# Disperse systems I.
# EMULSIONS

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# Emulsions

## Definition of emulsion

Emulsions – as dosage forms – are **externally** or **internally** used **liquid** pharmaceutical preparation, which contain **minimum two immiscible liquids** where one of the two phases is **dispersed** within the other liquid phase.

# Emulsions

## Definition of emulsion

Emulsions are liquid heterogeneous, L/L type, disperse systems.

Multi-phase and – multi-component systems.

If the size of the emulsified particles is in the colloidal range than the system is called **colloid emulsion.**

# Emulsions

## Definition of emulsion

The **externally** used emulsions are usually called

**liniments (linimentum),** but

**not the all** (in name) liniments are emulsion.

*(Linimentum scabicidum)*

# Theoretical basics of emulsions

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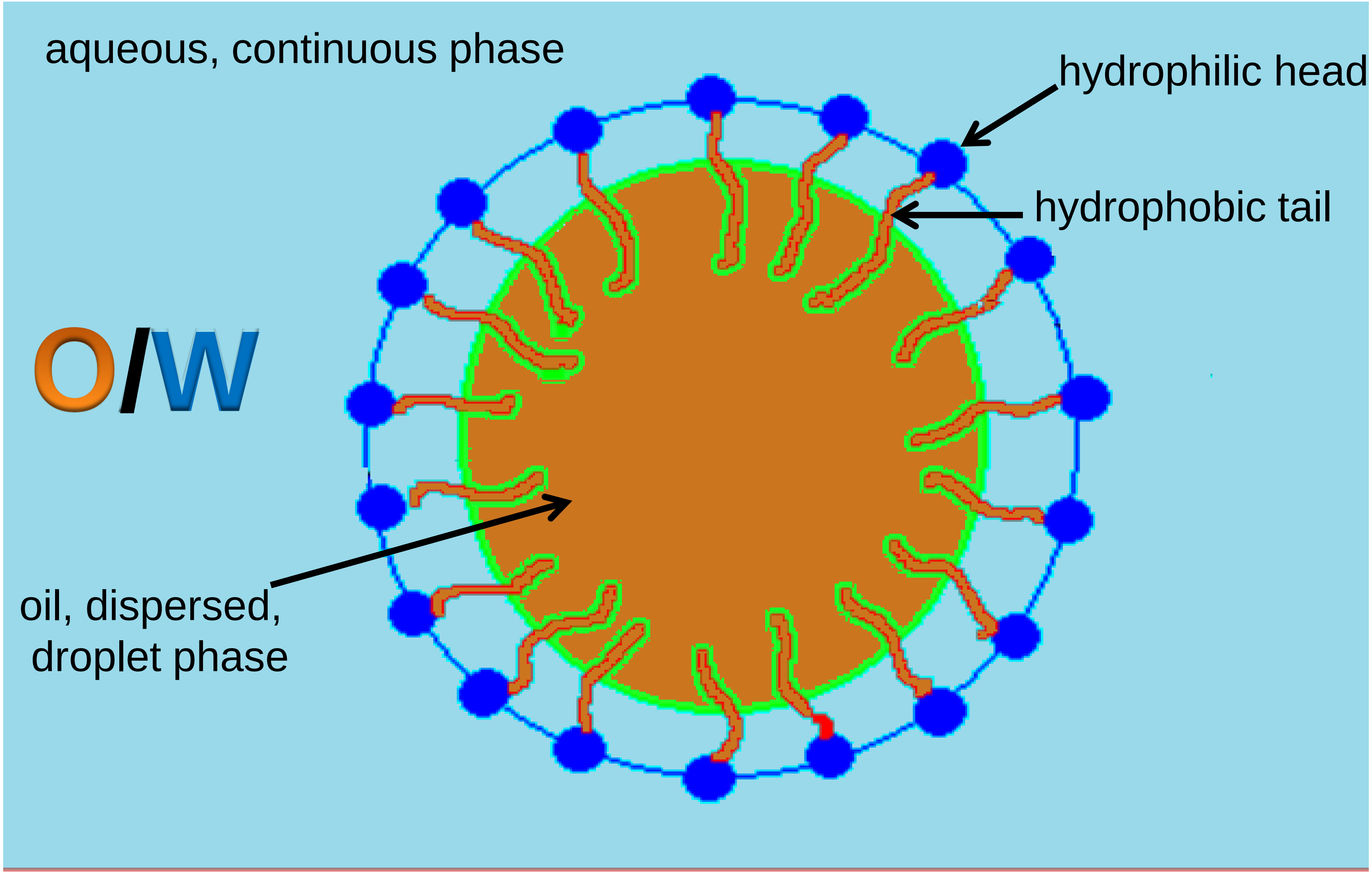
# Theoretical basics of emulsions

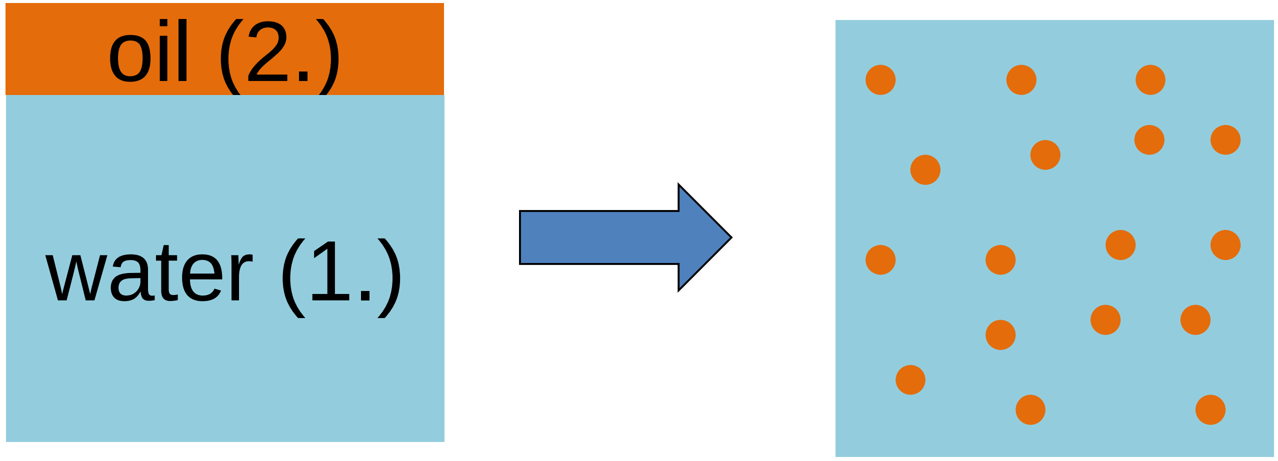


# Theoretical basics of emulsions

During the preparation of emulsions:

1. no changes in number of components or phases,

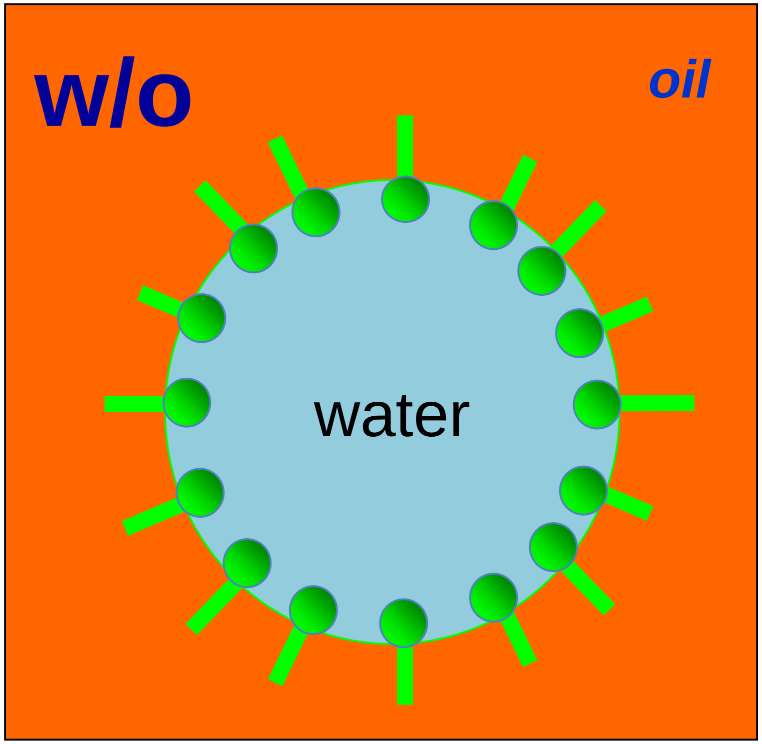
2. just the interfacial surface is increased

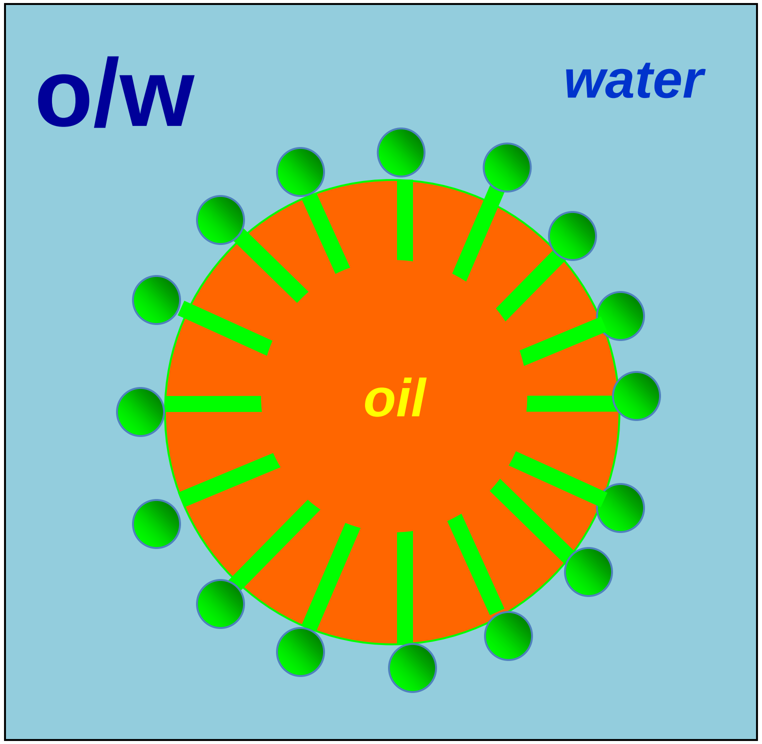


# Theoretical basics of emulsions

## Components of emulsions

1. Inner, disperse phase
2. Outer, continuous, disperse phase
3. Emulsifying agent, surfactant (generally)



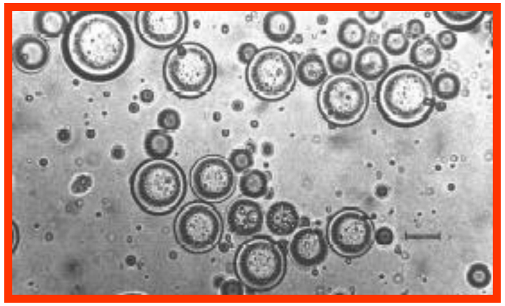



# Theoretical basics of emulsions

The **work/energy (*L*)** of manufacturing of emulsions is proportional to the surface tension and surface area.

The energy is necessary to ensure the formation of immiscible liquid droplets with small diameter in a continuous phase.

During this process, a **surface increasing** happens. (The work is necesary to overcome the surface tension.)



$$L = \gamma dF$$

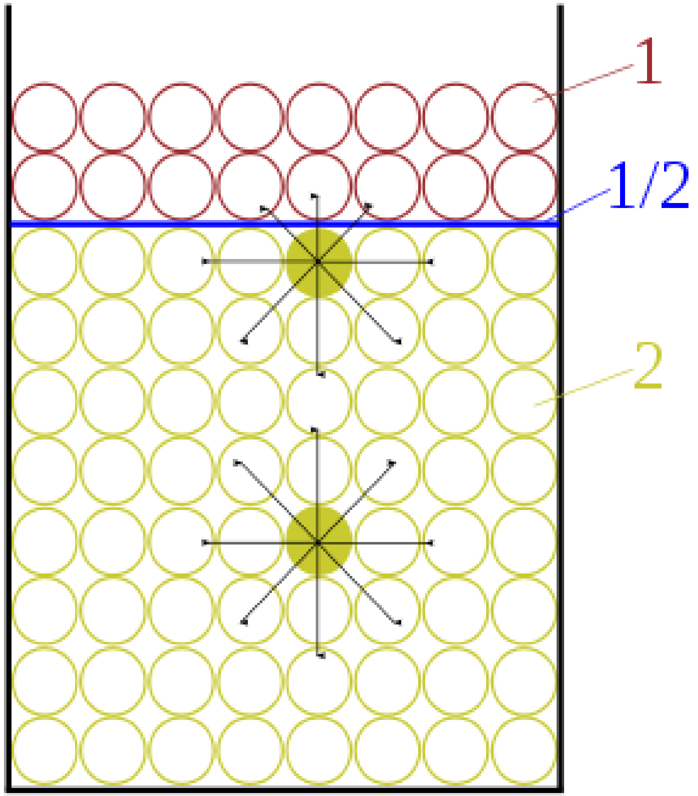
$L$ = work (the required energy)
$\gamma$ = surface tension
$F$ = surface area

# Theoretical basics of emulsions

## Surface tension

**Definition:**

**Surface tension** is a **contractive tendency** of the surface of a liquid that allows it to resist an external force.




Decreasing the surface tension with chemicals is not enough by its own for formation of an emulsion, but it is able to assist in it.

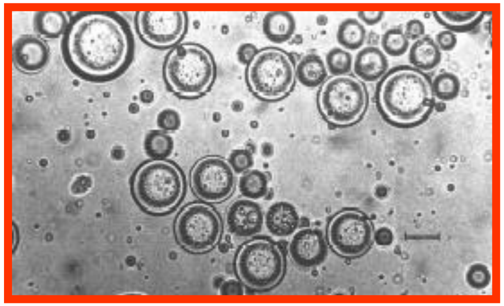
# Theoretical basics of emulsions

## Surface tension

**Antonov equation**

$$\gamma = \gamma_1 - \gamma_2$$

The **surface tension** can be calculated by the **interface voltage between two non-miscible fluids**.



$\gamma$ = surface tension

$\gamma_1$ = surface tension of liquid one

$\gamma_2$ = surface tension of liquid two

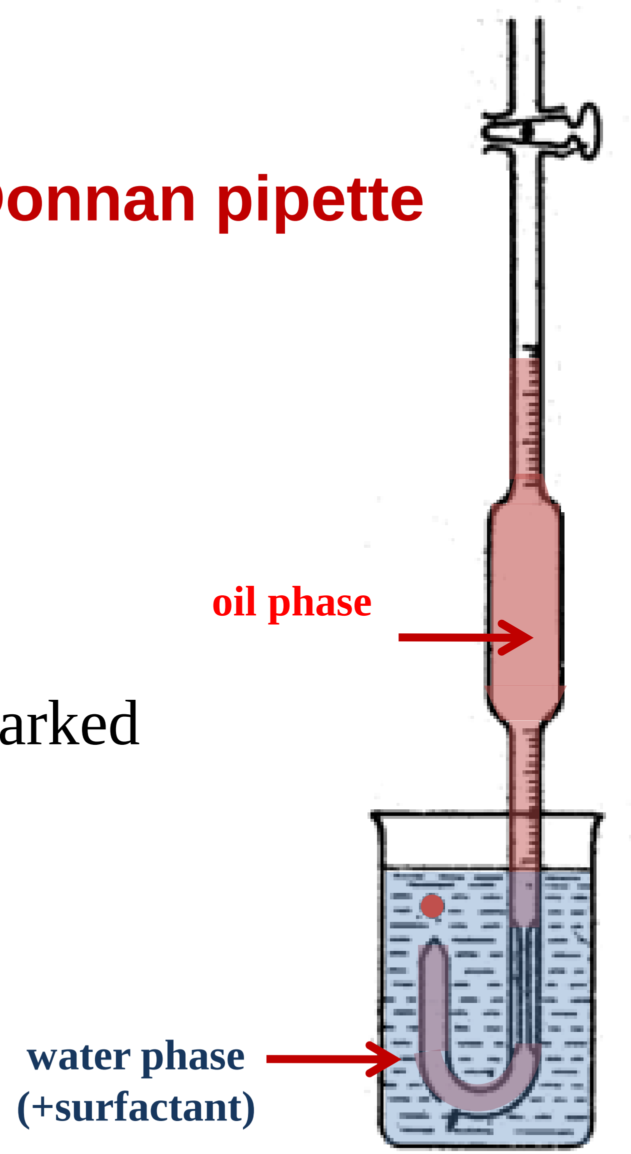
# Theoretical basics of emulsions

## Examination of surface tension

$$\gamma = \frac{v\,\Delta\rho\,g}{2\pi r k}$$

$$v = \frac{V}{n}$$

Donnan pipette




*v* volume of one drop

*n* drop number

*V* volume of Donnan-pipette what is marked between the two marked lines

*r* radius of the capillary,

*k* correction factor,

*Δρ* density difference

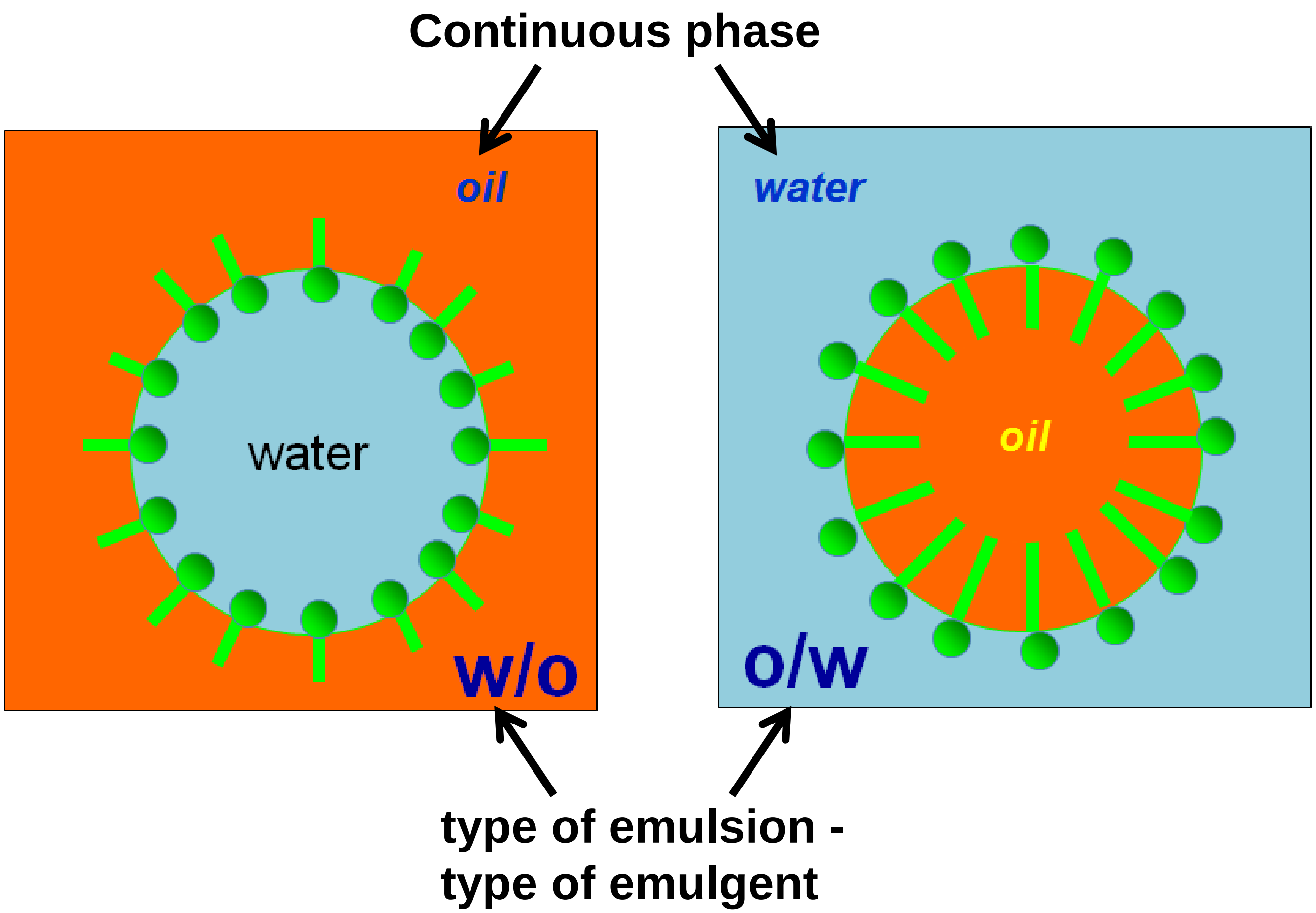
*g* gravity

# Theoretical basics of emulsions

## Orientation theory

**Bancroft‘s rule :**

***The liquid in which the surfactant has a higher solubility forms the continuous phase.***



# Theoretical basics of emulsions

## Phase-volume coefficient

$$F = \frac{V_i}{V_e}$$

$V_i$ = volume of the **internal** phase

$V_e$ = volume of the **external** phase

| | |
|---|---|
| $F < 0.3$ | low internal phase ratio (lotion) |
| $0.3 < F < 0.7$ | medium internal phase ratio (cream) |
| $F > 0.7$ | high internal phase ratio (ointment) |

**Phase inversion:**

**If the internal phase ratio is more than 0.74 (74%)!**

# Theoretical basics of emulsions

## Surfactants

Why do we ***add surfactants*** to the system at preparation of an emulsion?

- The type of the surfactant can **influence the type of the emulsion** (w/o, o/w) (*see Bancroft's rule*).

- The surfactant can **decrease the surface tension** and so the work needed during the preparation process.

- Surfactants are able to **enhance the stability** of the system.

# Theoretical basics of emulsions

**Emulsion number**

Characterizes the **emulsifying properties** of **emulsifying agents**

$$E_N = \frac{V_E - V_O}{V_E} * 100$$

*$E_N$ = emulsion number*
*$V_E$ = volume of the emulsified oil*
*$V_O$ = volume of separated oil*

# Stability of emulsions

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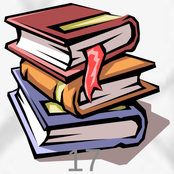
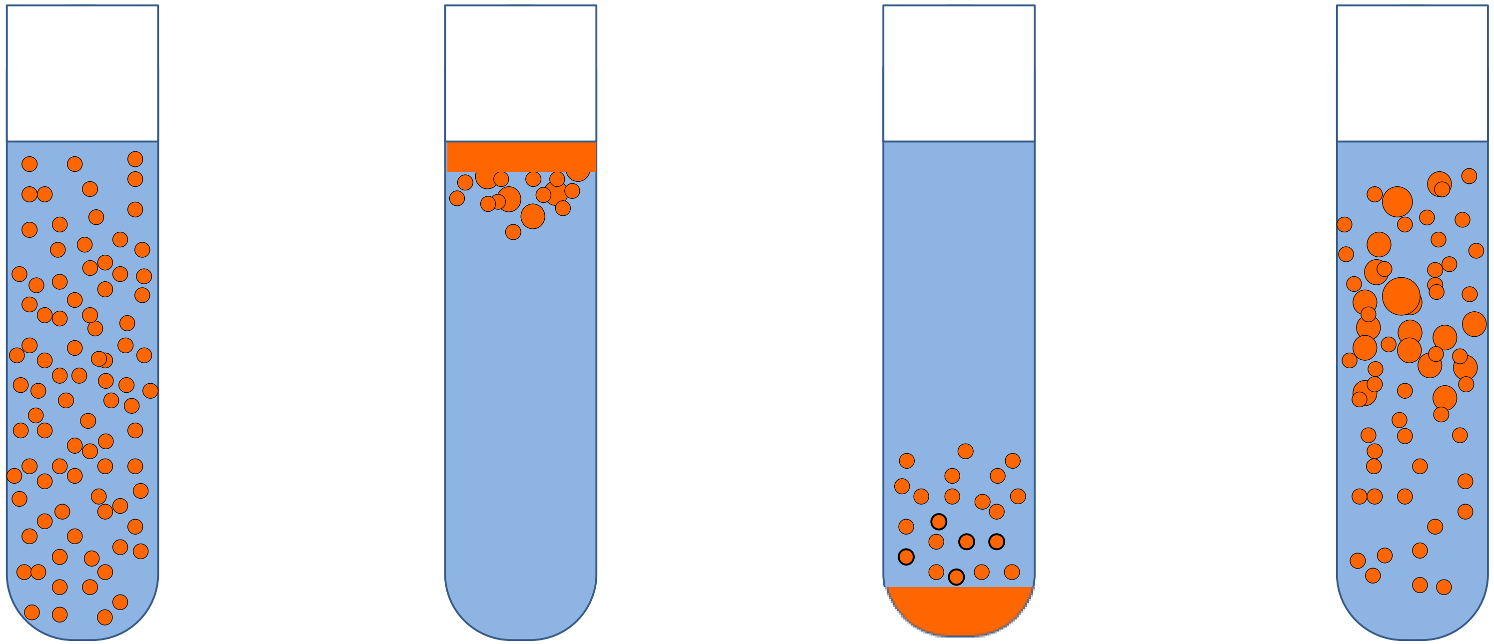


# Stability of emulsions

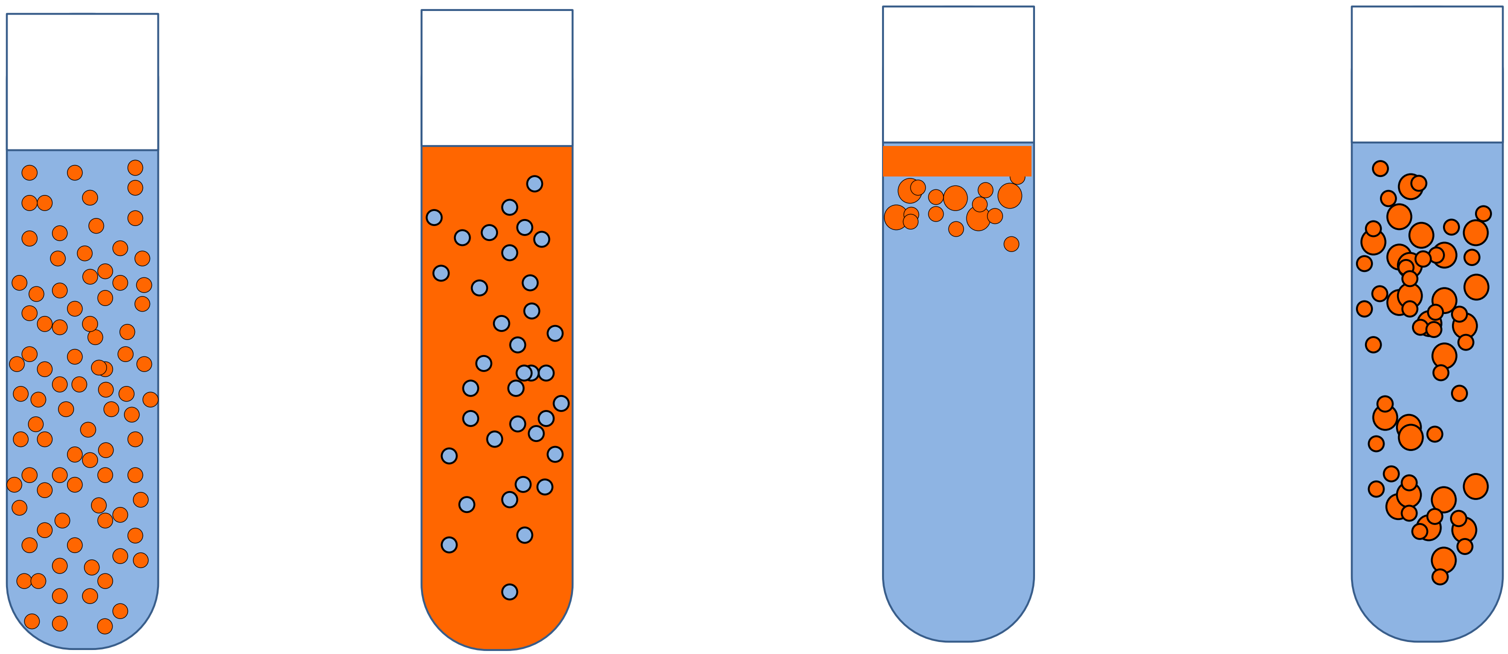
## Transforming



| | | | |
|---|---|---|---|
| initial emulsion or suspension | creaming emulsion | settling suspension, sedimentation | flocculation, aggregation, suspension, emulsion |

# Stability of emulsions

## Transforming



initial emulsion
or
suspension

phase
inversion
emulsion

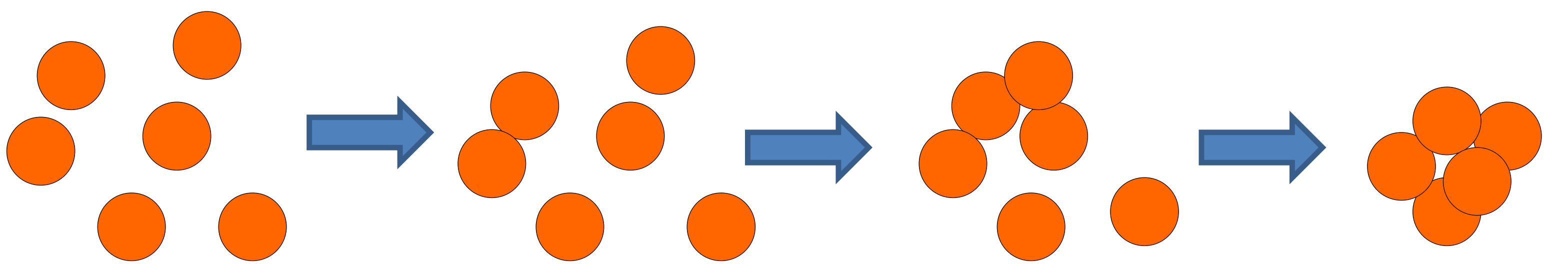
coalescence,
phase separation,
oiling emulsion

Ostwald
ripening
emulsion

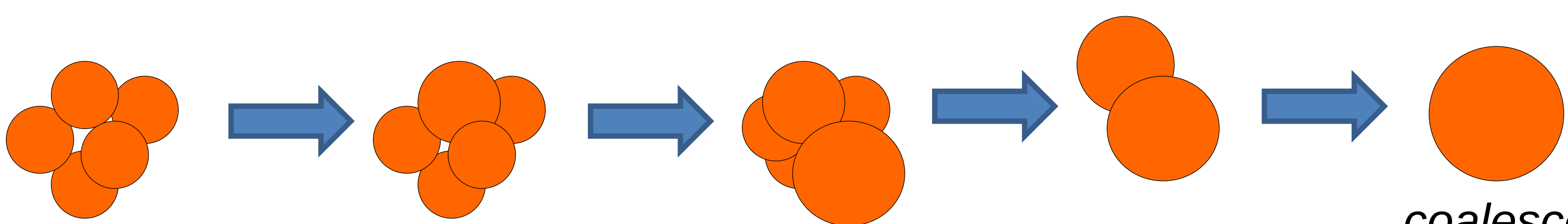
# Stability of emulsions

## Transforming

**Flocculation:** *aggregation of droplets* ***without coalescence****.*



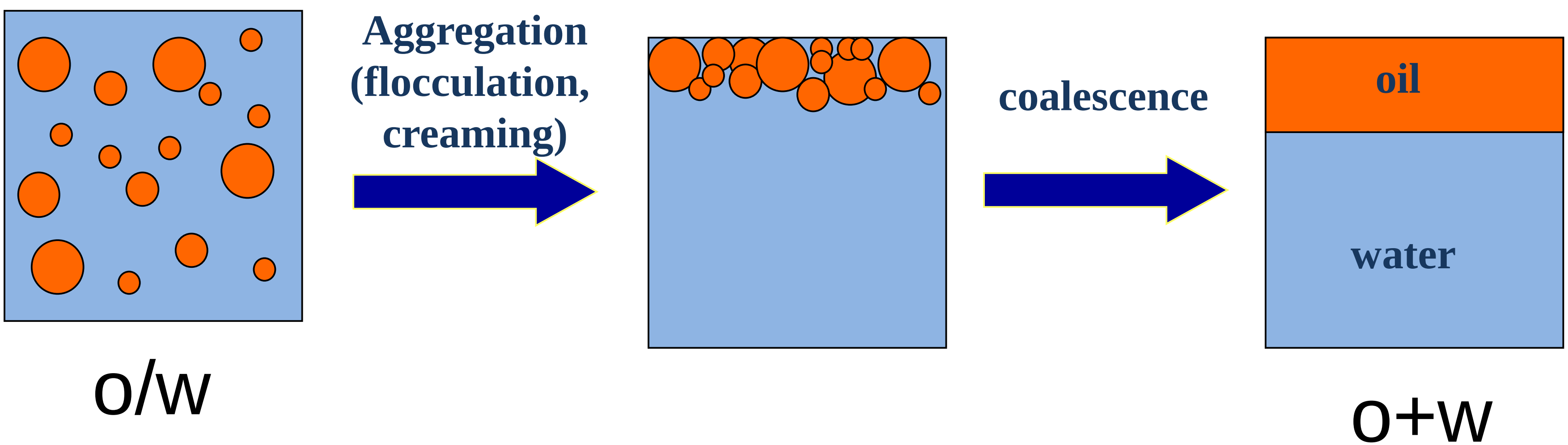

**Coalescence:** *aggregation due to* ***fusion*** *together of two or more individual droplets to* ***form a bigger drop****.*



# Stability of emulsions

## Transforming

Phase separation of emulsions



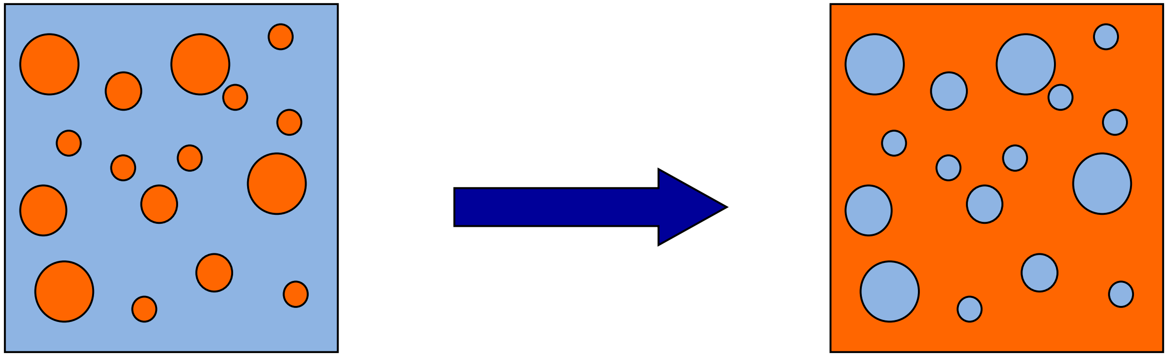
# Transforming

**Ostwald ripening:** *growth of large droplets* ***due to molecular diffusion*** *of oil molecules through the aqueous phase.*

# Stability of emulsions

## Transforming

Phase inversion



o/w

w/o

# Stability of emulsions

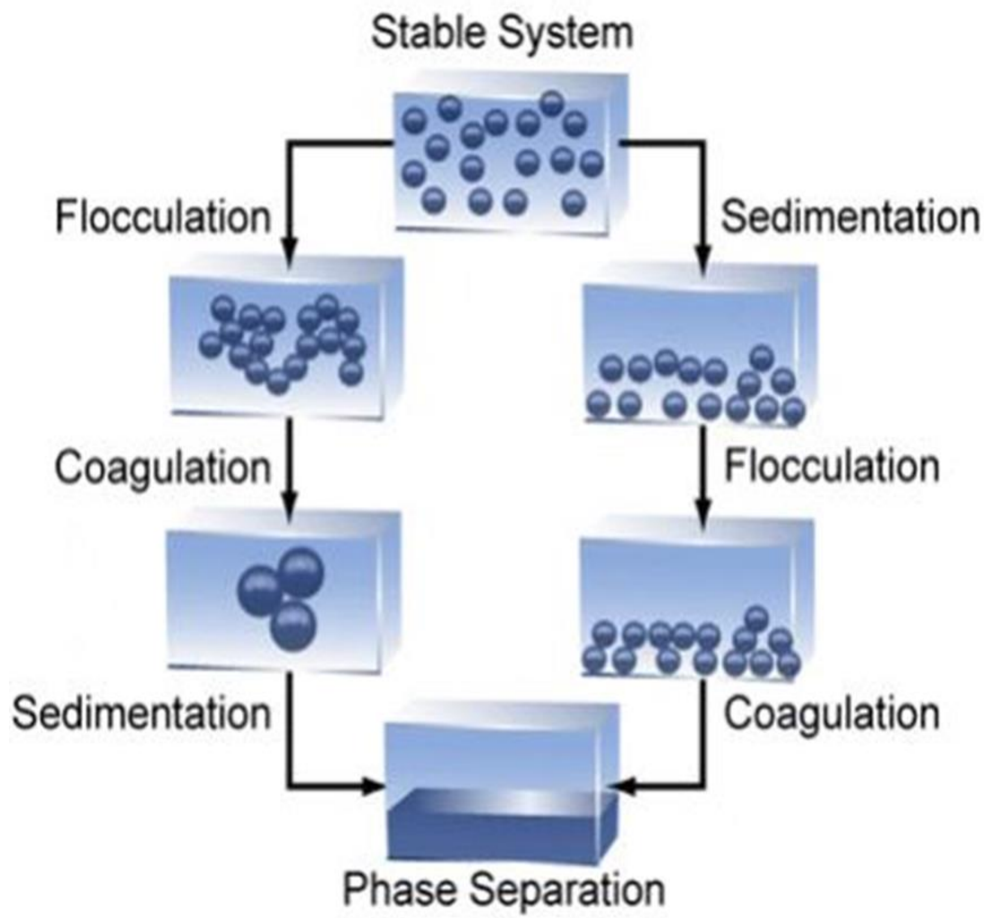
**The aggregative properties of the emulsions are influenced by:**

Interfacial **surface, charges, mechanical resistances**, (these can prevent to the confluence of the particles into a one whole (large) drop).

This layer depends on:
- the chemicals with polar and apolar groups,
- electrolytes,
- pH.

# Stability of emulsions

- Physical (kinetical) stability
- Chemical stability
- Microbiological stability



# Stability of emulsions

**The physical stability of emulsions depends on**

- Constancy of dispersion degree
- Drop size distribution
- Surface charge

# Stability of emulsions

**The surface layer depends on**

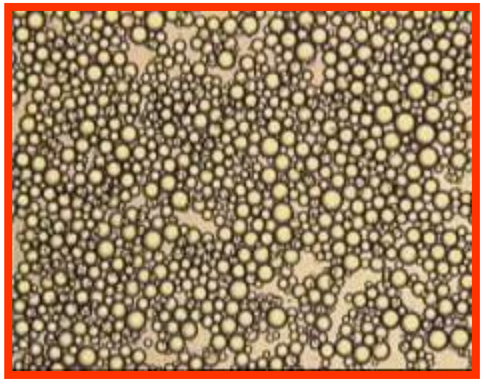
- compounds having **polar** and **apolar parts**,
- **electrolytes** (value),
- from **pH**.

# Physical stability of emulsions

## Stoke's law:

*stability of dispersion*
*(sedimentation, speed of separation)*

$$v_s = \frac{2r^2(\rho_2 - \rho_1)g}{9\eta}$$



$v_s$ = velocity of sedimentation
$r$ = radius of the droplet
$\rho_1$ = density of the dispersed phase
$\rho_2$ = density of the continuous phase
$\eta$ = viscosity of the medium

# Physical stability of emulsions

## Kinetics of flocculation

$$V_f = \frac{2\pi r^4(\rho_2 - \rho_1)g}{3k_B T}$$

$V_f$ = velocity of flocculation

$r$ = radius of the droplet

$\rho_1$ = density of the dispersed phase

$\rho_2$ = density of the continuous phase

$k_B$ = Boltzman constant

$T$ = absolute temperature

Boltzman constant = $1.38064852 \times 10^{-23}$ $m^2$ kg $s^{-2}$ $K^{-1}$

# Preparation of emulsions

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# Preparation of emulsions

1. **Formation of the drops**

- Energy is needed for the formation of the drops
- This energy can be decreased by application of surfactants

2. **Stabilization of drops**

- Surface charge,
- Polymer protective effect

# Preparation of emulsions

**Small amount of emulsion:**

Dissolve the ingredient in the proper phase (lipophilic or hydrophilic medium).

Disperse the internal phase in the external phase with mixing or shaking in 4-5 steps.

**Large amount (multi dose) emulsion:**

With high-speed (rpm) equipment.

In case of w/o emulsions the internal phase with the emulsifyier should be measured into the container and to this the addition of the external phase with surfactant should take place.

# Preparation of emulsions

## Commonly applied excipients:

1. **Surfactants** (polysorbates, tinctura saponariae;
   to external use: triethanolamine+oleic acid,
   sodium lauryl sulfate),

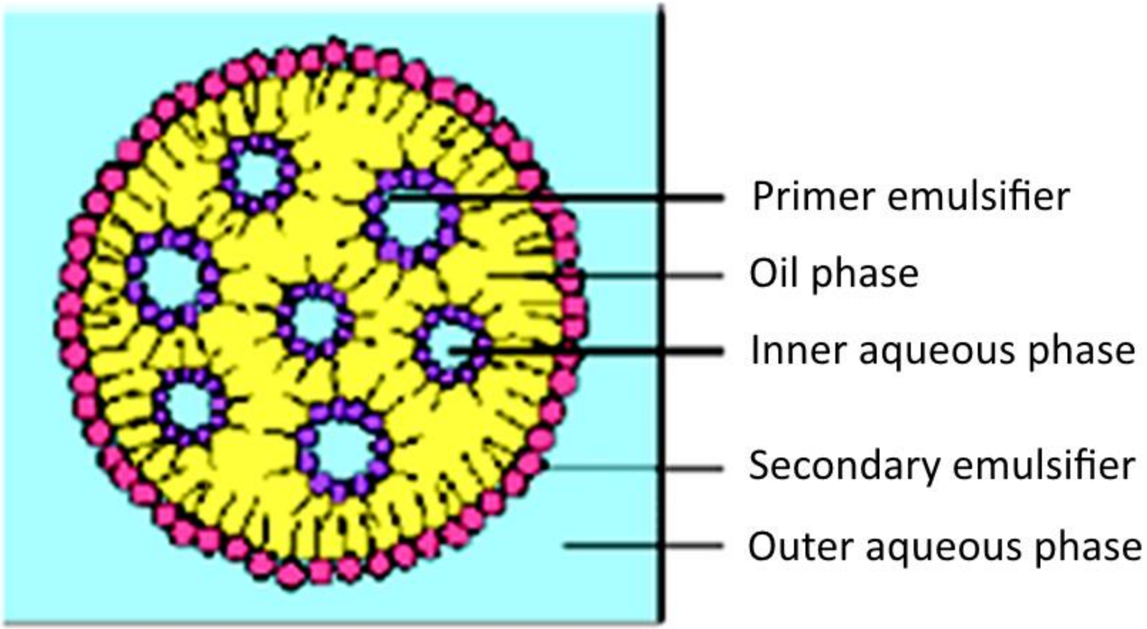
2. **Viscosity enhancers** (gelatin, cellulose derivatives, PVP)

3. **Preservatives** (Sol. conservans)

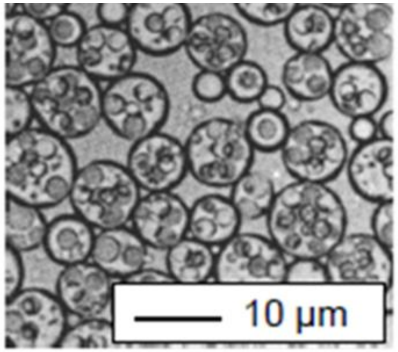
4. **Taste and smell masking materials** (vanillin, citric acid).

# Preparation of emulsions

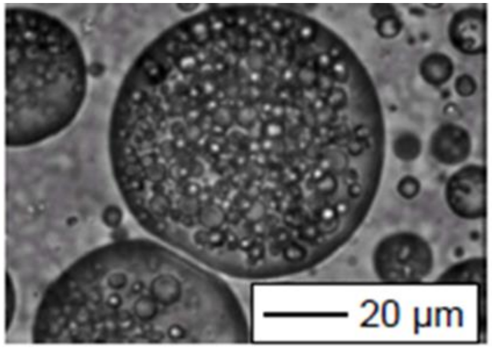
Complex emulsions




W/O/W emulsion



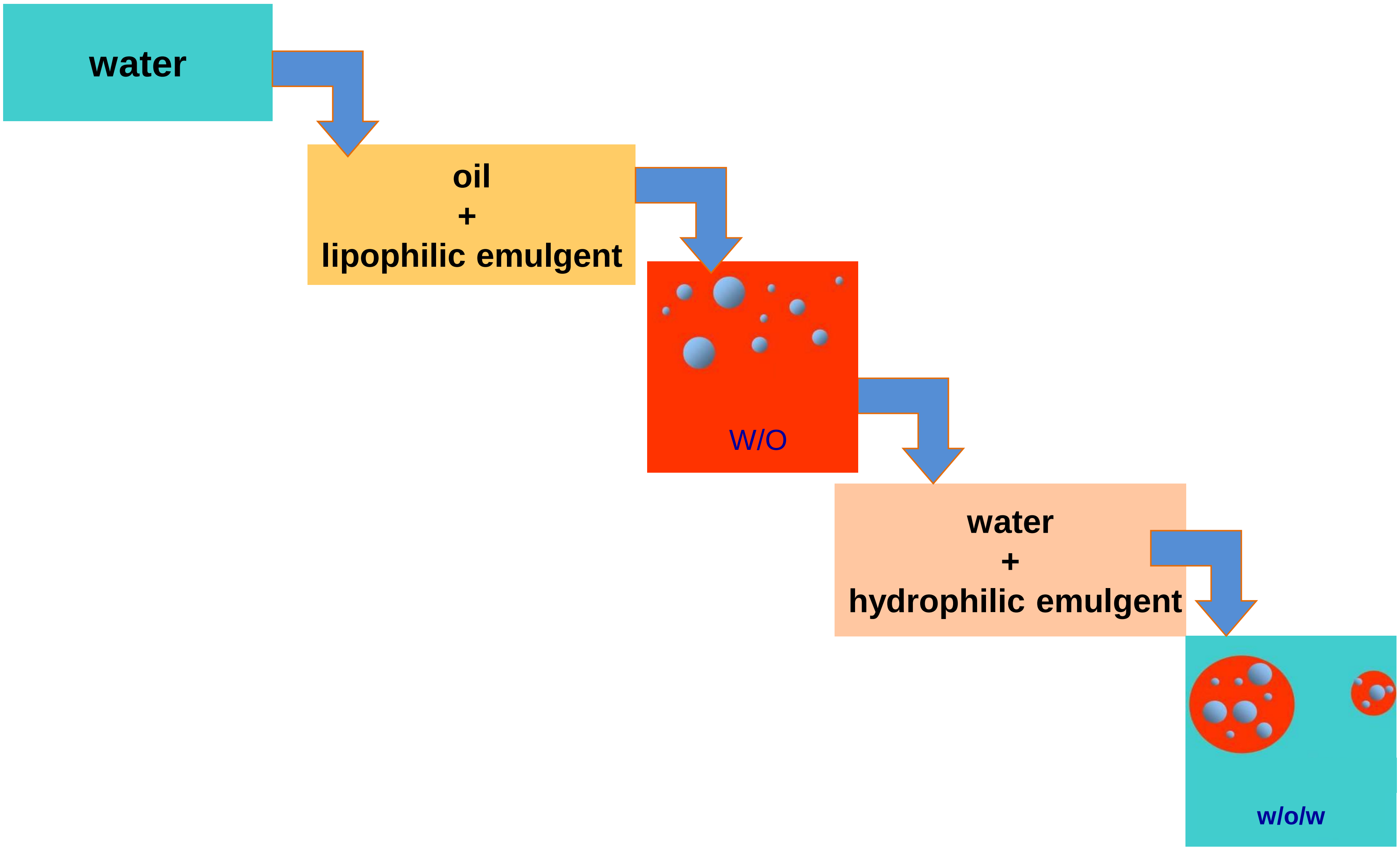

W/O/W




O/W/O

# Preparation of emulsions

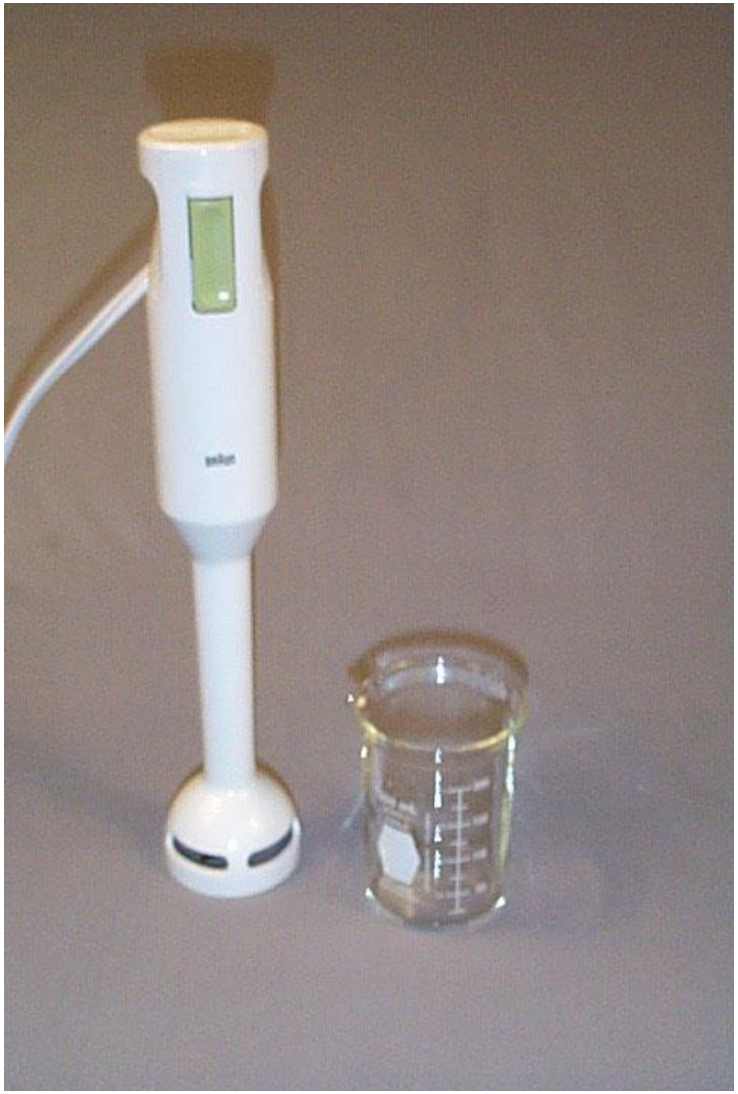
## Complex emulsions



# Preparation of emulsions

## <u>Hand mixer</u>

high shear forces



# Preparation of emulsions

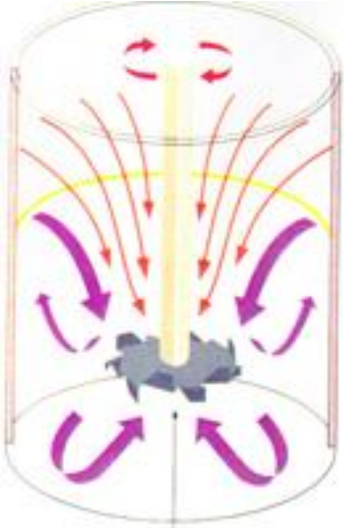
## High speed mixer

high shear forces

# Preparation of emulsions

## High speed mixer

**Dispenser**



3000 – 5000 rpm

suction, vortex effect, shear effect

high shear forces

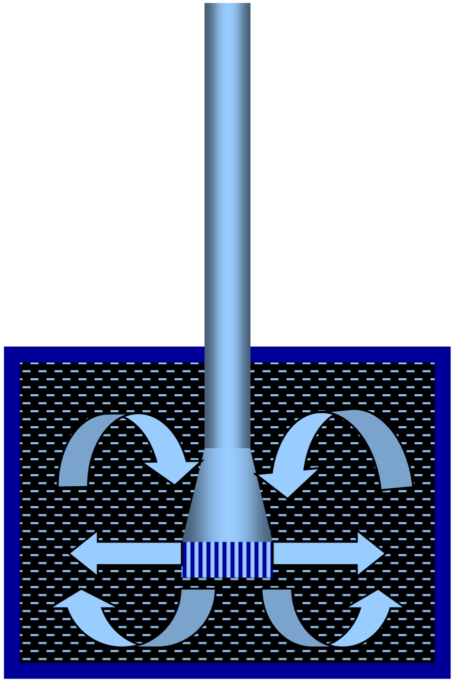
# Preparation of emulsions

## Ultrasonic homogenizer


# Preparation of emulsions

## UltraTurrax

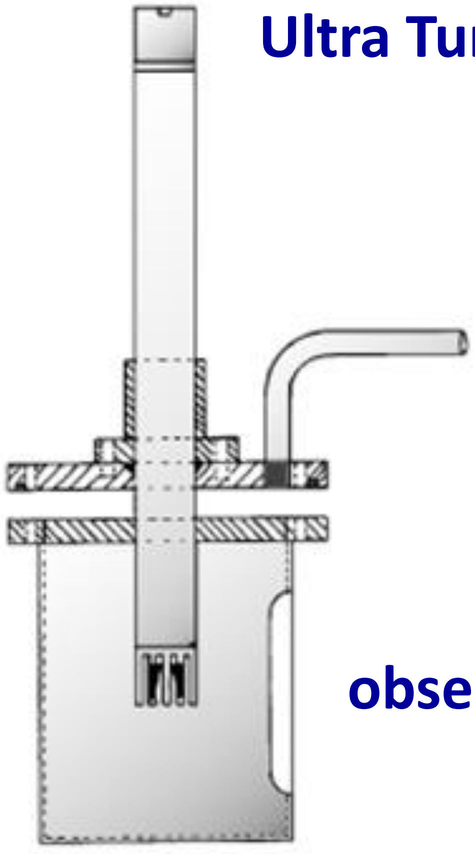


# Preparation of emulsions

## UltraTurrax

For closed system



# Preparation of emulsions

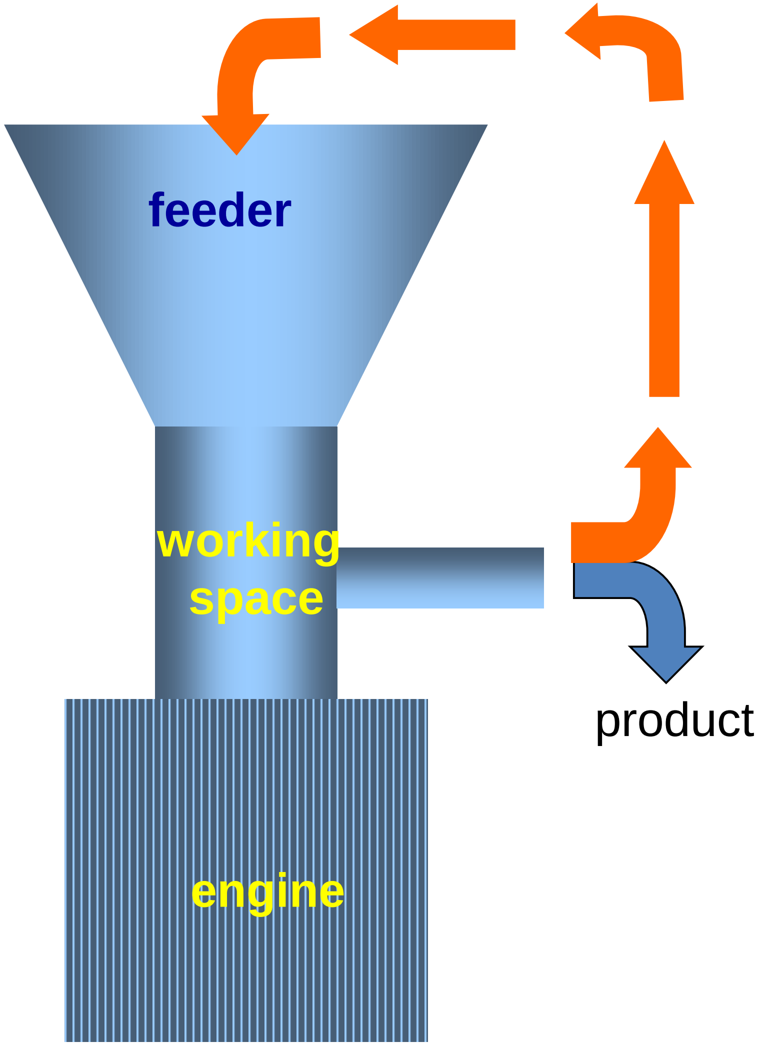
## Colloid mill

A colloid mills are frequently used to increase the stability of suspensions and emulsions by reducing the particle/ drop size.

This is done by applying high levels of hydraulic shear to the process liquid.

1-25µm particles
recirculation (option)

high shear forces

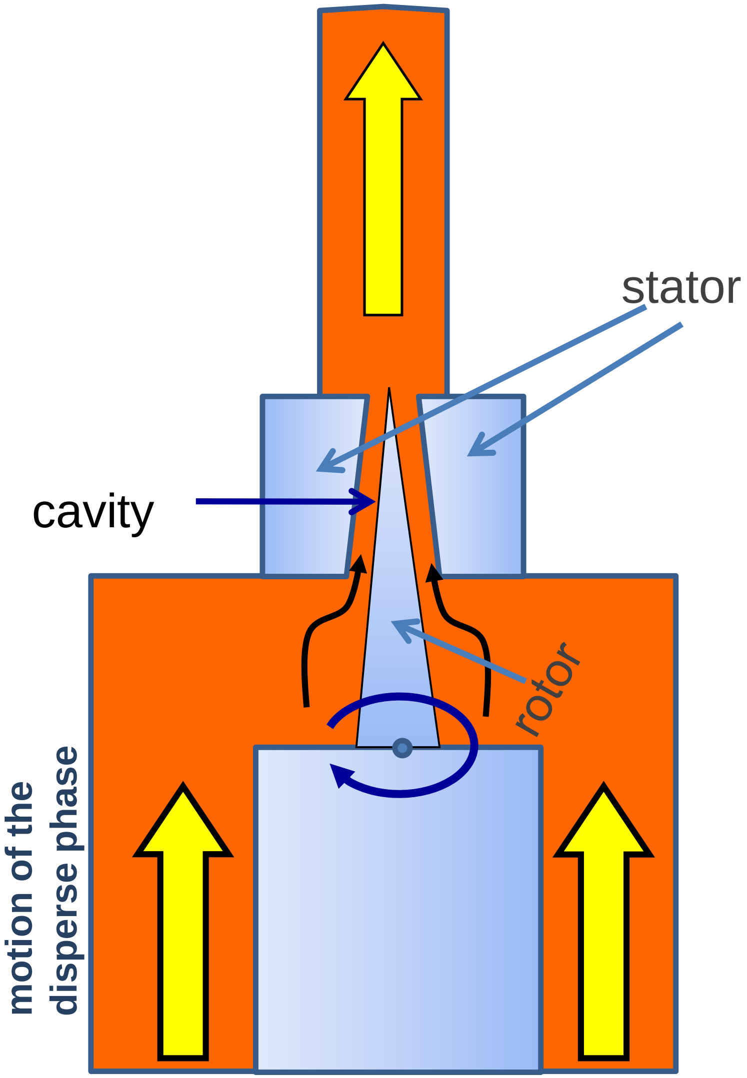


# Preparation of emulsions

## Colloid mill

Undispersed material is forced into a cavity formed by a **spinning rotor** and **fixed stator.**

Centrifugal force propels the material to the outside of the rotor, causing intense hydraulic shear that reduces the particle size breaking agglomerates and homogenizing the solids and liquids.



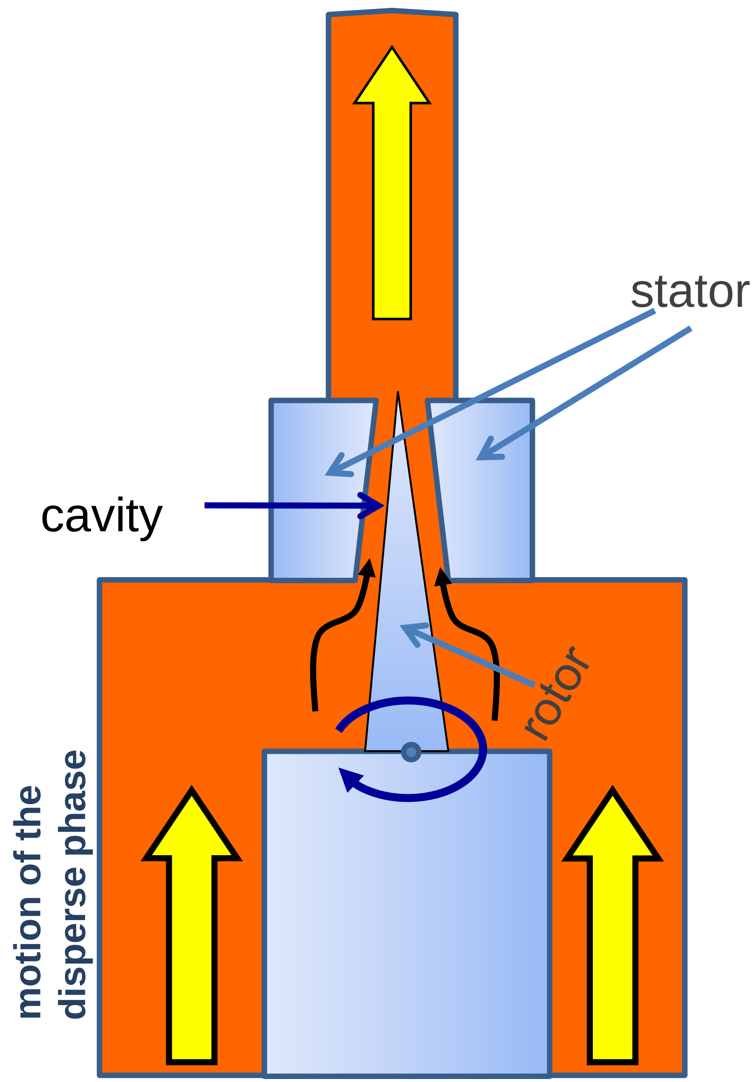

high shear forces

# Preparation of emulsions

## Colloid mill

Shearing can be regulate to decrease particle size by:

- increasing of rpm.
- reduction of the distance between the stator and rotor
- increasing of shearing time
- incerasing number of recirculation




high shear forces

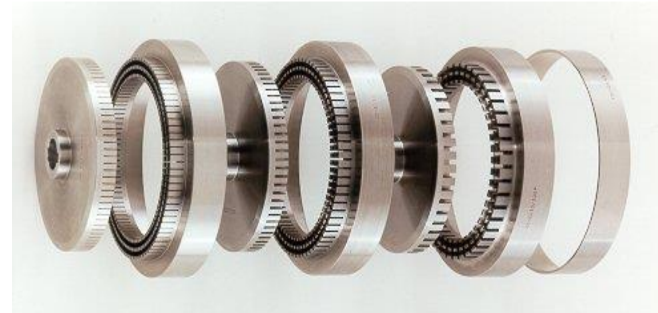
# Preparation of emulsions

## Colloid mill

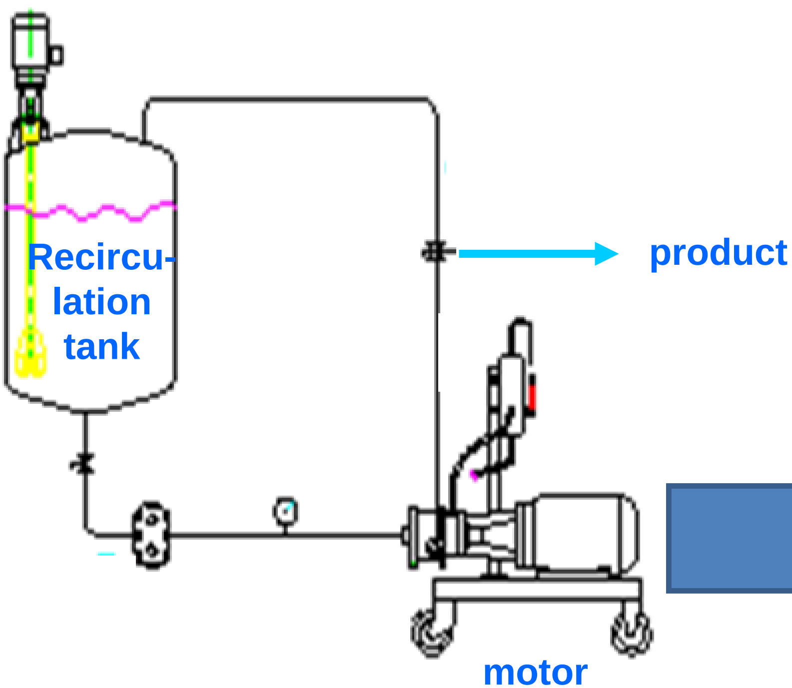
stator rotor

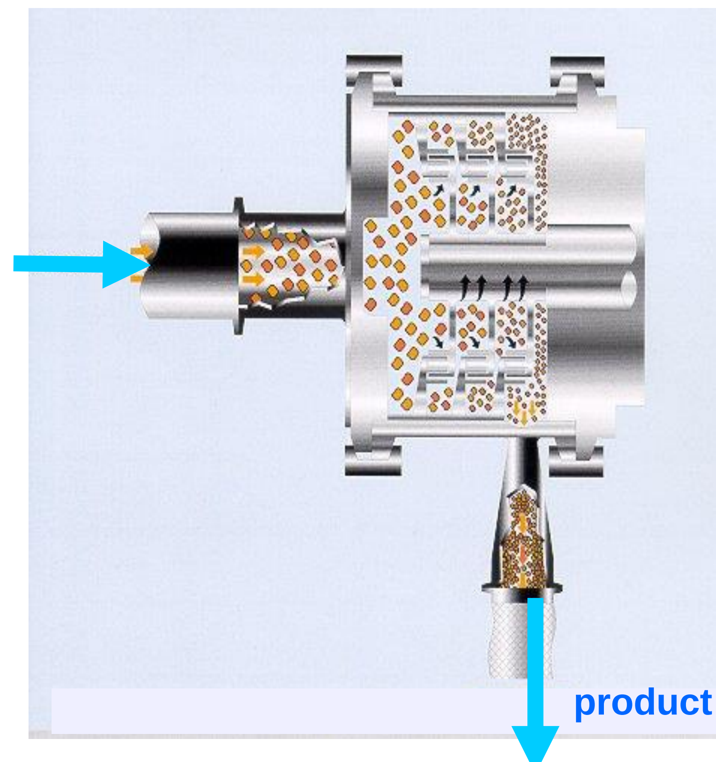
# Preparation of emulsions

## Ytron Jet mixer



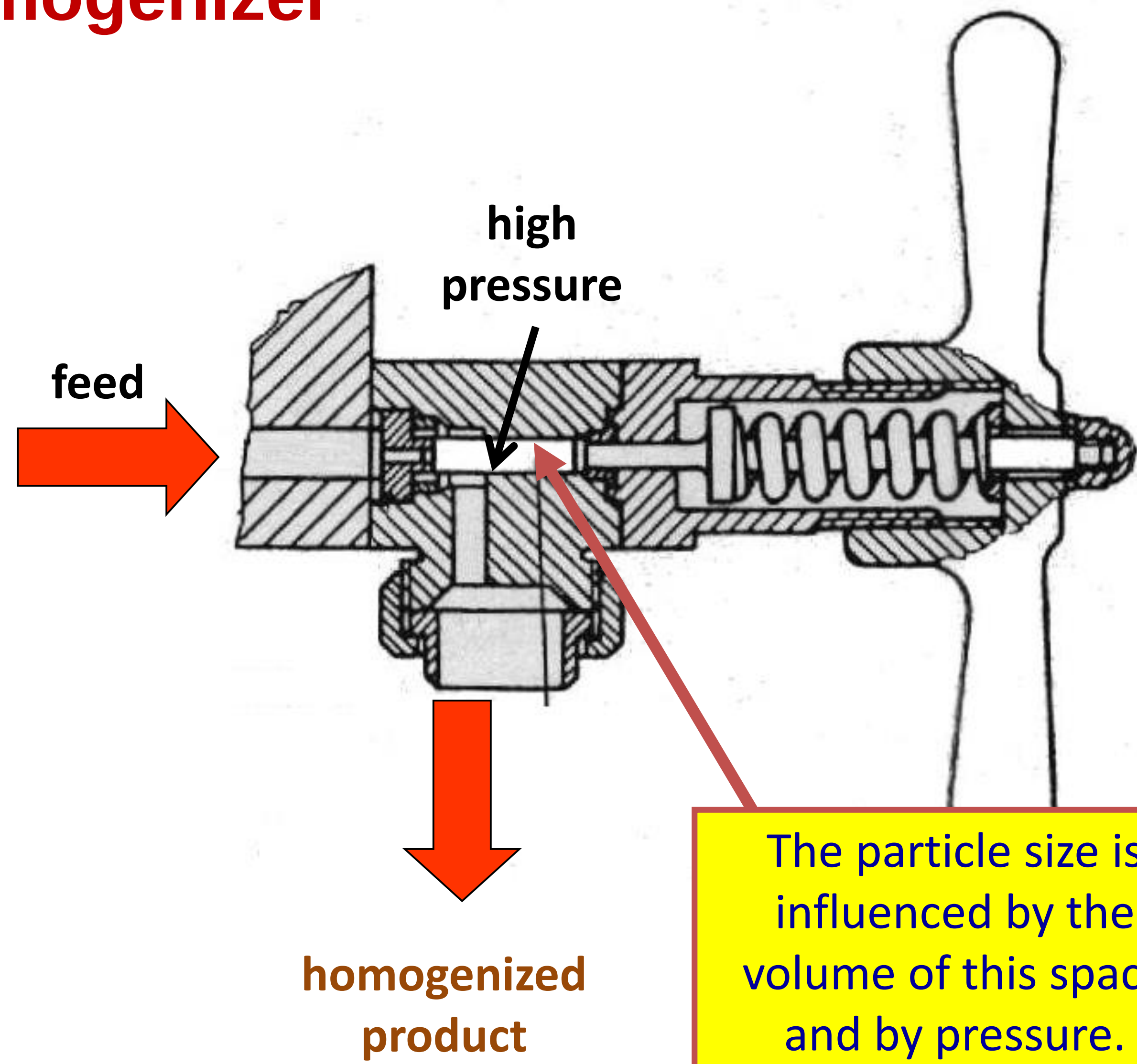
More units (unit = stator + rotor) in work space(s) one after the other.



# Preparation of emulsions

## Gaulin-type homogenizer

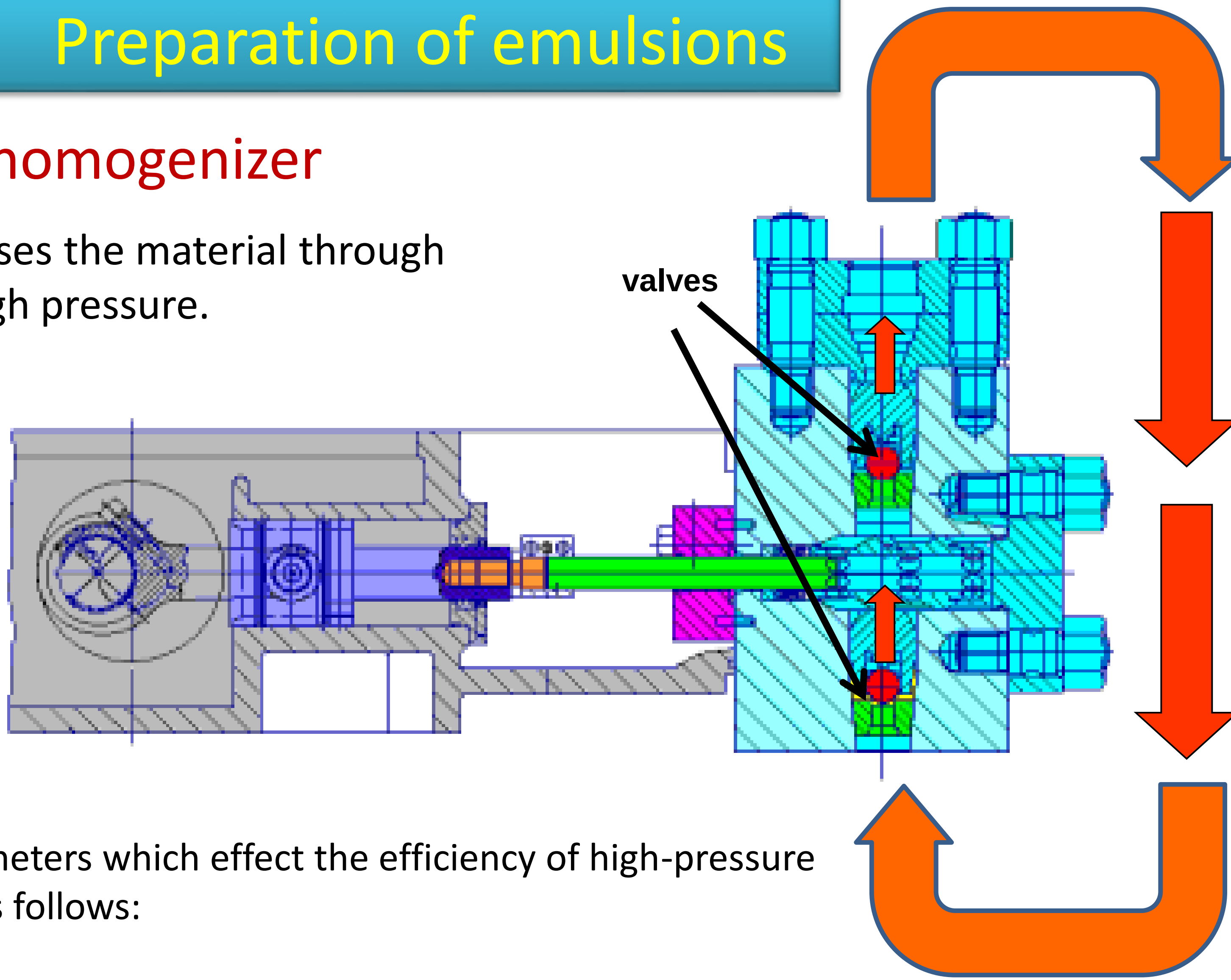



The particle size is influenced by the volume of this space and by pressure.

# Preparation of emulsions

## High pressure homogenizer

This equipment presses the material through a small hole with high pressure.




The operating parameters which effect the efficiency of high-pressure homogenizers are as follows:

- pressure
- temperature
- number of passes
- valve and impingement design
- flow rate

# Preparation of emulsions

## Microfluidiser - microchannel (MC) emulsification


This equipment applies high-pressure which forces the product through the interaction chamber, which consists of small channels (*microchannels*).

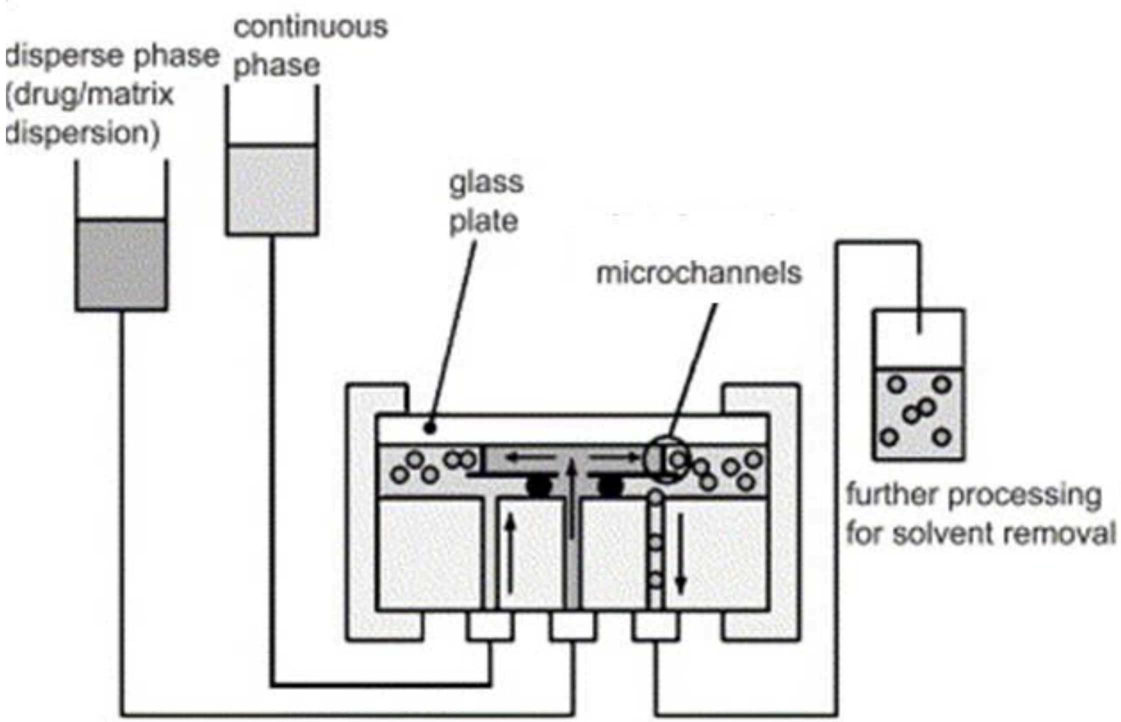
The product flows through the microchannels on to an impingement area resulting uniform particle size reduction in very fine particles of sub-micron range.

An equipment for parenteral feeding emulsions.

# Preparation of emulsions

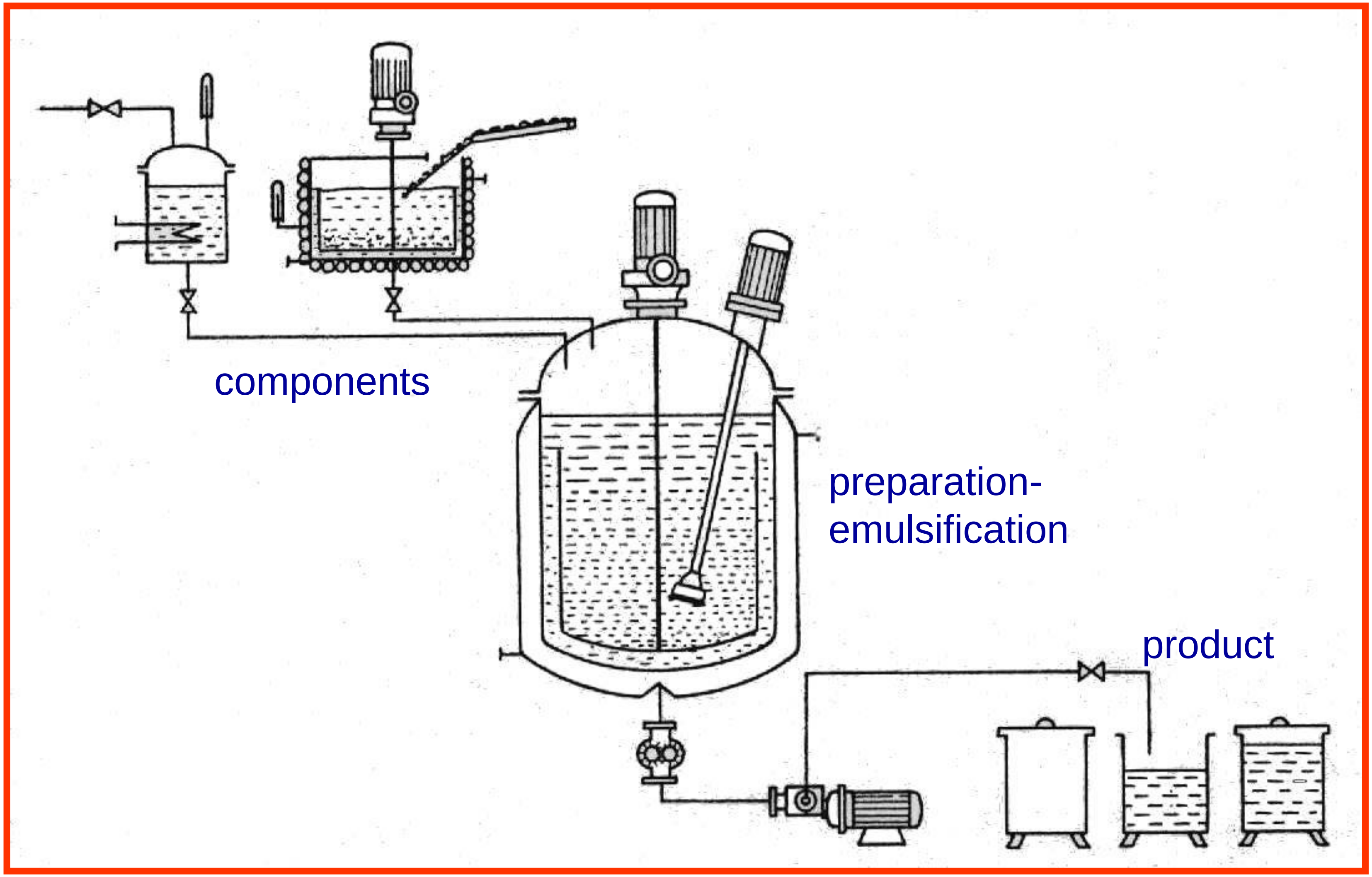
## Microfluidiser - microchannel (MC)emulsification


Product enters the system via the inlet reservoir and is powered by a high-pressure pump into the interaction chamber at given speed.




# Preparation of emulsions

In industry



# Emulsifying agents

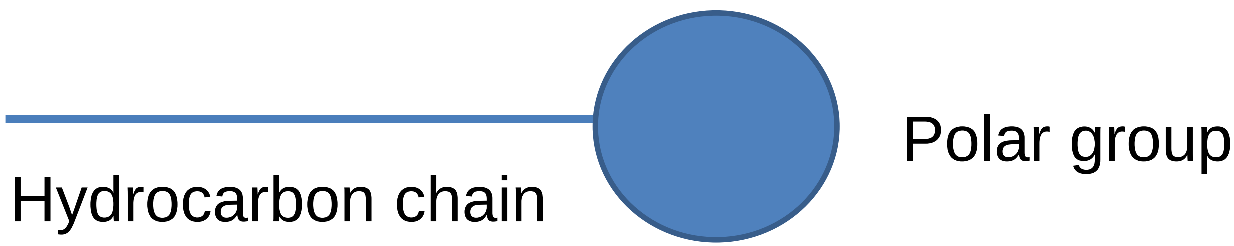


# Emulsifying agents

## Amphiphilic surface active materials

HLB value is essentially the proportion of ***hydrophilic and lipophilic molecule group***, namely the polarity of the particular molecule.

Stucture:




HLB = Hydrophilic-lipophilic balance

# Emulsifying agents

## Emulsifier Classification :

According to ionic composed of an organic lipophilic group (surface active portion)

- Naturally occurring materials and their derivatives
- Synthetic and semisynthetic surfactants:
  - Anionic
  - Cationic
  - Nonionic

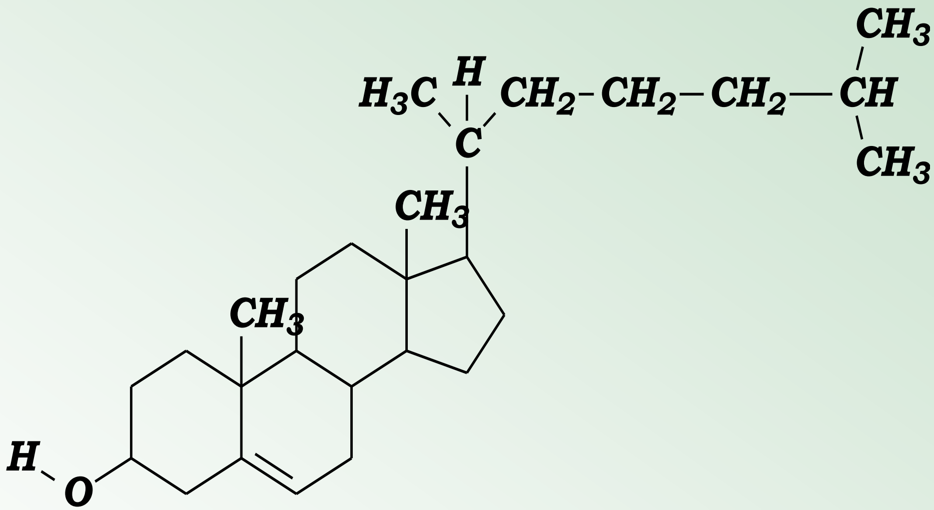
# Emulsifying agents

## Surfactants with natural origin

- **vegetable origin, carbohydrate polymer derivatives:**
  Acacia, tragakanta, agar-agar, pectin

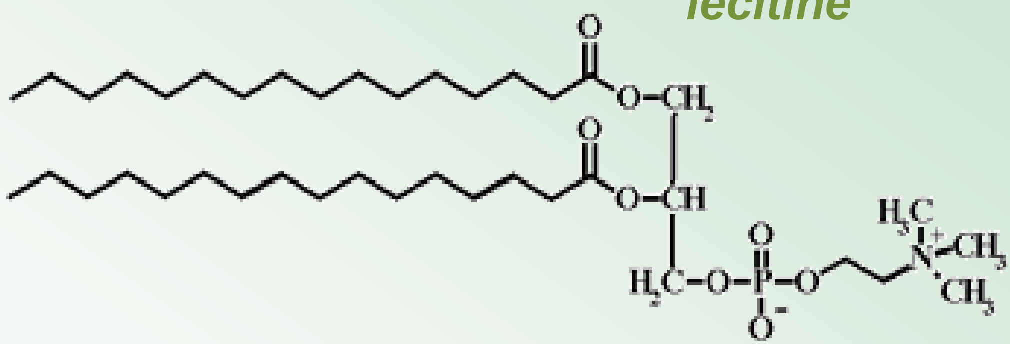
- **proteins:**
  gelatin, casein, o / w emulsion

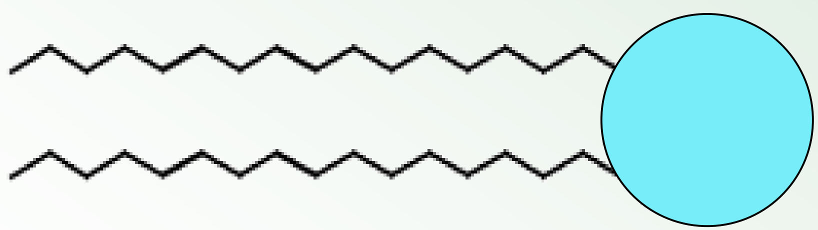
- **high molecular weight alcohols:**
  stearyl alcohol, cetyl alcohol, cholesterol



cholesterol

lecitine

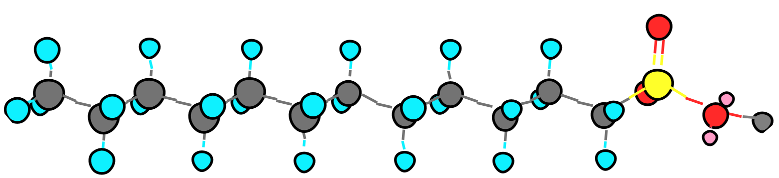


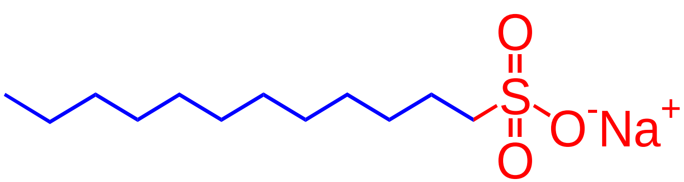


# Emulsifying agents

## Anionic surfactants

- alkali metal salts of fatty acids (soaps) (external use),
- salts of sulfuric acid esters, sodium-lauryl-sulphate, sulfonates.





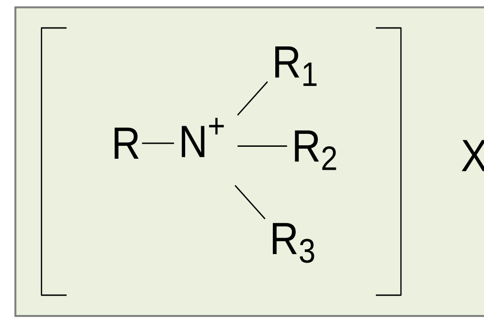

$CH_3(CH_2)_{10}CH_2OSO_3Na$

sodium-lauryl-sulphate, **HLB=40**

# Emulsifying agents

***Cation type surface -*** quaternary ammonium bases substituted with alkyl or aryl radicals

These are rarely used as emulsifying agents, primarily as ***preservatives***. (toxicity and irritancy)




**$R_1$=$R_2$=$CH_3$**

**$R_3$=$CH_3$ or $CH_2C_6H_5$**

**R= carbon chain ($C_{12}$-$C_{18}$)**

**Main type of cation type surface active substances:**

1) **cetavlon** type: alkyl trimethyl ammonium salts,

2) **sapamin** type: acyl amide alkyl trimethyl ammonium salts,

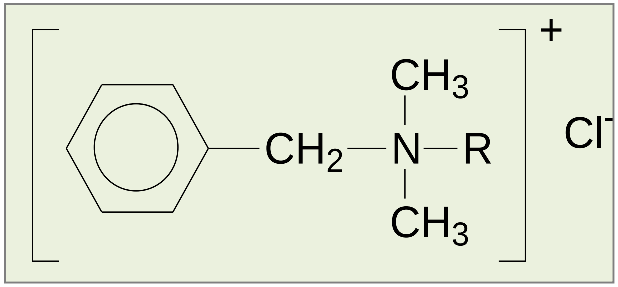
3) **zephirol** type: benzyl dimethyl alkyl ammonium salts,

4) **sterogenol** type: quaternary nitrogen compounds with long hydrocarbon chain that contain nitrogen aromatic ring

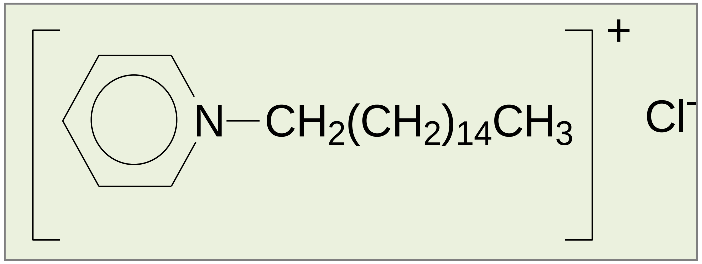
# Emulsifying agents

## Cationic surfactants

Benzalkonium chloratum (Zephirol),




Cetylpyridinium chloratum




The ionic surfactants must only be applied for external use.

# Emulsifying agents

## Non-ionic surfactants

- *Non-ionic surface active substances* **do not create ions in water**.

Low toxicity and irritancy → oral, parenteral use

Include: **fatty acid esters of polyvalent alcohols** (e.g. sorbitol, mannitol), **polyoxyethylene derivatives**, and compounds containing amide and ether bonds.

- Main type of **non-ionic surfactants**:
  1) polyethylene glycol ethers,
  2) polyethylene glycol esters,
  3) fatty acid esters,
  4) sorbitan fatty acid esters and polyethylene glycol ethers

- Polyethylene glycol-fatty alcohol ethers are so called **Brij**, generally **esters of PEG and palmitic or stearic acid**.

# Emulsifying agents

| Usage | HLB |
|---|---|
| Defoamers | 1-3,5 |
| Emulsifying agents | 3,5-8 |
| Moistening agent | 7-9 |
| O/W surfactants | 8-16 |
| Detergents | 13-16 |
| Solubilizing agents | 15-40 |

| HLB | Dispersion rate in water |
|---|---|
| 1-4 | Cannot be dispersed |
| 3-6 | Slightly dispersible |
| 6-10 | Milk-like dispersion |
| 10-13 | Opalescent solution |
| 15-40 | Clear solution |

# Examination of emulsions

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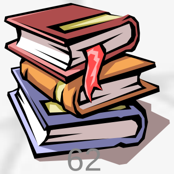


# Examination of emulsions

Parameters, what influence the emulsion’s behaviors

1. The viscosity increases with the internal phase ratio
2. The viscosity increases with the particle size of the dispersed phase
3. Viscosity of the external phase
4. The applied surfactant

# Examination of emulsions

Particle/drop size of emulsions can influence the

- viscosity
- light-transparency
- stability

# Examination of emulsions

Particle/drop size of emulsions depends on

- amount and type of surfactants
- the process time
- the intensity of the process (equipment)
- other substances

# Examination of emulsions

## Types of emulsions

**1. with dilution:**

**o/w** emulsion can be diluted with **water**

**w/o** emulsion can be diluted with **oil**

**2. with conductivity:**

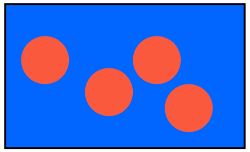
if the **water** is the **external** phase than the **conductivity is higher**

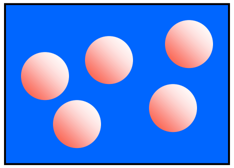
**3. with painting**

methylene blue – water, Sudan red – oil

**4. with fluorescency**

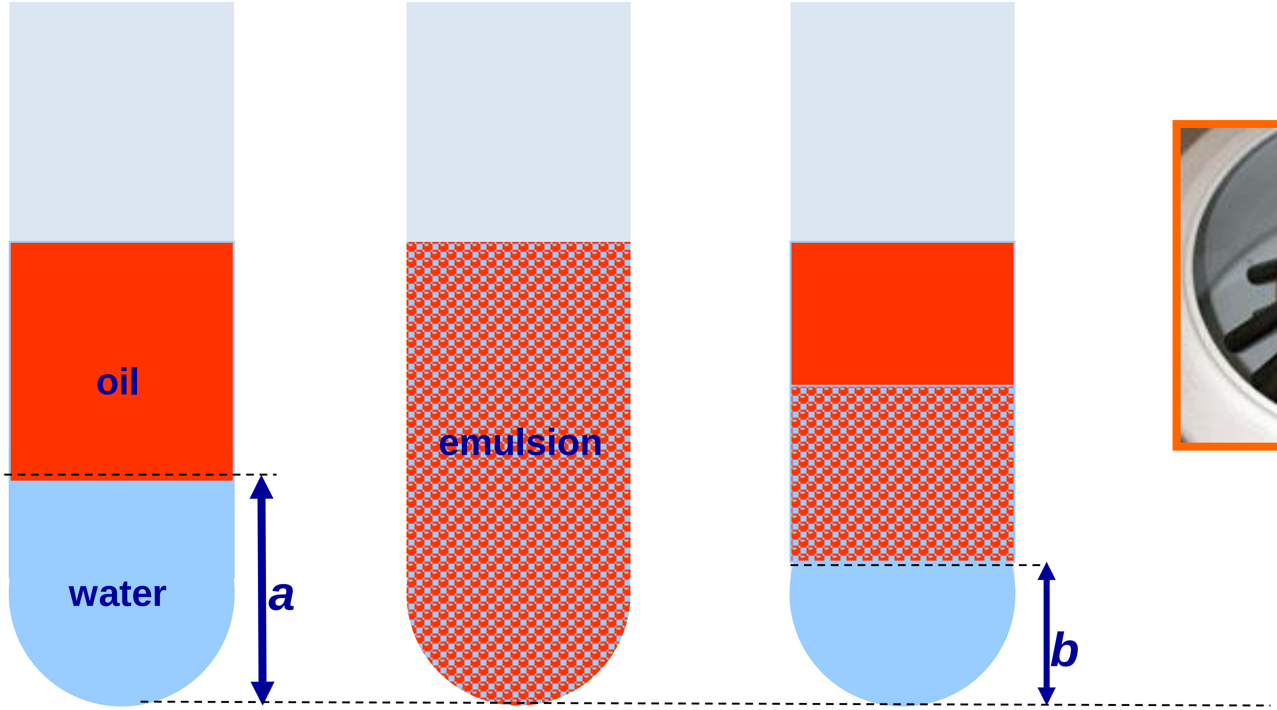
fluorescence of oil drops in UV light





# Examination of emulsions

Forced stability testing




**Before preparation** **After centrifugation**

# Examination of emulsions

Forced stability testing

$$S = \frac{a-b}{a}$$

*S* = stability (%)

*a* = volume of water phase **before** the preparation

*b* = volume of water phase **after** the centrifugation

# Examination of emulsions

## Phase inversion

If we have a w/o emulsion, and we enhance the internal phase ratio then the viscosity of the system increases.
After the phase inversion the viscosity of the system decreases.

**Phase inversion:**
**If the internal phase ration is more than 74%!**

# Application of emulsions

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# Application of emulsions

Disperse systems in drug therapy by:

1) oral,
2) peroral (e.g. O/W type emulsions for taste masking, antacid suspension),
3) intravenous (parenteral nutrition, nano products),
4) dermal and transdermal (e.g. medicinal ointments, creams, cosmetics),
5) vaginal (e.g. feminine washes),
6) rectal routes (e.g. enemas).

# Application of emulsions

- **External use**
  - injecting the active substances **into the skin**

- **Peroral use**
  - can be increased the bioavailability
  - regulation of drug release can be achieved
  - protecting the active substance against oxidation and hydrolysis
  - emulsions intended for oral use are o/w.

- **Parenteral use**
  - nanoemulsions

# Application of emulsions

## **Interal** administration

The Intralipid-infusion is a o/w emulsion, where the drop size is between 250-300 nm.

Phospholipids can stabilize the layers.
(lecithin is usually used)

# Application of emulsions

## Parenteral route

Propofol emulsion

iv. administration d<1000nm


20 ml ampule of 1% Propofol emulsion, intravenous injection

Soybean oil - lecithin mixture/ water

# Application of emulsions

## Nanoemulsions

They are usually o/w type emulsions.
The mean particle size is:

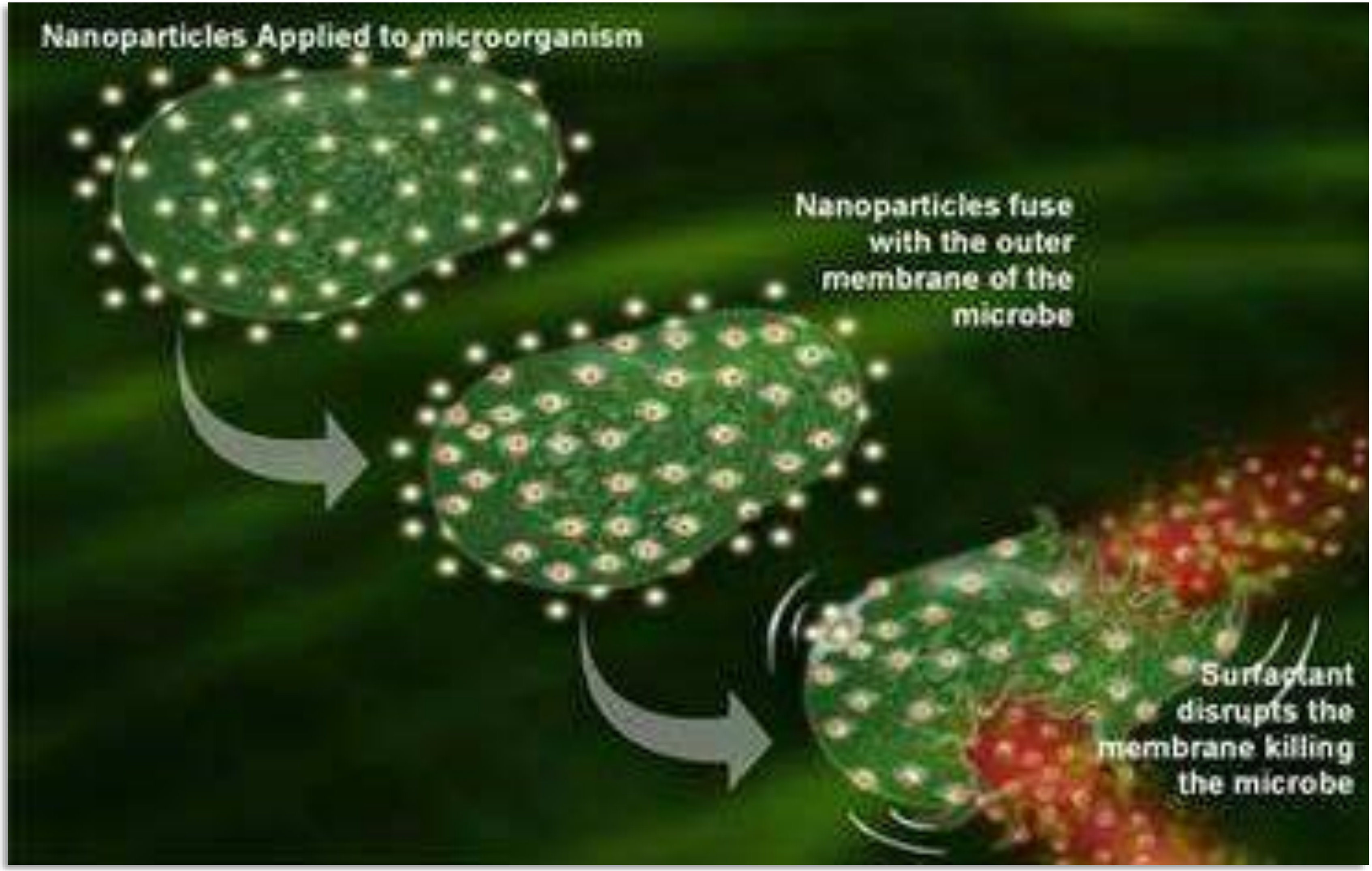
1-1000 nm, or
100 – 500 nm.

### Application

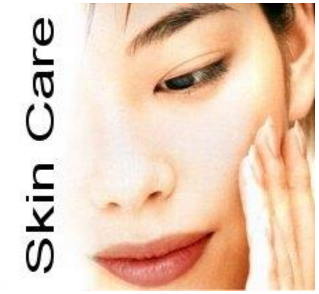
- skin (infections)
- cosmetics
- recombinated proteins, inactivated microorganisms

# Application of emulsions

## Nanoemulsions



# Application of emulsions




## Cosmetics

- o/w emulsions can be diluted with water and so they are washable and easily absorbed
- w/o emulsions: controlled drug liberation
- cleansing cream
- moisturizing cream (can hydrate the skin)

# Emulsions in FoNo VII.

- Emulsio olei jecoris Fo No VII.
- Emulsio olei jecoris composita Fo No VII.
- Emulsio olei ricini Fo No VII.
- Emulsio paraffini cum phenolphthaleino Fo No VII.
- Emulsio laxans Fo No Vet III.

- Linimentum ad pernionem Fo No VII.
- Linimentum ammoniatum Fo No VII.
- Linimentum scabicidum Fo No VII.

- Linimentum camphoratum Fo No Vet III.

# Emulsions

## Linimentum scabidium

External use. Shake before use! Expiry 3 month.

**LINIMENTUM SCABICIDUM**

(Linim. scabicid.)

| | | | |
|---|---|---|---|
| **I. Triaethanolaminum . .** | **1,0** | **g** | |
| **I. Acidum oleinicum . . .** | **4,0** | **g** | |
| **II. Benzylium benzoicum** | **25,0** | **g** | |
| **III. Aqua destillata** | **25,0** | **g** | |
| **IV. Aqua destillata** | **ad 100,0** | **g** | **(45,0 g)** |

**Készítés:** Az I. alatti alkotórészek elegyéhez a II-at hozzákeverjük és a III-ka! erőteljesen összerázzuk. Az emulzió tömegét a IV-kel kiegészítjük és ismét összerázzuk.

**Expedíció:** Sötét üvegben.

**Szignatúra:** Külsőleg. Bekenésre. Használat előtt felrázandó.

**Felhasználhatósági időtartam 3 hónap.**

**Dermatologicum. Scabicidum.**

# Emulsions

## Emulsio olei jecoris

Roborans. Antirachiticum.

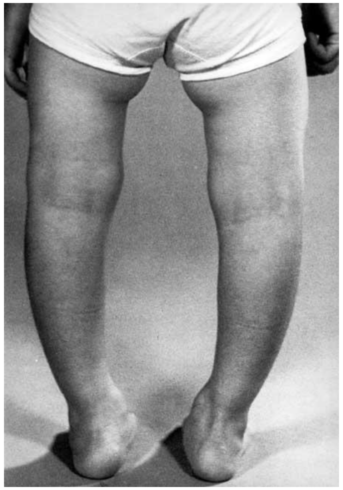
In case of rachitis, osteomalatia, spasmophilia, ceratomalatia, and reconvalescentia.

API: prepared from cod fish liver. Rich from Oleum jecoris: *D and A vitamines, and essential fatty acid. Used in rachitis, osteomalatia, spasmophilia, scrofulosis, ceratomalatia, reconvalescentia esetén használják.*

**EMULSIO OLEI JECORIS**

(Emuls. ol. jecor.)

| | | | |
|---|---|---|---|
| I. | **Tinctura saponariae** | 1,0 | g |
| I. | **Vanillinum** | 0,01 | g |
| I. | **Solutio conservans** | 1,0 | g |
| I. | **Aetheroleum citri** | XV | g« |
| I. | **Mucilago hydroxyaethylcellulosi .** | 92,0 | g |
| II. | **Saccharimidum natricum** | 0,50 | g |
| II. | **Acidum citricum** | 1,0 | g |
| III. | **Oleum jecoris** | 100,0 | g |
| IV. | **Aqua destillata** | . ad 200,0 | g |



**Készítés:** Az I. alatti alkotórészek elegyében a II. alatti alkotórészek homogén keverékét rázogatással feloldjuk úgy, hogy a szacharint előtte elporítjuk. A folyadékban a III-at 4-5 kb. egyenlő részletben, erőteljes összerázással emulgeáljuk. Az emulzió tömegét a IV-kel 200 g-ra kiegészítjük.

# Emulsions

## Cremor aquosus

*In case of Seborrhea.*
Dermatologicum. Antisenborrhoicum.
Skin softener cream. External use. Keep in a cool place.

**CREMOR AQUOSUS**
(Crem. aquos.)

| | | |
|---|---|---|
| I. Paraffinum microcrystallicum . . . . *vei* Paraffinum solidum | 6,0 | g |
| 1. Paraffinum liquidum | 10,0 | g |
| 1. Alcoholum cetylstearylicum . . . | 8,0 | g |
| 1. Glycerinum | 5,0 | g |
| II. Nátrium laurylsulfuricum | 1,0 | g |
| III. Solutio conservans | 1,0 | g |
| III. Aetheroleum citri | III | gtt |
| IV. Aqua destillata | . . ad 100,0 | g |

**Készítés:** Az I. alatti alkotórészek kb. 70 °C hőmérsékletű olvadékához az azonos hőmérsékletű II. kb. 65 g vízzel készült oldatát elegyítjük, az emulziót kihűlésig keverjük, majd hozzáadjuk a III. alatti alkotórészeket, és újra összekeverjük. A krémet vízzel 100,0 g-ra kiegészítjük.

# Emulsions

## Cremor refrigerans

*Dermatologicum. Adstringens. Antiphlogisticum.*
*In case of different skin inflammation.*
*Cooling cream. External use. Keep in a cool place.*
API: Aluminium aceticum tartaricum solutum as *adstringens.*
Side effect: Slightly irritatve.

**CREMOR REFRIGERANS**
(Crem. refrig.)

**I. Alumínium aceticum tartaricum**
**solutum. . . . . . . . . . . . . . . . . . . . . .2,5 g**
**II. Unguentum hydrophilicum**
**nonionicum. . . . . . . . . . . . . . . . . . .ad 50,0 g (47,5 g)**

# THANK YOU FOR ATTENTION!

**Important dates:**

**17. March**

**14. April**

**05. May**