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(54) **Titre : EMULSION DE CRISTAUX LIQUIDES DE TYPE HUILE DANS L'EAU ET PROCEDE DE PREPARATION DE L'EMULSION DE CRISTAUX LIQUIDES**

(54) **Title: LIQUID-CRYSTAL EMULSION OIL IN WATER TYPE AND A PREPARATION METHOD OF THE LIQUID-CRYSTAL EMULSION**

(57) **Abrégé/Abstract:**
The present invention relates to liquid-crystal emulsion for the use in a termo- optical matrix to an early diagnosis of mammary gland neoplasmic lesions. It contains a mixture of thermotropic liquid crystals and polyvinyl alcohol. The liquid-crystal emulsion contains 14 to 48% by weight (on a dry matter basis) of the thermotropic compounds mixture and 50 to 86% by weight (on a dry matter basis) of polyvinyl alcohol. The present invention also relates to a method for preparing liquid-crystal emulsion.

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(57) **Abstract**: The present invention relates to liquid-crystal emulsion for the use in a termo- optical matrix to an early diagnosis of mammary gland neoplasmic lesions. It contains a mixture of thermotropic liquid crystals and polyvinyl alcohol. The liquid-crystal emulsion contains 14 to 48% by weight (on a dry matter basis) of the thermotropic compounds mixture and 50 to 86% by weight (on a dry matter basis) of polyvinyl alcohol. The present invention also relates to a method for preparing liquid-crystal emulsion.

Liquid-crystal emulsion oil in water type and a preparation method of the liquid-crystal emulsion

A present invention relates to the emulsion of a thermotropic liquid crystals mixture in aqueous solution of polyvinyl alcohol (PAW) and the method for preparing this emulsion.

The thermotropic liquid crystals belong to a group of liquid crystals, that pass to the liquid-crystal phase during solid crystals heating, called as thermotropic mesophase, in which the crystals instead of melting to a conventional liquid, pass to the mesophase state at certain determined temperature, and isotropisation of the mesophase occurs only at higher temperature, that is a change of the liquid crystals into isotropic liquid. Dependently on the liquid crystal, it may pass through the different mesophases during reducing the temperature. Thermotropic liquid crystals are characterised by the thermooptical properties, based on the colour change effect of the light reflected by the mesophase, dependently on the temperature thereof.

From the patent specifications from the 1970s are known the emulsions, wherein the aqueous solutions of polyvinyl alcohol, which contained from 5 to 10% of formaldehyde, were used as a continuous phase. The emulsions according to these specifications were not suitable to the industrial applications due to low stability and strong and unpleasant odour release, both in the emulsification process and their storage, and the most importantly, their application on the large surfaces. The emulsification process required to use homogenizers with rotation speed above 12000 1/min and their cooling system. As a result of the problems with achieving (using said method) repeatable emulsion, in respect of significant thermooptical requirements, it was abandoned to use this method in the industrial processes.

Presently applied method of encapsulation is the microencapsulation process. The microencapsulation of the thermotropic liquid crystals, that is valid in the technical and advertising applications, is not appropriate as the encapsulation method for medical

applications, demanding for the field of observation of the thermographed surface assurance of optical continuity adjusted to optical resolution of coloured images registering, by means of human eye. The absence of the optical continuity results from dimensions and packing density of „capsules", with regard for a thickness of walls surrounding liquid-crystal aggregates (macroparticles) and is a disadvantage in case of medical applications, in particular applications in matrices to an early diagnosis of a breast cancer in women. That is why, there is a demand for a development the novel liquid-crystal emulsions and the methods for their preparation.

It is an object of the present invention to provide a liquid-crystal composition in a form of a thermooptically stable emulsion that does not release the unpleasant odour and is sufficiently stable from the point of view of a technological process for production of the thermooptical liquid-crystal matrices demands, and the method for the preparation of such composition. Moreover, such emulsion should be easy to prepare and should be characterised by repeatability and stability of parameters over time, such as viscosity and related to it average dimensions of the disperse phase aggregates.

It was found that demanded parameters, concerning „processing" conditions and physicochemical parameters of the liquid-crystal emulsion are possible to obtain by using for the continuous phase preparation appropriate, with regard for molecular weight and degree of hydrolysis, polyvinyl alcohol, in the form of water–acetone–alcohol solution containing from 5 to 20% by weight PAW, from 0.1 to 1.0% boric acid and from 1 to 2% nonoxynol-5 (ethoxylated nonylphenol, a product of addition about 5 molecules ethylene oxide to nonylphenol). The disperse phase content in relation to the continuous phase, on a dry matter basis, should be contained in a range from 14 to 48% by weight. Moreover it was found that easiness and repeatability of formation of the stable emulsion is strongly dependent on the conditions and conditioning time of the continuous phase solution.

Polyvinyl alcohol particularly convenient for the use according to the present invention has the molecular weight from 50000 to 130000 and degree of hydrolysis from 83% to 98 molar %. The emulsion according to the present invention will conveniently contain from 4 to 19% polyvinyl alcohol by weight. It is believed that the main function of polyvinyl alcohol in the emulsion, in combination with small amount, preferably from 1 to 2% by weight, of surfactant (nonoxynol-5) as a dispersing agent, is to act as a thickening agent. The function of polyvinyl alcohol in the phase after emulsion application, is in turn to act as a film-forming agent and partially encapsulating agent.

For the purposes of the application in the matrices to early diagnosis of breast cancer in women, the drop size of the oil phase (liquid-crystal phase) conveniently should be lesser than 5 μm, preferably lesser than 4 μm, and particularly preferably the drop size should be from 1 to 2 μm. Whereas, the emulsion viscosity conveniently should not be larger than 5000 mPa·s and preferably should be lesser than 4500 mPa·s. Particularly preferably the emulsions should have viscosity from 4000 to 4500 mPa·s.

Unexpectedly it was found that by using the emulsion composition according to the present invention and the method of their preparation, the liquid-crystal emulsion that meets the mentioned above requirements concerning the parameters such as the drop size of the oil phase and the emulsion viscosity is obtained.

The present invention relates also to the method for preparing liquid-crystal emulsion. The emulsion according to the present invention is conveniently prepared by vigorous pouring out the mixture of the thermotropic liquid crystals (oil phase), at the temperature near to the temperature of the transfer from the mesophase to the isotropic phase, to the aqueous phase containing polyvinyl alcohol, water, ethyl alcohol, acetone, emulsifying agent and boric acid, at the temperature conveniently lower by 5 to 10°C from the temperature of the oil phase. Mixing conveniently is carried out using the stirrer with the rotation speed from 500 to 5000 1/min. In order to obtain the droplets of the liquid-crystal aggregates with demanded size, pre-emulsion mass conveniently is mixed for 1 to 15 minutes. After cooling down to the room temperature the emulsion should be stored in a hermetically closed vessel, in a place not exposed to the direct action of sunlight. The emulsion is conveniently utilized during 1 to 10 days, preferably during 2 to 8 days, the most preferably during 4 to 6 days.

In order to obtain the aqueous phase, polyvinyl alcohol is added to the aqueous-alcoholic solution containing dissolved boric acid, preferably at the temperature 22 ± 2°C. The mixture is mixed until good dispersion of polyvinyl alcohol is obtained. Then, the temperature of the mixture, while continuously mixing, is rising to about 80 to 85°C and the mixture is maintained at this temperature until polyvinyl alcohol is completely dissolved. Next, the solution is cooled down to the temperature of 40°C, acetone and emulsifying agent are added and the whole is mixed to complete mass homogenisation. After cooling down to the room temperature the obtained mass is passed through the sieve of a number 29T, then it is transferred to the hermetically closed containers and placed in a

room at the temperature not lower than 20°C, conveniently for 10 to 15 days, preferably for 15 to 30 days, and the most preferably for 30 to 60 days.

Raw materials used in preparation of emulsion and the properties of composition

Oil phase:

Composition: the mixture of thermotropic liquid crystals with the mesophase range, being a function of, among other things, a purity of the mixture constituent compounds, preferably in the temperature range from 22.0°C to 48.0°C, containing: cholesteryl pelargonate, cholesteryl oleyl carbonate, cholesteryl propionate, cholesteryl chloride and 4,4´-dipentylazoxybenzene in appropriate ratios by weight.

Properties: any range of termooptical sensitivity (colour response) in visible spectrum range for indicated mesophase range; density at the temperature of 25°C preferably is 0.98 g/cm^3; and viscosity at the temperature of 25°C preferably is from 75 to 93 mPa·s.

Aqueous phase:

Composition: demineralised water with conductivity preferably lower than 10 µS; acetone preferably analytically pure; anhydrous ethyl alcohol; boric acid preferably analytically pure, nonoxynol-5 preferably with a water content lower than 1%.

Properties: homogenous, transparent mass with stabilised rheological parameters, in the form of polyvinyl alcohol solution in solvents with a density measured at the temperature of 25°C preferably of 1.004 g/cm^3 and viscosity preferably of 6300 mPa·s.

Physical properties of individual phases and final liquid-crystal emulsion were measured using the following measuring apparatus. Density was measured with a pycnometer from Zehner S/N. Viscosity was measured using a viscosimeter Brookfield RVT type. To measure the drop size of the oil phase in the emulsion, a photon correlation spectroscope (Zeta – Master 4, from Malvern, equipped with He-Ne laser of a power of 5 milliwatts) was used. The drop size was also confirmed in a finished product, by testing a cross-section of a film containing applied layer of emulsion by using scanning electron microscope BS-301/Tesla type.

Example 1

Preparation of the aqueous phase (continuous phase)

28.2 g of polyvinyl alcohol was added to the solution containing 90.5 g of demineralised water, 75.2 g of ethyl alcohol and 1.18 g of boric acid at the temperature of 22 ± 2°C. The mixture was mixed using the mechanical stirrer RD 50D type to obtain good dispersion of polyvinyl alcohol, then still mixing the temperature of the mixture was raised to about 80 to 85°C and the mixture was maintained at this temperature until polyvinyl alcohol was completely dissolved. Next, the solution was cooled down to the temperature of 40°C and 37.6 g of acetone and 2.35 g of nonoxynol-5 was added and obtained mixture was mixed to homogenous mass (235 g). After cooling to the room temperature, the obtained mass was passed through the sieve of a number 29T, transferred to the hermetically closed containers and placed in a room at the temperature of about 20°C for 22 days.

Preparation of the oil phase (disperse phase)

Cholesteryl pelargonate, cholesteryl oleyl carbonate, cholesteryl propionate, cholesteryl chloride and 4,4´-dipentylazoxybenzene was mixed in appropriate ratios by weight at the temperature of about 70°C, to obtain 15 g of the oil phase.

Preparation of the liquid-crystal emulsion

The mixture of the thermotropic liquid crystals (oil phase, 15 g) was vigorously poured into the aqueous phase (continuous phase, 235 g) at the temperature about 60°C. The whole was mixed using the mechanical stirrer RD 50D type with the rotation speed of 680 1/min. for 7 minutes to obtain 250 g of the liquid-crystal emulsion of a white colour, viscosity of 4200 mPa·s at the temperature of 25°C, density of 1.002 g/cm^3 at the temperature of 25°C and the average drop size of the oil phase of 3.1 μm.

Example 2

The liquid-crystal emulsion was prepared by following the procedure as described in Example 1, using the components in amounts given in Table 1.

Table 1

Component	Contents (g)
Polyvinyl alcohol	6.0
Demineralised water	40.4
Ethyl alcohol	35.0
Boric acid	0.1
Acetone	18.0
Nonoxynol-5	1.5
Mixture of thermotropic liquid crystals	2.0

As a result, the liquid-crystal emulsion of a white colour, viscosity of 4250 mPa·s at the temperature of 25°C, density of 1.003 g/cm^3 at the temperature of 25°C and the average drop size of the oil phase of 2.8 μm was obtained.

Example 3

The liquid-crystal emulsion was prepared by following the procedure as described in Example 1, using the components in amounts given in Table 2.

Table 2

Component	Contents (g)
Polyvinyl alcohol	19.0
Demineralised water	34.6
Ethyl alcohol	29.0
Boric acid	0.9
Acetone	14.5
Nonoxynol-5	2.0
Mixture of thermotropic liquid crystals	5.0

As a result, the liquid-crystal emulsion of a white colour, viscosity of 4350 mPa·s at the temperature of 25°C, density of 1.005 g/cm^3 at the temperature of 25°C and the average drop size of the oil phase of 2.4 μm was obtained.

WHAT IS CLAIMED IS:

1. A liquid-crystal emulsion oil in water type, characterised in that it consists essentially of

a) a continuous phase (aqueous phase) containing water, ethyl alcohol, acetone, polyvinyl alcohol, dispersing agent and boric acid,

b) a disperse phase (oil phase) containing a mixture of thermotropic liquid crystals.

2. The liquid-crystal emulsion according to claim 1, characterised in that the continuous phase contains polyvinyl alcohol in amount from 5 to 20% by weight.

3. The liquid-crystal emulsion according to claim 1 or 2, characterised in that the continuous phase contains dispersing agent in amount from 1 to 2% by weight.

4. The liquid-crystal emulsion according to any one of claims 1 to 3, characterised in that the continuous phase contains boric acid in amount from 0.1% to 1.0% by weight.

5. The liquid-crystal emulsion according to claim 1, characterised in that it contains 14 to 48% by weight (on a dry matter basis) of the mixture of thermotropic liquid crystals and 50 to 86% by weight (on a dry matter basis) of polyvinyl alcohol.

6. The liquid-crystal emulsion according to claim 1, characterised in that it contains polyvinyl alcohol of a molecular weight from 50000 to 130000 and hydrolysis degree of 83 to 98 molar %.

7. The liquid-crystal emulsion according to any one of claims 1 to 6, characterised in that the mixture of thermotropic liquid crystals comprises one or more compounds selected from the group consisting of cholesteryl pelargonate, cholesteryl oleyl carbonate, cholesteryl propionate, cholesteryl chloride and 4,4'-dipentylazoxybenzene.

8. The liquid-crystal emulsion according to claim 1, characterised in that it contains nonoxynol-5 as the dispersing agent.

9. The liquid-crystal emulsion according to claim 1, characterised in that the drop size of the oil phase (liquid-crystal phase) is less than 5 μm.

10. The liquid-crystal emulsion according to claim 1, characterised in that the drop size of the oil phase (liquid-crystal phase) is less than 4 μm.

11. The liquid-crystal emulsion according to claim 1, characterised in that the drop size of the oil phase (liquid-crystal phase) is from 1 to 2 μm.

12. The liquid-crystal emulsion according to claim 1, characterised in that the emulsion viscosity is less than 5000 mPa·s.

13. The liquid-crystal emulsion according to claim 1, characterised in that the emulsion viscosity is less than 4500 mPa·s.

14. The liquid-crystal emulsion according to claim 1, characterised in that the emulsion viscosity is from 4000 to 4500 mPa·s.

15. A method for preparing liquid-crystal emulsion, characterised in that it comprises steps of:

a) preparation of an oil phase by mixing thermotropic liquid crystals to yield a mixture of thermotropic liquid crystals;

b) preparation of an aqueous phase by adding polyvinyl alcohol to an aqueous-alcoholic solution containing dissolved boric acid and mixing and heating the resulting mixture until the polyvinyl alcohol is completely dissolved, cooling the obtained solution, adding acetone and emulsifying agent and mixing the mixture to obtain a homogenous mass, passing the obtained mass at room temperature through a number 29T sieve, transferring the mass to one or morehermetically closed containers and storing the mass at a temperature not lower than 20°C for 10 to 60 days; and

c) vigorously pouring the mixture of the thermotropic liquid crystals into the aqueous phase and mixing the whole using a stirrer with a rotation speed from 500 to 5000 1/min for 1 to 15 minutes to obtain a liquid-crystal emulsion.

16. The method according to claim 15, characterised in that in step b) the mixture is heated to a temperature of about 80 to 85°C.

17. The method according to claim 15, characterised in that in step b) the obtained solution is cooled down to a temperature of 40°C.

18. The method according to claim 15, characterised in that in step c) the mixture of thermotropic liquid crystals is poured into the aqueous phase at a temperature of about 60 to 65°C.

19. The method according to claim 15, characterised in that the aqueous phase is conditioned for 10 to 15 days before step c).

20. The method according to claim 15, characterised in that the aqueous phase is conditioned for 15 to 30 days before step c).

21. The method according to claim 15, characterised in that the aqueous phase is conditioned for 30 to 60 days before step c).

22. The method according to claim 15, characterised in that for stirring of the aqueous phase and the oil phase, a slow-rotating stirrer is used.