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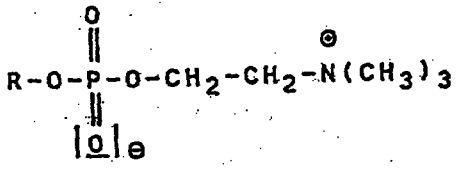
Stabilised hexadecylphosphocholine solutions in glycerol alkyl ethers

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

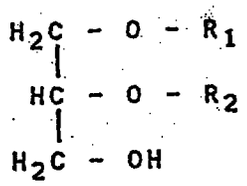
R represents an alkyl group with 12-20 carbon atoms which may optionally contain a double bond or a triple bond

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

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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