

OPHTHALMIC MEDICINES. MEDICINAL FORMS WITH ANTIBIOTICS

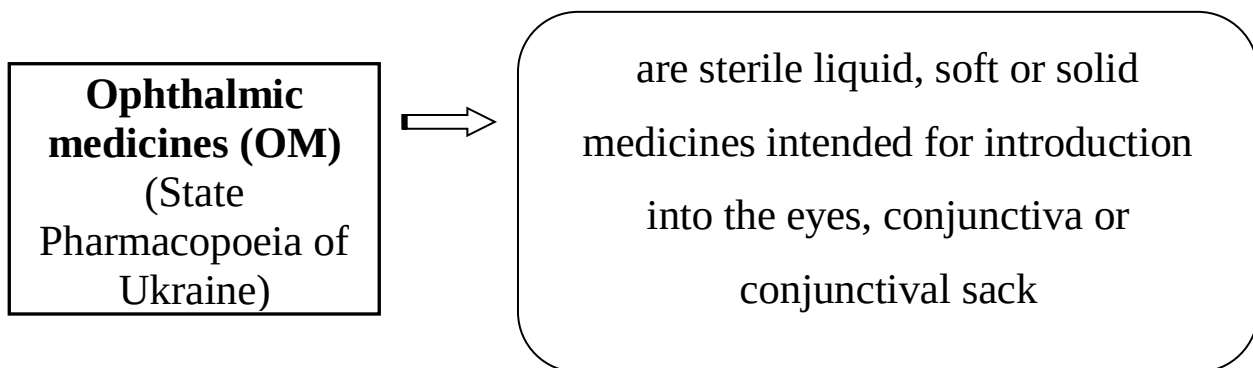
INTRODUCTION

Ophthalmic medicines are medicines intended for application on the mucous membrane of the eye, which is the most sensitive of all mucous membranes of the organism that sharply reacts on external irritants. Therefore, the same claims are laid to both ophthalmic medicines and solutions for injections: they should be maximally purified from visible and sub-visible particles, have exact concentration of substances, be isotonic, sterile and stable, and, in some cases, they should have the prolonged action and buffer properties. While preparing medicinal forms it is necessary to take into account specific mechanisms of absorption and distribution of medicines, the peculiarities of their interaction with tissues and liquids of the eye.

Drops are a simple and rather effective medicinal form used the most widely since old times. Compounding of medicines at the chemist's contains 5% - 15% of drops. The formulations of eye drops comprising two (to 35%), three (17-19%), four (22-25%), five (13-15%) medicinal substances are the most frequently met. Sometimes there are formulations with 8-9 components. Nowadays about 80 medicinal substances are applied in the ophthalmic practice, as well as a great amount of their various combinations.

It is still essential to prepare eye drops in the conditions of a chemist's because of the limited assortment of domestic manufactured ophthalmic medicines, difficult compositions in formulations and technological difficulties of their manufacturing.

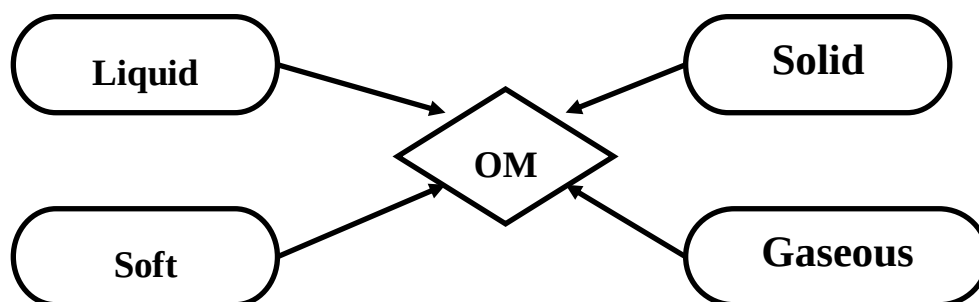
3.1. CHARACTERISTICS AND CLASSIFICATION OF OPHTHALMIC MEDICINES



Usually for treating ophthalmic diseases the following methods can be used:

- ✓ Instillation of solutions;
- ✓ Insertion of ointments, eye films, tablets, lamellas into the conjunctival sack;
- ✓ Introduction of medicinal substances by injections;
- ✓ Contact lenses and eye inserts;
- ✓ Electrophoresis.

DIFFERENT FORMS OF OPHTHALMIC MEDICINES (OM):



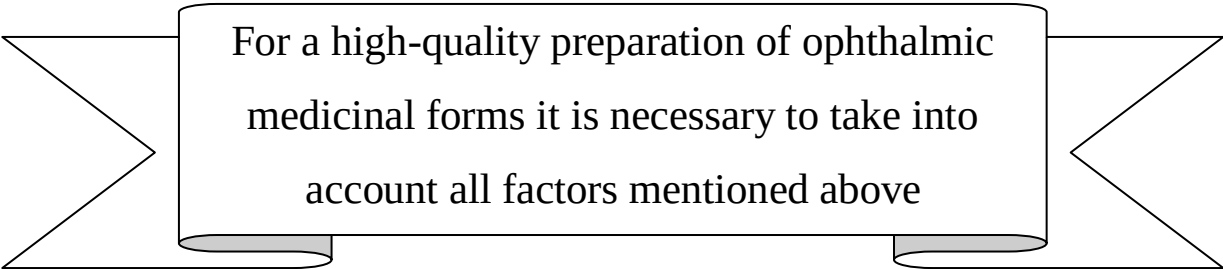
3.1. CHARACTERISTICS AND CLASSIFICATION OF OPHTHALMIC MEDICINES

FACTORS DETERMINING THE CHOICE OF A MEDICINAL FORM

- The state of a pathological process in the eye
- General indexes of the patient's organism state
- The presence of the corresponding traumatic lesions of the eye
- Degree of permeability of the blood-aqueous barrier
- Physical and chemical properties of medicinal substances
- Peculiarities of the pharmacological action of medicinal and auxiliary substances, etc.

In addition, the processes of activation or inhibition of the action of medicinal substances are affected by:

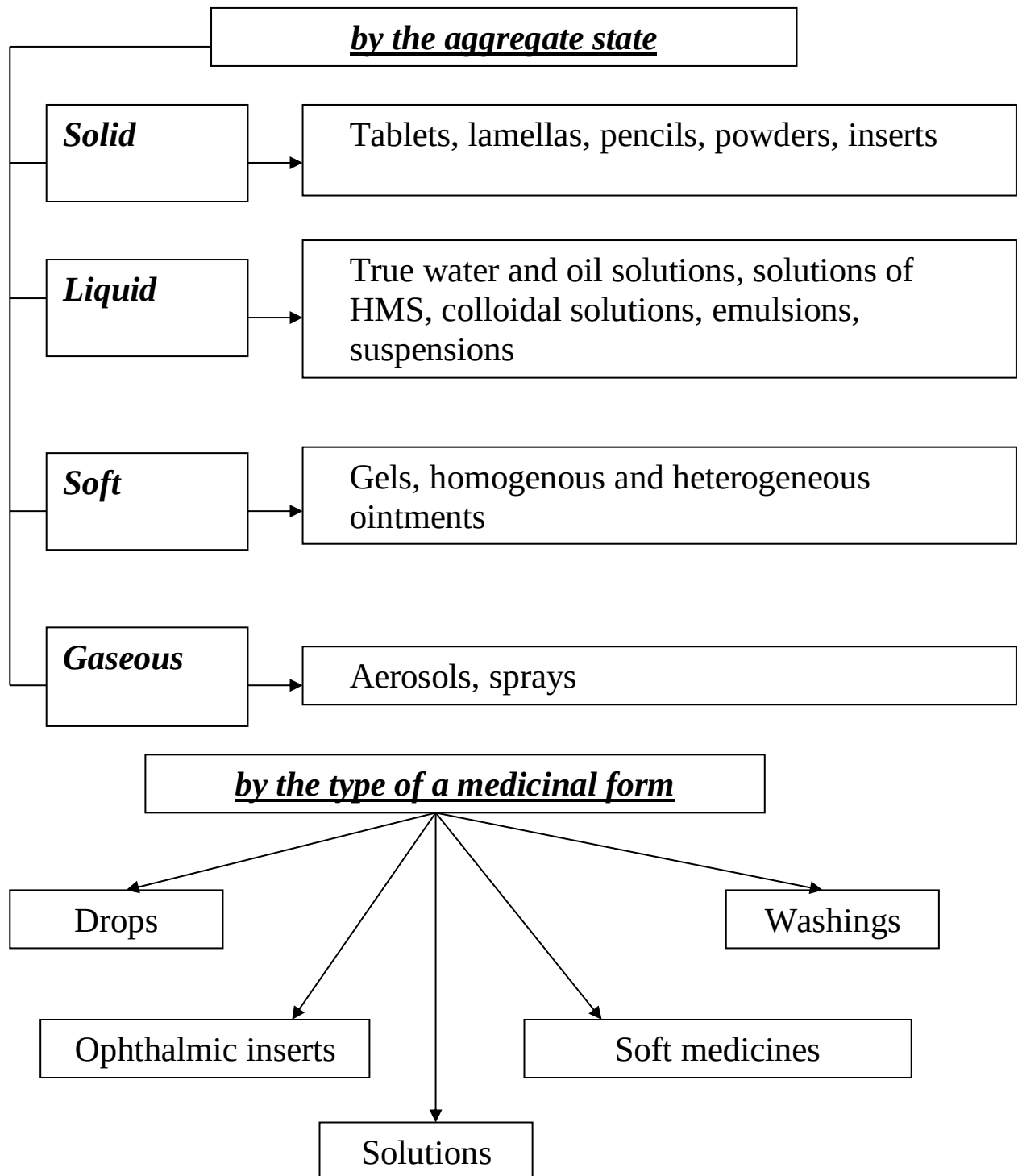
- ✓ pH value of the solution;
- ✓ the solution's osmotic pressure;
- ✓ the molecular weight of substances - carriers, etc.



For a high-quality preparation of ophthalmic medicinal forms it is necessary to take into account all factors mentioned above

Ophthalmic drops, lotions and ointments are prepared more often in the extemporal practice of the chemist's.

3.1. CHARACTERISTICS AND CLASSIFICATION OF OPHTHALMIC MEDICINES

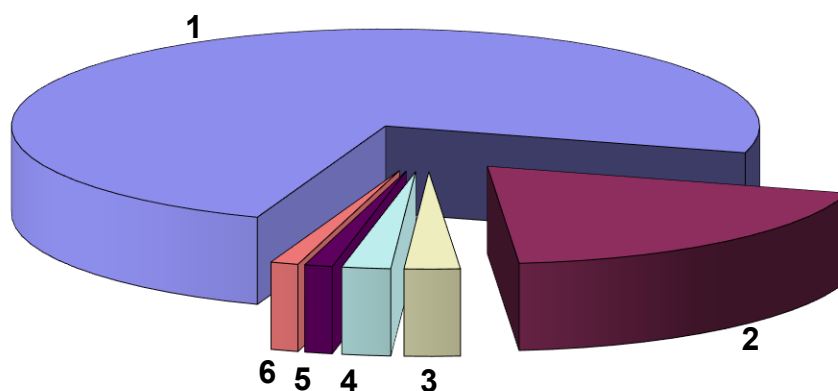


3.2. MODERN STATE OF OPHTHALMIC MEDICINES PRODUCTION IN UKRAINE

<i>Pharmacological group</i>	The number of medicines		
	Germany	Russia	Ukraine
1. Local anaesthetics	7	1	0
2. Antibiotics	51	16	18/1
3. Antiseptics	11	9	12/7
4. Antivirus medicines	8	5	4/0
5. Steroid anti-inflammatory medicines	64	11	18/0
6. Antiasthenotopic medicines	2	1	0
7. Medicines affecting vessels	26	9	1/0
8. Antiglaucoma medicines	130	45	41/3
9. Mydriatics	20	5	5/2
10. Anti-allergic medicines	24	14	14/0
11. Film-forming medicines (artificial tear)	31	4	4/0
12. Vitamins	14	-	0
13. Anticatarrrhal medicines	3	8	10/2
14. Organo-medicines	4	3	0
15. Others	27	1	6/1
TOTAL:	422	132	133/16

Note: Of 133 medicines only 16 ones are produced by Ukrainian manufactures (from 5 pharmacotherapeutical groups). The market of Ukraine is full of 88% of expensive foreign ophthalmic medicines.

The comparative analysis of quantitative and qualitative indexes of the ophthalmic medicines nomenclature



Medicines are produced in the different medicinal forms:

- 1) 73.9 % are ophthalmic drops on the water base;
- 2) 19.2 % are ophthalmic ointments and gels;
- 3) 2.4 % are drops on the oil base;
- 4) 2.1 % are solutions for eye irrigation and baths;
- 5) 1.2 % are ophthalmic suspensions;
- 6) 1.2 % are powders for dissolving "ex tempore".

Analysis of the market of ophthalmic medicines by the types of medicinal forms

Type of medicinal form	Country		
	Germany	Russia	Ukraine
1. Water drops	312	113	123
2. Solutions for eye irrigation	9	-	0
3. Ointments and gels	81	15	5
4. Oil drops	10	-	0
5. Suspensions	5	2	5
6. Dry substance + solvent	5	2	0
TOTAL:	422	132	133

3.3. OPHTHALMIC DROPS (GUTTAE OPHTALMICAЕ)

REQUIREMENTS FOR OPHTHALMIC DROPS

Ophthalmic drops

are liquid medicinal form, which are aqueous or oil solutions, thin suspensions of medicinal substances intended for instillation into eyes

Poor quality of eye drops and their contamination by microorganisms can cause severe consequences even the loss of vision.

That is why the **requirements** for eye drops are the same as for **solutions for injections**:

- sterility
- stability
- the absence of particulate matters
- isotonicity
- the prolongation of action (in some cases)

Ophthalmic drops are prescribed in small amounts (5-10 ml) taking into account their application for a short period.

3.3. OPHTHALMIC DROPS

STERILITY OF OPHTHALMIC DROPS

The character of preparatory measures, conditions of the technological process of eye drops and lotions are similar to those for solutions for injections, i. e. they are prepared in aseptic conditions with the subsequent sterilization.

The way of sterilization for eye drops depends on the stability of medicinal substances in solutions to temperature.

Medicinal substances can be divided into three groups:

1. Solutions of medicinal substances, which can be sterilized by thermal sterilization without adding stabilizers
2. Solutions of medicinal substances, which can be sterilized by thermal sterilization after adding stabilizers
3. Solutions of medicinal substances, which cannot be thermally sterilized and prepared in aseptic conditions without further sterilization

Solutions of medicinal substances, for which the modes of sterilization have not been developed, are also prepared in aseptic conditions.

3.3. OPHTHALMIC DROPS

STERILITY OF OPHTHALMIC DROPS

Microorganisms get into eye drops at the first opening of a vial, and depending on the composition of the solution, the following things can occur:

- *Reproduction and accumulation of individual species of microorganisms*

after the incubation period, which duration varies from several hours to several days

- *Retaining the amount of microorganisms at the same level*

when the solution's components have the bacteriostatic and fungistatic action

- *Decreasing the amount of microorganisms got into the solution*

when the solution's components have the bacteriostatic and fungistatic action

To preserve the sterility of eye drops after opening of a vial, **preservatives** - antimicrobial substances that prevent the growth of microorganisms - can be used.

- Preservatives should be compatible with other components of eye drops and keep their efficiency within the whole period of the medicine's application.
- Preservatives are not used if a medicinal substance provides a sufficient antimicrobial action independently.

3.3. OPHTHALMIC DROPS

STERILITY OF OPHTHALMIC DROPS

The limited assortment of preservatives is used in ophthalmic medicinal forms.

Classification of preservatives

Inorganic	boric acid – 1.9-2.0 % (pH approximately 5.0)
Organic	β-phenylethyl alcohol– 0.3-0.5% - benzyl alcohol – 0.9% - esters of <i>p</i>-hydroxybenzoic acid: nipagin – 0.05-0.23%, nipazol – 0.03-0.08% or their mixture (nipagin 0.18%, nipazol 0.02%) - levomycetin 0.15% - salts of quaternary ammonium bases (benzalkonium chloride, cetylpyridinium chloride, dodecyl methyl benzylammonium chloride) in the concentration of 1:10000 - sorbic acid – 0.05-0.2%
Organo-metallic	- ethanol mercury chloride 0.01% - merthiolate 0.005%

**Preservatives are added into a medicinal form
before sterilization of the solution**

3.3. OPHTHALMIC DROPS

STABILITY OF OPHTHALMIC DROPS

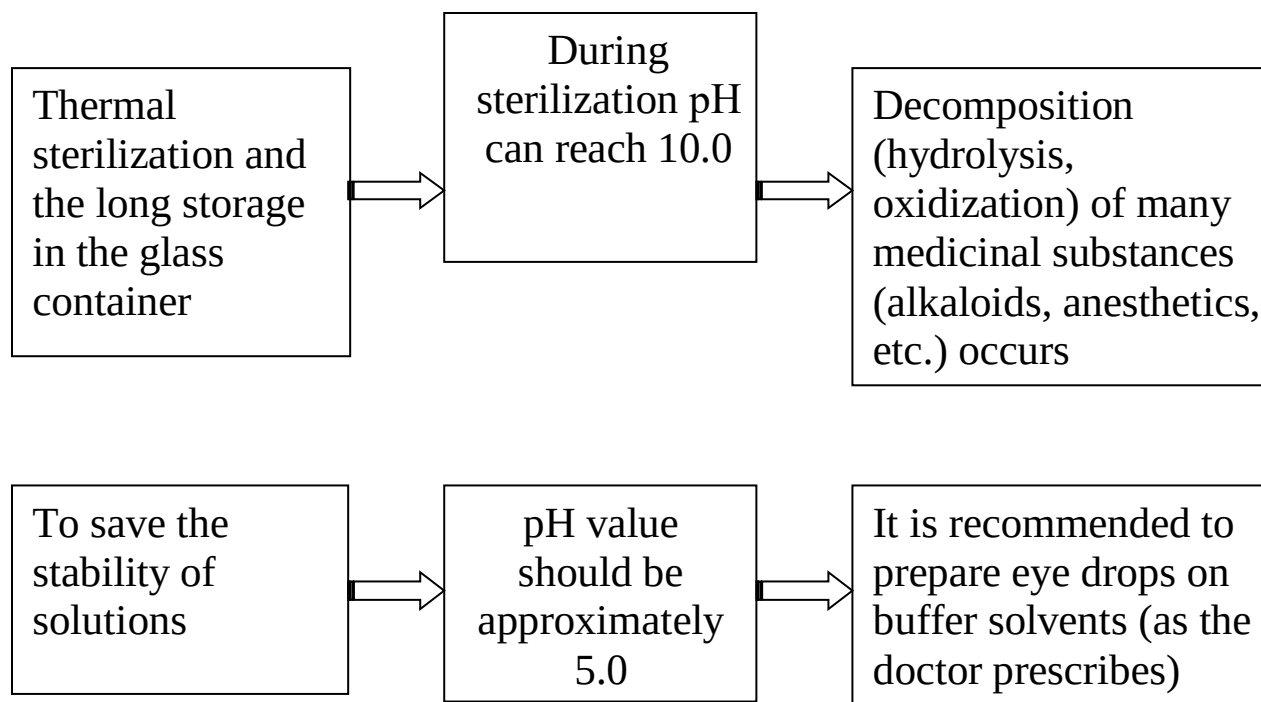
Different auxiliary substances are introduced to the composition of eye drops to provide their stability.

Components	The purpose of introduction	The mechanism of action
↓	↓	↓
preservatives	prevention of the microorganisms growth in the medicinal form in the process of its storage and use	▪ destruction of the cellular membrane ▪ protein coagulation ▪ blocking of free sulphohydril groups ▪ chemical antagonism
stabilizers	▪ increase of the chemical stability ▪ increase of the therapeutic activity ▪ decrease of the irritant action of ophthalmic solutions	▪ neutralization of acidic products of the vital activity in the place of application ▪ maintenance of pH value of the solution ▪ neutralization of the glass alkalinity
prolongation agents	▪ prolongation of medicines action ▪ reduction of the number of installations	▪ increase of density of solutions ▪ prolongation of the contact time of a medicine with the mucous membrane of the eye

3.3. OPHTHALMIC DROPS

STABILITY OF OPHTHALMIC DROPS

Disturbance of the stability of eye drops can take place during sterilization as the result of the temperature influence and the change of pH medium.



PREPARATION OF EYE DROPS ON BUFFER SOLUTIONS ALLOWS:

- to increase the chemical stability;
- to intensify the therapeutic action;
- to decrease the irritating action.

When choosing a buffer solution, its composition and pH should provide stability of a definite medicine.

3.3. OPHTHALMIC DROPS

STABILITY OF OPHTHALMIC DROPS

BUFFER SOLUTIONS

1. Medicines, which solutions should be with pH about 5.0	It is recommended to use the isotonic solution of boric acid (with the concentration of 1.9 %), its pH is below 5.0	They are used for preparing the following solutions: pilocarpine hydrochloride, dicaine, sovaine, mezaton and salts of zinc
2. Medicines, which solutions should be with pH about 6.8	It is recommended to use phosphate or borate buffer, which becomes isotonic with the help of sodium chloride	They are used for preparing solutions of salts of atropine, pilocarpine and scopolamine
Phosphate buffer	Solution of monobasic sodium phosphate 0.8 % – 30 ml Solution of dibasic sodium phosphate 0.94 % – 70 ml Sodium chloride – 0.43 g	
Borate buffer	Boric acid – 1.84 g Sodium tetraborate – 0.14 g Purified water (pH = 6.8) – 100 ml	
Borate-acetate buffer	1.9 % solution of boric acid 1.5 % solution of sodium acetate	
Borate-propionate buffer	1.9 % solution of boric acid 2 % solution of sodium propionate	

3.3. OPHTHALMIC DROPS

STABILITY OF OPHTHALMIC DROPS

3. Solutions of easily oxidized substances

Addition of antioxidants (sodium sulphite, sodium metabisulphite, etc.) is recommended

They are used for preparing the following solutions: physostigmine salicylate, adrenalin hydrochloride, etc.

Solutions of sodium sulphacyl 10, 20 and 30 %

1.0, 3.0, 5.0 g of sodium metabisulphite and 5, 17 and 18 ml of 0.1 M solution of sodium hydroxide per 1 litre of the solution, respectively

Solution of ascorbic acid 2 %

Solutions of sodium metabisulphite (0.1 %) or anhydrous sodium sulphite (0.2 %)

To stabilize eye drops the following methods can be used:

addition of high polymers, complexones

preparation of solutions under the atmosphere of inert gases

These methods of stabilization allow to increase the shelf life of eye drops

3.3. OPHTHALMIC DROPS

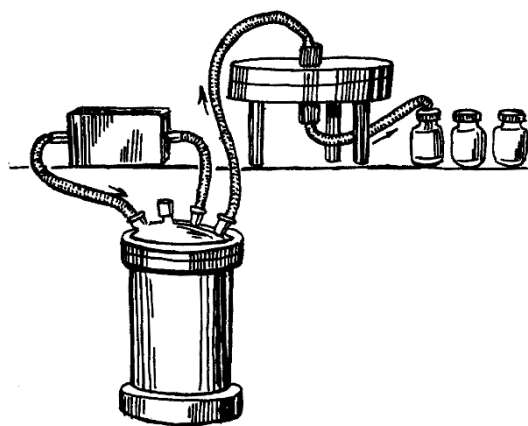
THE ABSENCE OF PARTICULATE MATTERS

All eye drops, excluding emulsions and the thinnest suspensions, should be carefully filtered.

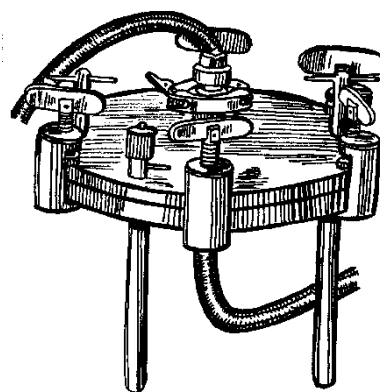
The following filters are used for filtration:

- ❖ **fold paper filters** where under the mouth of the funnel a piece of long fibrous cotton is put
- ❖ **glass filters** No.3 and No.4 (with the particles size of 20-30 μm)
- ❖ **membrane filters** – with the simultaneous mechanical sterilization (when preparing eye drops in large volumes)

When preparing eye drops in batches at the chemist's apparatuses for their filtration with the subsequent packing are expedient to use.



A



B

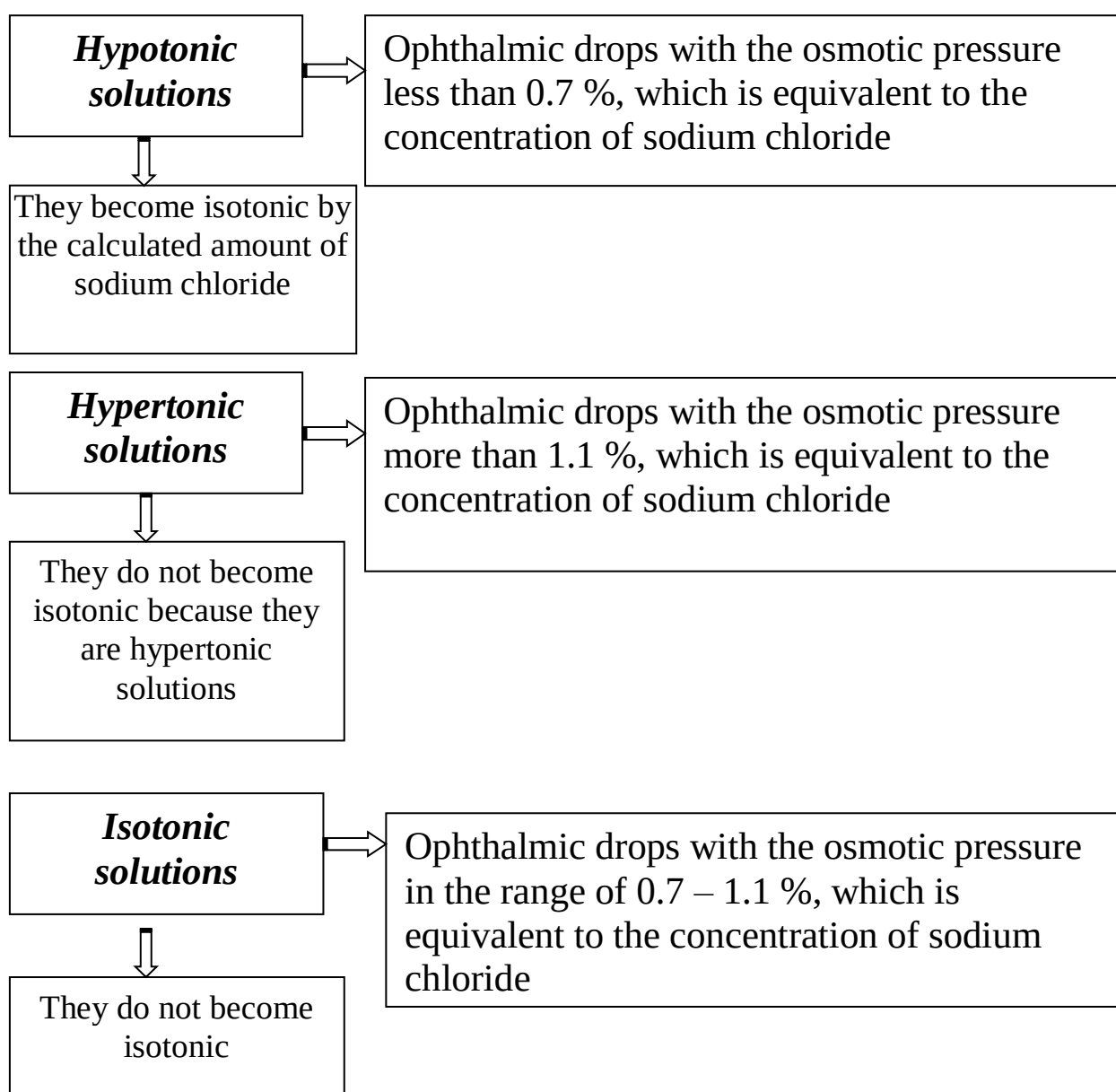
The scheme of USF-293-7 (A) filter apparatus and a general view of the FD-293 (B) filter holder.

3.3. OPHTHALMIC DROPS

ISOTONICITY OF OPHTHALMIC DROPS

In order to prevent discomfort eye drops should be isotonic to a human lachrymal fluid and correspond to the osmotic pressure of sodium chloride solutions with the concentration of $0.9 \pm 0.2 \%$.

**Depending on the osmotic pressure value eye drops
can be divided into 3 groups:**



3.3. OPHTHALMIC DROPS

ISOTONICITY OF OPHTHALMIC DROPS

To make the solution isotonic substances are used taking into account their compatibility with the drug components

- ❖ Sodium chloride
- ❖ Sodium sulphate
- ❖ Sodium nitrate

- ❖ Boric acid
- ❖ Glucose

Ophthalmic drops do not become isotonic in the case if colloidal substances (collargol, protargol) are prescribed as being powerful electrolytes isotonic agents can cause coagulation

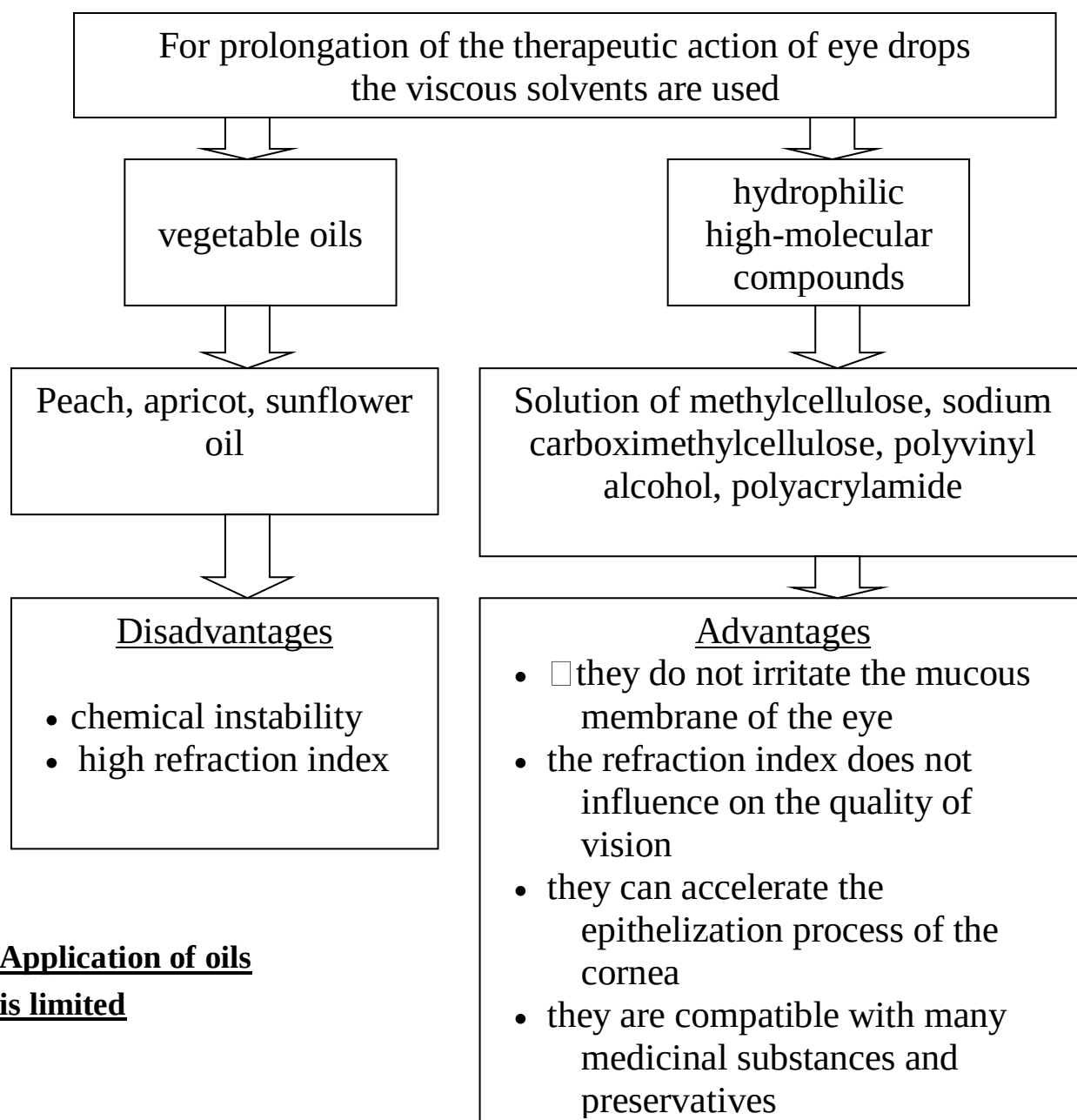
The isotonic concentration of ophthalmic drops can be calculated by the same methods as those for solutions for injections:

- using the equivalent by sodium chloride;
- using the Raoult law;
- using the Van't Hoff equation.

3.3. OPHTHALMIC DROPS

PROLONGATION OF THE THERAPEUTICALLY ACTION OF EYE DROPS

Frequent instillations of an aqueous solution washes off the lachrymal fluid containing lysozyme creating the conditions for occurrence of the infectious process.



**Application of oils
is limited**

All prolongation components mentioned can be added to the eye drops only by the doctor's prescription

3.4. TECHNOLOGY OF OPHTHALMIC DROPS

★ Ophthalmic drops are prepared by the mass-volume method in aseptic conditions with the subsequent sterilization of solutions of thermostable substances.

★ Such sterile solvents as purified water or water for injections, isotonic buffer solutions, oils, etc. are used in manufacture of ophthalmic drops.

★ When preparing ophthalmic drops in small amounts significant losses of medicinal substances take place:

- due to their absorption on the filters (up to 4.7 %);
- due to dilution of initial solutions while filtering through paper filters previously washed by water.

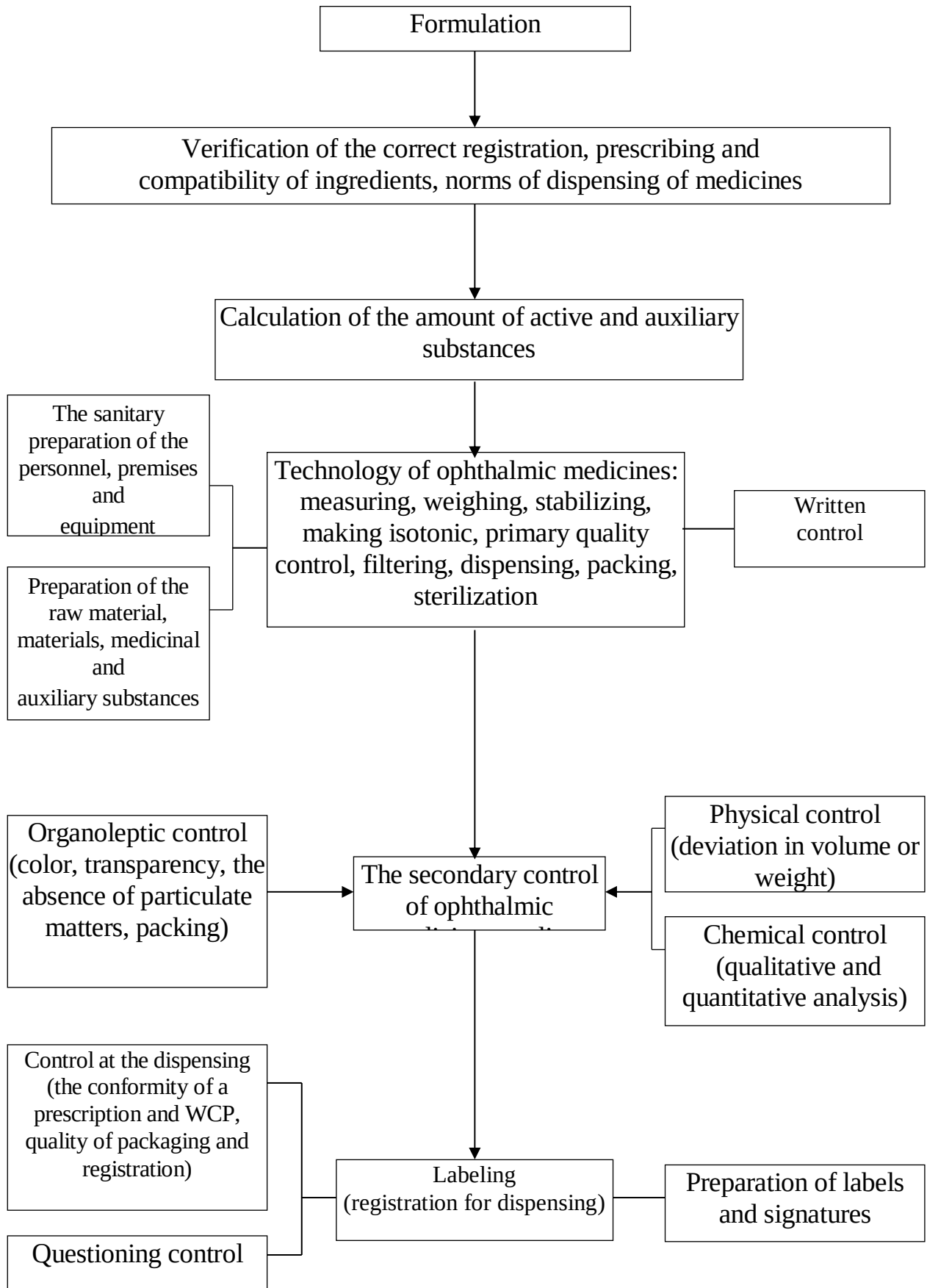
In order to decrease the loss of medicinal substances during the preparation of ophthalmic drops two ways are used:

1 Dissolve a medicinal substance, which is readily soluble in water, in a portion of water ($1/2$ from the solvent's volume), filter the solution in the bottle for dispensing through a paper filter previously washed by the sterile water for injections, and then wash the filter by the remaining portion of the solvent

2 If a medicinal substance is poorly soluble in water, dissolve it in all the solvent's quantity prescribed and filter in a graduated cylinder through a dry filter and cotton. Add the missing quantity of water through the same filter and cotton to make the required volume of the solution

3.4. TECHNOLOGY OF OPHTHALMIC DROPS

THE TECHNOLOGICAL SCHEME AND THE QUALITY CONTROL OF OPHTHALMIC MEDICINES



3.4. TECHNOLOGY OF OPHTHALMIC DROPS

Rp.: Sol. Mesatoni 1 % 10 ml isotonicae

D.S. 2 drops into both eyes for a night.



WCP (r. s.)

Mezaton 0.1

Sodium chloride ($E_{\text{mezaton}} = 0.28$):

$$1.0_{\text{mezaton}} - 0.28_{\text{sodium chloride}}$$

$$0.1_{\text{mezaton}} - X_{\text{sodium chloride}}$$

$$X = \frac{0.28 \times 0.1}{1.0} = 0.028 \text{ g of sodium chloride}$$

To make isotonic 10 ml of water it is necessary to take:

$$0.9 - 100 \text{ ml}$$

$$X - 10 \text{ ml}$$

$$X = 0.09 \text{ g of sodium chloride}$$

$$0.09 - 0.028 = 0.062 \approx 0.07 \text{ g}$$

Purified water – 10 ml

WCP (f. s.)

Date

№ Pr.

Aquae purificatae 10 ml

Mesatoni 0.1

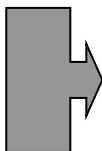
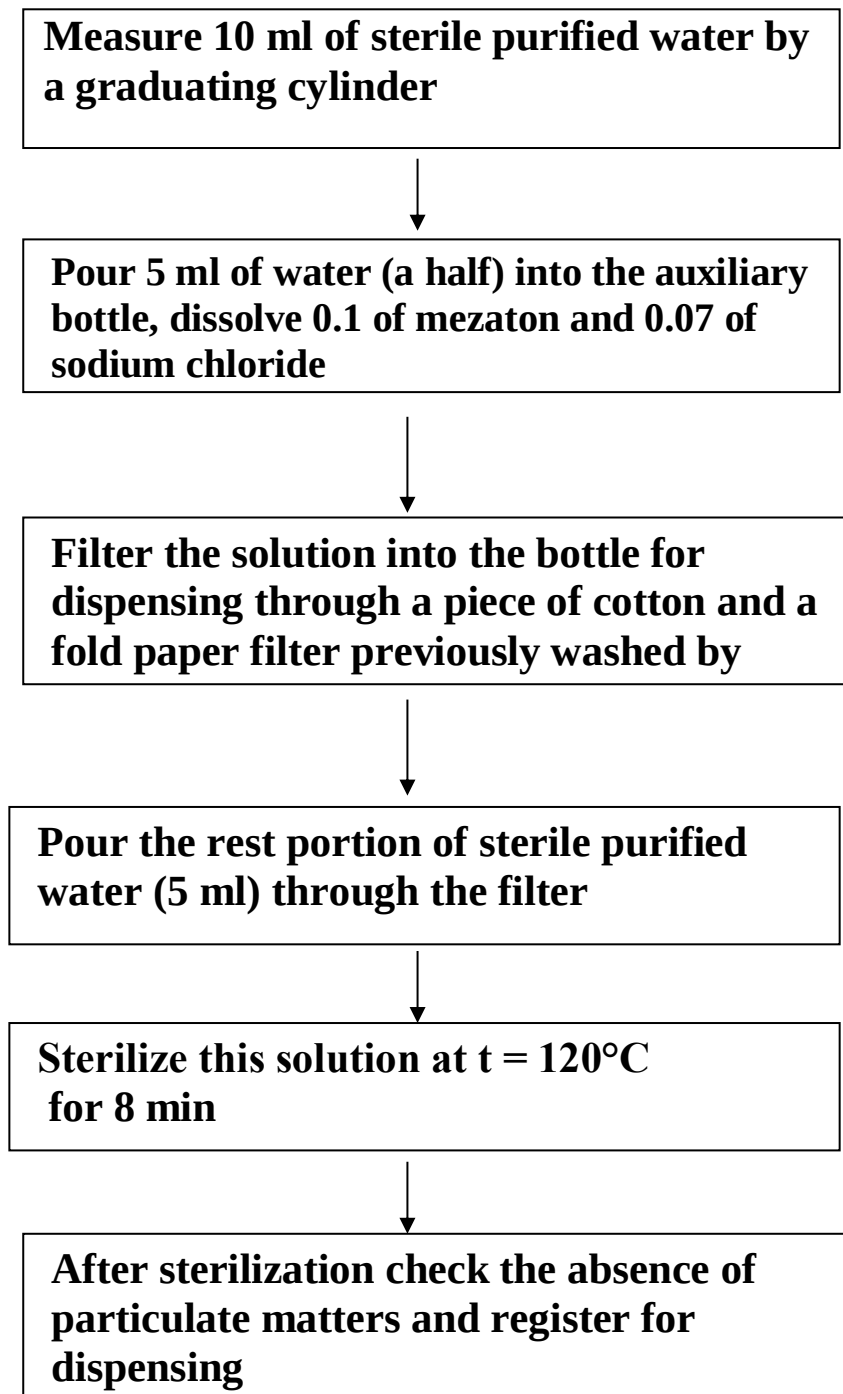
Natrii chloridi 0.07

Sterilis V = 10 ml

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Checked by: (signature)

3.4. TECHNOLOGY OF OPHTHALMIC DROPS



Introduction of an antioxidant (sodium metabisulphite) into the composition of eye drops with mezaton allows to increase the shelf life to 30 days.

3.4. TECHNOLOGY OF OPHTHALMIC DROPS

Rp.: Sol. Atropini sulfatis 1% 10 ml

Natrii sulfatis q.s.

ut fiat solutio isotonica

D.S. 2 drops into both eyes 3 times a day.



WCP (r. s.)

Atropine sulphate 0.1

Sodium chloride ($E_{\text{atropine sulphate}} = 0.1$):

1.0 atropine sulphate — 0.1 sodium chloride

0.1 atropine sulphate — X sodium chloride

X = 0.01

To make isotonic 10 ml of water it is necessary to take:

0.9 – 100 ml

X – 10 ml X = 0.09 g of sodium chloride

0.09 – 0.01 = 0.08 g of sodium chloride

Sodium sulphate ($E_{\text{sodium sulphate}} = 0.23$):

1.0 Sodium sulphate — 0.23 Sodium chloride

X Sodium sulphate — 0.08 Sodium chloride

X = 0.35

Purified water – 10 ml

3.4. TECHNOLOGY OF OPHTHALMIC DROPS

Rp.: Sol. Kalii iodidi 2% 10 ml

Riboflavini 0.001

Acidi ascorbinici 0.02

Glucosi 0.2

M.D.S. 2 drops into both eyes.



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WCP (r. s.)

Solution of riboflavin 0.02 %	0.02 – 100 ml	
	0.001 – x	x=5 ml

Potassium iodide 0.2

Ascorbic acid 0.02

Glucose:

$$X = \frac{a \times 100}{100 - b} = \frac{0.2 \times 100}{100 - 9} = 0.22 \text{ (humidity is 9 \%)}$$

Purified water: 10 ml – 5 ml = 5 ml

WCP (f. s.)

Date

№ Pr.

Sol. Riboflavini 0.02 % 5 ml sterile

Acidi ascorbinici 0.02

Glucosi 0.22 (hum. 9 %)

Aquae purificatae 5 ml

Sterilis V = 10 ml

Kalii iodidi 0.2

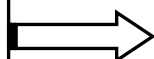
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3.5. OPHTHALMIC OINTMENTS

**OPHTHALMIC
SOFT MEDICINES**
(State
Pharmacopoeia of
Ukraine)



are homogenous sterile ointments,
creams or gels for application on the
conjunctive of the eye

REQUIREMENTS FOR OPHTHALMIC OINTMENTS:

➤ sterility

➤ stability

➤ even distribution of medicinal substances

➤ the absence of the irritant action and sticking of the eyelid

➤ uniform distribution on the mucus of the eye with
formation of the thinnest film

➤ maximal dispersion of medicinal substances

Bases for ophthalmic ointments

hydrophilic

hydrophobic

emulsion o/w

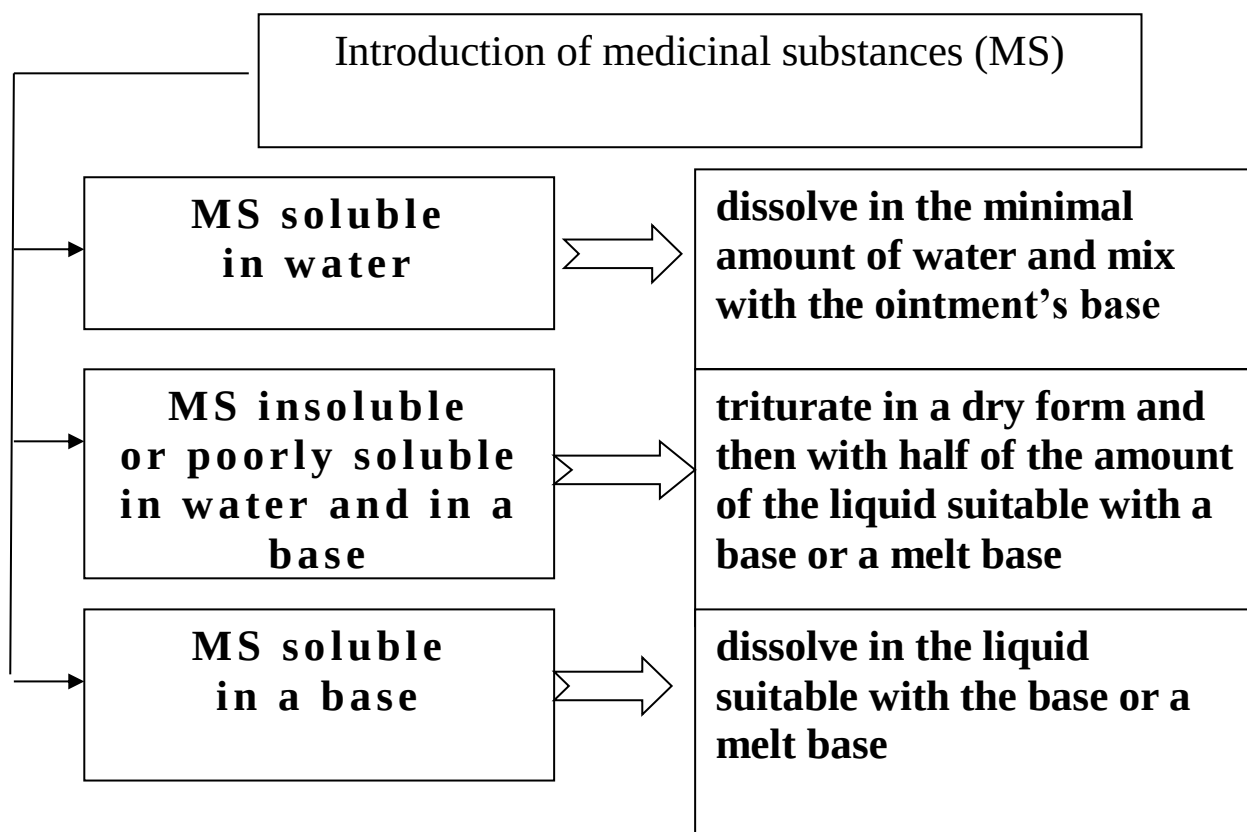
If the base for the ophthalmic ointment is not indicated in the prescription, the following one is usually used:

Vaseline of «for ophthalmic ointments» type - **9** or **8** portions

Anhydrous lanolin - **1** or **2** portions,
respectively

3.6. TECHNOLOGY OF OPHTHALMIC OINTMENTS

All ophthalmic ointments are prepared aseptically.



Resorcine and zinc sulphate into ophthalmic ointments can be introduced only after dissolving them in water

3.6. TECHNOLOGY OF OPHTHALMIC OINTMENTS

Rp.: Ung. Hydrargyri oxydi flavi 10,0
D.S. Put under the eyelid of the eye.



WCP (f. s)

Date

Nº Pr.

Hydrargyri oxydi flavi 0.2

Olei vaselini sterile gtts. V (1.–23 drops)

Vaselini pro oculi sterile 8.0

Lanolini anhydrici sterile 1.6

m = 10.0

Addita aseptice

Prepared by: (signature)

Checked by: (signature)

Rp.: Ung. Thiamini 0.5 % 10.0
D.S. Put under the eyelid for a night.



WCP (f. s.)

Date

Nº Pr.

Thiamini bromidi 0.05

Aquae purificatae sterile q.s. seu gtts. II

Basis pro oculi (9:1) sterile 10.0

m = 10.0

Addita aseptice

Prepared by: (signature)

Checked by: (signature)

3.7. OPHTHALMIC LOTIONS, WASHES, SUSPENSIONS, EMULSIONS AND OTHER MEDICINAL FORMS

Eye lotions are sterile aqueous solutions intended for moistening and washing of eyes, as well as for saturating materials applied on the eye. The technology of eye lotions is similar to those of eye drops

Liquids for treating contact lenses are sterile wetting, moistening, and disinfectant aqueous solutions for storing, cleaning and facilitating of application of contact lenses or contact glasses of the ophthalmological devices used for research

Suspensions and **emulsions** are prepared in conditions of the manufacture and at the chemist's diluting them with water to the required concentration. In the case of overcoming sedimentation instability of suspensions and keeping particles with the size not more than 10 μm in them, the medicines obtained are not felt by a patient and have the same effect as eye drops

Powders are used for powdering of the eye fluids. Prepare them in aseptic conditions from the medicinal substances of the thinnest dispersity subjecting the thermostable substances to sterilization

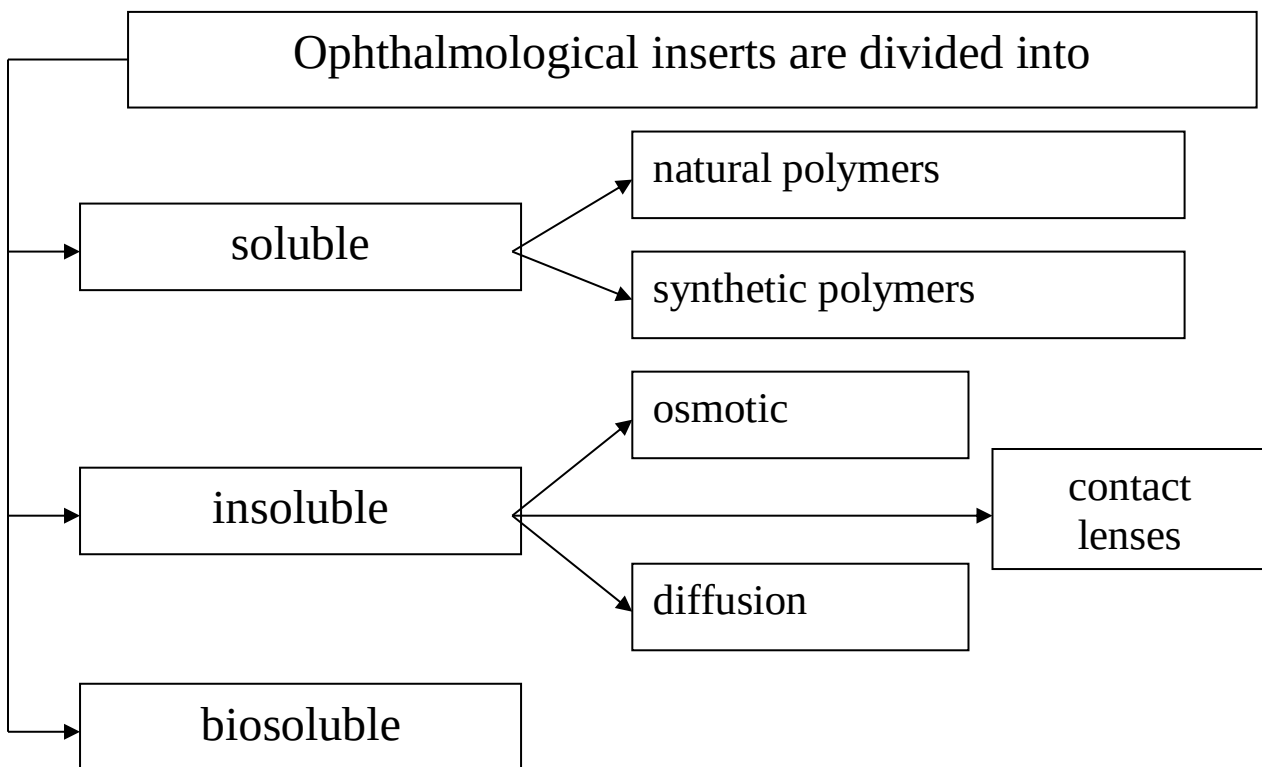
Eye sprays are solutions for injections, which are applied on the eye without contact. Nitrogen and nitrogen dioxide are used as a carrier for dosing aerosols. The index of pressure is limited in a balloon in order to be exactly dosed

3.8. OPHTHALMIC INSERTS

Ophthalmic inserts

are sterile dry or soft medicines with the proper size and shape intended for insertion in the conjunctival sack

Ophthalmic inserts usually consist of the matrix, in which the active substance is included, or the active substance is surrounded by the membrane that controls the rate of releasing.



Advantages of eye inserts:

- improvement of bioavailability of a medicinal substance due to the increase of the contact time with the mucous membrane;
- providing of the prolonged releasing of a medicine;
- diminishing of the systemic side effects;
- possibility of introducing the exact dose of a medicinal substance into the eye.

3.9. THE QUALITY CONTROL AND STORAGE OF OPHTHALMIC MEDICINAL FORMS

Quality control includes *all types of the intra-chemist's control*:

- Written;
- Questioning;
- Organoleptic (color, odor, uniformity) and the absence of particulate matters, transparency;
 - Physical (the total amount or the weight, which after preparation should not exceed the norms of permitted deviations, the size of particles in ointments);
 - Chemical control (primary and secondary (it is selective));
 - Control at the dispensing.

For dispensing and storages of eye drops use bottles of a neutral glass (bottles for antibiotics) closed by rubber corks and sealed by aluminium cover.

Conditions of storage of ophthalmic medicines depend on properties of the medicinal and auxiliary substances. If there are no special indications, eye drops, lotions and ointments are kept in a cool place for 10 days protected from light.

3.10. THE MAIN DIRECTIONS OF IMPROVING OPHTHALMIC MEDICINES TECHNOLOGY

Development of small high-performance devices and apparatuses for exploitation in the conditions of the chemist's and small productions

Introduction of new more improved auxiliary substances: polymers-carriers, preservatives, stabilizers, buffer solvents, prolongation agents, etc. possessing the minimal side effects

Development of packing materials for a single application; creation of medicinal forms for a single application: medicinal films (OMF), lamellas, aerosols, triturated tablets

Development of adequate express-methods for control of ophthalmic medicinal forms

3.11. MEDICINAL FORMS WITH ANTIBIOTICS

CLASSIFICATION OF MEDICINAL FORMS WITH ANTIBIOTICS

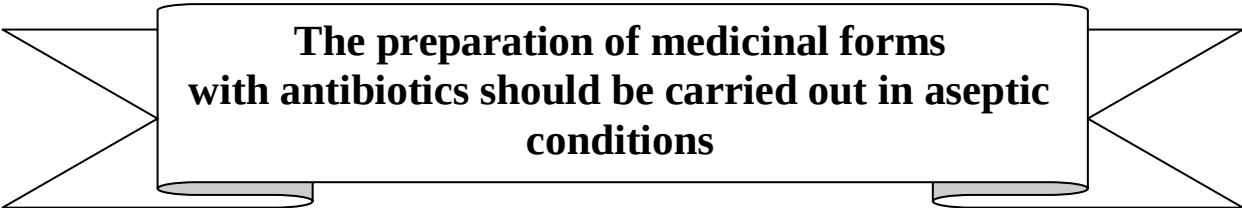
By the way of introduction:

for injections (water solutions and oil solutions, suspensions, emulsions);
for internal use (mixtures, tablets, capsules, pills);
for rectum and vagina;
for local application

By the form of medicines:

solutions;
eye drops;
drops for nose;
drops for ear;
washings;
suspensions;
ophthalmic and dermatological ointments;
suppositories;
tablets, powders, etc.

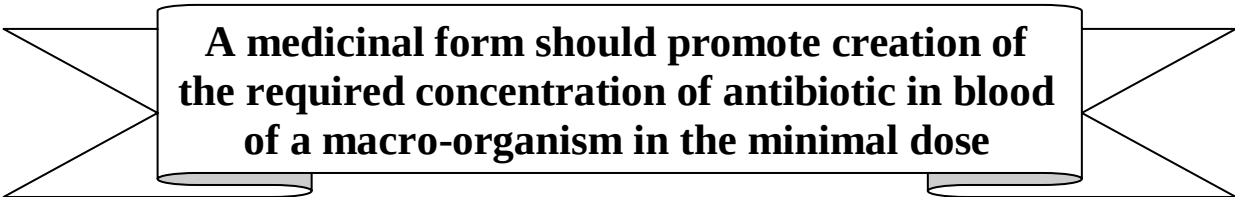
REQUIREMENTS FOR MEDICINAL FORMS WITH ANTIBIOTICS



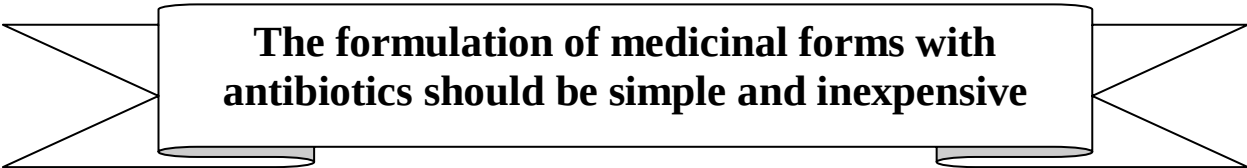
The preparation of medicinal forms with antibiotics should be carried out in aseptic conditions



The type of the medicinal form should provide stability of antibiotic in the process of technology and storage



A medicinal form should promote creation of the required concentration of antibiotic in blood of a macro-organism in the minimal dose



The formulation of medicinal forms with antibiotics should be simple and inexpensive

3.11. MEDICINAL FORMS WITH ANTIBIOTICS

are the low-molecular chemotherapeutic substances produced by microorganisms or obtained from natural sources, as well as their synthetic analogues or derivatives possessing the ability to suppress pathogens of a disease in the patient's organism or to inhibit development of malignant carcinomas.

PROPERTIES:

- They are unstable while storing;
- They are unstable at $\text{pH} < 7$ (penicillins);
- They interact with many auxiliary substances;
- They are poorly soluble in water (and aqueous solutions of some antibiotics are unstable);
- They have thermolability;
- They can show chemical or pharmacological incompatibility in combination with other substances.

Antibacterial activity of antibiotics is expressed in units of action (*U*) corresponding to the definite weight parts of a chemically pure medicine and it is determined by the method of biological standardization.

If there is no such conformity, while recalculating *U* of antibiotics in weight ratios it is necessary to use the data given in the corresponding individual articles of the State Pharmacopoeia of Ukraine, where the dependence between the weight and units of action of some antibiotics are specified.

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

Medicines with antibiotics in their composition are represented, as a rule, in such medicinal forms as for injections, for internal use, for external use, for use rectally and vaginally.

The invariance of the chemical structure, physical state and pharmacological action of antibiotics should be kept both while preparing medicines and during their storage and application by patients.

TECHNOLOGY OF POWDERS WITH ANTIBIOTICS

Complex powders with antibiotics are prepared according to the general rules of preparation of complex powders taking into account properties of the components. Antibiotics are added to the sterilized and cooled powders in aseptic conditions.

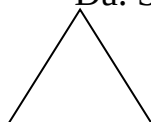
Rp.: Ephedrini hydrochloridi 0.2
Benzylpenicillini-natrii 200000 U
Streptocidi
Sulfadimezini ana 2.0
Misce fiat pulvis subtilissimus
Da. Signa. For inflation into the nose every 2 hours.

Triturate 2.0 g of streptocide with 20 drops of alcohol in a sterile mortar, then add 2.0 g of sulphadimezine. Pour out the mixture on the capsule and leave approximately 0.2 g in the mortar. Then put 0.2 g of ephedrine hydrochloride (list “A” with request) in the mortar, mix thoroughly and mix in some portions while stirring thoroughly with the mixture, which was previously placed on a capsule. Sterilize the mixture obtained at 150°C for 1 hour, then add 0.12 g of sodium salt of benzylpenicillin (a thermolabile substance) in aseptic conditions observing the rules of mixing.

Do not include antibiotics in powders in the pure state because of the possible allergic reactions of the patient.

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

Rp.: Ephedrini hydrochloridi 0.05
 Streptocidi
 Norsulfazoli ana 1.5
 Benzylpenicillini-natrii 250 000 U
 Misce, ut fiat pulvis
 Da. Signa. Inhale through the nose.



Issued:	Ephedrini hydrochloridi 0.05
	Date Signature
Received:	Ephedrini hydrochloridi 0.05
	Date Signature

WCP (front side)

Date	No	Pr.
Streptocidi		1.5
Ephedrini hydrochloridi		0.05
<u>Norsulfazoli</u>		<u>1.5</u>
Sterilis	m =	3.05
<u>Benzylpenicillini-natrii</u>		<u>0.15 (100 000 U = 0.06)</u>
	m =	3.2

Addita aseptice

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

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

TECHNOLOGY OF SOLUTIONS WITH ANTIBIOTICS

To give stability to eye drops and other liquid medicinal forms with antibiotics prepare isotonic solution of sodium chloride or use sodium chloride as a stabilizer.

Rp.: Benzylpenicillini-natrii 200 000 U
Sol. Natrii chloridi isotonicae 10 ml
Misce. Da.
Signa. 2 drops into both eyes.



WCP (front side)

Date	No	Pr.
	Sol. Natrii chloridi	0.9 % sterile 10 ml
	<u>Benzylpenicillini-natrii 0.12 (100 000 U =0.06)</u>	
	Addita aseptice	V = 10 ml

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

Rp.: Sol. Laevomycetini 0,25% 20 ml
Misce. Da. Signa. 2 drops into both eyes.



WCP (front side)

Date	No	Pr.
	<i>Aguae pro injectionibus 20 ml</i>	
	Laevomycetini 0.05	
	<u>Natrii chloridi 0.18</u>	
	Sterilis	V = 20 ml

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

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

TECHNOLOGY OF OINTMENTS WITH ANTIBIOTICS

When preparing ointments with antibiotics a special attention should be paid to the composition of a base and a way of introduction of antibiotics.

Ointments prepared on anhydrous bases are the most stable. The most suitable base for eye ointments is considered a mixture consisting of vaseline – 9.0 g («for eye ointments») and anhydrous lanolin – 1.0 g.

All bases for ointments with antibiotics are used only after their sterilization. They are kept in bottles of 10.0 g.

Ointments with antibiotics are prepared in aseptic conditions observing the general rules for preparing ointments using a mixture of 4 portions of anhydrous lanolin and 6 portions of vaseline («for eye ointments») as a base.

Ointments with benzylpenicillin salts are prepared similar the preparation of triturated ointments since an antibiotic is quickly inactivated in an aqueous solution.

Rp.: Unguenti Benzylpenicillini-natrii 20.0

Da. Signa. Put under the eyelid in 3-4 hours.

It is necessary to prepare the ointment according to the approved formulation (Pharmacopoeian Article 42-84-72): 0.65 g of sodium benzylpenicillin, 20.0 g of anhydrous lanolin, vaseline up to 100.0 g.

Open a bottle with penicillin previously washed with 10 % alcohol with the help of sterile tweezers and transfer 0.13 g of sodium benzylpenicilline into the sterile mortar, which is slightly warmed. Triturate the medicine in a fine powder, then triturate with a small amount of a sterile base (4.0 g of anhydrous lanolin and 16.0 g of vaseline) melt and cooled up to 40°C and add it to penicillin in the small portions while constantly stirring to form a homogeneous mixture. Place in a sterile bottle with a screwed lid. Prepare for dispensing. The shelf live of the ointment is 10 days.

Ointments with tetracycline are prepared on the sterile base in aseptic conditions. They are applied in treating trachoma, keratitis, acute conjunctivitis and other inflammatory ophthalmic diseases.

Rp.: Unguenti Tetracyclini hydrochloridi 1% 10.0

Da. Signa. Put on eyelids 2-3 times a day.

In preliminary sterilized mortar transfer 0.1 g (100000 U) of tetracycline hydrochloride, triturate thoroughly adding the melt half cooled base in portions (up to temperature 40°C). Keep the ointment in a cool dark place.

To prepare ointments with antibiotics use, as a rule, the base of lanolin - vaseline (4:6).

Rp.: Benzylpenicillini-natrii 100 000 U
 Lanolini anhydrici 4.0
 Vaselini pro oculi 6.0
 Misce, ut fiat unguentum
 Signa. Put under the eyelid.



WCP (front side)

Date		№ Pr.
	Benzylpenicillini-natrii 0.06 (100 000 U = 0.06)	
	<u>Basis pro oculi (6:4) sterile</u>	<u>10.0</u>
		m = 10.0
	Addita aseptice	
	Prepared by:	(signature)
	Checked by:	(signature)

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

TECHNOLOGY OF SUPPOSITORIES WITH ANTIBIOTICS

The absorption rate of antibiotics depends on the nature of a base, usually for this purpose cacao butter, wax and various surfactants are used.

Suppositories are prepared by the rolling method or the compression method as heating is impossible.

Suppositories with penicillin. Triturate penicillin with a small amount of lactose and introduce into the suppository base as a fine powder. The content of penicillin in one rectal suppository is 100000 - 500000 units. When storing in a cool place the activity of prepared suppositories can be preserved for 2 months.

Sometimes to accelerate the action of penicillin it is dissolved in the solution of sodium citrate (1:1000) and mixed with a suppository base. The stability of such suppositories is not more than 10 days.

Suppositories with tetracycline. More often tetracycline hydrochloride is used for this purpose. It is stipulated by the less expressed local irritating action of this antibiotic. Usually suppositories containing 0.3 g (300000 U) of tetracycline are prescribed to adults.

Rp.: Tetracyclini hydrochloridi 0.3
Olei Cacao **q.s.**
Misce, fiat suppositorium
Da tales doses № 6
Signa. Use 1 suppository 3 times a day.

Place 1.8 g of tetracycline hydrochloride in a sterile mortar, triturate thoroughly (without dilution in water) and while stirring add 16.2 g of the powdered cacao butter in portions. Mix to obtain the homogeneous plastic mass, from which roll out six suppositories and register them to dispensing.

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

TECHNOLOGY OF LIQUID MEDICINAL FORMS WITH ANTIBIOTICS

Use purified water, alcohol, glycerin, vegetable oils as solvents. Prepare solutions using the general rules of preparation. The peculiarity of preparation is the observance of aseptic conditions. It is necessary to avoid filtering of solutions through a common filter paper.

In most cases, only a sterile solvent is prepared at the chemist's, and dilution is performed directly before administration.

Aqueous solutions. *Solutions of sodium benzylpenicillin.* To prepare these solutions the following solvents are used:

- isotonic solution of sodium chloride;
- isotonic solution of glucose;
- novocain solution (0.25 and 0.5 %).

Therefore, *sodium benzylpenicillin* should be dissolved directly before administration.

Rp.: Benzylpenicillini-natrii 200000 U
Solutionis Natrii chloridi isotonicae 150 ml
Misce. Da. Signa. For washing of wounds.

At first prepare a sterile isotonic solution of sodium chloride, where dissolve 0.12 g of *sodium benzylpenicillin* salt.

Eye drops. *Eye drops with levomycetin.* Prepare solutions using fresh water for injections or isotonic solution of sodium chloride in aseptic conditions. Dilution of antibiotic can be carried out when heating.

Rp.: Laevomycetini **0.02**
Novocaini **0.1**
Solutionis Acidi borici 2 % 10 ml
Misce. Da. Signa. 2-3 drops 3 times a day into both eyes.

Solutions for injections with antibiotics are prepared with apyrogenic water for injections or isotonic solution of sodium chloride.

Alcoholic solutions. Levomycetin is also used as alcoholic solutions, frequently in combination with sulphonylamide medicines.

Rp.: Laevomycetini
Norsulfasoli-natrii aa 2.0
Spiritus aethylici 100 ml
Misce. Da. Signa. For rubbing of the skin.

Place 2.0 g of sterile sodium norsulphasol and 2.0 g of sterile levomycetin into sterile bottle for dispensing, add 100 ml of 90 % ethyl alcohol, close and shake to the complete dissolution.

Rp.: Laevomycetini 3.0
Solutionis Acidi borici 2 % 40.0
Spiritus aethylici 70 % 50.0
Misce. Da. Signa. To rub the face skin.

Dissolve levomycetin in alcohol, then add the boric acid solution.

Suspensions. Oil suspensions intended for intramuscular injections are more stable comparing to aqueous solutions of antibiotics. While preparing suspensions dispersity of the solid phase has a decisive importance.

Rp.: Benzylpenicillini-natrii 1000000 U
Olei Persicorum 100.0
Sterilisa!
Misce. Da. Signa. 1-2 ml intramuscularly 2 times a day.

Weigh 100.0 g of peach oil in the bottle for dispensing, close with a cotton tampon and sterilize at 180°C for 30-40 minutes. Then triturate sodium salt of benzylpenicillin in a sterile mortar in aseptic conditions with a small amount of sterile oil, gradually adding all oil. Place the suspension into a sterile bottle for dispensing.

3.13. REGISTRATION FOR DISPENSING OF MEDICINES WITH ANTIBIOTICS

Medicines with antibiotics are dispensed in sterile bottles preventing from microflora, as much as possible, and have the following labels:

- ❖ «For internal use» or «For external use»;
- ❖ «Prepared aseptically» or «Sterile»;
- ❖ «Keep in a cool place»;
- ❖ «Keep out of the reach of children»;
- ❖ «Keep away from direct light»;
- ❖ «Shake well before using» (if it is necessary).

3.14. QUESTIONS FOR SELF-CONTROL

1. What are the types of ophthalmic medicines?
2. Describe eye drops as a medicinal form.
3. What are the requirements to eye drops?
4. How can sterility of eye drops be achieved?
5. What are the peculiarities of technology for eye drops?
6. What requirements should the ophthalmic soft medicinal forms meet?
7. What is the peculiarity of introducing resorcline and zinc sulphate into ophthalmic ointments?
8. What are eye inserts?
9. Characterize medicinal forms with antibiotics and requirements to them.
10. What are the peculiarities of preparing liquid and solid medicines with antibiotics?
11. Describe formulation of ointments and suppositories with antibiotics.
12. Quality control, registration for dispensing and storage of medicines with antibiotics according to the normative documentation.

OPHTHALMIC MEDICINES. MEDICINAL FORMS WITH ANTIBIOTICS

INTRODUCTION

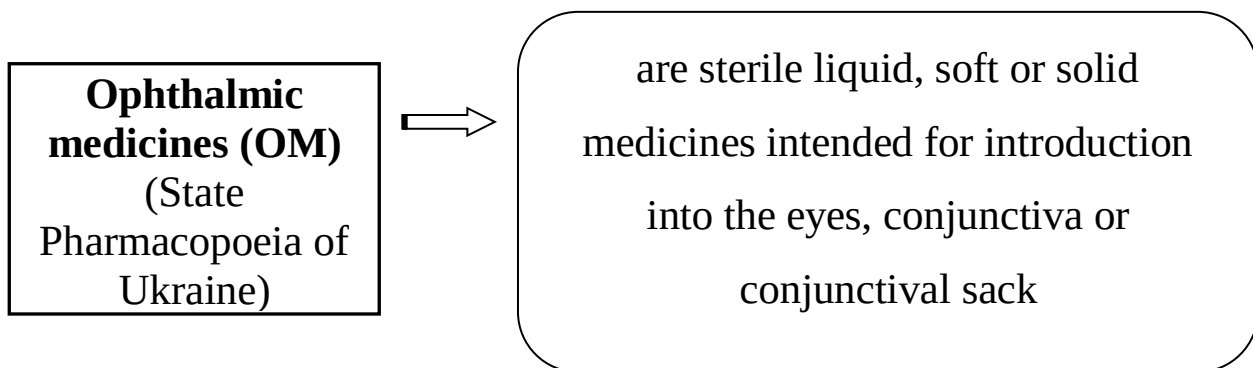
Ophthalmic medicines are medicines intended for application on the mucous membrane of the eye, which is the most sensitive of all mucous membranes of the organism that sharply reacts on external irritants. Therefore, the same claims are laid to both ophthalmic medicines and solutions for injections: they should be maximally purified from visible and sub-visible particles, have exact concentration of substances, be isotonic, sterile and stable, and, in some cases, they should have the prolonged action and buffer properties. While preparing medicinal forms it is necessary to take into account

specific mechanisms of absorption and distribution of medicines, the peculiarities of their interaction with tissues and liquids of the eye.

Drops are a simple and rather effective medicinal form used the most widely since old times. Compounding of medicines at the chemist's contains 5% - 15% of drops. The formulations of eye drops comprising two (to 35%), three (17-19%), four (22-25%), five (13-15%) medicinal substances are the most frequently met. Sometimes there are formulations with 8-9 components. Nowadays about 80 medicinal substances are applied in the ophthalmic practice, as well as a great amount of their various combinations.

It is still essential to prepare eye drops in the conditions of a chemist's because of the limited assortment of domestic manufactured ophthalmic medicines, difficult compositions in formulations and technological difficulties of their manufacturing.

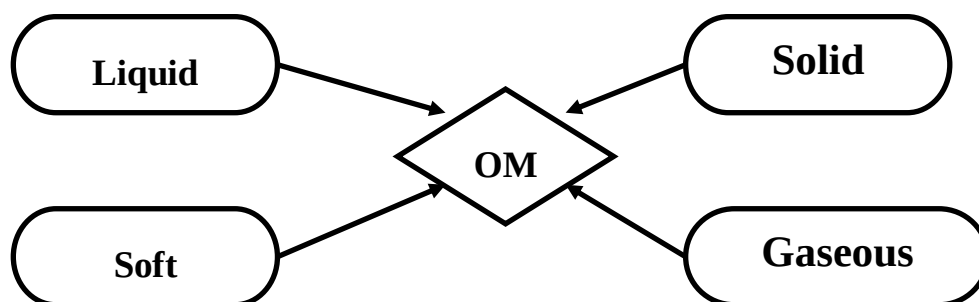
3.1. CHARACTERISTICS AND CLASSIFICATION OF OPHTHALMIC MEDICINES



Usually for treating ophthalmic diseases the following methods can be used:

- ✓ Instillation of solutions;
- ✓ Insertion of ointments, eye films, tablets, lamellas into the conjunctival sack;
- ✓ Introduction of medicinal substances by injections;
- ✓ Contact lenses and eye inserts;
- ✓ Electrophoresis.

DIFFERENT FORMS OF OPHTHALMIC MEDICINES (OM):



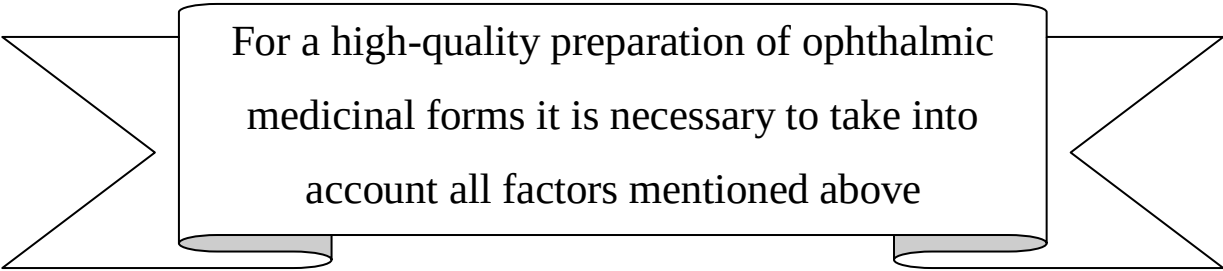
3.1. CHARACTERISTICS AND CLASSIFICATION OF OPHTHALMIC MEDICINES

FACTORS DETERMINING THE CHOICE OF A MEDICINAL FORM

- The state of a pathological process in the eye
- General indexes of the patient's organism state
- The presence of the corresponding traumatic lesions of the eye
- Degree of permeability of the blood-aqueous barrier
- Physical and chemical properties of medicinal substances
- Peculiarities of the pharmacological action of medicinal and auxiliary substances, etc.

In addition, the processes of activation or inhibition of the action of medicinal substances are affected by:

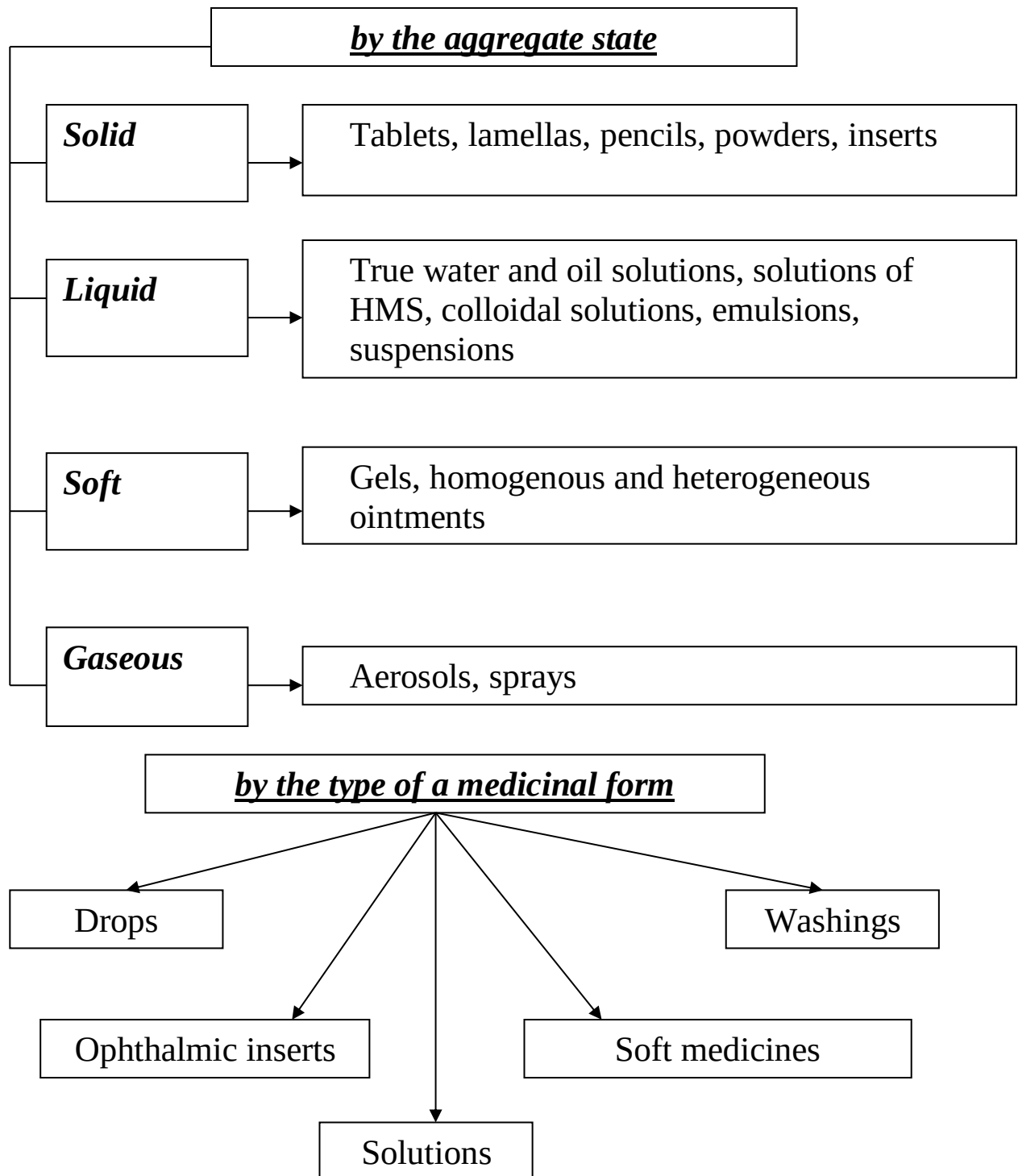
- ✓ pH value of the solution;
- ✓ the solution's osmotic pressure;
- ✓ the molecular weight of substances - carriers, etc.



For a high-quality preparation of ophthalmic medicinal forms it is necessary to take into account all factors mentioned above

Ophthalmic drops, lotions and ointments are prepared more often in the extemporal practice of the chemist's.

3.1. CHARACTERISTICS AND CLASSIFICATION OF OPHTHALMIC MEDICINES

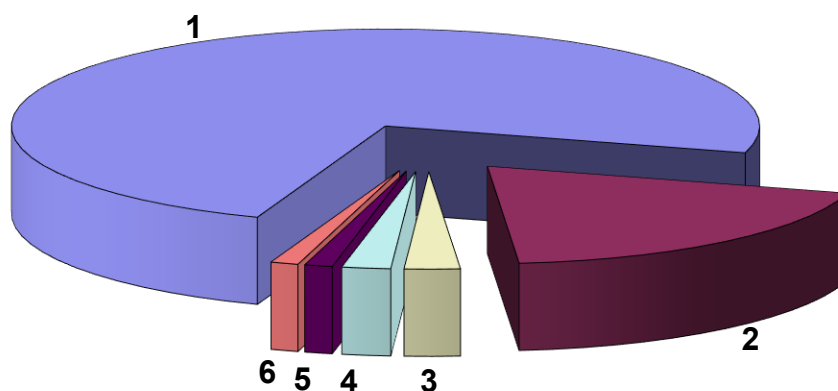


3.2. MODERN STATE OF OPHTHALMIC MEDICINES PRODUCTION IN UKRAINE

<i>Pharmacological group</i>	The number of medicines		
	Germany	Russia	Ukraine
1. Local anaesthetics	7	1	0
2. Antibiotics	51	16	18/1
3. Antiseptics	11	9	12/7
4. Antivirus medicines	8	5	4/0
5. Steroid anti-inflammatory medicines	64	11	18/0
6. Antiasthenotopic medicines	2	1	0
7. Medicines affecting vessels	26	9	1/0
8. Antiglaucoma medicines	130	45	41/3
9. Mydriatics	20	5	5/2
10. Anti-allergic medicines	24	14	14/0
11. Film-forming medicines (artificial tear)	31	4	4/0
12. Vitamins	14	-	0
13. Anticatarrrhal medicines	3	8	10/2
14. Organo-medicines	4	3	0
15. Others	27	1	6/1
TOTAL:	422	132	133/16

Note: Of 133 medicines only 16 ones are produced by Ukrainian manufactures (from 5 pharmacotherapeutical groups). The market of Ukraine is full of 88% of expensive foreign ophthalmic medicines.

The comparative analysis of quantitative and qualitative indexes of the ophthalmic medicines nomenclature



Medicines are produced in the different medicinal forms:

- 1) 73.9 % are ophthalmic drops on the water base;
- 2) 19.2 % are ophthalmic ointments and gels;
- 3) 2.4 % are drops on the oil base;
- 4) 2.1 % are solutions for eye irrigation and baths;
- 5) 1.2 % are ophthalmic suspensions;
- 6) 1.2 % are powders for dissolving “ex tempore”.

Analysis of the market of ophthalmic medicines by the types of medicinal forms

Type of medicinal form	Country		
	Germany	Russia	Ukraine
1. Water drops	312	113	123
2. Solutions for eye irrigation	9	-	0
3. Ointments and gels	81	15	5
4. Oil drops	10	-	0
5. Suspensions	5	2	5
6. Dry substance + solvent	5	2	0
TOTAL:	422	132	133

3.3. OPHTHALMIC DROPS (GUTTAE OPHTALMICAЕ)

REQUIREMENTS FOR OPHTHALMIC DROPS

Ophthalmic drops

are liquid medicinal form, which are aqueous or oil solutions, thin suspensions of medicinal substances intended for instillation into eyes

Poor quality of eye drops and their contamination by microorganisms can cause severe consequences even the loss of vision.

That is why the **requirements** for eye drops are the same as for **solutions for injections**:

- sterility
- stability
- the absence of particulate matters
- isotonicity
- the prolongation of action (in some cases)

**Ophthalmic drops are prescribed in small amounts (5-10 ml)
taking into account their application for a short period.**

3.3. OPHTHALMIC DROPS

STERILITY OF OPHTHALMIC DROPS

The character of preparatory measures, conditions of the technological process of eye drops and lotions are similar to those for solutions for injections, i. e. they are prepared in aseptic conditions with the subsequent sterilization.

The way of sterilization for eye drops depends on the stability of medicinal substances in solutions to temperature.

Medicinal substances can be divided into three groups:

4. Solutions of medicinal substances, which can be sterilized by thermal sterilization without adding stabilizers
5. Solutions of medicinal substances, which can be sterilized by thermal sterilization after adding stabilizers
6. Solutions of medicinal substances, which cannot be thermally sterilized and prepared in aseptic conditions without further sterilization

Solutions of medicinal substances, for which the modes of sterilization have not been developed, are also prepared in aseptic conditions.

3.3. OPHTHALMIC DROPS

STERILITY OF OPHTHALMIC DROPS

Microorganisms get into eye drops at the first opening of a vial, and depending on the composition of the solution, the following things can occur:

- *Reproduction and accumulation of individual species of microorganisms*

after the incubation period, which duration varies from several hours to several days

- *Retaining the amount of microorganisms at the same level*

when the solution's components have the bacteriostatic and fungistatic action

- *Decreasing the amount of microorganisms got into the solution*

when the solution's components have the bacteriostatic and fungistatic action

To preserve the sterility of eye drops after opening of a vial, **preservatives** - antimicrobial substances that prevent the growth of microorganisms - can be used.

- Preservatives should be compatible with other components of eye drops and keep their efficiency within the whole period of the medicine's application.
- Preservatives are not used if a medicinal substance provides a sufficient antimicrobial action independently.

3.3. OPHTHALMIC DROPS

STERILITY OF OPHTHALMIC DROPS

The limited assortment of preservatives is used in ophthalmic medicinal forms.

Classification of preservatives

Inorganic	boric acid – 1.9-2.0 % (pH approximately 5.0)
Organic	β-phenylethyl alcohol– 0.3-0.5% - benzyl alcohol – 0.9% - esters of <i>p</i>-hydroxybenzoic acid: nipagin – 0.05-0.23%, nipazol – 0.03-0.08% or their mixture (nipagin 0.18%, nipazol 0.02%) - levomycetin 0.15% - salts of quaternary ammonium bases (benzalkonium chloride, cetylpyridinium chloride, dodecyl methyl benzylammonium chloride) in the concentration of 1:10000 - sorbic acid – 0.05-0.2%
Organo-metallic	- ethanol mercury chloride 0.01% - merthiolate 0.005%

Preservatives are added into a medicinal form before sterilization of the solution

3.3. OPHTHALMIC DROPS

STABILITY OF OPHTHALMIC DROPS

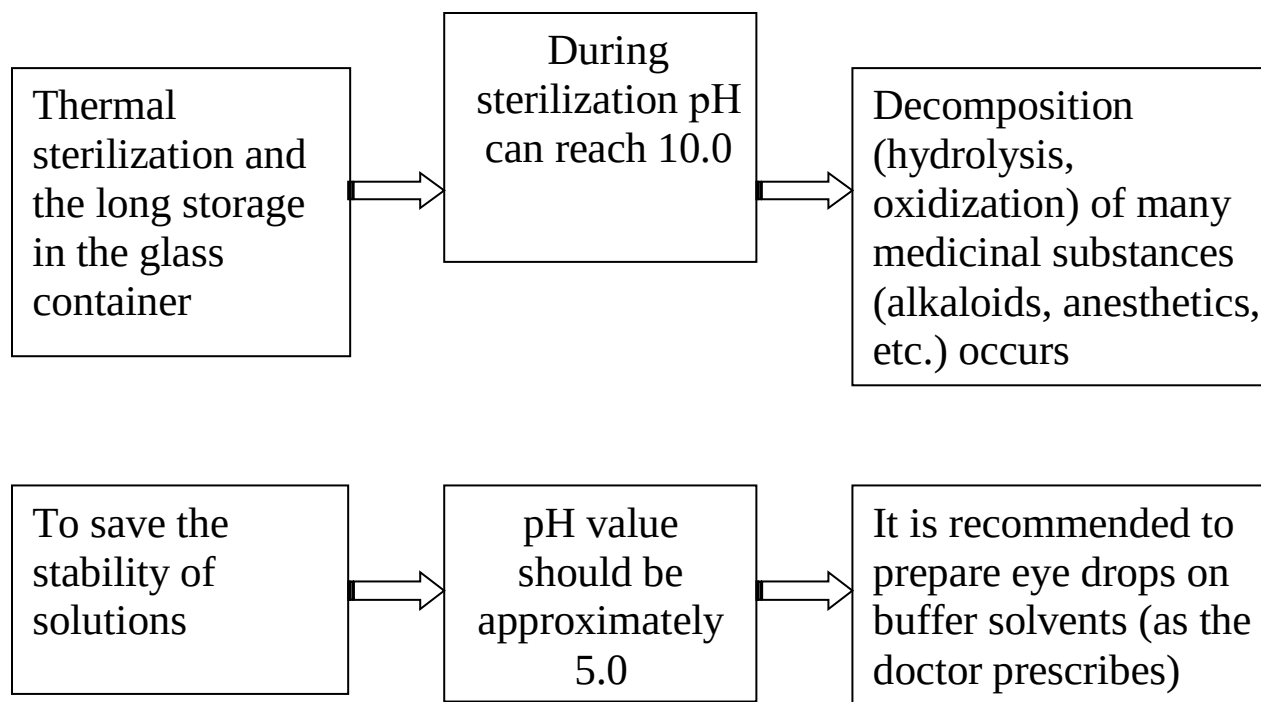
Different auxiliary substances are introduced to the composition of eye drops to provide their stability.

Components	The purpose of introduction	The mechanism of action
↓	↓	↓
preservatives	prevention of the microorganisms growth in the medicinal form in the process of its storage and use	▪ destruction of the cellular membrane ▪ protein coagulation ▪ blocking of free sulphohydril groups ▪ chemical antagonism
stabilizers	▪ increase of the chemical stability ▪ increase of the therapeutic activity ▪ decrease of the irritant action of ophthalmic solutions	▪ neutralization of acidic products of the vital activity in the place of application ▪ maintenance of pH value of the solution ▪ neutralization of the glass alkalinity
prolongation agents	▪ prolongation of medicines action ▪ reduction of the number of installations	▪ increase of density of solutions ▪ prolongation of the contact time of a medicine with the mucous membrane of the eye

3.3. OPHTHALMIC DROPS

STABILITY OF OPHTHALMIC DROPS

Disturbance of the stability of eye drops can take place during sterilization as the result of the temperature influence and the change of pH medium.



PREPARATION OF EYE DROPS ON BUFFER SOLUTIONS ALLOWS:

- to increase the chemical stability;
- to intensify the therapeutic action;
- to decrease the irritating action.

When choosing a buffer solution, its composition and pH should provide stability of a definite medicine.

3.3. OPHTHALMIC DROPS

STABILITY OF OPHTHALMIC DROPS

BUFFER SOLUTIONS

1. Medicines, which solutions should be with pH about 5.0	It is recommended to use the isotonic solution of boric acid (with the concentration of 1.9 %), its pH is below 5.0	They are used for preparing the following solutions: pilocarpine hydrochloride, dicaine, sovaine, mezonon and salts of zinc
2. Medicines, which solutions should be with pH about 6.8	It is recommended to use phosphate or borate buffer, which becomes isotonic with the help of sodium chloride	They are used for preparing solutions of salts of atropine, pilocarpine and scopolamine
Phosphate buffer	Solution of monobasic sodium phosphate 0.8 % – 30 ml Solution of dibasic sodium phosphate 0.94 % – 70 ml Sodium chloride – 0.43 g	
Borate buffer	Boric acid – 1.84 g Sodium tetraborate – 0.14 g Purified water (pH = 6.8) – 100 ml	
Borate-acetate buffer	1.9 % solution of boric acid 1.5 % solution of sodium acetate	
Borate-propionate buffer	1.9 % solution of boric acid 2 % solution of sodium propionate	

3.3. OPHTHALMIC DROPS

STABILITY OF OPHTHALMIC DROPS

3. Solutions of easily oxidized substances

Addition of antioxidants (sodium sulphite, sodium metabisulphite, etc.) is recommended

They are used for preparing the following solutions: physostigmine salicylate, adrenalin hydrochloride, etc.

Solutions of sodium sulphacyl 10, 20 and 30 %

1.0, 3.0, 5.0 g of sodium metabisulphite and 5, 17 and 18 ml of 0.1 M solution of sodium hydroxide per 1 litre of the solution, respectively

Solution of ascorbic acid 2 %

Solutions of sodium metabisulphite (0.1 %) or anhydrous sodium sulphite (0.2 %)

To stabilize eye drops the following methods can be used:

addition of high polymers, complexones

preparation of solutions under the atmosphere of inert gases

These methods of stabilization allow to increase the shelf life of eye drops

3.3. OPHTHALMIC DROPS

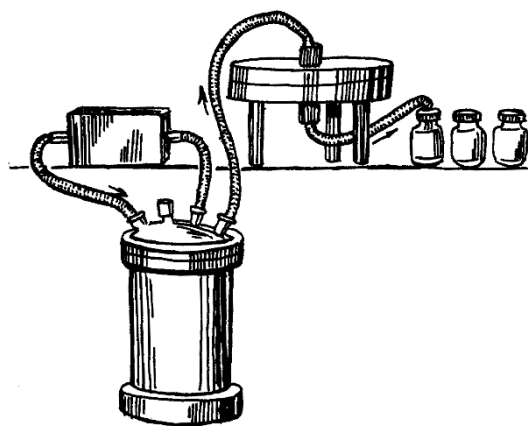
THE ABSENCE OF PARTICULATE MATTERS

All eye drops, excluding emulsions and the thinnest suspensions, should be carefully filtered.

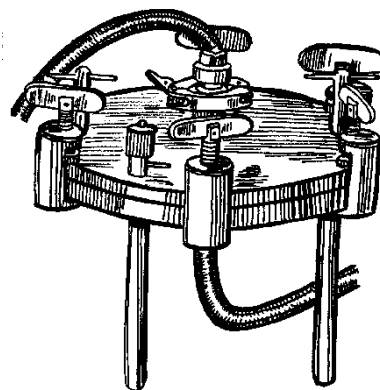
The following filters are used for filtration:

- ❖ **fold paper filters** where under the mouth of the funnel a piece of long fibrous cotton is put
- ❖ **glass filters** No.3 and No.4 (with the particles size of 20-30 μm)
- ❖ **membrane filters** – with the simultaneous mechanical sterilization (when preparing eye drops in large volumes)

When preparing eye drops in batches at the chemist's apparatuses for their filtration with the subsequent packing are expedient to use.



A



B

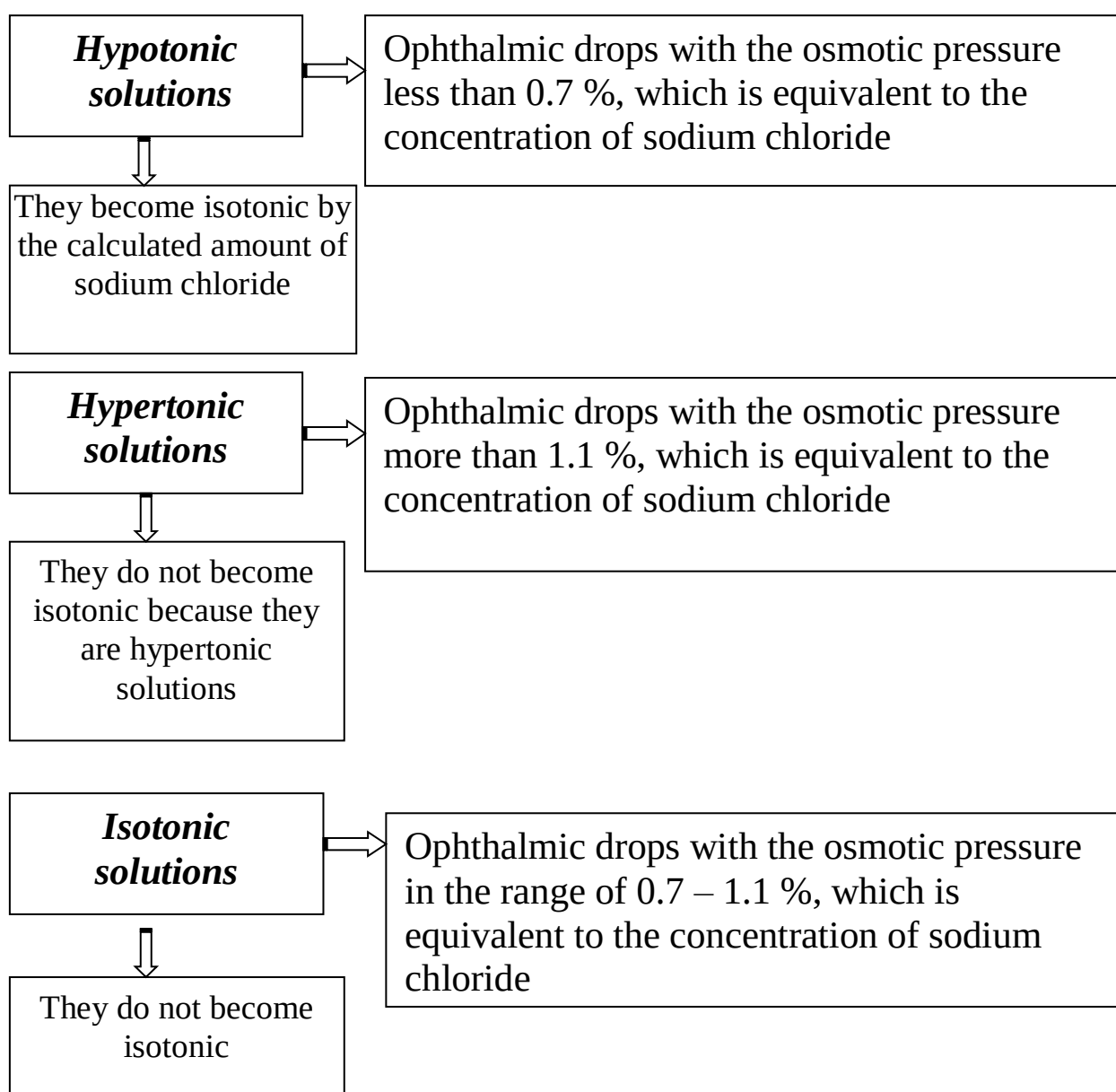
The scheme of USF-293-7 (A) filter apparatus and a general view of the FD-293 (B) filter holder.

3.3. OPHTHALMIC DROPS

ISOTONICITY OF OPHTHALMIC DROPS

In order to prevent discomfort eye drops should be isotonic to a human lachrymal fluid and correspond to the osmotic pressure of sodium chloride solutions with the concentration of $0.9 \pm 0.2 \%$.

**Depending on the osmotic pressure value eye drops
can be divided into 3 groups:**



3.3. OPHTHALMIC DROPS

ISOTONICITY OF OPHTHALMIC DROPS

To make the solution isotonic substances are used taking into account their compatibility with the drug components

- ❖ Sodium chloride
- ❖ Sodium sulphate
- ❖ Sodium nitrate

- ❖ Boric acid
- ❖ Glucose

Ophthalmic drops do not become isotonic in the case if colloidal substances (collargol, protargol) are prescribed as being powerful electrolytes isotonic agents can cause coagulation

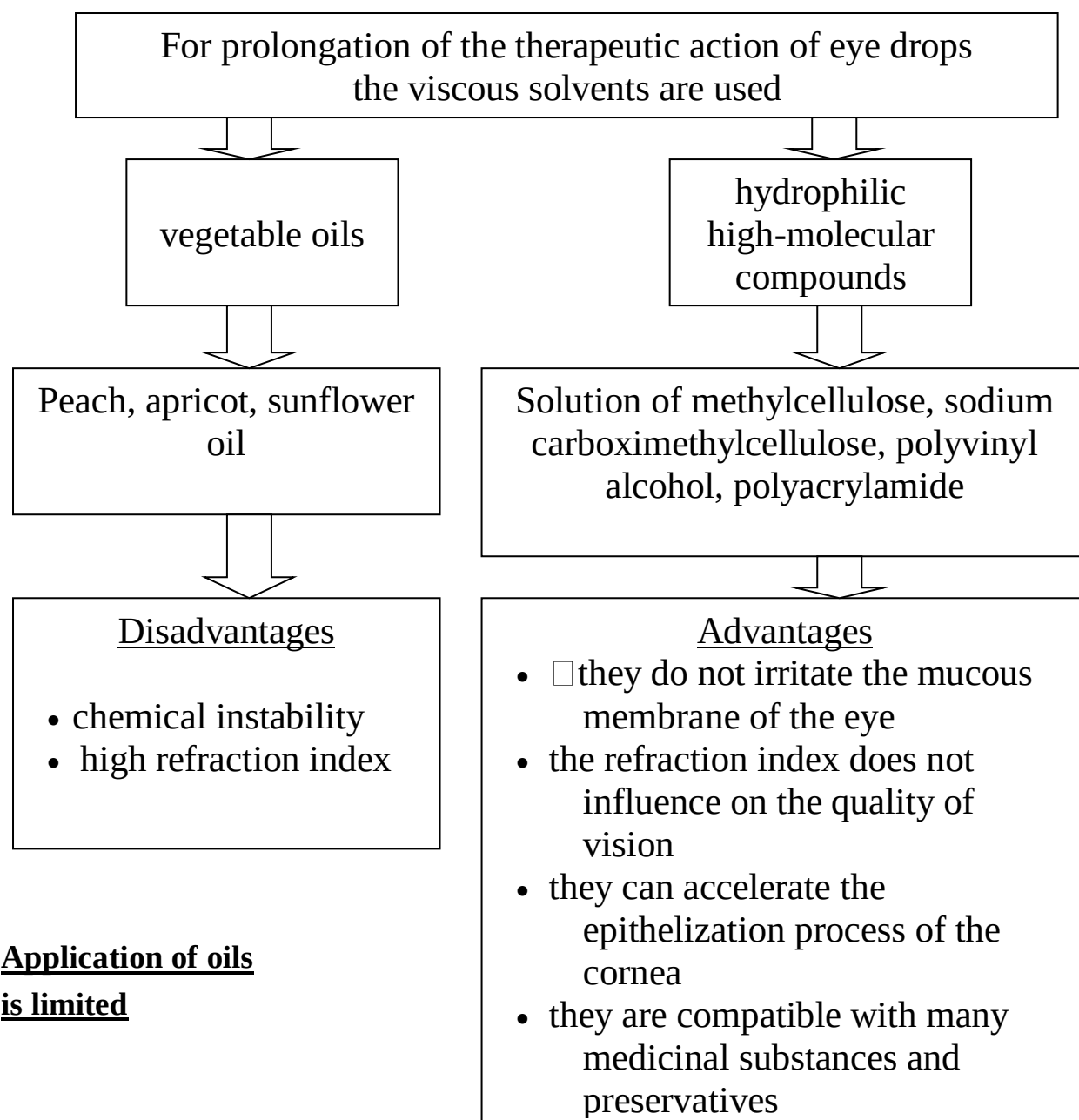
The isotonic concentration of ophthalmic drops can be calculated by the same methods as those for solutions for injections:

- using the equivalent by sodium chloride;
- using the Raoult law;
- using the Van't Hoff equation.

3.3. OPHTHALMIC DROPS

PROLONGATION OF THE THERAPEUTICALLY ACTION OF EYE DROPS

Frequent instillations of an aqueous solution washes off the lachrymal fluid containing liscyme creating the conditions for occurrence of the infectious process.



**Application of oils
is limited**

All prolongation components mentioned can be added to the eye drops only by the doctor's prescription

3.4. TECHNOLOGY OF OPHTHALMIC DROPS

★ Ophthalmic drops are prepared by the mass-volume method in aseptic conditions with the subsequent sterilization of solutions of thermostable substances.

★ Such sterile solvents as purified water or water for injections, isotonic buffer solutions, oils, etc. are used in manufacture of ophthalmic drops.

★ When preparing ophthalmic drops in small amounts significant losses of medicinal substances take place:

- due to their absorption on the filters (up to 4.7 %);
- due to dilution of initial solutions while filtering through paper filters previously washed by water.

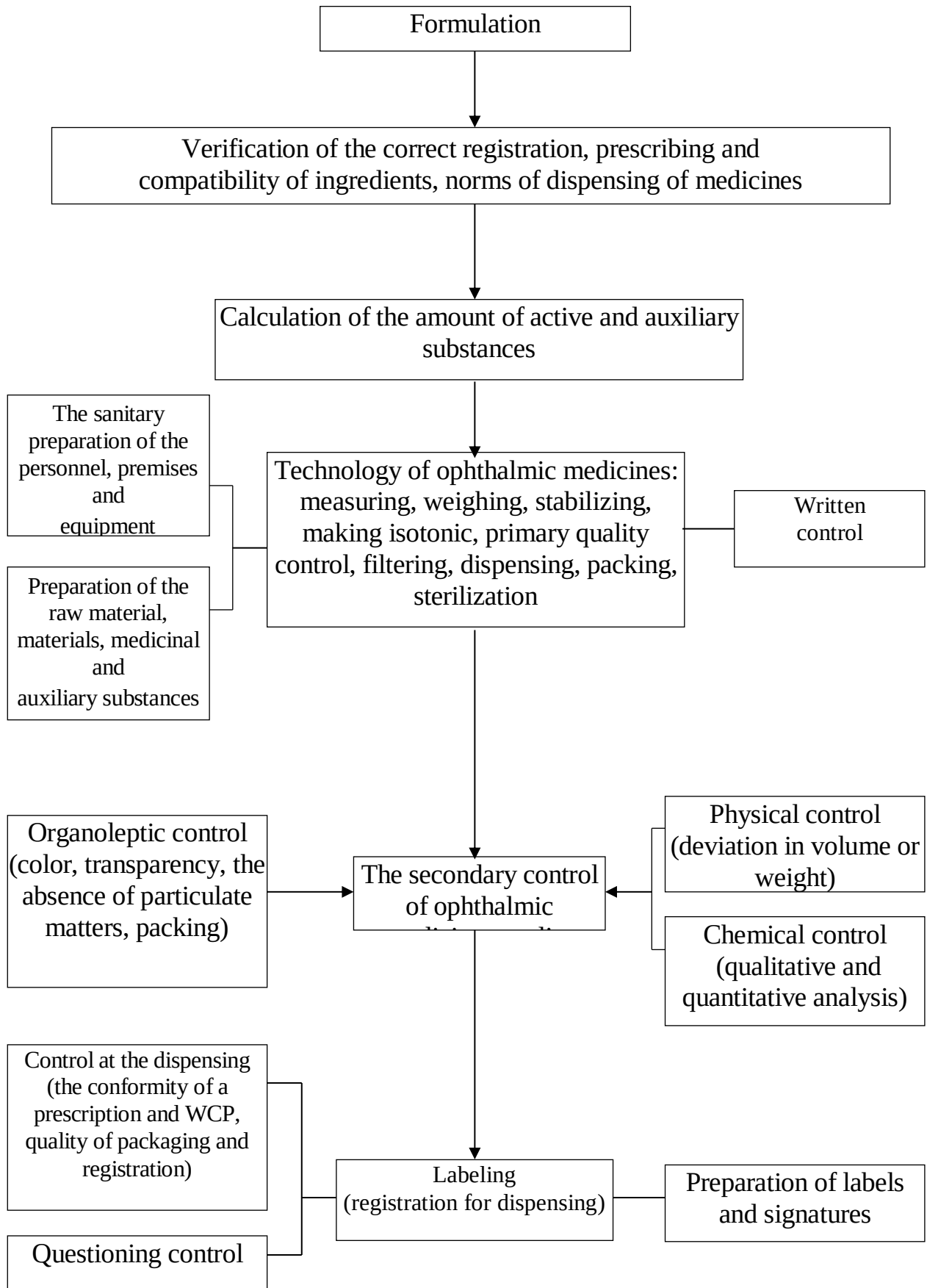
In order to decrease the loss of medicinal substances during the preparation of ophthalmic drops two ways are used:

2 Dissolve a medicinal substance, which is readily soluble in water, in a portion of water ($1/2$ from the solvent's volume), filter the solution in the bottle for dispensing through a paper filter previously washed by the sterile water for injections, and then wash the filter by the remaining portion of the solvent

3 If a medicinal substance is poorly soluble in water, dissolve it in all the solvent's quantity prescribed and filter in a graduated cylinder through a dry filter and cotton. Add the missing quantity of water through the same filter and cotton to make the required volume of the solution

3.4. TECHNOLOGY OF OPHTHALMIC DROPS

THE TECHNOLOGICAL SCHEME AND THE QUALITY CONTROL OF OPHTHALMIC MEDICINES



3.4. TECHNOLOGY OF OPHTHALMIC DROPS

Rp.: Sol. Mesatoni 1 % 10 ml isotonicae

D.S. 2 drops into both eyes for a night.



WCP (r. s.)

Mezaton 0.1

Sodium chloride ($E_{\text{mezaton}} = 0.28$):

$$1.0_{\text{mezaton}} - 0.28_{\text{sodium chloride}}$$

$$0.1_{\text{mezaton}} - X_{\text{sodium chloride}}$$

$$X = \frac{0.28 \times 0.1}{1.0} = 0.028 \text{ g of sodium chloride}$$

To make isotonic 10 ml of water it is necessary to take:

$$0.9 - 100 \text{ ml}$$

$$X - 10 \text{ ml}$$

$$X = 0.09 \text{ g of sodium chloride}$$

$$0.09 - 0.028 = 0.062 \approx 0.07 \text{ g}$$

Purified water – 10 ml

WCP (f. s.)

Date

№ Pr.

Aquae purificatae 10 ml

Mesatoni 0.1

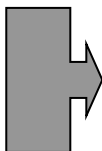
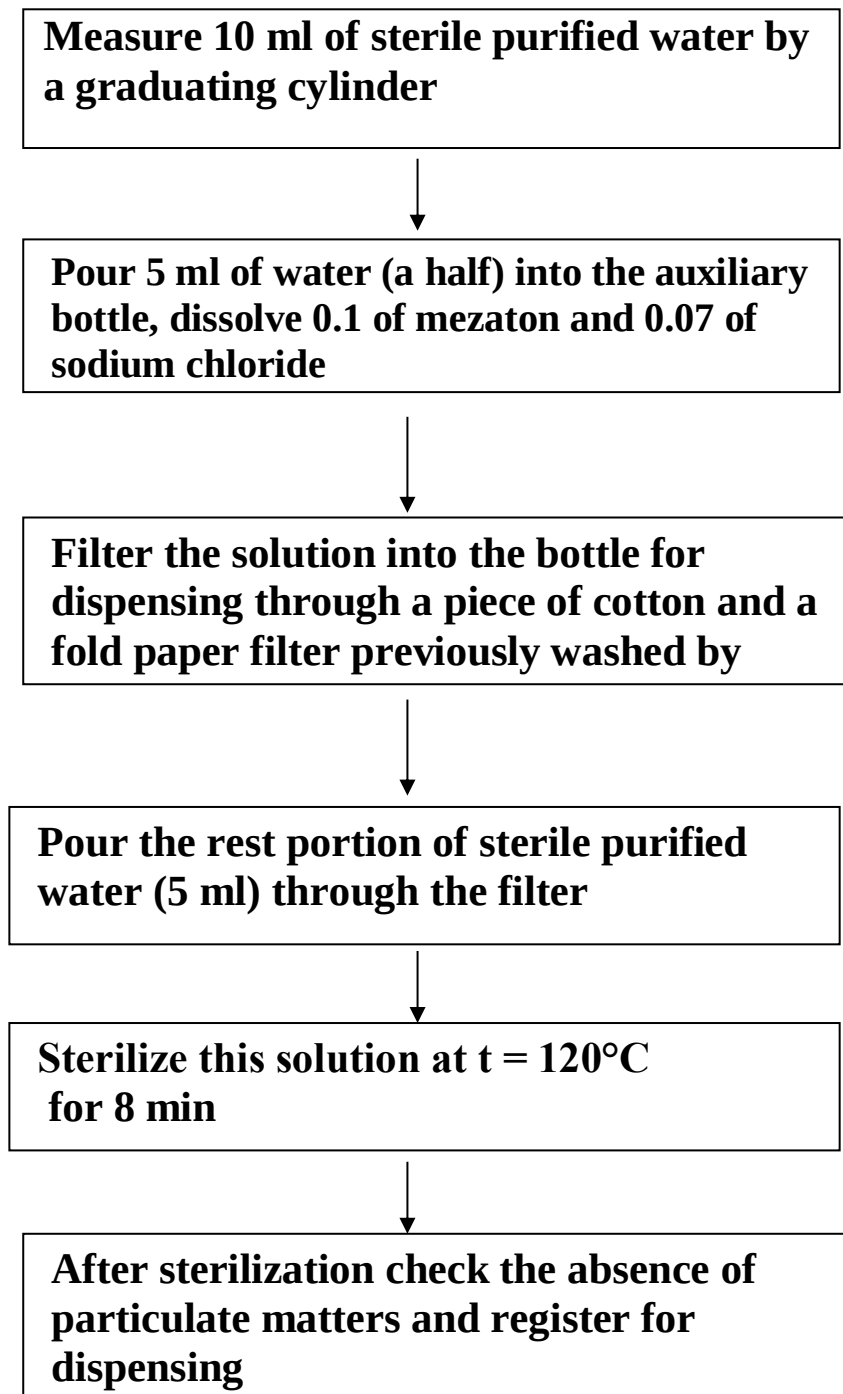
Natrii chloridi 0.07

Sterilis V = 10 ml

Prepared by: (signature)

Checked by: (signature)

3.4. TECHNOLOGY OF OPHTHALMIC DROPS



Introduction of an antioxidant (sodium metabisulphite) into the composition of eye drops with mezaton allows to increase the shelf life to 30 days.

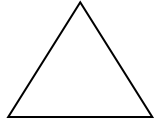
3.4. TECHNOLOGY OF OPHTHALMIC DROPS

Rp.: Sol. Atropini sulfatis 1% 10 ml

Natrii sulfatis q.s.

ut fiat solutio isotonica

D.S. 2 drops into both eyes 3 times a day.



WCP (r. s.)

Atropine sulphate 0.1

Sodium chloride ($E_{\text{atropine sulphate}} = 0.1$):

$$1.0 \text{ atropine sulphate} - 0.1 \text{ sodium chloride}$$

$$0.1 \text{ atropine sulphate} - X \text{ sodium chloride}$$

$$X = 0.01$$

To make isotonic 10 ml of water it is necessary to take:

0.9 – 100 ml

X – 10 ml X = 0.09 g of sodium chloride

0.09 – 0.01 = 0.08 g of sodium chloride

Sodium sulphate ($E_{\text{sodium sulphate}} = 0.23$):

$$1.0 \text{ Sodium sulphate} - 0.23 \text{ Sodium chloride}$$

$$X \text{ Sodium sulphate} - 0.08 \text{ Sodium chloride}$$

$$X = 0.35$$

Purified water – 10 ml

3.4. TECHNOLOGY OF OPHTHALMIC DROPS

Rp.: Sol. Kalii iodidi 2% 10 ml

Riboflavini 0.001

Acidi ascorbinici 0.02

Glucosi 0.2

M.D.S. 2 drops into both eyes.



WCP (r. s.)

Solution of riboflavin 0.02 %	0.02 – 100 ml	
	0.001 – x	x=5 ml

Potassium iodide 0.2

Ascorbic acid 0.02

Glucose:

$$X = \frac{a \times 100}{100 - b} = \frac{0.2 \times 100}{100 - 9} = 0.22 \text{ (humidity is 9 \%)}$$

Purified water: 10 ml – 5 ml = 5 ml

WCP (f. s.)

Date

№ Pr.

Sol. Riboflavini 0.02 % 5 ml sterile

Acidi ascorbinici 0.02

Glucosi 0.22 (hum. 9 %)

Aquae purificatae 5 ml

Sterilis V = 10 ml

Kalii iodidi 0.2

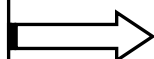
Addita aseptice

Prepared by: (signature)

Checked by: (signature)

3.5. OPHTHALMIC OINTMENTS

**OPHTHALMIC
SOFT MEDICINES**
(State
Pharmacopoeia of
Ukraine)



are homogenous sterile ointments,
creams or gels for application on the
conjunctive of the eye

REQUIREMENTS FOR OPHTHALMIC OINTMENTS:

➤ sterility

➤ stability

➤ even distribution of medicinal substances

➤ the absence of the irritant action and sticking of the eyelid

➤ uniform distribution on the mucus of the eye with
formation of the thinnest film

➤ maximal dispersion of medicinal substances

Bases for ophthalmic ointments

hydrophilic

hydrophobic

emulsion o/w

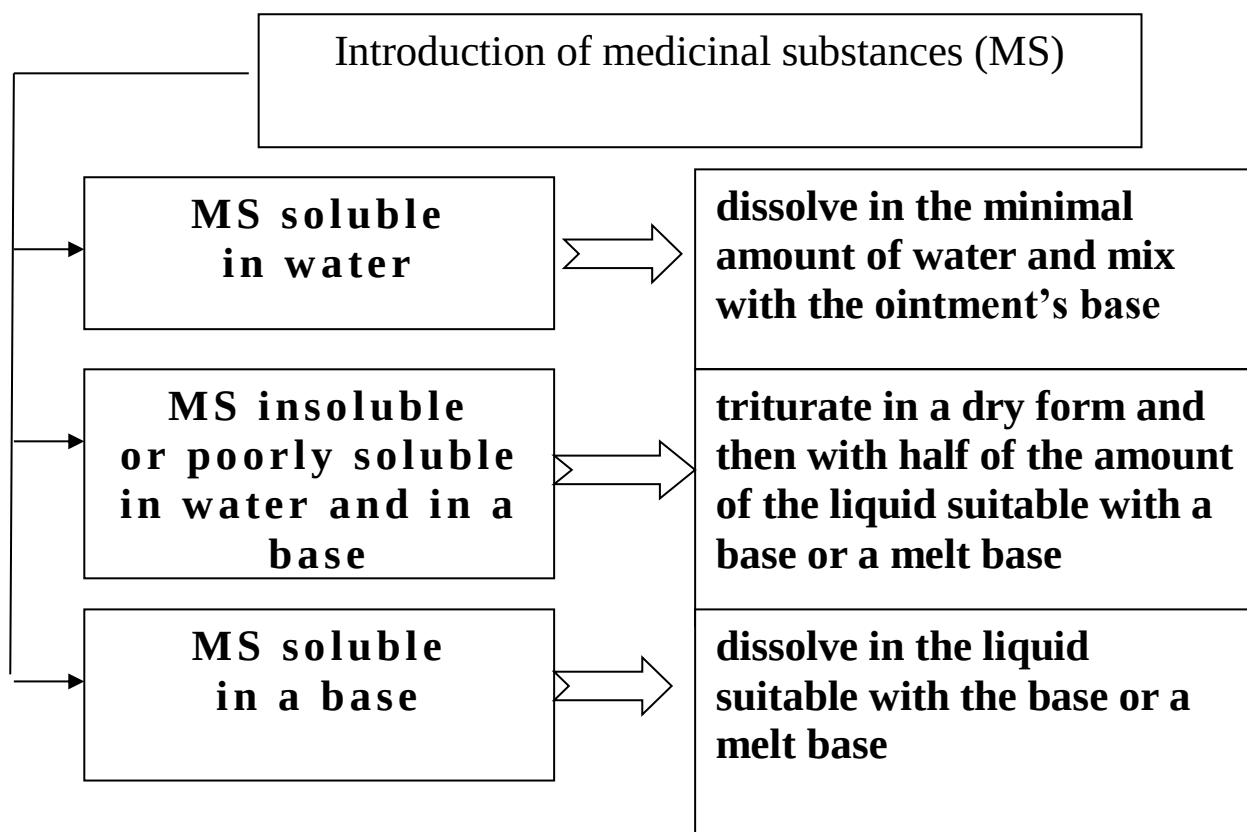
If the base for the ophthalmic ointment is not indicated in the prescription, the following one is usually used:

Vaseline of «for ophthalmic ointments» type - **9** or **8** portions

Anhydrous lanolin - **1** or **2** portions,
respectively

3.6. TECHNOLOGY OF OPHTHALMIC OINTMENTS

All ophthalmic ointments are prepared aseptically.



Resorcine and zinc sulphate into ophthalmic ointments can be introduced only after dissolving them in water

3.6. TECHNOLOGY OF OPHTHALMIC OINTMENTS

Rp.: Ung. Hydrargyri oxydi flavi 10,0
D.S. Put under the eyelid of the eye.



WCP (f. s)

Date

Nº Pr.

Hydrargyri oxydi flavi 0.2

Olei vaselini sterile gtts. V (1.–23 drops)

Vaselini pro oculi sterile 8.0

Lanolini anhydrici sterile 1.6

m = 10.0

Addita aseptice

Prepared by: (signature)

Checked by: (signature)

Rp.: Ung. Thiamini 0.5 % 10.0
D.S. Put under the eyelid for a night.



WCP (f. s.)

Date

Nº Pr.

Thiamini bromidi 0.05

Aquae purificatae sterile q.s. seu gtts. II

Basis pro oculi (9:1) sterile 10.0

m = 10.0

Addita aseptice

Prepared by: (signature)

Checked by: (signature)

3.7. OPHTHALMIC LOTIONS, WASHES, SUSPENSIONS, EMULSIONS AND OTHER MEDICINAL FORMS

Eye lotions are sterile aqueous solutions intended for moistening and washing of eyes, as well as for saturating materials applied on the eye. The technology of eye lotions is similar to those of eye drops

Liquids for treating contact lenses are sterile wetting, moistening, and disinfectant aqueous solutions for storing, cleaning and facilitating of application of contact lenses or contact glasses of the ophthalmological devices used for research

Suspensions and **emulsions** are prepared in conditions of the manufacture and at the chemist's diluting them with water to the required concentration. In the case of overcoming sedimentation instability of suspensions and keeping particles with the size not more than 10 μm in them, the medicines obtained are not felt by a patient and have the same effect as eye drops

Powders are used for powdering of the eye fluids. Prepare them in aseptic conditions from the medicinal substances of the thinnest dispersity subjecting the thermostable substances to sterilization

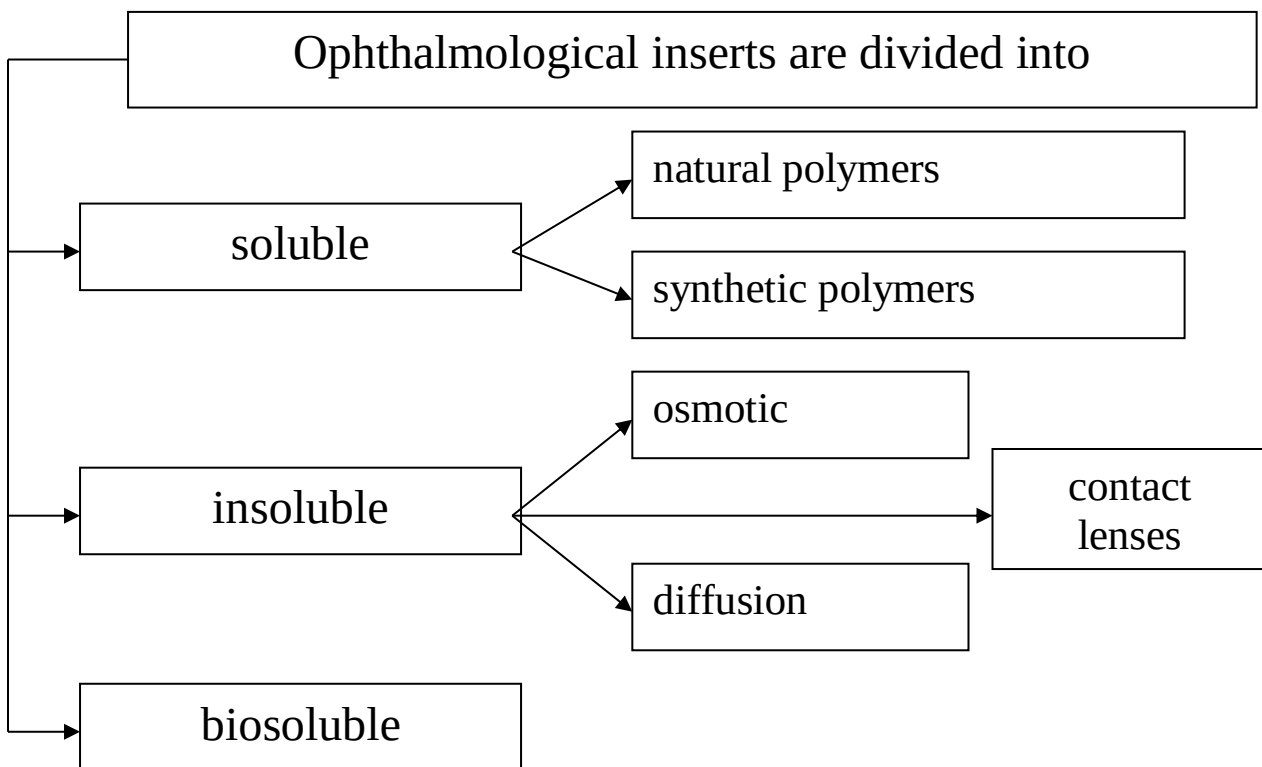
Eye sprays are solutions for injections, which are applied on the eye without contact. Nitrogen and nitrogen dioxide are used as a carrier for dosing aerosols. The index of pressure is limited in a balloon in order to be exactly dosed

3.8. OPHTHALMIC INSERTS

Ophthalmic inserts

are sterile dry or soft medicines with the proper size and shape intended for insertion in the conjunctival sack

Ophthalmic inserts usually consist of the matrix, in which the active substance is included, or the active substance is surrounded by the membrane that controls the rate of releasing.



Advantages of eye inserts:

- improvement of bioavailability of a medicinal substance due to the increase of the contact time with the mucous membrane;
- providing of the prolonged releasing of a medicine;
- diminishing of the systemic side effects;
- possibility of introducing the exact dose of a medicinal substance into the eye.

3.9. THE QUALITY CONTROL AND STORAGE OF OPHTHALMIC MEDICINAL FORMS

Quality control includes *all types of the intra-chemist's control*:

- Written;
- Questioning;
- Organoleptic (color, odor, uniformity) and the absence of particulate matters, transparency;
 - Physical (the total amount or the weight, which after preparation should not exceed the norms of permitted deviations, the size of particles in ointments);
 - Chemical control (primary and secondary (it is selective));
 - Control at the dispensing.

For dispensing and storages of eye drops use bottles of a neutral glass (bottles for antibiotics) closed by rubber corks and sealed by aluminium cover.

Conditions of storage of ophthalmic medicines depend on properties of the medicinal and auxiliary substances. If there are no special indications, eye drops, lotions and ointments are kept in a cool place for 10 days protected from light.

3.10. THE MAIN DIRECTIONS OF IMPROVING OPHTHALMIC MEDICINES TECHNOLOGY

Development of small high-performance devices and apparatuses for exploitation in the conditions of the chemist's and small productions

Introduction of new more improved auxiliary substances: polymers-carriers, preservatives, stabilizers, buffer solvents, prolongation agents, etc. possessing the minimal side effects

Development of packing materials for a single application; creation of medicinal forms for a single application: medicinal films (OMF), lamellas, aerosols, triturated tablets

Development of adequate express-methods for control of ophthalmic medicinal forms

3.11. MEDICINAL FORMS WITH ANTIBIOTICS

CLASSIFICATION OF MEDICINAL FORMS WITH ANTIBIOTICS

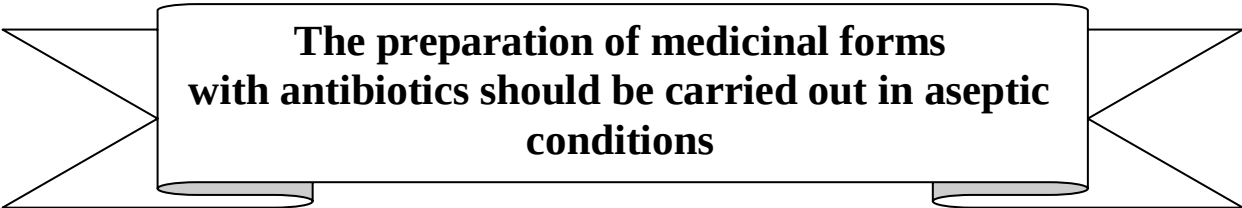
By the way of introduction:

for injections (water solutions and oil solutions, suspensions, emulsions);
for internal use (mixtures, tablets, capsules, pills);
for rectum and vagina;
for local application

By the form of medicines:

solutions;
eye drops;
drops for nose;
drops for ear;
washings;
suspensions;
ophthalmic and dermatological ointments;
suppositories;
tablets, powders, etc.

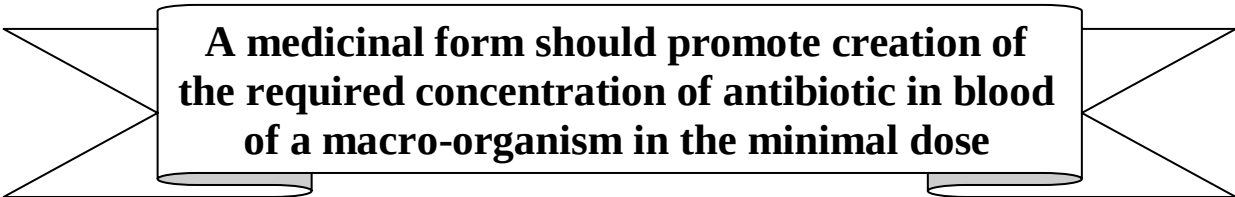
REQUIREMENTS FOR MEDICINAL FORMS WITH ANTIBIOTICS



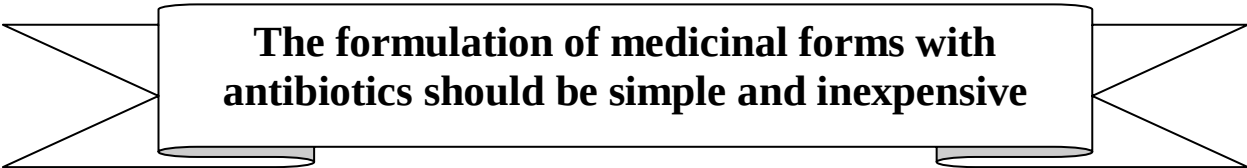
The preparation of medicinal forms with antibiotics should be carried out in aseptic conditions



The type of the medicinal form should provide stability of antibiotic in the process of technology and storage



A medicinal form should promote creation of the required concentration of antibiotic in blood of a macro-organism in the minimal dose



The formulation of medicinal forms with antibiotics should be simple and inexpensive

3.11. MEDICINAL FORMS WITH ANTIBIOTICS

are the low-molecular chemotherapeutic substances produced by microorganisms or obtained from natural sources, as well as their synthetic analogues or derivatives possessing the ability to suppress pathogens of a disease in the patient's organism or to inhibit development of malignant carcinomas.

PROPERTIES:

- They are unstable while storing;
- They are unstable at $\text{pH} < 7$ (penicillins);
- They interact with many auxiliary substances;
- They are poorly soluble in water (and aqueous solutions of some antibiotics are unstable);
- They have thermolability;
- They can show chemical or pharmacological incompatibility in combination with other substances.

Antibacterial activity of antibiotics is expressed in units of action (U) corresponding to the definite weight parts of a chemically pure medicine and it is determined by the method of biological standardization.

If there is no such conformity, while recalculating U of antibiotics in weight ratios it is necessary to use the data given in the corresponding individual articles of the State Pharmacopoeia of Ukraine, where the dependence between the weight and units of action of some antibiotics are specified.

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

Medicines with antibiotics in their composition are represented, as a rule, in such medicinal forms as for injections, for internal use, for external use, for use rectally and vaginally.

The invariance of the chemical structure, physical state and pharmacological action of antibiotics should be kept both while preparing medicines and during their storage and application by patients.

TECHNOLOGY OF POWDERS WITH ANTIBIOTICS

Complex powders with antibiotics are prepared according to the general rules of preparation of complex powders taking into account properties of the components. Antibiotics are added to the sterilized and cooled powders in aseptic conditions.

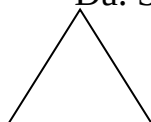
Rp.: Ephedrini hydrochloridi 0.2
Benzylpenicillini-natrii 200000 U
Streptocidi
Sulfadimezini ana 2.0
Misce fiat pulvis subtilissimus
Da. Signa. For inflation into the nose every 2 hours.

Triturate 2.0 g of streptocide with 20 drops of alcohol in a sterile mortar, then add 2.0 g of sulphadimezine. Pour out the mixture on the capsule and leave approximately 0.2 g in the mortar. Then put 0.2 g of ephedrine hydrochloride (list “A” with request) in the mortar, mix thoroughly and mix in some portions while stirring thoroughly with the mixture, which was previously placed on a capsule. Sterilize the mixture obtained at 150°C for 1 hour, then add 0.12 g of sodium salt of benzylpenicillin (a thermolabile substance) in aseptic conditions observing the rules of mixing.

Do not include antibiotics in powders in the pure state because of the possible allergic reactions of the patient.

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

Rp.: Ephedrini hydrochloridi 0.05
 Streptocidi
 Norsulfazoli ana 1.5
 Benzylpenicillini-natrii 250 000 U
 Misce, ut fiat pulvis
 Da. Signa. Inhale through the nose.



Issued:	Ephedrini hydrochloridi 0.05
	Date Signature
Received:	Ephedrini hydrochloridi 0.05
	Date Signature

WCP (front side)

Date	No	Pr.
Streptocidi		1.5
Ephedrini hydrochloridi	0.05	
<u>Norsulfazoli</u>	<u>1.5</u>	
Sterilis	m = 3.05	
<u>Benzylpenicillini-natrii</u>	<u>0.15 (100 000 U = 0.06)</u>	
	m = 3.2	

Addita aseptice

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

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

TECHNOLOGY OF SOLUTIONS WITH ANTIBIOTICS

To give stability to eye drops and other liquid medicinal forms with antibiotics prepare isotonic solution of sodium chloride or use sodium chloride as a stabilizer.

Rp.: Benzylpenicillini-natrii 200 000 U
Sol. Natrii chloridi isotonicae 10 ml
Misce. Da.
Signa. 2 drops into both eyes.



WCP (front side)

Date	Nº Pr.
Sol. Natrii chloridi	0.9 % sterile 10 ml
<u>Benzylpenicillini-natrii 0.12 (100 000 U =0.06)</u>	
Addita aseptice	V = 10 ml

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

Rp.: Sol. Laevomycetini 0,25% 20 ml
Misce. Da. Signa. 2 drops into both eyes.



WCP (front side)

Date	Nº Pr.
<i>Aguae pro injectionibus 20 ml</i>	
Laevomycetini 0.05	
<u>Natrii chloridi 0.18</u>	
Sterilis	V = 20 ml

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

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

TECHNOLOGY OF OINTMENTS WITH ANTIBIOTICS

When preparing ointments with antibiotics a special attention should be paid to the composition of a base and a way of introduction of antibiotics.

Ointments prepared on anhydrous bases are the most stable. The most suitable base for eye ointments is considered a mixture consisting of vaseline – 9.0 g («for eye ointments») and anhydrous lanolin – 1.0 g.

All bases for ointments with antibiotics are used only after their sterilization. They are kept in bottles of 10.0 g.

Ointments with antibiotics are prepared in aseptic conditions observing the general rules for preparing ointments using a mixture of 4 portions of anhydrous lanolin and 6 portions of vaseline («for eye ointments») as a base.

Ointments with benzylpenicillin salts are prepared similar the preparation of triturated ointments since an antibiotic is quickly inactivated in an aqueous solution.

Rp.: Unguenti Benzylpenicillini-natrii 20.0

Da. Signa. Put under the eyelid in 3-4 hours.

It is necessary to prepare the ointment according to the approved formulation (Pharmacopoeian Article 42-84-72): 0.65 g of sodium benzylpenicillin, 20.0 g of anhydrous lanolin, vaseline up to 100.0 g.

Open a bottle with penicillin previously washed with 10 % alcohol with the help of sterile tweezers and transfer 0.13 g of sodium benzylpenicilline into the sterile mortar, which is slightly warmed. Triturate the medicine in a fine powder, then triturate with a small amount of a sterile base (4.0 g of anhydrous lanolin and 16.0 g of vaseline) melt and cooled up to 40°C and add it to penicillin in the small portions while constantly stirring to form a homogeneous mixture. Place in a sterile bottle with a screwed lid. Prepare for dispensing. The shelf live of the ointment is 10 days.

Ointments with tetracycline are prepared on the sterile base in aseptic conditions. They are applied in treating trachoma, keratitis, acute conjunctivitis and other inflammatory ophthalmic diseases.

Rp.: Unguenti Tetracyclini hydrochloridi 1% 10.0

Da. Signa. Put on eyelids 2-3 times a day.

In preliminary sterilized mortar transfer 0.1 g (100000 U) of tetracycline hydrochloride, triturate thoroughly adding the melt half cooled base in portions (up to temperature 40°C). Keep the ointment in a cool dark place.

To prepare ointments with antibiotics use, as a rule, the base of lanolin - vaseline (4:6).

Rp.: Benzylpenicillini-natrii 100 000 U
 Lanolini anhydrici 4.0
 Vaselini pro oculi 6.0
 Misce, ut fiat unguentum
 Signa. Put under the eyelid.



WCP (front side)

Date		№ Pr.
	Benzylpenicillini-natrii 0.06 (100 000 U = 0.06)	
	<u>Basis pro oculi (6:4) sterile</u>	<u>10.0</u>
		m = 10.0
	Addita aseptice	
	Prepared by:	(signature)
	Checked by:	(signature)

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

TECHNOLOGY OF SUPPOSITORIES WITH ANTIBIOTICS

The absorption rate of antibiotics depends on the nature of a base, usually for this purpose cacao butter, wax and various surfactants are used.

Suppositories are prepared by the rolling method or the compression method as heating is impossible.

Suppositories with penicillin. Triturate penicillin with a small amount of lactose and introduce into the suppository base as a fine powder. The content of penicillin in one rectal suppository is 100000 - 500000 units. When storing in a cool place the activity of prepared suppositories can be preserved for 2 months.

Sometimes to accelerate the action of penicillin it is dissolved in the solution of sodium citrate (1:1000) and mixed with a suppository base. The stability of such suppositories is not more than 10 days.

Suppositories with tetracycline. More often tetracycline hydrochloride is used for this purpose. It is stipulated by the less expressed local irritating action of this antibiotic. Usually suppositories containing 0.3 g (300000 U) of tetracycline are prescribed to adults.

Rp.: Tetracyclini hydrochloridi 0.3
Olei Cacao **q.s.**
Misce, fiat suppositorium
Da tales doses № 6
Signa. Use 1 suppository 3 times a day.

Place 1.8 g of tetracycline hydrochloride in a sterile mortar, triturate thoroughly (without dilution in water) and while stirring add 16.2 g of the powdered cacao butter in portions. Mix to obtain the homogeneous plastic mass, from which roll out six suppositories and register them to dispensing.

3.12. TECHNOLOGY OF MEDICINAL FORMS WITH ANTIBIOTICS

TECHNOLOGY OF LIQUID MEDICINAL FORMS WITH ANTIBIOTICS

Use purified water, alcohol, glycerin, vegetable oils as solvents. Prepare solutions using the general rules of preparation. The peculiarity of preparation is the observance of aseptic conditions. It is necessary to avoid filtering of solutions through a common filter paper.

In most cases, only a sterile solvent is prepared at the chemist's, and dilution is performed directly before administration.

Aqueous solutions. *Solutions of sodium benzylpenicillin.* To prepare these solutions the following solvents are used:

- isotonic solution of sodium chloride;
- isotonic solution of glucose;
- novocain solution (0.25 and 0.5 %).

Therefore, *sodium benzylpenicillin* should be dissolved directly before administration.

Rp.: Benzylpenicillini-natrii 200000 U
Solutionis Natrii chloridi isotonicae 150 ml
Misce. Da. Signa. For washing of wounds.

At first prepare a sterile isotonic solution of sodium chloride, where dissolve 0.12 g of *sodium benzylpenicillin* salt.

Eye drops. *Eye drops with levomycetin.* Prepare solutions using fresh water for injections or isotonic solution of sodium chloride in aseptic conditions. Dilution of antibiotic can be carried out when heating.

Rp.: Laevomycetini **0.02**
Novocaini **0.1**
Solutionis Acidi borici 2 % 10 ml
Misce. Da. Signa. 2-3 drops 3 times a day into both eyes.

Solutions for injections with antibiotics are prepared with apyrogenic water for injections or isotonic solution of sodium chloride.

Alcoholic solutions. Levomycetin is also used as alcoholic solutions, frequently in combination with sulphonylamide medicines.

Rp.: Laevomycetini
Norsulfasoli-natrii aa 2.0
Spiritus aethylici 100 ml
Misce. Da. Signa. For rubbing of the skin.

Place 2.0 g of sterile sodium norsulphasol and 2.0 g of sterile levomycetin into sterile bottle for dispensing, add 100 ml of 90 % ethyl alcohol, close and shake to the complete dissolution.

Rp.: Laevomycetini 3.0
Solutionis Acidi borici 2 % 40.0
Spiritus aethylici 70 % 50.0
Misce. Da. Signa. To rub the face skin.

Dissolve levomycetin in alcohol, then add the boric acid solution.

Suspensions. Oil suspensions intended for intramuscular injections are more stable comparing to aqueous solutions of antibiotics. While preparing suspensions dispersity of the solid phase has a decisive importance.

Rp.: Benzylpenicillini-natrii 1000000 U
Olei Persicorum 100.0
Sterilisa!
Misce. Da. Signa. 1-2 ml intramuscularly 2 times a day.

Weigh 100.0 g of peach oil in the bottle for dispensing, close with a cotton tampon and sterilize at 180°C for 30-40 minutes. Then triturate sodium salt of benzylpenicillin in a sterile mortar in aseptic conditions with a small amount of sterile oil, gradually adding all oil. Place the suspension into a sterile bottle for dispensing.

3.13. REGISTRATION FOR DISPENSING OF MEDICINES WITH ANTIBIOTICS

Medicines with antibiotics are dispensed in sterile bottles preventing from microflora, as much as possible, and have the following labels:

- ❖ «For internal use» or «For external use»;
- ❖ «Prepared aseptically» or «Sterile»;
- ❖ «Keep in a cool place»;
- ❖ «Keep out of the reach of children»;
- ❖ «Keep away from direct light»;
- ❖ «Shake well before using» (if it is necessary).

3.14. QUESTIONS FOR SELF-CONTROL

1. What are the types of ophthalmic medicines?
2. Describe eye drops as a medicinal form.
3. What are the requirements to eye drops?
4. How can sterility of eye drops be achieved?
5. What are the peculiarities of technology for eye drops?
6. What requirements should the ophthalmic soft medicinal forms meet?
7. What is the peculiarity of introducing resorcline and zinc sulphate into ophthalmic ointments?
8. What are eye inserts?
9. Characterize medicinal forms with antibiotics and requirements to them.
10. What are the peculiarities of preparing liquid and solid medicines with antibiotics?
11. Describe formulation of ointments and suppositories with antibiotics.
12. Quality control, registration for dispensing and storage of medicines with antibiotics according to the normative documentation.