Description

Background of the Invention

The present invention is directed to tissue irrigating solutions and, more particularly, to an improved technique for formulating and packaging the components of a tissue irrigating solution containing glutathione, bicarbonate, and Ringer solution.

During the surgical procedures, it has been found extremely important to minimize disturbance of the environment of tissue and cells as much as possible. A traumatic change in the environment surrounding internal cells may lead to the destruction of such cells or the destruction of the function of such cells. The destruction of cell function may even lead to destruction of other cells which are dependent upon a proper functioning of the destroyed cells. Therefore, during surgical procedures such as, for example, intraocular surgery, it is very important that the exposed tissue be continuously irrigated with solutions which approximate natural body fluids. Such solutions are called "tissue irrigating solutions". One of the earliest tissue irrigating solutions for ophthalmic procedures was an isotonic saline. However, it was quickly recognized that the isotonic saline was not adequate as an ophthalmic irrigating solution because it resulted in endothelial cell swelling, cell damage, and consequent corneal clouding.

Alternatively, various electrolyte solutions have been proposed as tissue irrigating solutions, particularly in ophthalmic procedures, because such solutions more closely resemble the aqueous humor of the eye. The earliest electrolyte solution was known as Ringer's solution, which was a combination of sodium, calcium and potassium ions along with sodium lactate. Another solution intended for tissue irrigation is known as a balanced salt solution which contains the essential sodium, potassium, calcium, and magnesium salt ions along with an acetate-citrate buffer system. It has been somewhat successful and was used extensively until several years ago. Within the last 10-15 years, there has developed a tissue irrigating solution which is a combination of the Ringer solution along with glutathione and sodium bicarbonate. This is sometimes referred to GBR, and in recent years has become a recognized tissue irrigating solution, especially for ophthalmic procedures. When dextrose, sodium hydrogen phosphate (Na_2HPO_4), and sometimes adenosine are added to GBR, there results a fortified or enhanced balanced salt solution (sometimes referred to as "BSS Plus), which has proven to be the most effective for intraocular surgery.

The problem with all GBR solutions and particularly the fortified or enhanced balanced salt solution is that they are not stable. Because they must be mixed essentially at the operative site, it is difficult to control and maintain sterility. There are various reasons why GBR type solutions are not stable. First, bicarbonate and phosphate tend to precipitate in the presence of the magnesium and calcium ions. Therefore, once mixed, the sodium bicarbonate quickly loses its ability to act as a pumping agent for causing the endothelium to perform its fluid transport function of maintaining an outward fluid transport to the stromal layer, which results in damage to the cornea. Stated otherwise, the purpose of the bicarbonate is to act as a pump and, when mixed with the magnesium or calcium ions, it quickly loses its propensity for pumping. A second reason why the GBR solutions are not stable is that bicarbonate decomposes at a pH of less than 8 and becomes carbon dioxide which again causes the bicarbonate to fail to act as a chemical pump during the surgical procedure. Finally, the glutathione is unstable at a pH greater than 5. Therefore, the glutathione cannot exist in a basic solution and the bicarbonate cannot exist for extended periods in an acid solution.

A solution to this problem has been offered in United States Patents Nos. 4,443,432 and 4,550,022, both issued to Garabedian et al. According to these two patents, initially two solutions are prepared, one a basic solution providing the bicarbonate and sodium phosphate, and the second an acidic solution which provides the calcium and magnesium ions, as well as the dextrose and glutathione. The solutions are packaged and stored separately for extended periods of time and mixed within 24 hours of use. While the resulting irrigating product as described the Garabedian et al technique has achieved some degree of acceptance and success, there are some limitations as a result thereof. The long-term stability and maintenance of acceptable pH values is difficult in accordance with the method and technique described in the Garabedian et al patents. In order to steam sterilize the large solution, it is necessary to place the glutathione in the smaller package, because glutathione cannot stand steam sterilizing. Therefore, since the sodium bicarbonate is in the larger package, the large package must be glass, because it is difficult to maintain the stability of sodium bicarbonate in solution in a polymeric container. This occurs because sodium bicarbonate will not remain stable as a result of the transmission of vapors through the wall of the polypropylene bottle.

Summary of the Present Invention

In order to overcome the problems described hereinabove and offer an improved formulating and pack-

aging technique, the present invention contemplates a two-part intraocular or tissue irrigating system. A first part includes a stable, sterile pre-packaged acidic solution containing at least the calcium ions and magnesium ions. The second part includes a lyophilized powder containing at least the sodium bicarbonate and glutathione. The sodium hydrogen phosphate is preferrably included with the second part (powder). The potassium ions and dextrose may be provided in either the first or second part. When the first and second parts are mixed together, there is formed an extremely satisfactory irrigating solution. Preferably, the powder and solution should be aseptically mixed to maintain the sterility thereof.

More specifically, in the proposed irrigating product, a larger solution (on the order of 500mls) contains all the chlorides, i.e., sodium, potassium, calcium and magnesium, in a polypropylene bottle that is terminally steam-sterilized according to conventional processes. The second or smaller part is a lyophilized powder which includes sodium bicarbonate, disodium hydrogen phosphate, dextrose and glutathione disulphide. The second part is sterile-filtered before being aseptically filled into either a glass vial or a small polypropylene bottle for lyophil-ization. It has been found preferable to include the sodium hydrogen phosphate with the sodium bicarbonate. Thus the calcium and magnesium ions are placed in the large bottle. Both the bicarbonate and the glutathione are stabilized by the lyophilizing (freeze-drying) process. A special technique has been developed to eliminate any breakdown that could occur before the solution containing bicarbonate and glutathione are frozen. According to the improved technique, the sodium bicarbonate is first frozen, then the glutathione is frozen onto the surface of the sodium bicarbonate, then both frozen components are lyophilized (freeze-dried).

The large solution is preferably placed in a 500ml polypropylene bottle and the small solution containing the lyophilized powders are placed in a small 50ml glass or polypropylene vial. The two components are mixed aseptically through a transfer spike. One end of the spike is inserted through the stopper in the small vial. With the bottle containing the larger amount of solution in the upright position, the small vial is then inverted and the other end of the spike is inserted through the stopper into the large bottle. The large bottle, being polypropylene, is then squeezed which forces a small amount of fluid into the vial which promptly dissolves the lyophilized powder. When the polypropylene bottle is released, the fluid and powder dissolved therein will return to the large bottle. This process is repeated several times to flush all the contents of the vial into the bottle and to thoroughly mix the contents of the two containers.

It is, therefore, an object of the present invention to provide an improved formulating and packaging technique for the manufacture of glutathione/bicarbonate/Ringer solution type products.

Another object of the present invention is to provide an enhanced balanced salt solution of the type described in which the sodium bicarbonate, sodium hydrogen phosphate, and glutathione are packaged together in a powderous form.

Other objects and a fuller understanding of the invention will become apparent upon reading the following detailed description along with the accompanying drawings in which:

Figures 1 and 1A illustrate a two-part packaging system in which the components of the irrigating solution of the present invention are prepackaged and stored; and

Figure 2 is a schematic block diagram illustrative of the procedural steps involved in formulating the irrigating solution of present invention.

Detailed Description of a Preferred Embodiment

The present invention is directed generally to an improved technique for packaging a tissue irrigating solution of the type which includes glutathione/bicarbonate/Ringer solution, whereby the components are initially packaged in a two-component system. The composition and concentration of the two components of the system are such that they remain stable, even when stored for long periods of time. The two components are separately sterilized, then aseptically mixed so that the ultimate solution is completely sterile and available for use in surgery during the ensuing 24 hours. The mixed solution has been found to be extremely useful for maintaining the appropriate environment and preventing cell damage during surgical procedures, particularly procedures such as intraocular surgery.

The desired irrigating solution, when mixed, preferrably contains the following components in the amount indicated:

Ingredients for Enhanced Balanced Salt Solution

	mg /ml
Sodium chloride (NaCl)	7.14
Potassium chloride (KCl)	0.378
Calcium chloride ($CaCl_2$ $2H_2O$)	0.154
Magnesium chloride ($MgCl_2$ $6H_2O$)	0.20
Dextrose	0.916
Sodium carbonate ($NaHCO_3$)	2.096
Sodium hydrogen phosphate (Na_2HPO_4)	0.415
Glutathione disulphide	0.184

As has been described above, the irrigating solution identified hereinabove is supplied in two parts that will be mixed by the end user immediately prior to usage and will have usable life, when mixed, of 6-24 hours. One part is a mixed salt solution shown below in Formula 1 and the second part will be a powder containing the components shown in Formula 2. Formula 2 dissolves readily in Formula 1 and forms a clear solution consisting of the components in the amounts shown above. When packaged and before mixing the Formula 1 and Formula 2 powder contain the following ingredients in the indicated amounts.

Formula 1 (Solution)

Ingredients	mg /ml
Sodium chloride (NaCl)	7.14
Potassium chloride (KCl)	0.378
Calcium chloride ($CaCl_2$ $2H_2O$)	0.154
Magnesium chloride ($MgCl_2$ $6H_2O$)	0.20

Formula 2 (Powder)

Ingredients	Percentage by Weight
Dextrose	25.3
$NaHCO_3$	58.04
Na_2HPO_4	11.49
Glutathione disulphide	5.10

Looking now at the drawing, Formula 1 is placed in the large polypropylene container (500ml) 10 and Formula 2 is placed in the small container (50ml) 12. A mixing spike 14 is provided and utilized in the following manner. The mixed salt solution is carried in container 10 and the lyophilized in container 12. One end of the spike 14 is placed through the rubber stopper 13 in vial 12. The vial 12 and spike 14 are then inverted and the other end of the spike is placed through the rubber stopper 11 in the cap of bottle 10. The bottle 10 is preferrably formed of a resilient polypropylene material, so that when it is squeezed, a portion of the fluid is forced up into the small vial, where it mixes with and dissolves the powder therein. When the bottle 10 is released, the fluid then flows back down through spike 14 into the large container. When this process is repeated several times,

the powder is fully mixed, dissolved, and transferred into the large container 10. The small vial and spike are then disposed of, and the large container is ready for use in the operative procedure.

In the ensuing examples, there are explained several experiments which were conducted in order to determine the preferred manner for formulating the irrigating solution of the present invention. In preparation for experiments 1-6, the following solutions A and B were prepared.

Solution A

Ingredients	Amounts
Distilled water	10 liters
NaCl	71.4 g
KCl	3.79 g
$CaCl_2$	1.54 g
$MgCl_2$	2.00 g

Divide Solution A into four equal lots, each lot equaling approximately 2.5 liters, and adjust the pH of each lot with 1N.HCl as follows:

	Target	Actual
Lot 1A	pH 3.0	pH 2.9
Lot 2A	pH 4.0	pH 4.1
Lot 3A	pH 5.0	pH 5.5
Lot 4A	pH 6.0	pH 6.9

Fill nine 250ml plastic bottles from each pH lot, cap and sterilize. Retain the remainding 25ml of each lot of Solution A for further observation.

Solution B

Ingredients	Quantities
Distilled water	1 liter
$NaHCO_3$	42 g
Na_2HPO_4	8.32 g
Dextrose	18.4 g
Glutathione	3.68 g

Dissolve the Na_2HPO_4 and the dextrose in the one liter of distilled water. Check the pH (8.8). Add glutathione and check the pH again (7.38). Adjust the pH to 7.9-8.0 using 1 N.NaOH solution. Add $NaHCO_3$. Check pH (7.86). Divide the solution into three equal lots and ajdust the pH as follows:

Lot 1B	pH 7.9-8.0
Lot 2B	pH 7.7
Lot 3B	pH 7.4

Each of the above lots should be filled into 30ml glass vials there being 13.25ml in each of 18 vials of each pH. Freeze dry each vial as soon as possible after mixing.

EXPERIMENT 1

Samples of the freeze-dried Solution B were received and the following tests were performed. First 13.1mls of water was added to each of two vials of each of the three different types of pH samples and the pH checked immediately and after one hour.

Table 1

Original pH		Sample No.	Reconstituted pH
7.6		(1)	8.24
		(2)	8.23
After 1 hour	----	(2)	8.26
7.73		(1)	8.27
		(2)	8.28
After 1 hour	----	(2)	8.30
7.86		(1)	8.28
		(2)	8.28
After 1 hour	----	(2)	8.30

Preliminary tests excluded the pH 5 and pH 6 of Solution A as being too high initially. Thereafter, the pH 3 and pH 4 samples of Solution A were used to mix with the three pH levels of freeze-dried Solution B.

Table 2

Mix	Immediate	Three Hour
2.9/7.86	7.68	7.91
4.1/7.86	8.10	8.26
2.9/7.73	7.58	7.84
4.1/7.73	8.04	8.23
2.9/7.6	7.47	7.69
4.1/7.6	*8.26	8.32

*This is not a true result as a solution in water from Sample 1 had to be used.

In conclusion as to Experiment 1, it was determined that the pH of Solution B could not be reduced below about 7.9 before freeze-drying. The HCl used to reduce the pH appears to liberate CO_2 from the bicarbonate and eventually all free CO_2 is lost on freeze-drying. It would, therefore, probably be necessary to have a very low pH (2.0 or less) in Solution A to counteract the buffering effect of the phosphate and the bicarbonate.

EXPERIMENT 2

A fresh batch of Solution A and Solution B were prepared, and the pH of Solution B was adjusted to 7.89 before the $NaHCO_3$ was added. After the addition of $NaHCO_3$, the pH of Solution B was 7.98. The pH of Solution A was adjusted down to 2.5 by using 0.5 N HCl. When Solutions A and B were mixed in the correct proportions (10ml to 0.5ml), the pH of the initial mixture was 7.3. After 24 hours, this had risen to pH 8.2 and, thus, did not meet the necessary criteria of pH 7.4.

EXPERIMENT 3

The purpose of Experiments 3 and 4 are to determine by comparison in Experiment 5 what is the best technique for freeze-drying Solution B. In Experiment 3, 18.4 g of dextrose was dissolved in 1 liter of distilled water. 900ml of the distilled water/dextrose solution had dissolved in it 8.3 g of Na_2HPO_4 and 42.0 g of $NaHCO_3$ to form a Solution B-1 having a pH of 8.15.

Using 12ml of the remaining 100ml of the dextrose solution, dissolve therein .442 g of glutathione disulphide to form Solution B-2 having a pH of 2.63.

Pipette 11.9ml of Solution B-1 into each of twelve 30ml vials, cap and place in a freezer. Cool Solution B-2 to about the freezing point, and when Solution B-1 is frozen and thoroughly chilled, add 1.3ml of Solution B-2 to each of nine vials of Solution B-1 and return all twelve immediately to the freezer. The second layer of Solution B-2 froze almost immediately on contact with the first layer, which was expected and intended. Retain in the freezer one of the nine vials of the combination solution B-1 and B-2 and one of the three vials of Solution B-1 only. Freeze-dry the remainder for further tests in Experiment 5.

EXPERIMENT 4

Dissolve 18.4g of dextrose in 1 liter of distilled water. Into 900ml of the dextrose solution, dissolve therein 42g of NaHCO to form Solution B-1 with a pH of 8.03. Fill 11.9ml of Solution B-1 into each of twelve vials, stopper and freeze. To the remaining 100ml of the dextrose solution, add 8.32g of Na_2HPO_4. When completely dissolved (pH 8-9.5), transfer 12ml to another container and add .442g glutathione and dissolve forming a Solution B-2 at pH 7.36. Cool Solution B-2 to about the freezing point and, when Solution B-1 is frozen and thoroughly chilled, add 1.3ml of Solution B-2 to each of nine vials, and return all twelve immediately to the freezer. In the lab experiment, the second layer again froze almost immediately on contact with the first layer as was intended. Retain in the freezer one of the nine vials of the combination solution B-1 and B-2 and one of three vials of Solution B-1 only. Freeze-dry the remainder for further tests in Experiment 5.

EXPERIMENT 5

The freeze-dried samples from Experiments 3 and 4 were received and the following tests were performed on them. First, the four retained frozen samples were thawed and four equivalent freeze-dried samples were reconstituted with distilled water. The pH of all eight samples was measured with the following results:

Table I

	Sample	Frozen(A)pH	Freeze-dried(B)pH
Exp. 4, Solution 1	(1)	8.24	8.32
Exp. 4, Solution 1 & Glutathione	(2)	7.99	8.23
Exp. 5, Solution 1	(3)	8.15	8.26
Exp. 5, Solution 1 & Glutathione & Na_2HPO_4	(4)	8.10	8.33

It was observed that Sample 4-B did not dissolve as rapidly as the other samples, presumably because of "caking" of the phosphate in its anhydrous state.

Next, three samples each of the freeze-dried complete solution (Samples 2 and 4) were reconstituted with exactly 12mls of distilled water and the final pH checked.

Table II

	Sample	pH		
		1	2	3
Exp. 4, Solution 1 & Glutathione	(2)	8.26	8.21	8.27
Exp. 5, Solution 1 & Glutathione & Na_2HPO_4	(4)	8.28	8.25	8.27

Mixture 2 went easily into solution whereas Mixture 4 took five minutes to completely dissolve.

In conclusion as to Experiment 5, in both Experiments 3 and 4, there was an increase in the final pH after freeze-drying which indicates some slight loss of CO_2 during the process. The fact that the samples without glutathione showed a loss, although somewhat smaller, shows that the bicarbonate is inherently unstable - as is well known - and it will probably be necessary to match the Solution 1 to the freeze dried component in each lot in a production environment in order to produce a consistent pH in the final mixture. There was no marked difference in the apparant bicarbonate stability between the two experiments. In view of the solution difficulty with Experiment 4 material, it seems reasonable to concentrate on the Experiment 3 approach, i.e., using the $NaHCO_3$ and Na_2HPO_4 in Solution B-1 with only the glutathione in Solution B-2. This should help with any possible instability of the glutathione in an alkaline pH.

EXPERIMENT 6

The purpose of this experiment was to now determine whether a Solution A could be formulated with a Solution B-1 from Experiment 3 successfully. Again, it should be kept in mind the purpose of the line of experiments (Exp. 1-6) is to determine whether a solution having a final pH of approximately 7.4 when Solution B is dissolved into it can be attained and whether such pH will remain stable.

A 250ml bottle of Solution A from Experiment 1 at a pH of 2.9 was used. A vial of freeze-dried Solution B actually Solution B-1 from Experiment 3) was added and the pH checked at 7.65. A small amount (0.2ml) of 0.5 N HCl was added resulting in a pH of 7.54. A further small amount (0.2ml) of 0.5 N HCl was added providing a pH of 7.4. Thereafter, 0.4ml of .5 N HCl was added to a bottle (265ml) of pH 2.9 Solution A giving a pH of 2.58. When a vial of Solution B (actually Solution B-1 from Experiment 3) was added to this solution, there resulted a final mixture having a pH of 7.41. Four additional bottles of Solution A initially having a pH of 4.1 (Lot 2A) were similarly adjusted to pH values around 2.6 with the following results when mixed with vials of Solution B from either Experiment 3 or Experiment 4.

Table I

Final pH of Solution 1 + vial	pH After			
	5 min.	1 hr.	3 hr.	24 hr.
2.53 + Solution B (Exp. 3)	7.2	7.22	7.32	7.4
2.60 + Solution B (Exp. 3)	7.36	7.33	7.36	7.42
2.65 + Solution B (Exp. 4)	7.45	7.4	7.4	7.51
2.80 + Solution B (Exp. 4)	7.65	7.59	7.67	7.73

After 48 hours, there were obvious signs of degradation with deposits forming and in the case of the two higher pH values a strong smell of H_2S presumably from glutathione degradation. The two lower pH solutions appeared more stable, with less deposit and no odor.

In conclusion:

1. The bicarbonate phosphate in the first solution with glutathione only in the smaller second portion is the choice because it affords a better chance of stability for the glutathione with the lower pH and there is no problem of phosphate solubility when it is reconstituted.
2. A final pH of about 7.3 can be achieved by adjusting the chloride solution (Solution A) to about pH 2.6. The higher pH of the final solution appears to be less stable and it appears preferable to hold the final pH to or below 7.4.

EXPERIMENT 7

A pilot batch of the enhanced balanced salt solution in accordance with the above invention was produced to confirm the conclusion set forth in the experiments above. A 15 liter batch of Solution A was prepared as follows:

14 liters of WFI (distilled water which has been tested and qualified for injection) were measured into a graduated container and 107.1g of NaCl was dissolved therein.

1 liter of WFI had dissolved therein 22.7g KCl; 9.24g $CaCl_2$; and 12.00g of $MgCl_2$.

250ml of the potassium/calcium/magnesium solution was added to the 14 liters of the NaCl solution and the volume was made up to 15 liters by the addition of further WFI. The initial pH of Solution A was 6.03 and was lowered by the addition of 1 N HCl as follows:

9ml	HCl	pH 3.02
+4ml	HCl	pH 2.80
+6ml	HCl	pH 2.67
+6ml	HCl	pH 2.57

At this point, and after thorough mixing, the solution was filled into 250ml plastic bottles, stoppered, capped and sterilized with Dispersa Balansalt.

Solution B was prepared for freeze-drying in such a way that 10ml of the B-1 solution was frozen and then 1ml of the H-2 solution was added on top of of the surface of the B-1 solution. Solution B-1 was prepared by dissolving 22.0g of dextrose in 1 liter WFI. Approximately 800ml of this solution was transferred and had dissolved in it 50g of $NaHCO_3$ and 9.9g of Na_2HPO_4. Additional amount of the dextrose WFI was added to make up 900ml and equally distributed throughout 30ml vials at 10ml per vial and frozen. This made 90 samples.

90ml of the remaining dextrose solution was transferred to a flask and in it was dissolved 4.4g of glutathione disulphide. This glutathione disulphide solution was chilled to near freezing and 1ml thereof was added to each of the 90 frozen 10ml aliquots of the bicarbonate solution. The vials were immediately returned to the freezer and they were subsequently freeze-dried without allowing the material to thaw. Five frozen samples were retained as control samples and 85 were sent for freeze-drying.

After freeze-drying, five vials were taken and the contents mixed with each of the five bottles of Solution A at the pH of the mixtures were measured immediately and after one hour, six hours, and 24 hours, all at room temperature. The following results were obtained:

Sample		pH Value				
2mm		1 Hr.	5 Hrs.	24 Hrs.	48 Hrs.	72 Hrs.
1	7.35	7.40	7.50	7.50	7.40	7.60
2	7.40	7.40	7.45	7.50	7.40	7.60
3	7.35	7.40	7.45	7.45	7.40	7.60
4	7.40	7.40	7.40	7.45	7.50	7.60
5	7.40	7.40	7.50	7.50	7.55	7.65

From the preliminary pH measurements, it appears that the process used gives reproducible results and

that the mixed product is at least as stable as any other glutathione/bicarbonate/Ringer solution product on the market.

Claims

1. A tissue irrigating solution comprising:
   a) a first part including an acidic solution containing calcium ions and magnesium ions;
   b) a second part including a lyophilized powder containing sodium bicarbonate and glutathione;
   c) sodium ions, potassium ions, and dextrose, each being included in one of said first and second parts;
   d) said first and second parts when mixed together form a solution for irrigating body tissues during surgery.

2. The irrigating solution according to Claim 1 wherein said first part includes said sodium ions and said potassium ions, and said second part includes said dextrose.

3. The irrigating solution according to Claim 2 wherein said second part further includes sodium hydrogen phosphate.

4. The irrigating solution according to Claim 1 wherein said first part is steam-sterilized.

5. The irrigating solution according to Claim 1 wherein said first part and said second part are packaged in propylene bottles.

6. The irrigating solution according to Claim 3 wherein said solution includes ingredients in the following relation:

Ingredients for Enhanced Balanced Salt Solution

	mg /ml
Sodium chloride	7.14
Potassium chloride (KCl)	0.378
Calcium chloride ($CaCl_2$ $2H_2O$)	0.154
Magnesium chloride ($MgCl_2$ $6H_2O$)	0.20
Dextrose	0.916
Sodium carbonate ($NaHCO_3$)	2.096
Sodium hydrogen phosphate (Na_2HPO_4)	0.415
Glutathione disulphide	0.184

7. The irrigating solution according to Claim 3 wherein said first part of said solution includes ingredients in the following relation:

that the mixed product is at least as stable as any other glutathione/bicarbonate/Ringer solution product on the market.

Claims

1. A tissue irrigating solution comprising:
   a) a first part including an acidic solution containing calcium ions and magnesium ions;
   b) a second part including a lyophilized powder containing sodium bicarbonate and glutathione;
   c) sodium ions, potassium ions, and dextrose, each being included in one of said first and second parts;
   d) said first and second parts when mixed together form a solution for irrigating body tissues during surgery.

2. The irrigating solution according to Claim 1 wherein said first part includes said sodium ions and said potassium ions, and said second part includes said dextrose.

3. The irrigating solution according to Claim 2 wherein said second part further includes sodium hydrogen phosphate.

4. The irrigating solution according to Claim 1 wherein said first part is steam-sterilized.

5. The irrigating solution according to Claim 1 wherein said first part and said second part are packaged in propylene bottles.

6. The irrigating solution according to Claim 3 wherein said solution includes ingredients in the following relation:

Ingredients for Enhanced Balanced Salt Solution

	mg /ml
Sodium chloride	7.14
Potassium chloride (KCl)	0.378
Calcium chloride ($CaCl_2$ $2H_2O$)	0.154
Magnesium chloride ($MgCl_2$ $6H_2O$)	0.20
Dextrose	0.916
Sodium carbonate ($NaHCO_3$)	2.096
Sodium hydrogen phosphate (Na_2HPO_4)	0.415
Glutathione disulphide	0.184

7. The irrigating solution according to Claim 3 wherein said first part of said solution includes ingredients in the following relation:

* C L M S *

Formula 1 (Solution)

Ingredients	mg /ml
Sodium chloride (NaCl)	7.14
Potassium chloride (KCl)	0.378
Calcium chloride ($CaCl_2$ $2H_2O$)	0.154
Magnesium chloride ($MgCl_2$ $6H_2O$)	0.20

and wherein said second part includes ingredients in the following relation:

Formula 2 (Powder)

Ingredients	Percentage by Weight
Dextrose	25.3
$NaHCO_3$	58.04
Na_2HPO_4	11.49
Glutathione disulphide	5.10

8. The irrigating solution according to Claim 7 wherein the pH of the the first part is no greater than 2.8 and the pH of the final solution, when mixed, is no greater than 7.6.

9. A tissue irrigating product comprising:
   a) a first part including a stable sterile prepackaged acidic solution containing calcium ions and magnesium ions;
   b) a second part including a lyophilized powder containing sodium bicarbonate;
   c) sodium ions, potassium ions, and dextrose, each being included in one of said first and second parts;
   d) means for aseptically mixing said acidic solution and said lyophilized powder;
   e) said first and second parts, when mixed together, form a solution for irrigating body tissues during surgery.

10. The irrigating product according to Claim 9 wherein said first part includes said sodium ions and said potassium ions and said second part includes said dextrose.

11. The irrigating product according to Claim 10 wherein said second part further includes sodium hydrogen phosphate.

12. The irrigating product according to Claim 9 wherein said first part is steam-sterilized.

13. The irrigating product according to Claim 9 wherein said first part and said second part are packaged in polypropylene bottles and there is further included a double-ended mixing spike.

14. The irrigating product according to Claim 11 wherein said solution includes ingredients in the following relation:

* C L M S *

Ingredients for Enhanced Balanced Salt Solution

	mg /ml
Sodium chloride	7.14
Potassium chloride (KCl)	0.378
Calcium chloride ($CaCl_2$ $2H_2O$)	0.154
Magnesium chloride ($MgCl_2$ $6H_2O$)	0.20
Dextrose	0.916
Sodium carbonate ($NaHCO_3$)	2.096
Sodium hydrogen phosphate (Na_2HPO_4)	0.415
Glutathione disulphide	0.184

15. The irrigating product according to Claim 11 wherein said first part includes ingredients in the following relation:

Formula 1 (Solution)

Ingredients	mg /ml
Sodium chloride (NaCl)	7.14
Potassium chloride (KCl)	0.378
Calcium chloride ($CaCl_2$ $2H_2O$)	0.154
Magnesium chloride ($MgCl_2$ $6H_2O$)	0.20

and wherein said second part includes ingredients in the following relation:

Formula 2 (Powder)

Ingredients	Percentage by Weight
Dextrose	25.3
$NaHCO_3$	58.04
Na_2HPO_4	11.49
Glutathione disulphide	5.10

16. The irrigating product according to Claim 15 wherein the pH of said first part is no greater than 2.8 and the pH of the final solution is no greater than 7.6.

17. A method for preparing a prepackaged tissue irrigating solution comprising the steps of:
a) preparing an aqueous solution containing at least calcium ions and magnesium ions in distilled water;
b) preparing an aqueous dextrose solution having dissolved therein at least sodium bicarbonate and glutathione;
c) lyophilizing the solution of step (b);
d) packaging the solution of step (a) and the lyophilized powder of step (c) separately.

* C L M S *

18. The method according to Claim 17 wherein sodium ions and potassium ions are also introduced into the aqueous solution of step (a).

19. The method according to Claim 17 wherein the aqueous solution of step (a) is steam-sterilized.

20. The method according to Claim 18 wherein step (b) includes forming a first dextrose solution of said sodium bicarbonate and sodium hydrogen phosphate and a second dextrose solution containing said glutathione.

21. The method according to Claim 20 wherein step (c) includes freezing said first dextrose solution, then chilling said glutathione/dextrose solution to substantially the freezing point and introducing it onto the surface of the first dextrose solution immediately prior to the time the second dextrose/glutathione solution freezes, then freeze-drying the resulting combination of the frozen first solution and frozen second solution.

22. The method according to Claim 17 wherein the pH of the aqueous solution of step (a) is lowered to a point not exceeding 2.6 by adding hydrochloric acid thereto.

Patentansprüche

1. Gewebe-Berieselungslösung, gekennzeichnet durch:
   a) einen ersten Bestandteil, zu dem eine acidische Lösung gehört, die Kalziumionen und Magnesiumionen enthält;
   b) einen zweiten Bestandteil, zu dem ein gefriergetrocknetes Pulver gehört, das Natriumbikarbonat und Glutathion enthält;
   c) Natriumionen, Kaliumionen und Dextrose, die jeweils in einem der genannten ersten und zweiten Bestandteile enthalten sind;
   d) wobei die genannten ersten und zweiten Bestandteile, nachdem sie miteinander vermischt worden sind, eine Lösung zum Bespülen von Körpergeweben während chirurgischer Eingriffe ergeben.

2. Berieselungslösung nach Anspruch 1, dadurch gekennzeichnet, daß der genannte erste Bestandteil die genannten Natriumionen und die genannten Kaliumionen enthält und daß der genannte zweite Bestandteil die genannte Dextrose enthält.

3. Berieselungslösung nach Anspruch 2, dadurch gekennzeichnet, daß der genannte zweite Bestandteil außerdem Natriumhydrogenphosphat enthält.

4. Berieselungslösung nach Anspruch 1, dadurch gekennzeichnet, daß der genannte erste Bestandteil dampfsterilisiert ist.

5. Berieselungslösung nach Anspruch 1, dadurch gekennzeichnet, daß der genannte erste Bestandteil und der genannte zweite Bestandteil in Propylenflaschen verpackt sind.

6. Berieselungslösung nach Anspruch 3, dadurch gekennzeichnet, daß die genannte Lösung Inhaltsstoffe in folgendem Verhältnis enthält:

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Inhaltsstoffe für die verstärkte gleichgewichtige Salzlösung:

	mg/ml
Natriumchlorid	7,14
Kaliumchlorid (KCl)	0,378
Kalziumchlorid ($CaCl_2$ $2H_2O$)	0,154
Magnesiumchlorid ($MgCl_2$ $6H_2O$)	0,20
Dextrose	0,916
Natriumkarbonat ($NaHCO_3$)	2,096
Natriumhydrogenphosphat (Na_2HPO_4)	0,415
Glutathiondisulfid	0,184

7. Berieselungslösung nach Anspruch 3, dadurch gekennzeichnet, daß der genannte erste Bestandteil der genannten Lösung Inhaltsstoffe in folgendem Verhältnis enthält:

Formel 1 (Lösung)

Inhaltsstoffe	mg/ml
Natriumchlorid (NaCl)	7,14
Kaliumchlorid (KCl)	0,378
Kalziumchlorid ($CaCl_2$ $2H_2O$)	0,154
Magnesiumchlorid ($MgCl_2$ $6H_2O$)	0,20

und daß der genannte zweite Bestandteil Inhaltsstoffe in folgendem Verhältnis enthält:

Formel 2 (Pulver)

Inhaltsstoffe	Gewichtsprozent
Dextrose	25,3
$NaHCO_3$	58,04
Na_2HPO_4	11,49
Glutathiondisulfid	5,10

8. Berieselungslösung nach Anspruch 7, dadurch gekennzeichnet, daß der pH-Wert des ersten Bestandteils nicht größer ist als 2,8 und daß der pH-Wert der endgültigen Lösung nach dem Vermischen nicht größer ist als 7,6.

9. Gewebe-Berieselungsprodukt, gekennzeichnet durch:
a) einen ersten Bestandteil, zu dem eine stabile, sterile, vorverpackte acidische Lösung gehört, die Kal-

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ziumionen und Magnesiumionen enthält;
b) einen zweiten Bestandteil, zu dem ein gefriergetrocknetes Pulver gehört, das Natriumbikarbonat enthält;
c) Natriumionen, Kaliumionen und Dextrose, die jeweils in einem der genannten ersten und zweiten Bestandteile enthalten sind;
d) Einrichtungen zum aseptischen Vermischen der genannten acidischen Lösung und des genannten gefriergetrockneten Pulvers;
e) wobei der erste und der zweite Bestandteil, nachdem sie miteinander vermischt worden sind, eine Lösung zum Bespülen von Körpergeweben während chirurgischer Eingriffe ergeben.

10. Berieselungsprodukt nach Anspruch 9, dadurch gekennzeichnet, daß der genannte erste Bestandteil die genannten Natriumionen und die genannten Kaliumionen enthält und daß der genannte zweite Bestandteil die genannte Dextrose enthält.

11. Berieselungsprodukt nach Anspruch 10, dadurch gekennzeichnet, daß der genannte zweite Bestandteil außerdem Natriumhydrogenphosphat enthält.

12. Berieselungsprodukt nach Anspruch 9, dadurch gekennzeichnet, daß der genannte erste Bestandteil dampfsterilisiert ist.

13. Berieselungsprodukt nach Anspruch 9, dadurch gekennzeichnet, daß der genannte erste Bestandteil und der genannte zweite Bestandteil in Polypropylenflaschen verpackt sind und daß außerdem ein doppelseitiger Mischdorn (mixing spike) vorhanden ist.

14. Berieselungsprodukt nach Anspruch 11, dadurch gekennzeichnet, daß die genannte Lösung Inhaltsstoffe in folgendem Verhältnis enthält:

Inhaltsstoffe für die verstärkte gleichgewichtige Salzlösung:	mg/ml
Natriumchlorid	7,14
Kaliumchlorid (KCl)	0,378
Kalziumchlorid ($CaCl_2$ $2H_2O$)	0,154
Magnesiumchlorid ($MgCl_2$ $6H_2O$)	0,20
Dextrose	0,916
Natriumkarbonat ($NaHCO_3$)	2,096
Natriumhydrogenphosphat (Na_2HPO_4)	0,415
Glutathiondisulfid	0,184

15. Berieselungsprodukt nach Anspruch 11, dadurch gekennzeichnet, daß der erste Bestandteil Inhaltsstoffe in folgendem Verhältnis enthält:

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Formel 1 (Lösung)

Inhaltsstoffe	mg/ml
Natriumchlorid (NaCl)	7,14
Kaliumchlorid (KCl)	0,378
Kalziumchlorid ($CaCl_2$ $2H_2O$)	0,154
Magnesiumchlorid ($MgCl_2$ $6H_2O$)	0,20

und daß der genannte zweite Bestandteil Inhaltsstoffe in folgendem Verhältnis enthält:

Formel 2 (Pulver)

Inhaltsstoffe	Gewichtsprozent
Dextrose	25,3
$NaHCO_3$	58,04
Na_2HPO_4	11,49
Glutathionsulfid	5,10

16. Berieselungsprodukt nach Anspruch 15, dadurch gekennzeichnet, daß der pH-Wert des ersten Bestandteils nicht größer als 2,8 ist und daß der pH-Wert der endgültigen Lösung nicht größer als 7,6 ist.

17. Verfahren zum Herstellen einer vorverpackten Gewebe-Berieselungslösung, gekennzeichnet durch folgende Schritte:
a) Herstellen einer wäßrigen Lösung, die mindestens Kalziumionen und Magnesiumionen in destilliertem Wasser enthält;
b) Herstellen einer wäßrigen Dextroselösung, in der mindestens Natriumbikarbonat und Glutathion gelöst sind;
c) Gefriertrocknen der Lösung nach Schritt (b);
d) Getrenntes Verpacken der Lösung nach Schritt (a) und des gefriergetrockneten Pulvers nach Schritt (c).

18. Verfahren nach Anspruch 17, dadurch gekennzeichnet, daß der wäßrigen Lösung nach Schritt (a) außerdem Natriumionen und Kaliumionen zugesetzt werden.

19. Verfahren nach Anspruch 17, dadurch gekennzeichnet, daß die wäßrige Lösung nach Schritt (a) dampfsterilisiert wird.

20. Verfahren nach Anspruch 18, dadurch gekennzeichnet, daß zu dem Schritt (b) die Herstellung einer ersten Dextroselösung des genannten Natriumbikarbonats und Natriumhydrogenphosphats sowie einer zweiten Dextroselösung gehört, die das genannte Glutathion enthält.

21. Verfahren nach Anspruch 20, dadurch gekennzeichnet, daß zu dem Schritt (c) das Gefrieren der genannten ersten Dextroselösung gehört, sodann das Abkühlen der genannten Glutathion/Dextrose-Lösung im wesentlichen auf den Gefrierpunkt, das Aufbringen der letzteren Lösung auf die Oberfläche der ersten Dextroselösung unmittelbar vor dem Zeitpunkt, in dem die zweite Dextrose/Glutathion-Lösung gefriert, woraufhin die Kombination aus der gefrorenen ersten Lösung und der gefrorenen zweiten Lösung gefriergetrocknet wird.

22. Verfahren nach Anspruch 17, dadurch gekennzeichnet, daß der pH-Wert der wäßrigen Lösung nach

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Schritt (a) durch Hinzufügen von Salzsäure auf einen Wert gesenkt wird, der 2,6 nicht übersteigt.

Revendications

1. Solution pour irriguer un ou des tissus, cette solution comprenant :
   a) une première partie englobant une solution acide contenant des ions calcium et des ions magnésium ;
   b) une seconde partie englobant une poudre lyophilisée contenant du bicarbonate de sodium et du glutathion ;
   c) des ions sodium, des ions potassium et du dextrose, chacun étant inclus dans l'une desdites première et seconde parties ;
   d) lesdites première et seconde parties formant, lorsqu'elles sont mélangées ensemble, une solution pour irriguer des tissus du corps pendant une opération chirurgicale.

2. Solution pour irrigation selon la revendication 1, dans laquelle ladite première partie comprend lesdits ions sodium et lesdits ions potassium, et ladite seconde partie comprend ledit dextrose.

3. Solution pour irrigation selon la revendication 2, dans laquelle ladite seconde partie comprend en outre de l'hydrogénophosphate de sodium.

4. Solution pour irrigation selon la revendication 1, dans laquelle ladite première partie est stérilisée à la vapeur d'eau.

5. Solution pour irrigation selon la revendication 1, dans laquelle ladite première partie et ladite seconde partie sont emballées ou "conditionnées" dans des bouteilles en (poly)propylène.

6. Solution pour irrigation selon la revendication 3, dans laquelle ladite solution comprend des ingrédients selon la relation suivante :

Ingrédients pour une solution à équilibre amplifié entre des sels

	mg/ml
Chlorure de sodium	7,14
Chlorure de potassium (KCl)	0,378
Chlorure de calcium ($CaCl_2.2H_2O$)	0,154
Chlorure de magnésium ($MgCl_2.6H_2O$)	0,20
Dextrose	0,916
Carbonate de sodium ($NaHCO_3$)	2,096
Hydrogénophosphate de sodium (Na_2HPO_4)	0,415
Disulfure de glutathion	0,184

7. Solution pour irrigation selon la revendication 3, dans laquelle ladite première partie de ladite solution comprend des ingrédients (présents) selon la relation suivante :

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Formule 1 (solution)

Ingrédients	mg/ml
Chlorure de sodium (NaCl)	7,14
Chlorure de potassium (KCl)	0,378
Chlorure de calcium ($CaCl_2.2H_2O$)	0,154
Chlorure de magnésium ($MgCl_2.6H_2O$)	0,20

et dans laquelle ladite seconde partie comprend des ingrédients (présents) selon la relation suivante :

Formule 2 (poudre)

Ingrédients	% en poids
Dextrose	25,3
$NaHCO_3$	58,04
Na_2HPO_4	11,49
Disulfure de glutathion	5,10

8. Solution pour irrigation selon la revendication 7, dans laquelle le pH de la première partie n'est pas supérieur à 2,8 et le pH de la solution finale n'est pas supérieur, après mélangeage, à 7,6.

9. Produit pour irrigation de tissu(s), ce produit comprenant :
   a) une première partie, englobant une solution acide pré-emballée, stérile et stable, contenant des ions calcium et des ions magnésium ;
   b) une seconde partie, englobant une poudre lyophilisée contenant du bicarbonate de sodium ;
   c) des ions sodium, des ions potassium et du dextrose, chacun étant inclus dans l'une desdites première et seconde parties ;
   d) un moyen pour mélanger de manière aseptique ladite solution acide et ladite poudre lyophilisée ;
   e) lesdites première et seconde parties formant, lorsqu'elles sont mélangées ensemble, une solution pour irriguer des tissus du corps pendant une opération chirurgicale.

10. Produit pour irrigation selon la revendication 9, dans lequel ladite première partie comprend lesdits ions sodium et lesdits ions potassium, et ladite seconde partie comprend ledit dextrose.

11. Produit pour irrigation selon la revendication 10, dans lequel ladite seconde partie comprend en outre de l'hydrogénophosphate de sodium.

12. Produit pour irrigation selon la revendication 9, dans lequel ladite première partie est stérilisée à la vapeur d'eau.

13. Produit pour irrigation selon la revendication 9, dans lequel ladite première partie et ladite seconde partie sont emballées ("conditionnées") dans des bouteilles en polypropylène, et il y est également inclus un organe creux de liaison, à double extrémité pointue, pour mélangeage.

14. Produit pour irrigation selon la revendication 11, dans lequel ladite solution comprend des ingrédients (présents) selon la relation suivante :

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Ingrédients pour une solution à équilibre amplifié entre des sels

	mg/ml
Chlorure de sodium	7,14
Chlorure de potassium (KCl)	0,378
Chlorure de calcium ($CaCl_2.2H_2O$)	0,154
Chlorure de magnésium ($MgCl_2.6H_2O$)	0,20
Dextrose	0,916
Carbonate de sodium ($NaHCO_3$)	2,096
Hydrogénophosphate de sodium (Na_2HPO_4)	0,415
Disulfure de glutathion	0,184

15. Produit pour irrigation selon la revendication 11, dans lequel ladite première partie comprend des ingrédients (présents) selon la relation suivante :

Formule 1 (solution)

Ingrédients	mg/ml
Chlorure de sodium (NaCl)	7,14
Chlorure de potassium (KCl)	0,378
Chlorure de calcium ($CaCl_2.2H_2O$)	0,154
Chlorure de magnésium ($MgCl_2.6H_2O$)	0,20

et dans laquelle ladite seconde partie comprend des ingrédients (présents) selon la relation suivante :

Formule 2 (poudre)

Ingrédients	% en poids
Dextrose	25,3
$NaHCO_3$	58,04
Na_2HPO_4	11,49
Disulfure de glutathion	5,10

16. Produit pour irrigation selon la revendication 15, dans lequel le pH de ladite première partie n'est pas supérieur à 2,8 et le pH de la solution finale n'est pas supérieur à 7,6.

17. Procédé pour préparer une solution pré-emballée pour irriguer des tissus, le procédé comprenant les étapes consistant à :
    a) préparer une solution aqueuse contenant au moins des ions calcium et des ions magnésium dans de l'eau distillée ;
    b) préparer une solution aqueuse de dextrose comportant en dissolution au moins du bicarbonate de sodium et du glutathion ;
    c) lyophiliser la solution de l'étape b) ;
    d) "conditionner" ou emballer séparément la solution de l'étape a) et la poudre lyophilisée de l'étape c).

18. Procédé selon la revendication 17, dans lequel des ions sodium et des ions potassium sont également introduits dans la solution aqueuse de l'étape a).

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19. Procédé selon la revendication 17, dans lequel la solution aqueuse de l'étape a) est stérilisée à la vapeur d'eau.

20. Procédé selon la revendication 18, dans lequel l'étape b) comprend la formation d'une première solution de dextrose contenant ledit bicarbonate de sodium et l'hydrogénophosphate de sodium, et la formation d'une seconde solution de dextrose contenant ledit glutathion.

21. Procédé selon la revendication 20, dans lequel l'étape c) comprend la congélation de ladite première solution de dextrose, puis le refroidissement rapide de ladite solution de glutathion/dextrose sensiblement jusqu'au point de congélation et l'introduction de cette dernière solution à la surface de la première solution de dextrose immédiatement avant le moment où la seconde solution de dextrose/glutathion se congèle, puis la lyophilisation de la combinaison résultante de la première solution congelée et de la seconde solution congelée.

22. Procédé selon la revendication 17, dans lequel on abaisse, par addition d'acide chlorhydrique, le pH de la solution aqueuse de l'étape a) jusqu'à un point n'excédant pas 2,6.

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