**Maximum purified preparations (novogalenic preparations)**

Novogalenic drugs - phytopreparations containing the amount of biologically active substances of the original medicinal plant raw materials in their native state, maximally purified from accompanying substances.

Due to a deeper purification from accompanying substances, the following advantages appear in new galenic preparations compared to galenic ones:

1. Can be used as an injection.
2. Less side effects.
3. Great storage stability.

The first novogalene drug was developed at the end of the 19th century in Germany. In Russia in 1923. for the first time professor Stepun suggested the drug "Adonilen". Currently, VILAR is developing this group of drugs in Russia.

The technological scheme for obtaining novogalenic drugs is individual (depending on the properties of the amount of substances released), but general technological stages can be distinguished.

**Technological scheme for the production of novogalenic drugs**

**BP - 1.** Sanitary preparation of production

**BP - 1.1. Preparation of industrial premises**

**BP - 1.2. Processing equipment**

**BP - 1.3. Sanitary preparation of technological clothing**

**BP - 1.4. Sanitary training of personnel**

**BP - 2.** Preparation of raw materials and extractants

**BP - 2.1. Grinding raw materials**

**BP - 2.2. Preparation of extractants**

**TP - 3. Extraction**

**TP - 4. Concentration**

**TP - 5. Purification of concentrated extraction (obtaining a technical product)**

**TP - 6. Concentration and (or) drying**

**TP - 7. Standardization**

**UMO - 8. Packing, packaging, marking**

**PO - 9. Waste processing**

**BP - 1. Sanitary preparation of production** is carried out similarly to the previous groups of extraction preparations.

**BP - 2. Preparation of raw materials and extractants**

It is carried out similarly to galenic preparations. A feature is that the range of extractants used in the manufacture of this group of preparations is wider.

In the production of novogalene drugs, the choice of the extractant in each case is individually suited, taking into account:

* selectivity (selectivity) of extraction of a certain group of biologically active substances;
* desorbing capacity of the extractant;
* insignificant extraction of related substances.

*The following extractants have found the greatest application in the production of novogalenic preparations:*

1. Water.
2. Aqueous solutions of acids, salts, alkalis.
3. Ethanol in various concentrations.
4. Organic solvents (dichloroethane, acetone, chloroform, ethyl ether, methyl chloride).
5. Mixtures of solvents.

The composition of these mixtures is selected individually according to the criterion of maximum solubility in the BAS mixture.

Universal solvent: 95 parts chloroform and 5 parts ethanol.

**TP - 3. Extraction.** Of the extraction methods, the most widely used methods are those that make it possible to obtain concentrated extracts in a short time, such as:

1. Countercurrent extraction

- countercurrent multistage extraction (repercolation);

- continuous countercurrent extraction.

1. Circulating extraction (using volatile extractants).
2. Maceration with circulation or continuous stirring (with this method, the extraction is concentrated, but the depletion of the raw material is low).

**TP - 4. Concentration.** The resulting extracts may be too dilute or contain organic solvents that are non-indifferent to the human body and must be removed. Therefore, quite often the obtained extracts are concentrated by evaporation in vacuum evaporators at a temperature of 40-50 ° C (sometimes up to 70 ° C). During the concentration process, additional purification occurs, because impurities remaining in the solution precipitate. The concentrated extracts are filtered and purified.

**TP** - 5. Purification of concentrated extraction and obtaining a technical product.

Is a distinctive stage in the production of galenic and novogalenic preparations.

A wide variety of techniques and methods have been used to purify the obtained extracts from accompanying substances and isolate the required amount of substances. The following methods are most widely used:

1. Fractional deposition of biologically active substances or related substances.
2. Dialysis and electrodialysis.
3. Liquid extraction.
4. Chromatography.

**Fractional deposition of biologically active substances or related substances**

*Change of solvent*

The essence of this method lies in the fact that the solvent used for extraction is changed to the opposite one (i.e., an organic lipophilic solvent to an inorganic hydrophilic one and vice versa). In this case, as a rule, impurities precipitate, and biologically active substances remain in solution.

For example:

1. When biologically active substances are extracted with a non-polar or low-polar solvent (chloroform), the extraction is purified from lipophilic substances by removing the extractant and adding water to the remainder. In this case, the solubility of lipophilic substances decreases, and they precipitate, and the BAS remain in solution.
2. When ethyl ether is added to ethanol extracts from foxglove leaves, the saponins precipitate, while the cardinolides remain in solution.
3. When water is added to one stripped off chloroform-ethanol (95: 5) extraction from adonis grass, accompanying lipophilic substances precipitate, and cardiac glycosides remain in a dissolved state (Adonizid).

*Denaturation*

Almost any extract from medicinal plant materials contains proteins. These are complex organic compounds that are very sensitive to the effects of various external factors (heating, UV radiation, ultrasound, etc.). Under the influence of these factors, proteins are modified and form precipitates. This process is irreversible and is called protein denaturation. This phenomenon is used to purify extracts from proteins, while the extraction is boiled (BAS must be thermostable) and denatured proteins are precipitated.

*Salting out*

 Salting out can be carried out with the help oflarge amounts of a saturated solution of a strong electrolyte. In this case, such high-molecular compounds as proteins, gums, mucus, pectins precipitate. The mechanism of this phenomenon lies in the fact that when the electrolyte solution is added to the extraction, the resulting ions are hydrated, taking water away from the biopolymer molecules. This is followed by adhesion of particles and deposition of the biopolymer. Salting out is often used in the purification of organic protein products (pepsin, insulin).

 Different salts have different salting-out effectsit is explained by the ability of anions and cations to hydrate. The salting-out ability of electrolytes depends mainly on anions. According to their salting-out power, anions are located in the following lyotropic series:

*SO4 -> citrate -> acetate -> Cl-> NO3 -> CNS-*

For cations, there is the same lyotropic series:

*Li +> Na +> K +> Pb ++> Cs +*

 The greatest salting-out ability is possessed by litium sulfate, but cheaper sodium chloride is more widespread.

*Alcohol purification*

Ethyl alcohol is a highly hydrophilic substance, and therefore, when added to a solution of biopolymers, it takes away their protective hydration shell, as a result of which the IUDs precipitate. Partial purification from the IUD is achieved already during the extraction of raw materials, if ethyl alcohol is used as an extractant in a concentration of at least 70%.

**Dialysis**

 Dialysis is based on the property of low molecular weight molecules instill pass through semipermeable membranes, while biopolymer molecules cannot pass through these membranes. This phenomenon is used to purify extracts from medicinal plant materials from IUD molecules. For the dialysis process, semipermeable membranes are used made of gelatin, cellophane, collodion, cellulose derivatives, etc.

 Dialysis is usually very slownno. The speed of electrodialysis can be increased by increasing the temperature, increasing the area of ​​dialysis, applying an electric current. In the latter case, the phenomenon of electrodialysis is observed, which mainly affects substances that decompose into ions. A diagram of the simplest installation for electrodialysis is shown in Fig. twenty.



Figure: 20. Installation for electrodialysis

1 - electrodes; 2 - membranes; 3 - stirrer.

The installation for electrodialysis consists of a bath with a stirrer (3), divided by two semi-permeable partitions into three compartments. The cathode and anode (1) are lowered into the outer compartments, and the dialyzed extraction is poured into the middle compartment. Under the action of an electric current, cations move through semipermeable membranes (2) to the anode, anions - to the cathode. In the middle compartment, substances remain that do not pass through the semi-permeable partitions. In the course of work or continuously, the extraction and solutions of the dialyzed substances are removed.

**3. Liquid extraction**

The purification of extracts by liquid extraction is based on a diffusion process, in which one or several BAS are extracted from one liquid by another, insoluble or limitedly soluble in the first.

There are always two phases in solvent extraction. The transition of substances from one phase to another obeys the laws of mass transfer, solubility and interphase equilibrium. The efficiency of the transition of substances is determined by the Nernst law, according to which, when a substance is distributed between two immiscible phases, an equilibrium is formed between the concentrations of a substance in both phases.

The proportional constant is the distribution coefficient:

*K = C1 / C2*

Where:

*C1 is the equilibrium concentration of biologically active substances in refined sugar (residual initial solution);*

*C2 is the equilibrium concentration of biologically active substances in the extract or re-extract (solution of the extracted substances).*

The distribution coefficient depends on the solubility of the substance in each phase.

If C2> C1, then K <1;

If C2 <C1, then K> 1;

If C1 = C2, then K = 1.

Liquid extraction can be:

1. Stepped.

Staged extraction can be single-stage (one apparatus) and multi-stage (several apparatus); in addition, it can be direct-flow and counter-flow.

1. Continuous.

Liquid extraction equipment can be operated using:

- the forces of gravity;

- mechanical stirring or supply of any other energy for stirring liquids.

In gravitational apparatus (extractors), the difference in the densities of the solvents of different phases is used.

The following work on the principle of gravity:

1. Hollow spray extractors.
2. Packed extractors.
3. Extractors with sieve trays.

Extractors of the second group include:

 1. Mixing and settling extractors

 2. Rotary disc extractors.

 3. Column extractors with stirrers.

**Preparations of individual substances or substances**

**from medicinal plants**

At present, the range of preparations of individual substances from medicinal products is quite wide. This is due to the fact that biologically active substances isolated from medicinal plant materials have a variety of pharmacological properties and the following advantages over synthetic drugs:

1. More environmentally friendly in production.
2. More economical to manufacture.
3. Less toxic when applied.

Preparations of individual substances from medicinal plant materials are classified on the basis of their belonging to the groups of biologically active substances, that is, according to their chemical structure:

Preparations containing alkaloids, flavonoids, cardiac glycosides, saponins, coumarins, etc.

The process of obtaining preparations of individual substances is complex and multistage, specific for each type of raw material and isolated substances, and in many respects similar to the production of novogalenic preparations.

**Technological scheme of obtaining**

**preparations of individual substances**

**BP - 1.** Sanitary preparation of production

**BP - 1.1. Preparation of industrial premises**

**BP - 1.2. Processing equipment**

**BP - 1.3. Sanitary preparation of technological clothing**

**BP - 1.4. Sanitary training of personnel**

**BP –2.** Preparation of raw materials and extractant

**VR-2.1. Grinding raw materials**

**VR-2.2. Preparation of extractants**

**TP - 3. Extraction (obtaining extraction)**

**TP - 4. Concentration of extraction**

**TP - 5. Purification of extraction and production of technical product**

**TP - 6. Purification of technical product (isolation of individual substances)**

**TP - 7. Standardization**

**UMO - 8. Packing, packaging, marking**

**PO - 9. Waste processing**

**Stages VR - 1, VR - 2, TP - 3, TP - 4**are carried out similarly to these stages when receiving novogalenic drugs (see the previous section). The most optimal extraction method is selected for each preparation.

**TP - 5. Purification of extraction and receipt of a technical product.**

Purification of extracts from accompanying substances in the production of preparations of individual substances is carried out in the same ways as when obtaining new galenic preparations, the difference is that all operations are repeated many times.

* *Fractional sedimentation* most often carried out by changing the solvent.
* *Dialysis method* used for preliminary cleaning of extracts from IUD.
* *Liquid extraction* carried out by all methods is very wide, especially in the isolation of alkaloids.
* *Adsorption chromatography* - most often for the purification and separation of cardiac glycosides and their subsequent separation.
* *Ion exchange chromatography* - for the purification of aqueous extracts containing alkaloids (for example: serotonin hydrochloride from sea buckthorn bark can be isolated using ion exchange on the cation exchanger KB - 4P - 2).

**TP - 5. Purification of technical product (isolation and separation of individual substances)**...

As a result of the purification stage, a solution of individual substances is obtained in any solvent with a minimum content of related substances (technical product).

The extract purified at the previous stage is evaporated under vacuum at a residual pressure of 6666.1-10665.76 N / m2 and a total preparation is obtained.

 To divide the amount and isolate individual substances at the final stage, use:

1. Combination of chromatographic method with crystallization.
2. Combination of liquid extraction with crystallization.
3. Concentration.
4. Crystallization.

The final stage in obtaining individual preparations is always crystallization, which, as a rule, is carried out repeatedly, and it is called recrystallization.

*Crystallization is the process of separating a solid phase in the form of crystals from solutions or melts*... It is carried out mainly in three ways:

1. Removal of part of the solvent (evaporation).
2. By changing the temperature of the solvent.
3. A combination of both.

All methods lead to a decrease in the solubility of the substance and its isolation in the form of crystals.

Crystallization can be carried out from water, aqueous solutions of ethanol and other organic solvents. Usually, a solvent is selected for these purposes, the solubility of substances in which decreases with decreasing temperature. Crystallization with decreasing temperature is carried out from those substances that have positive solubility (directly proportional to the relationship between the solubility of a substance and temperature). Cooling is carried out with water, brine or air. So, when the extract from the emetic nut, purified from accompanying substances, is cooled, strychnine first of all precipitates, and other alkaloids remain in solution.

With negative solubility (inversely proportional relationship between solubility and temperature), crystallization is carried out by heating the solution with warm water or steam, but this method is rarely used.

For those substances whose solubility does not significantly depend on temperature, crystallization is carried out with the removal of part of the solvent. Part of the solvent is usually removed using vacuum, which protects the biologically active substances from destruction.

Sometimes crystallization is carried out by salting out with substances that bind water (high concentration ethyl alcohol, concentrated ammonia solutions and salt solutions containing the same ion with this mixture).

 Stages **TP - 6, UMO - 7, PO - 8** are carried out similarly to the drugs of the previous group.