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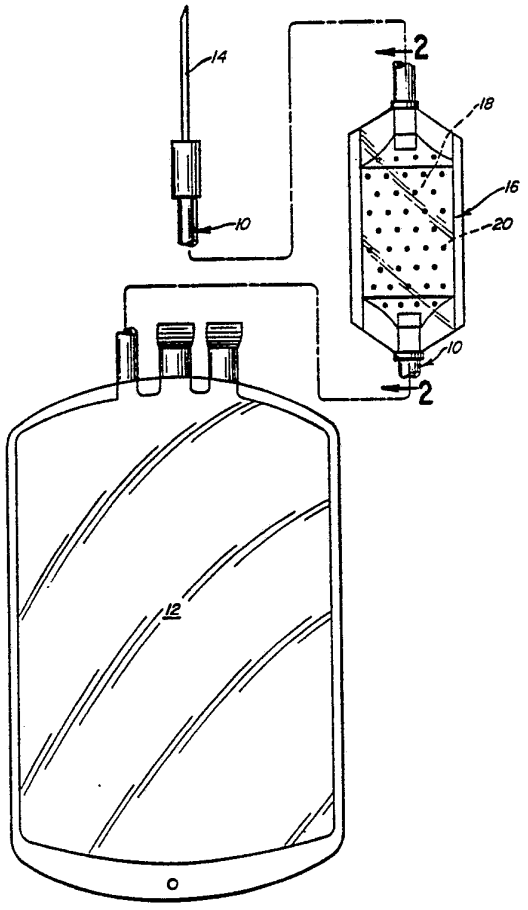
(54) Title: CONTROLLED ADMINISTRATION OF BENEFICIAL AGENT TO BLOOD

(57) Abstract

As one administers blood through a conduit (10) into a container (12), the blood is passed in the conduit across the supply of beneficial agent (18), such as anticoagulant, to cause a controlled amount of beneficial agent to enter the passing blood in a manner that is substantially uniform overtime. The beneficial agent (18) is typically in dry form until it enters into contact with the blood. Accordingly, no substantial portion of the blood is exposed to a significantly higher concentration of the beneficial agent than other portions of the blood.



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CONTROLLED ADMINISTRATION OF BENEFICIAL AGENT TO BLOOD

TECHNICAL FIELD

As blood is collected from the donor, it passes into a container such as a blood bag which contains an anticoagulant system. Such anticoagulant systems are typically a small amount of liquid solution which is stored in the bag and collection tubing, being typically ACD, CPD, CPD-adenine, or the like. Additionally, it has been suggested that the anticoagulant system may be placed as a dried coating or powder in the interior of the blood collection container.

With these systems, as the blood is introduced into the container, the ratio of the whole blood present to the anticoagulant present is undesirably low, consequently producing a significant and detrimental imbalance. While this problem is quickly corrected with the addition of subsequent amounts of blood, it can be damaging to the first aliquot of collected blood components.

Accordingly, there is a need for a blood handling system where beneficial agents such as anticoagulant/storage agents may be administered to the blood without the initial, undesirable osmotic shock effect that currently takes place at the beginning of the blood collection.

Additionally, in the manufacture of conventional blood storage bags which contain a liquid anticoagulant, a capital intensive and closely controlled manufacturing process is required, including a liquid filling operation (which requires a clean room), batch steam sterilization procedures, and packaging of the blood bag in an additional moisture

barrier container for storage. If it were possible to make use of blood bags which did not contain a liquid anticoagulant system, it would be possible to greatly simplify the manufacturing process, making use of radiation sterilization, and eliminating the additional moisture barrier packing which is currently necessary.

Additionally, blood storage bags which contain either a liquid anticoagulant or a dried coating thereof on the interior walls result in a container that must be completely filled with blood in order to be usable. If, for any reason, the donor is unable to donate one complete unit of blood, the entire, underfilled unit typically is not used, due to an excess concentration of anticoagulation agent present in the reduced volume of blood, since the anticoagulant present in the bag is intended for one complete unit of blood. If empty, anticoagulant-free blood storage bags were used in which the blood was still properly provided with anticoagulant/storage agents, these underfilled units could still be used for pediatric or partial transfusion purposes, and would not have to be discarded.

In accordance with this invention, the above problems, and other problems as well, may be solved, to permit the application of a beneficial agent such as anticoagulant/storage agents to blood while the blood is passing through a conduit into a container. Thus, blood storage containers without any beneficial agent therein may be manufactured and used, for the significant manufacturing advantages described above. Also, because of this invention, partial units of blood may be collected and used.

DESCRIPTION OF THE INVENTION

In this invention, the method of passing blood through a conduit into a container is improved as follows. The blood is passed into the conduit and across the supply of beneficial agent in such manner as to cause a controlled amount of beneficial agent to enter the passing blood in a manner that is substantially uniform over time. Accordingly, no substantial portion of the blood is exposed to a significantly higher concentration of the beneficial agent than other portions of the blood. Additionally, in the event that less than a unit of blood passes across the beneficial agent, less than the normal amount of the beneficial agent will enter the blood, so that the partial unit of blood contains substantially the same concentration of beneficial agent that a whole unit of blood would contain, permitting its use. Additionally, in those preferred circumstances where the container is substantially free of the beneficial agent, but for the beneficial agent passing into the container with the blood, simplified manufacturing methods may be used for manufacturing the container.

The beneficial agent is preferably provided in the form of a dry tablet or other solid mass, with means provided in the conduit for carrying the solid mass of beneficial agent and permitting blood flowing through the conduit to enter into contact with the solid mass. As blood passes through the solid mass, it picks up a substantially predetermined amount of beneficial agent, and carries it away. The solid mass may be engineered in accordance with any of a variety

of known ways, to provide a controlled, relatively constant release of the beneficial agent as the blood passes across it.

Typically, the beneficial agent is a dry, blood storage anticoagulant preparation, in its original state, prior to entering the passing blood. The dry beneficial agent may be a molded or pressed structure such as a tablet, a pressed solid structure having multiple flow channels through it for blood flow, a cylinder positioned so that blood flows through its bore, a powdery mass, or other shape or structure as desired.

Additionally, the beneficial agent may be impregnated in a controlled release matrix in accordance with known principles of the prior art. For example, the beneficial agent may be carried in the conduit on or in a porous, insoluble plastic mass such as polypropylene, through which the blood can flow as it passes through the conduit, for desired controlled release characteristics. The matrix may be embedded directly in the plastic material forming the conduit itself. Alternatively, masses of ion exchange resin may be placed in the conduit while carrying the desired beneficial agent so that blood flowing through the ion exchange resin will cause a controlled release of the beneficial agent.

When the beneficial agent desired is an anticoagulant/preservative preparation, it may comprise a solid mass of dextrose formed in a shape as described above, which contains an effective anticoagulating amount of a soluble, nontoxic citrate, so that the dextrose and the citrate dissolve together in a controlled release manner in the passing blood. Additionally, the anticoagulant/preservative formulation may include an amount of soluble, nontoxic

phosphate and/or adenine, which is effective to promote the blood storage of the anticoagulant preparation. Examples of usable citrates and phosphates include sodium citrate, citric acid, and monosodium or disodium phosphate. Another usable anticoagulant may be heparin.

Additionally, other dry ingredients may be incorporated in the glucose mass, such as mannitol, adenine, or any other desired beneficial agent. Additionally, other media for providing the solid, blood-soluble mass may be used such as sodium citrate per se, which serves as an anticoagulant in its own right.

By the term "blood", it is intended to include not only whole blood, but components of blood as may be desired, for example blood plasma (either platelet rich or platelet poor) or suspensions of packed cells, white cells, or platelets in saline, any other appropriate suspension of blood cells, or the like.

DESCRIPTION OF DRAWINGS

Fig. 1 is a plan view of a blood collecting set made in accordance with this invention, shown to be integrally connected to a blood storage bag.

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

DESCRIPTION OF SPECIFIC EMBODIMENT

Referring to the drawings, there is shown a set 10 for collecting blood from a patient or other donor and conveying it to blood storage container 12, which may be made in substantially conventional

manner. Set 10 carries at one end a conventional blood connection needle 14 for collecting blood from the venous system of the donor, which blood then passes through set 10 into blood bag 12.

In accordance with this invention, the conduit of set 10 defines an enlarged portion 16 which includes a solid mass 18 of dry blood storage anticoagulant preparation, typically having a water content on the order of no more than about 2% by weight. Anticoagulant tablet 18 is shown to be made in the form of a thin, rectangular member positioned within enlarged portion 16. The inner walls of both sides of enlarged portion 16 define an array of small projections 20 which project inwardly to define flow passages between the inner wall of enlarged portion 16 and the surface of anticoagulant preparation tablet 18.

Specifically, anticoagulant preparation tablet 18 may comprise, for example, a dried mixture of:

	Weight %
Dextrose	44
Sodium Citrate	46
Citric Acid	6
Sodium Biphosphate	4

Alternatively, another example of tablet 18 of this invention may be pressed together out of the following ingredients:

	Weight present
Dextrose	1.62 gm.
Sodium citrate	0.83 gm.
Citric acid	0.206 gm.
Sodium Biphosphate	0.140 gm.
Mannitol - as a binding agent	0.24 gm.
Poly(ethylene glycol) - as a tablet lubricant	2% of total wt.

Tablet 18 of either of the above mixtures of materials may be formed into a solid, pressed together matrix, or it may be mixed together with an aqueous vehicle, with the water being later evaporated away to form a glassy or microcrystalline composition.

Alternatively, member 18 may be a porous, insoluble plastic mass, for example porous polypropylene, having a mixture of citric acid and sodium citrate, for example, impregnated therein. Accordingly, as blood passes through such a porous, polypropylene mass, the citric acid and sodium citrate are leached into the blood at a generally constant rate, so that all portions of the blood passing through enlarged portion 16 receive a substantially similar amount of citric acid and sodium citrate. The proportions of citric acid and sodium citrate, and their concentrations, are selected to achieve the desired concentration and pH for the passing blood.

With a non-disintegrating mass such as polypropylene, there may be, towards the end of the dissolution time period for the anticoagulant, a reduction in the rate at which the anticoagulant enters the blood. This is due for example to the need for the last amount of anticoagulant or other agent to travel through the polypropylene, to the surface of that non-disintegrating mass.

Instead of citrate anticoagulant, the tablet 18 may alternatively include heparin anticoagulant, such as about 1800 to 2500 units of heparin for use with a single unit of whole blood. A single unit of whole blood is between about 400 to 500 ml. of liquid.

Blood bag 12 may be initially free of any anticoagulant. The entire system, including tablet 18, is typically radiation sterilizable, since it is substantially free of moisture. Additionally, no overpouch or other outer package is required to prevent the loss of water from a liquid anticoagulant system, which constitutes a significant advantage over the conventional present blood collection equipment.

For use, a conventional phlebotomy is made into a vein of a blood donor with needle 14, and the blood flows through conduit 10. As it flows, it enters enlarged portion 16, where it flows in a pair of opposed flow halves 22 between the walls 24 of enlarged portion 16 and the flat surfaces of tablet 18. As the blood so flows, the substance of tablet 18 is dissolved away into the flowing blood at a relatively uniform rate of dissolution, so that each individual portion of the flowing blood passing through conduit 10 picks up a substantially similar amount of the dissolved substance of tablet 18 as it flows across it. From there, the flowing blood, carrying the dissolved anticoagulant, glucose, etc. passes into bag 12 for storage, without encountering an excessive concentration of anticoagulant or other agent.

It may be generally desirable for the tablet 18 to be of such a thickness that it is not completely eroded away by the time that the last of the blood has passed across it to fill bag 12 to its desired amount.

When tablet 18 retains its basic rectangular shape to the end of the flow process, even though it becomes thinner, a relatively constant transfer of anticoagulant to all portions of the blood is achieved.

Other dry forms of beneficial agents, particularly anticoagulant/preservatives, may also be used as desired, as a substitute for the specific forms of beneficial agent illustrated above with respect to tablet 18.

Any design of blood bag or other container may also be utilized in accordance with this invention. If desired, the tablet 18 or an equivalent mixture of materials may be encapsulated and released via diffusion through a semipermeable membrane.

Additionally, the invention of this application may be used in conjunction with various other blood collection, separation, or handling procedures, for example plasma separation. Medications may be administered to blood in accordance with this invention by an apheresis procedure or the like.

The above has been offered for illustrative purposes only, and is not intended to limit the scope of the invention of this application, which is as defined in the claims below.

THAT WHICH IS CLAIMED IS:

1. The method of passing blood through a conduit, the improvement comprising:

passing said blood in the conduit across a supply of beneficial agent in such manner as to cause a controlled amount of beneficial agent to enter said passing blood in a manner that is substantially uniform over time, whereby no substantial portion of said blood is exposed to a significantly higher concentration of said beneficial agent than other portions of said blood.

2. The method of claim 1 in which said container is substantially free of said beneficial agent, but for beneficial agent passing into said container with said blood.

3. The method of claim 1 in which said beneficial agent is a dry anticoagulant preparation, prior to entering said passing blood.

4. The method of claim 3 in which said dry anticoagulant preparation is a solid mass of dextrose which contains an effective anticoagulating amount of citrate or citrate and phosphate.

5. The method of claim 3 in which said anticoagulant preparation is a suitable blood storage preparation.

6. The method of claim 3 in which said anticoagulant preparation is in the form of adhering particles, and includes mannitol in sufficient amount to promote the adhesion of said particles to each other.

7. The method of claim 3 in which said dry blood storage anticoagulant preparation is carried in said conduit on or in a porous, insoluble plastic mass through which blood flows as it passes through said

conduit.

8. The method of claim 1 in which said blood is whole blood.

9. In a set for conveying blood from one location to another which comprises a conduit, the improvement comprising: a portion of said conduit carrying a solid mass of dry blood storage anticoagulant preparation through which blood flowing through said conduit can pass.

10. The set of claim 9 in which said solid mass comprises dextrose which contains an effective anticoagulating amount of anticoagulant.

11. The set of claim 9 in which said solid mass is in the form of adhering particles, and includes mannitol in sufficient amount to promote the adhesion of said particles to each other.

12. The set of claim 9 having means for communication with the venous system of a blood donor at one conduit end.

13. The set of claim 12 which is connected to a blood storage bag at the other conduit end.

14. The set of claim 13 in which said anticoagulant comprises a soluble, nontoxic citrate.

15. The set of claim 13 in which said anticoagulant comprises heparin.

16. The set of claim 14 in which said anticoagulant includes an amount of soluble, nontoxic phosphate which is effective to promote the action of said blood storage anticoagulant preparation.

17. The set of claim 9 in which said dry, solid mass of anticoagulant is carried on or in a porous, insoluble plastic mass positioned within said conduit.

18. In a set for conveying blood from one

location to another, which comprises a conduit, the improvement comprising: a portion of said conduit carrying a solid mass of a dry blood storage anticoagulant preparation through which blood flowing through said conduit can pass, said solid mass comprising dextrose which contains an effective anti-coagulating amount of a soluble, nontoxic citrate, and also including an amount of soluble, nontoxic phosphate which is effective to promote the action of said blood storage anticoagulant preparation.

19. The set of claim 18 which is connected to a blood storage bag at at least of one of the conduit ends which is essentially free of said preparation.

20. The set of claim 19 having means for communication with the venous system of a blood donor at one conduit end.

21. The method of passing blood through a conduit into a container, the improvement comprising: passing said blood in the conduit across a supply of dry blood storage anticoagulant preparation in such manner as to cause a controlled amount of said preparation to enter said passing blood, and thereafter passing said blood into said container while said container is substantially free of said preparation but for the preparation which passes into said container with the blood, whereby no substantial portion of said blood is exposed to a significantly higher concentration of said beneficial agent than other portions of said blood.

22. The method of claim 21 in which said dry blood storage anticoagulant preparation is a solid mass of dextrose which contains an effective anticoagulating amount of soluble, nontoxic citrate.

23. The method of claim 22 in which said

anticoagulant preparation includes an amount of soluble, nontoxic phosphate which is effective to promote the action of said blood storage anticoagulant preparation.

24. The method of claim 23 in which said anticoagulant preparation is in the form of adhering particles, and includes mannitol in sufficient amount to promote the adhesion of said particles to each other.

25. The method of claim 24 in which said blood is whole blood.

26. The method of claim 21 in which said controlled amount of said preparation passes into the blood in a manner which is substantially uniform over time.

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FIG. 1

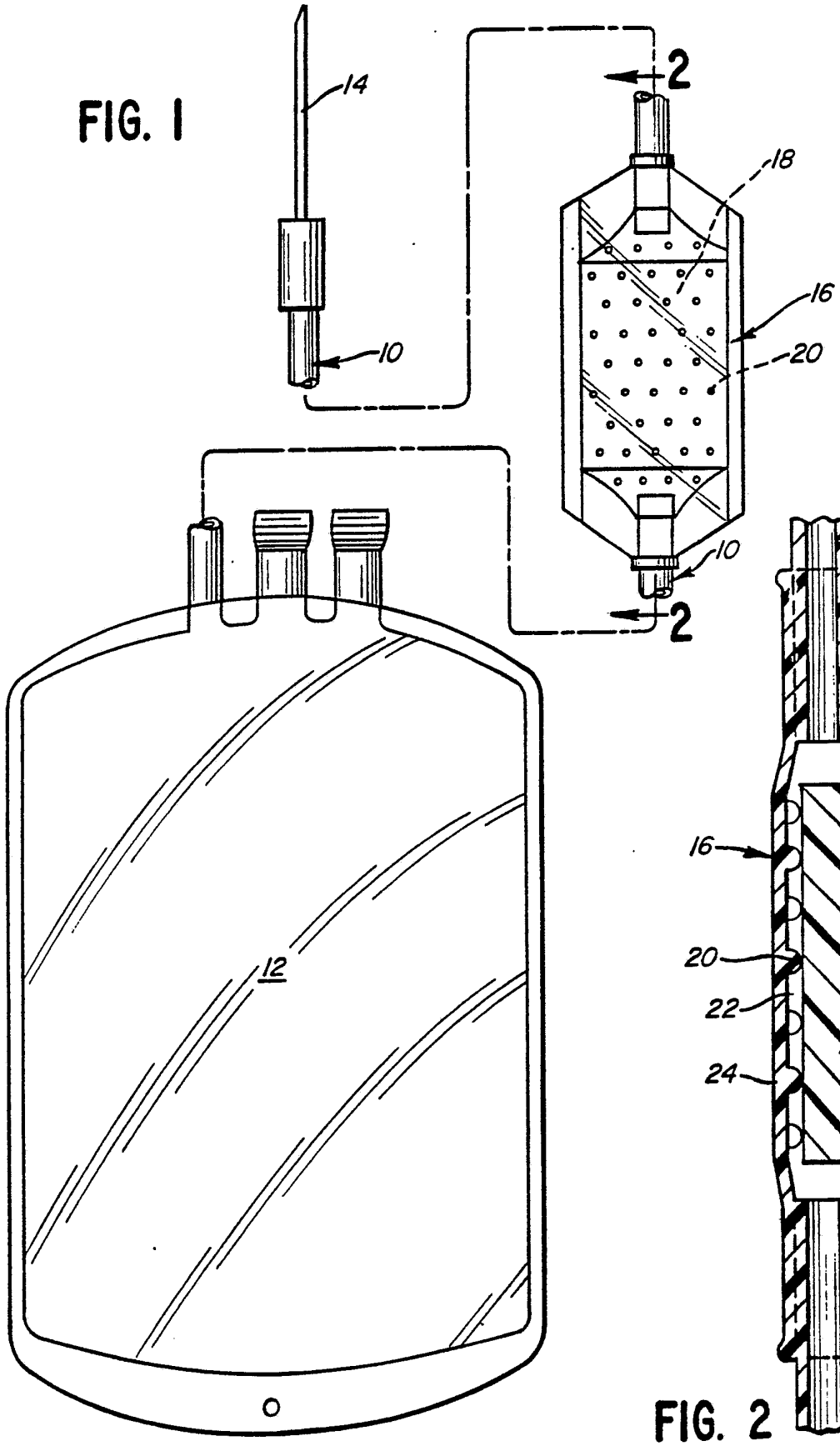

FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/03988

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4) A61K 9/22
US CL 604/890

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	604/4,6,56,82-85,92,185,251,252,262,890,892 424/467,479

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X Y	US,A, 4,552,555 (THEEUWES) 12 November 1985. See abstract, column 4, lines 8-36.	1, 2 3-26
Y	US,A, 4,235,236 (THEEUWES) 25 November 1980. See column 6, lines 10-28; col. 5, lines 20-21; col. 6, lines 51-60.	4,5,6,7, 10-26
Y,P	US,A, 4,758,430 (SABIN) 19 July 1988. See column 3, lines 47-2.	4,6,10,11
Y	US,A, 4,086,924 (LATHAM) 02 May 1978. See column 1, lines 65-5.	5,12-16,18-26
Y	Transfusion, Volume 24, No. 6, issued 1984 (Philadelphia), B.A. MYHER ET AL, "Preservastion of red cell antigens during storage of blood with different anticoagulants, see pages 499-501.	5,12-16, 18-26

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29 January 1989	10 APR 1989
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Mark O. Polutta Paul Sacher for

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	US,A, RE 25,129 (WALTER) 27 February 1962. See column 4, lines 15-25.	1-26
A	US,A, 4,257,426 (BAILEY), 24 March 1981. See abstract.	
A	CH, 497,181 (FOKIANOS), 30 November 1970. See Fig. 1, column 3, lines 5-10.	

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.