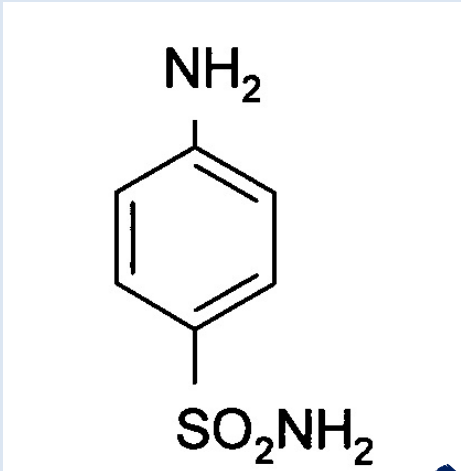
Biopharmacy

The plan of the lecture

1. Biopharmacy. Introduction.
2. Pharmaceutical Factors.
3. Biopharmaceutical Classification System (BCS).

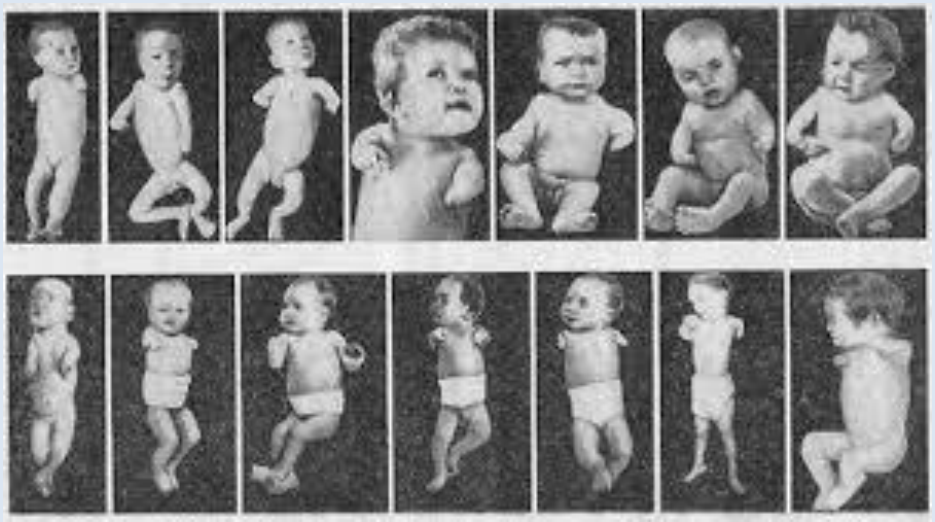
Intorduction

- Pharmaceutical companyS.E. Massengill (Bristol, Tennessee, USA)
- Liquid form of sulfanilamide based on diethylene glycol
- 1937 drug killed 107 children in 15 states
- In 1938, the United States introduced an indispensable requirement to confirm the non-toxicity of drugs by manufacturing companies.



** Скатков С.А. Разработка и регистрация лекарственных средств, 2013.*

Thalidomide tragedy



Francis O. Kelsey

THERAPEUTIC NON-EQUIVALENCE

Examples of therapeutic nonequivalence have been associated with the use of digoxin in the UK and USA in 1971 and phenytoin in Australia and New Zealand in 1968-69.

Prof. John G. Wagner (The University of Michigan) - one of the "founding fathers" of biopharmacy and pharmacokinetics

Dr. Gerhard Levy, Ph.D. (Gerhard Levy, University at Buffalo, SUNY) is a recognized leader in the field of pharmacokinetics and biopharmacy, whose research has led to important discoveries in drug therapy.

Biopharmacy in Russia

- From 1965 to 1985 A.I. Tentsova - Director of NIIF (formerly TsANII)
- From 1973 to 1989 she headed the departmentIn 1975
- A.I. Tentsova was the first elected Corresponding Member. RAMS department of biomedical sciences, specialty "biopharmacy".

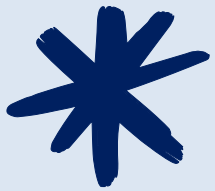
А.И. Тенцова, И.С. Ажгихин. Лекарственная форма и терапевтическая эффективность лекарств.- 1974.- 335 с.

Biopharmacy

- ***Biopharmacy*** is a science that studies the influence of pharmaceutical, biological and other factors on the therapeutic efficacy of drugs.

- The task of biopharmacy is the theoretical substantiation and creation of an optimal dosage form that provides the maximum therapeutic effect of the active substance with minimal side effects on the body.

- The content of biopharmacy is the study of the dependence of the therapeutic efficacy of drugs on ***pharmaceutical factors.***

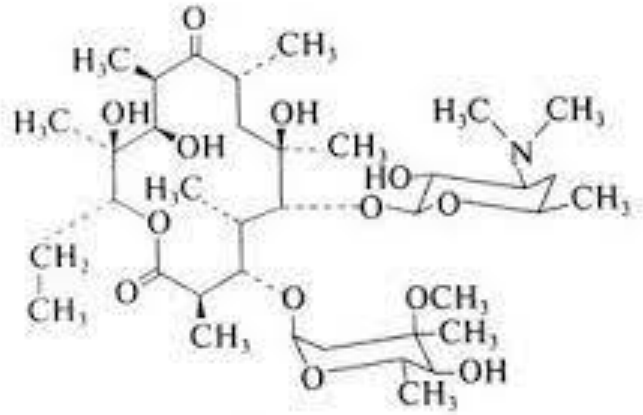


Pharmaceutical Factors

- simple chemical modification of active pharmaceutical ingredients (API);
- the physical state of the API;
- the nature and amount of excipients;
- technological operations, processes that take place when obtaining a medicinal product;
- dosage form.

SIMPLE CHEMICAL MODIFICATION OF ACTIVE PHARMACEUTICAL SUBSTANCES

- A simple chemical modification of API is understood as the use of substances in the form of various salts, acids, bases and other compounds, in which the part of the substance molecule responsible for the pharmacological effect is completely preserved.



Эритромицин

In the production of erythromycin tablets or capsules, erythromycin base is sometimes replaced with erythromycin propionate. The quantitative activity of the antibiotic is equivalent, however, the level of the substance in the blood plasma is 2-4 times higher when taking erythromycin propionate than when taking the base.

SIMPLE CHEMICAL MODIFICATION OF ACTIVE PHARMACEUTICAL SUBSTANCES

- Metoprolol tartrate has a relatively short half-life.
- Metoprolol succinate exhibits a b-blocking effect for 24 hours, i.e. salts provide different pharmacokinetics and change the rate of absorption of the substance into the blood.

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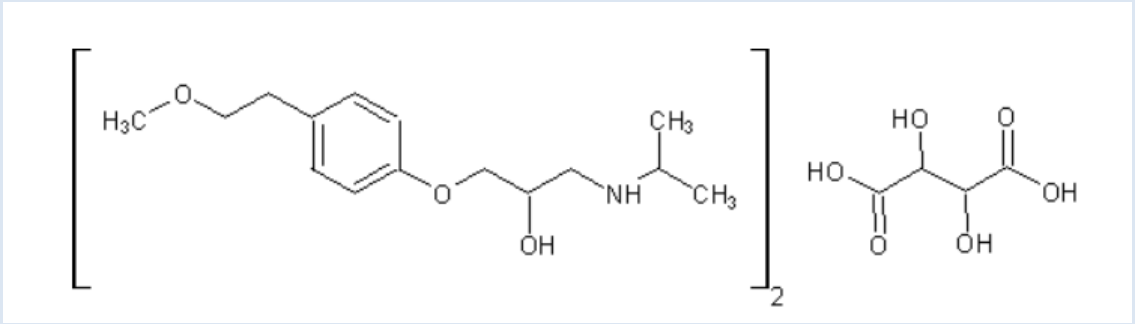
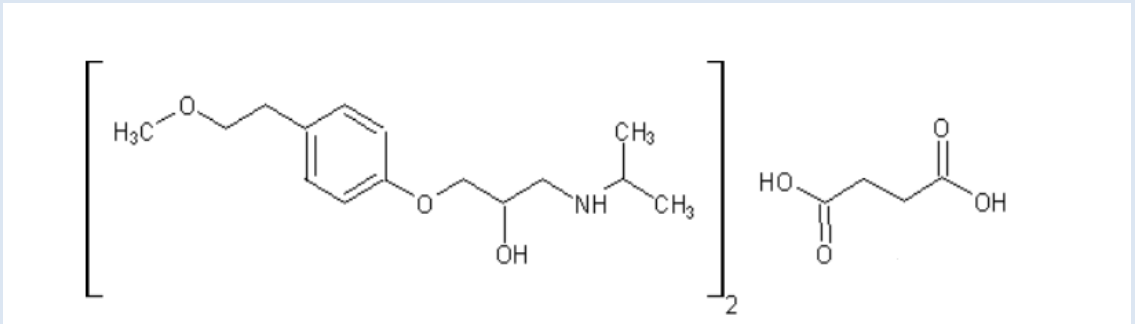
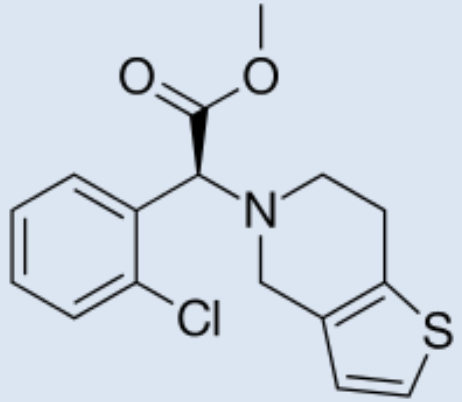
- Immediate release metoprolol tablets contain a highly soluble tartrate (water solubility over 700 mg/ml), while sustained release formulations are derived from the less soluble succinate salt (water solubility about 300 mg/ml).



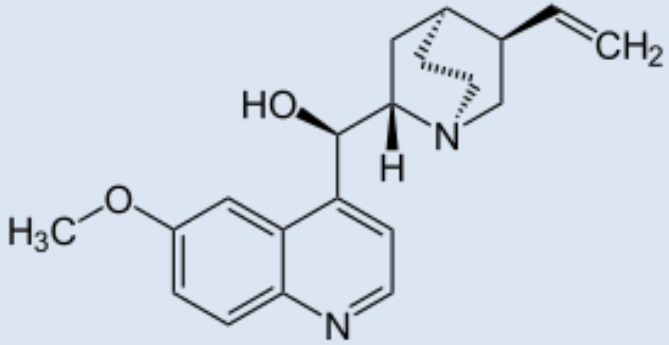


SIMPLE CHEMICAL MODIFICATION OF ACTIVE PHARMACEUTICAL SUBSTANCES. OPTICAL MODIFICATIONS

- Clopidogrel - S-enantiomer is active, R-enantiomer is an impurity.



- The dextrorotatory isomer of quinine sulfate has a stronger antiarrhythmic activity than the levorotatory.



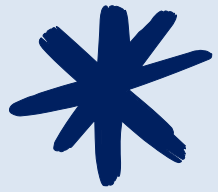
PHYSICAL STATE OF API

- Crystal shape
- Particle sizes
- Degree of crystallinity
- Grinding degree
- Polymorphism

PHYSICAL STATE OF APS. PARTICLES SIZES AND THEIR CHARACTERISTICS

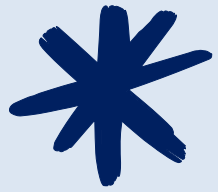
- An increase in the total surface area in contact with the liquid environment of the gastrointestinal tract contributes to an increase in solubility.

- The smaller the particle size, the larger the active surface area, the faster the dissolution rate and the higher the bioavailability.

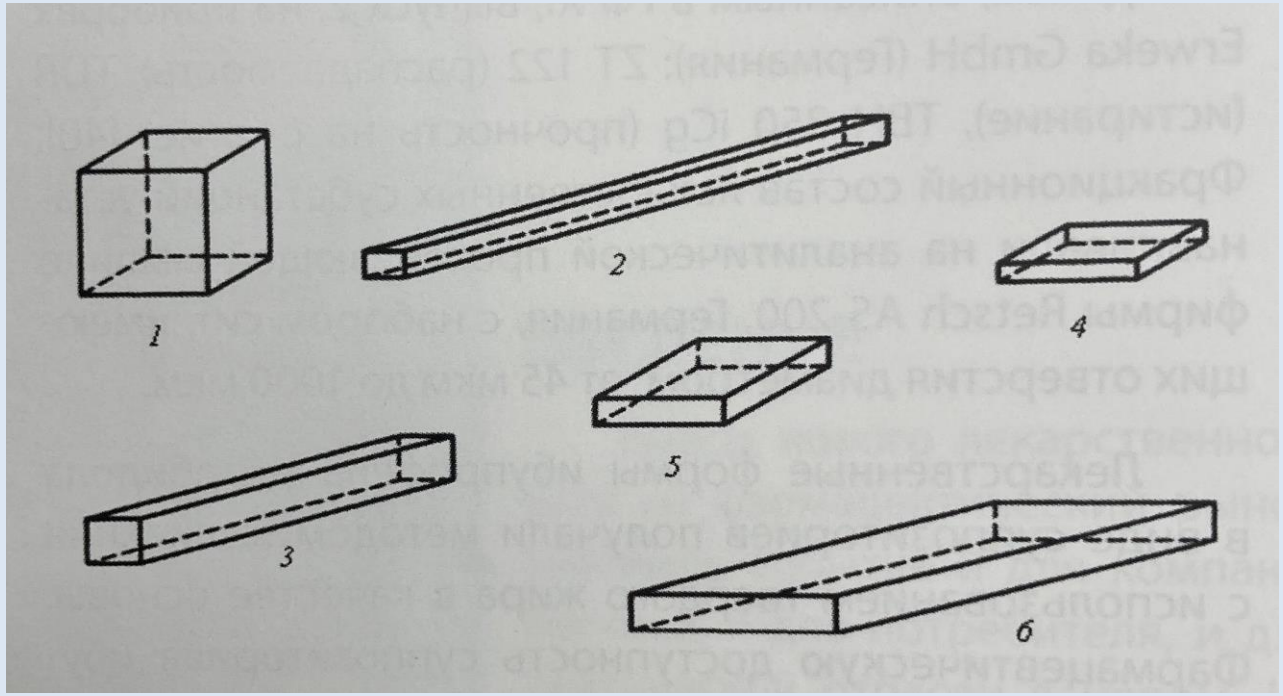


PHYSICAL STATE OF APS. DISPERSITY

- ***The dispersion*** of API particles has both technological (affects flowability, bulk mass, mixing uniformity, dosing accuracy) and biopharmaceutical significance (affects the rate and completeness of API absorption, concentration in biological fluids).
- There are ways to obtain API particles of controlled size and shape: changing the conditions of crystallization from solution, changing the solvent, mechanical or ultrasonic treatment, dehydration / desolvation of larger particles, conducting solid-phase reactions accompanied by dispersion of samples, etc.
- ***Micronization*** is the process of reducing the size of particles by grinding them to micron sizes.



Particle shape according to USP 31/NF 26



1 - equilateral volumetric: particles with the same length, width and thickness, including cubic and spherical particles;

2 - acicular: thin, needle-like particles or similar to it in terms of the ratio of length and thickness;

3 - columnar (rod-shaped): long, thin particles with a width and thickness greater than that of acicular;

4 - scaly (lamellar): thin, flat, with the same width and length;

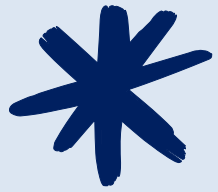
5 - lamellar (volumetric): flat, identical in length and width, but with a greater width than scaly;

6 - plank-shaped: large, tonic lamellar particles.

PHYSICAL STATE OF API

- ***Polymorphism*** - the ability to form crystalline structures that are chemically identical, but differ in physical properties: solubility, specific heat, melting point, etc.

- Different polymorphic modifications of medicinal substances differ in the effectiveness of the therapeutic action and stability.



Reasons for polymorphism

• Differences in:

The spatial arrangement of molecules, atoms and ions in the crystal lattice,

The value of the angle between the units of the crystal lattice,

Packing densities and crystal shapes (hexagonal, cubic, rhombic, etc.),

Degrees of association of molecules,

Coordination numbers (nearest units),Rotation of molecules or radicals of the crystal lattice

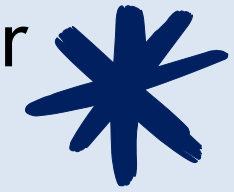
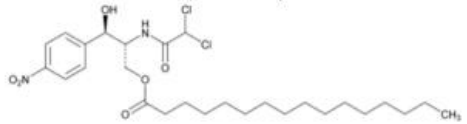
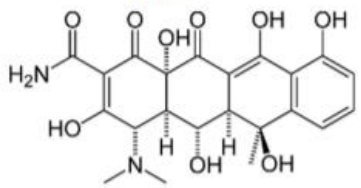
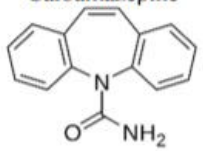


Table 2. Summarization of polymorphism of several drugs.

Drug Substance	Polymorphism Aspects	Bioavailability Issues
Chloramphenicol palmitate 	Chloramphenicol palmitate is a prodrug of chloramphenicol with antibiotic properties [64]. Chloramphenicol palmitate exist in three polymorphic forms: (A, B, C) [65,66], the stable form A (biologically inactive modification), the metastable form B (active modification) and unstable form C [67–69]. The three crystalline forms were also called α, β and γ. The α form is unstable at room temperature and gradually transforms to β on storage [70,71].	Form B (β) dissolves faster than Form A (α), and has a much higher solubility [72–74]. Low serum levels for the stable polymorph A were observed [75].
Oxytetracycline 	Oxytetracycline is a broad spectrum antibiotic. It exists in two different polymorphs [76].	Oxytetracycline showed differences in patients' blood levels [77] or differences in *in vitro* dissolution of tablets [78] because of differences in polymorphic forms.
Carbamazepine 	Carbamazepine is used in the treatment of epilepsy and trigeminal neuralgia. Different polymorphic forms were described [79–91]. Four anhydrous polymorphs were characterized: I, II, III, and IV, respectively identified as triclinic, trigonal, monoclinic, and monoclinic [77].	In spite different studies demonstrated similar pharmacokinetics in humans of anhydrous and dihydrate forms of carbamazepine [92] and no differences in bioavailability between a generic carbamazepine product and an innovator product [93], several clinical failures were reported concerning carbamazepine [94,95], in particular with generic carbamazepine tablets [96]. More recently, it was confirmed that the initial dissolution rate of carbamazepine was in the order of form III > form I > dihydrate, while the order of AUC values was form I > form III > dihydrate. This discrepancy may be attributed to the rapid transformation from form III to dihydrate in GI fluids [97].

Molecules 2015, 20, 18759-18776; doi:10.3390/molecules201018759

NATURE AND QUANTITY OF EXCIPIENTS

May affect therapeutic efficacy:

- action localization
- acceleration or delay of release
- Bioavailability
- safety

TECHNOLOGICAL OPERATIONS, PROCESSES OCCURING WHEN OBTAINING DOSAGE FORMS

Type of granulation:

hydration - hydrolysis, chem. reactions,

adhesive composition

drying - temperature effect, crystallization, mechanical effect

Pressing

tablet press brand - temperature effect,

pressing pressure

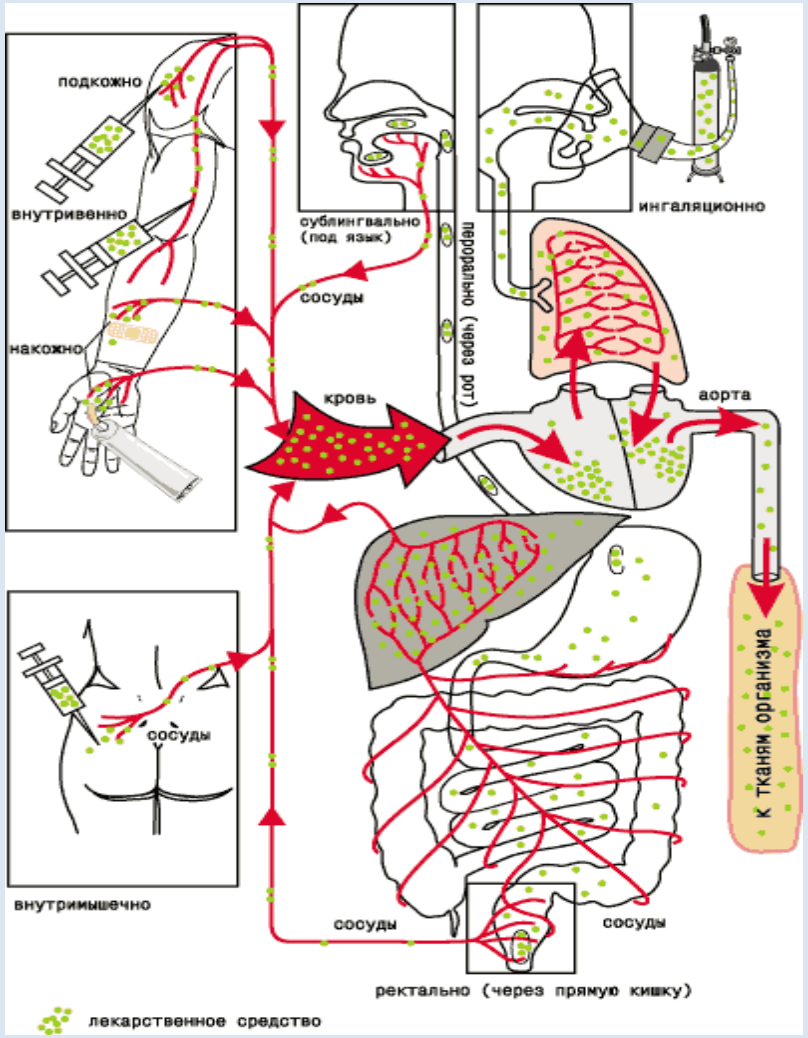
Occurrence, polarization of charges

The emergence of new connections

Coating - method, thickness, porosity, solubility, dissolution rate, etc.)

Composition of excipients

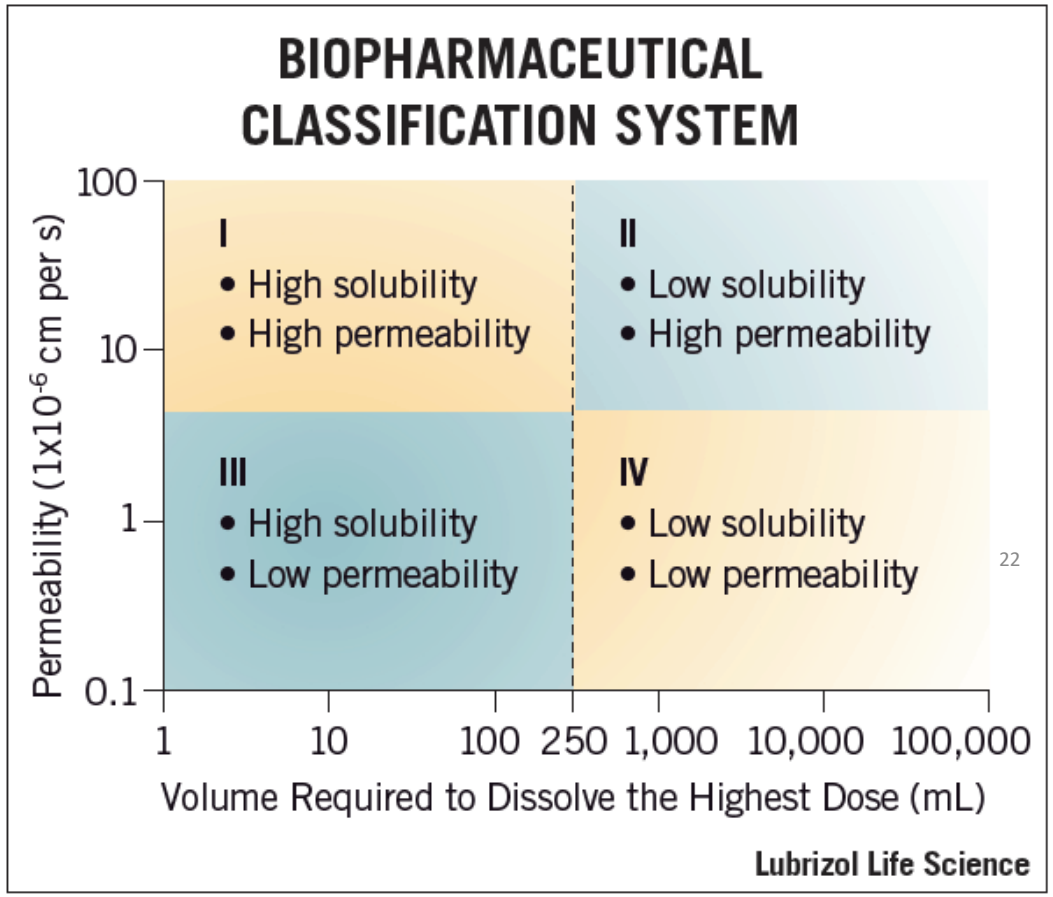
DOSAGE FORM, ROUTE OF ADMINISTRATION



- ***Dosage form*** is the state of the medicinal product, corresponding to the methods of its administration and use and ensuring the achievement of the desired therapeutic effect
- The most important task in the development and preparation of dosage forms is to provide optimal conditions for the release and subsequent absorption of API.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

Figure 1



Adopted by the FDA in 2001 as industry recommendation for the development of the Dissolution Test, later used to predict the bioavailability of substances and conduct the Biowaiver procedure

Amidon GL, et al. Pharm Res. 1995

https://lubrizolcdmo.com/technical-briefs/biopharmaceutical-classification-system/

Solubility

- ***Solubility*** of drugs in biofluids of the gastrointestinal tract (gastric juice, intestinal juice).
- Determined in the pH range corresponding to the pH of the biological fluids of the gastrointestinal tract - 1.2 - 6.8 (1.0-7.5).
- Carried out by shaking in a thermostated flask (Shake-flask method). Within 24 hours at a constant temperature of 37 ˚ C in triplicate, preferably at pH 1.2; 6.8; 7.4.
- Characteristics of biopharmaceutical solubility that allow classifying a drug as a drug with “high solubility” or “low solubility” are Dose/Solubility Ratio (D/S) and the Dose number (D_0)

Dose/Solubility Ratio

D/S ≤ 250 mL – «high solubility»

Dose Number

$$D_0 = \frac{M_0}{V_0 \cdot C_{s,min}}$$

250 ml - 1 glass of water, which is washed down with drugs when used for bioequivalence studies.

$D_0 \leq 1$ – high solubility
$D_0 > 1$ – low solubility

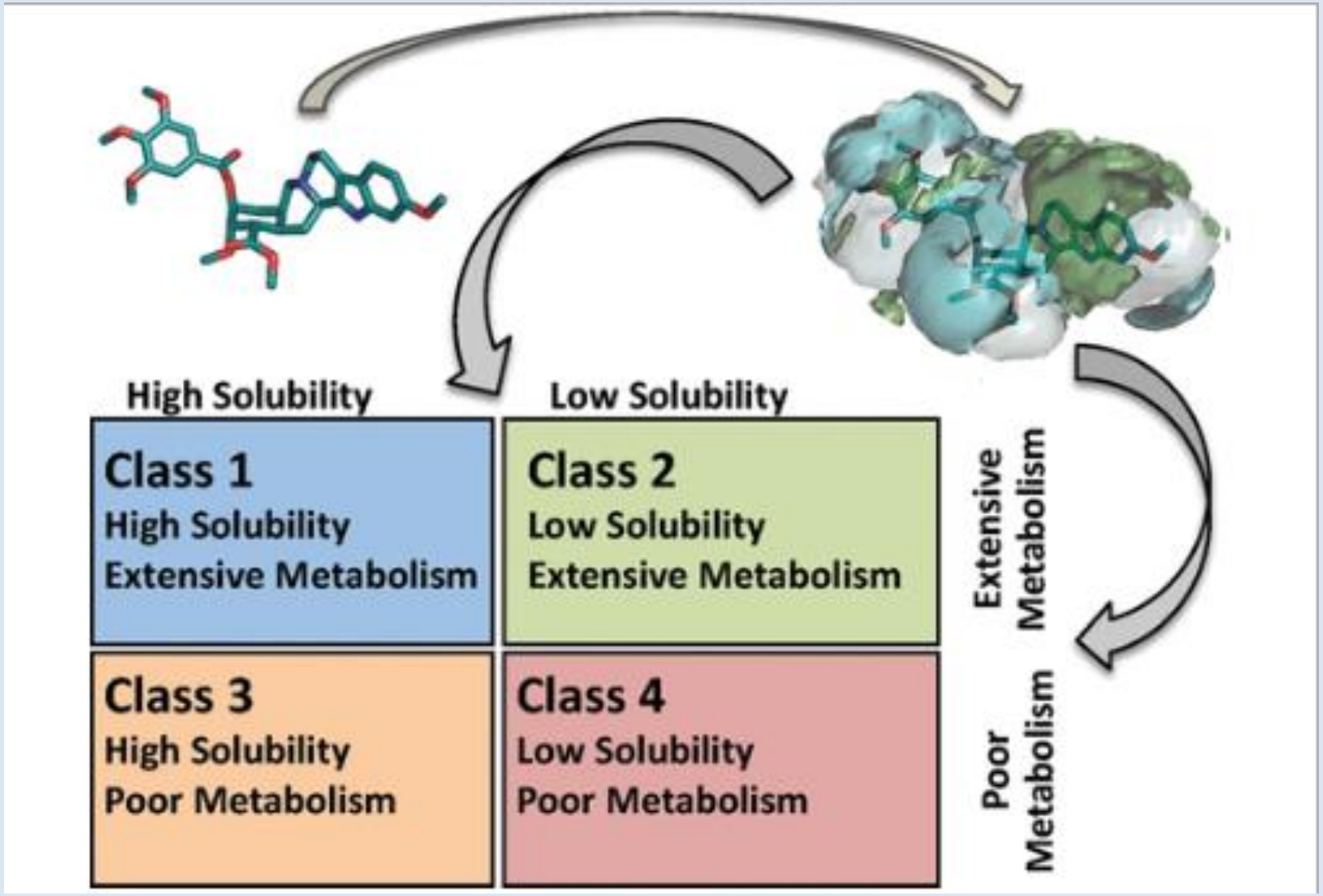
M_0 – maximum dose of API, mg
V_0=250 mL
Cs, min – minimum solubility, mL

PERMEABILITY

- ***Methods for determining permeability***
- In vivo method
- determination of bioavailability (absolute bioavailability greater than 85% - high permeability)
- determination of the permeability coefficient by the method of intestinal perfusion (Peff in vivo).
- In vitro
- determination of lipophilicity, distribution coefficient in the octanol-water system log P
- determination of permeability on a monolayer of epithelial cells of colon carcinoma Caco-2.

Criteria for high permeability determined on cell monoculture - the value of the apparent intestinal permeability Papp in vivo must exceed $1 \cdot 10^{-6}$ cm/s

Biopharmaceutics Drug Disposition Classification System (BDDCS)



https://pubs.acs.org/doi/10.1021/mp2004302