United States Patent [19]

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Isreeli et al.

[54] **PHASE SEPARATOR FOR CONTINUOUS FLOW OPERATION**

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[52] **U.S. Cl.** **210/532**, 23/253

[51] **Int. Cl.** **B01d 12/00**, G01n 29/02

[58] **Field of Search** 23/230, 253; 210/65, 210/83, 84, 532, 533, 536, 537, 538

[56] **References Cited**

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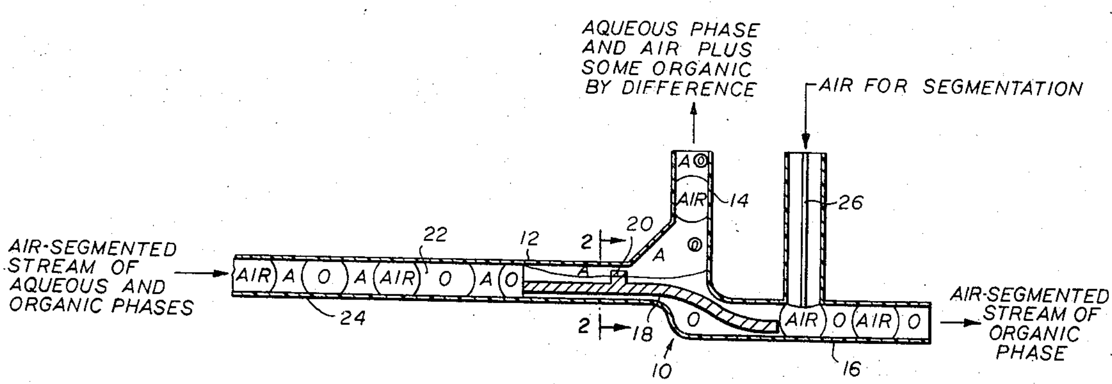
[57] **ABSTRACT**

A separator for separating multiphase fluid streams. The separator includes inlet and outlet means having wettable means positioned within the inlet means to direct the fluid to the outlet means.

8 Claims, 6 Drawing Figures



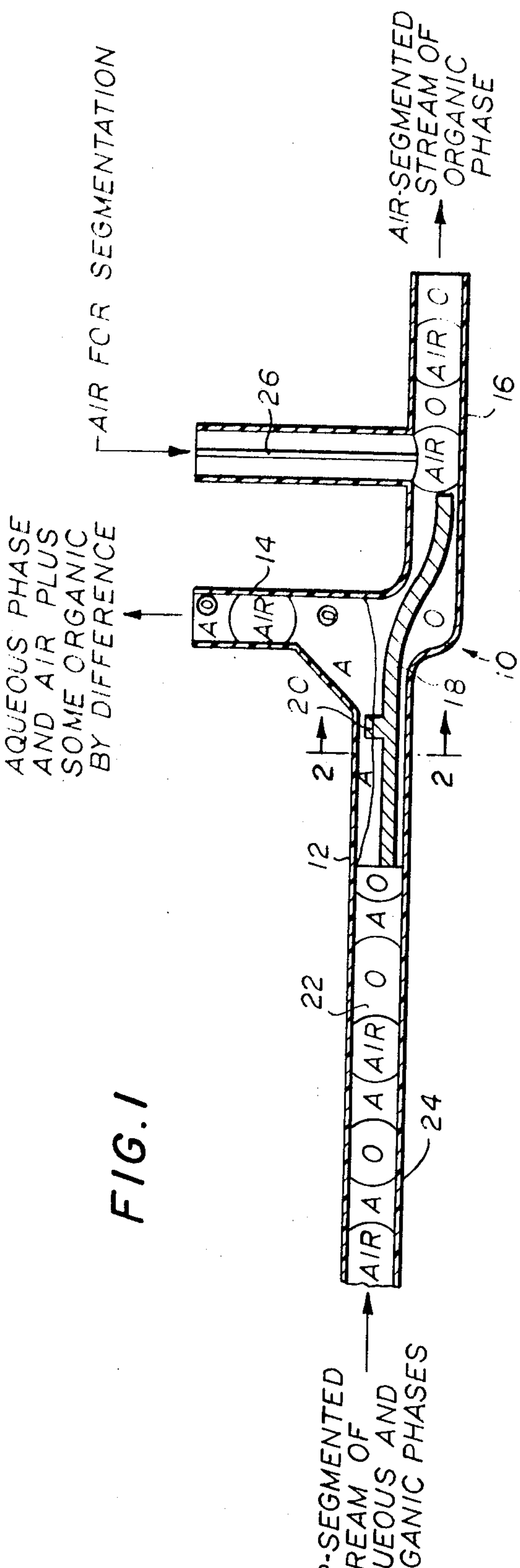

AIR FOR SEGMENTATION
AQUEOUS PHASE AND AIR PLUS SOME ORGANIC BY DIFFERENCE
AIR-SEGMENTED STREAM OF ORGANIC PHASE
AIR-SEGMENTED STREAM OF AQUEOUS AND ORGANIC PHASES
26
14
16
10
18
20
12
22
24
2
AIR
A
O

FIG. 1

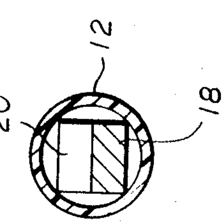

12
20
18

FIG. 2

FIG. 3

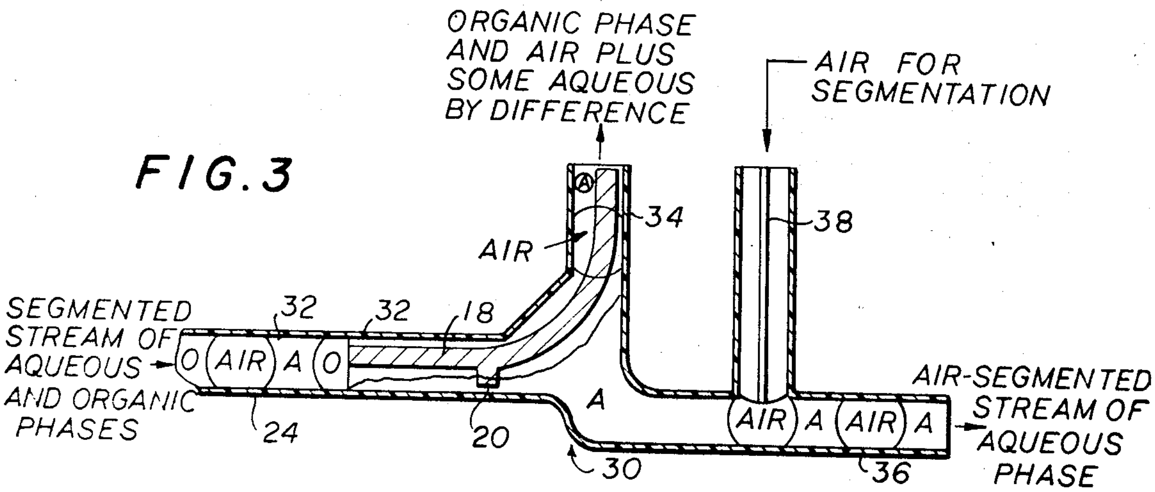


FIG. 4

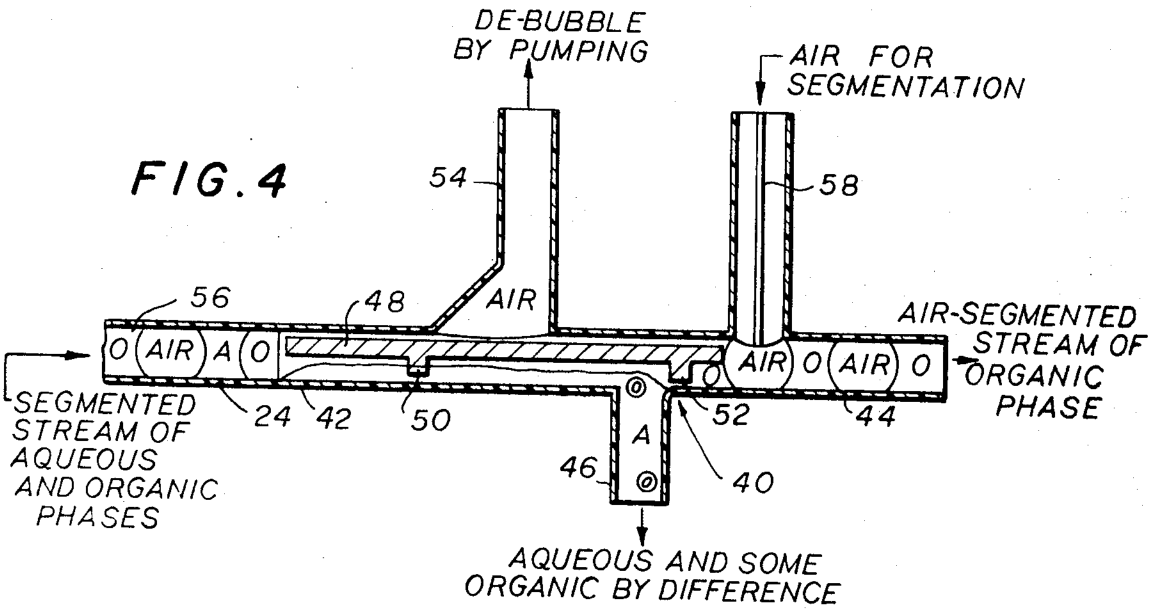
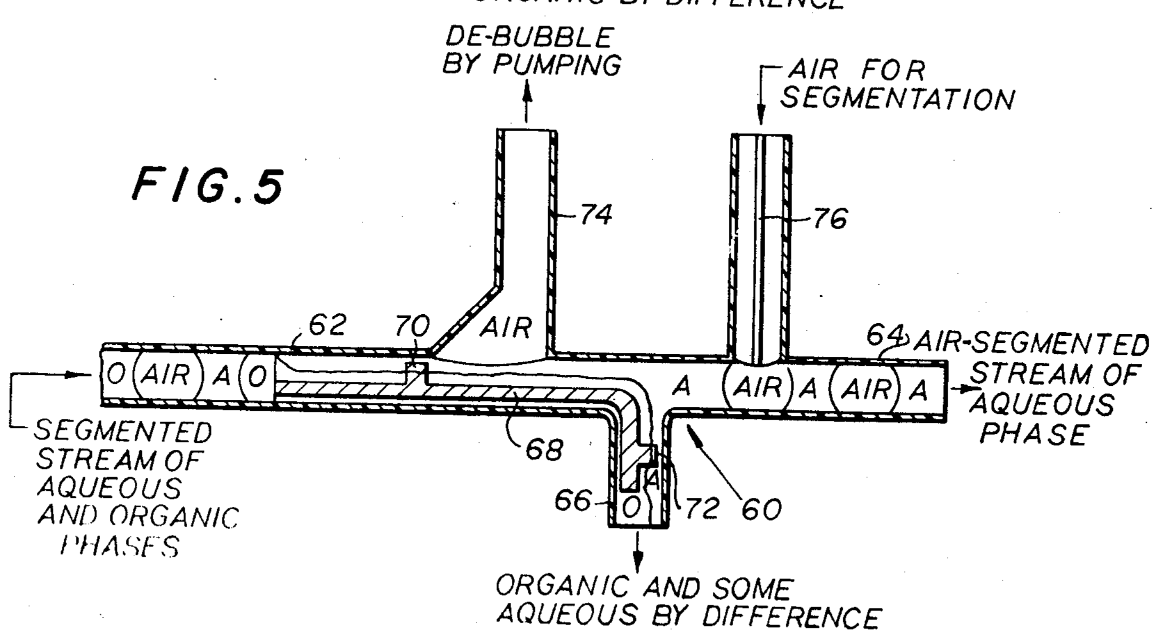


FIG. 5



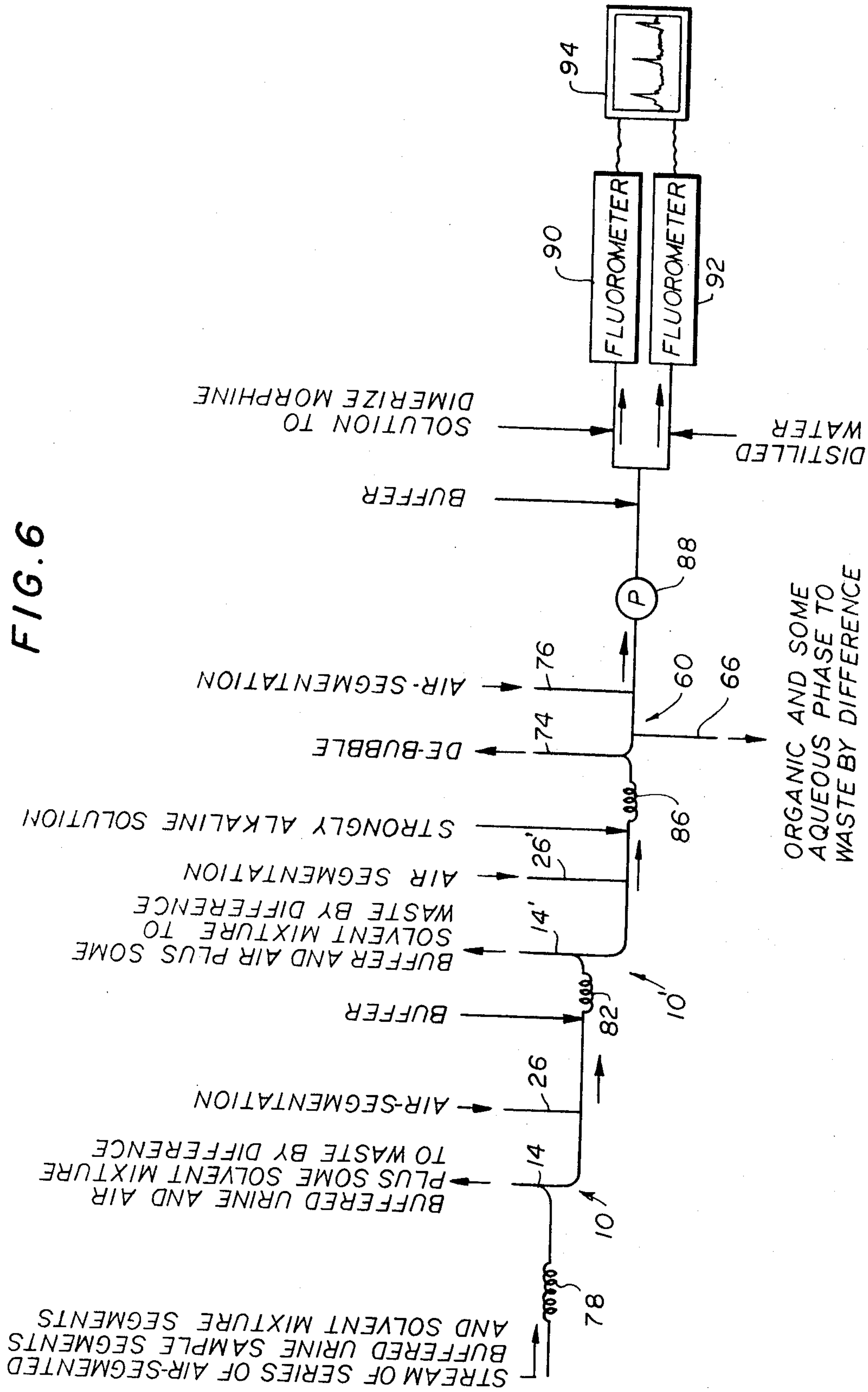

STREAM OF SERIES OF AIR-SEGMENTED BUFFERED URINE SAMPLE SEGMENTS AND SOLVENT MIXTURE SEGMENTS
78
BUFFERED URINE AND AIR PLUS SOME SOLVENT MIXTURE TO WASTE BY DIFFERENCE
14
10
AIR-SEGMENTATION
26
BUFFER
82
BUFFER AND AIR PLUS SOME SOLVENT MIXTURE TO WASTE BY DIFFERENCE
14'
10'
AIR SEGMENTATION
26'
STRONGLY ALKALINE SOLUTION
86
DE-BUBBLE
74
60
66
ORGANIC AND SOME AQUEOUS PHASE TO WASTE BY DIFFERENCE
AIR-SEGMENTATION
76
P
88
BUFFER
SOLUTION TO DIMERIZE MORPHINE
DISTILLED WATER
FLUOROMETER
90
FLUOROMETER
92
94

FIG. 6

PHASE SEPARATOR FOR CONTINUOUS FLOW OPERATION

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a new and improved phase separator for continuous flow operation.

2. Description of the Prior Art

Although phase separators for continuous flow operation are known, it may be understood that the same will, in general, be found to have relatively large hold-up volumes which function to limit the usefulness thereof in automated analysis apparatus. More specifically, and for use, for example, in automated analysis apparatus wherein a series of different samples which constitute an aqueous phase are formed into a stream and automatically and successively treated, as by solvent extraction, through interaction with a solvent phase, it may be understood that the relatively large hold-up volumes of the included prior art phase separators will function to unduly limit the sample analysis rate at which such analysis apparatus may be operated, and will not, in every instance, provide the complete phase separation as is required to insure the consistent accuracy of the sample analysis results. Too, said relatively large hold-up volumes are not particularly conductive to the required maintenance of sample integrity with resultant possility of unacceptable inter-sample contamination.

OBJECTS OF THE INVENTION

It is, accordingly, an object of this invention to provide a new and improved phase separator for cintinuous flow operation having a very small hole-up volume.

Another object of this invention is the provision of a phase separator as above including means to promote complete phase separation.

Another object of the invention is the provision of a phase separator as above which, when utilized with a stream of a series of different samples, includes means to preserve sample integrity and inhibit inter-sample contamination.

A further object of this invention is the provision of a phase separator as above which is particularly adaptable for use in an automated, continuous flow sample anslysis system which functions to determine the morphine level in a succession of different urine samples at a particularly high analysis rate.

SUMMARY OF THE DISCLOSURE

As disclosed herein, the new and improved phase separator for continuous flow operation of the invention takes the form of a fitting of a suitably inert material in the nature of glass having a body portion, an inlet for a multi-phase stream which includes aqueous and organic phases, and first and second outlets for said phases. Means which are preferentially wettable by said organic phase to promote phase separation and the accumulation of said organic phase and flow thereof to the outlet therefor are provided and take the form of a generally elongate member which is insertable into said separator to extend generally between said inlet and the outlet for said organic phase. For use in those instances wherein the organic is the heavier of the phases, the outlet therefore is disposed at a lower level than the aqueous phase outlet, while the reverse is true for instances wherein the aqueous phase is the heavier to thereby, in either event, take full advantage of the natural separational effects of gravity. Means may be included to segment one of the resultant separated phase streams with a suitable separating fluid when the separator is used in automated, sample analysis systems.

An application of the separator of the invention in an automated analysis system directed toward the determination of the morphine levels in a stream of different urine samples on a continuous flow basis is disclosed to clearly illustrate the advantages provided by the separator.

DESCRIPTION OF THE DRAWINGS

The above and other objects and significant advantages of the invention are believed made clear by the following detailed description thereof taken in conjunction with the accompanying drawings wherein:

FIG. **1** is a longitudinal cross-sectional view taken through a first embodiment of the phase separator of the invention;

FIG. **2** is a cross-sectional view taken along line **2—2** of FIG. **1**;

FIG. **3** is a longitudinal cross-sectional view taken through a second embodiment of the phase separator of the invention;

FIG. **4** is a longitudinal cross-sectional view taken through a third embodiment of the phase separator of the invention;

FIG. **5** is a longitudinal cross-sectional view taken through a fourth embodiment of the phase separator of the invention; and

FIG. **6** is a schematic flow diagram illustrating a utilization of the phase separator of the invention in an automated sample analysis system.

DETAILED DESCRIPTION OF THE INVENTION

Referring now to FIGS. **1** and **2**, a first embodiment of a new and improved phase separator for organic-aqueous phase separation in continuous flow analysis is indicated generally at **10** and comprises an inlet **12** and outlets **14** and **16**. The separator **10** is preferably made of glass. An insert **18** of a material which is preferentially wet by said organic phase is disposed as shown within the separator by friction fit, and the insert includes a nib or the like **20** to maintain the same positioned substantially as depicted. For use with a polar aqueous phase and a non-polar organic phase, the insert **18** is made of a suitable material in the nature of Teflon or polyethylene having a non-polar surface.

A stream **22** of alternating, substantially immiscible organic and aqueous (O and A) liquid phase segments, in which said organic phase is the heavier, is flowed as by pumping into separator inlet **12** through conduit **24.** For a typical continuous flow utilization of the separator **10,** the stream **22** will preferably be segmented as shown by a suitable separating fluid in the nature of air, and will consist of successive treated samples of an aqueous phase, a solute from which has been extracted into an organic solvent phase by preferential partitioning during flow through a mixing coil or the like as well understood by those skilled in the continuous flow solvent extraction art.

As the stream **22** enters the separator **10,** the non-polar surface of the insert **18** will be preferentially wet by the non-polar solvent phase, to the substantial exclusion of the polar aqueous phase, thereby causing the solvent phase to coalesce and pool at and on said insert.

This preferential wetting, in conjunction with the natural separational effects of gravity on said solvent phase, will cause the same to follow the insert to the lower portion of the separator **10** for flow therefrom through outlet **16**.

A very small portion of the organic phase, plus substantially all of the aqueous phase and the air will flow by difference from the separator through outlet **14**. Segmentation of the resultant organic phase stream for wash purposes and for maintaining sample integrity in a continuous flow separation system may be readily effected by the introduction of a suitable separating fluid in the nature of air to said stream as indicated through capillary **26**, although it is believed clear that such segmentation is not essential to efficient phase separation. In the same manner, it is believed clear that the incoming stream **22** need not be air-segmented for efficient operation of the separator **10**.

A second embodiment of the separator is indicated at **30** in FIG. **3** and comprises an inlet **32**, outlets **34** and **36**, and the insert **18**. The separator **30** is for use when the aqueous phase is the heavier, and would be particularly applicable for hase separation following the back-extraction of a solute from the organic to aqueous phases on a continuous flow basis. As the stream **22** enters the separator **30**, the solvent phase again preferentially wets and follows the insert **18**, to the substantial exclusion of the aqueous phase for flow by difference, with the air and a very small portion of the aqueous phase, from the separator **30** through outlet **34**. The substantial majority of the aqueous phase will, meanwhile, collect as shown under the influence of gravity in the lower portions of the separator **30** for flow therefrom through outlet **36**. Air-segmentation of the resultant aqueous phase may again be effected through a capillary as here indicated at **38**.

A third embodiment of the separator is indicated at **40** in FIG. **4** and comprises an inlet **42** and outlets **44** and **46**. The insert, here indicated at **48**, comprises nibs **50** and **52** for positioning. A debubbler is indicated at **54** and in included only when the incoming stream **56** is air-segmented. The separator **40** is for use when the organic phase is the lighter in, for example, a continuous flow solvent extraction process as described with regard to FIG. **1**. As the stream **56** enters the separator **40**, the organic phase will preferentially wet and follow the insert **48** with the result that the major portion thereof, as air segmented if required through capillary **58**, will flow from the separator through outlet **44**. The aqueous phase with a very small portion of the organic phase will flow by difference from the separator through outlet **46**.

A fourth embodiment of the separator is indicated at **60** in FIG. **5** and comprises an inlet **62** and outlets **64** and **66**. The insert, here indicated at **68**, comprises nibs **70** and **72** for positioning within the separator as shown. A debubbler is indicated at **74** and is included only when the incoming stream **76** is air-segmented. The separator **60** is for use when the aqueous phase is the lighter and would be particularly applicable for phase separation following back-extraction of a solute to the lighter aqueous phase on a continuous flow basis. As the stream **76** enters the separator **60**, the organic phase will preferentially wet and follow the insert **68** with the result that substantially all of said organic phase, with a very small portion of the aqueous phase will flow by difference from the separator through outlet conduit **66**. The ligher aqueous phase will meanwhile remain substantially above the preferentially wetted insert **68** for flow from the separator, as air-segmented if desired through capillary **76**, through outlet **64**.

"Purging" of each of the disclosed separator embodiments prior to the utilization thereof may, of course, be readily effected by the initial flow therethrough, for a sufficient period of time, of the phase which preferentially wets the insert to insure the absence of any of the other phase in the separator prior to the commencement of operation.

Of particular advantage with regard to each of the disclosed separator embodiments is the fact the hold-up volume, or volume thereof which must be filled for each phase separation, is substantially minimal, whereby the operational rates of the separators in terms of the number of treated samples which may be processed thereby per unit time is maximized. Too, the substantially complete separation provided with regard to the separated phase of interest is, of course, of particularly significant advantage as should be obvious.

A utilization of the separation of the invention in a system for the automated fluorometric determination of the morphine levels in urine samples to determine drug use on the part of the urine donors is illustrated schematically in FIG. **6** and, briefly described, comprises the supply of a continuous air-segmented stream of successive urine sample segments buffered to appropriate pH (the aqueous phase), generally alternating segments of a heavier solvent mixture (the organic phase), and appropriately spaced segments of a suitable wash liquid, respectively, to and through a suitable mixing coil **78** to effect the extraction of the free morphine base solute from the buffered urine sample segments to the adjoining solvent mixture segments through preferential solute partitioning. Following this, the stream is flowed through the separator **10** of FIG. **1** for separation of the organic phase as described, and which now contains the morphine solute of interest, and immediate re-segmentation of this phase with air through capillary **26** to thereby maintain sample integrity and inhibit inter-sample contamination.

Thereafter, a buffer solution at the same appropriate pH is added to the organic phase and the resultant stream flowed through mixing coil **82** to effect a "cleansing" of the organic phase by wash-extraction or back-extraction of amino acids and like compounds indiginous to urine therefrom into the buffer solution aqueous phase. Separation of the organic phase from this buffer is then effected in separator **10'** and is followed as indicated by the re-segmentation with air of the solvent phase.

A strongly alkaline solution is then added as indicated to the solvent phase stream and the resultant stream flowed through a mixing coil **86** to effect back-extraction of the morphine solute into this newly added alkaline solution aqueous phase. Following this, the resultant stream is flowed through the separator **60** of FIG. **5**, wherein the same is de-bubbled by debubbler **74** and the organic phase and a very small portion of the aqueous phase flowed to waste by difference through outlet **66**, while the major portion of said aqueous phase, now containing the morphine solute of interest, is immediately re-segmented with air and flowed from separator **60** to and through pump **88**.

A buffer at the appropriate pH is then added to the aqueous phase and the same divided as indicated into two streams. A pseudo-morphine solution to dimerize the morphine is added to one of said streams, and distilled water added to the other to provide a blank channel, whereupon said streams are simultaneously applied to and analyzed in fluorometers **90** and **92.** The results of these analayses are applied as indicated to a strip chart recorder to provide a readily readable and reproducible record of the morphine level in each of said urine samples.

A general discussion of the methodology involved in the determination of morphine levels in urine samples is provided in the article "Automated Analysis for Drugs in Urine" by D. V. Blackmore, et al., as published in CLINICAL CHEMISTRY, Volume 17, No. 9, of 1971; and such article is hereby incorporated by reference herein.

Utilization as described of the separator of the invention in an automated analysis system may be understood to make possible the operation of said system at a rate of between 40 and 60 samples per hour with the same clarity of analysis results as could be provided by such system utilizing the separators of the prior art at a maximum rate of between only 10 and 20 samples per hour.

Although disclosed as comprising a separately formed preferentially wettable insert, it is believed clear that the separator of the invention could, alternatively, be fabricated with said insert formed as an integral part thereof.

Too, and although disclosed by way of illustrative example as applied to the determination of morphine levels in urine samples, it is believed clear that the phase separator of the invention is by no means limited thereto, but rather, is advantageously utilizable for the phase separation function in a very wide variety of other and different applications.

While we have shown and described the preferred embodiment of our invention, it will be understood that the invention may be embodied otherwise than as herein specifically illustrated or described, and that certain changes in the form and arrangement of parts and in the specific manner of practicing the invention may be made without departing from the underlying idea or principles of this invention within the scope of the appended claims.

What is claimed is:

1. A separator for separating phases from a multiphase fluid stream on a continuous flow basis comprising, an inlet for said multi-phase stream, first and second outlets, and means in said separator which are preferentially wettable by one of said phases to promote phase separation and the accumulation of said one phase on and around said means and the flow of said phase to a predetermined one of said outlets, said last-mentioned means extending generally from said inlet and to said predetermined one of said outlets, so as to direct said one phase to said predetermined one of said outlets.

2. A separator as in claim **1** wherein, said multi-phase stream comprises an aqueous phase and an organic phase, and wherein said means are preferentially wettable by said organic phase.

3. A separator as in claim **1** wherein, said multi-phase stream comprises a polar phase and a non-polar phase, and wherein said means comprise a non-polar surface so as to be preferentially wettable by said non-polar phase.

4. A separator as in claim **1** wherein, said last-mentioned means comprises a generally elongate member which is insertable into said separator to extend generally from said inlet and to said predetermined one of said outlets.

5. A separator as in claim **2** wherein, said organic phase is heavier than said aqueous phase, said predetermined one of said outlets is disposed at a lower level than the other of said outlets.

6. A separator as in claim **2** wherein, said aqueous phase is heavier than said organic phase, said predetermined one of said outlets is disposed at a higher level than the other of said outlets.

7. A separator as in claim **1** further comprising, means to introduce a separating fluid after phase separation to segment the phase which flows to said predetermined outlet.

8. A separator as in claim **1** further comprising, means to introduce a separating fluid after phase separation to segment the phase which flows to the other of said outlets.

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