Modern drug delivery system I.

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Topics of this presentation

- Introduction
- Absorption from the mouth
- Modified drug release
  - Monolithic systems
  - Delayed release systems
  - Coated tablets and capsules
  - Two- and multilayer tablets

Drug therapy

The patients

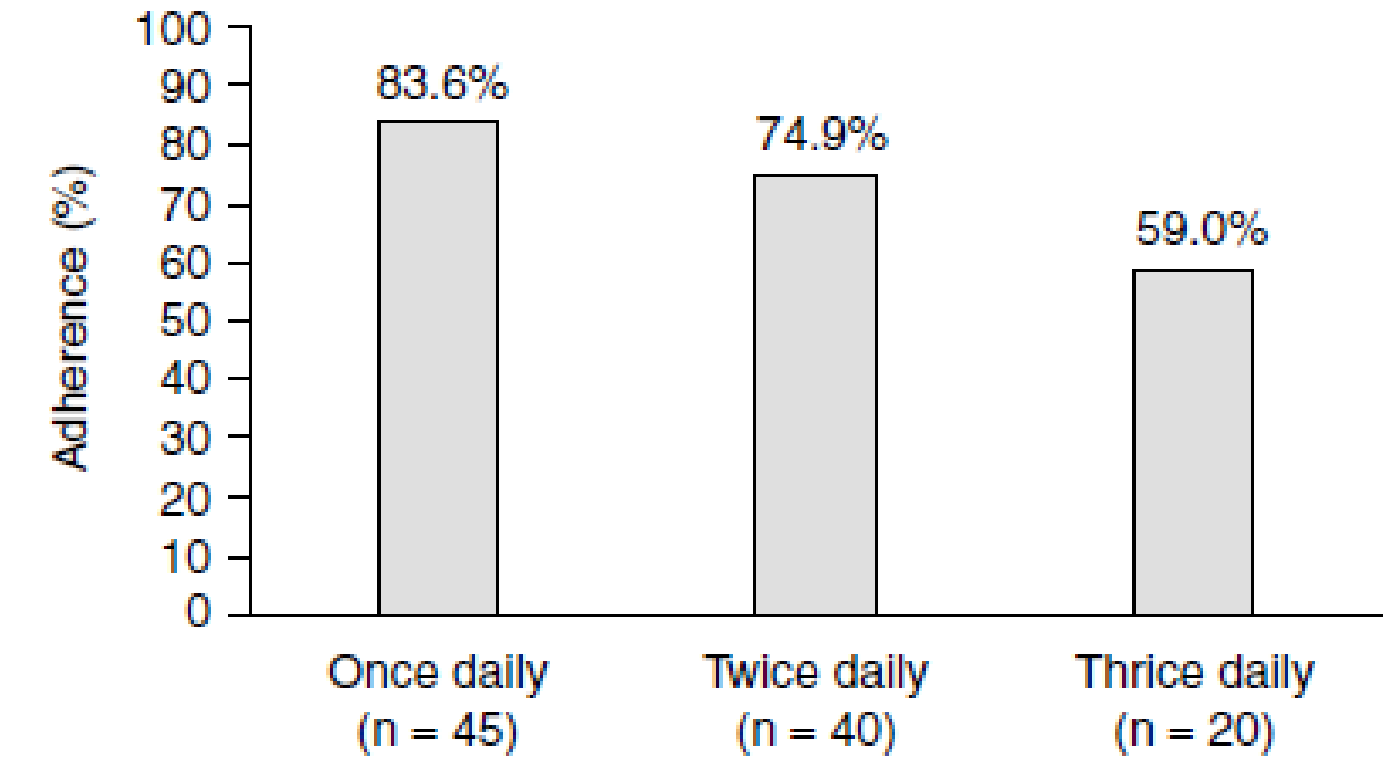
50 % of patients do not use appropriately the medication (patients with chronic disease),

60%- can not measure well the blood sugar level

65 %- can not reach the aimed level of blood pressure and (49 %) the colesterol level

The reason is the desorder in the patient's drug usage.

Adherency



Mean medication adherence according to administration frequency.

From the aspect of recovery the better choice is one pill/tablet per day.

Requirements of innovation in pharmaceutical industry

- new products
- quick marketing
- benefit

Results

- increasing in the role of pharmaceutical industry
- increasing in the innovation in pharmaceutical industry
- a lot of inventions and patents

Reasons of the wrong bioavailability:

1.) the dissolution is not complete,

2.) the API is not in dissolved form at the absorption site, because the delayed liberation from the DDS or the GI-transit is too fast,

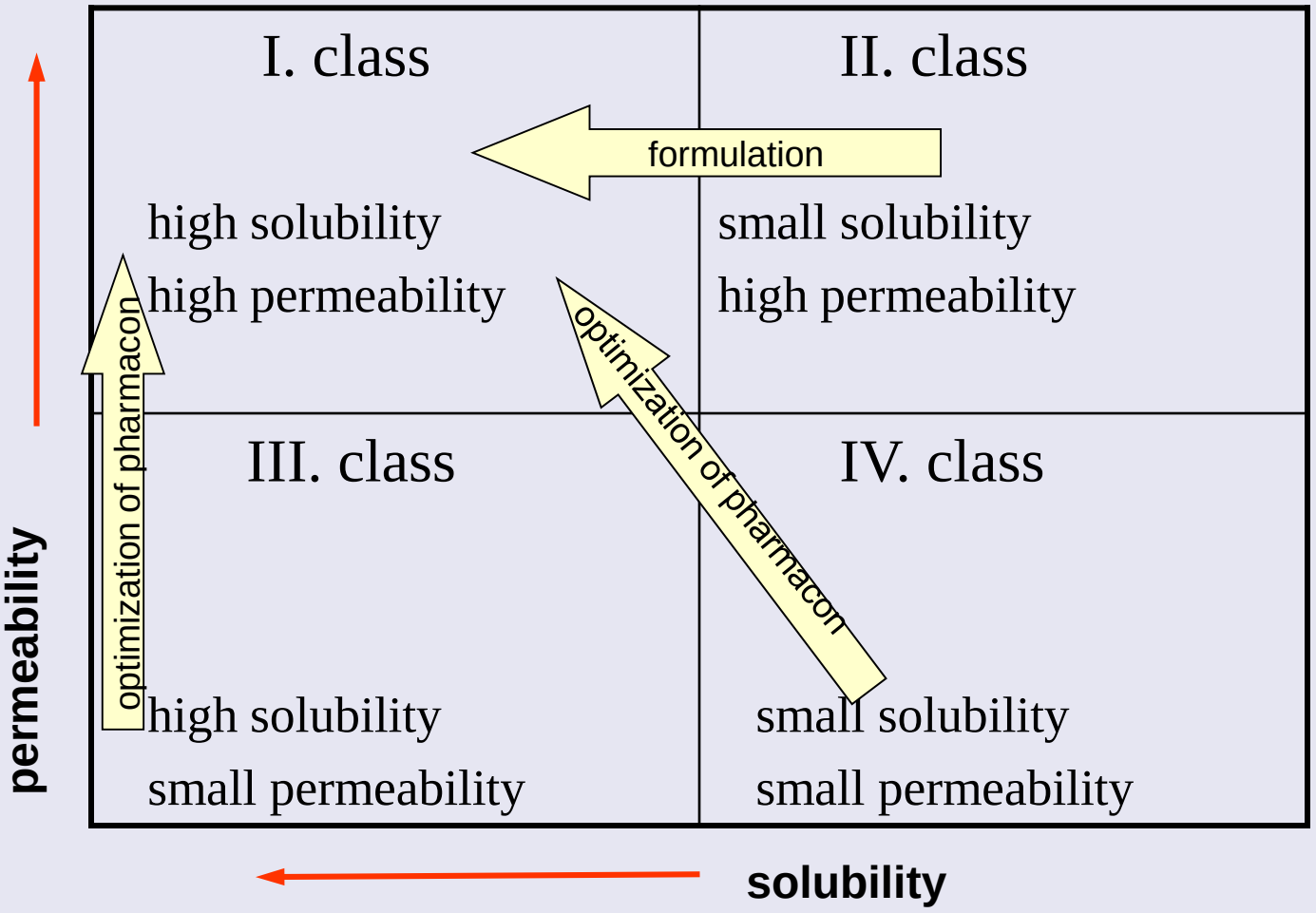
3.) after the liberation, it degrades/decomposes, absorbes to any surface or forms an inmiscible complex,

4.) the API can not go trough the membrane barrier,

5.) during the absorption (preabsorptive metabolism) or after this the API can be metabolised (first pass effect), or eliminated (biliar excretion).

Biopharmaceutical Classification System (1995)

(Prof. Gordon L. Amidon)



Drug therapy

Requirements of drug therapy

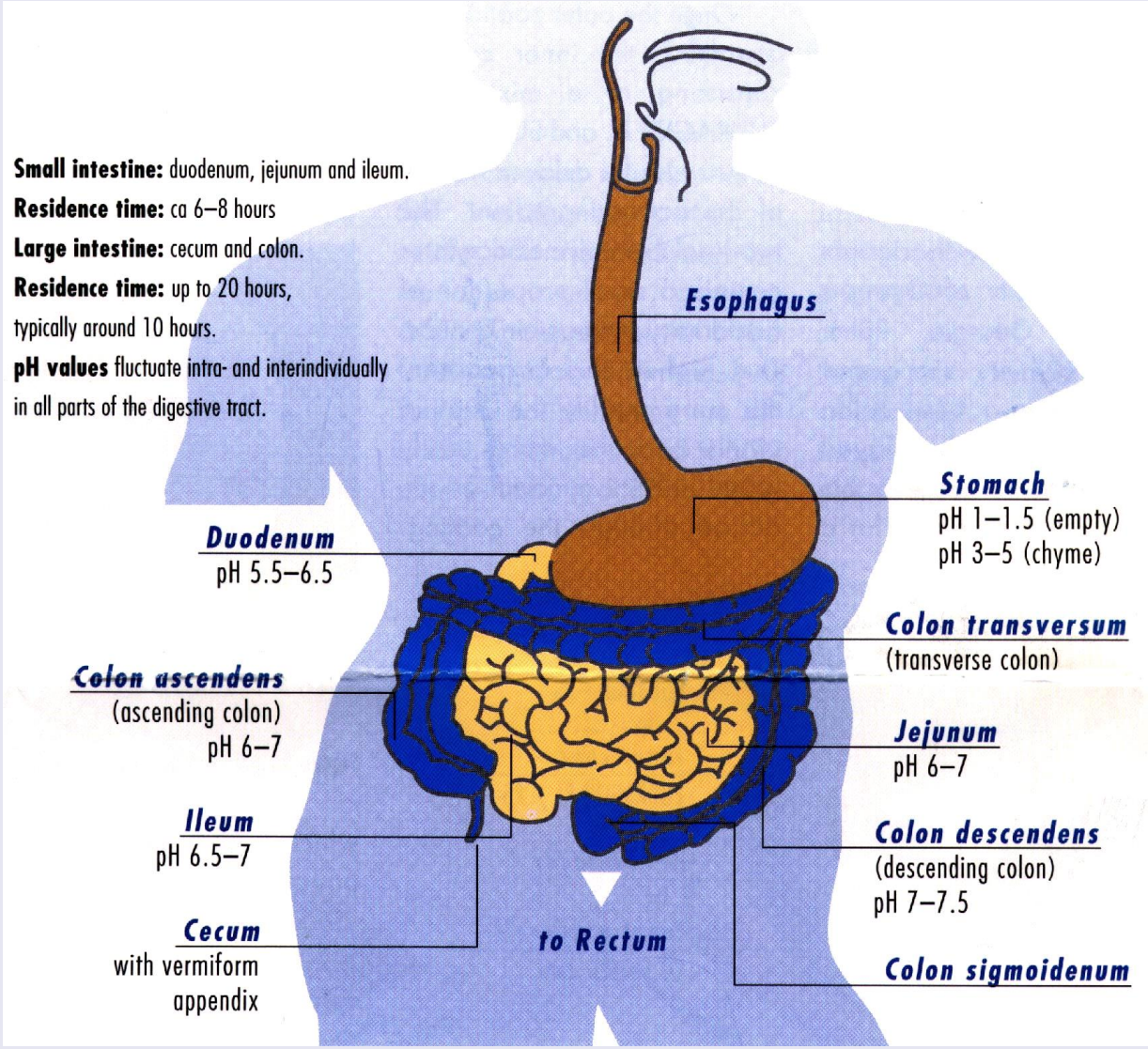
- reduction of the dose (side effects),

- perfect fitting for biological environment (absorption site depending of pH),

- perfect fitting for therapeutic requirements (systemic, local, immediate, prolonged, targeted release),

- design of the fate of drug from organism (metabolism, excretion)

pH in the gastrointestinal tract



Parameters of the sections of GI system

Per os	Length	Secretum/day	pH	Food pH	Retention time (h)	Absorption area (m^2)
Mouth Oesoph.	10 cm 20 cm	saliva 1-2 l secretum	5.0-8.5		10-20 s 10-20 s	0.02
Gastric	25 cm	gastric juice empty 50-100 ml chyme 2-3 l	1.0-1.5	3-5	0.5-3 h	0.1-0.2
Small intestine Duodenum Jejunum Ileum	 25-30 cm 2 m 3 m	pancreas secretum 7-1.5 l gall 0.6 l mucosal secretum 2-3 l water resorption 7 l	 5,5-6.5 6-7 kb. 7.6	 6-6.5 6-8	6-8 h	100
Colon	1.2-1.5 m	Water resorption 0.3-1 l		7.0-7.5	kb. 10 h	0.5-1
Rectum	10-12 cm	Secretum in rectum	7.2-7.4			0.04-0.07

Groups of products

1. generation: conventional products

Conventional drug delivery may not undergo a change – application of a particular composition or manufacturing method – that can intentionally alert the release of active substance.

Tablets, suppositories, ointments, etc.

The physico-chemical and pharmacokinetic (half time, bioavailability) behaviours of the API determine its fate in the human body (dissolution, plasma level, duration of action, side effects).

2. generation: modified release preparations

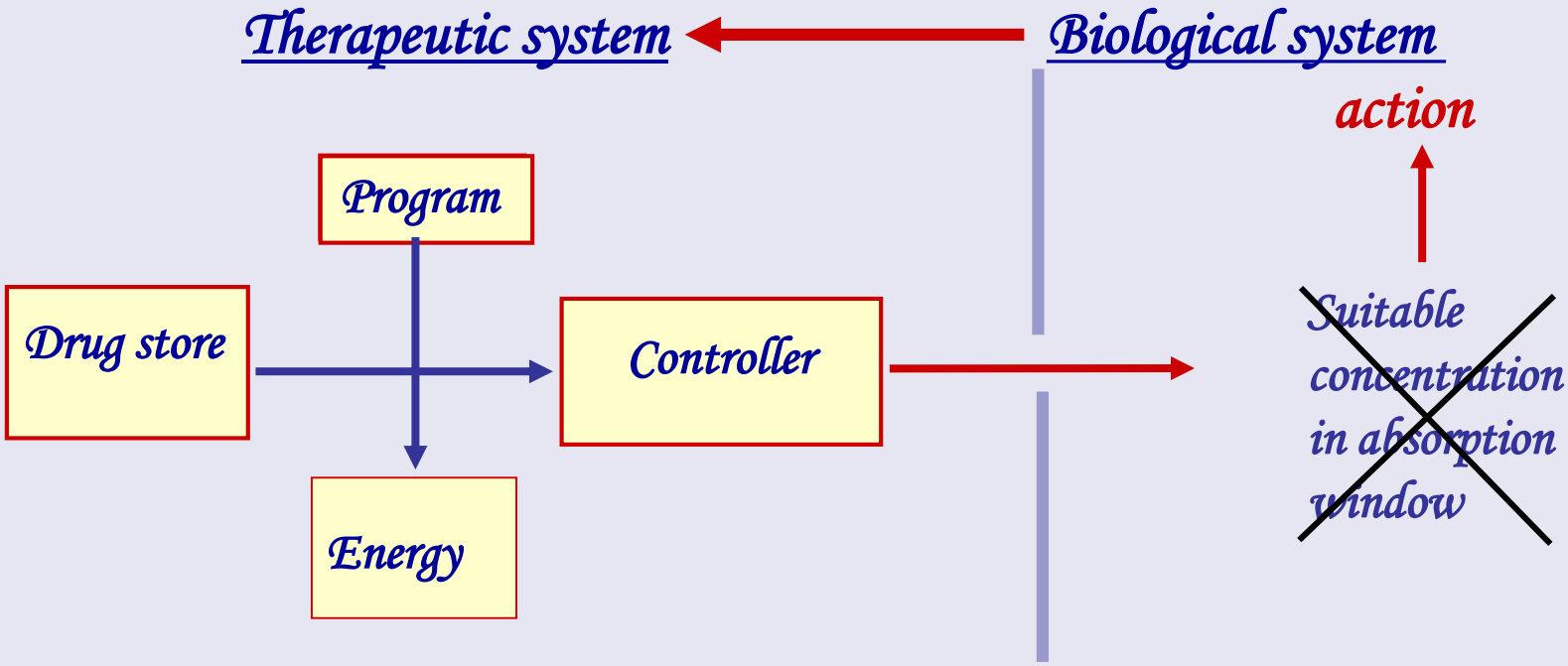
The modified release means the deliberated control of dissolution to achive a better therapeutic effect/effectiveness.

- *prolonged release, sustained release = SR)*
- *delayed release (cronotherapeutics systems also = DR)*
- *pulsatile release (cronotherapeutics = PR)*
- *immediate (accelerated) release (IR)*

Usually, it can improve the compliance, because the preparations with sustained release should be taken rarely so the reduction of the side effect is possible. The controlled drug release can reduce the API blood peaks so the likelyhood and severity of side effects.

3. generation: controlled drug delivery systems

The drug release is controlled in time and in space (therapeutic systems)

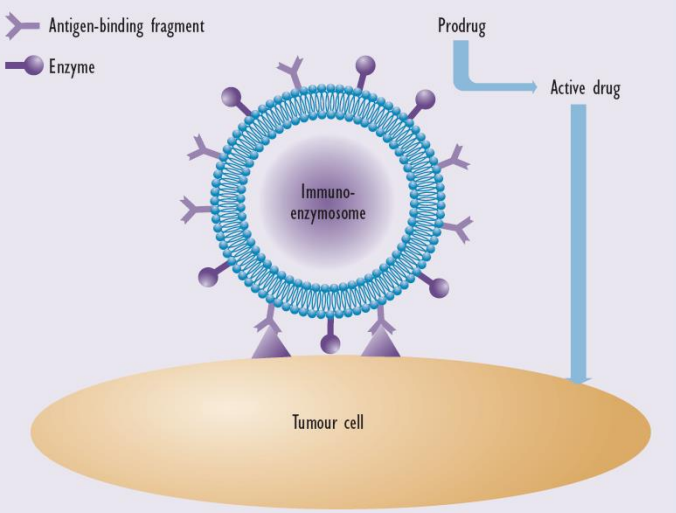


The therapeutic system contains 4 parts. The controller registers the decrease of the API in the blood and turns on the work of the therapeutic system.
The energy liberates the API according to program from the drug store and the API has to cross the human organism by the absorption window.

4. generation: space-controlled systems

- *Local-specified drug release preparations (delayed)*
  eg. gastroretentive systems

- *Targeted drug release preparations*



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

Drug release model

Noyes-Whitney model

Dissolution-diffusion

$$\frac{dm}{dt} = kA(C_s - C)$$

m	dissolved API at the ‘t’ time
t	time
k	kinetic of dissolution
A	surface area
C_s	solubility
C	concentration of the API at ‘t’ time

Korsmeyer-Peppas model

$$\frac{M_t}{M_\infty} = at^n$$

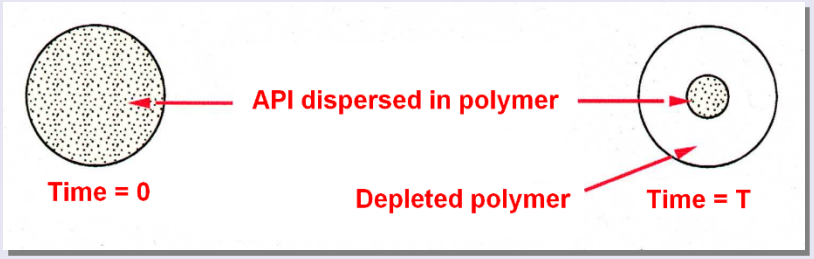
a constans
n dissolution factor

In the case of *lag time:*

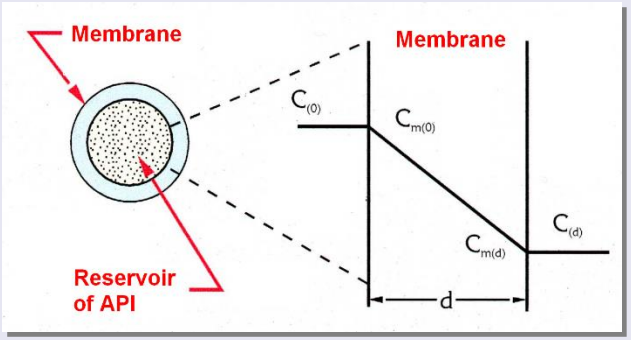
$$\frac{M_t}{M_\infty} = a(t-l)^n$$

Water-insoluble polymers

Matrix pellets



Reservoir pellets

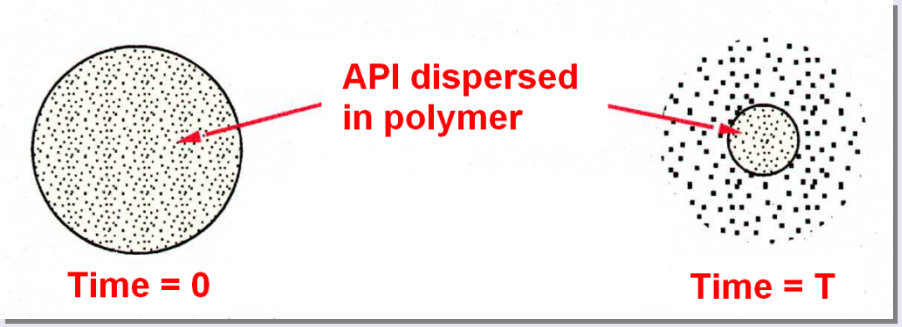


$$m = \sqrt{D(2C - C_s)C_s t}$$

(Higuchi)

m	*dissolved API at 't' time*
D	*diffusion constant*
C_s	*the solubility of the API*
C	*the initial concentration of the API*

Water-soluble or erodible polymer



$$\frac{M_t}{M} = 1 - \left(1 - \frac{k_0 t}{C_0 a}\right)^n$$

(Hopfenberg)

M_t= dissolved API at 't' time
M = total API
k_0 = erosion kinetic
C_0= initial concentration of API
t = time
a = eroding surface

Classification of pharmaceutical products

abbreviation	english	mean	example	Usually daily dose
CR	controlled release		Sinemet CR	2 x 1
Duo	-	The API is incorporated into two forms of pellets	Diclofenac Duo Pharmavit	1-2 x
EC	enteric coated	With enterosolvent coat	Videx EC	1 - 2 x
ER	extended release	Sustained release	Efectin ER	1 x
GITS	gastrointestinal therapeutic system	Special DDS with first order kinetic	Adalat GITS	1 x
HBS	hydrodynamically balanced system	(floating tablets)	Madopar HBS	3 x
LA	long acting	Sustained release	Inderal LA	1 x
MR	modified release	módosított hatóanyag-leadás	Preductal MR	2 x 1
OD	once daily	Sustained release preparation what should be taken once a day	Ciplox OD	1 x
SR	sustained release/slow release	Sustained release	Flugalin SR	1 x
TR	time release/ timed release	Sustained / time controlled release	Rondec TR*	2 x
XL	extended liberation extra long (release)	Sustained release	Cardura XL	1 x
XR	extended release	Sustained release	Glucophage XR	1 x
ZOK, Z	zero order kinetics	Sustained release preparation with first order kinetic	Betaloc ZOK Metoprolol Z Hexal	1 x

Absorption from the mouth

- *lot of capillary*
- *good absorption of some APIs*
- *the drug can go immadiatally into the blood*
- *avoiding of the „first pass effect”*
- *rapid action*

Ph.Eur: Tablets for use in the mouth

Sucker tablets

Buccal tablets

Sublingual tablets

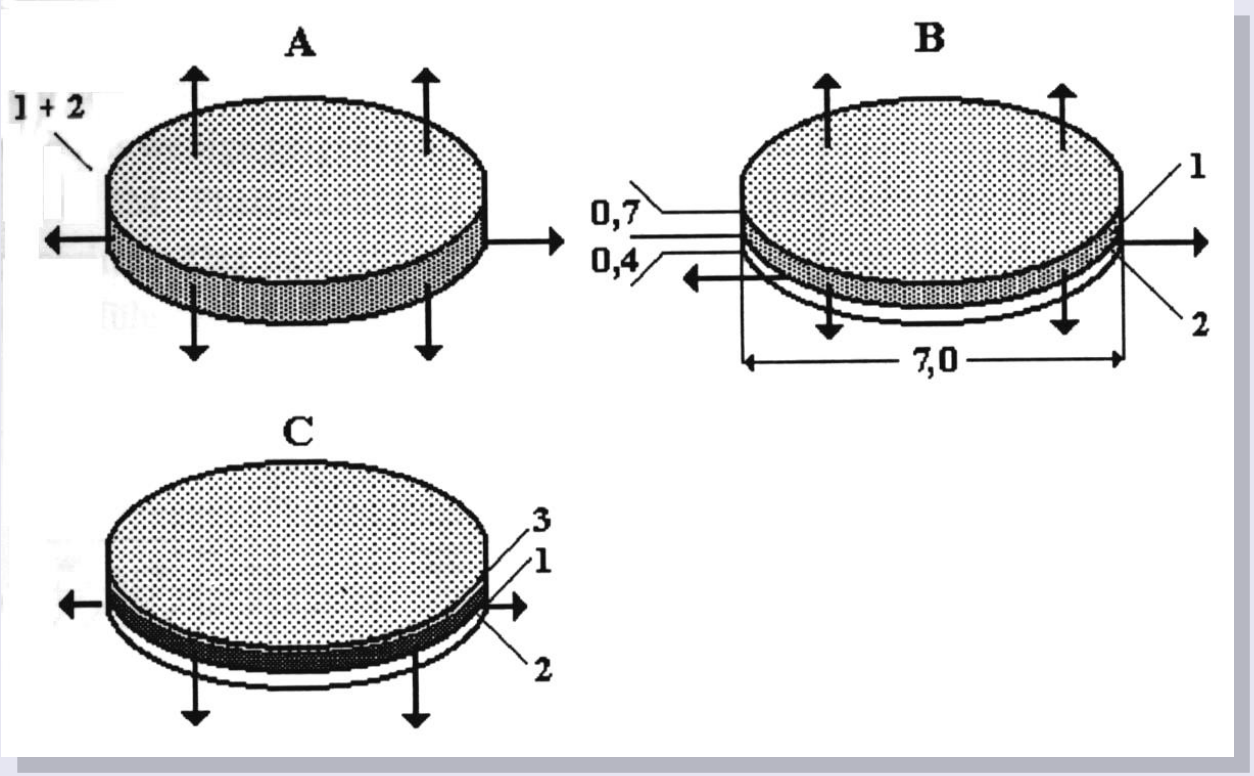
Mucoadhesive preparations (tablets, capsules, filmes)

Dispersable tablets *(1.* **disintegrate in water within 3 min or**

2. dispersible in mouth without water)

Chewable tablets and gums

Bioadhesive tablets



1. Drug layer *2. Biadhesive layer* *3. Impermeable cover layer*

Preparation may be diverse

Chewing gums

Components

API
Aromatic component
Sweeters: **Sorbitol** **Xylitol** **Maltitol**
Gum base

1848: first chewing gum
1869: first patent
1928: first medical chewing gum
ASA (Aspergum)
dimenhydrinate
1978: nicotinic chewing gum

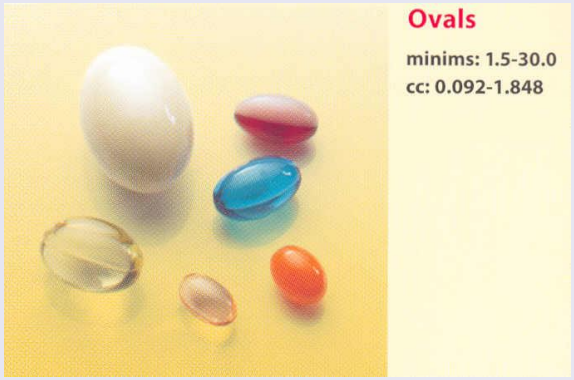
Local effect
pH (caries)
fluorid (caries)
oral infections : gingivitis, periodontitis, stb. (chlorhexidyne)
miconazole

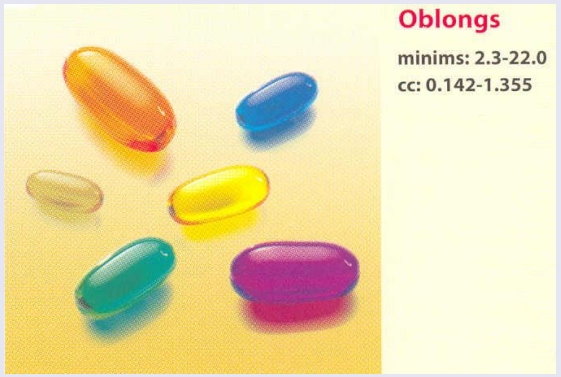
Systemic effect
pain (acetyl salicylic acid ,
methadone)
smoking (Nicorette, Nicotinell)
obesity (coffein, guarana, chrom- compounds)
others (allergy, coughing, sickness, diabetes, etc.)

Softgel

Soft capsules, filled with the solution of API, but the solvent is not water.

Pl.: Advil ultra, Nurofen soft capsule





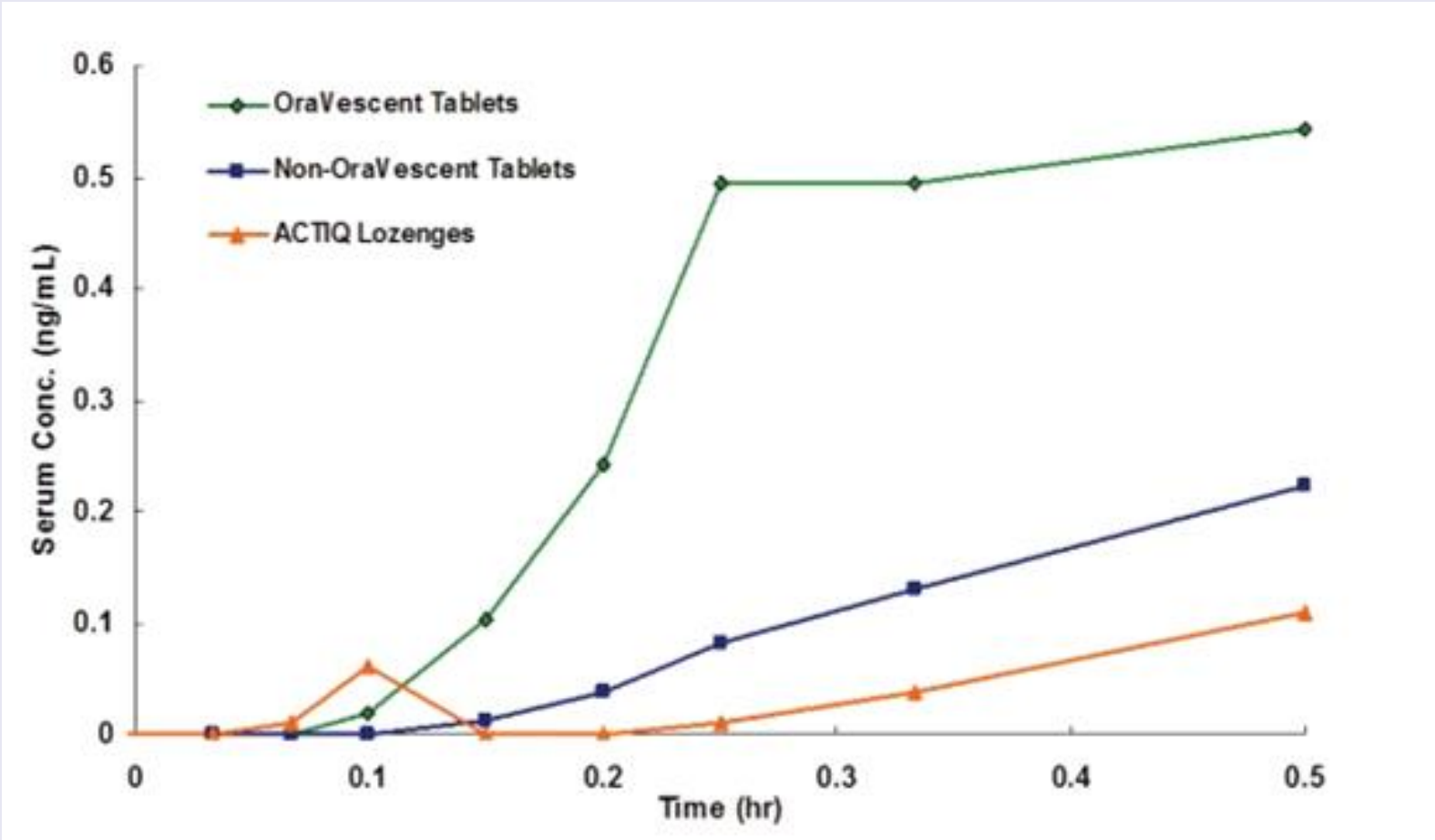
Absorption through the mucosa

OraVescent effervescent buccal tablets

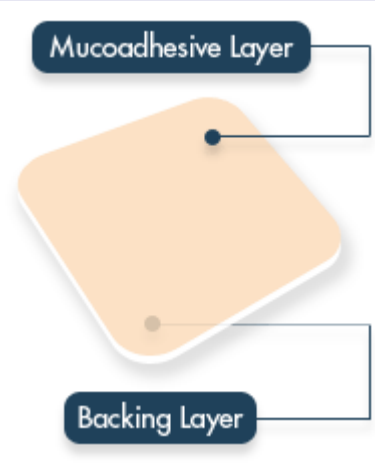
Reason: bioavailability of oral tablets: about 30%

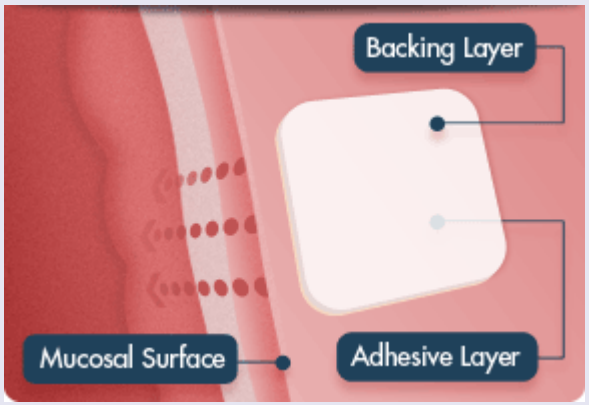
API: fentanyl-citrate

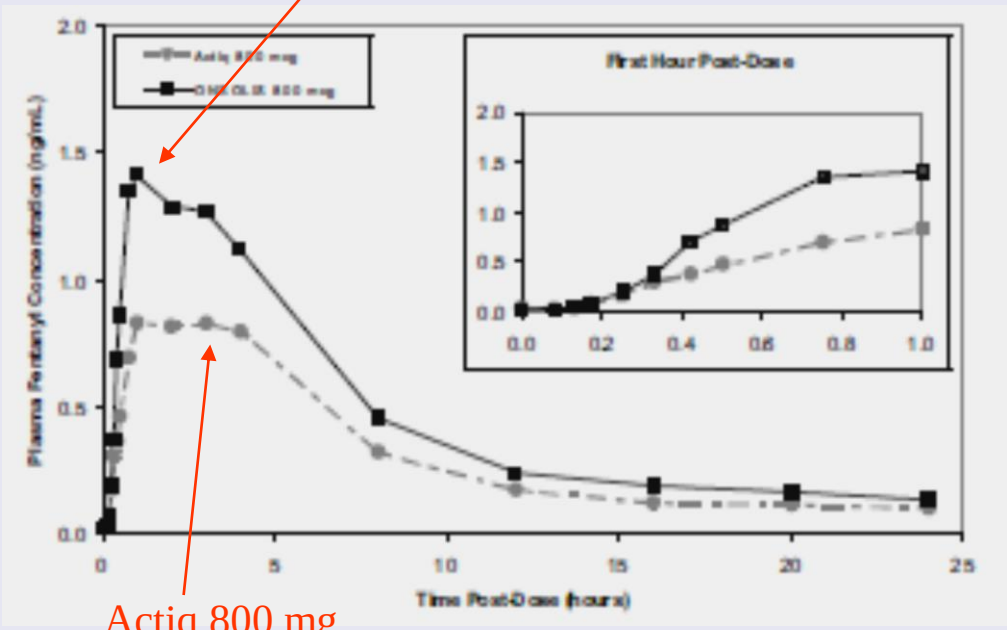
Oral Transmucosal System (OTS) (sucker)



Onsolis^{R} buccal film (erodeable)

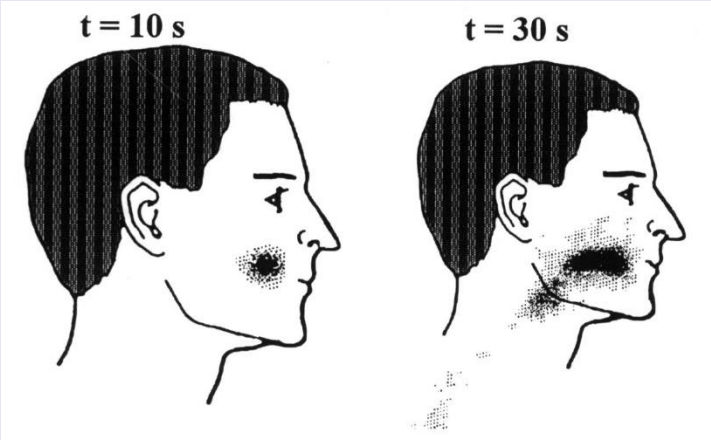






Dispersable tablets

FDDF = Fast Dissolving Drug Formulation
FDDT = Fast Dissolving Disintegrating Tablet



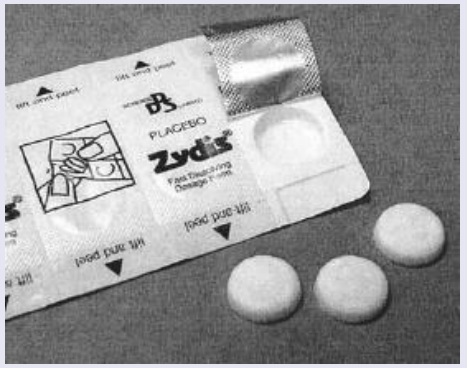
- *comfortable application*
- *without water*

10 mg technecium

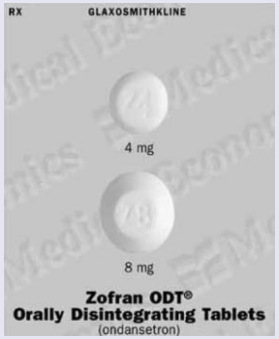
FDDF
(Fast Dissolving Delivery Formulation)

Excipients:

- polymer (dextrin, alginat, xanthan gum etc.)
- sugar alcohols (sorbitol, mannitol etc.)
- surfactant
- buffer (eg. citrate)
- taste masking



Preparation	API	Company	
Imodium lingual	Loperamid	Janssen,	1993
Feldene melt	Piroxicam	Pfizer,	1992
Zofran ODT	Ondansetron	Glaxo,	1999
Claritin Reditab	Loratadin	Schering Plough,	1997
Motilium	Domperidon,	Janssen,	1999
Zyprexa Zydis	Olanzapin	Eli Lilly,	2000



FDDT

Methods:

1. **Compression:**
   - **Micronized API**
   - **Solid dispersion**

2. **Pastille preparation (from wet mass)**
3. **Freez drying (Zydis technology):**
   - **aqueous solution or suspension of API**
   - **filling the formed blisters**
   - **freez drying**
   - **closing the blisters**

Zydis technology

Some patents

Patent	Method	Company	API
Zydis Quicksolv Lyoc	Cryo dehydration	R. P. Scherer, Inc. Germany Janssen Pharmaceutical Inc. USA Farmaloc, France	Olanzapine Cisaprid monohydrate Fluoroglucynol hydrate
Flashtab Orasolv Durasolv Wowtab Ziplets	Direct compression	Ethypharm, France Cima Labs, INC. USA Cima Labs, INC. USA Yamanouchi Pharma Tech. INC. Eurand International, Italy	Ibuprofen Paracetamol Zolmitriptane Famotidine Ibuprofen
Advatab	Microcapsuls and diffuscap CR	Eurand International, Italy	Cetryzine chloride
Flashdose	„Cotton candy" techn.	Fuisz Technology, Ltd, USA	Tramadol chloride
Oraquick	Micromasc taste masking	KV Pharm. Co. Inc., USA	Hioscyamine sulphate

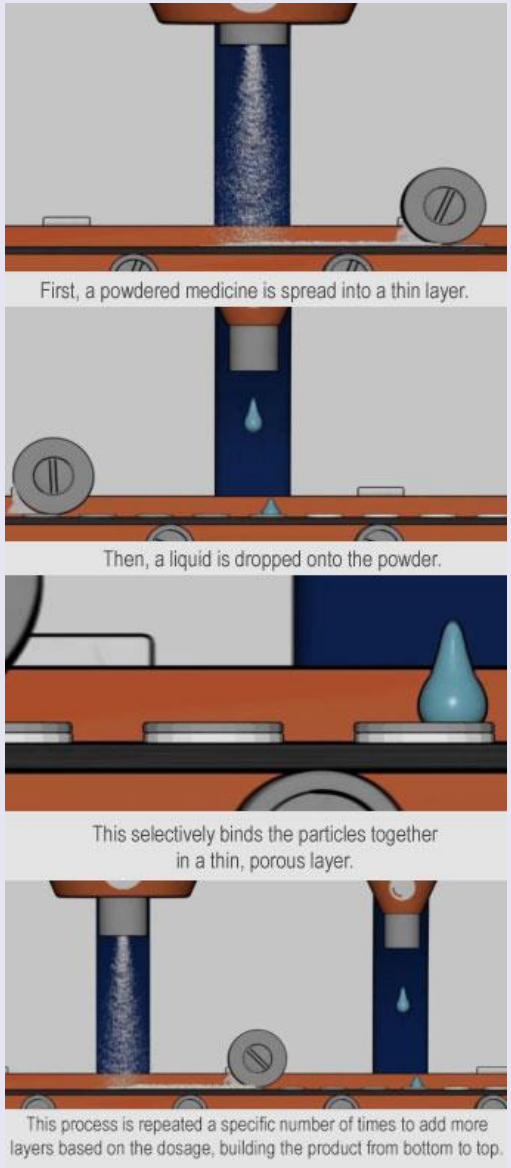
Important: high porosity, superdezintegrants, water soluble excipients

Jesmeen T., Uddin R.: Orodispersible Tablets: A Short Review. S. J. Pharm. Sci. 2011, 4, 96-99

Co-processed excipients

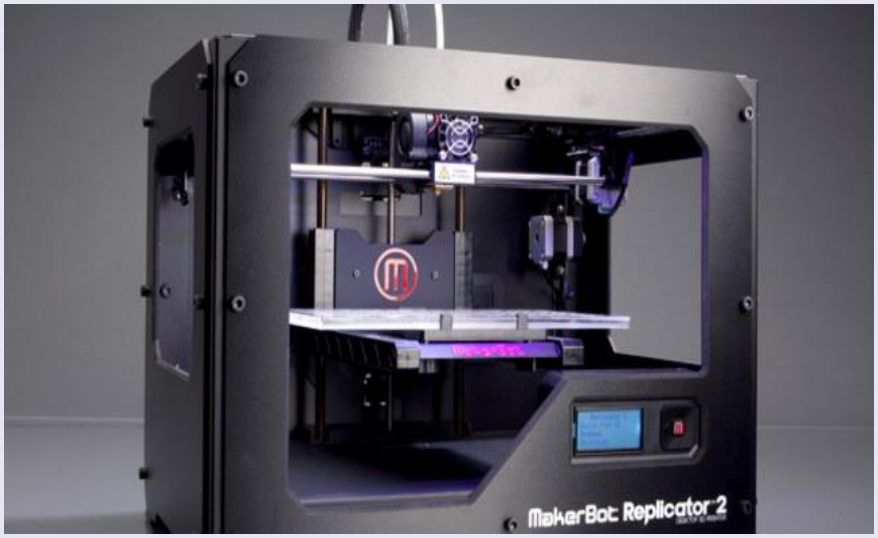
Brand name	Excipients	Company	Adventages
Ludipress	Laktose, 3,2% Kollidon 30, Kollidon CL	BASF AG	Small hygroscopicity. Good flowability.
Cellactose	Laktose, 25% cellulose	Meggle GmbH	Good compressibility, savouriness.
Prosolv	MCC, silica dioxid	Penwest	Good flowability, hardnes, and small friability.
Avicel CE-15	MCC, gum arabic	FMC corp.	Good taste masking
ForMaxx	Calcium carbonate, sorbitol	Merck	Homodispersity
Microcelac	MCC, laktose	Meggle	Suitable at high dosis too
Pharmatose DCL 40	95% β-laktose, 5% laktitol	DMV Veghel	Good compressibility
StarLac	85% α–laktose, 15% maize starch	Roquette	Good flowability

ZipDose technology



3D printed tablets

Spritam tabl.

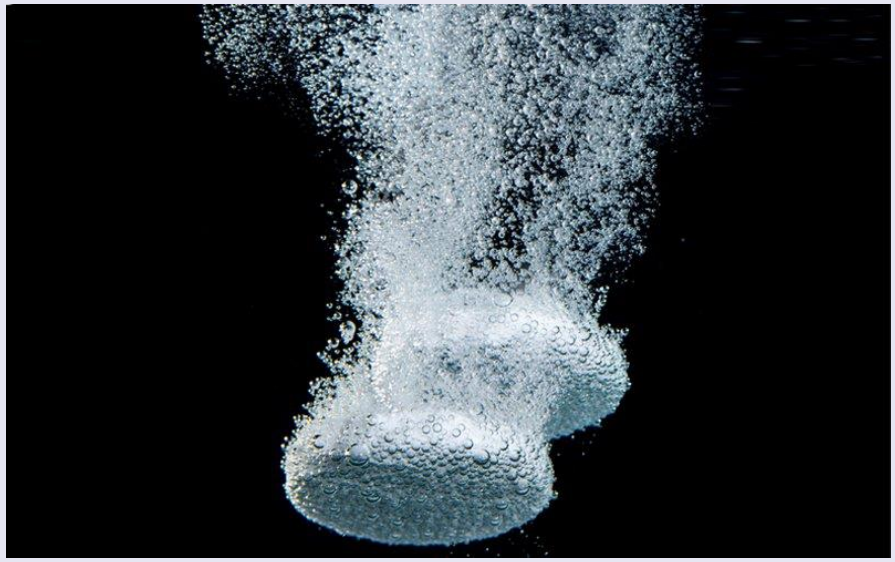


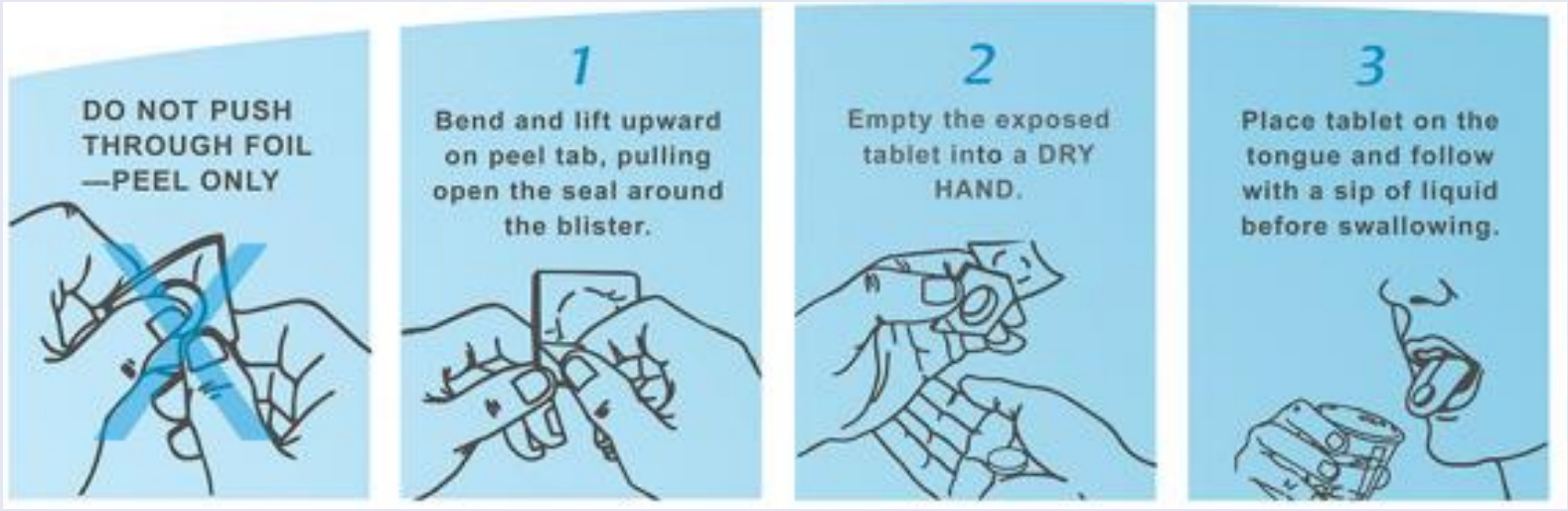
Printer

APRECIA Pharmaceuticals Company

ZipDose technology

- Unit dose
- High porosity
- Quick disintegration





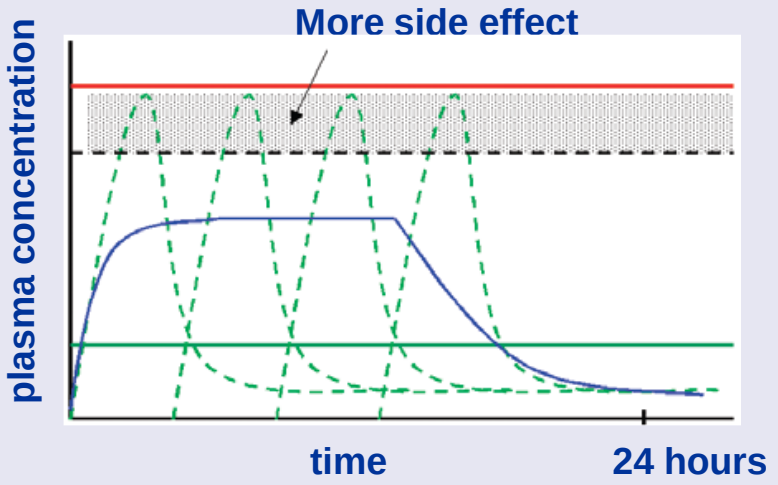
Excipents of Spritam tablet

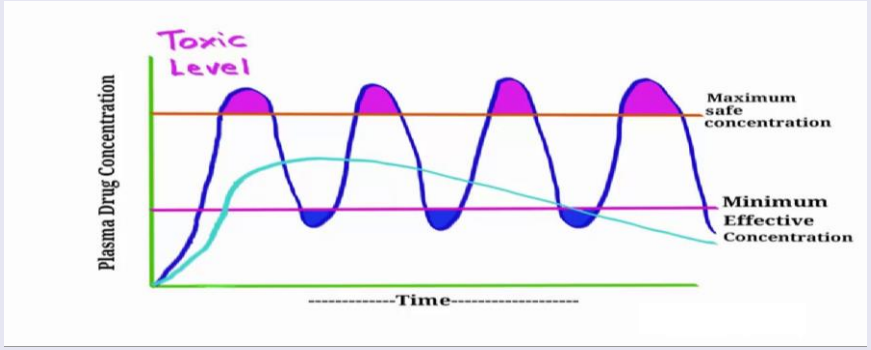
- colloidal silicon dioxide,
- glycerin, mannitol, microcrystalline cellulose, polysorbate 20, povidone,
- sucralose, butylated hydroxyanisole, and natural and artificial spearmint
- flavor.

Modified drug release

Advantages

- less medication,
- longer action,
- less side effect,
- steady plasma concentration,
- better complience.





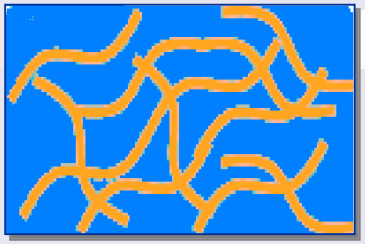
Modified drug release:

- sustained release
- delayed release
- pulsatile release
- (immediate release)

Methods:

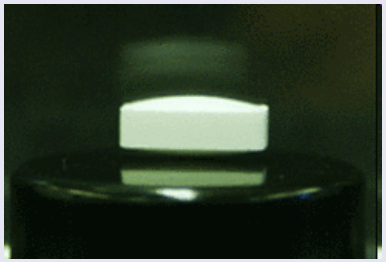
- monolitic matrix
- filmcoating
- Oral Osmotic System
- bi- or multilayer tablets

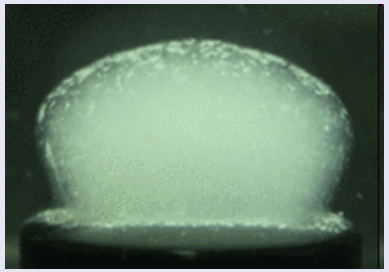
Monolithic systems



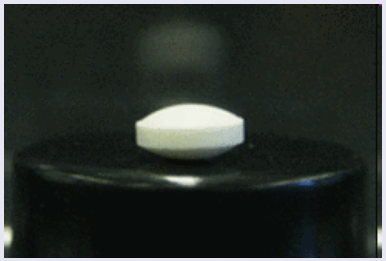
Drug release has happen by diffusion or by erosion.

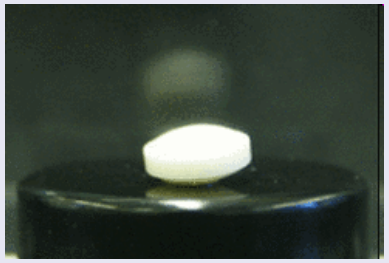
Swellable matrix



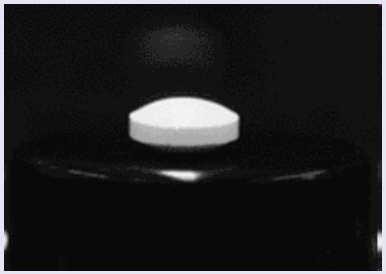


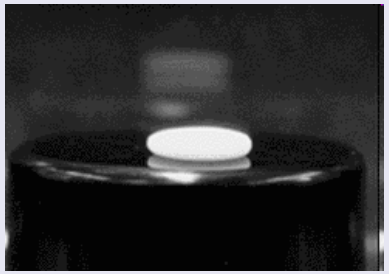
Non swellable matrix





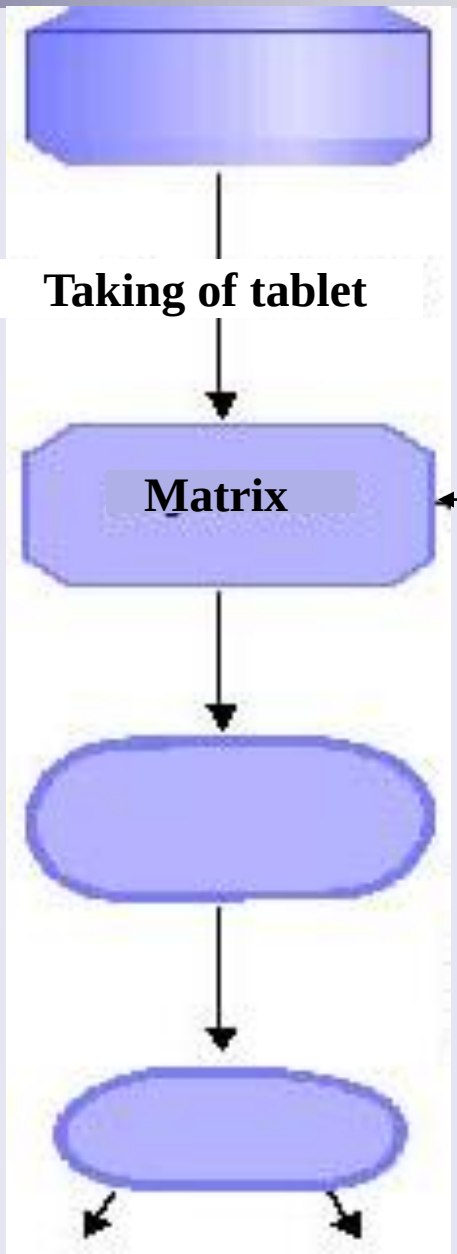
Erodeable matrix

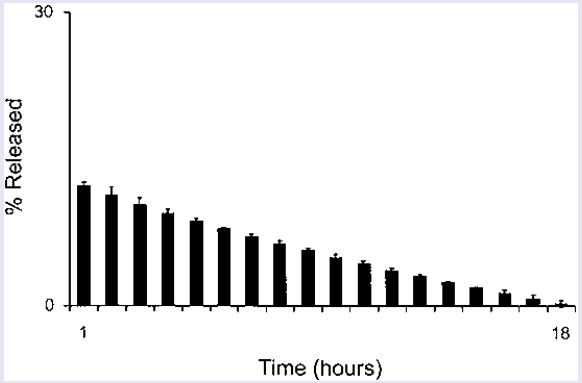




http://www.acino-pharma.com/html/index.php?id=4&L=1

Erodeable matrix





1. **Wetting**
- wetting of the surface
- hydratation of polymer
- gel barrier
- dissolution from the outer layer

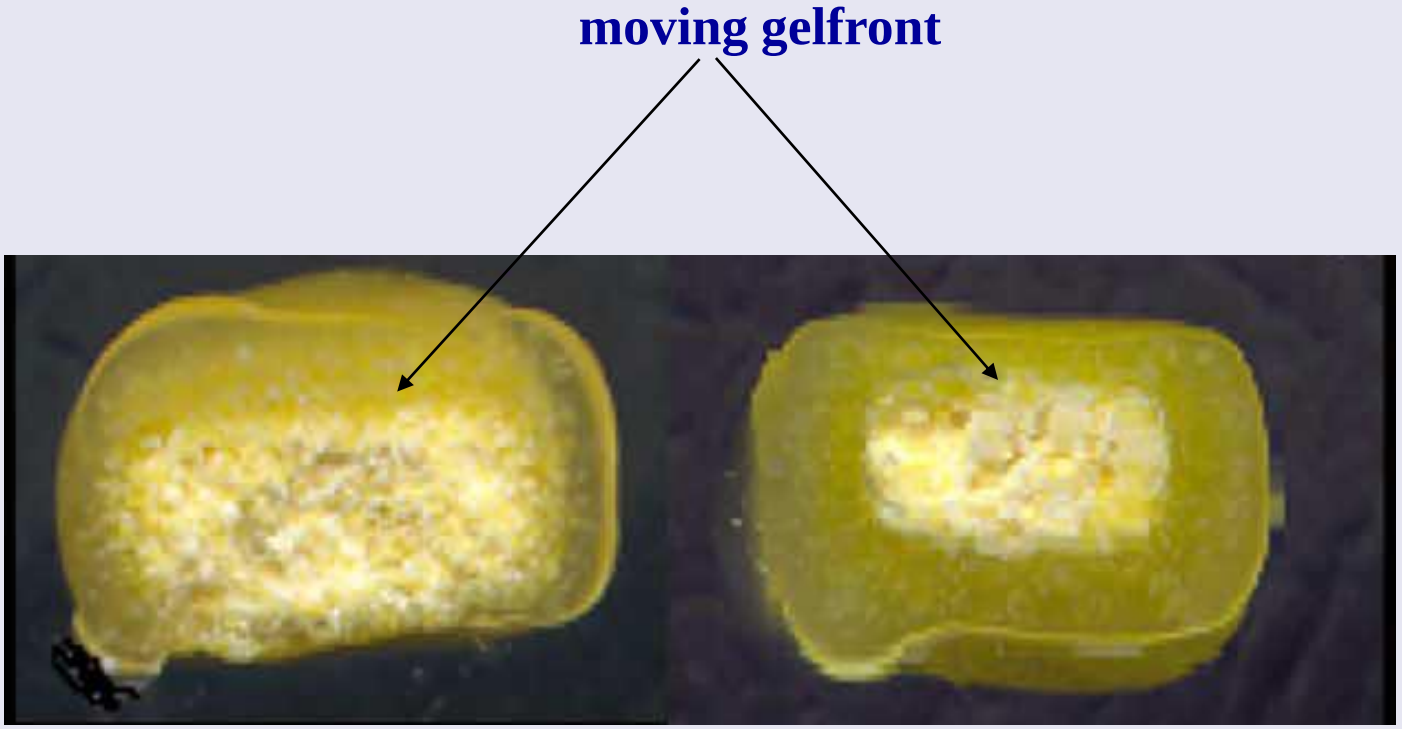
2. **Expansion of gel layer.**
- water penetration into tablet
- inreasing of thickness of gel layer
- liberation of API through the gel layer by diffusion

3. **Erosion**
- total hydratation of outer layer
- its resolvation in gastric juice
- water penetration into core

Water soluble API:dissolution by diffusion

Insoluble API: dissolusion by erosion

Swellable matrix

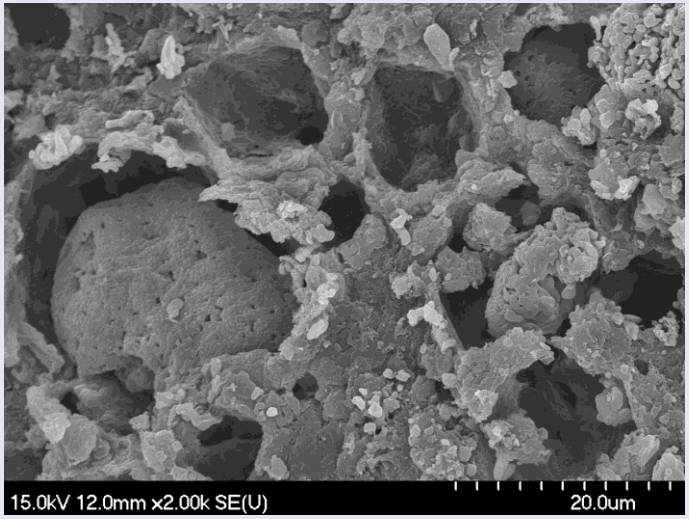


API: tetracyclin chloride
Polymer: HPMC

Shahla Jamzad et al.: Int. J. Pharm. 292 (2005) 75–85

Non swellable matrix

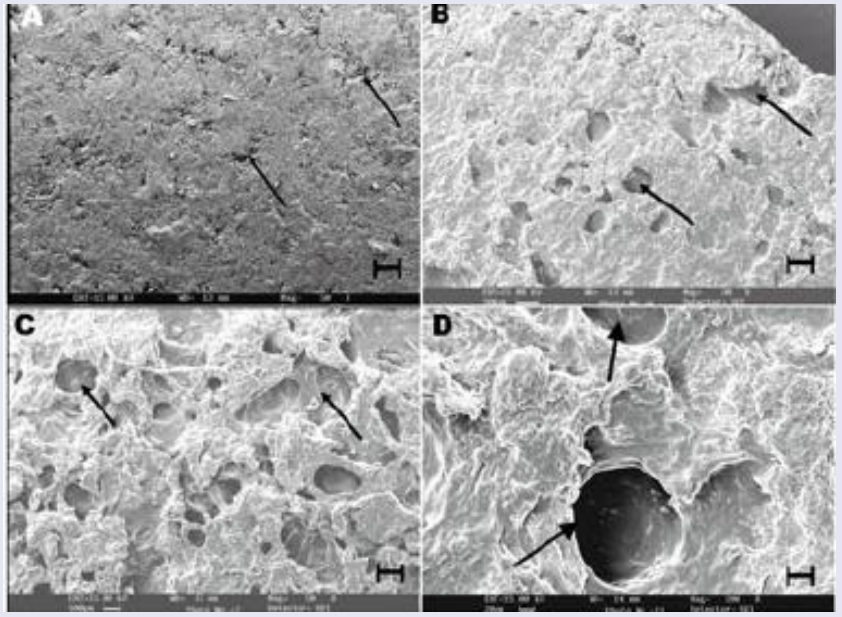
digestible



Elnazeer I. Hamedelniel: Development and characterization of matrix pellets prepared by extrusion and spheronization of Atenolol
PhD Thesis, Szeged, 2011.

non digestible

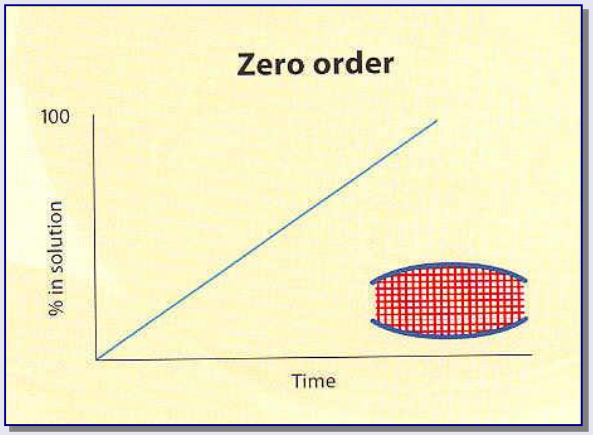
Surface of tablet (SEM, 5000x)

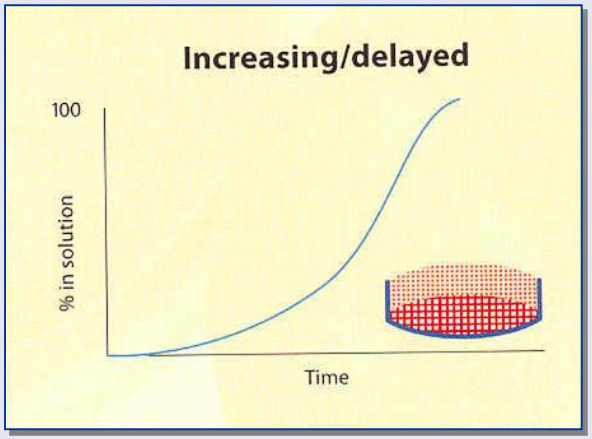


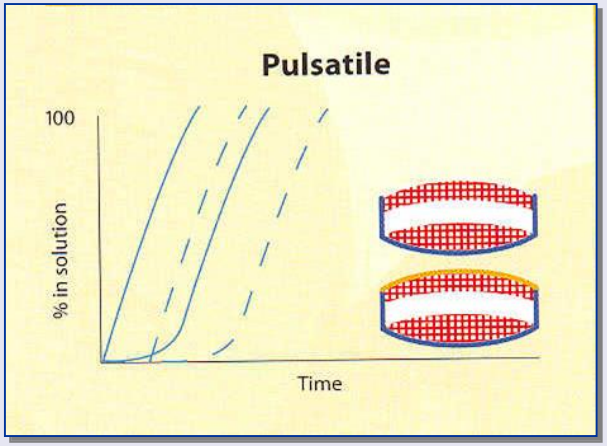
A: before dissolution
B: after 2 hours of dissolution
C: after 5 hours of dissolution
D: after 10 hours of dissolution

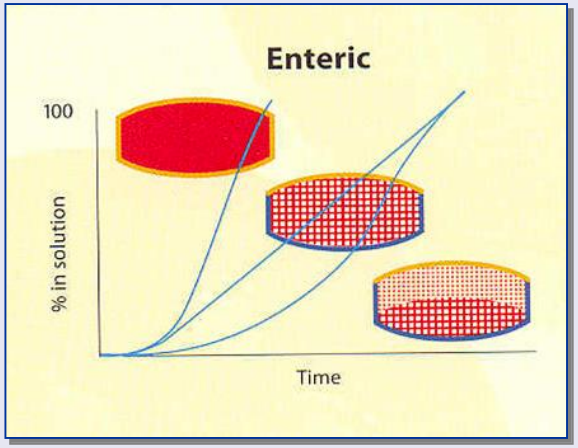
Film coating

Combination of film coating and matrix systems









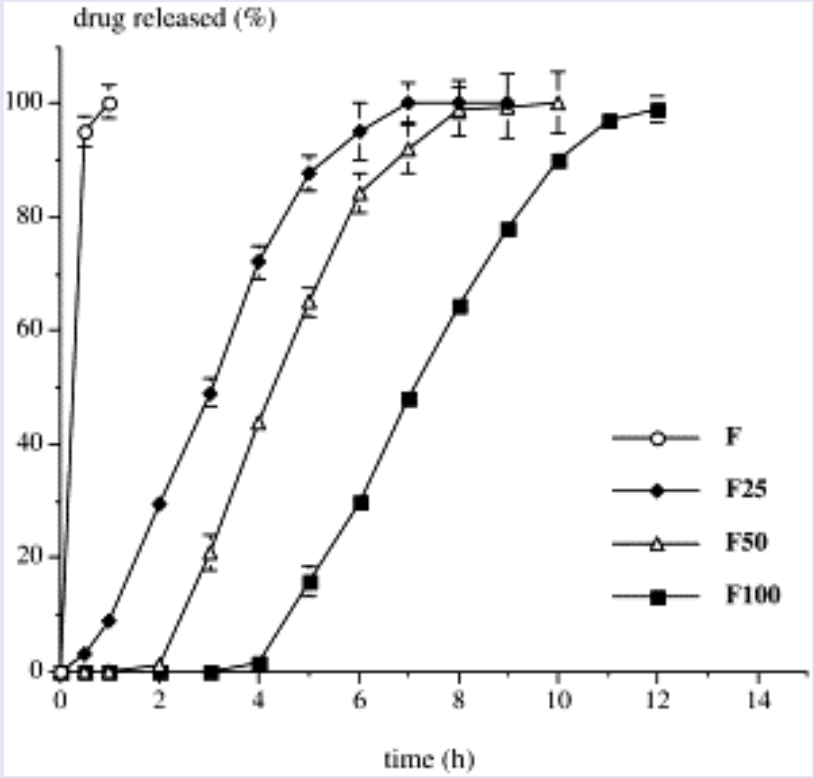
Delayed release

1. Drug release is started later (lag time).
2. Gastric resistent (intestinosolvent) preparations

Reasons:

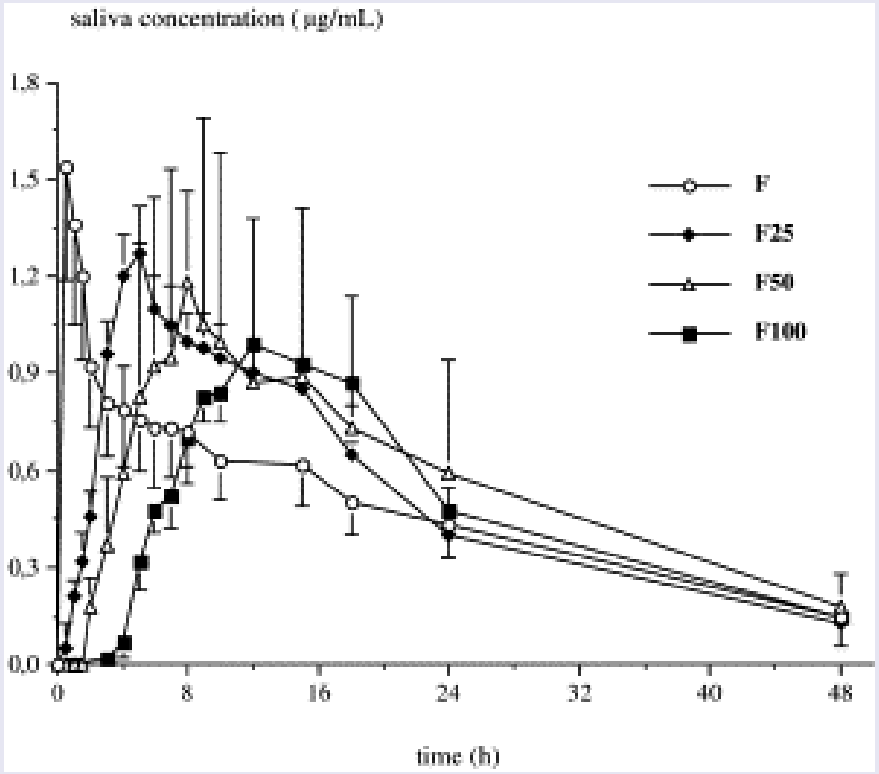
- Prevention of API against acidic milieu
- Prevention of mucous membrane against API
- Local therapy in GI system

Delayed release



In vitro

Film coating



In vivo

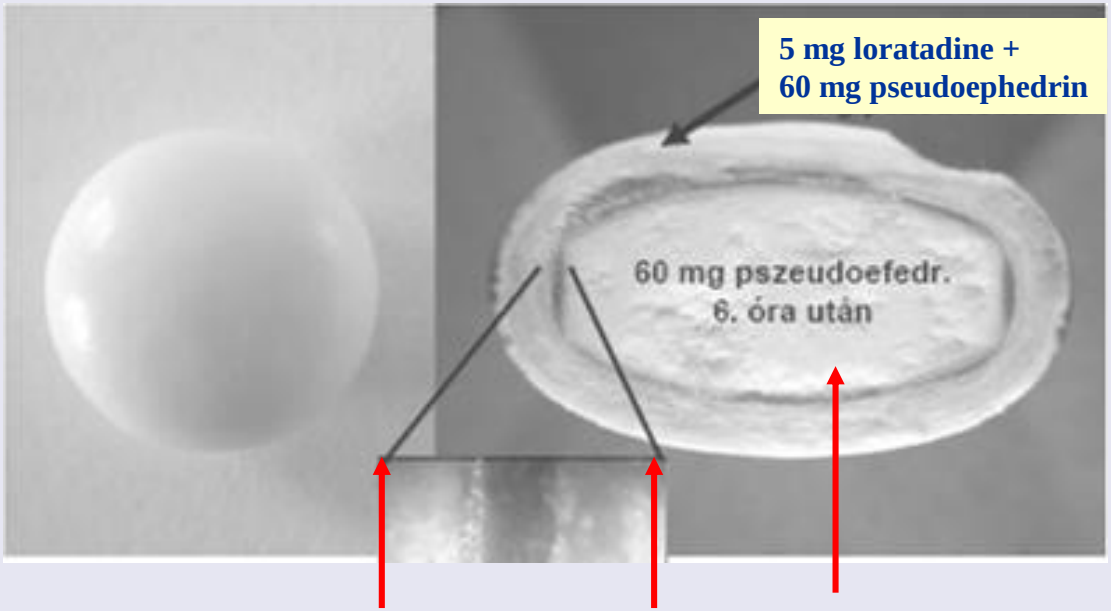
Tablet:

API: antipyrine

Coating: HPMC

Delayed release preparations

Multilayer coated tablets



coat

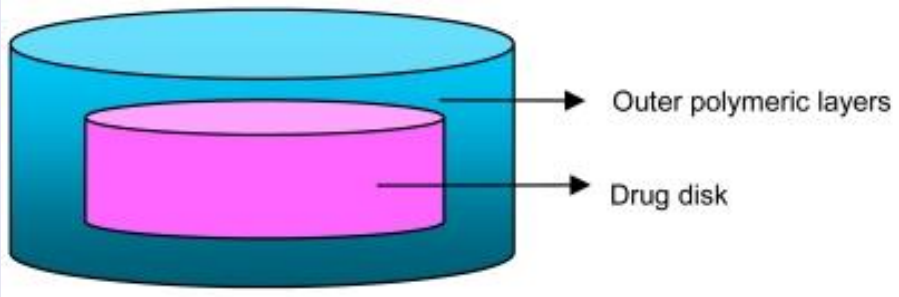
polymer coating

core

Coated tablets

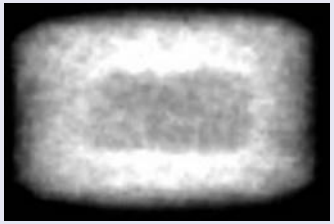
(Caped tablets)

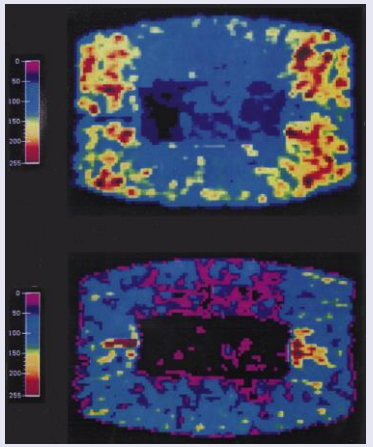
Geolock technology

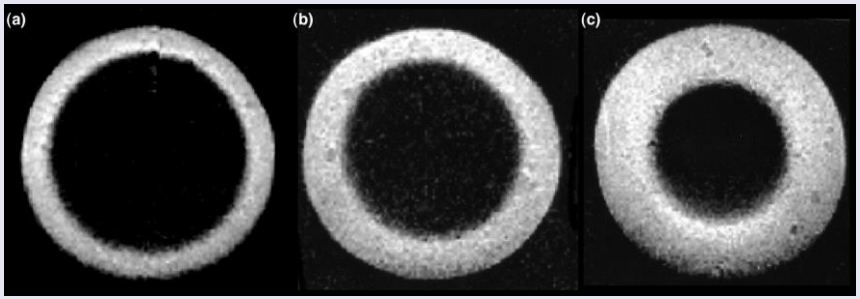


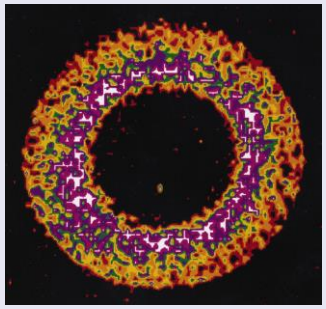
MRI

Cross section









Viewed from above

Colin D. Melia, Ali R. Rajabi-Siahboomi and Richard W. Bowtell: Magnetic resonance imaging of controlled release pharmaceutical dosage forms. PSTT Vol. 1, No. 1 April 1998, 32-39

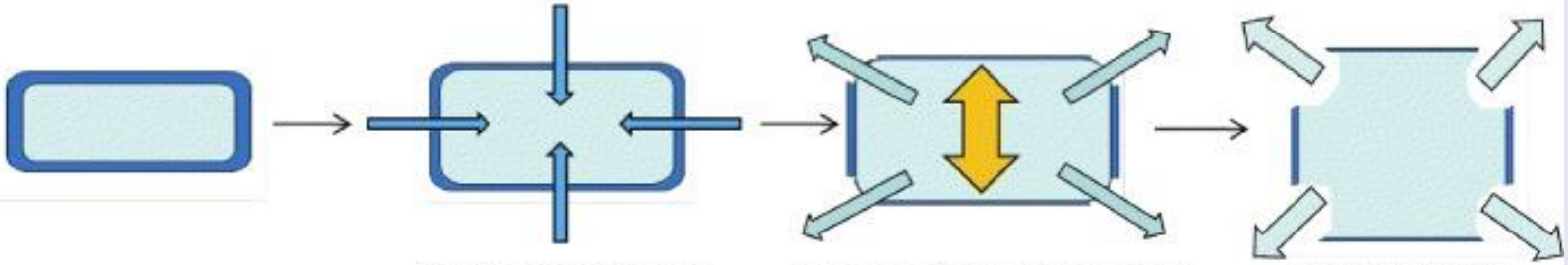
Uncoated Matrix Tablet:

Swelling of matrix; drug release

Further swelling of matrix; (axial and radial direction)

Erosion of matrix

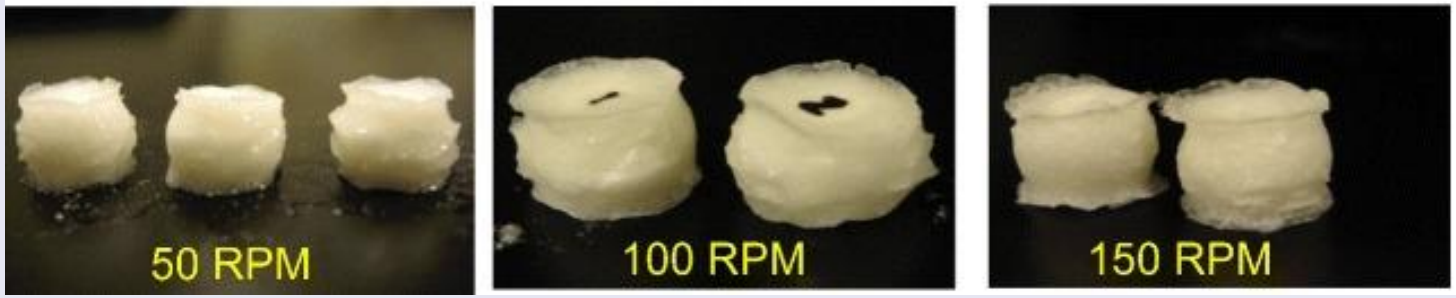
Ethylcellulose Coated Matrix Tablet:



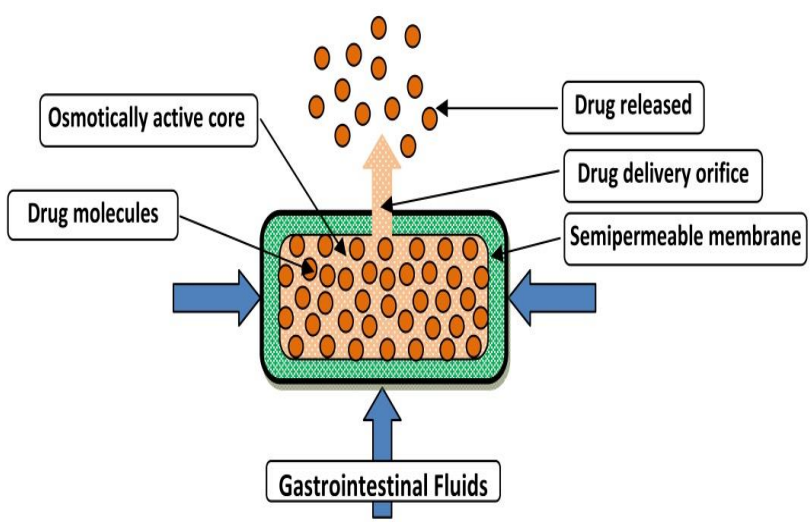
Swelling of matrix due to water permeation

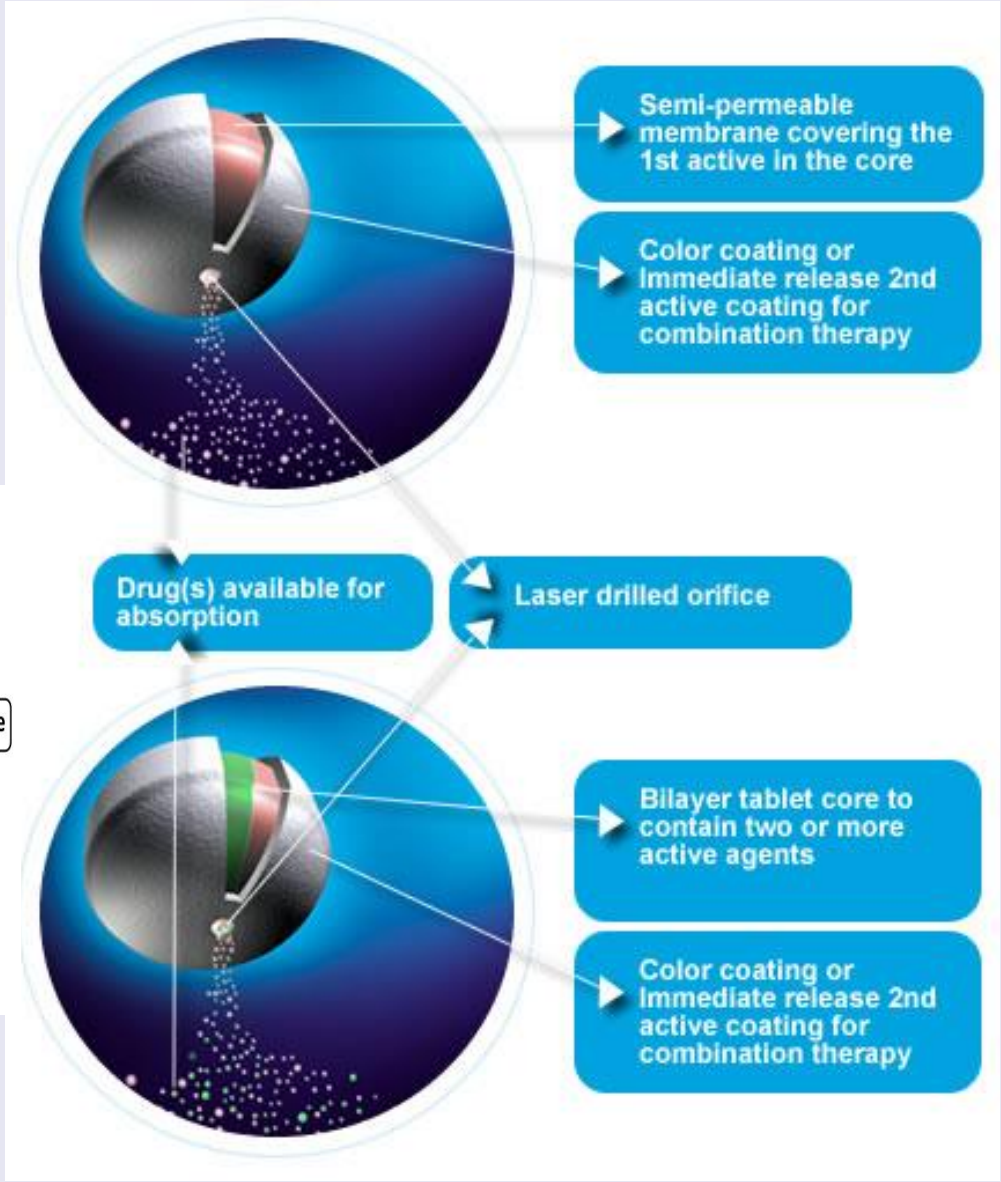
Rupture of barrier membrane; release of drug from tablet edges

Erosion of matrix



OROS technology





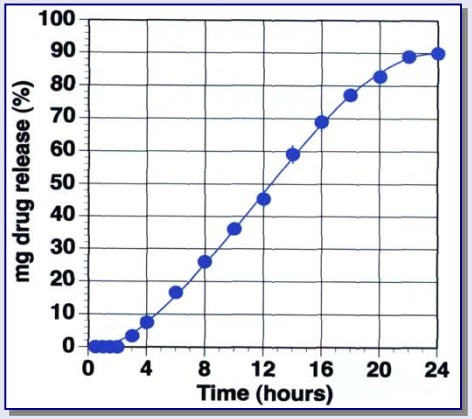
Adalat OROS tablet

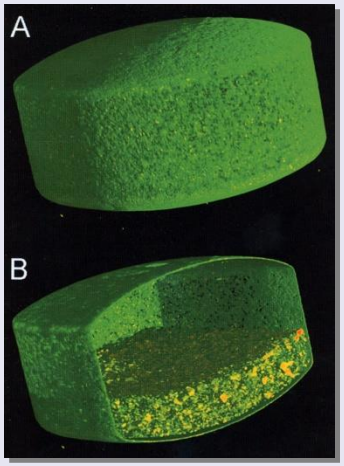
Components

API: nifedipine

Core and coating: magnesium stearate, hypromellose (5 cP), poliethylene oxide, cellulose acetate, hidroxy propyl cellulose, titan dioxide (E 171), hypromellose (3 cP), propylene glycol, red iron oxide (E 172), hypromellose (5 cP).

Colour: Opacode S-1-17823 (containing black iron oxide /E 172/).





Mikro-CT image

Cardura XL

intact tablet

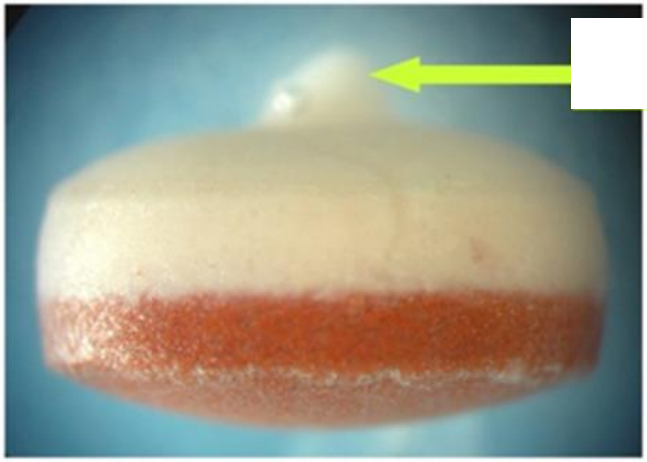
orifice

semipermeable membrane

drug store

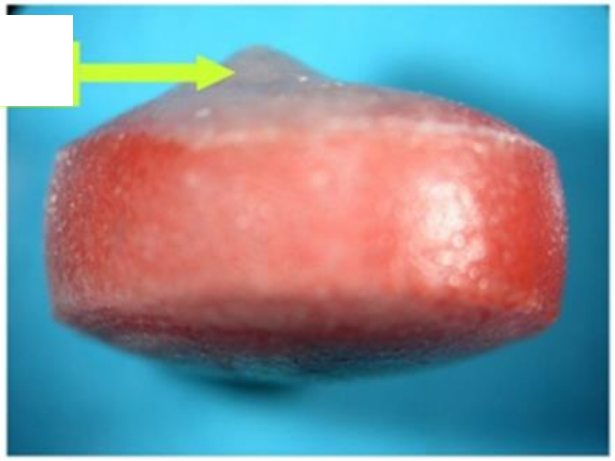
swellable hidrocolloid

cross section



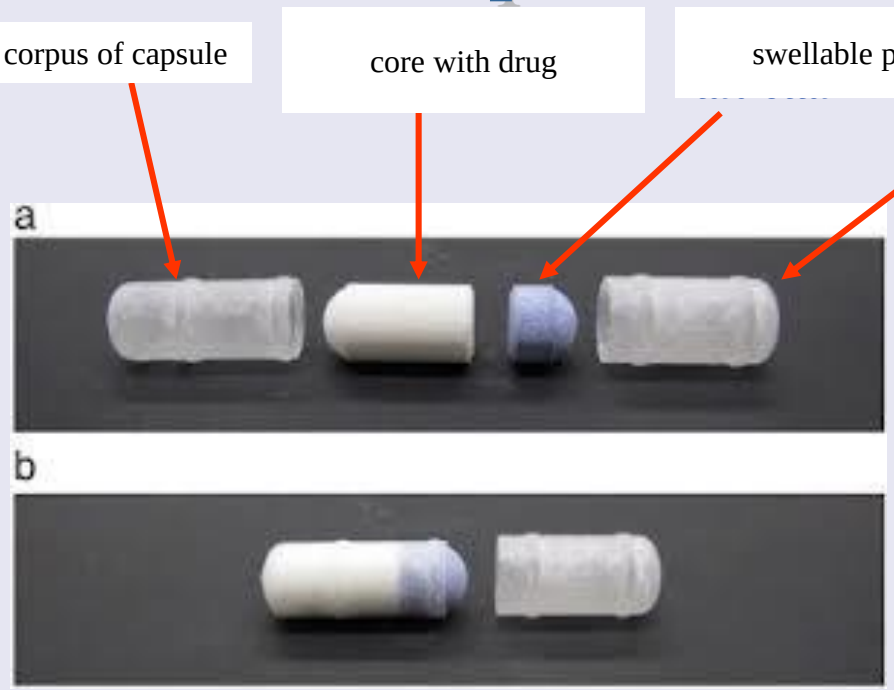
starting

drug release

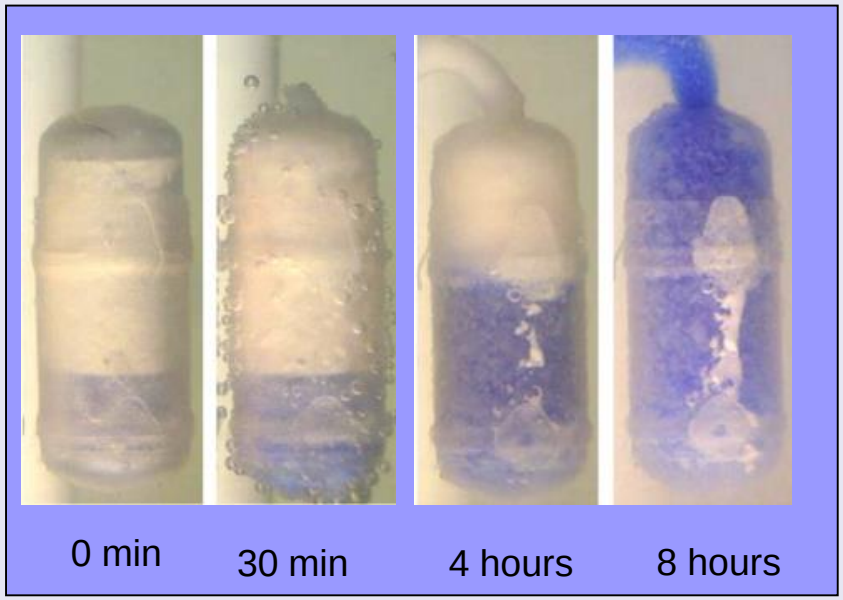


end

Osmotic capsules



Process of dissolution



Kenneth C. et al.:Osmotic capsules: An universal oral, controlled-release drug delivery dosage form. J. Controlled Release, 152, 264-269, 2011

Dissolution model of osmotic systems

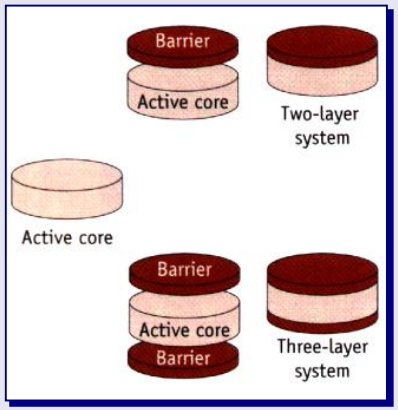
$$\frac{dm}{dt} = \frac{AK}{h(\Delta\pi - \Delta p)c}$$

$\Delta\pi$	osmotic pressure
Δp	hydrostatic pressure
A	surface of the membrane
c	concentration of API in the osmotic pump
K	constans

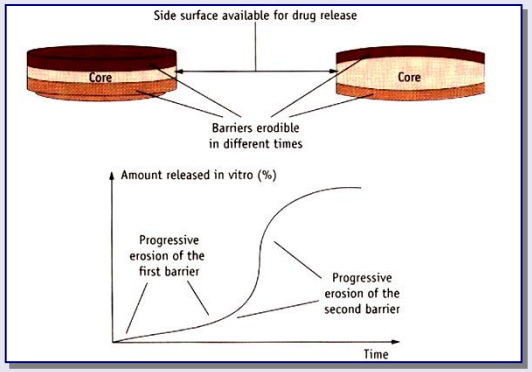
Two or multilayer tablets

- long time therapy
- combination-therapy
- different drugs (short and long life time) together
- rapid and slow release layer with the same drug
- decreasing the side effect

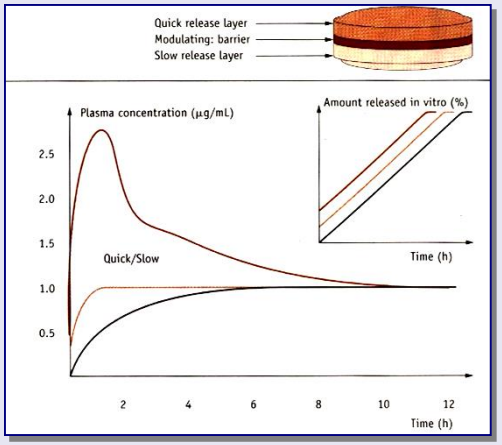
Elan Drug technology



Biomodale release tablet:
Two different erodeable barrier



rapid/slow release layer:



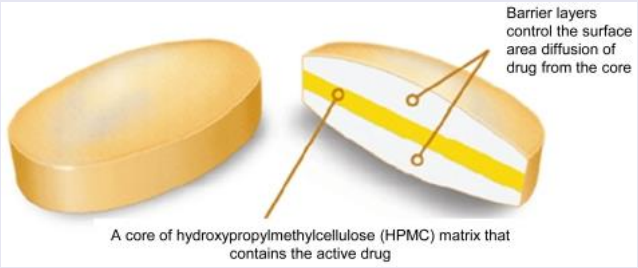
Conte, U., Maggi, L.: Multi-layer Tablets as Drug Delivery Devices, Pharm. Technol. Eur., February 1998, Vol 10, No 2, 18-25

Eg.: Multi-Tabs tabl., Coldrex tabl., Diclac retard tbl., MicardisPlus tabl., Ferrograd filmtabl., stb.

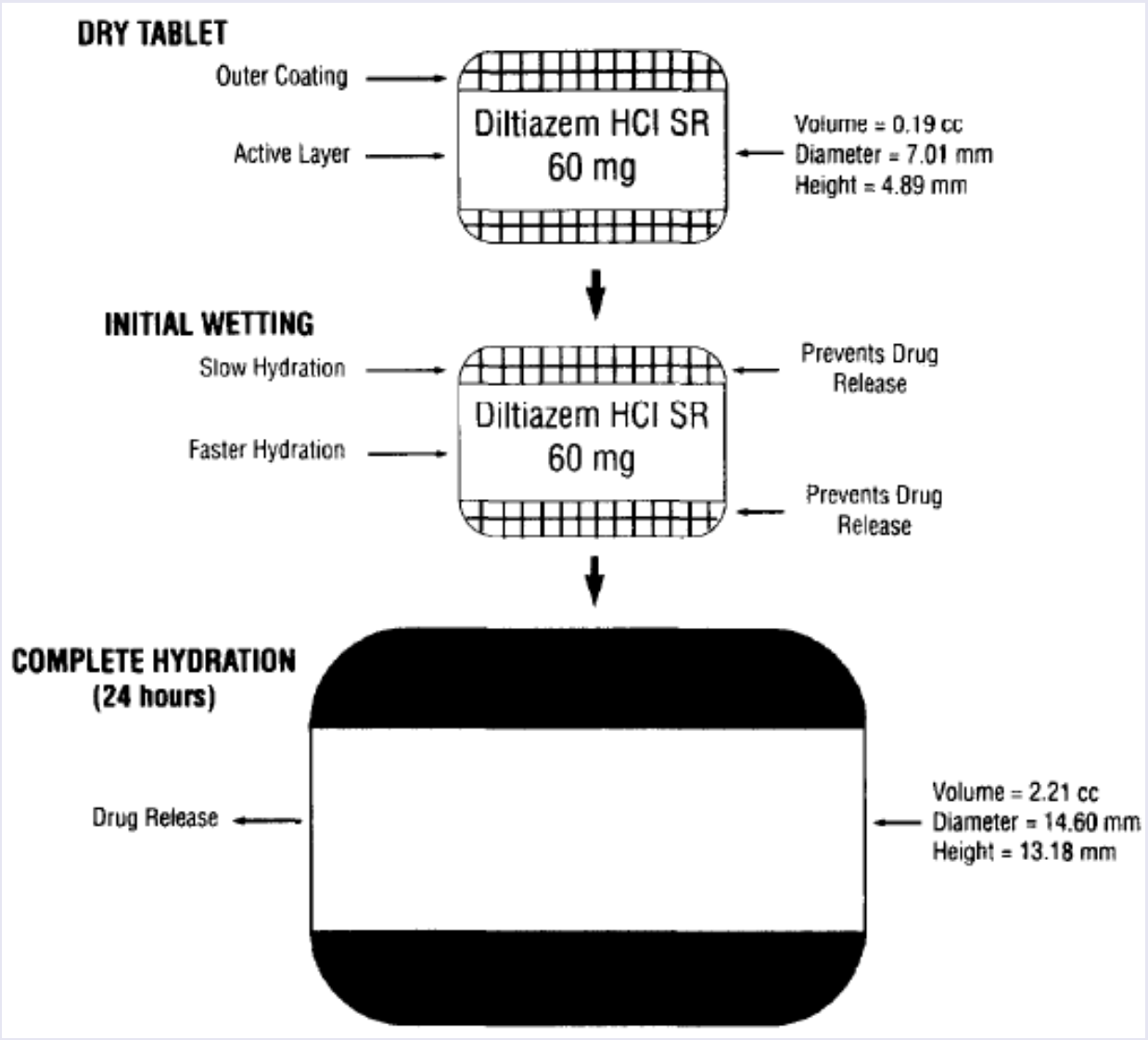
Combination:
0:120 mg (--), 30/120 mg (--) and 90/120 mg (--)

Multilayer tablets

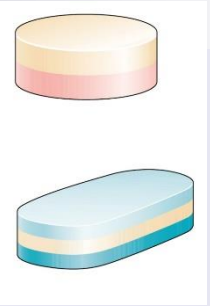
Geomatrix

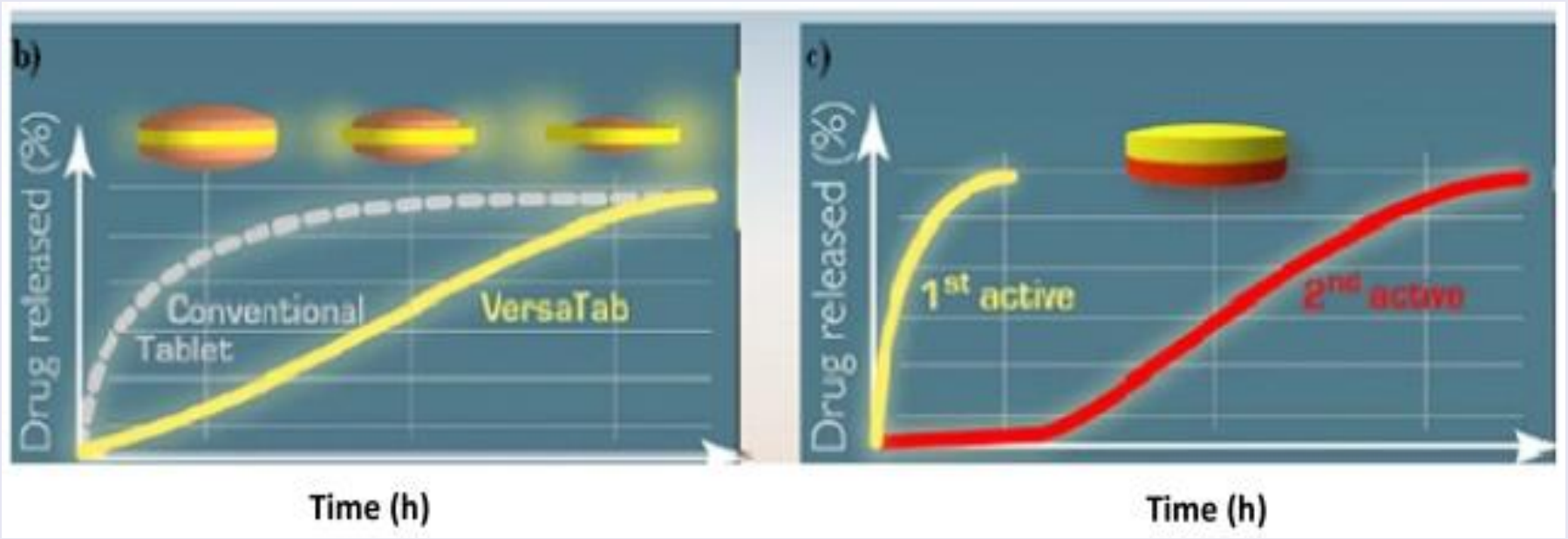


Skyepharma
Switzerland



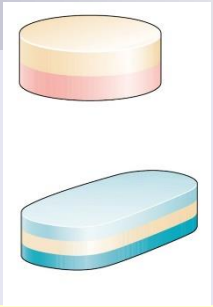
Multilayer tablet





SkyePharma

Solutions

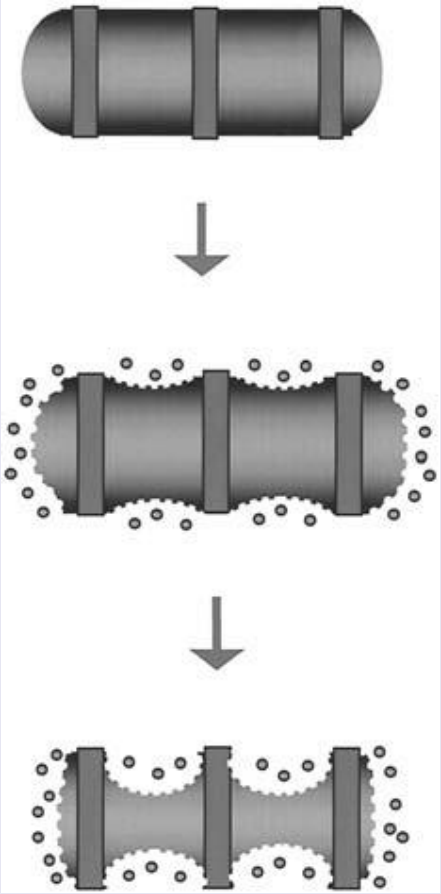


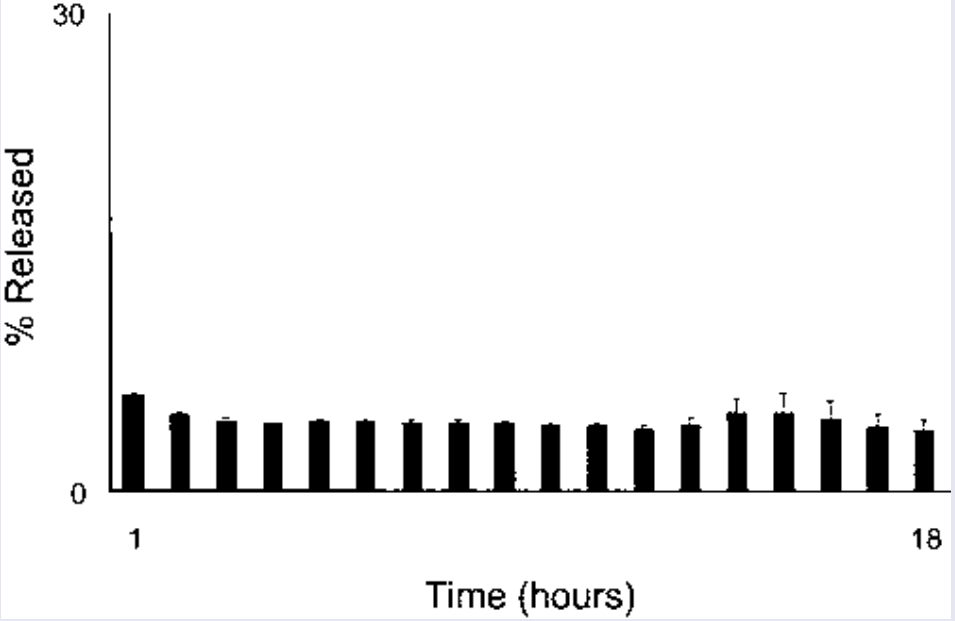
Basic polymer	Barrier	Type of tablet	Type of dissolution
Hydrophil	Hydrophil	Two layer	Sustained r.
Hydrophil	Hydrophob	Two layer	Sustained r.
Hydrophob	Hydrophil (Methocel® K4M)	Three layer	0 order k.
Hydrophob (CW)	Hydrophob (karnauba wax)	Three layer	Non-linear drug release
Hydrophob (CW)	Hydrophil (Methocel® K15M) and Hydrophob (CW)	Three layer	0 order k.
Hydrophil (HPMCAS&HPMC)	Hydrophob (EC)	Three layer	0 order k.

Ringcap

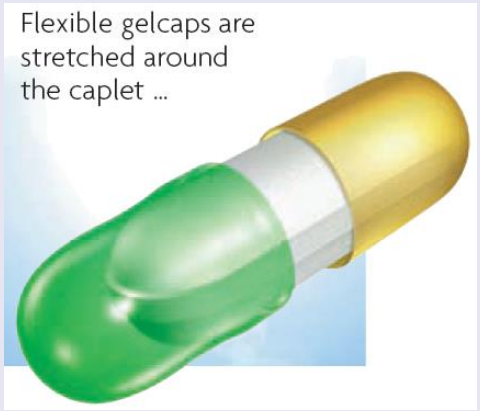
- ring-like coating
- unsoluble and non erodeable polymer
- number and thickness of rings

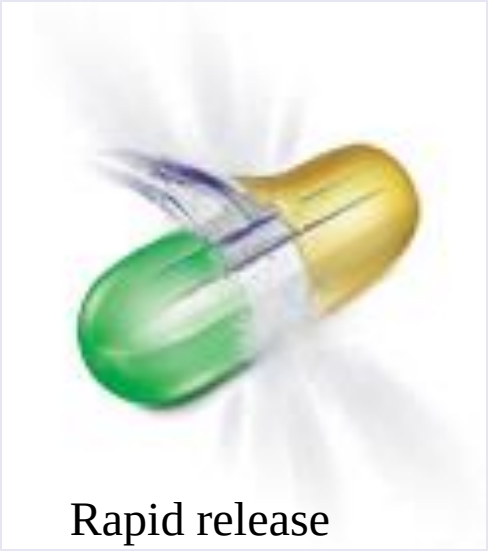
RINGCAP technology

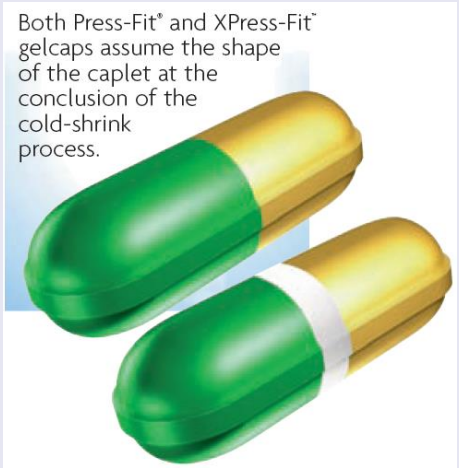




Press-Fit és XPress-Fit gelcap

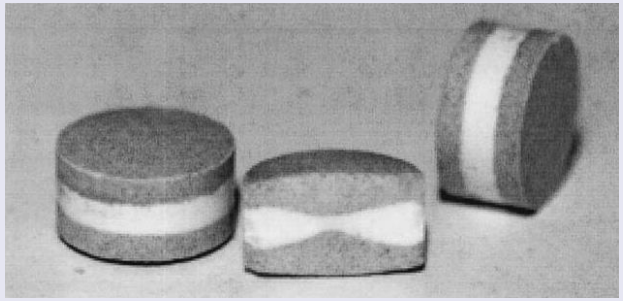


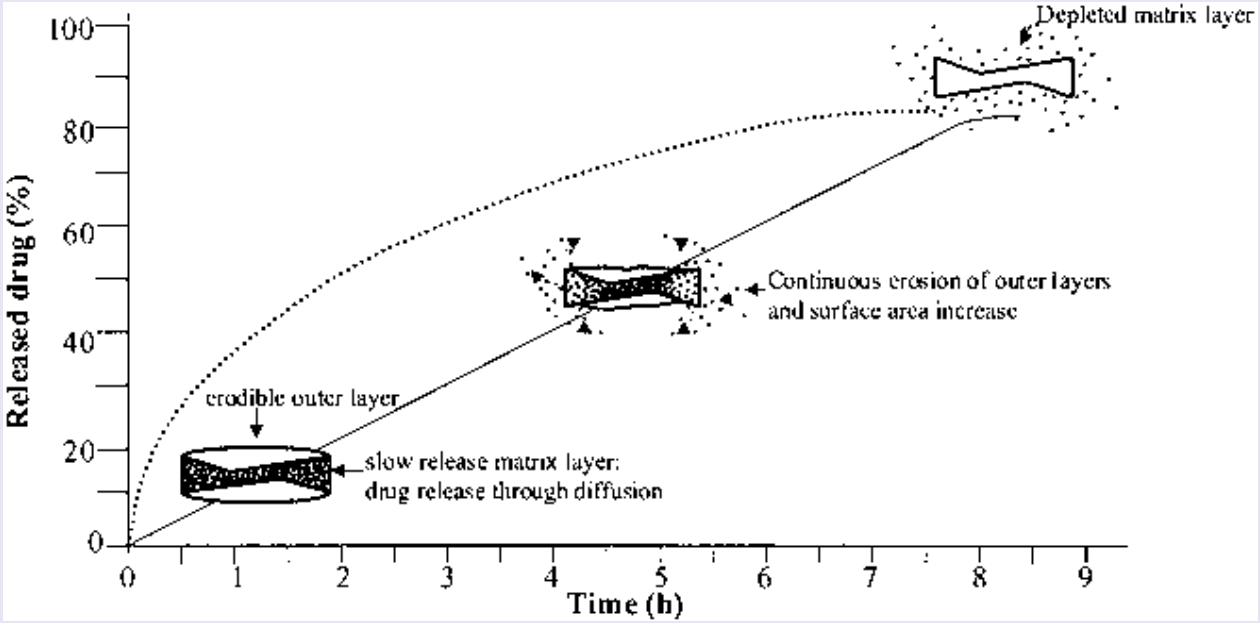

Rapid release



SMARTRIX technology

Controlling by geometry of matrix :





… and we are going on …