Research and development of pharmaceuticals 1/2

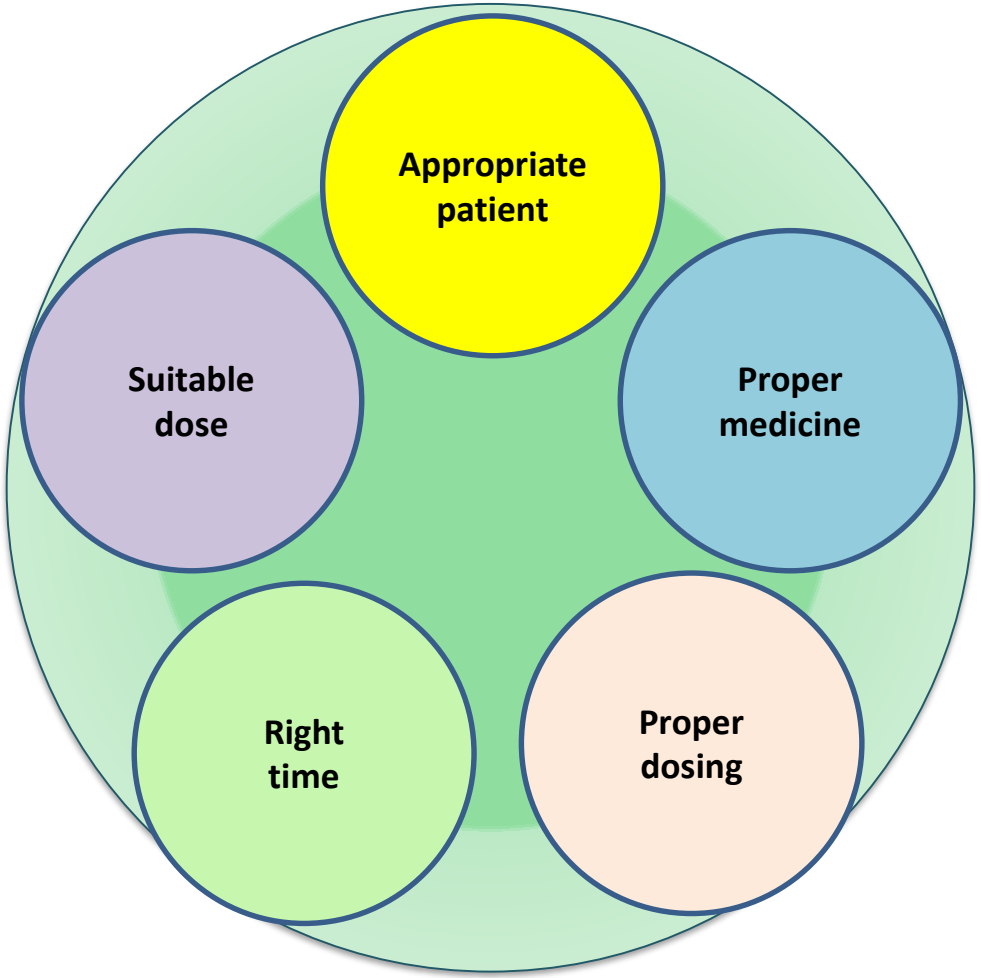
Luxembourg declaration, 2005.

Patients interest

Patient Safety – Making it Happen!

The right to access to high-quality healthcare is a fundamental right in the European Union.

Accordingly, patients, as recipients of health care services, are entitled to expect providers to make every effort to ensure their safety.



Before using any medicine, remember the 5 points:

- **appropriate patient,**
- **proper medicine,**
- **proper dosing,**
- **right time,**
- **in a suitable dose.**

Interests in medicines supplying

1. Patients' interests

- health promotion (prevention)
- healing / alleviation of symptoms
- individualized therapy (group of patients)

2. Social interest

- maintaining the workforce,
- minimization of health costs (rationalization, cost effective therapy, bed counting, drug prices)
- retention of specialized staff

3. Industrial interests

- profit making (R&D, market acquisition)

The pharmaceutical industry is profit-driven,
one of the most research-intensive industries.

An important factor for the economic competitiveness of pharmaceutical R&D is added intellectual value.

API
(original or
generic)

Pharmaceutical preparations
technological research
(in new dosage form)

Pharmaceutical preparations
technological development
(application in an existing
pharmaceutical form)

R&D
Research and Development

Pharmaceutical research

Refers to activities aimed at improving the scientific knowledge about

- **active pharmaceutical ingredients and**
- **pharmaceutical preparations**

in order to produce more effective medicines.

R&D
Research and Development

Drug development:

- targeted,
- a set of scheduled activities with the purpose,
- utilizing research-based insights,
- market entry of the drug.

R&D
Research and Development

Main components of research and development

- basic research and
- industrial or applied research.

The two research and development activities are closely related to each other and assume each other.

Effective applied research cannot be achieved without successful basic research, and vice versa.

R&D
Research and Development

Main components of research and development

Basic research - intended primarily to broaden general scientific and technical knowledge and is not directly linked to any industrial or commercial objective.

R&D
Research and Development

Main components of research and development

Industrial or applied research - research activity aimed at acquiring new knowledge, by which the acquired knowledge can be used for the development of new products, processes or to bring about a significant improvement in the existing products and processes.

R&D
Research and Development

Further opportunities for research and development

Experimental development:

Planning the results of applied research, ie designing new or improved products and processes.

Routine changes to products, production processes, existing services, even if they result in improvements to that product, process or service, are not considered experimental development.

R&D
Research and Development

Further opportunities for research and development

In order to strengthen or maintain the market position of enterprises, it is essential that they modernize and renew their products or the processes used in their manufacture, so they need continuous research, development and renewal in order to remain competitive.

Technological innovation:

Any activity of a scientific or technological nature, including investment in new knowledge, which actually or intentionally leads to the introduction of new or improved products or processes.

R&D
Research and Development

Invention:

The result of the invention is the knowledge gained so far
(a state of the art) technical solution somewhat (positively) exceeding.

Patent:

Legal protection of the technical solution created by the invention, exclusive exploitation right.

R&D
Research and Development

The invention is protected:

- patenting and
- keeping it secret

Advantage of patenting:

- may not be used by others for the duration of the protection
- time limited

The disadvantage:

- costs money

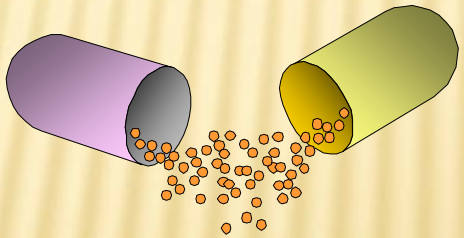
Advantage of secrecy:

- not time-limited
- it is for free

Disadvantage:

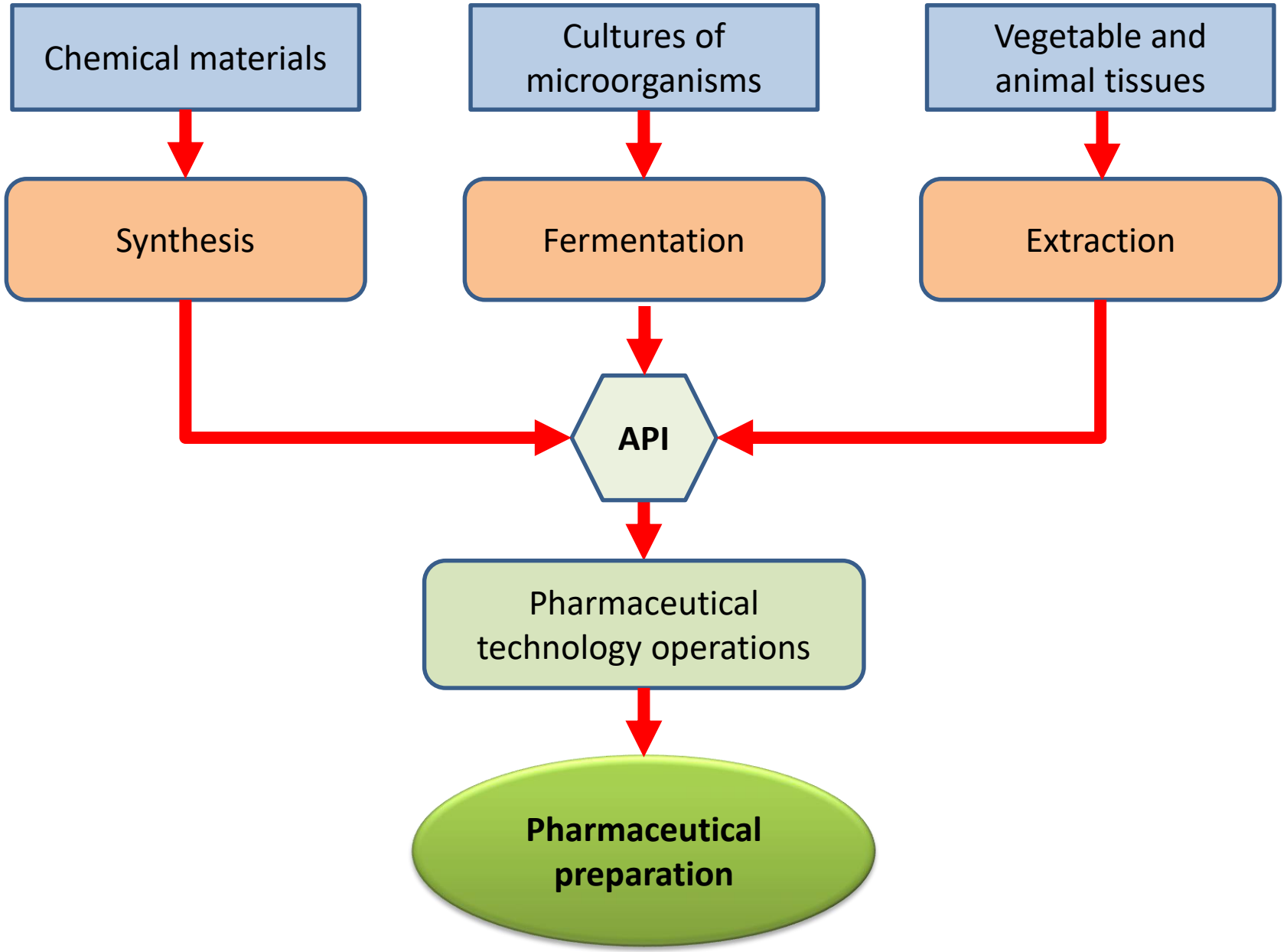
- can only be kept until it is patented by others (can no longer be used without legal consequences)

Research and development of active substances



R&D

Production and use of active substances



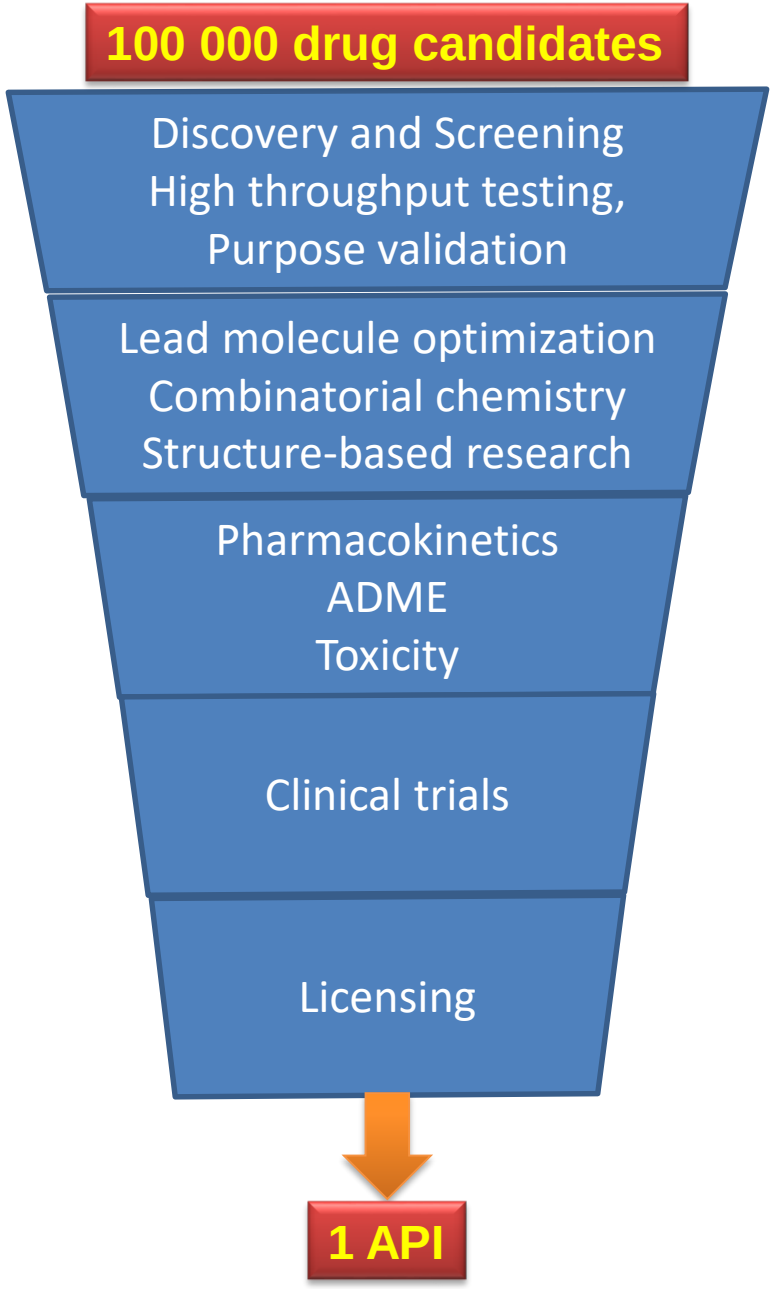
R&D

Major phases of drug development

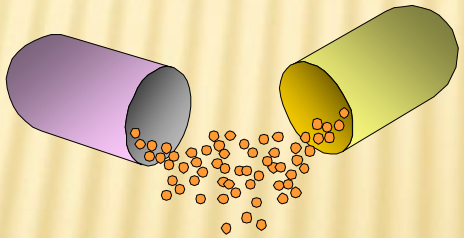
API
(original or generic)

Pharmaceutical preparations technological research (in new dosage form)

Pharmaceutical preparations technological development (application in an existing pharmaceutical form)



Pharmaceutical Technology research and development



R&D

The purpose and task of research and development of formulations is to develop drugs to meet the needs of therapy using pharmaceutical technology and special test methods based on biopharmaceutical aspects.

Product Design Required:

- when formulating a new active ingredient,
- modernization of a product containing a previously used API,
- to form a new dosage form.

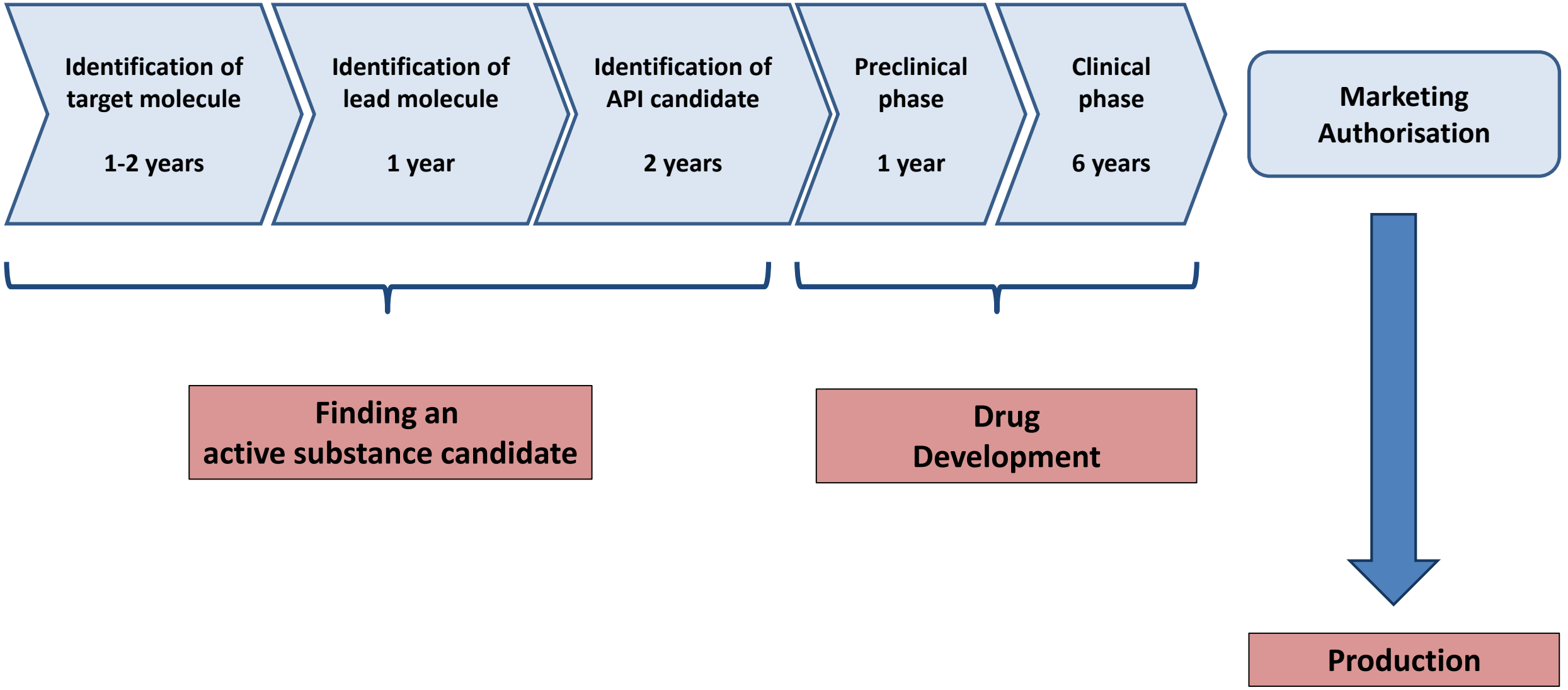
R&D

Not only do pharmaceutical formulations serve accurate dosage, shelf life, and safe drug delivery, they also play a critical role in controlling drug delivery.

Therefore, pharmaceutical, pharmaceutical technology and biopharmaceutical development begins at an early, pre-clinical stage of all research and development (R&D).

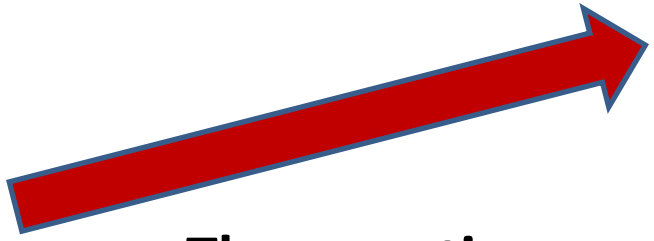
The active ingredient is then administered in the form of a formulation.

Main steps of R&D



Main steps of R&D

The active ingredient
physical,
chemical,
pharmacological,
pharmacokinetic,
biopharmaceutical,
parameters



Therapeutic purpose

Selection of a dosing regimen
appropriate to the therapeutic purpose
(biopharmacy, pharmaceutical technology)

Preformulation, drug product design
(biopharmacy, pharmaceutical technology)

Formulation, pharmaceutical product design
(biopharmacy, pharmaceutical technology)

Production
(biopharmacy, pharmaceutical technology)

R&D

First we discover the the drug and identify the market,

then we invent the disease.

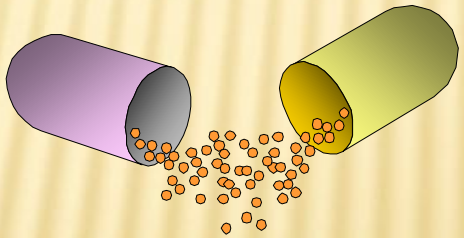
Main steps of R&D

Research and development activities on pharmaceuticals can be divided into two parts:

1. **Preformulation**

2. **Formulation**

Preformulation



Preformulation

Pharmaceutical companies in the 1960s began to introduce preformulation tests.

These are usually pre-tests designed to clarify that there are no significant barriers to the manufacture and marketing of the drug.

Preformulation

Definition:

Preformulation, as part of drug research and development, is the set of activities that we perform to prepare the product for reproducibility with quality parameters.

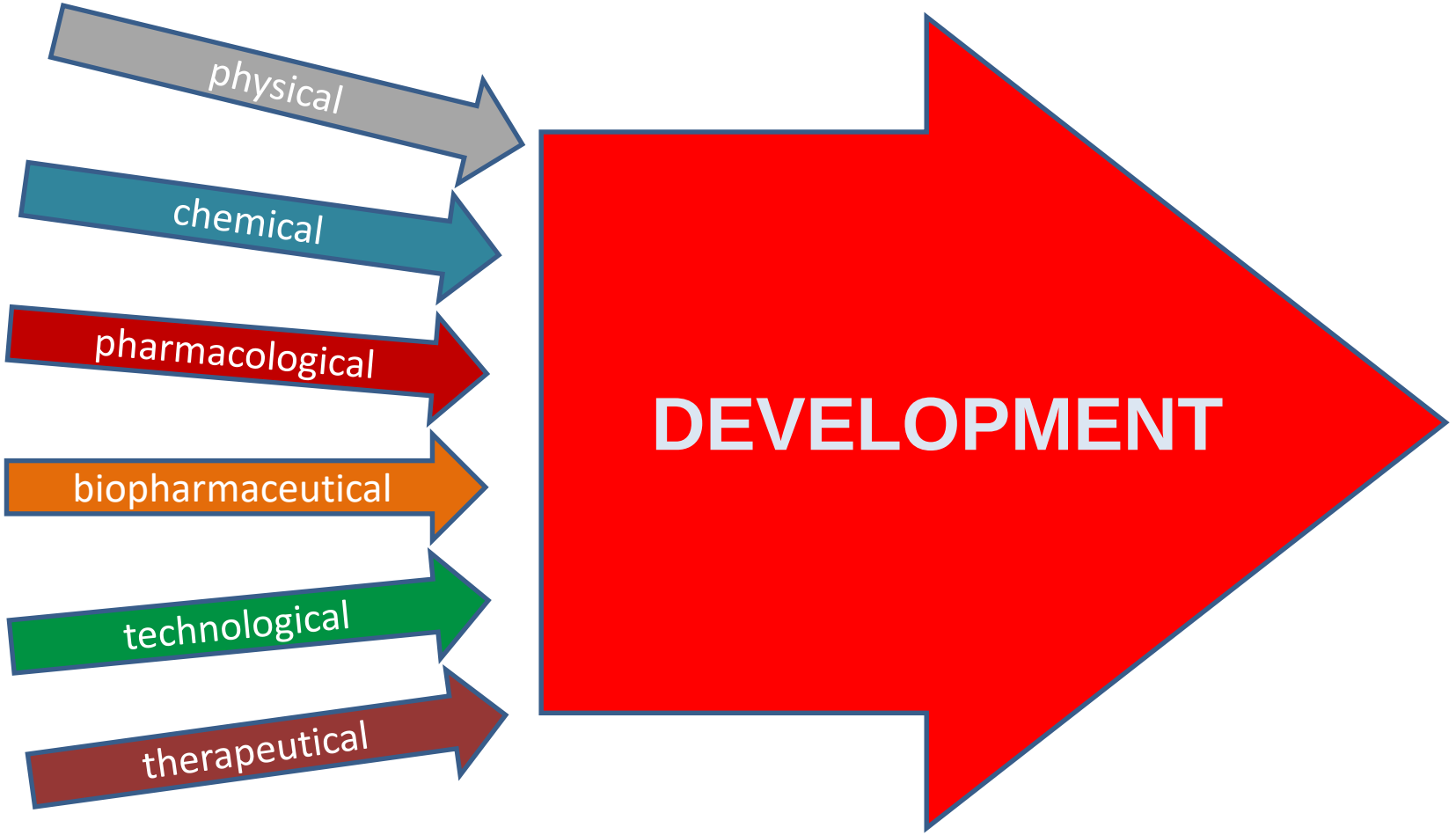
Preformulation

Aims of preformulation

1. Physico-chemical knowledge of the active ingredient of the preparation.
2. Exploration of the quality parameters of the reference preparation.
3. Formulation of the ideal formulation (composition) of the formulation by selecting suitable excipients to optimize the pharmaceutical and biopharmaceutical parameters of the formulation during the formulation phase.

Preformulation

Preformulation is a multidisciplinary development of a drug candidate.



Preformulation

The most important physical and chemical parameters of the active substance:

- crystallographic properties,
- melting point,
- solubility in various solvents,
- pH dependence of solubility,
- ionization constant (pKa),
- partition coefficient,
- dissolution rate,
- reactivity, incompatibility,
- stability,
- properties of solids
  - particle size, distribution,
  - crystalline structure properties,
  - polymorphism,
  - flow properties,
  - water sorption,
  - wetting ability,
- taste,
- color,
- smell.

Preliminary examinations:

Compatibility tests

1. Dual blends of active substance and potential excipients → forced stability test (50 ° C, 70 ° C / 1 month)

2. Challenge tests
light, heat, humidity, oxidation, acid, alkali? → active ingredient impurities?

3. Preformulation experiments

for solid dosage forms:
selection of appropriate dosage form, composition, operation

for liquid dosage forms:
selection of excipients and formulation materials

Development of test methods:

Development of test methods

chemical (if. content, contamination, stability),
physical (crystallography, particle size)
microbiology,
bioanalytical (parent compound, metabolites)
biopharmaceutical test methods (dissolution, prediction of absorption)

Validation of test methods

Stability

Liquid phase stability
pH effect
temperature effect

Solid phase stability
moisture effect
heat effect
light effect

Mechanism of degradation
hydrolysis
oxidation
activation energy
process order, kinetics
expiration date

Crystalline material
- physico-chemical parameters

Amorphous material
back formation
physico-chemical parameters

Hydrates / solvates
- physico-chemical parameters

Compatibility

- API - API
- API - excipient
- container

Preformulation

Common test methods used in preformulation

Test	Characterisation
1. UV specrtoscopy, TLC, HPLC, GC…	General methods
2. Solubility	Biological medium - UV, HPLC,GC
Water	intrinsic and pH-effect
pK_a	improving solubility e.g. by creating a salt form
Salts	solubility, hygroscopicity and stability
solvents	carriers or extracts
Distribution constant ($k_{o/v}$)	Lipophylicity, structural activity
Dissolution	Biopharmacy
3. Dissolution rate	Rotating disc method
4. Melting point	DSC
5. Particle size & distribution	Sieve analysis, microscopy, laser diffraction
6. Crystallography	DSC, RTG diffraction,electronmicroscopy
7. Stability	UV, HPLC,GC
liquid phase (dissolved state)	pH change, heat, hydrolysis – UV, HPLC,GC
solid phase	environmental effects (light, oxygen, heat)- UV,HPLC,GC
8. Density	Stamph volumeter
9. Rheological parameters	ASTM device…
10. Compressibility	Instrumented tabletting equipment,compression simulator
11. Compactibility (API and excipient)	DSC, TLC

Preformulation

Application of thermal energy in preformulation analysis

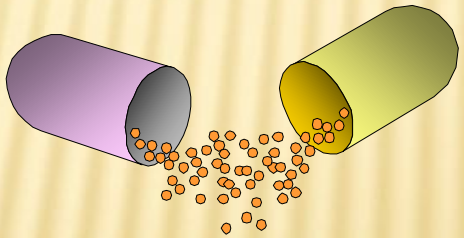
Method	Principle of measurement	Application
Differential Scanning Calorimetry (DSC)	Heat flow / heat capacity energy transfer as a function of temperature	crystallization polymorphism / pszeudopolimorfizmus glass transition temperature thermal decomposition melting point API Auxiliary Compatibility
Thermogravimetric analysis	weight change as a function of temperature and / or time	characterization of solvated / hydrated state loss of drying thermal decomposition sublimation
Modified DSC	change in heat flux / heat capacity as a function of temperature change in the sine program	glass transition point separating the reversible-irreversible heat flow in the overlapping region measuring enthalpy (stability) change upon return to rest

Preformulation

Application of thermal energy in preformulation analysis

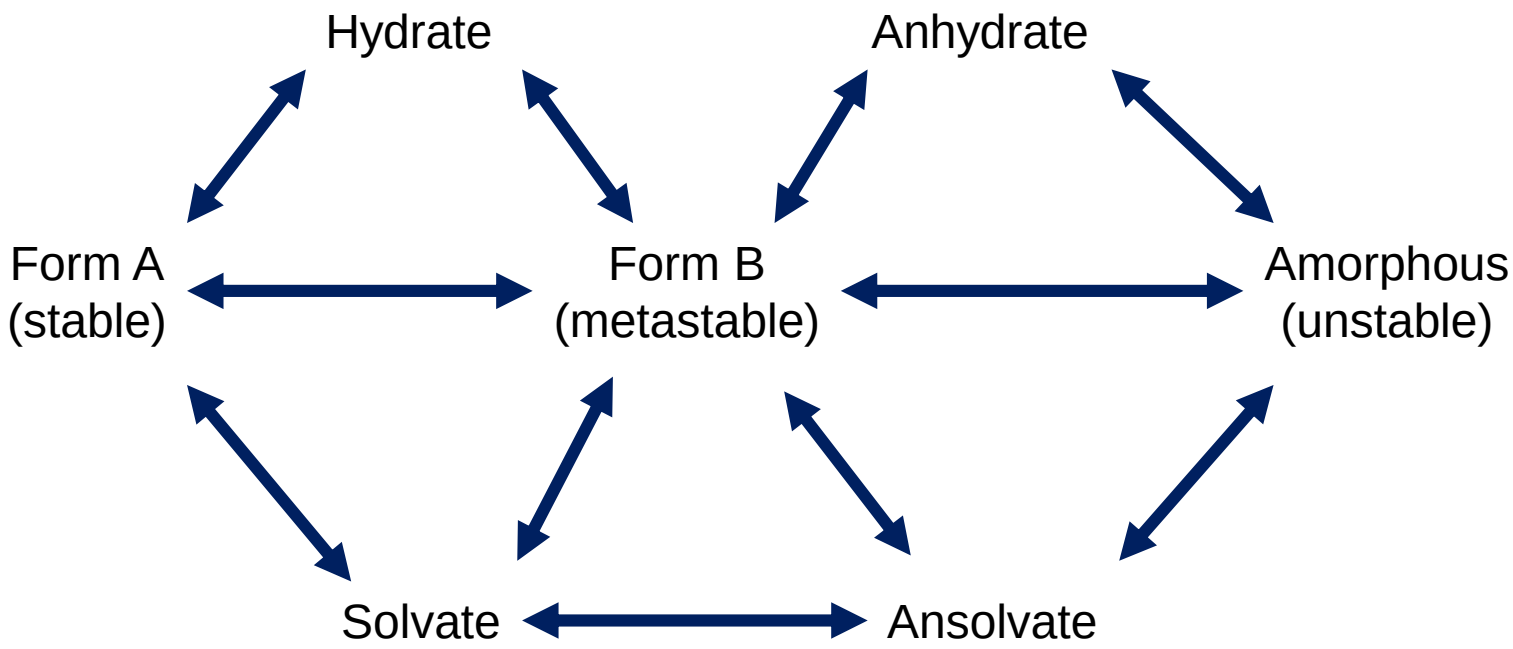
Method	Principle of measuring	Application
Thermo-microscopy	micro-photography of materials as a function of temperature	melting point decomposition polymorphism crystallization desolvation
Isothermal Microcalorimetry	high sensitivity heat flow measurement as a function of temperature / time	stability polymorphism measurement of amorphous content
Solution calorimetry	measurement of heat flow as a function of temperature / time	polymorphism measurement of amorphous content
Micro-thermal analysis	topography heat flow measurement as a function of temperature	melting point Glass transition temperature characterization of an amorphous state in a specific surface region
Thermal-mechanical analysis	expansion factor (softening)	Glass transition temperature
Dynamic-mechanic analysis	mechanical energy loss as a function of temperature	Glass transition temperature rheological properties

Preformulation Examples



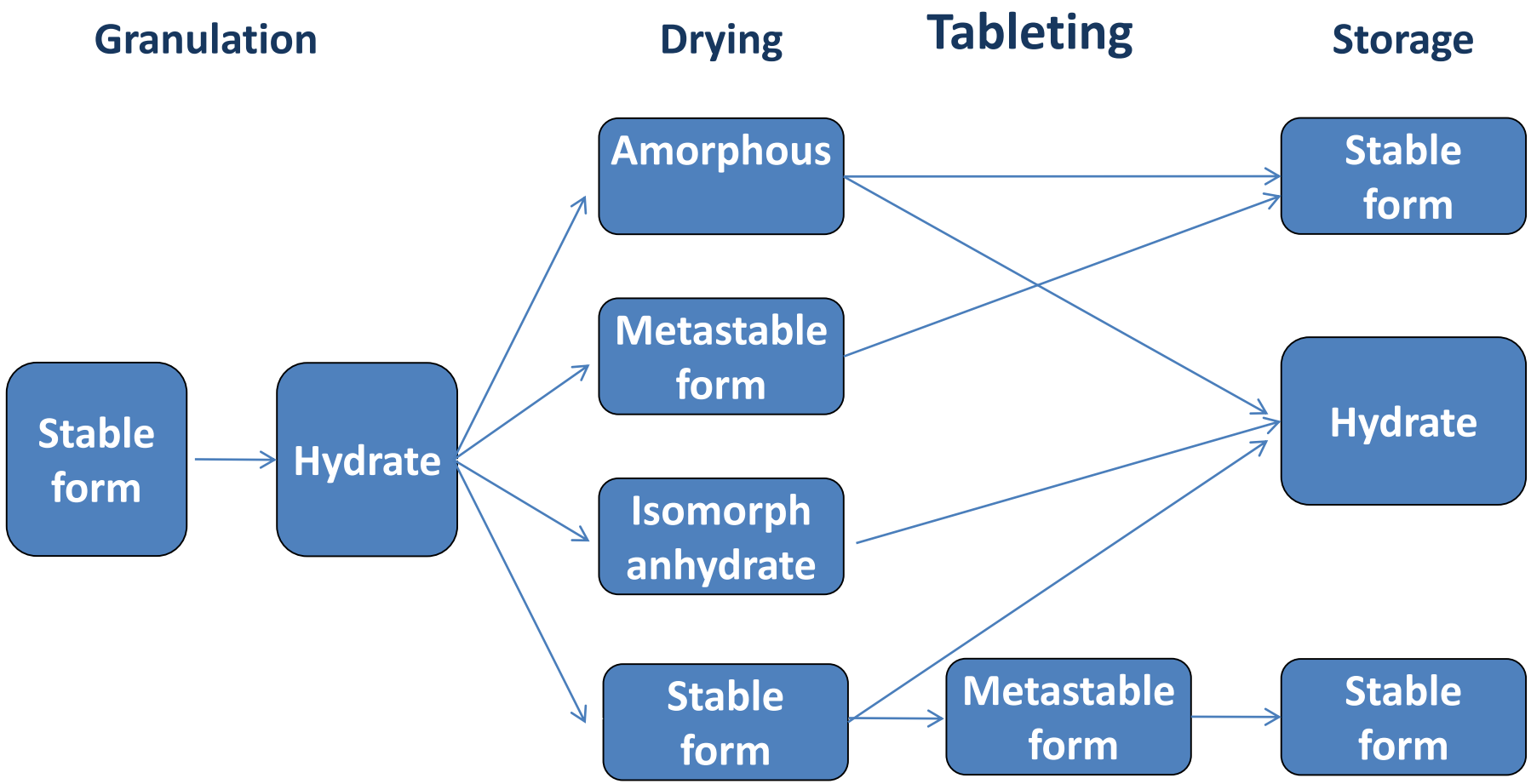
Importance of polymorphism

Possible manifestations of polymorphic materials:



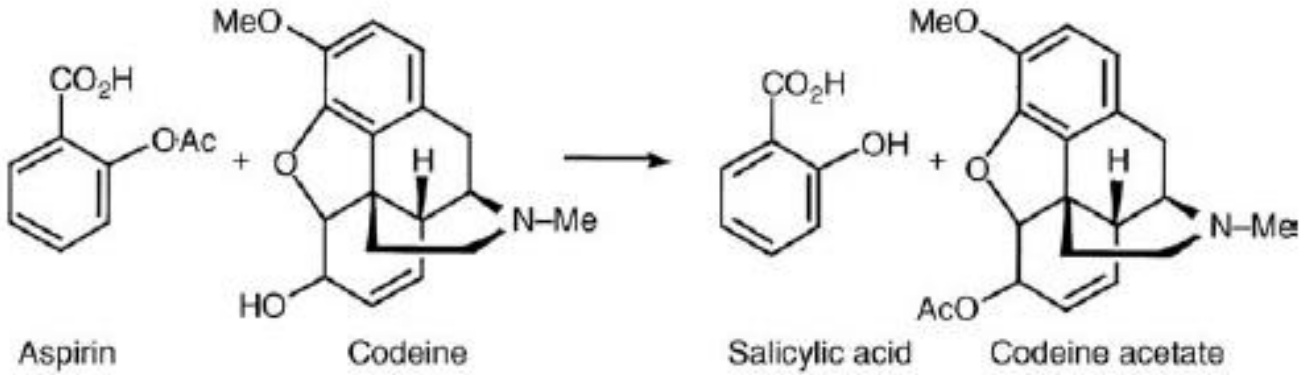
Importance of polymorphism

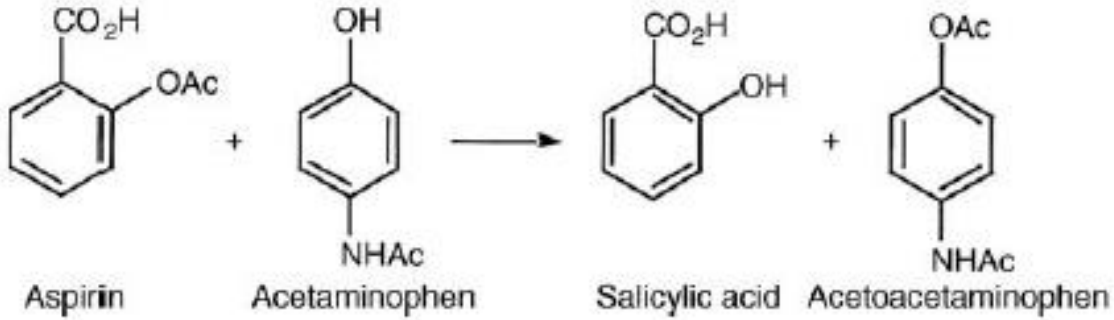
Possible phase transitions during tablet manufacturing:

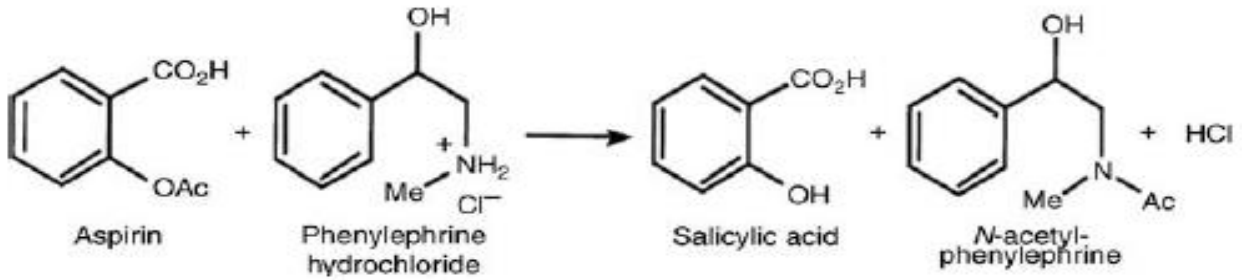


Preformulation

API interactions

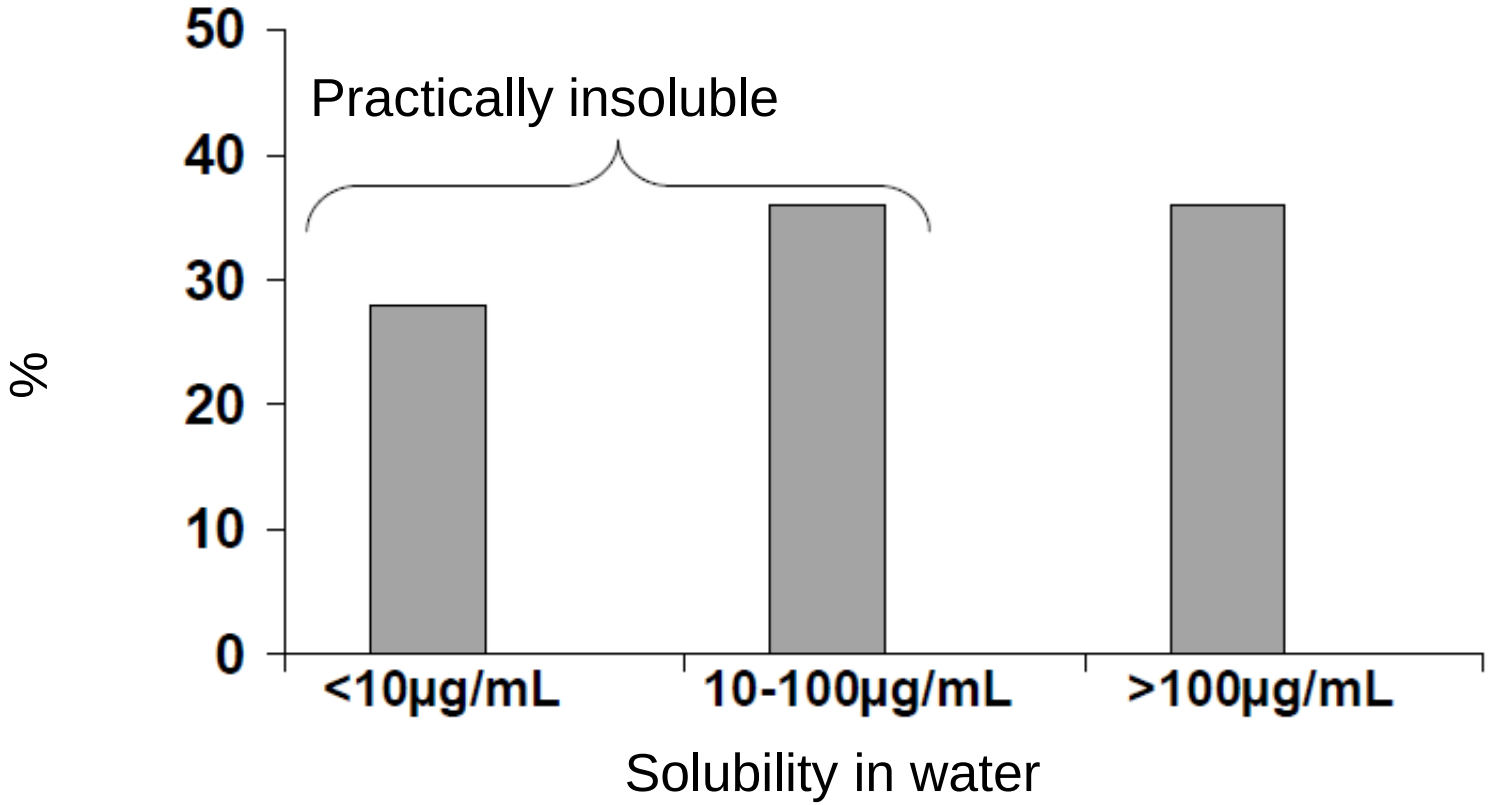






Solubility

Solubility trend in new API molecules



Preformulation

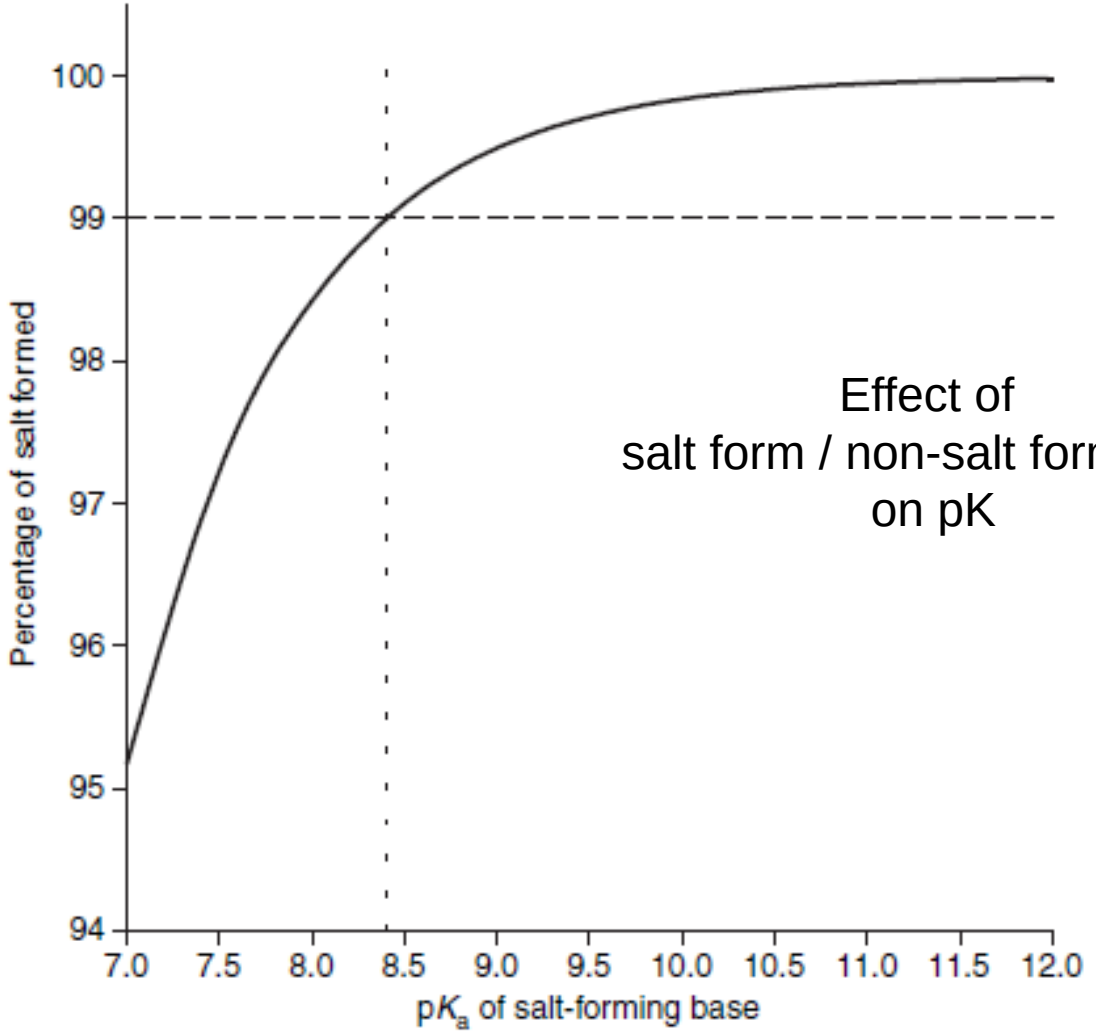
Salt formation

API type	Salt type
basic	Hydrochloride
	methansulfonate (mesilate)
	Hydrobromide
	Acetate
	Fumarate
	Sulfate
	Succinate
	Citrate
	Phosphate
	Maleate
	Nitrate
	Tartrate
	Benzoate
	Carbonate
	Pamoate
acidic	Sodium
	Calcium
	Potassium
	Trometamine

It may change during salt formation

- melting point,
- solubility,
- stability,
- crystalline characteristics,
- pK value,
- absorption,
- dose,
- pharmacokinetic and
- biopharmaceutical properties,
- toxicity
- bioavailability,
- bioequivalence.

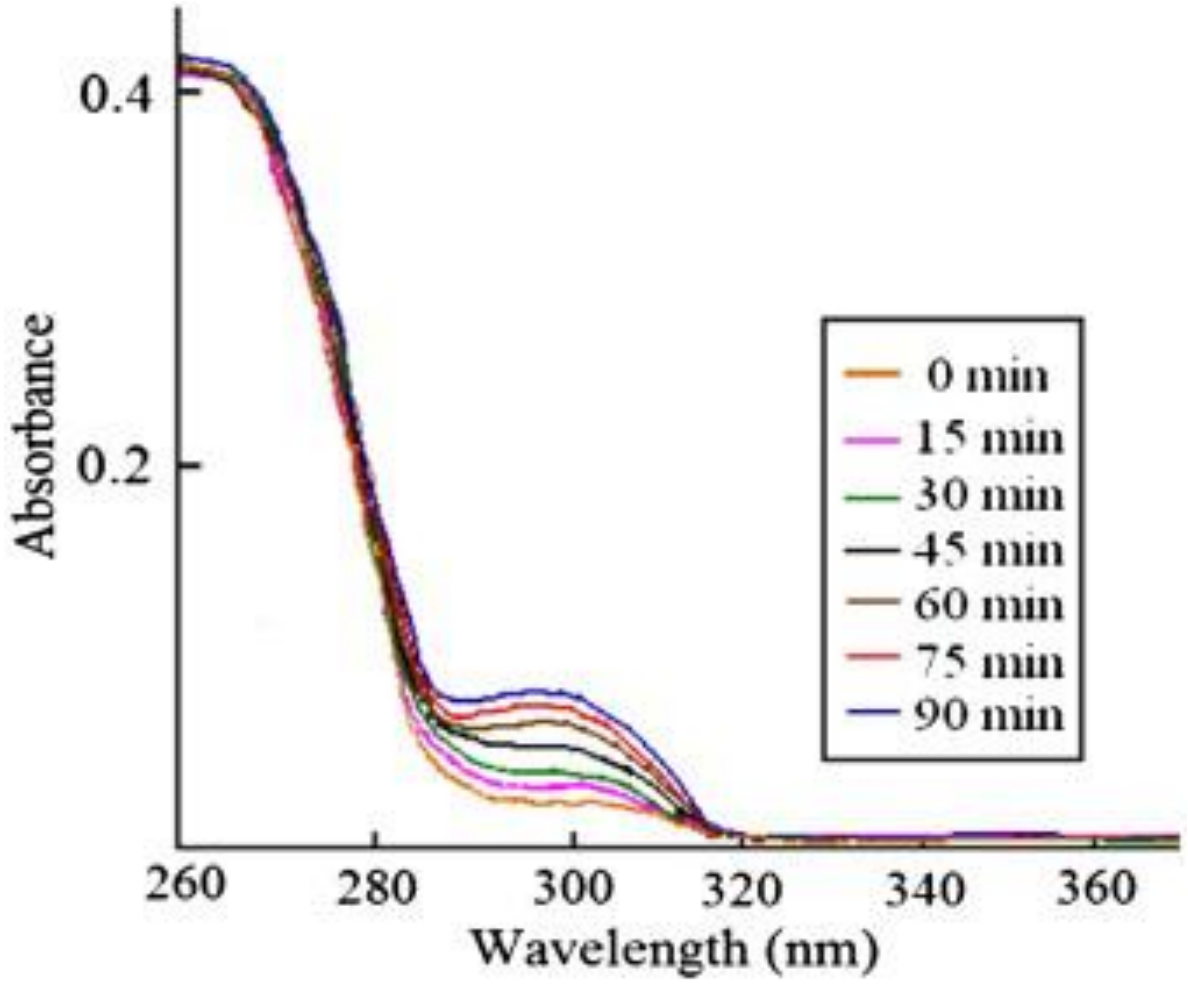
Salt form - pH dependence



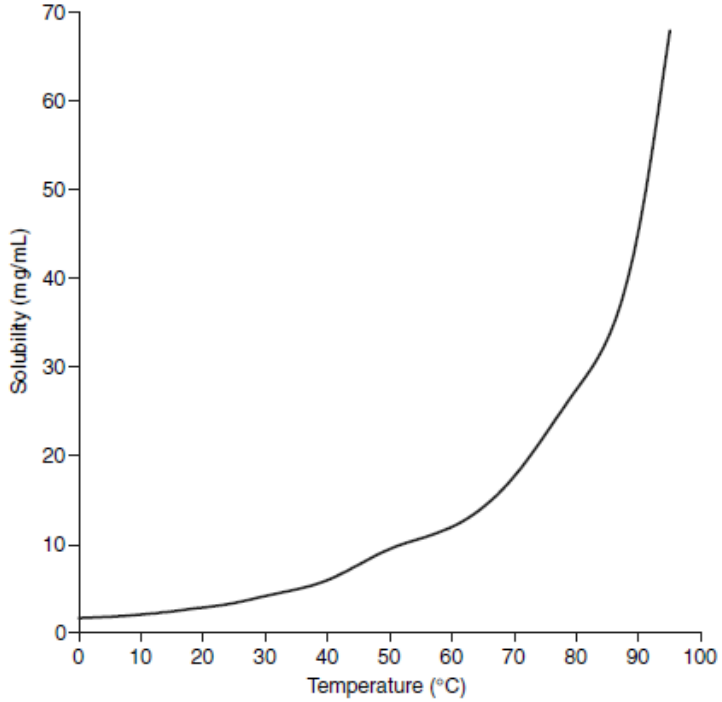
Effect of
salt form / non-salt form ratio
on pK

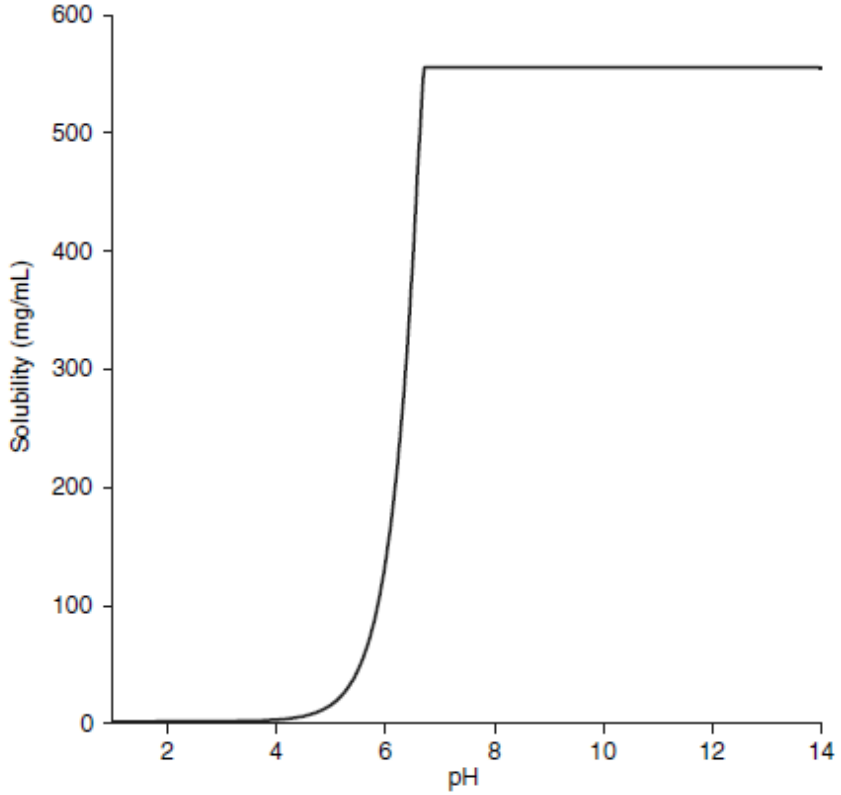
Figure 3 Degree of salt formation calculated for the reaction of ibuprofen with basic substances of varying pK values; note that the 99% formation criterion interacts with the curve at a pK_a value of 8.41.

Hydrolysis of ASA over time - UV spectrum change



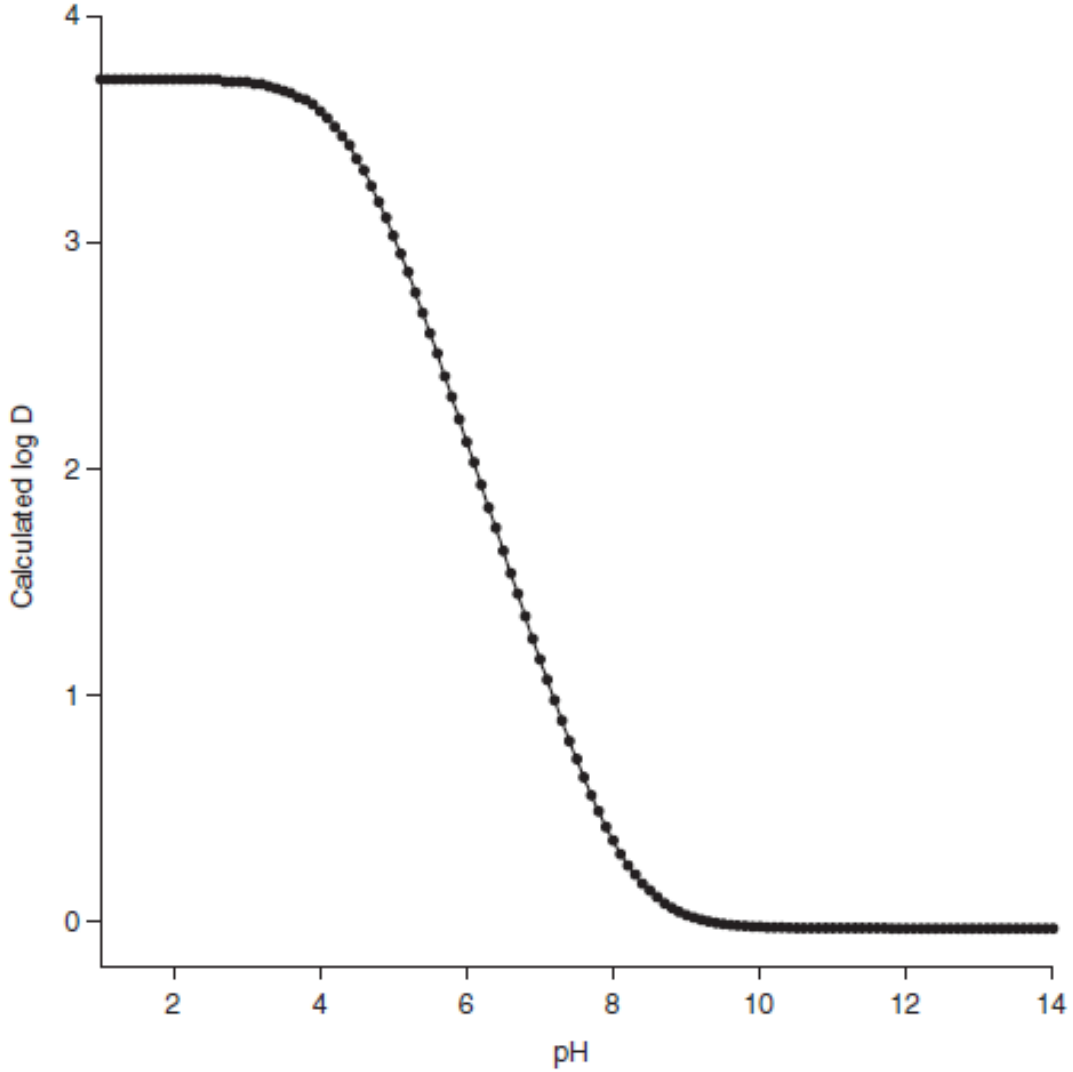
Temperature and pH dependence of solubility of benzoic acid



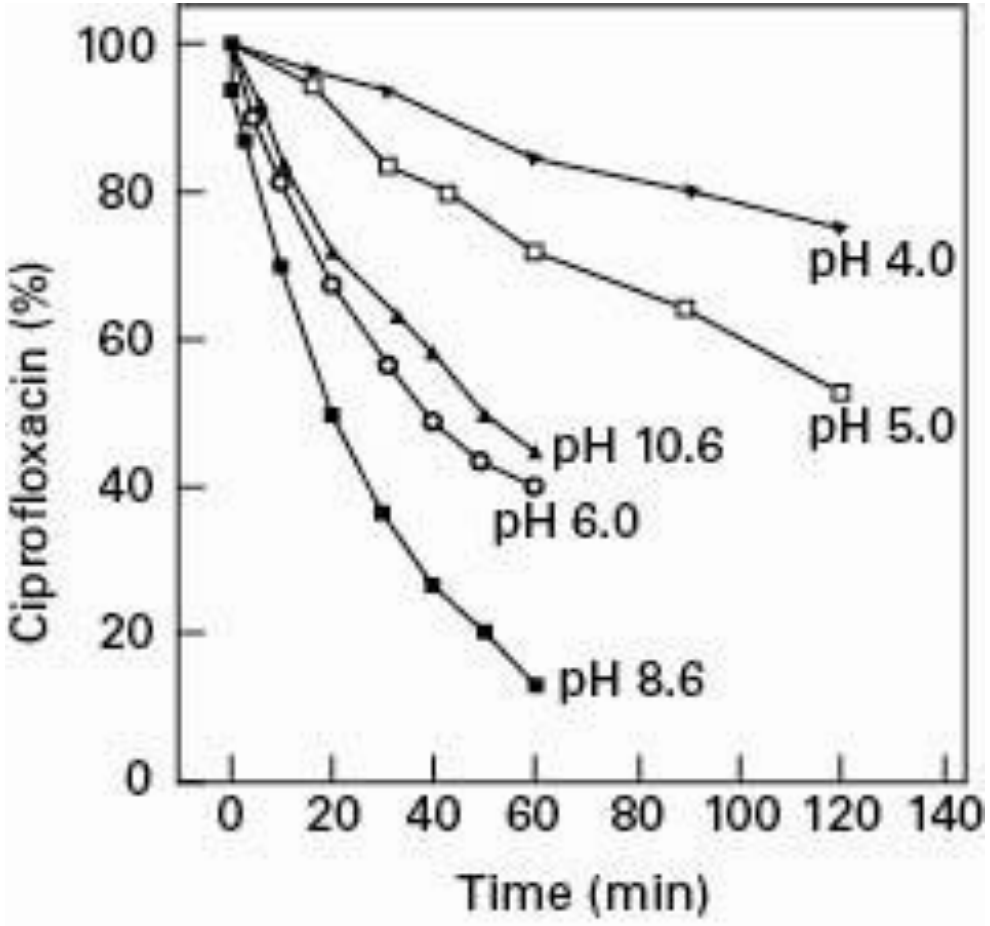


Preformulation

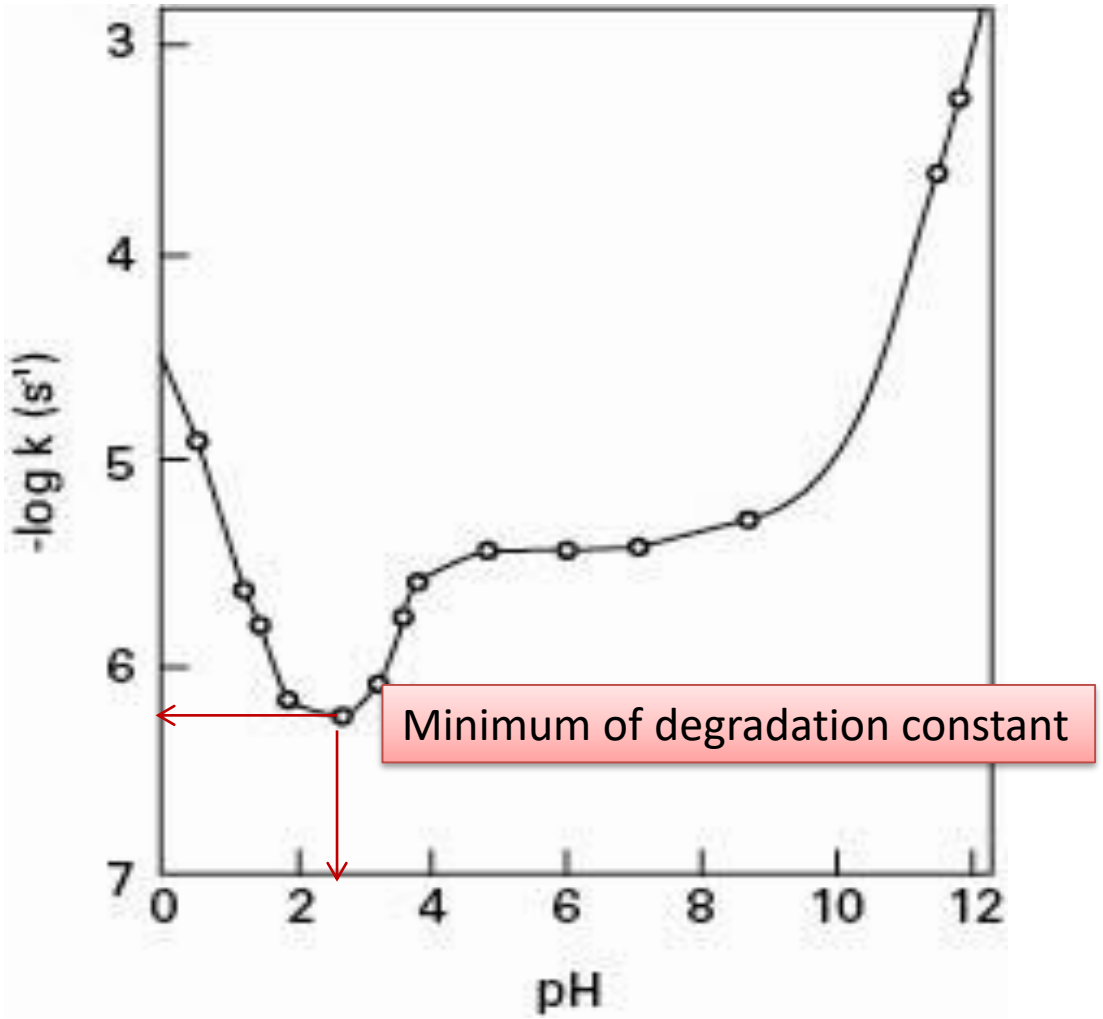
pH dependence of the partition coefficient of Ibuprofen



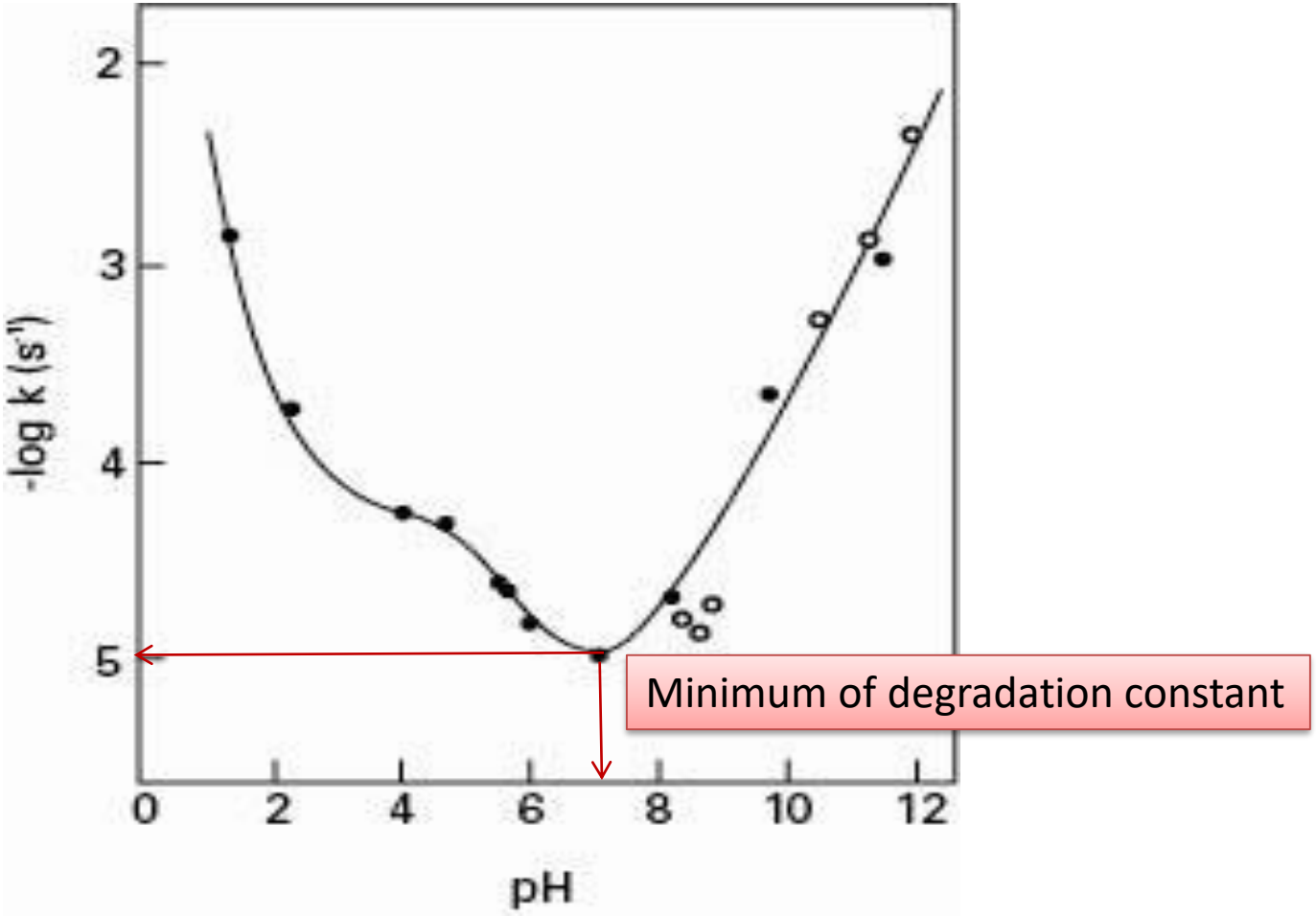
Decomposition of ciprofloxacin at different pH values over time



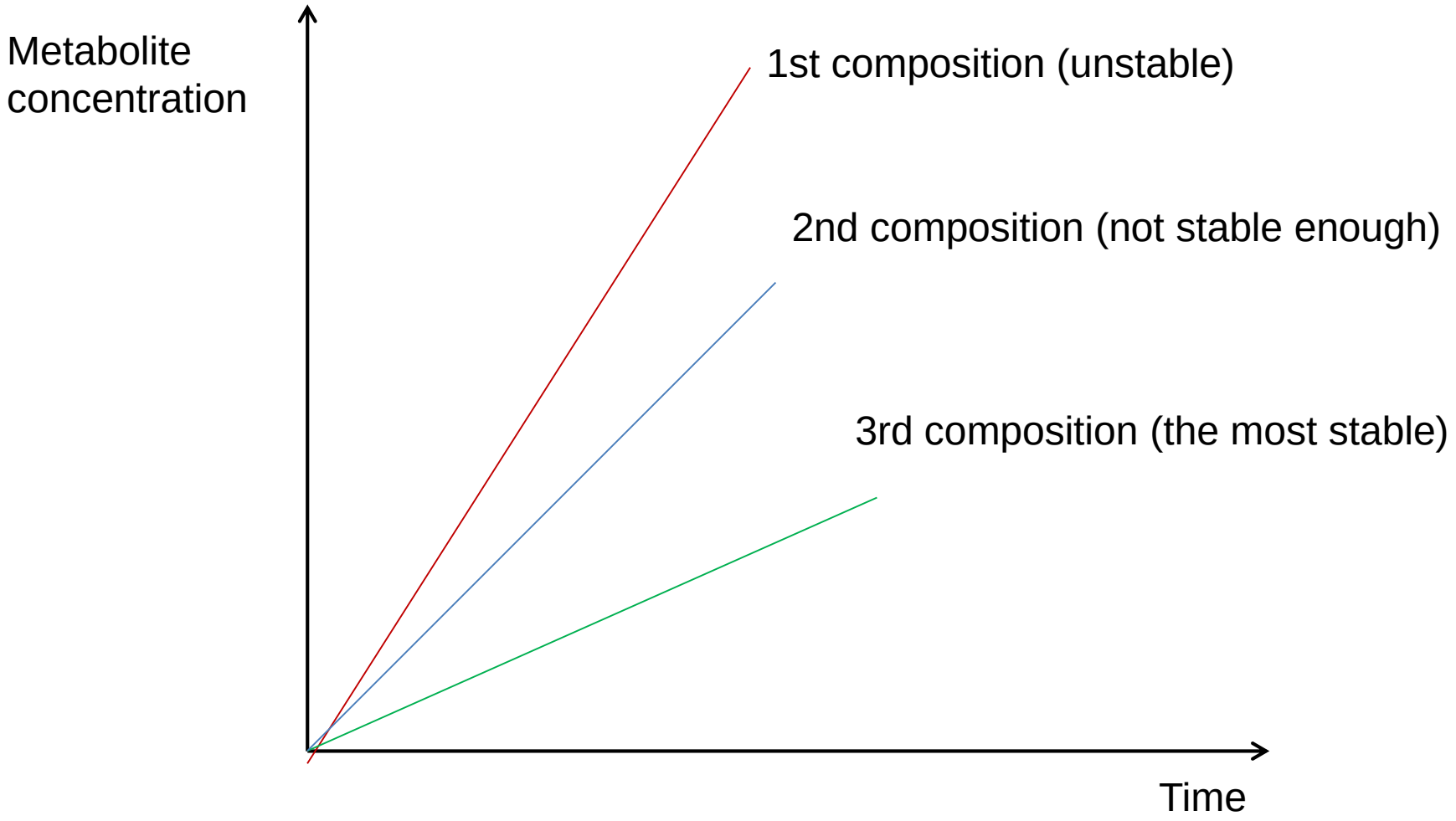
Changes in the degradation constant of aspirin as a function of pH



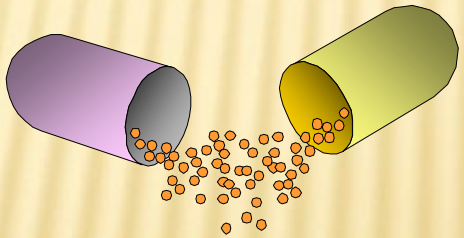
Change in the degradation constant of Methotrexat as a function of pH



Composition optimization based on degradation rate



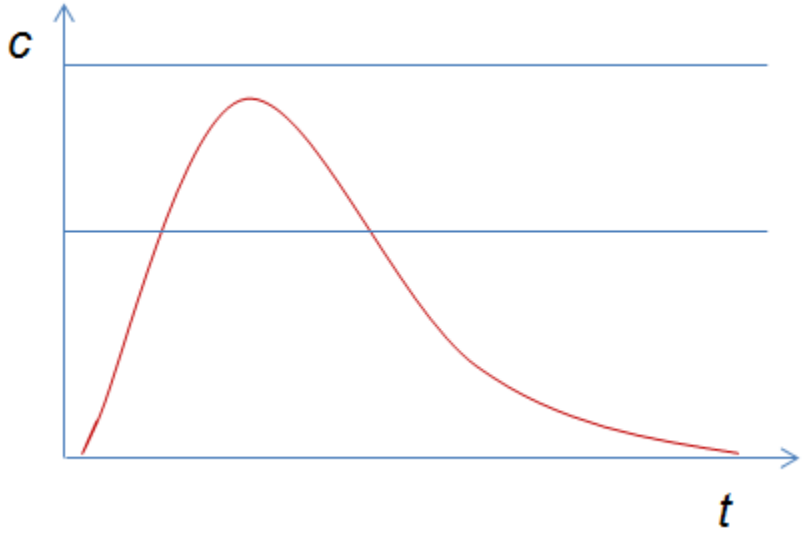
Aspects of preformulation in biopharmacy



Preformulation

The most important **pharmacological** - **pharmacokinetic** - **biopharmaceutical** parameters of the active substance

the nature of the effect (main effects, side effects),
dose,
therapeutic purpose,
the site of absorption,
absorption rate,
Cmax, tmax,
duration of action,
biological half-life,
volume of distribution,
binding to plasma proteins,
first pass effect,
metabolites,
elimination rate,
solubility,
permeability
biopharmaceutical class.



Preformulation

1. Biopharmaceutical aspects of preformulation:

- whether the active substance has the biopharmaceutical parameters required to achieve the desired therapeutic effect (eg solubility, absorption),

- if necessary, is it possible to modify the active ingredient to achieve the appropriate therapeutic effect,

- which formulation is best suited to achieve the desired therapeutic effect,

- what dosage of active ingredient is required in the particular dosage form,

- whether it is possible to develop a formulation with the biopharmaceutical parameters (eg, dissolution, absorption) required to achieve the desired therapeutic effect.

2. Pharmaceutical technology aspects of preformulation

- what excipients, in their particular form and composition, are capable of ensuring the proper quality of the preparation,

- by controlling the operational parameters, it is possible to produce this preparation in a safe, reproducible manner,

- it is capable of maintaining for a sufficient period of time the quality parameter values required to achieve the desired therapeutic effect
(eg dissolution, stability).

3. Relationships between biopharmaceutical and pharmaceutical technology and parameters of preformulation

Different crystalline forms of the same active ingredient may affect a

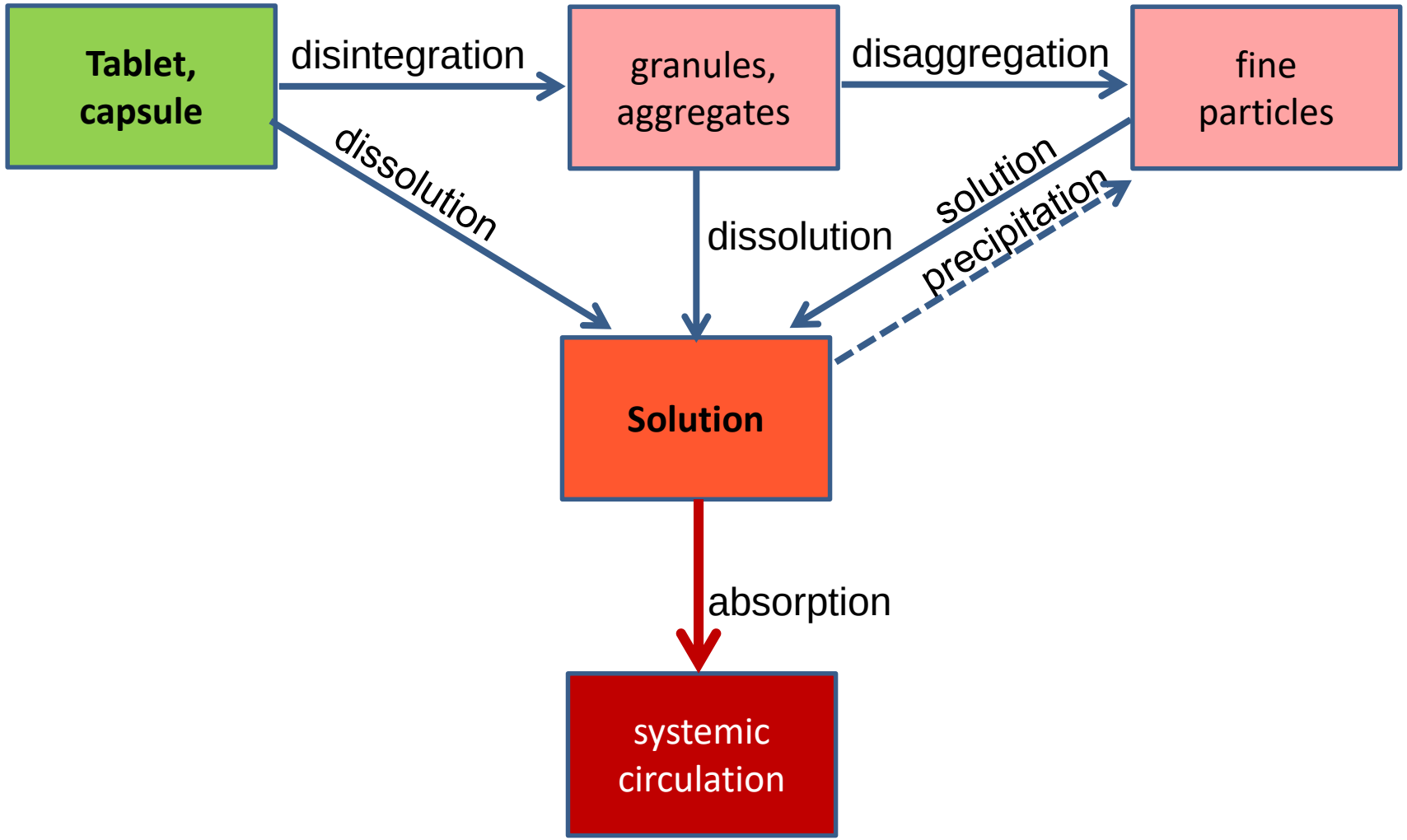
- release of the active ingredient (eg due to differences in solubility, dissolution rate),

- bioavailability (may be a disqualification if the alternative crystal form results in a different solubility or bioavailability product as a reference).

- stability (eg amorphization may impair stability)

- the manufacturability of the composition (eg compression properties)

Solubility - Absorption



Solubility, dissolution rate and absorption

In case of limited absorption by solubility

- the amount of API absorbed does not increase with dose increase,

- increasing the dissolution rate does not increase the absorption.

In the case of absorption limited by dissolution rate

- the dose increases the amount of API absorbed,

- particle size reduction or solution form may increase absorption.

Absorption limited by solubility

Poorly soluble pharmacons

- digoxin,
- penilcillin V,
- phenytoin,
- quinidin,
- tetracyclines.

Preformulation

Main biopharmaceutical aspects of product development

- the pharmaceutical composition should be suitable for the administration of API and develop its beneficial properties (biocompatibility)

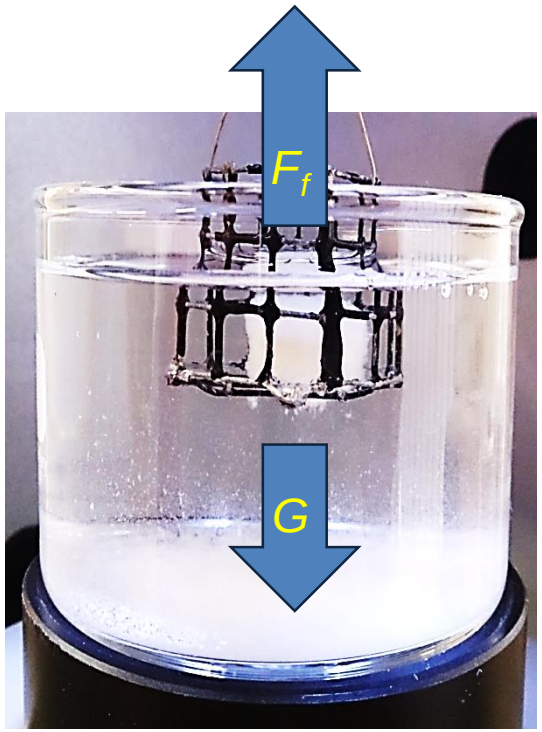
  allow accurate, simple and safe dosing,
- release the API from the preparation (controlled release), at the right time, place
- preferably in complete quantities without residues (bioavailability)
- the product should provide blood levels that are optimal for the therapeutic effect
- the excipients and any structural components of the preparation must be completely eliminated from the body

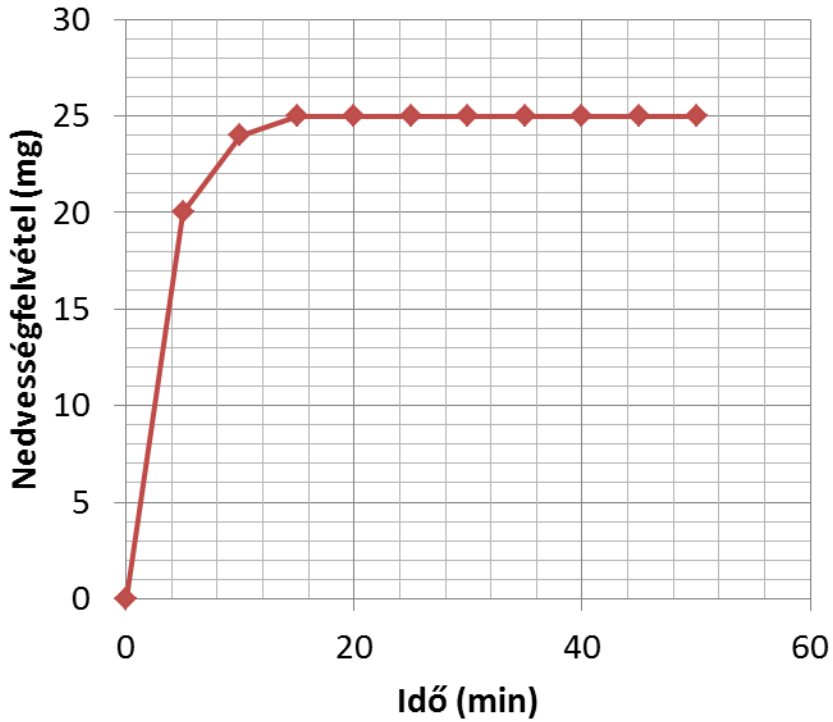
Preformulation

The most important biopharmaceutical parameters of the active substance

- moisture absorption,
- solubility,
- dissolution rate,
- absorption.

Moisture uptake





$F_b = G_{water} = m_{water} * g$ buoyancy

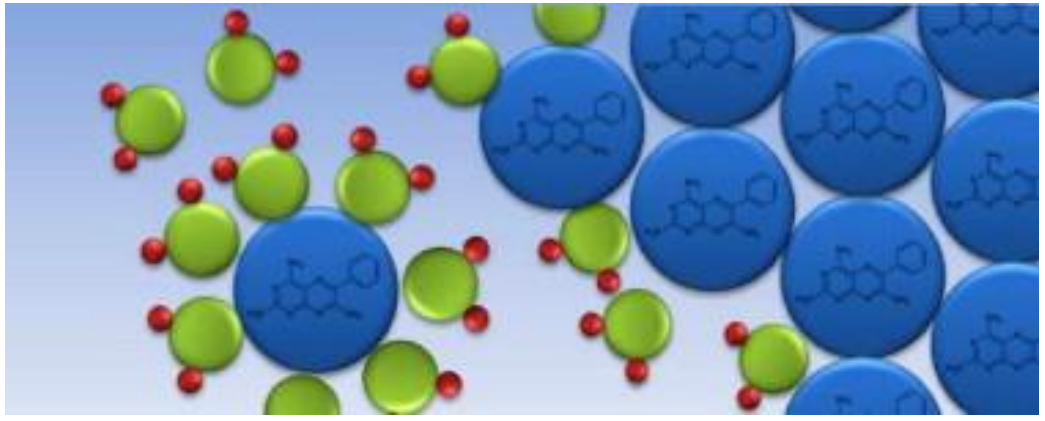
$G = m*g$ *weight force*

$F_r = G-G_{water}$ *resulting force*

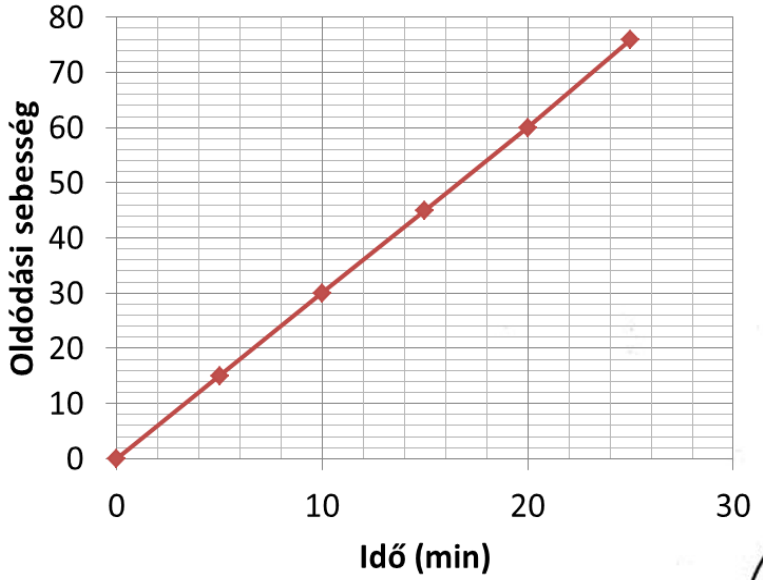
Solubility

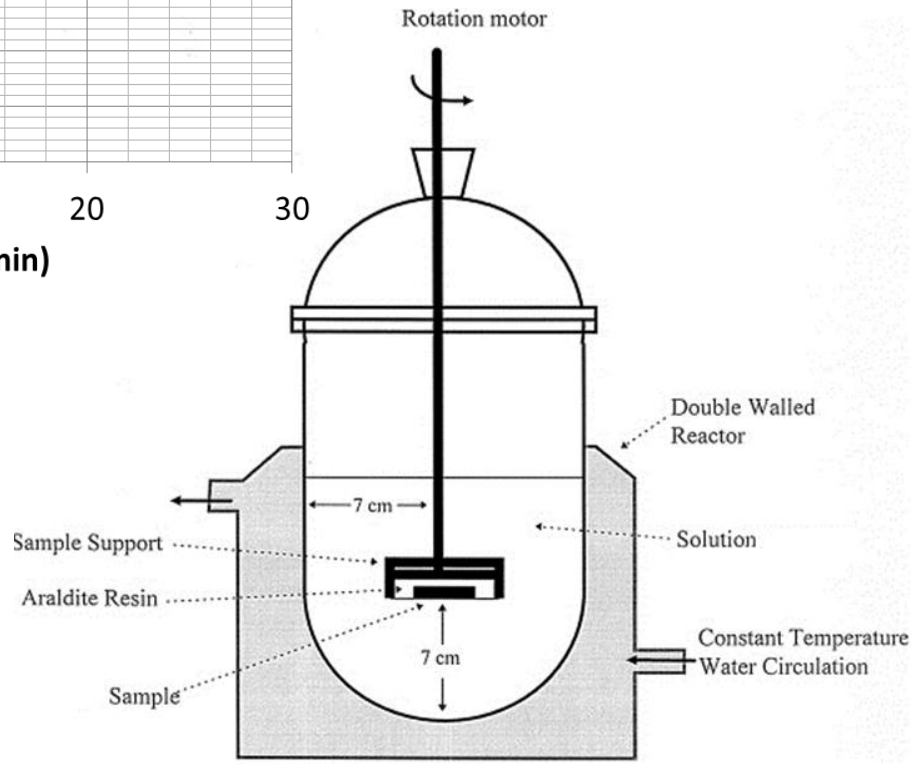
An active ingredient is considered to be readily soluble in biopharmaceuticals when the amount required for therapeutic effect is dissolved in an aqueous medium of 250 ml or less at a pH of 1-7.5 at 37 ° C.

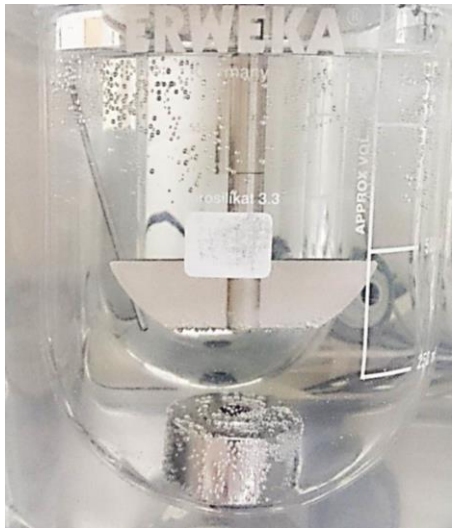
very soluble	1
freely soluble	1 - 10
soluble in	10 - 30
moderately soluble	30 - 100
poorly soluble	100 - 1000
hardly soluble in	1000 - 10 000
practically insoluble in	10,000



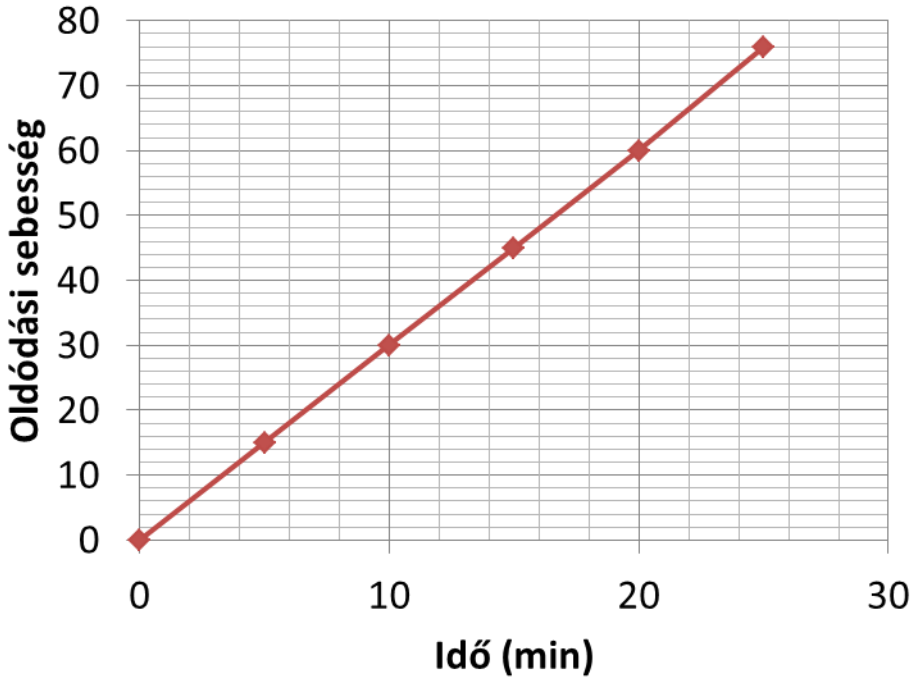
Dissolution rate







Dissolution rate



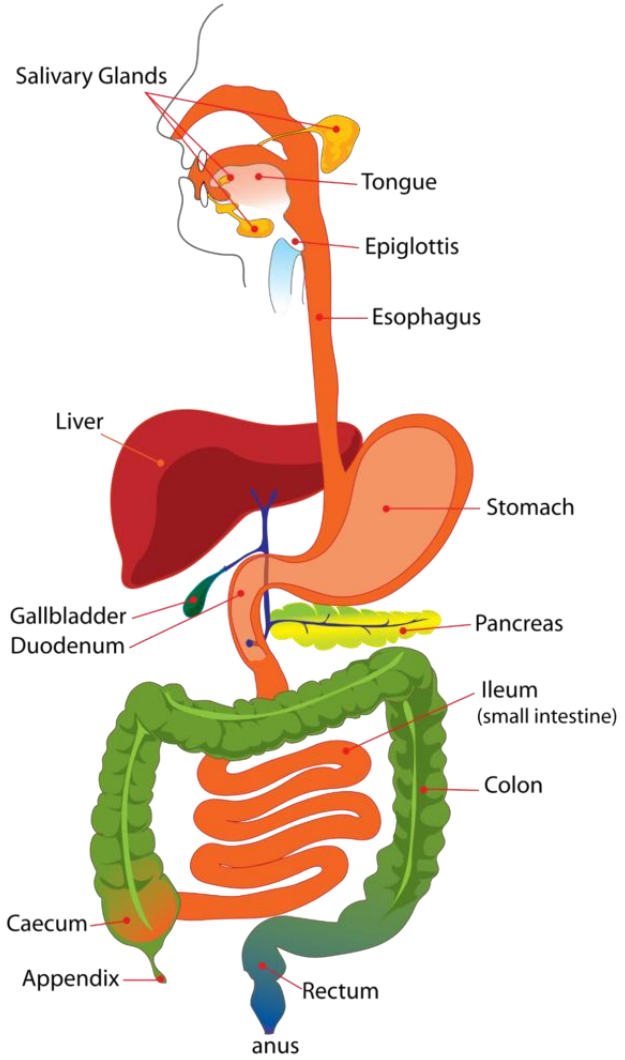
Noyes-Whitney equation

$$\frac{dm}{dt} = \frac{A\delta}{h}(C_s - C_t)$$

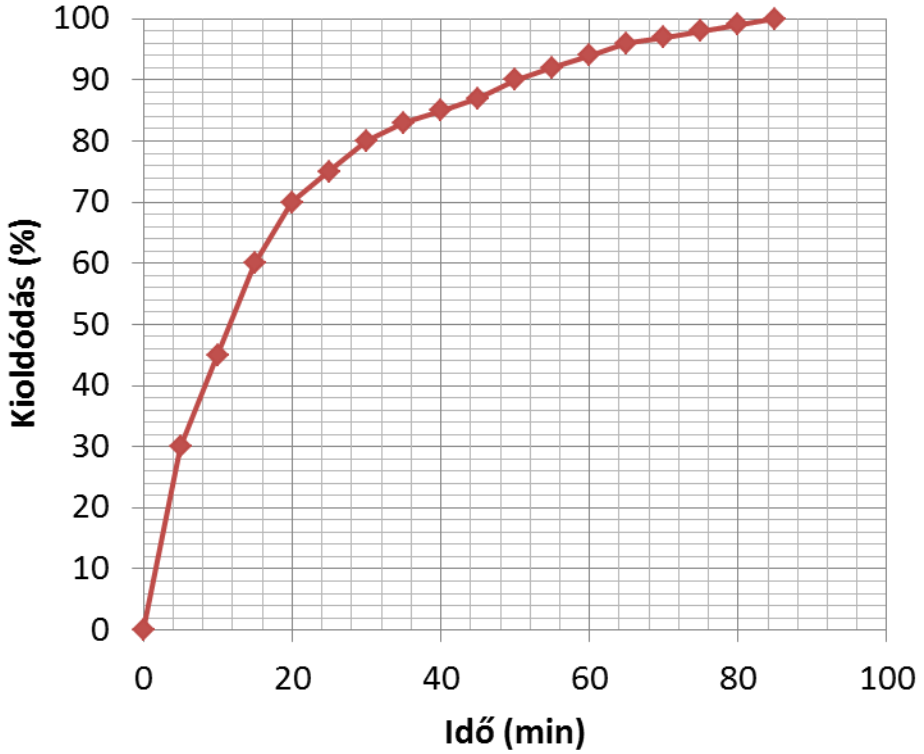
A = solvent-contacting surface of the active ingredient
δ = diffusion constant
h = diffusion layer thickness
C_s = saturation concentration
C_t = concentration at time t

A drug is considered to be biopharmaceutical rapidly soluble if
> 85% of the drug is dissolved within 30 minutes.

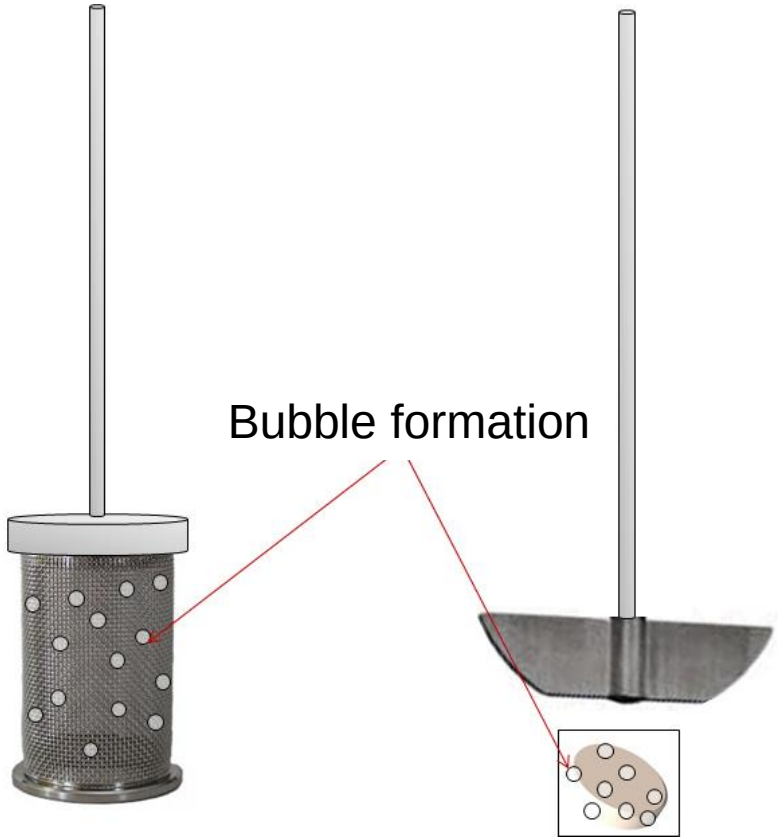
Dissolution

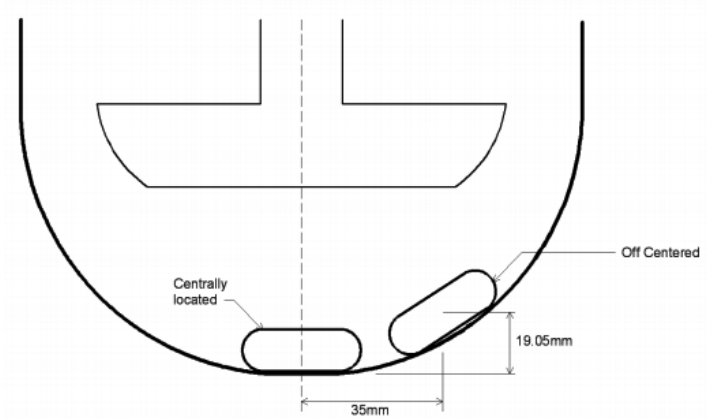


Dissolution



Dissolution





Wandering

Dissolution

Fully automated
dissolution tester

- preheating the release medium,
- filling up to a given volume,
- placement of tablets,
- release with specific parameters,
- evaluation,
- rinse
- resumption

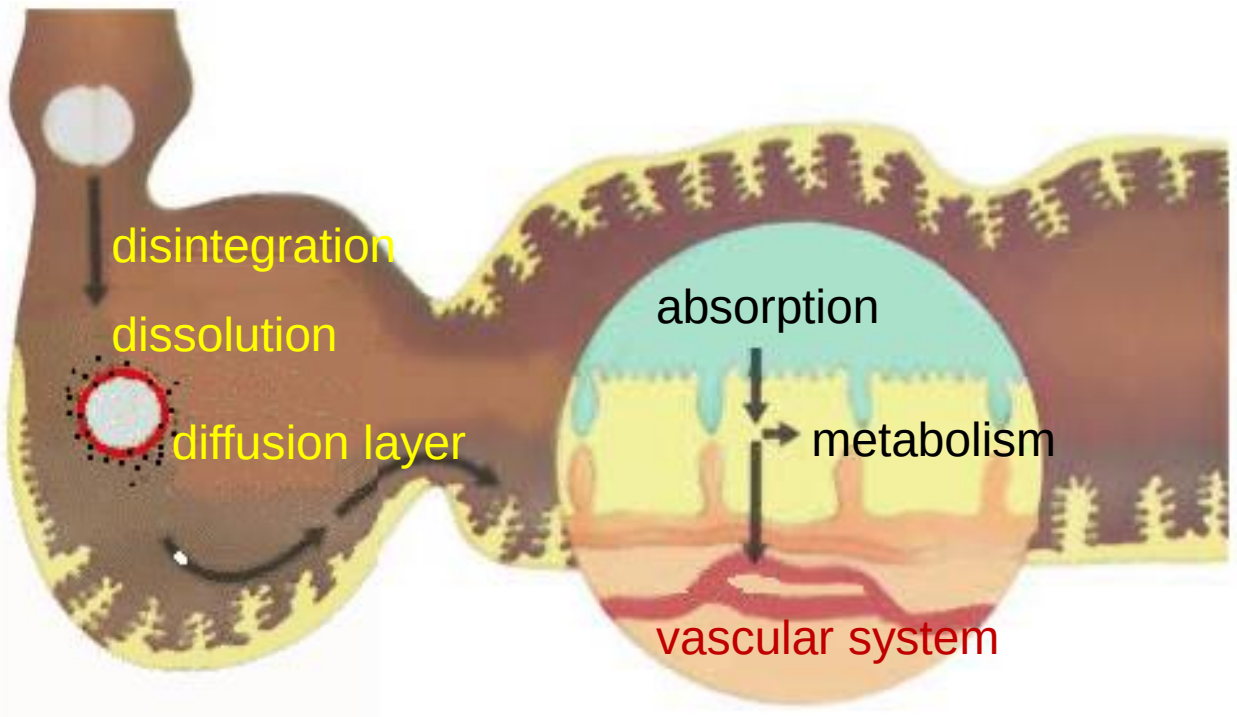
Dissolution

It is able to simulate physiological conditions (dissolution, absorption, membrane transport), that is, bio-relevant biopharmaceutical assays are very important in the development of the drug.

The in vitro modeling of physiological conditions is fraught with difficulties and it is difficult to approximate realistic, expected in vivo conditions.

Dissolution

API dissolution and absorption



External stimuli, dietary intake is determined by

- internal mixing conditions (peristalsis),
- the composition of the GI tract fluids,
- its pH,
- transit times.

Dissolution

Drug release testing is carried out under standardized conditions:

- the test in a dispenser of the same size as prescribed in the pharmacopoeia,
- fixed and properly positioned mixers (paddle, rotating basket),
- controlled speed (n),
- in a volume of solution (V), temperature (T), composition, pH, corresponding to the biological medium.

Biorelevant drug dissolution

1.) Gastric juice simulating a fasted state

(fasted state simulated gastric fluid, FaSSGF),

2.) an intestinal fluid that simulates starvation

(fasted state simulated gastric fluid, FaSSIF),

3.) gastric juice simulating a satiated condition

(fed state simulated gastric fluid, FeSSGF)

4.) intestinal fluid simulating a saturated state

(fed state simulated intestinal fluid, FeSSIF)

Product design

Gastric juice to simulate starvation

(fasted state simulated gastric fluid, FaSSGF)

pH 1.6		
Sodium taurocholate		80 µM
Lecithin		20 µM
Pepsin		0.1 mg/ml
NaCl		34.2 mM
HCl conc.	qs ad	pH 1.6
Deionized water	ad	1 l
pH		1.6
Osmolality (mOsmol/kg)		120.7 ± 2.5
Buffer capacity (mEq/pH/L)		–
Surface tension (mN/m)		42.6

Product design

Small intestine juice simulating starvation

(fasted state simulated gastric fluid, FaSSIF)

pH 6.5		
Sodium taurocholate		3 mM
Lecithin		0.75 mM
NaH_2PO_4		3.438 g
NaCl		6.186 g
NaOH	qs ad	pH 6.5
Deionized water	qs ad	1 l
pH		6.5
Osmolality (mOsmol/kg)		~270
Buffer capacity (mEq/pH/L)		~12
Surface tension (mN/m)		54

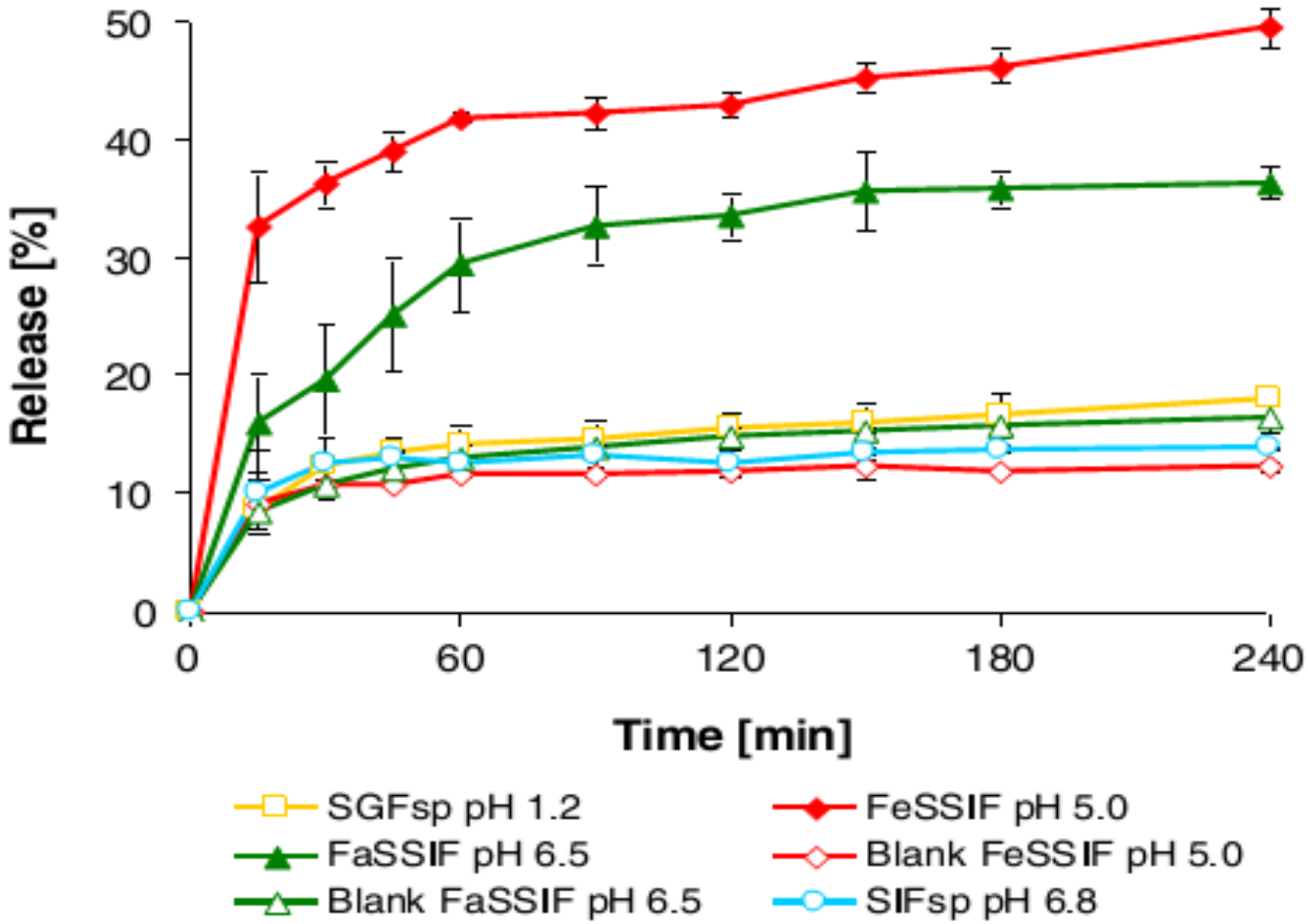
Product design

Small intestine juice simulating well-being

(fed state simulated intestinal fluid, FeSSIF)

pH 5.0		
Sodium taurocholate		15 mM
Lecithin		3.75 mM
CH_3COOH		8.65 g
NaCl		11.874 g
NaOH pellets		4.04 g
Deionized water	qs ad	1 l
pH		5.0
Osmolality (mOsmol/kg)		~670
Buffer capacity (mEq/pH/L)		~72
Surface tension (mN/m)		48

Product design



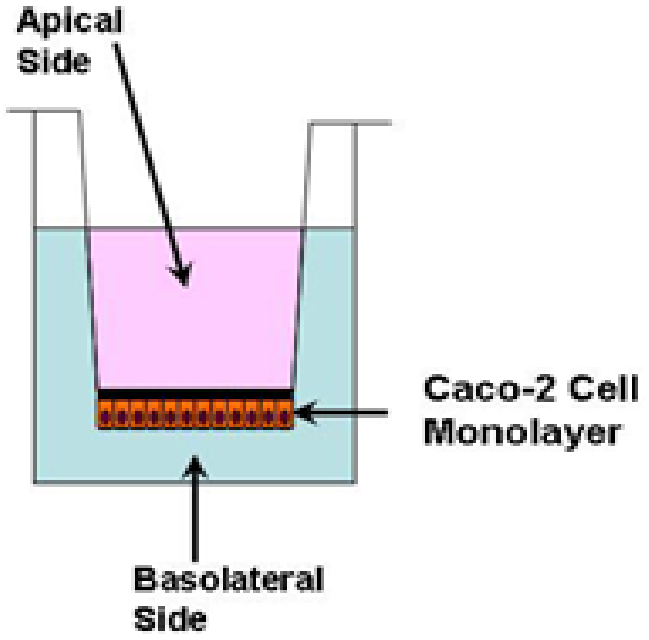
Dissolution profiles of Phenhydan® tablets obtained in compendial and biorelevant media simulating the intralumenal composition of stomach and small intestine before and after a meal ($n=3\pm SD$)

Alternative Names: Phenytoin, Phenytek, Epamin, Epanutin, Fenytoin, Eptoin, Dilantin

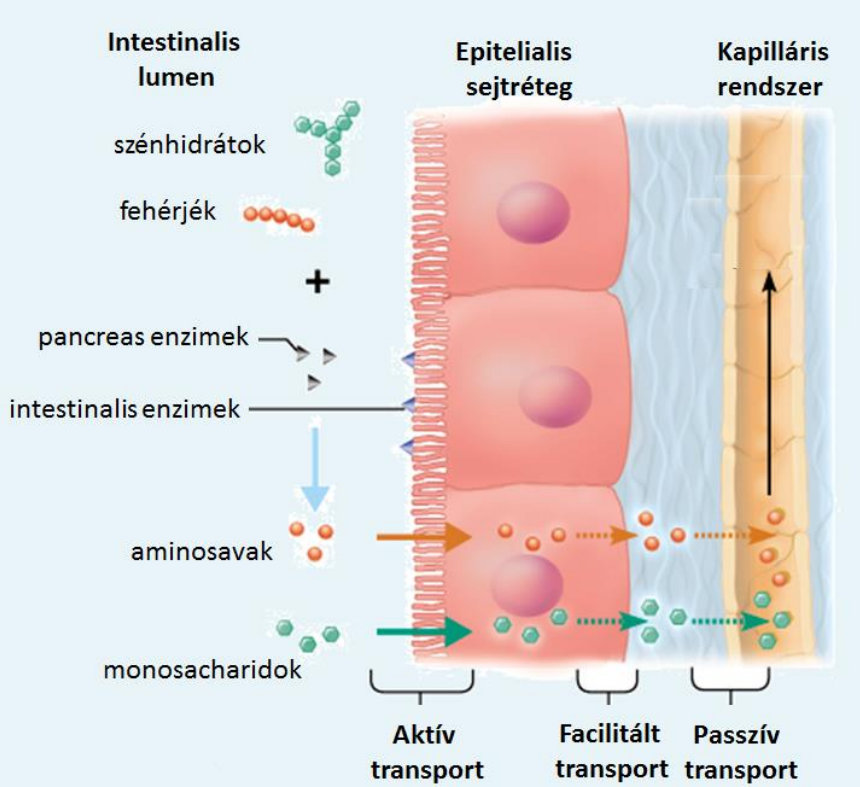
Absorption

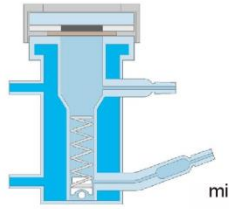
A drug is considered to be highly permeable when the extent of absorption (parent drug plus metabolites) is ≥ 90% of the administered dose in humans, as determined by weight retention law, or compared with an intravenous reference study (100% absorption).

Permeability can be determined in many ways, but most often by the use of colorectal adenocarcinoma (Caco-2) cell lines.
In this system, permeation through a single-layer cell culture is assayed.

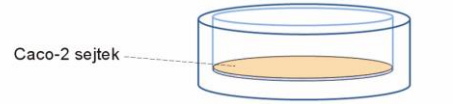


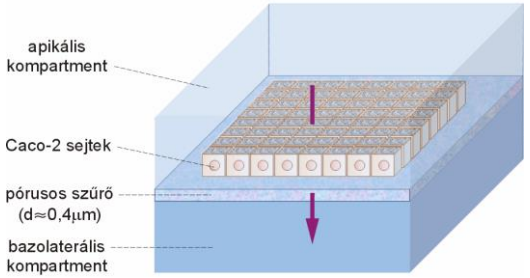
Absorption





Francz cell



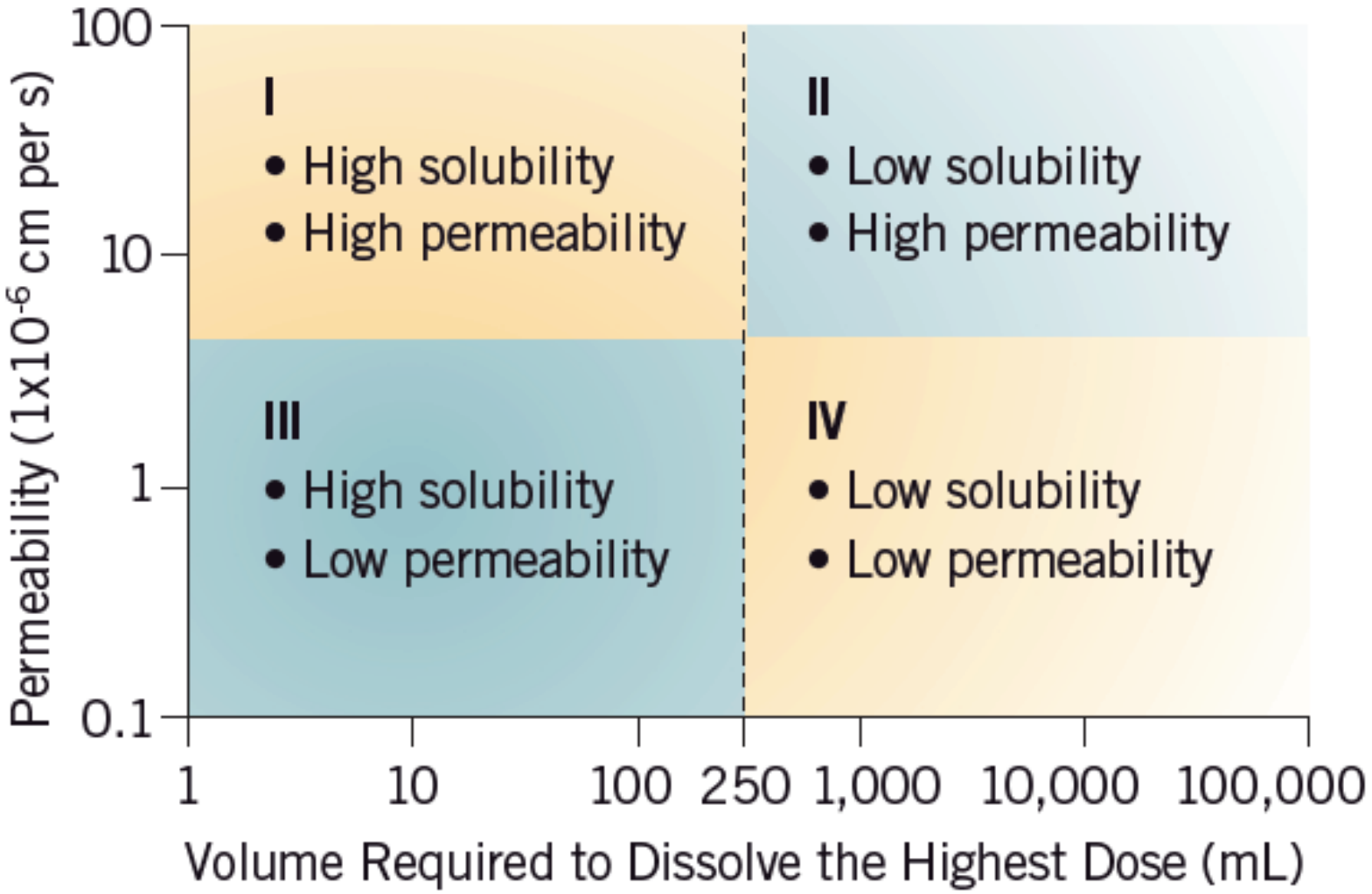


Bipharmaceutical Classification System (BCS)

Solubility and permeability are molecular properties derived from the structure of a substance, a characteristic of material quality

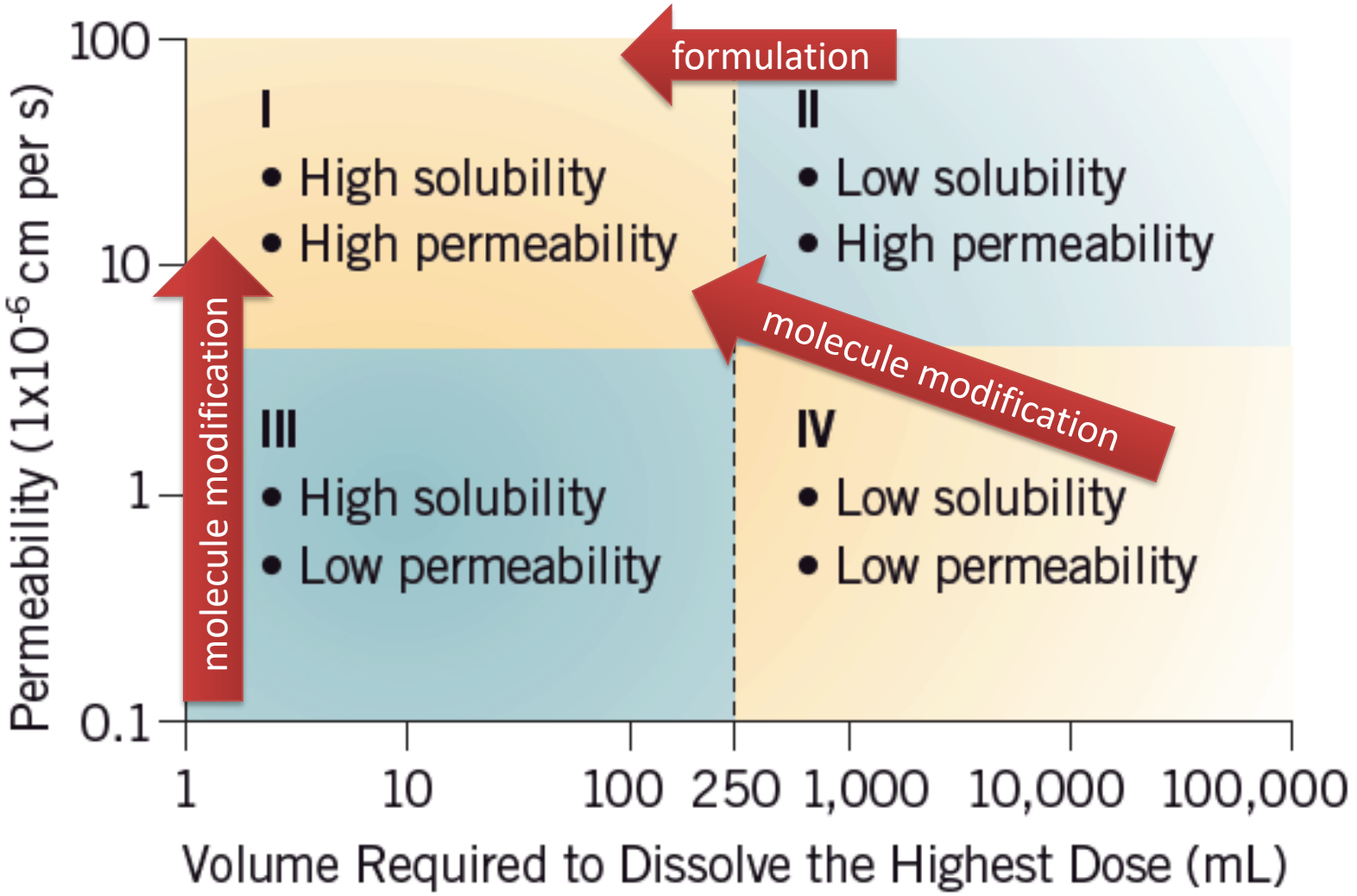
Bipharmaceutical Classification System (BCS)

Efficiency increasing



Bipharmaceutical Classification System (BCS)

Efficiency increasing



Biopharmaceutical fundamentals of R&D

BCS	API parameters		Formulation options		Dissolution IVIVC
	solubility	permeability	peroral	parenteral	
1	High	High	+	+	IVIVC is only expected **if the dissolution rate is less** than the gastric emptying time
2	Low	High	oldhatóság növelése, oldat forma, szilárd diszperzió, szemcseméret csökkentés	-	IVIVC can only be expected **if the in vitro dissolution rate is similar to the in vivo** one
3	High	Low	abszorpció elősegítése	+	Slow absorption is the determinant of speed, therefore, **IVIVC is limited**
4	Low	Low	2. és 3. kombinálása	-	**IVIVC is limited or non-existent**

End of Part 1.

Thank you
for your attention.