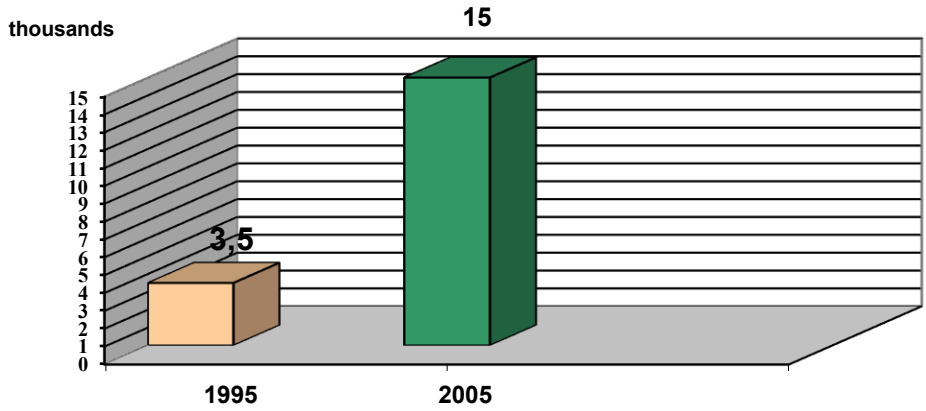
DIFFICULT CASES AND INCOMPATIBLE FORMULAS IN PRESCRIPTIONS

NTRODUCTION

The number of medicines has been considerably increased in recent years. More than 15 thousand manufactured medicines are used in medical practice.

Dynamics of the growth in nomenclature of medicines at the pharmaceutical market of Ukraine



In spite of the variety of manufactured medicines, the extemporaneous prescriptions have not lost its value. Modern prescriptions are complex formulas. Thoroughly considered combination of some medicinal substances simultaneously often gives more expressed therapeutic effect than their individual using. The formula itself can contain 4-5 and more ingredients, sometimes up to 10-15. Prescribing a complex formula, in some cases the doctor stipulates for intensification of a specific effect of ingredients, the so-called pharmacological synergism (from the Greek word «sinergia», which means the combined action), in other cases he intends to achieve weakening or removal of the side effect of one of the ingredients prescribed. To achieve the desirable therapeutic effect the phenomenon of antagonism (the opposite effect) of medicinal substances is also used. Thus, a doctor should pay serious attention to compatibility **of medicinal substances in the prescribed medicine.**

Sometimes in pharmaceutical practice doctors give prescriptions, which do not correspond these requirements. It happens in those cases when a doctor solves the task

of the selection of necessary medicinal substances unilaterally, i. e. takes into account only the pharmacological properties and does not take into account the possibility of combination of medicinal substances depending on their physical and chemical properties in one or another medicinal form, and it results in the incompatible formulas.

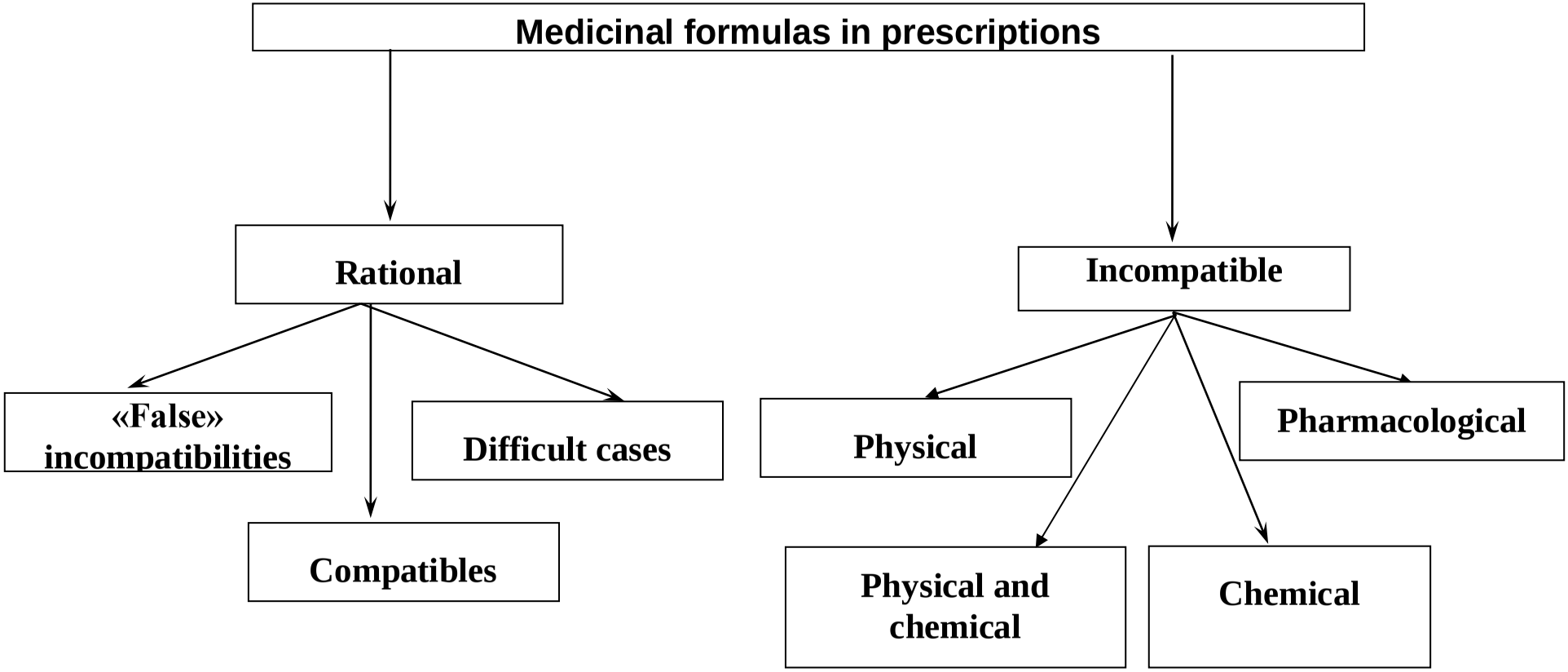
Formerly the terms «non-rational» and «incompatible» formulas were separated and meant different degree of uselessness of a medicine. Non-rational formulas were called the formulas, which did not render either medicinal or harmful action on the patient's organism. Incompatible formulas were the ones, where the prescribed medicines interacted with each other or with the organism, so that it resulted in decreasing the positive therapeutic effect and revealing some new physical and chemical properties of medicines. As a result, strong-effective and poisonous substances with a negative effect on the patient's organism are formed.

At present there is no difference between non-rational and incompatible formulas. One should remember at only medicines prepared in accordance with requirements can be dispensed from chemist's shops, therefore, all other formulas are incompatible.

The character of interaction between medicinal substances depends on:

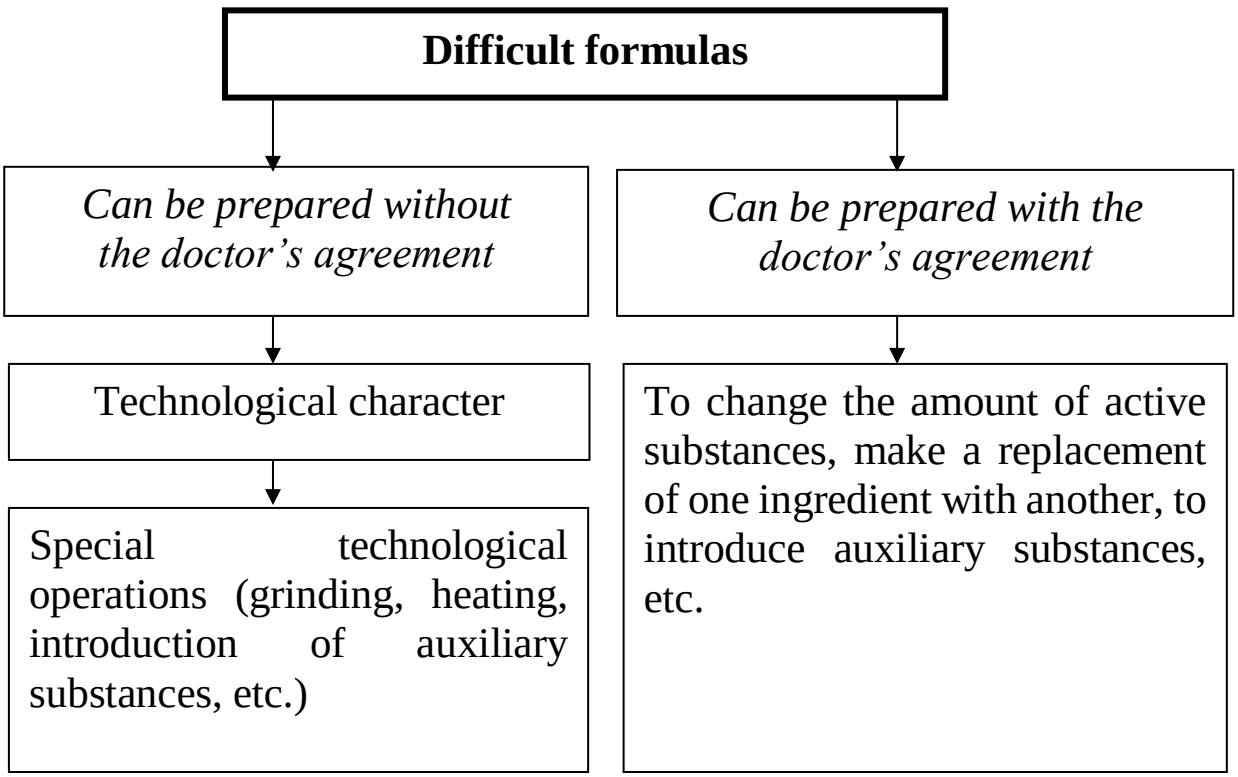
- *physical and chemical properties of these substances;*
- *dispersion medium;*
- *medicinal form;*
- *interaction of medicinal substances*.

CLASSIFICATION OF MEDICINAL FORMULAS IN PRESCRIPTIONS



4.1. DIFFICULT FORMULAS AND THE WAYS OF THEIR REMOVAL

The difficult formulas *are such combinations of medicinal substances when a pharmacist can prepare a medicine using special technological operations.* Thus, it is possible to avoid incompatibilities and to dispense a high-quality, effective medicine to the patient.

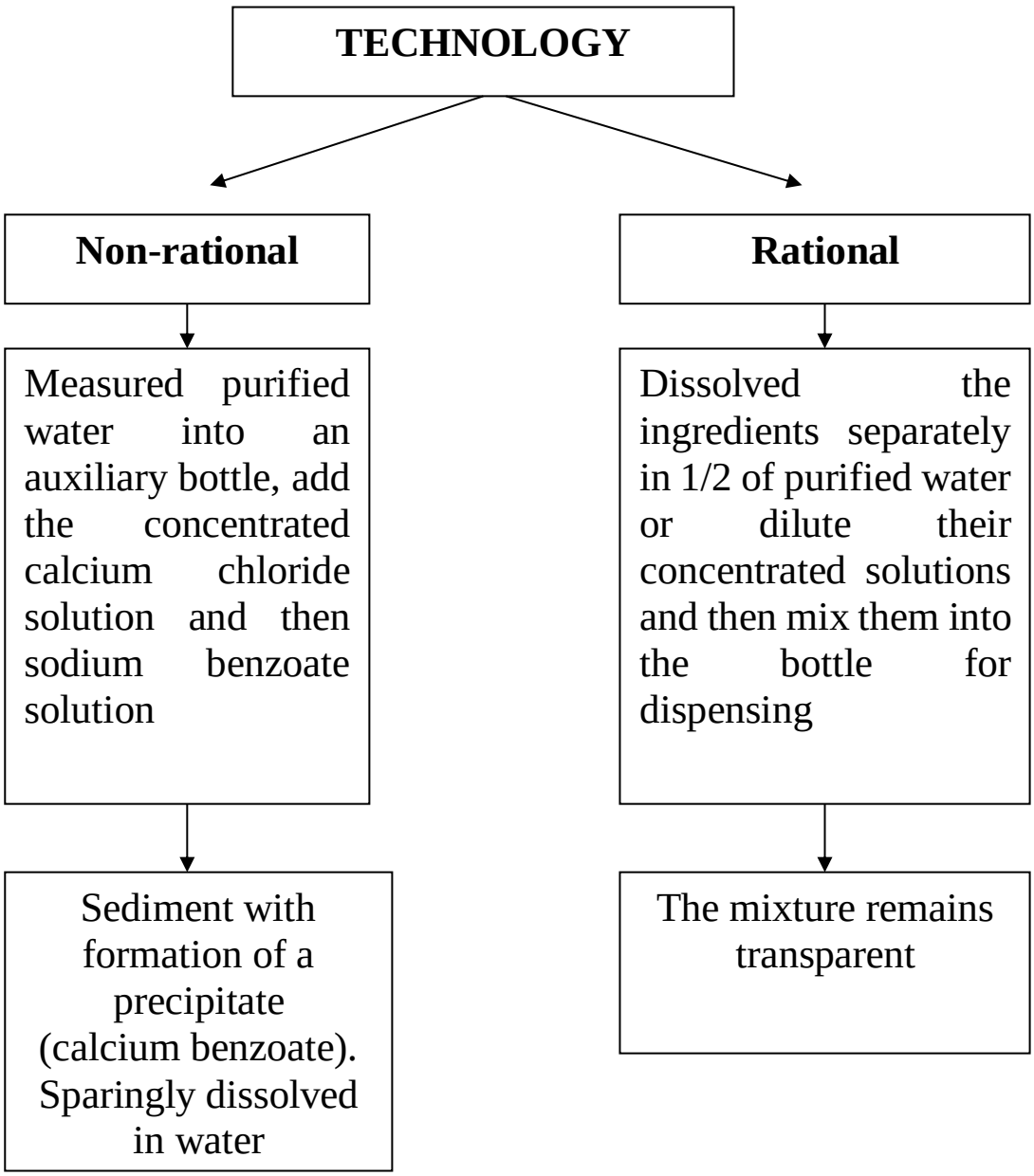


4.1. DIFFICULT FORMULAS AND THE WAYS OF THEIR REMOVAL

Rp.: Natrii benzoatis 4.0
Calcii chloridi 5.0
Aquae purificatae 150 ml
Misce. Da.

Signa. One tablespoon 3 times a day.

The given medicine is a difficult formula, which can be prepared without the doctor's agreement



4.1. DIFFICULT FORMULAS AND THE WAYS OF THEIR REMOVAL

Examples of difficult formulas, which can be prepared without the doctor's agreement

Name of the medicine	The causes of the difficulty and the ways of theirs removals
Solution of boric acid	Substances dissolved in cold water sparingly or partially should be dissolved in hot water
Solution of calcium gluconate	
Solution of ethacredine lactate	
Solution of riboflavine 0.02%	
Solution of furacilin (1:5000)	They are dissolved in hot water with sodium chloride (0.9 %)
Solution of copper sulphate	Poorly wetted large crystals of medicinal substances are ground with a small amount of warm water
Solution of potassium aluminium sulphate	
Solution of hydrochloric acid with pepsin	The changes in the order of preparing. Pepsin is dissolved in the hydrochloric acid solution at pH 2.0-3.5.
Zelenyn's drops	The absence of the solvent in the formula, the auxiliary substance is required. Potassium bromide is dissolved in the equal amount of purified water
Solution of osarsol	To improve solubility of osarsol sodium hydrocarbonate should be added as an auxiliary substance
Compound iodine solution	The changes in the order of preparing. Iodine is dissolved in the concentrated solution of potassium iodide.
Suspension with hydrophobic substances	Poor wettability of medicinal substances. A pharmacist should add a stabilizer
Liniment with menthol, sunflower oil, chloroform	Menthol is better dissolved in chloroform than in oil
Liniment with novocaine, chloroform, ammonium solution 10 %	Novocain salt is dissolved in 10 % ammonium solution and its base is dissolved in chloroform

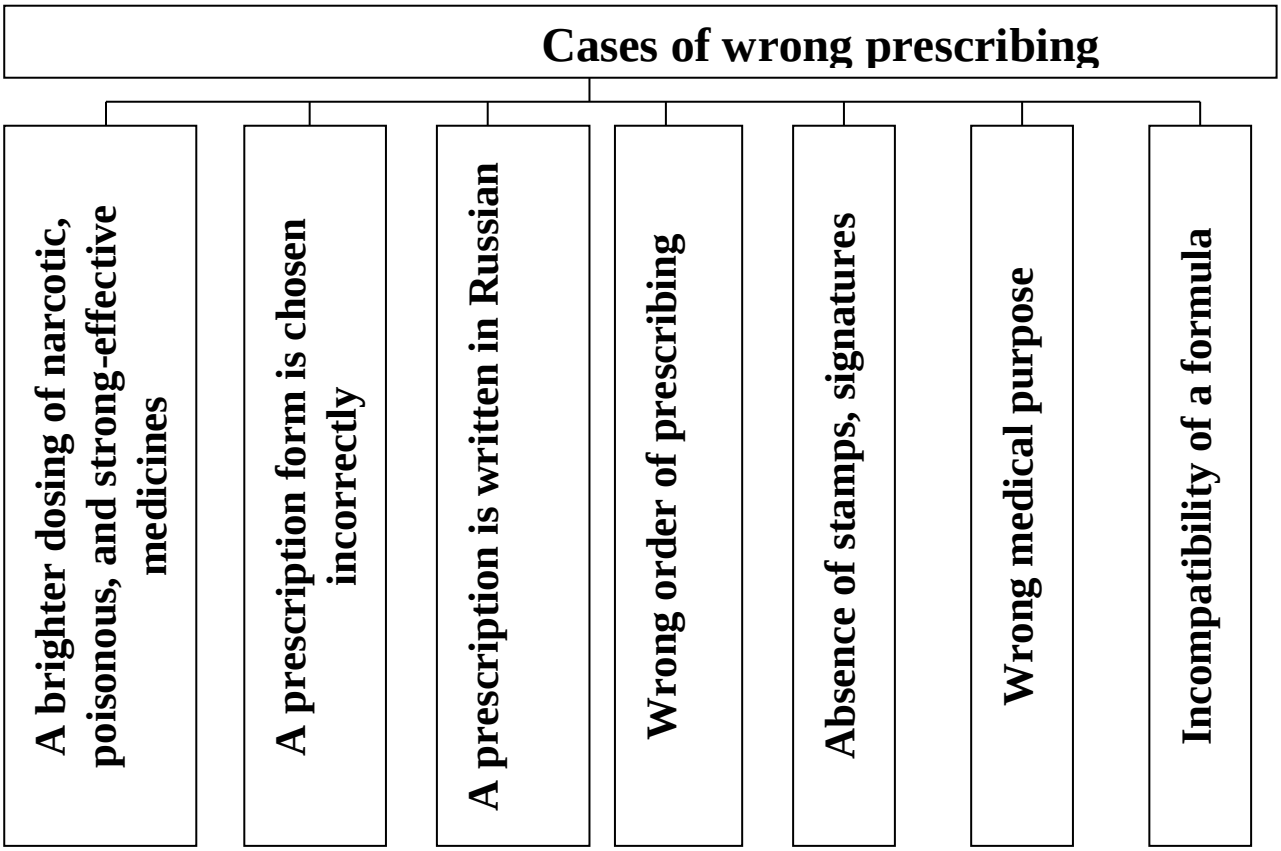
4.1. DIFFICULT FORMULAS AND THE WAYS THEIR REMOVAL

Examples of difficult formulas, which can be prepared with the doctor's agreement

Rp.: Acidi salicylici 2.0 Ichthyoli 10.0 Spiritus aethylici 40ml Misce. Da. Signa. For rubbing.	Rp.: Iodi 0.1 Kalii iodidi 1.0 Chloroformii 5.0 Olei Vaselini 5.0 Misce. Da. Signa. For rubbing.	Rp.: Mentholi 0.2 Natrii hydrocarbonatis 0.4 Spiritus aethylici 96 % 50 ml Misce. Da. Signa. For rubbing.
To dissolve ichthyol it is necessary to change ½ of alcohol amount to ether	It is necessary to exclude potassium iodide from the formula, because for its dissolution it purified water (immiscible with chloroform and vaseline oil) should be added	Sodium hydrocarbonate is not dissolved in 96 % ethyl alcohol, therefore, 70 % ethyl alcohol should be used

To summarize the information about difficult formulas it should be noted that they belong to the class of rational formulas. According to these formulas medicines are prepared and dispensed to the patients to the chemist's shops.

4.2. CASES OF WRONG FORMULAS IN PRESCRIPTIONS, GETTING INTO PHARMACIES. RIGHTS AND DUTIES OF A PHARMACIST-TECHNOLOGIST



The control of correctness of writing a prescription is laid upon a pharmacist-technologist who must follow the order of MPH of Ukraine № 360 dated from the 19th of July, 2005 «About the order of prescribing and dispensing medicines and items of medical purpose from chemist's shops», which provides rights and duties of a pharmacist in regard to prescriptions written in a wrong way or incompatibilities.

4.2. CASES OF WRONG FORMULAS IN PRESCRIPTIONS, GETTING INTO PHARMACIES. RIGHTS AND DUTIES OF A PHARMACIST-TECHNOLOGIST

The order of the Ukrainian MPH № 360 from 19.07.05 « About the order of prescribing and delivering medicines and products of medical purpose from pharmacies »

Prescriptions, which are made with violation of requirements these Rules or contain incompatible medicines, are considered to be invalid and the medicine should not be dispensed. *A prescription is provided with a stamp «Invalid prescription» and returns to the patient*
Doctors and other medical workers, who prescribe medicines, are responsible in accordance with the established procedure for prescribing medicines to the patient and observing the rules of prescribing
It is forbidden to certify by the stamps of health care institutions any forms unfilled and unsigned by a medical worker
A pharmacist-technologist is to inform the head of the corresponding health care institution about it, to contact the doctor of a polyclinic, who wrote the prescription, to specify the name of a medicine, its dosage and compatibility
The heads of health care authorities and the heads of health care institutions must (in all the cases of violation of the rules of prescribing) take urgent measures of disciplinary punishment to medical workers who broke the given Rules
If the prescribed medicine is not available, it is necessary to come to an agreement about the possibility to change it for an analogue.

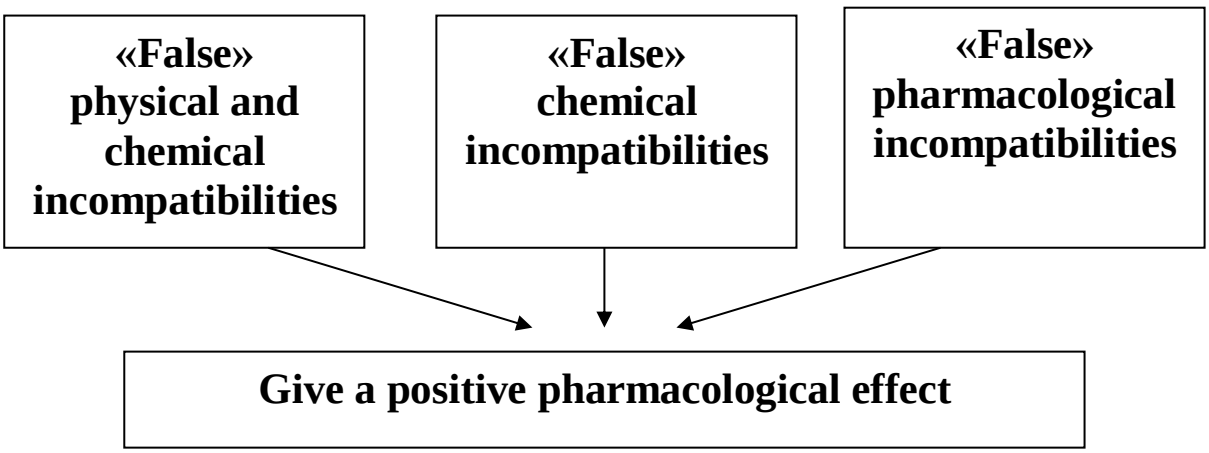
4.3. INCOMPATIBLE COMBINATIONS OF MEDICINAL SUBSTANCES IN FORMULAS.
CLASSIFICATION OF INCOMPATIBILITIES

Both a pharmacist and a doctor need to be informed well not only about therapeutic, but also about physical and chemical properties medicines:

- *solubility;*
- *pH of the medium;*
- *volatility;*
- *melting temperature;*
- *possible interaction*;
- *reactivity.*

There are two kinds of incompatibilities: «**obvious ones»** and «**false ones»**.

«**False» incompatibilities** *are formulas, in which antagonistic combinations of medicines (according to their pharmacological effect or to chemical interaction between ingredients), as well as the change in the physical state of medicines is envisaged by a doctor, as a therapeutic factor.*



4.3. INCOMPATIBLE COMBINATIONS OF MEDICINAL SUBSTANCES IN FORMULAS.
CLASSIFICATION OF INCOMPATIBILITIES

Obvious incompatibilities (**Incompatibilita pharmaceutica**) are *combinations of medicinal substances when while preparing them physical and chemical properties of medicines change, different chemical reactions occur, decrease of the therapeutic effect of a medicine or increase of toxic effects, i.e. different factors not envisaged by a doctor, are observed.*

When compounding difficult formulas the consultation of both a doctor and a skilled pharmacist is needed.

Depending on the character of changes, which can be formed when combining the ingredients in formulas the following incompatibilities can be distinguished:

- ***physical (physical and chemical) ones;***
- ***chemical ones;***
- ***pharmacological ones.***

The character of consequences, their degree of severity for a patient after preparation of medicines, which contain incompatible combinations, can be different:

- ***the therapeutic effect is reduced;***
- ***the therapeutic effect is not achieved;***
- ***the side effect is strengthened;***
- ***they can lead to a lethal outcome.***

Formulas containing incompatible combinations of ingredients, can not be used by a pharmacist for preparation of medicines for patients.

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

Physical incompatibilities *are the incompatibilities, when only physical state of medicinal substances included in medicines can change.*

Causes of physical incompatibilities:

- *insolubility or worsening of conditions of solubility;*
- *immiscibility of ingredients;*
- *dampening of a mixtures with solid substances;*
- *melting of a mixture of solid substances (eutectics);*
- *coagulation of colloid solutions and HMC;*
- *stratification of emulsions;*
- *absorption of active medicinal substances.*

Rather often along with the physical phenomena, the chemical reactions proceed; in the similar formulas, that is why this group of incompatibilities is often called **physical and chemical incompatibilities.**

The causes of obvious physical and chemical incompatibilities:

- *coagulation of colloidal solutions under the influence of electrolytes;*
- *formation of salts of metals with albuminic acids;*
- *the neutralization reaction between substances with acidic and alkali properties led to the loss of dryness of powders.*

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

This group of incompatibilities is unique when, in some cases, the cause of incompatibility is eliminated after having come to an agreement with a doctor, the medicine can be prepared.

The most typical examples of physical, physical and chemical incompatibilities are:

1. Insolubility or worsening of conditions of solubility:

- *the limit of solubility is exceeded;*
- *a wrong solvent is chosen;*
- *solubility becomes worse in the presence of the same ions;*
- *the solutions are mixed as a result of replacement of the solvent*

Ministry of Public Health Ukraine The Name of institution	The institution code Medical documentation. Form № 107/U
PRESCRIPTION (adult, children – choose the right position) “ 26 “ April 200 9.	
Name of patient Ivanov E.B. N ov A.I.	
Price	Rp.: Mentholi 0,1 Sol.Adrenalini hydrochloridi 0,1% 10 ml Misce. Da. Signa. Drops for nose.
Seal and signature of a doctor	
A prescription is valid for 10 days, 2 months (choose the right position)	

Prescription is not valid

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

This formula is a physical incompatibility. Menthol can not be dissolved in the aqueous solution of adrenaline hydrochloride. Medicine is not to be dispensed. The stamp “Prescription is not valid” is put into the prescription, then this fact is put down into the “Register of Wrong Prescriptions”, and the doctor, the head of the department or the head doctor is informed. The prescription should be returned to the patient.*

Rp.: Sol. Iodi spirituosae 10 % 0.5 ml
Sol. Acidi borici 2 % 100 ml
Misce. Da. Signa. For washing eyes.

While mixing aqueous and alcoholic solutions the solubility of iodine becomes worse. Iodine, as the tiniest crystals, provides the burning effect. Eye drops or lotions with a precipitate are not dispensed.

Rp.: Sol. Calcii chloridi 10 % 200 ml
Papaverini hydrochloridi 0.2
Misce. Da.

Signa. One tablespoon 3 times a day.

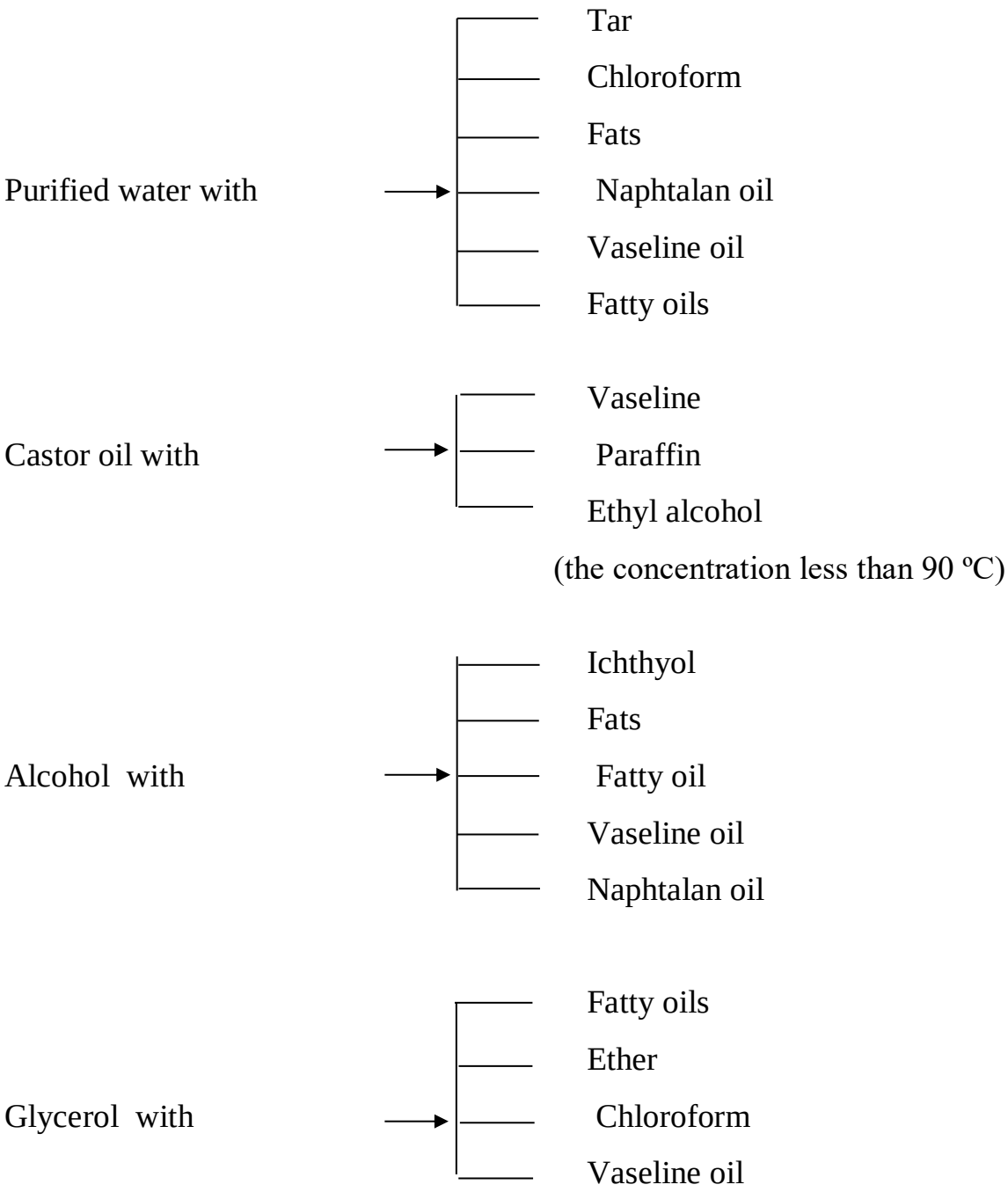
In this case there is papaverine hydrochloride (a strong effective substance) in the precipitate and as a result, under the influence of the same ion the solubility of the alkaloid salt will be decreased under the influence of calcium chloride.

** A pharmacist acts similarly in this situation and in all subsequent cases if the formula contains incompatibilities*

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

2. Immiscibility of ingredients

There is a number of substances, which are impossible to combine with each other, because they do not form any homogeneous system. Examples:



4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

Rp.: Sulfuris 1.0
Olei Ricini 10.0
Spiritus aethylici 70 % 20 ml
Misce. Da.
Signa. Apply to the affected areas.

In this case incompatibility is caused by immiscibility of castor oil and 70 % ethyl alcohol, it is necessary to prescribe 96 % alcohol.

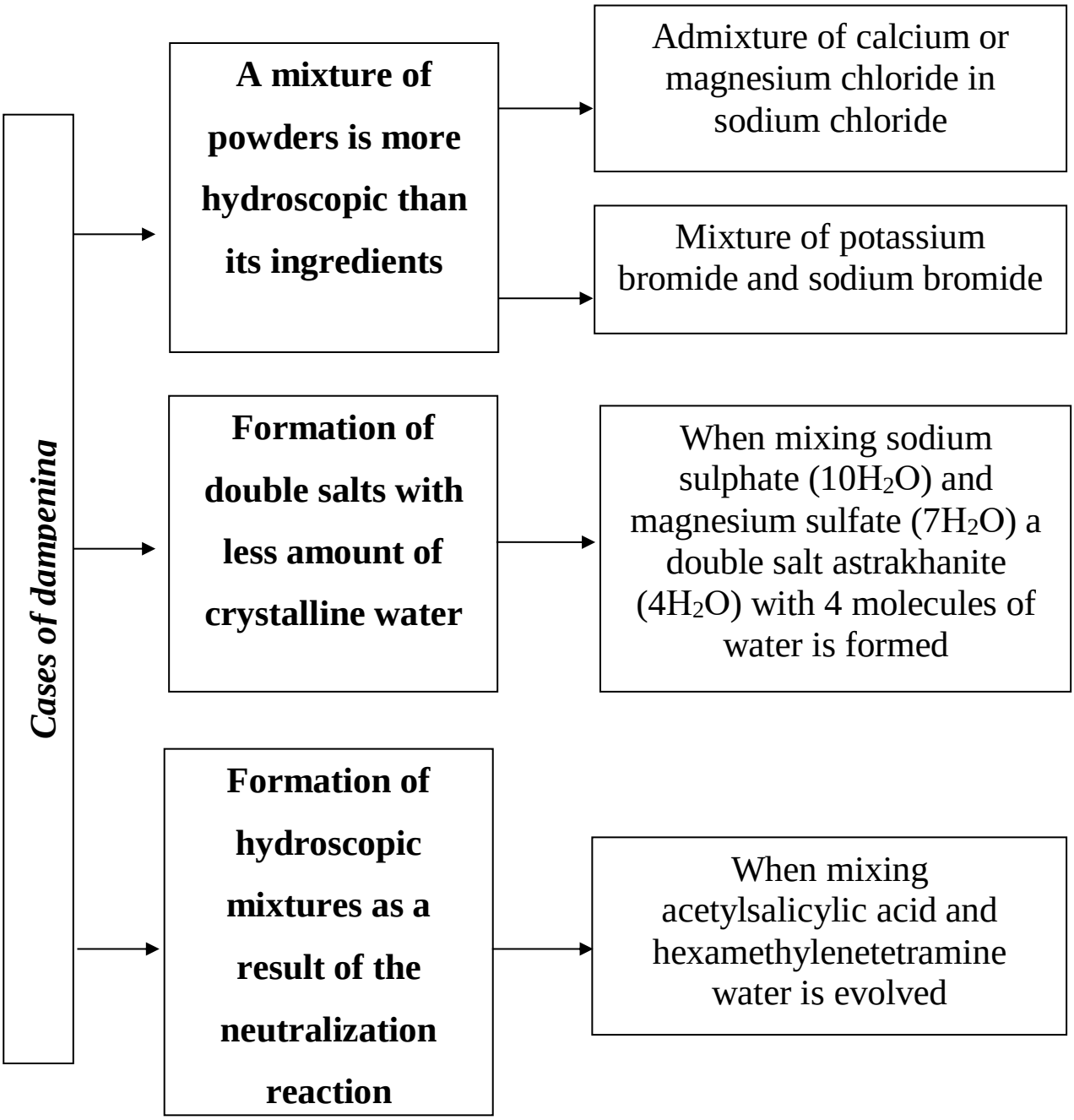
Rp.: Solutionis Natrii bromidi 2% 200 ml
Validoli 4 ml
Misce. Da.
Signa. One tablespoon 3 times a day.

Validol is immiscible with the aqueous solution of sodium bromide and is evolved on the surface of the mixture as oily drops.

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

3. Dampening of a mixture with solid substances.

Dampening of a mixture with solid substances is observed rather often in prescribing powders, as a result, their dryness is lost.



4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

The rate of dampening is influenced by the following factors:

- *humidity of the initial ingredients;*
- *the relative humidity of premises;*
- *the temperature of air in the premises;*
- *the character and duration of mixing;*
- *fineness;*
- *packing.*

Dampening of a mixture with solid substances can occur while mixing or storing. When powders are prepared from substances, which have the increased humidity, they dampen much more quickly, than the powders prepared from dry substances. The rate of the mixture damping depends on the relative humidity and the temperature in the premises. The more vigorously the substances are mixed, the quicker the mixture becomes damp. The relative air humidity in the premises has the main influence on dampening of substances. Most mixtures become damp if the relative humidity is higher than 60%. Packing material has also a substantial influence on damping.

The examples of mixtures with medicinal substances, which become damp are given bellow:

Antipyrine
Acetylsalicylic acid with → Analgine
Hexamethylenetetramine

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

Ascorbic acid

Aminophylline with → Salts of strong acids and weak bases

(ephedrine hydrochloride, dimedrol, spasmolythine)

Sodium hydrocarbonate
Ascorbic acid with → Euphylline
Ethaminal sodium
Vitamin P

If the similar medicinal substances are prescribed in small doses, the powder keeps dry for 7 days, in all other cases it is necessary to dispense euphylline (according to the agreement with a doctor) by a separate prescription.

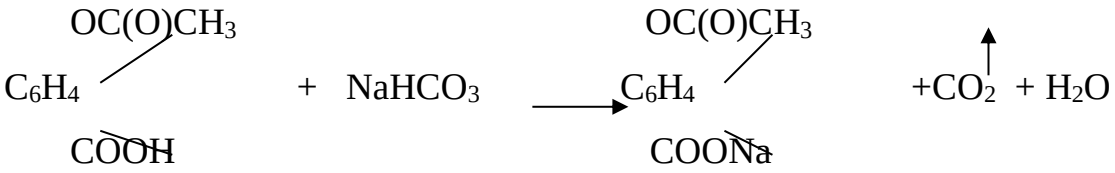
Rp.: Coffeini-natrii benzoatis 0.05
Hexamethylentetramini 0.3
Natrii salicylatis 0.5
Misce, fiat pulvis.
Da tales doses № 10.
Signa. One powder 3 times a day.

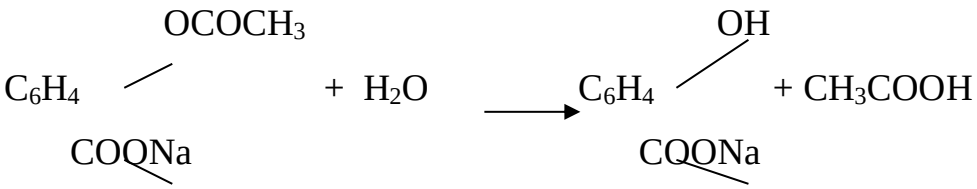
When the powders are prepared from dry substances, the mixture becomes damp on the second day. If damp hexametylentetramine (moisture is up to 3%) is put into the formula, the mixture loses its dryness immediately in the mortar.

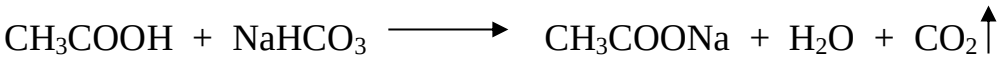
4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

Rp.: Acidi acetylsalicylici 0.3
Natrii hydrocarbonatis 0.2
Misce, fiat pulvis.
Da tales doses № 10.
Signa. One powder 3 times a day.

When combining acetylsalicylic acid with sodium hydrocarbonate at first hydroscopic sodium acetylsalicylate is formed, which is hydrolyzed to sodium salicylate and acetic acid. Powders at this stage have the smell of vinegar. Acetic acid turns into sodium acetate.







If these powders are prepared in summer time in a dry weather at the relative humidity of 30-40 %, they will undergo no changes in simple capsules for 10 days. The same powders prepared at the relative humidity of 70-80 % become damp by the end of the first day.

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

Rp.: Dimedroli

Papaverini hydrochloridi ana 0.03

Natrii nitritis 0.02

Acidi ascorbinici 0.3

Misce, fiat pulvis. Da tales doses numero 12.

Signa. One powder 3 times a day.

This given formula is a physical and chemical incompatibility. In this case moistening of the mixture occurs and the mixture becomes yellow as a result of the oxidation-reduction reaction. If 0.02 g of aerosil "A-175" per 1 powder or 0.05 g of a dried starch per one powder is added in the composition of the powder, the mixture remains without any changes for 10 days.

Rp.: Dimedroli 0.1

Natrii hydrocarbonatis 0.3

Misce, fiat pulvis.

Da tales doses numero 10.

Signa. One powder 3 times a day.

When mixing ingredients a damping mixture forms. Sodium hydrocarbonate creates the alkaline reaction, in the presence of moisture traces dimedrol-base of oily consistency, water and carbon dioxide are evolved. The reaction rate depends on the quantitative ratio of ingredients.

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

For example, if there is 0.1 of dimedrol in the mixture, a sticky mass will be formed in a day; if there is 0.05 of dimedrol – the mixture will be damp in a day; if there is 0.3 of dimedrol – the mixture will become damp only in 6 days. In order to prevent damping aerosil «À-175» (0.03 g per a powder) should be introduced in the mixture or, after coming to an agreement with a doctor a strong effective substance such as dimedrol should be dispensed in the form of tablets separately.

Rp.: Phenobarbitali 0.02

Euphyllini 0.15
Coffeini-natrii benzoatis 0.1

Acidi ascorbinici 0.1

Glucosi 0.2

Misce, fiat pulvis. Da tales doses № 10.

Signa. One powder 3 times a day.

When of ethylenediamine interact with dehydroascorbic acid, which always presents as traces in ascorbic acid, products of yellow color form as a result of the oxidation-reduction reaction. Replacement of euphyline by theophylline is inefficient in this case, as phenobarbital with euphylline form poorly soluble compound. After having come to an agreement with the doctor euphylline should be excluded from the formula and dispensed separately as tablets (a strong effective substance). It is also possible to avoid dampening for 10 days aerosil “A-175” is added in the amount of 0.03 g per a powder. The doctor should write a new prescription.

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

4. Melting of a mixture of solid substances

Eutectic alloys are the mixtures of the definite composition with a constant melting temperature, which is lower than the melting temperature of each substance individually (from the Greek word «eutektas» that means "melting well").

The phenomenon of eutectic can be used with a therapeutic purpose («false» incompatibilities):

- for obtaining of a liquid medicine;
- for more even distribution of a medicinal substance in the mixture of powders.

Examples of «false» physical and chemical incompatibilities:

Rp.: Thymoli 0.1 Mentholi 1.5 Acidi borici 10.0 Boli albae Talci ana 15.0 Misce, fiat pulvis. Da. Signa. External.	Rp.: Acidi carbolici cristallisati Mentholi Phenylii salicylatis Thymoli ana 4.0 Misce. Da. Signa. Dental drops.	Rp.: Chlorali hydrati Camphorae ana 3.0 Misce. Da. Signa. Dental drops.
Thymol and menthol as an eutectic alloy are more evenly distributed in the mixture of powders than when adding them in the crystalline form. Little amount of the forming liquid does not influence on dryness of powders	A liquid medicine. When mixing the prescribed ingredients an eutectic alloy envisaged by a doctor as a therapeutic factor is formed	When mixing chloral hydrate and camphor the eutectic mixture used as dental drops is formed

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

When prescribing obvious incompatibilities, as a result of the interaction between substances, dense, slightly mobile liquids are formed; they are difficult to crystallize neither mixing with water nor with oil, and, therefore, they are not used with a therapeutic purpose.

The influence of different factors on the rate of eutectic alloys formation

Factor	Effect
Nature of initial substances	Eutectic mixtures form antipyrine, menthol, phenacetin, thymol, camphor, chloralhydrate, resorcinol, phenylsalicylate, bromocamphor, phenol, etc.
Contact surface between the particles of substances	It influences intensively
Environmental temperature	The higher the temperature is, the quicker the process of melting occurs
Degree of mechanical influence	It influences strongly
Relative air humidity	It does not have any essential influence

To eliminate incompatibilities in complex powders the following technological methods are recommended:

- *Elimination of a reactivity component* (except list "A" and "B").
- *Separate dispensing of medicinal substances* (except strong effective substances).
- *After coming to an agreement with the doctor replacement of reactivity component by a pharmacologically active part*, namely, sodium caffeine-benzoate can be replaced by caffeine in the amount of 40 %, codeine phosphate by codeine (75 %), euphillyn – by theophillyne (80 %).

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

- *Introduction of auxiliary substances – regulators of moisture into the mixture*, their purpose is to adsorb moisture (clay minerals, aerosil, magnesium carbonate, dried starch). The amount and the type of regulators are chosen experimentally taking into account compatibility of ingredients.
- *Fractional mixing.*
- *Drying of crystalline hydrates while preparing powders.*
- *Choice of packing material (waxed or paraffin capsules).*

In every special case, elimination of the ingredients incompatibility is solved with or without the agreement of a doctor.

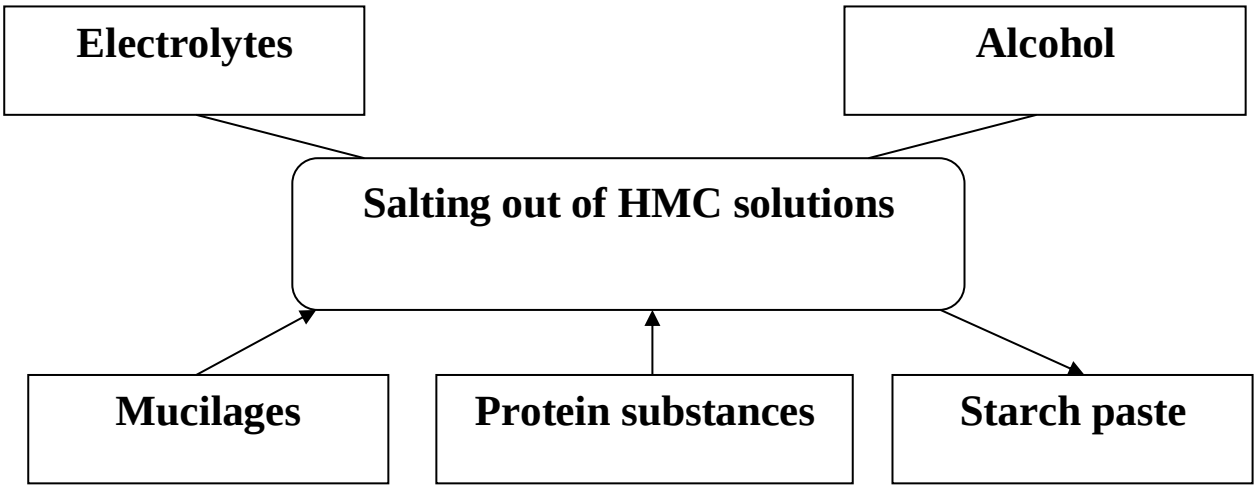
5. Coagulation of colloidal solutions and high molecular compounds (HMC)

Solutions of HMC and protected colloids are instable while storing.

Under the influence of external factors the processes causing their destruction occur in the solutions of HMC:

- *salting out* (solubility decreasing and precipitating);
- *coacervation* – (stratification);
- *syneresis* – (gelatinization).

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES



Salting out is caused when the ions of neutral salts hydrate and absorb water from compounds. Salting out activity of electrolytes depends on the ability of ions to hydrate it does not depend on the valency and diminishes in such sequence:

anions – sulphate→ citrate→ acetate→ chloride→ nitrate;

cations – lithium→ sodium→ potassium→ rubidium→ cesium.

Therefore, electrolytes must be added very carefully and only in the dissolved state.

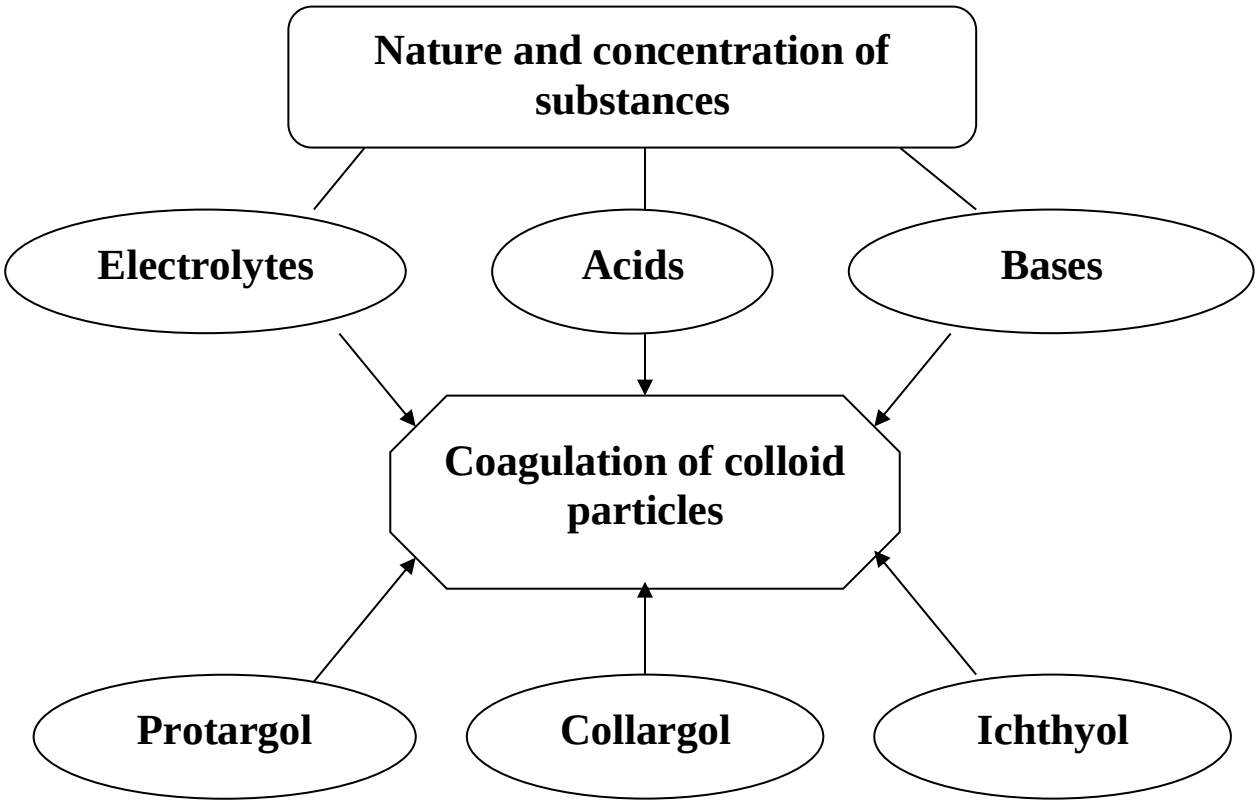
4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

Rp.: Solutionis Calcii chloridi 5 % 180 ml
Extracti Polygoni hydropiperis fluidi 20 ml
Misce. Da. Signa. One tablespoon an hour.

Under the influence of sodium chloride a flake – like resinous residue, which sticks to the walls of the bottle, forms.

***Colloid solutions* undergo:**

- *spontaneous aging*;
- *coagulation* – it is the enlargement of the disperse phase particles due to their sticking together



4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

Rp.: Solutionis Protargoli 2 % 100 ml
Zinci sulfatis 0.5
Misce. Da.
Signa. Eye drops.

In this case the coagulation of protargol is caused by taking the electric charge from the particles of protargol. The simultaneously precipitate of zinc albuminate is formed. Eye drops are not to be dispensed.

Solutions of ichthyol also undergo coagulation when the medicines of silver, iron, copper, mercury, lead, calcium are added. Thus, the reaction of exchange takes place; as a result, an insoluble precipitate of sulphoichtyol acids salts is formed and thiophenes are isolated as oily mass.

Rp.: Solutionis Ichthyoli 5 % 200 ml
Zinci sulfatis 4.0
Glycerini 10.0
Misce. Da.
Signa. For irrigation.

The formula is incompatible, since the therapeutic value of the medicine is lost. The insoluble precipitate of zinc ichthyolsulphate is formed.

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

6. Stratification of emulsions

One of the causes of physical and chemical incompatibilities is stratification of emulsions (coalescense). These processes take place under the influence of:

- *electrolytes;*
- *heating;*
- *concentrated syrups.*

Solutions of electrolytes are added into the emulsion only in the diluted state and in small amounts.

Rp.: Emulsi oleosi 100.0
Natrii sulfatis 10.0
Misce. Da.
Signa. One tablespoon 3 times a day.

Sodium sulphate, which prescribed in a large quantity, causes stratification of the emulsion.

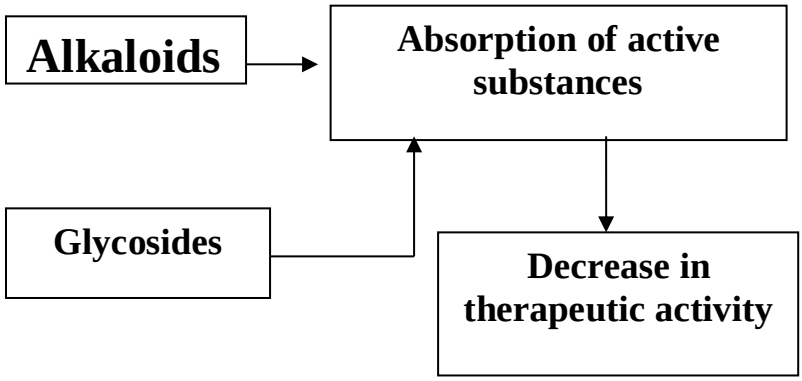
Rp.: Emulsi Olei Ricini 100.0
Sirupi Cerasi 10.0
Misce. Da.
Signa. One tablespoon 3 times a day.

Berries syrups (raspberry, cherry) are acid-reacting liquids, which cause flocculation of emulsions. If the prescribed syrup is substituted by a simple one, the process of emulsion decomposition will also occur as a result of dehydration of the concentrated solutions of sugar.

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

7. Adsorption of active medicinal substances

- coal
- aluminum hydroxide
- white clay;
- vegetable powders



The phenomenon of adsorption of active substances can be observed when combining alkaloid salts and vegetable powders. Taking into account the fact that vegetable powders are not digested, and consequently are not assimilated by the organism, the valuable medicinal substances can be lost. In some occasion, vegetable powders combined with medicinal substances form sparingly soluble compounds; as a result, their medicinal properties are lost. It is easily to avoid this undesirable phenomenon if vegetable powders are replaced by sugar or glucose.

The phenomenon of adsorption can be observed when isolating non-toxic precipitates in the mixtures they can adsorb the medicinal substances contained in the mixture on their surface. It is especially dangerous when some poisonous or strong effective substances are included into the medicine.

4.4. PHYSICAL, PHYSICAL AND CHEMICAL INCOMPATIBILITIES

Rp.: Codeini 0.2
Infusi radicis Valerianae ex 10.0 200 ml
Calcii chloridi 10.0
Misce. Da.
Signa. One tablespoon 3 times a day.

In this case as a result of the interaction of calcium chloride with organic acids, which are present in the valerian root extract, a precipitate is formed and, besides, coagulation of the extractive substances and starch by a strong electrolyte occurs. The precipitate is not toxic itself, but it can partially adsorb codeine. Therefore, this formula is incompatible, since the dosage of the strong effective substance of codeine becomes incorrect.

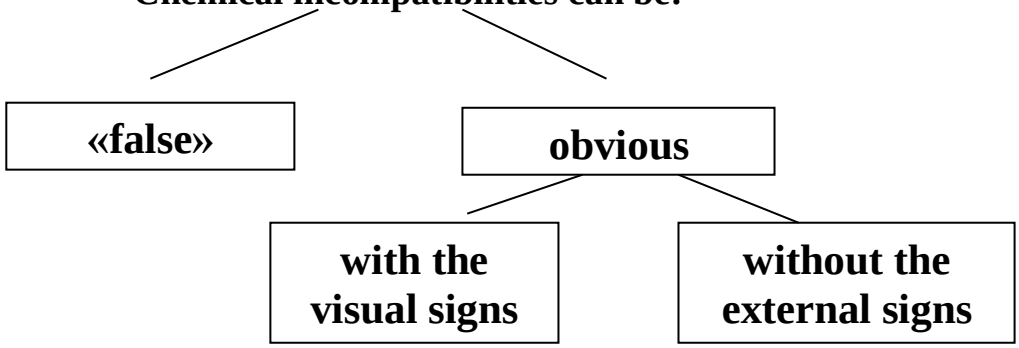
Rp.: Extr. Belladonnae 0.15
Decocti foliorum Uvae ursi 20.0 200 ml
Hexamethylentetramini 5.0
Misce. Da.
Signa. One tablespoon 3 times a day.

When dissolving of hexamethylenetetramine in bearberry decoction tannins precipitate and alkaloids of belladonna extract are adsorbed on the precipitate. However, in pharmaceutical practice the formula containing bearberry decoction and hexamethylenetetramine can meet more often. In this case hexamethylenetetramine can be dispensed separately as a powder per doses.

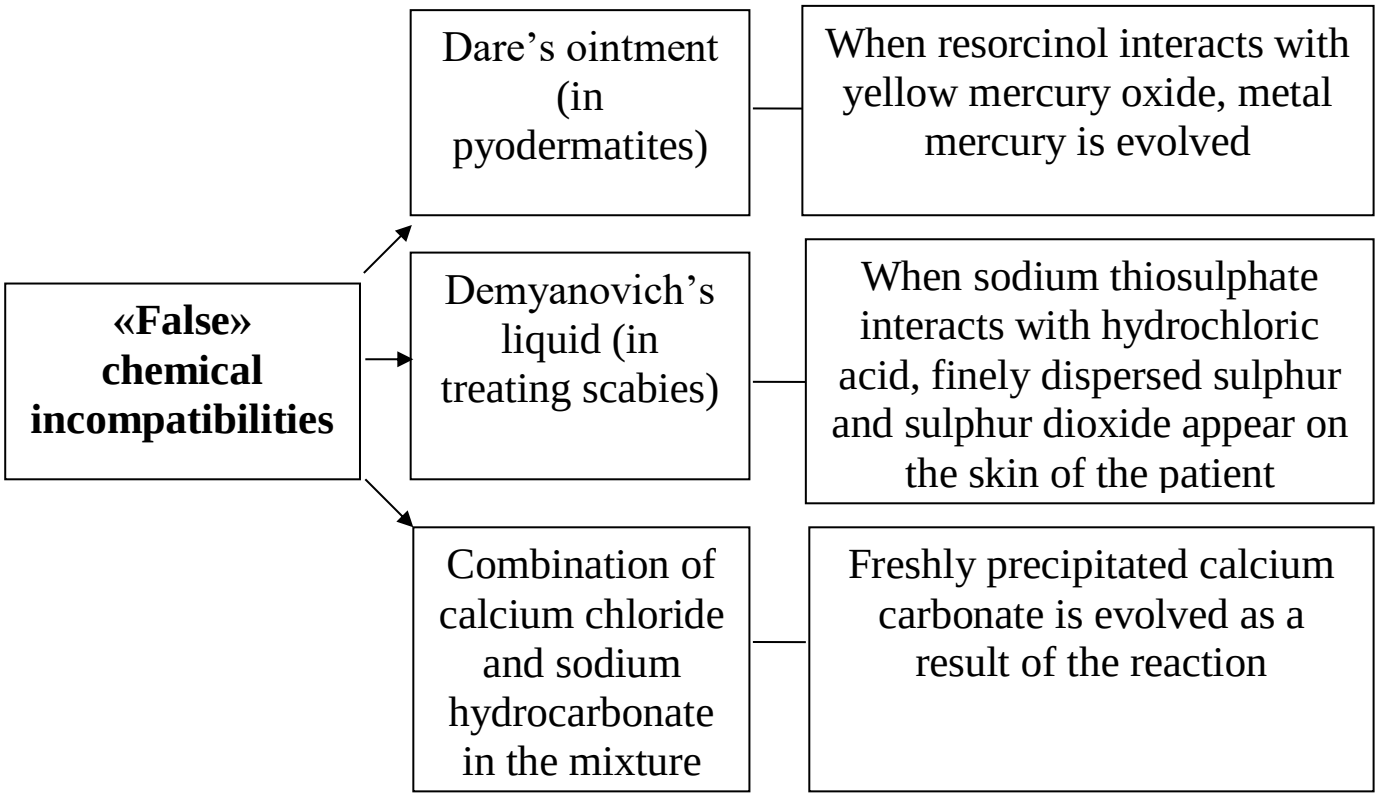
4.5. CHEMICAL INCOMPATIBILITIES

Chemical *incompatibilities are incompatibilities, which are accompanied by the unforeseen chemical reactions between medicinal substances, as a result, weakening or complete loss of the drug therapeutic effect, as well as intensification of toxic effects occur.*

Chemical incompatibilities can be:



«False » chemical incompatibilities *are the chemical reactions (envisaged by a doctor beforehand) between components, where a therapeutic effect is rendered by the newly formed substances.*



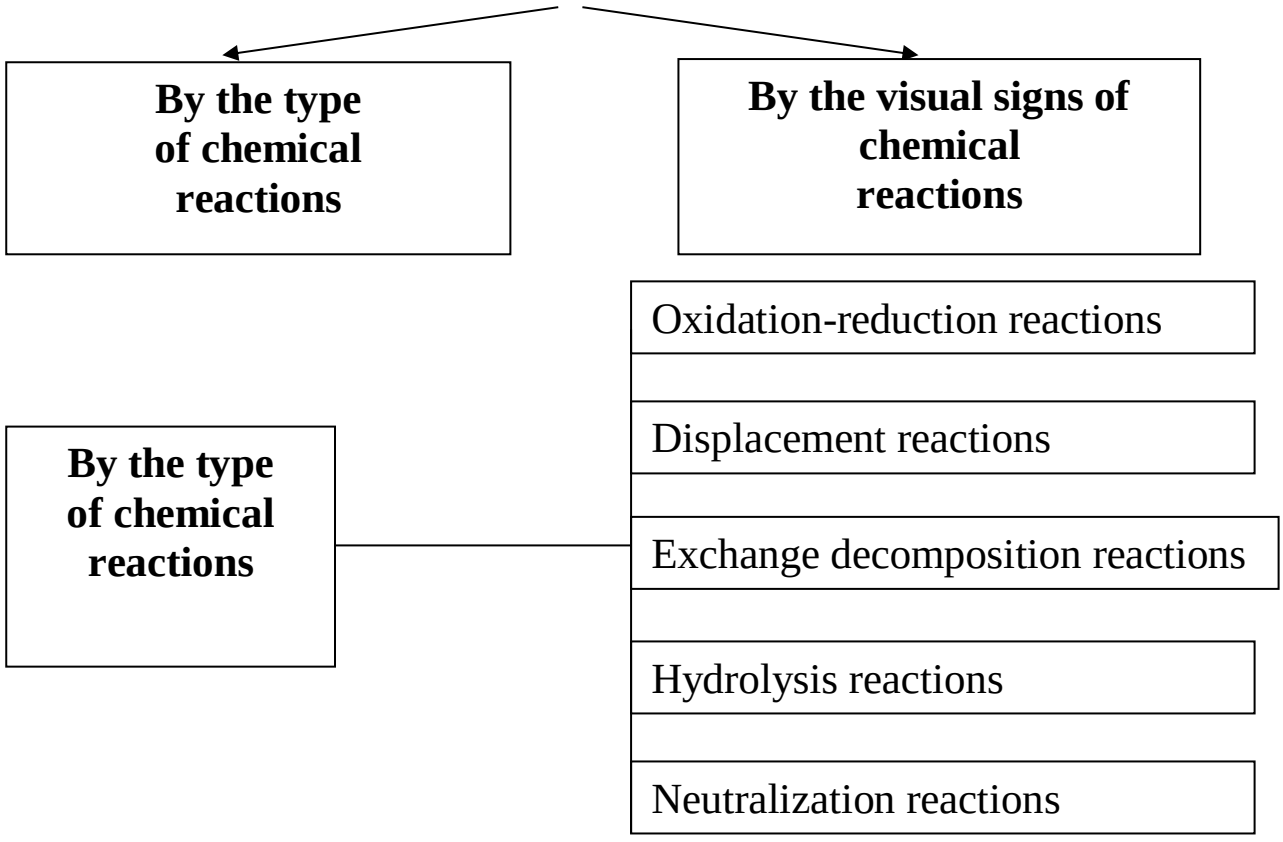
4.5. CHEMICAL INCOMPATIBILITIES

Chemical incompatibilities occur in liquid medicinal forms more often, but they are also observed in powders, ointments, etc.

The character of interaction between medicinal substances depends on:

- *physical and chemical properties of medicinal substances;*
- *type of medicinal form;*
- *properties of dispersion medium and character of its interaction with medicinal substances.*

Classification of chemical incompatibilities



4.5. CHEMICAL INCOMPATIBILITIES

The examples of chemical incompatibilities:

Oxidation-reduction reactions

Rp.: Argenti nitratis 0.5

Anaesthesini 1.0

Vaselini 25.0

Misce fiat unquentum.

Da. Signa. Apply for the affected area.

The given formula is chemically incompatible. Anaesthesine is oxidized in this combination and silver nitrate is reduced to metallic one. The ointment turns black. The medicine can not be prepared and dispensed.

Rp.: Unguenti Hydrargyri oxydi flavi 10.0

Resorcini 0.2

Misce fiat unquentum.

Da. Signa. Place behind the eye-lids for the night time.

Resorcinol reduces yellow mercury oxide to the metallic mercury and is oxidized itself. The ointment becomes dark.

Rp.: Tincturae Belladonnae 5 ml

Kalii permanganatis 0.1

Aquae purificatae 200 ml

Misce. Da.

Signa. One tablespoon 3 times a day.

The given medicine is chemically incompatible. Potassium permanganate oxidizes alkaloids of Belladonna tincture (organic compounds) and is reduced to marganese dioxide (a dark-brown residue). The color of the mixture turns to dark green.

4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Iodi 0.05
Kalii iodidi 0.1
Zinci oxydi 0.5
Ichthyoli 0.1
Olei Cacao q.s.
Da tales doses numero 10.
Signa. One suppository 3 times a day.

When iodine interacts with ichthyol the oxidation-reduction reaction also takes place and the suppository mass becomes dark.

Rp.: Hydrargyri monochloridi 3.0
Perhydroli 3 ml
Lanolini 5.0
Vaselini 25.0
Da. Signa. Ointment for freckles.

This formula is chemically incompatible without any visible external signs. Under the influence of mercury perhydrol, monochloride (calomel) is oxidized to mercury dichloride (corrosive sublimate), and the presence of lanolin in the formula increases absorption of medicinal substances, i. e. the ointment of the surface action becomes resorptive, and it can result in poisoning.

4.5. CHEMICAL INCOMPATIBILITIES

Displacement reactions

Rp.: Solutionis Natrii benzoatis 2 % 100 ml
Acidi hydrochlorici diluti 1 ml
Misce. Da.
Signa. One tablespoon 3 times a day.

As a result of the displacement reaction when the strong hydrochloric acid displaces the weak benzoic acid from sodium benzonate, the white crystalline precipitate of benzoic acid, which irritates the mucous membrane of the gastrointestinal tract is evolved.

Rp.: Acidi nicotinici 1.0
Natrii nitritis 0.6
Aquae purificatae 200 ml
Misce. Da.
Signa. One tablespoon 3 times a day.

Nicotinic acid displaces nitrogen oxides from sodium nitrite. A doctor can be advised to neutralize the acid by sodium hydrocarbonate (we take 0.7 sodium hydrocarbonate per 1.0 of the acid). The medicine can be prepared in this case.

Rp.: Natrii thiosulfatis
Acidi hydrochlorici diluti 25 ml
Aquae purificatae 200 ml
Misce. Da.
Signa. External.

As a result of the displacement reaction the strong hydrochloric acid evolves an abundant sulphur precipitate and sulphur dioxide (a gaseous product) from sodium thiosulphate.

4.5. CHEMICAL INCOMPATIBILITIES

Exchange decomposition reactions

Rp.: Unguenti Kalii iodidi 30.0

Solutionis Plumbi subacetatis 2 ml

Misce. Da.

Signa. Apply for the affected area.

When mixing the ointment of potassium iodide with the solution of basic lead acetate it gets a bright-yellow color as a result of lead iodide formation.

Rp.: Zinci sulfatis

Natrii tetraboratis aa 0.05

Aquae purificatae 20 ml

Misce. Da.

Signa. Two drops 3 times a day in each eye.

A precipitate of zinc metaborate is formed as a result of the exchange decomposition and under the influence of the alkaline medium hydrolysis of sodium tetraborate takes place and the flake-like precipitate of zinc hydroxide is evolved.

Rp.: Infusi herbae Adonidis 180 ml

Calcii chloridi 10.0

Magnesii sulfatis 12.0

Misce. Da.

Signa. One tablespoon 3 times a day.

The cause of this incompatibility is formation of calcium sulphate precipitate, cardiac glycosides of spring Adonis can be absorbed on it.

4.5. CHEMICAL INCOMPATIBILITIES

Reactions of hydrolysis

Rp.: Infusi foliorum Digitalis 0.5 200 ml

Acidi hydrochlorici 4 ml

Misce. Da.

Signa. One tablespoon 3 times a day.

The given formula is chemically incompatible without any visible external sings. Hydrochloric acid hydrolyzes cardiac glycosides containing in the foxglove leaves infusion.

Cardiac glycosides also undergo hydrolysis under the influence of sodium salts of barbituric acid, sulphanilamide medicines and other alkaline components of the formula.

Rp.: Barbitali-natrii

Chlorali hydrati ana 2.0

Infusi radicis Althaeae

Aquae Menthae ana 60 ml

Misce. Da.

Signa. One tablespoon 3 times a day.

The given medicine is chemically incompatible. Decomposition of chloral hydrate occurs with formation of chloroform in the alkaline medium due to sodium barbital. The latter can be sensed by a clearly expressed smell, and the drops of chloroform appear in a day. Besides, the barbital base is precipitated gradually (solubility 1:170).

4.5. CHEMICAL INCOMPATIBILITIES

Neutralization reactions

Nowadays there is a tendency complicate the mixture of hydrochloric acid with pepsin and pancreatine by adding tinctures of mint, wormwood, belladonna, vitamins, ascorbic acid, etc.; it leads to decrease in digesting ability of enzymes.

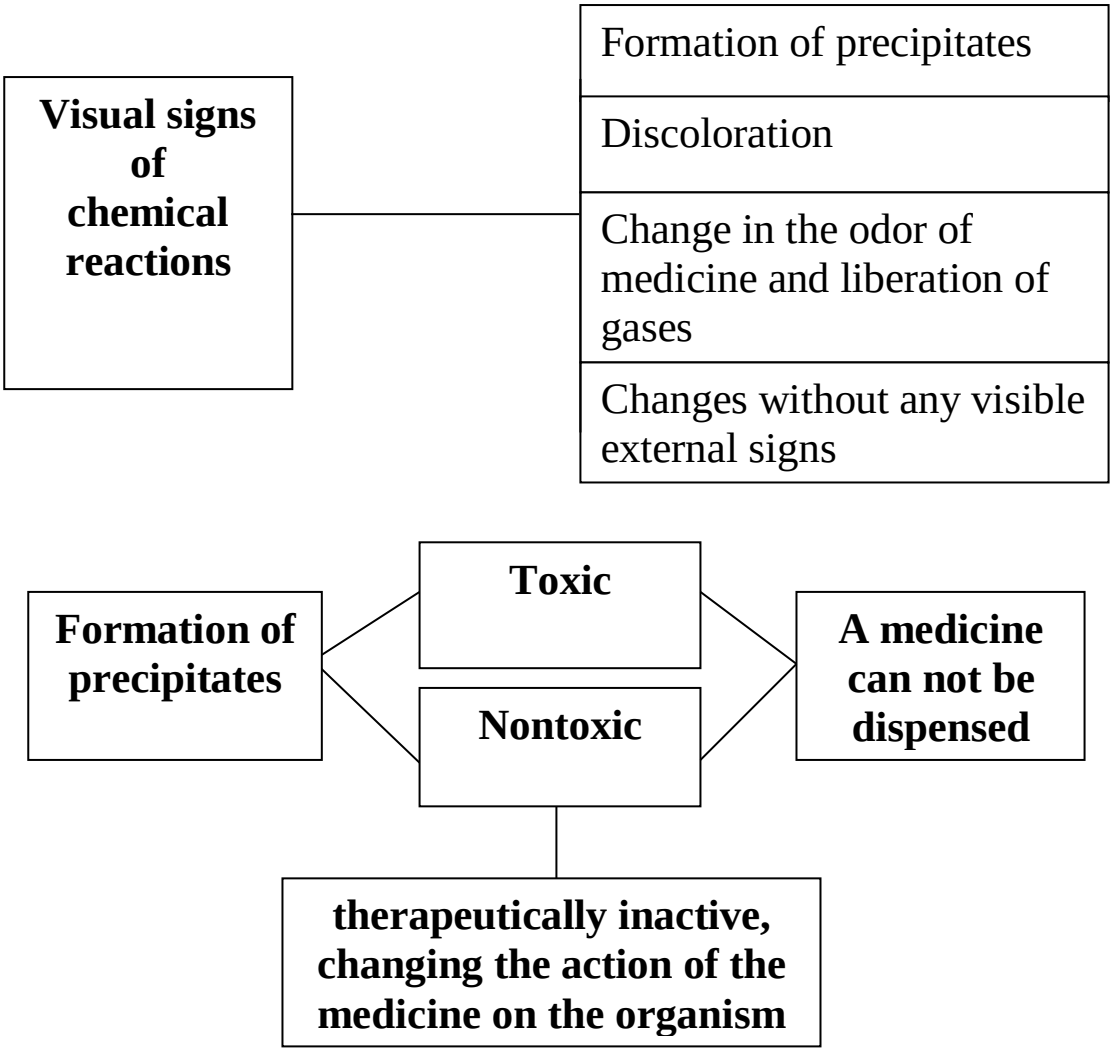
Rp.: Solutionis Acidi hydrochlorici 2% 200 ml
Pepsini 4.0
Acidi ascorbinici 2.0
Tincturae Absinthii 5 ml
Misce. Da.
Signa. One tablespoon 3 times a day.

The amount of ascorbic acid prescribed contributes to inactivation of pepsin.

Rp.: Zinci oxydi 10.0
Acidi salicylici 4.0
Glycerini 6.0
Aquae purificatae 40 ml
Misce. Da.
Signa. Rub into the skin.

There is the reaction of neutralization in this formula, and as a result, the insoluble compound of zinc salicylate is formed. The precipitation in the medicinal form, which is a suspension, proceeds without any external signs, but in some hours zinc salicylate becomes hard and “cements” the medicine.

4.5. CHEMICAL INCOMPATIBILITIES



The causes of precipitate formation:

- *precipitation of alkaloids and nitrous bases;*
- *precipitation of cardiac glycosides;*
- *precipitation of tannins;*
- *precipitation of barbituric acid derivatives;*
- *precipitation of sulphanylamides;*
- *precipitation of heavy metals compounds;*
- *precipitation of antibiotics;*

4.5. CHEMICAL INCOMPATIBILITIES

as well as the result of chemical reactions:

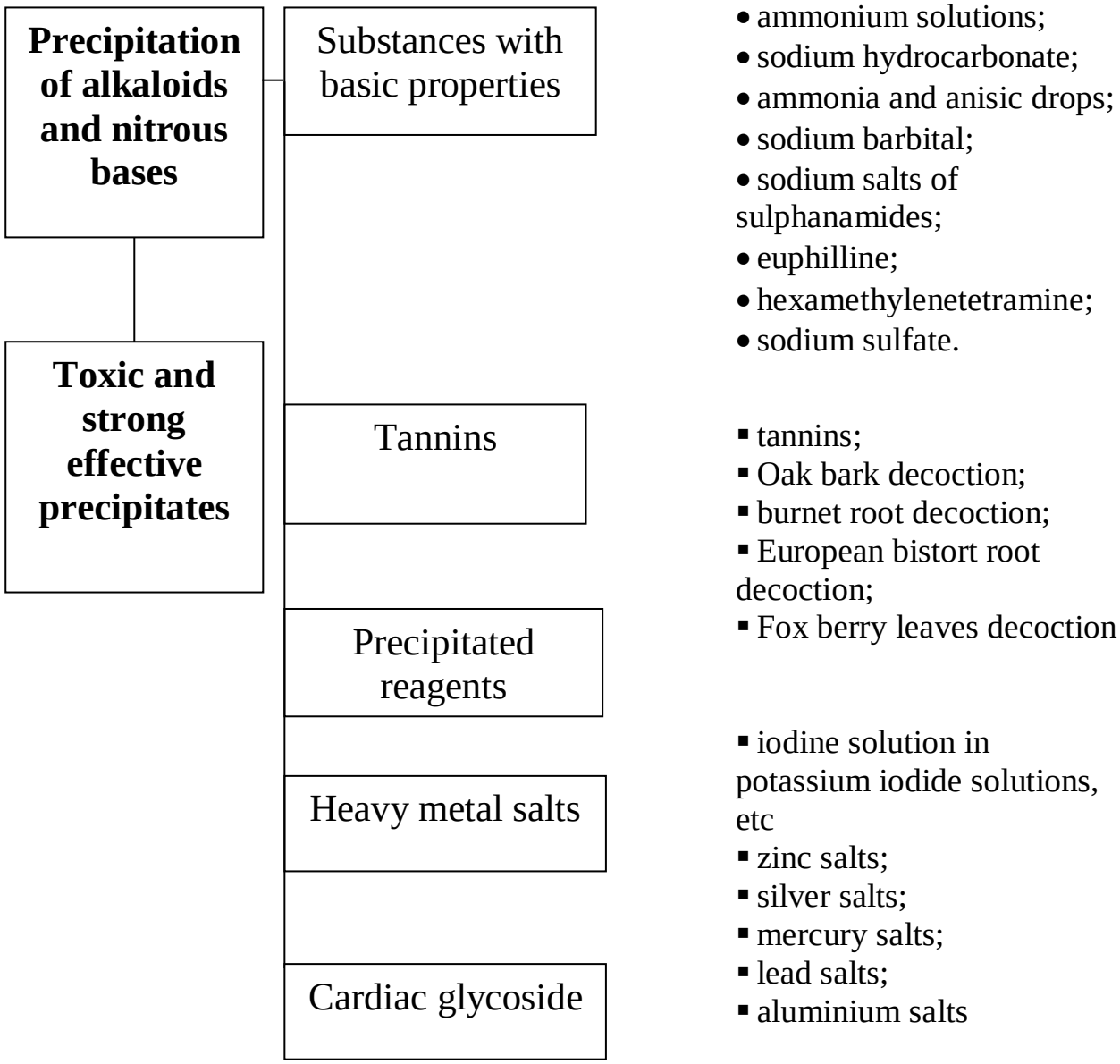
- *displacement of weak acids from salts by stronger acids;*
- *oxidization-reduction reactions;*
- *neutralization reactions;*
- exchange decomposition *reactions.*

Examples of such combinations of medicinal substances that are most often met in the compounding formulas at the chemist's, are given below:

Bases of alkaloids are very difficult to dissolve in water, excluding:

- *caffeine;*
- *codeine;*
- *pylocarpine;*
- *termopsine;*
- *citisine;*
- *nicotine and some others.*

4.5. CHEMICAL INCOMPATIBILITIES



The following salts are especially sensible to the alkaline environment:

Alkaloid salts:

- Papaverine
- Strychnine
- Apomorphine
- Scopolamine
- Atropine, etc.

Nitrate base salts:

- Proserine
- Spasmolytin
- Dibasol
- Promedol
- Diphenhydramine hydrochloride
- Novocaine
- Dicaine
- Etacridine, etc.

4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Papaverini hydrochloridi 0.15

Natrii hydrocarbonatis 5.0

Aquae purificatae 100 ml

Tincturae Valerianae 5 ml

Misce. Da.

Signa. One tablespoon 3 times a day.

In this case the base of papaverine displaced by sodium hydrocarbonate precipitates in the alkaline medium. The part of sodium hydrocarbonate is spent on neutralization of organic acids of valerian.

Rp.: Codeini 0.15

Solutionis Aethylmorphini hydrochloridi 1% 10 ml

Misce. Da.

Signa. Fifteen drops 3 times a day.

Codeine being a strong base should not be combined with salts of alkaloids formed by weaker bases. In this case under the influence of codeine which is alkaline reactive, ethylmorphine precipitates.

Rp.: Dicaini 0.15

Solutionis Sulfacyli-natrii 30 % 10 ml

Misce. Da.

Signa. Two drops 3 times a day.

When preparing a medicine according to this prescription the liquid at first becomes opalescent. Then if in is allowed to stand, a finely dispersed precipitate of dicaine base appears under the influence of the alkaline medium formed by sodium sulphacyl, which if sparingly soluble in water (1:200).

4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Novocaini
Dimedroli ana 0.15
Glucosi 0.2
Norsulfazoli-natrii 2.5
Aquae purificatae 25 ml
Misce. Da.
Signa. Two drops 3 times a day in each eye.

Sodium salt of norsulfazol creates the alkaline medium, where dimedrol and novocaine decompose with precipitation of bases.

Alkaloid bases can precipitate not only as a result of their displacement from salts but also as a result of decomposition of salts.

Rp.: Papaverini hydrochloridi 0.3
Coffeini-natrii benzoatis 1.0
Aquae pro injectionibus 10 ml
Sterilisa!
Misce. Da. Signa. On one ml intramuscularly.

Papaverine hydrochloride is the salt of a weak base and a strong acid, and sodium caffeine-benzoate is the salt of a strong base and a weak acid. As a result of interaction bases of papaverine and caffeine (solubility 1:60), as well as benzoic acid (solubility 1:400) precipitate.

Precipitates alkaloid salts can be also observed in those cases when as the result of exchange reaction poorly soluble alkaloid salts are formed.

4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Chinini hydrochloridi 0.1
Zinci sulfatis 0.05
Solutionis Acidi borici 2 % 10 ml
Misce. Da. Signa. Two drops in each eye.

A precipitate of poorly soluble quinine sulphate (solubility 1:800) and water-soluble zinc chloride, which irritates the mucous membrane, is formed.

Tannins give insoluble precipitates with alkaloids (in the form of alkaloid tannaete).

The exceptions are:

- quinine hydrochloride
- morphine hydrochloride
- codeine

} are not precipitated by tannins.

Rp.: Omnoponi 0.1
Decocti foliorum Uvae Ursi ex 6.0 200 ml
Misce. Da.
Signa. One tablespoon 3 times a day.

As a result of interaction tannats of opium alkaloids are formed and precipitated.

4.5. CHEMICAL INCOMPATIBILITIES

When combining solutions of alkaloid salts with *sedimentary reagents* (for example, with iodine solution in potassium iodide solution), precipitates in the form of polyiodides are formed. The exceptions are:

- caffeine;
- theobromine;
- theophilline.

Rp.: Tincturae Strychni 8 ml
Iodi 0.5
Kalii iodidi 5.0
Aquae purificatae 20 ml
Misce. Da. Signa. Ten drops 3 time a day.

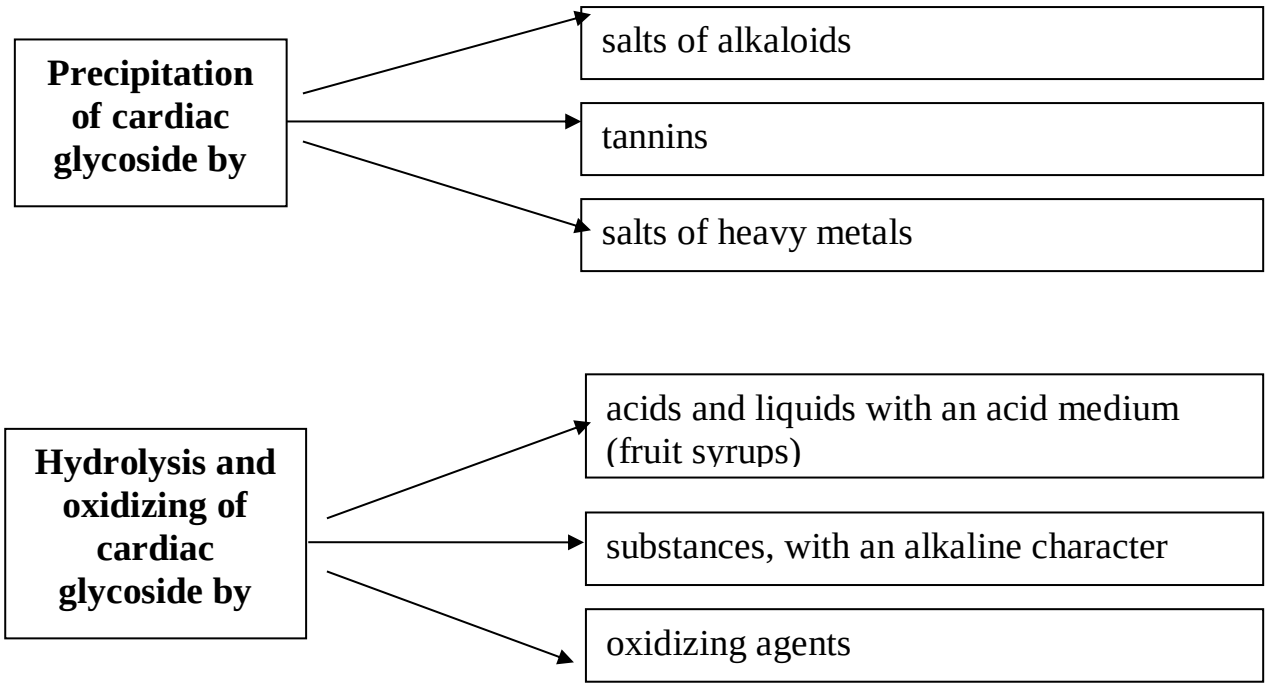
The polyiodides of strychnine, brucine and other alkaloids of S*trichnos nux-vomica are precipitated*.

Salts of alkaloids and salts of nitrogen-containing substances should not be combined with the *salts of heavy metals*, because insoluble precipitates are formed.

Rp.: Physostigmini salicylatis 0.1
Plumbi acetatis 0.05
Aquae purificatae 10 ml
Misce. Da. Signa. Two drops in each eye.

As a result of the exchange decomposition reaction, lead salycilate, where the base of physostigmine is absorbed precipitates.

4.5. CHEMICAL INCOMPATIBILITIES



Formation of precipitates in interaction of cardiac glycosides with salts of alkaloids takes place with a comparatively high concentration (more often – in drops).

Rp.: Omnoponi 0.3

Coffeini 0.1

Tincturae Strychni 5 ml.

Tincturae Convallariae 15 ml

Misce. Da.

Signa. Ten drops 3 times a day.

A brown amorphous toxic precipitate appears as a result of the interaction.

4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Infusi herbae Adonidis ex 8.0 200 ml
Kalii bromidi 5.0
Extracti Crataegi fluidi 25 ml
Misce. Da.
Signa. One tablespoon 3 times a day.

Tannins of hawthorn extract interact with cardiac glycosides of Adonis extract forming an amorphous brown toxic precipitate.

Rp.: Infusi herbae Adonidis ex 6.0 180 ml
Sirupi Rubi idaei 20 ml
Tincturae Valerianae 10 ml
Misce. Da.
Signa. One tablespoon 3 times a day.

This formula is chemically incompatible. The hydrolysis of cardiac glycosides of Adonis by organic acids of raspberry syrup takes place. The reaction occurs without any visible changes, and the medicine loses its therapeutic effect completely. However, fruit syrup is a flavor in this formula, that is why the medicine can be dispensed if the raspberry syrup is replaces by a simple syrup.

4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Papaverini hydrochloridi 0.5

Analgini 3.0

Solutionis Natrii bromidi 2 % 200 ml

Natrii nitritis 1.0

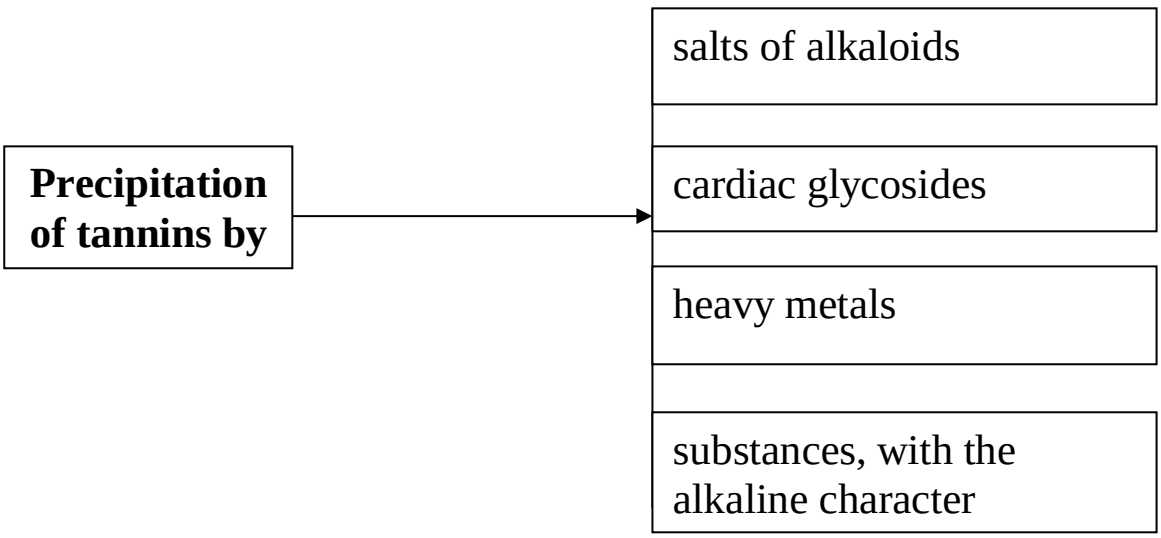
Adonisidi 8 ml

Tincturae Crataegi 10 ml

Misce. Da.

Signa. One tablespoon 3 times a day.

In this case papaverine base precipitates in the alkaline medium created by analgin under the influence of sodium nitrite and tannins of hawthorn tincture. Nitrous acid formed decomposes to nitrogen oxides, which oxidize cardiac glycosides of adoniside, and the precipitate of cardiac glycosides is formed under the action of tannins. Their saponification occurs in the alkaline medium. The medicine gets an unpleasant odor and contains a toxic precipitate.



The examples of formation of alkaloids tannats and cardiac glycosides are given above.

4.5. CHEMICAL INCOMPATIBILITIES

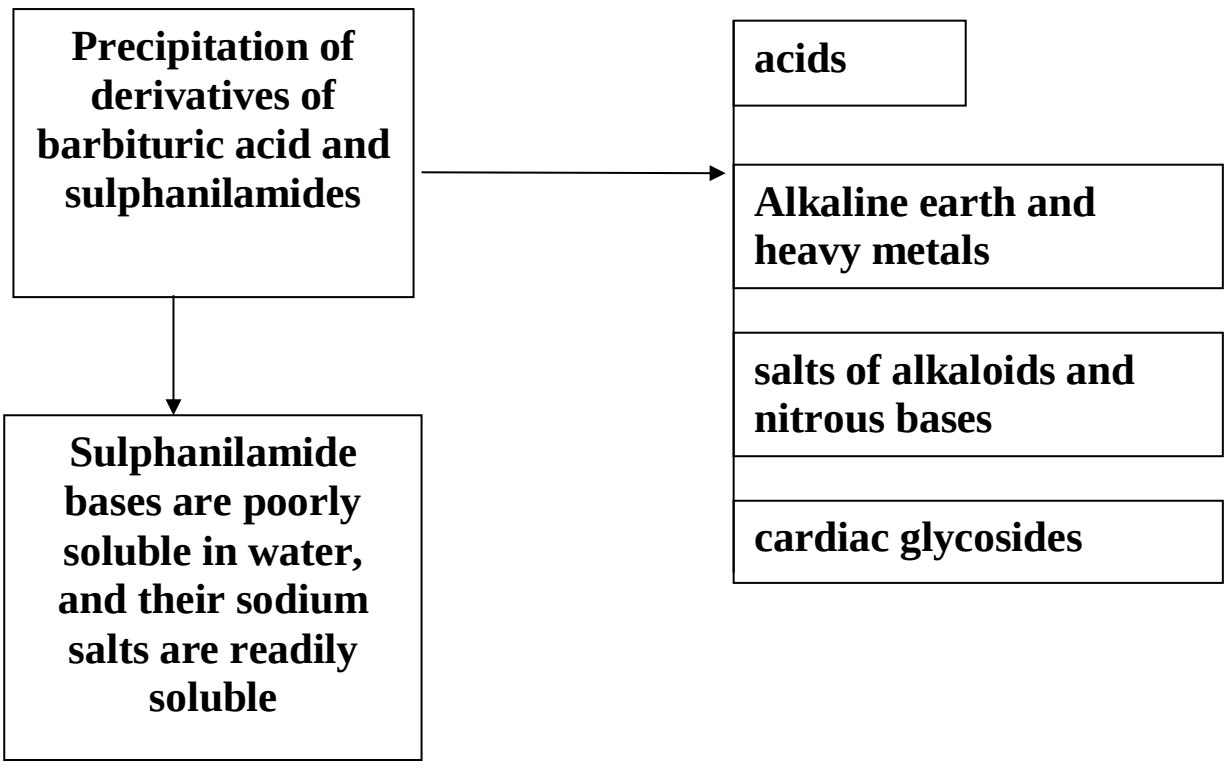
Rp.: Decocti corticis Quercus 200 ml

Plumbi acetatis 2.0

Misce. Da.

Signa. A lotion.

Tannins of oak bark under the influence of lead acetate precipitate in the form of an abundant brown residue of tannat lead. However, the astringent and anti inflammatory action of the medicine remains. It can be dispensed after coming to an agreement with a doctor with a label «Shake well before using», since this precipitate is distributed well.



4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Barbitali-natrii 2.0
Solutionis Natrii bromidi 3 % 100 ml
Acidi ascorbinici 1.0
Tincturae Valerianae 10 ml
Misce. Da.
Signa. One tablespoon 3 times a day.

As a result of interaction of sodium barbital and ascorbic acid a white crystalline precipitate of barbital is formed. The part of barbital will be also displaced by acids of valerian tincture.

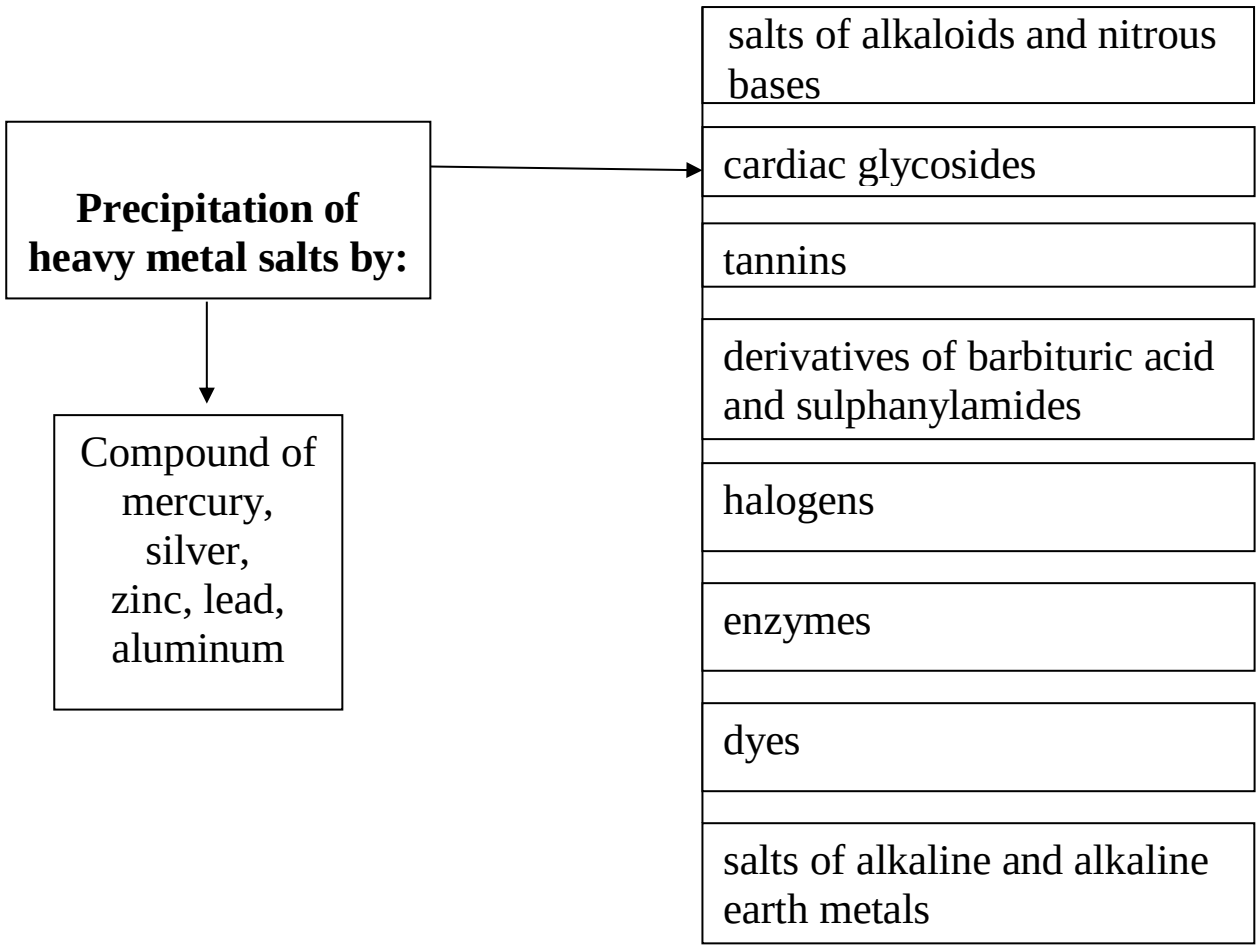
Rp.: Solutionis Sulfacyli-natrii 30 % 10 ml
Acidi ascorbinici 0.15
Misce. Da.
Signa. Two drops in each eye.

Ascorbic acid neutralizes of sodium sulfacyl solution and precipitates sulfacyl, which has the solubility of 1:200. After having come to an agreement with a doctor the formula can be made rational if at first ascorbic acid is neutralized by sodium hydrocarbonate (0.7 of sodium hydrocarbonate per 0.15 of ascorbic acids). A precipitate of sulfacyl is not formed in this case.

Rp.: Solutionis Sulfacyli-natrii 30 % 10 ml
Zinci sulfatis 0.05
Misce. Da.
Signa. Two drops in each eye.

Zinc hydroxide precipitate under the influence of the alkaline medium created by sodium sulfacyl.

4.5. CHEMICAL INCOMPATIBILITIES



Rp.: Solutionis Argenti nitratis 0.4 200 ml

Natrii hydrocarbonatis 4.0

Misce. Da.

Signa. One tablespoon 3 times a day.

A flake-like precipitate of silver hydrocarbonate is formed as a result of interaction of the prescribed ingredients.

Rp.: Hydrargyri dichloridi 0.5

Natrii tetraboratis 4.0

Spiritus aethylici 70 % 15 ml

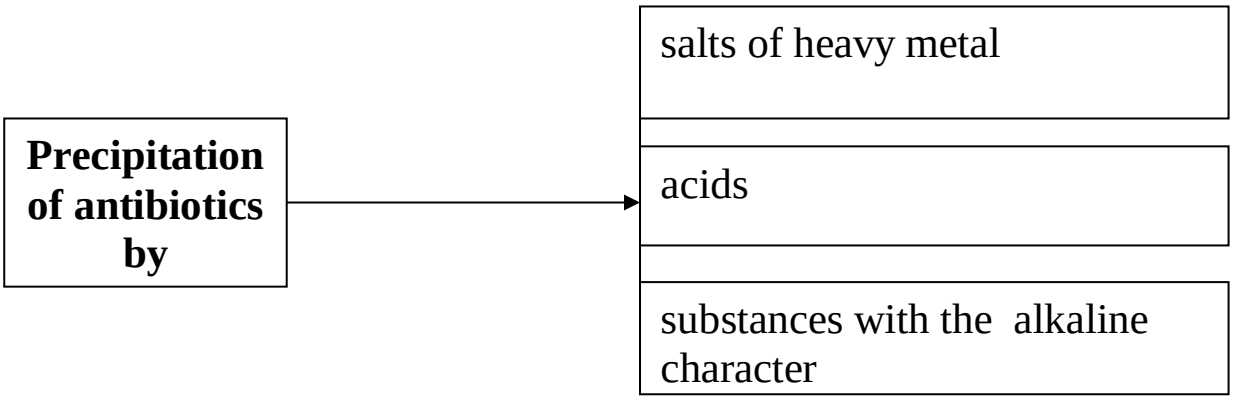
Aquae purificatae ad 100 ml

Misce. Da.

Signa. For disinfection.

4.5. CHEMICAL INCOMPATIBILITIES

When preparing the medicine the yellow mercury oxide is formed, it is obtained in the reaction of mercury dichloride with sodium hydroxide isolated in hydrolysis of borax.



Rp.: Ephedrini hydrochloridi 3 % 20 ml
Zinci sulfatis 0.03
Benzylpenicillini-kalii 200 000 ED
Sol. Adrenalini hydrochloridi 0.1% gtts. X
Misce. Da.
Signa. Nasal drops.

Under the influence of zinc sulphate the inactivation of penicillin take place and the precipitate of benzylpenicillin acid is formed.

Rp.: Benzylpenicillini-natrii 125 000 ED
Sol. Àcidi ascorbinici 5 % 5 ml
Misce. Da.
Signa. Two drops in the right eye.

The unstable lactam ring of penicillin is hydrolised in the acidic medium created by the ascorbic acid and as a result, the inactive benzylpenicillin acid precipitates.

4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Streptomycini sulfatis 250 000 ED

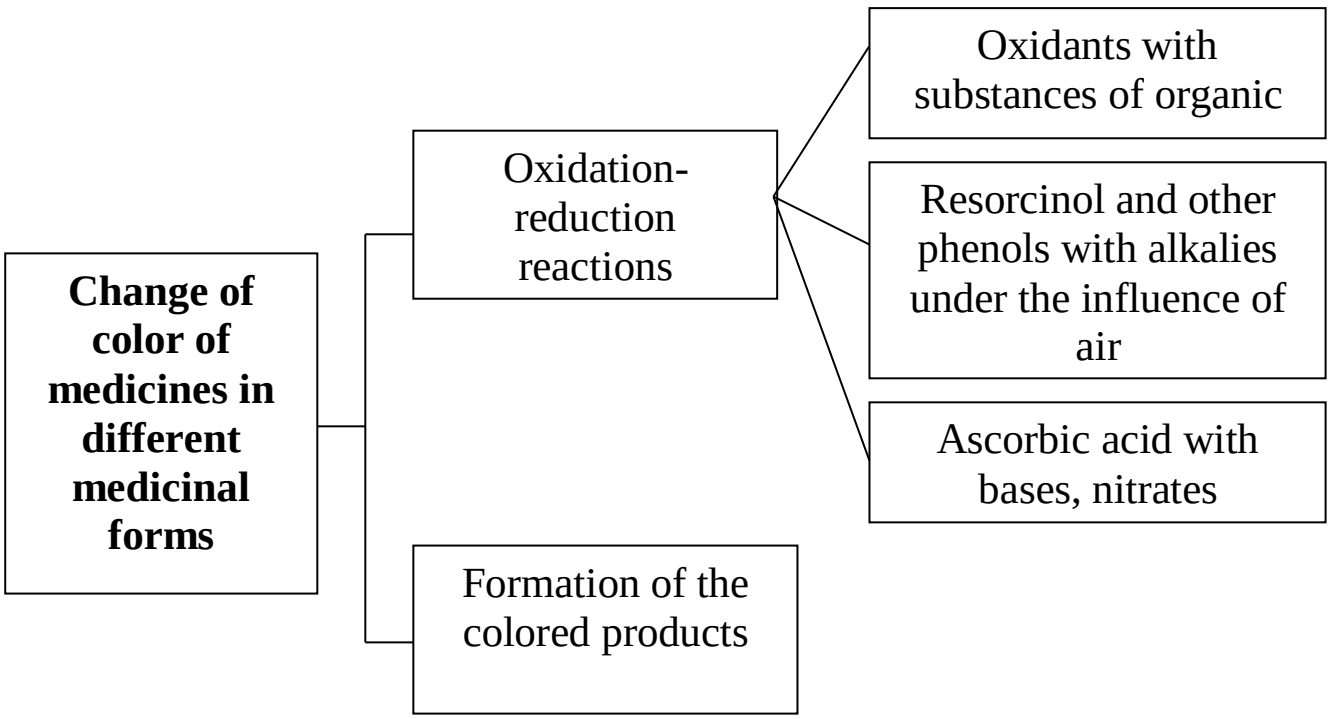
Sol. Norsulfazoli-natrii 2 % 100 ml

Misce. Da.

Signa. One tablespoon 3 times a day.

As a result of exchange decomposition the base of norsulpaasole precipitates; streptomycin become non active in the alkaline medium and the insoluble base of streptomycin is formed.

Formation of precipitate *as a result of proceeding exchange decomposition reactions*, displacement weak acids by strong acids, oxidization-reduction, neutralization, were considered in the first section.



4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Kalii permanganatis 0.1
Chinini hydrochloridi 0.5
Misce fiat pulvis
Da tales doses N 20
Signa. One powder 3 times a day.

The color of powders changes gradually from violet to black because potassium permanganate oxidizing quinine hydrochloride is restored to marganese dioxide.

Rp.: Extracti Belladonnae 0.15
Antipyrini
Resorcini
Natrii hydrocarbonatis ana 3.0
Aquae purificatae 200 ml
Misce. Da.
Signa. 1 tablespoon 3 times a day.

Resorcinol, in presence of sodium hydrocarbonate, is oxidized by oxygen from air, changing the color of medicines from red to violet, and the products of oxidization emetic action.

Rp.: Solutionis Sulfacyli-natrii 10 % 10 ml
Solutionis Adrenalini hydrochloridi 0.1 % 2 ml
Misce. Da.
Signa. Two drops in each eye.

Adrenaline is oxidized by oxygen from the air in the alkaline medium created by sodium sulfacyl, the medicine becomes gradually brown.

4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Solutionis Adrenalini hydrochloridi 0.1% 1 ml
Solutionis Hydrogenii peroxydi diluti 15 ml
Misce. Da.
Signa. Nasal drops.

Adrenaline is oxidized by hydrogen peroxide with formation of the brown decomposition products.

Rp.: Papaverini hydrochloridi 0.03
Natrii nitritis 0.02
Acidi ascorbinici 0.1
Sacchari 0.3
Misce fiat pulvis.
Da tales doses N 12.
Signa. One powder 3 times a day.

Sodium nitrite oxidizes ascorbic acid and powders become damp at first, turn yellow gradually, and then have a brown color and an odor of nitrogen oxides.

Rp.: Antipyrini 4.0
Solutionis Nàtrii nitritis 1 % 200 ml
Misce. Da.
Signa. One tablespoon 3 times a day.

The mixture is colored in emerald green color as a result of formation of nitroso-antipyrine.

4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Extracti Belladonnae 0.3

Acidi ascorbinici 3.0

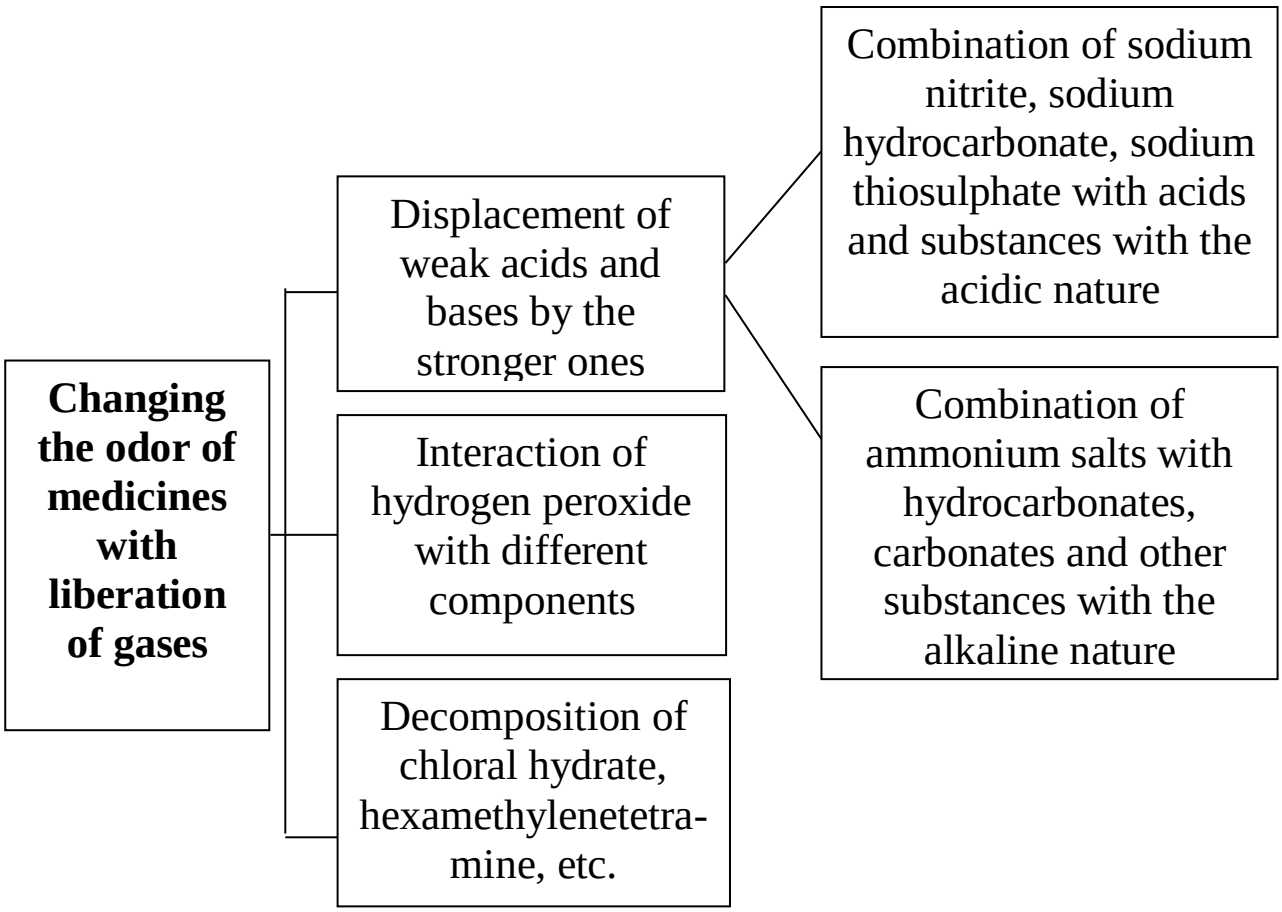
Ferri lactatis 9.0

Misce fiant pulvis

Da. Signa. One powder 3 times a day.

As a result of interaction between iron lactate and ascorbic acid, iron ascorbate of violet color is formed (the exchange decomposition reaction).

The similar example of changing color of a medicine as a result of exchange decomposition reaction was given earlier: it is a bright yellow coloring of potassium iodide ointment with lead acetate as a result of formation of lead iodide.



4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Solutionis Natrii bromidi 3 % 200 ml

Acidi ascorbinici 5.0

Natrii nitritis 0.6

Misce. Da.

Signa. One tablespoon 3 times a day.

Ascorbic acid displaces the red-brown vapors of nitrogen oxides with an unpleasant odor from sodium nitrite; the mixture becomes of light yellow color.

Similarly hydrochloric and nicotinic acids and alkaloid salts (papaverine hydrochloride, etc.) act to sodium nitrite. Acids displace carbon dioxide from salts of carbonates and hydrocarbonates, and they displace sulfurous gas from thiosulfate.

Rp.: Infusi herbae Adonidis ex 6.0 200 ml

Hexamethylentetramini 8.0

Ammonii bromidi 6.0

Misce. Da.

Signa. One tablespoon 3 times a day.

Ammonium is isolated from ammonia bromide under the influence of the alkaline medium created by hexamethyltetramine.

Rp.: Collargoli 0.3

Solutionis Hydrogenii peroxydi 20 ml

Misce. Da.

Signa. For washing of purulent wounds.

Hydrogen peroxide decomposes with a rapid liberation of oxygen under the influence of the colloid medicine collargol.

4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Solutionis Hydrogenii peroxydi 5 ml

Olei Persicorum 4.0

Vaselini 20.0

Misce fiat unguentum.

Da. Signa. Cover the affected areas.

Hydrogen peroxide decomposes with the liberation of oxygen under the influence of fats, and as a result, the ointment foams actively.

Rp.: Chlorali hydrati 6.0

Infusi radicis Althaeae 180 ml

Natrii hydrocarbonatis 4.0

Misce. Da.

Signa. One tablespoon 3 times a day.

Chloroform with a characteristic odor liberates under the influence of the alkaline medium of sodium hydrocarbonate from chloral hydrate. The mixture becomes muddy, because chloroform does not mix with water.

Rp.: Infusi radicis Valerianae ex 8.0 200 ml

Acidi ascorbinici 3.0

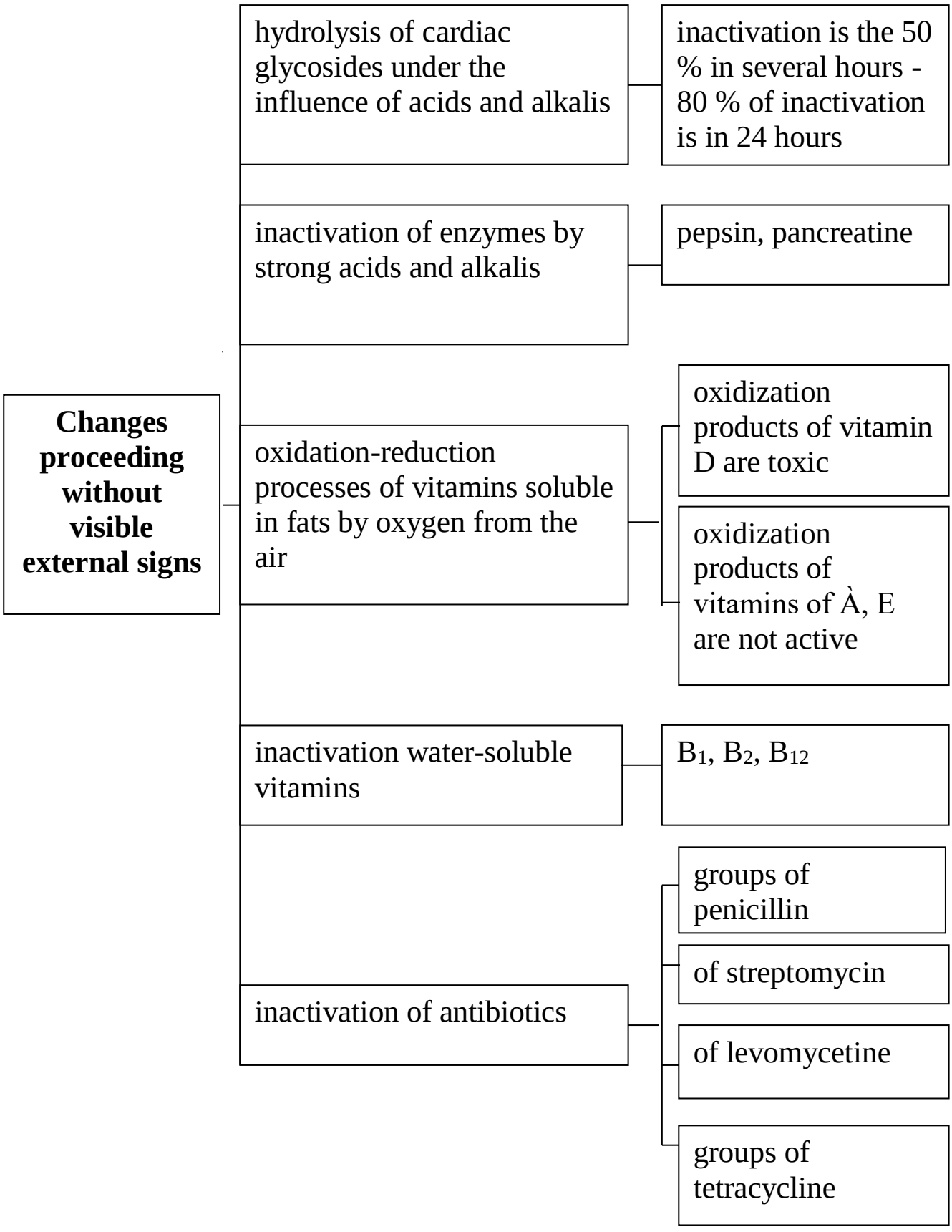
Hexamethylentetramini 1.0

Misce. Da.

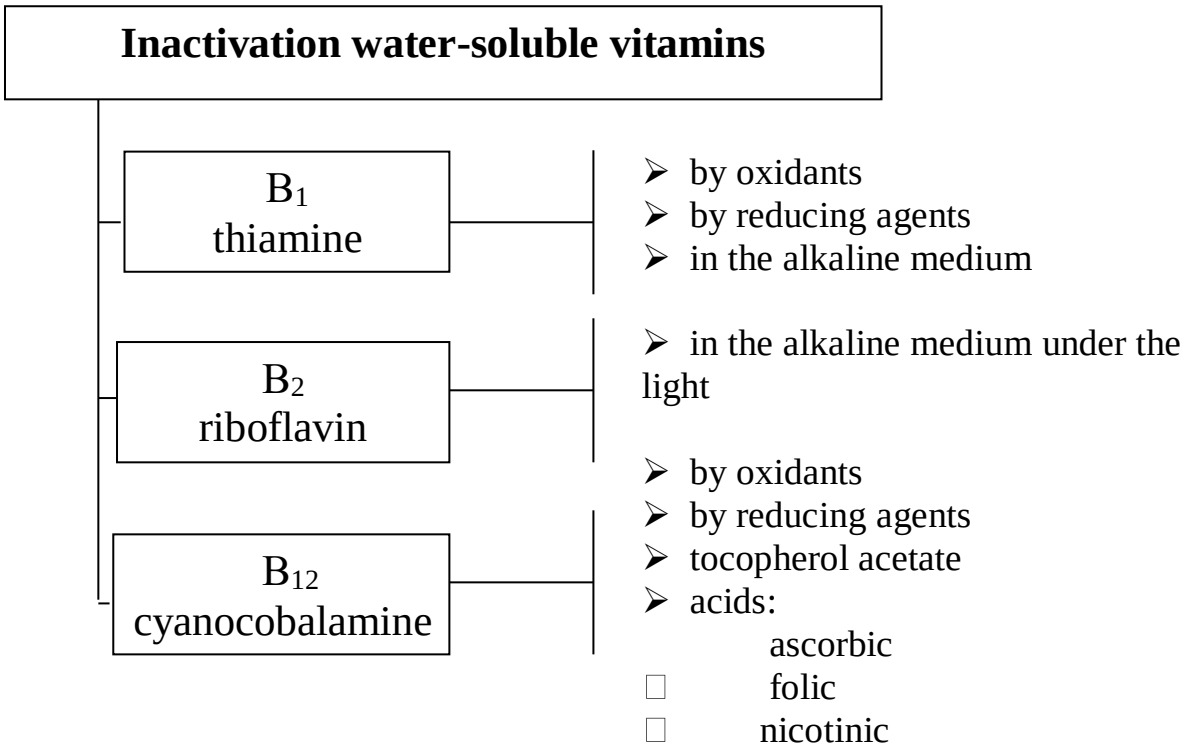
Signa. One tablespoon 3 times a day.

Hexamethylenetetramine is subjected to hydrolysis in the acidic medium with the liberation of formaldehyde with a specific odor.

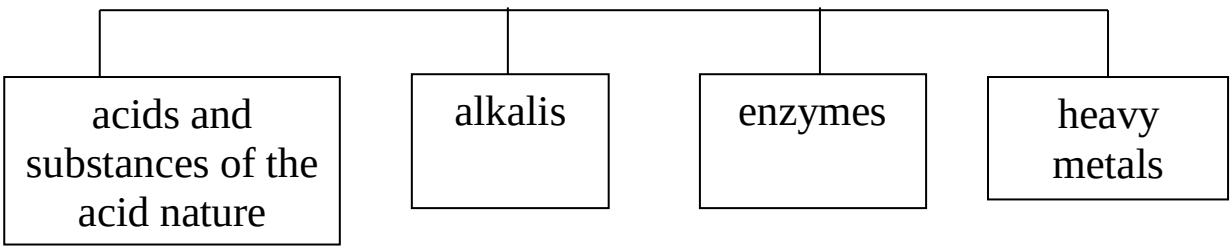
4.5. CHEMICAL INCOMPATIBILITIES



4.5. CHEMICAL INCOMPATIBILITIES



Penicillin is a derivative of thiasolidine containing the unstable lactam ring subjected to hydrolysis under the influence of:



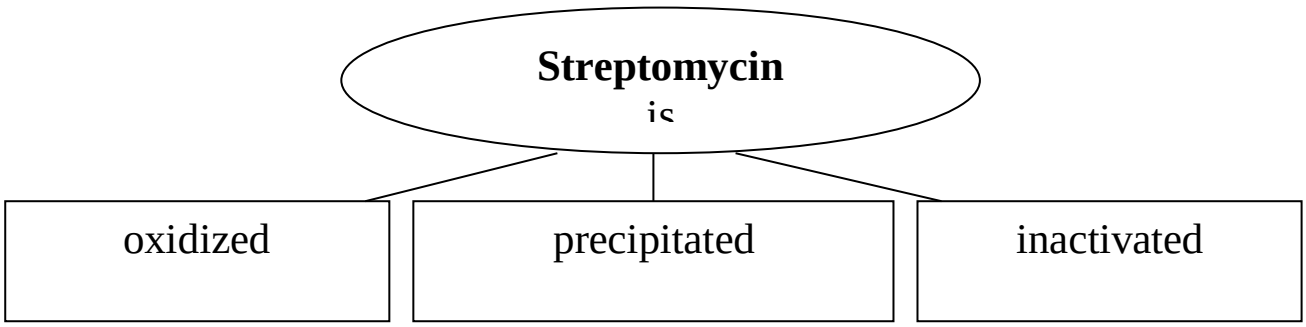
It is impossible to combine penicillin in liquid medicinal forms and ointments with:

- glycerin;
- naftalan;
- resorcinol;
- zinc oxide;
- thiamine;
- ephedrine;
- adrenaline;
- iodine;
- iodides;
- hydrogen peroxide.

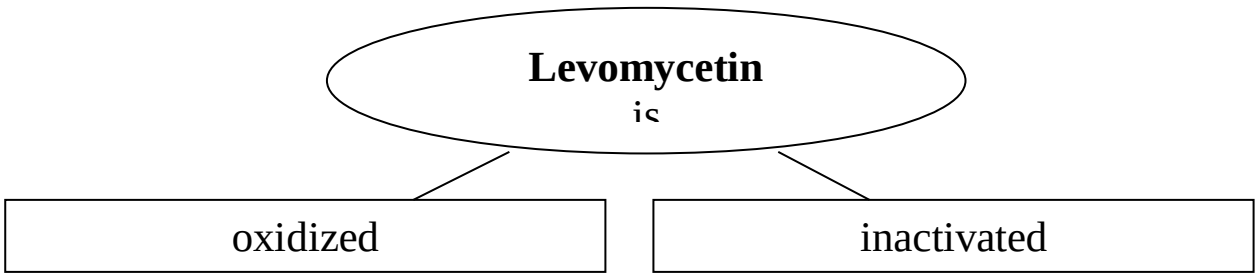
4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Benzylpenicillini-kalii 500 000 ED
Solutionis Hydrogenii peroxydi
Spiritus aethylici ana 5 ml
Misce. Da.
Signa. Three drops in the ear 2 times a day.

Inactivation of potassium salt benzylpenicillin by hydrogen peroxide is accelerated by ethyl alcohol; as a result, there is break of the lactam ring with formation of non active water-soluble products - penicilamine and penicilaldehyde.

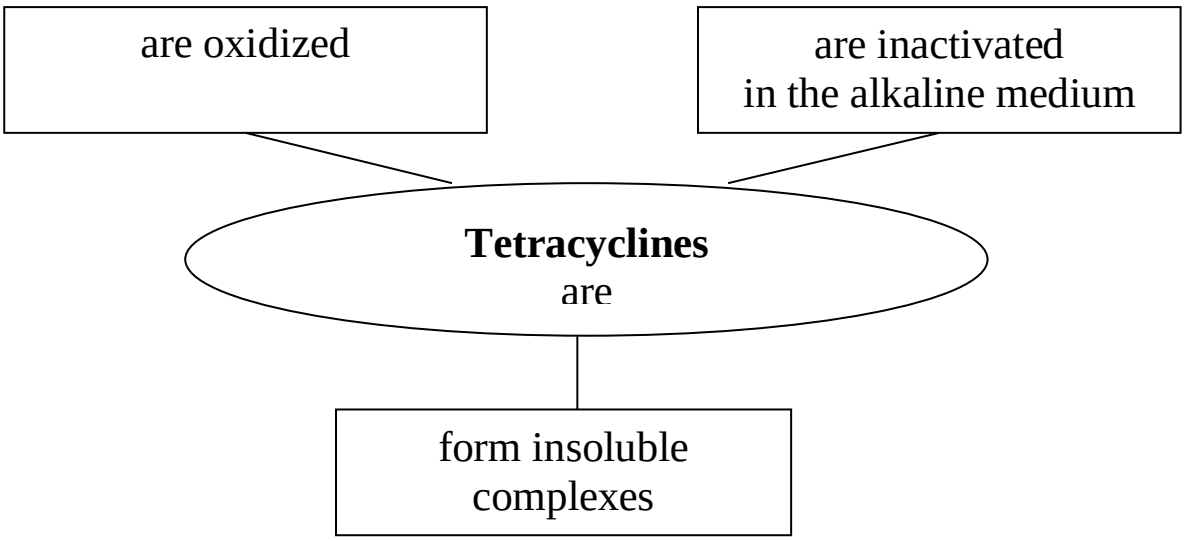


by:
- alkaloid reagents ;
- dyes
- blood serum,
- in the alkaline medium
- in the presence of glucose
- nucleic acids.



- in the alkaline medium at pH > 9.5;
- during sterilization at t > 100°C.

4.5. CHEMICAL INCOMPATIBILITIES



- with salts of polyvalent metals;
- of boric and phosphoric acids and their salts.

Besides, ***tetracyclines*** are incompatible with ascorbic and nicotinic acids, sodium sulfacyl, sodium tetraborate, calcium chloride, zinc sulphate, tannin, ephedrine.

Oxytetracyclines are inactivated in the acidic medium.

Chlortetracyclines form incompatibilities characteristic for chlorides and salts of alkaloids.

Sodium salts of tetracyclines reaction are incompatible with acids, salts of metals and salts of organic bases because of the alkaline.

In some cases no changes are observed in the prepared medicine, and the interaction between ingredients takes place in the gastrointestinal tract.

4.5. CHEMICAL INCOMPATIBILITIES

Rp.: Analgini 5.0

Solutionis Natrii bromidi 1 % 200 ml

Kalii iodidi 4.0

Natrii nitritis 2.0

Misce. Da.

Signa. One tablespoon 3 times a day.

After dispensing the medicine a patient came to the chemist's complains of headaches.

The research has shown that there is no interaction between the ingredients in the weak alkaline medium created by analgin. In the acidic medium of the stomach sodium nitrite oxidizes potassium iodide with the liberation of iodine.

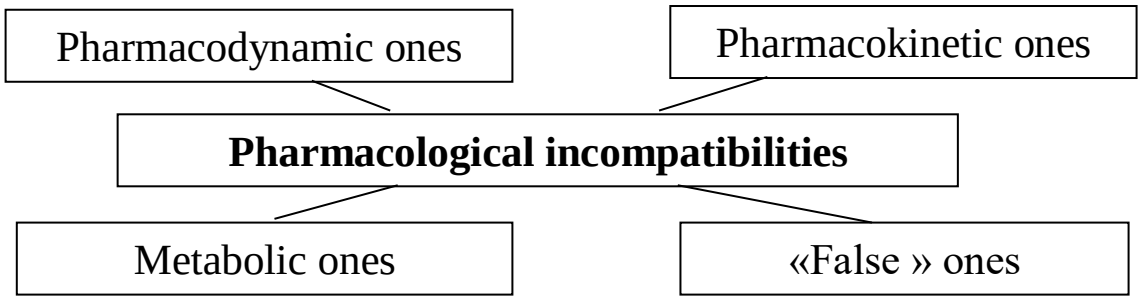
There are 14 tablespoons in the mixture, thus i. e. 14 intakes. There is 4.0/14=0.285 g of potassium iodide in a tablespoon. Taking into account that highest single dose (H.S.D.) of iodine is 0.02 g, the single dose of iodine in the mixture is exceeded in 11 times.

Consequently, such medicine can not be prepared and dispensed.

4.6. PHARMACOLOGICAL CONCEPT OF INCOMPATIBILITY

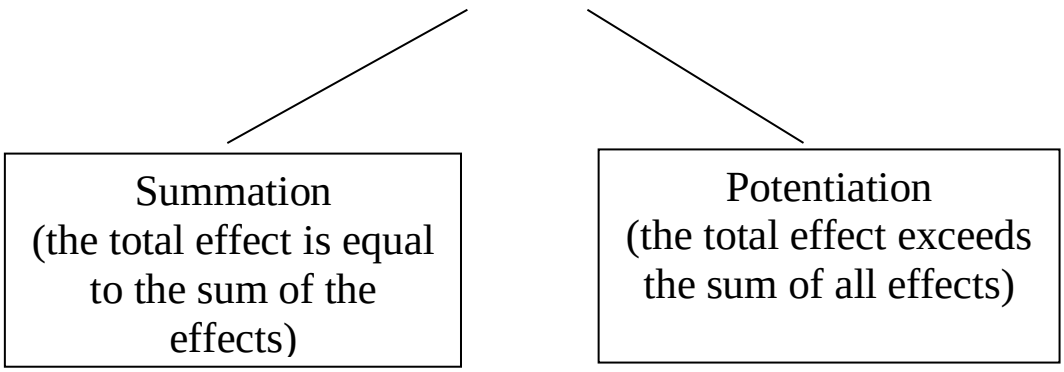
Pharmacological incompatibility *is the combination of medicinal substances, which in some cases result in decrease or complete loss of the therapeutic effect, in other cases –it intensifies or reveals undesirable side effects.*

Pharmacological incompatibility suggests the change of the phermacodynamic effects, but not the medicinal substances themselves, i. e. antagonistic effects of medicines influence on certain structural and functional systems of the organism.



Pharmacodynamic *interaction of medicinal substances reveals as synergism and antagonism.*

Synergism is the simultaneous action in one direction of two or several medicines providing more expressed effect than each of them individually in the form of:



4.6. PHARMACOLOGICAL CONCEPT OF INCOMPATIBILITY

Antagonism is weakening or complete elimination of all effects of the basic substance by other substances, added simultaneously or consistently.

Pharmacokinetic incompatibility *is the manifestation of interaction in absorption, distribution and excretion of medicinal substances from the organism expressed in the change of the rate of these processes, which can result in weakening of the therapeutic effect or in intensifying of the side effect.*

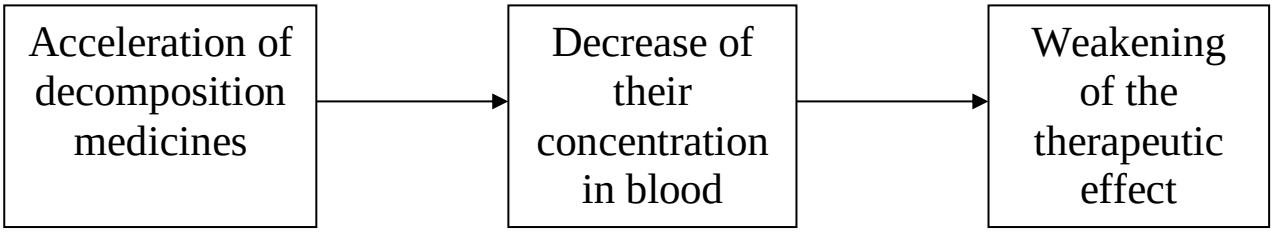
Some cases of combined therapy with antibiotics can be considered as the examples:

- streptomycin with neomycin, monomycin → provide intensification of the oto-toxic effect of streptomycin, irreversible changes of the acoustic nerve;
- streptomycin with tetracycline → pathology of the liver is complicated by adipose infiltration of the liver;
- streptomycin with penicillin → intensification of the toxic effect on the myocardium, dramatic decrease in its contractive activity.

Metabolic incompatibility *is the change of metabolism of medicinal substances with their simultaneous administration.* It can be the result of metabolism acceleration under the influence of simultaneous or successive administration of medicines inducing enzymes (e. g., phenobarbital, butadion, reopyrin, alcohol, etc).

4.6. PHARMACOLOGICAL CONCEPT OF INCOMPATIBILITY

When such medicines are used the following effects are observed:



- if phenobarbital and anticoagulants are prescribed together, the increase of doses for anticoagulants is required, as they decompose in the organism
- when administration of Phenobarbital is discontinued, bleeding can appear since decomposition of anticoagulants becomes slower, and their toxic concentration is accumulated in blood.

Pharmacological incompatibility based on the mutual inactivation of pharmacological effects (functional antagonism) can be of a great variety.

There are several types of antagonism:

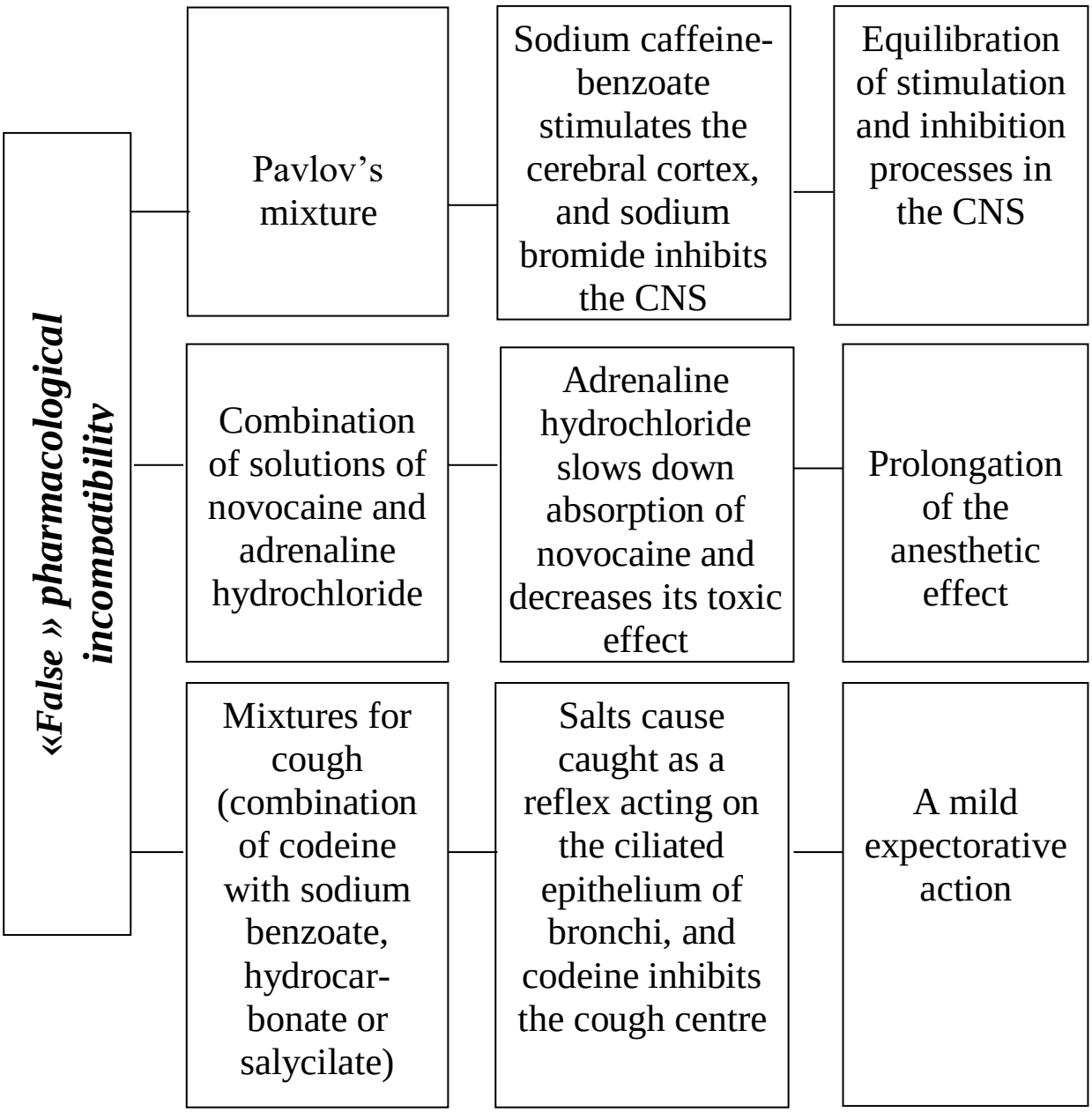
Direct (true)	***Bilateral***
Competitive	***Unilateral***
Indirect	***Partial (synergism-antagonism)***

Sometimes the phenomenon of antagonism is used for treating patients:

- antidotes;
- *«false»* pharmacological incompatibilities.

4.6. PHARMACOLOGICAL CONCEPT OF INCOMPATIBILITY

«False» incompatibility is **the** *combination of components, which are antagonists, rendering a positive therapeutic effect depending on their dose.*



4.6. PHARMACOLOGICAL CONCEPT OF INCOMPATIBILITY

Direct antagonism *(monosystemic) is the opposite action of medicinal substances that is realized within the same system.*

For example, the use of atropine sulphate in poisoning with fly agarics - the mushroom poison muscarin stimulates M-cholinoreceptors, and atropine has an opposite action blocking them.

Competitive antagonism *is the variety of direct antagonism occurring if there are two compounds with the similar chemical nature and spatial structure in the organism simultaneously, and as the consequence what both substances can bind with the same receptor of the cell.*

The substance wins, which is either in the organism in a greater concentration or contacts with receptors quicker in such competitive activity. It can be illustrated by the interaction of morphine and nalorphine - the substance used to treat acute morphine poisoning. They are structural antagonists; however, nalorphine has a greater affinity to the opiate receptors and binds with them, thus making toxic effect of morphine on the respiratory centre weaker.

This antagonism can be illustrated by the combination of antibiotics and sulphanilamides in treating inflammatory diseases, where the solution of novocain (para-aminobenzoic acid derivative) is used as the solvent for antibiotics. Para-aminobenzoic acid is included in the structure of folic acid synthesized by many microorganisms. As a result the bacteriostatic action of sulphanilamyde decreases since its mechanism is bound by competitive antagonism with para-aminobenzoic acid.

4.6. PHARMACOLOGICAL CONCEPT OF INCOMPATIBILITY

Indirect antagonism *is the opposite action of medicinal substances, which occurs within the range of different structures, i. e. they act purpose fully on different pharmacological receptors.*

For example:

- the combination of curare with strychnine for stopping convulsion in acute poisoning by strychnine - the convulsive reaction caused by excitement of one system (intrareceptoral bonds of the spinal cord) - is removed due to inhibition of the other system (direct transmission of the impulse from the nerve to the muscle);
- simultaneous introduction of atropine sulphate with promedol is inexpedient, because it leads to decreasing of the analgetic effect of promedol under the influence of atropine;
- aminazine should not be introduced with adrenaline hydrochloride, since the former reduces the vasoconstrictive action of the latter;
- aminazine should not be prescribed to patients with cardiovascular diseases who receive glycoside – containing medicines, as it decreases the effect of cardiac glycosides, arterial pressure, contributes to the occurrence of tachycardia and the myocardial ischemia is also possible.

Aminazine combined with soporific medicines decreases diuresis, because reabsorption of the liquid by the tubules apparatus of the kidneys changes.

4.6. PHARMACOLOGICAL CONCEPT OF INCOMPATIBILITY

Bilateral antagonism *occurs when the effects of medicinal substances mutually decrease regardless of order of their administration:*

- administration of substances stimulating and inhibiting the CNS. For example, in poisoning by somnolent medicines caffeine, corazol, phenamine are used. In the conditions of previous administration of stimulants the somnolent effect weakens.
- the effect atropine sulphate and pilocarpine hydrochloride on the pupil of the eye (its expansion or narrowing).

Unilateral antagonism *is when the use of one medicine eliminates the possibility of the subsequent action of another one.*

For example, aminazin removes the effects of noradrenaline and adrenaline completely. Additional introduction of these substances on the background of aminazin the previous introduction will not be accompanied by the increase in arterial pressure.

Partial antagonism *is when one of the substances removes only some effects of other substances.* It is the positive moment of medical practice for decreasing of sides effects of some medicines.

For example, when treating shock morphine hydrochloride is widely used, it removes the phenomena of overexcitement of the CNS, inhibits the respiratory centre, and that is extremely undesirable. Simultaneous introduction of atropine allows to avoid inhibition of the respiratory centre, without reducing the antishock effect of morphine on the cerebrum.

4.6. PHARMACOLOGICAL CONCEPT OF INCOMPATIBILITY

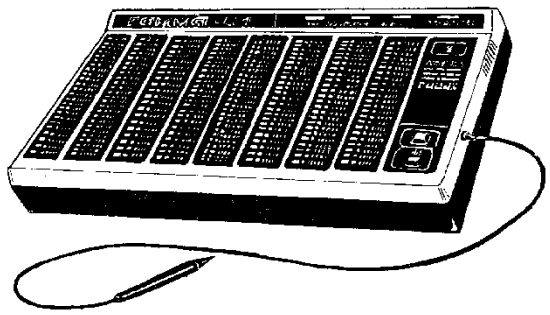
Synergism - antagonism *is the example of partial antagonism when medicinal substances are synergic in some effects and antagonistic in other ones.* This phenomenon is positive for medical practice. For example, combining of antituberculous remedies with vitamins:

- in treating acute pneumonia by streptomycin and ascorbic acid toxicity of antibiotics decreases notably and the dynamics of roentgenologic, laboratory and clinical indexes improves. Similar results are noted at combination of antituberculous medicines with pyridine-containing vitamins (nicotinic acid and pyridoxine).
- the wide-spread prescription of corticosteroid medicines under protection of antibiotics is also based on the phenomenon of synergism-antagonism.

In conclusion, it is necessary to draw your attention to the fact that there is no systematic approach to the solution of the question about compatibility of medicines in Ukraine. Pharmaceutical workers of each chemist's face such situations, and, revealing incompatibilities and overcoming difficulties, first of all, depend on the professional level of the specialist. In our opinion, one possible method of solving this problem is to use ***electronic database*** at the chemist's shops it allows find out the type of incompatibilities quickly and objectively, defer mine the risk of the during interaction. In some chemist's to verify the compatibility of a medicine the following device is used:

4.6. PHARMACOLOGICAL CONCEPT OF INCOMPATIBILITY

Gamma-FN-01



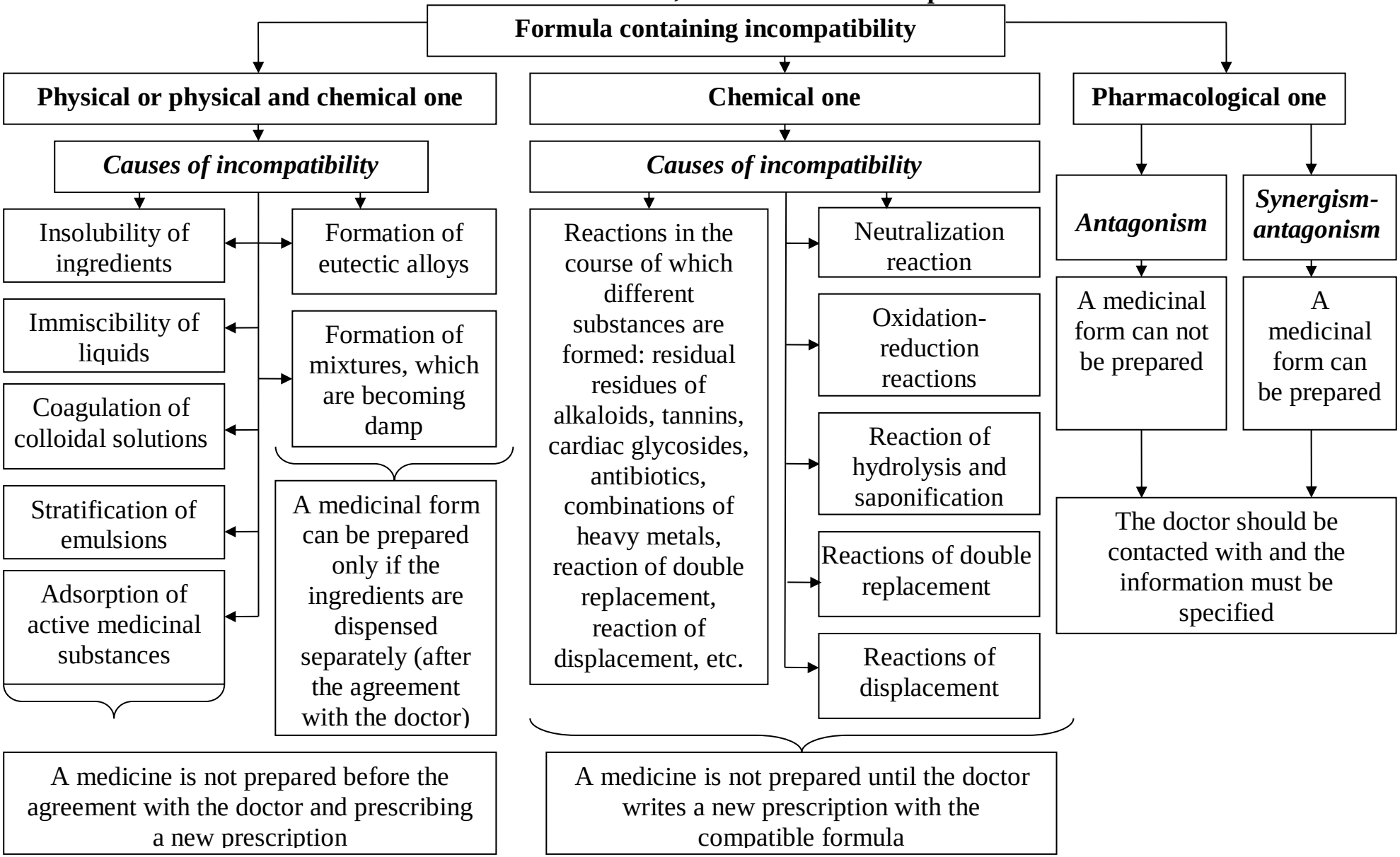
It contributes to the accessible quick and qualified solution of the combined pharmacotherapy problem. The only agreed actions of pharmaceutical and medical professionals allow to prescribe or determine the rational variants of combination of medicines.

In conclusion we would like to give the scheme of work with formulas containing incompatible combinations of ingredients (this scheme should make the work of the pharmacist easier when he has to decide what to do with such a formula).

4.7. QUESTIONS FOR SELF-CONTROL

1. Definition of difficult formulas and the ways of their removal (with giving the exact examples in different medicinal forms).
2. Cases of wrong prescribing of prescription for pharmacies.
3. Definitions of incompatibilities. Rights and duties of a pharmacist-technologist in regard to the wrong written prescriptions in accordance with to the requirements of the order of MPH of Ukraine dated the 30th of June, 1994.
4. Classification of incompatibilities.
5. Reasons of physical and physical and chemical incompatibilities.
6. Ways of removal of physical incompatibilities.
7. Definition and classification of chemical incompatibilities.
8. Classification of chemical incompatibilities by the types of chemical reactions.

Scheme of work with formulas, which contain in compatibilities



9. Classification of chemical incompatibilities by the visible signs of proceeding reactions in interaction of ingredients in different medicinal forms.

10. Reasons of formation of a residual substance in different medicinal forms.

11. Chemical incompatibilities, proceeding with discoloration, smell, selection of gases.

12. Chemical incompatibilities, proceeding without the visible external signs.

13. Incompatible combinations in medicinal forms with antibiotics.

14. Incompatibility of vitamin remedies.

15. Incompatibility in solid and liquid medicinal forms.

16. Incompatibility in soft medicinal forms.

17. «False» incompatibilities and their classification.

18. Concepts about pharmacological incompatibilities and their classifications.

19. Types of antagonism.

TESTS

1. Substances which increase chemical stability of medicines in solutions for injections are called:

A Stabilizers
B Regulators of osmotic pressure
C Preservatives
D Regulators of pH
E Regulators of viscosity

2. What the stabilizer used for preparation of Novocain solution for injection?

A Sodium methabisulfite
B Trilon B
C 0.1 M Hydrochloric acid solution
D Sodium hydroxide
E Sodium bromide

3. A pharmacist prepared a solution for anti-shock therapy. The concentration of alcohol in this solution is:

A 70 %
B till 33 %
C 40 %
D 60 %
E 90 %

4. What the isotonic agent used for 3 % solution of glucose?

A Sodium chloride
B Sodium sulphite
C Sodium bisulphate
D Sodium salicylate
E Sodium benzoate

5. What is the easily-oxidized substance requiring of antioxidants?

A Ascorbic acid
B Dimedrol
C Sodium chloride

D Sodium iodide
E Calcium gluconate