

PHYSICO-CHEMICAL PROPERTIES OF NITROXANE SUBSTANCE IN AQUEOUS MEDIA.

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Abstract

In this work the solubility of bioactive compound "Nitroxane" with acaricidal and fungicidal action has been investigated. Nitroxane is a mixture of 4,6-dinitro-5,7-dichlorobenzofuroxane (30%) and 5-nitro-4,6-dichlorobenzofuroxane (70%). Nitroxane is soluble in ethyl alcohol, dimethylformamide, dimethylsulfoxide, but it is insoluble in water, which considerably limited its practical applications.

In the present work condensation method for obtaining nitroxane medicinal forms in water media is presented. The conditions and procedure of introduction of stabilizers, such as non-ionic surfactants and polyethylene oxides have been selected. Different types of medicinal preparations in the form of colloidal solutions and suspensions have been developed.

Introduction

One of the perspective trends of scientific studies carried out at the department of chemistry and technology of organic compounds of nitrogen is the search for biologically active compounds, among which of special interest is nitroxane - benzofuroxane derivative [1, 2].

Medicinal preparations which are presently applied in veterinary practice to treat scabies and fungous diseases have been proved to be rather ineffective. Many acaricide preparations belong to the derivatives of phosphorus and chlorocompounds. They are high-toxic for warm-blooded animals. For treatment of fungous skin diseases polyene antibiotics are used, which cause allergic reactions and by-effects.

Advantage of biologically active compound nitroxane is the wide spectrum of biological action. Nitroxane shows at small concentration (0.1-1.0%) acaricide and fungicidal activity. Its competitiveness is much greater as compared to the above mentioned preparations with one-purpose action [3]. Having high biological activity, nitroxane remains small-toxic for warm-blooded animals (LD50 = 5000 mg/kg for external use), which allows to attribute it to the 4-th class toxicity.

However, practical use of nitroxane is limited because of its insolubility in water.

In the present work the study of physico-chemical properties of the medicinal forms of nitroxane in water is carried out with the purpose of their improvement.

The aims of the present work included:

1. Detailed development of separate stages of commercial pharmaceutical preparation of medicinal forms;
2. Search and choice of components of the medicinal forms: the solvent, auxiliary substances, stabilizers of suspensions and colloidal solutions;
3. Matching the structural components of the medicinal forms;
4. Estimation of physico-chemical characteristics of the offered medicinal forms.

To solve the tasks in hand the joint scientific studies of the chair of physical and colloidal chemistry and the department of chemistry and technology of organic compounds of nitrogen of the Kazan state technological university were carried out in the field of development and improvement of medicinal forms on the basis of biologically active substance nitroxane. In work [3] the study of biological properties has shown 5-nitro-4,6-dichlorobenzofuroxane to be highly active.

Objects and Methods of Research

Table 1. Nitroxane solubility.

Conditional terms	Amount of solvent (ml), necessary for dissolving 1g of the substance	Solvent		
		Water	DMSO	Ethyl alcohol
Very easily soluble	up to 1		+	
Easily soluble	more than 1 up to 10			+
Soluble	»10 »30			
Medium soluble	»30 »100			
weakly soluble	»100»1000			
Rather weakly soluble	»1000»10000			
Practically not soluble	»10000	+		

in water. The general formula of PEO is: $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$ [6]. In this work PEO-400 and PEO-3000 were used. PEO-400 has high osmotic activity and its application is highly perspective in manufacturing medicinal forms for treatment of purulent wound surfaces.

Sedimentation test was carried out using the method of determining precipitation rate of a deposit with the help of torsion balance [7]. Surface tension was measured by Williami method [8].

The measurement of turbidity of the suspension was carried out by the method of photoelectrocalorimetric analysis on spectrophotometer «Specol-10». Turbidity of the system τ is associated with optical density (D) in the ratio: $\tau = (2.3D)/L$, where L – cuvette length, L=5 cm.

The synthesis of a mixture of two components with the common name «Nitroxane» was carried out according to [3]. The product is whity-yellow crystals, $T_{\text{mp}} = 114-116^\circ \text{C}$. The qualitative composition was determined by the method of spectrophotometric analysis [1]. Nitroxane has the following composition:

4,6-dinitro-5,7-dichlorobenzofuroxane 30%;
5-nitro-4,6-dichlorobenzofuroxane 70%.

The content of nitroxane in the product should be no less than 95% (after recrystallization in ice acetic acid). The solubility of nitroxane in various solvents is indicated in table 1.

Official solubility is determined as the ability of a substance to be dissolved in various solvents accepted in (Russian) State pharmacopoeia. From table 1 it is seen, that the best solvent for nitroxane is dimethylsulfoxide [4], which in chemical practice is known under the name «Dimexide». Being a good solvent of nitroxane, dimexide easily penetrates through biological barriers and is depoted as a medicinal substance in tissues [5].

As a surfactant we used oxyethylized alkylphenol of general formula $\text{C}_n\text{H}_{2n+1}\text{O}(\text{C}_2\text{H}_4\text{O})_m\text{H}$.

Recently in pharmaceutical practice polyethylene oxides (PEO) with various molecular mass have received a wide circulation. PEO are easily dissolved

Results and Discussion

To study the ways of obtaining new more perfect forms sedimentation analysis of nitroxane water suspension was carried out. Sedimentation analysis of nitroxane suspension in water comes to determination of deposit accumulation rate. Nitroxane is hydrophobic powder, poorly moistened with water. On introducing nitroxane portion (1%) into water polydisperse system is formed, which is settled immediately after preparation. In fig. 1 the dependence between the mass of precipitated deposit Q and settling time t is given. The experimental data are processed according to [7].

The size of particles (r) is calculated by the formula:

$$r = \sqrt{(9\mu_0 \cdot u) / (2g(\gamma - \gamma_0))}$$

Where g - acceleration of free fall

μ_0 - water viscosity;

u - deposition rate of particles;

γ - nitroxane density, $\gamma = 1.8 \text{ g/cm}^3$;

γ_0 - water density, $\gamma_0 = 1 \text{ g/cm}^3$.

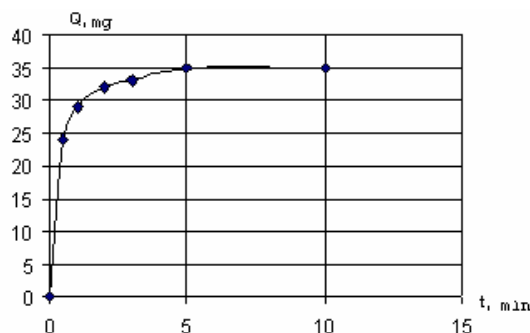


Fig. 1. Precipitation curve of nitroxane suspension in water.

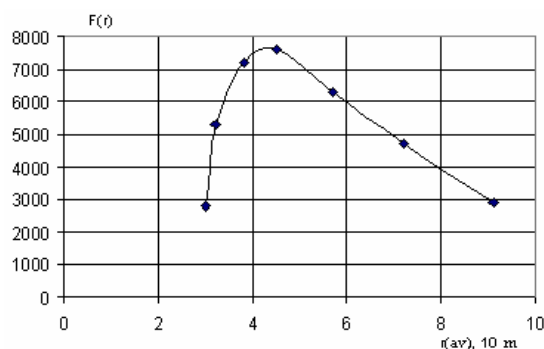


Fig. 2. Distribution curve of nitroxane suspension in water.

Using the results, obtained at processing precipitation curve, we drew the curve of distribution (fig. 2). It shows the weight content $F(r)$ in suspension of various fractions. The value $F(r)$ - weight content of each fraction is expressed by the area of appropriate rectangular. Having constructed such rectangulars for all fractions and having connected medium points of their upper sides by a smooth line, we shall obtain the curve of distribution. The fraction corresponding to the distribution curve maximum is a preferred fraction of polydisperse suspension.

From fig. 2 it is seen, that nitroxane suspension in water is enriched with particle fractions having the sizes $r = 4.5 \cdot 10^{-5} \text{ m}$. Apparently, nitroxane suspension in water can be attributed to polydisperse system. The distribution curve is an important characteristic of nitroxane suspension in water.

It has been shown above that nitroxane suspension in water is a disperse system with quite large particles having practically complete kinetic instability.

For preparation of nitroxane dispersion stable in water we have already used the condensation method of obtaining colloidal nitroxane solution, but not that of suspension. The possibility of preparation of nitroxane medicinal forms with the use of the condensation method of preparation have been investigated.

The creation of medicinal forms on the basis of nitroxane by condensation method needed detailed development of separate stages of preparation

technology, composition, order of components mixing. With this purpose the solution of nitroxane in DMSO was prepared which was added dropwise in water. However, for the purpose of stability, stabilizers were added in colloidal solution. As stabilizers of stable nitroxane colloidal solutions in water a number of surfactants and polymers were chosen allowed for use in the technology of medicinal forms of chemist's manufacturing [9]. In the presence of stabilizers the stability of colloidal solutions gradually increased. The change of optical density in time did not occur and this is reflected in table 2, where the types correspond to 2-nd and 3-rd types of medicinal forms given in table 3.

Table 2. Change of optical density in time.

Type of medicinal forms	13-th day	14-th day	17-th day	18-th day	19-th day
2	1.9	1.85	1.8	1.45	1.4
3	1.7	1.7	1.6	1.29	1.25

The measurement of surface tension of stabilizers in water has shown, that they are surfactants (fig. 3). Stabilizers are adsorbed on the surface of colloidal solution particles, giving it the adsorption-solvation stability factor.

We systematized the data on the study of physico-chemical properties of medicinal forms based on chemically prepared nitroxane. It has been shown, that medicinal forms are stable systems at the expense of formation of adsorption layers of stabilizers on the surface of nitroxane particles, condensation method being the basis of their preparation.

Change of quantitative composition and order of components mixing have allowed (table 3) to create new medicinal forms. As a result of improvement of preparation technique and stabilizers selection the composition, which has stable medical effect at the expense of smaller particle size and greater homogeneity of colloidal solution, has been offered. «Ex tempore» colloidal solution has been developed, the use of which excludes transportation of great amounts of water, which facilitates its delivery to the consumers.

Thus, thanks to the use of condensation method of medical

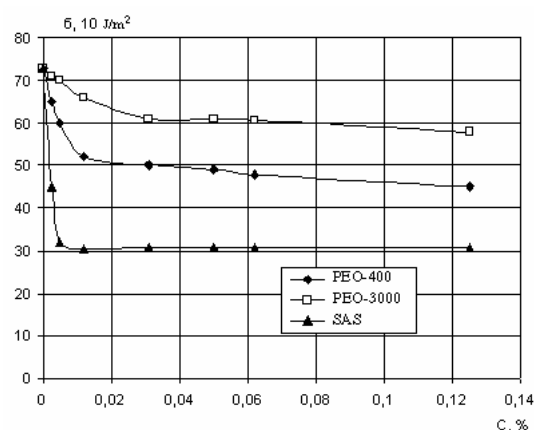


Fig. 3. Isothermal curve of surface tension in aqueous stabilizers solutions ($T = 25^\circ \text{C}$)

forms preparation new types of medical nitroxane forms have been created: colloidal solution and concentrate «*ex tempore*», their stability in time has also been studied.

Table 3. The nature and properties of medicinal forms based on substance «Nitroxane».

Type of medicinal form	Method of preparation	Content (mass.%)	Physico-chemical properties of various medicinal forms	area of external use in veterinary practice
1. Combined: coarse and microheterogeneous suspension	On Patent №2067863 [10] a) grinding of nitroxane with surfactant in mortar б) adding water	Nitroxane 1.0 Surfactant 2.0 Water - up to 100	Opaque dispersion, not breaking down for 10-15 min. Raver= 10^{-5} m	effective mean against and fungous dise.
2. a) True solution б) ultramicro heterogeneous system - colloidal solution	a) Nitroxane solution in dimethylsulfoxide б) adding surfactant and PEO б) colloidal solution obtaining in water by means of condensation method (solvent replacement) r) straining	a) Nitroxane 1.0 DMSO 5.0 б) Nitroxane 1.0 DMSO 5.0 surfactant 1.25 PEO 0.82 Water - up to 100	Fine system with particle size Raver= $10^{-7} - 10^{-9}$ m. Kinetically stable for 15 days system.	Same
3. Colloidal solution "ex tempore"	a) Nitroxane solution in dimethylsulfoxide б) colloidal solution obtaining in water by means of condensation method	a) Nitroxane 1.0 DMSO 5.0 б) Nitroxane 1.0 DMSO 5.0 surfactant or PEO 2.0 Water - up to 100	Heterogeneous system, stable for 90 min.	Same

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