Excipients in the technology of dosage forms

International Pharmaceutical Excipients Council (IPEC)

The **IPEC Federation** is a global organization that promotes the **quality of pharmaceutical excipients**. Represents the five existing regional international pharmaceutical excipient boards - IPEC Americas, IPEC Europe, IPEC Japan, IPEC China, IPEC India - and provides a harmonized opinion to promote the best use of excipients in medicines.

Modern requirements for excipients

- Should help to ensure the required therapeutic effect with a minimum dose of the drug;
- Should not show toxic and allergenic effects on the body;
- Should not interact with medicinal and other auxiliary components, packaging materials;
- Should not impair the organoleptic properties of the medicinal product

Modern requirements for excipients

- Should provide a given dosage form, its consistency, strength and degradation properties;
- The quality of excipients must be stable and comply with regulatory documentation.

Classification of excipients

Depending on origin

- ❖ natural
- ❖synthetic and semi-synthetic
- ❖microbiological synthesis

Classification of excipients

Depending on destination

- form-building
- stabilizers
- prolongators
- flavors
- dyes improving the solubility and bioavailability of drugs

Forming substances

Purpose is the creation of a dosage form, its mass, volume, consistency

The nature of the excipient largely determines the stability of the drug and the rate of API release.

- dispersed media in the technology of liquid dosage forms;
- fillers for solid dosage forms;
- bases for ointments;
- bases for suppositories;
- pushing dispersion media in the production of aerosols;
- medicated patch bases and carriers for transdermal therapeutic systems

Stabilizers

Chemical stabilizers | **Disperse system stabilizers** | **Antimicrobial Preservatives**

- chemical stability of the medicinal substance during storage and processing into a medicinal product;
- aggregative (consistent) stability of the dosage form;
- ensuring microbiological purity and sterility.

Chemical stabilizers

To prevent hydrolysis and inhibition of redox processes

- hydrochloric acid, sodium bicarbonate, surfactants, buffer systems, macromolecular substances (to prevent hydrolysis);
- antioxidants that can react with free radicals (butyl hydroxyanisole, alkyl gallates, tocopherol);
- antioxidants that can be oxidized due to the low redox potential (derivatives of sulfurous acid, organic sulfur compounds, ascorbic acid);
- antioxidant synergists with little intrinsic antioxidant activity (ethylenediaminetetraacetic acid).

Disperse system stabilizers

To increase the aggregative stability of microheterogeneous systems (suspensions, emulsions, ointments, gels, aerosols). Thickeners and surfactants.

Functions of surfactants (emulsifiers):

- ✓ stabilize dispersed systems, increasing their stability as a result of lowering surface tension at the interface;
- ✓ regulate bioavailability by increasing the permeability of cell membranes and improving the affinity of the particles of the dispersed phase to the biofluids of the body.

The effectiveness of surfactants is estimated by the value of the hydrophilic-lipophilic balance (HLB), i.e. balance between hydrophilic and hydrophobic groups in a molecule (0-40)

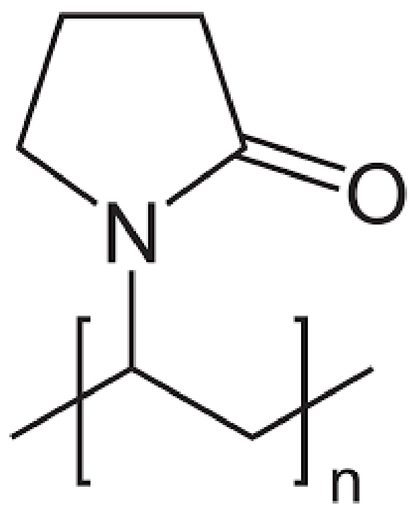
The value of the hydrophilic-lipophilic balance of surfactants

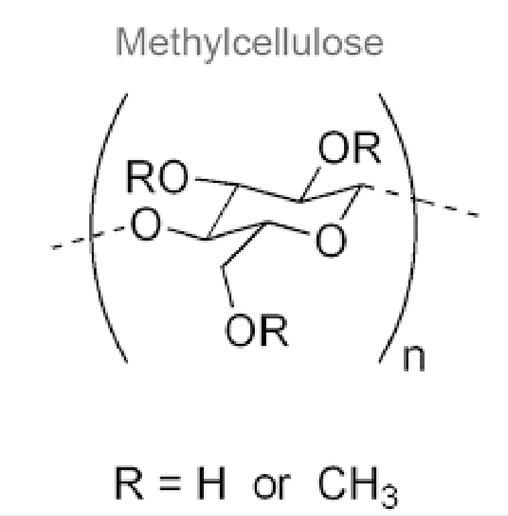
HLB	Type of surfactant	Application area	Examples
3-6	Lipophilic	Water/oil type emulsion stabilizers	Polyoxyethylene sorbites
10-17	Hydrophilic	Oil/Water Emulsion Stabilizers	Twins
> 17	Hydrophilic	Solubilizers	Polyoxyethylene Stearate

*Алексеев К.В., 2011

Prolongators

For liquid dosage forms - increasing the viscosity of the dispersion medium by introducing thickeners - sugar syrup, glycerin, macromolecular compounds (gelatin, polyvinylpyrrolidone (PVP), cellulose derivatives, etc.)





Prolongators

For solid dosage forms - materials used to create matrix dosage forms are introduced into dosage forms, they are classified into hydrophobic (synthetic, lipophilic), hydrophilic (forming hydrogels, soluble), biodegradable.

Polymers for obtaining inert hydrophobic matrices - ethyl cellulose, methacrylic copolymers, products based on polyvinyl acetate.

Lipophilic prolongators - carnauba wax, stearyl alcohol, paraffin, stearic acid, vegetable oils.

Prolongators

To obtain hydrophilic matrices - hydroxypropyl methylcellulose (hypromelose, HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), etc.

Biodegradable materials - L-, D-polylactic acid, polyglycolic acid, chitosan, sodium alginate, pectin.

Substances that improve the solubility of pharmaceutical substances

Increasing the bioavailability and therapeutic efficacy of drugs containing sparingly soluble APIs

- use of complex solvents;
- solubilization;
- complexation;
- use of solid dispersed systems

Substances that improve the solubility of pharmaceutical substances

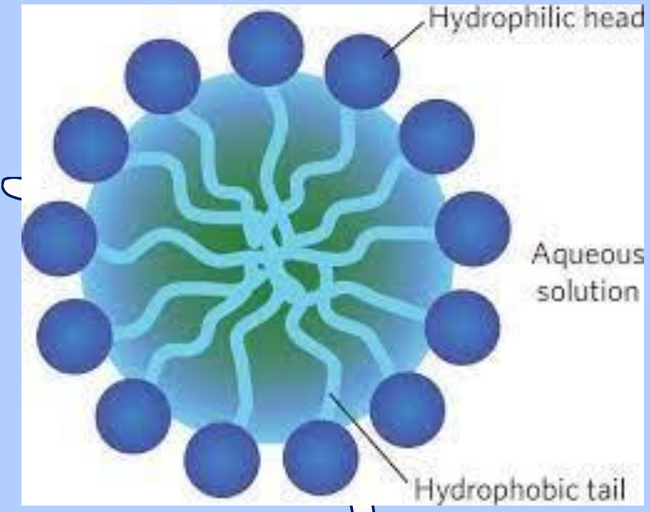
Complex solvents are used in the production of liquid dosage forms and aerosols, complex extractants are used in the production of highly purified extractive herbal preparations.

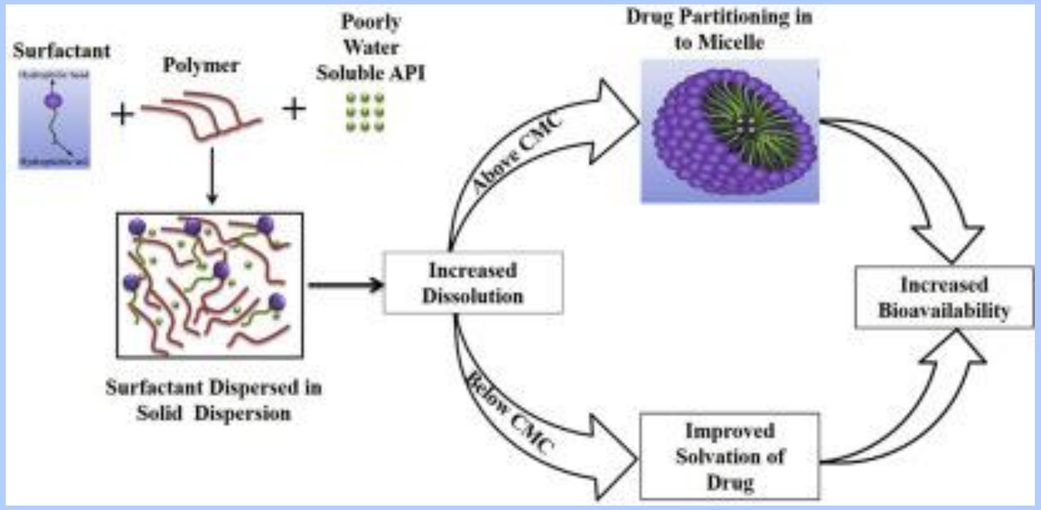
Co-solvents - glycerin, polyethylene glycol, benzyl alcohol, benzyl benzoate, etc.

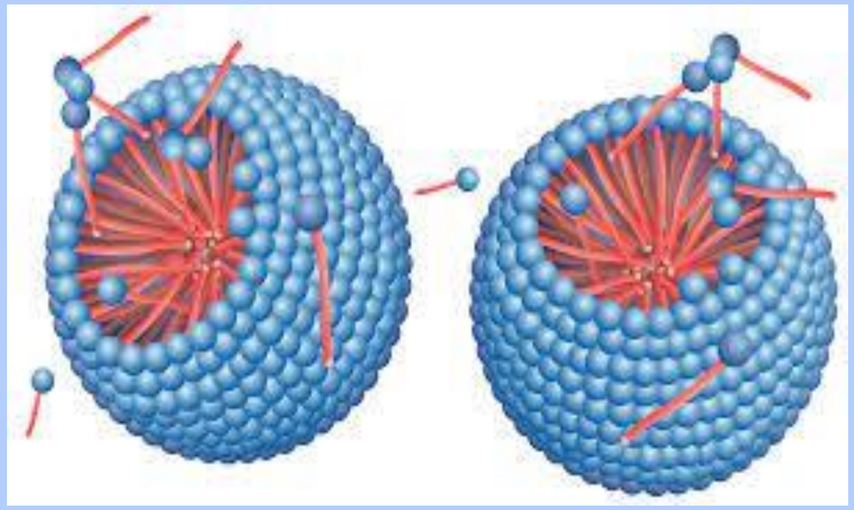
Substances that improve the solubility of pharmaceutical substances

Solubilization of insoluble and sparingly soluble substances using surfactants.

"Solubilization" **is the spontaneous penetration of a low molecular weight substance into surfactant micelles or macromolecular coils of a polymer.**







Solubilization of insoluble and sparingly soluble substances using surfactants

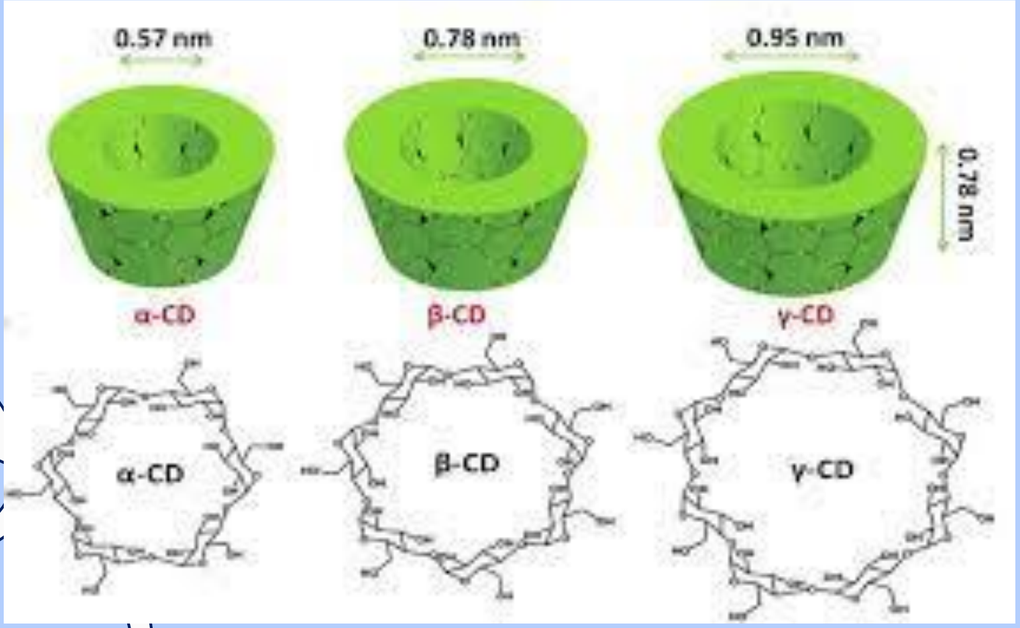
For solubilization, the concentration of surfactant in the drug must be greater than the critical micelle concentration, but not too high, because. this can lead to undesirable effects on the body.

- polyethylene oxides
- twins

Complexation

Excipients capable of forming inclusion compounds due to the special structure of the molecule (complexes "guest-host")

Cyclodextrins are cyclic oligosaccharides consisting of a different number of glucose units (6-8)



Technology for obtaining complexes with cyclodextrins - microgrinding, drying of a solution of cyclodextrin and API after prolonged stirring while heating, co-crystallization, etc.

- increase in the ability to oxidize, hydrolyze, temperature;
- reduced volatility;
- improved solubility and bioavailability

Solid disperse systems

Two- and multi-component systems, including a medicinal substance and a carrier, which contain a highly dispersed solid phase of the medicinal substance or its solid solutions in the carrier matrix with the possible partial formation of complexes of variable composition with the carrier material.

The carrier is water-soluble polymers (polyvinylpyrrolidone). When the solid dispersion system enters an aqueous medium, the carrier dissolves and the drug substance is released in colloidal/molecular form with a high surface area. As a result, the rate of dissolution of a poorly water-soluble substance and its bioavailability increase.

Disintegrants

Disintegrating agents are introduced into tablets in order to improve their disintegration in the gastrointestinal tract, which is necessary for the release and subsequent absorption of active substances, as well as to prevent cementation of tablets during storage. All disintegrators ensure the destruction of the tablet into small particles upon contact with the liquid, resulting in a sharp increase in the total surface of the particles, which contributes to the release and absorption of active substances.

By the nature of the action, loosening agents are distinguished:

- Swelling
- improving solubility
- hydrophilizing
- gas generating

Disintegrants

- **Swelling substances** include pectin, cellulose, gelatin, starch, alginates, bentonites, MCC.
- Sugar and glucose **Improve the solubility**.
- Surfactants are used as **hydrophilizing agents**, the action of which is based on improving wettability due to a decrease in surface tension at the interface between tablets and liquid and the penetration of liquid into tablets.
- **Gas-forming substances** (usually a mixture of bicarbonate with tartaric or citric acid) are of limited use for effervescent, as well as for vaginal tablets.

Superdisintegrants

Along with the classic baking powder, in recent years, the so-called "super disintegrants" have been increasingly widely used.

They are cross-linked polymers derived from potato starch, CMC or PVP. Swelling in water, but not dissolving, they create conditions for the accelerated disintegration of the tablet. Compared to conventional disintegrants, they are much stronger and are used in smaller quantities.

manufacturer	Superdesintegrant	trademark	Properties/application
ISP, USA	crospovidone	Polyplasdon XL	in the production of large tablets with a drug content of about 500 mg or more
		Polyplasdon XL-10	in the manufacture of small tablets and capsules
AVEBE, Netherlands	croscarmellose sodium	Primellose	medium swelling capacity
FMC, USA		AcDiSol	
AVEBE, Netherlands	sodium starch glycolate	Primojel	high swelling capacity