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See the video-film "Preparation of sterile medicines and medicines requiring aseptical conitions of preparation in pharmaceutical conditions"

STABILIZATION OF SOLUTIONS FOR INJECTIONS

INTRODUCTION

Every year solutions for injections are more and more widely adopted in medicine. The Ukrainian State Pharmacopoeia states a number of requirements to medicinal forms for injections, one of which is stability. A stability of a medicine is really important, because it determines the economy and profitability of a factory and pharmacy production to a large extent. Besides, stability during storage is the major condition of successful treatment and main characteristic of qualitative medicines. However, the process of their stabilizing has not been studied well enough. Therefore, at present the problem of medicinal forms stability for injections in the conditions of their assortment expansion and in the volume of their production has the highest priority.

Many medicinal substances collapse in formation of non-active and toxic products under influencing of many factors in the process of preparation and storage of solutions. For example, during the process of sterilization of solutions for injections and their subsequent storage some medicinal substances can possibly change. The problem of stability can be solved by studying the nature of reactions occurring in medicinal forms and applying physical and chemical research methods to reach these aims.

Production of stable solutions involves the maximal removal of factors contributing to decomposition of medicinal substances and it is achieved by using auxiliary substances – stabilizers, as well as by application of the complex of technological methods in the process of medicinal forms preparation. The rational selection of stabilizers will allow to prepare a high-quality and therapeutically effective medicinal form. Practical necessity to study the given topic can be explained by the study of substances concerning the stabilization of medicinal forms for injections.

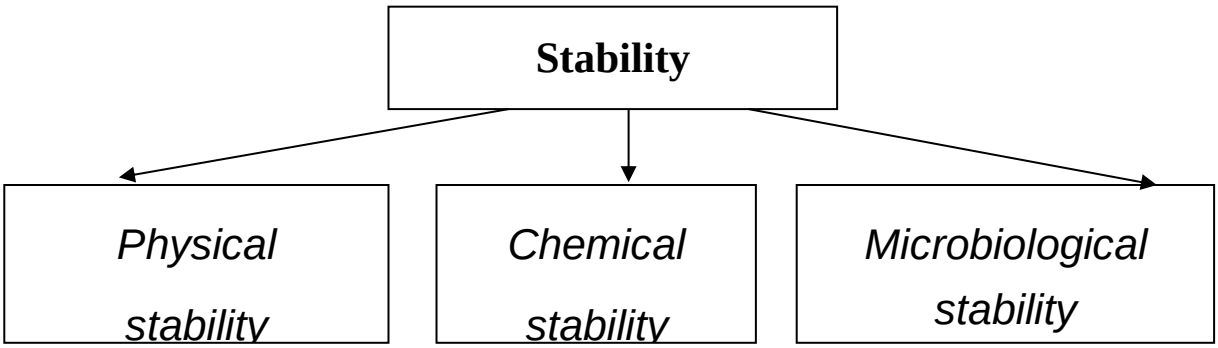
1.1. STABILITY AND ITS TYPES

Stability is ability of medicines to preserve their physical and chemical properties and pharmacological activity during some definite term of their storage stipulated by the requirements of normative documentation.

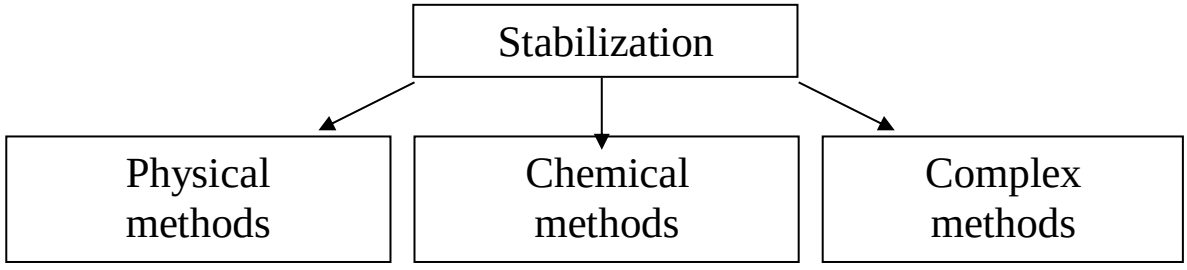
The study of stabilization aspects is an important technological task, because 90 % of medicinal substances require application of a stabilizer or special terms of preparation.

Stability of medicines depends on:

- *temperature of storage;*
- *light intensity;*
- *environmental composition;*
- *method of preparation;*
- *auxiliary substances;*
- *type of medicinal form (especially the aggregate state);*
- *packing.*



The main principle of stabilizing medicines involves the maximum removal of factors contributing to the change in qualities of medicinal substances.



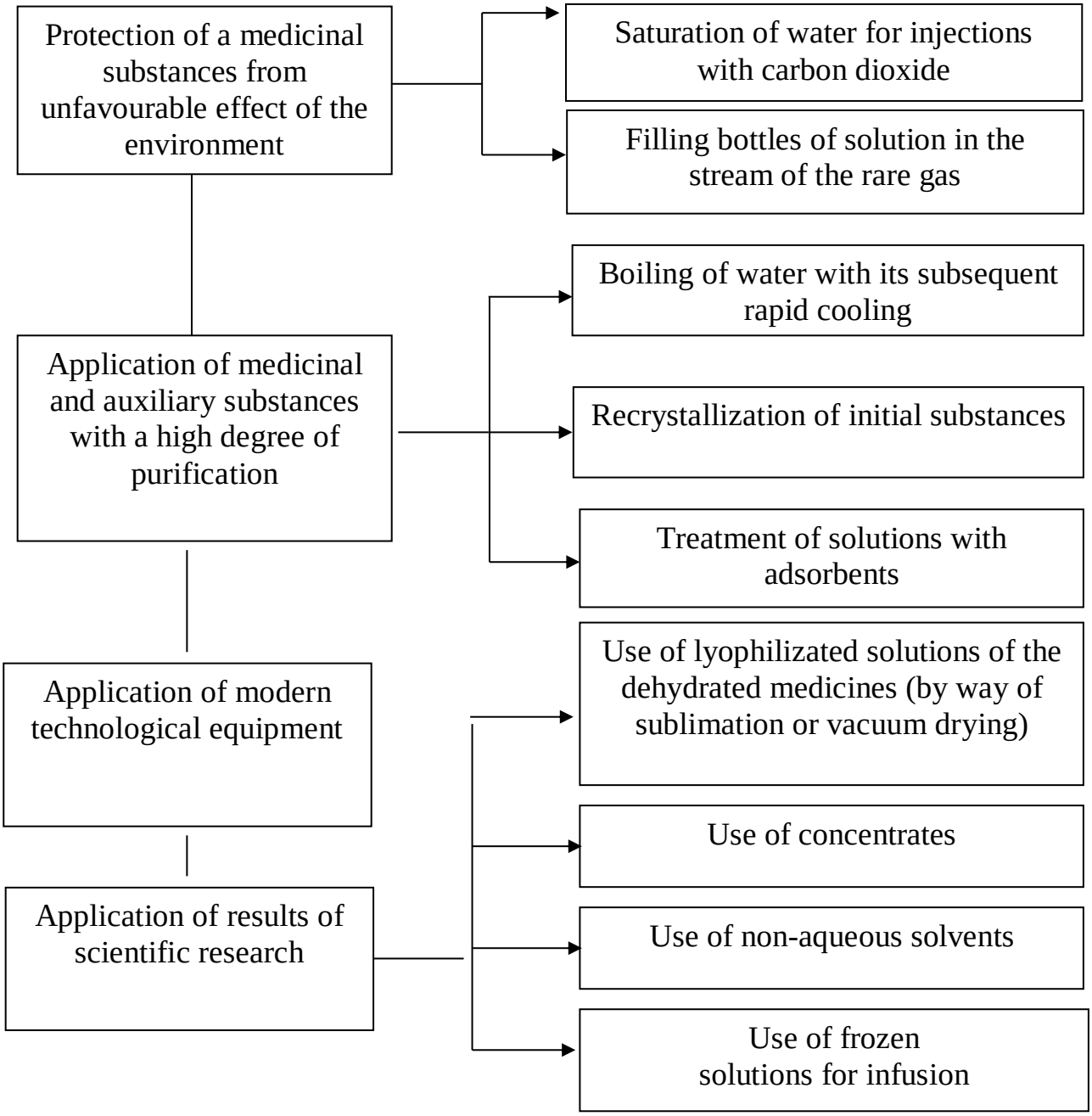
1.2. THE METHODS OF STABILIZATION

PHYSICAL METHODS OF STABILIZATION

Physical processes **that take place in medicines:**

- enlargement of particles of the dispersion phase;
- stratification;
- change of consistency;
- evaporation;
- sublimation.

Methods of physical stabilization



1.2. THE METHODS OF STABILIZATION

CHEMICAL METHODS OF STABILIZATION

Chemical stability of solutions depends on:

- ***properties of solvents and medicinal substances;***
- ***class and sort of bottles glass;***
- ***presence of oxygen in water and in solutions;***
- ***pH of solutions;***
- ***temperature and time of sterilization;***
- ***presence of ions of heavy metals;***
- ***terms of storage of medicines.***

Chemical processes that take place in medicine:

- ***hydrolysis;***
- ***saponification;***
- ***reaction of reduction-oxidization;***
- ***decarboxylation;***
- ***isomerization;***
- ***racemization;***
- ***polymerization;***
- ***photochemical destruction.***

Chemical methods involve the increase in the stability of medicinal substances and medicines on the whole by adding the substances – stabilizers.

The choice of stabilizers depends on:

- ***nature of medicinal substances;***
- ***description of processes, which take place in the solutions***

1.3. STABILIZERS

Stabilizers *are the substances increasing chemical stability of medicinal substances in solutions for injections.*

Requirements to a stabilizer:

- *it must be safe for the patient both in its pure state and in combination with the components of medicines (pharmacological indifference);*
- *it must be approved for application in medical practice;*
- *it must be effective in the applied concentrations (to perform its functional purpose);*
- *chemical purity;*
- *availability.*

The mechanism of stabilizers' effect

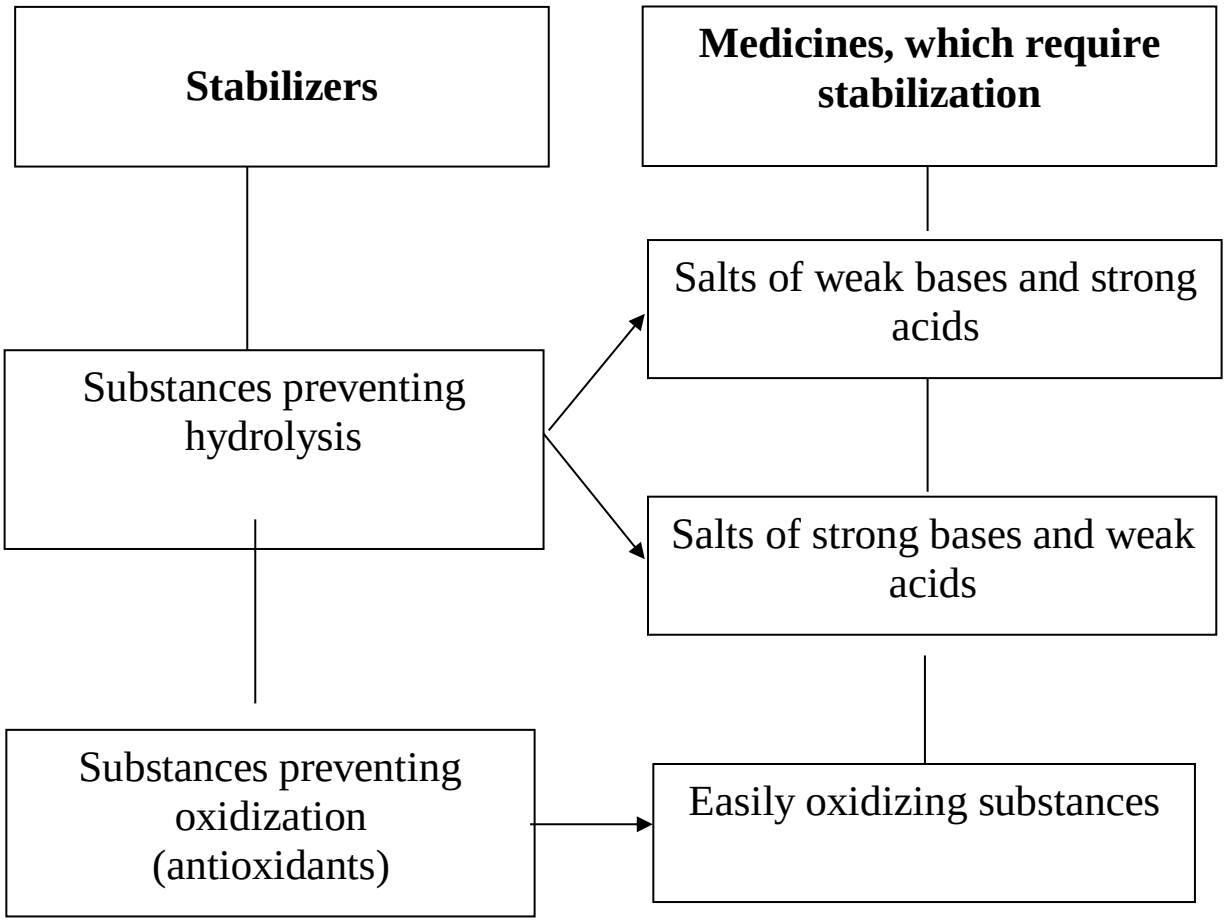
- *turning insoluble active substances into a soluble salt or complex compounds;*
- *creation of a definite value of the pH medium;*
- *selection of the proper systems of solvents;*
- *prevention of reduction-oxidization processes.*

1.3. STABILIZERS

CLASSIFICATION OF MEDICINAL SUBSTANCES

AND STABILIZERS

(Prozorovsky A.S., Kudakova N.A.)



The name of a stabilizer and its amount indicated in the normative and technical documentation, as well as in valid orders of the Ukrainian Ministry of Public Health and instructions is marked on the reverse side of the prescription and in the front side of WCP.

1.4. STABILIZATION OF HYDROLYSABLE SOLUTIONS

Hydrolysis is a reaction of ion exchange between different substances (salts, esters, etc.) and water

THE SCHEME OF HYDROLYSIS PROCESS

$$BA + HOH \rightarrow HA + BOH$$

where: **BA – is a hydrolyzing substance;**

HA and BOH – are products of hydrolysis.

Factors, which influence on the degree of hydrolysis:

- ***the chemical nature of a salt,***
- ***temperature;***
- ***the concentration of a salt.***

THE SCHEME OF HYDROLYSIS OF A STRONG BASE SALT AND A WEAK ACID

$$BA + HOH \leftrightarrow B^+ + OH^- + HA$$

where: **BA – is a hydrolyzing substance;**
HA – is a weakly dissociated acid.

Salts of solutions of strong bases and weak acids are stable

When adding (as a stabilizer) sodium hydrocarbonate or 0.1 M sodium hydroxide solution

Solutions:

- Sodium thiosulphate;
- Sodium caffeine benzoate;
- Sodium nitrite.

1.4. STABILIZATION OF HYDROLYSABLE SOLUTIONS

Rp.: Sol. Coffeini-Natrii benzoatis 10 % 50 ml
Sterilisa!
D. S. 2 ml 2 times a day for intramuscular injections.

The solution of sodium caffeine benzoate is stabilized by 0.1 M sodium hydroxide solution in the amount of 4 ml per 1 litre of the solution, irrespective of sodium caffeine benzoate concentration for adjusting pH – 6.8 –8.5 (SPh. X)

The given medicine is the solution of a strong-effective substance - a strong basic salt and a weak acid for injections requiring stabilization. Put 10.0 g sodium caffeine benzoate in a volumetric flask, then dissolve in one part of water for injections, add 8 drops of 0.1 M sodium hydroxide solution and dilute with water for injections to 50 ml. After the qualitative and quantitative analysis, filter the solution in a bottle for dispensing, check the presence of particulate matters, then cork the bottle hermetically by a rubber cap under aluminium cover and sterilize.

Perform the secondary control of quality and register the medicine for dispensing, by the number of prescription and labels “For injections”, “Sterile”.

WCP (reverse side)

Sodium caffeine benzoate:
10.0 / 2 = 5.0
0.1M sodium hydroxide solution
1000 ml – 4 ml
50 ml – X X = 0.2 ml
1 ml – 20 drops
0.2 ml – X X=4 drops

Water for injections up to 50 ml

WCP (front side)

Date № Pr.
Coffeini-Natrii benzoatis 5.0
Sol. Natrii hydroxydi 0.1 M gtts IV
(1 ml – 20 drops)
Aquae pro injectionibus ad 50 ml
V_{total}=50 ml
Sterilis
Prepared by: (signature)
Checked by: (signature)

1.4. STABILIZATION OF HYDROLYSABLE SOLUTIONS

THE SCHEME OF HYDROLYSIS OF A WEAK BASE SALT AND STRONG ACID

The scheme of hydrolysis

$BA + HOH \leftrightarrow BOH + H^+ + A^-$

where: BA – is a hydrolyzing substance;

BOH – a weakly dissociated base.

Solutions of the weak base salt and the strong acid are stable

Without adding the stabilizers

Solutions:

- Dimedrol
- Papaverine hydrochloride
- Trimecain
- Emetine hydrochloride
- Ephedrine hydrochloride

When adding 0.1 M hydrochloric acid solution

Solutions:

- Atropine sulphate
- Dibasol
- Dicain (0.1%; 0.2%; 0.3%)
- Novocain (0.25%; 0.5%; 1%; 2%)
- Scopolamine hydrobromide
- Spasmolithin
- Strychnine nitrate

When adding 0.1 M hydrochloric acid solution and antioxidants

Solutions:

- Apomorphine hydrochloride
- Novocain (5%; 10%)

1.4. STABILIZATION OF HYDROLYSABLE SOLUTIONS

Rp.: Sol. Novocaini 0.5% 200 ml
Sterilisa!
D. S. For infiltrative anesthesia.

Novocain solutions are stabilized by 0.1 M hydrochloric acid solution to adjust pH 3.8-4.5 (SPh X). The amount of it depends on the concentration of novocain in the solution.

The amount of 0.1 M hydrochloric acid solution per 1 liter of novocain solution for injections

Novocain solution, %	The volume of hydrochloric acid, ml
0.25	3
0.5	4
1	9
2	12

The given medicine is a solution of a strong-effective substance –the weak base salt and the strong acid for injections requiring stabilization.

WCP (reverse side)

Novocaini: 0.5 x 2 = 1.0
0.1 M hydrochloric acid solution:
1000 ml – 4 ml
200 ml – X
X = 0.8 ml
1 ml – 20 drops
0.8 ml – X
X = 16 drops
Water for injection up to 200 ml

WCP (front side)

Date № Pr.

Novocaini 1.0
Sol. Acidi hydrochlorici 0.1 M gtts XVI (1 ml – 20 drops.)
Aquae pro injectionibus ad 200 ml
V_{total}=200 ml
Sterilis

Prepared by: (signature)
Checked by: (signature)

1.5. STABILIZATION OF SOLUTIONS OF EASILY OXIDIZABLE SUBSTANCES

Oxidation of medicinal substances in the process of preparing solutions for injections takes place in the presence of oxygen contained in water and over the solution. The process of oxidization considerably strengthens under the influence of sensitizing factors:

- ***light;***
- ***warmth;***
- ***value of the pH medium, etc.***

THE SCHEME OF OXIDATION

$$\mathbf{RH \xrightarrow{O_2} R \xrightarrow{RH} RO_2 \xrightarrow{RH} ROOH \rightarrow R}$$

where: RH – is an oxidized substance;
R– is an alkyl radical;
RO_2– is a radical peroxide;
ROOH – is a hydroperoxide.

Stabilization of solutions of easily oxidizable substances is carried out by:

- introduction of antioxidants;
- introduction of complexones for binding ions of heavy metals;
- adjustment of the optimal pH range;
- decrease of oxygen content in a solvent and over the solution (saturation of CO_2, filling in the stream of a rare gas);
- use of a light-resistant container for reducing influence of the light.

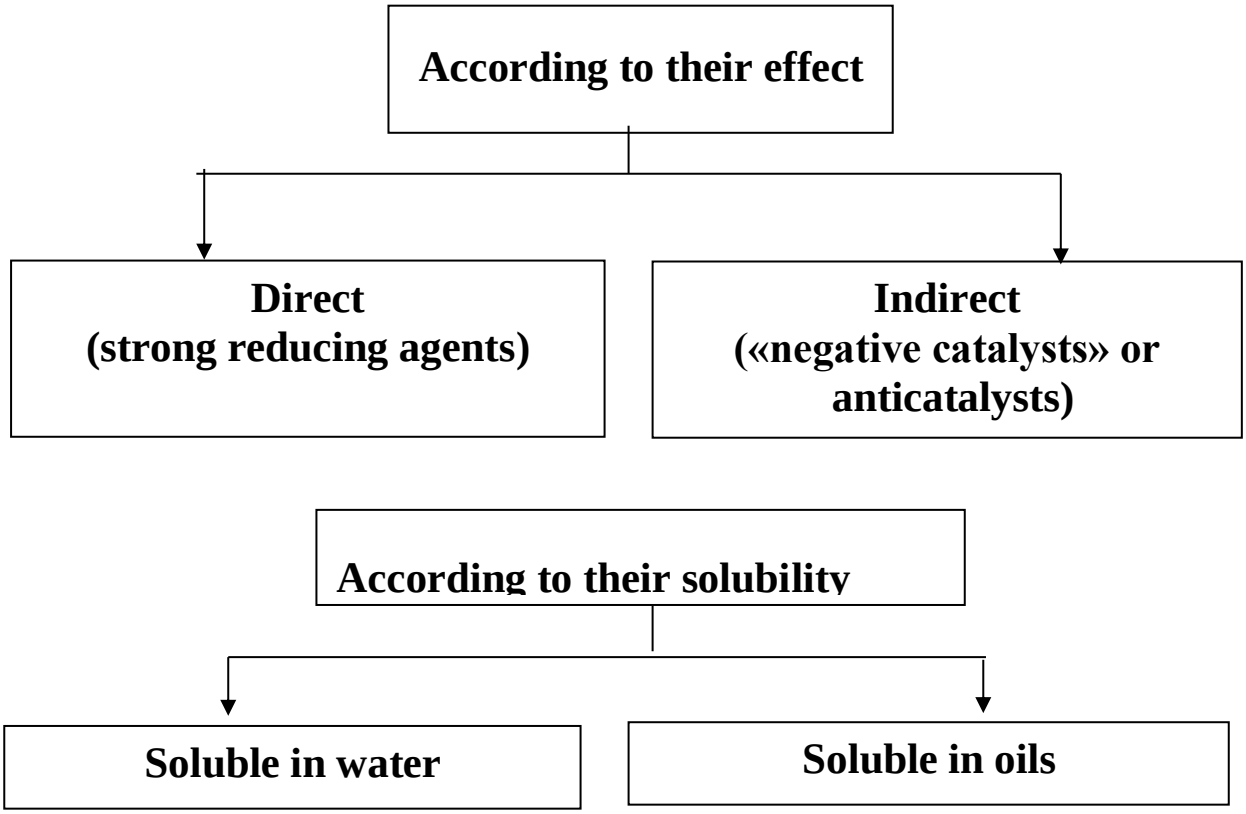
1.6. CHARACTERISTICS OF ANTIOXIDANTS

Antioxidants are auxiliary substances preventing oxidation; in pharmaceutical practice they are applied to stabilize solutions of easily oxidizable substances.

Requirements to antioxidants:

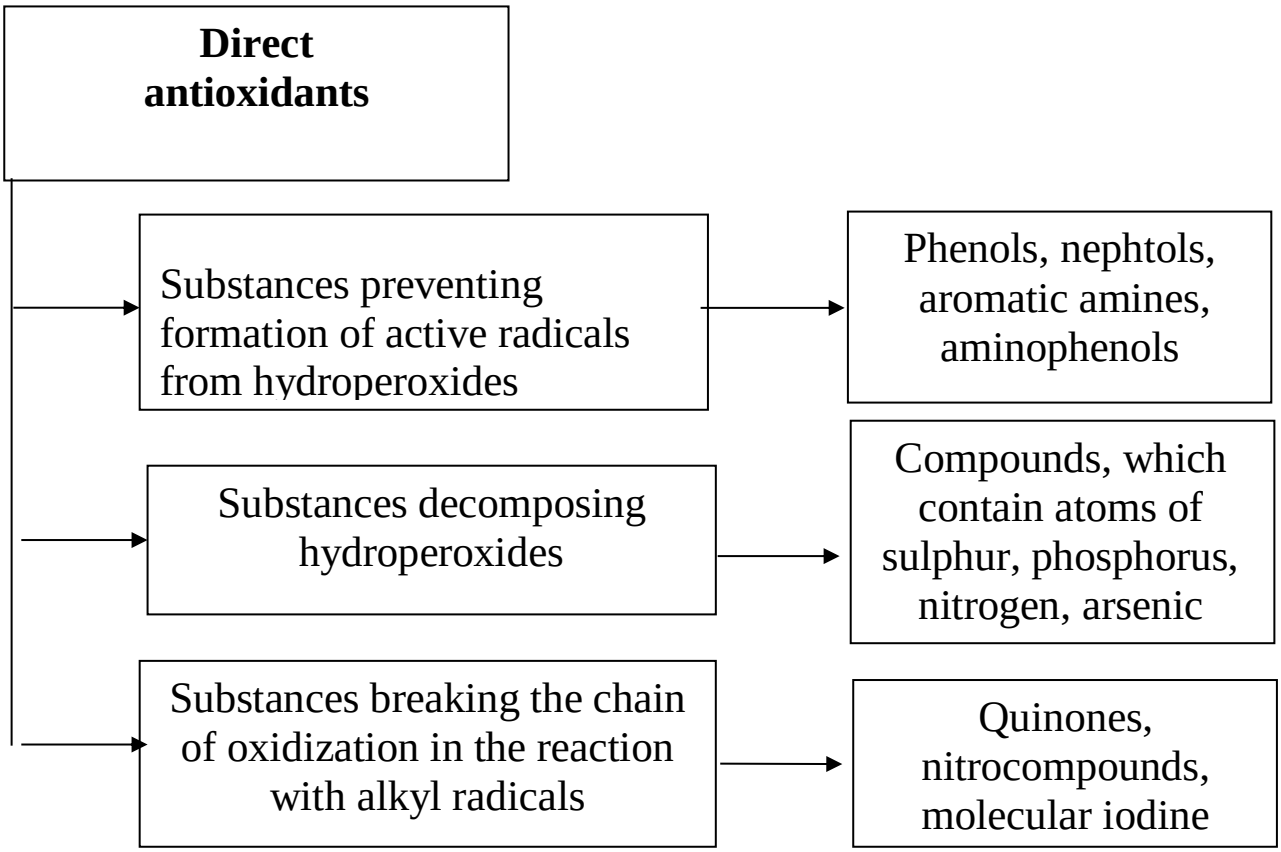
- harmlessness of both antioxidants and products of their metabolism, as well as ingredients formed in the doses applied (absence of non- irritating and allergic effect);
- efficiency at minimal concentrations;
- a good solubility in a dispersion medium.

Classification of antioxidants

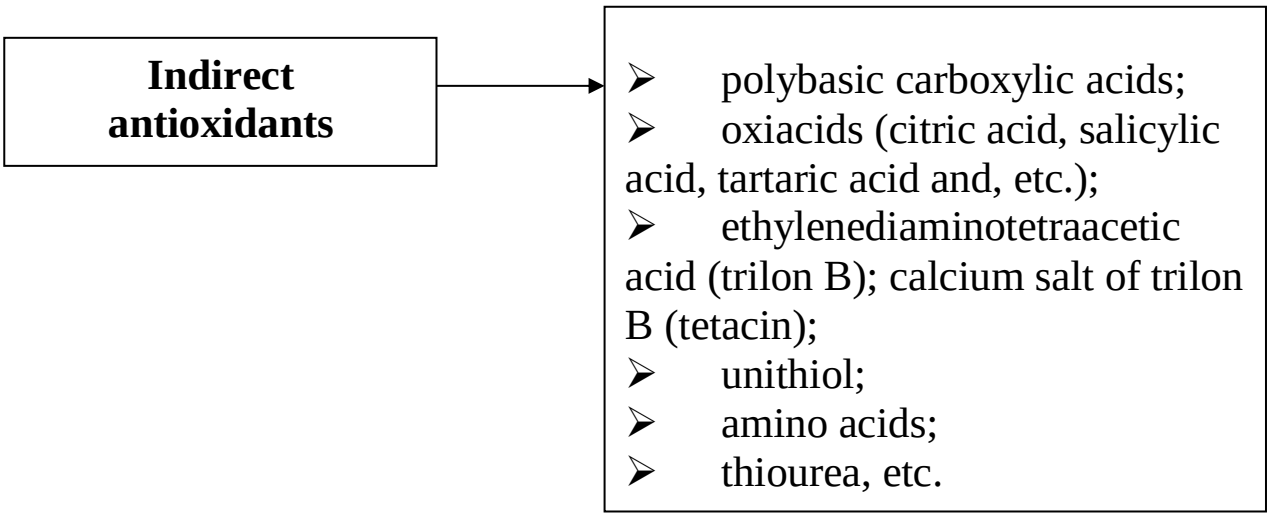


1.6. CHARACTERISTICS OF ANTIOXIDANTS

Direct antioxidants *are strong reducing agents, which are characterized by a higher ability to oxidization than medicinal substances stabilized by them, belong to the class of.*



Indirect antioxidants are the substances, which bind cations of metals occurring in solutions of medicinal substances as admixtures from medicines and being the catalysts of oxidation processes into practically non-dissociated compounds.



1.6. CHARACTERISTICS OF ANTIOXIDANTS

APPLICATION OF ANTIOXIDANTS IN SOLUTIONS FOR INJECTIONS

Stabilizers	Medicinal substance, which is stabilized
Direct antioxidants: Analgin Sodium sulphite (Na_2SO_3)	Apomorphine hydrochloride Ascorbic acid Sodium p-aminosalicylate Streptocide dissoluble (0.5%, 5%, 10%) Ethazol sodium
Sodium metabisulphite ($Na_2S_2O_5$)	Vikasol Ascorbic acid Sodium salicylate
Sodium bisulphite ($NaHSO_3$)	Novocainamide (procainamide hydrochloride)
Sodium thiosulphate ($Na_2S_2O_3$)	Vikasol Dicain (1%, 2%) Novocain (5%, 10%) Dissoluble streptocide (5%, 10%)
Unithiol	Thiamine bromide (3%, 6%) Thiamine chloride (2.5 %, 5%)
Cysteine	Apomorhine hydrochloride
Indirect antioxidants («negative catalysts»): Trilon B (ethylene diaminetetracetic disodium salt)	Sodium hydrocarbonate (3%, 4%, 5%, 7%)

1.7. PREPARATION OF SOLUTIONS OF EASILY OXIDIZABLE SUBSTANCES

Rp.: Sol. Acidi ascorbinici 5% 100 ml
Sterilisa!
D. S. For intravenous injections.

The given medicine is a solution for injections, which consists of an easily oxidizable substance, which requires stabilization. pH = 6.0 –7.0 (SPh. X).

WCP (reverse side)

Ascorbic acid 5.0
Sodium metabisulphite 0.1
(or sodium sulphite 0.2)
Sodium hydrocarbonate 2.38
Water for injections up to 100 ml
or
100 - (5.0 x 0.61 + 2.38 x 0.3) = 96.24 ml

WCP (front side)

Date № Pr.
Natrii methabisulfitis 0.1
(seu Natrii sulfitis 0.2)
Acidi ascorbinici 5.0
Natrii hydrocarbonatis 2.38
Aquae pro injectionibus ad 100 ml
V_{total}=100 ml
Sterilis
Prepared by: (signature)
Checked by: (signature)

Place 0.2 g of sodium metabisulphite (or 0.1 g of sodium sulphite) into a volumetric flask, dissolve in a large amount of water for injections for binding of free oxygen, add subsequently 5.0 g of ascorbic acid and 2.38 g of sodium hydrocarbonate and dilute with water for injections to 100 ml. After the qualitative and quantitative analysis, filter the solution into a bottle for dispensing, then check the presence of particulate matters, cork the bottle hermetically by a rubber cap under aluminium cover and sterilize in autoclave: at 120ºC for 8 min.

Perform the secondary control of quality and register for dispensing by the number of prescription, labels “For injections”, “Sterile”.

1.7. PREPARATION OF SOLUTIONS OF EASILY OXIDIZABLE SUBSTANCES

Rp.: Sol. Natrii hydrocarbonatis 5% 100 ml
Sterilisa!
D. S. For intravenous injections.

The given medicine is a solution for injections. ***(pH 8.1 – 8.9).***

WCP (reverse side) WCP (front side)

Sodium hydrocarbonate 5.0
Water for injections up to 100 ml
or
100 – (5.0 x 0.3) = 98.5 ml

Date № Pr.
Natrii hydrocarbonatis 5.0
Aquae pro injectionibus ad 100 ml
V_{total}=100 ml
Sterilis
Prepared by: (signature)
Checked by: (signature)

If sodium hydrocarbonate contains more than 0.05 % of calcium salts as an admixture, its solutions are stabilized by trilon B

The amount of trilon B per 1 l of sodium hydrocarbonate solution for injections

The content of sodium hydrocarbonate solution, (%)	Amount of trilon B, (g)
3	0.02
4	0.03
5	0.04
7	0.05

Peculiarities of formulation of sodium hydrocarbonate solutions for injections:

- a substance with the mark «chemically pure», «pure for analysis», «suitable for injections» (amount of calcium and magnesium ions should be less than 0.05 %);
- dissolution is performed at of 15-20º C without shaking thoroughly;
- bottles are filled up to 2/3 of volumes (70 %);
- bottles are sterilized, when they are turned upside-down or when they are in the horizontal position;
- the medicine is used in 2-3 hours after complete cooling and shaking (to dissolve carbonic acid, which is over the solution).

1.7. PREPARATION OF SOLUTIONS OF EASILY OXIDIZABLE SUBSTANCES

Stabilization of glucose solutions is carried out by adjusting the solution, which consists of sodium chloride, hydrochloric acid and purified water (Weibel liquid), to pH 3.0 – 4.0.

The content of Weibel liquid	
For volumes more than 1 l (per 1 l of the solution)	**For volumes less than 1 l** (5 % of the volume of glucose solution)
Sodium chloride 0.26 0.1 M hydrochloric acid 5 ml	Sodium chloride 5.2 8.3 % hydrochloric acid 4.4 ml Water for injections up to 1 l

Rp.: Sol. Glucosi 10% 100 ml
Sterilisa!
D. S. For intravenous injections.

The given medicine is a solution for injections containing glucose – a hygroscopic substance and requiring stabilization.

WCP (reverse side)

Glucose (humidity is 9 %)

$$X = \frac{a \times 100}{100 - b} = \frac{10 \times 100}{100 - 9} = 11{,}0$$

Weibel liquid
100 ml – 100 %
X – 5 %; X = 5 ml
Water for injections up to 100 ml
or
100 – (11.0 x 0.69 – 5 ml) = 92.4 ml

WCP (front side)

Date № Pr.
Glucosi 11.0 (hum. 9%)
Liquoris Wejbeli 5 ml
Aquae pro injectionibus ad 100 ml
V_{total}=100 ml
Sterilis

Prepared by: (signature)
Checked by: (signature)

The role of sodium chloride is:

- formation of the aldehyde group complex;
- shifting the equilibrium toward formation of a cyclic form of glucose.

1.8. CHARACTERISTICS OF PRESERVATIVES

Microbiological instability is a change in medicines of oxidizing, hydrolytic and other character under the influence of microorganisms and products of their vital activity (toxins or enzymes).

It is possible to prevent microbiological instability of solutions for injections by addition different chemical antibacterial substances – ***antimicrobial stabilizers (preservatives) to them.***

Preservatives are the auxiliary substances used for prevention of contamination and reproduction of microorganisms in medicines.

The choice of a preservative is determined by:

- ***the composition of a medicine;***
- ***pH of the medium;***
- ***the scheme of drug administration.***

Medicine for intracavitary, intraocular or other injections reaching the spinal fluid, as well as a single dose exceeding 150 ml must not contain any preservatives.

1.8. CHARACTERISTICS OF PRESERVATIVES

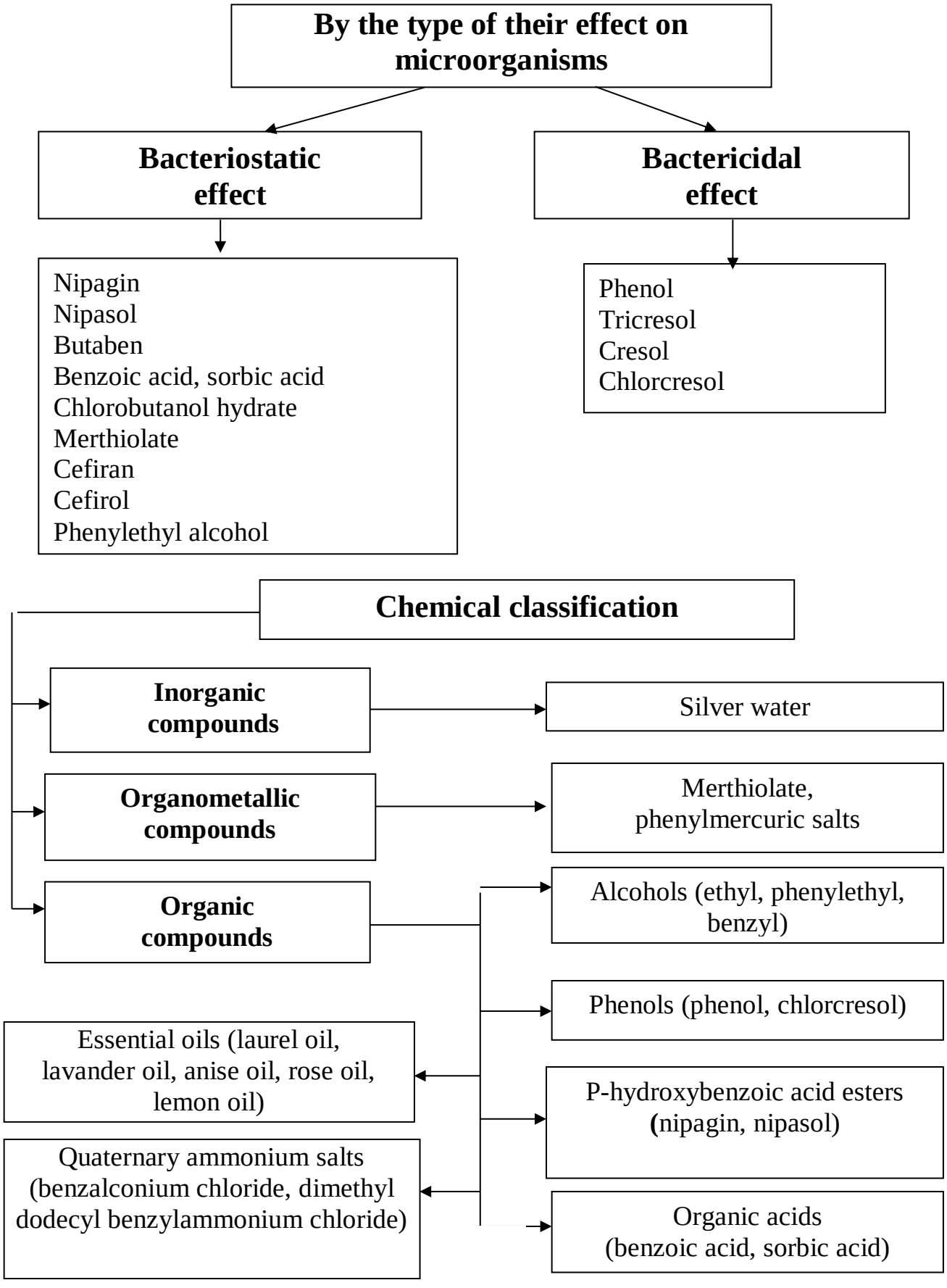
Requirements to preservatives:

- pharmacological indifference in the concentration used (absence of generally toxic, allergenic and locally irritable effect);
- a wide spectrum of antimicrobial action at low concentrations;
- a good solubility in a dispersion medium;
- chemical indifference (absence of chemical interaction with medicinal and auxiliary substances and packing materials;
- stability within a wide range of pH and temperatures during the shelf life of medicines;
- absence of the effect on organoleptic properties of medicines;
- support of sterility of medicinal forms for the whole period of their application (a reliable antimicrobial activity);
- absence of ability to form stable strains of microorganisms.

Preserving does not exclude the observance of sanitary rules of a manufacturing process, which should promote to the maximal decrease of microbical contamination of medicines

1.8. CHARACTERISTICS OF PRESERVATIVES

CLASSIFICATION OF PRESERVATIVES



1.8. CHARACTERISTICS OF PRESERVATIVES

Application of preservatives in the formulation of sterile and aseptically prepared solutions for injections

Nomenclature of preservatives	Concentration
Inorganic compounds	
Silver water	1-10 mg/l
Organometallic compounds	
Merthiolate	0.005 % 0.02 % 0.01 %
Phenylmercuric acetate	to 0.02 %
Phenylmercuric nitrate	0.001 – 0.002 % 0.004 %
Organic compounds	
Alcohol: lethyl alcohol	0.3 –0.5 %
l alcohol	1-2 %
butanol hydrate	0.5 %
Phenol and its derivatives: phenol	0.25-0.3(0.5) %
chlorcresol	0.05 % 0.1 %
p-hydroxybenzoic acid esters (nipagin, nipasol, butabene)	to 0.5 %
Organic acids: – sorbic acid	0.1-0.2 %
Quaternary ammonium salts: benzalconium chloride	0.01 %
dimethyl dodecyl benzylammonium chloride	0.01 %

Stabilization of solutions for injections **by complex methods** is carried out by introduction of several stabilizers of different types:

- some direct antioxidants;
- a direct and indirect antioxidant;
- an antioxidant and a substance providing pH of the medium;
- an antioxidant and a preservative.

1.9. QUESTIONS FOR SELF-CONTROL

1. Specify the types of instability and the causes of changes in injections solutions.
2. Name physical processes occurring in solutions for injections and methods of physical stabilization.
3. Name chemical processes occurring in solutions for injections and explain what they depend on.
4. Name the requirements to stabilizers and their classification.
5. Name the peculiarities of technology of sodium hydrocarbonate solutions for injections.
6. Specify the features of stabilization of glucose.
7. Name the requirements to preservatives and their classification.

SOLUTIONS FOR INJECTIONS WITH THERMOLABILE SUBSTANCES. SUSPENSIONS FOR INJECTIONS

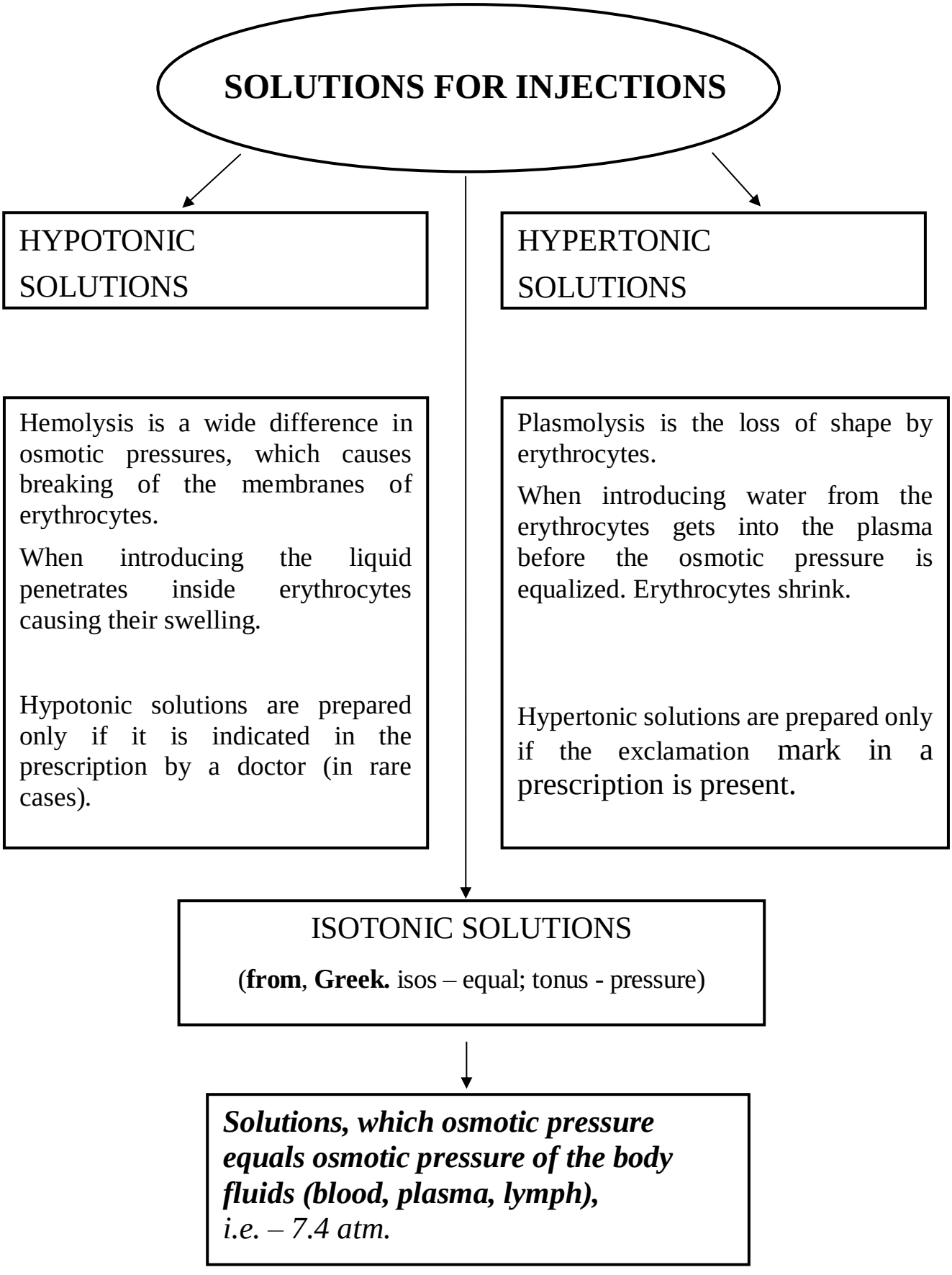
INTRODUCTION

Introduction of solutions for injections, which osmotic pressure differs from osmotic pressure of blood plasma, causes evident pain: the stronger it feels; the greater the osmotic difference is. The practical necessity to study this topic is in the possibility to remove the feeling of violent pain when using solutions for injections by introduction of auxiliary substances for isotonicity.

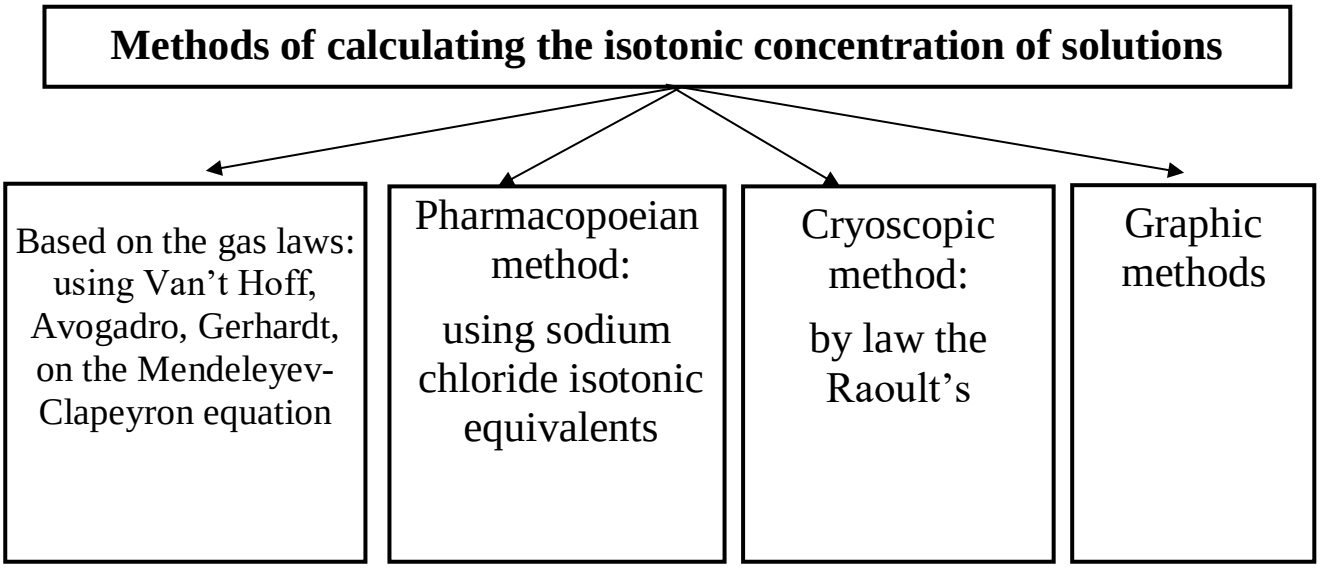
The assortment of medicines for supporting and restoring of the volume and composition of intracellular and extracellular fluid is represented rather great by both domestic and foreign manufacturers. Infusion therapy is an integral part of the complex of the therapeutic measures carried out when treating diseases and damages accompanied with the considerable pathological changes in basic organs and systems and widely used primarily while rendering emergency first aid and in intensive therapy. The basis of infusion therapy is the prolonged (within several hours and even some days) parenteral introduction lies of considerable amounts of the liquid containing metabolically active components in to the organism.

Infusion medicines should meet the requirements included into the corresponding normative and technical documentation. The general article related to these medicinal forms is included in the State Pharmacopoeia of Ukraine: «Medications for parenteral use».

2.1. CLASSIFICATION OF SOLUTIONS FOR INJECTIONS



2.2. METHODS OF CALCULATING THE ISOTONIC CONCENTRATION OF SOLUTIONS



THE CALCULATION OF ISOTONIC CONCENTRATIONS OF SOLUTIONS FOR NON-ELECTROLYTES BASED ON THE GAS LAWS

THE CALCULATION BY THE VAN'T-HOFF EQUATION

1 g/mol – at 0º C or 273 K and 1 atm occupies the volume of 22.4 l

The amount of water for dissolving 1 g/mol of a substance is:

$$22.4 : 7.4 = 3.03 \text{ l}$$

Correction to the temperature of the human body:

$$273 \text{ K} + 37 \text{ K} = 310 \text{ K}$$

273 K – 3.03 l
310 K – x l x = 3.44 l
To prepare of 1 liter of the solution:
1 g/mol – 3.44 l
x g/mol – 1 l x = 0.29 g/mol

$$\mathbf{m = 0.29xM}$$

where: **m** – is the mass of a substance, g;
0.29 – is the isotonicity factor of a non-electrolyte;
M – is the molecular weight of a substance.

2.2. METHODS OF CALCULATING THE ISOTONIC CONCENTRATIONS OF SOLUTIONS

By the Mendeleyev-Clapeyron equation

$$\mathbf{PV = nxRT}$$

P **–** is the osmotic pressure of blood plasma, 7.4 atm;

V – is the volume of the solution, l;

R – is the universal gas constant, 0.082 (atmxl)/molxgrad;

T – is the absolute body temperature, 310 K;

n – is the number of g/mol of the dissolved substance.

$$\mathbf{n} = \frac{\mathbf{PV}}{\mathbf{RT}} \text{ or } \mathbf{n} = \frac{\mathbf{m}}{\mathbf{M}}; \quad \frac{\mathbf{m}}{\mathbf{M}} = \frac{\mathbf{PV}}{\mathbf{RT}} \qquad \mathbf{m} = \frac{\mathbf{MPV}}{\mathbf{RT}} = \frac{\mathbf{M \cdot 7.4 \cdot 1}}{\mathbf{0.082 \cdot 310}} = \mathbf{M \cdot 0.29} \text{ g/mol}$$

$$\mathbf{m = 0.29 \text{ x } M}$$

where: **m** – is the mass of a substance, g;

0.29 – is the isotonicity factor of an non-electrolyte;

M – is the molecular weight of a substance.

2.2. METHODS OF CALCULATING THE ISOTONIC CONCENTRATION OF SOLUTIONS

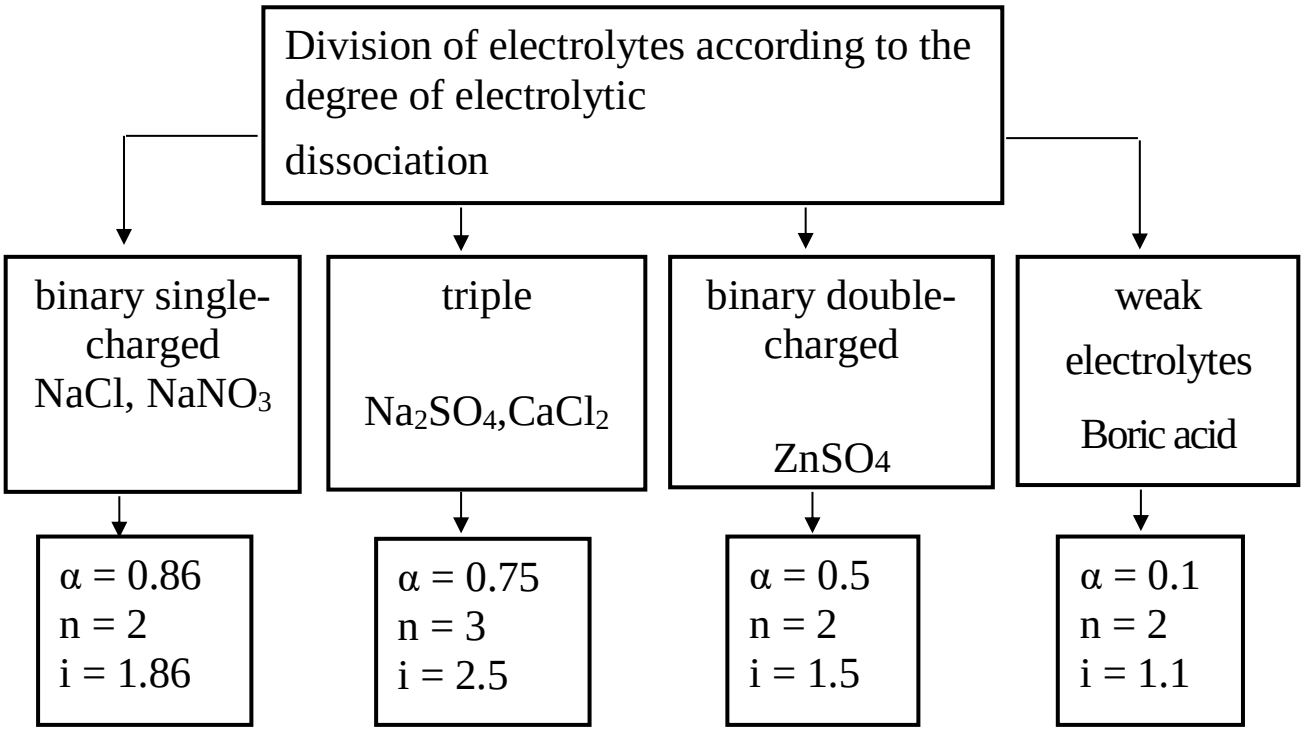
THE CALCULATION OF ISOTONIC CONCENTRATIONS OF SOLUTIONS FOR NON-ELECTROLYTES

$$m = (0.29xM) / i$$

i – *is the isotonic coefficient, which shows how many times the number of elementary particles of the dissolved substance increase due to electrolytic dissociation*.

$$i = 1 + \alpha (n - 1)$$

i – is the isotonic coefficient – is the electrolytic dissociation degree – is the number of particles formed from 1 molecule of the substance during the process of dissociation.



2.2. METHODS OF CALCULATING THE ISOTONIC CONCENTRATION OF SOLUTIONS

THE CALCULATION OF ISOTONIC CONCENTRATIONS OF SOLUTIONS USING OF SODIUM CHLORIDE ISOTONIC EQUIVALENTS

Advantages of the method (it is the Pharmacopoeian method):

- universal;
- accurate;
- the most frequently applied in the pharmacy practice.

Sodium chloride isotonic equivalent (E) – is the quantity of sodium chloride, which at equal conditions creates the osmotic pressure that is equal to the osmotic pressure created by 0.1 g of a medicinal substance

The name of medicinal substances	**The equivalent of substances by NaCl**	**Isotonic concentration, %**
Sodium chloride (NaCl)	-	0.9
Sodium nitrite ($NaNO_2$)	0.66	1.3
Sodium sulphate (Na_2SO_4)	0.23	3.9
Glucose (anhydrous) ($C_6H_{12}O_6$)	0.18	5.2
Boric acid (H_3BO_3)	0.53	1.7

2.2. METHODS OF CALCULATING THE

ISOTONIC CONCENTRATION OF SOLUTIONS

THE CALCULATION OF ISOTONIC CONCENTRATIONS OF SOLUTIONS USING RAOULT'S LAW (CRYOSCOPIC METHOD)

Raoult's law : ⟶ Pressure of vapour over the solution is proportional to the molar fraction of the dissolved substance

↓

The conclusion from the Raoult's law:

- decrease in the freezing temperature (depression) is proportional to the decrease in the vapor pressure and proportional to the concentration of the dissolved substance in the solution;
- isotonic solutions of different substances freeze at the same temperature, i.e. have identical temperature depression of 0.52°C (depression of the blood serum).

If the prepared solution of a substance has the depression equal to 0.52°C, it will be isotonic to the blood serum.

Depression (decrease) in the freezing temperature point of 1 % solution of a medicinal substance (Δt) in comparison with the freezing temperature point 1 % solution of sodium chloride decreases in comparison with the freezing temperature point of solvent.

1 % – Δt (reference data)
x – 0.52ºC

$$X = \frac{0.52\ C \times 1\%}{\Delta t}$$

m – is the amount of a medicinal substance required for isotonicity, g;
V – is the volume, ml.

$$m = \frac{0.52^{o}\ C \times V}{\Delta t \times 100}$$

2.2. METHODS OF CALCULATING THE ISOTONIC CONCENTRATION OF SOLUTIONS

Rp.: Sol. Glucosi 3% 100 ml isotonicae
Sterilisa!
D. S. For intravenous introduction.

The given medicine is a solution for injections for intravenous introduction, requiring stabilization.

WCP (reverse side)

Control of isotonicity:

1) b*y the van't-Hoff equation*: m = 0.29 x M; M = 180
m = 0.29 x 180 = 52 g/l
i.e. the isotonic concentration of the glucose solution– 5.2%

2) *by the Raoult's law*: 1% – 0.104 ºC
x – 0.52 ºC x = 5 %

3) *by sodium chloride isotonic equivalent*: $E_{glucose}$ = 0.18
0.18 $_{NaCl}$ – 1.0 of glucose
0.9 – x x = 5.0
i.e. the isotonic concentration of glucose - 5 %

The amount of sodium chloride for making the solution more isotonic

- 1.0 of glucose – 0.18 NaCl 3.0 of glucose – x x = 0.54
  0.9 – 0.54 = 0.36

The volume isotonised by 3.0 g of glucose

5.0 – 100 ml
3.0 – x x = 60 ml

- *The volume of water without isotonisation:* 100 – 60 = 40 ml
Sodium chloride 0.9 – 100 ml
x – 40 ml x = 0.36
- *The amount of glucose necessary to reach the isotonicity of the solution:*

5.0 – 3.0 = 2.0

2.2. METHODS OF CALCULATING THE ISOTONIC CONCENTRATION OF SOLUTIONS

The amount of sodium chloride:

0.18 $_{NaCl}$ – 1.0 of glucose

x – 2.0 of glucose x = 0.36

Anhydrous glucose 3.0

Glucose (hum. 9%)

$$x = \frac{a \ x \ 100}{100 \ - \ в} = \frac{3 \ x \ 100}{100 \ - \ 9} = 3.3$$

a – the weight of anhydrous glucose, g;
b – humidity, %

Weybel stabilizer: 5 ml
(5 % of the volume irrespective of the glucose concentration)

Water for injections up to 100 ml

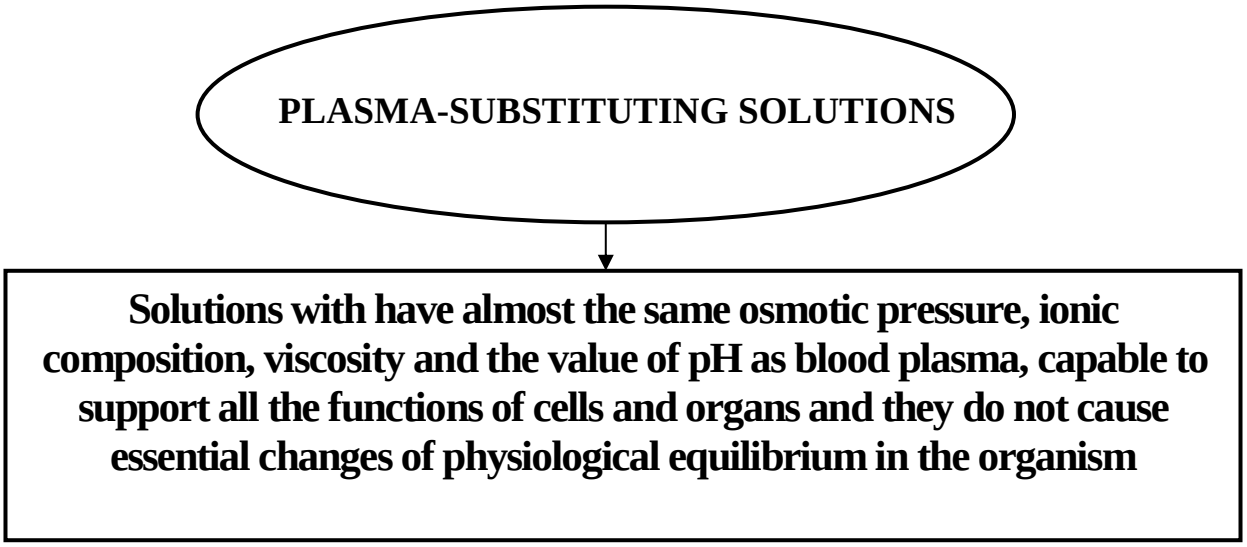
In aseptic conditions place 3.3 g of glucose (humidity 9 %) and 0.36 g of sodium chloride into a sterile 100 ml volumetric flask, add one part of water for injections and dissolve, then add 5 ml of the Weybel stabilizer, mix, and dilute with water for injections.

Perform the quantitative and qualitative analysis, filter the substance and cork with a rubber cap. After that check the presence of particulate matters, cork the bottle by aluminium cover and sterilize at 120°C for 8 minutes immediately after preparation. After sterilization perform the secondary quality control. Then register the medicine for dispensing by the number of prescription and labels «For injections» and «Sterile».

WCP (front side)

Date № Pr.
Glucosi 3.3 (hum. 9 %)
Natrii chloridi 0.36
Liquoris Wejbeli 5 ml
Aquae pro injectionibus ad 100 ml
V = 100 ml
Sterilis
Prepared by: (signature)
Checked by: (signature)

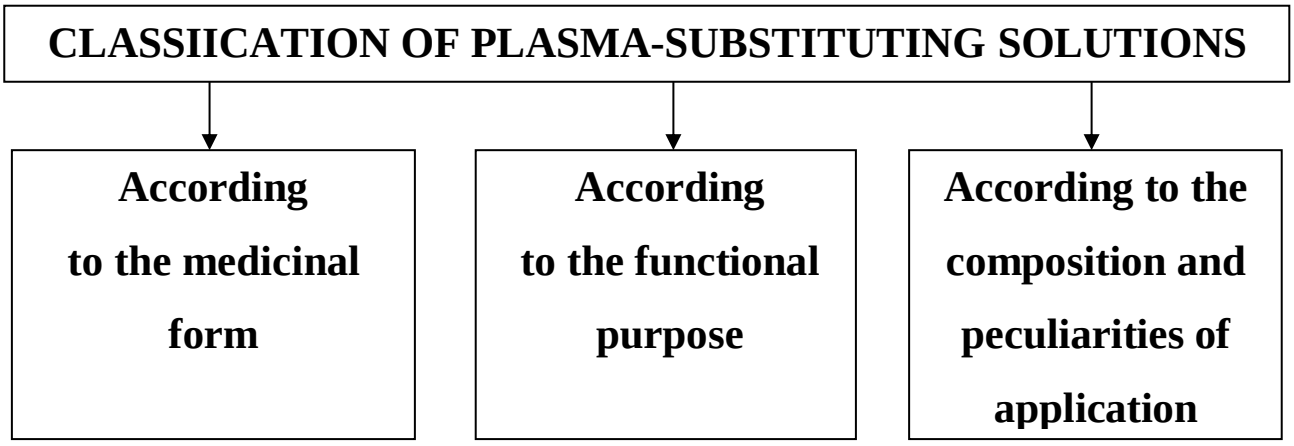
2.3. PLASMA-SUBSTITUTING SOLUTIONS



TASKS OF INFUSION THERAPY

- of the normal volume and composition of extracellular fluid including the volume of circulatory blood;
- normalization of the organism is electrolyte balance taking into account the natural need in electrolytes and their pathological losses;
- correction of shifts in the acid-base balance;
- normalization of homeostatic and rheological properties of blood;
- maintenance of the normal macro- and microcirculation;
- preventive measures and treatment of functional disorders of the heart, lungs, liver, kidneys, gastro-intestinal tract, endocrine glands;
- providing of the adequate metabolism, i.e. compensation of energy losses of the organism and correction of protein, lipid and carbohydrate metabolism.

2.4. CLASSIFICATION OF PLASMA-SUBSTITUTING SOLUTIONS

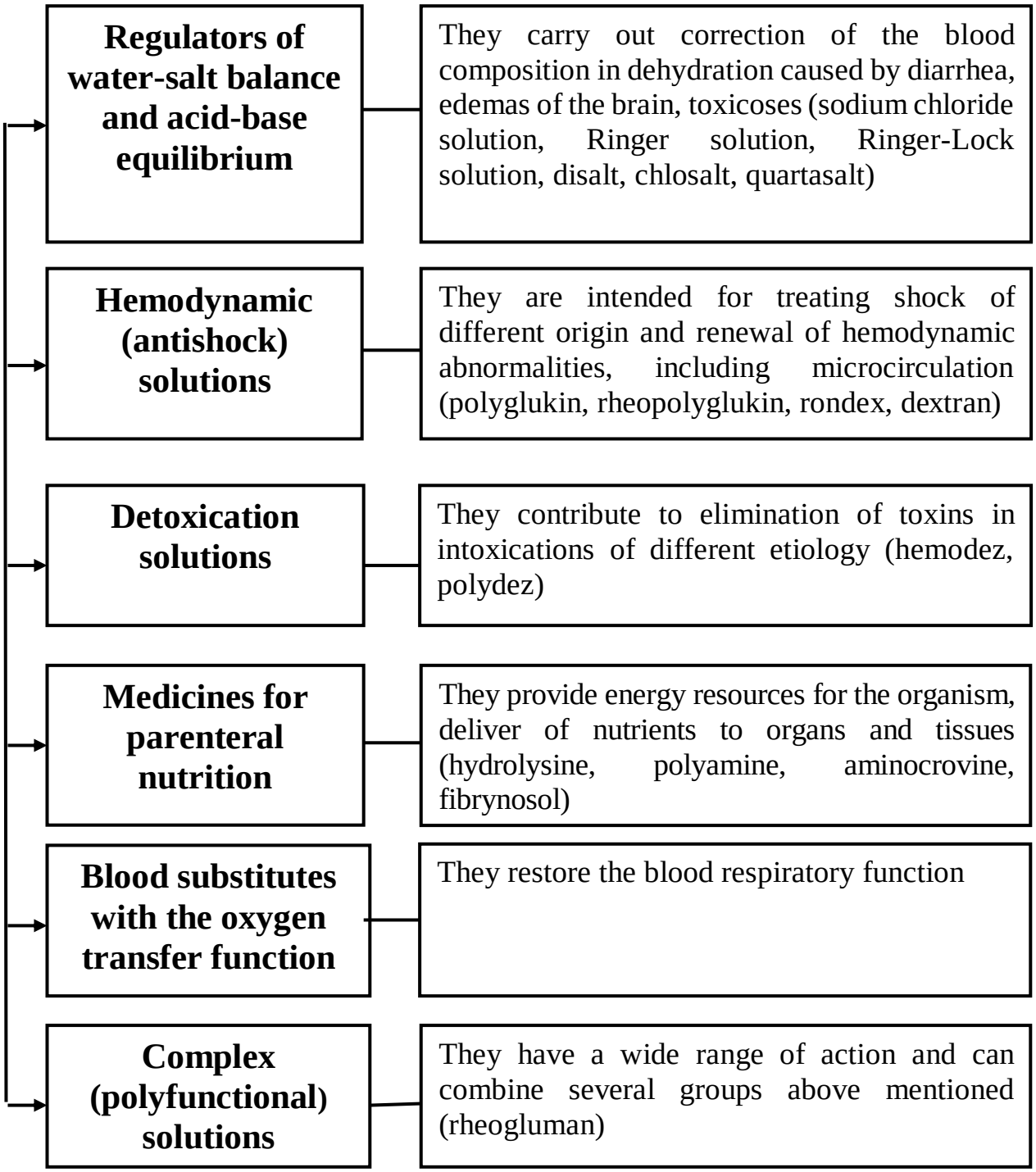


Classification according to the medicinal form:

- solutions for intravenous infusions;
- emulsions;
- concentrates for intravenous infusions;
- powders and lyophilisated medicinal forms for intravenous infusions;
- infusion medicines prepared by the freezing method.

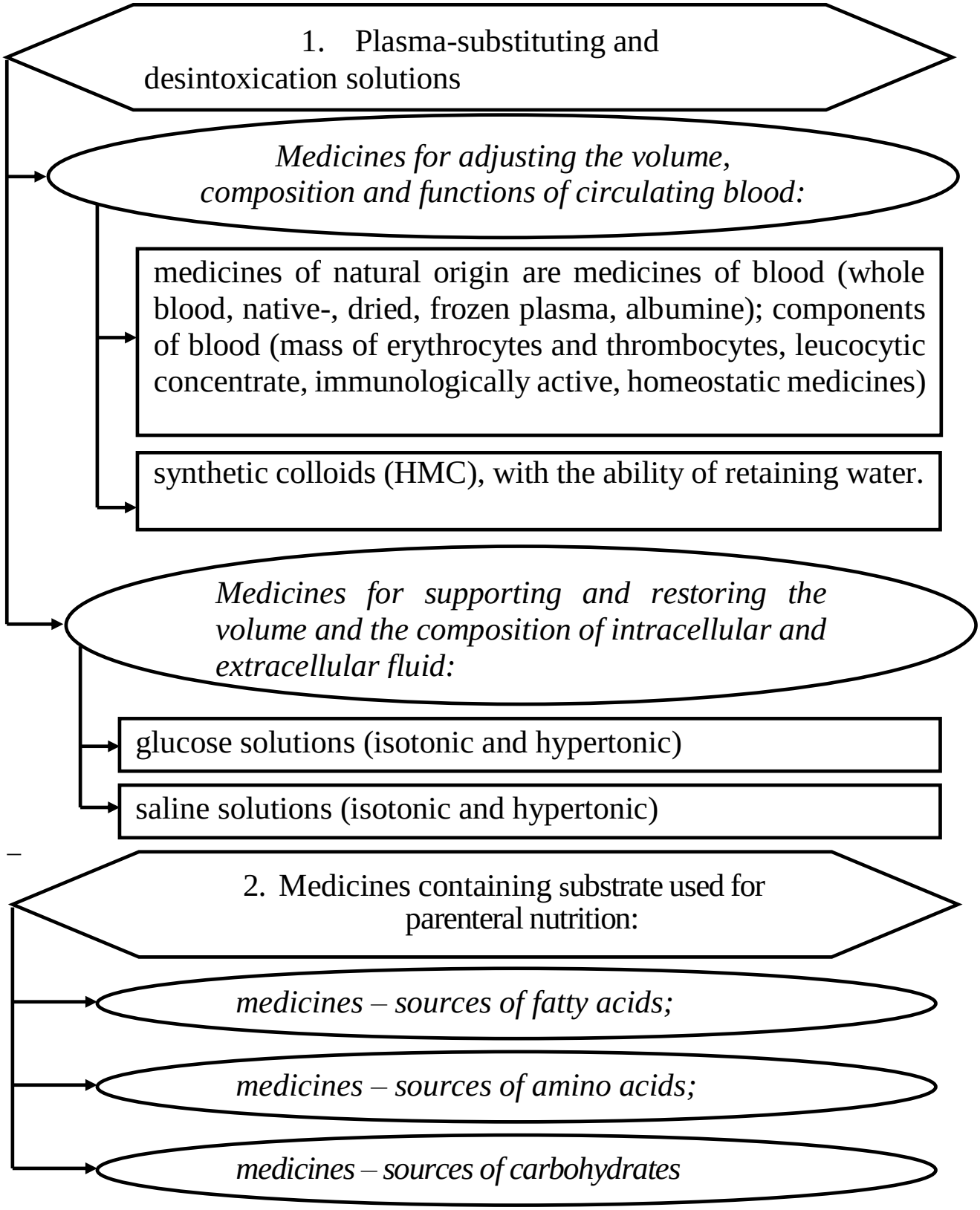
2.4. CLASSIFICATION OF PLASMA-SUBSTITUTING SOLUTIONS

Classification according to the functional purpose

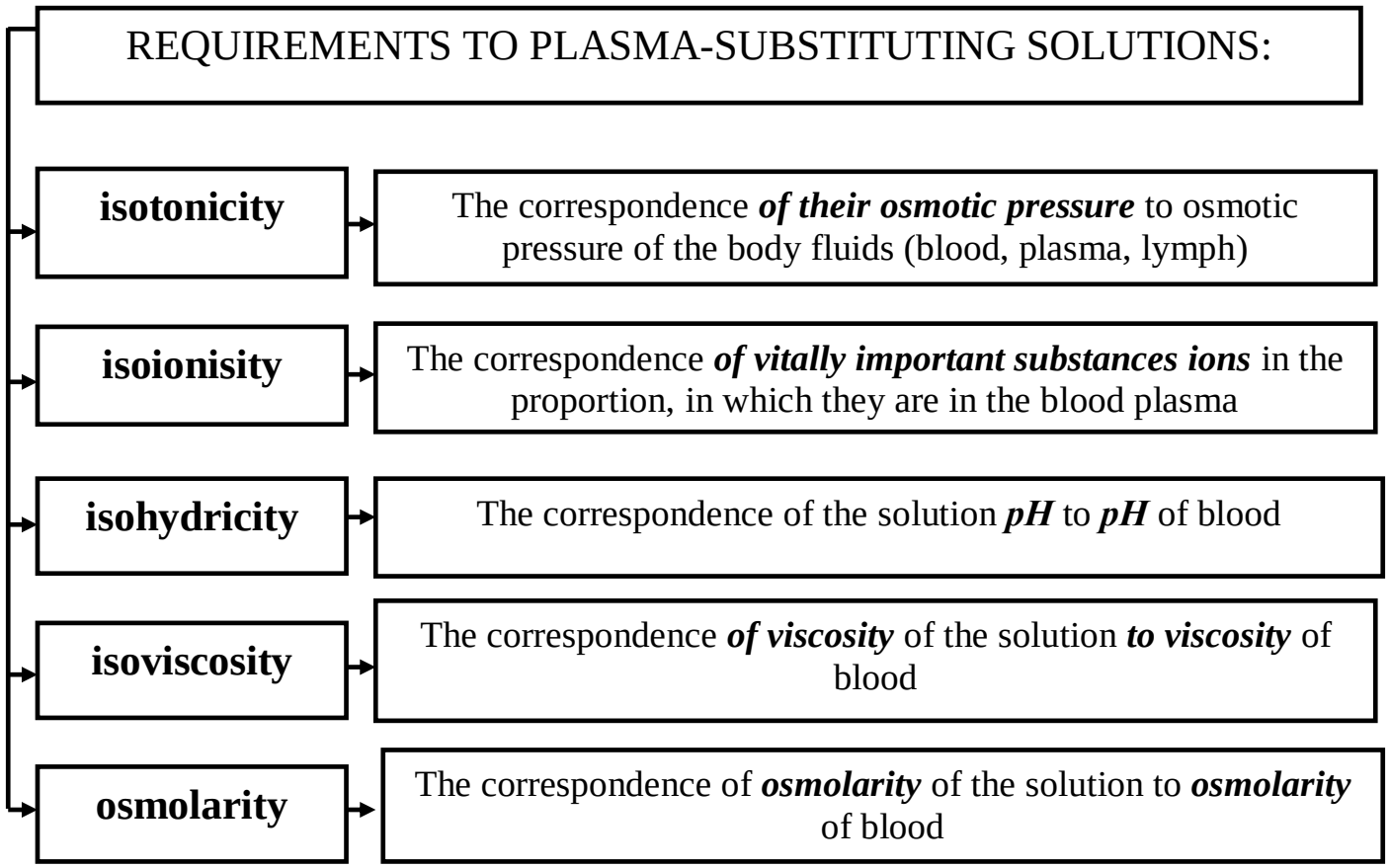


2.4. CLASSIFICATION OF PLASMA-SUBSTITUTING SOLUTIONS

Classification according to the composition and peculiarities of application



2.5. REQUIREMENTS TO PLASMA-SUBSTITUTING SOLUTIONS



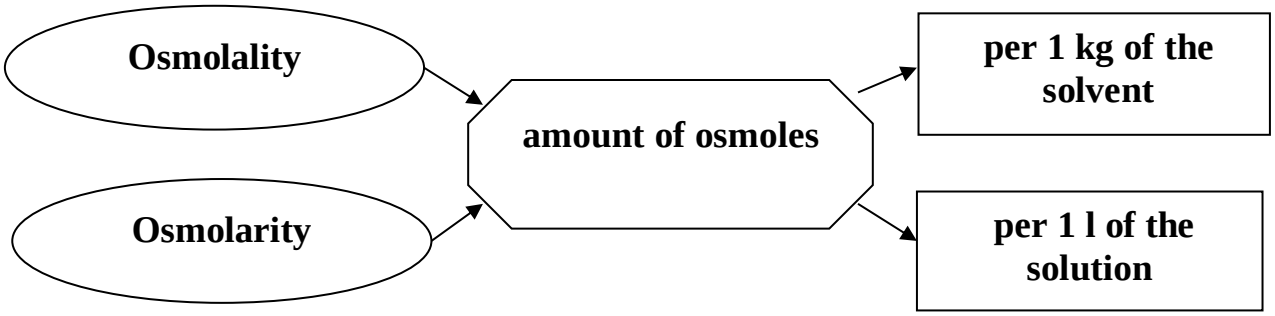
PHYSIOLOGICAL CONSTANTS OF HUMAN BLOOD PLASMA

Osmotic pressure, Pa	72.52×10^4
Ionic composition	Cations: K^+, Na^+, Ca^{2+}, Mg^{2+} Anions: Cl^-, SO_4^{2-}, HPO_3^{2-}, HCO_3^-, PO_4^{3-}
pH value	7.36 – 7.47 (carbonate, phosphate and albuminous systems of ampholytes are applied)
Viscosity, H×c/m²(sP)	0.0015 – 0.0016 (1.5 – 1.6)
Osmolarity, mosmol/l	appr. 300 (corresponds to the pressure ≈ 780 kPa)

2.5. REQUIREMENTS TO PLASMA-SUBSTITUTING SOLUTIONS

***Osmolarity* – is the value of estimating the total contribution of different dissolved substances into the osmotic pressure of the solution. Osmotic pressure is expressed in milli-osmoles (mosmol)**

Along with the concept of «osmolarity» the concept of «osmolality» is used. The difference of these values consists in using in calculations. Different expressions of concentrations of solutions as: *molar and molal*.



The example of theoretical osmolarity calculation of 2 l of 0.9 % sodium chloride solution.

1 mmol of sodium chloride = 2 mosmol ($Na^+ + Cl^-$)

The molecular weight of sodium chloride = 58.44

Two liters of 0.9 % solution contain 18.0 g (18 000 mg) of sodium chloride.

Therefore, there are:

18 000 mg / 58.44 = 308 mosmol per every ion.

The total value of the theoretical osmolarity is:

308 x 2 = 616 mosmol.

2.5. REQUIREMENTS TO PLASMA-SUBSTITUTING SOLUTIONS

Theoretical osmolarity of infusion solutions

№№ п/п	Name		Theoretical osmolarity, mosmol/l
1	Acesalt solution		227.4
2	Solution of glucose:	5 %	262.1
		10 %	514.4
		20 %	1019.0
		25 %	1271.3
3	Disalt solution		234.6
4	Petrov's liquid, a blood substitute		532.4
5	Quartasalt solution		264.8
6	Solution of sodium hydrocarbonate:	3 %	713.4
		4 %	952.2
		7 %	1664.7
7	Solution of sodium chloride:	0,9 %	308.0
		10 %	3422.0
8	Ringer solution		320.9
9	Ringer-Lock solution		325.9
10	Trisalt solution		293.2
11	Chlosalt solution		255.6
12	Solution of aminocapronic acid, 5 %		381.2
13	Solution of mannitol, 15 %		1131.1
14	Solution of sodium hydrocitrate:	4 %	456.1
		5 %	570.0
		6 %	1684.1
15	Solution of sodium citrate:	4 %	448.0
		5 %	660.0
16	Ringer-acetate solution		302.4

2.5. REQUIREMENTS TO PLASMA-SUBSTITUTING SOLUTIONS

COMPOSITIONS OF PLASMA-SUBSTITUTING LIQUIDS

Names of solutions	The content of salts included into thesolution, g/l										
	sodium chloride	potassium chloride	sodium hydrocarbonate	sodium acetate	calcium chloride	magnesium chloride	magnesium sulphate	sodium phosphate	sodium hydrophosphate	glucose	other additives
Ringer-Lock solution	9.0	0.2	0.2	–	0.2	–	–	–	–	1.0	–
Tirode solution	8.0	0.2	1.0	–	0.2	0.1	–	0.05	–	1.0	–
Saline infuzine CLOBTI[1]	8.0	0.2	0.8	–	0.25	–	0.05	0.138	–	–	CO_2 to pH 6.0-6.4
LIBT[2] liquid	15.0	0.2	0.1	–	0.2	–	–	–	–	–	–
Atsler-Leman solution	8.0	0.2	1.2	–	0.2	0.1	–	–	–	–	0.7 g gummy-arabic
Petrov's liquid	15.0	0.2	–	–	0.1	–	–	–	–	–	10 % of blood
Sulphur- transfuzine CLOBTI	7.5	0.2	–	–	–	0.1	–	0.052	0.476	10.0	When using it is mixed with the human serum in the ratio of 4:1
Disalt	6.0	–	–	2.0	–	–	–	–	–	–	–
Trisalt	6.0	1.0	4.0	–	–	–	–	–	–	–	–
Quartasalt	4.75	1.5	1.0	2.6	–	–	–	–	–	–	–
Acesalt	5.0	1.0	–	2.0	–	–	–	–	–	–	–
Chlosalt	4.75	1.5	–	3.6	–	–	–	–	–	–	–

Note:

[1] Saline infuzine CLOBTI was offered by the Central Lenin order Blood Transfusion institute (I.A. Fedorov and P.S. Vasilyev).

[2] LIBT – Leningrad Institute of Blood Transfusion (I.R. Petkov and A.M. Filatov).

2.5. REQUIREMENTS TO PLASMA-SUBSTITUTING SOLUTIONS

PLASMA-SUBSTITUTING AND NUTRIENT SOLUTIONS

Group	Medicine	Method of application
Solutions based on polyvinylpyrrolidone and polyvinyl alcohol	Hemodez Hemodez N Polydez Enterodez	Intravenously drop wise
Medicine based on gelatin	Gelatinol	Intravenously drop wise
Medicines based on dextran	Polyglukin Rheopolyglukin Rondex Rheogluman	Intravenously jet, drop wise
Medicines based on protein hydrolyzate or amino acids	Hydrolyzine Aminopeptide Amikine Aminocrovin Protein Casein hydrolyzate Polyamine Phibrinosol	Intravenously drop wise
Medicine based on oil and phosphates	Lipofundine	Intravenously drop wise

2.6. FORMULATION OF PLASMA-SUBSTITUTING SOLUTIONS

Rp.: Natrii chloridi 1.8
Kalii chloridi 0.04
Calcii chloridi 0.04
Natrii hydrocarbonatis 0.04
Glucosi 0.2
Aquae pro injectionibus ad 200 ml
Sterilisa!
D. S. For intravenous introduction.
Ringer-Lock solution.

This medicine is a saline plasma-substituting solution for intravenous introduction.

WCP (reverse side)

Sodium chloride 1.8
Glucose (humidity 9 %)

$$X = \frac{ax100}{100-b} = \frac{0.2x100}{100-9} = 0.22$$

Potassium chloride 0.04
Calcium chloride solution 20 % (1:5)
0.04 x 5 = 0.2 ml
1 ml – 20 drops
0.2 ml – x x = 4 drops
Water for injections up to 100 ml

WCP (reverse side)

Sodium hydrocarbonate 0.04
Water for injections up to 100 ml

The medicine is prepared in aseptical conditions. Prepare the saline composition with glucose (Ringer-Lock solution № 1) in a 100 ml volumetric flask and the sodium hydrocarbonate solution (Ringer-Lock solution № 2) in another one.

After the qualitative and quantitative analysis, filter the solution into a bottle for dispensing, then check the presence of particulate matters, cork the bottle hermetically by a rubber cap under aluminium cover and sterilize in autoclave: at 120ºC for 8 min.

Perform the secondary control of quality and register for dispensing by the number of prescription, labels “For injections”, “Sterile”.

NB! The medicine is made by mixing two solutions prepared separately (immediately before use) in aseptical conditions

WCP (front side)

Date № Pr.
Natrii chloridi 1.8
Glucosi 0.22 (hum. 9 %)
Kalii chloridi 0.04
% (1:5) gtts IV (1 ml = 20 drops)
Aquae pro injectionibus ad 100 ml
V=100 ml
Sterilis

Prepared by: (signature)
Checked by: (signature)

WCP (front side)

Date № Pr.
Natrii hydrocarbonatis 0.04
Aquae pro injectionibus ad 100 ml
V=100 ml
Sterilis

Prepared by: (signature)
Checked by: (signature**)**

2.7. SOLUTIONS FOR INJECTIONS WITH THERMOLABILE SUBSTANCES

PECULIARITIES OF FORMULATION OF SOLUTIONS FOR INJECTIONS WITH THERMOLABILE SUBSTANCES

- they are not sterilized;
- they are prepared in aseptical conditions;
- all thermostable ingredients are sterilized;
- they are filtered through sterile filters.

Rp.: Sol. Hexamethylentetramini 20 % 100 ml
Sterilisa!
D. S. For injections

This medicine is a solution for injections with hexamethylenetetramine, a thermolabile substance, in the amount exceeding 3 %.

WCP (reverse side)

Hexamethylenetetramine 20.0
CVI $_{\text{hexamethylenetetramine}}$ = 0.78
Water for the injections:
100.0 – (20.0 x 0.78) = 84.4 ml

The solution is prepared in aseptical conditions, using sterilized water for the injections, filtering material and crockery. In aseptical conditions pour 84.4 ml of water for injections into the auxiliary bottle, then add 20.0 g of hexamethylenetetramine and mix. Perform the complete chemical analysis, filter the solution into a bottle for dispensing, cork, after that check particulate matters and roll with cover. Then put the number of prescription on the bottle and fill WCP (front side). Stick the labels «For injections» and «Aseptically prepared».

WCP (front side)

Date № Pr.
Aquae pro injectionibus sterile 84.4 ml
Hexamethylentetramini 20.0
V = 100 ml
Addita aseptice
Prepared by: (signature)
Checked by: (signature)

2.8. SOLUTIONS FOR INJECTIONS BASED ON THE NON-AQUEOUS SOLVENTS

NON-AQUEOUS SOLVENTS → Are used for preparation of injectional medicinal forms of hormones, vitamins, camphor, antibiotics, sulphur and etc.

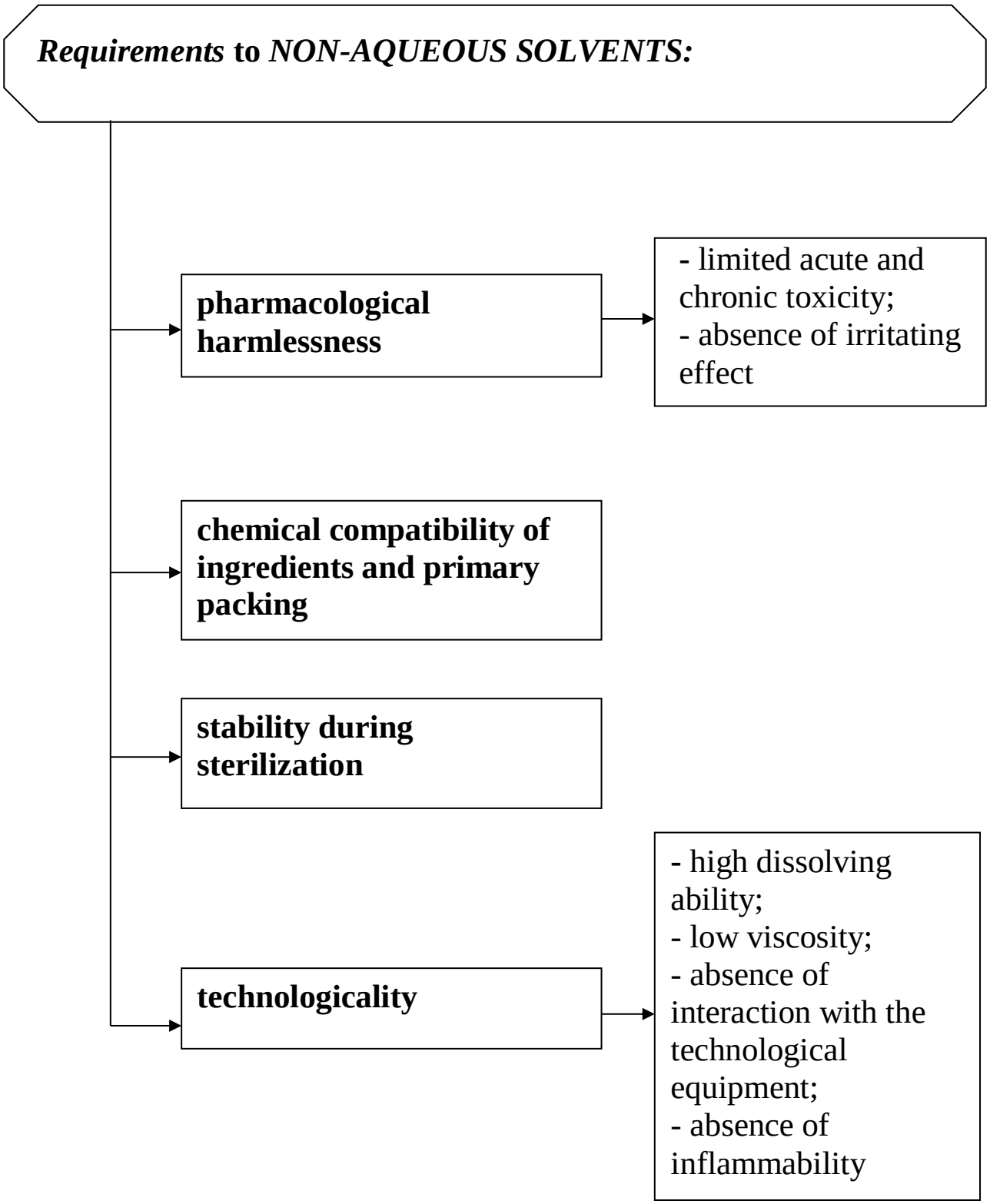
***NON-AQUEOUS SOLVENTS have*:**

- **different dissolving capability**
- **properties against hydrolysis**
- **bactericidal properties**
- **stabilizing properties**

With the help of *NON-AQUEOUS SOLVENTS it is possible to obtain*:

- **solutions with a prolonged effect**
- **solutions with a greater shelf life**
- **solutions of substances insoluble and unstable in the aqueous medium**

2.8. SOLUTIONS FOR INJECTIONS BASED ON THE NON-AQUEOUS SOLVENTS



2.8. SOLUTIONS FOR INJECTIONS BASED ON THE NON-AQUEOUS SOLVENTS

CLASSIFICATION OF NON-AQUEOUS SOLVENTS

In accordance of their chemical nature

Monoatomic alcohols	Ethyl alcohol and benzyl alcohol
Polyatomic alcohols	Glycerol, propyleneglycol, butyleneglycol, polyethylenoxide-400, polyvinyl alcohol
Esters	Methyl- or ethyl- esters of oleinic acid benzylbenzoate
Amides	Methylacetamide, dimethylacetamide
Vegetable oils	Oils of almond, peach, apricot, olive

To prepare sterile solutions **non-aqueous solvents** both individual and **mixed** are used, they possess greater dissolving ability comparing to each indivial solvent:

- **hydroglyceric;**
- **hydropropylene;**
- **alcohol- water – glycerine;**
- **mixtures of vegetable oils with benzylbenzoate;**
- **mixtures of vegetable oils with ethyloleate, etc.**

2.8. SOLUTIONS FOR INJECTIONS BASED ON THE NON-AQUEOUS SOLVENTS

REQUIREMENTS OF THE STATE PHARMACOPOEIA OF UKRAINE TO OILS:

- acid number – not more than 0.56;
- iodine number – from 79 to 137;
- saponification number – from 185 to 200;
- transparency;
- at tº of 10ºC they must not have any smell and any bitter taste.

PECULIARITIES OF THE TECHNOLOGY OF NON-AQUEOUS SOLUTIONS FOR INJECTIONS

VISCOUS LIQUIDS

- they are prepared by mass;
- the sterilized solvent is used (it is sterilized at 180ºC for 30 minutes or at 200ºC for 15 minutes (in autoclave at 120ºC for 2 hours).

fatty oils, ethyl oleate, complex solvents

VOLATILE LIQUIDS

ethyl alcohol

1. They are added to the solution *before sterilization*:

- in the concentration up to 33 %;
- fill a small bottle up to ¾ volume;
- corks must not have any punctures;
- corks from rubber of beige (IR-21) or a grey (IR-119) colour;
- corks from rubber of a red colour (25 P) with a gasket from parchment;
- during sterilization the solution must not touch the cork.

2. They are added aseptically *after sterilization*.

2.8. SOLUTIONS FOR INJECTIONS BASED ON THE NON-AQUEOUS SOLVENTS

Rp.: Sol. Camphorae oleosae 20 % 100.0
Sterilisa!
D. S. For 2 ml subcutaneously

This medicine is an oily solution for hypodermic introduction.

WCP (reverse side)

Camphor	20.0
Peach oil	100.0 - 20.0 = 80.0

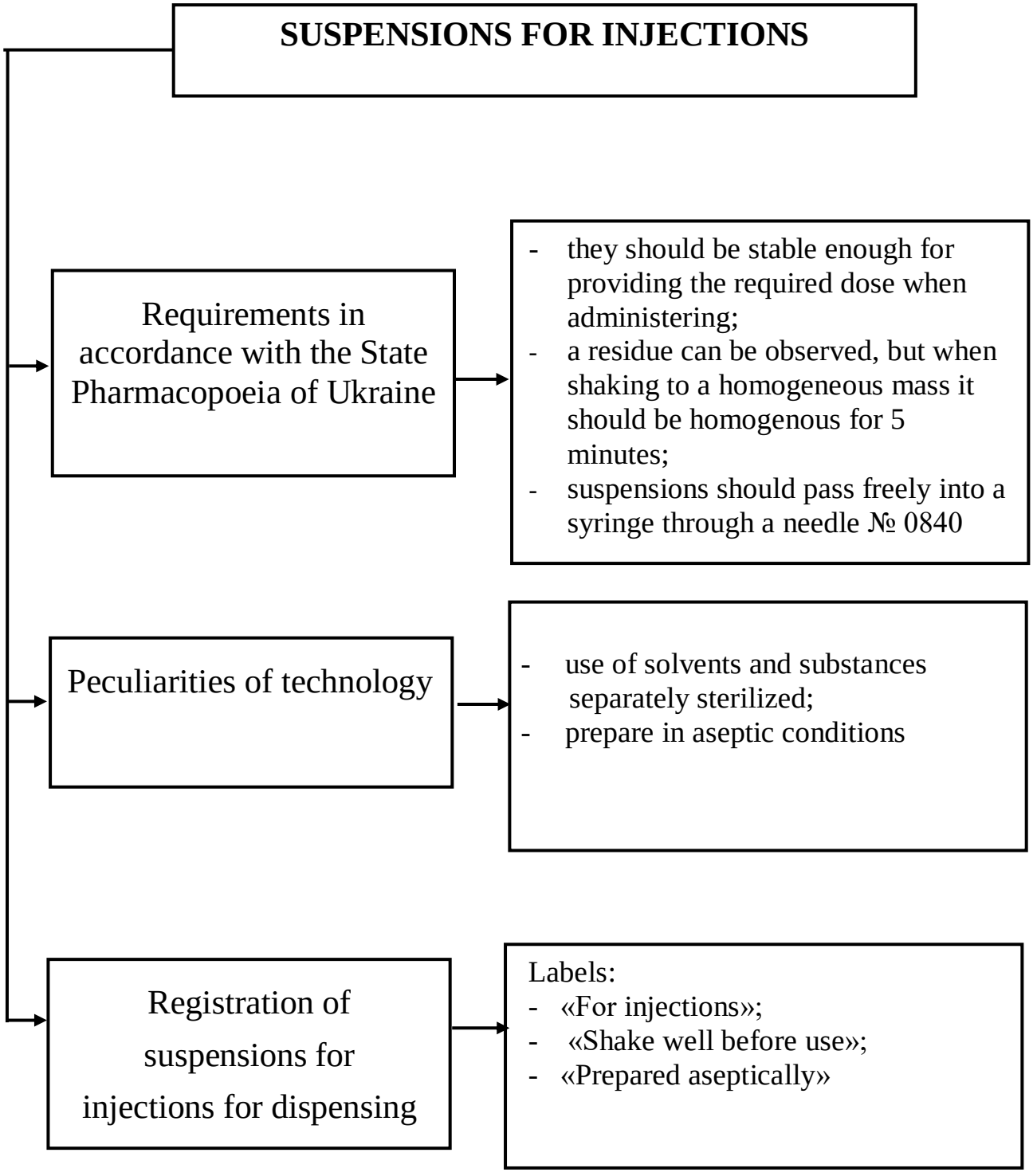
In aseptic conditions weigh 20.0 g of camphor, dissolve in 80.0 g of the warm sterilized oil (peach, almond, olive oil). Then filter in a sterile bottle for dispensing the heated drying cabinet, close by a rubber cap check particulate matters and sterilize the bottle. Perform the control of particulate matters. Put the number of prescription and fill in WCP (front side). Stick the labels «For injections» and «Sterile».

WCP (front side)

Date № Pr.
Camphorae 20.0
Olei Persicorum sterile 80.0
m = 100.0
Sterilis

Prepared by: (signature)
Checked by: (signature)

2.9. SUSPENSIONS FOR INJECTIONS



The difficult technological problem is the choice of the sterilization method, since size enlargement of particles of the disperse phase can occur in suspensions at a high temperature

2.9. SUSPENSIONS FOR INJECTIONS

Rp.: Streptocidi 6.0
Olei Persicorum pro injectionibus 30.0
Misce. Da.
Signa. For intramuscular injections

This medicine is a suspension for parenteral use with a difficultly powdered, strong effective substance – streptocide.

WCP (reverse side)

Peach oil 30.0
Streptocide 6.0
Ethyl alcohol 95 % for streptocide powdering:

1.0 - 5 drops
6.0 - x x = 30 drops

In a dry bottle for dispensing filter 30.0 g of peach oil and sterilize at t°=180°C for 30 minutes or at t°=200°C for 15 minutes (in autoclave at 120°C for 2 hours). Powder 6.0 g of streptocide sterilized for 1 hour at t^o=150°C and 30 drops of 95 % ethyl alcohol in a sterile mortar in aseptical conditions. Then by Deryagin is rule mix with 3.0 g of peach oil. Gradually add the rest of oil. Transfer the mixture into a bottle for dispensing and seal it. Put the number of prescription and fill in WCP (front side). Stick the labels «For injections», «Shake well before use» and «Prepared aseptically».

WCP (front side)

Date № Pr.
Streptocidi sterile 6.0
Olei Persicorum sterile 30.0
m=36.0
Addita aseptice
Prepared by: (signature)
Checked by: (signature)

2.10. EMULSIONS FOR PARENTERAL NUTRITION

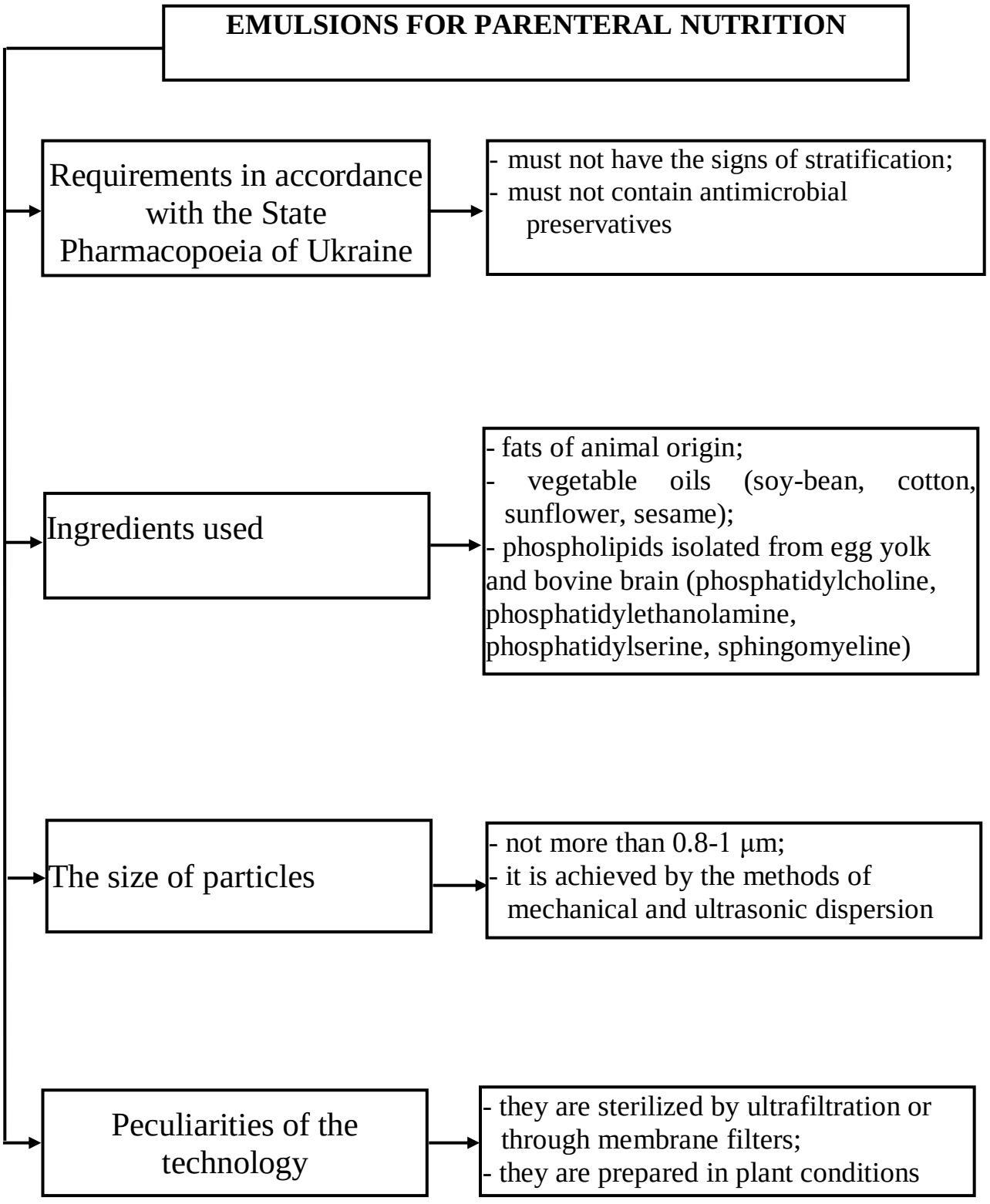
Emulsions for parenteral nutrition – are high-dispersed heterogeneous systems represented by a medicinal form homogeneous in appearance consisting of mutually insoluble liquids.

***Positive qualities** of emulsions for intravenous infusions*:

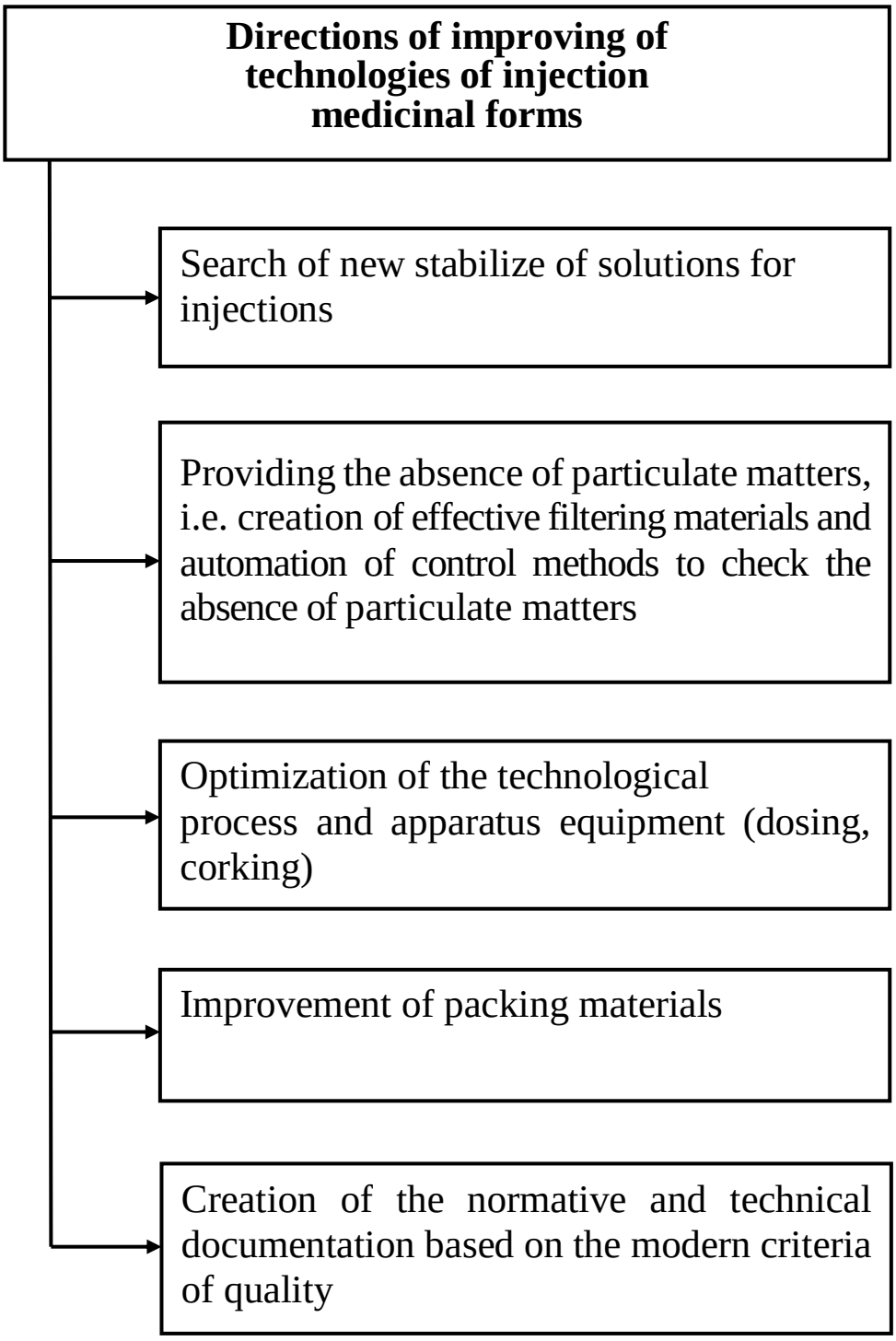
- possibility of solubilize medicinal substances with a low solubility in water;
- possibility to obtain stable medicines from compounds subjected to the hydrolysis in the aqueous medium;
- possibility to reduce the irritating or toxic effect of medicinal substances administered intravenously;
- possibility to obtain medicinal forms with the prolonged action;
- possibility to deliver medicinal substances directly to the target organs.

Due to the high caloric value of fat (more than 9 kcal/g), as well as the presence of carbohydrates in lipid emulsions, their caloric content exceeds considerably the similar index of other medicines for parenteral nutrition

2.10. EMULSIONS FOR PARENTERAL NUTRITION



2.11. IMPROVEMENT OF TECHNOLOGY OF INJECTION MEDICINAL FORMS



NB! Osmolarity, the composition of the medicine and the ionic composition of the medicine (in mmol/l) are specified on the label in addition to labeling for injection medicines

2.12. QUESTIONS FOR SELF-CONTROL

1. Give the definition of isotonic solutions. Importance of isotonic solutions for injections.
2. Name the methods of isotonic concentration calculation of solutions. Which of them is pharmacopoeian one?
3. Name plasma-substituting solutions and their classification.
4. Specify the peculiarities of preparing solutions for injections with thermolabile substances.
5. Name the peculiarities of technology of non-aqueous solutions for injections.
6. Name the peculiarities of technology of suspensions for injections.
7. Specify directions of improving the technology of injection medicinal forms.