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Preparation of the high purity perfluorodecalin

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Abstract: The preparative method for the perfluorodecalin purification using the low temperature crystallization in the presence of organic compound (diluent) has been developed.

Keywords: Perfluorodecalin, crystallization.

It is known that perfluorocarbones are good solvents for the gases (oxygen, nitrogen, carbon dioxide) without forming any chemical compounds with them. Moreover, the perfluorocarbones have high chemical resistance. The listed properties of perfluorocarbones were used when blood substituents were developing.

The first Russian blood substituent “Perftoran”™ is represented as 26-30% water emulsion of perfluorodecalin with a range of additives. However the single dose of the perfluorodecalin inserted into a blood channel can be equal 100 g. Such a high dose of the product leads to the extreme tough requirements to its purity. Content of impurities for the usual medicinal products is acceptable at the level of 0,5-1%, that in case of the 500 mg dose (for the most part of the medicinal products the doses are far less) there are 2,5-5 mg of impurities. Experience has proven that intaking of such quantity of impurities is acceptable and doesn't lead to the serious adverse events. Consequently, the purification of technical perfluorodecalin to the higher level than it is required for the most medical products, is necessary.

In the industry, the technical perfluorodecalin is obtained through the formation of the naphthalene mixture in decalin at 350°C with the use of cobalt trifluoride [1]. It is known that the formation process flows through the radical mechanism, and therefore differs with low selectiveness and formation of many different impurities. The technical perfluorodecalin consists of the mixture of cis- and trans-isomers in the ratio about 1 : 1 (93 - 95%), and also contains perfluorobutylcyclohexane and perfluoromethyloctahydroindene impurities, that have close to the basic substance boiling temperatures which can't be removed by distillation.

There is underlined in the work [2], that the first samples of perfluorinated blood substituents had serious side effect, the content of impurities in these products changed from batch to batch, and only after development of the special methods of purification (which

are mostly confidential) , it became possible to raise the purity of commercial preparations up to 98%. However the requirements to the perfluorodecalin as essence are higher, that is why the content of the basic substance must be not less than 99,9%.

There is a known method of purification of the technical perfluorodecalin [3]. This method is based on the perfluorodecaline's double crystallization at the low temperatures (minus 17 – minus 15°C) with obtainment of samples that contain 99,0 — 99,3% of the basic substance. A weak point of such method is that using it, it's impossible to get the perfluorodecalin with the purity 99,9%, which is necessary for producing of medical preparations based on it. In practice, in case of this way of crystallization, the capture of impurities by the crystals takes place: the cooling speed variation in the interval 0,5 – 2°C/min doesn't reduce impurities in solid phase.

We used the process of the low temperature crystallization of perfluorodecalin in the presence of small amount of appropriate organic compound (dilutant) for purification of technical perfluorodecalin. The low specificity and an intermolecular energy is unique feature of perfluorodecalin (the same as other perfluorinated hydrocarbons), and this leads to the easy building of molecules of perfluorinated impurities into the growing crystal's grid. An introduction of a dilutant reduces concentration of impurities in the growing crystal's zone and increases perfluorodecalin's molecules binding selectivity in the growth step, that leads to the obtainment of higher-end crystals and as a consequence – to its higher purity. Organic compounds that have the boiling temperature not more than 80°C and the freezing temperature not less than minus 30°C were chosen in the quality of the delutant.

It has been discovered that several factors affect the purification rate, and main of them are: delutant's nature and it's quantity.

For example, when using aliphatic hydrocarbons (pentane, hexane and so on) an added dilutant's quantity hardly affected the purification rate. To our opinion this is connected with the limited solubility of the above listed dilutants at 20°C in perfluorodecalin. We have found out that the single low temperature crystallization both solutions and aliphatic hydrocarbons emulsions in the technical perfluorodecalin leads to the impurities reduction only in 2 – 3 times (in crystal sediment the perfluorodecalin content increases to 97,5 - 98,3%). In order to obtain the perfluorodecalin with the content of basic substance not less than 99,9% not less than 4 – 5 crystallizations are required.

Chloroorganic compounds also limitedly dissolve in perfluorodecalin. The solubility of methylene chloride at a room temperature is 2%. However the perfluorodecalin's purification efficiency in the presence of methylene chloride is higher than in the presence of aliphatic hydrocarbons: the single crystallization reduces quantity of impurities to 1%. There are required 3-4 crystallizations in order to obtain 99,9% perfluorodecalin.

Polyfluorinated compounds at a room temperature are mixed with perfluorodecalin in every respect, that's why the quantity of the added polyfluorinated compound influences essentially on the impurities' removal rate. We have shown that in the presence of 5 – 6 % 1,2,2-trichloro-1,1,2-trifluoroethane there is a sample with the content of 99,4% perfluorodecalin crystallized, while using 10 - 12% 1,2,2-trichloro-1,1,2-trifluoroethane – 99,6%. Similar results were obtained using perfluorotriethylamine.

Consequently, for obtaining perfluorodecalin with the content of the basic substance not less than 99,9%, only two crystallizationes by applying 1,2,2-trichloro-1,1,2-trifluoroethane or perfluorotriethylamine are required.

However it ought to be noted that at every crystallization an isomeric composition changes (enrichment with trans-isomer). In order to save an isomer balance cross crystallization is

required.

EXPERIMENTAL

The crystallization was carried out on the Cyrstallizer BuchiGlasUster 316L, (drukfilter, volume 500 ml provided with jacket and additional coil over filter membrane). An impurities content was determined using the method GLC on the chromatograph «HP 6890-5973 GC-MS EI» with mass detector, column HP-5MS, vapor's and detector's temperature 250 °C. The definition was made with the programmed temperature rise – initial temperature 60 °C, then with the speed 10 deg/min, the temperature rise to 250 °C. Electron binding energy 70 eV.

The crystallization in the presence of1,2,2-trichloro-1,1,2-trifluoroethane.

In the machine there was put 800 g of 93,14% perfluorodecalin and 80 g 1,2,2-trichloro-1,1,2-trifluoroethane. Using the coolant delivery with the temperature minus 25°C in vessels jacket the mixture is cooled to minus 5°C, then the cooling is made with a speed 0,5°C/hour until the temperature is minus 20°C. The drain valve is opened and under the dry nitrogen pressure there is made a filtration until the supernatant liquid stops its separation. The perfluorodecalin crystals are melt by inputting the coolant with a temperature 0°C. 40 g of 1,2,2-trichloro-1,1,2-trifluoroethane are added and one more cycle of crystallization, filtration and melting is made, than it is held in vacuum for one hour (10 mm Hg). 473 g of distilled perfluorodecalin is obtained, the content of the basic substance is 99,93% (according to GLC).

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