

Identification of the complex composition of substances that migrate from rubber stoppers and patterns of research using mass spectrometry methods

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Keywords: mass spectrometry, identification, migration, impurities, butyl rubber, infusion drugs, rubber plugs.

Abstract

Mass spectrometry and chromatography-mass spectrometry methods were used to identify the unknown and complex composition of substances migrating and accumulating in sterile forms of infusion drugs. Organic substances have been identified for their greater content in the investigated samples of butyl rubbers and rubber stoppers on their basis, extra-gyrated with methylene chloride and distilled water. The need for special sample preparation for the study of extracts is shown, and certain regularities of the studies of substances migrating from the plugs are established. The results of the research showed that the carcinogenic accelerator of vulcanization of tetramethylthiuram-disulfide is used in the manufacture of plugs based on butyl rubber. Its disintegration and transformations are accompanied by the formation of new gaseous and soluble carcinogenic organic compounds. These compounds have a greater chemical activity and are able to minimize the therapeutic effect of the active pharmaceutical substance of the drug or enhance it up to a toxic manifestation, or completely change its therapeutic properties.

Rubber medical plugs based on butyl rubbers are complex high-molecular organic compositions and, as shown by the literature and patent publications of domestic and foreign authors, their properties have not been studied. Rubbers and rubber compounds for the production of medical jams have never been developed, despite the importance of these drugs, which are used in large volumes in intensive care units.

Medical rubber stoppers, produced and used both in Russia and abroad for the capping of infusion and injection preparations, according to the studies conducted by the specialists of Kazan National Research Technological University on identification of their compositions showed that they are all made on the basis of butyl and halobutyl rubbers using carcinogenic vulcanization accelerators and, as it turned out, the same geometric dimensions according to ISO 8536-2-2001, ISO 8362-2, which are developed and used for their control in the manufacture and supplies to pharmaceutical companies and pharmacies.

References

- [1] A.A. Saminski, J.J. Rozhavskiy, T.S. Ryabysheva, N.F. Krivonosov, V.S. Altizer, V.A. Beresnev. Polymer basis for the rubber pharmaceutical stoppers. *FGUP "scientific research Institute of rubber and latex products. Moscow. Russia.*
- [2] S.V. Guzhova, N.N. Simonova, A.G. Liakumovich, D.R. Sharafutdinova, A.F. Fatkullina, K.V. Kholin. Sanitary and chemical studies of multicomponent composition of substances migrating from rubber medical tubes based on butyl rubber. *Herald of Roszdravnadzor.* **2013.** No.5. P.44-48. (russian)
- [3] S.V. Guzhova, N.N. Simonova, N.K. Romanova, A.G. Liakumovich, R.Z. Musin, K.V. Kholin, A.F. Fatkullina. Study of composition of substances migrating to the infusion medicines of sealing tubes on the basis of galo bytil rubber. *Herald of Roszdravnadzor.* **2014.** No.2. P.37-44. (russian)
- [4] S.V. Guzhova, N.K. Romanova, Yu.N. Khakimullin, N.N. Simonova, E.N. Tcherezova, R.S. Yarullin. Identification of "invisible pollutants" of infusion and injection drugs migrating from medical stoppers. *Herald of Kazan Technological University.* **2014.** Vol.17. No.20. P.167-171. (russian)

- [5] S.V. Guzhova, N.K. Romanova, A.A. Chizhevsky, N.N. Simonova, E.N. Tcherezova, Yu.N. Khakimullin, R.S. Yarullin. Use of the atomic emission spectrometry to evaluate degradation of medical rubber stoppers. *J. Herald of Kazan Technological University*. **2015**. Vol.18. No.1. P.110-115. (russian)
- [6] S.V. Guzhova, N.K. Romanova, N.N. Simonova, E.N. Cherezova, Yu.N. Khakimullin, and R.S. Yarullin. The role of detergents used in sanitary-and-hygienic treatment of stopper in the contamination of drugs. *Butlerov Communications*. **2015**. Vol.42. No.5. P.78-83. DOI: 10.37952/ROI-jbc-01/15-42-5-78
- [7] *GOST R 52770-2007*. Medical products. Safety requirements. *Methods of sanitation-chemical and toxicological tests*. **2007**. P.20. (russian)
- [8] V.G. Zaikin. Mass spectrometry of synthetic polymers. Moscow: VMSO. **2009**. 330p. (russian)
- [9] V.O. Sheftel, S.E. Kataev. Migration of harmful substances from polymeric materials. *Moscow: Chemistry*. **1978**. P.168. (russian)
- [10] Hygienic standards 1.1.725-98 "List of substances, products, production processes, household and natural factors carcinogenic to humans". *Ministry of health of the Russian Federation Moscow*. **1999**. (russian)
- [11] Russian register of potentially hazardous chemical and biological substances. *MH RF, Moscow*. **2000**. (russian)
- [12] *GOST R 52249-04*. Rules of production and quality control of medicines. (russian)