Modern drug delivery system 2.

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PTE Institute of Pharmaceutical Technology and Biopharmacy, Pécs, 17 April 2018.

Topics

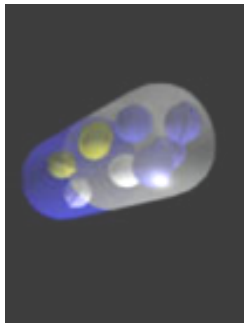
Multiparticulate dosage forms
Gastroretentive preparation
Cronotherapy/cronotechnology/pulsatile dosage forms
Colon therapy
Self-controlled systems
Implants
Pediatrics preparations
Excipients
Halving/breaking problems
Other innovative solutions
Targeted drug delivery systems

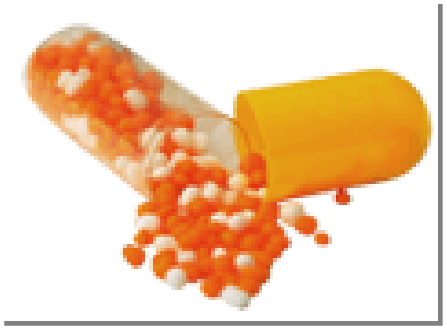
Multiparticulate dosage forms

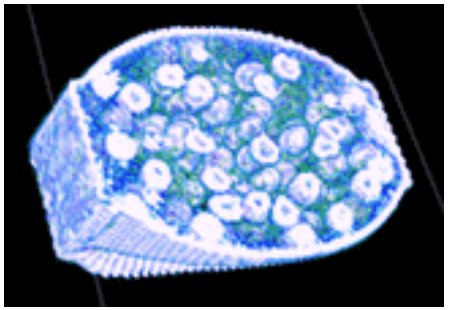
These consist of many mini-depots (pellets or microencapsulated crystals) in a capsule or a tablet, or minitablets in a capsule.

These mini-depots are dispersed and distributed throughout the GI tract when the capsule or tablet disintegrates.

The tablet may be divided without loss of the depot effect.



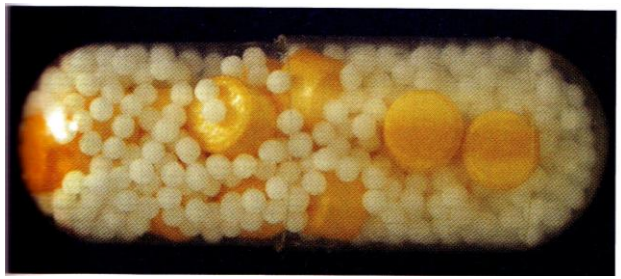




http://www.acino-pharma.com

Minitablets

Multiple-tip tooling

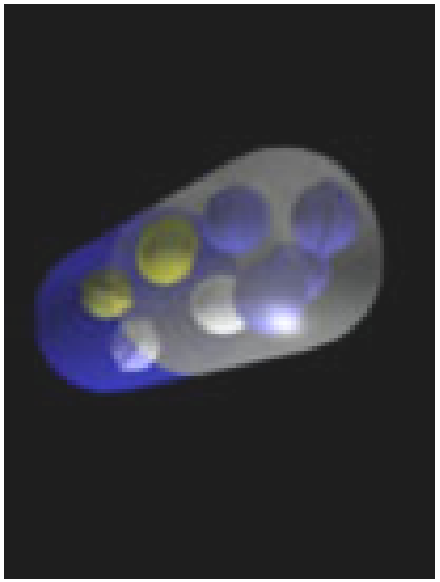


Advantages:

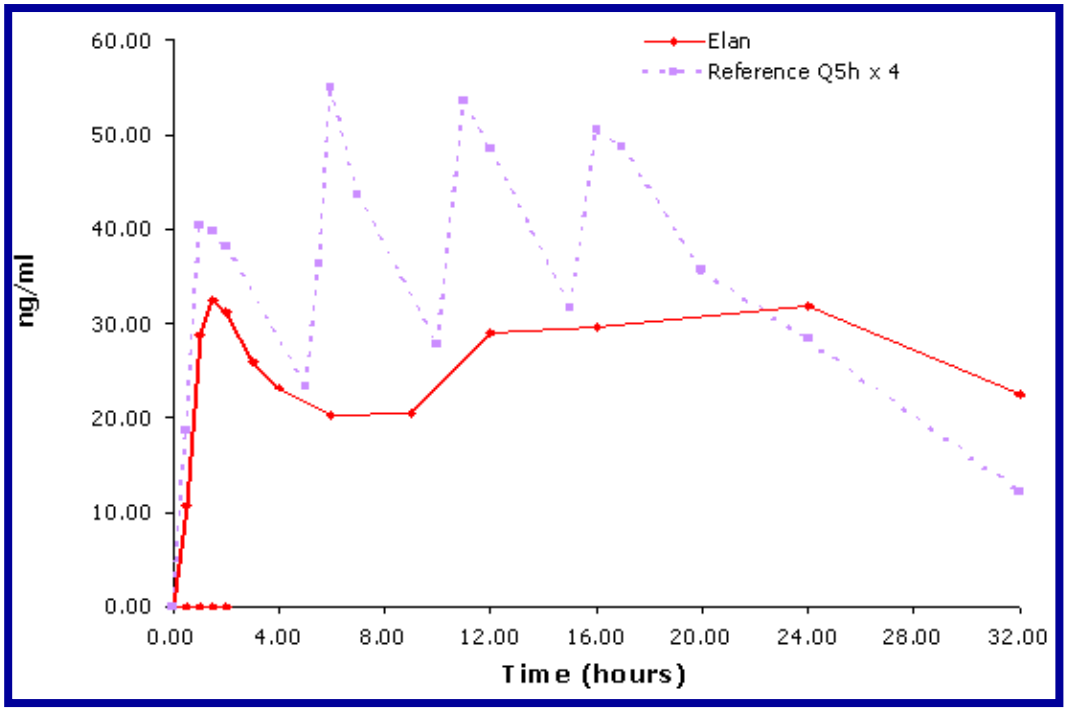
- Easy to swallow
- Good alternative to pellets
- Direct compression is possible
- Coating is possible (in a perforated coating pan or a fluid bed apparatus)
- Complex release profiles is possible (i.e. initial and maintenance dose in one capsule)
- Several chemically incompatible drugs pressed into minitablets, coated and combined in one single capsule
- May offer a solution for pediatrics

Disadvantage: The punches can easily break

Minitablets

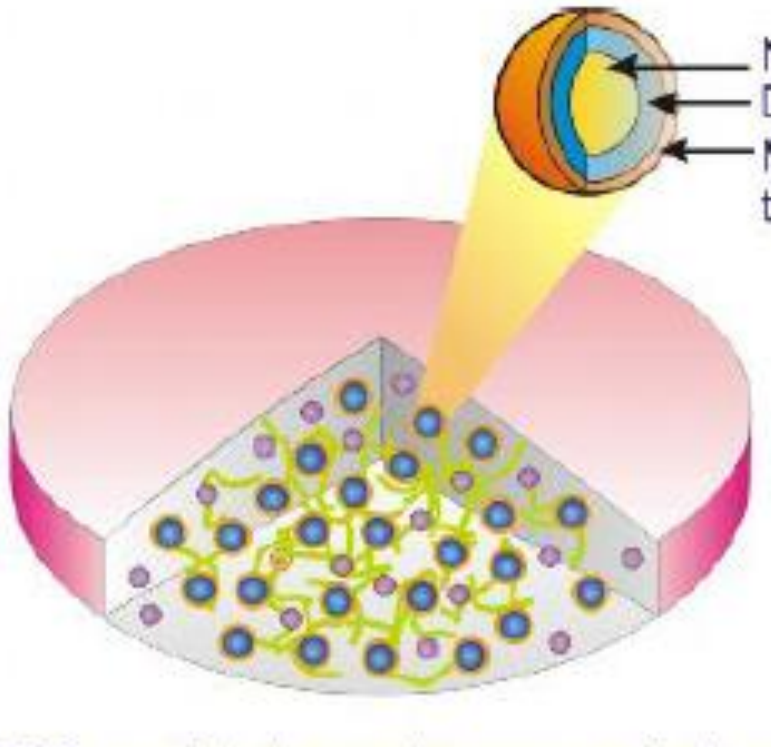


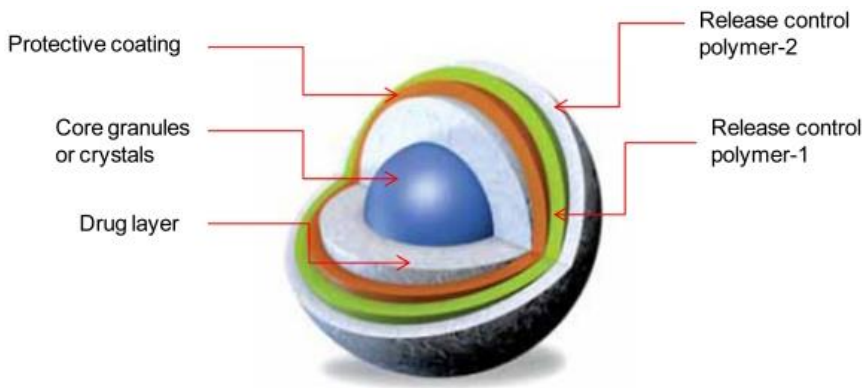
Controlled release preparation



"Reservoir" systems"

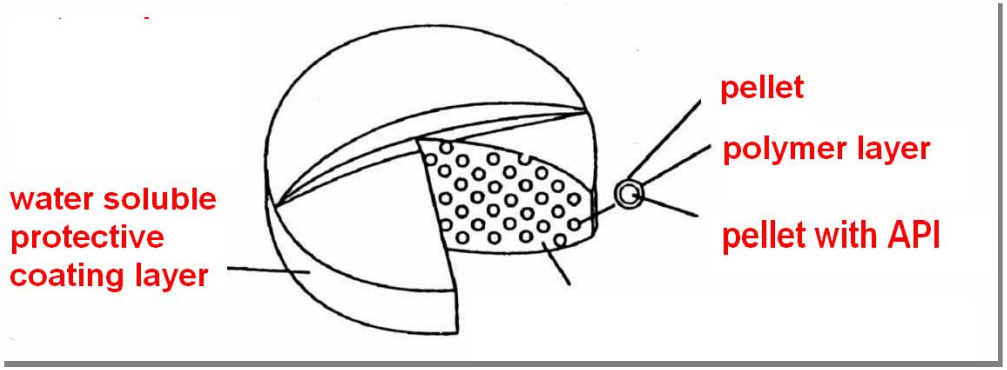
MUPS = Multiple Unit Pellet System



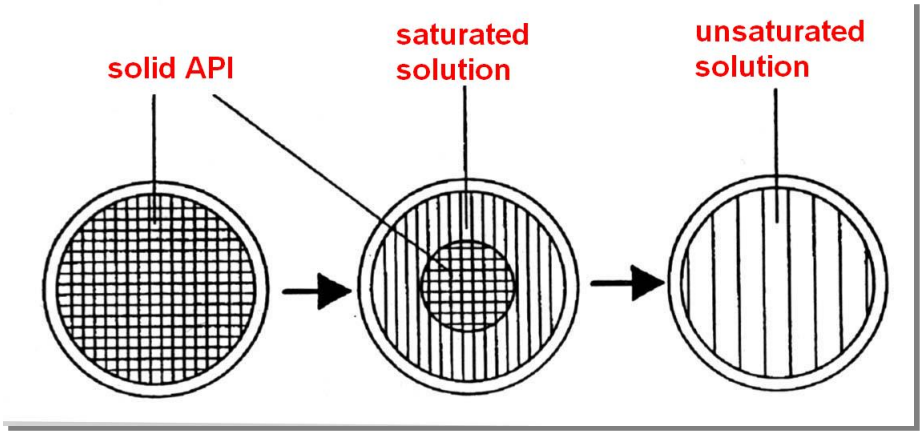


MUPS = Multiple Unit Pellet System

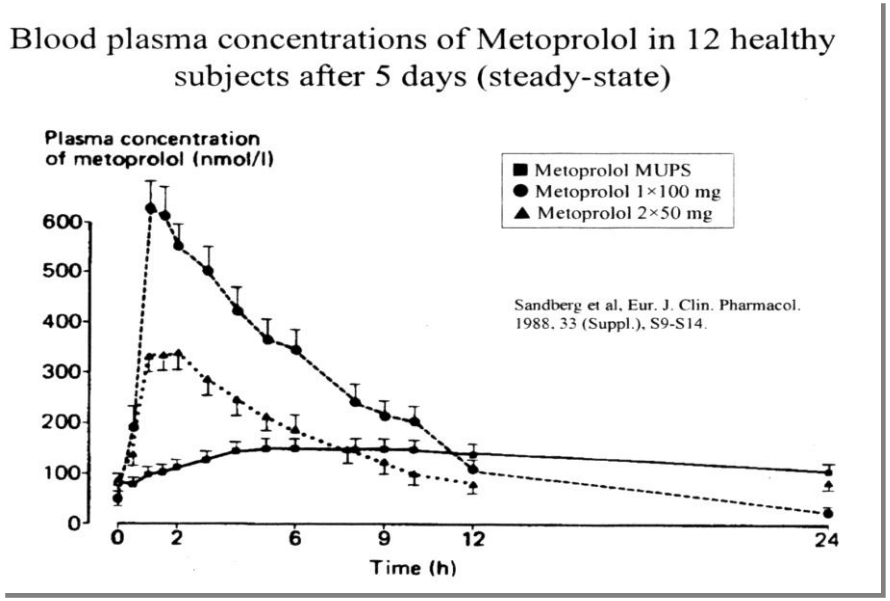
Structure



Preparation in the gastric

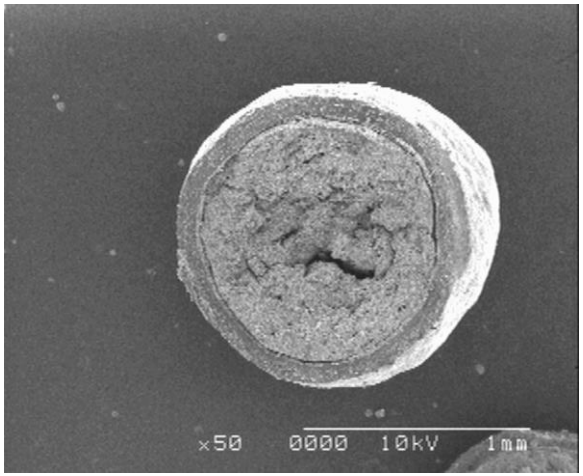


Belok-Zok (metoprolol-succinate)

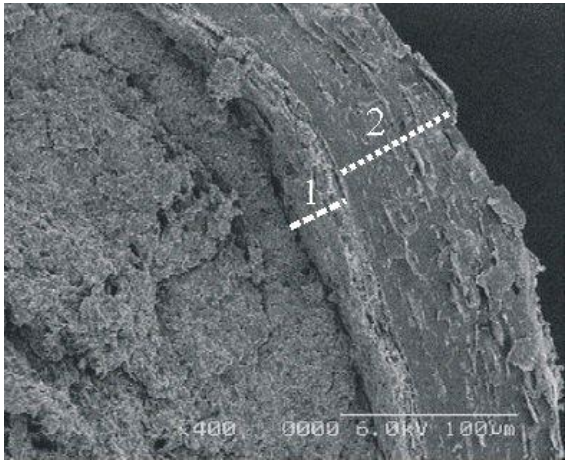


Müller, R.H., Hildebrand, G.E.: Pharmazeutische Technologie: Moderne Arzneiformen, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 1998

Matrix pellet with pH-dependent coating

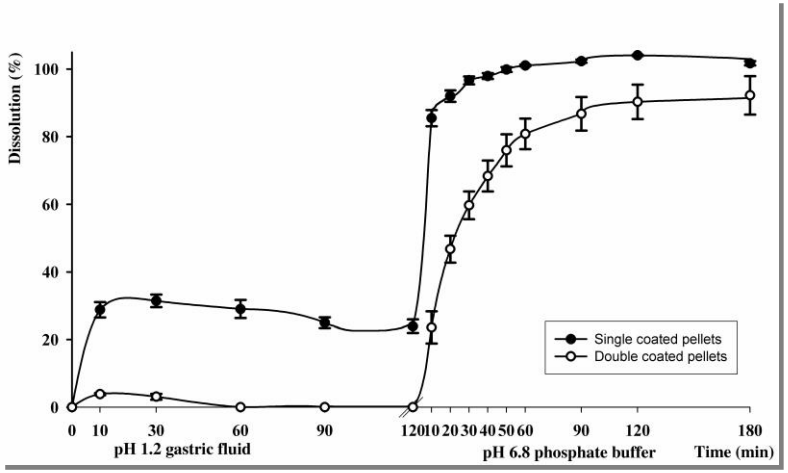


Cross-section of the double-coated pellet (SEM). Magn.: 50x



Cross-section of the double-coated pellet (SEM). Magn.: 400x
1: protective layer; 2: functional layer

Atenolol could not dissolve from the double-coated pellets in gastric juice because the protective layer closed the pores of the core and did not allow the migration of any component in the outer layer.

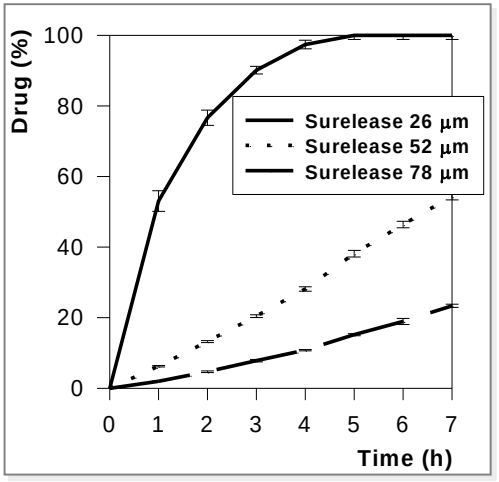


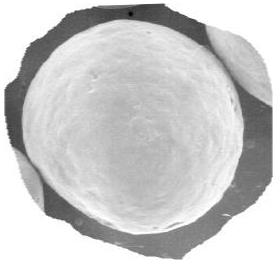
Dissolution profiles of Atenolol from the single-coated and double-coated pellets

E.I. Hamedelniel, J. Bajdik, T.Sovány, K. Pintye-Hódi: Delayed release matrix pellet preparation containing an alkalizing pore-former agent, Chem. Eng. Res. Des. 2011, 89, 1006-1010

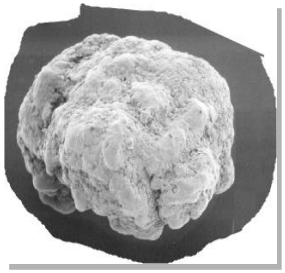
Pellets coated with pH-independent polymer

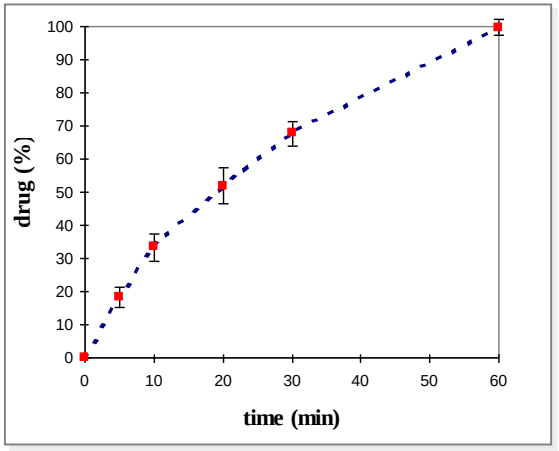
In vitro testing of coated pellets



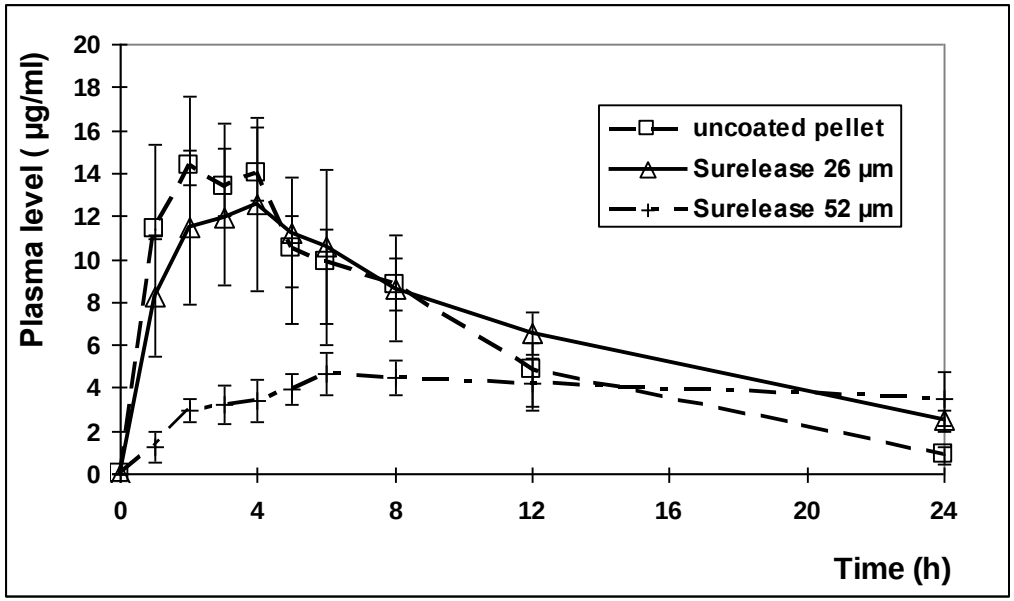


In vitro testing of uncoated pellets





In vivo testing of coated pellets in rabbits



Muskó Zs., et al.: Study of in vitro and in vivo dissolution of theophylline from film-coated pellets
Eur. J. Pharm. Biopharm. 2001, 51, 143-146

Some information of the characteritics

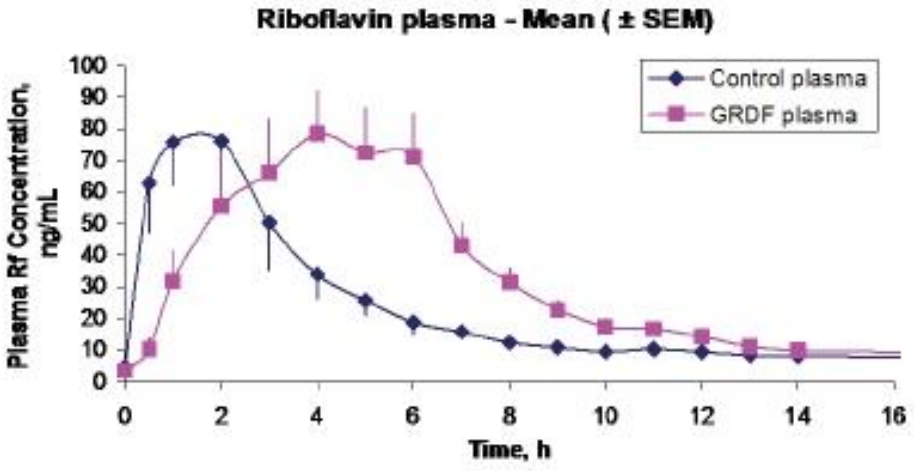
Single unit dose	Multiparticulate unit dose
• Transport dependent on gastric emptying	• Transport virtually independent of gastric emptying
• Transport strongly influenced by intestinal motility and transit time of food	• Transport only moderately affected by intestinal motility and transit time of food
Varying rate and extent of bioavailability	Reproducible bioavailability
Risk of accumulation of doses Risk of high local drug concentrations Risk of local irritations	No risk of accumulation of doses and its consequences
• Tablets non-dividable	• Tablets dividable

Gastroretentive preparations

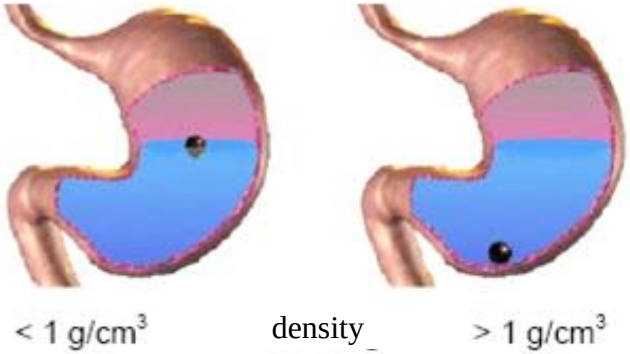
Gastroretentive preparations can prolong the residence time in the stomach for hours. They are perfect for the therapy of proximal region of the small intestine.

Application

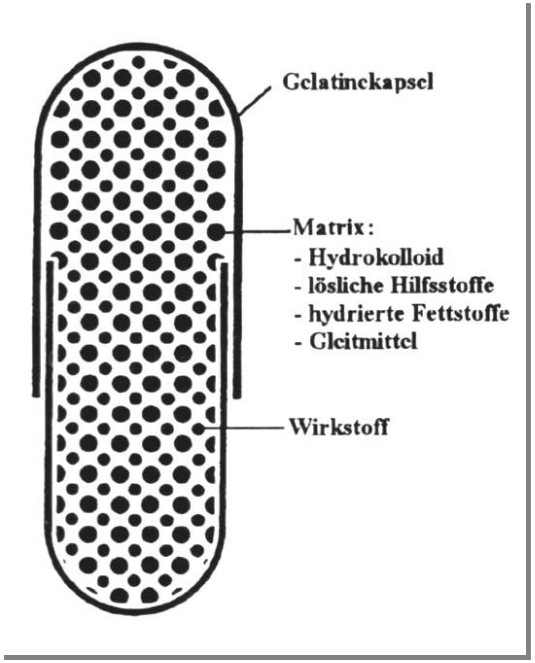
- extended local effect (antacids, ulcer)
- improved bioavailability because of the most proper site of absorption of an API
  API's with narrow absorption vindow: aciklovir, atenolol, diltiazem, furosemide, itrakonazol, levodopa, riboflavin, etc.
- avoidance of the other parts of the GI tract (amoxicillin trihydrate - colon flora)
- stability is suitable in intestine: captopril
- protection of the API (ranitidine-HCl and metronidazole)



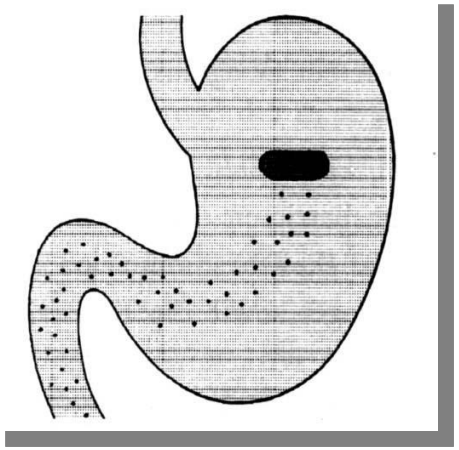
Mean plasma concentration of RF dosed after a light meal with an IR formulation (blue) or a GRDF (purple).

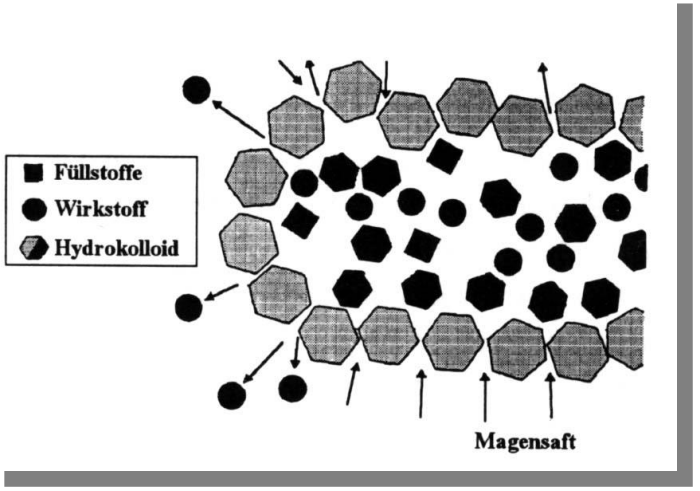


Floating systems



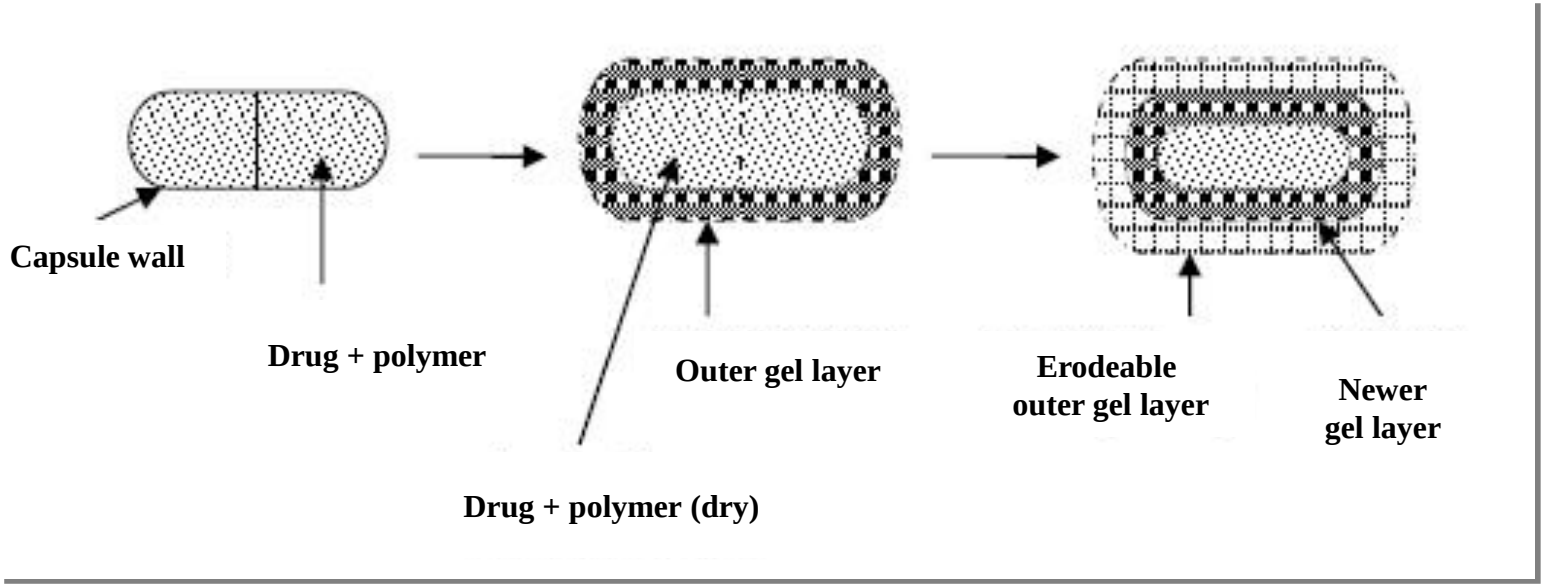
Madopar HBS



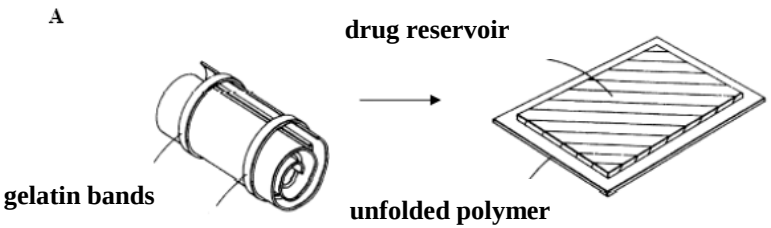


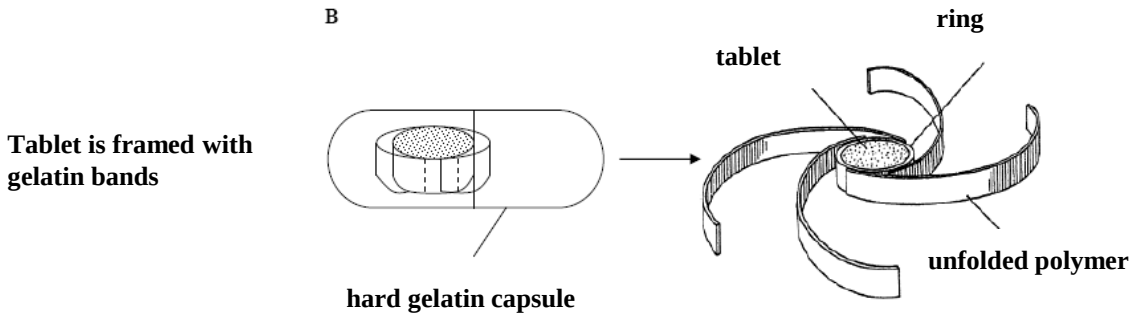
Matrix pellet: methyl-hydroxy-propyl-cellulose
hydrogenized vegetable oil etc.

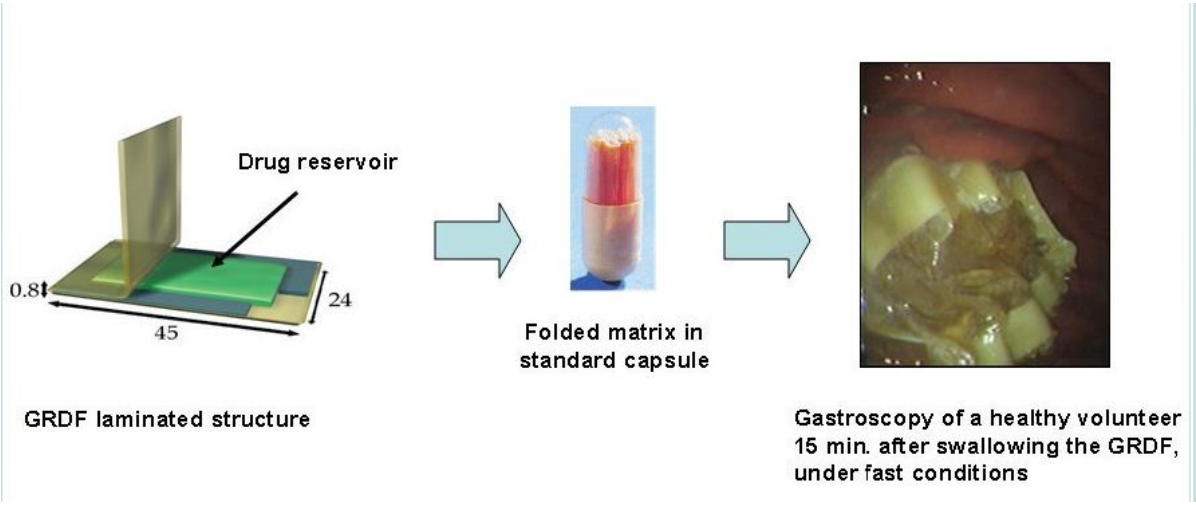
Swellable systems



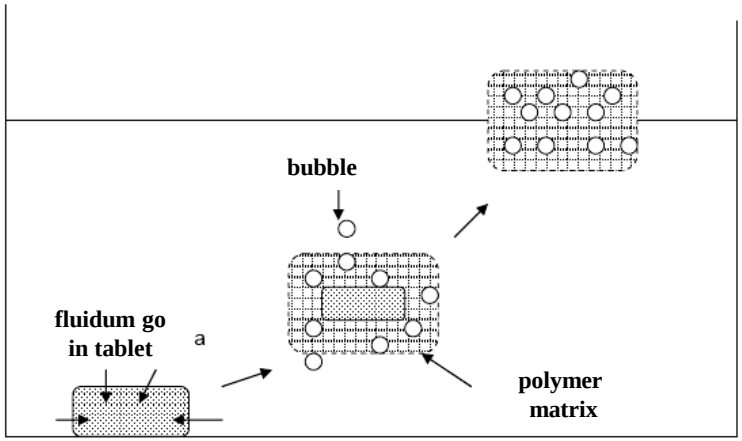
Unfolded systems







Systems based on gase forming



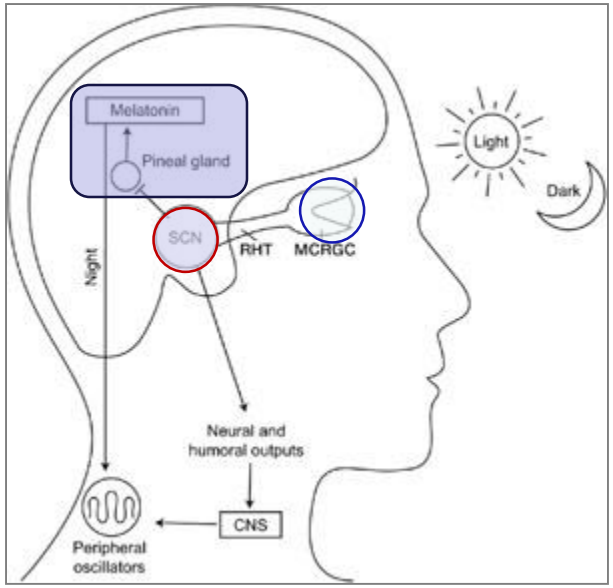
0-3 min

The gastric floating system involved sodium bicarbonate as a gas-forming agent dispersed in the hydrogel matrix. On reacting with hydrochloric acid, the bicarbonate ion is converted to carbon dioxide in the form bubbles on the surface of the tablets, which caused the tablets to float in the fluid for more than 4 h *in vitro*.

Patients keep seat!

Chronobiology

Circadian rhythm of human body (day cycle)



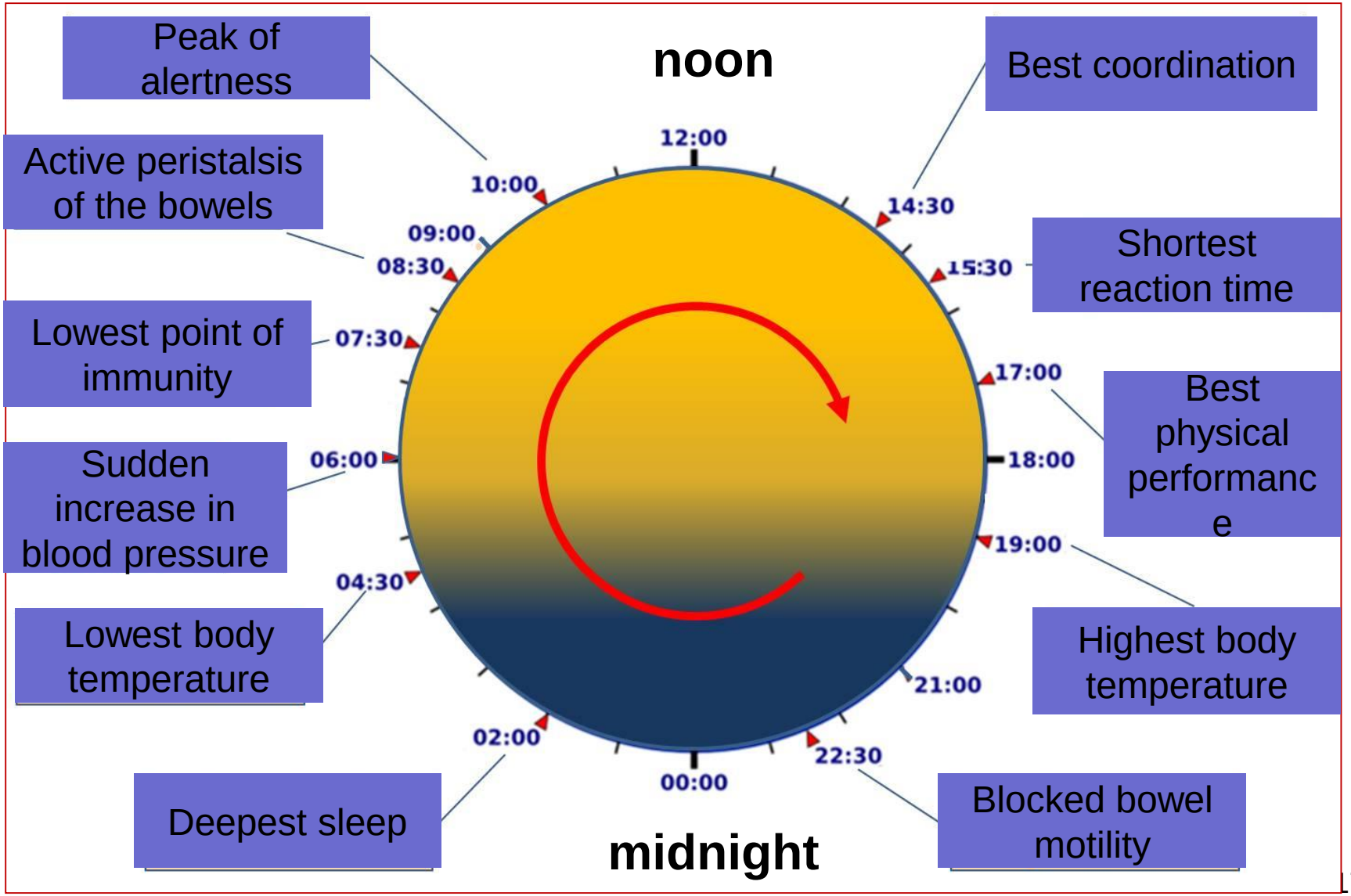
The circadian rhythm is determined by exogenous and endogenous processes.

The cycles are regulated by the hypothalamic nuclei (the suprachiasmatic neurons, SCN).

The rhythm of day and night is detected by light-sensitive cells of the retina.

The pineal gland get a signal for the emptying of "darkness hormone" melatonine.

Chronotherapy



Chronopharmacotherapy diseases

- *Asthmatic attack* during early morning
- *Heart attacks* in the middle of the night
- Morning *stiffness in arthritis*
- *Peptic ulcer* during afternoon and night

Asthma

Heart attack

Arthritis

Chronotechnology

Possibility of regulation

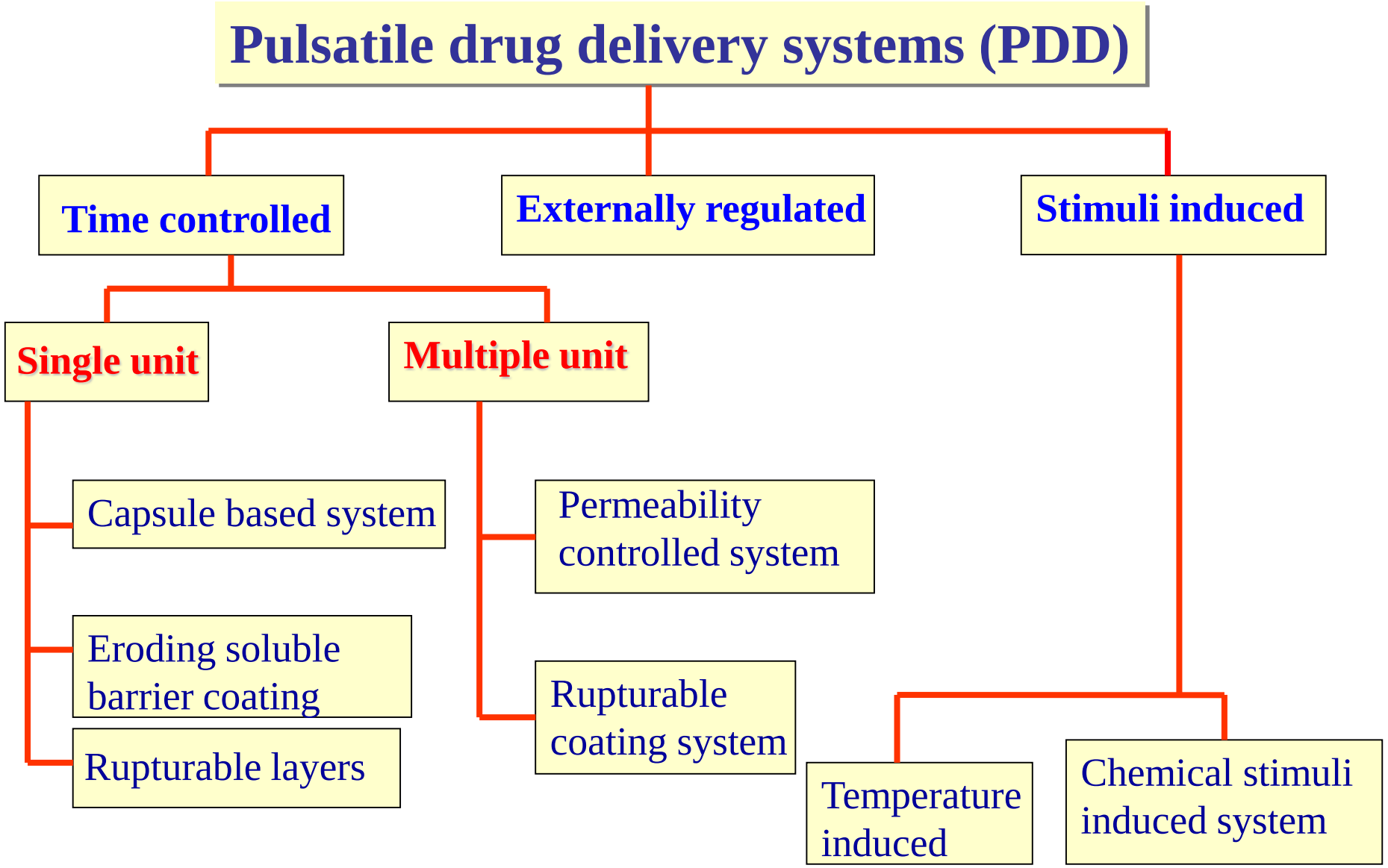
Lag time: decrease
increase

Speed of the drug release: decrease
increase

Duration of drug release: decrease
increase

Kinetic of the drug release: zero order
first order

Design of drug release: site controlled
time controlled


Pulsatile drug delivery systems (PDD)
Time controlled
Externally regulated
Stimuli induced
Single unit
Multiple unit
Capsule based system
Eroding soluble barrier coating
Rupturable layers
Permeability controlled system
Rupturable coating system
Temperature induced
Chemical stimuli induced system

Technological possibility

a.) controlled systems

- time (delayed release)
- site („local release”) pH, enzymes, bacterium

Disadvantage: rigidity

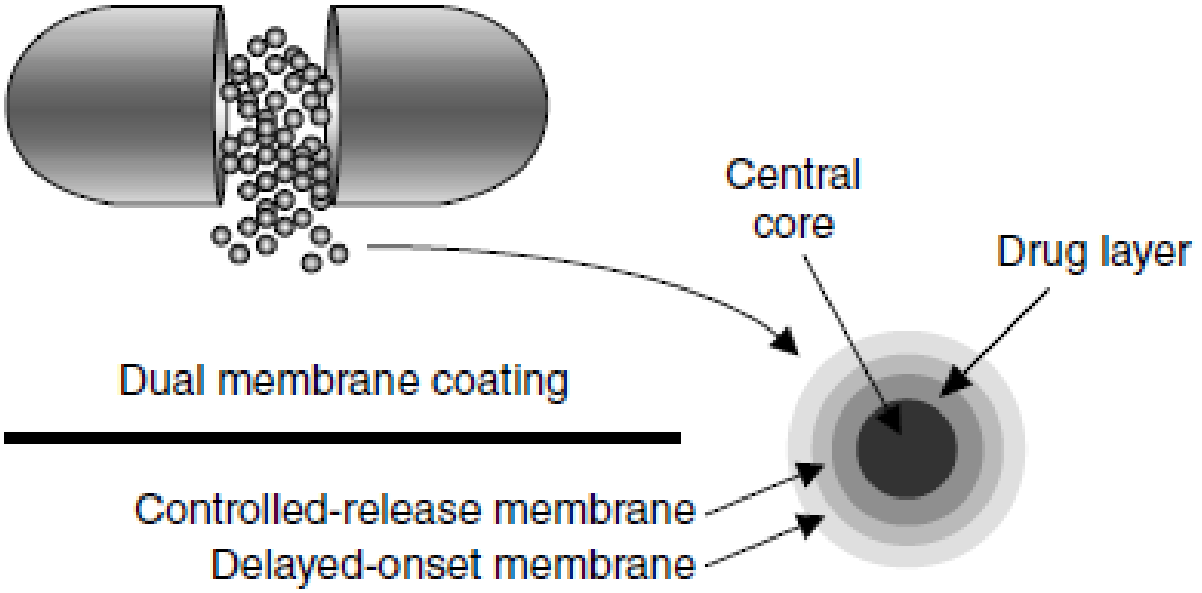
b.) systems that are sensitive to biologic signals

- stimuli-sensitive polymers (pH, temperature…)
- self-control systems

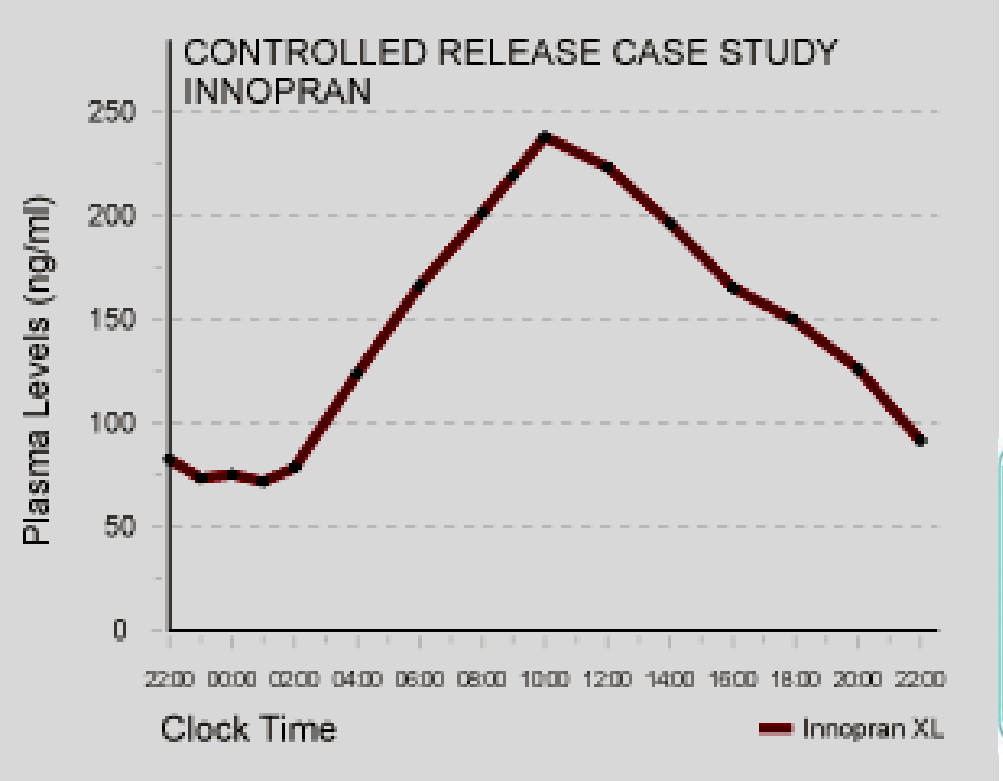
Disadvantage: „high quality” technology, expensive

Diffucaps® chronotherapeutic system

- **Propranolol (InnoPran XL™)**
- Multipartculate system
- After the administration at pm. 22 o'clock, c_{max} will be at 10 o'clock am.

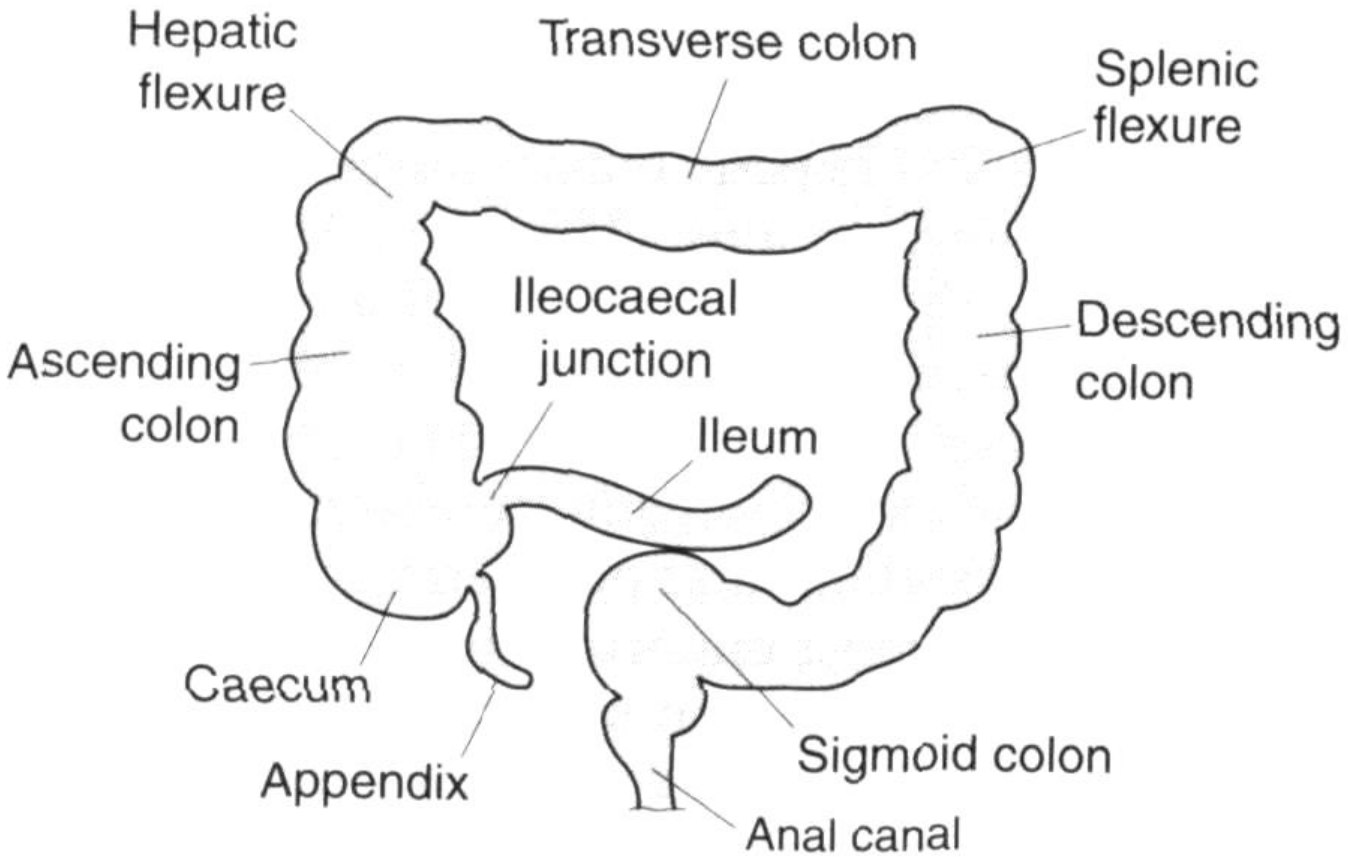


Diffucaps® chronotherapeutic system



Colon therapy

Anatomy of colon



Specific environment

- low amount of dissolution medium,
- pH 6,8-7,8
- no digestion,
- intestinal flora,
- water reabsorption.

Preparations must to reach the colon without no damage.

Advantages of colon therapy

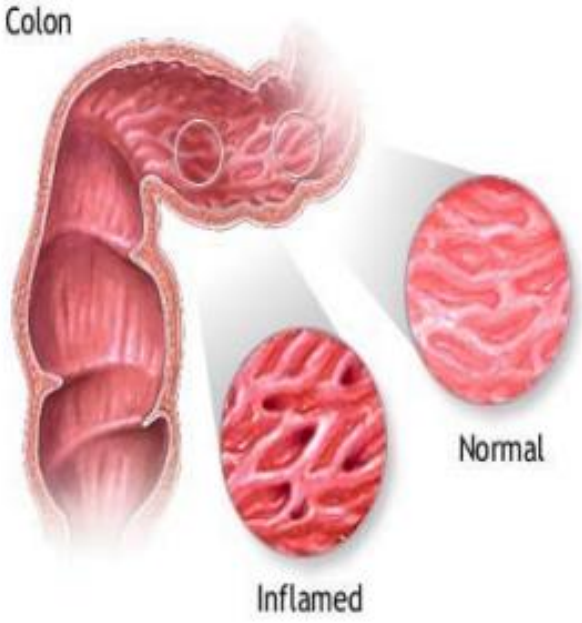
Target therapy
Decrease the dose
Decrease the side effect
Increase the bioavailability

Deseases in colon

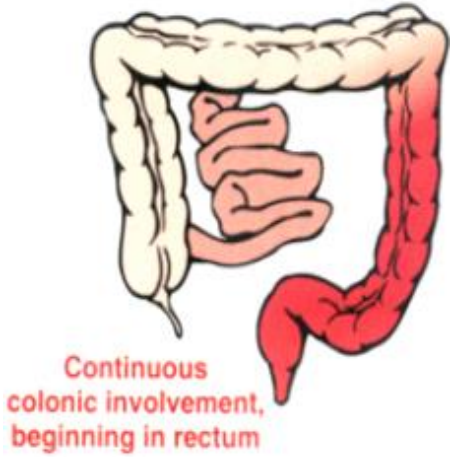
	Desease	APIs
Local action	Inflamation in colon Crohn desease Chronic pancreatitis	Hydrocortisone, prednisolone, sulfasalazine, olsalazine, mesalazine, balsalazine
	Removal the pancreas, cistic fibrosis, cancer in colon	Peptic enzimes, 5-fluorouracyl
Systematic action	Avoiding the irritation in gastric, Avoiding the „first pass" effect, Administration some peptids, Administration some vaccines	NSAIDS Steroids Insulin Typhoid

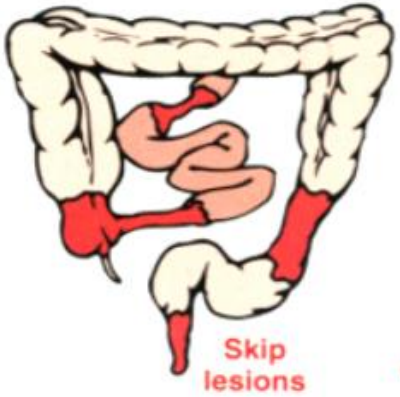
Deseases in colon

Colon inflamation



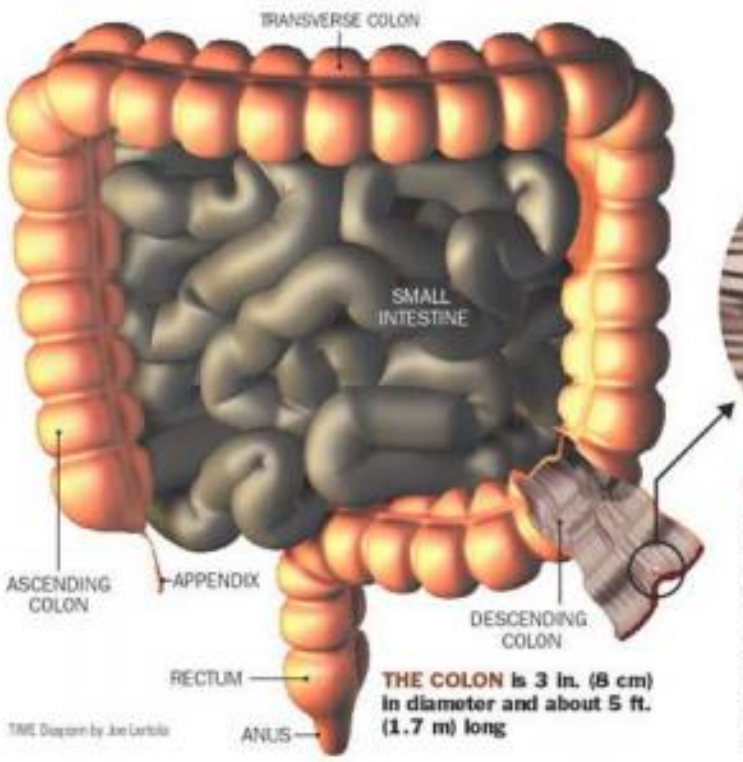
Colitis ulcerosa



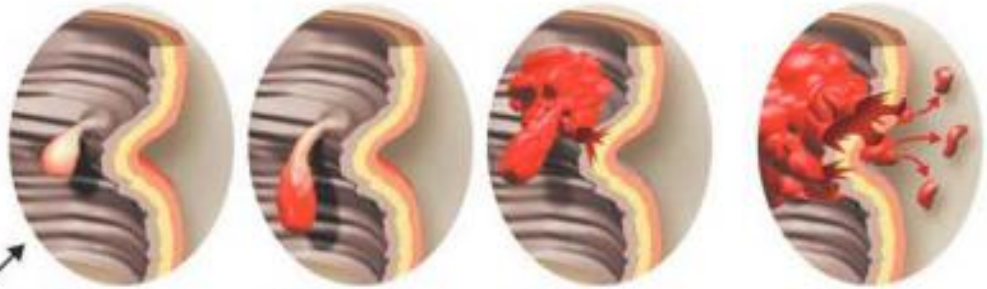


Chron desease

Cancer in colon



Malignant tumour



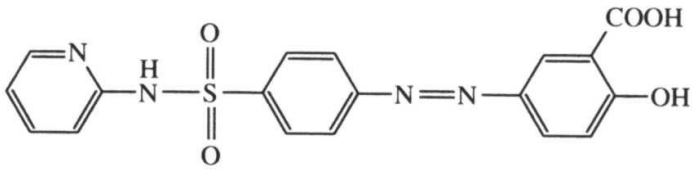
1 Cells that line the colon are very active, constantly dividing and creating buds, known as polyps. Most polyps are small, benign growths that eventually stop growing

2 But a tiny percentage of these polyps keep growing, sometimes for 10 years or more. Various genetic mutations can transform them into cancerous tumors

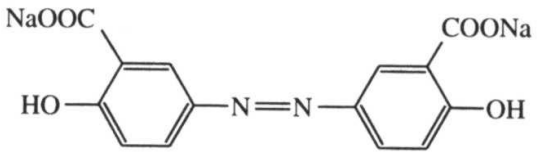
3 As these tumors grow larger, they gather more mutations and begin to burrow deeper and deeper into the muscle wall that surrounds the colon

4 Once the cancer invades the blood and lymph systems, malignant cells can break off and spread to other organs, such as the liver, lungs and stomach

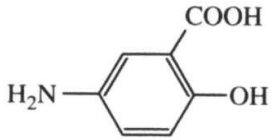
Prodrug



(I)



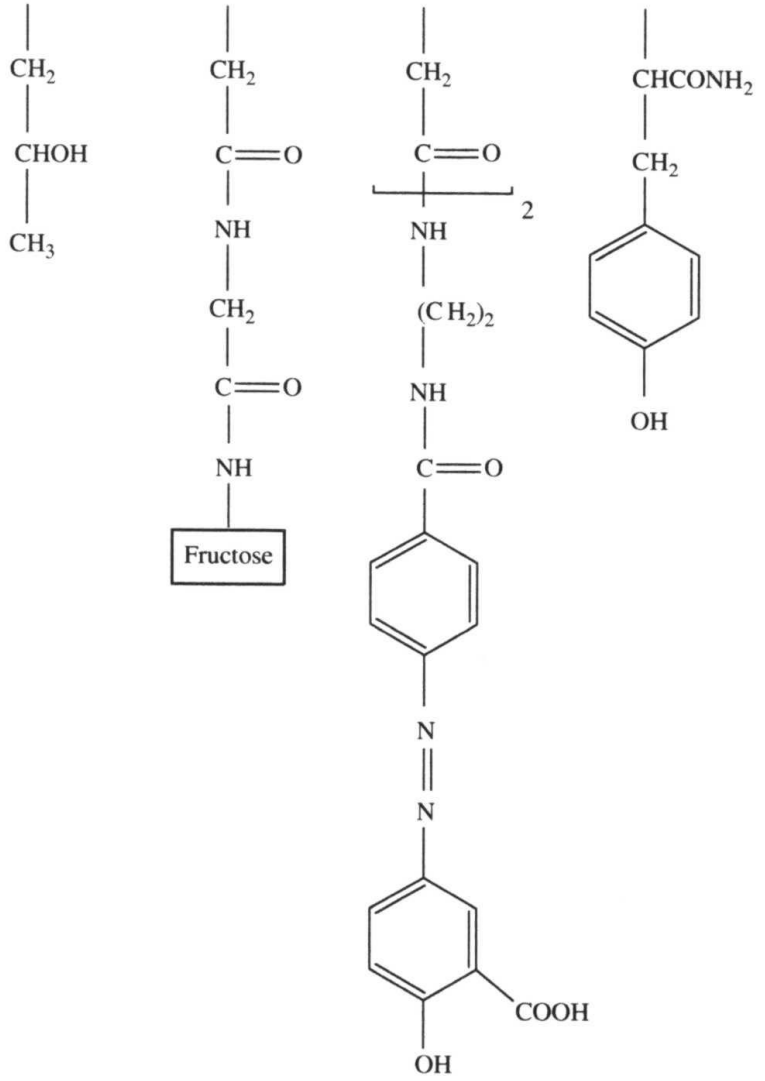
(II)



(III)

I. Sulfasalazine
II. Olsalazine
III. 5-Amino-salicylic acid

(diazoreductase enzyme)

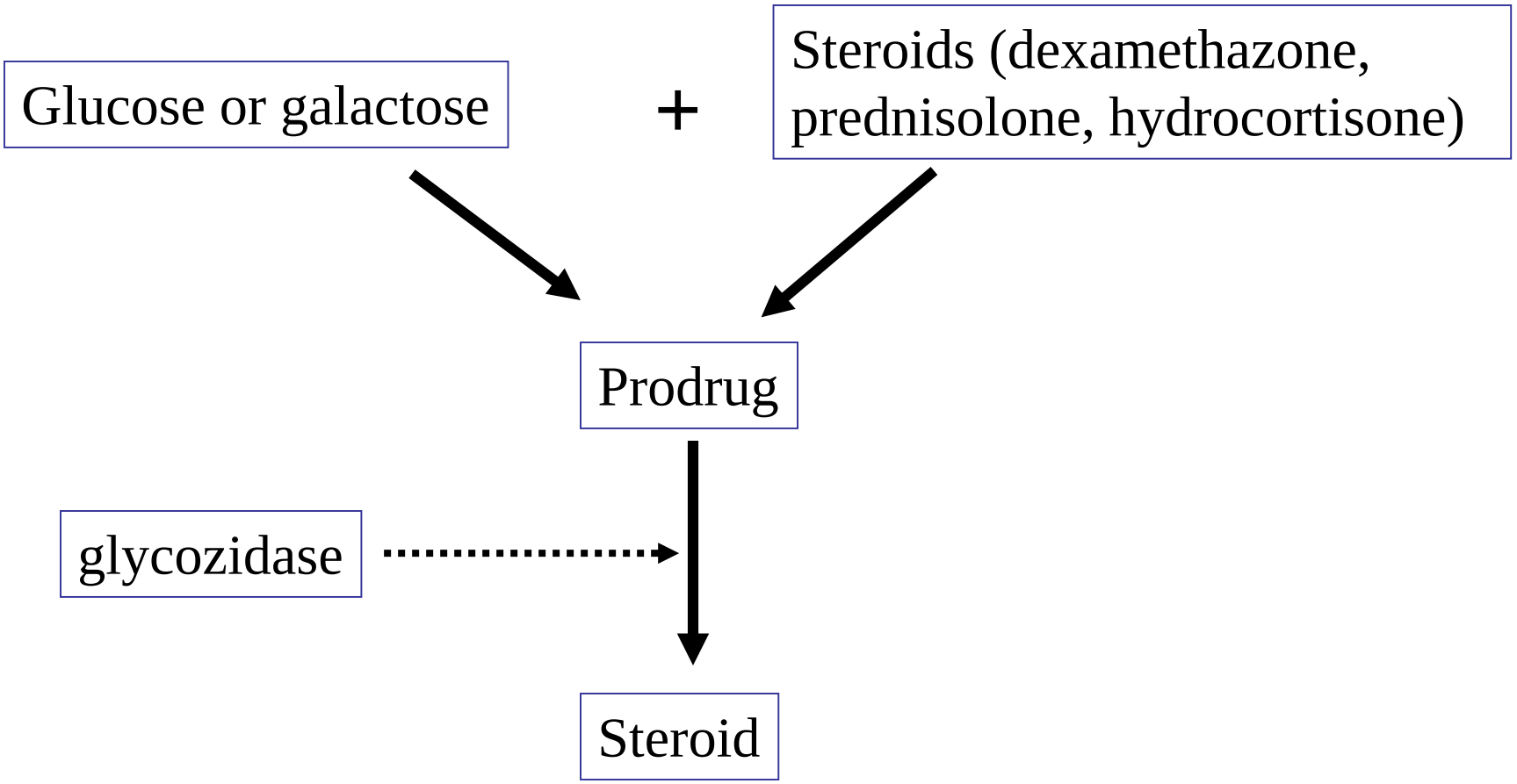


Polymer-prodrug

Polymer molecule: poly-sulfonamido-etilene

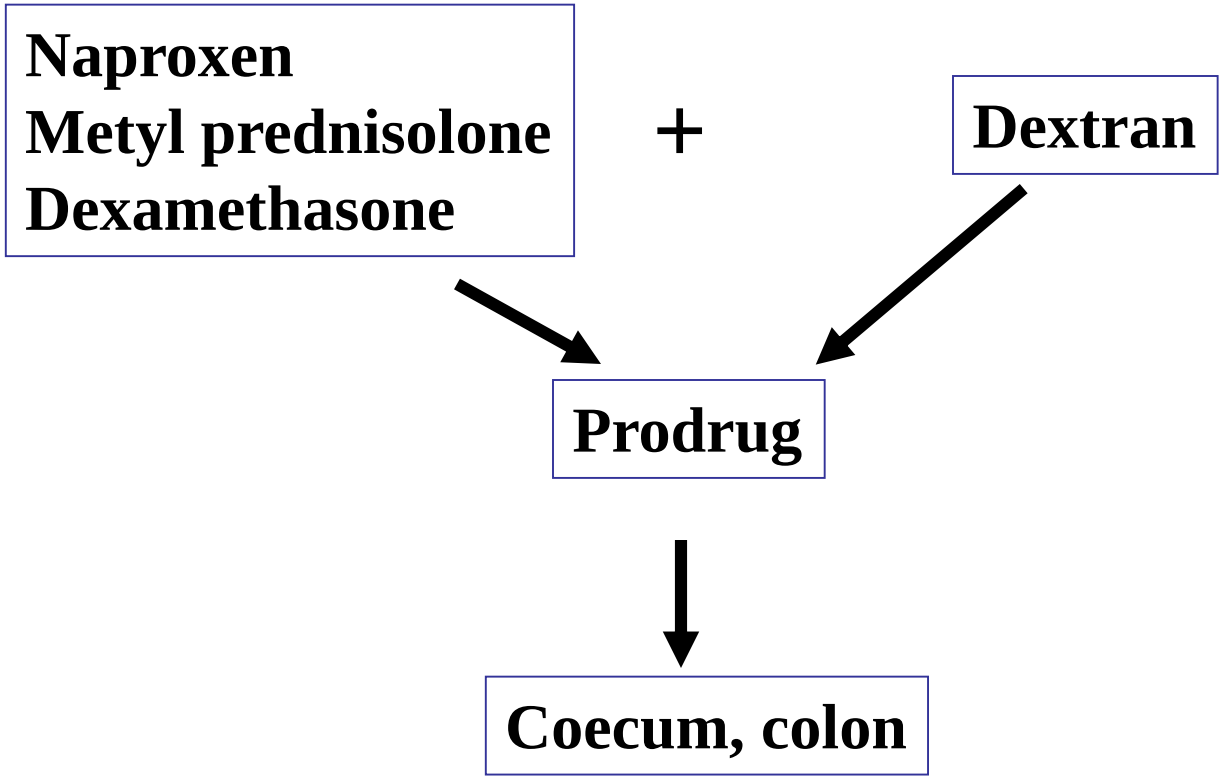
Prodrug

Enzyme degradation

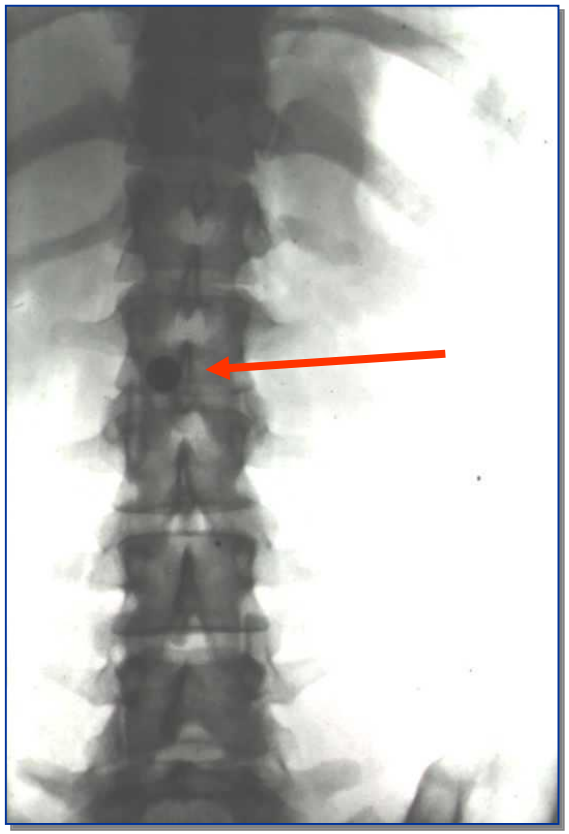


Prodrug

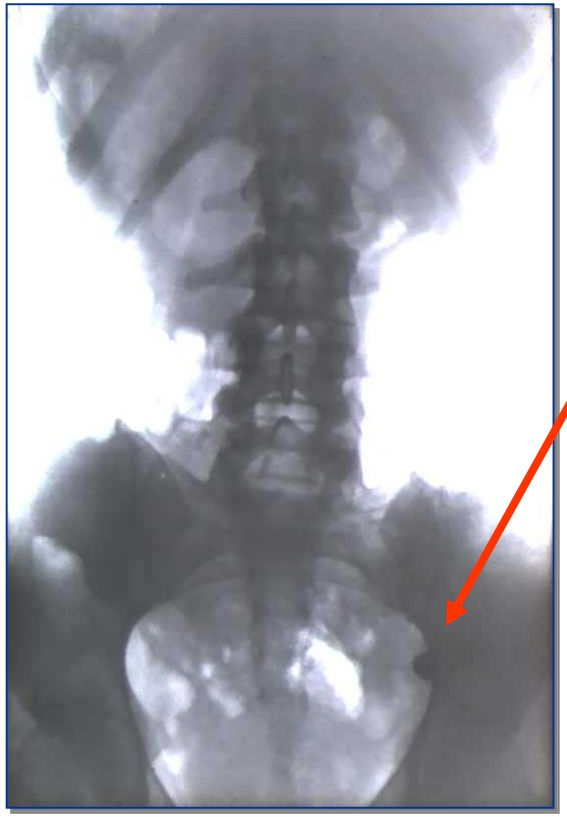
Ester bonds



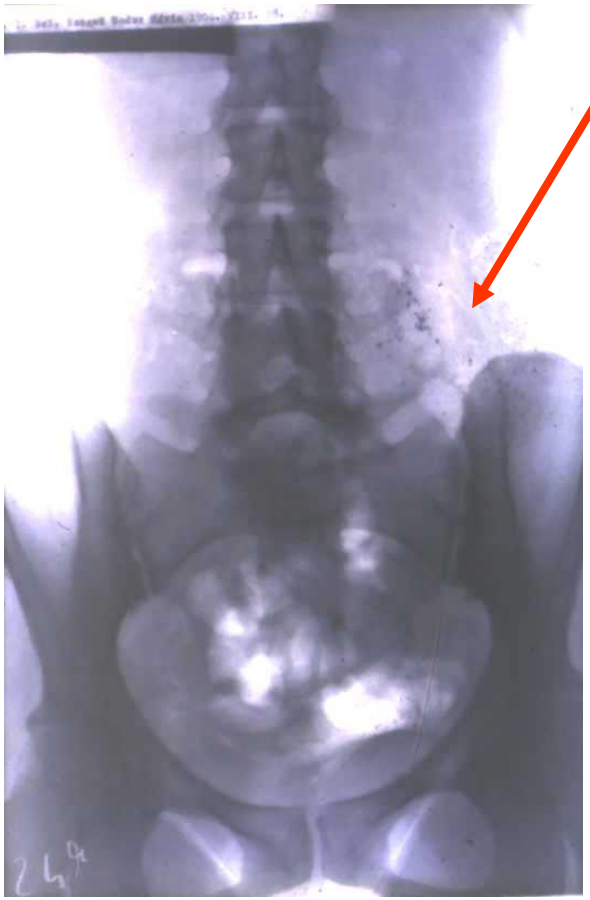
Film coating



0 min



300 min



24 h

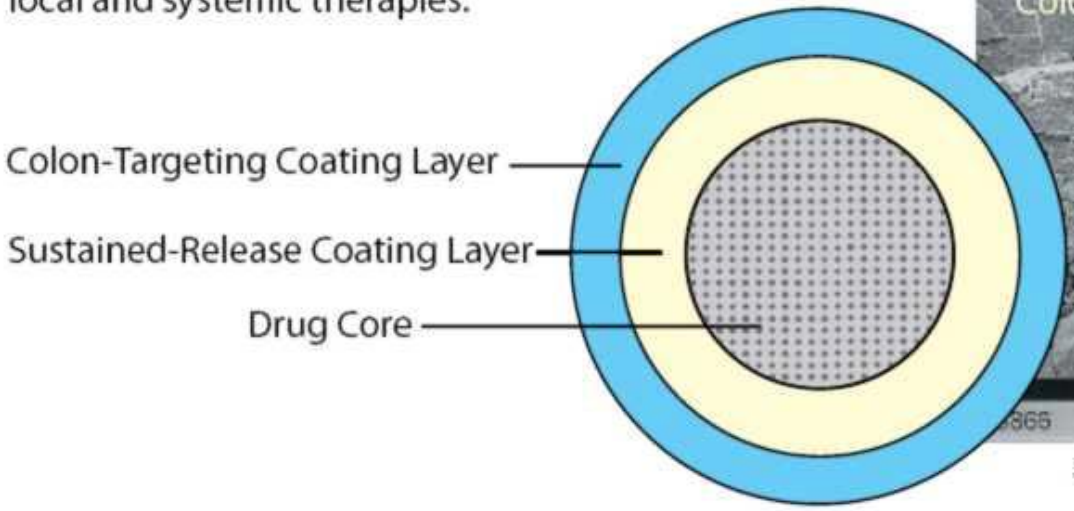
Film coated tablet after administration

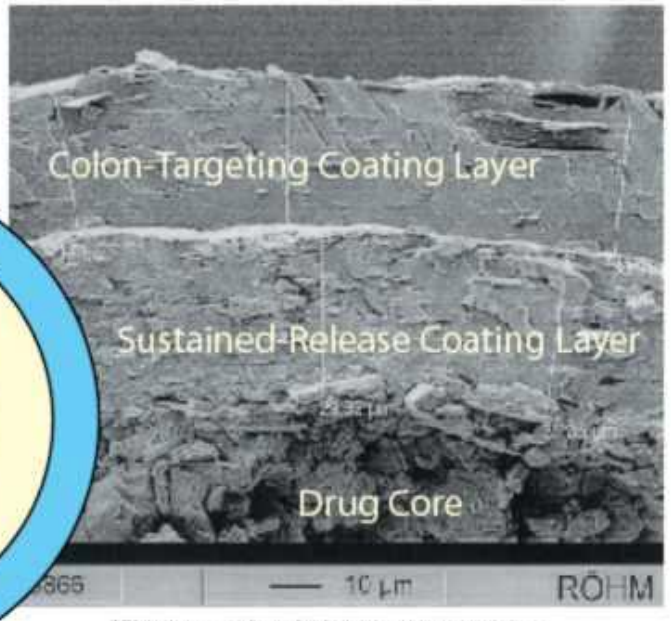
Core: $BaSO_4$

Coating material: Eudragit S

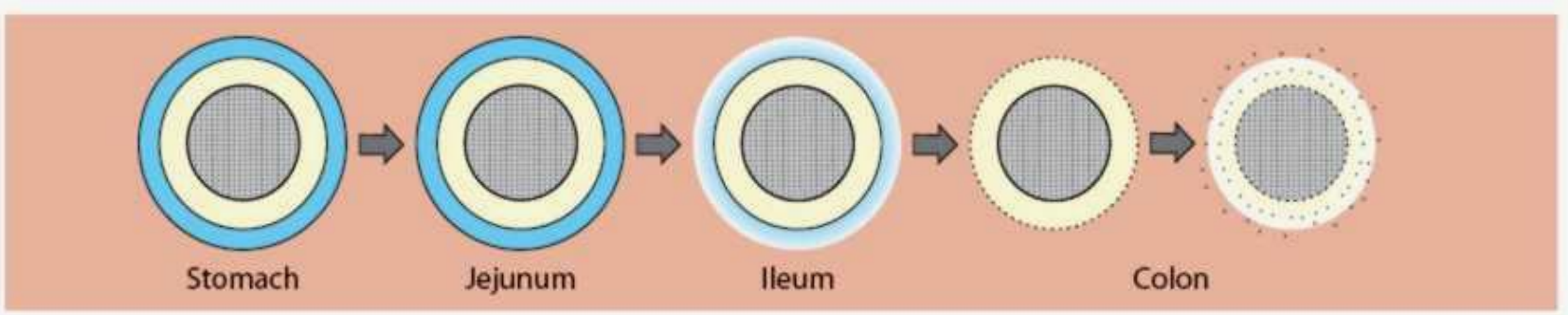
Eudracol

EUDRACOL™ is a colon-targeted, pH-triggered and sustained-release oral drug delivery technology for multi-unit dosage forms, for both local and systemic therapies.





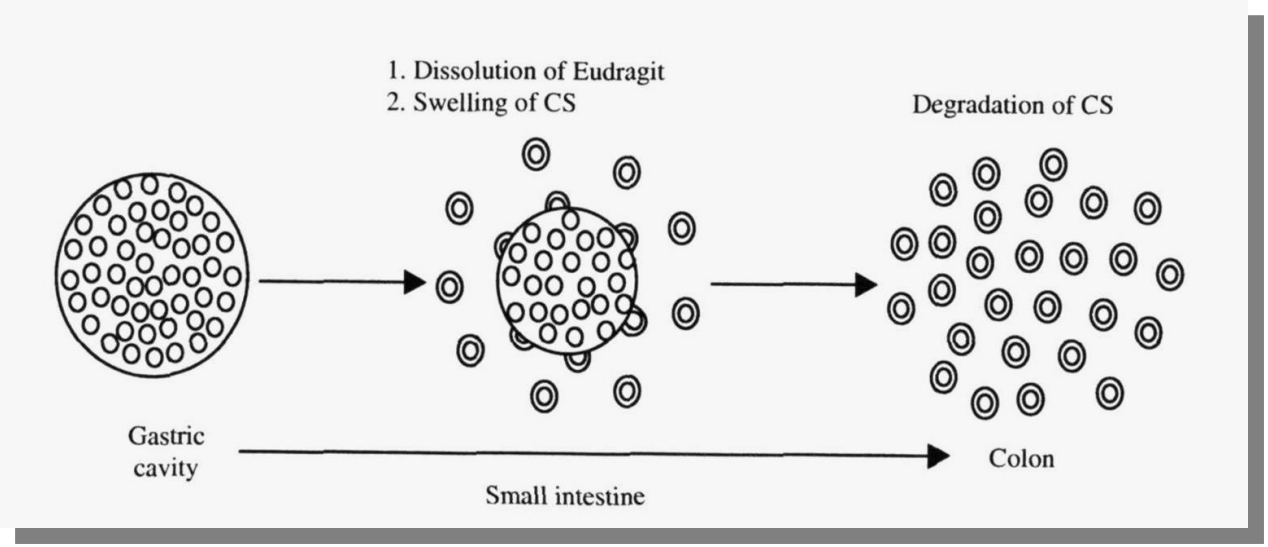
SEM picture of multi-layer coating systems



Coating

Degradation by enzymes

The natural polysaccharids (pectine, xylane, chitosane etc.) are not digestible in stomach or in small intestine, bat they degradate in the colon by the bacteriums, which are in the colon.



API: diclofenac

Self-controlled systems

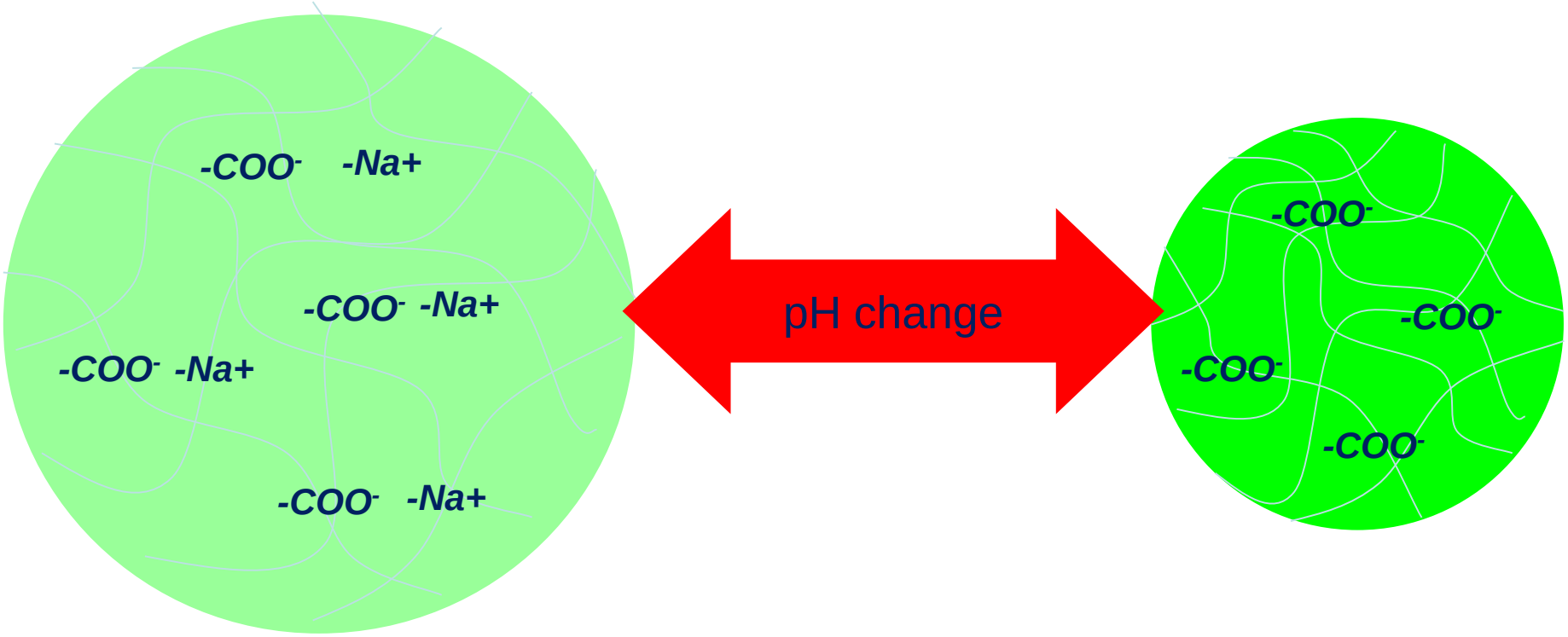
37

Self-controlled systems

Volume change of hydrophil gels

swelling

constriction



pH=5,5

pH=4,5

Self-controlled systems

Effect	Hidrogel	Mechanism
pH	Acid, base hidrogel	pH change — swelling — API release
Ionic strength	Ionic hidrogel	The ion concentration in the matrix is alerted by the ion strength — swelling — API release
Chemical	Electron-acceptor hidrogels	Complex formation (aceptor-donor molecula) — swelling — API release
Ensim-substrate	Ensim containing hidrogel	The substrate activates the enzyme — enzymatic transformation — swelling — API release

Self-controlled systems

Effect	Hidrogel	Mechanism
Temperature	Thermal sensitive hidrogel	Temperature change — danger in the polymer-polymer and water-polymer interaction — swelling — API release
Electric field	Polyelectrolyte hidrogels	It can alert the — charge of the membrane — electrophoretic release of the API — wetting — liberation of the API
Ultrasound	Ethylene-vinyl alcohol	The US can — increase the temperature — enhanced dissolution rate

We can use these effects. E.g. such polymer is chosen, which phase transition temperature is around 40 ˚C. In lower temperature these polymers are in dissolved phase, above 40 ˚C in aggregated phase. Given material accumulated around tumour because of increased temperature of tumour cells.

Some other possibility

Accu-Break Pharmaceuticals Inc.

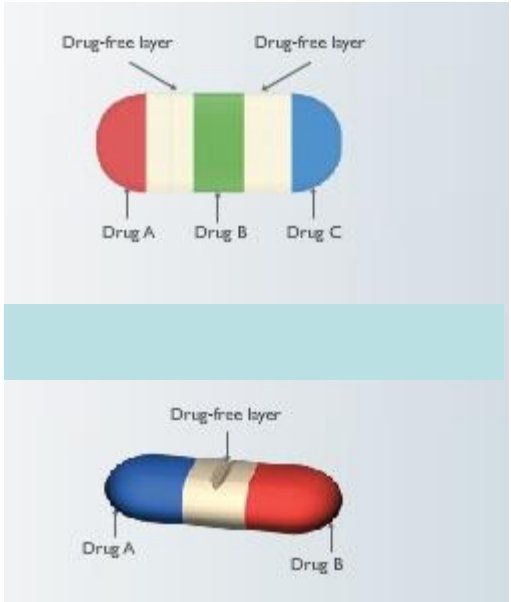
Caterpillar-tablet

„split-dose”

„fixed dose”

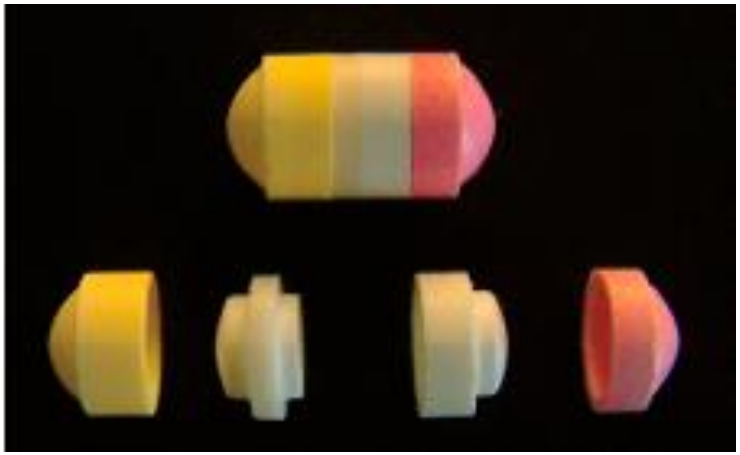
Multidose tablet

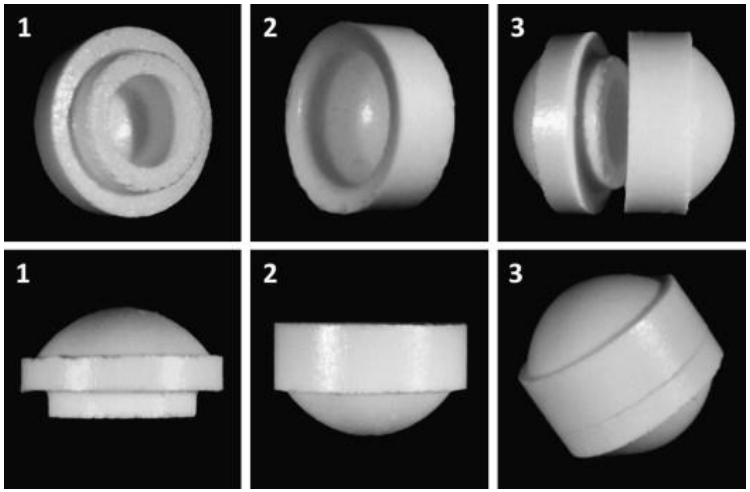
Incompatible drugs

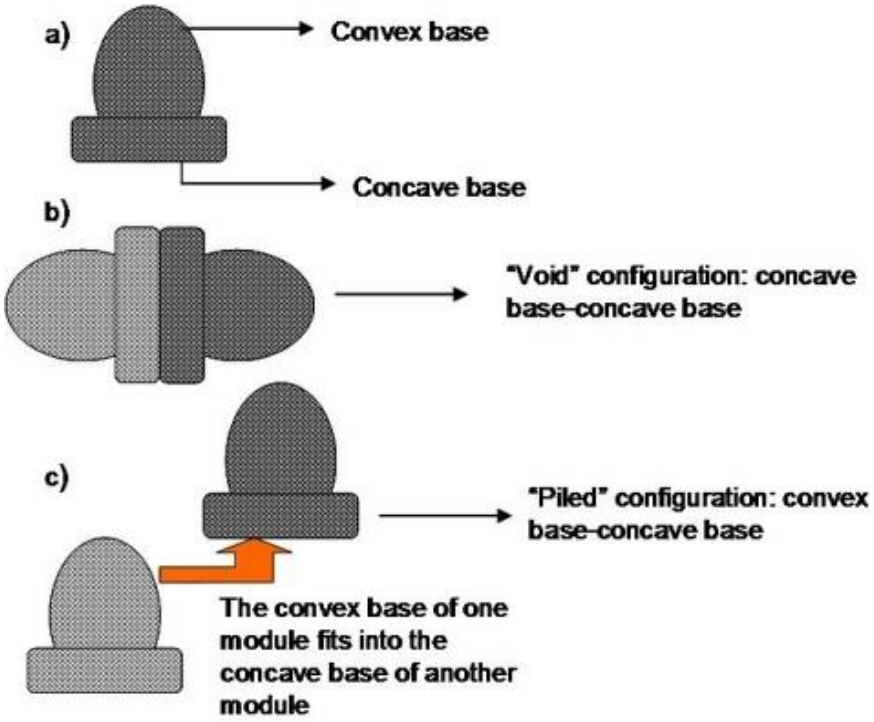


Controlled drug release

„LEGO" tablets (Dome matrix module)







Moodley K, Pillay V, Choonara YE, du Toit LC, Ndesendo VM, Kumar P, Cooppan S, Bawa P : Oral Drug Delivery Systems Comprising Altered Geometric Configurations for Controlled Drug Delivery, Int J Mol Sci (2011)

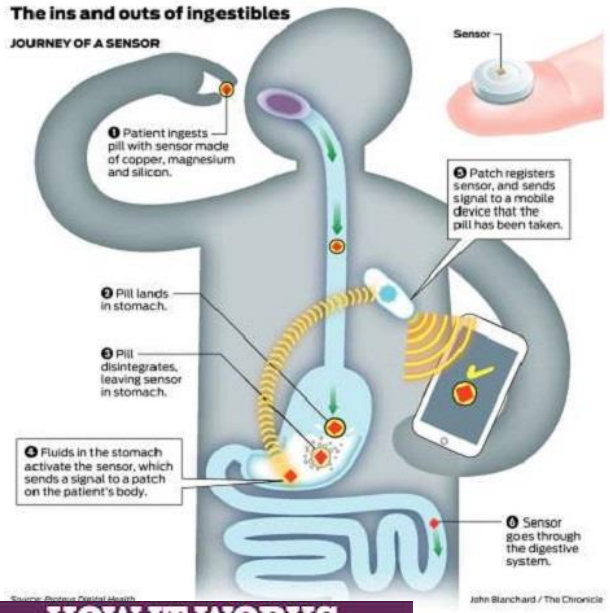
Tablets with sensors

Otsuka Pharmaceutical Co., Ltd

Proteus Digital Health

Abilify MyCite®
(aripiprazole tablets with sensor)
2, 5, 10, 15, 20, 30 mg

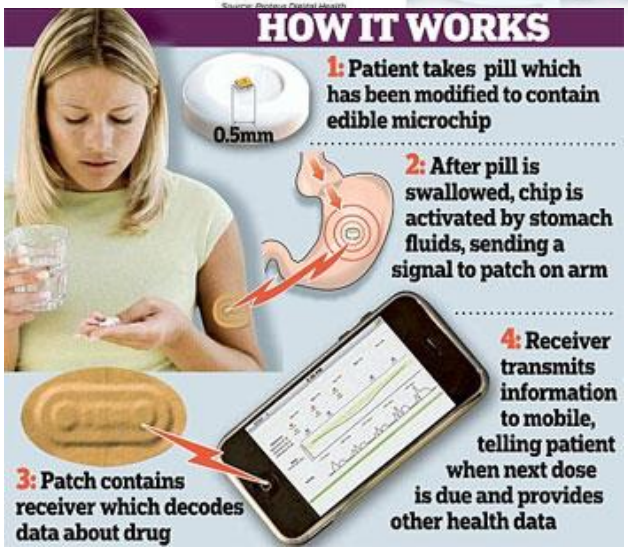
(schizophrenia, bipolar disorder, depression)



Parts of the administration:

sensitive patch (to put on the thorax

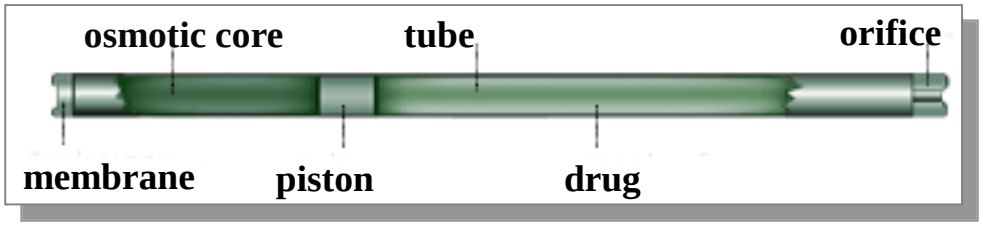
the information transmit to a mobil

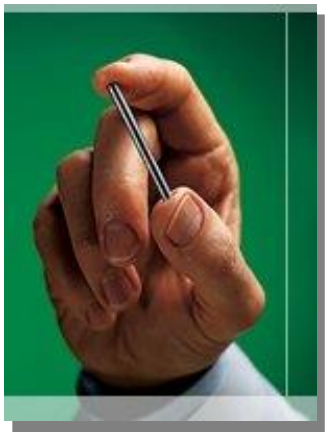


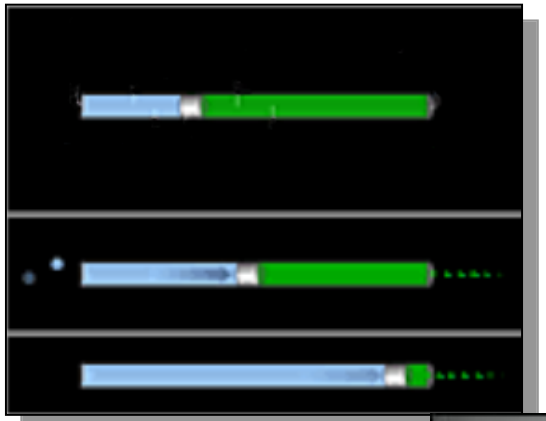
Implants

Osmotic systems

Subcutaneous application





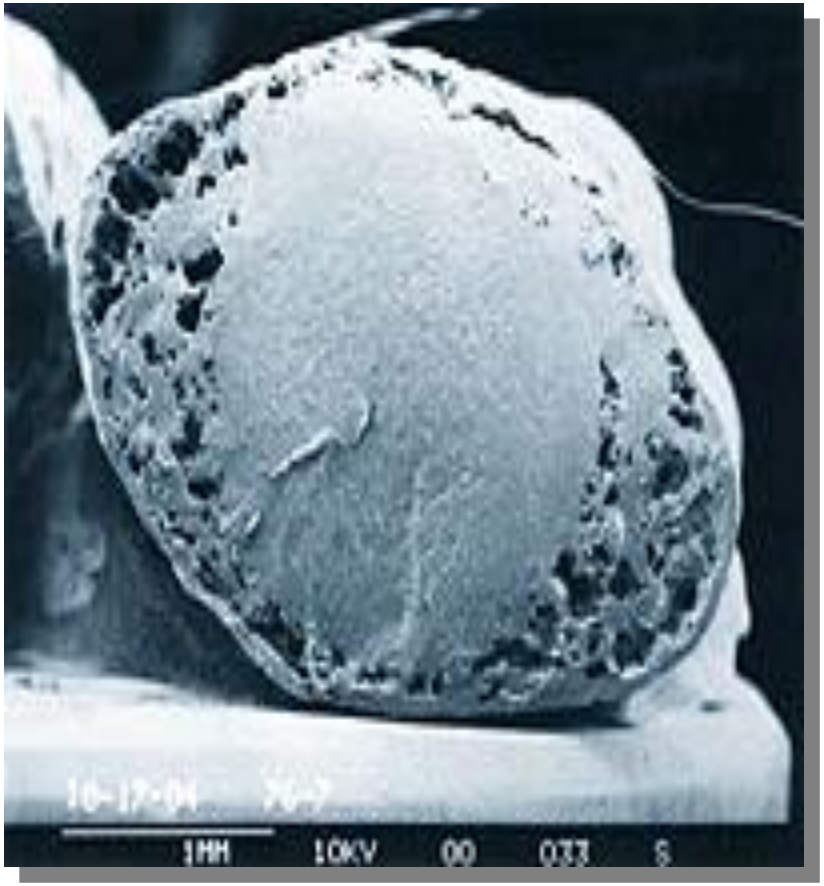


Norplant

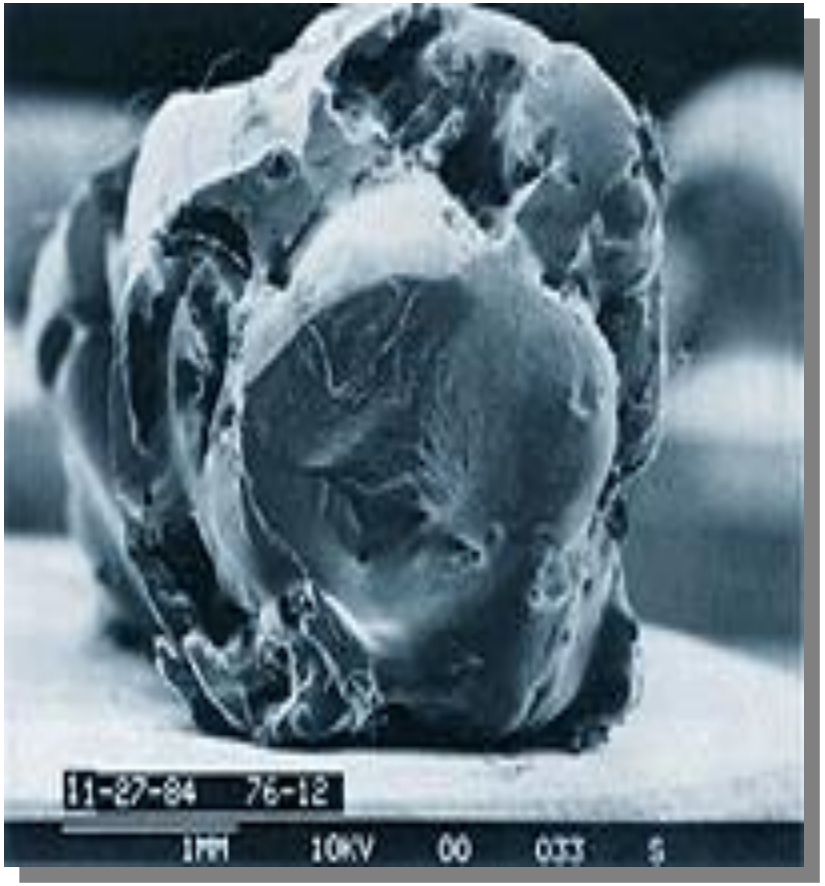
Drug release: 5 years

Biodegradable rod after implantation

Erodable implants



9 weeks

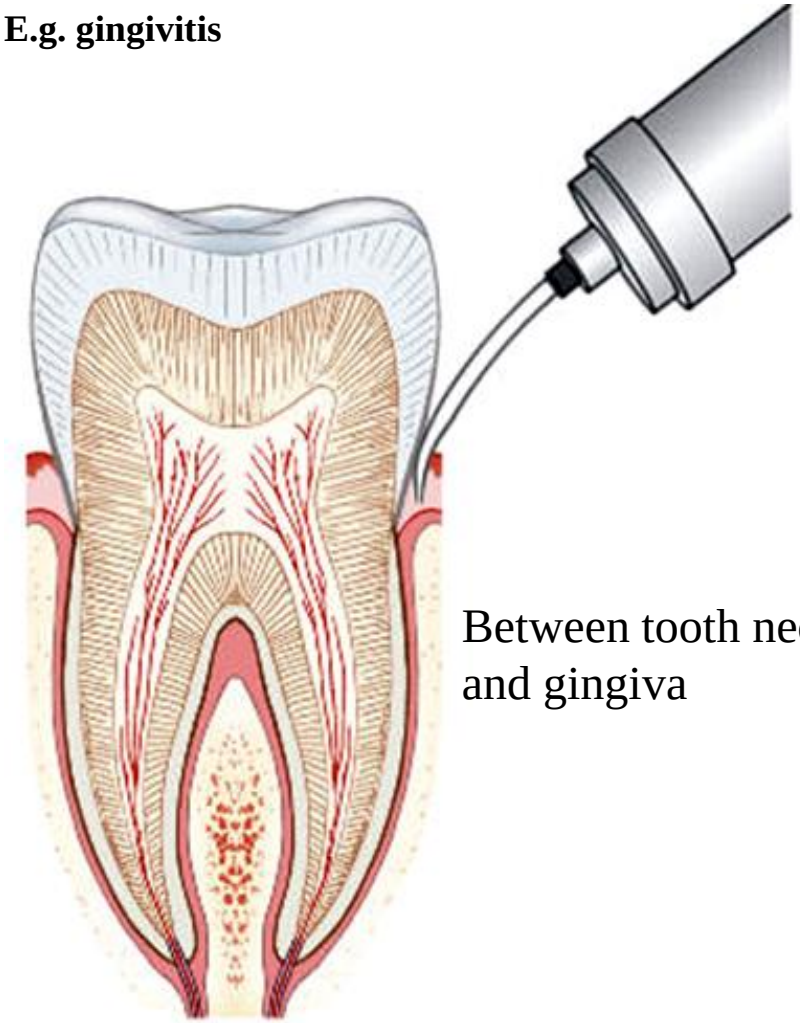


16 weeks

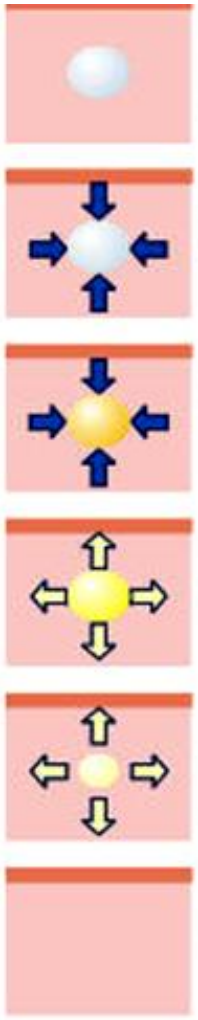
Local „implant” in dental administration

Local depot

E.g. gingivitis



Between tooth neck and gingiva



After administration

Inflow of the endogenous liquid

Gel formation

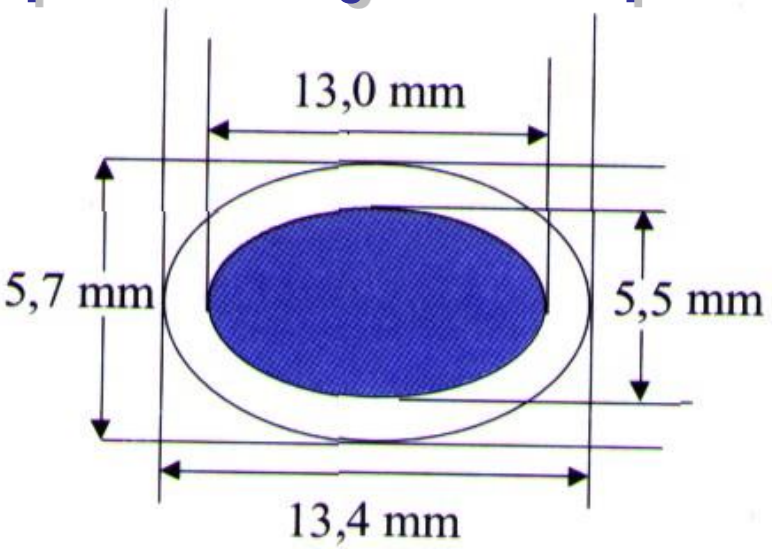
Drug release

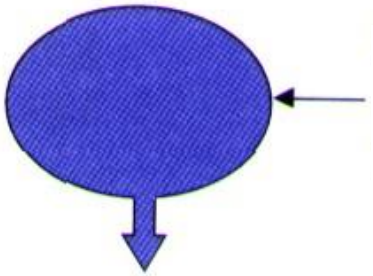
Drug release and erosion of the gel matrix

Total absorption

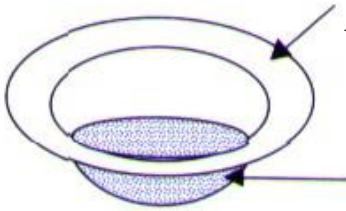
Ophthalmological therapeutic system

Ocusert





diffusion controlling
EVA membrane



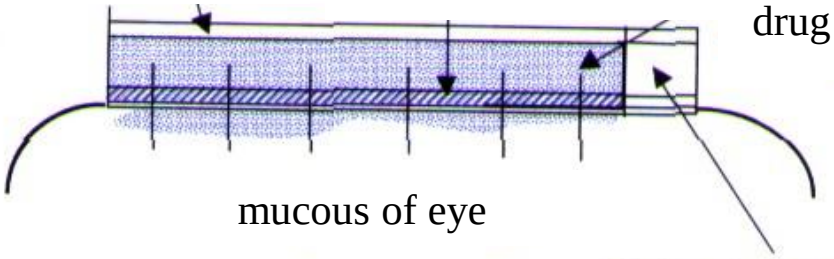
white layer for application

drug depo

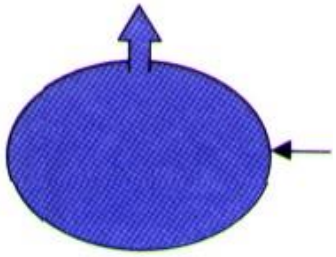
EVA polymer
cover membrane

diffusion controlling
EVA membrane

drug depo



mucous of eye



EVA polymer
membrane

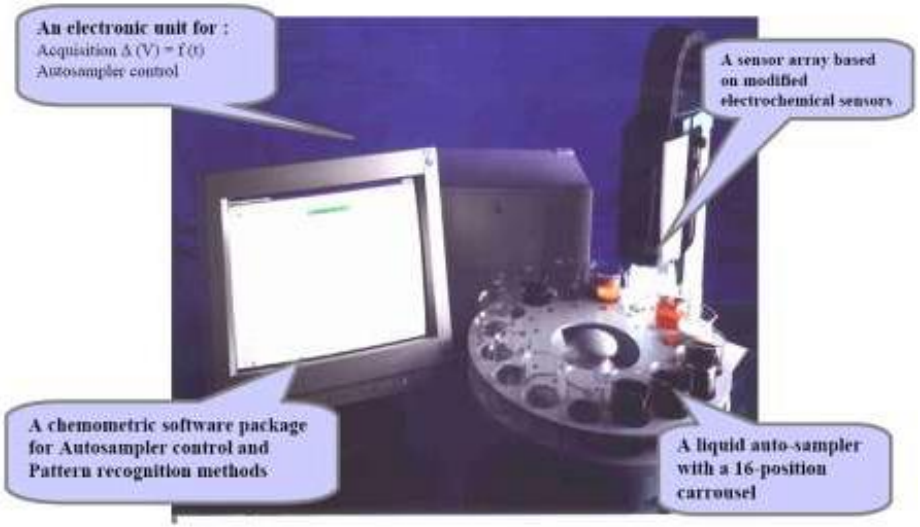
layer for application

API: pilocarpine
Drug release: 18 μg/h, 7 day

Pediatrics preparations

Pediatrics preparations

FDDF tablets
ODT preparations
Mucoadhesive films
„Suckers”

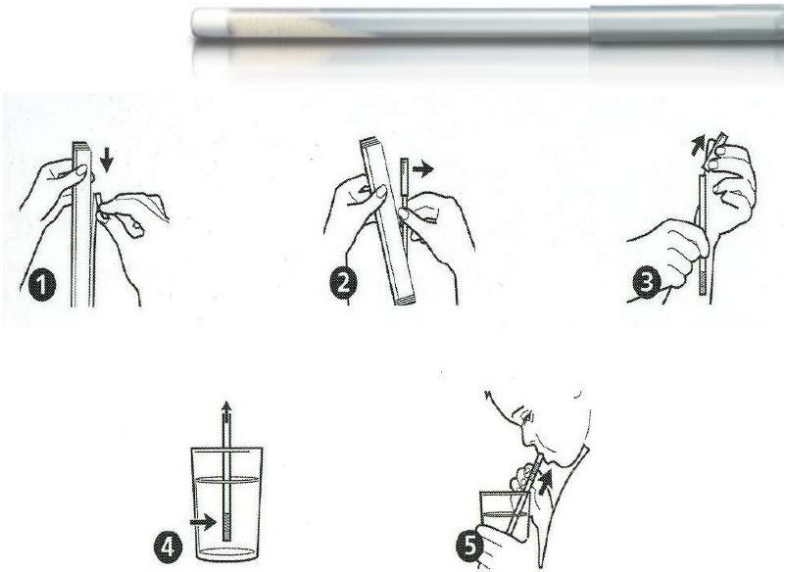


Electronic tongue

SIP technology

www.bbc.co.uk/2/hi/health

Granules or pellets in sucker



Clarosip (klaritromicin)
(Grünenthal GmbH)

Excipients

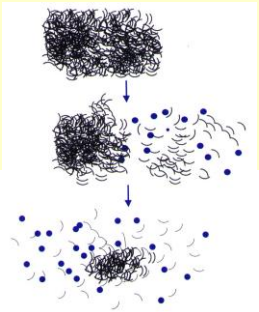
Excipients

Excipients for influence of drug release

Hidrogels: (unsoluble)
- poly hidroxyethyl metacrylate (PHEMA)
- cross linked poly vinyl alcohol (PVA)
- cross linked poly vinyl pyrrolidone (PVPP)
- poly ethylene oxide (PEO
- poly acrylamide (PA)

Soluble polymers:
- poly ethylen glycol (PEG)
- poly vinyl alcohol (PVA)
- poly vinyl pyrrolidone (PVPP)
- hidroxypropil methylcellulose (HPMC)

Biodegredable polimers:
- polylactic acid (PLA)
- polyglycol acid (PGA)
- polycapro lacton (PCL)
- polyanhydrids
- polyorthoesters



Non biodegredable polymers:
- poly vinyl acetate (PVA)
- poly dimethyl syloxane (PDS)
- poly ether urethane (PEU)
- poly vinyl chloride (PVC)
- cellulose acetate (CA)
- ethylcellulose (EC)

Mucoadhesive polymers:
- carboxy methylcellulose sodium (CMCNa)
- poly acryl acid
- tragacantha
- methylcellulose
- pectin

Natural polysaccharids:
- xanthan gum
- guar gum

Osmotic materials

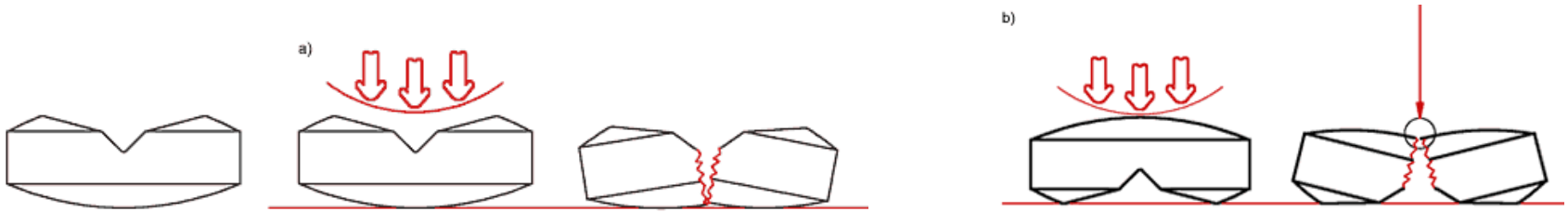
Unorganic water soluble compounds:

$MgSO_4$, NaCl, KCl, Na_2SO_4, $NaHCO_3$

Organic polymers:

CMCNa, HPMC, hydroxy-ethyl- methylcell., MC, PEO, PVP

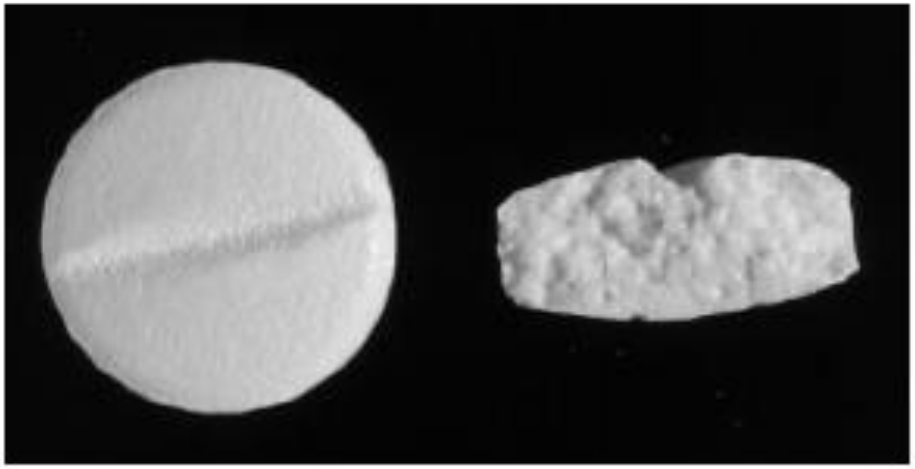
To break or not to break? When is it possible?



…if the mechanism of drug release is not influenced.

To break or not to break?

Multiparticulate systems

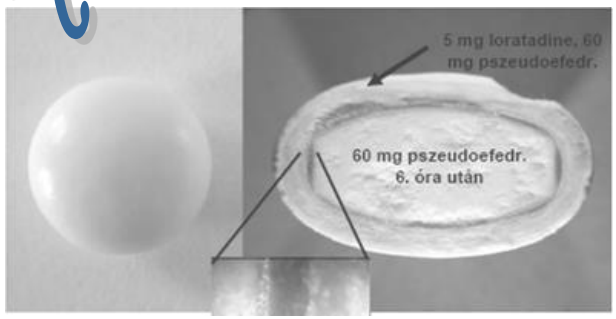


Pl. Betaloc ZOK, Metoprolol Z

…breaking is possible, but the pulverize and mastication is vorbidden!

To break or not to break?

Practical tips



No breaking

- ***buccal and sublingual tabletsk***
- ***bélben oldódó bevonatú tabletták***
- ***sustained release or slow release non multiparticulate tablets (SR, LA, CR, SA, TD, TR, XL)***
- ***coated tablets***
- ***layered tablets***
- ***multiparticulate tablets prepared from pellets with different drug contents***
- ***matrix tablets***
- ***OROS tablets***
- ***gastroretentive preparations***

To break or not to break?

Breaking is possible

- ***gastric soluble coated and sugar coated tablets***
- ***chewing tablets***
- ***some mucoadhesive preparations***

Is it possible to open or chew the capsules?

Open is possible

- **content is powder - mix with liquid (incompatibility!)**
  - dust on the surface of food
  (pl. ampicillin, doxycyclin)

No open and no chewing:

- **sustained release capsules (with pellets, crystals or granules)**
- **OROS capsuls**

No chewing:

- **modified release capsules**
- **coated capsules**
- **content is enterosolvent pellets**

Targeted drug delivery systems

Targeted drug delivery systems

Chemotherapy

Side effects of chemotherapy

methotrexate **– liver and kidney damage, loss of hair,**

doxorubicin **– myocardial damages,**

vincristine **- peripheral nerve injury, alopecia,**

daunorubicin- **muscle and bone marrow damage,**

cytarabine **- bone marrow and intestinal damage**

Important:
Only the liberated substance can be absorbed in the target cell.

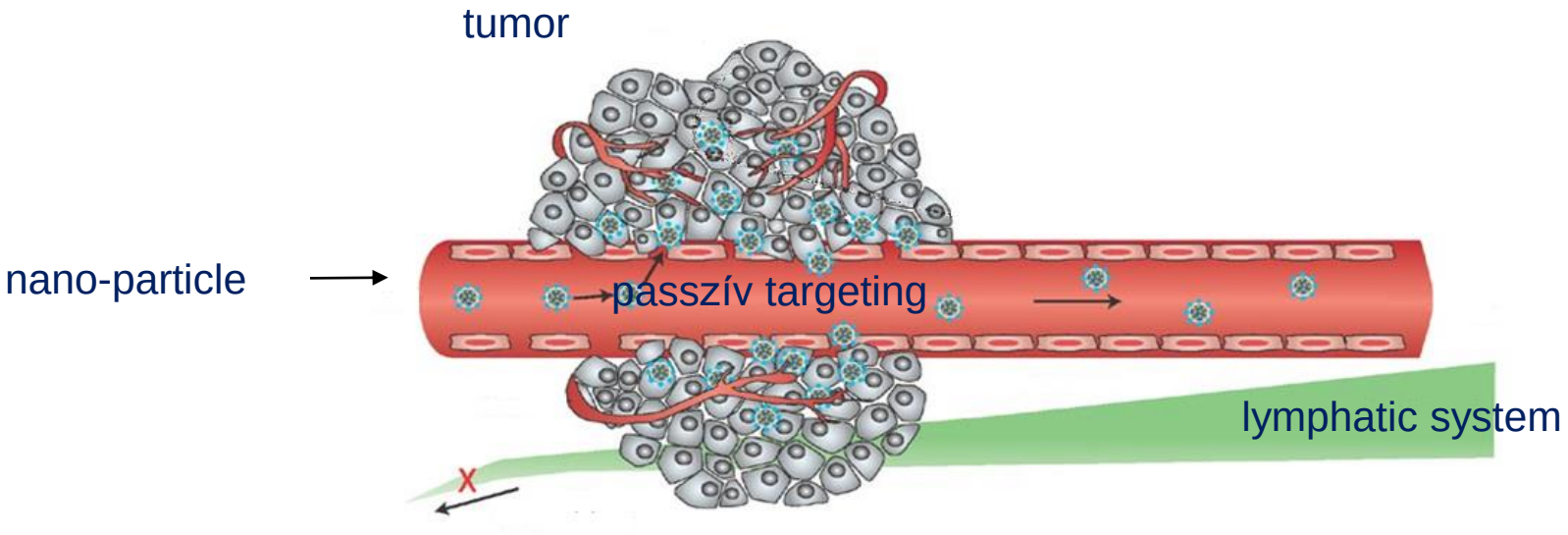
Targeted drug delivery systems

Passive targeting

Passive tumor deposition by non targeted is accomplished by extravasation from leaky vessels adjacent to the tumor and retention of nanoparticles at the tumor site due to slow clearance.

Cancer tissues are different of healthy tissues:

- enhanced vascular permeability.
- decreased lymphatic flow.



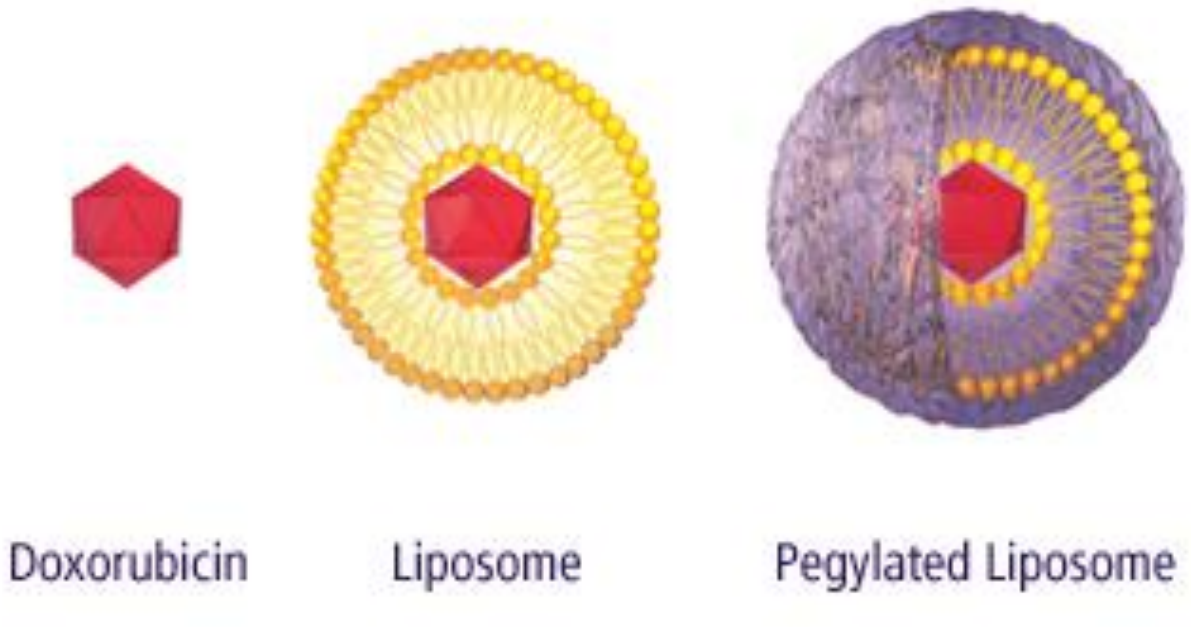
The residence time of nanoparticles increase in the tumor.

Nature Reviews Drug Discovery ***2, 347-360 (May 2003)***

Liposome

Doxil^{R}

- natural polyphospholipids
- the heads of hydrophil phosphates stand outwards respectively inward



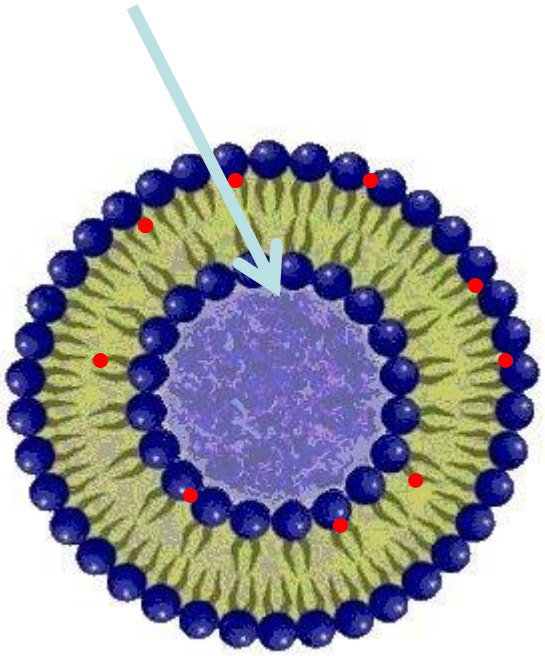
Application of nanoparticles in nuclear medicine

András Polyák PhD thesis, 2011, SE
^{99m}Tc-tracer doxorubicin

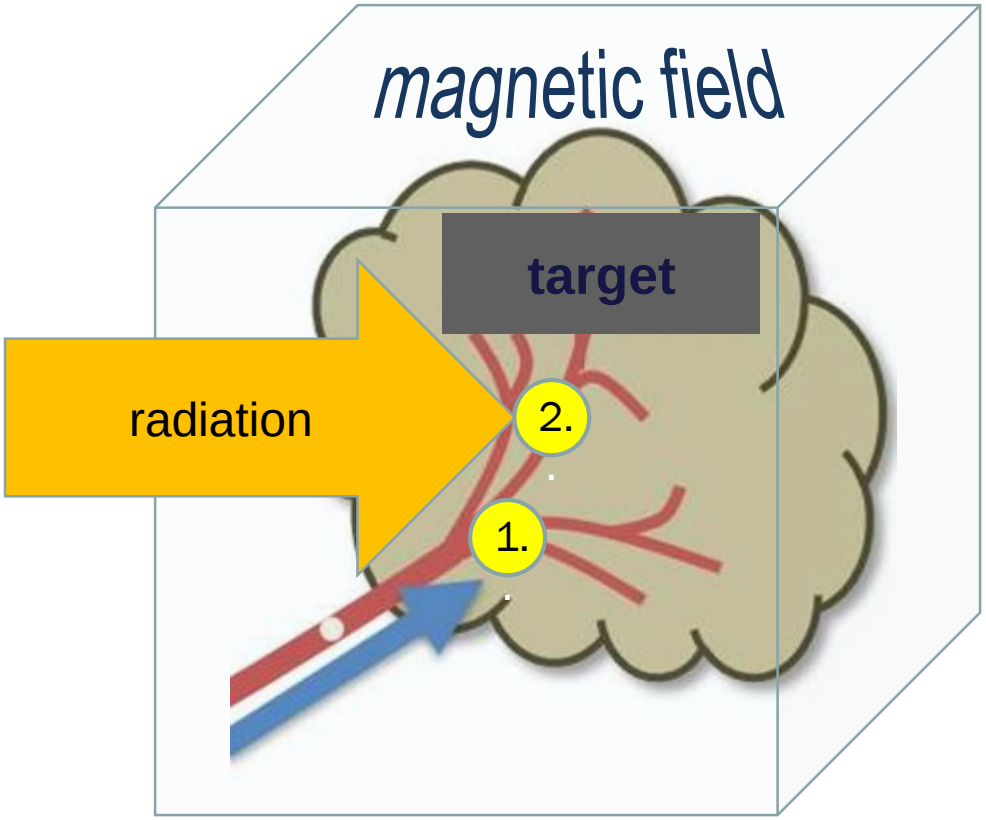
Targeted drug delivery systems

Passive targeting

magnetic core



Structure of magnetic liposomes

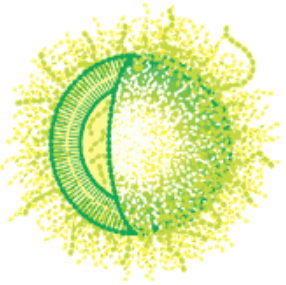


1st step: collection of the particles in the magnetic field

2nd step: liberation of the API

Targeted drug delivery systems

Active targeting



Three levels of active targeting:

1. First order targeting - organ targeting.
   DDS release the drug only in a specific predetermined target site, *organ or tissue* including lymphatics, peritoneal cavity, plural cavity, cerebral ventricles, eyes, joints, etc.

2. Second order targeting - cellular targeting.
   DDS particles release the drug to a particular *cell* within an organ or tissue. Selective delivery of drugs as tumour cells and not to the normal cells(e.g. selective drug delivery to kupffer cells in the liver). Usually an antibody is attached to the surface of a DDS particle, which able to specifically recognize and to bound to a specific antigen on a cell surface.

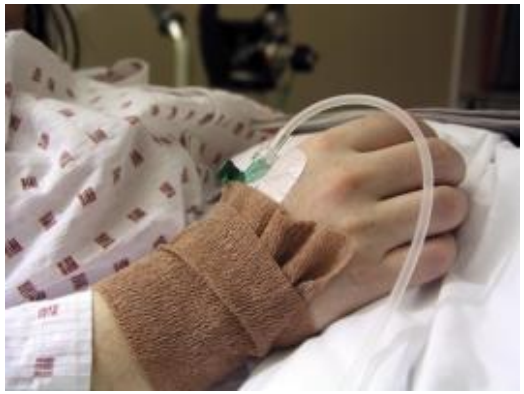
3. Third order - subcellular targeting.
   It is defined as drug delivery specifically to the intracellular site of targeted cells (eg. receptor based ligand mediated entry of a drug complex into a cell by endocytosis.) *For example: gen delivery.*

Externaly controllable systems

66

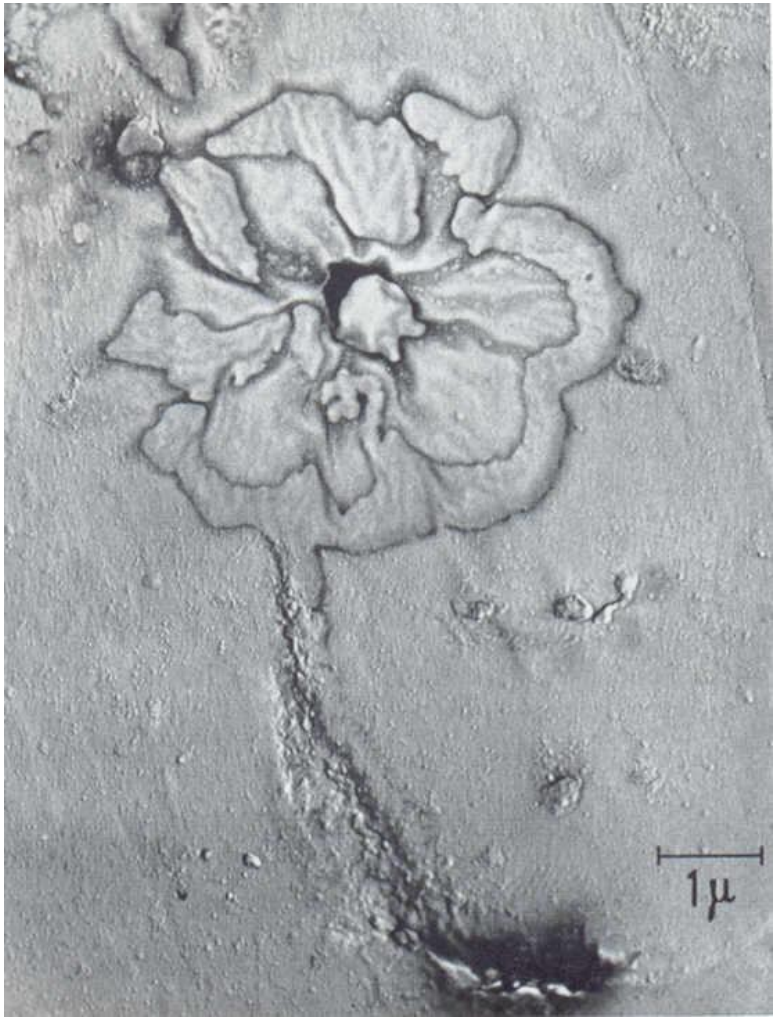
Externaly controllable systems

Patient Controlled Analgesia (PCA)



The patient can administers the pain relief.
The infusion is programmable by the prescriber.

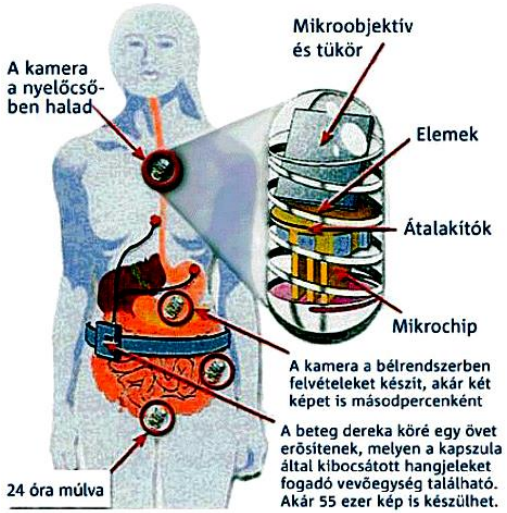
Thank you for your attention!

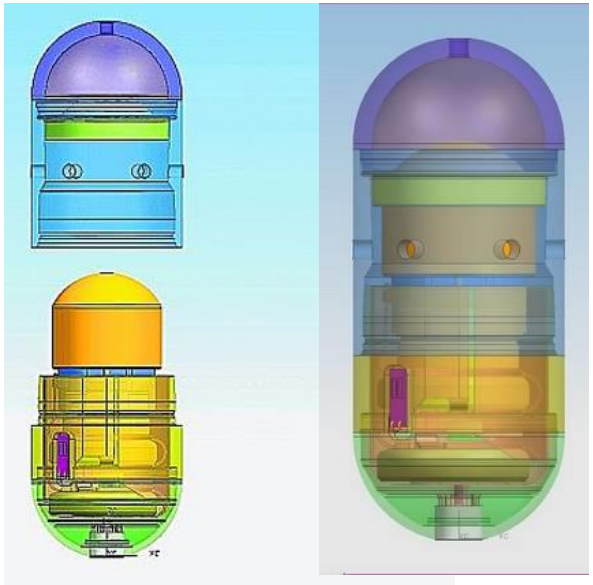


Artifact during preparation for TEM

Externally controlled DDSs

iPill diagnostic





iPill drug therapy