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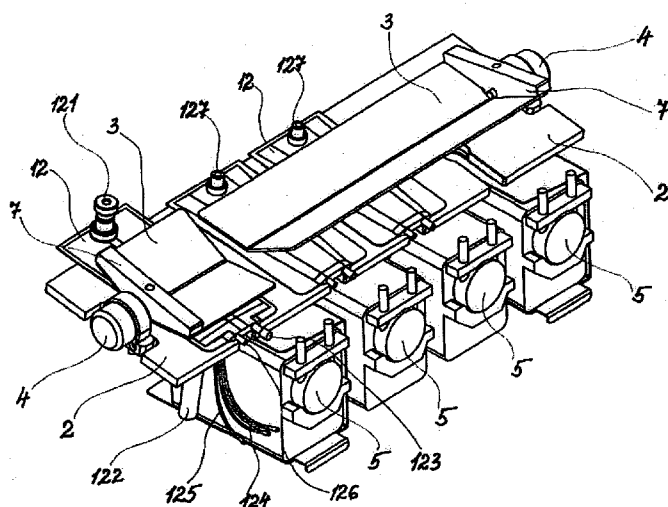
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[Continued on next page]

(54) Title: DIGESTIVE TRACT SIMULATOR

Fig. 1



(57) Abstract: A digestive tract simulator, comprising hydraulically interconnected at least two elastic bags (12) kept at the constant temperature and a controllable heating source, wherein a heating source is represented by a heated temperating plate (2) over whose working surface intended for placing of elastic bags (12) two levers (7) are arranged in an axial distance, swinging around a common axis; to these levers (7) a deflected wing (3) placed in parallel with the temperating plate (2) and having working arms opened in a wide angle in direction from the temperating plate (2) is mounted on the lever's side near to the temperating plate (2); at least one of levers (7) is connected to a pendulum engine (4) having an adjustable motion so that elastic bags (12) are in operating state situated between the working surface of the temperating plate (2) and the deflected wing (3); each of bags (12) is equipped by an air cock (127) and an input and output pipe channel (126) for working medium, connecting bags (12) together via tubing coupled through a peristaltic pump (5).



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Digestive Tract Simulator

Technical field

The invention relates to the simulation of the human digestive system, consisting of a set of at least two deformable chambers kept at constant temperature during operation and formed by interconnected elastic bags. Each of the bags is equipped by outlets for hydraulic interconnection, as well as by outlets for measuring probes connection and by outlets for sample withdrawal and refilling of titration solvent into bags respectively.

State of the Art

For prediction of biological accessibility of medical drugs, especially for the solid drug's formulations, "*in vitro*" tests are used. So called dissolution equipments belong among the most widely used tools, e.g. of type 1 or 2 according to US pharmacopoeia (USP). However, they have considerable limits due to their simplicity.

To increase the predictability and better simulate processes in the human digestive tract, the equipment simulating these processes was designed. Such an apparatus simulating peristaltic movements, which contribute to dissolution of the drug and its passage through digestive tract, is described for example in the US patent No. 5,525,305. This apparatus includes the unit, consisting of at least two pressurized chambers, each of them containing the elastic tube. Each end of this tube is tightly connected to the wall of pressure chamber, so the space between the wall of chamber and the tube is hermetically closed. Obviously, the unit has a connecting hardware for inlet and outlet of gas or liquid into (and out of, respectively) the spaces between walls of pressure chamber and tubes, as well as the hydraulic hardware for connection of chambers together or to terminal or intermediate pieces. The unit has also connecting systems in terminal and intermediate pieces for introduction of working medium components into tubes or removal of them respectively. Medium present in spaces between walls of pressure chamber and the tube can be exploited also for heating of components taking part in a reaction within the tube.

For control of frequencies and force of peristaltic movements, controlling systems and regulating units are used for increasing and decreasing the inner pressure between the tube

and wall of the chamber. These units utilize pumps controlled by the computer.

This kind of apparatus is very complicated and very expensive, whereas the human digestive system is simulated only roughly.

A similar arrangement is known from the published abstract no. 5592130 of Japanese patent application no. 55-2924. It consists of two bags, connected by an interface, made up of channels, inlet and outlet tubes, or pipes. A modularity of this equipment is hardly possible to enlarge, so neither in this case is it possible to simulate the human digestive tract accurately. The relevant apparatus is also offered in a Dutch patent n. 9201907.

The purpose for designing the human digestive system simulator according to this invention was to eliminate drawbacks of improve upon the above mentioned apparatuses, possibly using readily commercially available components.

Invention Description

The above mentioned deficiencies are eliminated by the human digestive system simulator, which uses a unique system for modulation of hydraulically interconnected elastic bags, kept at constant temperature. According to this invention the bags represent a stomach and a small intestine. The subject matter of the invention is the fact that the heating source is represented by a heated plate, having two levers swinging around a common axis and arranged in an axial distance over its working surface intended for the placing of elastic bags. A bent wing, having working arms opened in a wide angle in direction away from the working surface, is mounted to these levers on the side near to heating plate. The wing is placed in parallel with the heating plate, whereas at least one of levers is connected to the pendulum engine with adjustable motion. Elastic bags are in an operating state situated side by side and symmetrically across at the axis of levers between the working surface of the heating plate and the wing. Each of them is equipped by an air cock and an input and output pipe channel for working medium, connecting bags together via tubing coupled through peristaltic pump.

The deflected (bent) wing can be advantageously divided so it's one part works with the elastic bag, which represents a stomach, while the second part works with the bags representing a small intestine. Each of the levers is operated by its own pendulum engine.

It is advantageous, if at least one of elastic bags is equipped by a filler hole with a plug for inserting the solid form of drug and cleaning solvent, by a socket for pH probe, by inputs of titration components of working solution, by the inlet for a temperature probe, by an input for a digestive juice and finally by an output for sample collection.

The next advantage of the human digestive simulator according to the invention consists in the fact that the assembly of the heating plate with elastic bags, the tiltable steering deflected wing on levers connected to pendulum motion engine(s) and with the peristaltic pumps is placed in a closeable box which is heated by an air heater and equipped with at least two linear dosing equipments of working medium components.

It is advantageous that for operation and regulation of the unit (pendulum motion engines, the heating element of heating plate, peristaltic pumps, air heating, and delivery system) as well as for collecting and processing the data, the system is connected to computer controlling unit.

Brief Description of the Figures

The invention will be clearly explained using one example of concrete implementation displayed on attached drawings, where:

Fig. 1 shows the view of the assembly of the main part of the simulator in accordance with the invention.

Fig. 2 shows the view of overall configuration of the digestive tract simulator, including the closeable box in which it is placed.

Fig. 3 shows the view of the possible realization of the semi-product of elastic bag representing stomach.

Fig. 4 shows the side view of the elastic bag for the small intestine simulation.

Fig. 5 shows the ground plan view of the elastic bag from the figure 4.

Fig. 6 shows an axonometric view of the bag from figures 4 and 5.

Examples

As evidenced by the Figure 1 the main part of this equipment forms the main unit, which consists of the heating resp. temperature regulating plate 2, on which elastic bags 12

are placed during operating state. These bags are advantageously realized by readily available bags for infusion solutions, which are modified by adding air cock 127, inlet and outlet sockets 126 for inputs of working solutions as acids or alkalis for automatic titration of their content, as well as by adding hydraulic cross connection 12 of bags, output for sample collection and pH probes.

Swing levers 7 with gimbal are assembled to the ends of heating plate 2, heated by flat resistor body. The levers 7 are removably connected with parts of divided, longitudinally deflected wing 3 which are arranged over all bags 12 and touching on filled bags 12 by a part of their working surface. Each of levers 7 is operated by the common pendulum pneumatic motor 4 with adjustable speed. Peristaltic pumps 5 for pumping of each bag 12 volume from one bag 12 to the next or outward of the apparatus, are placed under the temperature regulating plate 2.

It is evident from Figure 1 that the first (or left) elastic bag 12 representing stomach is equipped by the filler hole 121 with a plug for inserting the solid form of the drug and perhaps even for inserting the cleaning solution or gas purging input. Into this bag 12, the volume of which is with advantage larger than the inner volume of bags 12 representing parts of the small intestine, see Figures 3, 4 and 5. The pH probe 122 is loaded into the bag 12 through an independent socket. The bag 12 is equipped by inlets 124 for titration components, by the outlet 125 for sample collection and by the inlet for a temperature probe 123.

Heating plate 2 is manufactured advantageously as metallic board equipped with temperature probes, which are not displayed on figures.

The central unit mentioned above, as shown in Figure 2, is placed inside the closeable box, containing also air heating unit 11 and at least two linear dosing equipments 10 connected to computerized control unit.

Although the purpose and the functionality of the apparatus would be clear on grounds of technical description described above, it is important to mention, that the softened, flattened, buckled or truncated lower rim of deflected wing 3 doesn't push flanks of elastic bags 12 to one another, but it is set to the level allowing during operation, it means during swinging motion of wing, the transit of working liquid together with solid form of drug

between one part of the bag 12 from which a liquid is squeezed out into its second part which is not pressed.

While the stomach 12 is represented by a unique bag, a small intestine in which the final stage of digestion is performed as well as absorption of nutrients happens is represented by three bags linearly ordered on the heating plate 2 across the direct-axis of it and of the deflected wing 3 too. These bags 12 represent jejunum, duodenum and ileum.

The transit of liquids between discrete elastic bags 12 of the digestive tract simulator according to the invention is provided by peristaltic pumps 5, whose action is controlled, as well as the action of the air heating unit 11, the linear dosing equipments 10, the temperature regulating plate 2 heating, and speed of the pneumatic pendulum motor 4, by the computer control unit placed outside of closeable box 1 of the simulator.

The digestive tract simulator according to this invention imitates the human digestive tract very accurately. Moreover, the individual parts of the simulator are easily removable and replaceable. The volume of each elastic bag 12 is periodically mixed during the operation by periodically compressing upper side of the bag 12 by parallel surface of bent wing 3. At the same time the pH value and the temperature of inner volume are measured.

CLAIMS

1. A digestive tract simulator, comprising hydraulically interconnected at least two elastic bags (12) kept at constant temperature and a controllable heating source, **characterized in that** the heating source is represented by a heated tempering plate (2) over whose working surface intended for placing of elastic bags (12) two levers (7) are arranged in an anaxial distance, swinging around a common axis;
to these levers (7) a deflected wing (3) placed in parallel with the tempering plate (2) and having working arms opened in a wide angle in direction from the tempering plate (2) is mounted on the lever's side near to the tempering plate (2);
at least one of levers (7) is connected to a pendulum engine (4) having an adjustable motion so that elastic bags (12) are in operating state situated between the the working surface of the tempering plate (2) and the deflected wing (3);
each of bags (12) is equipped by an air cock (127) and an input and output pipe channel (126) for working medium, connecting bags (12) together via tubing coupled through a peristaltic pump (5).
2. Digestive tract simulator according to claim 1, **characterized in that** each of levers (7) is connected to its own pendulum hydraulic and/or air-operated engine (4), these engines being advantageously synchronous, and is attached to the divided deflected wing (3), one part of which is destined for a cooperation with the elastic bag (12) representing a stomach and second part is destined for the plastic bag and/or bags (12), representing a small intestine.
3. Digestive tract simulator according to claim 1 or claim 2, **characterized in that** at least one of elastic bags 12 is equipped by a closeable filler hole (121) for inserting the solid form of drug and cleaning solution, by a socket (122) for pH probe insertion, by inputs (124) of titration components of working solution, by an inlet (123) for a temperature probe, by an output (125) for sample collection as well as for an input of digestive juice.
4. Digestive tract simulator according to any of claims 1 to 3, **characterized in that** the deflected wing (3) and/or divided wings (3) are vertically adjustable above the tempering plate (2).
5. Digestive tract simulator according to any of claims 1 to 4, **characterized in that** the

temperating plate (2) is formed by a metallic board heated by a resistor body and equipped with temperature probes.

6. Digestive tract simulator according to any of claims 1 to 5, **characterized in that** the assembly comprising the temperating plate (2) with elastic bags (12), the deflected wing (3) on levers (7) attached to the pendulum engine and/or engines (4) and the peristaltic pumps (5) is placed inside a closeable box (1) in which an air heating unit (11) and at least two linear dosing equipments (10) for dosing of working solution components are arranged.

7. Digestive tract simulator according to any of claims 1 to 6, **characterized in that** the pendulum engines (4), a temperating plate (2) heating, the peristaltic pumps (5), the probes, the air heating unit (11) and dosing equipments (10) are connected to a computer control unit.

8. Digestive tract simulator according to any of claims 1 to 7, **characterized in that** the elastic bag (12) equipped by the filler hole (121), by the socket (122) for pH probe insertion, by the inputs (124), by the inlet (123) for temperature probe and by the output (125) for sample collection representing the stomach is of bigger volume than other, advantageously three elastic bags (12) representing parts of the small intestine.

9. Digestive tract simulator according to any of claims 1 to 8, **characterized in that** the elastic bags (12) are represented by modified bags for infusion solutions.

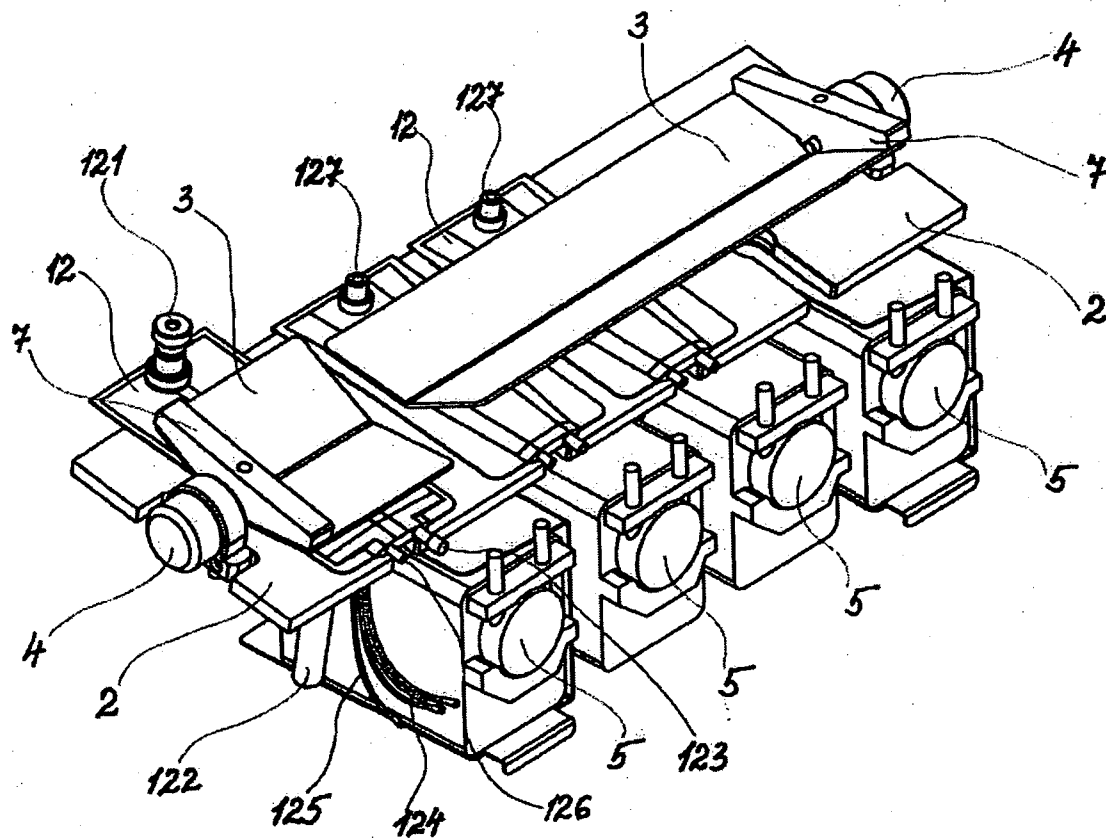
Figures**Fig. 1**

Fig. 2

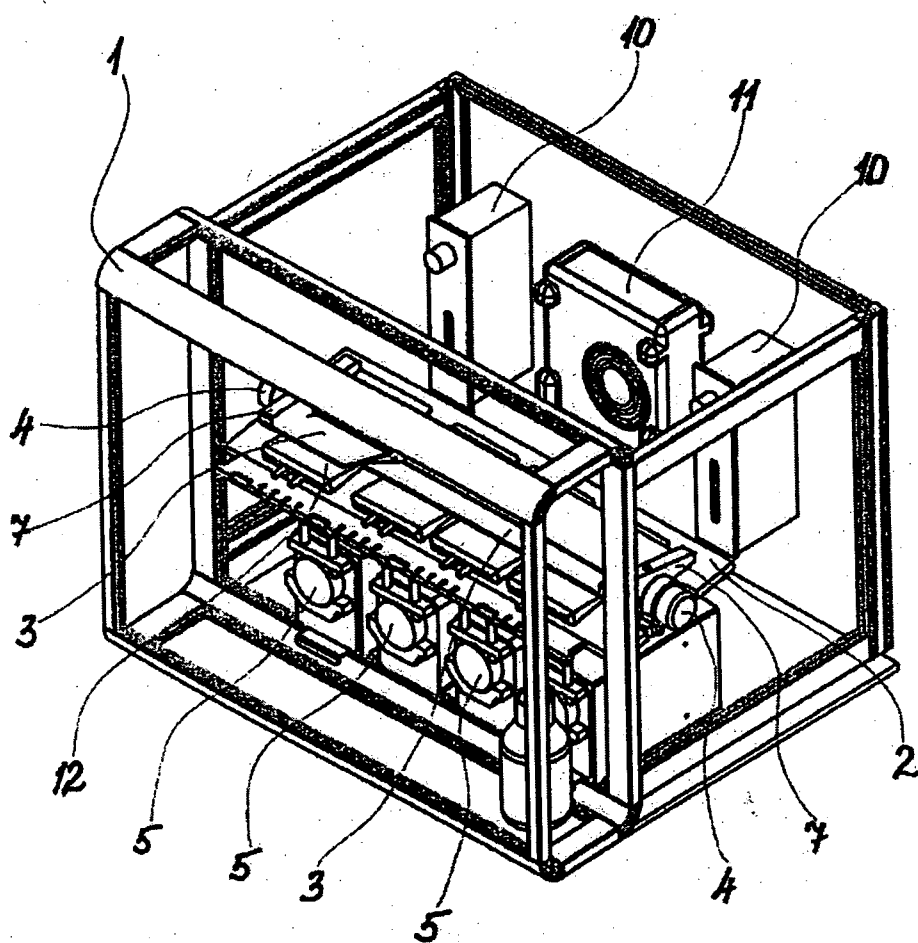


Fig. 3

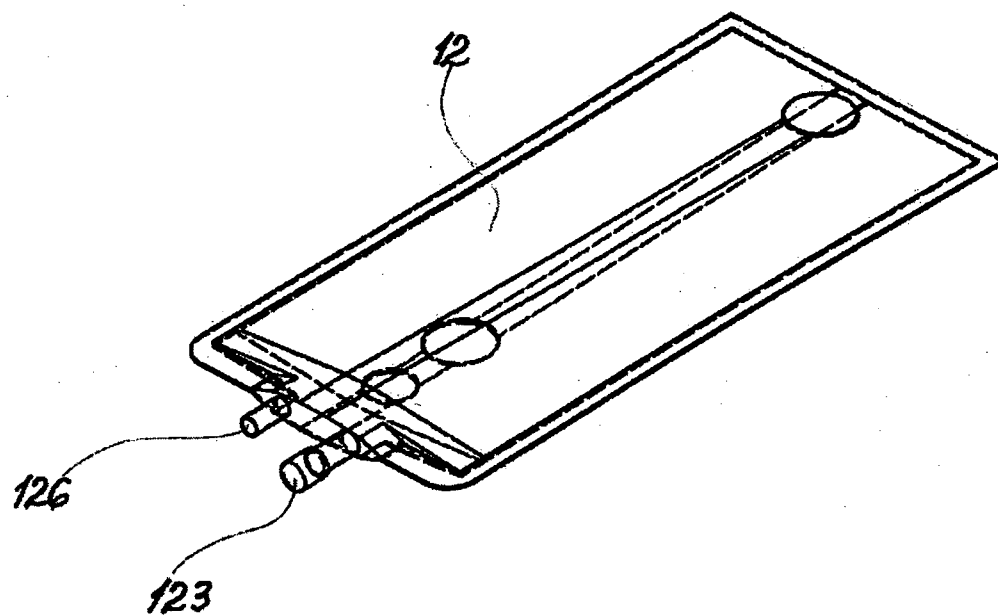


Fig. 4

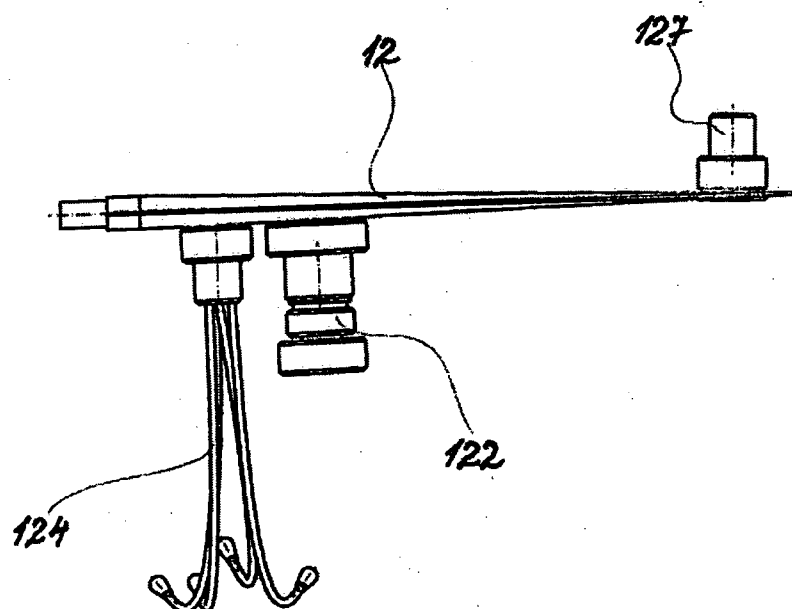


Fig. 5

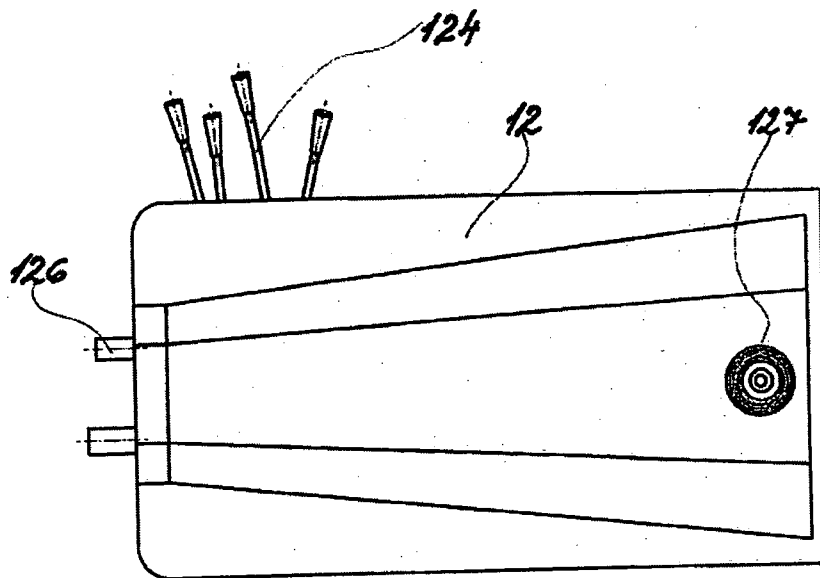
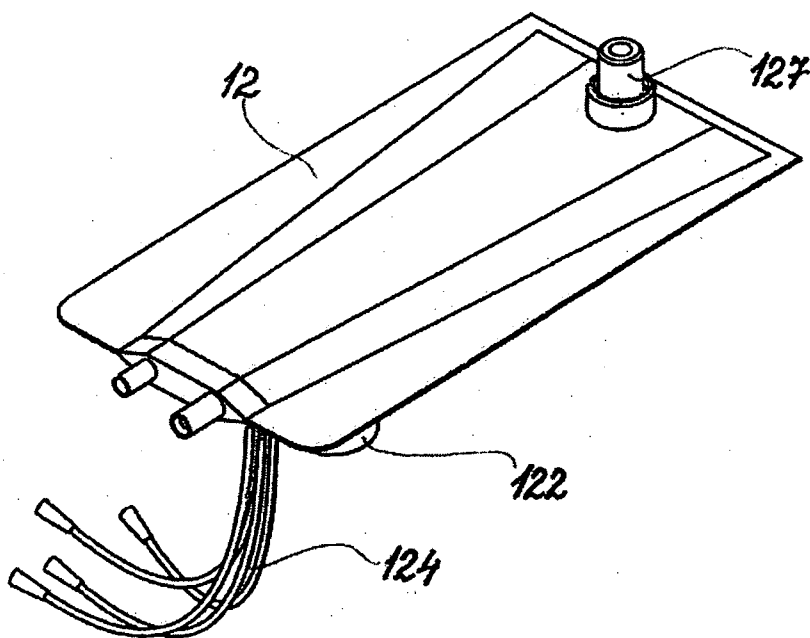


Fig. 6



INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2010/000123

A. CLASSIFICATION OF SUBJECT MATTER
INV. G09B23/30 G09B23/32 B01F11/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G09B B01F

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94/09895 A1 (TNO [NL]; MINEKUS MANNES [NL]; HAVENAAR ROBERT [NL]) 11 May 1994 (1994-05-11) page 4, lines 1-7; figure 1 page 3, line 5 page 4, lines 11-14 page 5, lines 30-32; figure 3 -----	1-9
A	JP 55 002924 A (KAGAWA ATSUKO) 10 January 1980 (1980-01-10) the whole document -----	1-9
A	FR 2 923 065 A1 (UNIV D AUVERGNE CLERMONT 1 ETA [FR] UNIV D AUVERGNE CLERMONT 1 [FR]) 1 May 2009 (2009-05-01) claim 1; figure 1 ----- -/-	1-9



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/010238 A1 (PLANT BIOSCIENCE LTD [GB]; WICKHAM MARTIN [GB]; FAULKS RICHARD [GB]) 25 January 2007 (2007-01-25) claim 1; figure 1 -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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