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(54) METHOD FOR HEAT-STERILIZING ARTIFICIAL KIDNEYS

(71) We, TEIJIN LIMITED a Japanese Body Corporate of 11, 1-chome, Minamihon-machi, Higashi-ku, Osaka, Japan, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to a method for heat-sterilizing artificial kidneys.

An artificial kidney is already known which include a receptacle having accommodated therein perm-selective hollow flaments and comprising blood inlet and outlet ports and dialyzate inlet and outlet ports. The artificial kidney performs the function of kidneys of the living body by the removal of wastes from the blood into the dialyzate and the ultrafiltration of excess water in the blood. The importance of hollow filaments-containing artificial kidneys has increased rapidly because of their small sizes for the available area of membrane and of their ease of use.

It is necessary to sterilize artificial kidneys during production so as to avoid microbial contamination, and to supply them in the microbe-free state to the users. The users perform a necessary pretreatment on the sterilized artificial kidneys prior to use.

In the past, pre-use sterilization of artificial kidneys has been performed mainly by the following two typical methods.

According to one method, the manufacturers sterilize the artificial kidneys by filling them with an aqueous solution of formaldehyde which is relatively concentrated, and usually has a concentration of 1 to 5%, and ship them in the sterilized state. Prior to use for dialysis, the users remove the formaldehyde by washing, warm the artificial kidneys to the body temperature, and perform other necessary treatments (for example, fill a physiological saline solution containing heparin into the blood-flowing section of the artificial kidneys). This method permits effective sterilization. However, since the formaldehyde used as a sterilizing agent is toxic to man, it must be completely removed from the artificial kidneys. This requires the flowing of a great quantity of water for a long period of time. Such a washing operation is troublesome, and the users must spend considerable labor and time. There is an additional defect that if washing is stopped after the formaldehyde concentration in the washing effluent has decreased and no substantial formaldehyde is detected, the formaldehyde remaining in the hollow filaments gradually oozes.

According to the other method, the manufacturers sterilize the artificial kidneys by passing a gaseous mixture consisting of 10 to 30% ethylene oxide or propylene oxide as a sterilizing ingredient and the remainder being Freon (Registered Trade Mark) or CO_2 as a carrier ingredient into the artificial kidneys in the dried state, and ship them in the sterilized condition. Prior to use, the users perform necessary treatments on the dried sterilized artificial kidneys; for example, they fill a dialyzate and an isotonic saline solution. This method has the defect that gases such as ethylene oxide or propylene oxide are adsorbed onto the hollow filaments, and the gases remaining in the filaments react with chloride ion in the physiological saline solution to form a toxic chlorohydrin compound. Washing of these residual gases require the passing of a physiological saline solution in an amount of as

large as more than 2 liters. Furthermore, since the hollow filaments of the artificial kidneys are capillary tubes, in order to remove the bubbles completely, the washing liquid must be passed for long periods of time, or the washing liquid must be passed after replacing the air in the hollow filaments by aseptic carbon dioxide gas. In the latter case, the users require various devices such as a carbon dioxide gas cylinder, a sterilizing filter, a pressure control device, or a flow rate controlling device. If the bubbles remain in the hollow filaments, minute bubbles are very likely to flow into the body during dialysis, or may cause coagulation of the blood within the hollow filaments, thus increasing the amount of the blood remaining in the dialyzer after dialysis, and also losses of blood.

Furthermore, since by the gas sterilizing method, artificial kidneys in the dried state are rendered wet by pretreatment, the performance of the artificial kidneys tends to change, and has poor reproducibility.

A third sterilizing method suggested involves applying gamma-rays in a dose of 0.5 to 5 Mrads to artificial kidneys. This radiation sterilizing method is free from the problem of residual toxicity, but, in the same manner as second method, tends to cause changes in the performance of the artificial kidneys in pretreatments, such as the filling of a physiological saline solution and a dialyzate into the artificial kidneys in the dried state. In addition, the materials which constitute the artificial kidneys are susceptible to degradation by application of ionizing radiation, and problems are still left unsolved in the improvement and choice of materials.

Generally, sterilization also includes heat sterilization which is widely practised for the sterilization of injection syringes and instruments for surgical operation. For example, Japanese Pharmacopoeia, the 9th revised edition, sets forth a method for controlling microorganisms by a high-pressure steam sterilizing method which comprises heating the material to be sterilised in saturated steam at 115°C. for 30 minutes, at 121°C. for 20 minutes, or at 126°C. for 15 minutes. The Japanese Pharmacopoeia also permits the use of an intermittent sterilizing method which comprises heating the material to be sterilized for 30 to 60 minutes in water or flowing steam at 80 to 100°C. every 24 hours, and repeating this heating operation 3 to 5 times.

Since heat sterilization is advantageous because of the freedom from residual toxicity and the ease of washing, it would be very convenient if this method can be applied to artificial kidneys. In fact, the heat sterilizing method has never been applied to artificial kidneys, and no attempt at it has been made because it has been considered as quite impossible to heat sterilize artificial kidneys filled with a primer. The reason for this is that upon heating, the artificial kidneys undergo deformation, cracking or breakage owing to the thermal expansion of the primer and the air contained in the artificial kidneys and the generation of the autogenous pressure of steam, and consequently, leakage of the primer occurs, and that it is difficult to seal artificial kidneys aseptically after sterilization.

According to the present invention, there is provided a method for heat sterilizing an artificial kidney comprising a receptacle having accommodated therein permselective hollow filaments and including inlet and outlet ports for the blood and inlet and outlet ports for a dialyzate, which method comprises

(a) providing a fluid-containing and sealed artificial kidney containing a liquid primer which is water or an aqueous solution wherein at least one of the inlet and outlet ports is connected to a pressure buffer container and the remaining ports are sealed,

(b) heating the fluid-containing and sealed artificial kidney to a temperature of 80 to 130°C to heat sterilize it and cause thermally expanded fluid to pass from the artificial kidney to the pressure buffer container,

(c) cooling the heat sterilized artificial kidney while sealed to reduce the pressure therein, and

(d) either aseptically sealing the port connected to the pressure buffer container or maintaining the connection.

The important feature of the heat sterilization method of this invention is that a pressure buffer container having a special function is connected to at least one of the inlet and outlet ports for the blood and inlet and outlet ports for the dialyzate of an artificial kidney containing a liquid primer and the remaining ports are sealed, and in this condition the artificial kidney is heat sterilized at a temperature of 80 to 130°C. Heating under these conditions results in the expansion of the primer and residual gases such as air present in the artificial kidney, the increase in volume being accommodated by the pressure buffer container. As a result, the internal pressure of the artificial kidney which is caused by the thermal expansion of fluids (the primer and gases) and an increase in steam pressure is prevented from rising to the extent that deformation, cracking or breakage of the artificial kidney would occur.

Thus, the pressure buffer container used in the method of this invention has the dual function of storing expanded fluids (primer and gases) from the artificial kidney, and of

checking the increase in the pressure within the artificial kidney which occurs at the time of heating.

The pressure buffer container used in the method of this invention may communicate with the outer atmosphere in regard to pressure but is aseptically shielded from the outer atmosphere, or may be shielded from the outer atmosphere both in regard to pressure and microbes (for example, a closed bag). When a closed bag is used, it is preferably one which can expand itself according to the movement of the expanded fluids (primer and gases) inside so that it can exhibit a pressure buffer action.

When the connection between the artificial kidney and the pressure buffer container is released after the heat sterilization of the artificial kidney by the method of this invention, the port connected to the pressure buffer container should be sealed to prevent leakage of the primer. According to the method of this invention, it is easy to perform this sealing aseptically. This is another important feature of the invention.

In the present invention, heat sterilization is carried out preferably in accordance with the Japanese Pharmacopoeia, the 9th. revised edition. The heat sterilization is carried out at a temperature of 80 to 130°C. since the high-pressure steam sterilization method (115 to 120°C.) and the intermittent sterilization method (80 to 100°C.) can be applied.

The invention is specifically described below by reference to the acompanying drawings in which:-

Figure 1 is a schematic view showing one embodiment of the method of heat sterilization in accordance with this invention;

Figure 2 is a view showing another embodiment of the heat sterilizing method of this invention;

Figure 3 is a view showing a further embodiment of the heat sterilizing method of this invention;

Figures 4 to *6* show typical examples of a buffer bag for use in the embodiment shown in Figure 3;

Figure 7 is a view showing a method of aseptic sealing in the method of this invention; and *Figures 8* and *9* show connecting tubes suitable for use in the method shown in Figure 7, Figures 8(a) and 9(a) being longitudinal sectional views, and Figures 8(b) and 9(b) being cross-sectional views taken along the lines A-A′ of Figures 8(a) and 9(a), respectively.

Referring to Figure 1 which schematically shows the heat sterilization of an artificial kidney by the method of this invention, an artificial kidney 1 comprises a receptacle 2 having accommodated therein a number of perm-selective hollow filaments 3. A pair of partition walls 5 are provided within the receptacle 2 to support the hollow filaments 3. The receptacle 2 includes a blood inlet port 6 and a blood outlet port 6′ both normally composed of narrow tubing having an open end and a dialyzate inlet port 7 and a dialyzate outlet port 7′ both normally composed of thick tubing having an open end. One end of the receptacle 2 is a blood distributing section 4 and the other end is a blood gathering section 4′, which are both separated by the partition walls 5 from a centrally located chamber for dialysis in the receptacle 2. The receptacle 2, the hollow filaments 3, the partition walls 5, and the ports 6, 6′, 7 and 7′, are made of materials which do not substantially deform upon heating at the temperature of 80 to 130°C, employed for heat sterilization.

In performing the heat sterilization of the artificial kidney 1 in accordance with the method of this invention, a liquid primer composed of water or an aqueous solution is used to fill the artificial kidney 1. As a result, the primer fills substantially all the spaces of receptacle 2, i.e. the spaces in the hollow filaments which are passages for the blood, the spaces between the hollow filaments which are passages for the dialyzate, the spaces inside the blood distribution section 4 and the blood gathering section 4′, and the spaces within the ports 6,6′,7,7′. At least one (port 6′ in Figure 1) of the ports 6,6′,7,7′ is connected to a pressure buffer container 10 through a conduit 9, and the other ports are sealed to prevent leakage of the primer (for example, by using stoppers or by weld sealing). In this condition, the artificial kidney 1 is heated to a temperature of 80 to 130°C. to heat sterilize it. At this time, the pressure buffer container 10 may be heated together with the artificial kidney 1. Or the pressure buffer container 10 may be disposed outside the heater, to heat only the artificial kidney 1. When the artificial kidney 1 is heat-sterilized, the expansion of the primer and any residual air in the artificial kidney caused by the rise in temperature and the autogenous pressure of steam cause fluid to pass from the artificial kidney 1 to the pressure buffer container 10. As a result, the pressure within the artificial kidney can be buffered.

Cooling of the artificial kidney after the end of sterilization causes the fluids remaining in it to shrink, and reduces the pressure of steam. Hence, the inside of the artificial kidney is under reduced pressure. As a result, the artificial kidney tends to return to the normal atmospheric pressure from the reduced pressure, and the liquid primer stored in the pressure buffer container 10 flows into the artificial kidney 1 through the conduit 9.

The heat sterilization method of this invention can be performed by either of the two

embodiments described hereinbelow.

According to one embodiment, a pressure buffer container having liquid primer therein is used, and connected to the artificial kidney so that the primer in the artificial kidney communicates with the primer in the pressure buffer container, prior to performing the heat sterilization. Figure 2 shows this embodiment. Referring to Figure 2, a plurality of artificial kidneys 1 are connected to one pressure buffer container 10, and the primer in each of the artificial kidneys communicates with a primer phase 12 of the pressure buffer container 10. A gaseous phase 13 is present over the liquid phase 12. The reference numeral 14 represents a bellows for pressure buffering, and the reference numeral 15, a sterilizing filter. Preferably, the pressure buffering is carried out by using one or both of the bellows and the sterilizing filter. In this first embodiment, the fluids (primer and air) expanded during heat sterilization move from the artificial kidney to the pressure buffer container 10. On cooling, only the primer returns to the artificial kidney 1, and the air remains in the gaseous phase 13 and never returns. Thus, the amount of a gaseous ingredient such as residual air present in the artificial kidney decreases correspondingly after the heat sterilization treatment.

The amount of any gaseous ingredient present in the artificial kidney is desirably as small as possible, and therefore, a decrease in the amount of the gaseous ingredient brought about by the heat sterilization treatment is advantageous. In this specification, the decrease in the content of such a gaseous ingredient is sometimes referred to as the "improvement of the primed condition of an artificial kidney". When the artificial kidney is insufficiently filled with liquid, bubbles present in the path of blood may induce coagulation and other undesirable phenomena. The bubbles present in the bath of dialyzate reduce both the available membrane area of the hollow filaments and the dialyzing efficiency. The first embodiment of the method of the present invention is preferred because it can achieve this improvement in the primed condition of artificial kidneys. In the first embodiment, the pressure buffer container 10 is made of such a material as metals, glass and thermally stable resins, and the conduit 9 is made preferably of such a material as a silicone rubber or a thermally stable synthetic rubber.

A second embodiment of the method of this invention involves using a pressure buffer container which does not contain liquid primer and therefore occupied only with a gas phase, and connecting to at least one of the ports of the artificial kidney, prior to heat sterilization. Figure 3 shows one example of the second embodiment, and pressure buffer container 10 shaped like a balloon is connected to a port 7' of the artificial kidney. According to this method, steam and/or gases from within the artificial kidney, the contents of which have been expanded by heat sterilization, are taken up by the expansion of the pressure buffer container (buffer bag) itself. As a result, the pressure in the artificial kidney is reduced, and the load on the receptacle, the blood distributing section and the blood gathering section of the artificial kidney becomes small. An improvement in the primed condition cannot be achieved by the second embodiment.

The material for the buffer bag is required to have the properties of not breaking upon expansion, wet heat resistance at 80 to 130°C., and safety and nontoxicity for medical uses. Examples are natural rubbers, synthetic rubbers such as polyisoprene rubber or polybutadiene rubber, silicone rubbers, and rubbery elastomers such as polyurethane elastomers, or materials not having rubbery elasticity such as polypropylene, polyesters, nylon, and polypropylene/polyester laminate films. The volume of the buffer bag is such that its maximum volume on expansion within the limit of pressure is larger than the increase in the volume of fluids (primer and air) in the artificial kidney which is ascribable to heat expansion.

The buffer bag used in the second embodiment may be of various shapes such as a bag-like, balloon-like or tubular shape. An especially preferred buffer bag is a bag having an cross-linking from at least one prepolymer and a curing agent, without any substantial thick portion is a neck portion to be fitted to a port of the artificial kidney, and the thin portion is an expansible portion. The thickness (T mm) of the thick portion and the thickness (t mm) of the thin portion have the relation shown by the following equations (1) to (3).

$$0.05 \text{ mm} \leqq t \leqq 2.0 \text{ mm} \quad \ldots\ldots (1)$$

$$0.25 \text{ mm} \leqq T \leqq 5.0 \text{ mm} \quad \ldots\ldots (2)$$

$$1 < T/t \leqq 30 \quad \ldots\ldots (3)$$

The volume of the buffer bag under zero gauge pressure (atmospheric pressure) is usually 2 to 100 ml, preferably 4 to 50 ml. The maximum volume on expansion of the bag differs according to the type of the artificial kidney and the amount of expansion fluids in it. For example, when the amount of liquid primer in the artificial kidney is 400 ml and the amount of residual air is 0 to 20 ml, the expansion fluids are expected to have a volume of 20 to 70

ml. Hence, the buffer bag is expansible when its volume at zero gauge pressure is less than its maximum volume on expansion. Preferably, at the time of connecting the buffer bag, it is flattened, or is filled with a small amount of water or an aqueous solution so as to admit no gas into it. The thin portion of the bag should have a thickness of usually 0.05 to 2.0 mm. preferably 0.10 to 1.0 mm, so that the bag can be expanded and flattened. When it is necessary to expand the bag, it should have a break elongation of preferably 100 to 1500%, more preferably 300 to 1000%.

The neck portion of the bag to be secured to a port of the artificial kidney is a fixing part of the bag, and is thick so as to provide a sealing action for the prevention of leakage of the primer, etc. and contamination after heat sterilization. The thickness (T) is usually 0.25 to 5.0 mm, preferably 0.4 to 3.0 mm. The thick portion and thin portion are usually fabricated into a unitary structure. Alternatively, they may be separatedly fabricated, and formed into a unitary structure by, for example, bonding. The thicknesses of these two portions should satisfy the equation (3) given hereinabove.

Figure 4 shows a buffer bag suitable for connection to a port of the artificial kidney comprising thin tubing, for example, a blood inlet or outlet port. The inside diameter and length of the neck portion 21 to be connected to the port should preferably be of magnitudes which permit engagement with the port.

Figure 5 shows a buffer bag suitable for connection to a port of the artificial kidney comprising thick tubing, for example, a dialyzate inlet or outlet port.

Figure 6 shows a buffer bag in which the inside surface of the neck portion conforms to the outer shape of a port. In this case, the thickness T of the thick portion in an average of the minimum thickness T_1 and the maximum thickness T_2.

The shape of the expanded portion 22 may be substantially cylindrical or elliptic, or may be generally oval as shown in Figure 6.

According to the method of this invention, the openings connected to the pressure buffer container should be aseptically sealed before the connection between the artificial kidney and the pressure buffer container is released after the heat treatment. The following two major methods are available for achieving the aseptic sealing.

A first method comprises connecting a conduit 9 with a thicker tip portion to a port 6′ of an artificial kidney 1 as shown at the left end of Figure 2, suspending a stopper 11 for prevention of leakage of a primer in the thicker portion of the conduit 9, and fitting the stopper 11 into the port 6′ after the end of the heat sterilization treatment and before disconnecting the port 6′ and the conduit 9. Since after heat sterilization, the inside of the artificial kidney and the inside of the pressure buffer tank are microbe-free, the above operation can achieve an aseptic sealing of the port 6′.

A second method comprises connecting a port 7′ and a conduit 9 through a connecting tube 30 having a weld-sealable part 31 as shown in Figure 7, and welding the weld-sealable part 31 after the heat sterilization treatment and before the disconnection of the port 7′ and the conduit 9 thereby to achieve an aseptic sealing. The connecting tube 30 may be made of any material which can be sterilized in high pressure steam and can be welded at the weld-sealable part 31 by heat, high frequency or ultrasonic waves. Examples are polyvinyl chloride, polyolefins, and polyurethane.

When the ports of the artificial kidney or the conduit 9 are weld-sealable, the aseptic sealing may be achieved by weld-sealing these portions. When the aforesaid pressure buffer bags are used, they may be used as a seal without separation after heat sterilization.

The connecting tube suitable for use in the second method is a cylindrical tube composed of a cylindrical connecting part 32, a weld-sealable part 31 and a cylindrical conduit part 33, as shown in Figures 8 and 9. The weld-sealable part 31 is a thin neck-like structure having a maximum outside sectional dimension of 2 to 15 mm, and a maximum inside sectional dimension of 1 to 14 mm, and is made of a material which can be welded. The weld-sealable part 31 is centrally located in the connecting tube 30, and the connecting part 32 and the conduit part 33 are located at the ends of the connecting tube 30.

The shapes and dimensions of the connecting part 32 and the conduit part 33 are determined in consideration of the shape and sealability of the port and conduit to be connected. The weld-sealable part 31 preferably has an inside sectional size of at least 1 mm from the viewpoint of serviceability as a conduit. Preferably, its upper limit is 14 mm in view of the size of the parts of the artificial kidney and the area to be welded. The maximum outside dimension of the weld-sealable part 31 is preferably 2 to 15 mm so that it holds little liquid while yet providing sufficient area to be welded. More preferably, the weld-sealable part 31 has a maximum outside sectional dimension of 3 to 8 mm and an inside sectional dimension of 2 to 7 mm. The sectional shape of the connecting tube may be circular, elliptical, oval or rectangular. If the weld-sealable part 31 is of a fine diameter, its sectional shape is preferably circular for ease of a welding operation. If it is of a relatively large diameter, the sectional shape is preferably a flattened ellipse, an oval shape or a rectangle

for the same reason. However, the shape is not limited to these examples.

Figure 8 shows a connecting tube 30 suitable for connection to a port of thin tubing (a blood inlet or outlet port) of the artificial kidney. The connecting part 32 and the conduit part 33 are of cylindrical shape in order to achieve fitting and sealing. The section taken along the line A-A′ of the weld-sealable part 31 is circular.

Figure 9 shows a connecting tube suitable for connection to a port ot thick tubing (a dialyzate inlet or outlet port) of the artificial kidney. The shape of the connecting part 32 is a cylinder having a conical top 34. A collar 35 is provided in the tube 30 so as to achieve fitting and sealing with the port and facilitate the operation of removing the connecting tube at the time of using the artificial kidney in patients. In this connecting tube, the A-A′ section of the weld-sealable part 31 is a flattened oval shape.

According to the method of this invention, artificial kidneys can be easily heat sterilized. The heat sterilization treatment does not cause the breakage and deformation of the artificial kidneys filled with water or an aqueous solution and a poor seal. Furthermore, the flow paths of the blood can be maintained in an operable condition. In addition, the artificial kidneys after heat sterilization can be aseptically sealed to prevent secondary microbial contamination.

Furthermore, the artificial kidneys heat sterilized by the method of this invention are improved in their primed condition, and can exhibit excellent substance exchange performance and affinity for the blood. The artificial kidneys heat sterilized by the method of this invention, as a whole, have a high level of assurance of the freedom from microbes, are free from residual toxocity, and can be easily washed for use.

An artificial kidney particularly suitable for heat sterilisation in accordance with the method of the invention consists essentially of a receptacle, hollow filaments accommodated therein and partition walls supporting the hollow filaments in place, wherein the hollow filaments, the partition walls and the receptacle have substantial thermal stability at a temperature within the range of 40 to 130°C., and the coefficient of linear expansion (A[ℓ/°C.]) of the partition walls, at a temperature within the range of 40 to 130°C., has the following relation to the coefficient of linear expansion (B[ℓ/°C.]) of the receptacle and the termperature (Θ[°C.])

$$4.13 \times 10^{-5} \exp(0.00769\ \Theta) \leqslant A \leqslant 2B$$

and the partition walls do not have a second order transition point between 50 and 120°C.

An artificial kidney having this structure does not undergo deformation, breakage and poor sealing by heat sterilization, and the blood flow paths and the dialyzate flow paths can be maintained in good condition. As a result, the artificial kidney can exhibit superior performance owing also to the thermal stability of the hollow filaments.

The artificial kidneys which meet the above conditions can be constructed by a method known *per se* using the following materials.

Examples of the materials for the hollow filaments are cellulose, cellulose esters, polyacrylonitrile, polyvinyl alcohol, poly(aromatic amides) such as polyamidebenzohydrazide, isophthalamide, polycarbonate, polysulfones and polyethers. Of these, cellulose and polyacrylonitrile are especially preferred.

The material for the receptacle may, for example, by polycarbonate, poly(4-methylpentene-1), polyvinylidene fluoride and polyacetal. The polycarbonate and poly(4-methyl-pentene-1) which have a high level of transparency are especially preferred materials.

High-molecular-weight polymers are preferred as materials for the partition walls. Preferred polymers are those which are obtained by addition polymerization and cross-linking from at last one prepolymer and a curing agent, without any substantial change in total amounts of the reactants before and after the reaction. Specific examples of such polymers are urethane resins and epoxy resins. In particular, poly(ester-type urethanes) obtained by addition polymerization of (I) an isocyanato-terminated prepolymer and (II) a polyol derived from a hydroxy-containing fatty acid and a glycerin ester are preferred.

The following examples illustrate the present invention in more detail.

Example 1 and Comparative Example 1

A bundle of 10,000 cellulosic hollow filaments having an inside diameter of 250 microns and membrane thickness of 30 microns was accommodated in a polycarbonate receptacle. Both ends of the bundle were fixed by a urethane resin to form partition walls. A blood distributing plate made of polypropylene was fixed by clamping with a bag cap (or cap nut) of polycarbonate.

The blood-flowing section and the dialyzate flowing section of the resulting artificial

kidney containing hollow filaments were filled with distilled water. A silicone rubber tube was connected to one opening for the dialyzate and the other opening of the tube was connected to 200 ml of distilled water placed in a glass pressure buffer container. Using a high-pressure steam sterilizing machine, the artificial kidney was heat sterilized at 115°C. for 30 minutes, cooled gradually to room temperature, and withdrawn from the sterilizer.

The weight (a) of the resulting artificial kidney before priming, its weight (b) after priming, and its weight (c) after heat sterilization were measured, and from these values, the amounts of a primer before and after heat sterilization were calculated. The results are shown in Table 1.

For comparison (Comparative Example 1), in order to improve the primed condition, the blood flowing section and the dialyzate flowing section of the artificial kidney were first purged with carbon dioxide gas, and then filled with distilled water but the primed artificial kidney was not connected to the rubber tube and glass pressure buffer container. The results obtained are also shown in Table 1. It is seen from the results that the heat sterilized artificial kidney obtained by this invention showed improvement both in the substantial amount of the primer and in appearance.

TABLE 1

(Unit of weight: g)

Items	Example 1	Comparative Example 1
Weight (a) before priming	422	422
Weight (b) after priming	844	853
Amount (b-a) of primer before heat sterilization	422	431
Weight (c) after heat sterilization	862	-
Amount (c-a) of primer after heat sterilization	440	
Primed condition	No bubbles were seen, and the primed condition was very uniform.	Small bubbles were observed.

The artificial kidney obtained was subjected to a sterility test. Negative results were obtained both in regard to Schizomycetes and Eumycetes. It was also confirmed that no leak occurs in the hollow filaments in the artificial kidney. Then, it was examined for dialyzing performance.

At this time, in order to confirm the effect of the improvement of the primed condition, the dialyzing performance was measured in the primed condition of the present invention. Then, the primer in the dialyzate-flowing section was pulled out in an amount of 10 g, 20 g, and 30 g, respectively, and the artificial kidney was well shaken to decrease the size of the bubbles and render their distribution uniform. Then, the performance of the artificial kidney in the dialysis of urea was measured. (Dialyzing performance evaluated in dialysance D (ml/min). The dialysance (D) is an operational parameter that focusses on the removal of a solute from the blood stream so that $D = Q_B \times C_{Bi} - C_{Bo}/C_{Bi}$ where Q_b is a blood flow rate (ml/min), C_{Bi} is a concentration at the blood inlet, and C_{Bo} is a concentration at the blood outlet.)

The results are shown in Table 2.

TABLE 2

	Amount of the primer withdrawn (g)	Dialyzing performance (mℓ/min.)
Example 1	0	176
	10	171
Comparative Example 1	20	163
	30	154

Model blood: 0.01% aqueous urea solution (flow rate (Q_B) = 200 mℓ/min.)
Dialyzate: Water (Countercurrent flow rate (Q_D) = 500 mℓ/min.)

The results of Table 2 demonstrate that the primed condition affects the dialyzing performance.

Examples 2 to 4

Hollow filament-containing artificial kidneys constructed under the same conditions as in Example 1 and filled with distilled water were heat sterilized in the same way as in Example 1 at varying temperatures.

The weights of each of these artificial kidneys before and after priming (a and b) and its amount after heat sterilization (c) were measured, and from these values, the amounts of the primer in each artificial kidney before and after heat sterilization were calculated. The results are shown in Table 3.

The artificial kidneys so heat-sterilized were subjected to a sterility test, and it was found that negative results were obtained both in regard to Schizomycetes and Eumycetes.

The results show that the present invention can afford artificial kidneys having improved primed conditions.

TABLE 3

Items	Example 2	Example 3	Example 4
Sterilizing temperature (°C.)	80	121	126
Sterilizing time (minutes)	120 (5 times)	20	15
Sterilizing pressure (kg/cm^2)	1.0	2.2	2.6
Weight before priming (a) (g)	425	420	423
Weight after priming (b) (g)	846	843	845
Amount of the primer before heat sterilization (b-a) (g)	421	423	422
Weight after heat sterilization (c) (g)	859	862	862
Amount of the primer after priming (c-a) (g)	434	442	439
Primed condition	Scarcely any bubbles	No bubbles	No bubbles

Example 5

A hollow filament-containing artificial kidney was constructed in the same way as in Example 1. The blood flowing section and the dialyzate flowing section of the artificial kidney was filled with distilled water at 20°C. A silicone rubber buffer bag of the type shown in Figure 6 and having a capacity of 50 ml with the thickness of the thin portion being 0.5 mm was fitted to one opening for the dialyzate with care taken not to admit air into the bag. The amount of the water filled in the artificial kidney was 422 ml, and the amount of the residual air was 17 ml when measured after the heat sterilization. Two openings for the blood and one opening for the dialyzate were sealed by silicone rubber stoppers to prevent leakage of the filled liquid.

The artificial kidney to which the buffer bag had been secured was heat sterilized at 115°C. and 2.0 kg/cm^2 for 30 minutes using a high-pressure steam sterilizer. The pressure of the inside of the sterilizer was maintained at 2.0 kg/cm^2 by the introduction of microbe-free

air, and the artificial kidney was cooled slowly down to room temperature and withdrawn from the sterilizer.

There was no difference between the weights of the artificial kidney before and after the heat sterilization. No leakage of the filled liquid occurred. A sterility test on the artificial kidney showed negative results both in regard to Schizomycetes and Eumycetes. It was also found that there was no leak in the hollow filaments in the artificial kidney.

Examples 6 to 12 and Comparative Examples 2 to 4

Hollow filament-containing artificial kidneys were constructed in the same way as in Example 5. The blood flowing section and the dialyzate flowing section of each of the artificial kidneys were filled with distilled water kept at 20°C. A buffer bag was secured to one opening for the dialyzate with a care taken not to admit air into it. Each of the artificial kidneys was heat sterilized under the various conditions shown in Table 4. The results are shown in Table 4.

A sterility test performed on the artificial kidneys in Examples 6 to 12 showed negative results.

The silicone rubber buffer bags were expansible balloon-like bags as shown in Figures 5 and 6. The polypropylene buffer bags were made of polypropylene films.

The breakage of the buffer bags used in Comparative Examples 2 to 4 as shown in Table 4 was presumably because the volume of each buffer bag was smaller than the increase in the volume of primer and residual air in the artificial kidney caused by heat expansion.

TABLE 4

Example (Ex.) or Comparative Example	Sterilizing temperature	Sterilizing time	Sterilizing pressure	Buffer bag			Amount of primer	Amount of residual air	Results	
				Volume (mℓ) (*1)	Material	Thickness			Breakage of the buffer bag	Coming off of the stopper
(CE.)	(°C.)	(mm)	(kg/cm²)	30	Silicone rubber	0.5	424	17	No	No
Ex. 6	115	30	2.0	30	"	0.5	432	8	No	No
Ex. 7	121	20	2.2	40	"	0.5	445	1	No	No
Ex. 8	126	15	2.6	20	Polypropylene	0.2	420	20	No	No
Ex. 9	80	120 (5 times)	1.0	30	"	0.2	422	18	No	No
Ex.10	100	60 (3 times)	1.2	100	"	0.2	447	0	No	No
Ex.11	115	30	2.0	30	Silicone rubber	0.7	445	1	No	No
Ex.12	126	15	2.6	10	Polypropylene	0.2	422	17	Yes	No
CE. 2	115	30	2.0	20	"	0.2	434	9	Yes	No
CE. 3	121	20	2.2	20	Silicone rubber	0.2	446	0	Yes	No
CE. 4	126	10	2.6							

(* 1) Maximum volume within the limit of pressure.

Example 13

A hollow filament-containing artificial kidney constructed in the same way as in Example 1 was filled with a 15% by weight aqueous solution of sodium chloride, and a polyvinyl chloride connecting tube for medical use having the shape shown in Figure 9 was fitted to an opening for a dialyzate and disposed as shown in Figure 7. A sterilizing filter was secured to the buffer tank, and the artificial kidney was sterilized at 115°C. for 30 minutes. The artificial kidney was cooled, and the seal-weld portion of the connecting tube was welded by an ultrasonic welder to shield the artificial kidney aseptically from the buffer means. Then, the conduit part of the connecting tube was cut off to provide a heat sterilized artificial kidney.

A sterility test on the product showed that the results were negative in regard to both Schizomycetes and Eumycetes.

WHAT WE CLAIM IS:-

1. A method for heat sterilizing an artificial kidney comprising a receptacle having accommodated therein permselective hollow filaments and including inlet and outlet ports for the blood and inlet and outlet ports for a dialyzate, which method comprises

(a) providing a fluid-containing and sealed artificial kidney containing a liquid primer which is water or an aqueous solution wherein at last one of the inlet and outlet ports is connected to a pressure buffer container and the remaining ports are sealed,

(b) heating the fluid-containing and sealed artificial kidney to a temperature of 80 to 130°C to heat sterilize it and cause thermally expanded fluid to pass from the artificial kidney to the pressure buffer container,

(c) cooling the heat sterilized artificial kidney while sealed to reduce the pressure therein, and

(d) either aseptically sealing the port connected to the pressure buffer container or maintaining the connection.

2. A method according to claim 1 wherein after aseptically sealing the port in step (d), the connection is released.

3. A method according to claim 1 or 2 wherein the pressure buffer container of step (a) contains liquid primer in communication with the liquid primer in the artificial kidney.

4. A method according to claim 3 wherein the pressure buffer container communicates with the outside atmosphere in regard to pressure, but is shielded aseptically from the outside atmosphere.

5. A method according to claim 1 or 2 wherein the pressure buffer container is a closed bag made of a material having rubbery elasticity so that it expands upon an increase in internal pressure.

6. A method according to claim 5 wherein said bag is an integrated structure comprising a thick portion and a thin portion, said thick portion being a neck portion which is to connect with an inlet or outlet port of the artificial kidney and the thin portion being an expansible portion, and the thickness (T mm) of the thick portion and the thickness (t mm) of the thin portion have the relation shown by the following equations (1) to (3):

$$0.05 \text{ mm} \leqq t \leqq 2 \text{ mm} \quad \ldots\ldots (1)$$

$$0.25 \text{ mm} \leqq T \leqq 5 \text{ mm} \quad \ldots\ldots (2)$$

$$1 < T/t \leqq 30 \quad \ldots\ldots (3)$$

7. A method according to claim 1 or 2 wherein a conduit is provided between the port and the pressure buffer container, and one end of the conduit is connected to the port and the other end to the pressure buffer container thereby to connect the port to the pressure buffer container.

8. A method according to claim 7 wherein a continuous cylindrical tube having a cylindrical connecting part at one end, a centrally located weld-sealable part and a cylindrical conduit part at the other end is provided between the port and the said one end of the conduit, and the connecting part is connected with the port and the conduit part with said one end of the conduit.

9. A method according to claim 8 wherein the aseptic sealing of step (d) is performed by welding the weld-sealable part.

10. A method according to claim 8 or 9 wherein the outside diameter of the weld-sealable part is smaller than the outside diameter of the connecting part and the outside diameter of the conduit part, and the cross-section of the weld-sealable part has a maximum outside dimension of 2 to 15 mm and a maximum inside dimension of 1 to 14 mm.

11. A method according to any one of the preceding claims wherein the artificial kidney comprises (a) a permselective membrane composed of a bundle of hollow filaments, (b)

partitions walls and (c) a receptacle provided with inlet and outlet ports for the blood and inlet and outlet ports for a dialyzate, wherein the hollow filaments, the partition walls and the receptacle are made of materials which do not substantially deform by heat at a temperature of 80 to 130°C., and the following relation exists between the coefficient of linear thermal expansion (A, ℓ/°C.) of the partition walls and the coefficient of linear thermal expansion (B, ℓ/°C) of the receptacle

$$4.13 \times 10^{-5} \exp (0.00769\ \Theta) \leqq A \leqq 2B$$

wherein Θ represents temperatures in °C., and the partition walls have no second order transition point at a temperature within the range of 50 to 120°C.

12. A method according to claim 1 substantially as described with reference to any one of the Examples.

13. A method according to claim 1 substantially as described by reference to any one of Figures 1, 2, 3 (in conjunction with any one of Figures 4 to 6) and 7 (in conjunction with Figures 8 or 9).

14. An artificial kidney when heat sterilized by a method as claimed in any one of the preceding claims.

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1575377 COMPLETE SPECIFICATION

4 SHEETS *This drawing is a reproduction of the Original on a reduced scale*

Sheet 1

Fig. 1

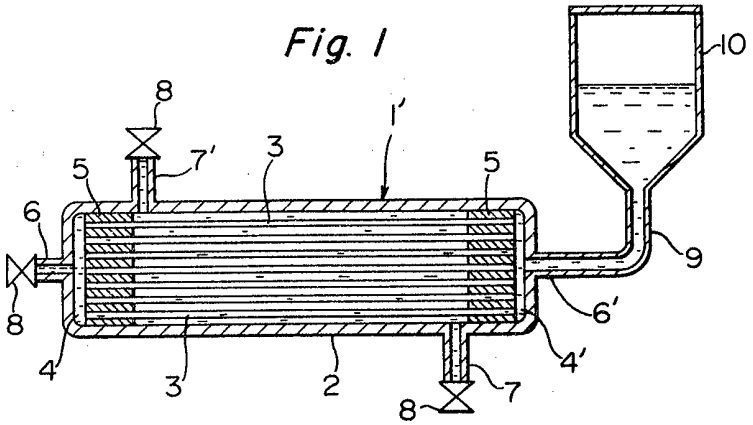


Fig. 2

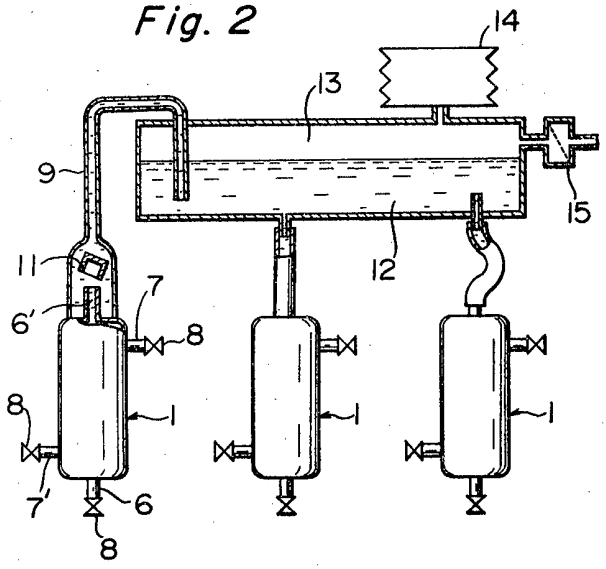


Fig. 3

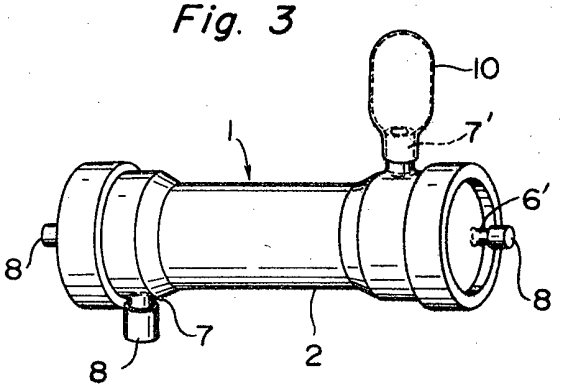


Fig. 7

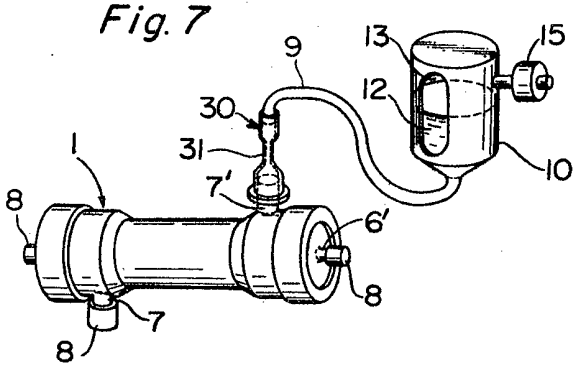
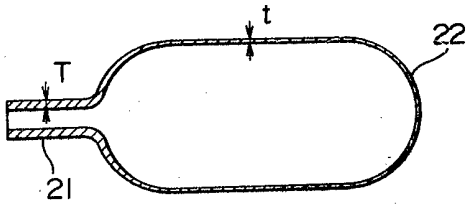


Fig. 4



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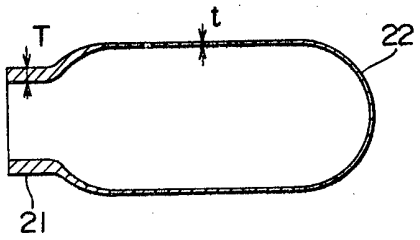

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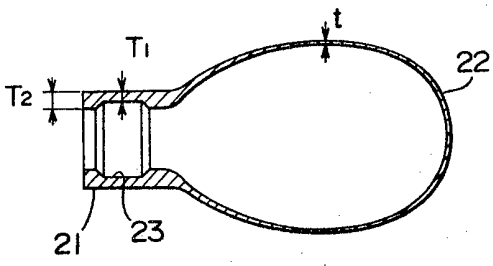

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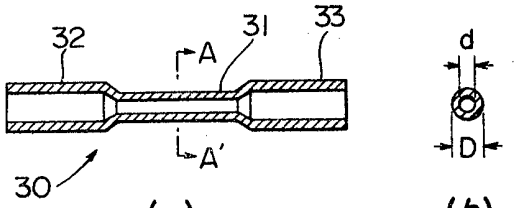
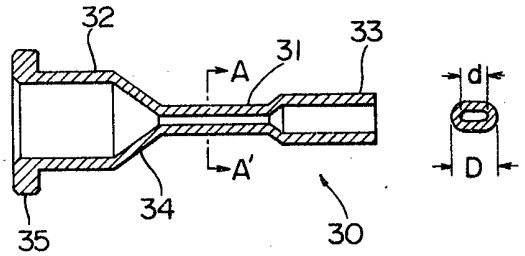
Fig. 8



(a) (b)

Fig. 9



(a) (b)