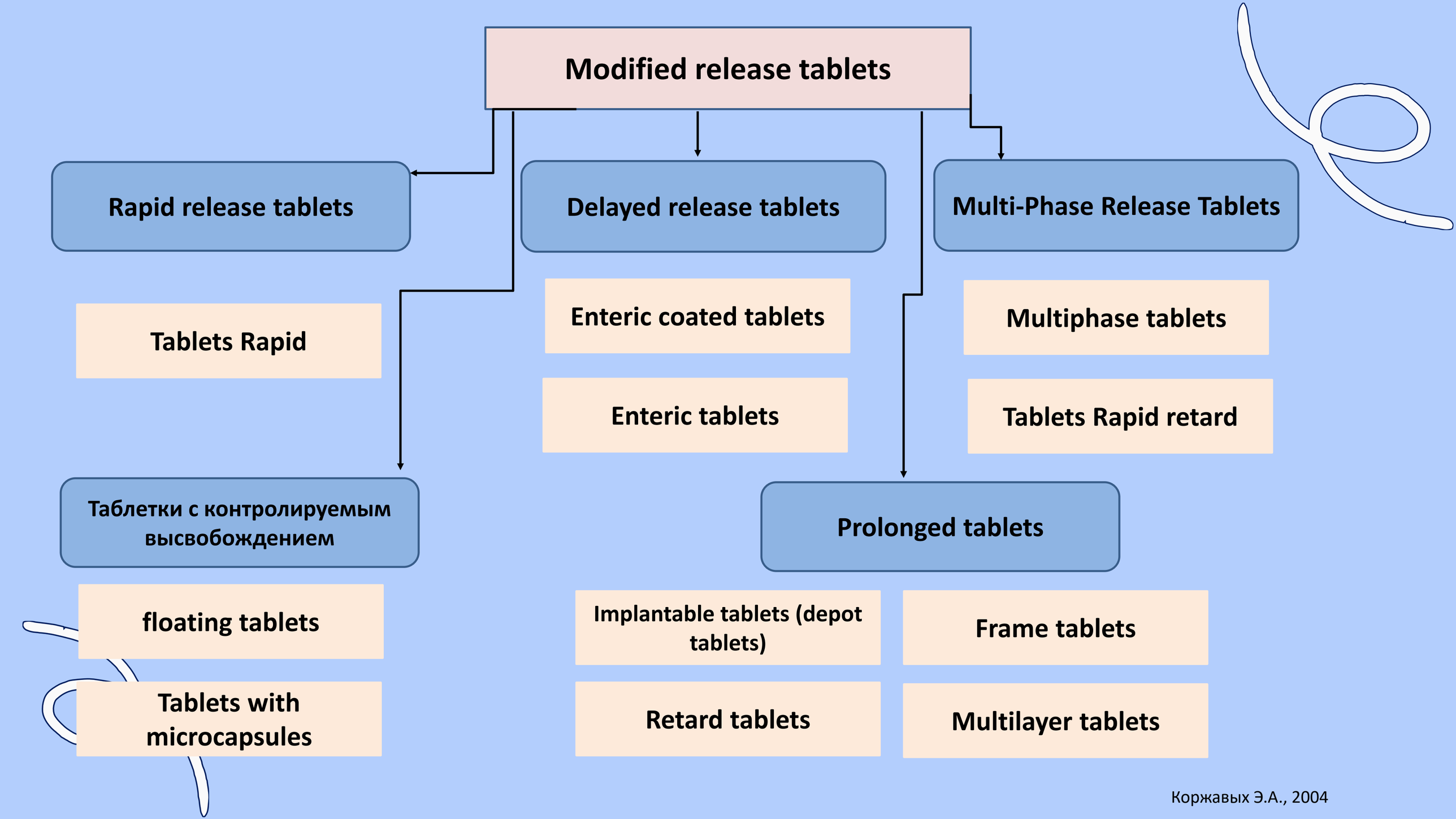
Medicines with improved biopharmaceutical properties. Solid dosage forms.

# Tablets

***Tablets is a solid dosage form obtained by pressing powders and granules containing one or more medicinal substances with or without the addition of excipients.***

***Modified release tablets are tablets with a modified, compared with the usual form, mechanism and nature of the release of medicinal substances.***

***They are coated or uncoated tablets containing special excipients or obtained by special technology, which allows you to change the speed or place of release of the drug.***



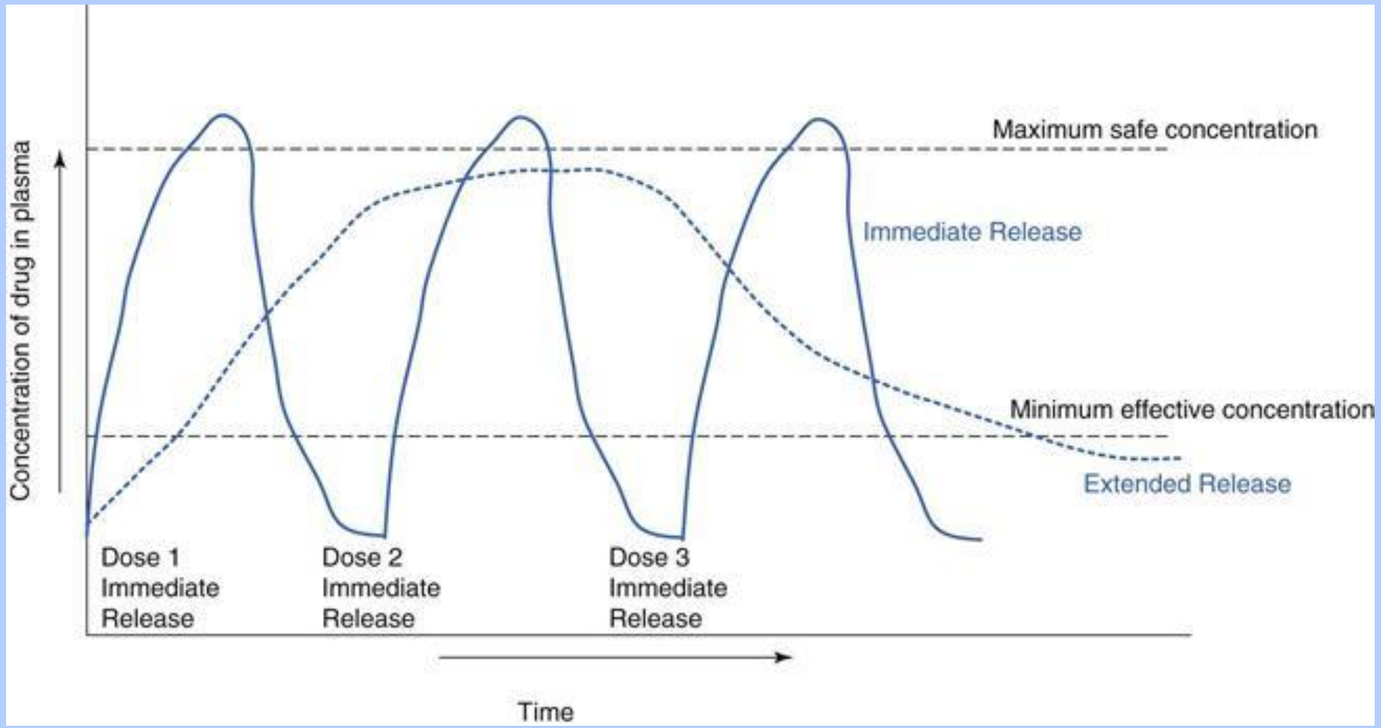

Коржавых Э.А., 2004

# Features to Consider When Designing Modified Release Tablets

- conditions for ***absorption*** of API in the gastrointestinal tract: place, rate and mechanism of absorption;
- ***solubility*** in the gastrointestinal tract;
- features of ***pharmacokinetics***: the presence of first pass metabolism, the relationship between the absorption rate and the concentration of the drug in the blood plasma;
- features of ***pharmacodynamics***: concentration-effect relationship, the likelihood of developing tolerance with a constant intake of APIs in the body

# Advantages of modified release tablets

- allow you to change the speed and duration of release, the place of release, the intensity of the therapeutic effect of the drug substance;
- protection of the medicinal substance from degradation in the gastrointestinal tract;
- increased transit time in the upper gastrointestinal tract;
- improved permeability across epithelial barriers




Modified-release formulations may be important for drugs with a very short half-life (T1/2) that require multiple doses per day, or those that have a very long half-life to eliminate "peak" blood concentrations, as well as to drugs with a narrow therapeutic index to prevent the development of toxic concentrations in the blood.

Obtaining more stable and predictable concentrations of drugs in blood plasma within the therapeutic corridor, which is accompanied by the stability of the therapeutic effect during the dosing interval, a decrease in the development of concentration-dependent side effects, and an increase in patients' adherence to therapy

# Modification methods

- ***physical:*** the use of substances that slow down the absorption, metabolism and excretion of a medicinal substance;
- ***chemical:*** obtaining sparingly soluble salts, replacing some functional groups with others, introducing new chemical groups into the composition of the molecule of the original substance;
- ***technological:*** incorporation into a matrix, coating with special shells.

# Rapid release tablets

***Tablets with accelerated release (rapid)*** are tablets with a modified (accelerated) onset of the action of a medicinal substance.

- creation of soluble salts of a medicinal substance;
- increasing the solubility of sparingly soluble substances;
- obtaining solid dispersed systems.

# Delayed release tablets

***The release of the drug starts later and lasts longer, providing a delayed onset of drug action.***

- enteric tablets (gastric-resistant, gastro-resistant, tablets soluble in intestinal juice, enteric tablets, entero-tablets) - tablets that are stable in gastric juice and release medicinal substances in the intestine.
- enteric coated tablets.

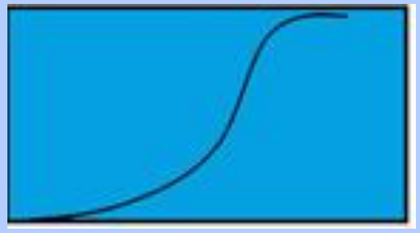
# Multi-Phase Release Tablets

- multiphase tablets are tablets of prolonged action, obtained by pressing a mixture of granulates with different release rates of the same drug substance.

- Rapid retard tablets are biphasic release tablets containing a mixture of fast and sustained release microgranules. They provide a quick onset of effect and a long-term effect of the drug.

**Classification of existing modified release profiles,presented on the Colorcon® website- www.colorcon.com/formulation/app/tailoring-release-profiles**

Delayed / Sustained



Ascending

Enteric

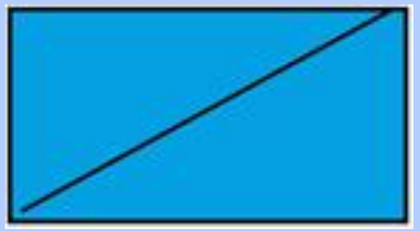
Intestinal

First Order

Modified Enteric

Pulsatile

Biphasic



Zero Order

# Controlled release tablets

***They provide rapid achievement and long-term maintenance at a constant level of the therapeutic concentration of the drug in the blood plasma, the constancy of the pharmacological effect.***

***They are characterized by a prolongation of the time of entry of the medicinal substance into the biophase and its release, corresponding to the real needs of the body.***

# The release will be controlled under the following conditions:

- ✓ the type of mathematical dependence of the amount of the released drug substance on the parameters affecting the release process is known;
- ✓ the drug substance is released according to the pharmacokinetic rational rate or speed program;
- ✓ the release rate is not affected or only slightly affected by physiological conditions (pH and enzymatic composition of gastrointestinal fluids, etc.).
- ✓ The speed is determined by the properties of the tablet itself and can be theoretically predicted with sufficient accuracy.

***If any of these conditions is not met, then the tablets are classified as prolonged forms.***

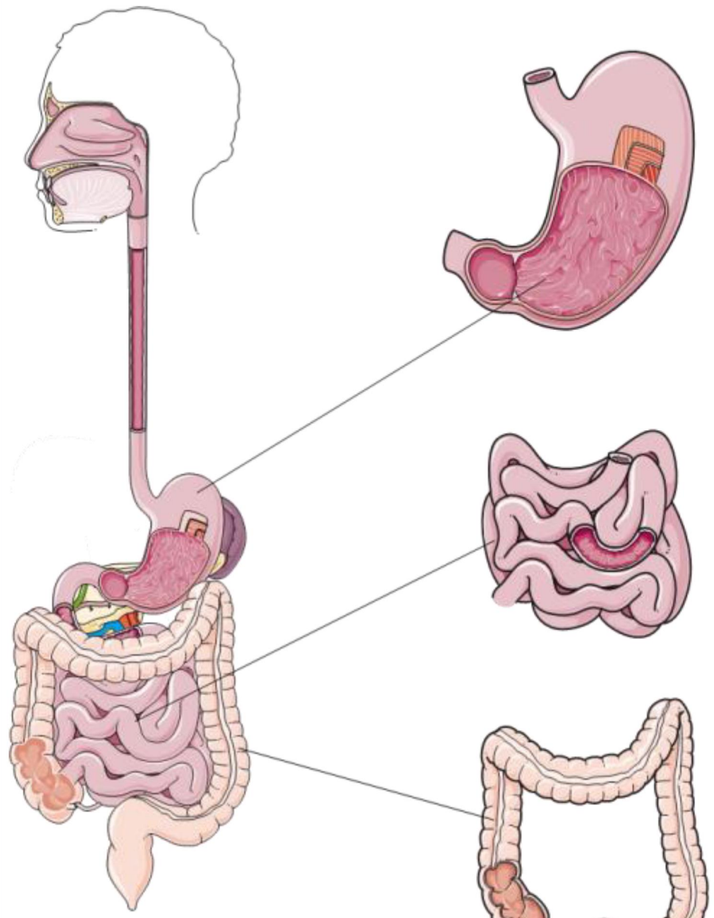
# Mathematical models of controlled release

| Model | Mathematical Equation |
|---|---|
| Zero order | $1 - \frac{M_t}{M_0} = M_0 - k_0 t$ |
| First order | $ln(M_0 - M_t) = lnM_0 - k_1 t$ |
| Higuchi | $M_t = k_H \sqrt{t}$ |
| Hixson–Crowell | $\sqrt[3]{\left(1 - \frac{M_t}{M_0}\right)} = 1 - k_\beta t$ |
| Baskar | $-ln\left(1 - \frac{M_t}{M_0}\right) = ln\left(\frac{M_0}{M_0 - M_t}\right) = 1.59\left(\frac{6}{d_p}\right)^{1.3}(Dt)^{0.65}$ |

Mt - amount of substance released over time t;
M0 - initial amount of the drug;
k – release constant;
D – diffusion constant

Eulálio et al., Pharmaceutics 2023.
https://doi.org/10.3390/pharmaceutics15030955

# Oral controlled drug delivery systems



## Gastroretentive Drug Delivery Systems

- gastric floating formulations
- gastric expandable formulations
- Bioadhesive formulations
- high-density formulations

## Small intestine Targeting Drug Delivery Systems

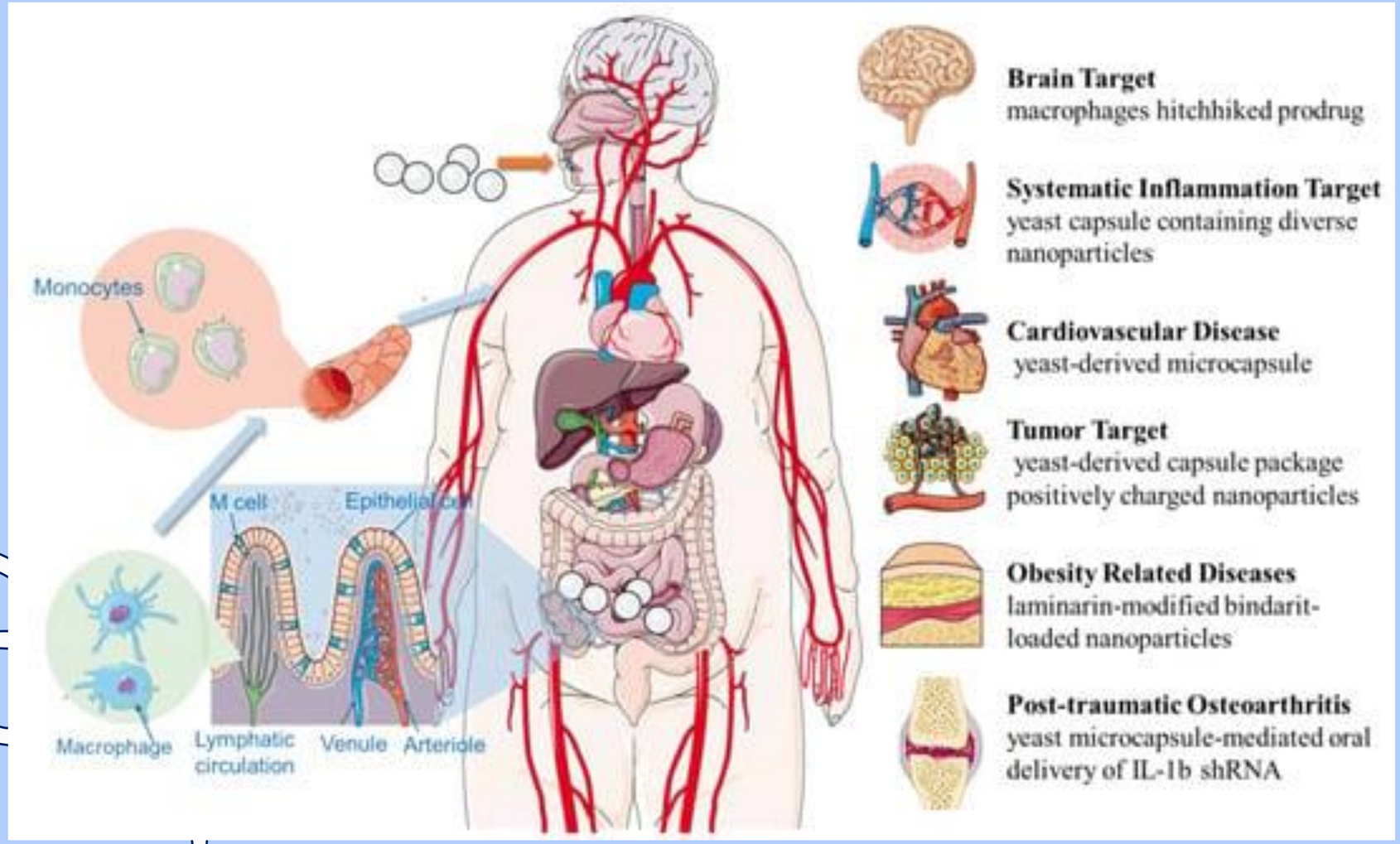
- pH-responsive formulations
- enteric-coated formulations
- mucoadhesive formulations

## Colon Targeting Drug Delivery Systems

- prodrugs
- enzyme responsive formulations
- ROS-responsive formulations
- pH-dependent formulations
- microbiota-dependent formulations

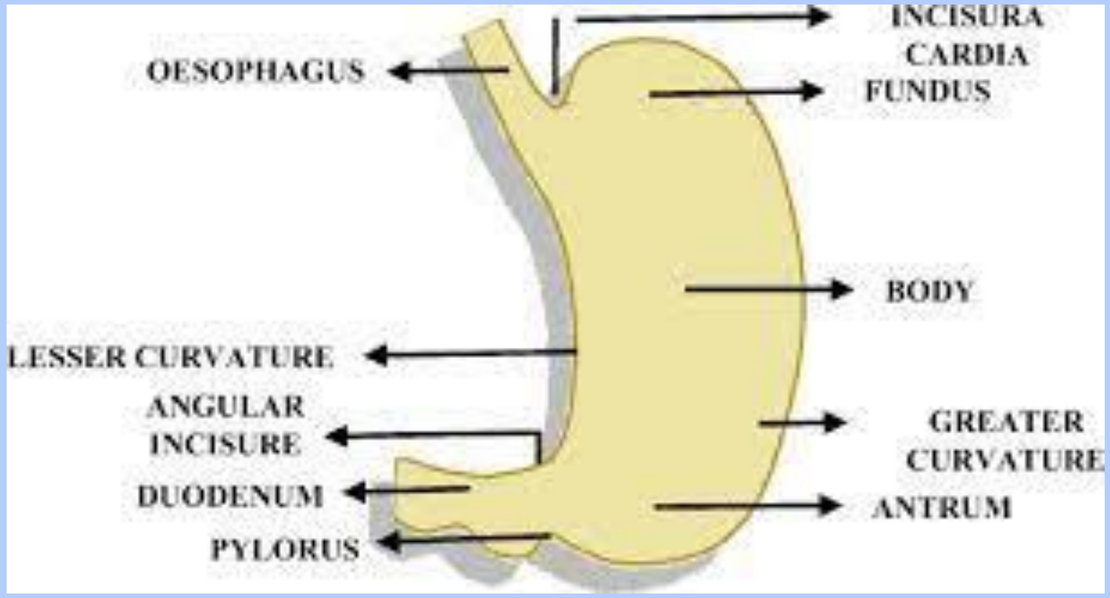
Lou et al., Pharmaceutics 2023
https://doi.org/10.3390/pharmaceutics15020484

# Oral controlled drug delivery systems




Lou et al., Pharmaceutics 2023
https://doi.org/10.3390/pharmaceutics15020484

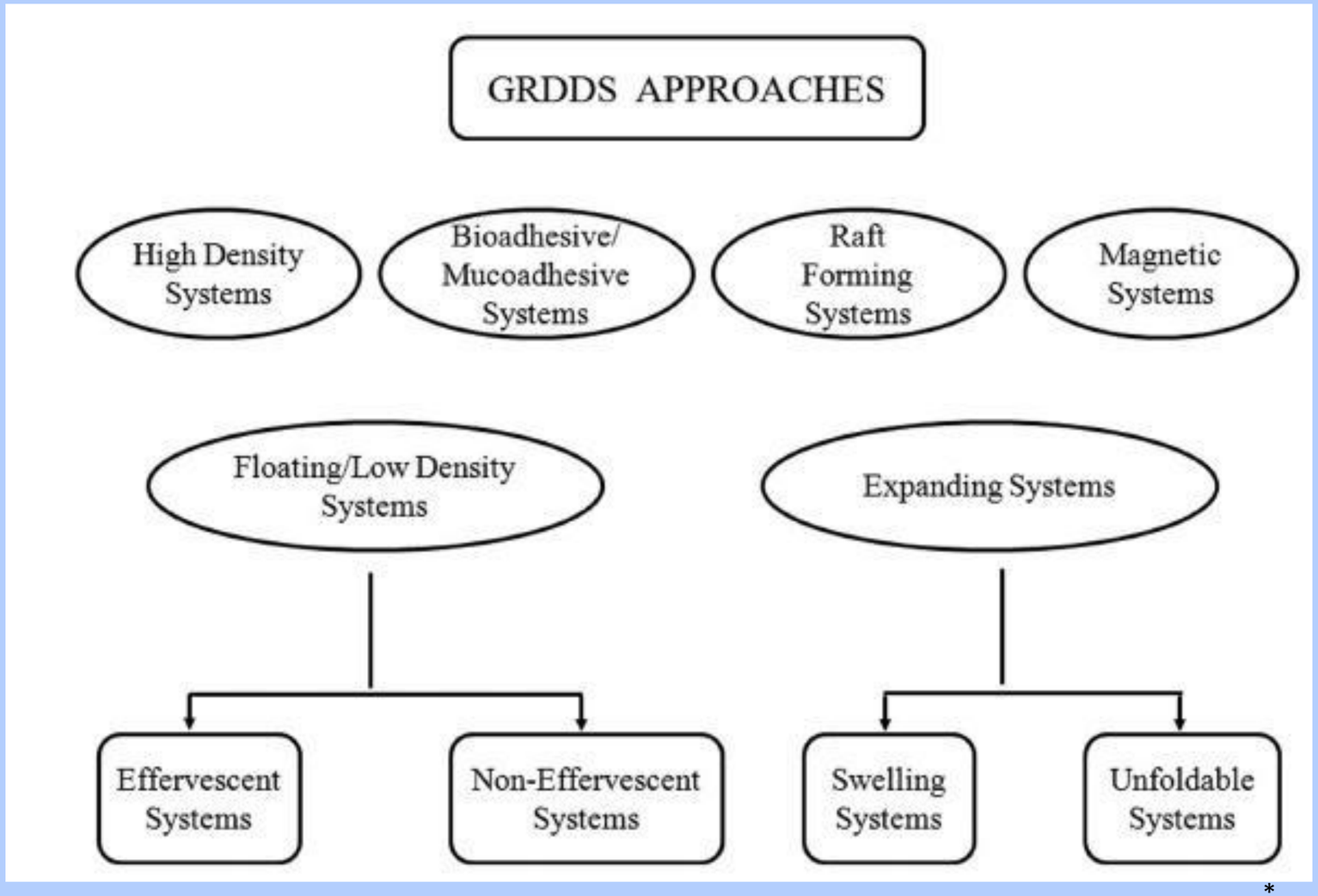
# Gastroretentive drug delivery systems (retained in the stomach)




analgesics, tranquilizers, antidepressants, diuretics, vitamins, antibiotics, antacids, sedatives, antiparkinsonian, antiasthma prophylactic drugs, anti-inflammatory, anthelmintic, antianginal drugs, hormonal drugs

- ✓There are a number of medicinal substances that are effectively absorbed only in the upper part of the gastrointestinal tract, namely: in the stomach and the proximal region of the small intestine.
- ✓At present, one of the promising ways to increase the effectiveness of pharmacotherapy is the creation of long-acting drugs with a gastroretentive effect, that is, they are retained in the stomach for a long time.

# Classification of gastroretentive dosage forms

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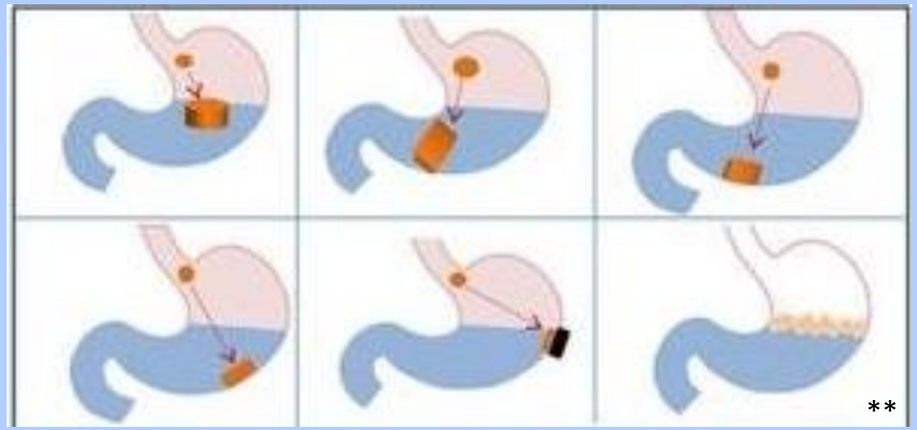

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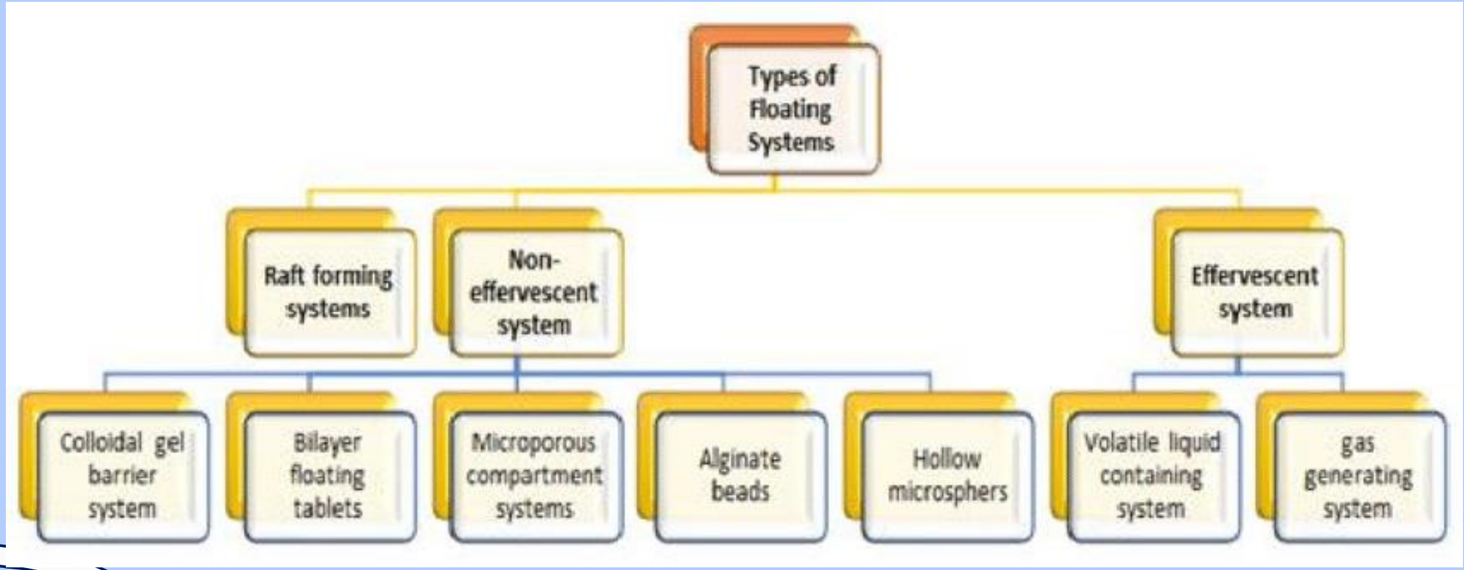
*Arora et al., 2005

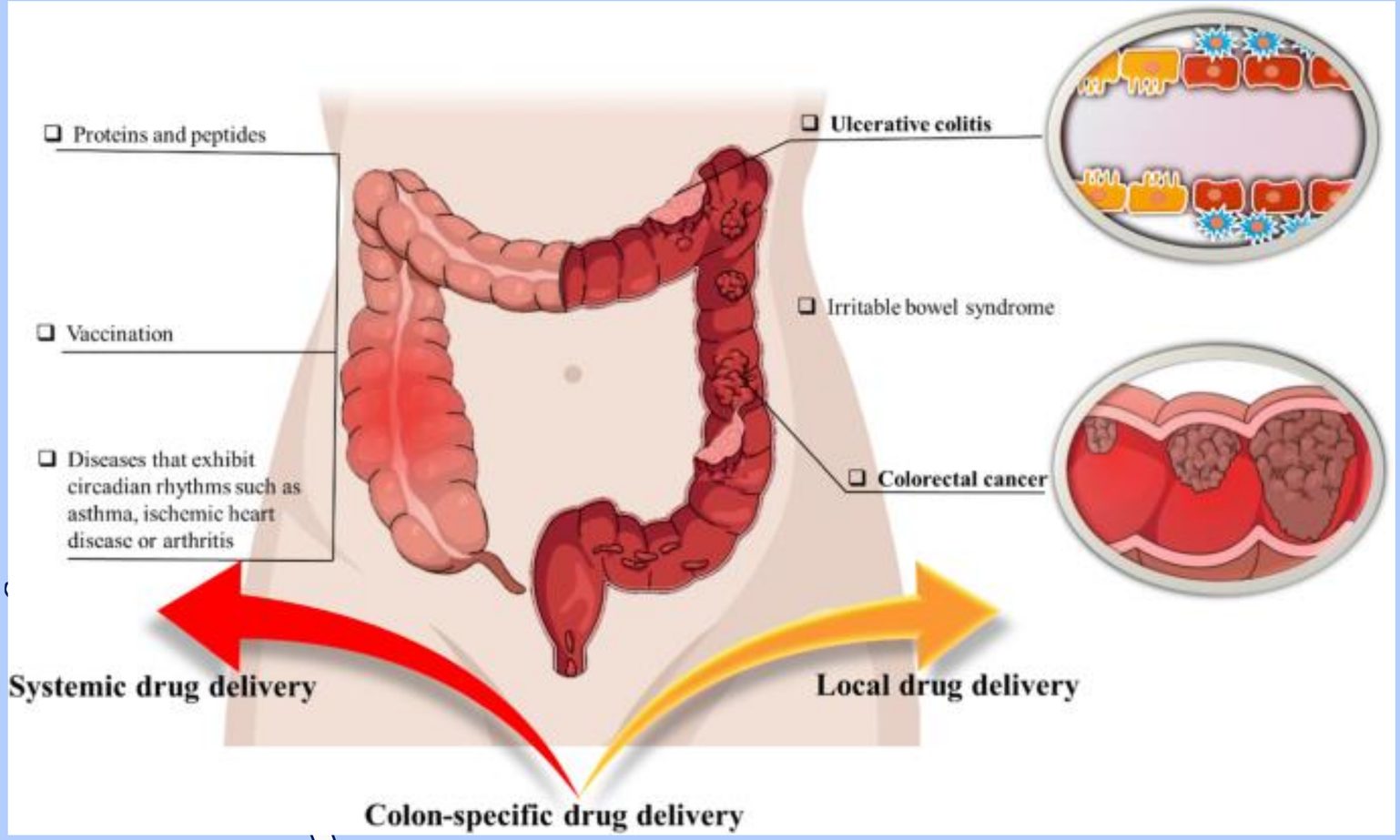
** Tripathi et al., 2019

# Floating drug delivery systems



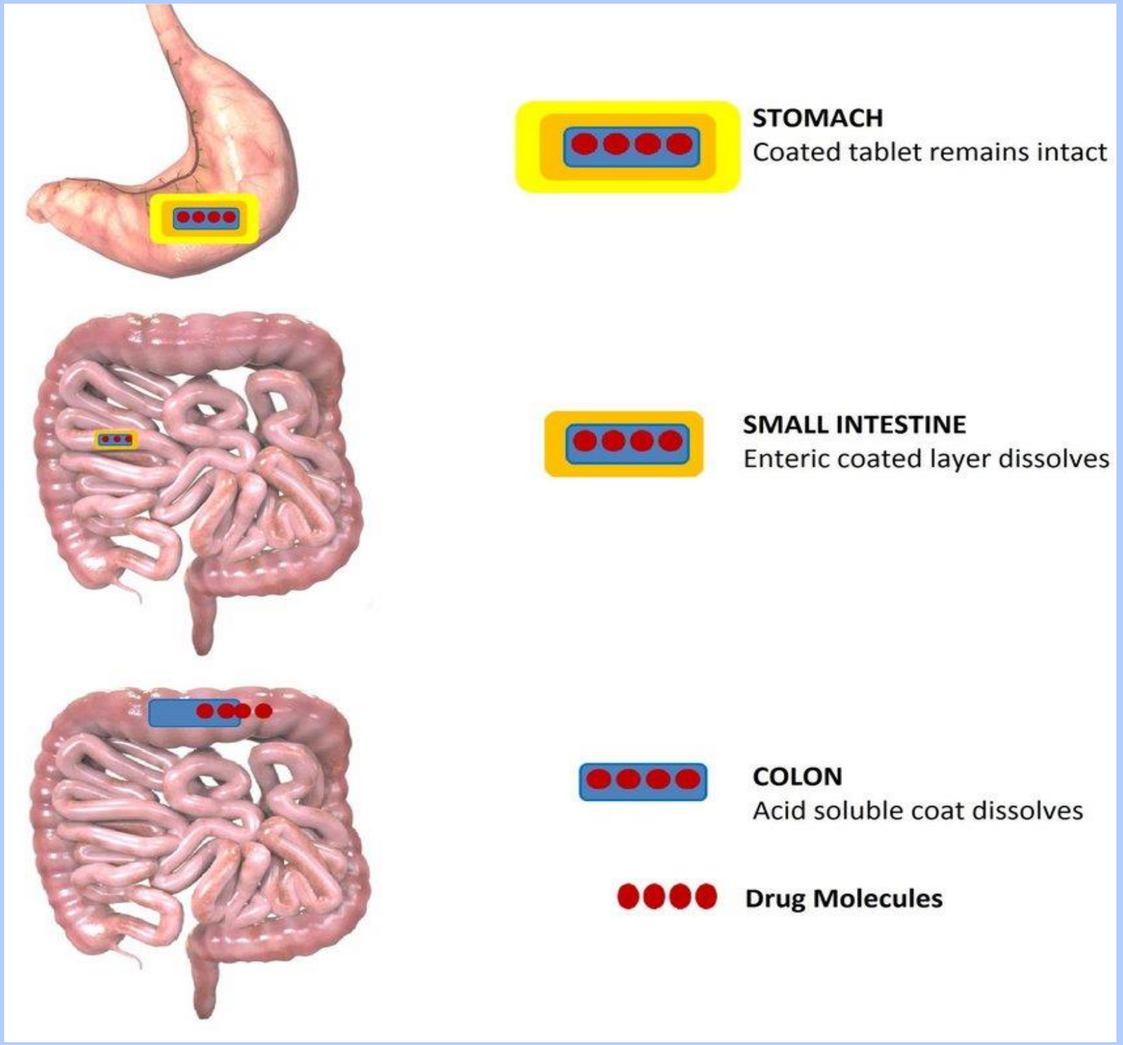

- ✓ Floating systems are hydrodynamically balanced systems with a density less than gastric juice.
- ✓ As a result, they float on the surface for a long time without affecting the rate of emptying.
- ✓ While the system is floating, the drug is gradually released at the required rate.
- ✓ After the drug is released, the matrix is removed from the stomach.

# Colon targeted drug delivery system



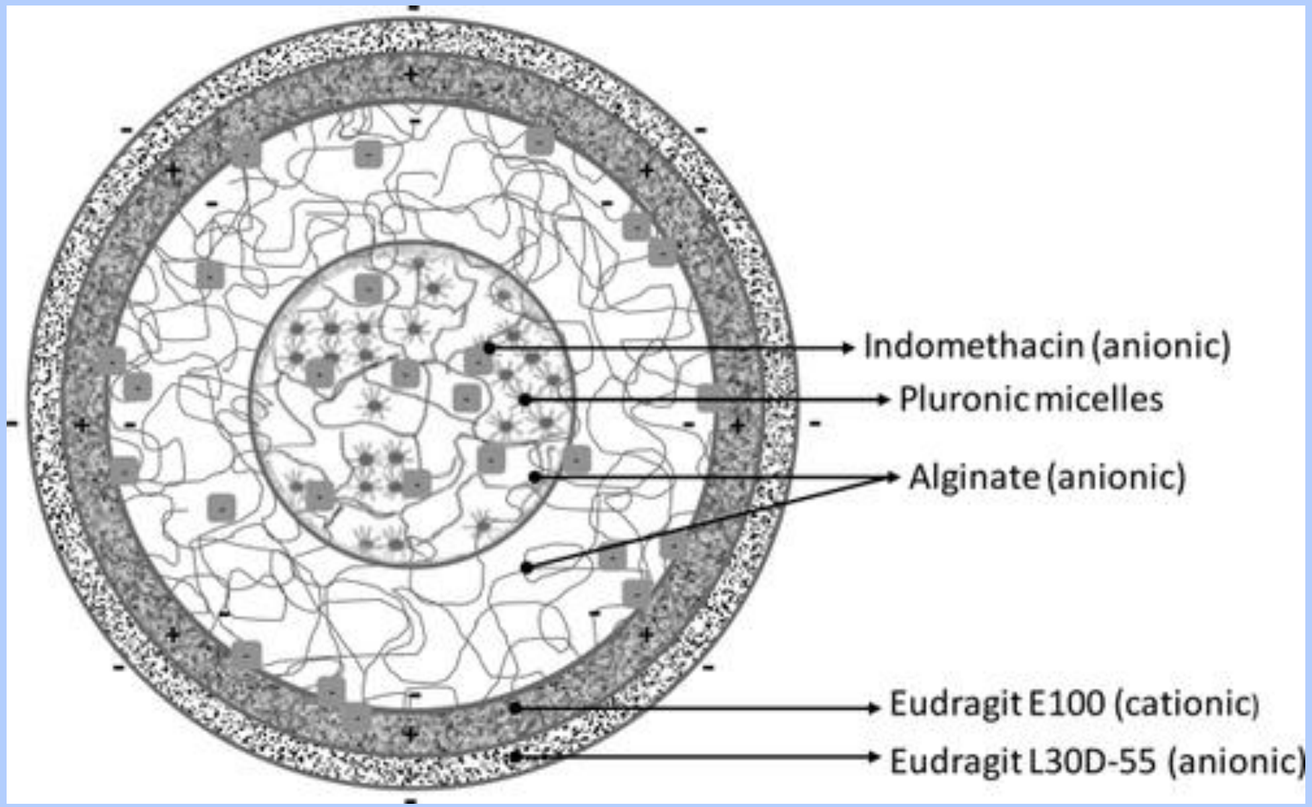

- ✓ This delivery method makes it possible to achieve success both in the treatment of diseases of the large intestine (ulcerative colitis, Crohn's disease, colorectal cancer, chronic pancreatitis, irritable bowel syndrome) and in the treatment of systemic diseases by increasing the bioavailability of APIs, the optimal absorption zone of which is this area of the gastrointestinal tract.
- ✓ API: mesalazine, sulfasalazine, dexamethasone, hydrocortisone, prednisolone, loperamide, curcumin, as well as NSAIDs (aspirin, indomethacin, sodium diclofenac, celecoxib, meloxicam), 5-fluorouracil, capecitabine, etc.

# Colon targeted drug delivery system



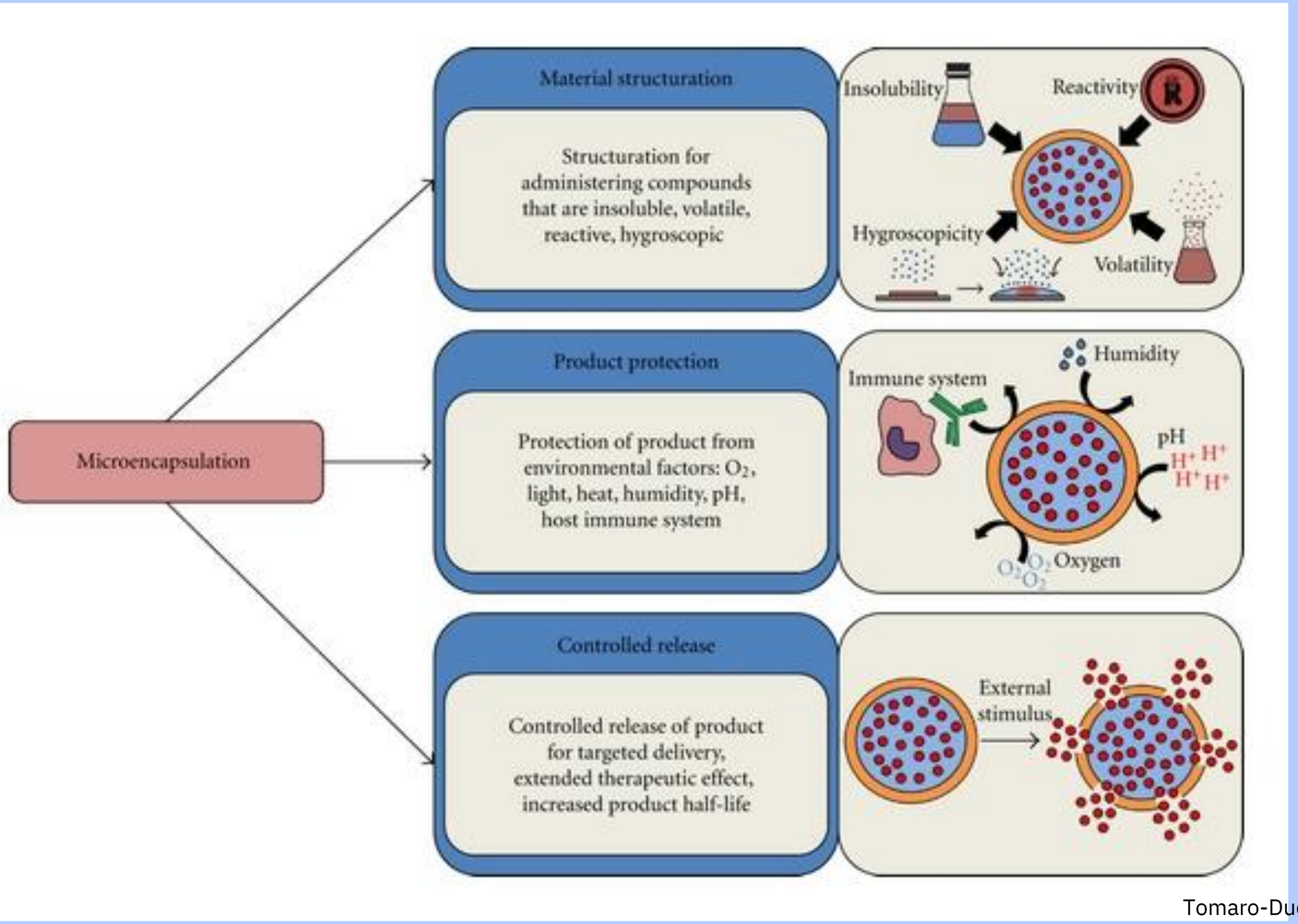

- ✓ use of prodrugs;
- ✓ the use of biodegradable materials that are destroyed by intestinal microflora or enzymes;
- ✓ creation of time-dependent systems;
- ✓ creation of bioadhesive systems;
- ✓ use of enteric film coatings;
- ✓ microencapsulation.

# Microencapsulated dosage forms




- ✓ ***Microcapsules are capsules consisting of a thin shell based on a polymer or other material, spherical or irregular in shape, ranging in size from 1 to 2000 microns, containing solid or liquid active ingredients with or without the addition of excipients.***

A. Dalmoro et al., 2016
https://doi.org/10.1002/app.42976




Tomaro-Duchesneau et al., 2013
https://doi.org/10.1155/2013/103527

# Prolonged tablets

***Tablets from which the drug substance is released either in several portions or slowly and evenly, providing an increase in the duration of action of the drug substance by slowing down its release.***

- Retard tablets are prolonged tablets that provide the body with a supply of a medicinal substance and its subsequent slow release.
- Matrix tablets - tablets with continuous, evenly extended release and supportive action of medicinal substances.
- Intermittent-release tablets are prolonged-release tablets that release the drug in portions.

# Prolonged tablets

- ***Sustained-release tablets*** are sustained-release tablets that, when administered, release the initial dose of the drug substance and release the remaining (maintenance) doses at a constant rate corresponding to the elimination rate and ensuring the desired therapeutic concentration is constant.
- ***Delayed-release tablets*** are prolonged-release tablets that, when administered, release the drug substance later and last longer than from the conventional dosage form.
- ***Reservoir-type tablets*** are a core containing a medicinal substance, and a polymer shell that determines the release rate.
- ***Implantable tablets*** are sterile extended-release tablets in the form of a disk or cylinder for implantation under the skin.

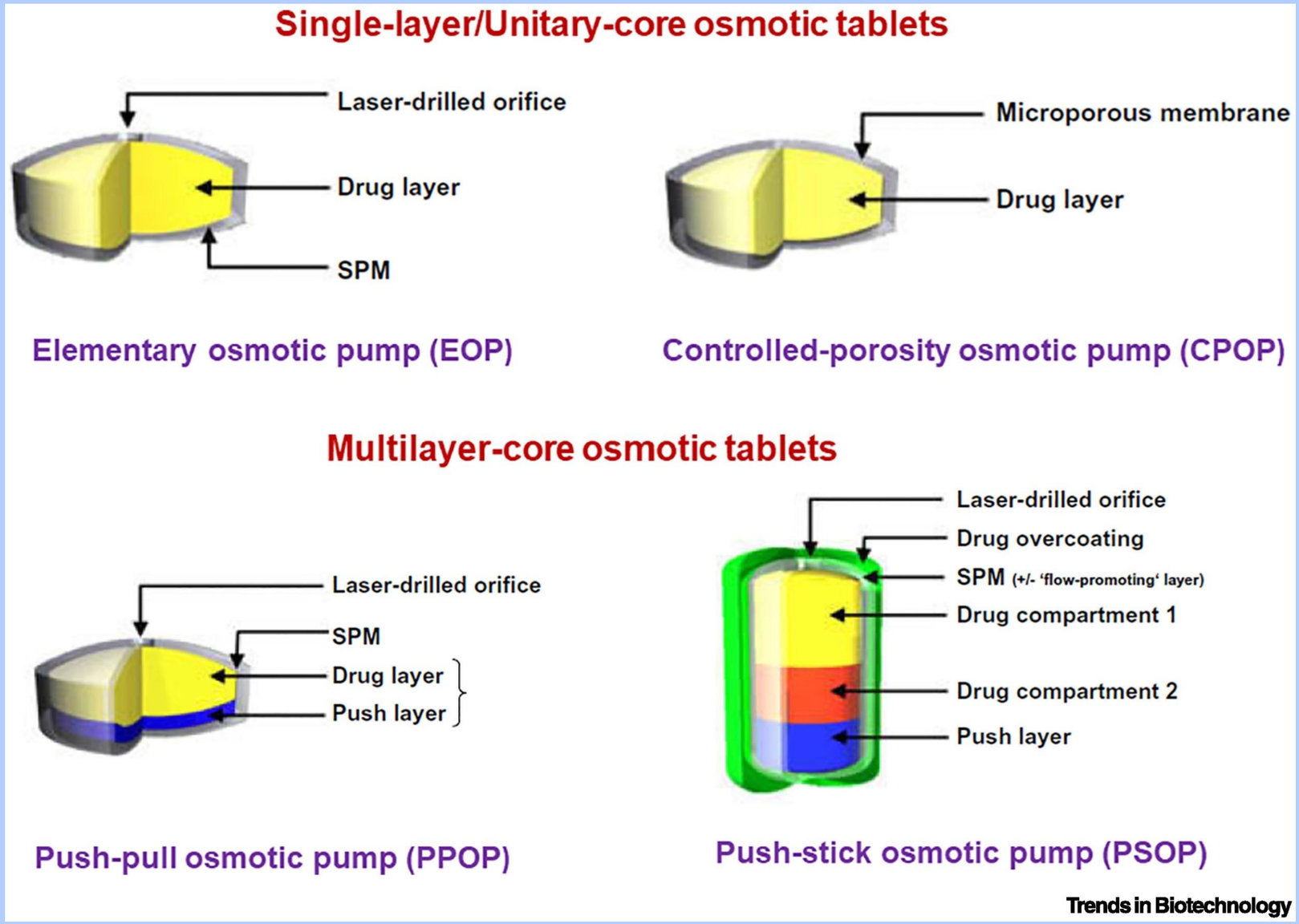
# Therapeutic drug delivery systems

***Dosage forms with controlled release of a drug substance at a rate set in advance, after a certain time, in a certain place, in accordance with the actual need of the body.***

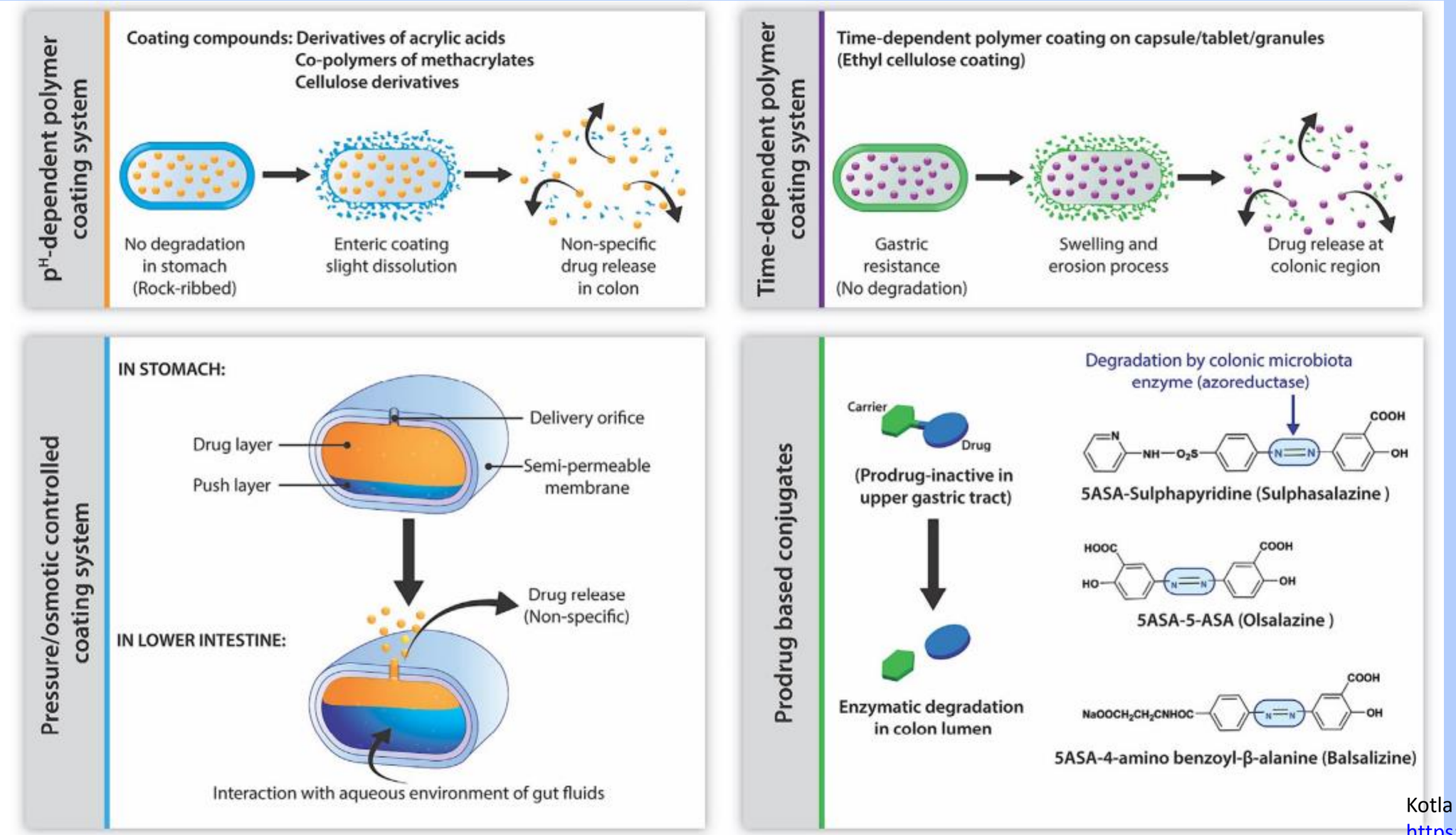
Main elements:

- medicinal substance;
- An element that controls the release of a medicinal substance;
- The platform on which the system is hosted;
- Therapeutic program.

# Therapeutic drug delivery systems. Osmotic tablets



# Therapeutic drug delivery systems




Kotla et al., 2019
https://doi.org/10.1016/j.addr.2018.06.021

# Therapeutic drug delivery systems. CODES TM