

**NATIONAL UNIVERSITY OF PHARMACY
TECHNOLOGY OF DRUGS DEPARTMENT**
Discipline “Pharmacy-based technology of drugs”
The topic of the lecture :



**“Difficult cases of
preparing medicinal
forms at the
chemist’s ”**

***A LECTURE FOR ENGLISH STUDENTS of THE 3-RD
COURSE IN THE SPECIALTY “PHARMACY”
Edited by associate professor Herasymova I.V.***

PLAN OF THE LECTURE

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1. Classification of medicinal formulas.
2. Difficult cases of preparation medicines.
3. Examples of difficult formulas
4. Classification of incompatibilities.
5. Insolubility or bad solubility.
6. Unmixing of ingredients.
7. Absorption of water by powders.
8. Melting a mixture of solid substances.
9. Coagulation of colloidal solutions and HMC.
10. Destruction of emulsions.
11. Absorption of active substances.

Questions for self-control

**Peculiarities of different substances
introduction into medicinal forms**

References:

1. Tikhonov A.I., Yarnykh T.G., Yuryeva A.B., Garkavtseva O.A. **Chemist's Technology of Drugs: The manual for students of higher schools** / Ed. by A.I. Tikhonov and T.G. Yarnykh. – Kharkiv: NUPh; Original, 2011. – 424 p
2. **Dry, liquid and soft medicinal forms.** A textbook for English students in speciality “Pharmacy” / A.I. Tikhonov, T.G. Yarnykh, A.B. Yuryeva, L.N. Podorozhna, S.S. Zuykina; Ed. by A.I. Tikhonov. – Kharkiv: NUPh; Original, 2011. – 208 p.
3. Tikhonov A.I., Yarnykh T.G., Yuryeva A.B., Podorozhna L.N., Zuykina S.S. **Biopharmaceutics.** Lectures for English students on the speciality “Pharmacy”: a handbook for the out-of-class work of students/ edited by acad. A.I. Tikhonov. – Kharkiv: NUPh, Original, 2011. – 140 p.

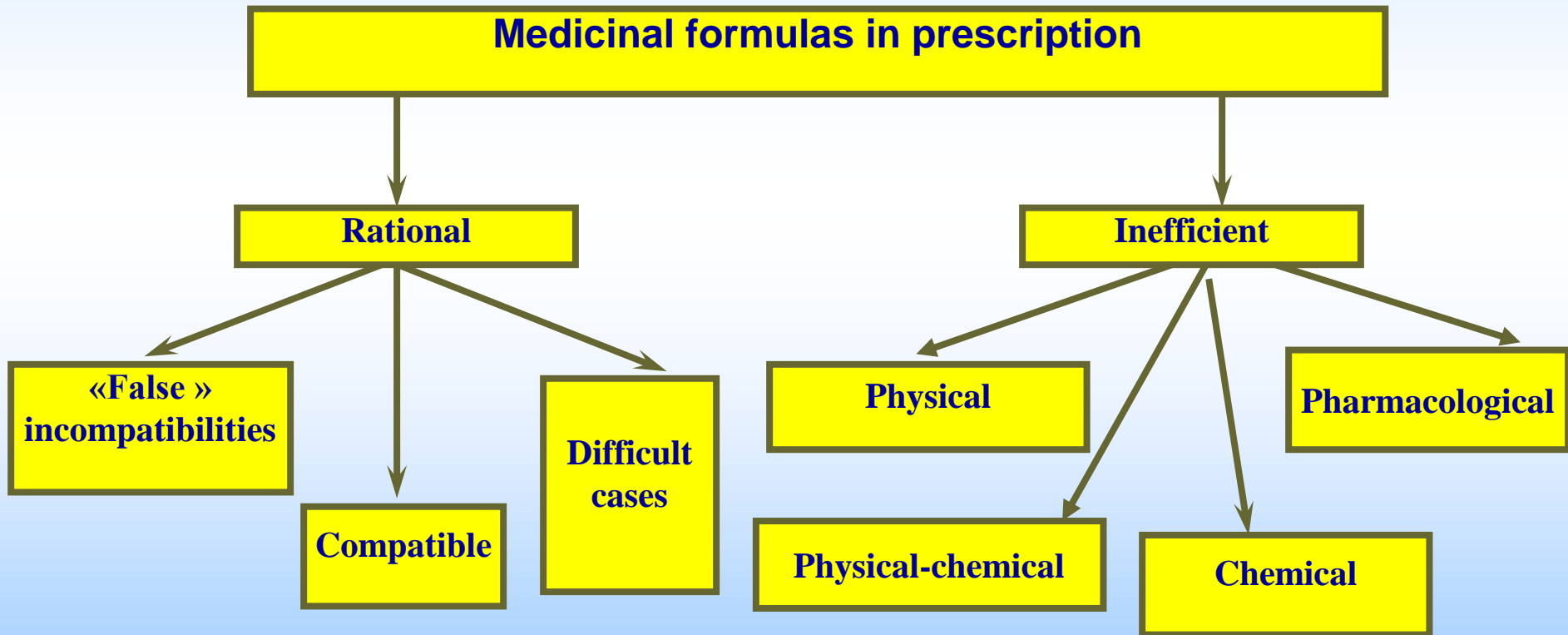
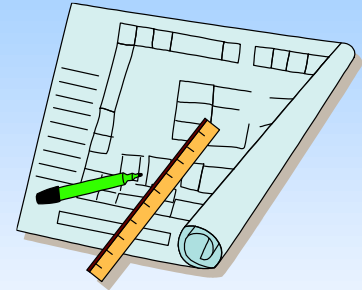
1. Classification of medicinal formulas

Sometimes in pharmacy practice a doctor decides the task of selection of necessary medicinal substances one-sided : takes into account only a pharmacological side and does not take into account a possibility of combination of medicinal substances depending on physical and chemical properties in one medicinal form.

In this case are form incompatibilities as a result.

1. Classification of medicinal formulas

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2. Difficult cases of preparation

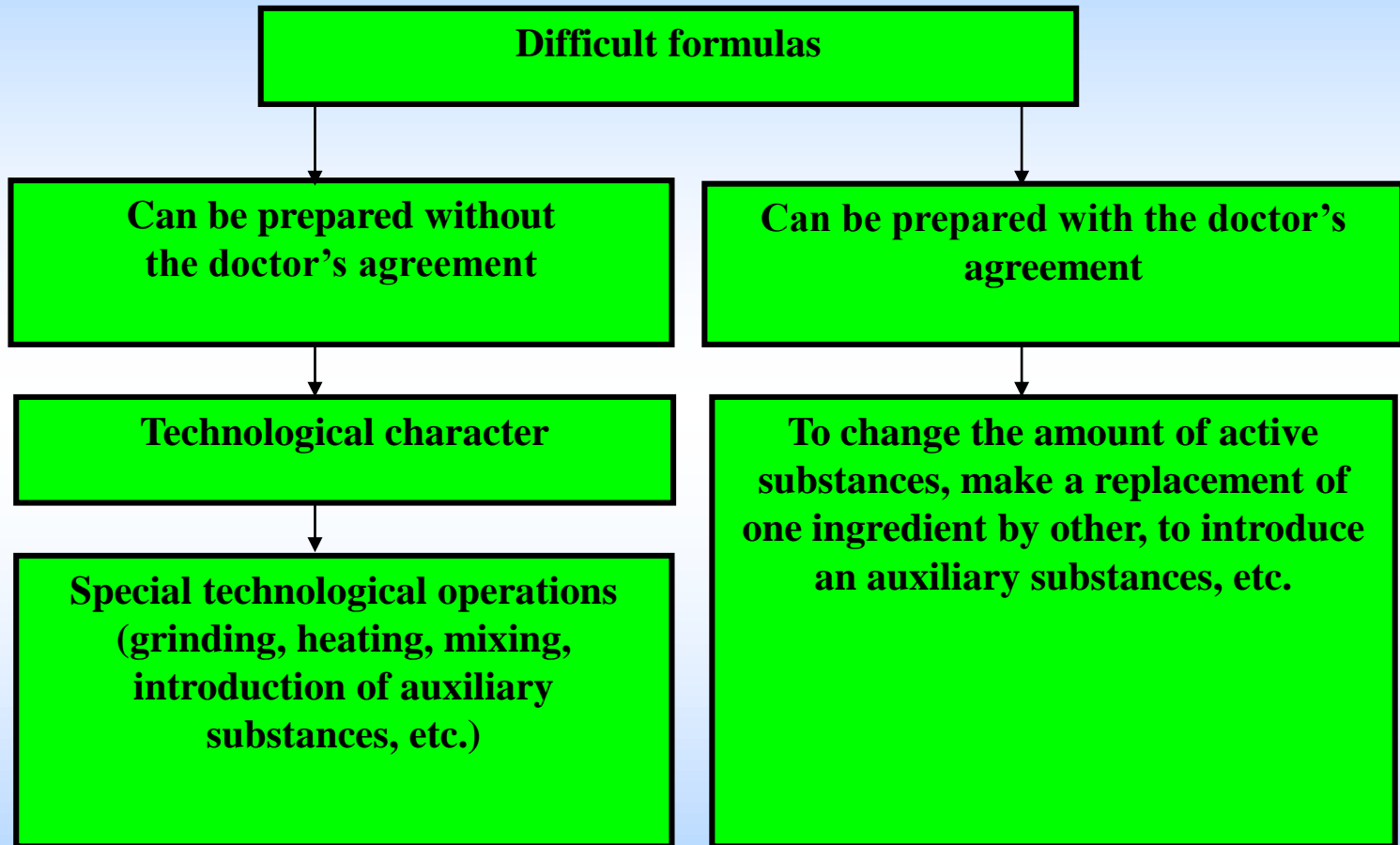
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The difficult formulas are such combinations of medicinal substances when a pharmacist can prepare a medicine using special technological operations. Thus, it is possible to avoid incompatibilities and to dispense a high-quality effective medicine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



2. Difficult cases of preparation

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3. Examples of difficult formulas

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

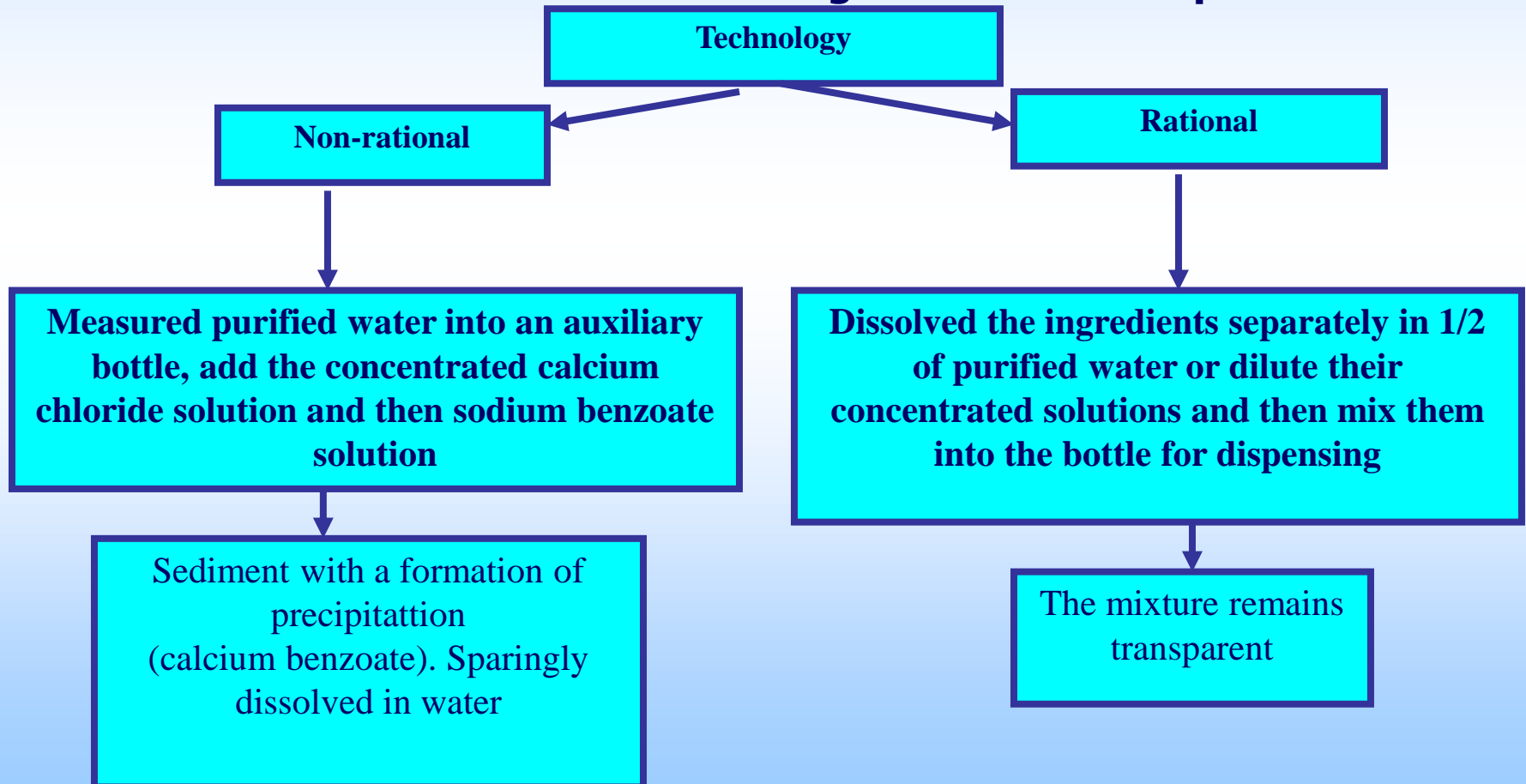
Rp.: Natrii benzoatis 4.0

Calcii chloridi 5.0

Aquae purificatae 150 ml

Misce. Da.

Signa. Use 1 table spoon 3 times a day.



3. Examples of difficult formulas

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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

3. Examples of difficult formulas

**Rp.: Acidi salicylici 2.0
Ichthyoli 10.0
Spiritus aethylici 40 ml
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 $\frac{1}{2}$ 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

4. CASES OF WRONG FORMULAS IN PRESCRIPTIONS, GETTING INTO PHARMACIES.

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Cases of wrong prescribing

A brigher dosing of narcotic, poisonous, and strong-effective medicines

A prescription form is chosen incorrectly

A prescription is written in Russian

Wrong order of prescribing

Absence of stamps, signatures

Wrong medical purpose

Incompatibility of a formula

**“Physical-chemical
incompatibilities”**

1. Classification of incompatibilities.

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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.

1. Classification of incompatibilities.

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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.*

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

2. Insolubility or bad solubility

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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.*

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

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.

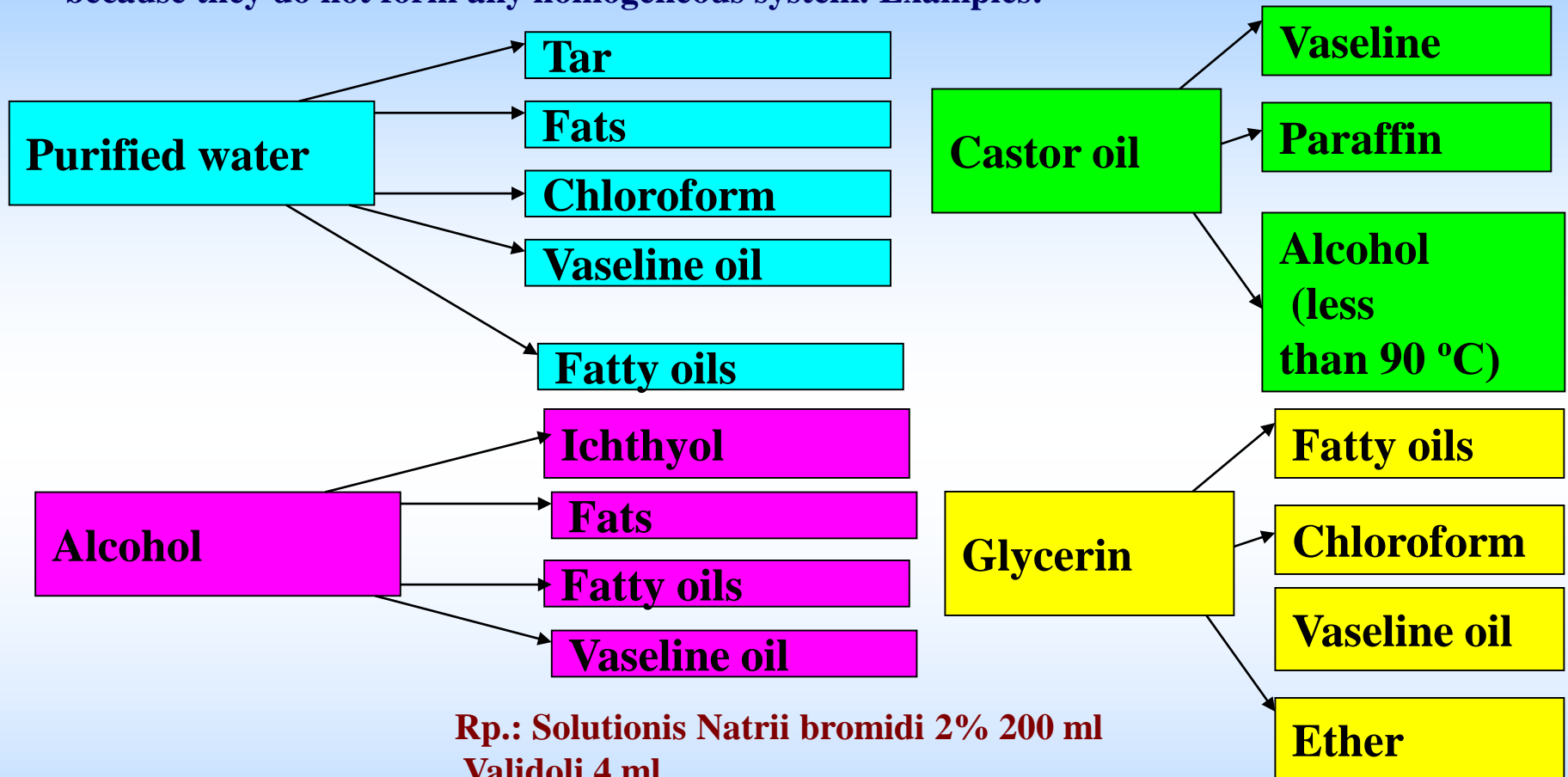


Rp.: Sol. Calcii chloridi 10 % 200 ml
Papaverini hydrochloridi 0.2
Misce. Da. Signa. Use 1 table spoon 3 times a day.

3. Immiscibility of ingredients

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



Rp.: Solutionis Natrii bromidi 2% 200 ml
Validoli 4 ml
Misce. Da.
Signa. 1 table spoon 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. Dampening of a mixture with solid substances

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Cases of dampening

A mixture of powders is more hygroscopic than its ingredients

Admixture of calcium or magnesium chloride in sodium chloride

Mixture of potassium bromide and sodium bromide

Formation of double salts with less amount of crystalline water

When mixing sodium sulphate ($10\text{H}_2\text{O}$) and magnesium sulfate ($7\text{H}_2\text{O}$) a double salt astrakhanite ($4\text{H}_2\text{O}$) with 4 molecules of water is formed

Formation of hygroscopic mixtures as a result of the neutralization reaction

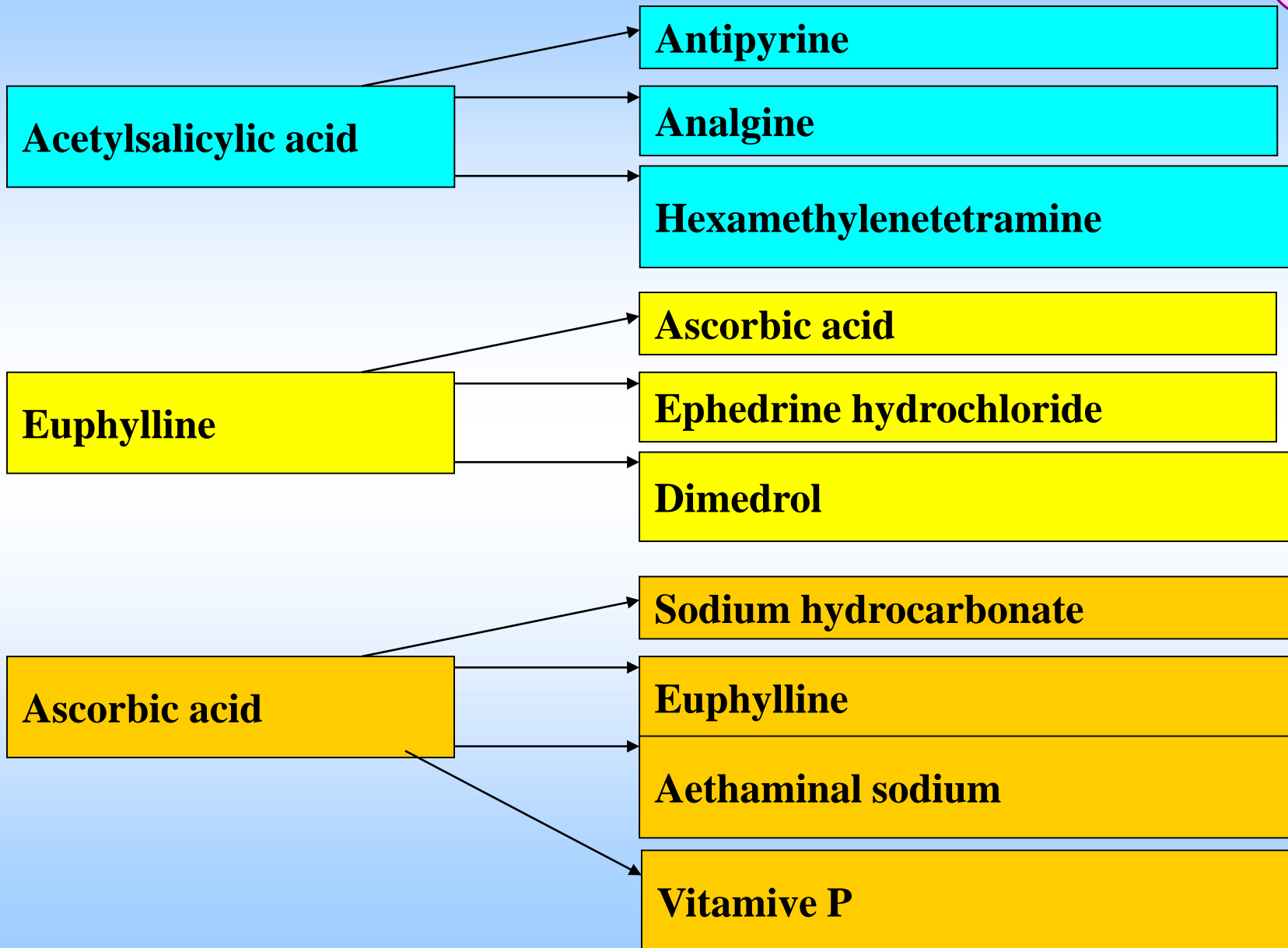
When mixing acetylsalicylic acid and hexamethylenetetramine water is evolved

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.*

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

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5. Melting of a mixture of solid substances

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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):

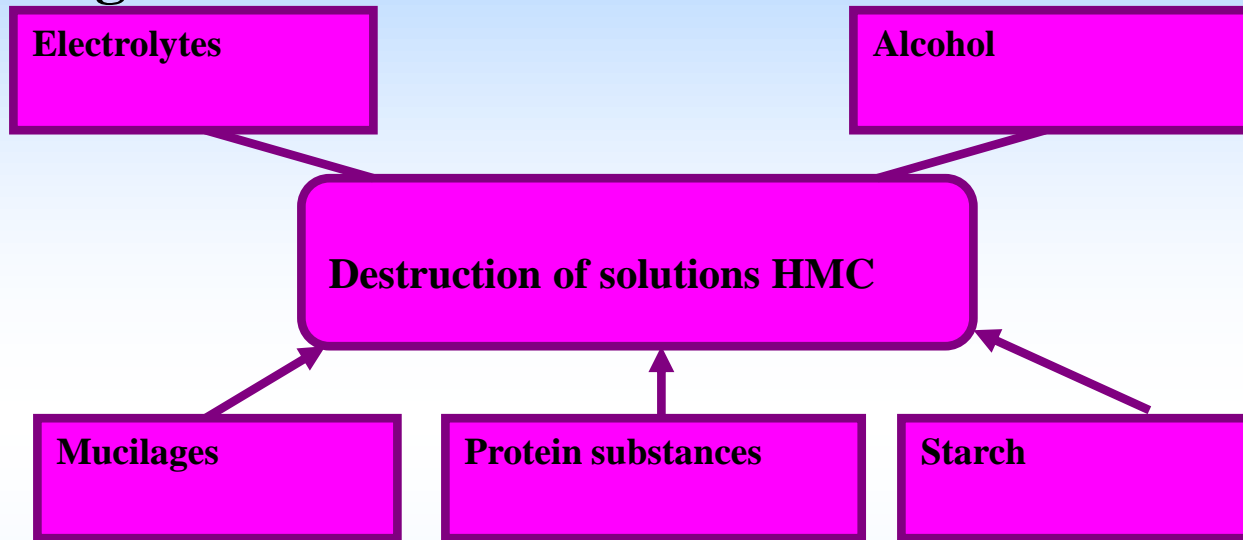
- for obtaining of a liquid medicine;
- for more even distribution of a medicinal substance in the mixture of powders.

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 Phenylis 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

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

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Solutions of HMC and protected colloids are instable while storing.



Rp.: Solutionis Calcii chloridi 5 % 180 ml
Extracti Polygoni hydropiperis fluidi 20 ml
Misce. Da.
Signa. 1 table spoon each hour.

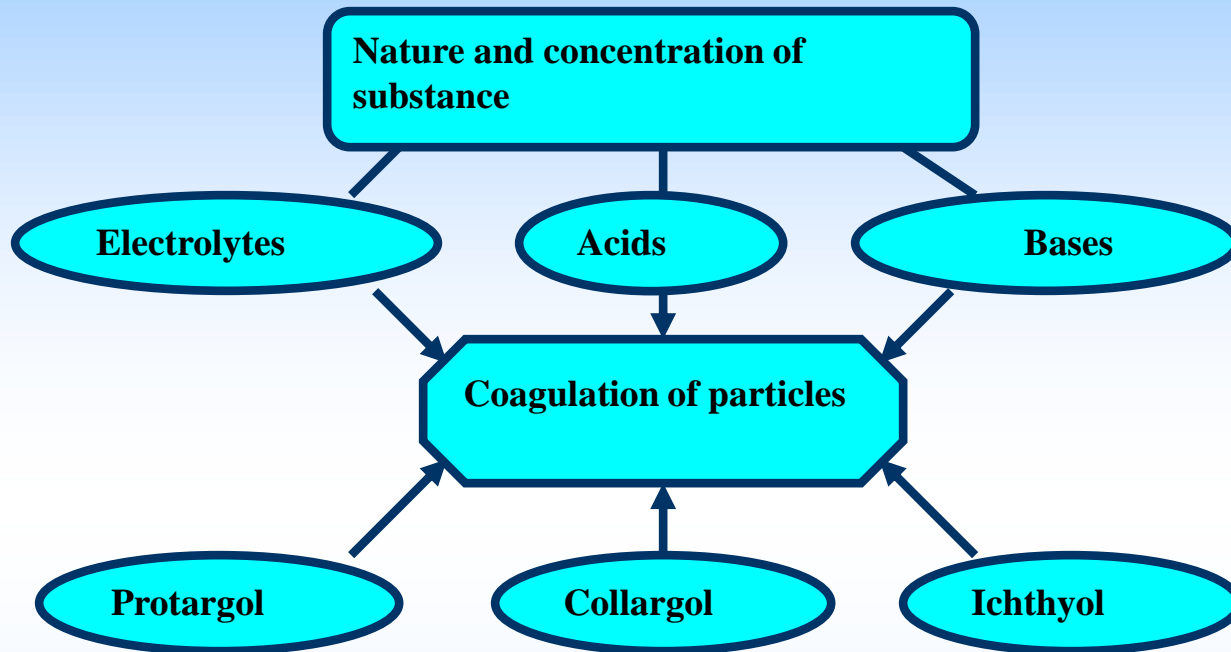
Under the influence of external factors the processes causing their destruction occur in the solutions of HMC:

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

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

6. Coagulation of colloidal solutions and HMC

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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.

7. Destruction of emulsions

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One of reasons of physical-chemical incompatibilities is destruction of emulsions. These processes take place at influencing:

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

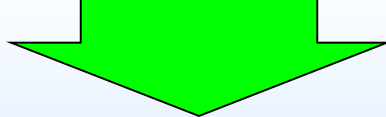
Rp.: Emulsi oleosi 100.0

Natrii sulfatis 10.0

Misce. Da.

Signa. 1 table spoon 3 times a day.

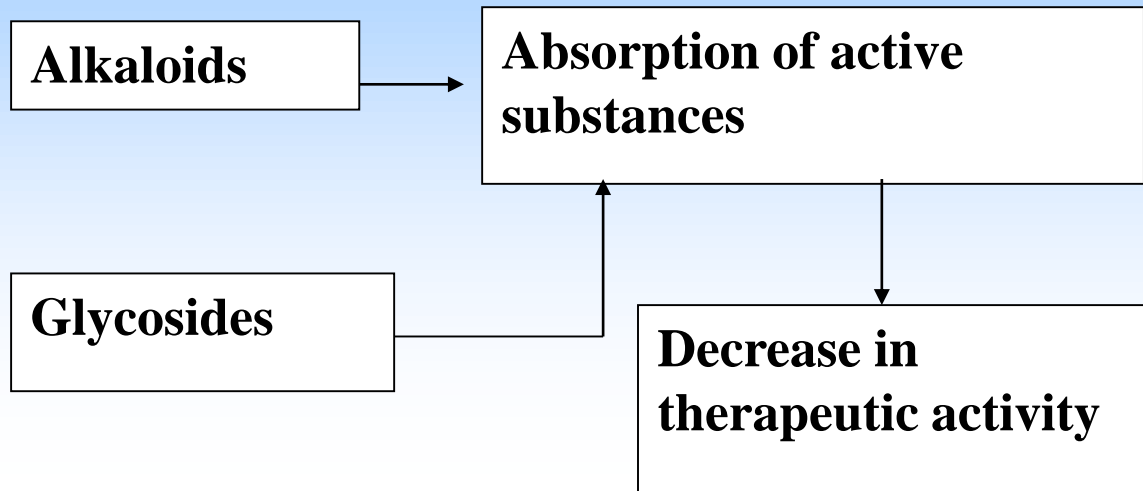
Solutions of electrolytes add
in emulsion only in the
dilute state and by portion.



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

8. Absorption of active substances

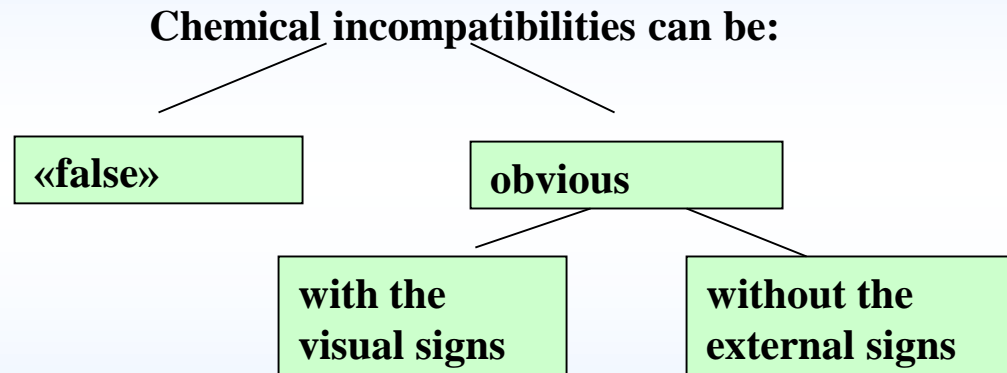
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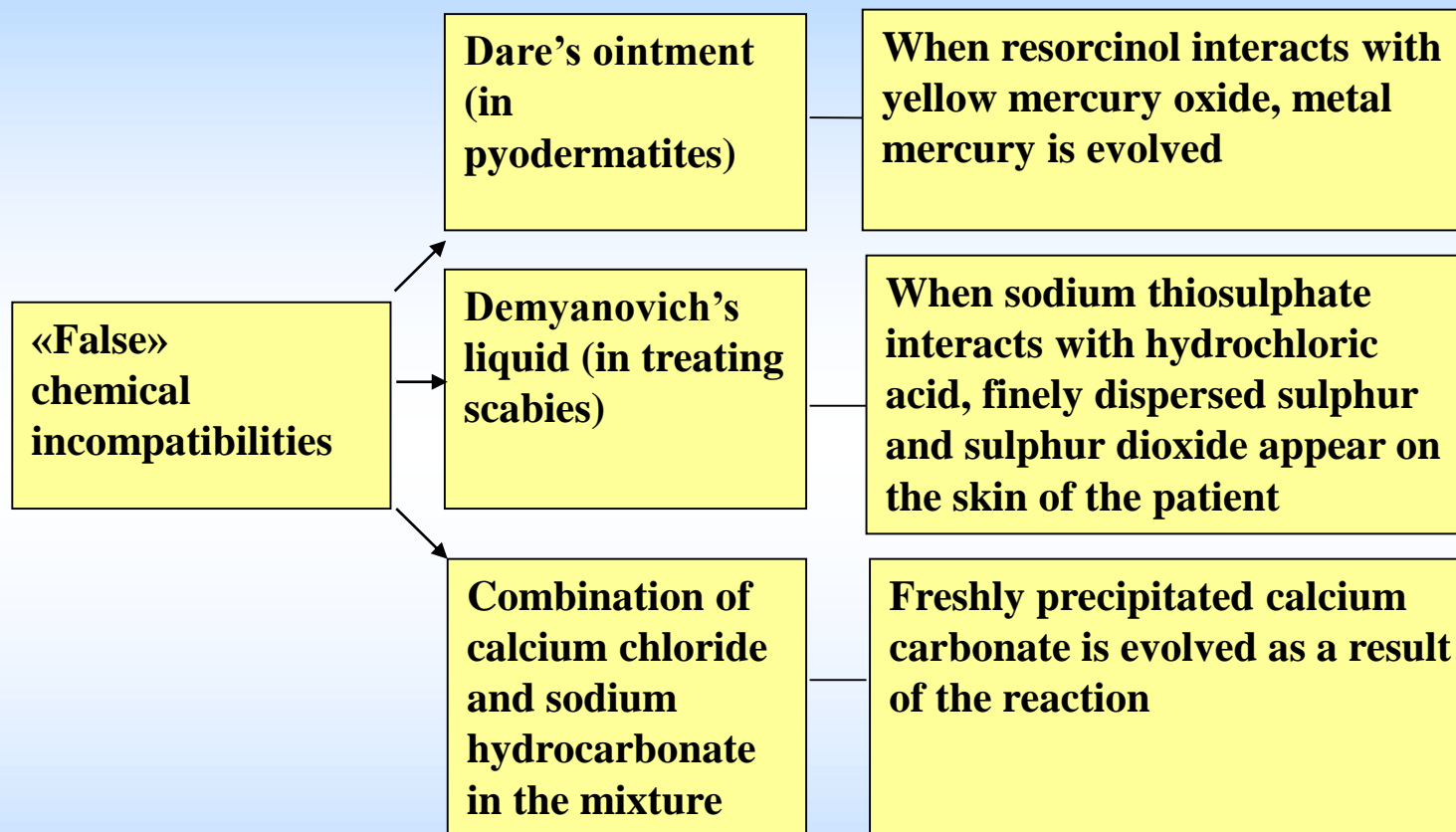
- coal
- aluminum hydroxide
- white clay;
- vegetable powders

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.*



«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.



The character of interaction between medicinal substances depends on:

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

Classification of chemical incompatibilities

**By the type
of chemical
reactions**

**By the visual signs of
chemical
reactions**

**By the type
of chemical
reactions**

Oxidation-reduction reactions

Displacement reactions

Exchange decomposition reactions

Hydrolysis reactions

Neutralization reactions

Oxidation-reduction reactions

Rp.: Argenti nitratis 0.5

Anaesthesini 1.0

Vaselini 25.0

Misce fiat unguentum.

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 unguentum.

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 manganese dioxide (a dark-brown residue).


The colour of the mixture turns to dark green.

Conclusions


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1. **Classification of medicinal formulas was discussed.**
2. **Difficult cases of preparation medicines were explained.**
3. **Examples of difficult formulas were considered.**
4. **Classification of incompatibilities was discussed.**

A pharmacist refused preparation of nasal drops to a patient because of incompatibility between collargol and dimedrol written in the prescription. What is the reason for incompatibility between these ingredients?

- A. Coagulation 
- B. Immiscibility
- C. Adsorption
- D. Dissection
- E. Eutectic formation

A pharmacist has revealed an incompatibility in the prescription. What drug substances form an eutectic mixture?

- A. Sodium hydrocarbonate + hexamethylenetetramine
- B. Chloral hydrate + camphor 
- C. Antipyrine + analgin
- D. Calcium chloride + sodium chloride
- E. Ephedrine hydrochloride + glucose

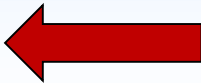
A pharmacist revealed physical incompatibility caused by coagulation. This process takes place in a solution if the combination of the following substances is present:

- A. Dimedrol and sodium chloride
- B. Dimedrol and glucose
- C. Dimedrol and collargol
- D. Dimedrol and novocaine
- E. Dimedrol and diazoline



What technology should be chosen by a pharmacist to make a liquid dosage form, if it contains calcium gluconate?

- A. Dissolve it in hot solvent or heat it up to full dissolution
- B. First grind it to powder when it is dry or with small amount of solvent added
- C. Dissolve in water free of redox substances
- D. Add equal amount of sodium chloride



A pharmacist prepared the 2% aqueous solution by dissolving the drug substance triturated in a mortar. What substance is this technology typical for?

- A. Potassium permanganate
- B. Calcium gluconate
- C. Osarsolum
- D. Boric acid
- E. Potassium bromide



It is required to prepare furacilin solution (1:5000). What is the dissolution peculiarity of furacilin?

- A. It dissolves in the cold purified water
- B. It dissolves in a minimal amount of ethyl alcohol
- C. It dissolves in the purified water after the trituration
- D. It dissolves in the filtered purified water
- E. It dissolves in the boiling water purified in the presence of sodium chloride





Thank you for attention!