A STUDY OF THE INFLUENCE OF SOLVENTS ON CRYSTALLOGRAPHIC CHARACTERISTICS OF LOCAL ANESTHETICS

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Introduction

The actuality of search for rational therapy of anorectal diseases is associated with the widespread occurrence of this pathology among the able-bodied population in Ukraine [4]. An important step in the treatment of this group of diseases is the reduction of pain. Esters of para-aminobenzoic acid (PABA) – benzocaine and substituted amides – lidocaine and trimecaine are used in suppositories as substances with anesthetics effect [1]. When benzocaine is used to reduce pain the effect develops for 1 minute after applying of rectal dosage forms and lasts for 20-30 minutes. The maximum effect of lidocaine is manifested within 15-30 minutes after using the medications. Trimecaine is absorbed rapidly and has a period of action of 60 minutes, but in the presence of inflammation, it is possible to decrease the anesthetic activity. The above local anesthetics have a low toxicity, which is an essential aspect in the formation of medications [3].

The aim of the work was to study solubility of anesthetic substances: benzocaine, lidocaine, trimecaine.

Materials & methods

The study objects were benzocaine (Changzhou Sunlight Pharmaceutical Co., Ltd., China), lidocaine hydrochloride (Societa Italiana Medicinali Scandicci srl (S.I.M.S. srl), Italy) and trimecaine hydrochloride (Interpharma Praha, a.s., Czech Republic). Definition of crystallographic characteristics in a solvent was carried out a microscopic method using a Konus Academi Microscope of Italian production with a DLT-Cam Basic 2MP camera. DLTCamViewer ™ software was used to visualize images for definition of the shape and size of particles over time. [5]. The solvents used to have different dielectric conductivity: (water - 78.3, propylene glycol - 32.0, ethanol - 25.2, macrogol -400 - 14.1, Witepsol - 2.5).

The crystallographic characteristics of the substance established on value of the Fere's diameter (Df) and shape factor (k) calculated by the formula (1):

$$k = \frac{W}{L}, \text{ where} \quad (1)$$

k – shape factor;
W – width;
L – length.

The particles are considered as isodiametric, if k → 1. The sphericity coefficient was calculated by the formula (2):

$$Ks = \frac{d_{max}}{d_{min}}, \text{ where} \quad (2)$$

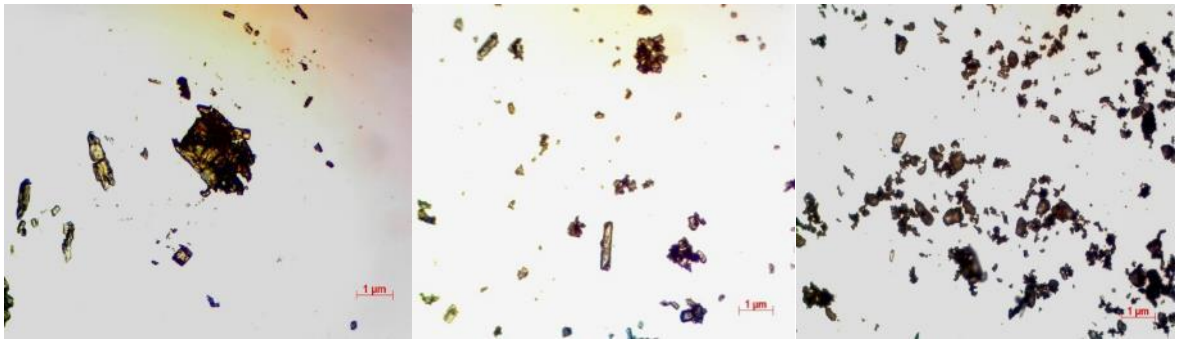
Ks – sphericity coefficient;
d_{max} – maximum diameter;
d_{min} – minimum diameter [2].

The shapes of the particles are considered as spherical, if 1 ← Ks.

Definition of these parameters is necessary to determine the influence on the crystallographic characteristics of anesthetics [2]. The statistical processing of result carried out in accordance with the requirements of the SPhU using the software Microsoft Excel 2007.

Results & discussion

Results of the study are showing that the form and size of benzocaine (Fig. 1A), lidocaine (Fig. 1B), trimecaine (Fig. 1C) significantly differ from each other. Benzocaine (Fig. 1A) has volumetric particles, which are close to the rectangular shape, with a linear size of 0.5 to 7 μm in maximum measurements, k = 0.2 - 0.5 μm, Df = 2 μm, with an uneven surface and numerous debris. Lidocaine (Fig. 1B) has particles that are capable of agglomeration, linear size 0.1-1.2 μm, k = 0.4, Df = 0.6 μm. In the sample of trimecaine (Fig. 1C) there is a uniform distribution of transparent particles that are close to the rectangular shape, capable of agglomeration, with a linear size of 0.05-1 μm, k=0,7, Df = 0,9 μm.



1A 1B 1C

Fig.1 Photo of dry substances: 1A-benzocaine; 1B-lidocaine; 1C-trimecaine

The resulting data are indicating that the particle samples of benzocaine and trimecaine have a significant difference in linear values. Benzocaine has large number of particles with isodiametric form and oscillation in the linear sizes of fractions. Lidocaine and trimecaine are characterized by a more homogeneous distribution of fractions.

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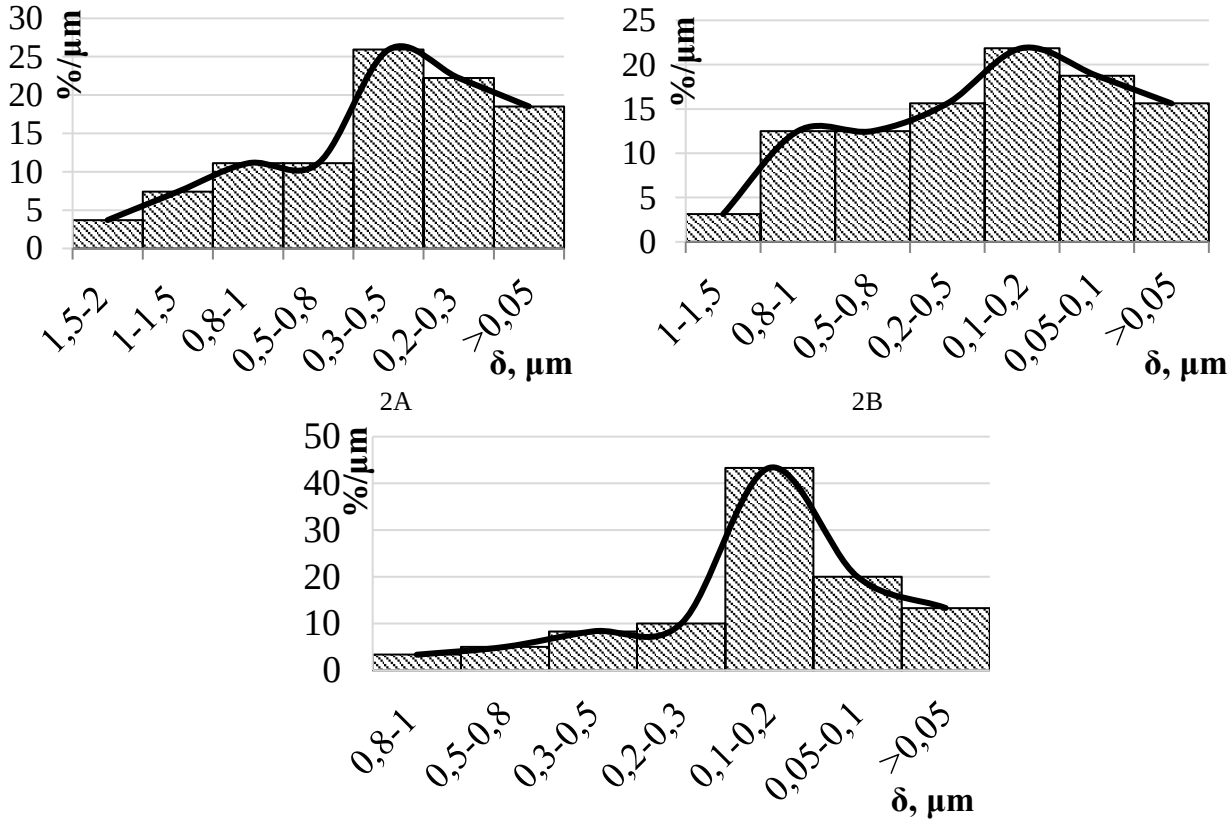
The resulting data are confirmed by the results of the dispersion analysis of the particle size distribution (Fig. 2).



2A 2B

2C

Fig. 2. Differential curve of particle distribution by microscopic study: 2A-benzocaine; 2B-lidocaine; 2C-trimecaine

As can be seen from data Fig. 2. to the law of normal distribution is obeyed in a sample of trimecaine [2]. The differential curve of this substance has one maximum similar to a fraction with a particle size of 0.1-0.2 µm. In other samples, the height of the maximum are reducing, the curve becomes more stretched, that indicating about their polydispersity. Lidocaine has the largest area between the differential curve and x-line (Fig. 2), which indicates that it has almost equally particle ratio of all fractions. In a sample of benzocaine a fraction with size of 0.5 µm is prevailing.

3A 3B 3C

Fig. 3. Solubility of substances in water: 3A-benzocaine; 3B-lidocaine; 3C-trimecaine

The next step was to define the effect of solvents with different values of dielectric conductivity on crystallographic characteristics (fig. 3-10). As can be seen from Fig. 3, the addition of purified water to the samples significantly changed the linear size and shape of their particles. Benzocaine is changing the size due to the disintegration of conglomerates. In the samples of lidocaine and trimecaine the size is changing due to dissolution.

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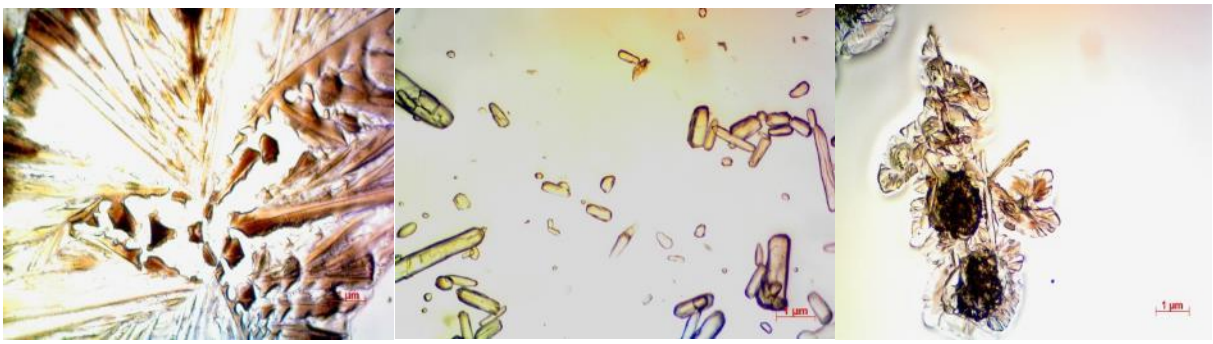
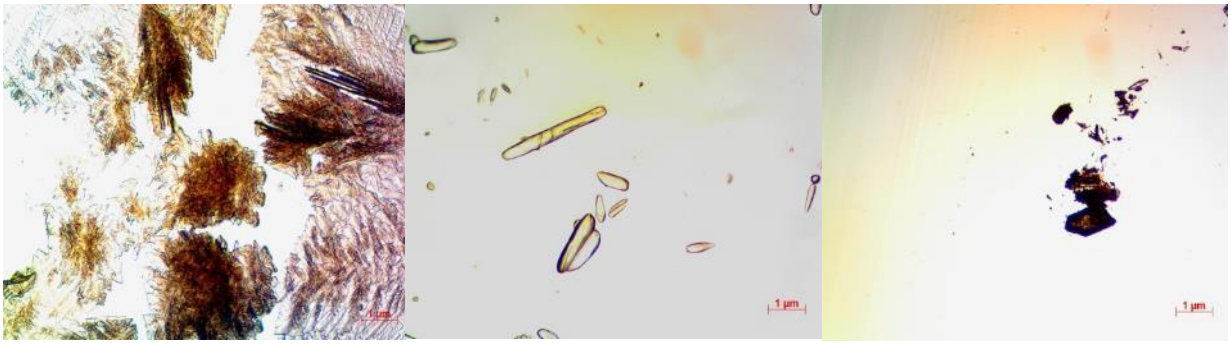


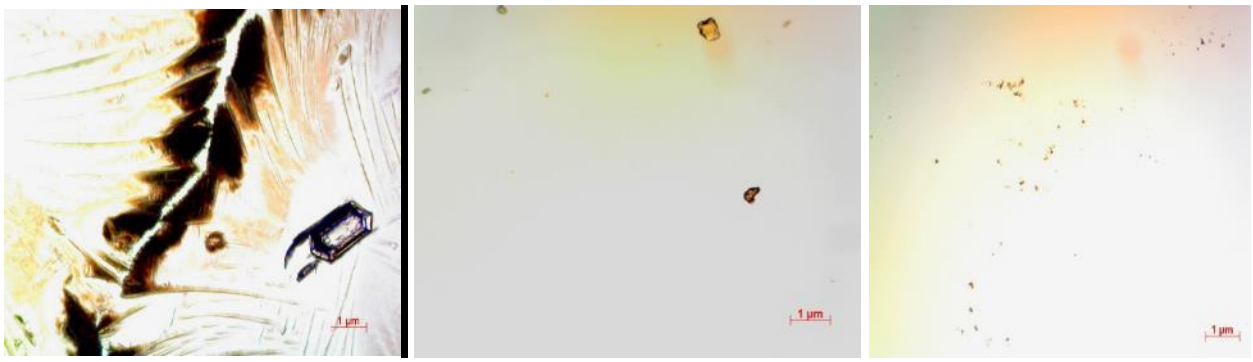
4A 4B 4C

Fig. 4. Solubility of substances in ethanol 96%: 4A-benzocaine; 4B-lidocaine; 4C-trimecaine



5A 5B 5C

Fig. 5. Solubility of substances in ethanol 70%: 5A-benzocaine; 5B-lidocaine; 5C-trimecaine



6A 6B 6C

Fig. 6. Solubility of substances in ethanol 45%: 6A-benzocaine; 6B-lidocaine; 6C-trimecaine

Studies of the substances behavior in ethanol - water solutions with different concentrations (45% - 70% - 90%) showed, that decreasing the content of ethanol leads to increased the solubility of trimecaine and lidocaine. Ethanol is dissolving benzocaine in the concentration of 70% and 96%, but after the removal of ethanol, the formation of crystals with their agglomeration is observed, that can prevent the homogeneous distribution of the active pharmaceutical ingredient in the dosage forms [6].

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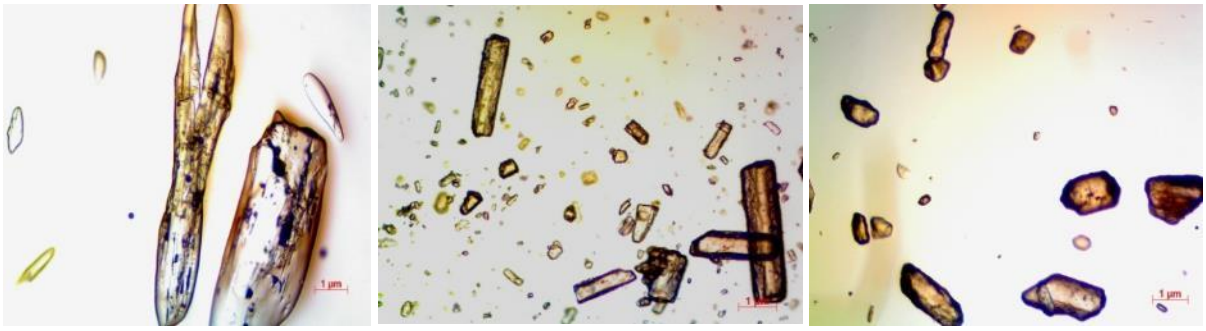
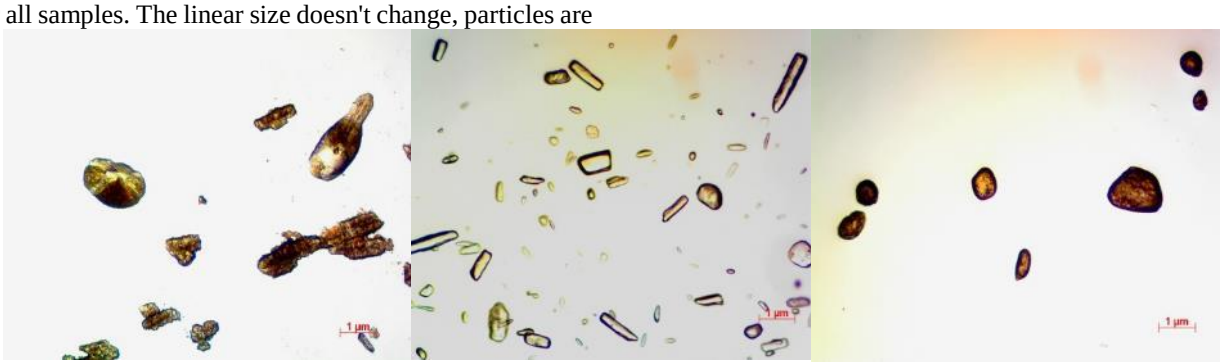


7A 7B 7C

Fig. 7. Solubility of substances in polysorbate-80: 7A-benzocaine; 7B-lidocaine; 7C-trimecaine

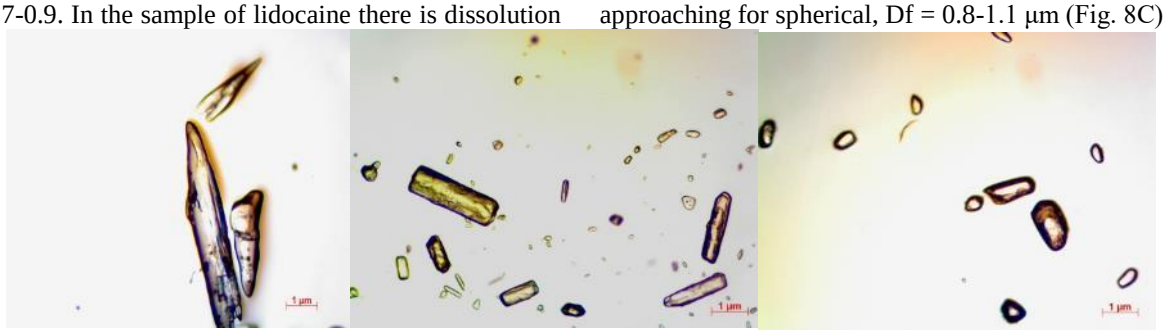
The effect of polysorbate-80 is almost the same for all samples. The linear size doesn't change, particles are well wetted, transparent, with uniform distribution.



8A 8B 8C

Fig. 8. Solubility of substances in propylene glycol: 8A-benzocaine; 8B-lidocaine; 8C-trimecaine

The results of solubility of substances in an environment of a low-polar solvent of propylene glycol shows that benzocaine (Fig. 8A) is a partially soluble, as evidenced by the change in the linear size of particles. There is a change in the shape of the crystals due to wetting of the particle, when propylene glycol is added, Df = 1 μm, k = 0.7-0.9. In the sample of lidocaine there is dissolution of particles with a size of 0.3-0.5 μm (Fig. 8B). The dissolution of the fraction over 0.5 μm occurs slowly with the wetting of the entire surface. In the process of dissolution, the particles are capable to agglomeration, Df = 0.1-0.3 μm. Trimecaine is partially soluble in this environment over a period of time. At the same time there is a deformation of the crystal due wetting, the shape is approaching for spherical, Df = 0.8-1.1 μm (Fig. 8C).



9A 9B 9C

Fig. 9. Solubility of substances in macrogol-400: 9A-benzocaine; 9B-lidocaine; 9C-trimecaine

The study of samples in an environment of the macrogol-400 (Fig. 9) shows the identical characteristics of particle dissolution with a size less than 0.5 μm and partial wetting of particles more than 0.5 μm. For benzocaine crystallographic characteristics were k = 0.5-0.6; Df = 1 μm. For trimecaine and lidocaine there is a characteristic of the same value of Df = 0.3 μm.

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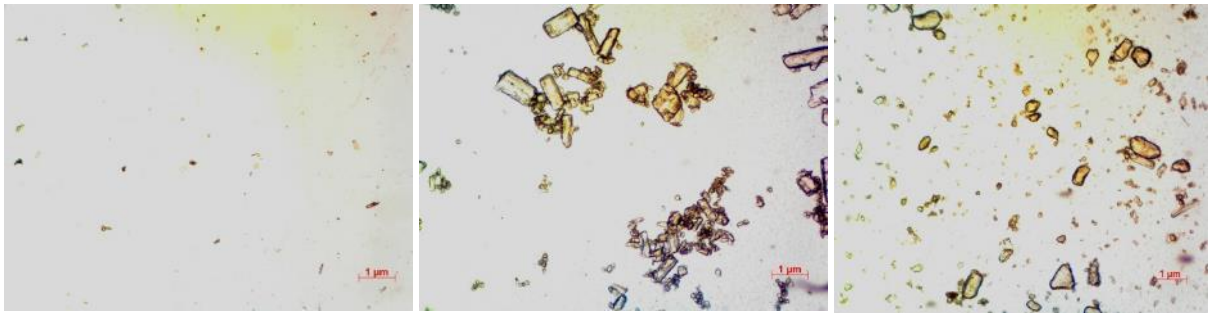

10A 10B 10C

Fig. 10. Solubility of substances in witepsol: 10A benzocaine; 10B-lidocaine; 10C-trimecaine

According to the research results, benzocaine is well soluble in witepsol (Fig. 10). The sparse particles are observed in the field of vision, but they completely dissolve over a period of time, linear sizes from 0.05 to 0.2 μm, Df = 0.05 μm (Fig. 10A). Lidocaine and trimecaine aren`t dissolved in this environment (Fig. 10B and Fig. 10C), which indicates the immutability of their linear sizes. The particles of substance are transparent, single in the field of vision, which points to the wetting.

The obtained results show the dependence of the samples of dissolution degree on the index of dielectric conductivity. Thus, the solubility of the witepsol decreases with increasing dielectric conductivity and reaches maximum at 2.5. The property of the dissolution of lidocaine and trimecaine is different - the solubility increases with increasing dielectric conductivity, the maximum dissolution at 78.3. Taking into account the obtained data, we can conclude about advisability of benzocaine introduction into suppositories in the form of a solution in the environment with dielectric permittivity to 2.5 and for lidocaine and trimecaine in the range 25-78. The substance can be introduced by suspension in the environment with different dielectric permittivity. To do this, the sphericity coefficient must be taken into account, which influence on the degree of sedimentation and the rate of active substances release from dosage forms [6].

Table.1. Definition of the linear size, sphericity coefficient and shape factor of particles

№ з/п	Solvent	Sample №		
		Benzocaine (№1)	Lidocaine (№2)	Trimecaine (№3)
a	Water	l=2-3 k=0.65±0.001 Ks=1.3±0.003	-	-
b	Ethanol	l=4.3-5	-	-
c	Polysorbate-80	l=1-7 k=0.21±0.0004 Ks=2.2±0.005	l=0.2-3 k=0.33±0.001 Ks=1.8±0.004	l=0.2-1 k=0.7±0.001 Ks=1.1±0.002
d	Propylene glycol	l=1-3 k=0.82±0.002 Ks=1.19±0.002	l=0.1-1.5 k=0.8±0.002 Ks=1.15±0.002	l=0.3-1 k=0.9±0.002 Ks=1.09±0.002
e	macrogol-400	l=3.5-4.8 k=0.4±0.001 Ks=2.2±0.005	l=0.1-1.2 k=0.45±0.001 Ks=1.9±0.004	l=0.3-1 k=0.84±0.002 Ks=1.21±0.002
g	Witepsol	-	l=0.3-1 k=0.5±0.001 Ks=1.36±0.003	l=0.1-1 k=0.6±0.001 Ks=1.23±0.003

Note: P=95%, l- linear size (μm), k – shape factor, Ks – sphericity coefficient, - – dissolution.

As can be seen from Table - 1 the biggest values of sphericity have samples №2- d, e, g; №3 -c, d, g;

Thus, the obtained results show about advisability of benzocaine introduction into the rectal form as a solution with witepsol, lidocaine and trimecaine – with water. The sphericity coefficient show about advisability of lidocaine and trimecaine introduction as a suspension in propylene glycol.

Conclusion

1. The influence of solvents with different dielectric conductivity on solubility of benzocaine, lidocaine and trimecaine substances has been investigated. It was found that benzocaine dissolves in witepsol, and trimecaine and lidocaine in water and ethanol.

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2. The particle size distribution has been studied. It was found that trimecaine relate to monodisperse, and benzocaine, trimecaine to polydispersed substances, as evidenced by the area under the differential curve of particle distribution.
3. The crystallographic characteristics of the substances of anesthetics have been studied. It is determined that they belong to isodiametric substances, the shape factor of which is approaching 0. The particles are capable of agglomeration, with an uneven surface and numerous debris.
4. On the basis of research it can be concluded, that benzocaine should be introduced as solution in witepsol and trimecaine, lidocaine - as suspension in the dosage forms.

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Introduction. Esters of para-aminobenzoic acid (PABA) – benzocaine and substituted amides – lidocaine and trimecaine are used in suppositories as substances with anesthetics effect. When benzocaine is used to reduce pain the effect develops for 1 minute after applying of rectal dosage forms and lasts for 20-30 minutes. The maximum effect of lidocaine is manifested within 15-30 minutes after using the medications. Trimecaine is absorbed rapidly and has a period of action of 60 minutes, but in the presence of inflammation, it is possible to decrease the anesthetic activity. The above local anesthetics have a low toxicity, which is an essential aspect in the formation of medications. **Material & methods.** The study objects were benzocaine (Changzhou Sunlight Pharmaceutical Co., Ltd., China), lidocaine hydrochloride (Societa Italiana Medicinali Scandicci srl (S.I.M.S. srl), Italy) and trimecaine hydrochloride (Interpharma Praha, a.s., Czech Republic). Definition of crystallographic characteristics in a solvent was carried out a microscopic method using a Konus Academi Microscope of Italian production with a DLT-Cam Basic 2MP camera. DLTCamViewer ™ software was used to visualize images for definition of the shape and size of particles over time. The solvents used to have different dielectric conductivity: (water - 78.3, propylene glycol - 32.0, ethanol - 25.2, macrogol -400 - 14.1, witepsol - 2.5). The crystallographic characteristics of the substance established on value of the Fere's diameter (Df) and shape factor (k). The statistical processing of result carried out in accordance with the requirements of the SPhU using the software Microsoft Excel 2007. Results of the study are showing that the form and size of benzocaine, lidocaine, trimecaine significantly differ from each other. Benzocaine has volumetric particles, which are close to the rectangular shape, with a linear size of 0.5 to 7 μm in maximum measurements, k = 0.2 - 0.5 μm, Df = 2 μm, with an uneven surface and numerous debris. Lidocaine has particles that are capable of agglomeration, linear size 0.1-1.2 μm, k = 0.4, Df = 0.6 μm. In the sample of trimecaine there is a uniform distribution of transparent particles that are close to the rectangular shape, capable of agglomeration, with a linear size of 0.05-1 μm, k=0,7, Df = 0,9 μm. The resulting data are confirmed by the results of the dispersion analysis of the particle size distribution, shown that to the law of normal distribution is obeyed in a sample of trimecaine. The differential curve of this substance has one maximum similar to a fraction with a particle size of 0.1-0.2 μm. In other samples, the height of the maximum are reducing, the curve becomes more stretched, that indicating about their polydispersity. Lidocaine has the largest area between the differential curve and x-line (Fig. 2), which indicates that it has almost equally particle ratio of all fractions. In a sample of benzocaine, a fraction with size of 0.5 μm is prevailing. The obtained results show the dependence of the samples of dissolution degree on the index of dielectric conductivity. Thus, the solubility of the witepsol decreases with increasing dielectric conductivity and reaches maximum at 2.5. The property of the dissolution of lidocaine and trimecaine is different - the solubility increases with increasing dielectric conductivity, the maximu m dissolution at 78.3.Taking into account the obtained data, we can conclude about advisability of benzocaine introduction into suppositories in the form of a solution in the environment with dielectric permittivity to 2.5 and for lidocaine and trimecaine in the range 25-78. The substance can be introduced by suspension in the environment with different dielectric permittivity.
Keywords: benzocaine, lidocaine, trimecaine, solubility, shape factor, sphericity.

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