

# Liberation 2.

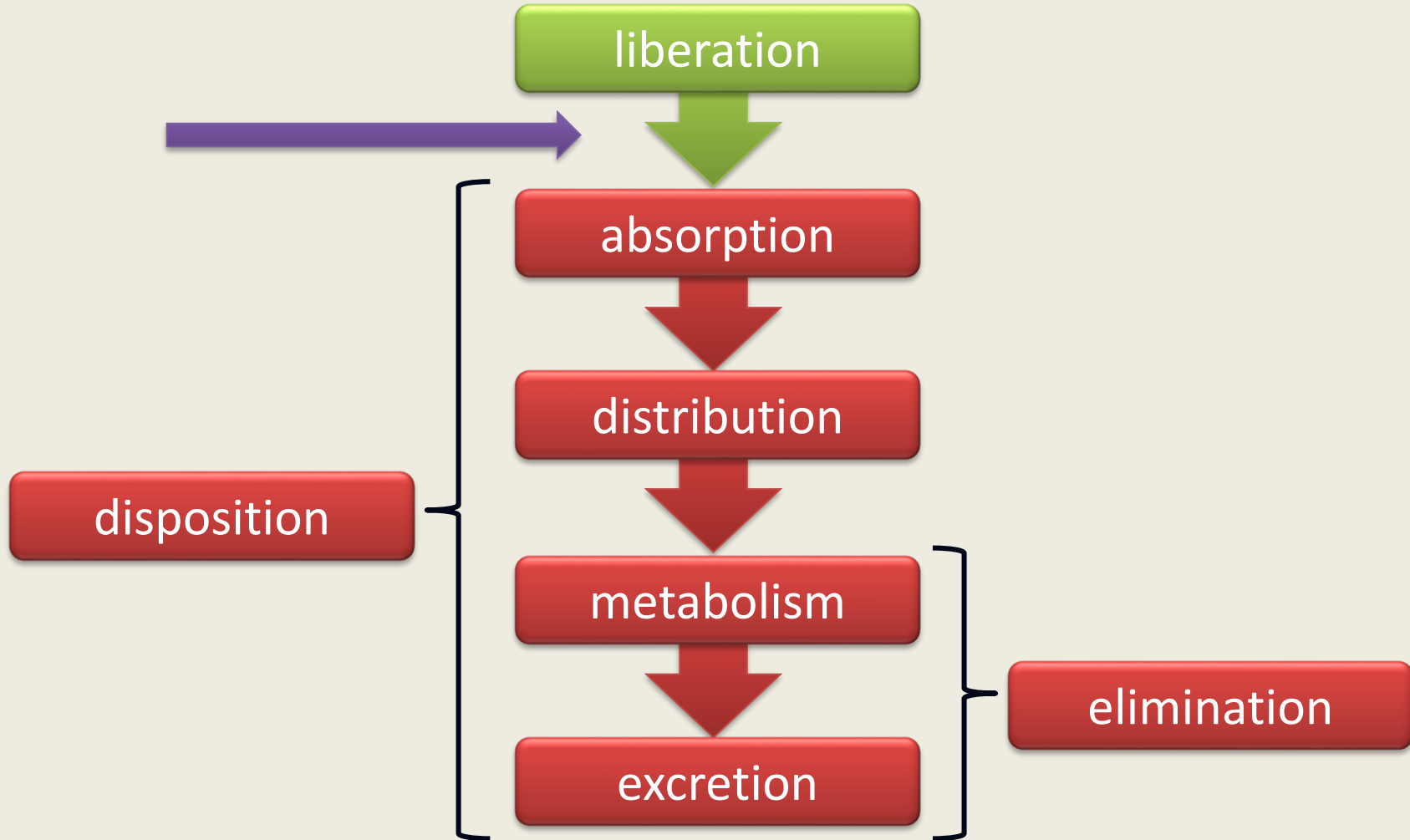
## Drug release types

**SZILÁRD PÁL**

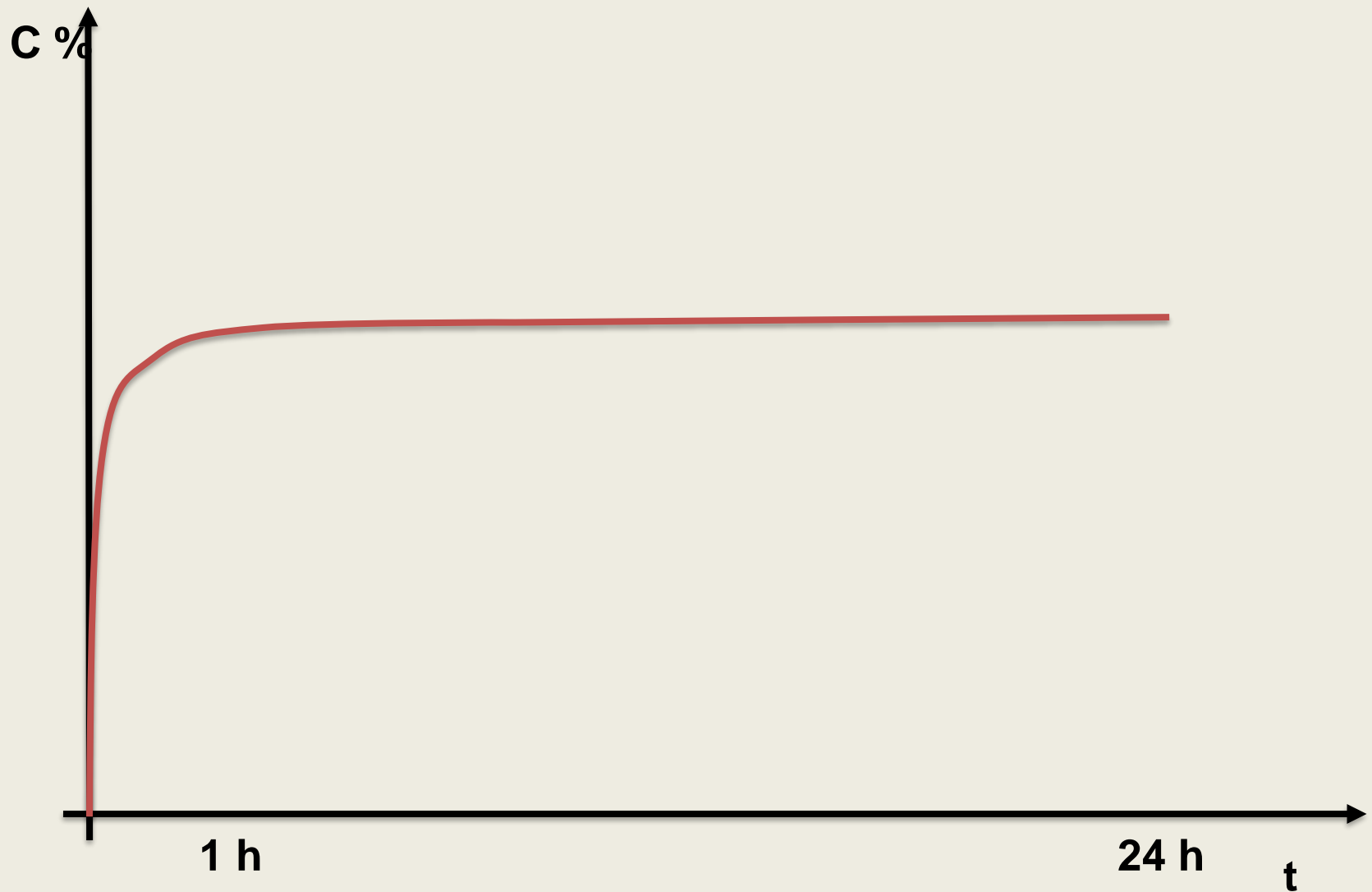
**UNIVERSITY OF PÉCS**

**INSTITUTE OF PHARMACEUTICAL TECHNOLOGY AND  
BIOPHARMACY**

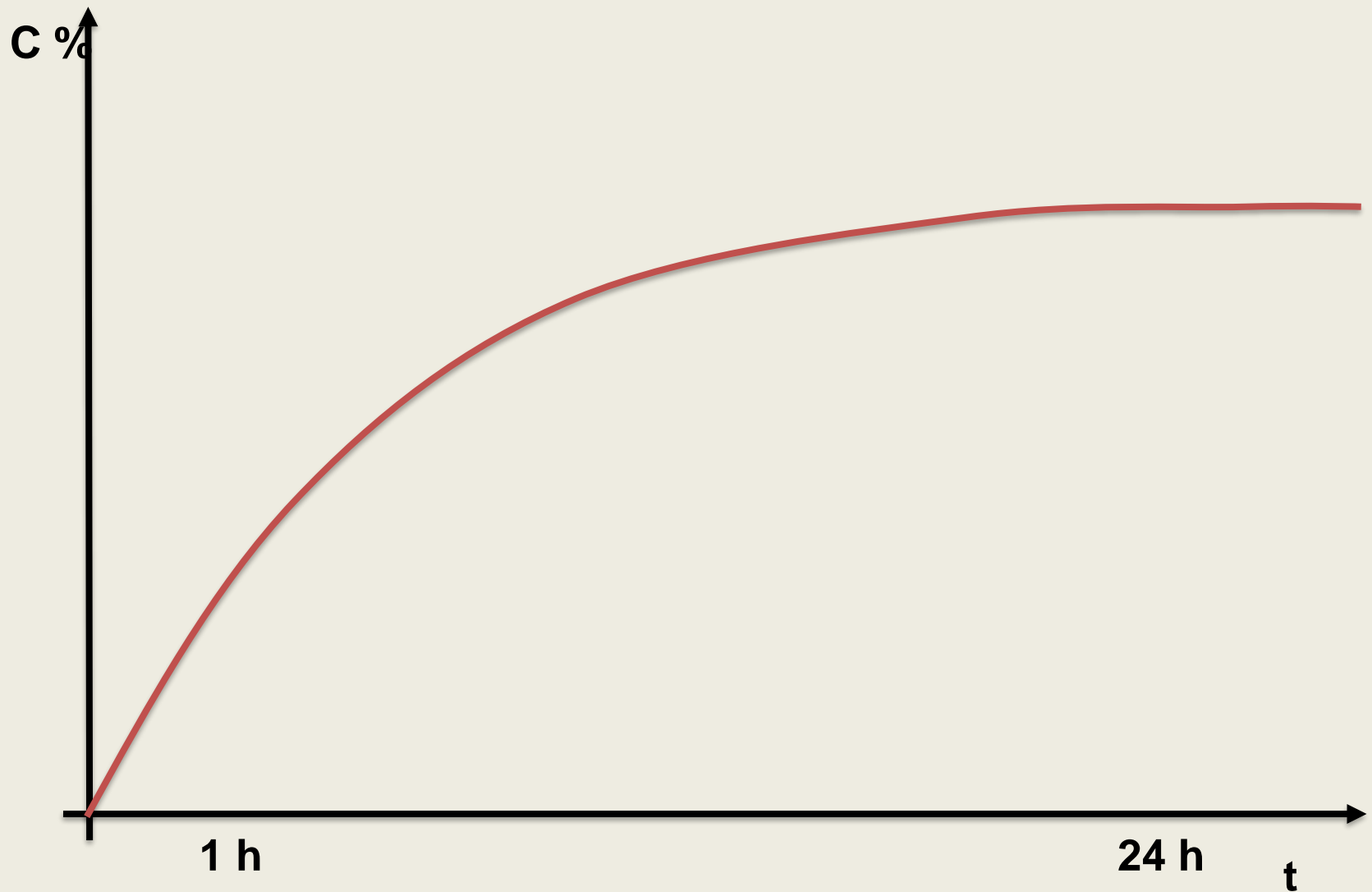
# LADME system



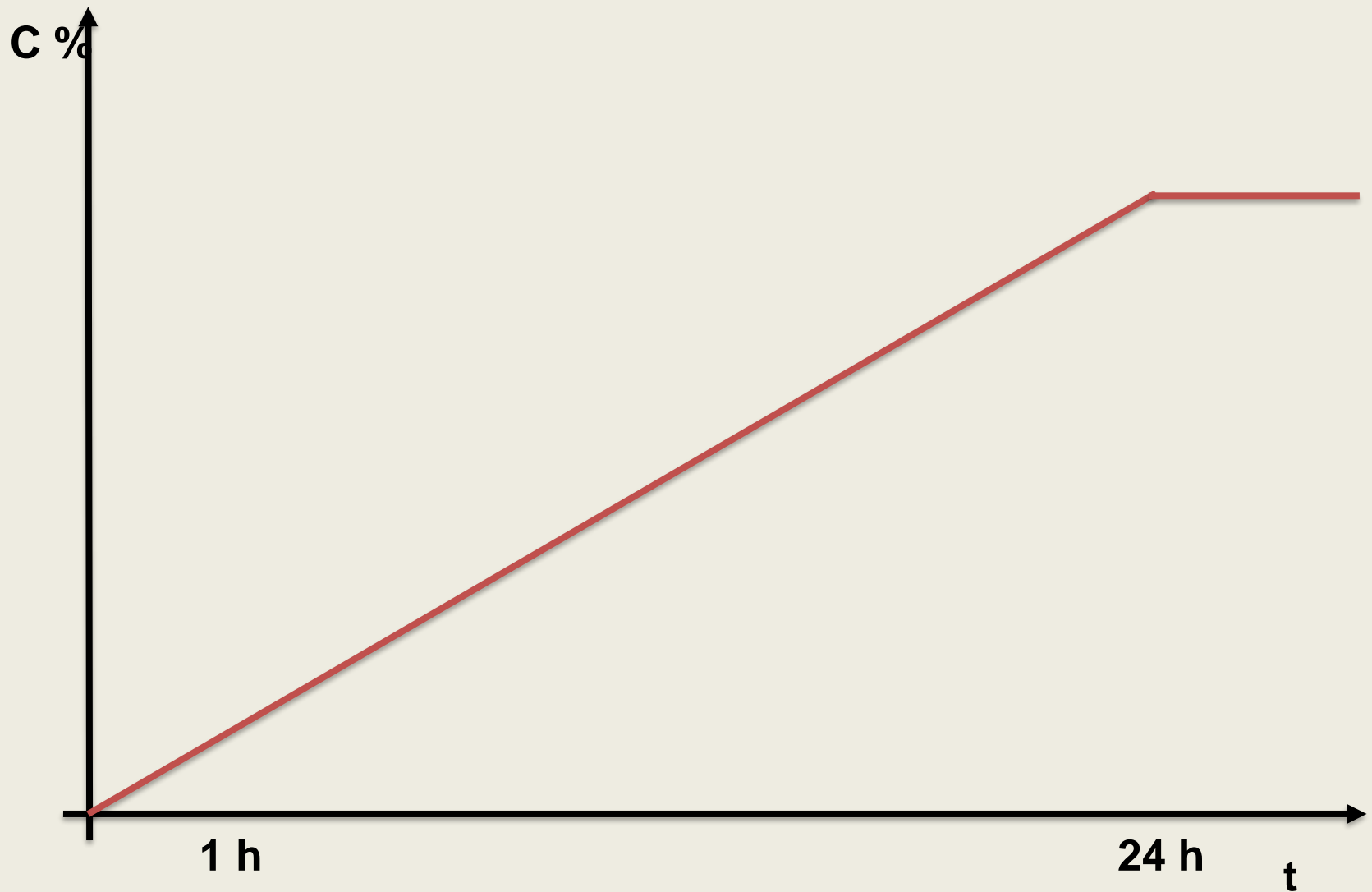
What is the dissolution type of the preparation below?



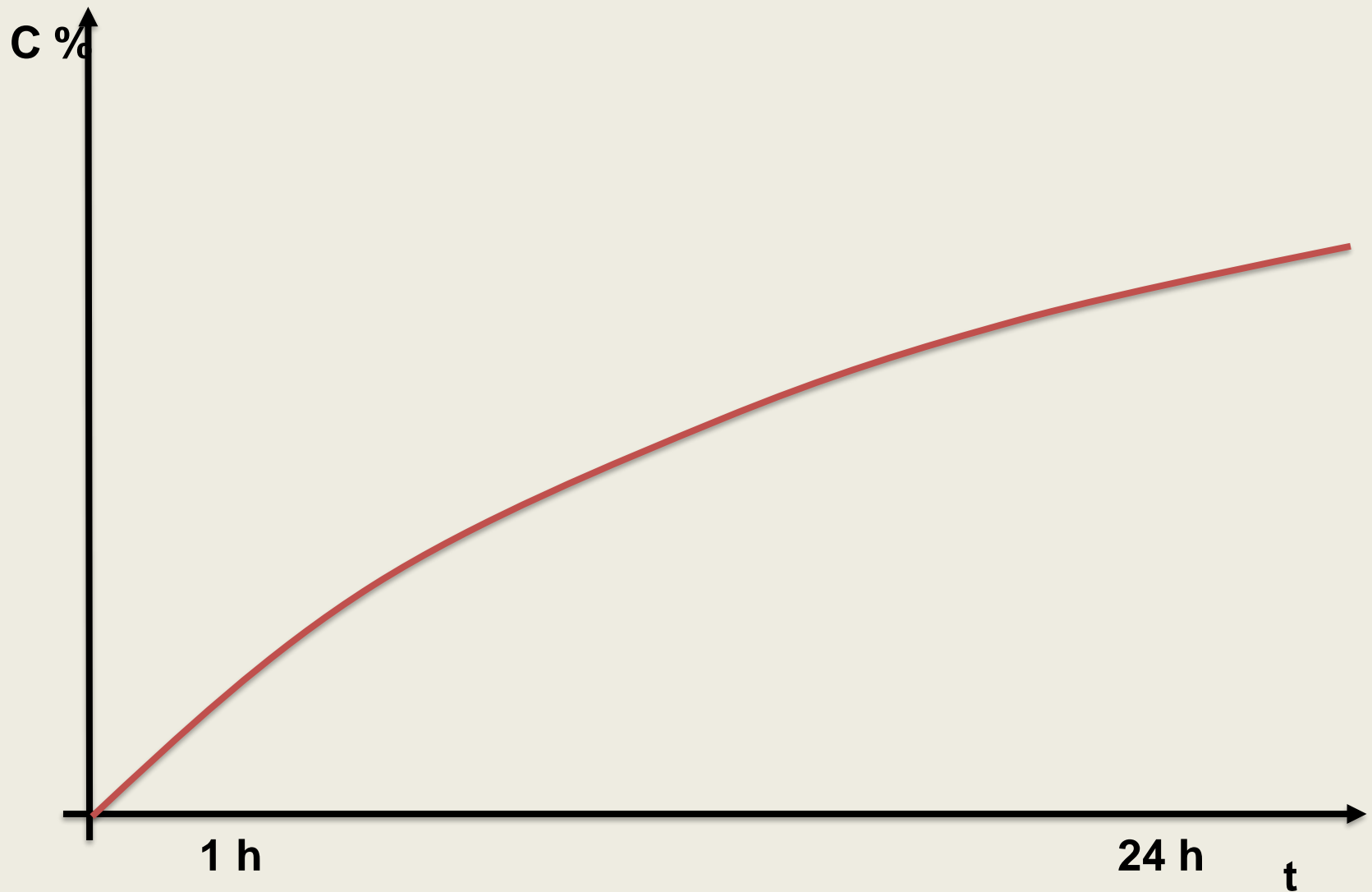
What is the dissolution type of the preparation below?



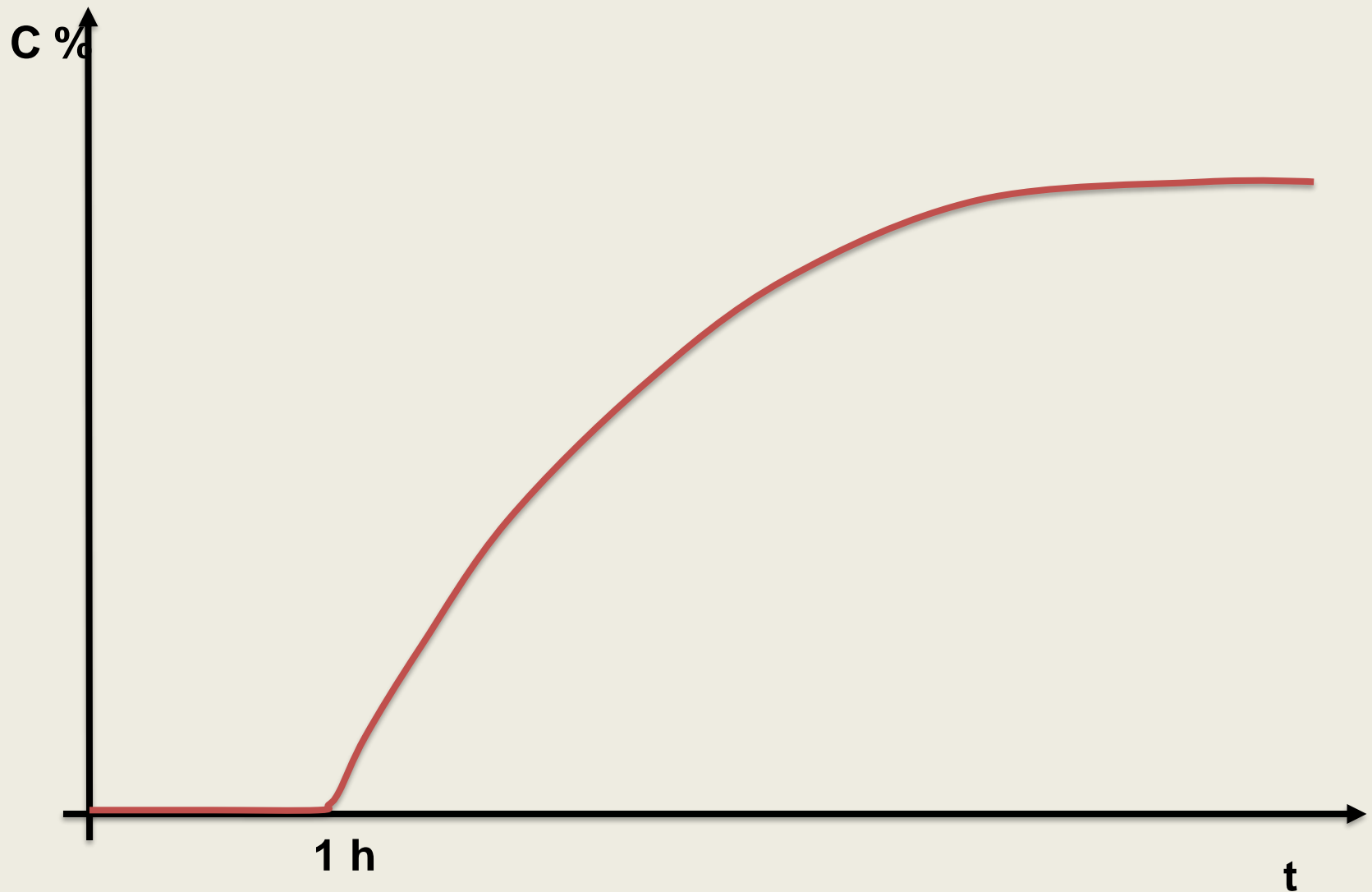
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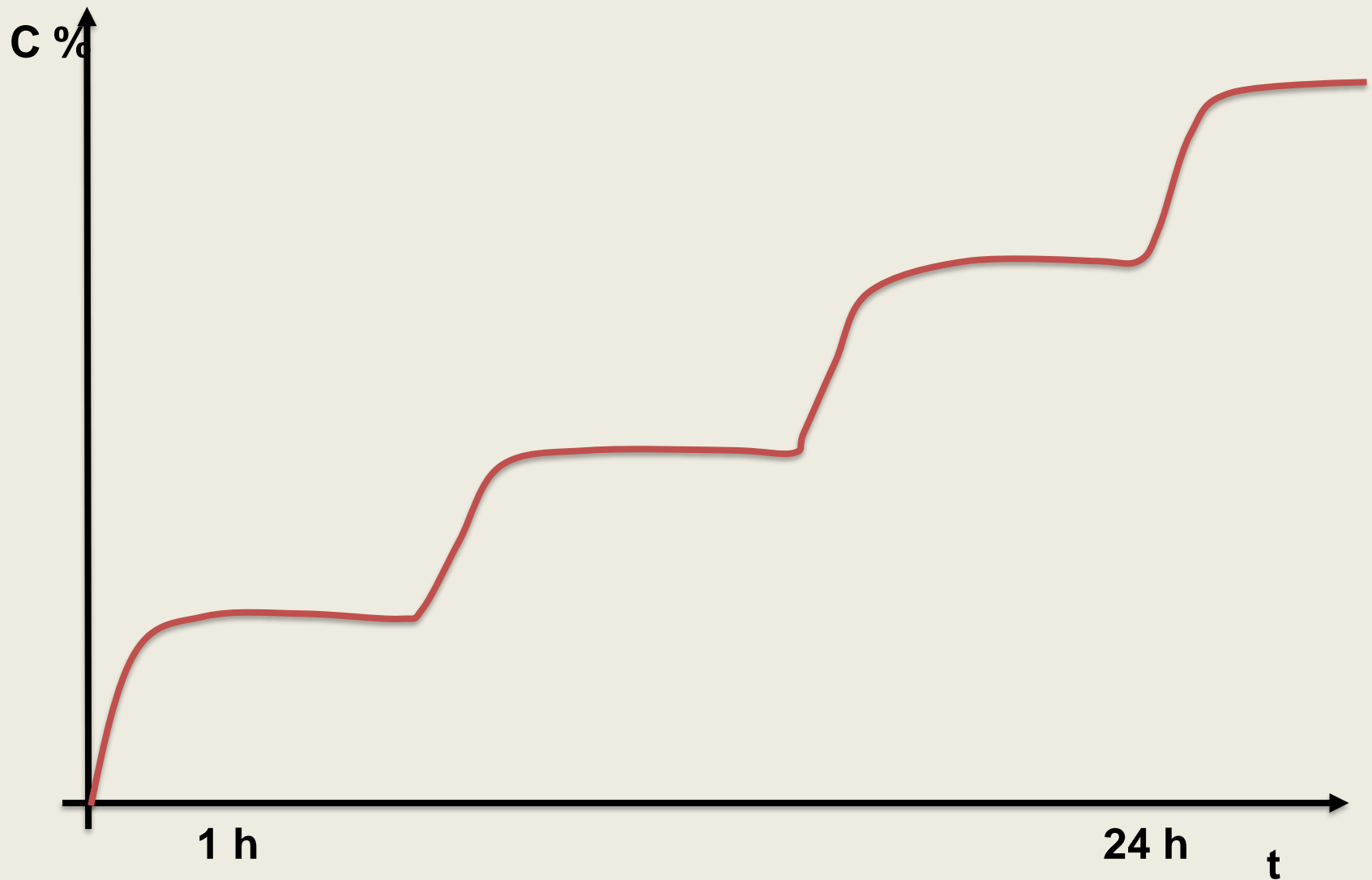
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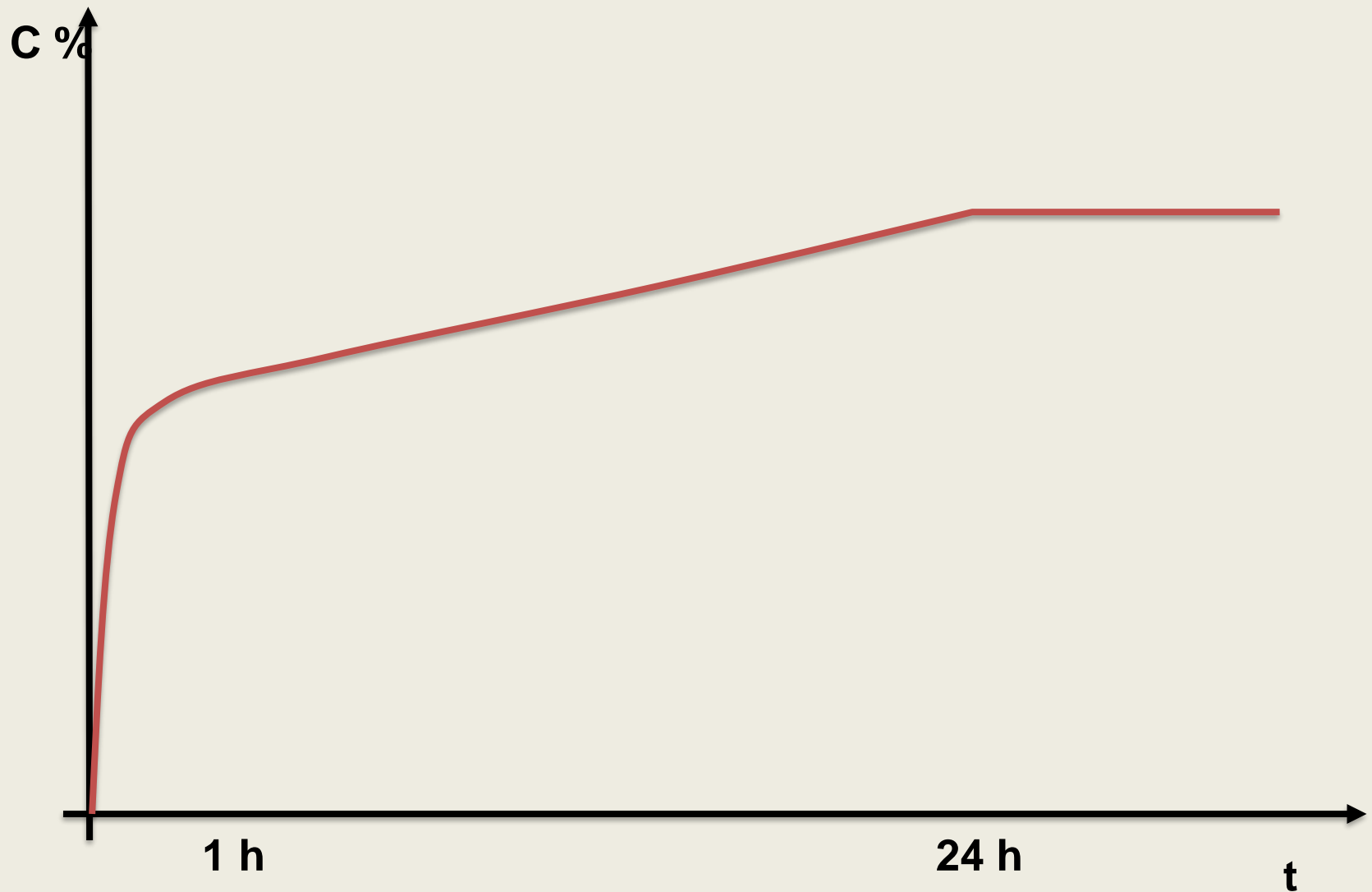


What is the dissolution type of the preparation below?





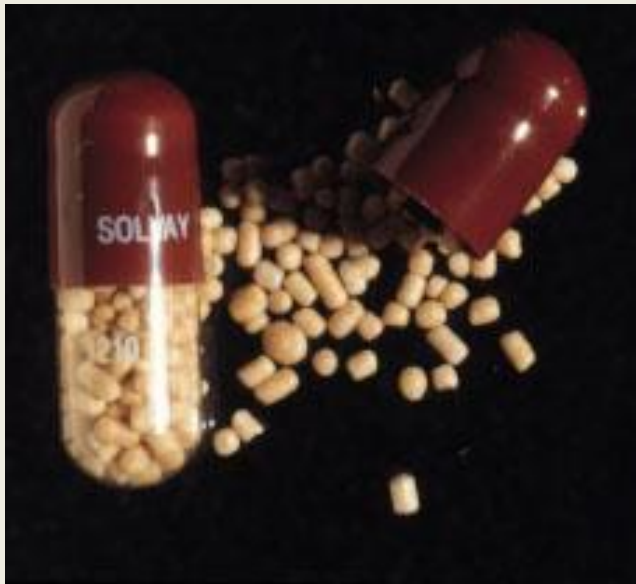
What is the dissolution type of the preparation below?



# Drug release types

- Conventional drug release
- Modified drug release
  - Rapid drug release
  - Delayed drug release
  - Slow drug release
  - Pulsatile drug release
  - Local drug release
- Self-regulating drug release
- Targeted drug release

# Technologies





# Abbreviations After Brand Name

- **R** ▶ Kalium R ▶ RETARD
- **RETARD** ▶ Euphylong Minor Retard ▶ RETARD
- **DEPOT** ▶ Zoladex LA Depot ▶ H.A. RAKTÁR
- **LA** ▶ Zoladex LA Depot ▶ LONG ACTING
- **SR** ▶ Isoptin SR ▶ SUSTAINED RELEASE
- **SL** ▶ Tramadol SL ▶ SUSTAINED LIBER.
- **MR** ▶ Preductal MR ▶ MODIFIED RELEASE
- **ZOK** ▶ Betaloc ZOK ▶ ZERO ORDER KIN.
- **CR** ▶ Sinemet CR ▶ CONTROLLED REL.
- **RD** ▶ Isospan RD ▶ RAPID DISSOLUTION
- **HBS** ▶ Madopar HBS ▶ HYDROD. BAL. SYS.
- **GITS** ▶ Adalat GITS ▶ G.I. THER. SYSTEM

# Conventional drug release

- There is no technological modification during the manufacture to change the dissolution rate
- Drug release is determined by physico-chemical characters

# Factors affecting drug dissolution

- Physico-chemical properties of the API
  - Polimorphism
  - Chemical structure
  - Particle size
  - Complexation
  - Wettability
  - Impurities

# Aspirin 500 mg tbl.

- Acetyl salicylic acid
  - Maize starch
  - Microcrystalline cellulose





# Modified drug release

- Aims:
  - Optimizing the therapeutic effect by slowing, accelerating or delaying the drug release
  - Decrease toxic adverse effects
  - Increase patient compliance

# Rapid drug release

- Aim:
  - Accelerating the liberation in order to reach a quick absorption

# Calcium 500 mg effervescent tbl.

- Calcium carbonate (API)
  - Sodium bicarbonate
  - Anhydrous citric acid



# Panadol Rapid (Optizorb®) tbl.

- Paracetamol
  - Alginic acid
  - Calcium carbonate
  - Crospovidone



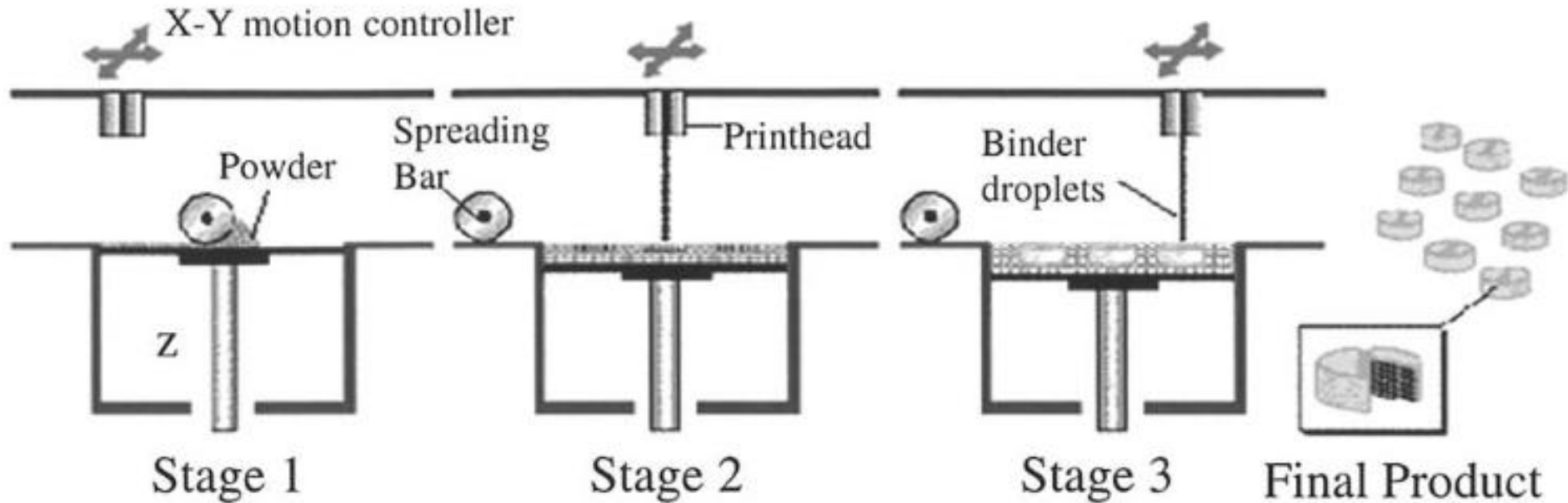
# 3D printing (ZIPDOSE, THERIFORM tech.)

MJ Cima, JS Haggerty, EM Sachs, PA Williams. Three-dimensional printing techniques. US patent 5,204,055, **1993**.

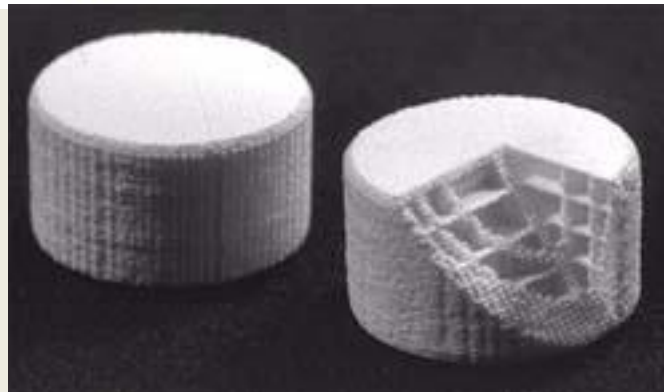
**Disintegrates in less than 1 s!**



# THERIFORM technology

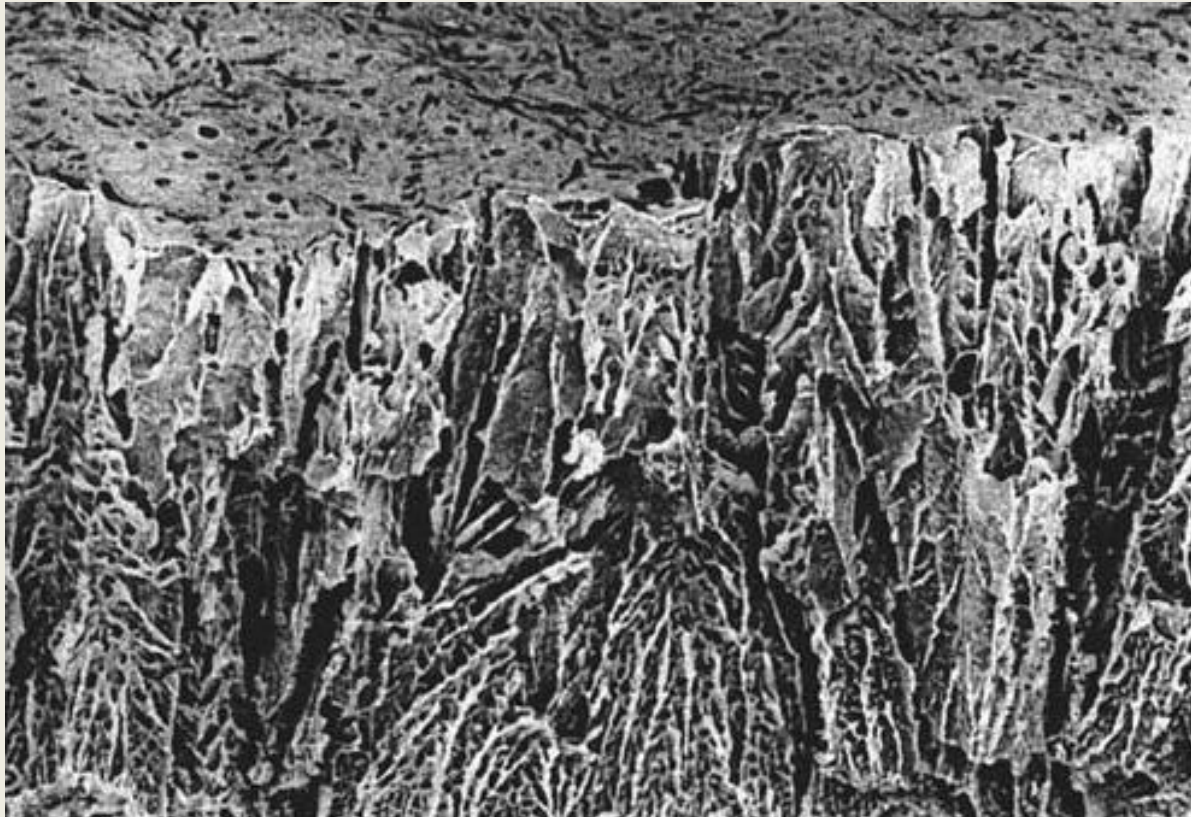


**Figure 1** Schematic TheriForm process. (See color insert.)

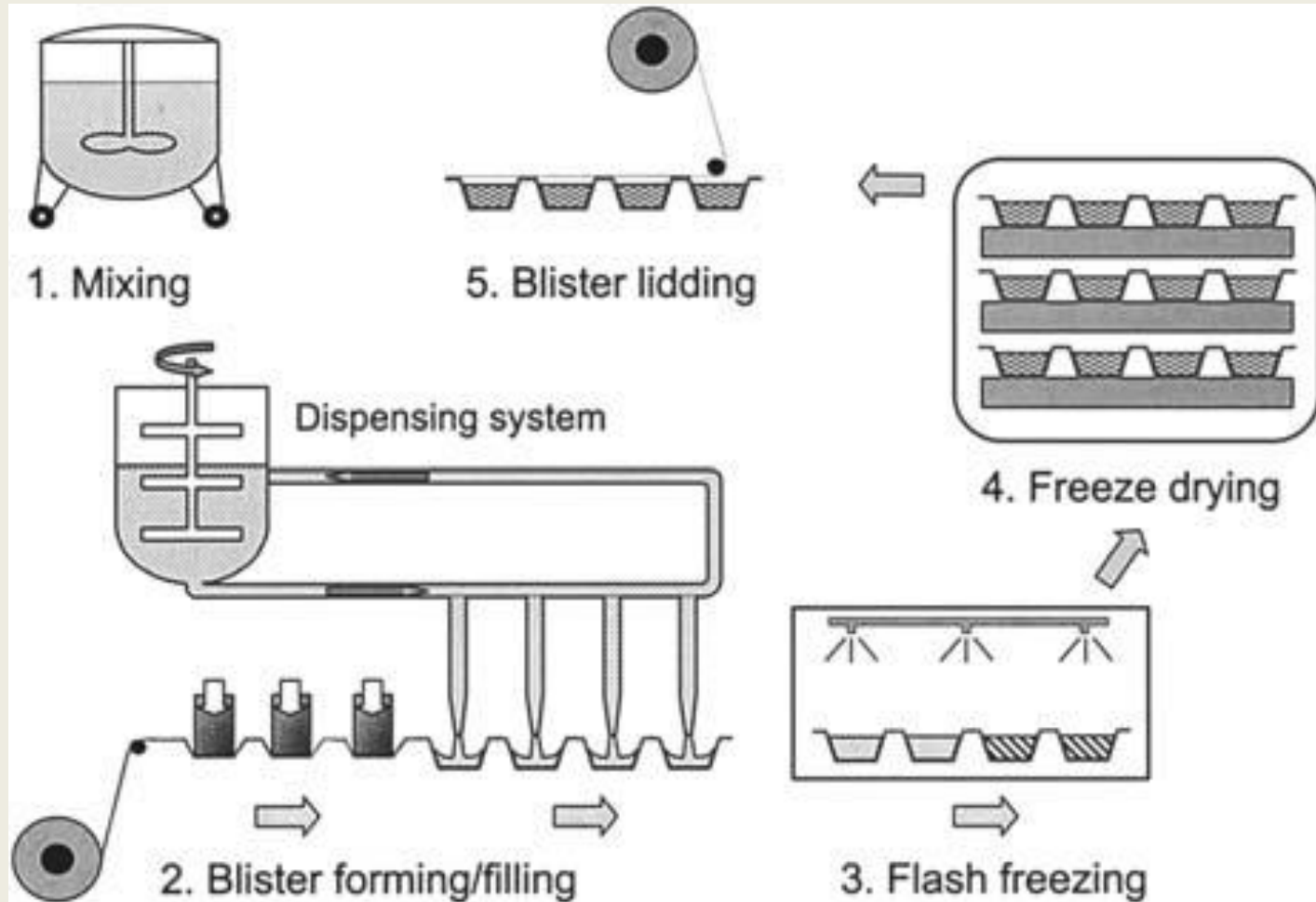


# ZYDIS technology

- SEM image:



# ZYDIS technology





# ZYDIS technology

- Feldene (Piroxicam, Pfizer, 1992)
- Imodium (Loperamid, Janssen, 1993)
- Claritine (Loratadin, Schering Plough, 1997)
- Zofran (Ondansetron, Glaxo, 1999)
- Motilium (Domperidon, Janssen, 1999)
- Zyprexa (Olanzapin, Eli Lilly, 2000)



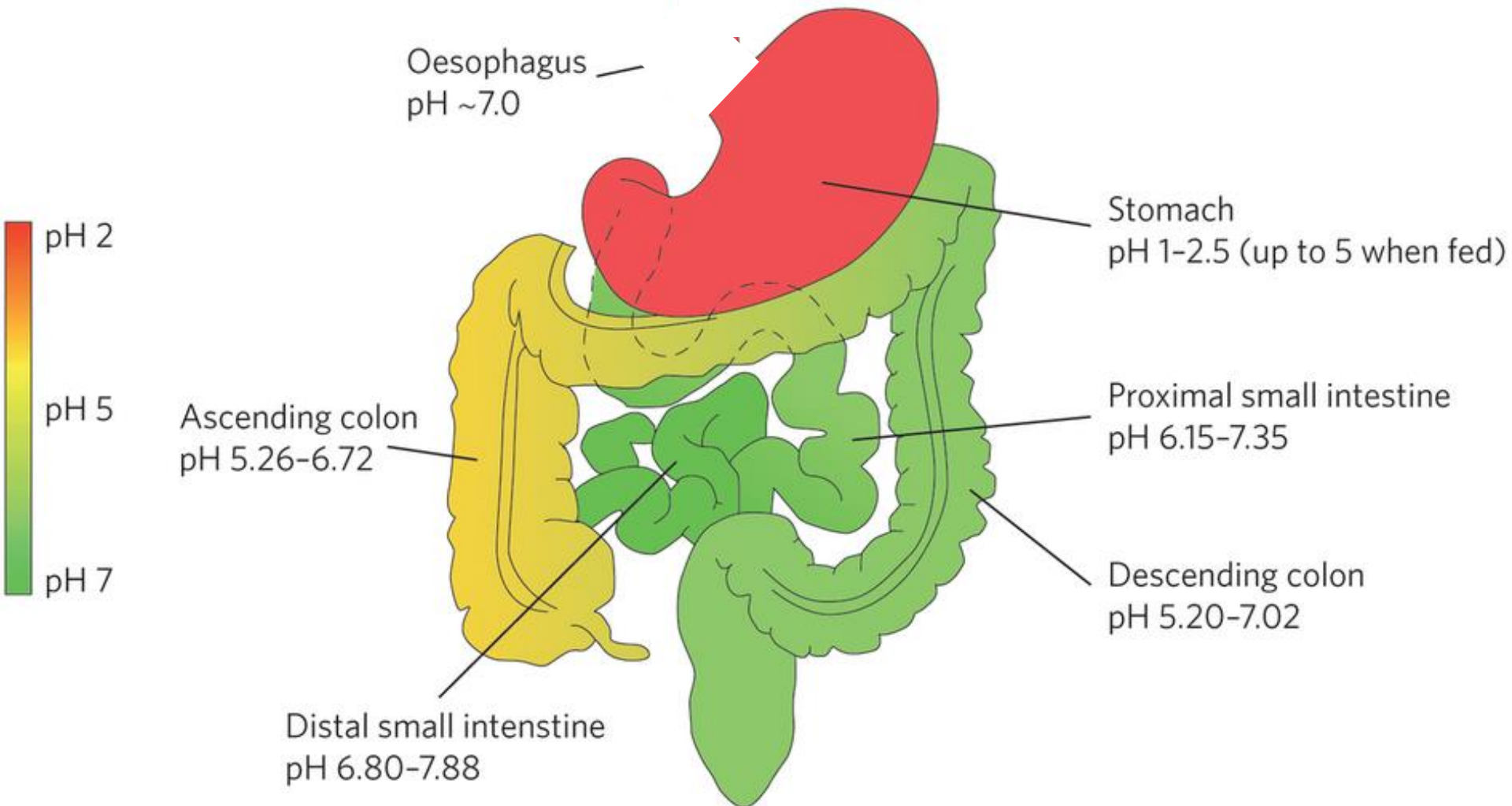
# ZYDIS technology



# Delayed drug release

- Liberation of the API is delayed by a lag time
  - Intestinosolvent preparations (gastric juice resistant preparations)
    - HCl can damage the API
    - API can damage the gastric mucosa

# Delayed drug release



# Pharmaceutical Excipients used to create delayed release preparations

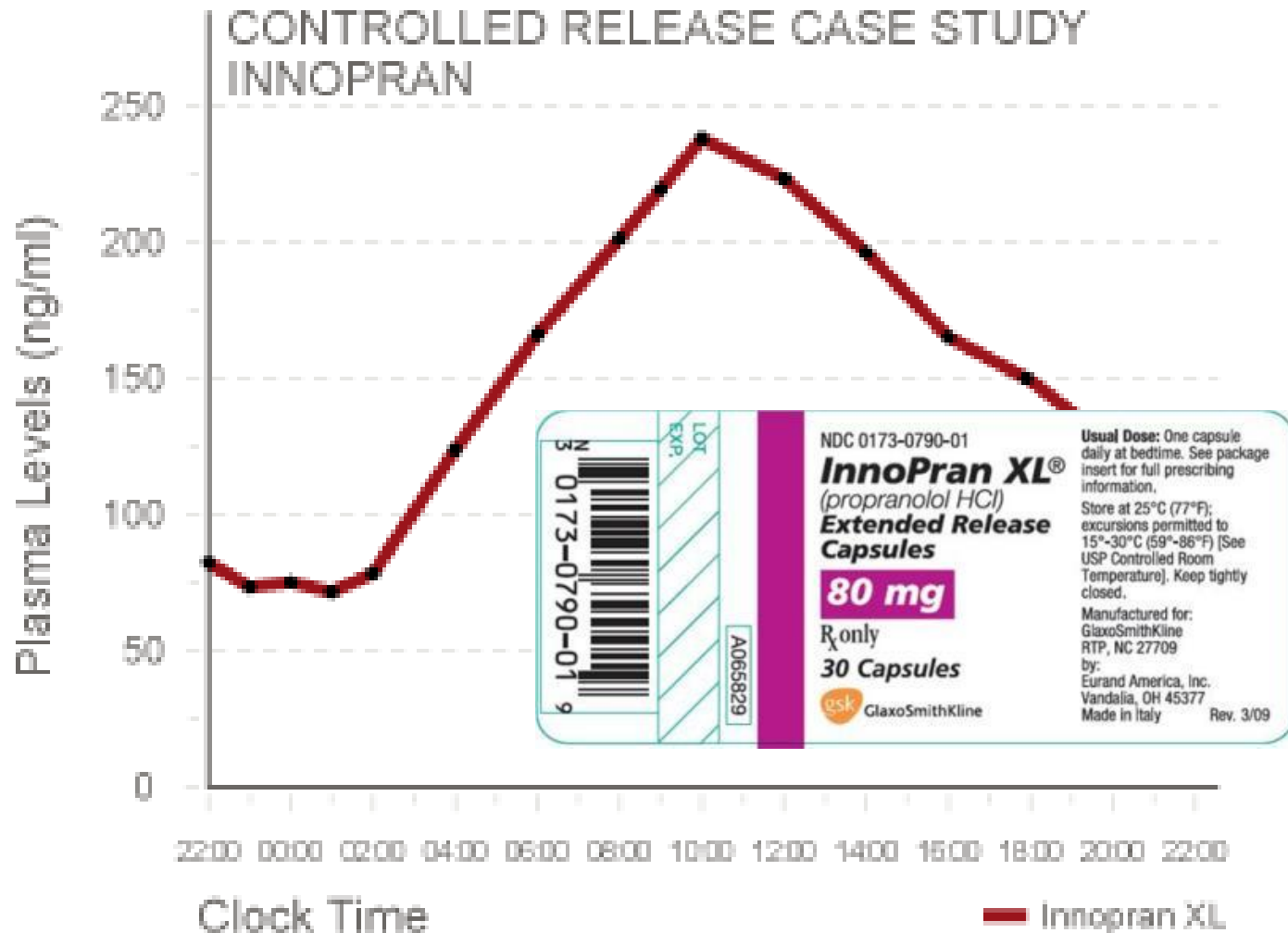
- pH sensitive coating
  - **Intestinosolvent/gastroresistant coating**
    - Cellulose acetate phtalate (CAP)
    - Eudragit L,S (metacrylic acid copolimers)

# Kreon 10000 cps.

- Pancreas powder

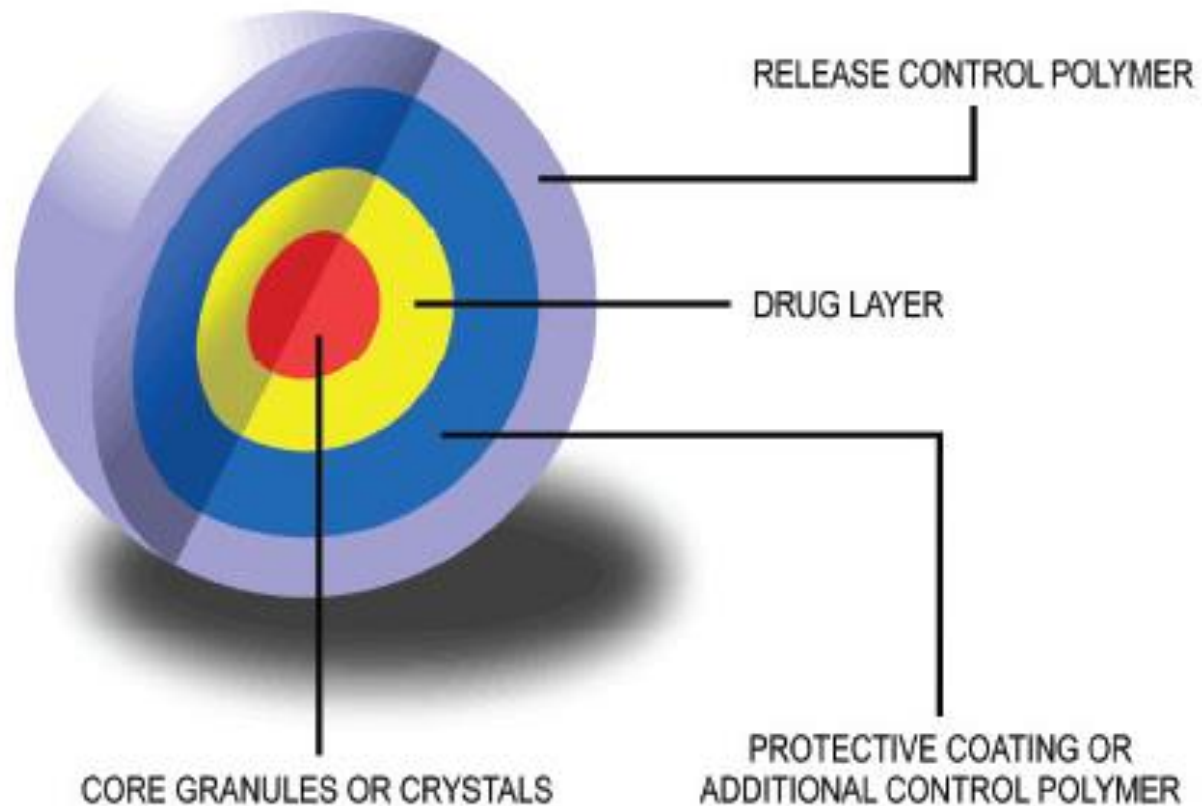


# Diffucaps<sup>®</sup> - delayed release Chronotherapeutic system (2003)



# Diffucaps<sup>®</sup> - delayed release Chronotherapeutic system (2003)

## Diffucaps<sup>®</sup> Bead Technology





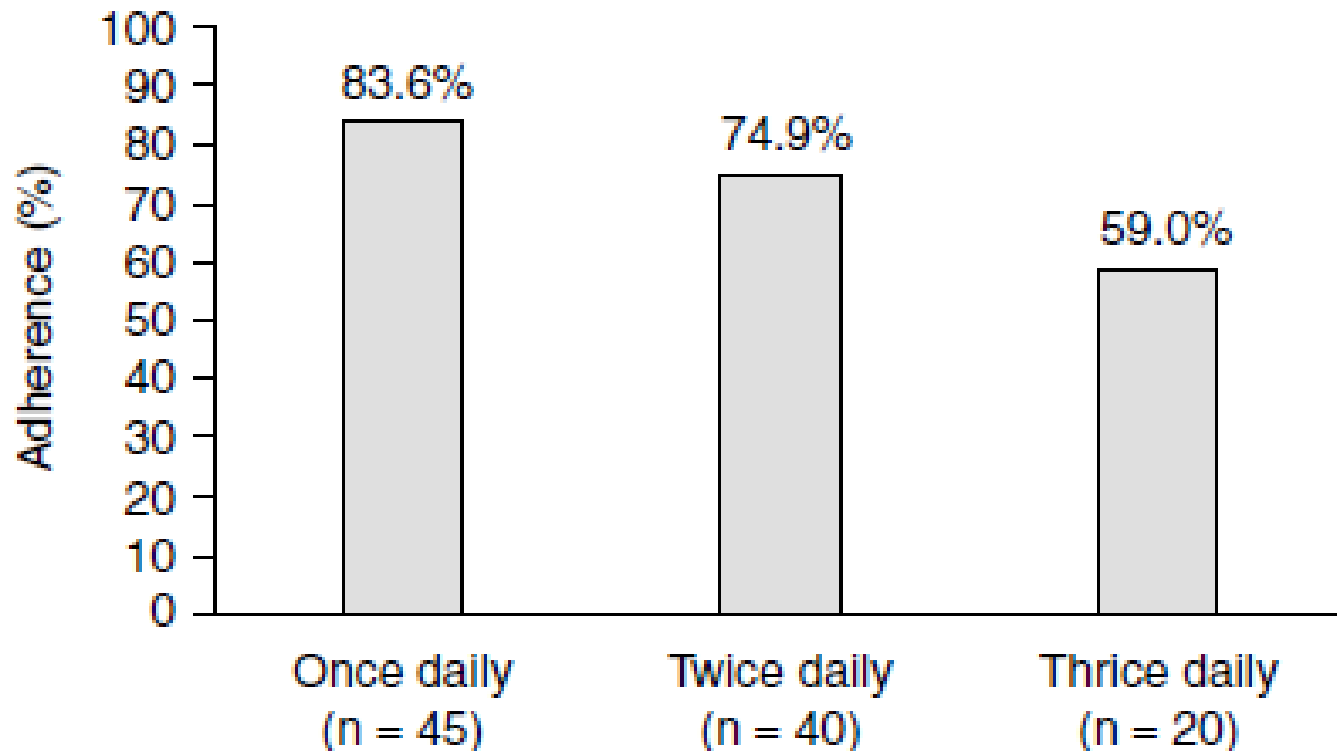
# Slow/sustained drug release

- Release of API is slow, thus the step of the liberation is determinant for the absorption
- It is reasonable at APIs with short half-life and to avoid plasm fluctuations

# Slow/sustained release

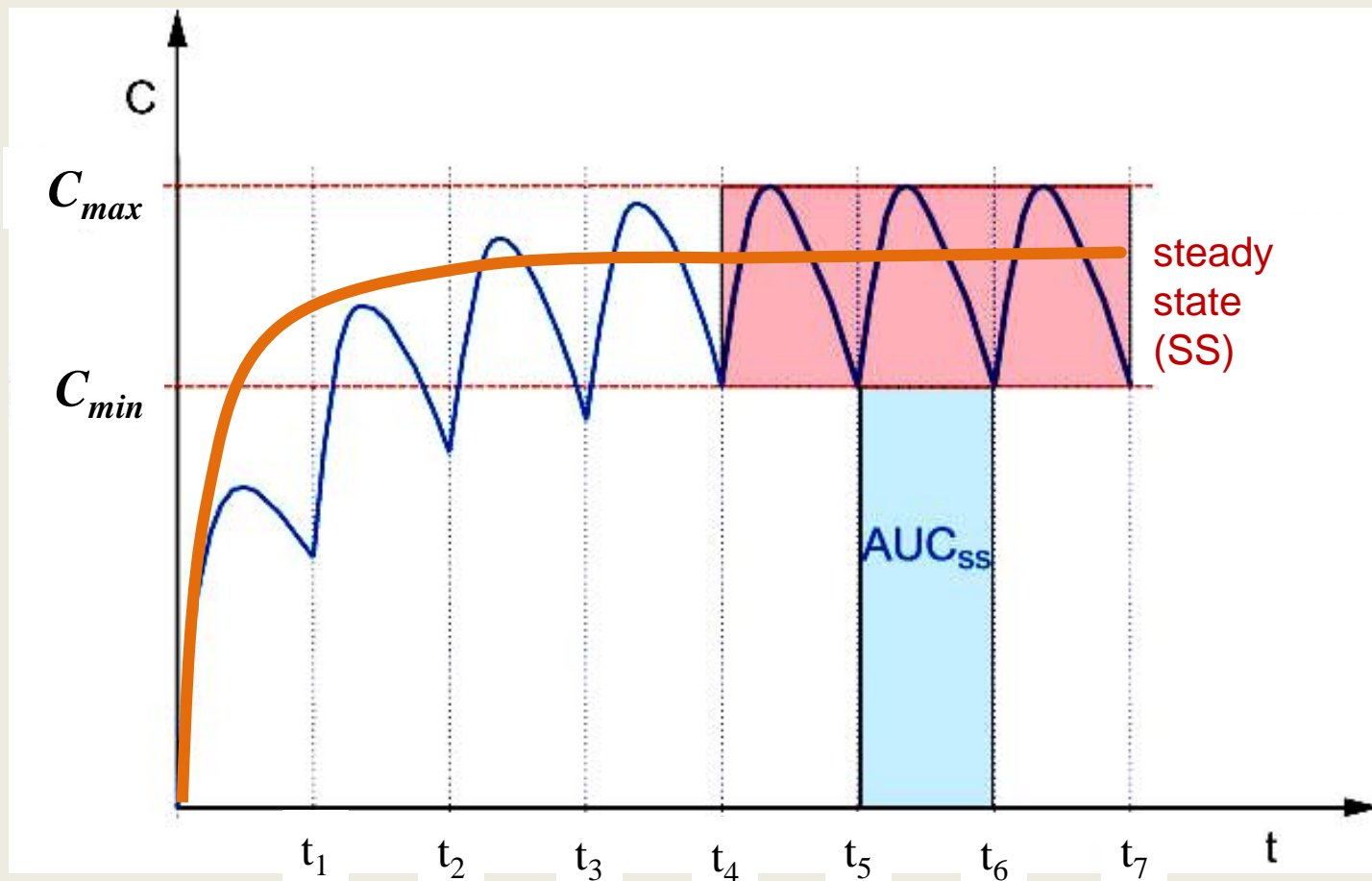
- **Special case**
  - Drug dissolution at constant rate, Zero Order Kinetics (ZOK)

# Modified drug release

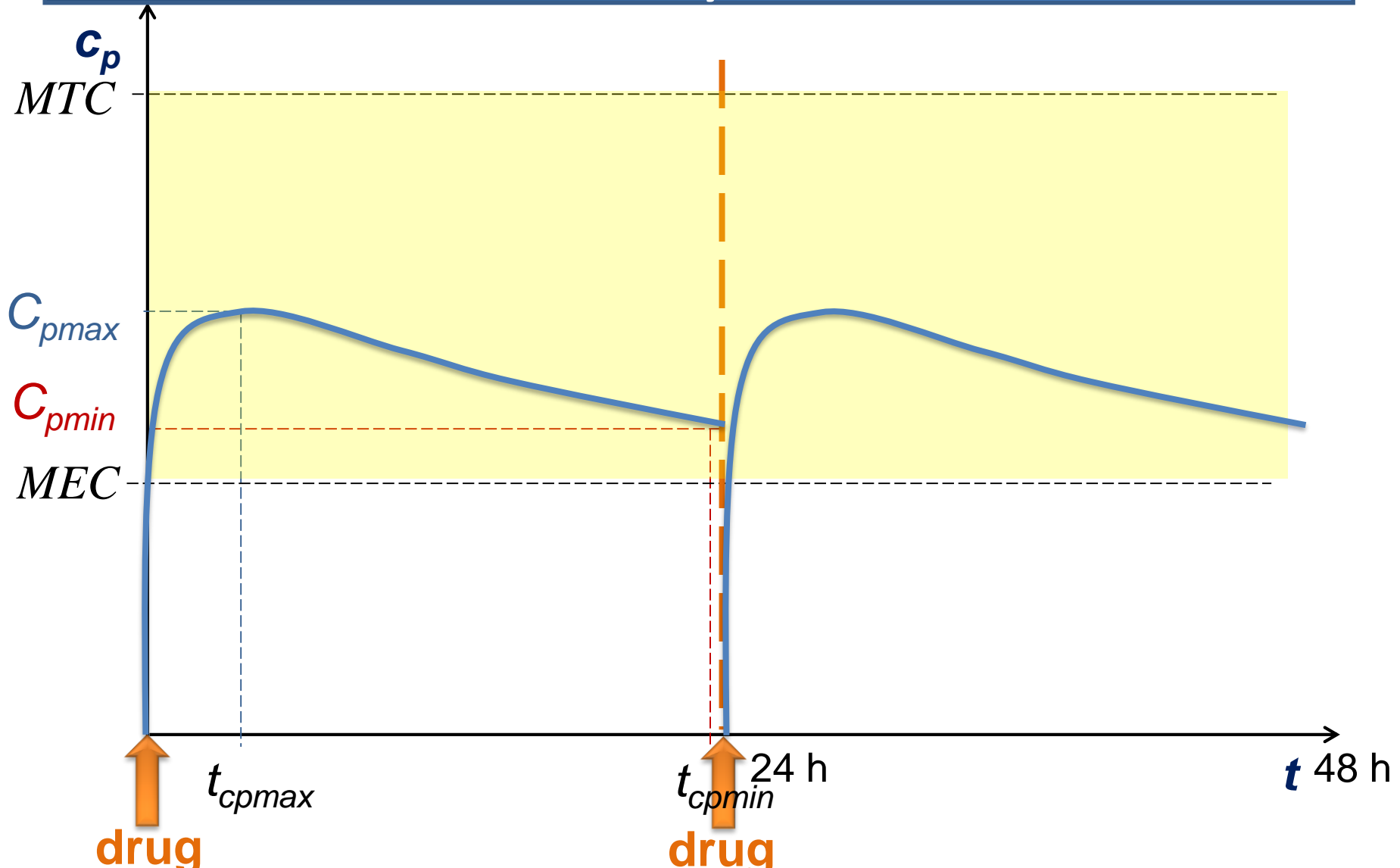


**Fig. 2.** Mean medication adherence according to administration frequency. Medication adherence is defined as the percentage of dose removed from the device divided by the number of doses prescribed.<sup>[10]</sup>

# API blood plasm curve at repeated doses



# Sustained Release Drug Repeated Daily 1x



# Pharmaceutical Excipients to create slow/sustained release preparations

1. Biodegradable matrix
2. Film coating
  - Eudragit RL, RS, NE (metacrylester copolimers)

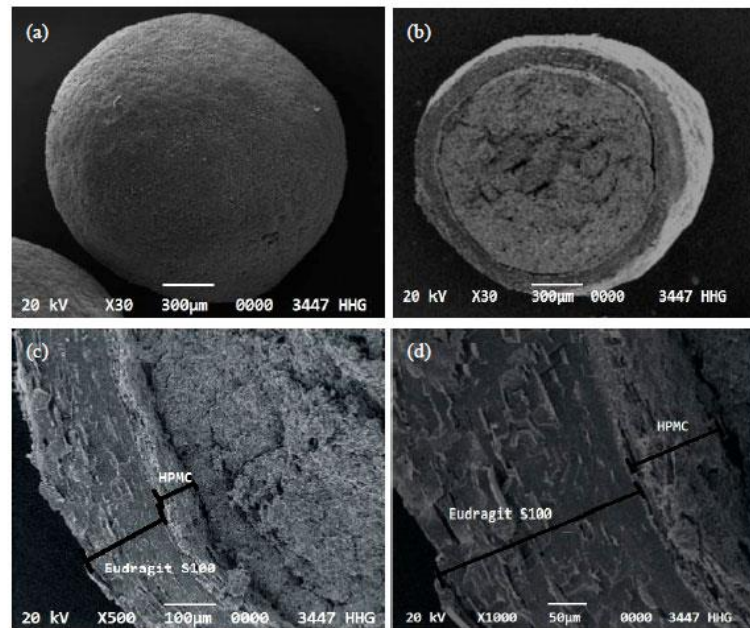


Fig. 8(a-d): Scanning electron micrographs of Budesonide layered HPMC K100M and Eudragit S100 coated pellets (a): at X30, (b): at X30, (c): at X500 and (d): at X1000 magnification

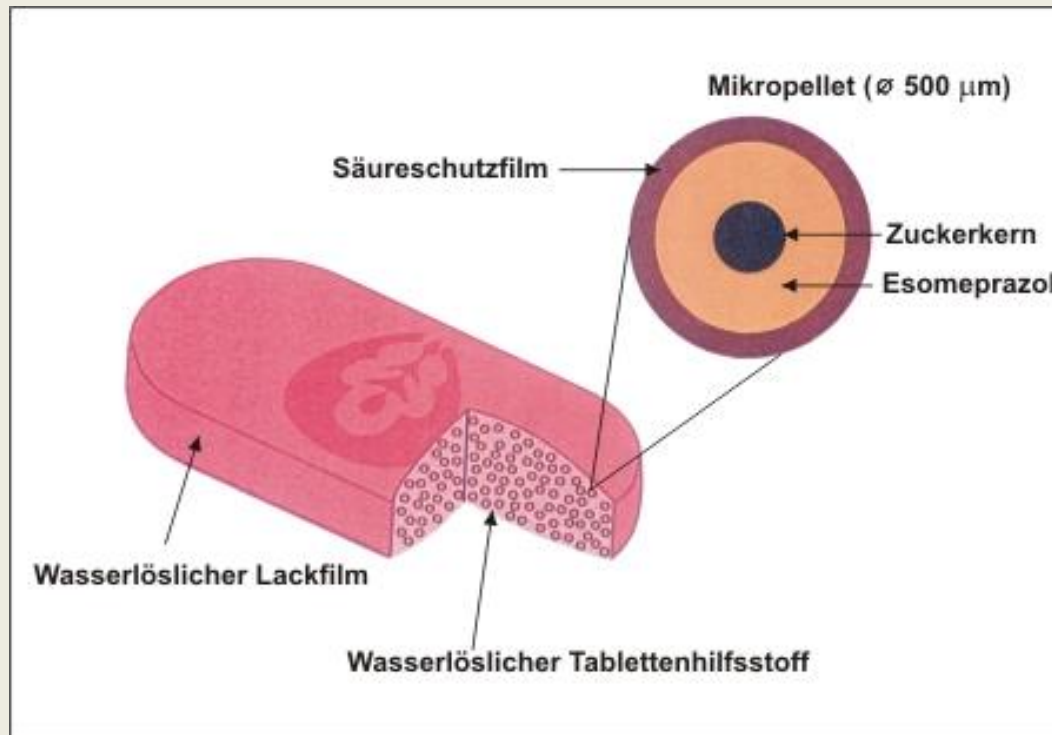
# Kaldyum

- Potassium-chloride
  - 30%-os polyacrylate aqueous dispersion



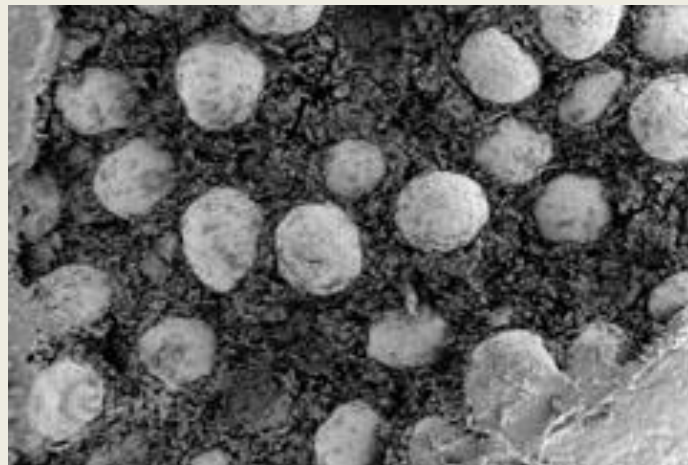
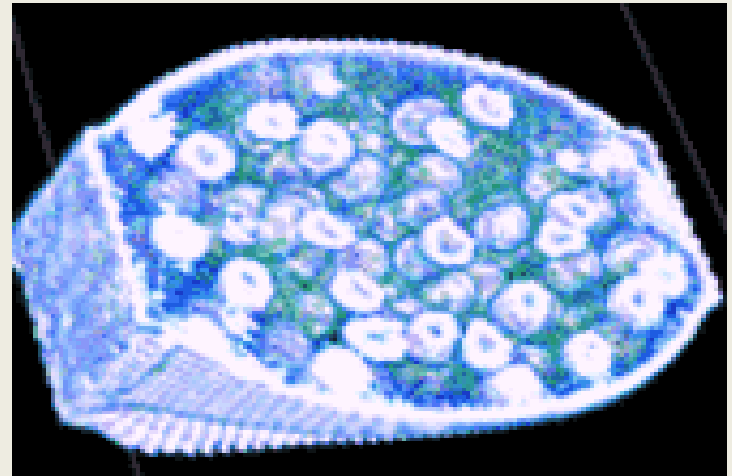
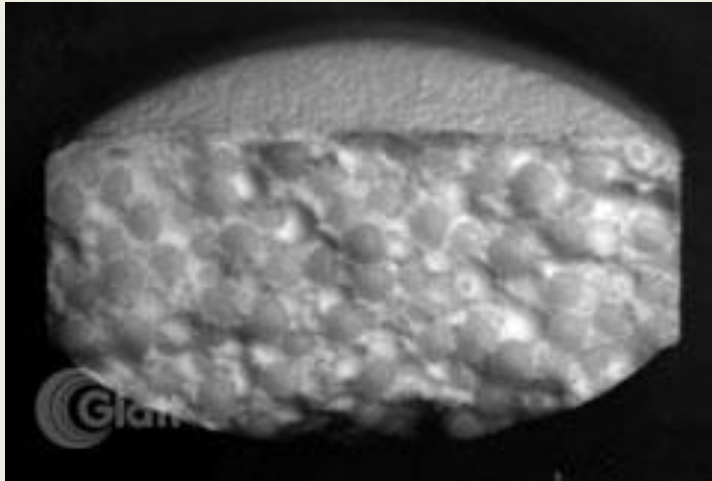
# Slow/sustained release

- Multiple unit pellet system (MUPS)





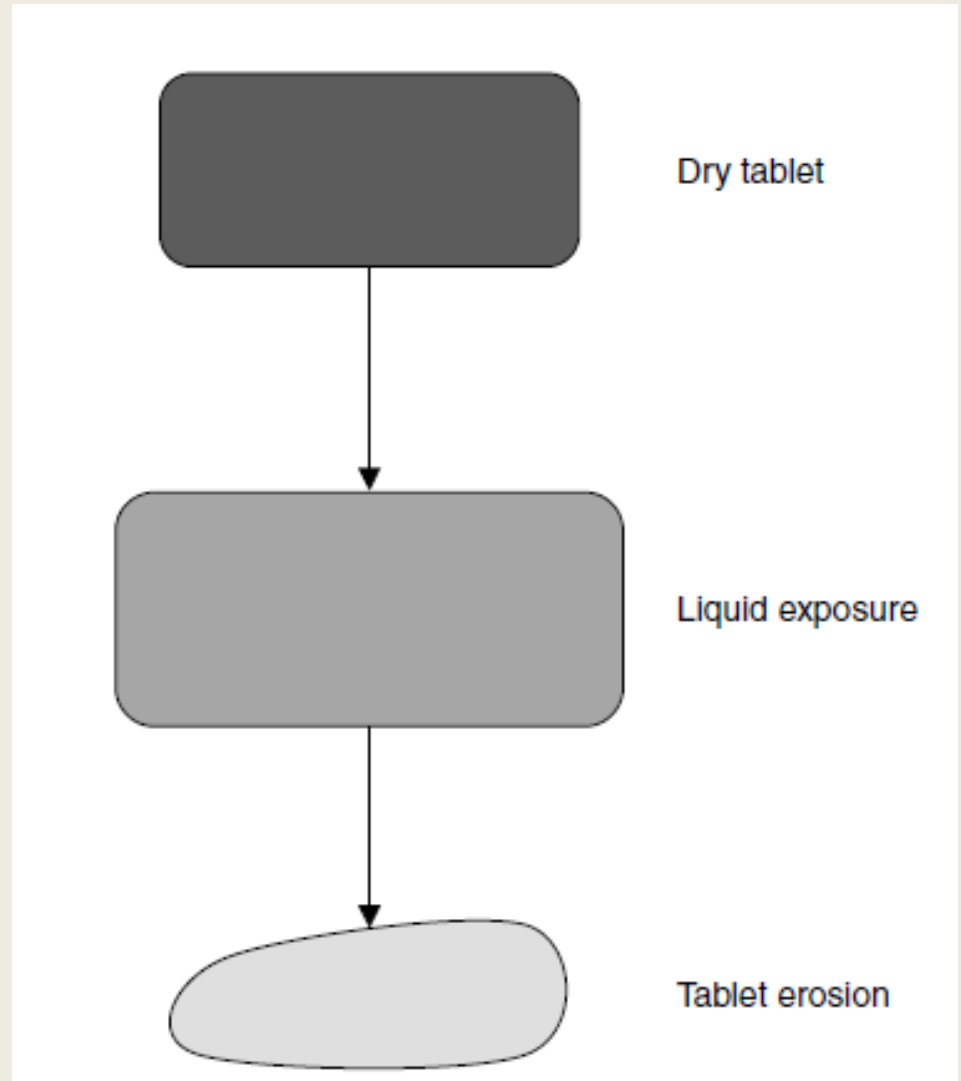
# MUPS (1991)



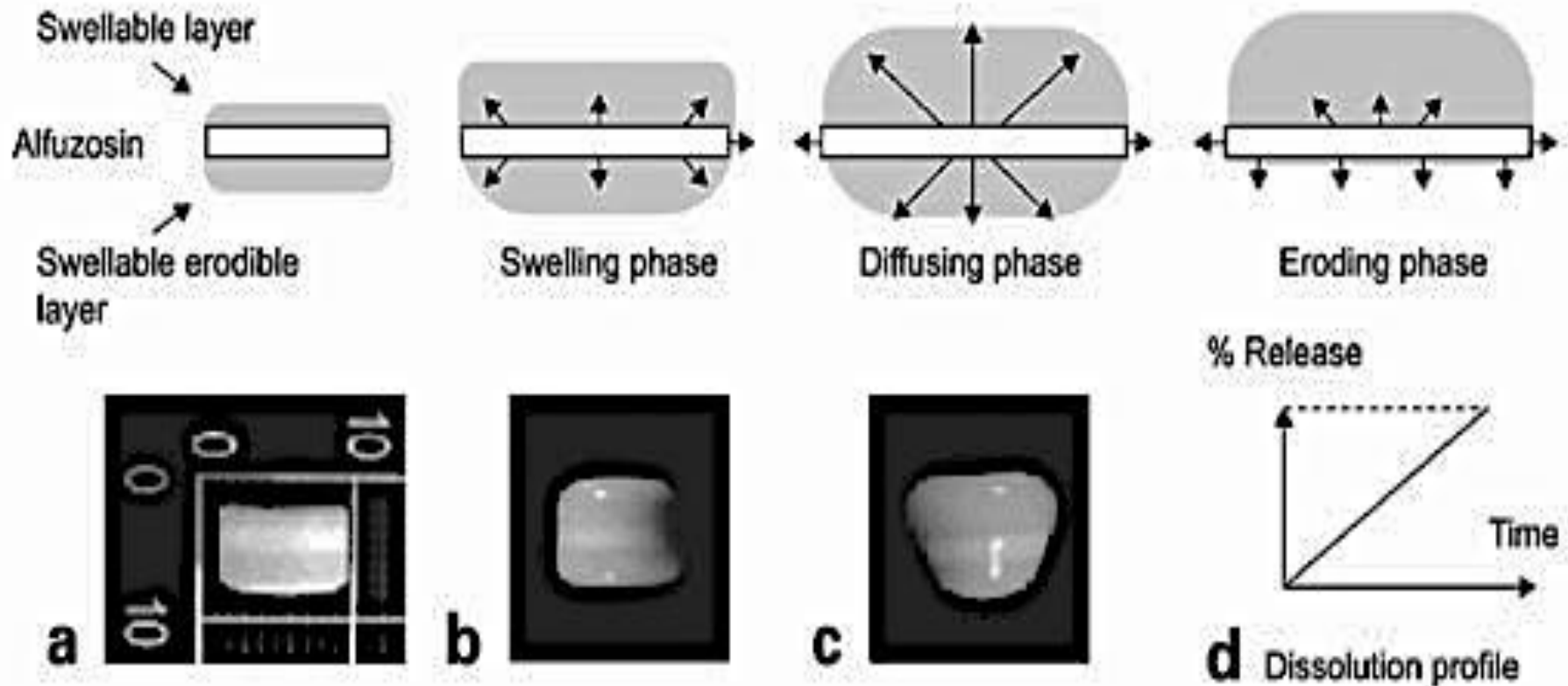
# Slow/sustained release

- Matrix systems
  - pH sensitive
  - Biodegradable.
  - Hidrophilic (alginic acid and derivatives)
  - Hidrophobic (ethyl-cellulose)

# Sodium alginate based hydrophilic matrix (1986)



# Geomatrix™ Sandwich Tablet 1992



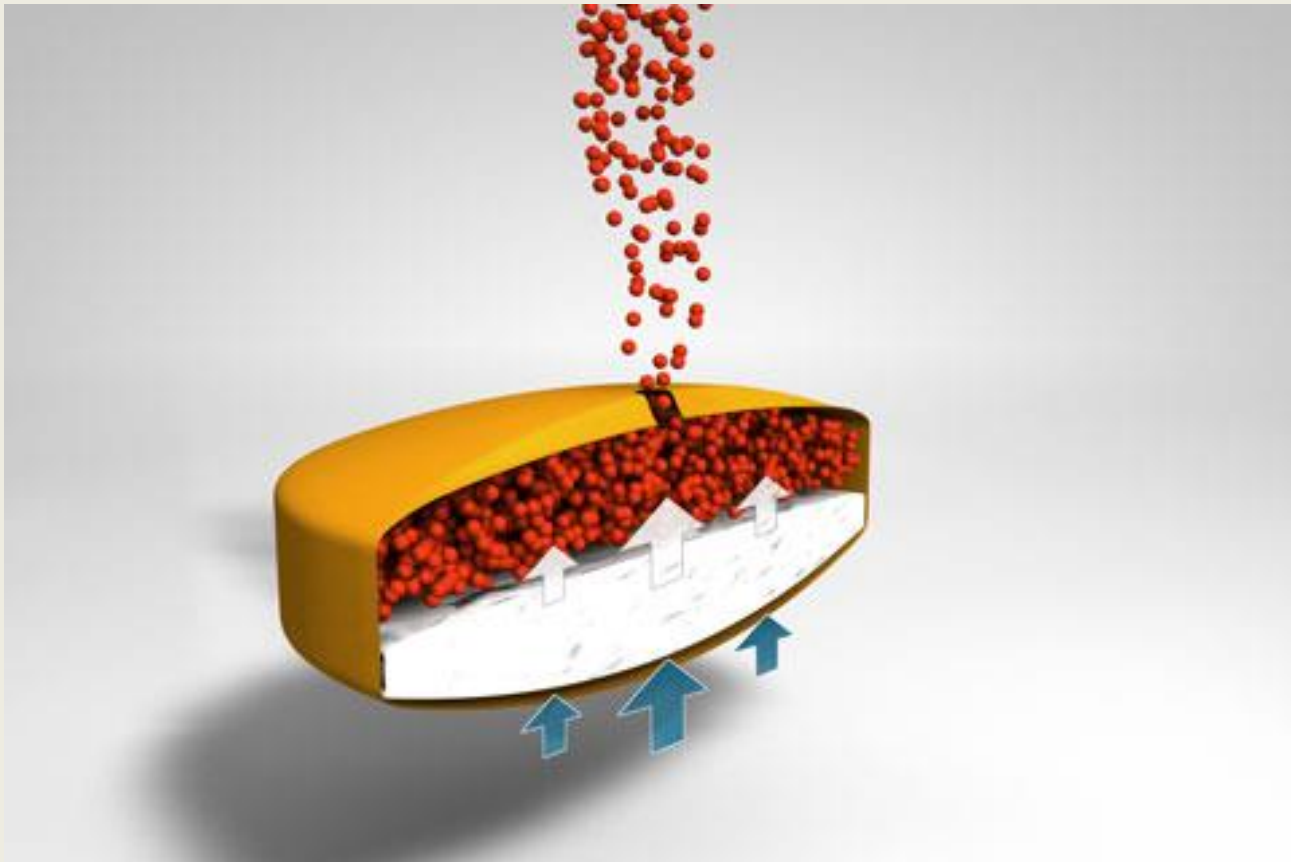
# Slow/sustained release preparations

- Osmotic systems:
  - Osmotic Release Oral System (OROS)
  - GastroIntestinal Therapeutic System (GITS)



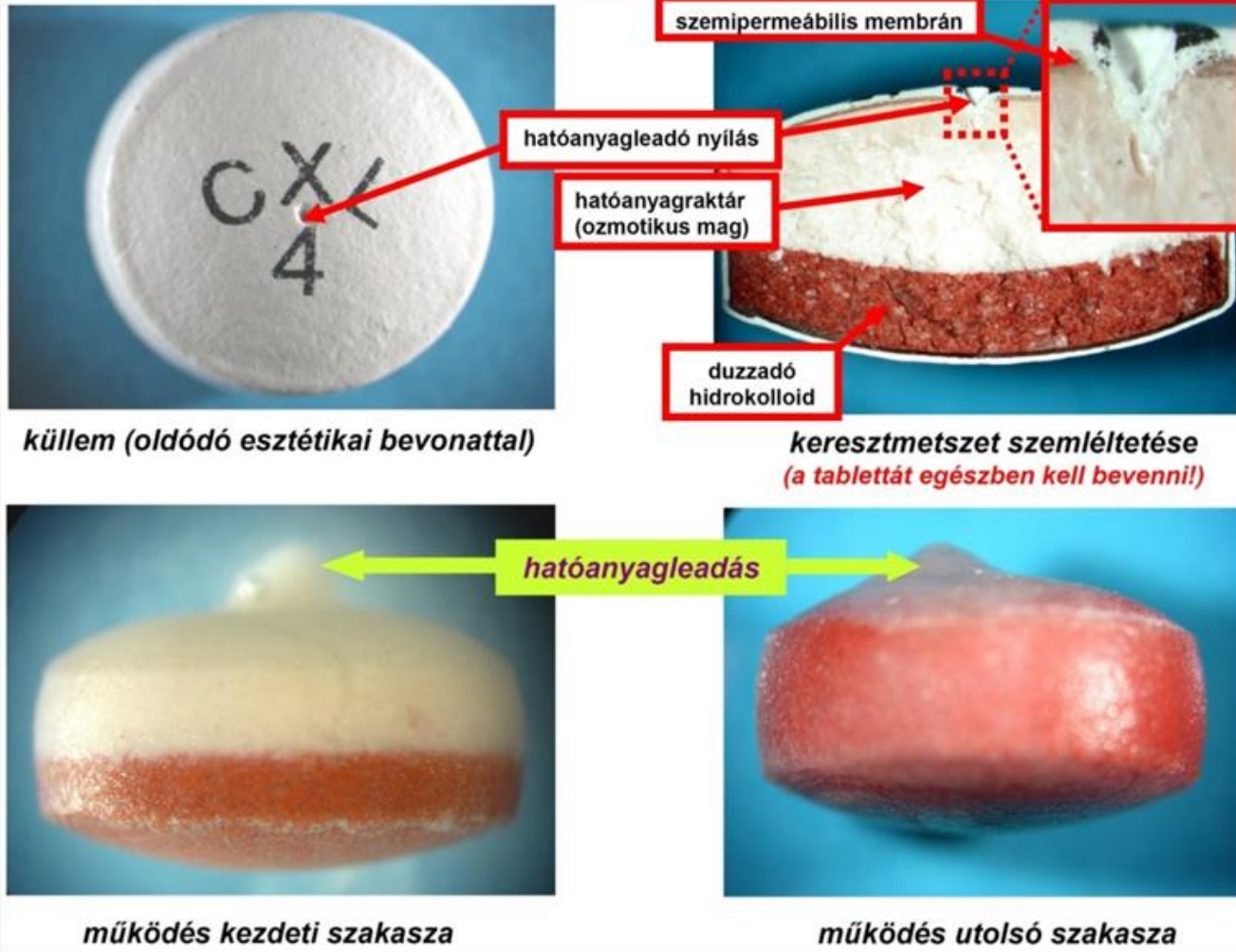
# Osmotic technologies

- ALZA Corp. 1970 – Dr. Alejandro Zaffaroni





# Gastrointestinal Therapeutic System



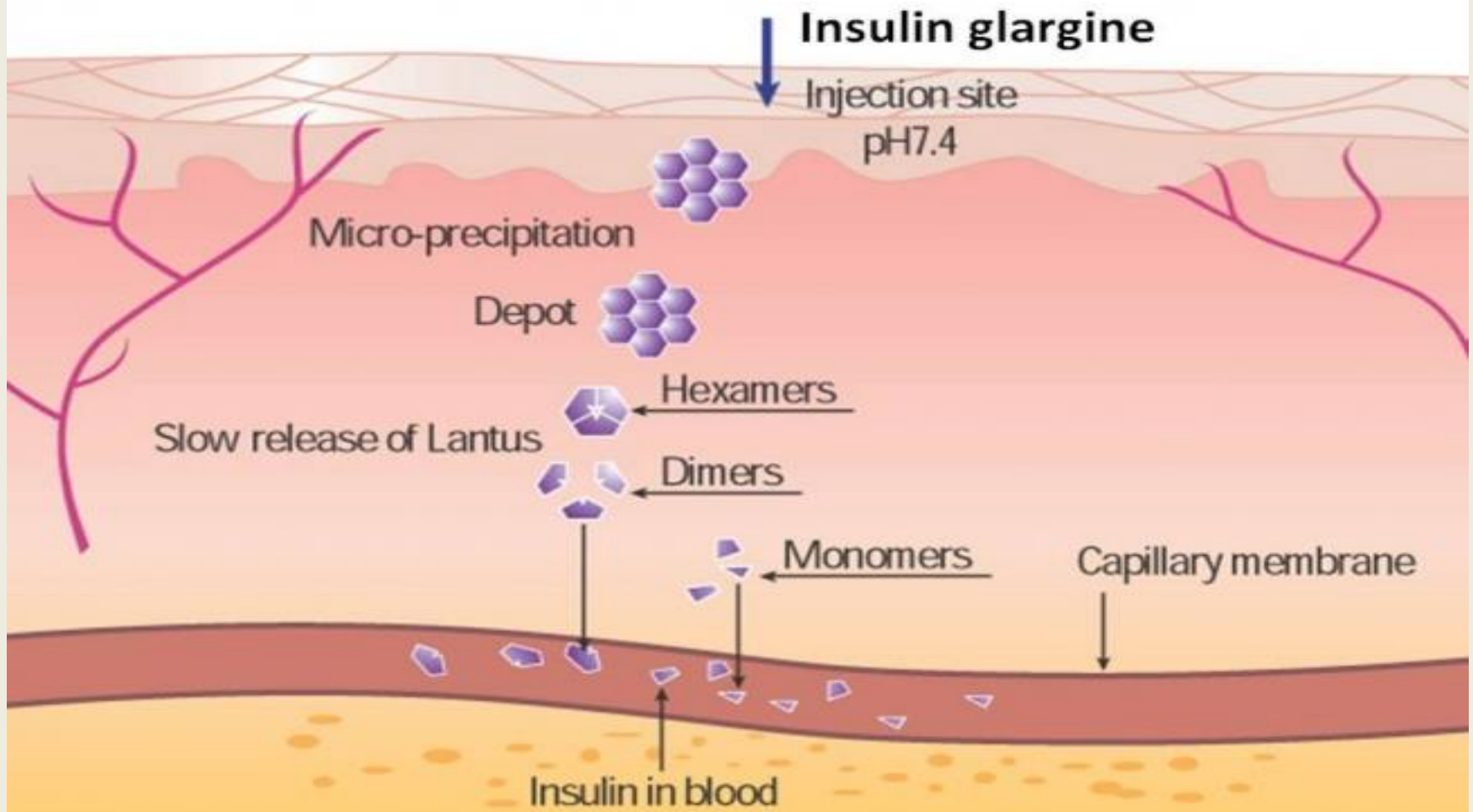
# Glargin analog insulin (Lantus<sup>®</sup> SoloStar<sup>®</sup>)

**Once-A-Day.  
24 Hours.**





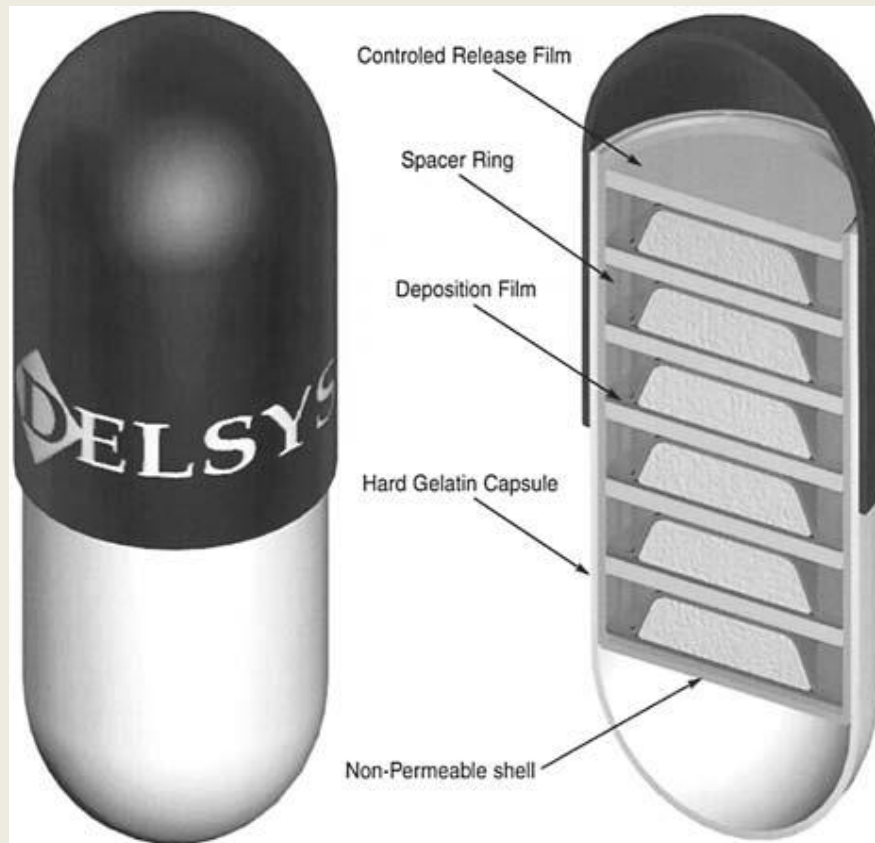
# Glargin analog insulin



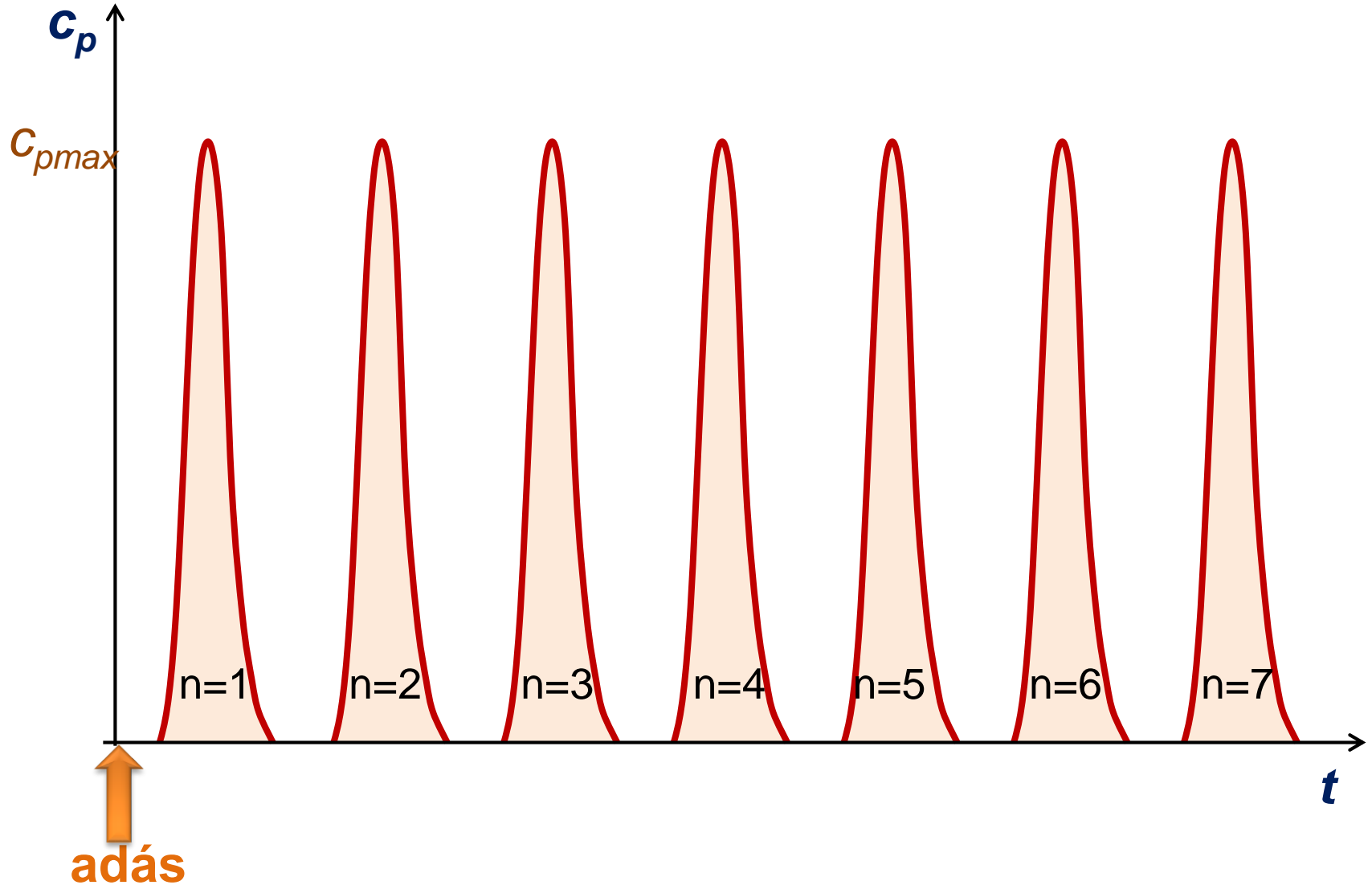
# Pulsatile drug release

- Drug release shows a pulsatile pattern
- Reasonable at circadian diseases

# Pulsatile drug release



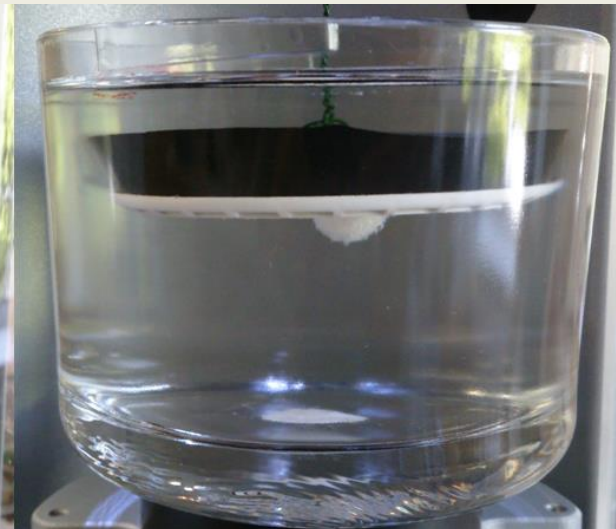
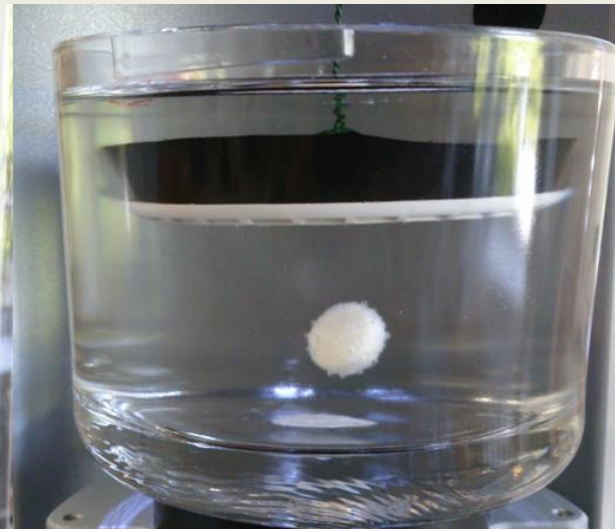
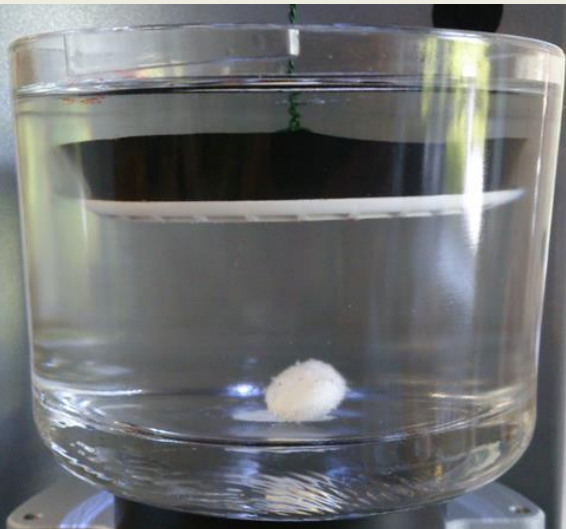
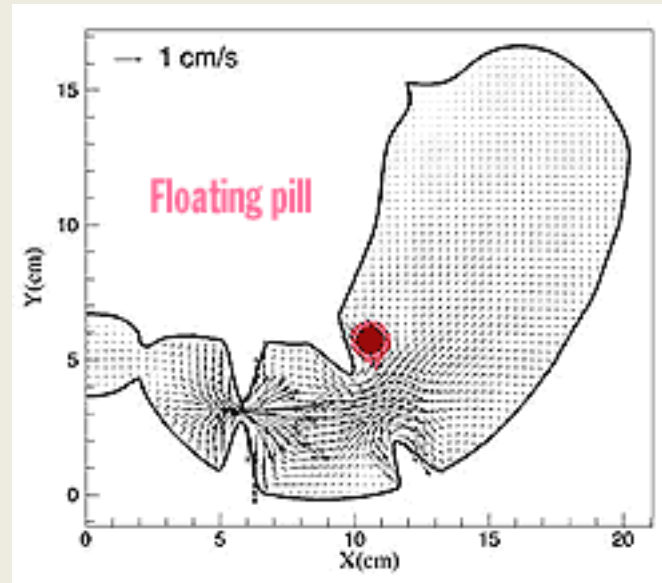
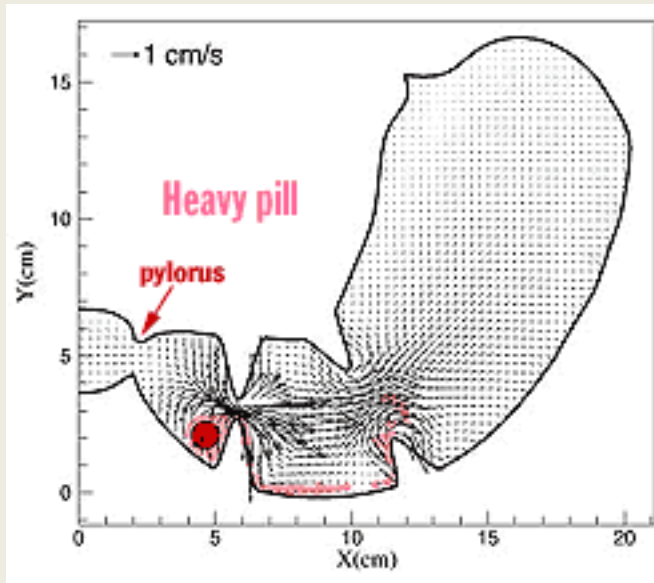
# Pulsatile drug release



# Local drug release

- Reasonable:
  - If the API absorbs from a definite section of the GI tract
  - Stability is adequate at low pH
  - Colon-specific drug delivery

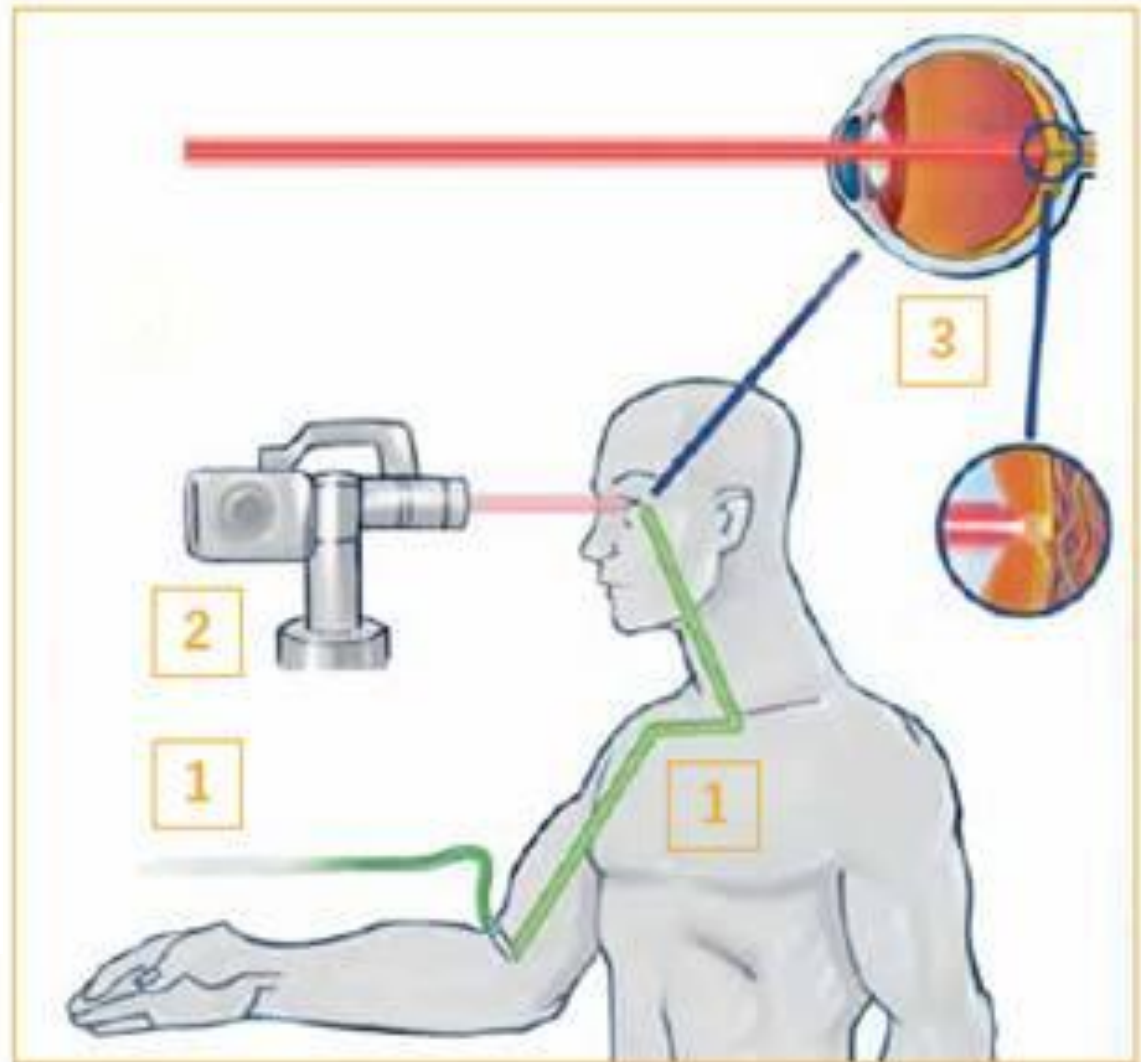
# Local drug release (Gastroretentive tablets)



# Targeted drug release

- Significant at cancer diseases
- API...
  - Injected to the target organ
  - Transferred to the blood vessel of the cancerous tissue
  - Targeting is realised by magnetic field
  - Sonic waves, ultrasound, heat trigger the drug release
  - Applied by targeting molecule

# Visudyne<sup>®</sup> - liposome containing targeted drug release





**Thank you for your attention!**