



(22) Date de dépôt/Filing Date: 2000/05/26

(41) Mise à la disp. pub./Open to Public Insp.: 2000/12/07

(45) Date de délivrance/Issue Date: 2010/08/03

(62) Demande originale/Original Application: 2 373 939

(30) Priorité/Priority: 1999/05/26 (GB9912356.4)

(51) Cl.Int./Int.Cl. *A61K 9/12* (2006.01),
A61J 1/20 (2006.01), *A61K 31/08* (2006.01),
A61K 31/185 (2006.01), *A61M 11/00* (2006.01),
A61M 5/178 (2006.01)

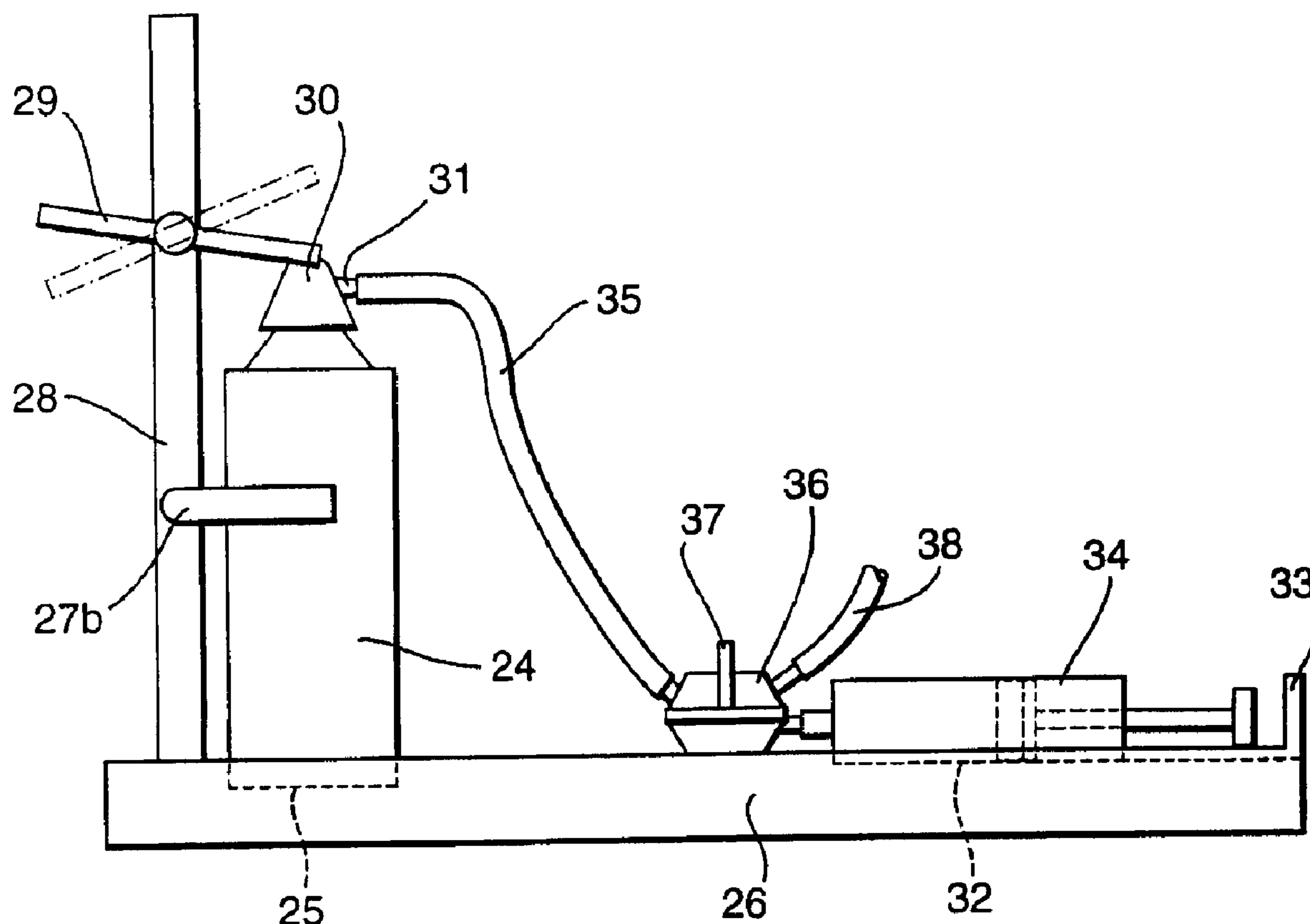
(72) Inventeurs/Inventors:
OSMAN, TARIQ, GB;
FLYNN, SHEILA BRONWEN, GB;
WRIGHT, DAVID DAKIN IORWERTH, GB;
HARMAN, ANTHONY DAVID, GB;
BOORMAN, TIMOTHY DAVID, GB

(73) Propriétaire/Owner:
BTG INTERNATIONAL LIMITED, GB

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : GENERATION DE MICROMOUSSE THERAPEUTIQUE

(54) Title: GENERATION OF THERAPEUTIC MICROFOAM



(57) Abrégé/Abstract:

Improved therapeutic sclerosing microfoams and methods and devices for making them are provided that have advantage in producing a consistent profile injectable foam with minimal input by the physician yet using high volume percentages of blood dispersible gases, thus avoiding use of potentially hazardous amounts of nitrogen.

23410-647D

5

ABSTRACT

Improved therapeutic sclerosing microfoams and methods and devices for making them are provided that have advantage in producing a consistent profile injectable foam with minimal input by the physician yet using high volume percentages of blood dispersible gases, thus avoiding use of potentially hazardous amounts of nitrogen.

23410-647D

GENERATION OF THERAPEUTIC MICROFOAM

This application is a divisional of Canadian National Phase Patent Application Serial Number 2,373,939, filed May 26, 2000.

The present invention relates to the generation of microfoam comprising a sclerosing material, particularly a sclerosing liquid, which is suitable for use in the treatment of various medical conditions involving blood vessels, particularly varicose veins and other disorders involving venous malformation.

Sclerosis of varicose veins is based on the injection into the veins of liquid sclerosant substances which, by *inter alia* causing a localised inflammatory reaction, favour the elimination of these abnormal veins. When a sclerosing substance is injected in liquid form, it is mixed with the blood contained in the vein and is diluted in an unknown proportion. The results are uncertain, owing to over- or under-dosage, and are limited to short varicose segments. As the size of the varicose veins to be injected decreases, this dilution is less and the results obtained are more predictable.

Until recently, sclerosis was a technique selected in cases of small and medium varicose veins, those with diameters equal to or greater than 7 mm being treated by surgery. Sclerosis and surgery complemented one another but sclerosis treatment continued not to be applicable to large varicose veins. In these large varicose veins, if a sclerosing substance was injected, its concentration in the vein, its homogeneous distribution in the blood, and the time for which it is in contact with the internal walls of the vessel treated were not known.

In 1946, Orbach injected a few cubic centimetres of air into small varicose veins and confirmed a displacement of the blood inside the vessel which was occupied by the injected air. A sclerosing solution introduced immediately afterwards was more effective than if it had been injected into the blood. However, in thick varicose veins, when air is injected the phenomenon described of the displacement of the blood by the injected air does not occur but the air forms a bubble inside the vein which makes the method ineffective in these vessels.

The same author had the idea, a few years later, of injecting foam obtained by agitation of a container containing sodium tetradecyl sulphate, which is an anionic

23410-647D

sclerosing detergent with a good foaming capability. The method was of little use owing to the large size of the bubbles formed and was dangerous owing to the side effects of atmospheric nitrogen which is only slightly soluble in blood. Both methods had limited practical repercussion being used only in small varicose veins.

5 An injectable microfoam suitable for therapeutic uses has now been developed and is described in EP 0656203 and US 5676962. These patents describe a microfoam produced with a sclerosing substance which, when injected into a vein, displaces blood and ensures that the sclerosing agent contacts the endothelium of the vessel in a known concentration and for a controllable
10 time, achieving sclerosis of the entire segment occupied.

 The advantages of use of this foam are that it allows the concentration of the sclerosing agent in the blood vessel to be known, since the microfoam displaces the blood and is not diluted therein in to the same extent as a simple liquid would be. Furthermore it allows homogeneous distribution of the sclerosis product in the vein to
15 be ensured and the time for which it is kept in contact with the internal walls of the vein to be controlled. None of which factors is known precisely or is controllable with the use of sclerosing agents in simple liquid form.

 The preparation of such a microfoam may be carried out with a solution of any sclerosing substance, particularly polidocanol, alkali metal tetradecyl sulphate eg.
20 sodium salt, hypertonic glucose or gluco-saline solutions, chromic glycerol, ethanolamine oleate, sodium morrhuate or iodic solutions.

 However, this known method requires production of microfoam by the physician, pharmacist or an assistant immediately prior to administration to the patient. Such procedure allows for variation of agent depending upon the person
25 preparing it, with content of gas, bubble size and stability all needing attention with respect to the condition being treated. It also requires a high degree of care and knowledge that may be difficult to replicate under pressure, ie. when time available to prepare the foam is short.

The method particularly described in the aforesaid patents uses a high speed beating action with a brush to generate a foam of correct property. Other reported techniques in use do not produce such uniform, stable or injectable microfoam and notably include those where gas is bubbled, eg sparged into the sclerosant, eg. by leakage into a sclerosant filled syringe from around the side of the syringe plunger.

Furthermore, a problem in using air as the gas for producing the foam is the perception that large volumes of nitrogen should not unnecessarily be introduced into patients, particularly where large vessels are being filled with foam and eliminated. Gas embolism with nitrogen remains a possibility.

The solubility of physiological gases in aqueous fluids, such as blood, varies considerably. Thus while nitrogen is almost twice as insoluble in water as oxygen at STP, carbon dioxide is over fifty times as soluble in aqueous liquids as nitrogen and over twenty five times as soluble as oxygen.

Table 1: Solubility of Gases in water at STP

Gas	Mole Fraction Solubility 10^{-5}
Helium	0.7
Nitrogen	1.18
Oxygen	2.3
Xenon	7.9
Nitrous oxide	43.7
Carbon dioxide	61.5

At the present time it is perceived that production of such microfoam with gases incorporating high proportions of gas that is readily dispersed in blood, such as carbon dioxide, would be desirable for the purposes of minimising the prospect of the treatment producing a gas embolism. However, it is also perceived by practitioners that this is difficult task due to its high solubility in water.

It would also be desirable to provide a relatively stable microfoam of uniform character that is readily producible by use of a relatively simple and reliable mechanism, rather than one involving use of high speed mixing or beating, the time of performance of which may affect foam property.

- 5 It is particularly desirable that the microfoam so produced may be passed through a needle of gauge suitable for injecting into blood vessels without being significantly converted back to its separate gas and liquid components and/or changing characteristics such as significantly increasing bubble sizes.

Such a needle may be of very small diameter, eg a 30 gauge needle (0.14 mm
10 interior diameter). More typically it will be larger eg. an 18 to 22 gauge needle (interior diameter 0.838 to 0.394mm), more preferably 19 to 21 gauge (interior diameter. 0.686mm).

The rate at which the foam is passed down the needle can be such that any foam might be broken down, but it is desirable that a foam is produced that does not
15 break down under normal injection conditions, ie. at rates compatible with control of entry of foam into a vein. For example, it should withstand injection at rates of 0.1 to 0.5ml/second, more preferably 0.3 to 1ml/second for a 19 to 21 gauge needle.

It is still further desirable to provide a device that is of sterile type with regard to the foam it generates particularly with regard to micro-organisms and pyrogens.

- 20 It is particularly desirable to provide a sealed device that operates to produce foam of set property suitable for a given medical procedure without technical input from the physician who will perform the procedure, or assistants thereof.

One form of device that could potentially provide these desired properties would be an aerosol dispenser of a type that produces foams. However, for the
25 purposes of generating a microfoam to be injected into a human or animal body, it is undesirable to have a propellant gas of the type usually employed in aerosol canisters, eg such as isopropane. This determines that the gas from which the foam is to be made must itself be pressurised to allow production of foam.

Water soluble gases such as carbon dioxide have been found by the inventors to be incapable of producing a stable foam when generated by merely being passed through a standard aerosol valve under pressure, such as might be expected to convert a detergent solution such as one of polidocanol or sodium tetradecylsulphate to a foam. They have determined that when this gas is used under pressure to propel a sclerosing agent solution through a conventional aerosol valve the foam produced, while initially containing at least some microfoam structure, is not sufficiently stable to be applied to the treatment of blood vessels as described in EP 0656203 and US 5676962. Such foam is furthermore incapable of being passed through a syringe needle without significant reversion to liquid and gas phases. It will be realised by those skilled in the art that the microfoam technique exploits the ability of the gas to deliver the sclerosant solution to the wall of the vessel to be treated, rather than to allow its dilution in blood as in the liquid phase.

Aerosol units that are capable of producing foam have been described in the prior art. US 3,471,064 describes a device wherein air is drawn into a foamable liquid through a series of small holes in the dip tube of the unit. Such a device is not sterile in operation as it relies on its contents being open to the air. Foam so produced would appear to vary in properties dependent upon how much air is drawn in. A further device is described in US 3,428,222 and utilises a wicking and foaming element in a compressible container that again draws in air to produce foam.

US 3,970,219 describes sealed aerosol devices which are capable of using pharmacologically inert gases to foam and expel liquid compositions. It describes devices which produce foam by passage of the propellant through a material having pores of 0.01 to 3mm diameter from a lower propellant gas holding chamber to an upper foam holding chamber. The liquid to be foamed sits in the upper chamber or is absorbed onto the porous material by shaking the container or is wicked up from a lower chamber. This patent teaches that liquid from foam in the upper chamber drains down into the lower chamber, such that the thinnest walled bubbles are expelled, and

teaches that the propellant gas should be 'less soluble', such as nitrogen, fluorocarbon or hydrocarbon, where aqueous liquids are to be foamed.

Similar bubbler devices are used in accessories for use with 'environmentally friendly' aerosol devices that operate using air under low pressure, ie. hand pump conditions. Two such devices are supplied by Airspray International as the
5 'Airspray^{RTM} Finger Pump Foamer' and 'Airspray Mini-Foamer'. The former is said to be suitable for simple water based formulations while the latter is suggested for cosmetics, hair or skin care preparations. A second such device is provided as an optional extra in the Swedspray/Eurospray^{RTM} hand pump device as a foaming
10 nozzle. This device is marketed as being suitable for use to 'make you own cleansing foam or shaving lather'.

However, the present inventors have found that use of the available hand-pump devices themselves, which in any case are not sterile, cannot produce good microfoam with high loadings of carbon dioxide due to outgassing, nor with inclusion
15 of significant amounts of glycerol which otherwise stabilises microfoam. Furthermore, when significant back-pressure is applied to the outlet of such device, such as when attached to a syringe to be loaded for injecting the foam, stuttering occurs. Use of low ejection velocity with this device can cause wetting at the nozzle which results in large bubbles caused by air entrapment. In any case the foams so
20 produced, whether with oxygen or carbon dioxide, tend to be very dry, with resultant need for high concentration of sclerosant to be included, and tendency to break up on passage down a needle.

It is preferred not to unnecessarily use high concentrations of sclerosant in the solution as this could result in overdosage should a dispensing device fail and deliver
25 a more dense microfoam, ie. including a higher proportion of liquid than intended.

Thus there is a need to provide a method and device that are capable of producing a uniform injectable microfoam made with a relatively low concentration of a sclerosing agent and a significant amount of a blood dispersible gas in sterile

23410-647D

fashion without volatile liquid propellants or the need for the operator to directly be concerned in control of its parameters.

The present applicants have now provided a method and devices capable of addressing at least some of the aforesaid needs and have produced a
5 novel stable injectable sclerosing microfoam with that method and devices.

For the purpose of this application terms have the following definitions: Physiologically acceptable blood dispersible gas is a gas that is capable of being substantially completely dissolved in or absorbed by blood. A sclerosant liquid is a liquid that is capable of sclerosing blood vessels when
10 injected into the vessel lumen. Scleropathy or sclerotherapy relates to the treatment of blood vessels to eliminate them. An aerosol is a dispersion of liquid in gas. A major proportion of a gas is over 50% volume/volume. A minor proportion of a gas is under 50% volume/volume. A minor amount of one liquid in another liquid is under 50% of the total volume. Atmospheric pressure and bar are
15 1000 mbar gauge. Half-life of a microfoam is the time taken for half the liquid in the microfoam to revert to unfoamed liquid phase.

In a first aspect of the present invention there is provided a method for producing a microfoam suitable for use in scleropathy of blood vessels, particularly veins, characterised in that it comprises passing a mixture of a
20 physiologically acceptable blood dispersible gas and an aqueous sclerosant liquid through one or more passages having at least one cross-sectional dimension of from 0.1 to 30 μm , the ratio of gas to liquid being controlled such that a microfoam is produced having a density of between 0.07 g/ml to 0.19 g/ml and a half-life of at least 2 minutes.

25 The microfoam may be such that 50% or more by number of its gas bubbles of 25 μm diameter and over are no more than 200 μm diameter.

The gas/liquid ratio in the mix may be controlled such that the density of the microfoam is 0.09 g/ml to 0.16 g/ml, possibly 0.11 g/ml to 0.14 g/ml. The microfoam may have a half-life of at least 2.5 minutes, possibly at least 3
30 minutes. The half-life may be as high as 1 or 2 hours or more, but may be less

23410-647D

than 60 minutes, possibly less than 15 minutes and less than 10 minutes in some embodiments.

Half-life is conveniently measured by filling vessel with a known volume and weight of foam and allowing liquid from this to drain into a graduated vessel, the amount drained in a given time allowing calculation of half-life ie. of conversion of microfoam back into its component liquid and gas phases. This can be carried out at standard temperature and pressure, but in practice ambient clinic or laboratory conditions will suffice.

The method may provide a foam characterised in that at least 50% by number of its gas bubbles of 25 μm diameter and over are of no more than 150 μm diameter, more preferably at least 95% of these gas bubbles by number are of no more than 280 μm diameter. At least 50% by number of these gas bubbles might be of no more than 130 μm diameter and in some embodiments at least 95% of these gas bubbles by number are of no more than 250 μm diameter.

The mixture of gas and sclerosant liquid may be in the form of an aerosol, a dispersion of bubbles in liquid or a macrofoam. By macrofoam is meant a foam that has gas bubbles that are measured in millimeters largest dimension, eg. approximately 1 mm and over, and over such as can be produced by lightly agitating the two phases by shaking. The gas and liquid could be provided in the form of an aerosol where a source of pressurised gas and a means for mixing the two is provided to the point of use. It may be that a macrofoam is first produced where the liquid and gas are brought together only at the point of use.

The ratio of gas to liquid used in the mixture is important in order to control the structure of the microfoam produced such that its stability is optimised for the procedure and the circumstances in which it is being carried out. For example, 1 gram sclerosant liquid is mixed with from approximately 6.25 to 14.3 volumes (STP), and possibly 7 to 12 volumes (STP), of gas in some embodiments.

The physiologically acceptable blood dispersible gas may comprise a major proportion of carbon dioxide and/or oxygen. Conveniently it may comprise a minor proportion of nitrogen or other physiologically acceptable gas. While a

23410-647D

proportion of nitrogen may be present, as in air, embodiments of the present invention may provide for use of carbon dioxide and/or oxygen without presence of nitrogen.

In one form the gas used is a mixture of carbon dioxide and other physiological gases, particularly containing 3% or more carbon dioxide, illustratively from 10 to 90% carbon dioxide, and possibly 30 to 50% carbon dioxide. The other components of this gas may be oxygen with a minor proportion only of nitrogen in some embodiments. The other component is oxygen in some embodiments.

A further form of gas comprises 50% vol/vol or more oxygen, the remainder being carbon dioxide, or carbon dioxide, nitrogen and trace gases in the proportion found in atmospheric air. One gas is 60 to 90% vol/vol oxygen and 40 to 10% vol/vol carbon dioxide, possibly 70 to 80% vol/vol oxygen and 30 to 20% vol/vol carbon dioxide. A gas including 99% or more oxygen is also contemplated.

It is found that passing a stream of the sclerosant liquid and the gas under pressure through one or more passages of 0.1 μm to 30 μm as described provides a stable blood dispersible gas based sclerosant injectable microfoam that was previously thought to be only producible by supply of high amounts of energy using high speed brushes and blenders.

The sclerosing agent could be a solution of polidocanol or sodium tetradecylsulfate in an aqueous carrier, eg. water, particularly in a saline. In some embodiments the solution is from 0.5 to 5% v/v polidocanol, illustratively in sterile water or a physiologically acceptable saline, eg. in 0.5 to 1.5% v/v saline. Concentration of sclerosant in the solution could be advantageously increased for certain abnormalities such as Klippel-Trenaunay syndrome.

Polidocanol is a mixture of monolaurylethers of macrogols of formula $\text{C}_{12}\text{C}_{25}(\text{OCH}_2\text{CH}_2)_n\text{OH}$ with an average value of n of 9. It will be realised that mixtures with other alkyl chains, oxyalkyl repeat units and/or average values of n might also be used, eg. 7 to 11, but that 9 is most conveniently obtainable, eg. from Kreussler, Germany, eg. as Aethoxysklerol.

23410-647D

The concentration of sclerosant in the aqueous liquid is a 1-3% vol/vol solution in some embodiments, of polidocanol for instance, in water or saline, possibly about 2% vol/vol. The water or saline also, in some cases at least, may contain 2-4% vol/vol physiologically acceptable alcohol, eg. ethanol. Saline is buffered in some embodiments. Buffered saline may be phosphate buffered saline. The pH of the buffer could be adjusted to be physiological, eg. from pH 6.0 to pH 8.0, illustratively about pH 7.0.

The sclerosant may also contain additional components, such as stabilising agents, eg. foam stabilising agents, eg. such as glycerol. Further components may include alcohols such as ethanol.

The aerosol, dispersion or macrofoam could be produced by mixing the gas and liquid from respective flows under pressure. The mixing conveniently is carried out in a gas liquid interface element such as may be found in aerosol canisters. The interface device may however be very simple, such as a single chamber or passage of millimetre dimensions, ie. from 0.5 to 20 mm diameter, preferably 1 to 15 mm diameter, into which separate inlets allow entry of gas and liquid. Conveniently the interface is of design which is commonly found in aerosol canisters but which is selected to allow the correct ratio of gas to liquid to allow formation of a foam of the presently defined density. Suitable inserts are available from Precision Valves (Peterborough UK) under the name Ecosol and are selected to produce the ratio specified by the method above.

However, the mixing of gas and liquid may also be brought about within a dip-tube leading from the sclerosant solution located in the bottom of a pressurized container where holes in the dip-tube allow gas to enter into a liquid stream entering from the bottom of the tube. In this case the holes may be of similar diameter to the Ecosol holes. Such holes may be conveniently produced by laser drilling of the dip-tube.

The one or more passages through which the aerosol or macrofoam so produced are passed to produce the stable microfoam may have diameter of from 5 μm to 25 μm , possibly from 10 μm to 20 μm where simple passages are provided, such as provided by openings in a mesh or screen, eg. of metal or

23410-647D

plastics, placed perpendicular to the flow of gas/liquid mixture. The passage is conveniently of circular or elliptical cross section, but is not necessarily so limited. A number of such meshes or screens may be employed along the direction of flow.

- 5 The passages could be provided as multiple openings in one or more elements placed across the flow. The elements are from 2 to 30 mm diameter, illustratively 6 to 15 mm diameter, face on to the flow, with 5 to 65% open area, eg. 2% to 20% open area for woven meshes and 20% to 70% open area for microporous membranes in some embodiments. Openings in a porous material, such as provided in a perforated body, may provide several hundreds or more of
10 such passages, even tens or hundred of thousands of such passages, eg. 10,000 to 500,000, presented to the gas liquid mixture as it flows. Such material may be a perforated sheet or membrane, a mesh, screen or sinter. A number of sets of porous material may be provided arranged sequentially such that the gas and
15 liquid pass through the passages of each set. This leads to production of a more uniform foam.

Where several elements are used in series these may be spaced 1 to 5 mm apart, illustratively 2 to 4 mm apart, eg. 3 to 3.5 mm apart.

- For some embodiments of the present invention it is found that the
20 passage may take the form of a gap between fibres in a fibrous sheet placed across the path of the gas/liquid flow, and the dimension described is not necessarily the largest diameter, but is the width of the gap through which the gas/liquid aerosol or macrofoam must flow.

- Alternatively the method provides for passing the mixture of gas and
25 liquid through the same set of passages, eg. as provided by one or more such porous bodies, a number of times, eg. from 2 to 2,000, illustratively 4 to 200 times, or as many times as conveniently results in a microfoam of the density set out above. It will be realised that the more times the microfoam passes through the meshes, the more uniform it becomes.

23410-647D

The pressure of the gas used as it is passed through the passages will depend upon the nature of the mechanism used to produce the foam. Where the gas is contained in a pressurized chamber, such as in an aerosol canister, in contact with the liquid, suitable pressures are typically in the range 0.01 to 9 bar over atmosphere. For use of meshes, eg. 1 to 8 meshes arranged in series, having apertures of 10-20 μm diameter, 0.1 to 5 atmospheres over bar will, *inter alia*, be suitable. For use of 3-5 meshes of 20 μm aperture it is found that 1.5-1.7 bar over atmospheric is sufficient to produce a good foam. For a 0.1 μm pore size membrane, a pressure of 5 bar or more over atmospheric pressure might be used.

10 In one embodiment of the invention the passages are in the form of a membrane, eg. of polymer such as polytetrafluoroethylene, wherein the membrane is formed of randomly connected fibres and has a rated effective pore size which may be many times smaller than its apparent pore size. A particularly suitable form of this is a biaxially oriented PTFE film provided by TetratexTM USA under the
15 trademark Tetratex^{RTM}, standard ratings being 0.1 to 10 μm porosity. Pore sizes for the present method and devices are 3 to 7 μm in some embodiments. This material may be laminated with a porous backing material to give it strength and has the advantage that one pass through may be sufficient to produce a foam that meets the use parameters set out above with regard to stability. However, it will
20 be evident to those skilled in the art that use of more than one such membrane in series will give a still more uniform foam for given set of conditions.

It is believed that the combination of provision of a stream of solution and gas under pressure through an aerosol valve and then flow through the passages, eg. pores in a mesh, screen, membrane or sinter provides energy
25 sufficient to produce a stable aqueous liquid soluble gas, eg. carbon dioxide and/or oxygen, based sclerosant microfoam that was previously thought to be only producible by supply of high amounts of energy using high speed brushes and blenders as described in the prior art.

An embodiment of the invention provides a microfoam having at
30 least 50% by number of its gas bubbles of 25 μm diameter or over being no more than 120 μm diameter. At least 95% of its gas bubbles of 25 μm diameter or over

23410-647D

are of no more than 250 μm diameter in some embodiments. Diameter of such bubbles may be determined by the method set out in the Example 6 set out herein.

Another embodiment of the invention provides a housing in which is situated a pressurisable chamber. For sterile supply purposes this will at least be partly filled with a sterile and pyrogen free solution of the sclerosing agent in a physiologically acceptable aqueous solvent but otherwise may be charged with such at the point of use. This provides a pathway by which the solution may pass from the pressurisable chamber to exterior of the housing through an outlet and possibly a mechanism by which the pathway from the chamber to the exterior can be opened or closed such that, when the container is pressurised, fluid will be forced along the pathway and through one or more outlet orifices.

The housing may incorporate one or more of (a) a pressurised source of the physiologically acceptable gas that is readily dispersible in blood, and (b) an inlet for the admission of a source of said gas; the gas being contacted with the solution on activation of the mechanism.

The gas and solution are caused to pass along the pathway to the exterior of the housing through the one or more, preferably multiple, passages of defined dimension above, through which the solution and gas must pass to reach the exterior, whereby on contact with, eg. flow through, the passages the solution and gas form the microfoam.

In some embodiments, the gas and liquid pass through a gas liquid interface mechanism, typically being a junction between a passage and one or more adjoining passages, and are converted to an aerosol, dispersion of bubbles or macrofoam before passing through the passages, but as explained they may be converted first to a macrofoam, eg. by shaking of the device, eg., by hand, or mechanical shaking device.

In a second aspect of the present invention there is provided a device for producing a microfoam suitable for use in scleropathy of blood vessels, particularly veins, comprising a housing in which is situated a pressurisable chamber containing a solution of the sclerosing agent in a physiologically

23410-647D

acceptable solvent referred to in the first aspect; a pathway with one or more outlet orifices by which the solution may pass from the pressurisable chamber to exterior of the device through said one or more outlet orifices and a mechanism by which the pathway from the chamber to the exterior can be opened or closed such that, when the container is pressurised and the pathway is open, fluid will be forced along the pathway and through the one or more outlet orifices said housing incorporating one or more of (a) a pressurised source of physiologically acceptable gas that is dispersible in blood and (b) an inlet for the admission of said gas; the gas being in contact with the solution on activation of the mechanism such as to produce a gas solution mixture said pathway to the exterior of the housing including one or more elements defining one or more passages of cross sectional dimension, illustratively diameter, 0.1 μm to 30 μm , through which the solution and gas mixture is passed to reach the exterior of the device, said passing of said mixture through the passages forming a microfoam of from 0.07 to 0.19 g/ml density and of half-life at least 2 minutes.

In some embodiments, the microfoam has 50% or more by number of its gas bubbles of 25 μm diameter and over of no more than 200 μm diameter.

In some embodiments, the microfoam is from 0.09 to 0.16 g/ml density and illustratively of 0.11 g/ml to 0.14 g/ml.

In some embodiments, the microfoam has a half-life of at least 2.5 minutes, illustratively at least 3 minutes.

This device may provide a microfoam wherein at least 50% by number of its gas bubbles of 25 μm diameter and over are of no more than 150 μm diameter or less, illustratively at least 95% by number of these gas bubbles are of diameter 280 μm or less. In some embodiments at least 50% by number of these gas bubbles are of no more than 120 μm diameter and possibly at least 95% of these gas bubbles are of no more than 250 μm diameter.

The apparatus may include a chamber, eg. such as in a sealed canister, charged with the blood dispersible gas and the sclerosant liquid, eg. in a single chamber, the device pathway including a dip tube with an inlet opening

23410-647D

under the level of the liquid in this chamber when the device is positioned upright. The dip-tube may have an outlet opening at a gas liquid interface junction where the gas, which resides in the chamber above the liquid, has access to the pathway to the device outlet. The pathway is opened or closed by a valve element which is
5 depressed or tilted to open up a pathway to the exterior of the device, whereby the liquid rises up the dip tube under gas pressure and is mixed in the interface junction with that gas to produce an aerosol, dispersion of bubbles in liquid or macrofoam.

Either inside the pressurisable chamber disposed in the pathway to
10 the valve, or on the downstream side of the valve, is provided an element having the one or more passages described in the first aspect mounted such that the gas liquid mixture, ie. dispersion of bubbles in liquid, aerosol or macrofoam, passes through the passage or passages and is caused to foam. This element may conveniently be located in a cap on the canister in between the valve mounting
15 and an outlet nozzle. Conveniently depression of the cap operates the valve. Alternatively the element is within the canister mounted above the gas liquid interface.

In an alternate embodiment of this device the gas liquid interface may comprise holes in the dip tube above the level of the liquid in the canister
20 inner chamber.

The gas pressure employed will be dependent upon materials being used and their configuration, but conveniently will be 0.01 to 9 bar over atmospheric, illustratively 0.1-3 bar over atmospheric, and illustratively 1.5-1.7 bar over atmospheric pressure.

25 A device of this aspect of the invention is of the 'bag-on-valve' type. Such device includes a flexible gas and liquid tight container, forming a second inner chamber within the pressurisable chamber, which is sealed around the dip-tube and filled with the liquid. The dip-tube may have a one-way valve located at a position between its end located in the sclerosant liquid and the gas liquid
30 interface junction, which when the passage to the exterior is closed, remains closed such as to separate the liquid from the physiologically acceptable blood

23410-647D

dispersible gas around it in the chamber. On opening the pathway to the exterior, the one way valve also opens and releases liquid up the dip-tube to the gas liquid interface where an aerosol is produced which is in turn then passed through the passages to be converted to microfoam. A suitable one-way valve is a duck-bill
5 type valve, eg. such as available from Vernay Labs Inc., Yellow Springs, Ohio, USA. Suitable bag-on-valve constructions are available from Coster Aerosols, Stevenage, UK and comprise an aluminium foil/plastics laminate.

Conveniently the one way valve is located at the top of the dip-tube between that and the gas liquid interface junction, ie. an Ecosol device. This
10 allows filling of the bag before application of the one way valve, followed by sterilisation of the contents, whether in the canister or otherwise.

Such a device has several potential advantages. Where oxygen is the gas, this is kept separate from the liquid before use and thus reduces possibility of oxygen radicals reacting with organic components in the liquid, eg.
15 during sterilisation processes such as irradiation. Where carbon dioxide is the gas, storage can lead to high volumes of gas dissolving in the liquid, which on release to the atmosphere or lower pressure, could out-gas and start to destroy the microfoam too quickly. Such separation also prevents the deposition of solidified sclerosing agent components in the dimension sensitive orifices of the
20 device in an unused can in storage or transit, particularly should that be oriented other than upright.

The gas liquid interface may be provided as a defined orifice size device such as the Ecosol device provided by Precision Valve Peterborough UK. For a device where the passages of defined dimension are outside of the
25 pressurised chamber, ie. mounted on the valve stem, the ratio of area of the gas holes to the liquid holes should be of the order of 3 to 5, preferably about 4. Where the passages are inside the pressurised chamber this may be higher.

A third aspect of the invention provides a device for producing a microfoam suitable for use in sclerotherapy of blood vessels, particularly veins,
30 comprising a housing in which is situated a pressurisable chamber, at least part filled or fillable with a solution of a sclerosing agent in a physiologically acceptable

23410-647D

solvent and/or a physiologically acceptable blood dispersible gas; a pathway by which the contents of the chamber may be passed to exterior of the housing through one or more outlet orifices and a mechanism by which the chamber can be pressurized such that its contents pass to the exterior along the pathway and
5 through one or more outlet orifices said pathway to the exterior of the housing or the chamber including one or more elements defining one or more passages of cross sectional dimension, illustratively diameter, 0.1 μm to 30 μm through which the contents of the chamber may be passed, whereby on passing through the passages the solution and gas form a microfoam of from 0.07 to 0.19 g/ml density
10 and having a half-life of at least 2 minutes.

In some embodiments, the microfoam is such that 50% or more by number of its gas bubbles of 25 μm or more diameter are of no more than 200 μm diameter.

In some embodiments, the microfoam is of density 0.09 to 0.16 g/ml
15 and illustratively of 0.11 g/ml to 0.14 g/ml. The limits on bubble size may also be as for the first and second aspects.

In some embodiments, the microfoam has a half-life of at least 2.5 minutes, illustratively at least 3 minutes.

The elements defining the passages in the pathway or chamber may
20 be static or may be movable by manipulation of the device from outside of its interior chamber.

23410-647D

Such device may be conveniently constructed in the form of a syringe device, comprising a syringe barrel and a functionally co-operating syringe plunger defining a chamber, the plunger being the means for pressurising the chamber, that chamber containing the gas and liquid in use, but which is particularly characterised by being formed with the passages of aforesaid dimension adjacent or at the needle affixing end of the syringe body, eg at a luer connection opening.

In use such a device is partially charged with the required sclerosant liquid and then charged with the physiologically acceptable gas, or vice versa, by withdrawing the syringe plunger while connecting the luer opening to a source of each in turn. Alternatively these may be mixed beforehand as a macrofoam, or even as a microfoam which by its nature will be breaking down. Where the gas and liquid are charged as separate phases the syringe contents may be agitated such as to produce a foam. The plunger is then pushed into the syringe body whereby this foam passes through the passages and is converted to a microfoam having the required stability for the procedure concerned. Where the gas and liquid are charged together as a foam, operation of the plunger will provide the microfoam.

In one embodiment of this device two chambers are provided and are linked to each other through a passage, eg including the syringe body luer connector orifice, via the one or more passages of $0.1\mu\text{m}$ - $30\mu\text{m}$ dimension. In this manner reciprocation of a plunger in one or both of the chambers results in the gas and liquid being passed through the passages of defined dimension a desired number of times to produce the desired foam.

In an alternative embodiment an element defining a number of the passages of said dimension is provided within the chamber such that it can be moved in either direction to pass chamber contents through its passages. Conveniently this element may be mounted on a support, such as a support plunger rod coaxial to the syringe plunger rod. The element may incorporate any of the porous passageway defining items referred to above, but conveniently includes meshes or a porous membrane mounted with major surfaces perpendicular to the syringe barrel/chamber longitudinal

23410-647D

axis such that movement of the support rod in either direction longitudinally results in a sweeping action by the element such that chamber contents, gas and liquid, are passed through the passages together. It will be realised that once such a device is charged with a suitable ratio of gas and liquid, it may also be shaken to
5 give a loose macrofoam as a first step.

The housing may be a container defining a chamber in which is situated the solution and gas under pressure and the pathway is a conduit leading from the chamber in the interior of the container to a valve closing an opening in the container wall.

10 Forms of the one or more elements defining the multiple passages for use in the device include meshes, screens or sinters. Thus one or more meshes or perforated screens or sinters will be provided, with some forms employing a series of such elements arranged in parallel with their major surfaces perpendicular to the path of solution/gas expulsion.

15 All elements of any of the devices according to embodiments of the invention having a critical dimension may be made of a material that does not change dimension when exposed to aqueous material. Thus in some embodiments elements with such function such as the air liquid interface and the element defining the passages of 0.1 μm -30 μm dimension are not to be of a
20 water swellable material such as Nylon 66 where they are likely to be exposed to the solution for more than a few minutes. Where such exposure is likely these parts are fashioned from a polyolefin such as polypropylene or polyethylene in some embodiments.

The canister or syringe device may be sized such that it contains
25 sufficient gas and solution to form up to 500 ml of microfoam, illustratively from 1 ml up to 200 ml and possibly from 10 to 60 ml of microfoam. Particularly the amount of gas under pressure in such canisters should be sufficient to produce enough foam to treat, ie. fill, at least one varicosed human saphenous vein. Thus canisters of embodiments of the invention may be smaller than those currently
30 used for supply of domestic used mousse type foams. The canister device might

23410-647D

be disposable after use, or cannot be reused once opened such as to avoid problems of maintaining sterility.

A device which maintains gas pressure in the canister as foam is expelled is provided in some embodiments. Suitable devices are such as
5 described under trademarked devices PECAP and Atmosol. However, where a significant headspace or pressure of gas is provided this will not be necessary.

In order to ensure that the microfoam delivered from devices of embodiments of the invention is not 'outside' specification, ie. falls within the desired density, bubble size and half life parameters set out above, a further,
10 fourth, aspect of the invention provides a device which is positioned to receive microfoam emitted from the device of the second and third aspects of the invention, which device allows venting of the first portion of microfoam to waste and passage of a second portion of microfoam to a delivery device, such as a syringe, in sterile fashion.

15 A device of the fourth aspect comprises an inlet conduit being adapted to engage the outlet of a microfoam producing device of the second or third aspect in a microfoam tight fashion, the conduit being connected to and leading through a multipath tap capable of being set to direct microfoam passing down the conduit to one or both of first and second contiguous outlet conduits or to close the inlet
20 conduit, at least one of the first and second outlet conduits being adapted to receive the luer connector of a syringe. The device may also comprise one or more elements for engaging the device of the second or third aspect other than by its outlet nozzle to hold it securely, eg. upright in the case of a canister with a dip-tube.

The device of the fourth aspect may comprise a three-way tap. In some
25 embodiments the device of the fourth aspect comprises a base element, sufficiently stable to mount a microfoam producing device of the second or third aspects when engaged thereby. The microfoam producing device could be engaged by resilient elements which locate it securely adjacent the three-way tap whereby the inlet conduit can be attached to the microfoam producing device outlet conduit.

23410-647D

The device of the fourth aspect may comprise a base element adapted to mount the microfoam dispensing device and an activating element which operates to cause the pathway to be opened to the inlet conduit. In this manner when the multi-way tap is shut, the dispensing device contents remain therein, but when the multi-way
5 tap is opened to either of its outlet conduits it immediately causes release of foam generated by the device.

A further aspect of the present invention provides improved microfoams for use in the elimination of blood vessels and vascular malformations that are made available by the method and devices of embodiments of the invention, comprising a
10 physiologically acceptable gas that is readily dispersible in blood together with an aqueous sclerosant liquid. In some embodiments the microfoam has a density of from 0.07 to 0.19 g/cm and is capable of being passed down a 21 gauge needle without reverting back to gas and liquid by more than 10%, based on liquid content reverting back to unfoamed liquid phase.

15 In some embodiments, the microfoam, on passage through said needle, does not revert back to unfoamed liquid by more than 5% based on liquid content, illustratively by no more than 2%.

In some embodiments, the microfoam is capable of being passed down a needle while retaining at least 50% by number of its gas bubbles of at least 25 μm
20 diameter at no more than 200 μm diameter. This is conveniently measured under ambient conditions, more preferably at STP.

In some embodiments, at least 50% by number of said gas bubbles remain at no more than 150 μm diameter and at least 95% of these bubbles at no more than 280 μm diameter. The microfoam has a half-life as measured by drainage through
25 a funnel of 2 cm neck diameter and drainage path 10 cm of at least 2 minutes in some embodiments, illustratively 2.5 minutes and possibly 3 minutes. This may be carried out at ambient temperature or STP. The funnel may be pre-equilibrated in a water bath to ensure a temperature of 25°C before drying and application of foam. Placing of a microfoam filled syringe upside down, without its plunger, above the funnel leading into
30 a graduated receptacle allows convenient measurement of this parameter.

23410-647D

In some embodiments, the gas includes less than 40% v/v nitrogen. The density of the microfoam may be from 0.09 to 0.16 g/ml, illustratively 0.11 g/ml to 0.14 g/ml.

Advantageously at least 50% by number of the gas bubbles of 25 μ m diameter or more are of no more than 120 μ m diameter and illustratively at least 95% of these gas bubbles are of diameter 250 μ m or less.

In some embodiments, the foam density, which is a measure of liquid/gas ratio, is from 0.13 to 0.14 g/cm and the half-life is at least 2.5 minutes. The foam does not move outside of its parameters of bubble size set out above in such time in some embodiments.

The gas consists of at least 50% oxygen or carbon dioxide, illustratively 75% or more oxygen or carbon dioxide and possibly at least 99% oxygen or carbon dioxide, eg. substantially 100% oxygen or carbon dioxide, in some embodiments. The oxygen or carbon dioxide is medical grade in some embodiments.

The sclerosant may be aqueous polidocanol or sodium tetradecyl sulfate.

When the sclerosant is aqueous polidocanol the concentration of polidocanol is from 0.5 to 4% vol/vol in the liquid, may be 1 to 3% vol/vol polidocanol and illustratively 2% vol/vol in the liquid.

Advantageously the sclerosant is made up in water, but may be made up in a saline solution, particularly 10 to 70 mM phosphate buffer saline, eg. 50 mM phosphate buffered saline, and of pH 6 to pH 8.0 eg. about pH 7.0 in some embodiments. Advantageously the aqueous solution contains a minor amount of an alcohol, such as 96% ethanol, eg. at between 2 and 6% vol/vol, illustratively at about 4% vol/vol of 96% ethanol.

Addition of glycerol to the aforesaid sclerosant imparts a longer half-life to the resultant foam. However, glycerol also produces a tendency for the meshes to block up when using a mesh device as described above, so should be used carefully where the device it is produced from may be used multiple times or the bag-on-valve concept is used.

23410-647D

According to one particular aspect of the invention, there is provided a microfoam comprising a physiologically acceptable blood dispersible gas capable of being dissolved in or absorbed by blood, and an aqueous sclerosant liquid, wherein the aqueous sclerosant liquid is a solution of polidocanol or sodium tetradecylsulphate in an aqueous carrier, the gas contains 10 to 90% vol/vol carbon dioxide, the microfoam has a density of from 0.07 to 0.19 g/ml, at least 50% by number of the microfoam gas bubbles of 25µm diameter and over are of no more than 150µm diameter and at least 95% of the microfoam gas bubbles of 25µm diameter and over are of no more than 280µm diameter at STP, the microfoam is capable of being passed down a 21 gauge needle without reverting back to gas and liquid by more than 10% based on liquid content reverting back to unfoamed liquid phase at STP, and has a half-life as measured by time for drainage of half the liquid in the microfoam as unfoamed liquid through a funnel of 1 cm neck diameter and 10cm drainage path of at least 2 minutes at STP.

There is also provided a use of such a microfoam for the manufacture of a medicament for the treatment of sclerotherapy.

Embodiments of the present invention will now be described further by way of illustration only by reference to the following Figures and Examples. Further embodiments falling within the scope of the invention will occur to those skilled in the art in the light of these.

FIGURES

Figure 1: Shows a cross-sectional view of a canister device of the second aspect of the invention as further described in Example 2 below.

Figure 2: Shows a cross-sectional view of a canister device of the second aspect incorporating a bag-on-valve reservoir for the sclerosant with the gas being in the outer chamber and separated therefrom by a one way duck-bill valve.

Figure 3: Shows a cross-sectional view of a syringe-like device of the third aspect incorporating a set of meshes across its dispensing chamber.

23410-647D

Figure 4: Shows a cross-sectional view of a syringe-like device of the third aspect incorporating a porous membrane supported on an inner plunger rod such that it can be reciprocated within the syringe chamber contents.

Figure 5: Is a bar chart and graph illustrating distribution of gas bubble
5 diameter in a 0.13 g/ml oxygen/air/polidocanol microfoam of the fourth aspect.

Figure 6: Is a graph illustrating distribution of gas bubble diameter in microfoams of 0.09 g/ml and 0.16 g/ml of the fourth aspect.

Figure 7: Is a graph showing the effect of passing a foam of the fourth
10 aspect down a 21 gauge needle as compared to control fresh and similarly aged microfoams.

Figure 8: Is a bar chart and graph showing the effect of passing a 2% vol polidocanol solution dry microfoam of density 0.045 g/ml, such as producible by use of a prior art bubbler device (Swedspray valve, Ecosol insert and head), down a 21 gauge needle.

15 Figure 9: Is a graph showing the effect of passing a 1% vol polidocanol dry microfoam of density 0.045 g/ml such as producible by use of the prior art bubbler device (Swedspray valve, Ecosol insert and head), down a 21 gauge needle.

23410-647D

Figure 10: is an elevation view of a syringe filling device of the fourth aspect.

Figure 11: Is a plan view of the device of Figure 10.

EXAMPLES

5 EXAMPLE 1.

A standard aerosol canister with a one way depressible action valve is charged half full with a 3% v/v solution of polidocanol in sterile water and pressurised to 3 atmospheres with a 50:50 mix of carbon dioxide and oxygen. On the valve stem is mounted an actuator and delivery head which carries four plastics screens, just under
10 0.5 mm thick, perforated with 20µm diameter passages, these screens being of the general type provided in the Swedspray-Eurospray foaming actuator cap ApRisC (RTM) device. The valve is fed through an Ecosol gas liquid interface insert from a dip-tube and the surrounding chamber. Gas inlet sizes (x2) into the insert are 0.006" x 0.01" while the single liquid inlet is 0.024", as controlled by selecting Ecosol insert
15 size. On depression of the head the aerosol valve releases pre-mixed solution and gas onto the screens whereupon a microfoam suitable for scleropathy and that is dimensionally stable for at least 2 minutes, preferably 5 minutes, using glycerol in the polidocanol formulation is produced.

20 EXAMPLE 2.

Figure 1 illustrates a further canister design of the invention wherein the passages through which the gas liquid mixture must travel are placed within the pressurised chamber, thus increasing hygiene of the device.

The canister is of standard 500ml design with an aluminium wall (1), the
25 inside surface of which is coated with an epoxy resin resistant to action of polidocanol and oxygen (eg Hoba 7940-Holden UK)) . The bottom of the canister (2) is domed inward. The canister inner chamber (4) is pre-purged with 100% oxygen for 1 minute, containing 15ml of a 2% vol/vol polidocanol/20mmol phosphate buffered saline solution (3) then filled with the oxygen at 2.7 bar gauge (1.7 bar over atmospheric).

This is provided by overpressuring the polidocanol part filled can with 1.7 bar oxygen.

The dome provides a perimeter area around the bottom of the inner chamber in which a level of polidocanol solution is retained sufficient for the bottom open end of a dip tube to be submerged therein when the top of the dome is no longer covered with the solution. In this manner, by use of an indicia on the outside of the canister to indicate the position of the dip tube, the canister can be oriented to extract the last fraction of solution if desired. In practice a vertical orientation is sufficient.

A standard 1" diameter aerosol valve (5) (Precision Valves, Peterborough) is crimped into the top of the canister after sterile part filling with the solution and is activatable by depressing an actuator cap (6) to release content via an outlet nozzle (13) sized to engage a luer fitting of a syringe or multi-way connector (not shown). A further connector (7) locates on the bottom of the standard valve and mounts, preferably by interference fit, four Nylon 66 meshes held in high density polyethylene (HDPE) rings (8) all within an open ended polypropylene casing. These meshes have diameter of 8mm and have a 15% open area made up of 20µm pores, with the meshes spaced 3.5mm apart by the HDPE rings.

A further connector (9) locates on the bottom of the connector holding the meshes and receives a housing (10) which mounts the dip tube (12) and includes gas receiving holes (11a, 11b) which admit gas from chamber (4) into the flow of liquid which rises up the diptube on operation of the actuator (6). These are conveniently defined by an Ecosol device with insert as before. Holes (11a,11b) have cross-sectional area such that the sum total ratio of this to the cross-sectional area of the diptube is controlled to provide the required gas/liquid ratio. This is for example 0.010" x 0.013" each hole (11a, 11b) to 0.040" liquid receiving hole.

EXAMPLE 3.

A further canister embodiment of the present invention is shown in Figure 2, which is broadly as shown in Figure 1, but for the inclusion of a modified 'bag-on-

valve' arrangement. In this embodiment the polidocanol sclerosing solution (3) is enclosed in a foil bag (22), comprising an aluminium foil/plastics laminate (Coster Aerosols Stevenage UK) sealed in gas tight fashion to dip-tube (12). At the top end of the dip-tube is a one-way duck-bill valve (Vernay Labs Inc Ohio USA) that serves to prevent contact of polidocanol with the contents of the dip-tube (12) and chamber (4) until the valve (5) is operated. On said operation the valve (21) opens and polidocanol solution (3) is caused to rise up the dip-tube (12), whereby it becomes mixed with the air/oxygen gas mixture entering through holes (11a, 11b). In this manner the can may be safely sterilised with ionising radiations which may otherwise cause interactions between radical species in the gas and the organic component of the polidocanol solution. Such arrangement can also improve the operation of the canister with regard to start up of foam delivery. The bag (22) preferably substantially only contains the liquid (3), with no head-space gas above it.

15 EXAMPLE 4.

The device of this example is identical with that of Example 3, save that the polidocanol in the liquid is replaced with a sodium tetradecylsulphate at 1% vol/vol, all other ingredients being the same.

20 EXAMPLE 5.

Figure 3 shows a syringe device that is specifically designed to produce microfoam according to the invention using the method of the invention. Syringe body (13) has a luer opening (14) and locating flanges (15) and cooperates with a plunger (16) to define a chamber (19). Chamber (19) is prefilled, or filled in use, with sclerosing solution (18), in this case polidocanol as above. The plunger has a sealing face (17) that is inert with respect to the polidocanol solution and which ensures that said solution does not escape around the sides of the plunger when that is depressed to pressurise the contents of chamber (19).

Located between the plunger sealing face (17) and luer opening (14) is a series of three spaced meshes (20) of the type and configuration referred to in Example 2. In this example the meshes are located such as to leave a space between them and the luer opening such that a physician can see the foam produced by passage of gas/liquid mixture through the meshes.

In operation such a syringe is preferably provided with the plunger pushed in such as to define a reduced chamber (19) volume filled with sclerosing solution with the luer opening sealed in a sterile fashion, eg. by a foil seal cap attached to its exterior. The cap is peeled off, the luer attached to a source of required blood dispersible gas and the plunger withdrawn to admit a required amount of gas to give a ratio of gas to liquid suitable such that when agitated, eg. by shaking the syringe, a macrofoam is produced containing a 7:1 to 12:1 ratio gas to liquid. For production of foam the plunger is depressed with an even pressure, such as to depress at 1ml/second, and the macrofoam is converted to microfoam.

It will be realised that the microfoam could be directly applied to a patient, but more conveniently would be transferred directly to a chamber, eg a second syringe, where viewing of a large volume of foam such as would be required to eliminate a large saphenous vein, would be more readily performed. In this manner, should it be desired, the microfoam could be passed between the two chambers via the meshes in order to render it still more uniform in nature.

EXAMPLE 6.

Figure 4 shows a further syringe device embodiment of the invention designed to produce microfoam according to the invention using the method of the invention. Syringe body (13) has a luer opening (14) and locating flanges (15) and cooperates with a plunger (16) to define a chamber (19). Chamber (19) is prefilled, or filled in use, with sclerosing solution (18), in this case polidocanol as above. The plunger has a sealing face (17) that is inert with respect to the polidocanol solution and which

ensures that said solution does not escape around the sides of the plunger when that is depressed to pressurise the contents of chamber (19).

Passing down the central longitudinal axis of the plunger is a rod (21) mounting a porous Tetratex membrane (22) of effective pore size about 5µm in a double ring mounting. The rod (21) has a handle (23) located outside the syringe chamber which allows the membrane to be moved independently of the plunger such as to force the contents of chamber (19) to pass through its pores.

In operation such a syringe is preferably provided with the plunger pushed in such as to define a reduced chamber (19) volume filled with sclerosing solution with the luer opening sealed in a sterile fashion, eg. by a foil seal cap attached to its exterior. The cap is peeled off, the luer attached to a source of required blood dispersible gas and the plunger withdrawn to admit a required amount of gas to give a ratio of gas to liquid. Eg. a 7:1 to 12:1 ratio gas to liquid. For production of foam the handle (23) on rod (21) is operated to pass the membrane up and down the chamber a number of times, eg 2 to 10 times, causing the gas and liquid to mix and produce foam. For dispensing of foam directly to a patient, or to another syringe or container, the rod (21) is withdrawn such that membrane mounting (22) abuts the plunger sealing face and the plunger is such depressed with an even pressure, eg. at 1ml/second. Obviously when the foam is passed directly into a patient a suitable needle is affixed to the luer connection.

EXAMPLE 6.

A microfoam of the invention is produced in a device as described in Example 1, having critical passage and gas mixing dimensions as set out in Example 2 but differing therefrom in that mesh is located in the dispensing cap, downstream of the valve, while gas/liquid mixing occurs in an Precision Valves Ecosol insert device upstream of the valve. The chamber (500ml) is charged with 15ml of an aqueous solution containing per 100ml polidocanol (Kreussler-Germany) (2ml), 96% ethanol (4ml) and 55mmol Phosphate Buffer (pH7.0) (94ml) with gas being air overpressured

with 1.5bar 100% oxygen. The characteristics of the microfoam produced on operation of the valve are shown in Figures 5 and 6. Figure 5 shows bubble size distribution immediately after microfoam generation; foam density being 0.138g/ml. Figure 6 shows bubble size produced with varying ratio of gas to liquid, provided by altering the gas/liquid interface hole size (11a, 11b) to give foams of 0.09g/ml (closed diamonds) and 0.16g/ml (open circles). Figure 7 shows the effect on bubble size distribution of a preferred microfoam (0.13g/ml) after passage through a 21G needle: Open circles show fresh foam, crosses control foam aged to match injection time and closed diamonds show after passage through the needle. Figure 8 shows the effect of passing a microfoam made using a Swedspray device density 0.045g/ml through the needle. Closed diamonds are control aged while open circles are after needle passage.

Note, when 5% glycerol is added to the formulation, half life was increased to approximately 4 minutes.

Bubble sizes are calculated by taking up foam into a syringe through its luer opening, optionally attaching a 21G needle, and injecting foam between two glass slides that are separated using 23.25 micron diameter beads (eg. available as microspheres from Park Labs USA). Maxtascan/Global Lab Image technique was used to analyse bubble size. Diameters of uncompressed bubbles (D_r) were calculated from diameters of bubbles between slides (D_f) using the equation $D_r = 3 \sqrt{3} D_f^2 x / 2$ where x is the distance between the slides. These measurements thus are made at ambient temperature and pressure.

It will be realised that bubbles much smaller than 25µm diameter may be present but not counted. The % figures given with respect to bubble thus relate to bubbles in the range 25µm and above.

EXAMPLE 7.:

For filling of a syringe with microfoam of the invention the bottom of a canister of Example 1, 2 or 3 is placed into a receiving recess in the base of a syringe filling device as shown in elevation in Figure 10 and plan (Figure 11). Canister (24) is

inserted into a 1 cm deep recess (25) in a plastics base element (26), the recess being approximately 1mm in diameter more than the canister such that a snug fit is provided. The canister is further supported by two resilient fixed arms (27a, 27b), fixed on vertical support rod (28) that deform to receive the canister diameter.

5 Just above the top of the position of the canister cap in use, the support rod (28) mounts an actuator arm that is lockable between a first actuating position (full lines) an and an off position (dotted lines). In the actuating position the arm depresses the canister actuator cap (30), thus opening the canister valve and causing microfoam to be released.

10 Also on the base (26) is a recess (32) sized to snugly receive a syringe (34) with its plunger. A stop element (33) is provided that is positioned such that on filling the plunger is limited in its range of longitudinal movement such that the syringe cannot be overfilled.

A flexible transparent plastics tube (35), inert to the sclerosant foam, is
15 attached to the canister outlet nozzle (31) in use and is fixed to a three way valve (36) affixed to the base (26). The valve is operated by turning a tap (37) to one of three positions: (a) valve shut-no microfoam passage (b) valve open to waste (38) whereby any microfoam that by visual inspection of the contents of tube (35) appears unsuitable, is vented and (c) valve open to syringe, whereby a set amount of
20 microfoam passes through the syringe luer and fills it until the syringe plunger abuts the stop (33)

EXAMPLE 8.

20 mls microfoam of Example 6 is loaded into a 20ml syringe using the device
25 of Example 7 and the syringe disengaged from the device. A 19 gauge needle is attached either directly to the syringe luer fitting or via a catheter. The microfoam is administered into to a varicose vein while its advance and final position is monitored using a hand held ultrasound scanner such that the fresh foam is restricted in location

WO 00/72821

PCT/GB00/02045

to the vein being treated. After between 1 and 5 minutes the vein contracts and subsequently becomes fibrosed.

23410-647D

CLAIMS:

1. A microfoam comprising a physiologically acceptable blood dispersible gas capable of being dissolved in or absorbed by blood, and an aqueous sclerosant liquid, wherein
 - 5 the aqueous sclerosant liquid is a solution of polidocanol or sodium tetradecylsulphate in an aqueous carrier,
 - the gas contains 10 to 90% vol/vol carbon dioxide,
 - the microfoam has a density of from 0.07 to 0.19 g/ml,
 - at least 50% by number of the microfoam gas bubbles of 25µm diameter
 - 10 and over are of no more than 150µm diameter and at least 95% of the microfoam gas bubbles of 25µm diameter and over are of no more than 280µm diameter at STP,
 - the microfoam is capable of being passed down a 21 gauge needle without reverting back to gas and liquid by more than 10% based on liquid content reverting back to unfoamed liquid phase at STP, and
 - 15 has a half-life as measured by time for drainage of half the liquid in the microfoam as unfoamed liquid through a funnel of 1 cm neck diameter and 10cm drainage path of at least 2 minutes at STP.
2. A microfoam as claimed in claim 1 comprising 50% vol/vol or more oxygen with the remainder being carbon dioxide or carbon dioxide, nitrogen and trace
 - 20 gases in the proportion found in atmospheric air.
3. A microfoam as claimed in claim 1, wherein the gas is of 60 to 90% vol/vol oxygen and 40 to 10% vol/vol carbon dioxide.
4. A microfoam as claimed in claim 1 or claim 2, wherein the sclerosant liquid is 0.5 to 5% vol/vol polidocanol.
- 25 5. A microfoam as claimed in claim 1 or claim 4, wherein the concentration of the sclerosant in the liquid is from 1 to 3% vol/vol.

23410-647D

6. A microfoam as claimed in any one of claims 1 to 5, wherein it is capable of being passed down a 21 gauge needle such that 50% or more by number of its gas bubbles of at least 25 μm remain at 150 μm diameter or less and at least 95% of these bubbles at 280 μm diameter or less.
- 5 7. A microfoam as claimed in any one of claims 1 to 6, wherein it has a density of from 0.09 to 0.16 g/ml.
8. A microfoam as claimed in any one of claims 1 to 6, wherein it is of density of from 0.11 to 0.14 g/ml.
9. A microfoam as claimed in any one of claims 1 to 8, wherein the saline is
10 phosphate buffered saline pH 6.0 to pH 8.0.
10. A microfoam as claimed in any one of claims 1 to 9, wherein the aqueous solution contains a minor amount of alcohol.
11. A microfoam as claimed in any one of claims 1 to 10, wherein it contains 1 to 10% vol/vol glycerol.
- 15 12. A microfoam as claimed in any one of claims 1 to 11 for use in therapy.
13. Use of a microfoam claimed in any one of claims 1 to 12 for the manufacture of a medicament for the treatment of sclerotherapy.
14. A microfoam as claimed in any one of claims 1 to 12 for sclerotherapy.

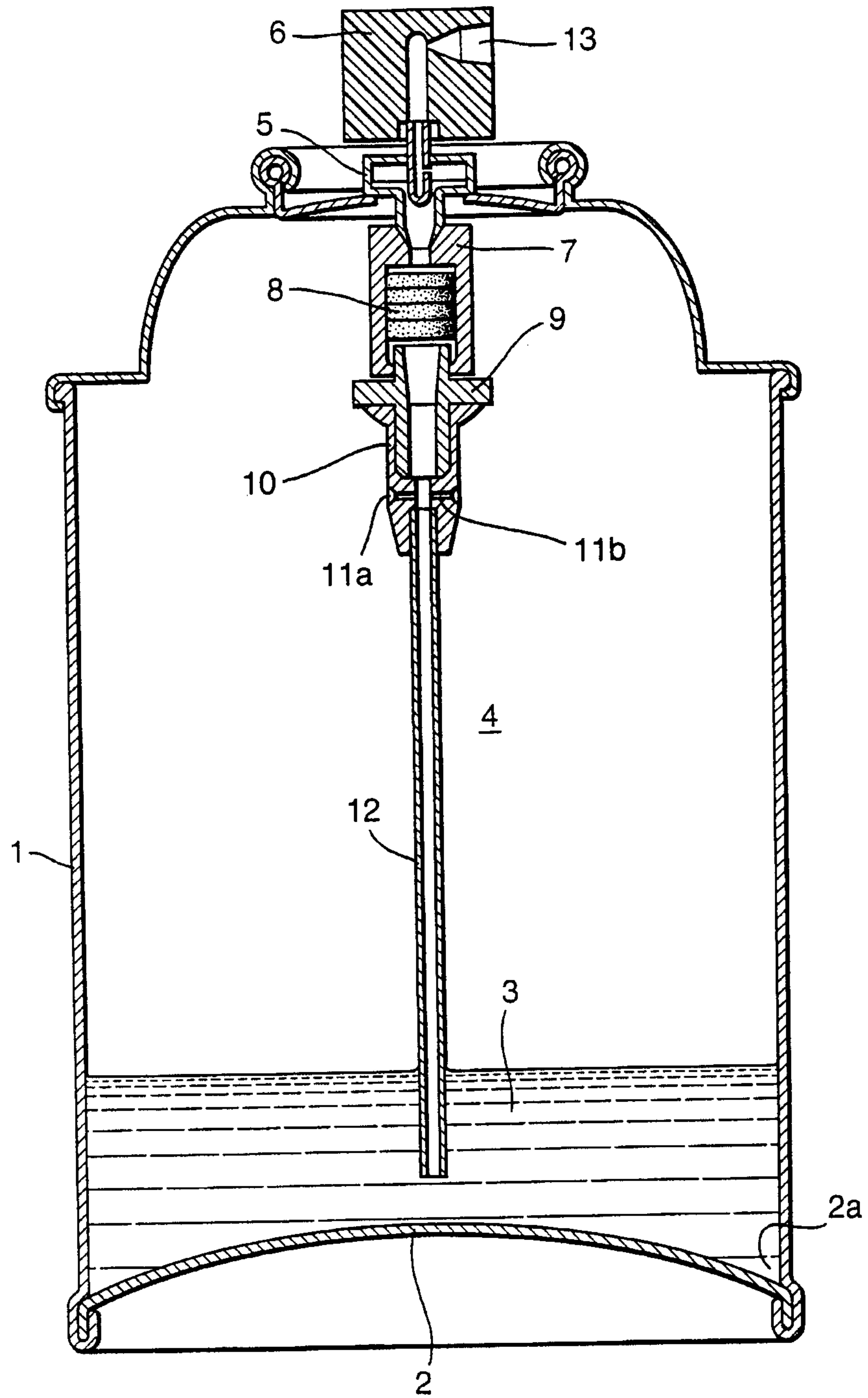
FETHERSTONHAUGH & CO.

OTTAWA, CANADA

PATENT AGENTS

1/9

Fig.1.



SUBSTITUTE SHEET (RULE 26)

2/9

Fig.2.

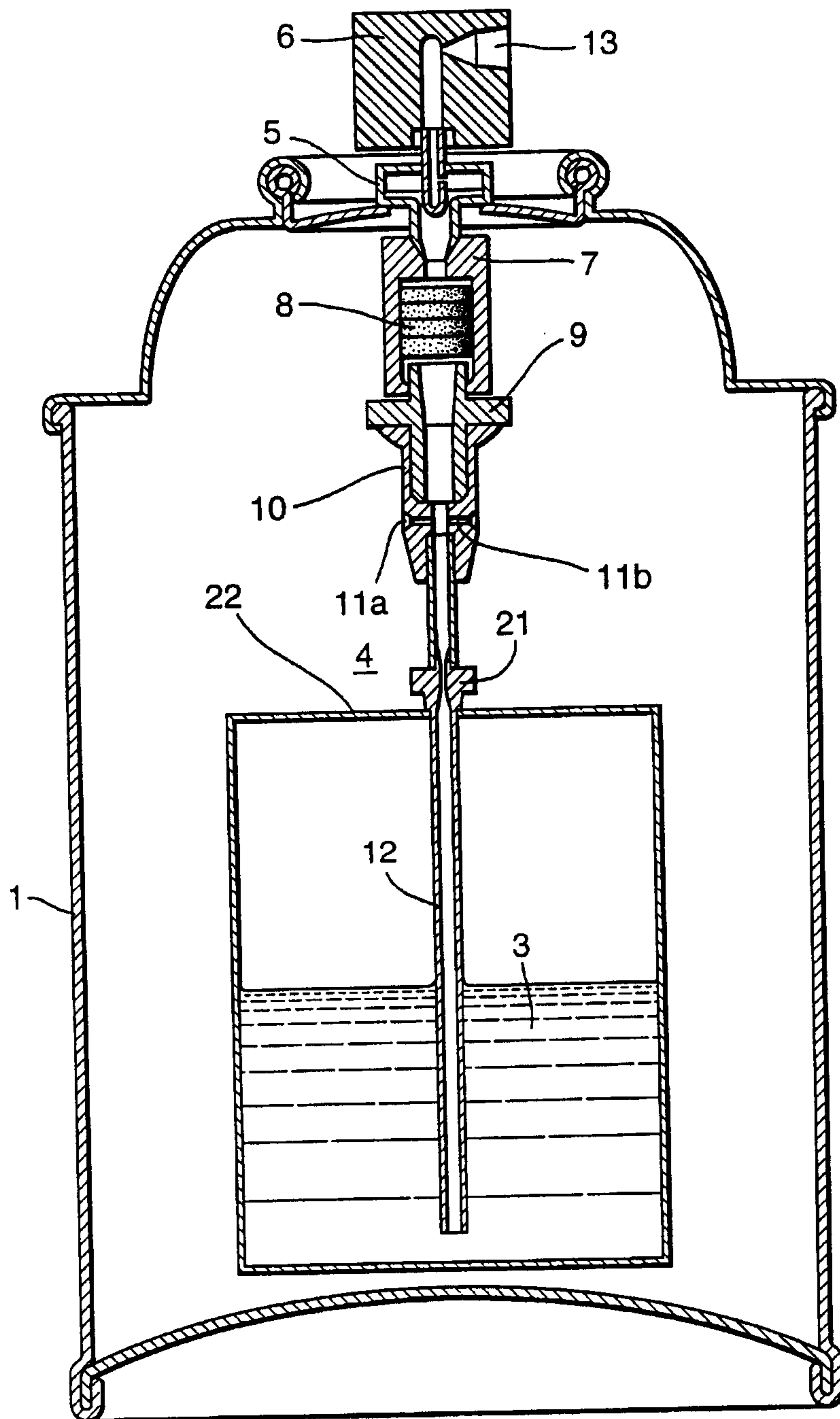


Fig.3.

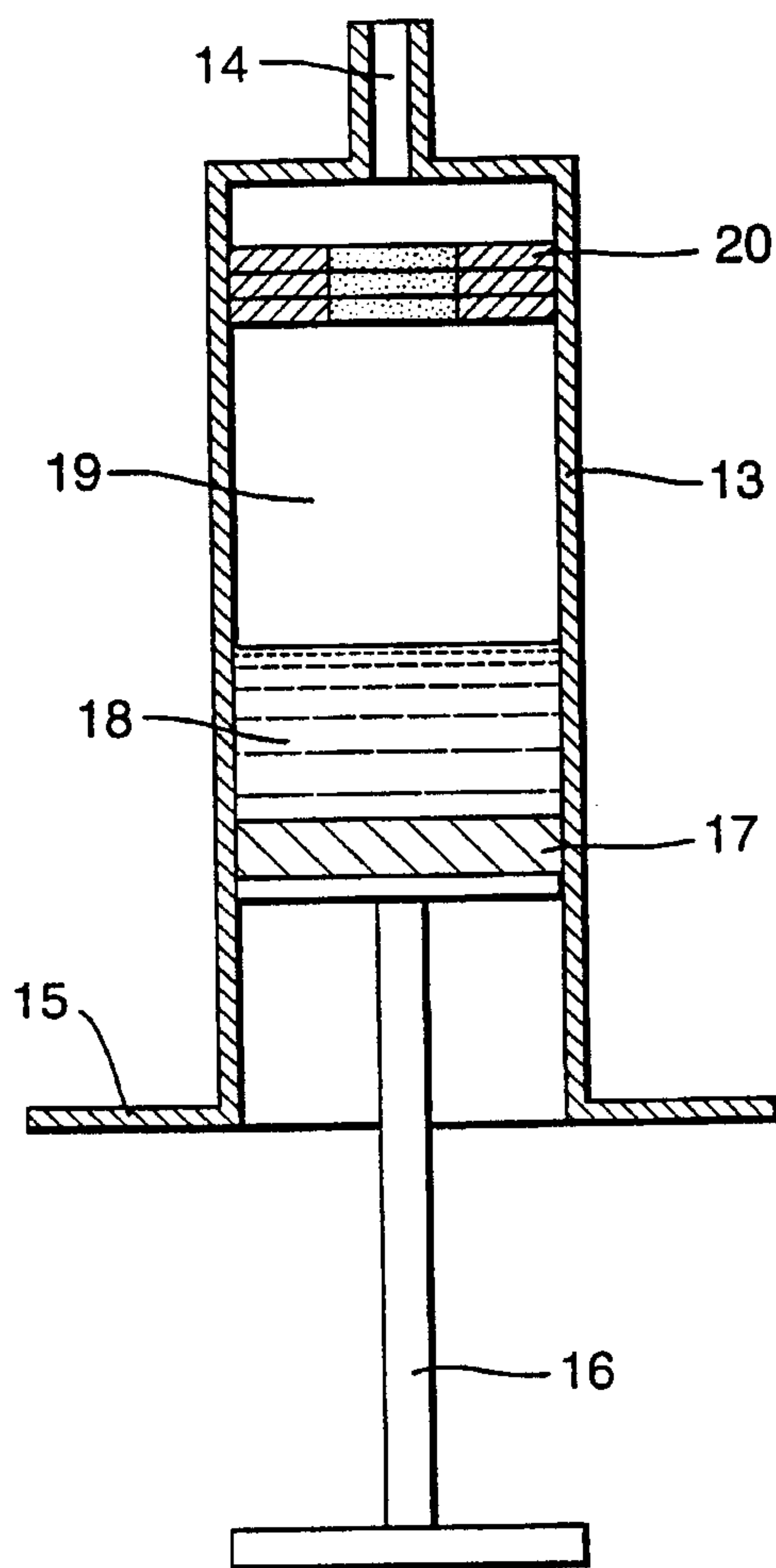
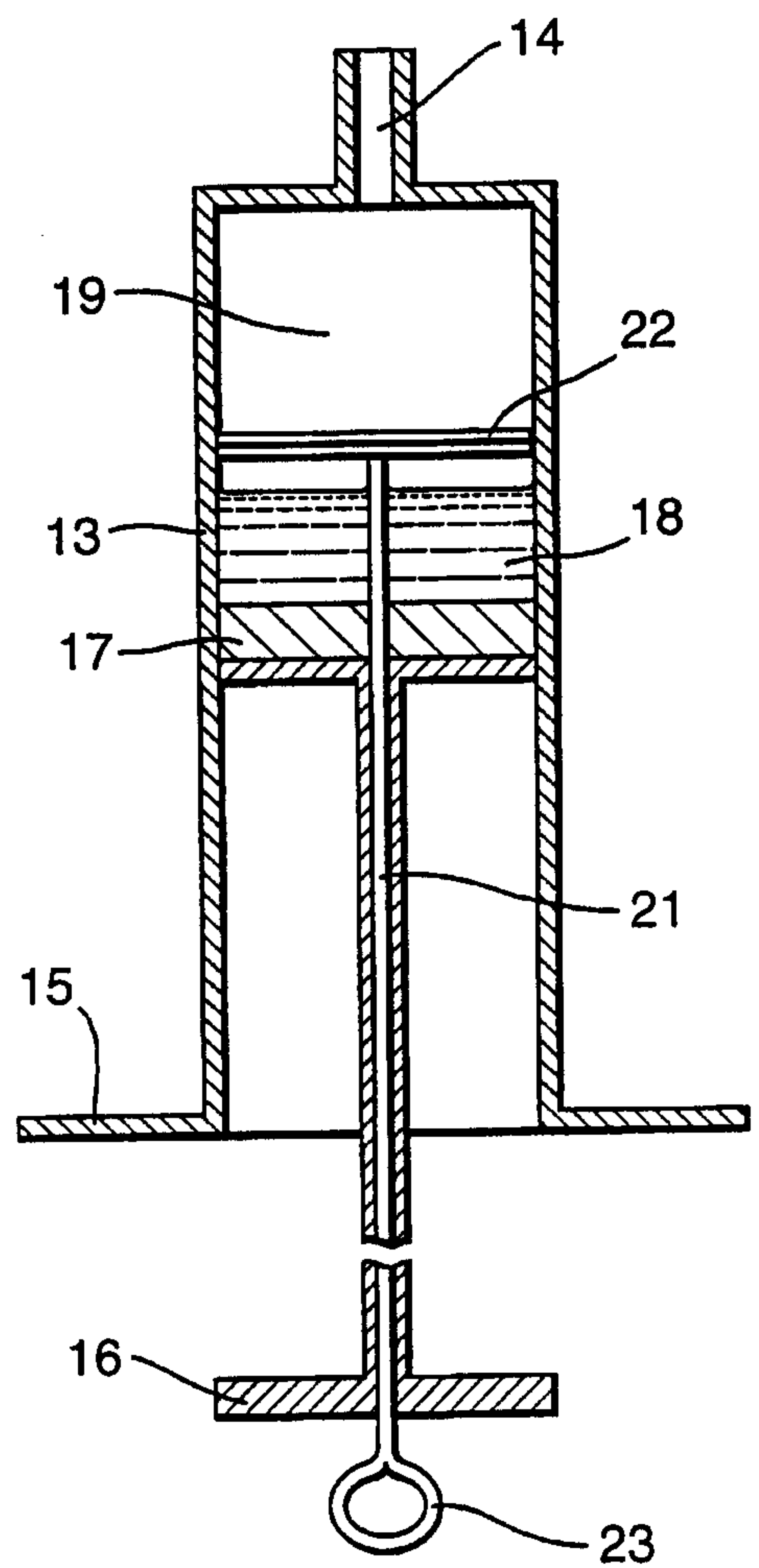
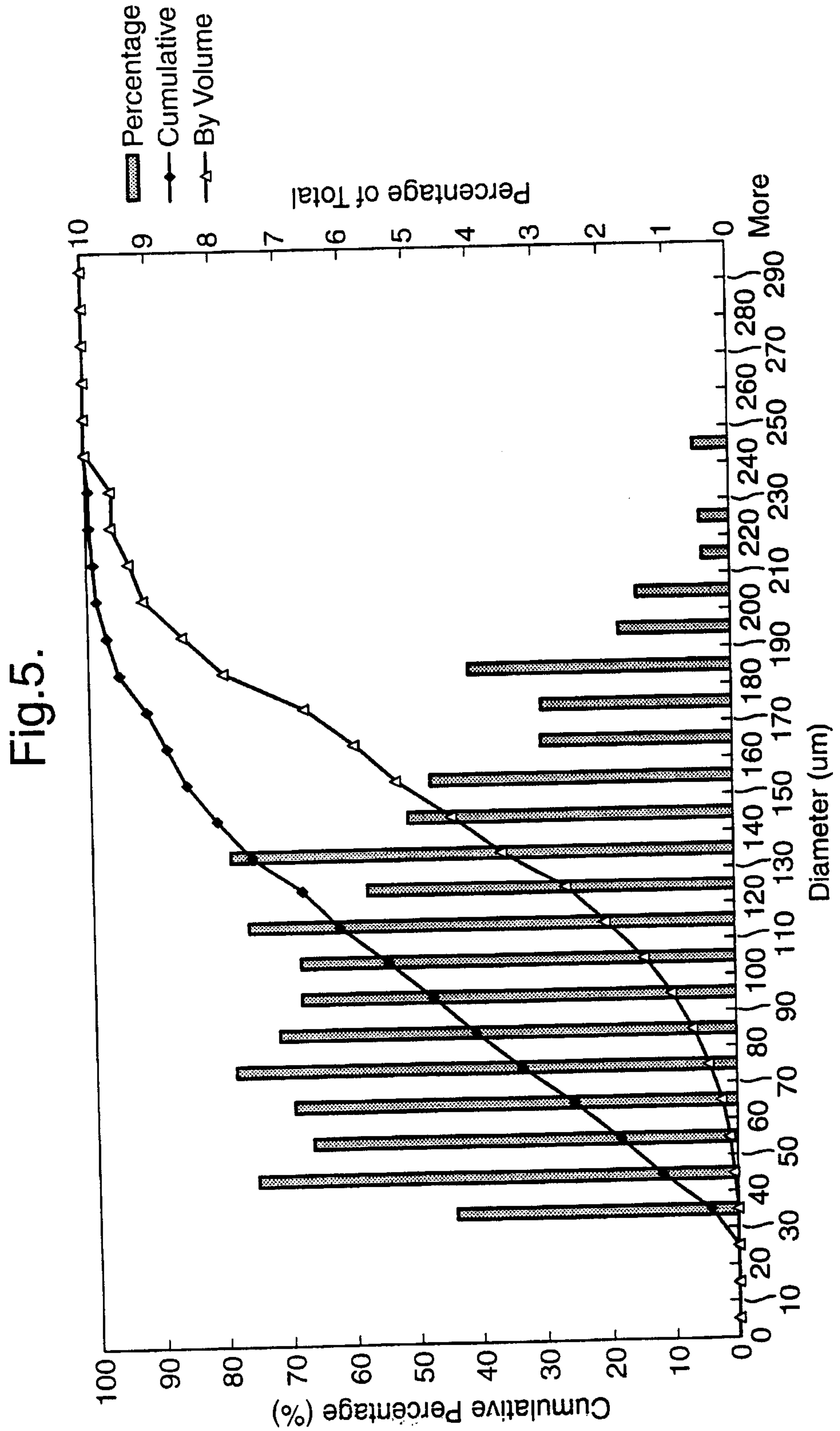


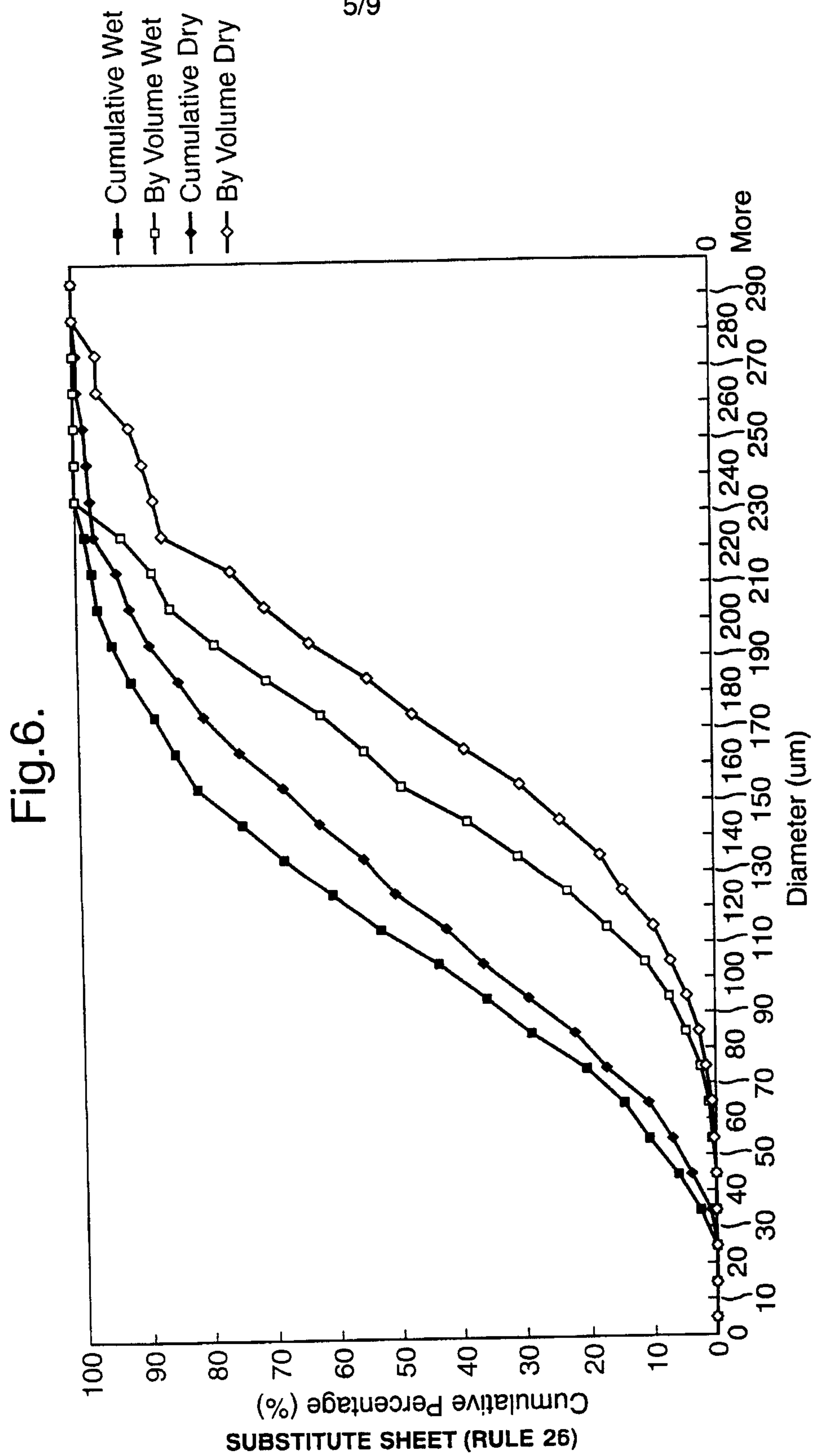
Fig.4.



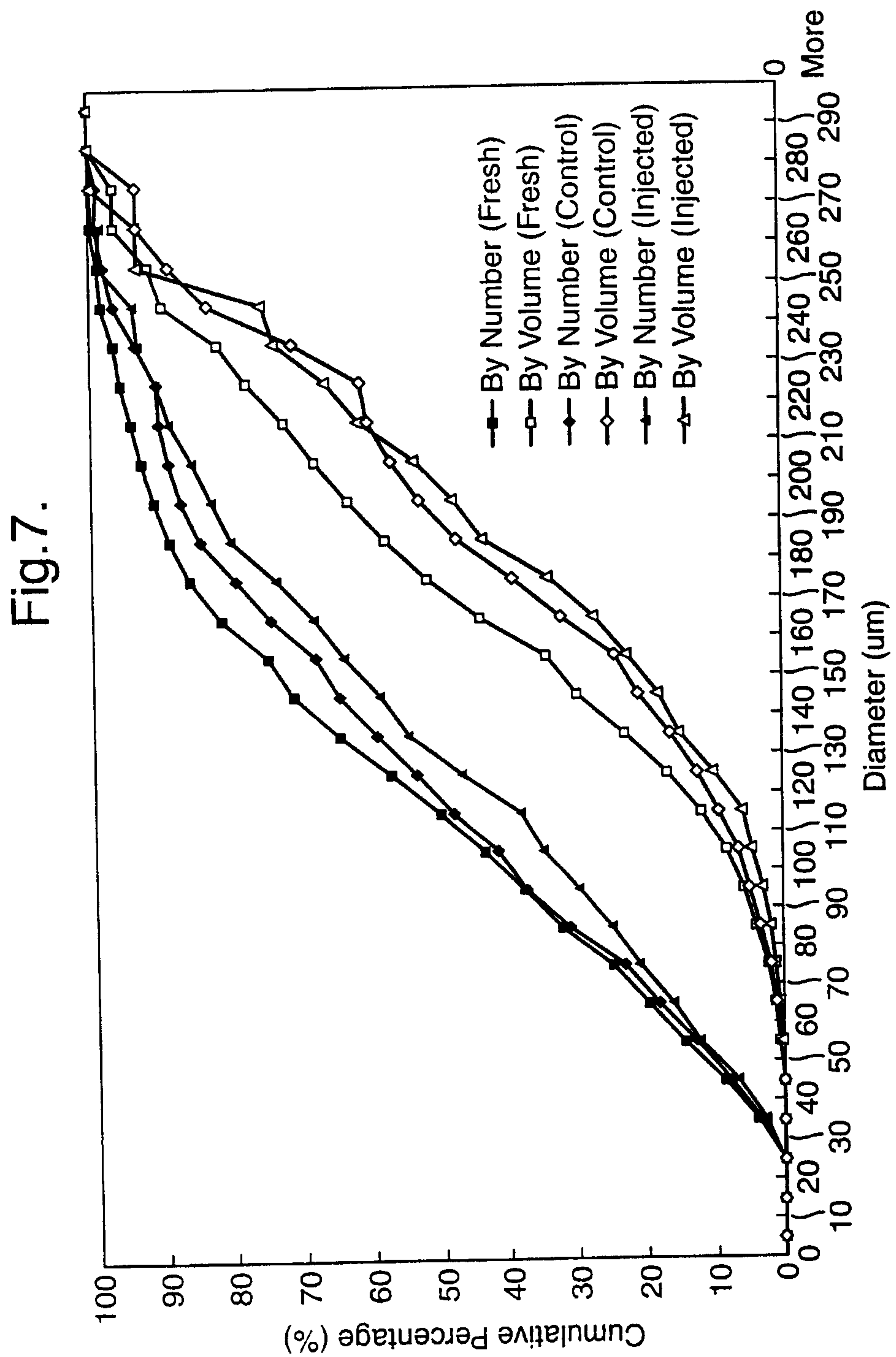
4/9



5/9



6/9



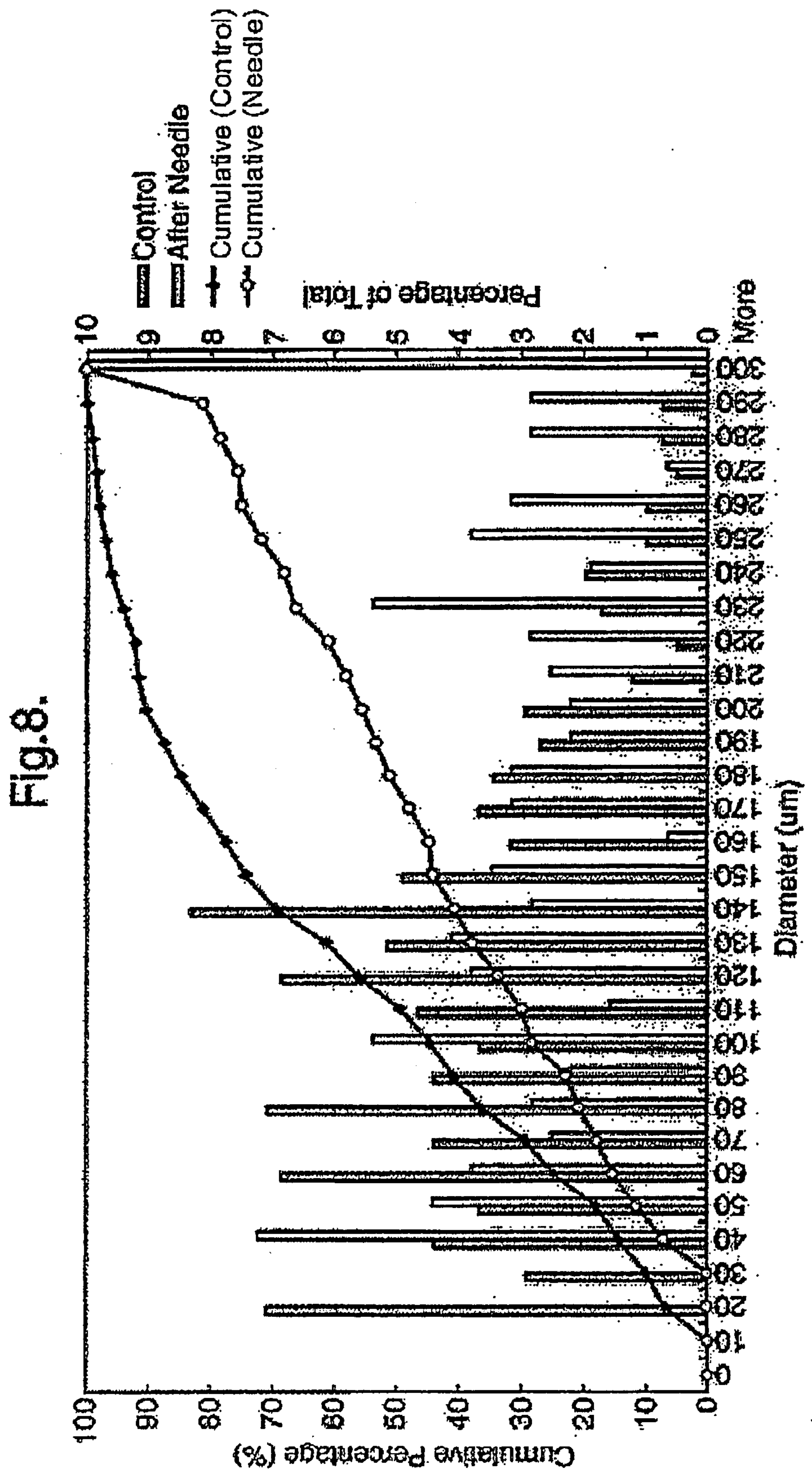
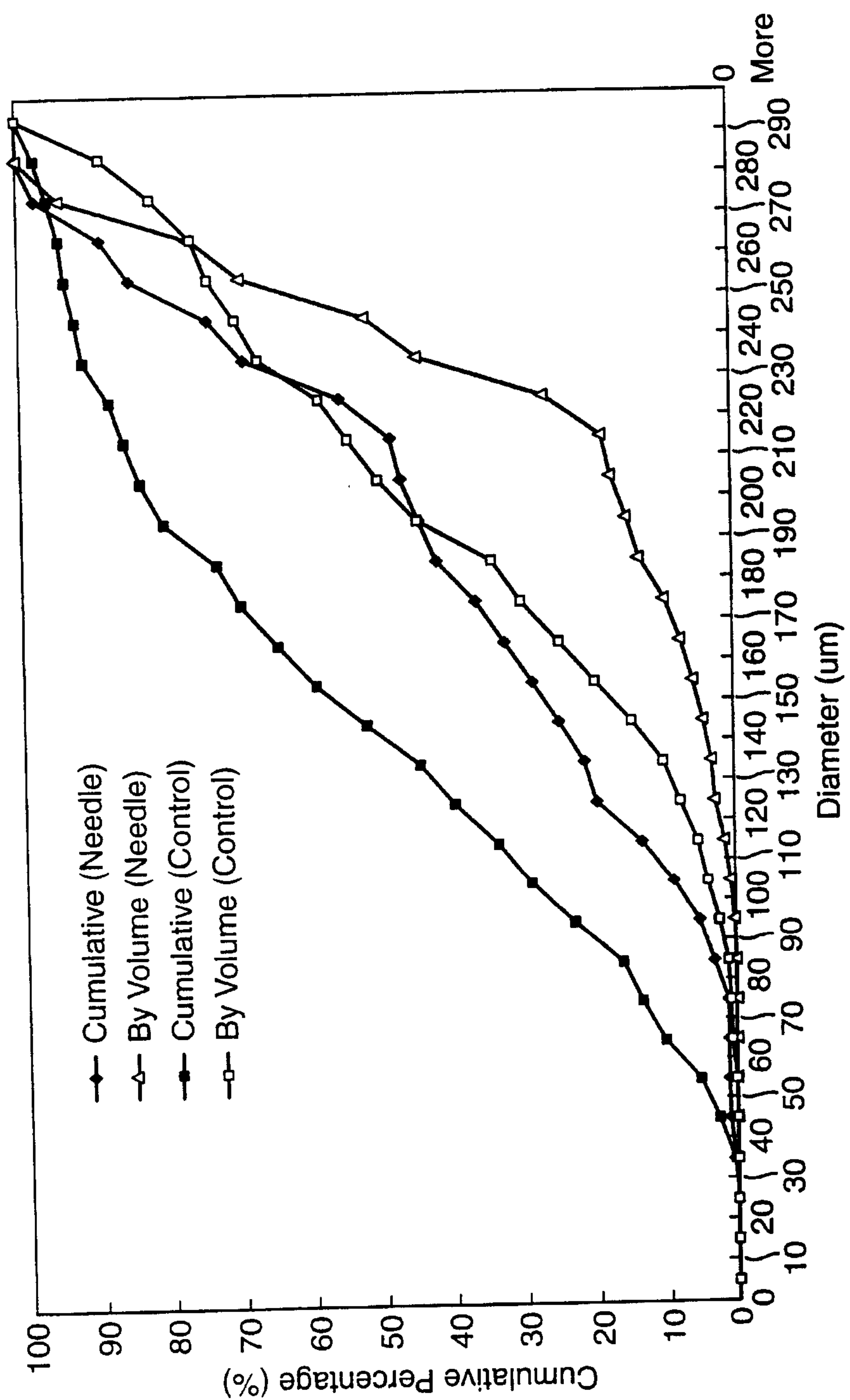


Fig.9.



9/9

Fig.10.

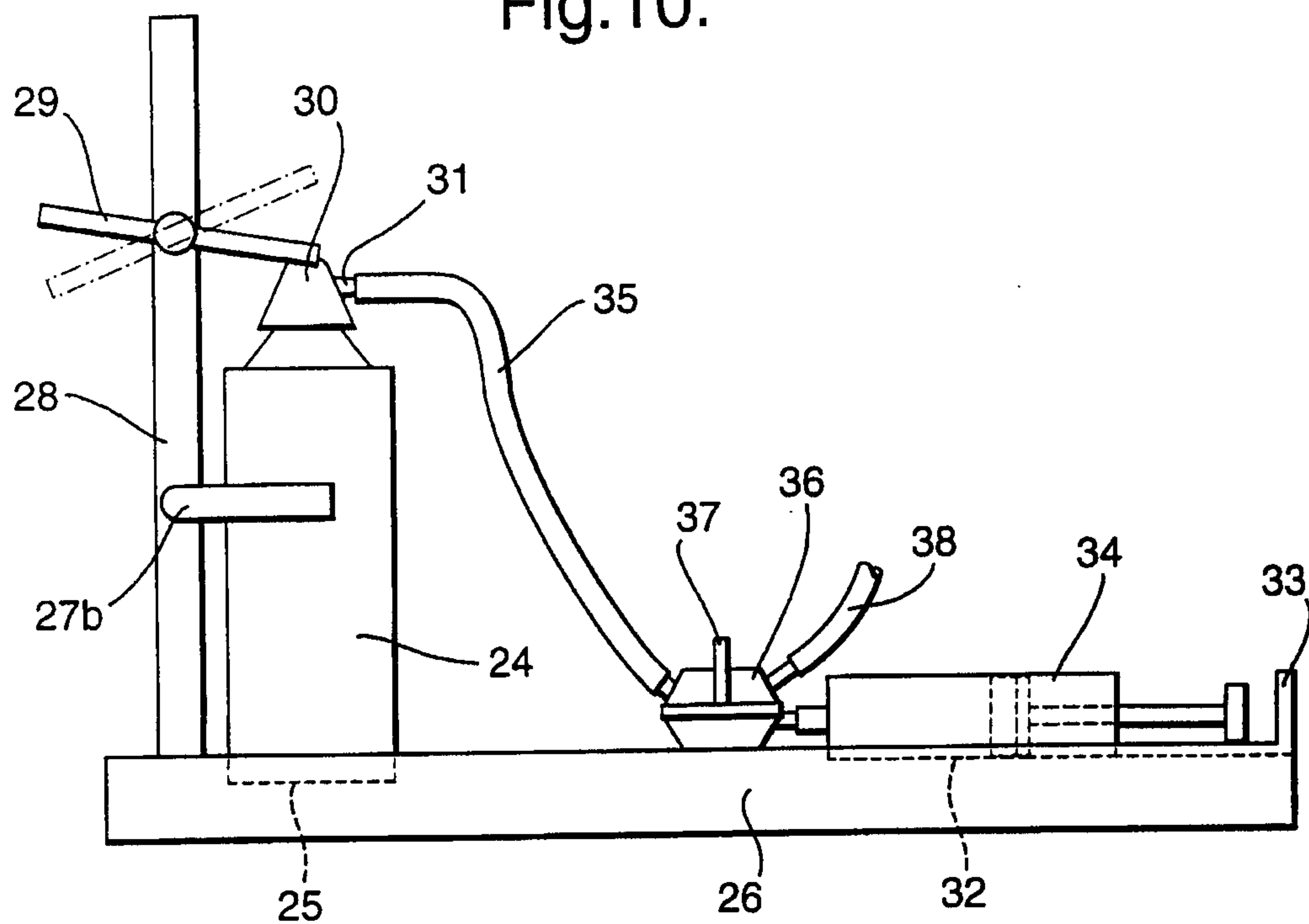
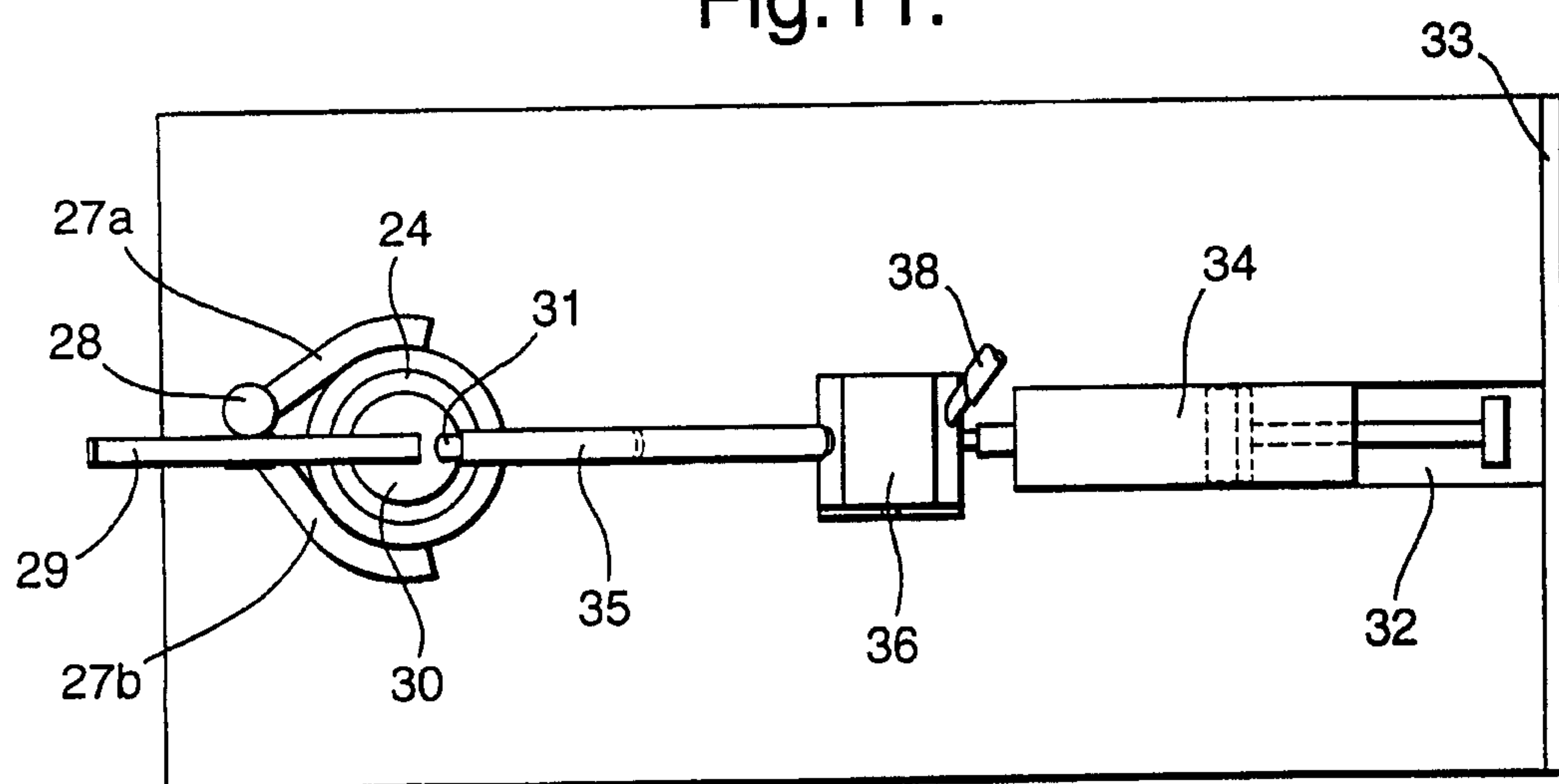


Fig.11.



SUBSTITUTE SHEET (RULE 26)

