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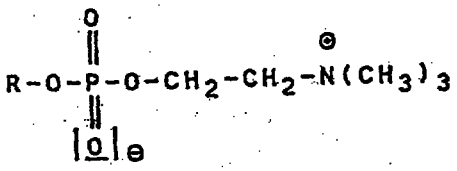
Stabilised hexadecylphosphocholine solutions in glycerol alkyl ethers

Description

Alkylphosphoric acid compounds are known substances with anti-tumour effects. German published patent 33 43 530.8 discloses the anti-tumour effect and the preparatory presentation of the compounds. Water or physiologically acceptable organic solvents such as glycerol alkyl ether are used as solvents for these active substances.

It has, for example, been found favourable for topical application to use the active substance together with at least one alkyl glycerol with 2-12 carbon atoms in the alkyl radical that may be present in the form of an ether group bound to one of the primary or secondary OH groups of the glycerol. Alkyl glycerols of this type raise or improve the effect of alkylphosphoric acid compounds. Preference is given here to alkyl glycerols with 3-9 carbon atoms used alone or in mixtures. Particularly favourable effects are therefore displayed by a medicament containing

a) one or several alkylphosphoric acid compounds of the general formula I



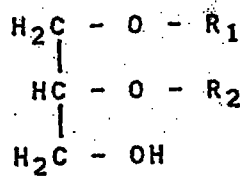
I

R represents an alkyl group with 12-20 carbon atoms which may optionally contain a double bond or a triple bond

b) an alkyl glycerol of the general formula II

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II

in which one of the radicals R_1 and R_2 represents an alkyl group with 2 to 12 carbon atoms and the other radical represents a hydrogen atom, as well as optionally additional conventional additives and dilutants.

It is preferable to consider a mixture of water and an alkyl glycerol mixture of nonyl or octyl glycerol, hexyl or pentyl glycerol and propyl or ethyl glycerol. An appropriate formulation for topical application contains for example 1-100 mg alkylphosphoric acid compound per ml alkyl glycerol or a corresponding alkyl glycerol mixture with water.
A mixture of this type is hereinafter also referred to as cascade.
Alkyl glycerol-water mixtures containing, for example, nonyl glycerol, hexyl glycerol, propyl glycerol are for example preferred. Such mixtures preferably contain 3 of the glycerol ethers mentioned, namely a lower (propyl), a medium (hexyl) and a higher (nonyl), the amounts by weight of the lower ether being approximately as much as the sum of the amounts by weight of the two other glycerol ethers. The amount of water is about the same as the amount of the lower glycerol ether and is for example half the total amount of the glycerol ethers present.
Examples of this type of glycerol ether / water mixtures are listed hereinbelow:

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	Water	Glycerol propyl ether	Glycerol hexyl ether	Glycerol nonyl ether
Parts by weight	2 :	2 :	1 :	1

	Water	Glycerol ethyl ether	Glycerol pentyl ether	Glycerol octyl ether
Parts by weight	2 :	2 :	1 :	1

In addition to water it is also possible to utilize all solvents usable for topical medicaments.

A particular favourable carrier mixture for the alkylphosphoric acid compound hexadecylphosphocholine consists of a mixture of about 4 parts by weight of water, 4 parts by weight of propyl glycerol and 2 parts by weight each of hexyl glycerol and nonyl glycerol.

It is not necessary to add preservatives to solutions of this type since microbiological load tests showed these solutions to have optimum antiseptic properties.

A 6 % hexadecylphosphocholine solution is for example composed as follows:

hexadecylphosphocholine	0.600 g
glycerol-1-n-propyl ether	3.145 g
glycerol-1-n-hexyl ether	1.570 g
glycerol-1-n-nonyl ether	1.570 g
water	3.145 g
	10.030 g = 10 ml

It was regrettably found during stability storage that oxidative processes cause peroxides to be formed in the solution which later lead to acids and hence a drop in pH due to further decomposition. The pH value was set at 4-6 in the specification.

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pH and peroxide number of a 6 % hexadecylphosphocholine solution in cascade (untreated)

	-4°C	+2°C	RT	31°C	41°C
Initial investigation					
pH value			5.6		
peroxide number			0.4		
3 months					
pH value	5.0	5.0	4.0	3.6	3.3
peroxide number	0.81	0.95	0.91	3.6	6.0
6 months					
pH value	7.4	6.0	3.8	3.5	3.1
peroxide number	0.55	0.18	1.9	4.9	7.8

To control peroxide formation hexadecylphosphocholine cascade solutions were gassed with nitrogen and covered with nitrogen after filling into 10 ml bottles. An attempt was also made to prevent peroxide formation by adding antioxidants. pH and peroxide number in a 6 % hexadecylphosphocholine solution in cascade (after gassing with nitrogen)

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	-4°C	+2°C	RT	31°C	41°C
Initial investigation					
pH value			4.6		
peroxide number			0.0		
3 months					
pH value	4.6	5.0	4.2	3.9	3.6
peroxide number	0.1	0.11	0.97	0.94	5.1
6 months					
pH value	4.5	4.4	4.1	3.9	3.5
peroxide number	0.0	0.0	1.73	1.1	4.6

RT = room temperature

As may be seen, the pH value falls and the peroxide content rises in this case, too.
As shown in the following table, the addition of antioxidants did not bring any improvement.

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pH value of hexadecylphosphocholine cascade solutions with addition of antioxidants

With 0.1 % sodium disulfite

	-4°C	+2°C	RT	31°C	41°C
Initial pH value					
3-month pH value	3.8	3.7	3.3	3.1	2.8

With 0.01 % ascorbyl palmitate and 0.05 % α-tocopherol

	-4°C	+2°C	RT	31°C	41°C
Initial pH value			3.8		
3-month pH value	3.8	3.7	3.3	3.1	2.8

Experiments have confirmed that the conventional formulation is not storage stable.
The use of conventional agents to suppress peroxide formation, such as gassing with nitrogen to remove the oxygen from the solution, and the addition of antioxidants did not lead to storage stable solutions.

In an experiment a citrate buffer system was added in addition to the antioxidant sodium disulfite. It was then found that the pH value could be maintained within the specification.

pH value of miltefosine cascade solutions with added 0.1 % sodium disulfite and citrate buffer (0.1 molar in the water phase)

	-4°C	+2°C	RT	31°C	41°C
Initial pH value			5.6		
3-month pH value	5.6	5.6	5.3	5.1	5.2

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Since sodium disulfide did not exert any positive influence as an antioxidant, a miltefosine cascade solution was prepared containing only citrate buffer to reduce the peroxide formation.

It was surprisingly found that the addition of buffer was able to suppress the peroxide formation and thus a fall in the pH value.

Hexadecylphosphocholine cascade solution with citrate buffer

	-4°C	+2°C	RT	31°C	41°C
initial pH value			5.8		
peroxide number			0.58		
3 months					
pH value	5.8	5.8	5.8	5.8	5.7
peroxide number	0.33	0.29	0.41	0.51	0.58
6 months					
pH value	5.8	5.8	5.8	5.7	5.6
peroxide number	0.02	0.39	0.11	0.36	0.54
12 months					
pH value	5.8	5.8	5.7	5.6	5.3
peroxide number	0.06	0.04	0.18	0.11	0.3

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10 ml of a 6 % buffered hexadecylphosphocholine cascade solution are composed as follows:

hexadecylphosphocholine	0.6000 g
D,L-glycerol-1-n-propyl ether	3.1600 g
D,L-glycerol-1-n-hexyl ether	1.5800 g
D,L-glycerol-1-n-nonyl ether	1.5800 g
citric acid anhydrous	0.0484 g
sodium hydroxide	0.0227 g
purified water	3.0889 g
	10.0800 g = 10 ml

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The following mixtures are additional suitable buffer mixtures: mixtures of
disodium hydrogen phosphate/citric acid,
succinic acid/sodium hydroxide,
potassium dihydrogen phosphate/disodium hydrogen phosphate
sodium hydrogen maleate/sodium hydroxide,
tris-maleate/sodium hydroxide,
potassium dihydrogen phosphate/sodium hydroxide.
A mixture of citric acid and sodium hydroxide of pH value 5.3 is particularly preferred.

Example 1

Buffered 6 % (W/V) hexadecylphosphocholine solution for topical application

Hexadecylphosphocholine solution is prepared by dissolving hexadecylphosphocholine in a buffered solvent termed a cascade. 6.27 kg DL-glycerol-1-ethyl ether, 3.135 kg DL-glycerol-1-n-pentyl ether and 3.135 kg DL-glycerol-1-n-octyl ether are mixed and 1.19 kg hexadecylphosphocholine dissolved in this mixture.

Preparation of citrate buffer pH 5.3
0.0965 kg citric acid anhydrous are dissolved in 5.8 kg purified water and 0.047 sodium hydroxide in 0.3 kg purified water. The sodium hydroxide solution is now added to the citric acid solution until a pH value of 5.3 is reached. Water is then added to make up to 6.27 kg. 6.27 kg citrate buffer are now combined with 13.73 kg solution of the hexadecylphosphocholine in the ether mixture. A uniform solution is obtained with nitrogen gassing. The solution is filtered through a membrane filter, pore size 0.2 µm, filled in 10 ml portions into brown dropper bottles and closed with pipette and protective cap.

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* C L M S *

Stabilised hexadecylphosphocholine solutions in glycerol alkyl ethers

Claims

1. A solution of one or several alkylphosphocholines and glycerol ethers according to formula I in water, characterised in that a buffer solution is added.

2. A solution according to Claim 1, characterised in that a solution of citric acid and sodium hydroxide in water is used as buffer solution.

3. A solution according to Claim 1, characterised in that the pH value of the solution lies between 4 pH and 6 pH.

4. A process for the preparation of a solution according to Claim 1, characterised in that one or several alkylphosphocholines according to Formula I in a mixture of glycerol-1-n-alkyl ethers according to Formula II are dissolved in water and a buffer solution added so that a pH value of 4 pH to 6 pH is reached.

5. A process according to Claim 4, characterised in that a solution of citric acid and sodium hydroxide is used as buffer solution.

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6. A medicament for the treatment of tumours, characterised in that it constitutes a buffered solution according to Claim 1.

7. The use of the solution according to Claim 1 for preparing an agent for combating tumour diseases.

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Stabilised hexadecylphosphocholine solutions in glycerol alkyl ethers

Summary

The solutions of alkylphosphocholines in glycerol alkyl ethers can be prepared in a storage stable manner and without preservatives and oxidation protection agents by adjusting the pH value to a range between 4 pH and 6 pH.

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☑ Description : paged .1... to paged .8...
☑ Claim(s) : paged .9.. to paged .10..
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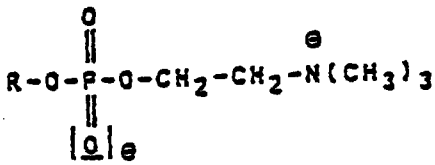
Stabilised hexadecylphosphocholine solutions in glycerol alkyl ethers

Description

Alkylphosphoric acid compounds are known substances with anti-tumour effects. German published patent 33 43 530.8 discloses the anti-tumour effect and the preparatory presentation of the compounds. Water or physiologically acceptable organic solvents such as glycerol alkyl ether are used as solvents for these active substances.

It has, for example, been found favourable for topical application to use the active substance together with at least one alkyl glycerol with 2-12 carbon atoms in the alkyl radical that may be present in the form of an ether group bound to one of the primary or secondary OH groups of the glycerol. Alkyl glycerols of this type raise or improve the effect of alkylphosphoric acid compounds. Preference is given here to alkyl glycerols with 3-9 carbon atoms used alone or in mixtures. Particularly favourable effects are therefore displayed by a medicament containing

a) one or several alkylphosphoric acid compounds of the general formula I

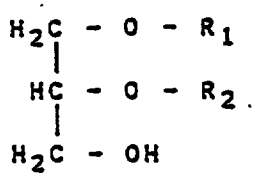


I

R represents an alkyl group with 12-20 carbon atoms which may optionally contain a double bond or a triple bond

b) an alkyl glycerol of the general formula II

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II

in which one of the radicals R_1 and R_2 represents an alkyl group with 2 to 12 carbon atoms and the other radical represents a hydrogen atom, as well as optionally additional conventional additives and dilutants.

It is preferable to consider a mixture of water and an alkyl glycerol mixture of nonyl or octyl glycerol, hexyl or pentyl glycerol and propyl or ethyl glycerol. An appropriate formulation for topical application contains for example 1-100 mg alkylphosphoric acid compound per ml alkyl glycerol or a corresponding alkyl glycerol mixture with water.
A mixture of this type is hereinafter also referred to as cascade.
Alkyl glycerol-water mixtures containing, for example, nonyl glycerol, hexyl glycerol, propyl glycerol are for example preferred. Such mixtures preferably contain 3 of the glycerol ethers mentioned, namely a lower (propyl), a medium (hexyl) and a higher (nonyl), the amounts by weight of the lower ether being approximately as much as the sum of the amounts by weight of the two other glycerol ethers. The amount of water is about the same as the amount of the lower glycerol ether and is for example half the total amount of the glycerol ethers present.
Examples of this type of glycerol ether / water mixtures are listed hereinbelow:

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	Water		Glycerol propyl ether		Glycerol hexyl ether		Glycerol nonyl ether
Parts by weight	2	:	2	:	1	:	1

	Water		Glycerol ethyl ether		Glycerol pentyl ether		Glycerol octyl ether
Parts by weight	2	:	2	:	1	:	1

In addition to water it is also possible to utilize all solvents usable for topical medicaments.

A particular favourable carrier mixture for the alkylphosphoric acid compound hexadecylphosphocholine consists of a mixture of about 4 parts by weight of water, 4 parts by weight of propyl glycerol and 2 parts by weight each of hexyl glycerol and nonyl glycerol.

It is not necessary to add preservatives to solutions of this type since microbiological load tests showed these solutions to have optimum antiseptic properties.

A 6 % hexadecylphosphocholine solution is for example composed as follows:

hexadecylphosphocholine	0.600 g
glycerol-1-n-propyl ether	3.145 g
glycerol-1-n-hexyl ether	1.570 g
glycerol-1-n-nonyl ether	1.570 g
water	3.145 g
	10.030 g = 10 ml

REPLACEMENT SHEET
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It was regrettably found during stability storage that oxidative processes cause peroxides to be formed in the solution which later lead to acids and hence a drop in pH due to further decomposition. The pH value was set at 4-6 in the specification.

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pH and peroxide number of a 6 % hexadecylphosphocholine solution in cascade (untreated)

	-4°C	+2°C	RT	31°C	41°C
Initial investigation					
pH value			5.6		
peroxide number			0.4		
3 months					
pH value	5.0	5.0	4.0	3.6	3.3
peroxide number	0.81	0.95	0.91	3.6	6.0
6 months					
pH value	7.4	6.0	3.8	3.5	3.1
peroxide number	0.55	0.18	1.9	4.9	7.8

To control peroxide formation hexadecylphosphocholine cascade solutions were gassed with nitrogen and covered with nitrogen after filling into 10 ml bottles. An attempt was also made to prevent peroxide formation by adding antioxidants. pH and peroxide number in a 6 % hexadecylphosphocholine solution in cascade (after gassing with nitrogen)

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REPLACEMENT SHEET
01 AUG 1996

	-4°C	+2°C	RT	31°C	41°C
Initial investigation					
pH value			4.6		
peroxide number			0.0		
3 months					
pH value	4.6	5.0	4.2	3.9	3.6
peroxide number	0.1	0.11	0.97	0.94	5.1
6 months					
pH value	4.5	4.4	4.1	3.9	3.5
peroxide number	0.0	0.0	1.73	1.1	4.6

RT = room temperature

As may be seen, the pH value falls and the peroxide content rises in this case, too.
As shown in the following table, the addition of antioxidants did not bring any improvement.

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pH value of hexadecylphosphocholine cascade solutions with addition of antioxidants

With 0.1 % sodium disulfite

	-4°C	+2°C	RT	31°C	41°C
Initial pH value					
3-month pH value	3.8	3.7	3.3	3.1	2.8

With 0.01 % ascorbyl palmitate and 0.05 % α-tocopherol

	-4°C	+2°C	RT	31°C	41°C
Initial pH value			3.8		
3-month pH value	3.8	3.7	3.3	3.1	2.8

Experiments have confirmed that the conventional formulation is not storage stable.
The use of conventional agents to suppress peroxide formation, such as gassing with nitrogen to remove the oxygen from the solution, and the addition of antioxidants did not lead to storage stable solutions.

In an experiment a citrate buffer system was added in addition to the antioxidant sodium disulfite. It was then found that the pH value could be maintained within the specification.

pH value of miltefosine cascade solutions with added 0.1 % sodium disulfite and citrate buffer (0.1 molar in the water phase)

	-4°C	+2°C	RT	31°C	41°C
Initial pH value			5.6		
3-month pH value	5.6	5.6	5.3	5.1	5.2

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Since sodium disulfide did not exert any positive influence as an antioxidant, a miltefosine cascade solution was prepared containing only citrate buffer to reduce the peroxide formation.

It was surprisingly found that the addition of buffer was able to suppress the peroxide formation and thus a fall in the pH value.

Hexadecylphosphocholine cascade solution with citrate buffer

	-4°C	+2°C	RT	31°C	41°C
initial pH value			5.8		
peroxide number			0.58		
3 months					
pH value	5.8	5.8	5.8	5.8	5.7
peroxide number	0.33	0.29	0.41	0.51	0.58
6 months					
pH value	5.8	5.8	5.8	5.7	5.6
peroxide number	0.02	0.39	0.11	0.36	0.54
12 months					
pH value	5.8	5.8	5.7	5.6	5.3
peroxide number	0.06	0.04	0.18	0.11	0.3

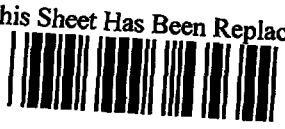
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10 ml of a 6 % buffered hexadecylphosphocholine cascade solution are composed as follows:

hexadecylphosphocholine	0.6000 g
D,L-glycerol-1-n-propyl ether	3.1600 g
D,L-glycerol-1-n-hexyl ether	1.5800 g
D,L-glycerol-1-n-nonyl ether	1.5800 g
citric acid anhydrous	0.0484 g
sodium hydroxide	0.0227 g
purified water	3.0889 g
	10.0800 g = 10 ml

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The following mixtures are additional suitable buffer mixtures: mixtures of
disodium hydrogen phosphate/citric acid,
succinic acid/sodium hydroxide,
potassium dihydrogen phosphate/disodium hydrogen phosphate
sodium hydrogen maleate/sodium hydroxide,
tris-maleate/sodium hydroxide,
potassium dihydrogen phosphate/sodium hydroxide.
A mixture of citric acid and sodium hydroxide of pH value 5.3 is particularly preferred.

Example 1

Buffered 6 % (W/V) hexadecylphosphocholine solution for topical application

Hexadecylphosphocholine solution is prepared by dissolving hexadecylphosphocholine in a buffered solvent termed a cascade. 6.27 kg DL-glycerol-1-ethyl ether, 3.135 kg DL-glycerol-1-n-pentyl ether and 3.135 kg DL-glycerol-1-n-octyl ether are mixed and 1.19 kg hexadecylphosphocholine dissolved in this mixture.

Preparation of citrate buffer pH 5.3
0.0965 kg citric acid anhydrous are dissolved in 5.8 kg purified water and 0.047 sodium hydroxide in 0.3 kg purified water. The sodium hydroxide solution is now added to the citric acid solution until a pH value of 5.3 is reached. Water is then added to make up to 6.27 kg. 6.27 kg citrate buffer are now combined with 13.73 kg solution of the hexadecylphosphocholine in the ether mixture. A uniform solution is obtained with nitrogen gassing. The solution is filtered through a membrane filter, pore size 0.2 µm, filled in 10 ml portions into brown dropper bottles and closed with pipette and protective cap.

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Stabilised hexadecylphosphocholine solutions in glycerol alkyl ethers

Claims

1. A solution of one or several alkylphosphocholines and glycerol ethers according to formula I in water, characterised in that a buffer solution is added.

2. A solution according to Claim 1, characterised in that a solution of citric acid and sodium hydroxide in water is used as buffer solution.

3. A solution according to Claim 1, characterised in that the pH value of the solution lies between 4 pH and 6 pH.

4. A process for the preparation of a solution according to Claim 1, characterised in that one or several alkylphosphocholines according to Formula I in a mixture of glycerol-1-n-alkyl ethers according to Formula II are dissolved in water and a buffer solution added so that a pH value of 4 pH to 6 pH is reached.

5. A process according to Claim 4, characterised in that a solution of citric acid and sodium hydroxide is used as buffer solution.

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6. A medicament for the treatment of tumours, characterised in that it constitutes a buffered solution according to Claim 1.

7. The use of the solution according to Claim 1 for preparing an agent for combating tumour diseases.

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ABSTRACT

Stabilised hexadecylphosphocholine solutions in glycerol alkyl ethers

Summary

The solutions of alkylphosphocholines in glycerol alkyl ethers can be prepared in a storage stable manner and without preservatives and oxidation protection agents by adjusting the pH value to a range between 4 pH and 6 pH.

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STABILISED HEXADECYLPHOSPHOCHOLINE SOLUTIONS IN GLYCEROL ALKYL ETHERS

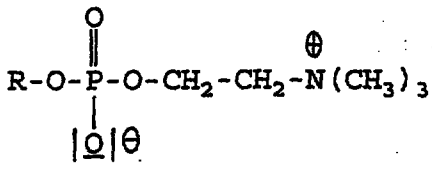
Description

Alkylphosphoric acid compounds are known substances which have anti-tumour action. DE-OS 33 42 530.8 discloses their anti-tumour action and the preparation of these compounds. The solvents used for these active ingredients are water or physiologically compatible organic solvents, such as for example glycerol alkyl ethers.

A composition prepared from hexadecylphosphocholine and a glycerol alkyl ether for tumour treatment is also known from USP 4,837,023.

For topical application, it has, for example, proved advantageous to use the active ingredient together with at least one glycerol alkyl ether with 2-12 carbon atoms in the alkyl residue, which may be present in the form of an ether group attached to one of the primary or secondary OH groups of the glycerol. Such glycerol alkyl ethers promote or improve the action of the alkyl phosphoric acid compounds. Glycerol alkyl ethers with 3-9 C atoms were here preferably used alone or in mixtures. Particularly favourable action is thus possessed by a pharmaceutical preparation which contains

a) one or more alkylphosphoric acid compounds of the general formula I

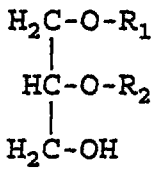


I

in which R means an alkyl group with 12 to 20 C atoms, which may optionally contain a double bond or a triple bond,

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b) glycerol alkyl ethers of the general formula II



II

in which one of the residues R_1 and R_2 means an alkyl group with 2 to 12 C atoms and the other residue means an H atom,

optionally together with further conventional additives and diluents.

A mixture prepared from water and a glycerol alkyl ether mixture of glycerol nonyl or glycerol octyl ether, glycerol hexyl or glycerol pentyl ether and glycerol propyl or glycerol ethyl ether is preferably considered. A corresponding formulation for topical application contains, for example, 1-100 mg of alkylphosphoric acid compound per ml of glycerol alkyl ether or of a corresponding glycerol alkyl ether mixture with water. Such a mixture is also below termed a cascade. By way of example, glycerol alkyl ether/water mixtures are preferred which contain, for example, glycerol nonyl ether, glycerol hexyl ether, glycerol propyl ether. Such aqueous mixtures preferably contain 3 of the stated glycerol alkyl ethers, namely one lower (propyl), one medium (hexyl) and one higher (nonyl), wherein the quantity by weight of the lower ether is approximately the same as the sum of the quantities by weight of the other two glycerol alkyl ethers. The quantity of water is approximately equal to the quantity of the lower glycerol alkyl ether and is, for example, half the total quantity of the glycerol alkyl ethers present.

Examples of such glycerol alkyl ether water mixtures are listed below:

REPLACEMENT SHEET
04 DEC 1997

	Water	Glycerol propyl ether	Glycerol hexyl ether	Glycerol nonyl ether
Parts by weight	2 :	2 :	1 :	1

	Water	Glycerol ethyl ether	Glycerol pentyl ether	Glycerol octyl ether
Parts by weight	2 :	2 :	1 :	1

Apart from water, any solvents usable for topical pharmaceutical preparations may also be used.

A particularly favourable excipient mixture for the alkyl phosphoric acid compound hexadecylphosphocholine consists of a mixture of approximately 4 parts by weight of water, 4 parts by weight of glycerol propyl ether and 2 parts each of glycerol hexyl ether and glycerol nonyl ether.

Preservation is not required for such solutions as the solutions were found to have optimal antiseptic properties in microbiological exposure tests.

For example, a 6% hexadecylphosphocholine solution is of the following composition:

hexadecylphosphocholine	0.600 g
glycerol 1-n-propyl ether	3.145 g
glycerol 1-n-hexyl ether	1.570 g
glycerol 1-n-nonyl ether	1.570 g
water	3.145 g
	10.030 g = 10 ml

Unfortunately, during the stability storage period, it was found that peroxides are produced in the solution by oxidative processes, which subsequently further decompose into acids and thus reduce pH. The pH value set in the specification was 4-6.

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pH and peroxide number of a 6% hexadecylphosphocholine solution in cascade (untreated)

	-4°C	+2°C	RT	31°C	41°C
Initial investigation					
pH value			5.6		
peroxide number			0.4		
3 months					
pH value	5.0	5.0	4.0	3.6	3.3
peroxide number	0.81	0.95	0.91	3.6	6.0
6 months					
pH value	7.4	6.0	3.8	3.5	3.1
peroxide number	0.55	0.18	1.9	4.9	7.8

In order to inhibit peroxide formation, hexadecyl-phosphocholine cascade solutions were perfused with nitrogen and, once filled into 10 ml bottles, provided with a nitrogen blanket. It was also attempted to prevent peroxide formation by adding anti-oxidants. pH and peroxide value of a 6% hexadecylphosphocholine solution in cascade (after perfusion with nitrogen).

	-4°C	+2°C	RT	31°C	41°C
Initial investigation					
pH value			4.6		
peroxide number			0.0		
3 months					
pH value	4.6	5.0	4.2	3.9	3.6
peroxide number	0.1	0.11	0.97	0.94	5.1

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6 months					
pH value	4.5	4.4	4.1	3.9	3.5
peroxide number	0.0	0.0	1.73	1.1	4.6

RT = room temperature

As may be seen, in this case too the pH value falls and the peroxide content rises.

The addition of anti-oxidants brought about no improvement either, as is shown by the following table.

pH value hexadecylphosphocholine cascade solutions with added anti-oxidants.

With 0.1% sodium disulphite

	-4°C	+2°C	RT	31°C	41°C
Initial pH value					
3 month pH value	3.8	3.7	3.3	3.1	2.8

With 0.01% ascorbyl palmitate and 0.05% α-tocopherol

	-4°C	+2°C	RT	31°C	41°C
Initial pH value			3.8		
3 month pH value	3.8	3.7	3.3	3.1	2.8

The tests demonstrate that the conventional formulation is not stable in storage.

Even the use of conventional means of suppressing peroxide formation, such as for example perfusion with nitrogen, in order to remove the oxygen from the solution, and the addition of anti-oxidants did not result in solutions which were stable in storage.

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In one test, a citrate buffer system was used in addition to the anti-oxidant sodium disulphite. It was then observed that the pH value could be maintained within the specification.

pH value of Miltefosin cascade solutions with the addition of 0.1% of sodium disulphite and citrate buffer (0.1 molar in aqueous phase). (Chemically, Miltefosin is 0-hexadecyl-0-(2-trimethylaminoethyl) phosphate.)

	-4°C	+2°C	RT	31°C	41°C
Initial pH value			5.6		
3 month pH value	5.6	5.6	5.3	5.1	5.2

Since sodium disulphide exerted no positive influence as an anti-oxidant, a Miltefosin cascade solution was produced containing only citrate buffer to reduce peroxide formation.

Surprisingly, it was observed that peroxide formation and consequently a reduction in pH could be suppressed by addition of the buffer.

Hexadecylphosphocholine cascade solution with citrate buffer

	-4°C	+2°C	RT	31°C	41°C
Initial pH value			5.8		
Peroxide number			0.58		
<u>3 months</u>					
pH value	5.8	5.8	5.8	5.8	5.7
Peroxide number	0.33	0.29	0.41	0.51	0.58

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6 months					
pH value	5.8	5.8	5.8	5.7	5.6
Peroxide number	0.02	0.39	0.11	0.36	0.54
12 months					
pH value	5.8	5.8	5.7	5.6	5.3
Peroxide number	0.06	0.04	0.18	0.11	0.3

10 ml of a 6% buffered hexadecylphosphocholine cascade solution are of the following composition:

hexadecylphosphocholine	0.6000 g
D,L-glycerol 1-n-propyl ether	3.1600 g
D,L-glycerol 1-n-hexyl ether	1.5800 g
D,L-glycerol 1-n-nonyl ether	1.5800 g
Anhydrous citric acid	0.0484 g
Sodium hydroxide	0.0227 g
Purified water	3.0889 g
	10.0800 g = 10 ml

The following mixtures constitute further suitable buffer mixtures: mixtures of disodium hydrogen phosphate/citric acid, succinic acid/sodium hydroxide, potassium dihydrogen phosphate/disodium hydrogen phosphate, sodium hydrogen maleate/sodium hydroxide, tris-maleate/sodium hydroxide. A mixture prepared from citric acid and sodium hydroxide of a pH value of 5.3 is particularly preferred.

Example 1

Buffered 6% (wt./vol.) hexadecylphosphocholine solution for topical application

Hexadecylphosphocholine solution is produced by dissolving hexadecylphosphocholine in a buffered solvent described as a cascade.

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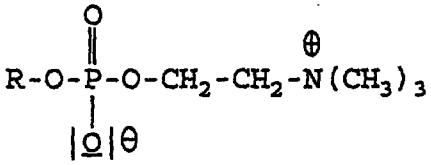
6.27 kg of DL-glycerol 1-n-ethyl ether, 3.135 kg of DL-glycerol 1-n-pentyl ether and 3.135 kg of DL-glycerol 1-n-octyl ether are mixed together and 1.19 kg of hexadecylphosphocholine is dissolved in this mixture.

Production of citrate buffer pH 5.3
0.0965 kg of anhydrous citric acid is dissolved in 5.8 kg of purified water and 0.047 kg of sodium hydroxide is dissolved in 0.3 kg of purified water. The sodium hydroxide solution is then added to the citric acid solution until a pH value of 5.3 is reached. The solution is then made up to 6.27 kg with water. 6.27 kg of citrate buffer are then combined with 13.73 kg of the hexadecylphosphocholine solution in the ether mixture. A uniform solution is produced while being is perfused with nitrogen. The solution is filtered through a membrane filter, pore size 0.2 µm, transferred in 10 ml portions into brown dropping bottles and sealed with a dropper and protective cap.

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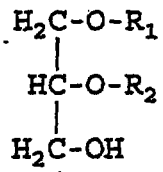
Patent Claims

1. Stabilised solutions of alkylphosphocholines and glycerol alkyl ethers in water consisting of one or more alkylphosphocholines of the formula



I

in which R means an alkyl group with 12 to 20 C atoms, and glycerol alkyl ethers of the formula



II

in which one of the residues R_1, R_2 means an alkyl group with 2 to 12 C atoms and the other residue means an H atom, characterised by an added buffer solution.

2. Solution according to claim 1,
characterised in that
the buffer solution consists of a solution of citric acid and sodium hydroxide in water.

3. Solution according to claims 1 and 2,
characterised in that
the pH value of the solution is between 4 and 6.

4. Process for the production of a solution according to claims 1 to 3,
characterised in that
one or more alkylphosphocholines according to the formula I is/are dissolved in a mixture of glycerol alkyl ethers according to the formula II and a buffer

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solution is added such that a pH value of 4 to 6 is achieved.

5. Process according to claim 4, characterised in that a solution of citric acid and sodium hydroxide is used as the buffer solution.

6. Pharmaceutical preparation for tumour therapy, characterised in that it constitutes a buffered solution according to claim 1.

7. Use of the solution according to claim 1 for the production of a topical agent to combat tumorous conditions.

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