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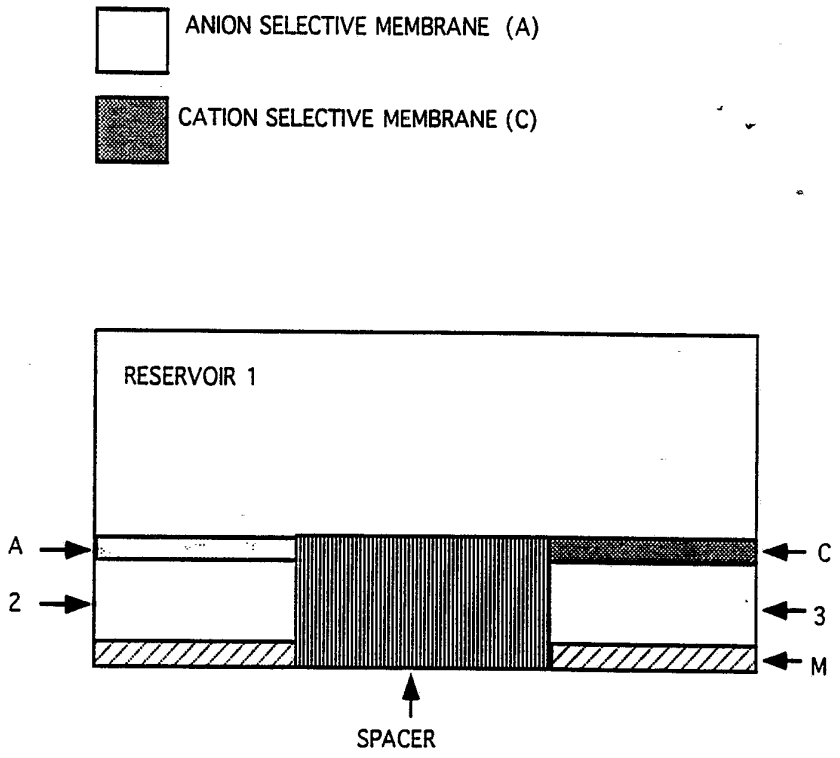
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(54) Title: ELECTROCHEMICAL METHOD AND DEVICE FOR DRUG DELIVERY



(57) Abstract

An iontophoretic device for drug delivery may be powered by producing the necessary electropotential to deliver the drug using a difference in concentration of a salt across an anion selective membrane and a cation selective membrane, thereby creating an electropotential between the membranes. A membrane M that is permeable to electrolyte ions and, if present, drug borders the salt reservoirs and makes contacts with body to be treated.

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ELECTROCHEMICAL METHOD AND DEVICE FOR DRUG DELIVERY

The present invention relates to an iontophoretic method for drug delivery and a device suitable for use in carrying out this method.

In the present method, an electric current is generated by creating Galvani potential differences across at least two different ion selective membranes via a salt concentration difference over the membranes and bringing one anion selective membrane and one cation selective membrane into contact with human or animal body either directly or indirectly. According to a feature of the invention at least one reservoir containing a salt solution is needed, the concentration of which differs from the salt concentration of the extracellular fluids in human or animal tissues. The method of the invention can be specially used with transdermal preparations but also with mucoadhesive preparations and implants. For simplicity, the description which follows will refer to devices which are transdermal preparations, but it is to be understood that the method and device may be adapted to apply to mucoadhesive preparations and implants.

Iontophoresis or iontophoretic therapy is the delivery into human or animal tissue of a drug by the use of an electric field or current. Reviews of methods, devices and drugs suitable for iontophoretic delivery are contained in e.g. Journal of Controlled Release Vol. 7, 1988, pp. 1-24, Drug Design and Delivery Vol. 4, 1989, pp. 1-12 and Journal of Pharmaceutical Sciences Vol. 78, 1989, No. 5 , pp. 376-383. In addition to transdermal applications the methods have also been used in ophthalmologic therapy (A.K. Banga & Y.W. Chien, J.Controlled Release Vol. 7, 1988, pp. 1-24).

For the generation of electric current some kind of a battery is always needed, and current is introduced into the tissues of the body via wires and electrodes. The electric circuit is closed through the body of a patient after attaching a device on the surface of the body or by the implantation of a device. The flux of a drug is enhanced mainly due to the migration of ionized drug molecules but also secondary effects e.g. electroosmotic convective flow and tissue alteration due to current can be responsible for the flux enhancement. Due to these secondary effects also the flux of neutral drug

molecules is enhanced in the presence of electric field (L. Wearley & Y.W. Chien, Pharmaceutical Research Vol. 7, 1990, pp. 34-40).

When current is passing in the circuit electrochemical reactions take place at the electrodes, and possibly harmful reaction products can be generated or useful compounds consumed at the electrodes. Such a reaction is usually the splitting of water which results in the change of pH and in the need to buffer the solutions (see e.g. EP 369945). Iontophoretic burns, skin irritation and electric shocks have been reported (P. Tyle, Pharmaceutical Research, Vol. 3, No. 6, 1986, pp. 318-326 and A.K. Banga & Y.W. Chien, Journal of Controlled Release, Vol. 7, 1988, pp. 1-24).

The present invention provides an iontophoretic device in which the power to generate the necessary electropotential to deliver the drug is provided by a difference in concentration of a salt across an anion selective membrane and a cation selective membrane. There is no need for a conventional battery or any electrodes. The present invention therefore provides a method of aministering a drug, which is ionized or ionizable *in situ*, to a human or animal body which method comprises forming a circuit by placing in electrolytic contact:

(i) the body and

(ii) one or more electrolyte solutions of which at least one is contained in a compartment, having a boundary which comprises a membrane selective to cations and a membrane selective to anions, the concentration of electrolyte in the compartment(s) being such that on formation of the circuit ions move through the ion selective membranes; the drug being present, at least initially, in one or more of said solutions such that the movement of ions causes movement of the drug in ionized form into the body.

The present invention also provides a drug delivery device comprising a compartment containing:

i) a drug which is in ionized form or ionizable *in situ* ; and

ii) an electrolyte solution of a concentration higher than the concentration of electrolyte in extracellular fluids in human or animal tissue

said compartment having a boundary which comprises a membrane which selectively allows cations to pass through and a membrane which selectively allows anions to pass through.

An alternative device is one which comprises at least three compartments 1, 2 and 3, each containing an electrolyte solution and in which:

i) compartment 1 contains a solution of different concentration from the solutions of compartments 2 and 3, 1 being in electrolytic contact with 2 via a membrane C which selectively allows cations to pass through, and in electrolytic contact with reservoir 3 via a membrane A which selectively allows anions to pass through;

ii) at least one of 2 and 3 further contains a drug which is in ionized form or capable of being ionized *in situ* ;

iii) 2 and 3 each have as part of their boundaries a membrane M that is permeable to electrolyte ions and, if present, drug;

said device being capable of forming a circuit when brought into contact with a human or animal body, the concentrations of electrolyte solutions being such that on formation of the circuit ions move through membranes A and C causing the drug in ionized form to move into the body.

The drug administered by the device is ionized or ionizable *in situ* , i.e. it is capable of existing in ionized form under the conditions in which the device is used. It is also possible that the drug may be capable of associating with an ionic species during use of the device.

In the following description of the invention reference is made to the figures of the drawings.

Figure 1 shows the principle of the invention.

Figure 2 shows an example of a one compartment design of the device.

Figure 3 shows an embodiment of a device.

Figure 4 shows an embodiment of a device for transdermal therapy.

Figure 5 shows a side-view of an embodiment of a circular device for transdermal therapy.

Figure 6 shows a bottom-view of an embodiment of a circular device for transdermal therapy.

Figure 7 shows an embodiment of a device which comprises alternating dilute and concentrated salt solutions and anion and cation selective membranes.

When two salt solutions I and II of different concentrations are separated by an ideal ion selective membrane which allows only one of the ions, with a charge number z_i, to cross the membrane but excludes all the other ions, a Galvani potential difference, $\Delta\Phi$, across the membrane is created, and it is given by Equation (1)

$$\Delta\Phi = \frac{RT}{z_i F} \ln \frac{a_i(I)}{a_i(II)} \qquad (1)$$

where a_i(I) and a_i(II) are the activities of the ion in the solutions I and II, R = 8.314 J K^{-1} mol^{-1}, F = 96487 As mol^{-1} and T is the thermodynamic temperature (K). However, the ion cannot cross the membrane because of the electroneutrality condition $\sum z_i \cdot c_i = 0$ wherein c_i is concentration, but if electrodes which are reversible with respect to any of the ions are placed in the solutions and connected with each other, ions begin to flow through the membrane because electrode reactions equilibrate the loss and the excess of the ion. This phenomenon is known in concentration cells with transference and ion selective membranes.

When a concentrated salt solution is separated from two dilute solutions with two different ion selective membranes and the dilute solutions are connected via a salt bridge with the same dilute concentration as presented in Figure 1., ion fluxes i.e. electric current can be obtained because the removal of an equivalent of cations is balanced with the corresponding removal of anions. If the salt bridge is replaced by reversible electrodes which are in contact, the process known as reverse electrodialysis is obtained (J.N. Weinstein & F.B. Leitz, Science, Vol. 191, pp. 557-559 and US 4171409). A Human or animal body can be considered to form a salt bridge and thus an iontophoretic method for drug delivery is obtained. No electrodes or conventional batteries are needed to generate current.

The drug is placed in the appropriate dilute salt solution according to the drug's electric charge: positively charged drugs are placed in solution that is separated from the reservoir by a cation selective membrane and negatively charged drugs in the solution that is separated by an anion selective membrane.

The magnitude of current generated can be calculated by Ohm's law $I = \Delta\Phi/R_C$, where R_C is the resistance of the half-circuit. The flux of a drug, J_D, in this case with a perfect sink condition is approximately given by Equation (2)

$$J_D = D_D \frac{C_D}{h} \frac{v}{1-e^{-v}}; v = \frac{z_D F I R \Omega}{RT} \qquad (2)$$

where c_D is the concentration of a drug in the reservoir, D_D is the integral diffusion coefficient of a drug in the tissue which limits the flux, and h and R_Ω are the thickness and resistance of that tissue. The limiting value $z_D = 0$ for electrically neutral drugs yields the passive flux $J_{D,p} = D_D \cdot c_D/h$.

Suitable drugs for the method of the invention are those which have electric charge in water solution. It is therefore particularly suitable for the delivery of ionized drugs. Neutral drugs such as peptides may be delivered using this method by causing the drug to ionize e.g. by selecting an appropriate pH of the drug solution.

The present method may be used for delivering any drug capable of being ionized and which is appropriate for iontophoretic administration. Such drugs include local anaesthetics e.g. lignocaine and lidocaine; antibiotics and antibacterials e.g. streptomycin and penicillin; peptides and proteins, such as insulin; vasodilators; steroids; beta-blockers, such as metoprolol, sotalol and propranolol; and other drugs such as papaverine. Further drugs are listed in the reviews of iontophoretic techniques mentioned earlier. It is possible to deliver more than one drug at the same time.

The maximum salt concentration of the concentrated solution is due to the solubility of the salt. The lowest limit of the concentration of the dilute solution is that the solution must be capable of conducting current. The salt concentration in the dilute solution can also be less than that in the extracellular fluids of human or animal tissues. All pharmaceutically acceptable salts can be used. Typical salts include e.g. NaCl and KCl.

The ion selective membranes can be of any of the commercial types available, such as Ionics (Ionics, USA), Nafion (a perfluorosulfonic acid membrane of DuPont Limited), Neosepta (Tokoyama Soda Limited), Tosflex (Tasoh Corporation), Ionac (Sybron Chemicals) and Selemion (Asahi Glass).

The device for carrying out the method of the present invention can be of several different types of design. The following types of design presented are not by any means limiting but only illustrative. Figure 1, which shows the principle of the invention, presents a three compartment design where a reservoir of the concentrated salt solution is placed between the two reservoirs of dilute salt solution with different ion selective membranes, and the drug is added in the appropriate one of the dilute solutions depending on the charge of the drug. A very dilute solution can also be placed between two concentrated solutions maintaining the design otherwise the same. In this case the drug is placed in the concentrated solution appropriate to the charge on the drug. Now greater potential differences can be obtained but at the same time the resistance of the circuit increases. Both designs described above have the similarity that drug is not passed through the ion selective membranes.

In a one compartment design there is only one reservoir. This reservoir contains both salt solution and drug as illustrated in Figure 2, and the tissues of a body itself provides the other compartments. The solution in the device should in this embodiment be more concentrated than the salt concentration of extra cellular fluids of human or animal tissues. In this case drug has to transfer through one of the ion selective membranes, depending on this charge, and this may lead to use of tailor-made membranes in order to allow the passage of drug molecules with great size.

An example of a practical embodiment of the device is illustrated in Figure 3. For example, the body of the device may be formed of a silicon material e.g. Silastic and the ion-selective membranes may be e.g. Neosepta and Tosflex. The device comprises a reservoir 1 connected to a reservoir 2 by an anion selective membrane A, and connected to a cation selective membrane C, the reservoir 2 and membrane A being separated from the reservoir 3 and membrane C by a spacer S which is non-porous to the solutions being used. The membrane M borders reservoirs 2 and 3 and is intended to make contact with the body to be treated.

The reservoir 1 may contain a concentrated salt solution and the reservoirs 2 and 3 may contain dilute salt solutions or vice versa; preferably the reservoir 1 contains a concentrated salt solution.

The drug is placed in either of the reservoirs 2 or 3 depending on its charge. The drug may also be placed in the reservoir 1, but in this case the

drug has to penetrate also one of the ion selective membranes as described before. The membrane M depicted below the reservoirs 2 and 3 may be an ordinary membrane which allows the penetration of the drug and the salt ions. It is intended that the reservoirs 2 and 3 be brought into contact with the human or animal body via that membrane. A spacer separates the ion selective membranes from each other. The spacer may be for instance an empty space or an impermeable wall.

For transdermal therapy the device may have an adhesive layer as illustrated in Figure 4, which further may be covered by a tape. After the covering tape is removed the device is attached to the skin. The adhesive layer may contain one or more penetration enhancers to reduce the resistance of the skin. The salt solutions may be immobilized in a hydrogel, such as agar-agar or agarose, since it has been noticed that the transport properties of ions are reduced surprisingly little in such a gel (Y.B. Bannon et al., Drug Development and Industrial Pharmacy, Vol. 14, No. 15-17, 1988, pp. 2151-2166).

A wide range of salt concentrations may be used in a device, e.g. concentrations from 0.005 M to 5 M. Typically a difference in initial concentrations in two adjacent reservoirs separated by an ion-selective membrane will be 60 to 130 fold, preferably about 100 fold e.g. 0.01 M and 1M NaCl or 0.05 M and 5 M NaCl. This can be expected to produce a potential difference of 120 mV over the ion-selective membranes.

The life-time of the device is determined by the concentrations of the salt solutions and can be calculated from the Faraday's law as follows:

$$\frac{dn}{dt} = \frac{I}{z_i F} - \Delta t = \frac{z_i F \Delta n}{I} \qquad (3)$$

where Δt is the time used, Δn is the amount of salt consumed (mol) and I, z_i and F are as defined before.

The life-time of the device is also dependent on the volume of the salt solutions because the transfer of ions tends to equalize, though slowly, the concentrations. The power of the device is determined by the area and ideality of the membranes: the greater these quantities are the greater is the current. A circular, concentric form is an example of a device in which a long life time and high current are combined. A side-view and a bottom-view of an

embodiment of a circular device are presented in Figure 5 and Figure 6, respectively.

The electric potential supplied by the salt concentration difference across membranes in a single cell device e.g. as shown in Figure 1, is lower than the electric potential which may be obtained from conventional batteries. However, the unit presented in Figure 1 may be connected in series to provide a higher potential and greater current. Reservoirs of dilute and concentrated solutions and anion selective and cation selective membranes alternate and a drug to be administered is in one of the outer reservoirs. An example of that kind of a device is presented in Figure 7. The outer reservoirs are brought into contact with human or animal body via a membrane that is permeable to the drug and salt ions. If the salt concentrations between adjacent reservoirs would result in a potential difference of 120 mV in a single cell, connection of four units in series will produce a potential difference of 500 mV.

Referring to equation 2, the term $v / (i\text{-}e^{-v})$ may be regarded as an enhancement factor, which indicates how the flux of a drug varies with the electric potential and the charge on the drug ion. This relationship is shown in Figure 8 for ionic charges (z) of ± 1, ± 2 and ± 3. For example when the drug ion has a charge of ± 1, an electric potential of 500 mV results in a 20-fold increase in the drug flux compared with the passive flux.

The examples of devices presented in Figures 4 to 7 are designed specially for transdermal purposes but they can easily be modified for other purposes, such as mucoadhesive purposes, for example, where the resistance of the flux limiting tissue is much less than that of skin which results in greater currents.

The iontophoretic method of the present invention has several advantages. In the absence of electrodes no reactions take place and the changes in composition or pH of the solutions and degradation of drug are avoided. The absence of a battery and electrodes removes the need for safety precautions and problems with disposal of the device. Furthermore, ordinary commercial membranes and salts can be utilized which means low costs. Since the current produced is relatively low, there is the further advantage that adjusting the current to avoid skin irritation is not required. From Faraday's law it can be calculated that changes of the concentrations due to current are

negligible for several weeks. The device may therefore be used to administer the drug over a long time.

Experiment 1

The principle of the method was experimentally verified using a reverse electrodialysis set up: a 1.5 mol dm^{-3} NaCl solution was separated with Ionics 103-PZL-389 anion exchange and Nafion 423 cation exchange membrane from 0.15 mol dm^{-3} NaCl solutions which mimic the salt content of the blood circulation; snake skin preparates (*Elaphe obsoleta*) with 1,0 cm^2 area to mimic human *stratum corneum* were placed between membranes and Ag/AgCl electrodes, and current was monitored between the electrodes.

The device was able to maintain a current of 5 - 10 µA for several days which ensures the validity of Equation 1 and proves that the current was limited by the resistance of snake skin. It has been noticed in separate measurements that the resistance of snake skin with 1,0 cm^2 area varies between ca. 5 kΩ and 20 kΩ according to its hydration. It must be noticed that both membranes create approximately the same potential difference which has to overcome the resistance in its own branch of the circuit only. Also, it must be emphasized that the use of electrodes for the monitoring of current increases the entropy production of the system, and a device without electrodes is capable of maintaining higher current.

Experiment 2

The principle of a device which comprises alternating dilute and concentrated salt solutions and anion and cation selective membranes was tested using the system depicted in Figure 9.

A indicates an Ionics 103-PZL-389 anion exchange membrane and C indicates a Nafion 423 cation exchange membrane.

The test revealed that the potential difference achieved from this system was twice as great as the potential difference achieved when only two ion selective membranes were used.

Claims

1. A drug delivery device comprising a compartment containing:

i) a drug which is in ionized form or ionizable *in situ* ; and

ii) an electrolyte solution of a concentration higher than the concentration of electrolyte in extracellular fluids in human or animal tissue

said compartment having a boundary which comprises a membrane which selectively allows cations to pass through and a membrane which selectively allows anions to pass through.

2. A drug delivery device which comprises at least three compartments 1, 2 and 3, each containing an electrolyte solution and in which:

i) compartment 1 contains a solution of different concentration from the solutions of compartments 2 and 3, 1 being in electrolytic contact with 2 via a membrane C which selectively allows cations to pass through, and in electrolytic contact with 3 via a membrane A which selectively allows anions to pass through;

ii) at least one of 2 and 3 further contains a drug which is in ionized form or capable of being ionized *in situ* ;

iii) 2 and 3 each have as part of their boundaries a membrane M that is permeable to electrolyte ions and, if present, drug;

said device being capable of forming a circuit when brought into contact with a human or animal body, the concentrations of the electrolyte solutions being such that on formation of the circuit ions move through membranes A and C causing the drug in ionized form to move into the body.

3. A device according to claim 2 in which the solution in 1 is more concentrated than that in 2 or 3.

4. A device according to claim 3 in which the concentration of solutions in each of 2 and 3 is at least as great as the electrolyte concentration in the extracellular fluids in human or animal tissue.

5. A device according to claim 3 in which the concentration of solutions in each of 2 and 3 is less than the electrolyte concentration in the extracellular fluids in human or animal tissue.

6. A device according to claim 2 in which the solution in 1 is more dilute than that in 2 or 3.

7. A device according to claim 2 in which the device is circular, and the ion-selective membranes are concentric rings or ring portions.

8. A drug delivery device comprising:

i) at least four compartments which are connected in series and separated alternately by membranes which selectively allow passage of cations and membranes which selectively allow passage of anions, the two outer membranes being of different ion selectivties;

ii) the compartments each contain an electrolyte solution the relative concentrations of solutions in adjacent compartments being alternate;

iii) one of the outer compartments further containing a drug which is in ionized form or capable of being ionized *in situ*, the two outer compartments each having as part of their boundaries, in addition to an ion selective membrane, a membrane M that is permeable to electrolyte ions and, if present, the drug;

said device being capable of forming a circuit when brought into contact with a human or animal body, the concentrations of electrolyte solutions being such that on formation of the circuit ions move through the ion-selective membranes causing the drug in ionized form to move into the body.

9. A device according to claim 2 in which the drug is in the form of a salt whose cation is pharmacologically active, the compartment containing the drug being in contact with an adjacent compartment via a cation selective membrane.

10. A device according to claim 8 in which the drug is in the form of a salt whose cation is pharmacologically active, the compartment containing the drug being in contact with an adjacent compartment via a cation selective membrane.

11. A device according to claim 2 in which the drug is in the form of a salt whose anion is pharmacologically active, the compartment containing the drug being in contact with an adjacent compartment via an anion selective membrane.

12. A device according to claim 8 in which the drug is in the form of a salt whose anion is pharmacologically active, the compartment containing the drug being in contact with an adjacent compartment via an anion selective membrane.

13. A method of administering a drug, which is ionized or ionizable *in situ*, to a human or animal body which method comprises forming a circuit by placing in electrolytic contact:

(i) the body and

(ii) one or more electrolyte solutions of which at least one is contained in a compartment having a boundary which comprises a membrane selective to cations and a membrane selective to anions, the concentration of electrolyte in the compartment(s) being such that on formation of the circuit ions move through the ion selective membranes; the drug being present, at least initially, in one or more of said solutions such that the movement of ions causes movement of the drug in ionized form into the body.

14. A method according to claim 13 in which the anion selective membrane and cation selective membrane are each in direct contact with the body when the circuit is formed.

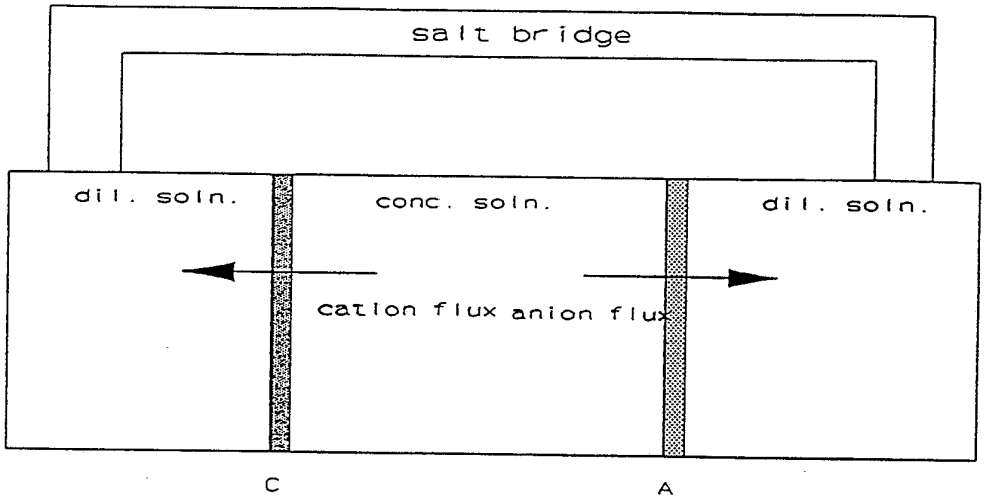
15. A method according to claim 13 in which the anion selective membrane and cation selective membrane are not in direct contact with the body when the circuit is formed.

16. A method of drug delivery which comprises contacting human or animal body tissue with a device as defined in claim 1.

17. A method of drug delivery which comprises contacting human or animal body tissue with a device as defined in claim 2.

18. A method of drug delivery which comprises contacting human or animal body tissue with a device as defined in claim 8.

Figure 1.



A = Anion selective membrane

C = cation selective membrane

Figure 2.

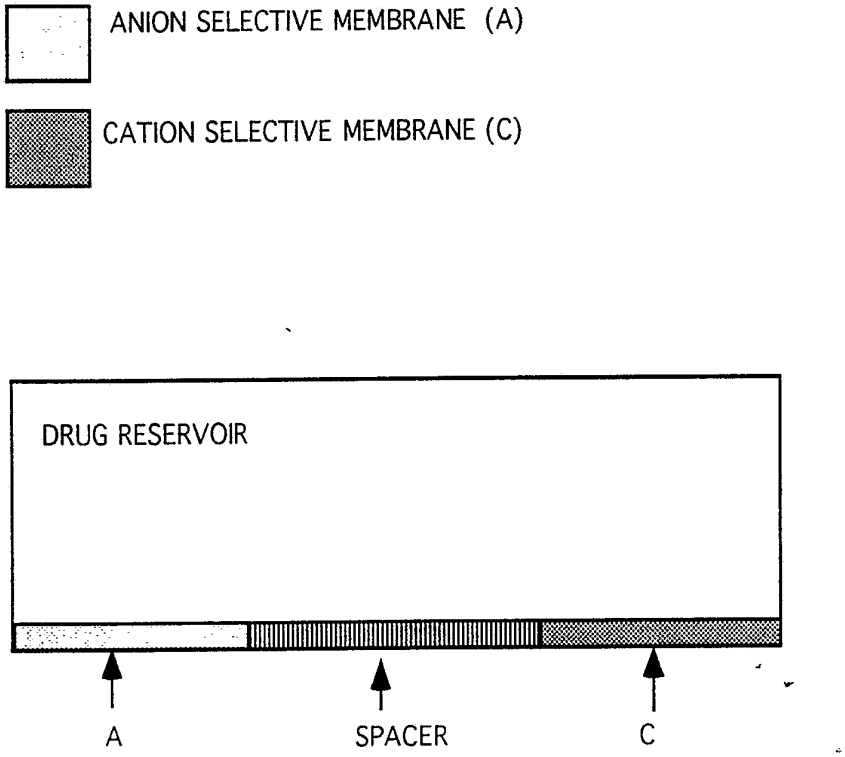

ANION SELECTIVE MEMBRANE (A)
CATION SELECTIVE MEMBRANE (C)
DRUG RESERVOIR
A
SPACER
C

Figure 3.

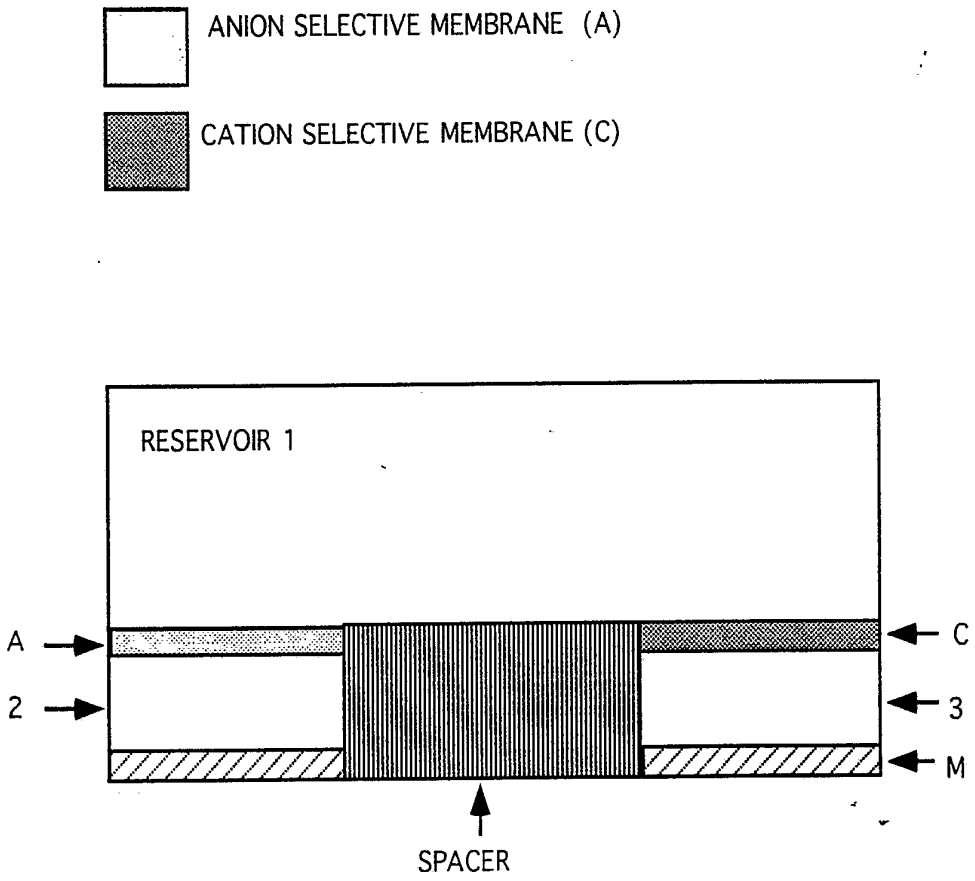

ANION SELECTIVE MEMBRANE (A)
CATION SELECTIVE MEMBRANE (C)
RESERVOIR 1
A
2
C
3
M
SPACER

Figure 4.

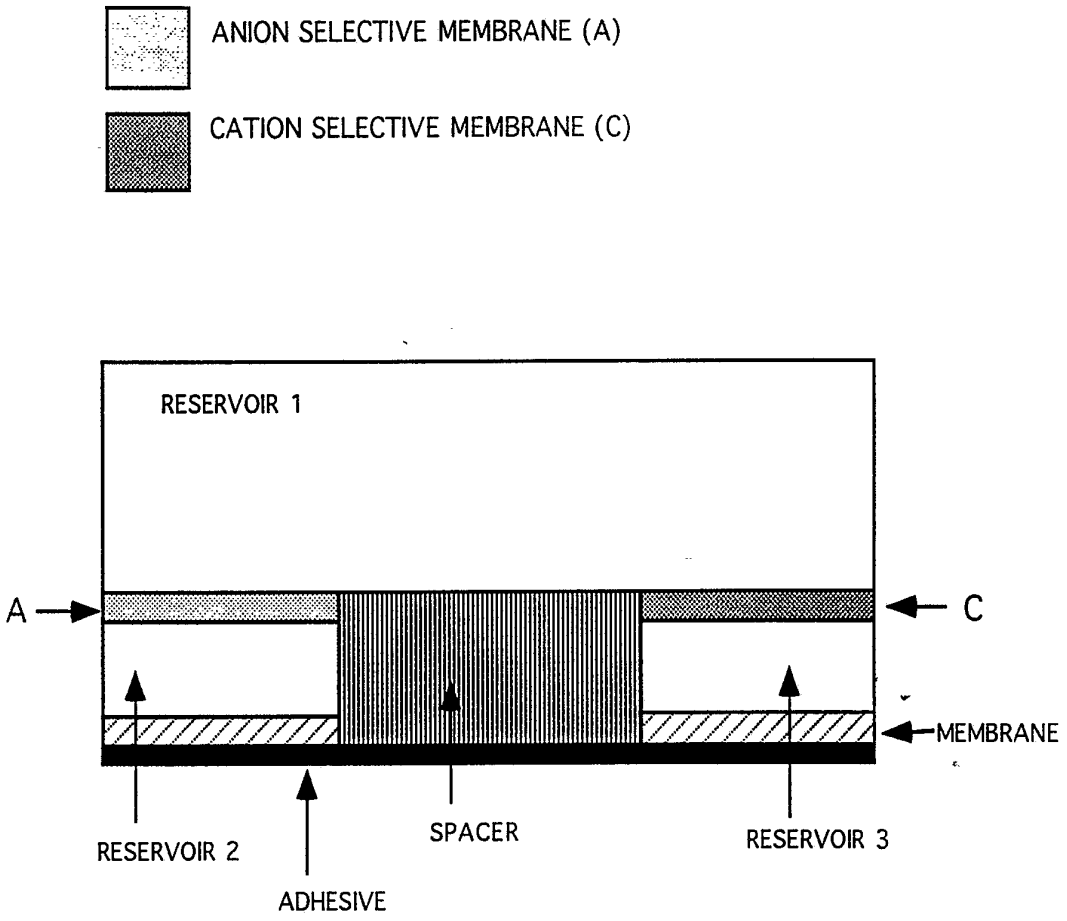

ANION SELECTIVE MEMBRANE (A)
CATION SELECTIVE MEMBRANE (C)
RESERVOIR 1
A
C
MEMBRANE
RESERVOIR 2
ADHESIVE
SPACER
RESERVOIR 3

Figure 5.

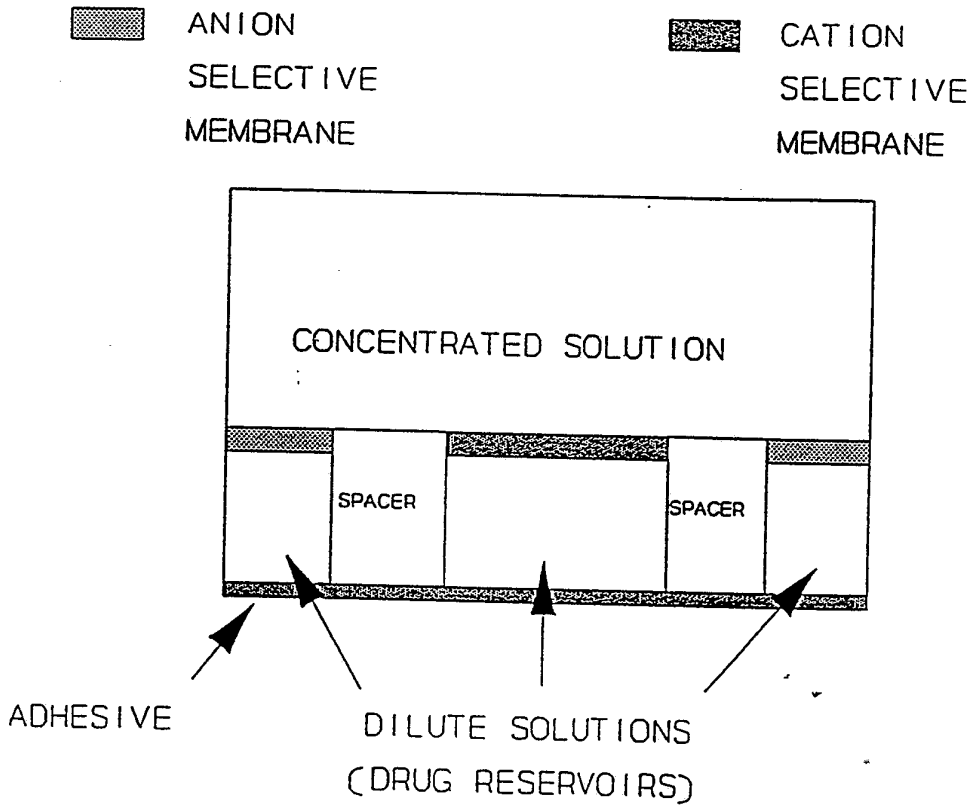
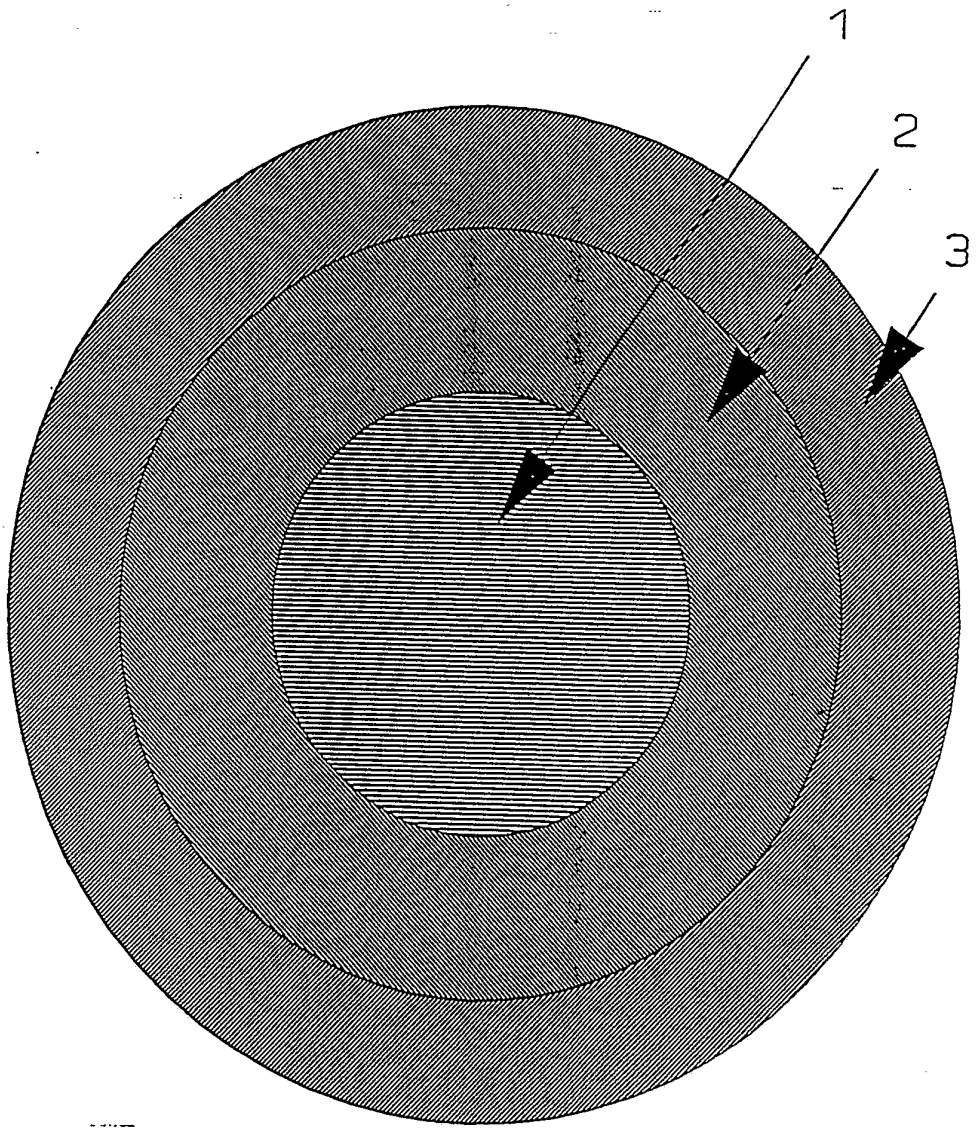

ANION
SELECTIVE
MEMBRANE
CATION
SELECTIVE
MEMBRANE
CONCENTRATED SOLUTION
SPACER
SPACER
ADHESIVE
DILUTE SOLUTIONS
(DRUG RESERVOIRS)

Figure 6.



1 = cation selective membrane
2 = spacer
3 = anion selective membrane

Figure 7.

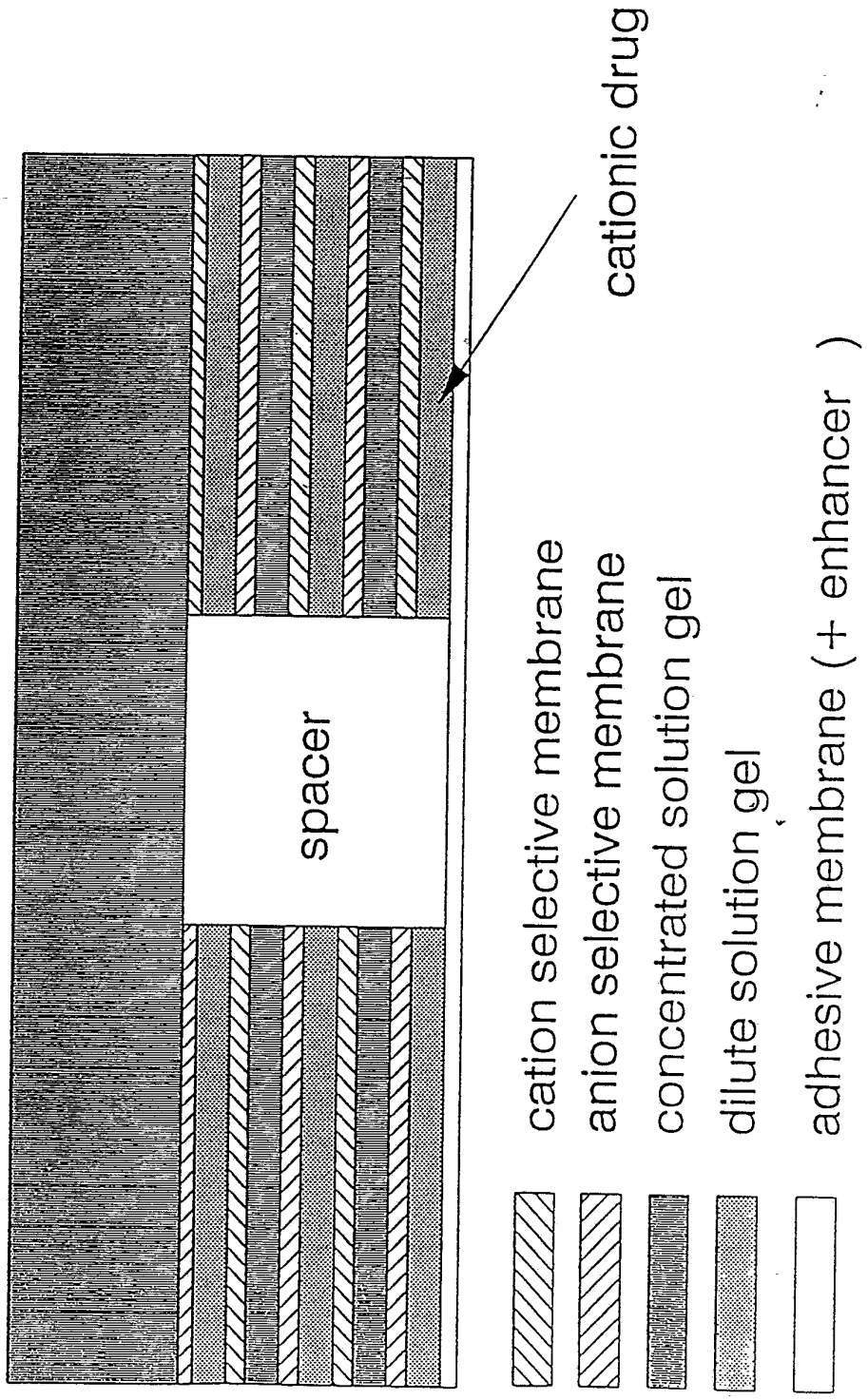

cationic drug
spacer
cation selective membrane
anion selective membrane
concentrated solution gel
dilute solution gel
adhesive membrane (+ enhancer)

Figure 8.

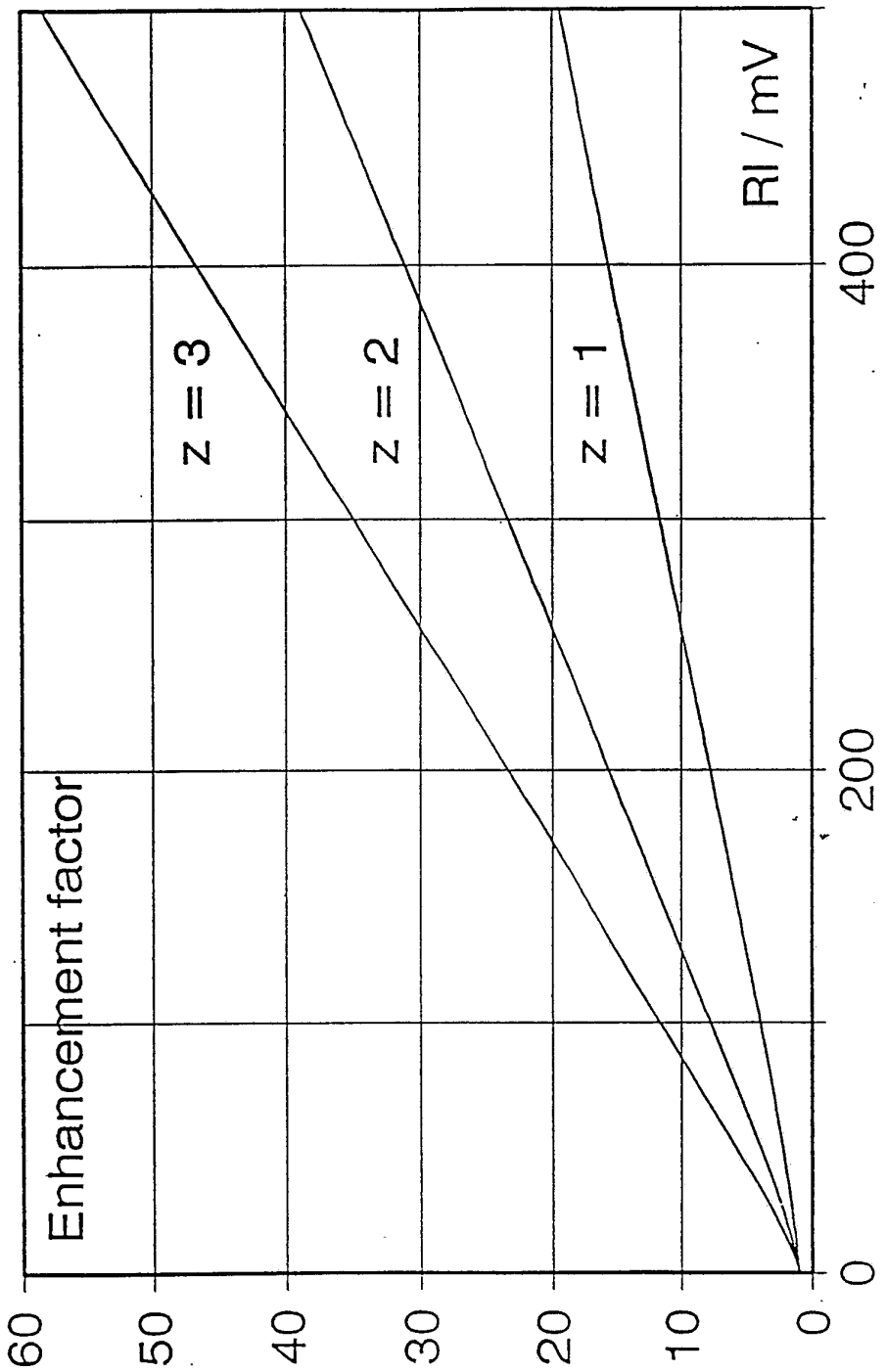
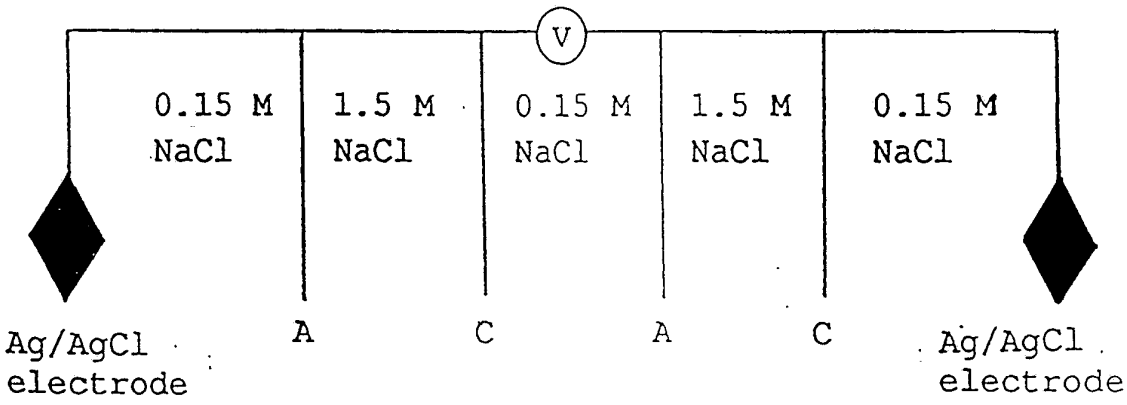


FIGURE 9.


V
0.15 M NaCl
1.5 M NaCl
0.15 M NaCl
1.5 M NaCl
0.15 M NaCl
Ag/AgCl electrode
A
C
A
C
Ag/AgCl electrode

INTERNATIONAL SEARCH REPORT

International Application No PCT/FI 93/00083

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

Int.Cl. 5 A61N1/30

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61N ; A61M

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	US,A,4 722 726 (J.E. SANDERSON ET AL.) 2 February 1988 see the whole document	1,13
A		2,7, 8-12, 14-18
A	FR,A,762 259 (D. DEUTSCH) 9 April 1934 see the whole document	1,2
A	EP,A,0 316 065 (ALZA CORPORATION) 17 May 1989 see the whole document	1

° Special categories of cited documents :[10]

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

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

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"&" 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
17 JUNE 1993	24 JUN 1993
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FERRIGNO A.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

FI 9300083
SA 71428

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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		EP-A- 0258392	09-03-88
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