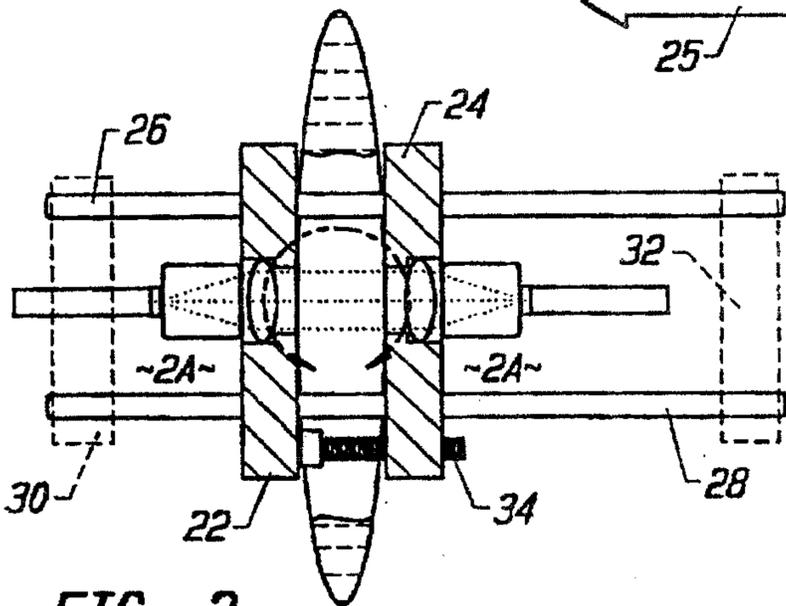
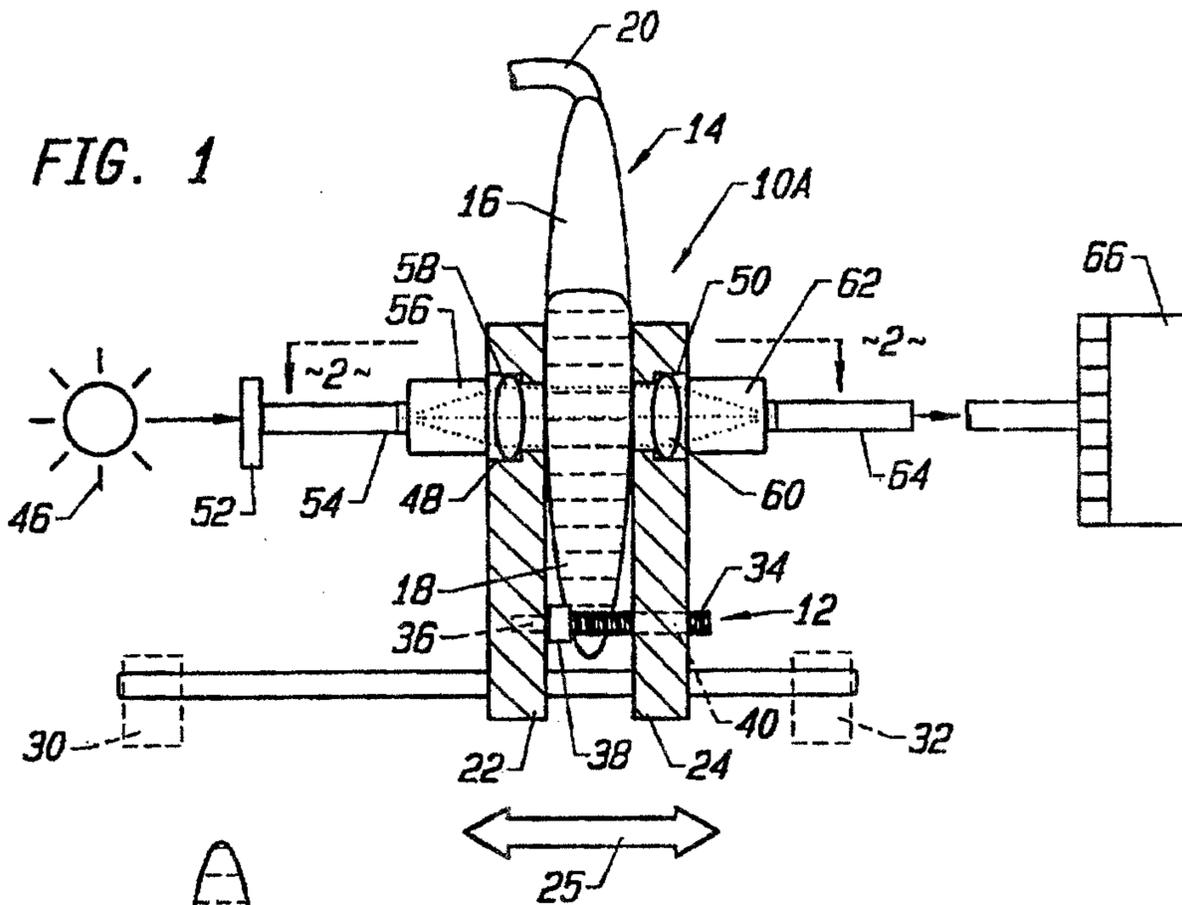


FIG. 2

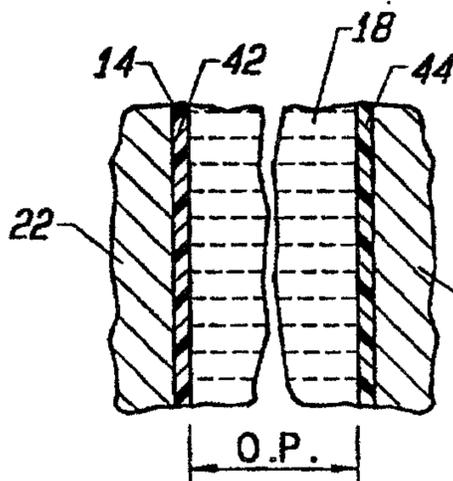


FIG. 2A

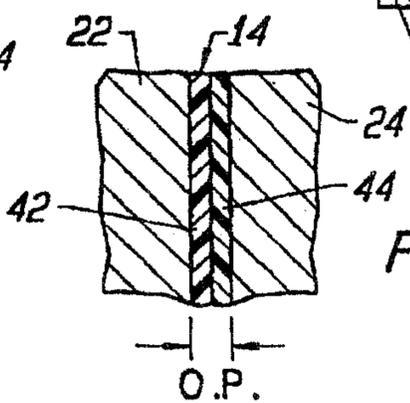


FIG. 2B

FIG. 3

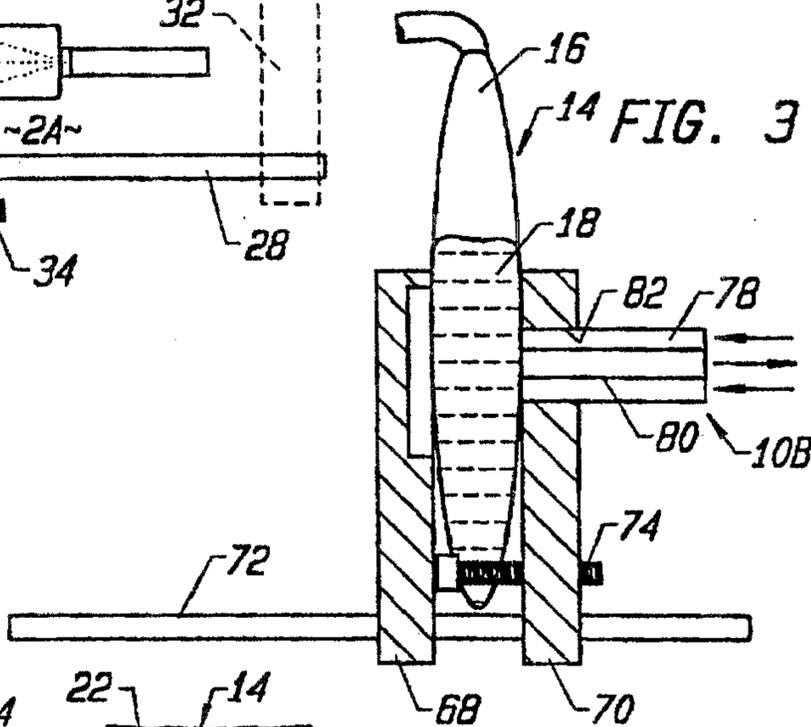
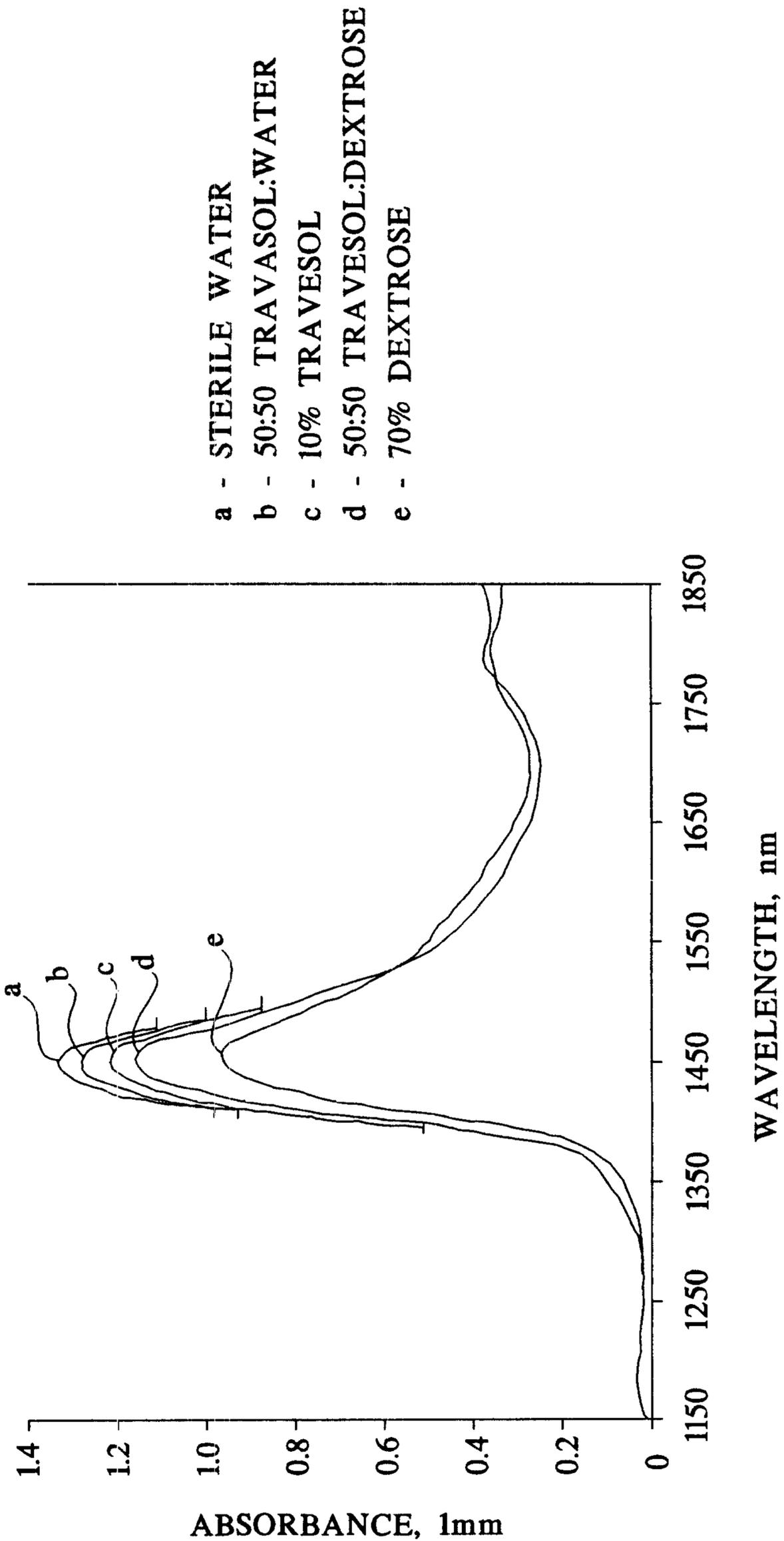
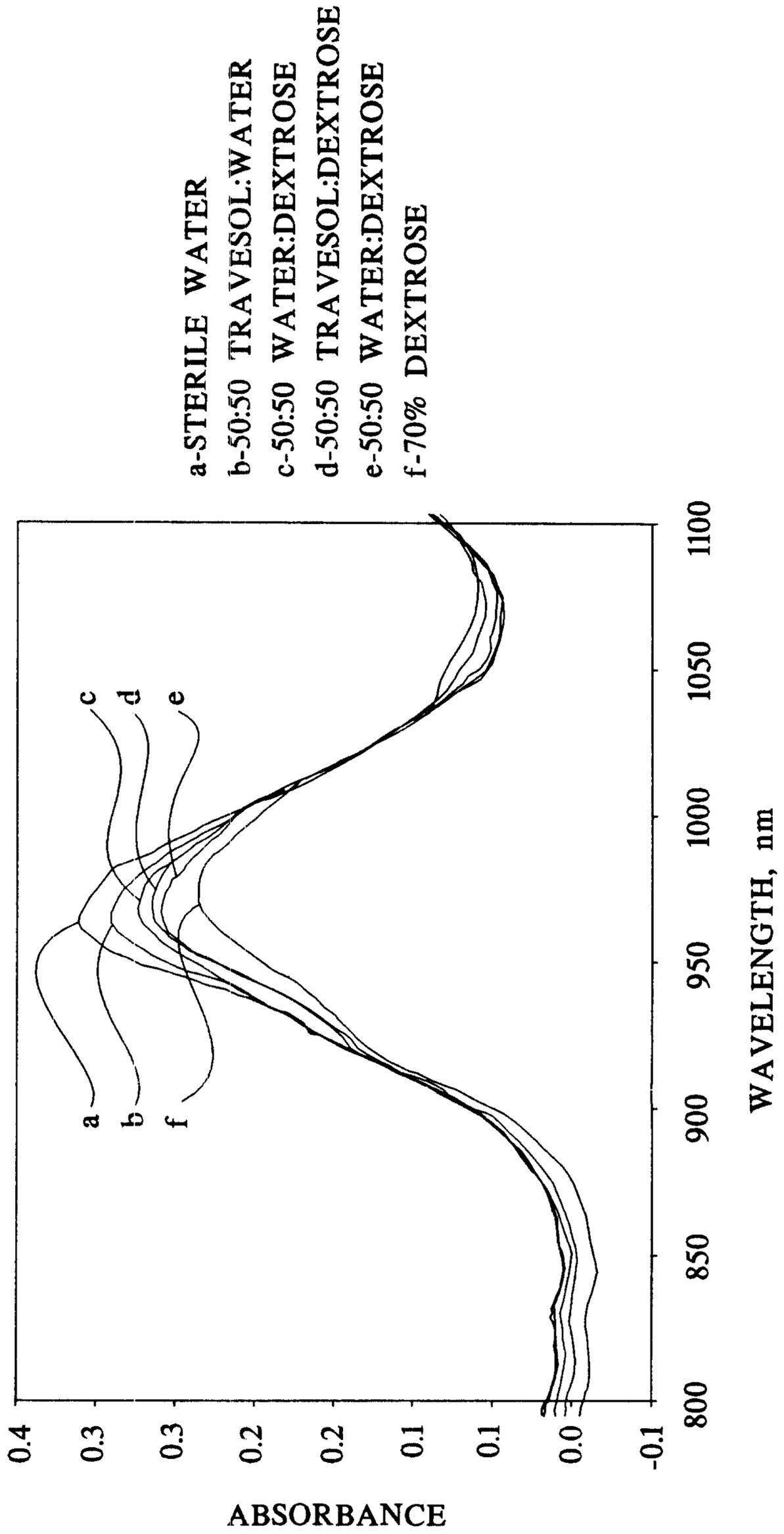


FIG.4



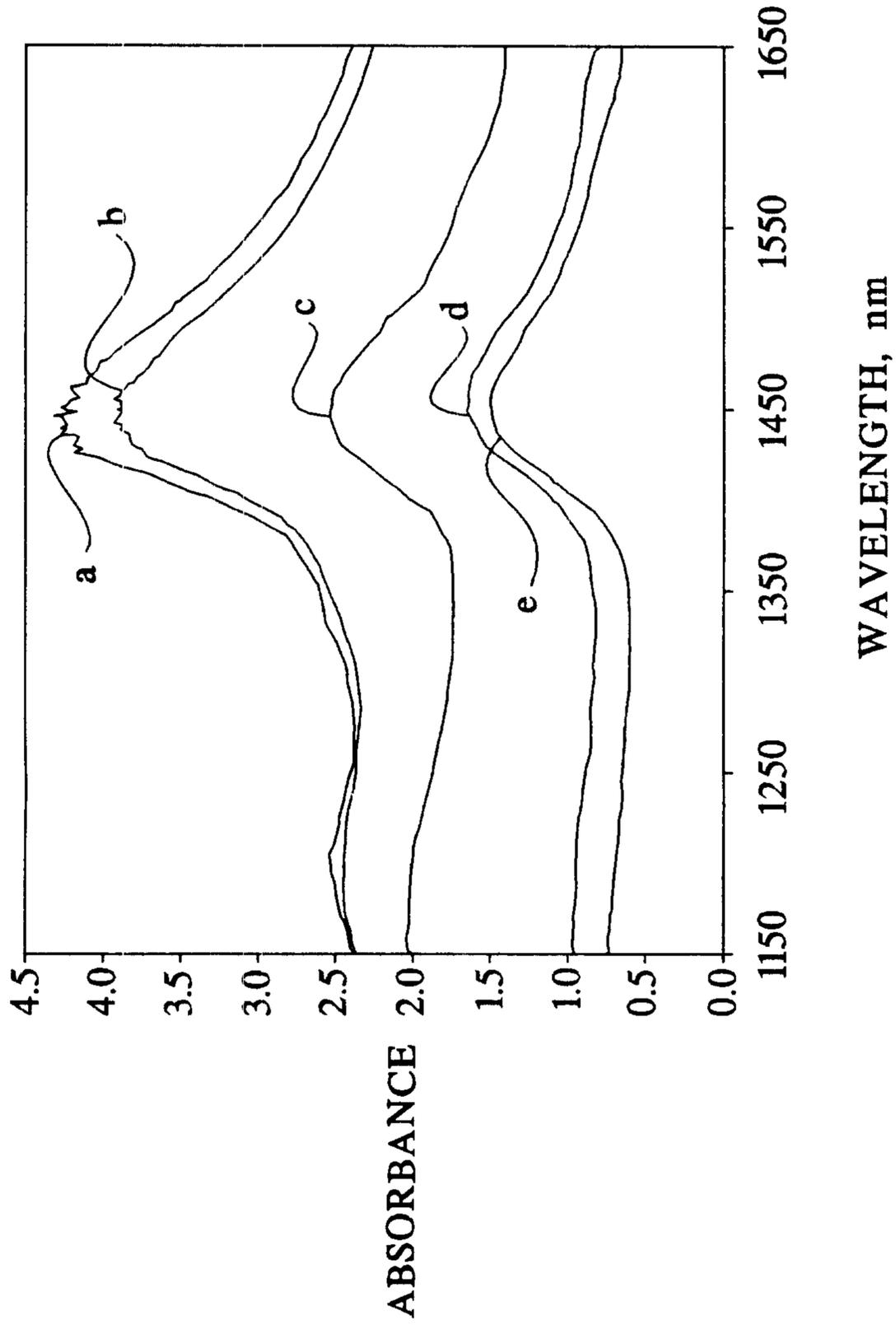
*Sim; M. Bunnell*

FIG.5



*Simon, M. G. Bunnell*

FIG.6

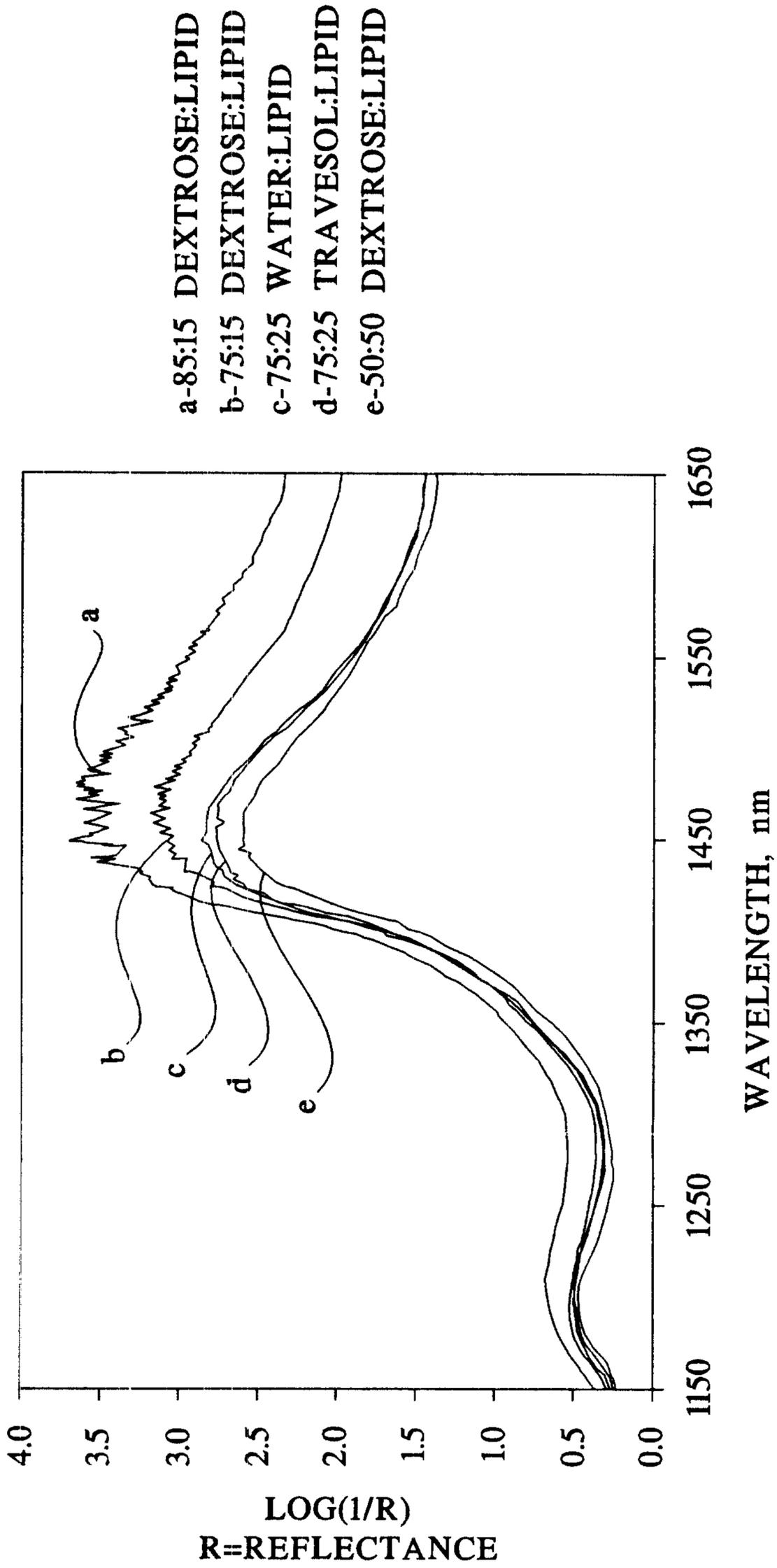


- a-50:50 WATER:LIPID
- b-50:50 TRAVESOL:LIPID
- c-50:50 DEXTROSE:LIPID
- d-75:25 DEXTROSE:LIPID
- e-85:15 DEXTROSE:LIPID

2 1 5 9 2 3 5

*Simon, M. Samuel*

FIG.7



*Singh, N. Kumar*

FIG.8

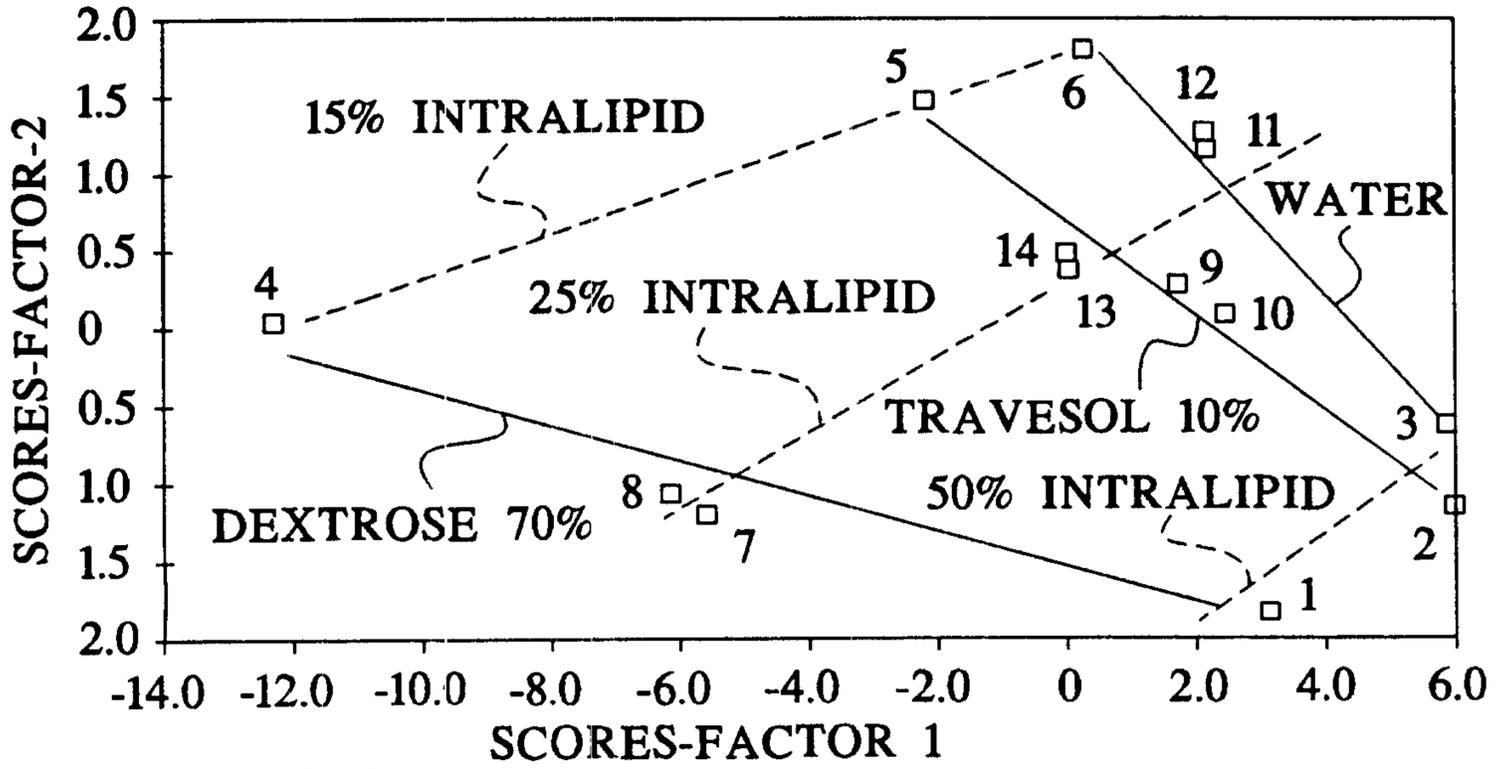


FIG.9

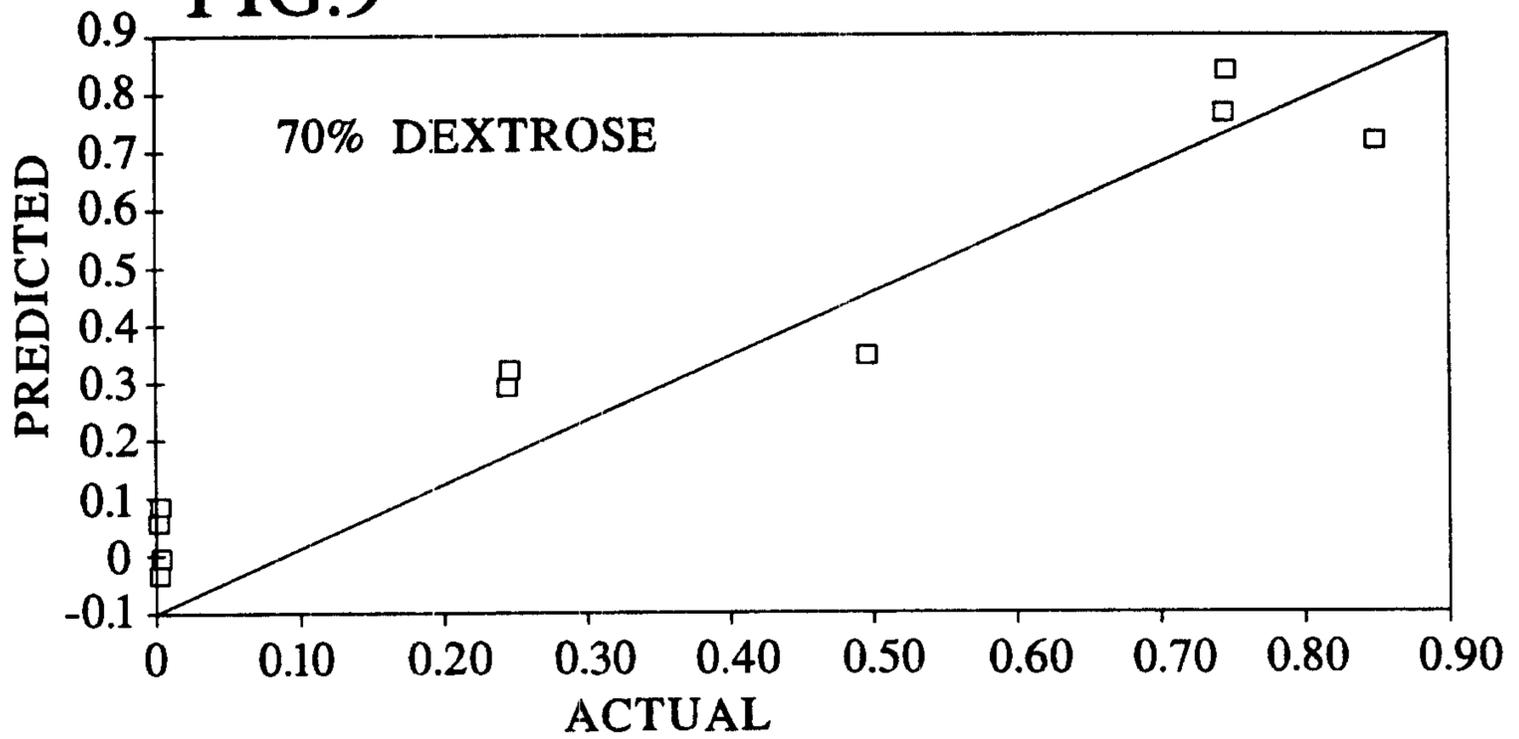
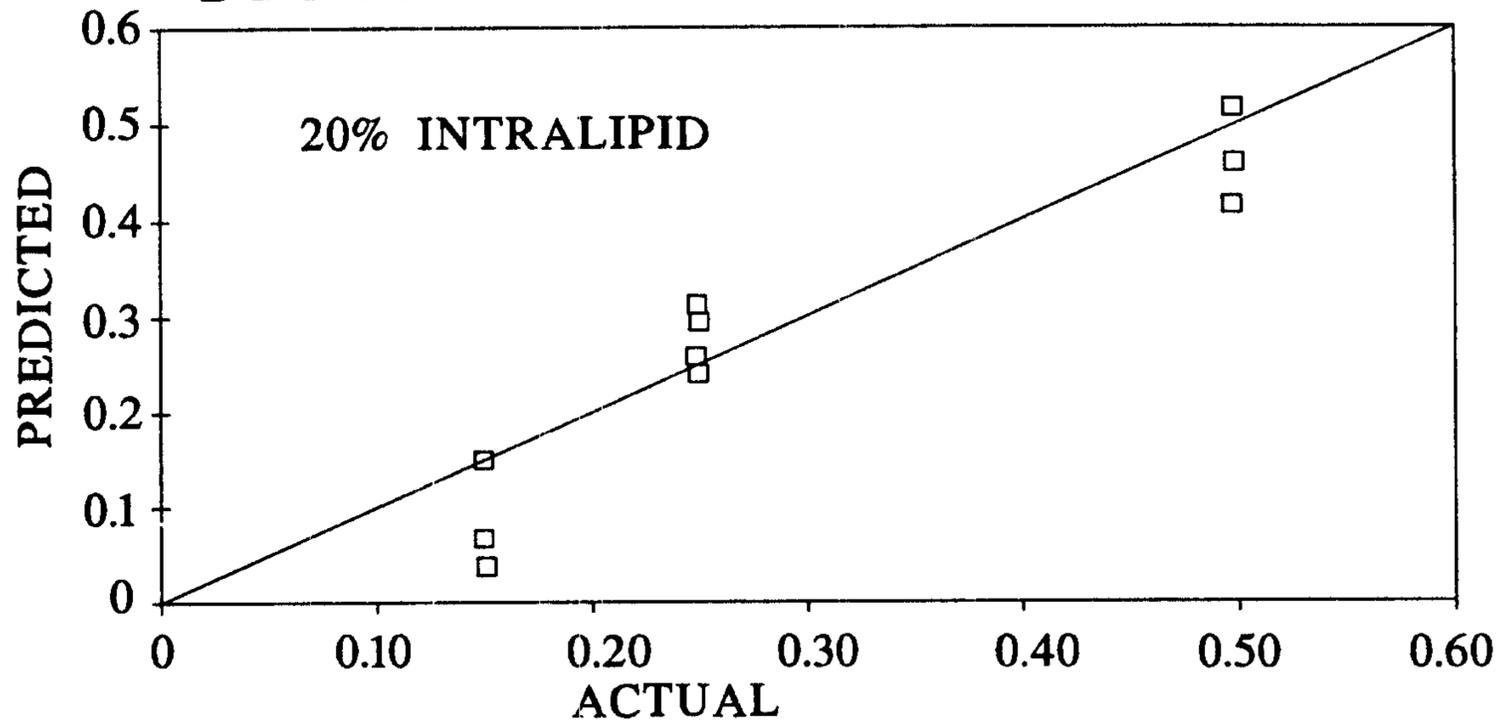
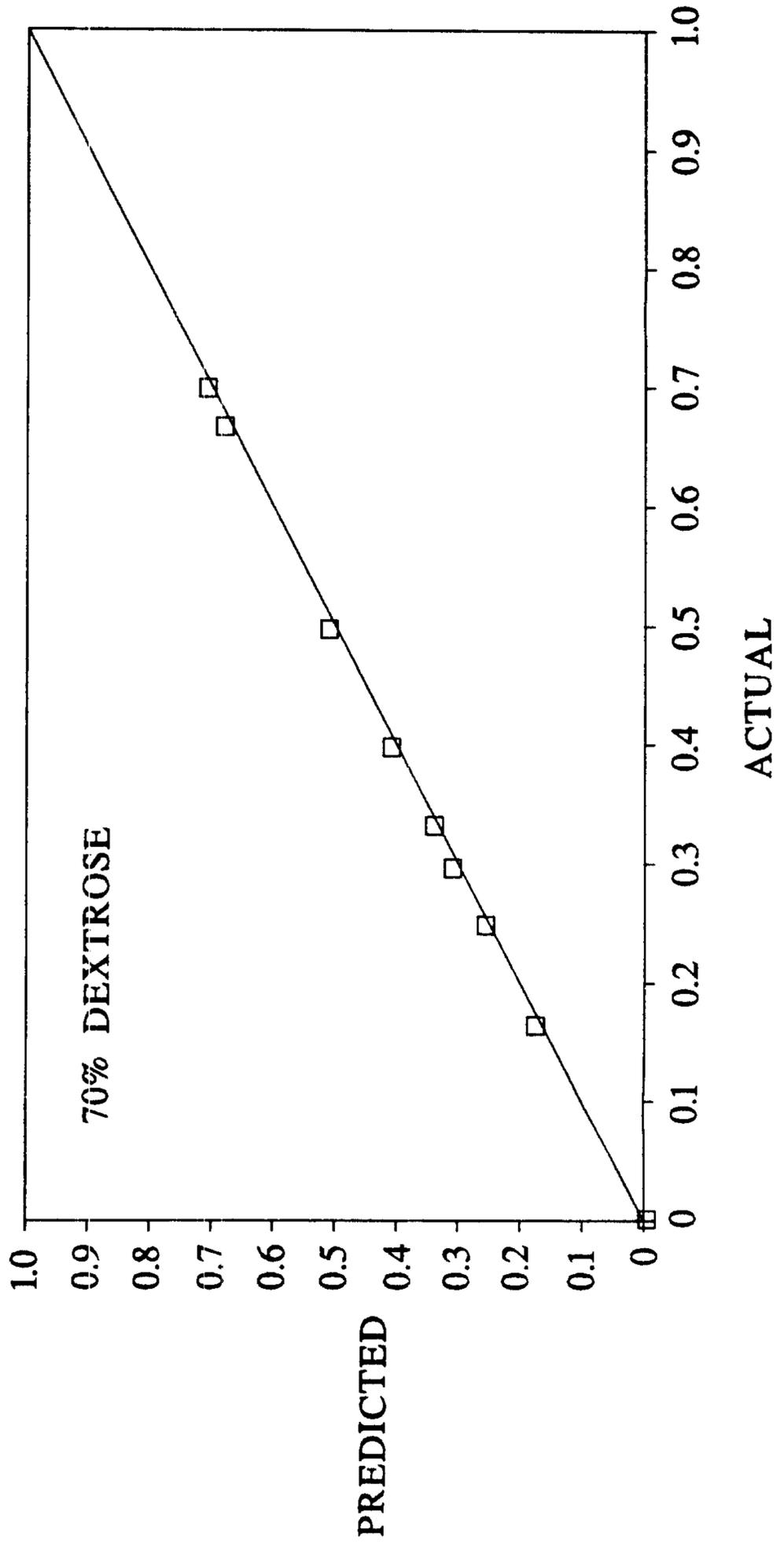


FIG.10



*Sim; M. Suman*

FIG.11



*Sim, J. M. L.*

FIG.12

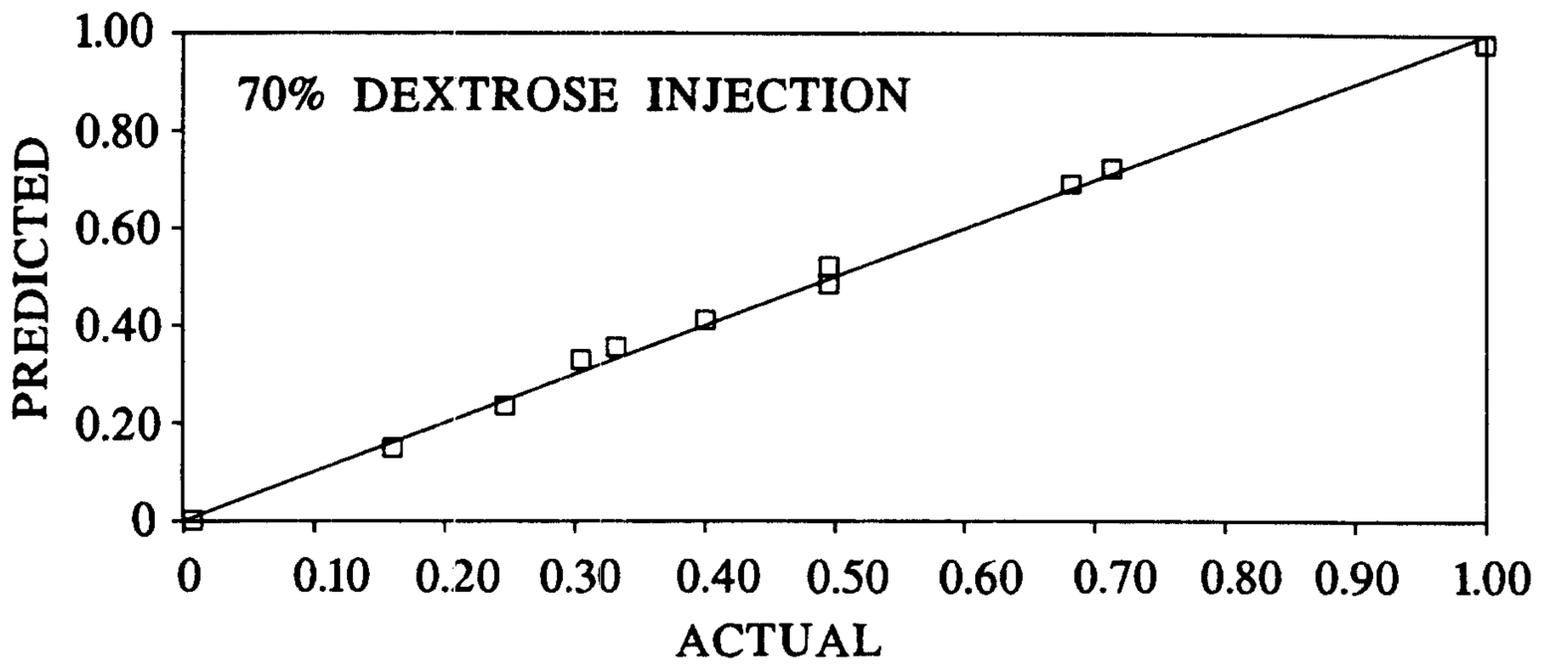


FIG.13

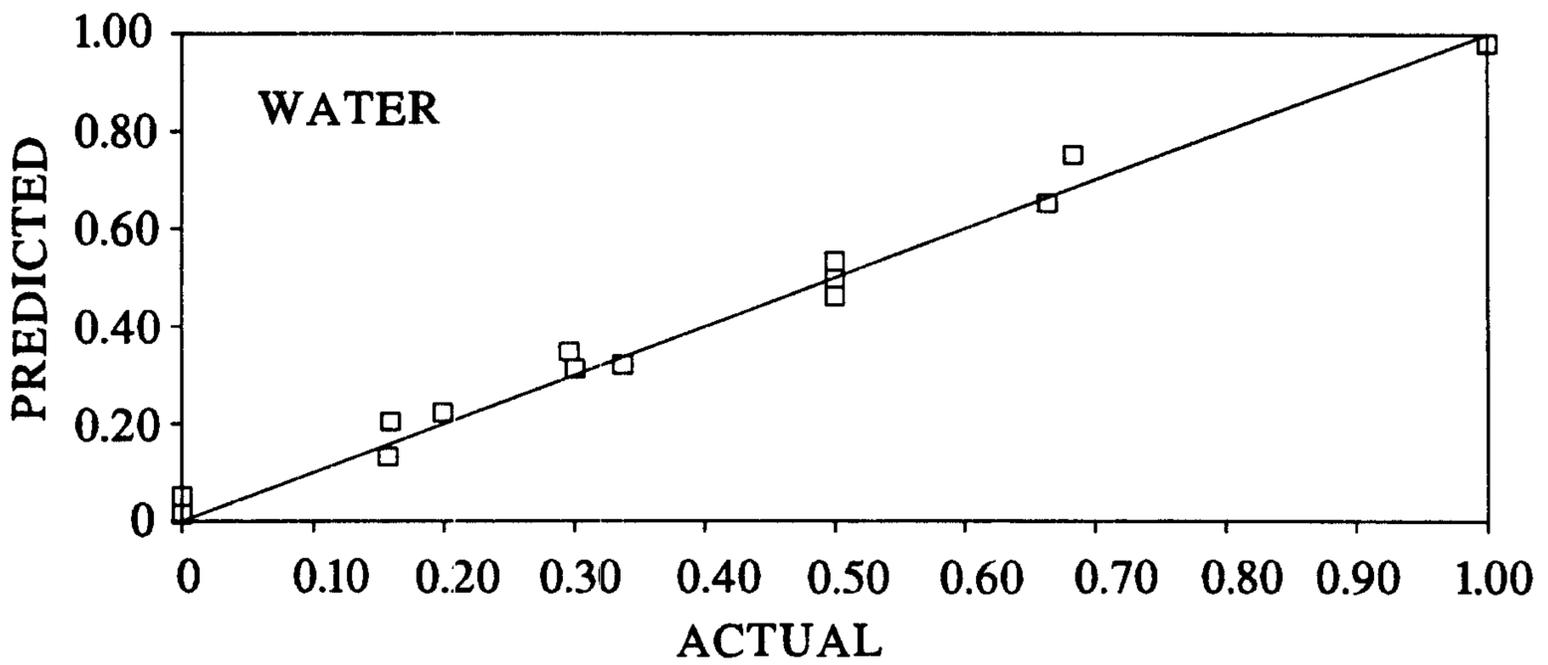
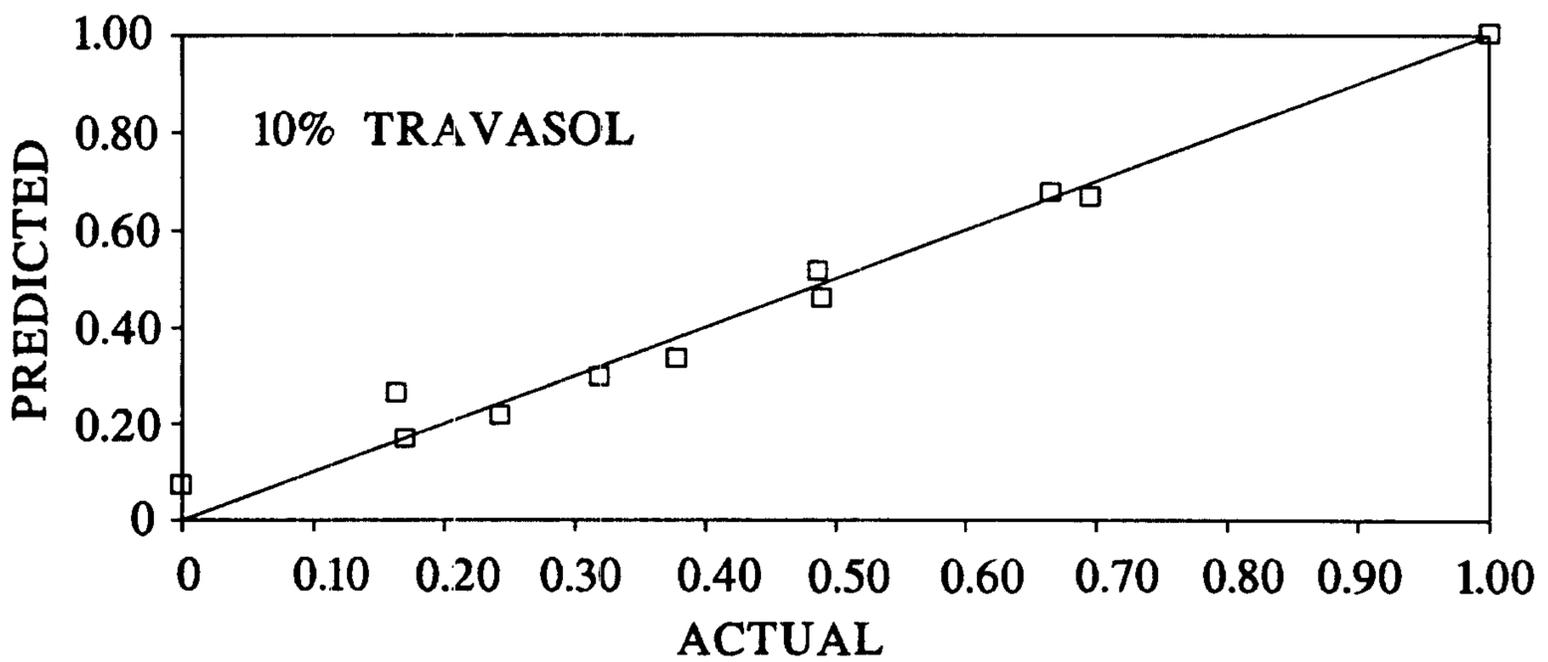


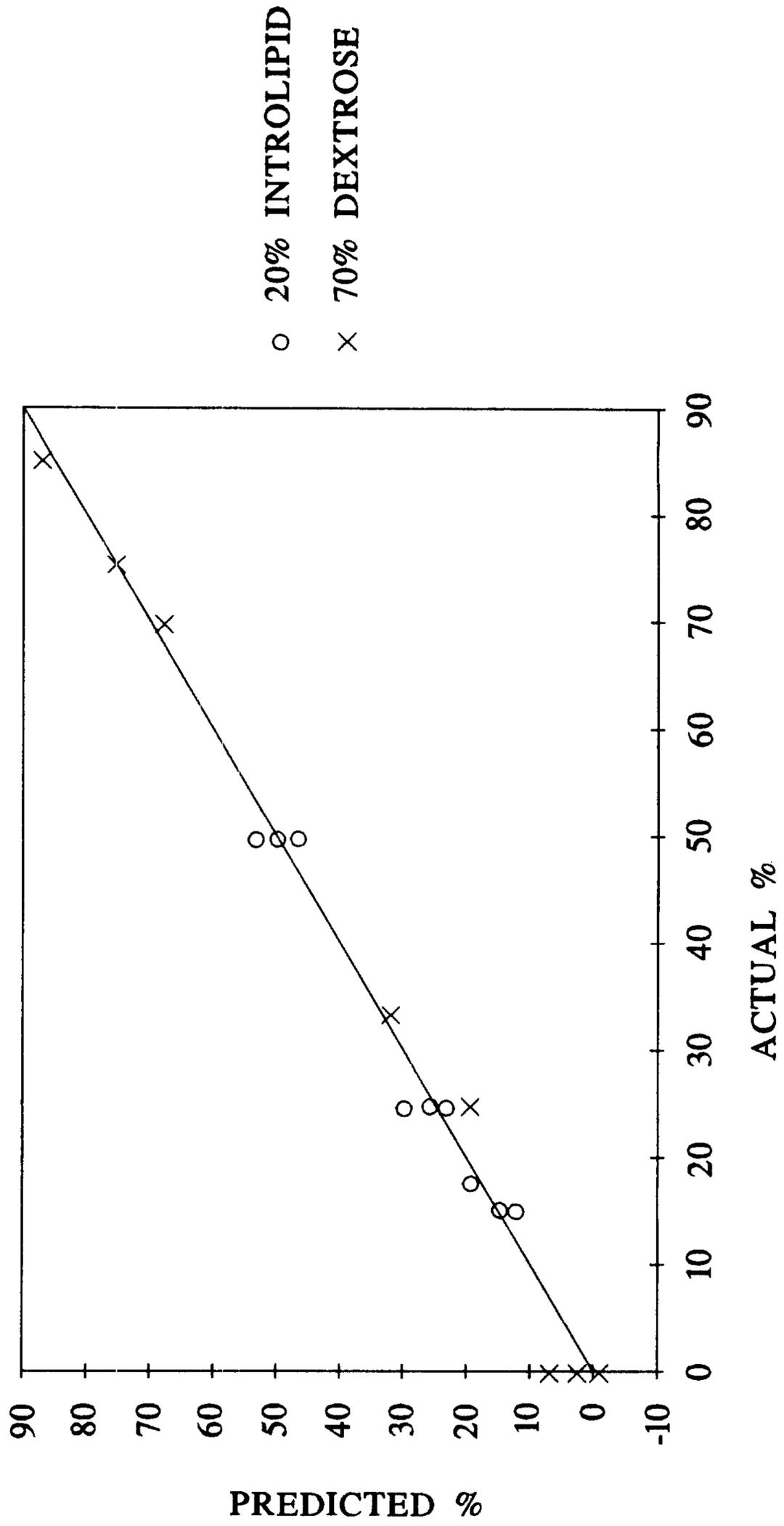
FIG.14



*Srinivasulu Reddy*

2159235

FIG.15



*Simon, M. Bennett*

