D2HP – OTU 05

Pharmaceutical engineering : practical works

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FOCUS ON TABLETS FOR CONTROLLED RELEASE

PLANNING

Timetable D2HP– 2024/2025

		Room	
08 nov. 2024	13h30 – 16h45	1402a	Intro + Matrix class (EBM)
14 nov. 2024	13h30 – 16h45	4208 a et 4208b	Tutorial: Preparation to Practical (EBM)
18 nov. 2024	9h30 – 12h45	4208 a et 4208b	PW Matrix group 1 (EBM)
22 nov. 2024	13h30 – 17h45	4208 a et 4208b	PW Matrix group 1 (EBM
29 nov. 2024	9h00 – 12h15	4208 a et 4208b	PW Matrix group 1 (JPM)
29 nov. 2024	13h30 – 17h45	4208 a et 4208b	PW Matrix group 2 (EBM)
03 dec. 2024	13h30 – 17h45	4208 a et 4208b	PW Matrix group 2 (EBM)
04 dec. 2024	9h30 – 12h45	4208 a et 4208b	PW Matrix group 2 (EBM)

EBM : Eloisa Berbel Manaia

JPM : Jean Philippe Michel

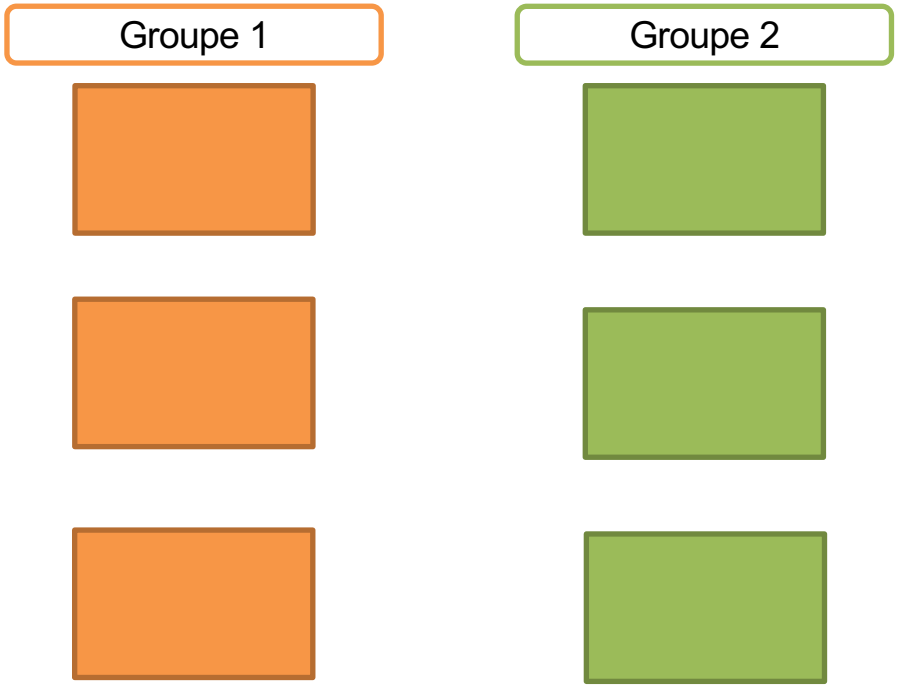
Note: Groups will be formed during the first class.

Evaluation:

- report of Practical classes
- participation at the tutorial and PW

GROUPES

1	AWAD SALMAN	Diana
2	AZEEM	Muhammad
3	Batool	Farwa
4	Bharwani	Ziyana
5	BRIKA	Eleanna
6	CHAIB	Kinda
7	EL HAJJ	Liana
8	Eze	Chinwendu
9	Habinger	Leila
10	Iusupova	Madina
11	KAZMA	Marwa
12	Khan	Insharah
13	KHANGTRAGOOL	Waristha
14	LE	Hoang Linh
15	Mourad	Reem
16	NGUYEN	Lucie
17	NOOH	Mdrmah
18	REZA Md.	Sakib
19	RODRIGUEZ LUA	Karen
20	TEOVA GONZALEZ	Veneta
21	Toshtemirov	Shuhrat
22	TULEGENOVA	Alina
23	WONG	Zhi Chin
24	ZELMANOVICH	Maya



-Respect your groupe Practical classes
- Practical classes are mandatory

AGENDA

1. Introduction
2. Matrix tablets: overview
3. Inert matrix tablets
4. Swellable matrix tablets
5. Erodible matrix tablets
6. Other excipients / some reminders on tablets
7. Controls
8. Conclusion

CONVENTIONNAL DDS*

*** DDS = Drug Delivery Systems**

Oral route
(ex: solutions, tablets, capsules)

- Easy to use
- Good compliance
- Exposure to digestive fluids
- Low absorption of some API (Mw, low water solubility))

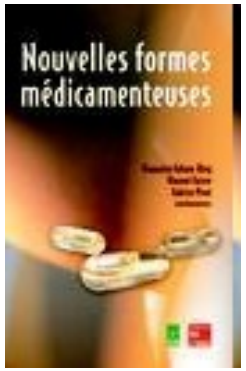
Parenteral
(ex: solution for IV injection)

- Rapid action
- No absorption step
- Lower compliance
- Rapid clearance

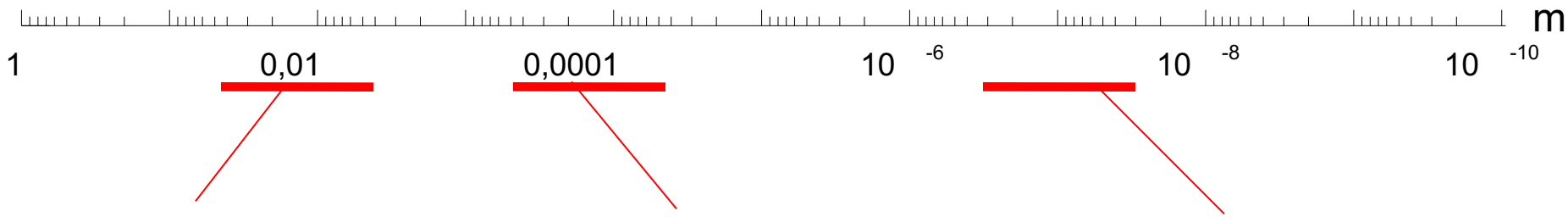
Absorption and distribution depend essentially on the API physico-chemical properties.

NOVEL DDS

The DDS (shape, size, excipients…) controls API release and/or distribution into body



1985……2004



Monolithic DDS

- **Matrix tablets**
- Reservoirs
- Inserts, implants
- Adhesive systems

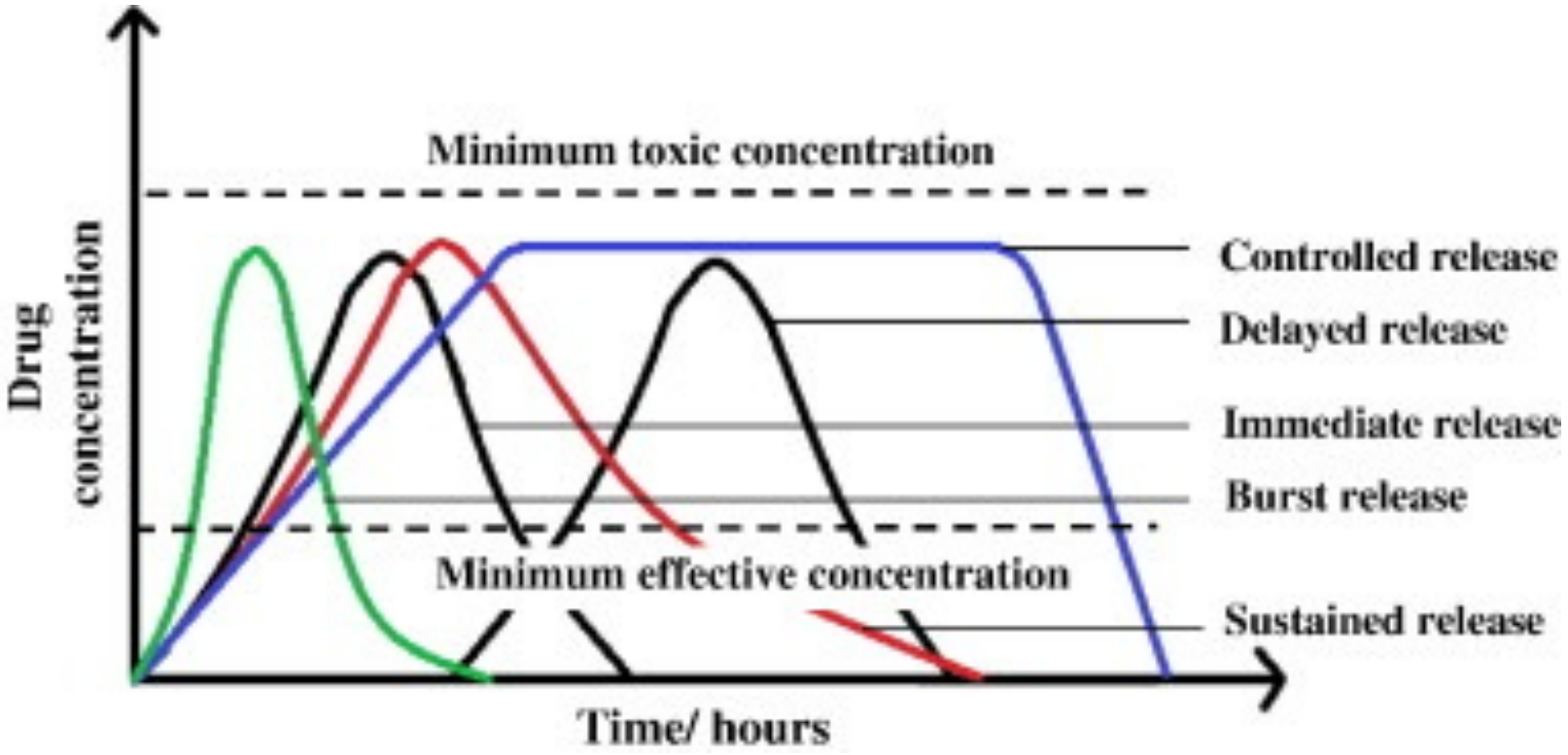
Divided DDS

- Microparticles ("simples", bioadhesives, implantables)

Colloïdal drug carriers

- Nanoparticles
- Liposomes

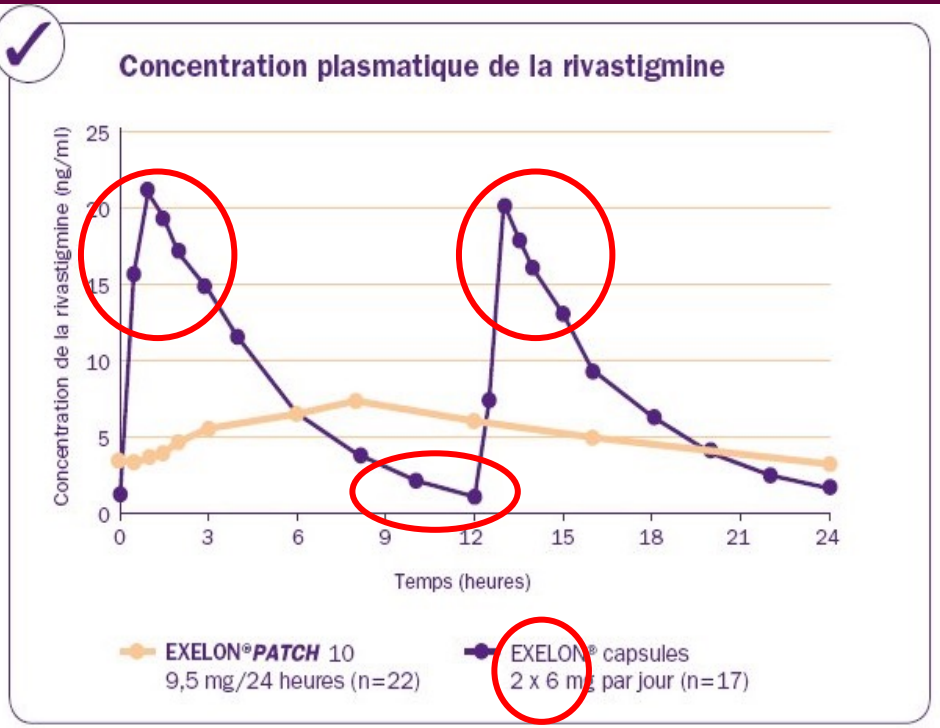
MODIFIED RELEASE DDS



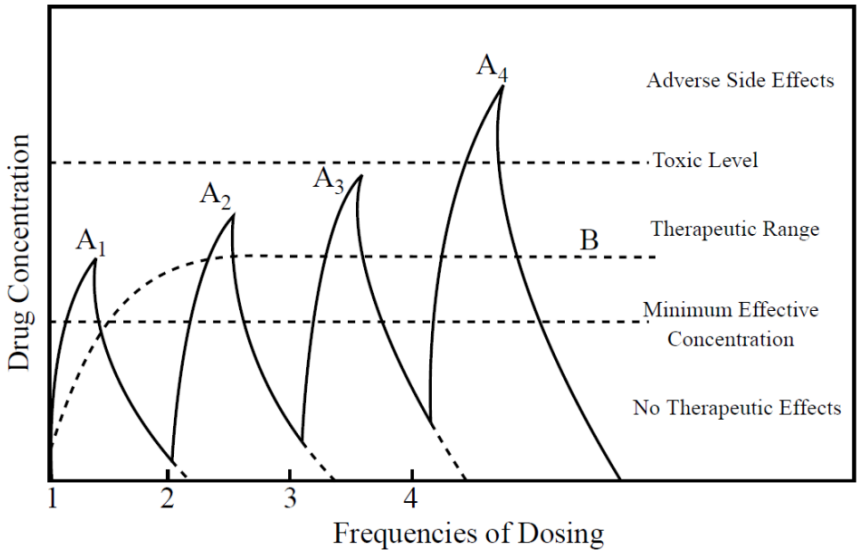
In Eur. Ph. « modified release » because of modification of…

- **release rate**
- **release site**
- **release moment**

MODIFIED RELEASE DDS



D'après Cummings et al.[4]



Therapy for Alzheimer's disease

A lot of commercial products

LP,
Chrono,
CR,
Retard,
…

MODIFIED RELEASE DDS

Advantages

- Compliance
- Lower amount of API delivered per unit of time
- Reduction in the incidence and severity of both local and systemic side effects
- Reduced blood level oscillation (night)
- Economy

…

Limitations

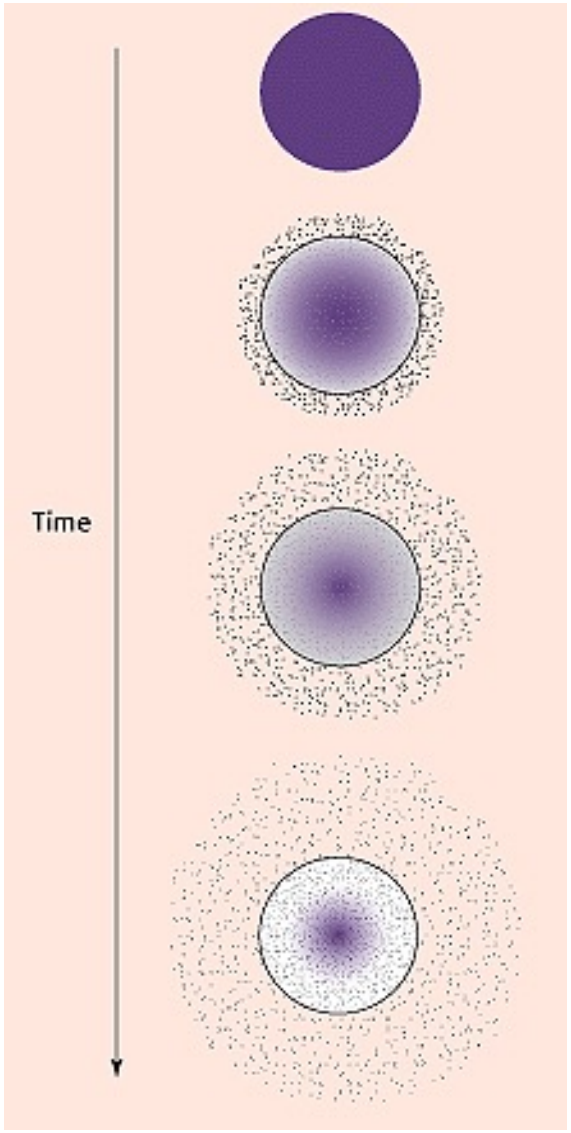
- Accumulation (in case of slow elimination)
- Overdosage (default, bad use)
- Problem in case of intolerance or « poisoning »
- Size of the dosage form
- Complex formulation development

…

TWO DESIGNS

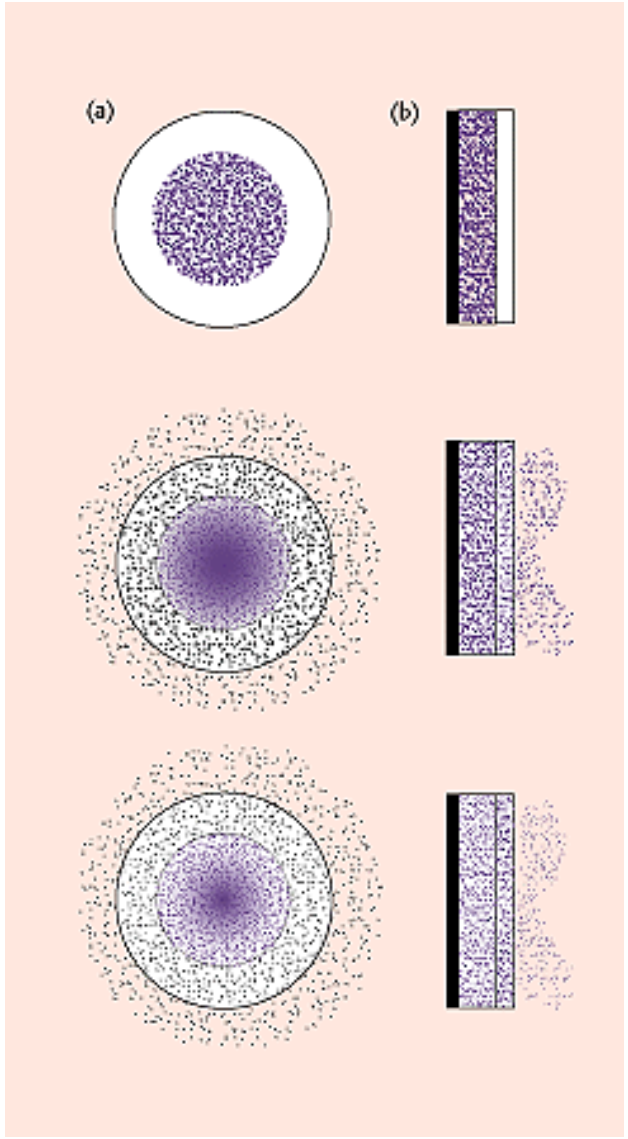
In case of tablets:
obtained by compression

Matrix



Reservoir

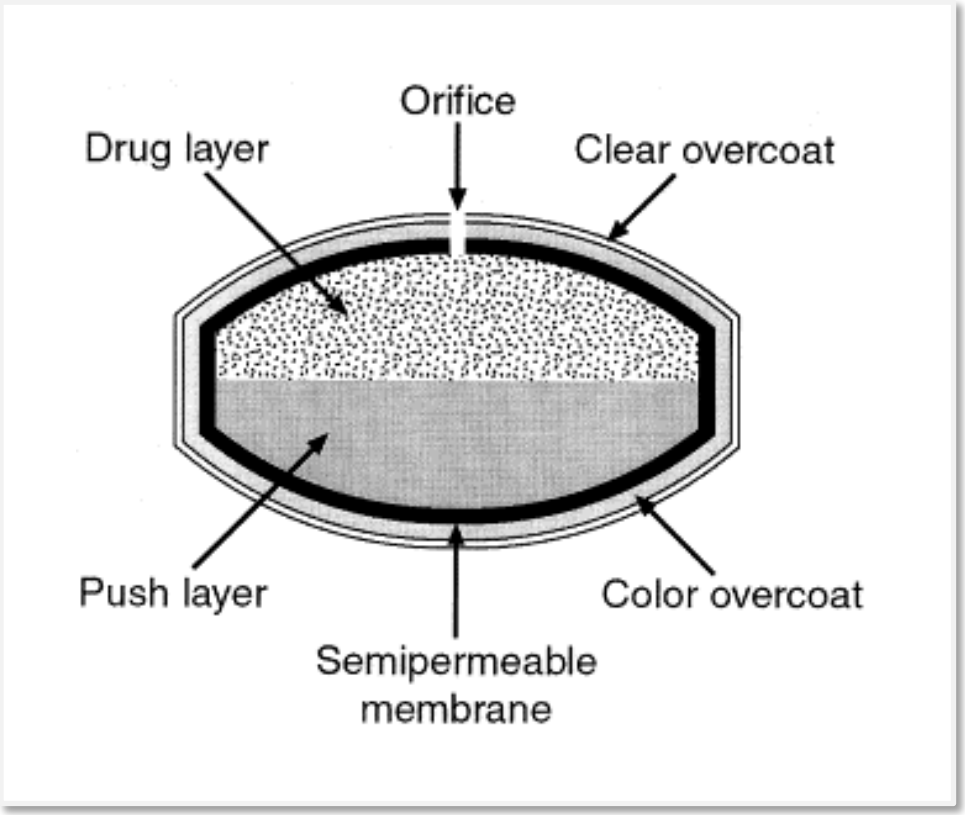
In case of tablets:
obtained by coating



OTHER CR TABLETS

More original systems

Ex: - **Osmotic-controlled Release Oral delivery Systems**



- **Prolonged gastric residence time**

…

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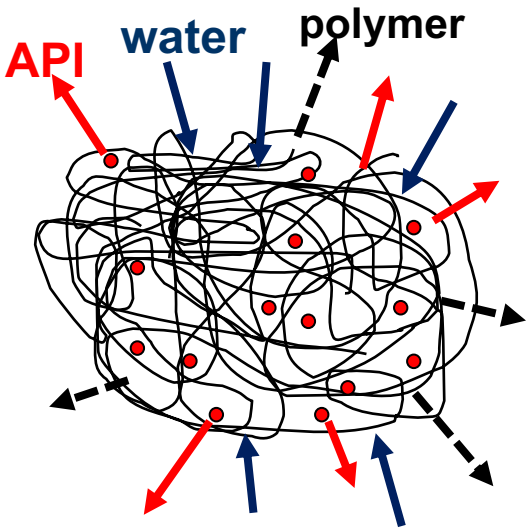
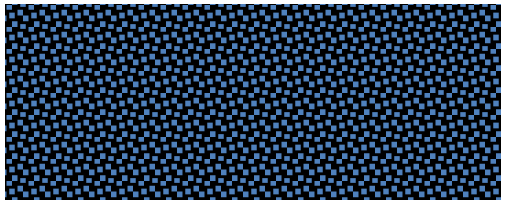
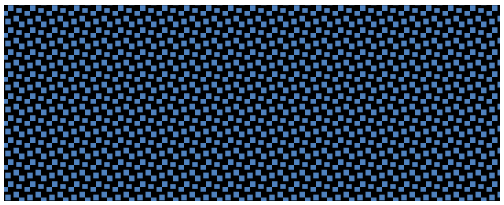
MATRIX TABLETS

Release controlled by diffusion mechanism into polymer network

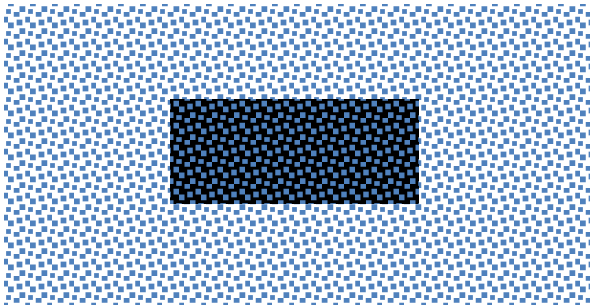




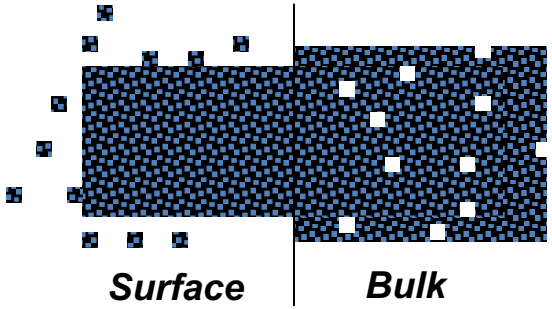
+ dissolution medium



Inert Matrix tablet

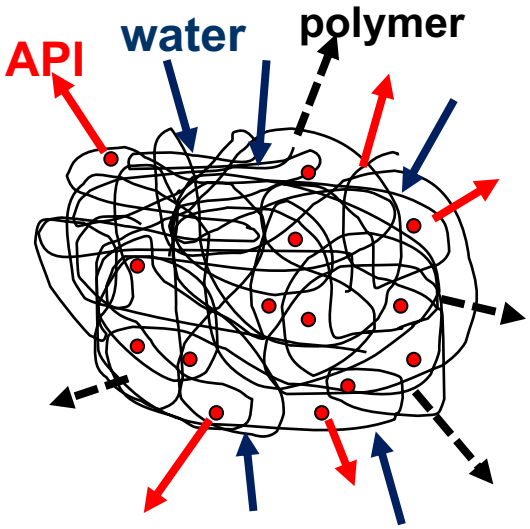


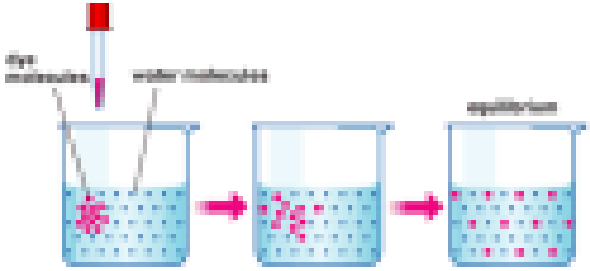
Matrix tablet with swelling



Matrix tablet with erosion

CRITICAL POINT: DIFFUSION PROCESSES





For all the diffusing species, the diffusion rate follows the Fick law:

$$\frac{dQ}{dt} = -S \cdot D \cdot \frac{dc}{dx}$$

S = Diffusion surface

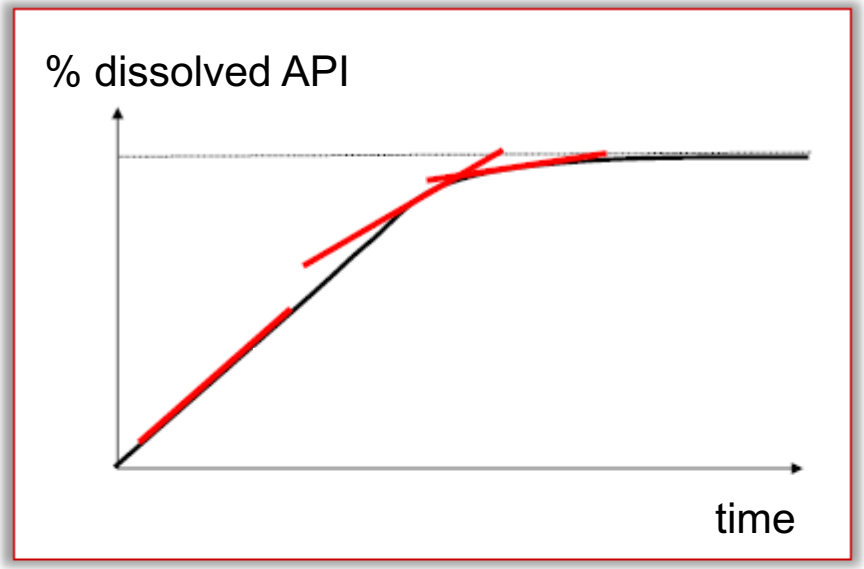
D = Diffusion coefficient

dc/dx = Concentration gradient

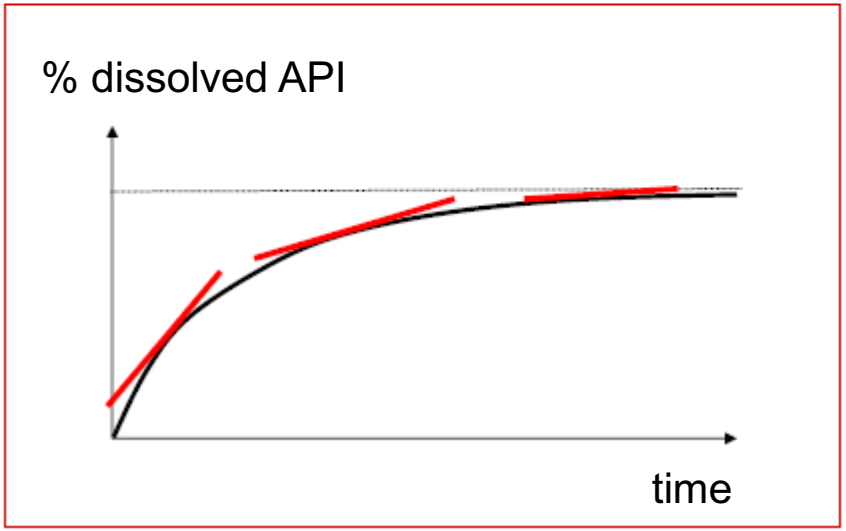
Into matrices, modulation of the diffusion coefficient D

RELEASE KINETICS ORDERS

Zero-order
Release rate is constant
(except at the end)

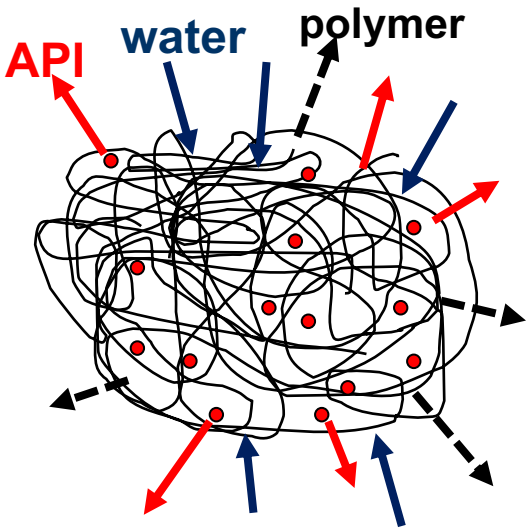


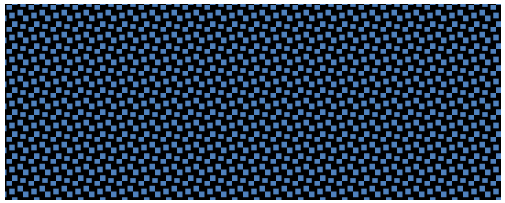
First-order
Release rate decreases with time



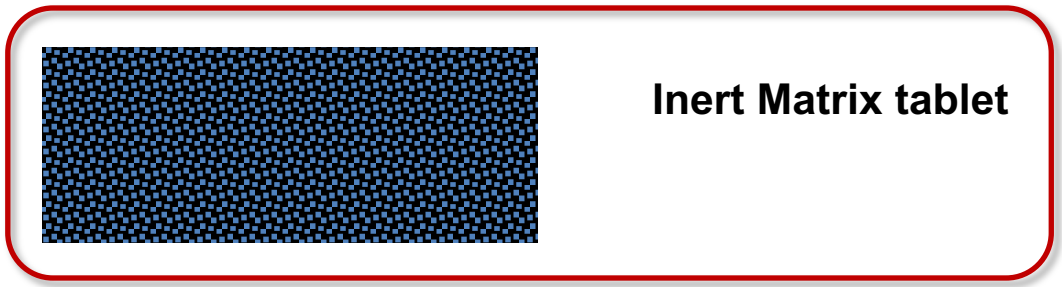
MATRIX TABLETS

Release controlled by diffusion mechanism into polymer network

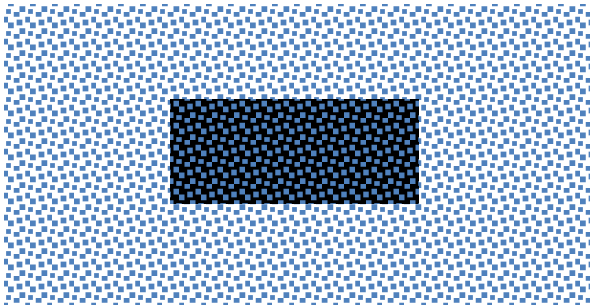




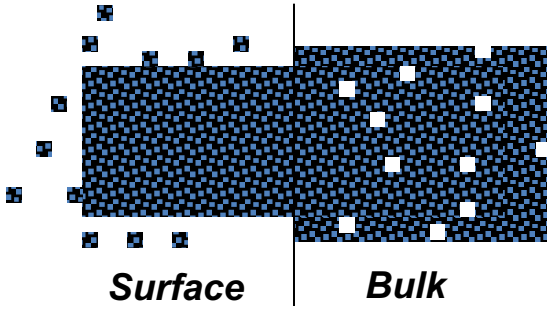
+ dissolution medium



Inert Matrix tablet

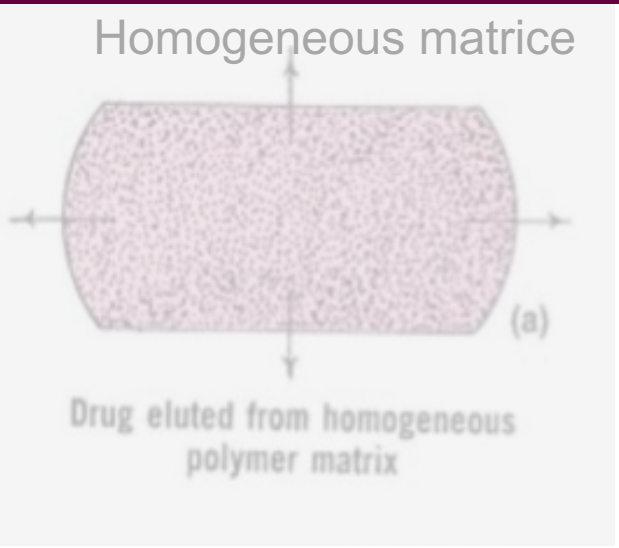


Matrix tablet with swelling

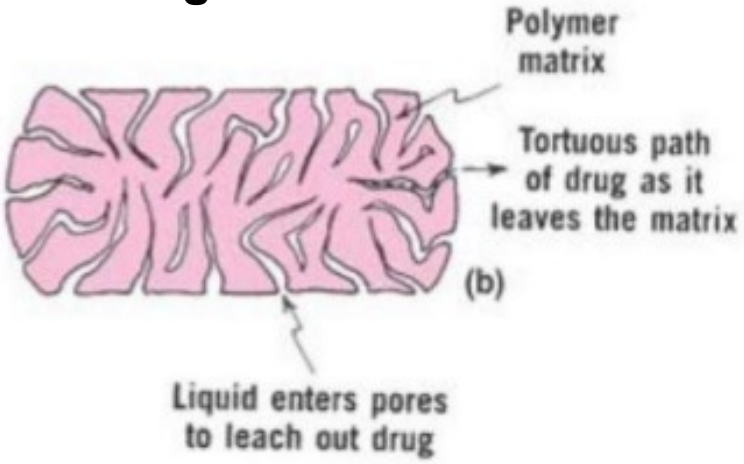


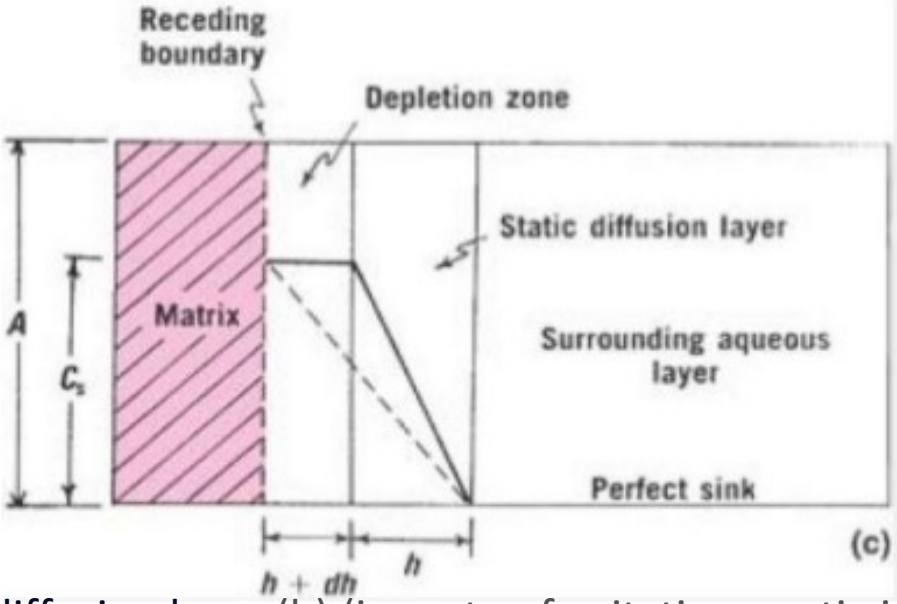
Matrix tablet with erosion

INERT MATRIX TABLETS



Heterogeneous matrices





Noyes-Withney

$$\frac{dC}{dt} = \frac{DS(Cs - Ct)}{h}$$

the **rate of dissolution** of a solid is dependent upon its **solubility**, **the concentration of solute in solution at a particular time, diffusivity**, and the **surface area of the solid**

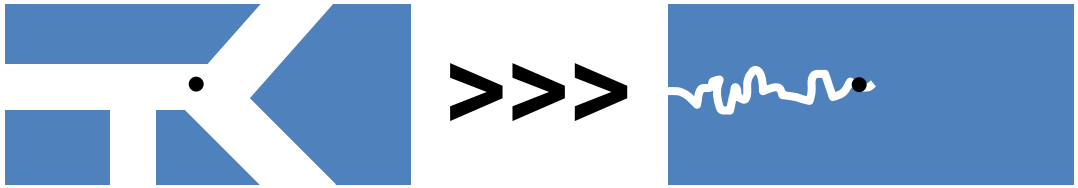
Thickness of diffusion layer (h) (i.e. rate of agitation or stirring). The saturation solubility of a drug is a key factor in the Noyes- Whitney equation. The driving force for dissolution is the concentration gradient across the boundary layer.

HETEROGENEOUS INERT MATRIX

In heterogeneous inert matrices, dissolved API diffuse through the pore

The API diffusion coeffcient depends on matrix porosity (ε) and tortuosity (τ)

$$D_{eff.} = \frac{\varepsilon}{\tau} D_{API\ into\ diss.med.}$$



HETEROGENEOUS INERT MATRIX

Higuchi simplified model for heterogeneous inert matrices:
ex: Ethylcellulose

if Q is the released amount per surface (S) at time (t),

Then

$$Q / S = \left[D_{PA}.C_S.(\varepsilon/\tau).(2.A - \varepsilon.C_S).t \right]^{1/2}$$

with

D_{PA} = **diffusion coefficient of the API into the dissolution medium**

A = Initial concentration of the API into the matrix

C_S = API solubility into the dissolution medium

ε = matrix porosity

τ = matrix tortuosity

Hypothesis:
- one-direction release
- Sink conditions
- Instantaneous dissolution of the API
- …

INERT MATRIX - POROSITY

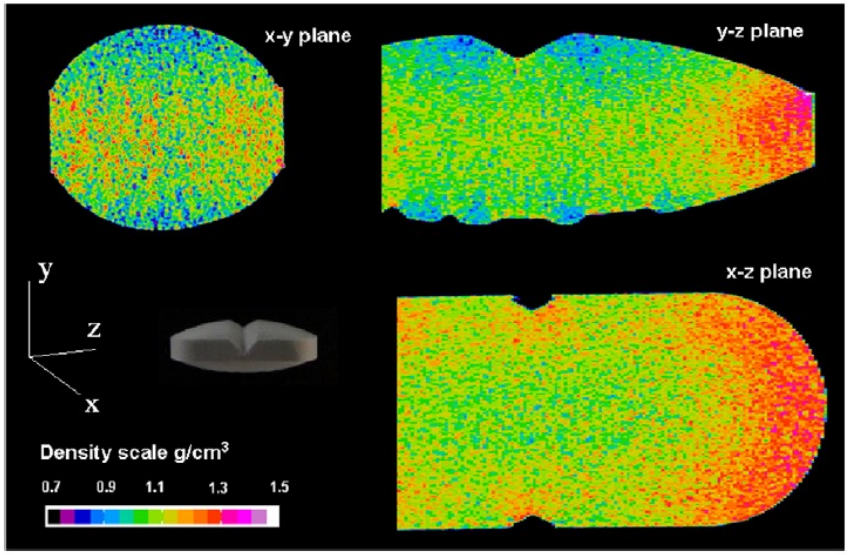
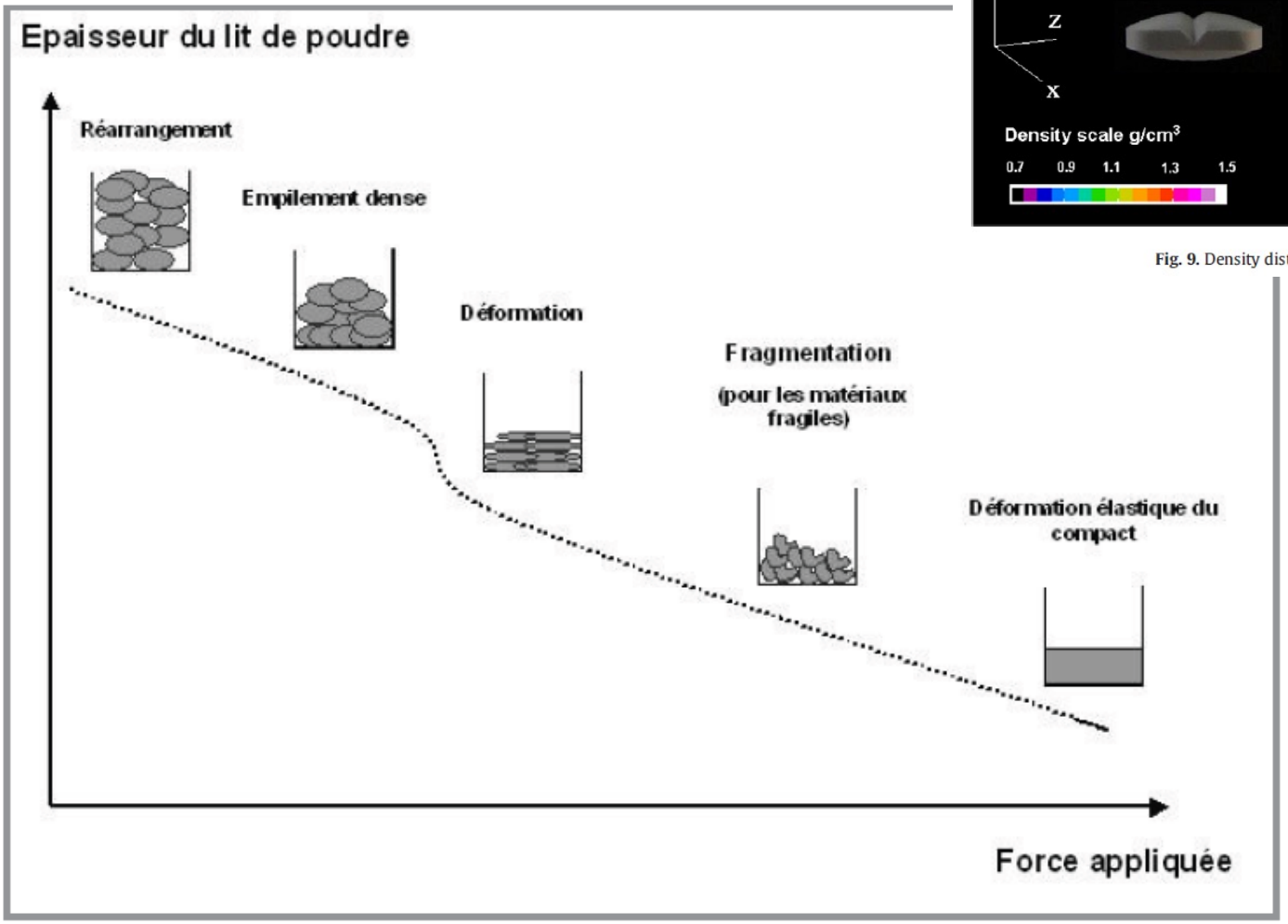
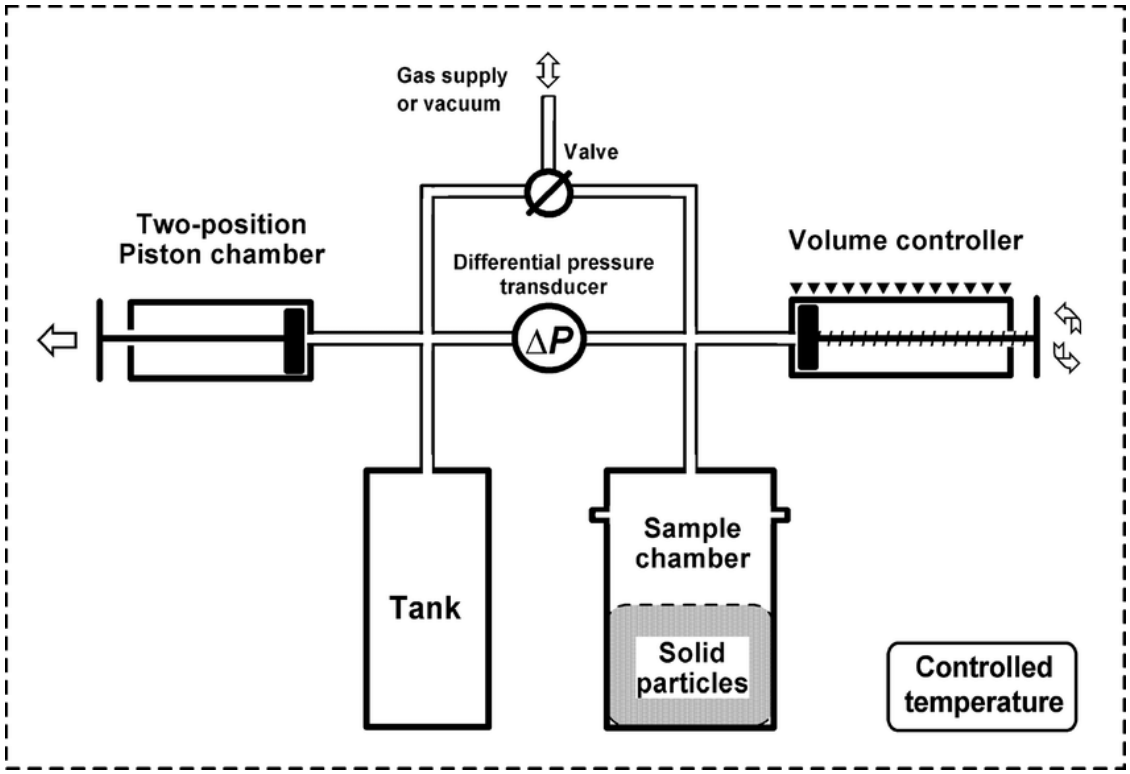


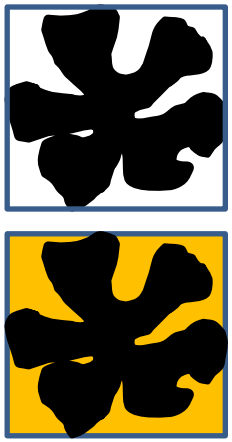
Fig. 9. Density distribution in tablets using X-ray CT [19].



INERT MATRIX - POROSITY

- **Pycnometry** (gaz or liquid)





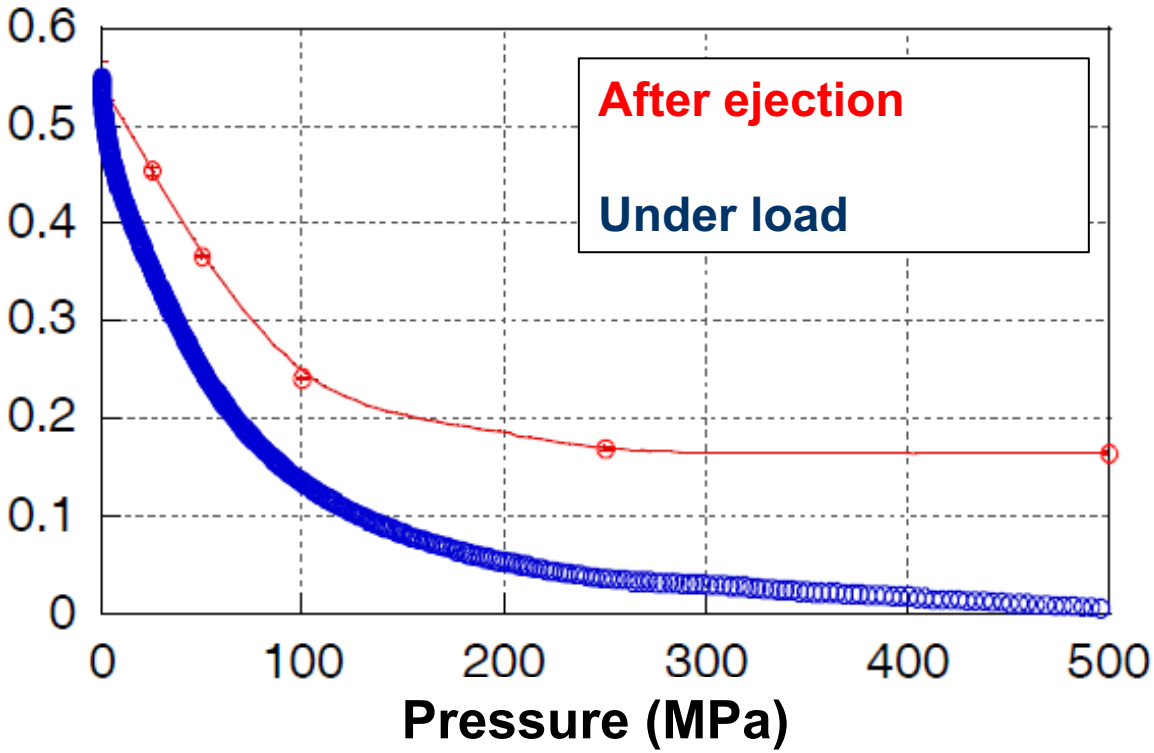
$$\text{Compacity (\%)} = (D_{\text{compact after ejection}} / D_{\text{pycnometry}}) \times 100$$

$$\text{Porosity (\%)} = \varepsilon = 100 - \text{compacity}$$

INERT MATRICX - POROSITY

Effect of compression force on starch tablets

Porosity



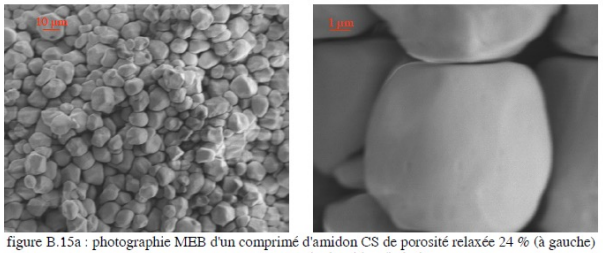


figure B.15a : photographie MEB d'un comprimé d'amidon CS de porosité relaxée 24 % (à gauche) avec un zoom sur un grain d'amidon (à droite)

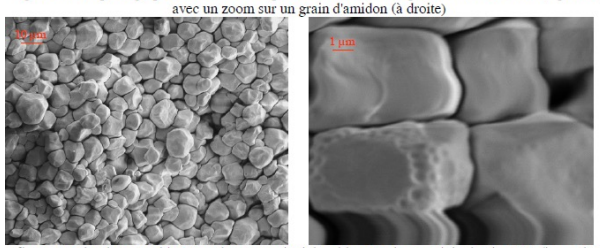


figure B.15b: photographie MEB d'un comprimé d'amidon CS de porosité relaxée 17 % (à gauche) avec un zoom sur un grain d'amidon (à droite)

Thèse E. Serris, Ecole des Mines 2002

INERT MATRICES - POROSITY

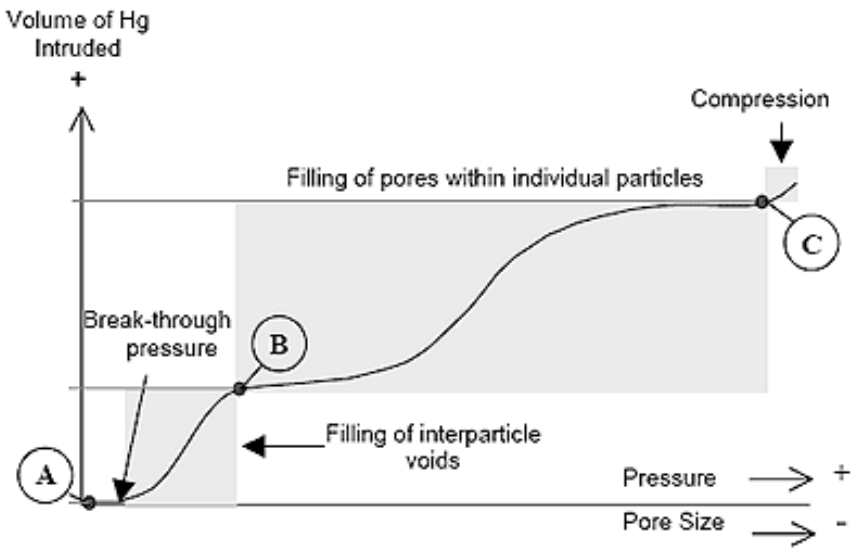
- **Porosity**: Mercury porosimetry

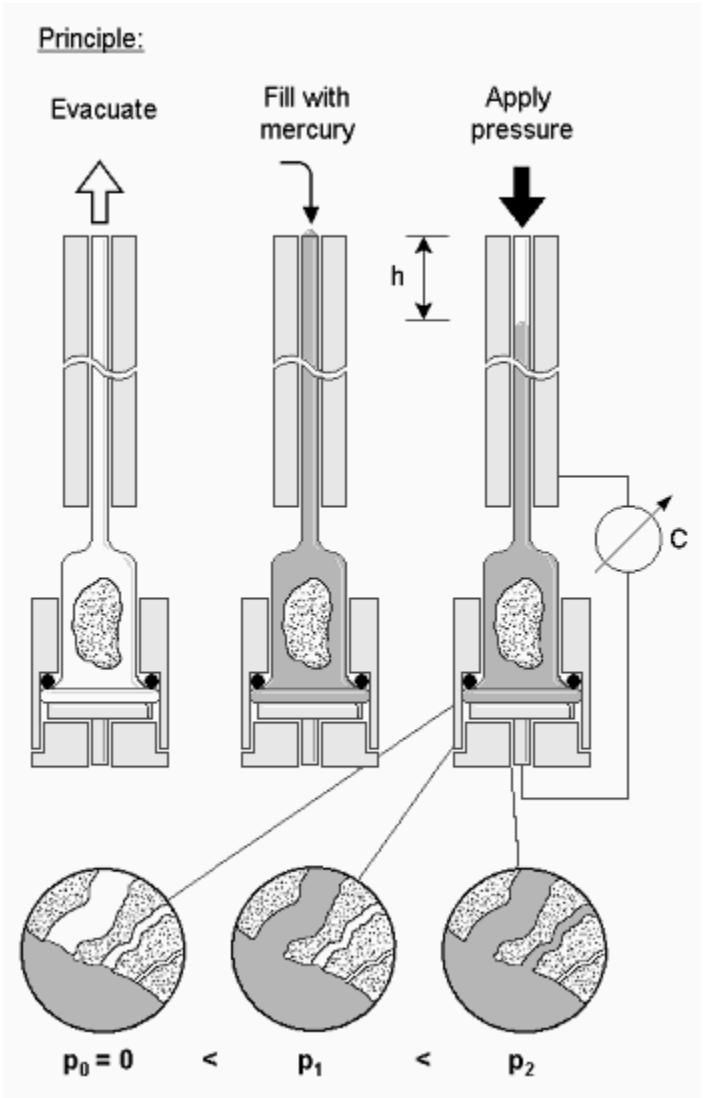
The relation between the applied pressure and the smallest filled pores is:

$$p = \frac{2\,\sigma\,\cos\theta}{r} \quad \text{(Washburn)}$$

σ = Surface tension (0.48 N/m) p = Pressure

θ = Wetting angle (140°) r = Pore radius

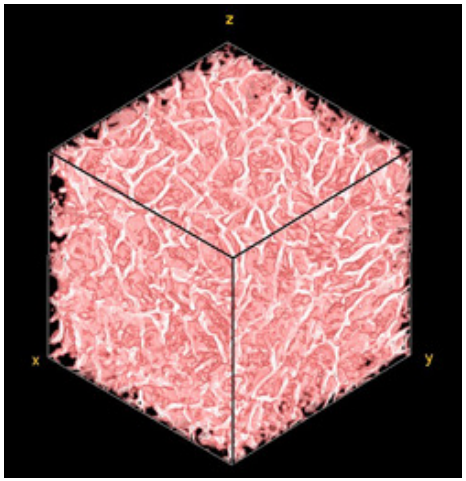


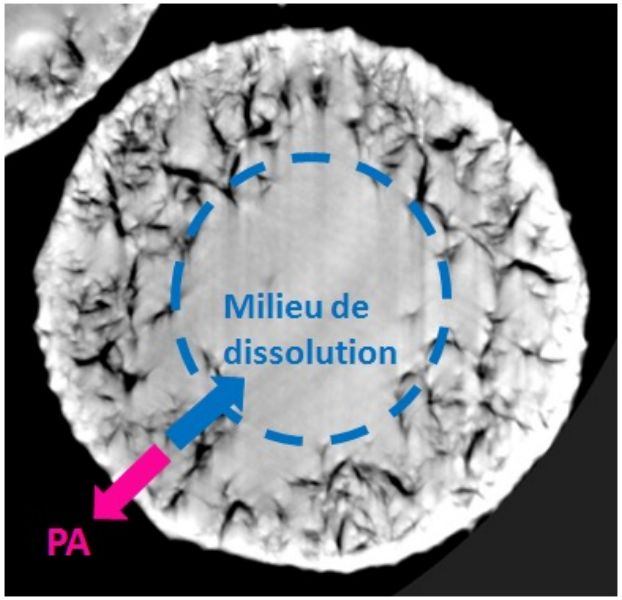


INERT MATRICES - TORTUOSITY

Experimental quantification

Ex: microtomography X





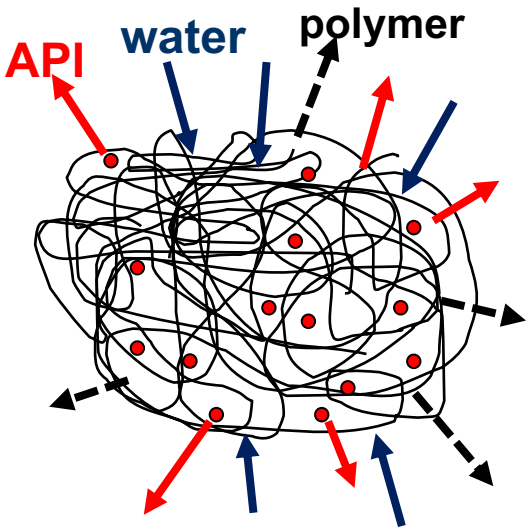
Theoretical quantification

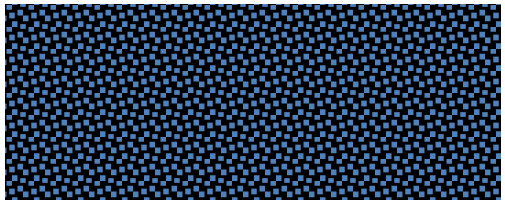
$$\frac{1}{\tau} = 1 - \frac{2}{3}(1+\varepsilon)(1-\varepsilon)^{2/3}$$

In general between 1 and 3

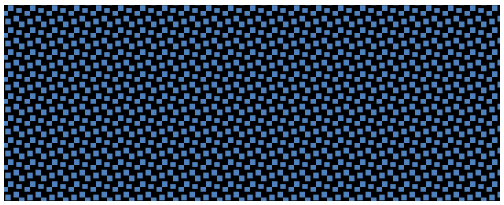
MATRIX TABLETS

Release controlled by diffusion mechanism into polymer network

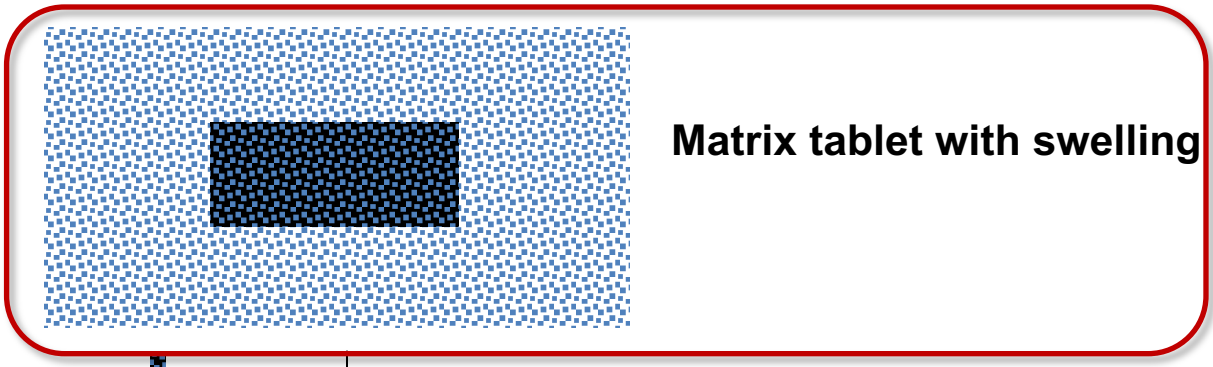




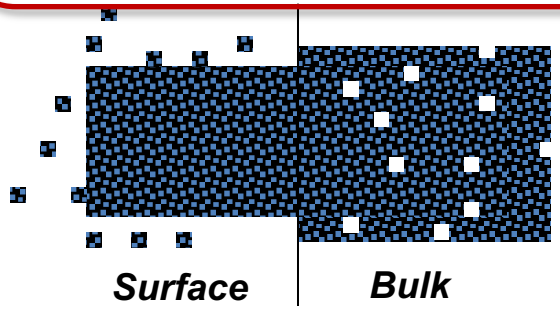
+ dissolution medium



Inert Matrix tablet



Matrix tablet with swelling



Matrix tablet with erosion

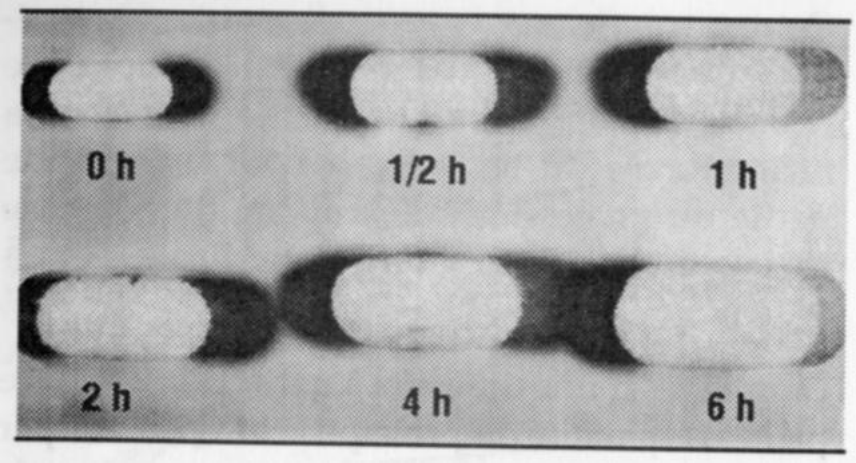
MATRIX WITH SWELLING

Creation of a gel layer (hydrated polymer with high-molecular weight) at tablet surface.

API release depends on gel layer properties.

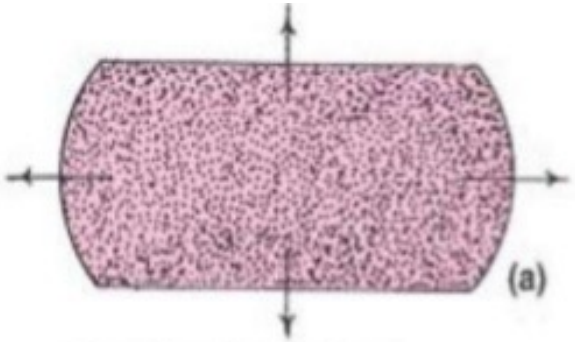
Strong effect of hydrated polymer viscosity on the stability and thickness of this layer or on API diffusion.

Ex: *Hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC),…*

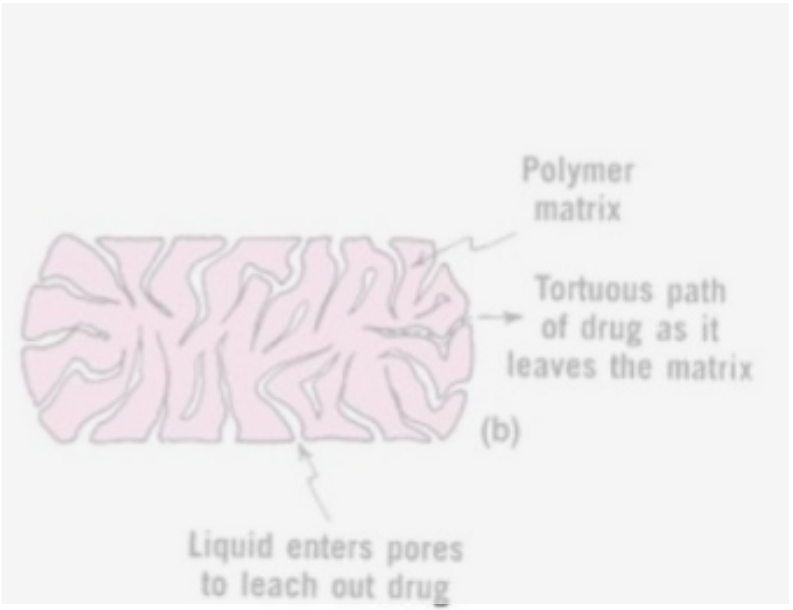


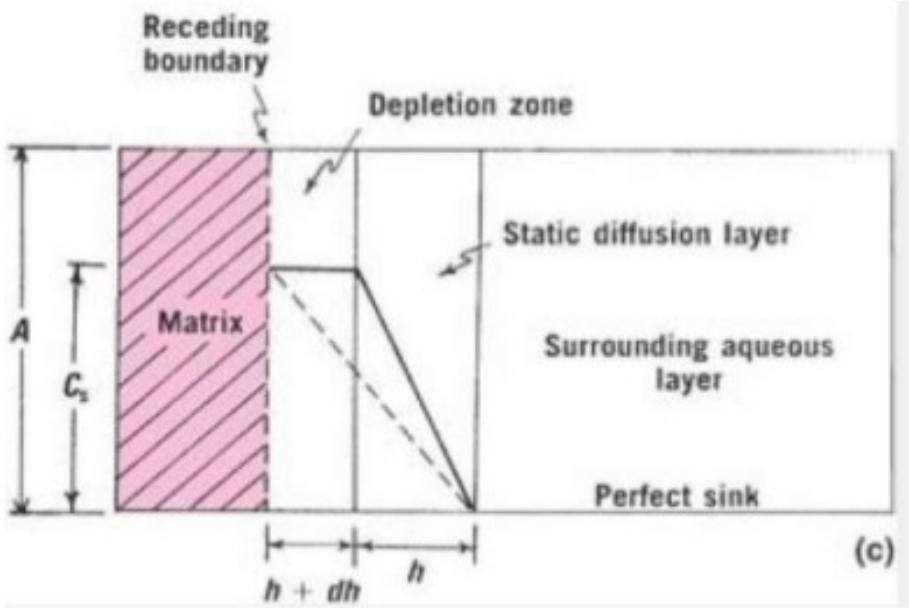
Special case: HOMOGENEOUS MATRIX

Homogeneous matrix



Drug eluted from homogeneous polymer matrix





Noyes-Withney

$$\frac{dC}{dt} = \frac{DS(Cs - Ct)}{h}$$

Special case: HOMOGENEOUS MATRIX

Higuchi simplified model for homogeneous matrix

if Q is the released amount per surface (S) at time (t),

Then

$$Q / S = \left[D_{PA} . C_S \left(2.A - C_S \right) . t \right]^{1/2}$$

With

D_{PA} = **diffusion coefficient of the API into hydrated polymer**

A = Initial concentration of the API into the matrix

C_S = API solubility into the dissolution medium

Hypothesis:

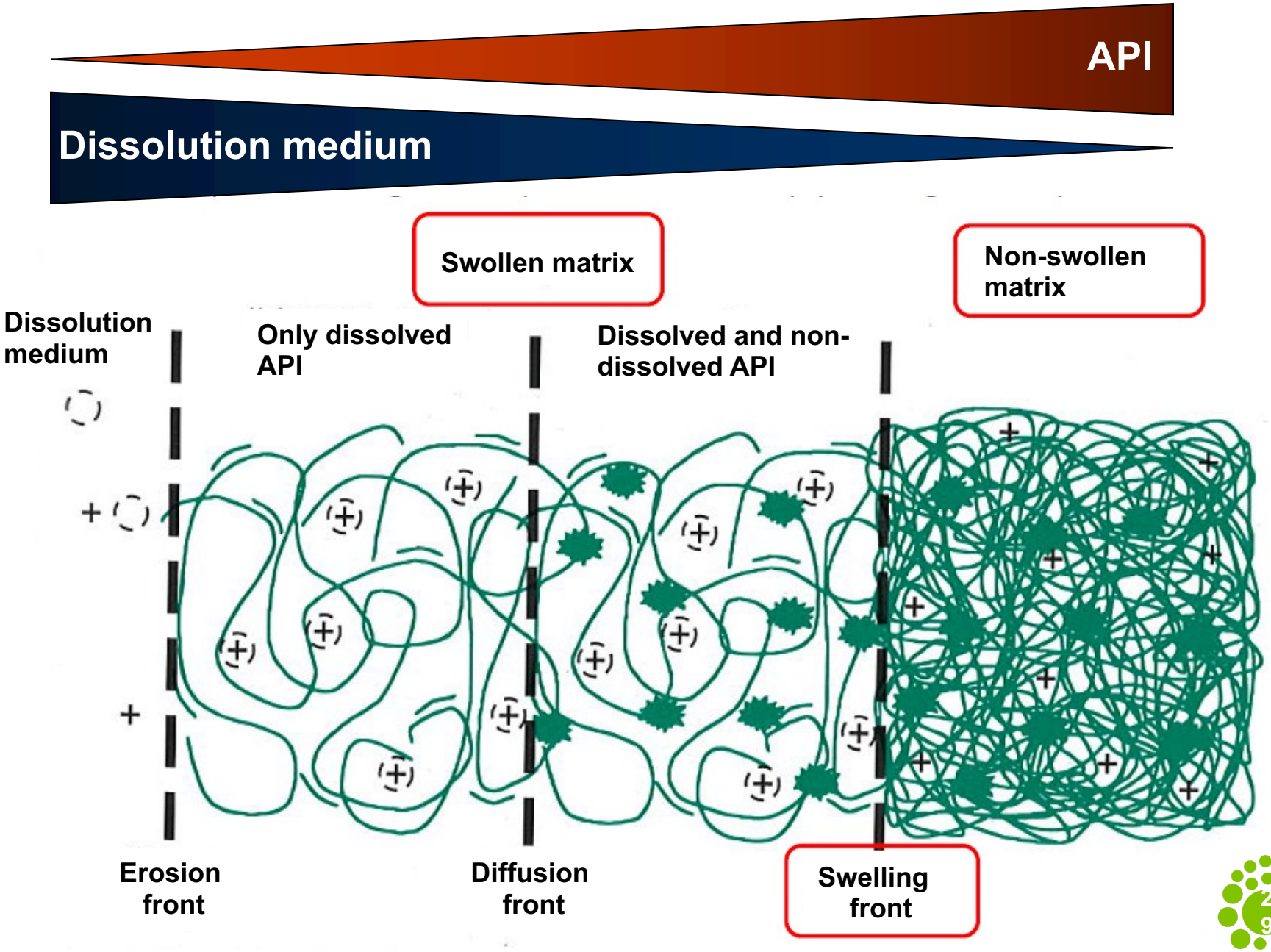
- one-direction release

- Sink conditions

- Instantaneous dissolution of the API

- Instantaneous fully hydration of the polymer

MATRIX WITH SWELLING



MATRIX WITH SWELLING

Principal consequences of swelling:

- increase of the diffusion path length for API
  = decrease of the release rate

- increase of polymer chain mobility (and then also for API)
  = increase of the release rate

Modelisation is complex because of simultaneous phenomena.

Simple model: Peppas-Korsmeyer model

$$M_t/M_\infty = kt^n$$

with n = 0,5 essentially diffusion* (* cf. previous slides)

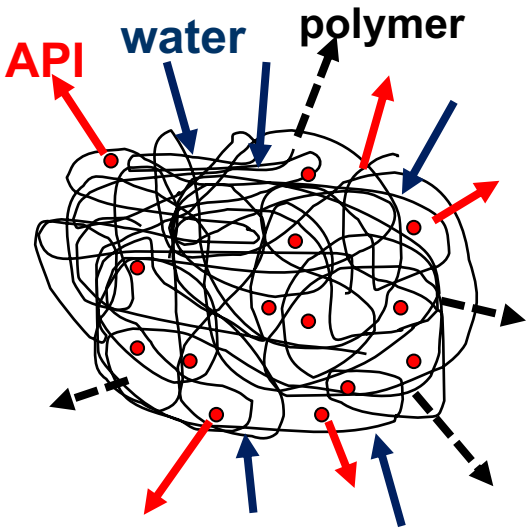
0,5< n<1 diffusion + polymer relaxation + erosion

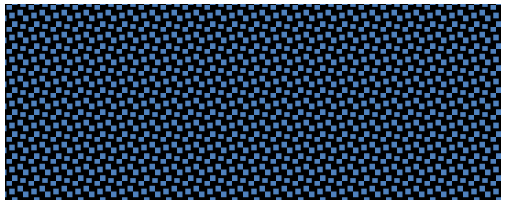
More complex models exist:

$$\frac{M_t}{M_\infty} = 4\left[\frac{Dt}{\ell^2}\right]^{1/2}\left[\frac{1}{\pi^{1/2}} + 2\sum_{n=1}^{x}(-1)^n \mathrm{ierfc}\left(\frac{n\ell}{2\sqrt{Dt}}\right)\right]$$

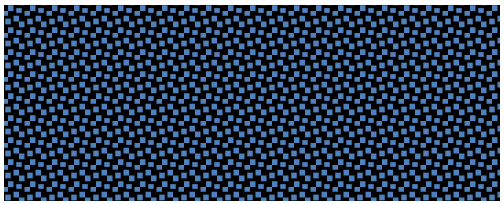
MATRIX TABLETS

Release controlled by diffusion mechanism into polymer network

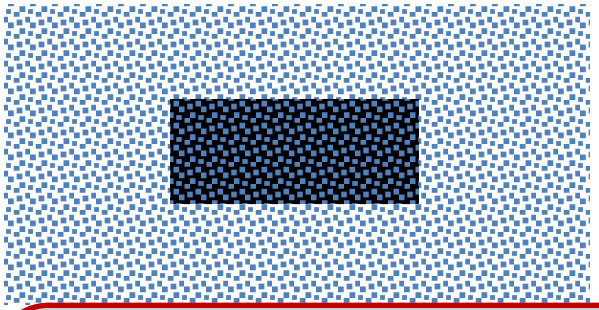




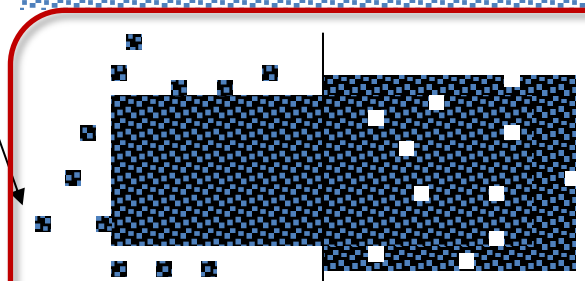
+ dissolution medium



Inert Matrix tablet



Matrix tablet with swelling



Matrix tablet with erosion

MATRIX WITH DEGRADATION

- **Erosion** = polymer chain lysis

  Ex.: Poly(lactic-co-glycolic) acids

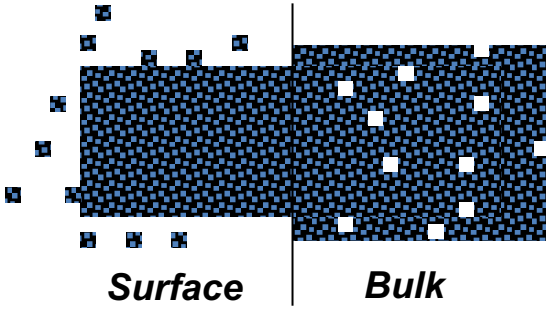
- **Dissolution** = polymer chain solubilization

  Exemple: Polymethacrylates

Matrix degradation depends on balance between two rates:
water penetration vs. polymer dissolution/degradation rates.

Surface degradation
Volume degradation

Erosion kinetics control the API release

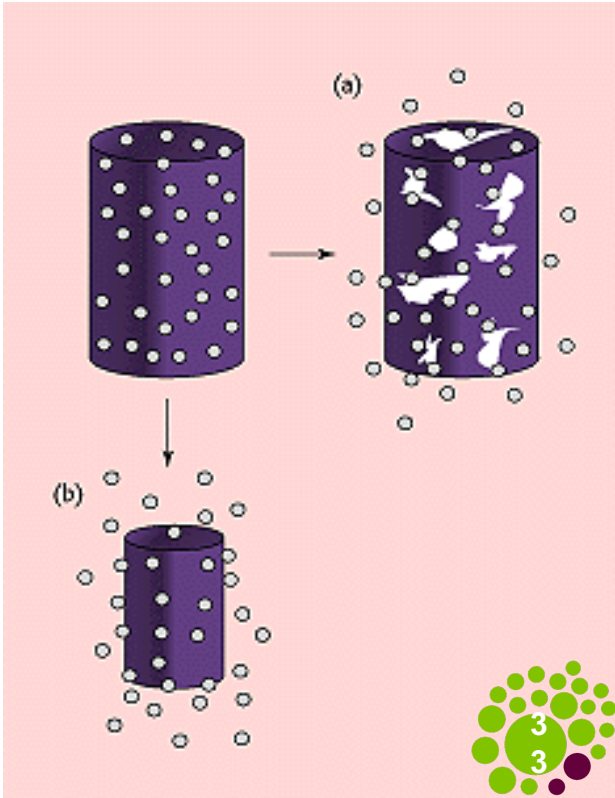


Ex: *Polylactic-co-glycolic acids (PLGA), polymethacrylates, HPMC and HPC with low viscosity,…*

MATRIX WITH DEGRADATION

- **HETEROGENEOUS EROSION = Surface erosion**
  - Hydrophobic polymers
  - Physical integrity of the matrix is maintained
  - Zero-order kinetics are possible (erosion >> diffusion)

- **HOMOGENEOUS EROSION = Volume erosion**
  - More hydrophilic polymer
  - Physical integrity of the matrix is lost
  - Erosion + diffusion
  - Kinetics less related to the time



PARAMETERS RELATED TO API

Solubility

Only solubilized fraction can diffuse
Dissolution rate increases with solubility
Si solubilité < 0,01 mg/ml, libération souvent incomplète
Influence du pKa

Dosage

If more than 500 mg, hard to formulate matrix

Molecular weight

If > 500 Da, diffusion coefficient into polymer network could be low

Granulometry

Influence intrinsic dissolution of the API

PARAMETERS RELATED TO POLYMER

Viscosity

Granulometry

Crystallinity

Glass transition temperature

Polymer proportion

Interactions with API

- Cationic polymers (NaCMC, chitosan) + Anionic API
- Carbopol-based matrices + Basic API

AGENDA

1. Introduction
2. Matrix tablets: overview
3. Inert matrix tablets
4. Swellable matrix tablets
5. Erodible matrix tablets
6. Other excipients / some reminders on tablets
7. Controls
8. Conclusion

DILUENTS

Function : to act as a bulking agent or filling material

Ideal diluent: Chemically and physiologically inert
Easy tabletted
Inexpensive
Non-hygroscopic
Soluble or not, taste, acid or alcalin,...

Examples: Starch, Lactose, Sucrose, Glucose, Mannitol, Sorbitol, Calcium Phosphate, Calcium Carbonate, Cellulose…

DILUENTS

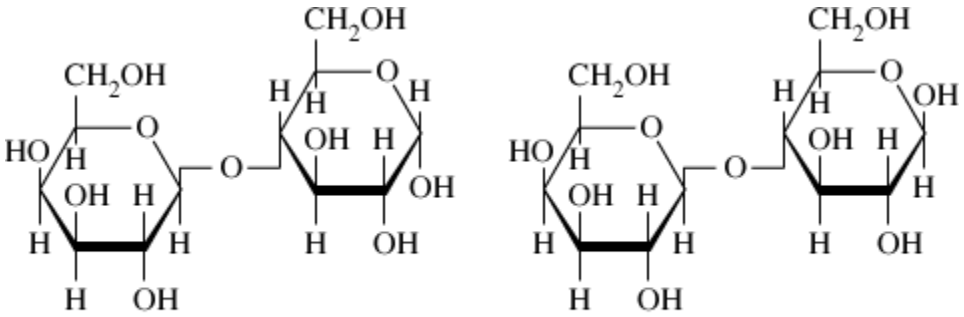
True density : The mass of a particle divided by its volume, excluding open and closed pores

Bulk density: The bulk density of a material. It is the ratio of the mass to the volume (including the inter-particle void volume) of an untapped powder sample

Tapped density : The tapped density of powders or granulates is an increased bulk density attained after mechanically tapping a cylinder containing the sample.

DILUENTS

LACTOSE

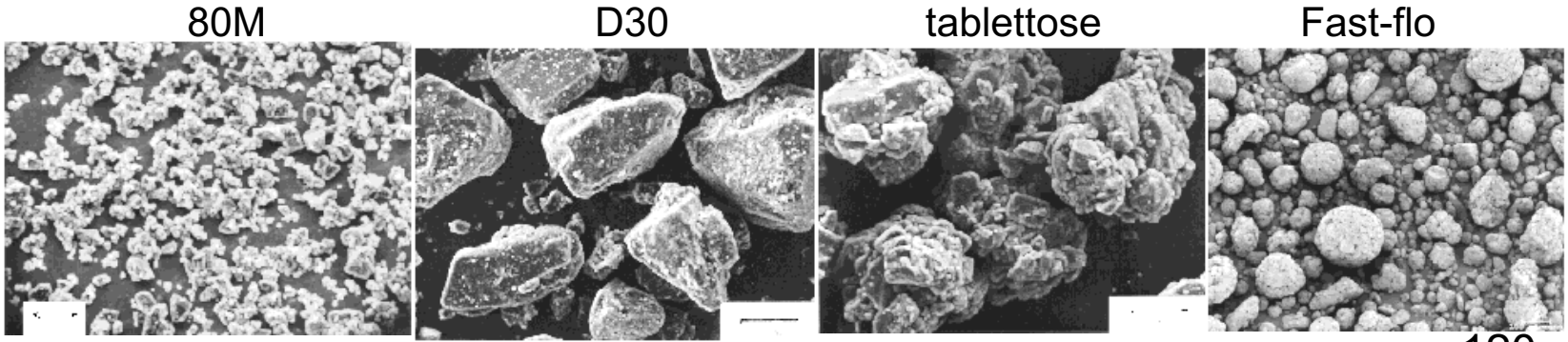


True density
1.540 for α-lactose monohydrate;
1.589 for anhydrous β-lactose.

Bulk density: 0.619 g/cm^3 .
Tapped density: 0.935 g/cm^3

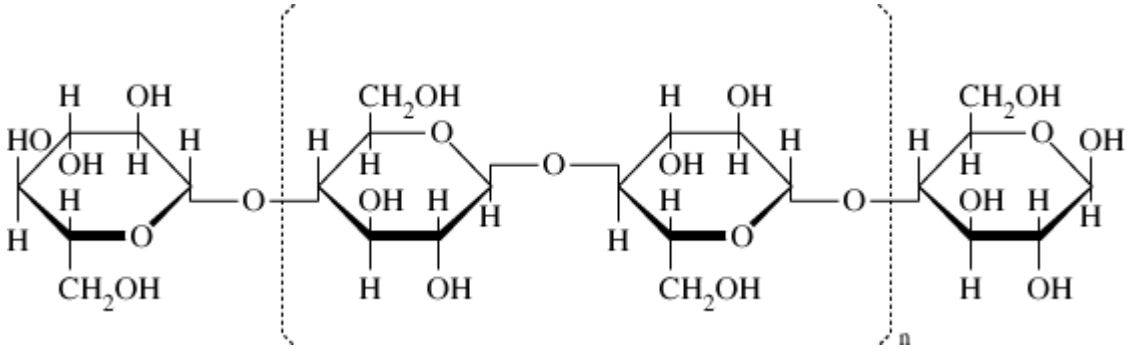
Different kind of lactoses: anhydrous α-lactose, monohydrate α-lactose, anhydrous β-lactose (in general 70/30 β/α mixtures),…

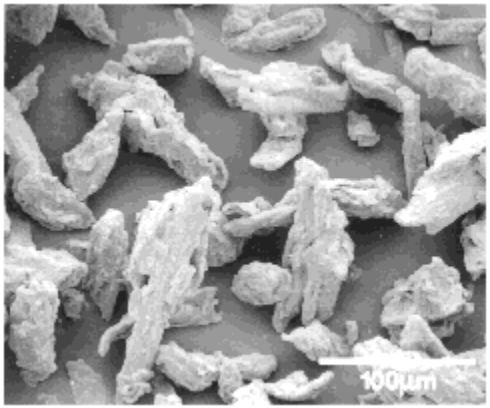
Examples of commercial monohydrate lactoses



DILUENTS

MICROCRYSTALLINE CELLULOSE





***Angle of repose*:** 34.4° for Emcocel 90M

Bulk density:
0.337 g/cm^3
0.32 g/cm^3 for Avicel PH-101
0.29 g/cm^3 for Emcocel 90M

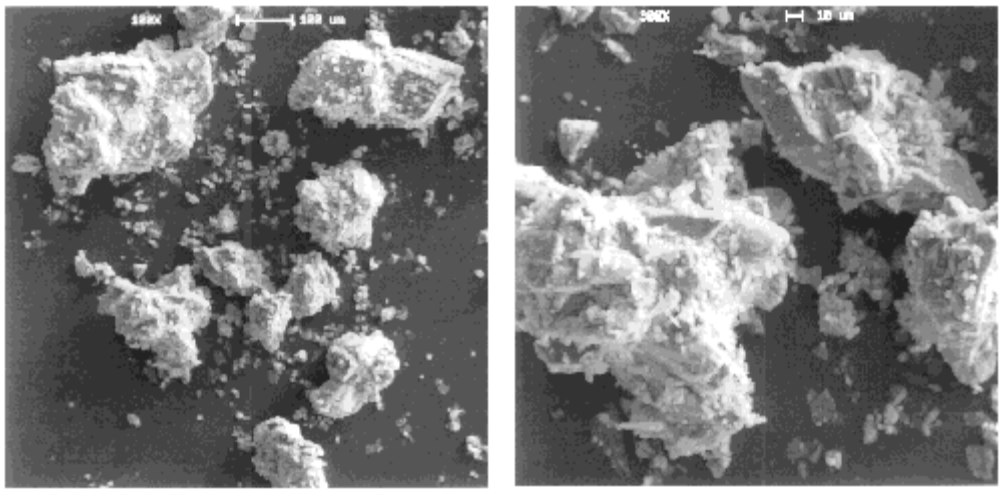
Tapped density:
0.478 g/cm^3
0.45 g/cm^3 for Avicel PH-101
0.35 g/cm^3 for Emcocel 90M

***True density*:** 1.512-1.668 g/cm^3

DILUENTS

CALCIUM PHOSPHATE (DIHYDRATE)

$CaHPO_4 (+2H_20)$



x 100 x 300

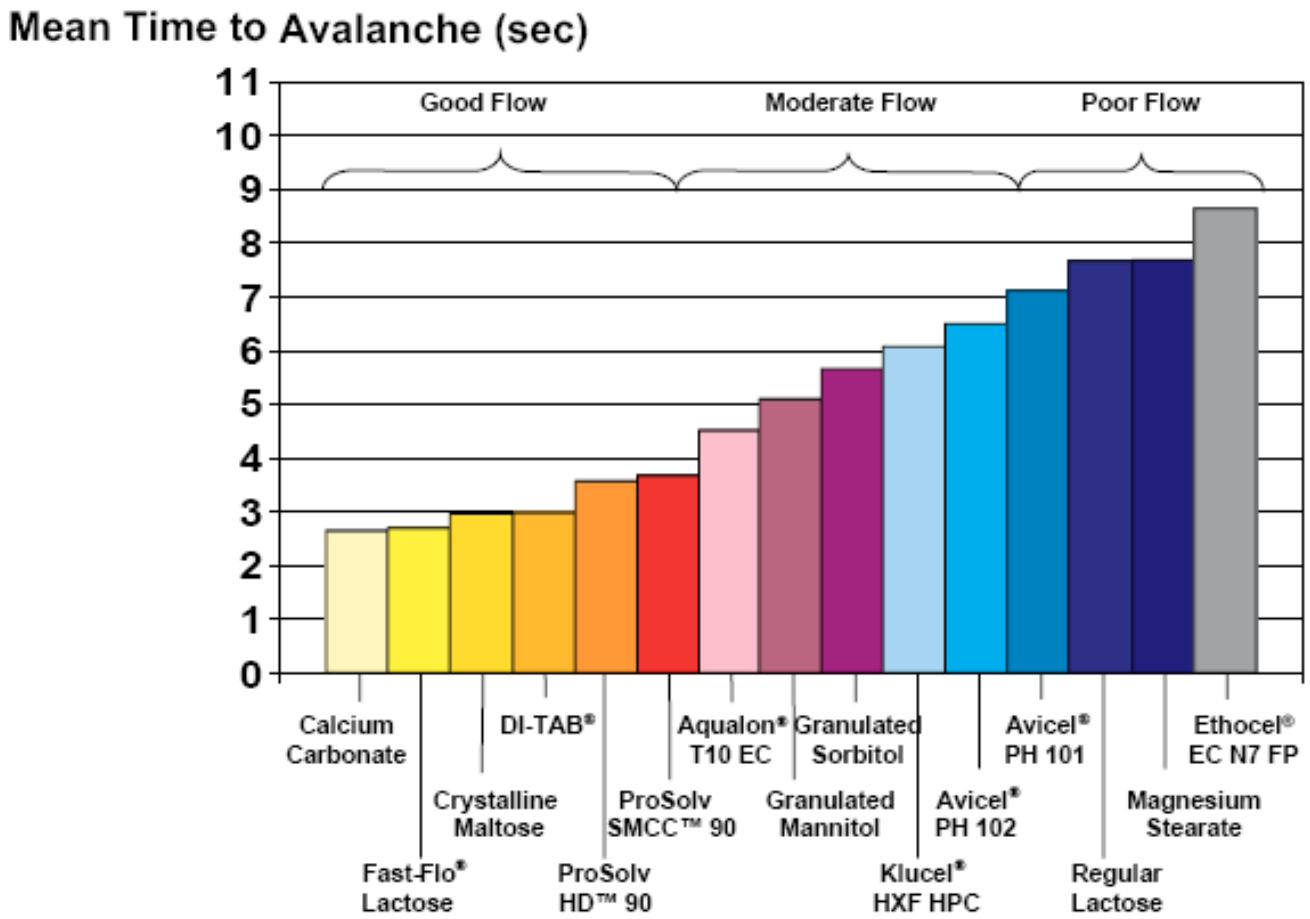
True density: 2.89 g/cm^3 for A-TAB
2.39 g/cm^3 for DI-TAB

Bulk density: 0.78 g/cm^3 for A-TAB

Tapped density: 0.82 g/cm^3 for A-TAB

FLOWABILITY

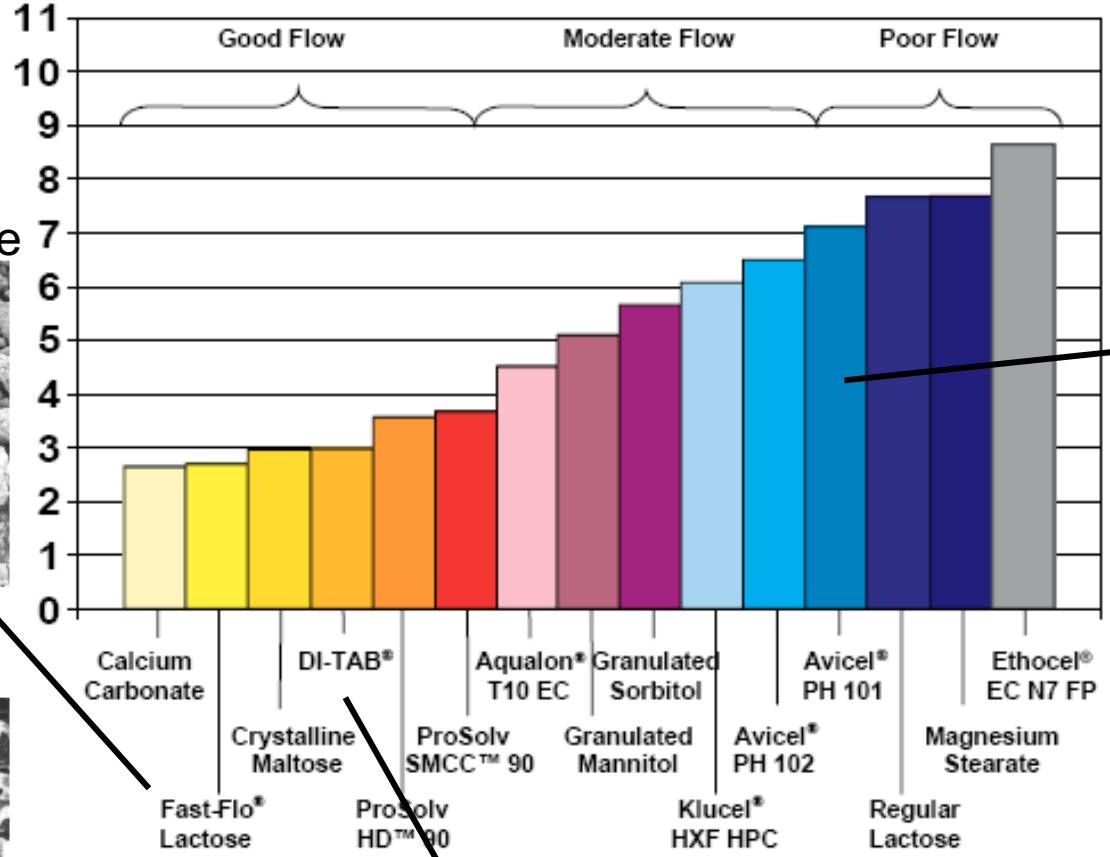
Powder Flowability of Pharmaceutical Excipients



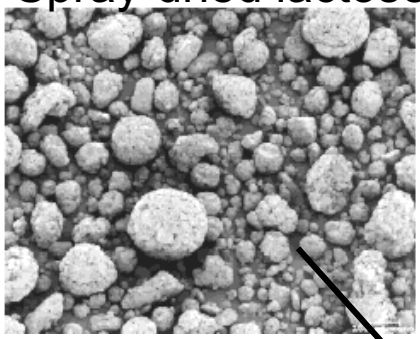
FLOWABILITY

Powder Flowability of Pharmaceutical Excipients

Mean Time to Avalanche (sec)

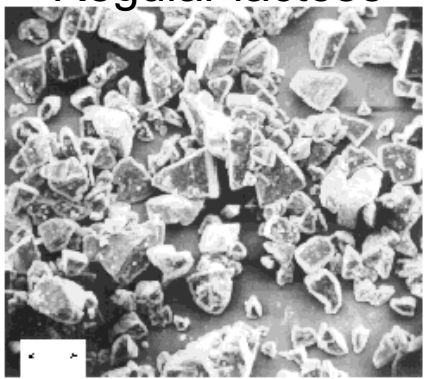


Spray-dried lactose

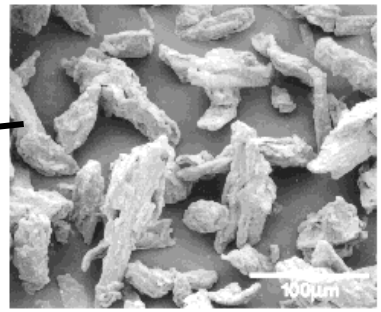


vs.

Regular lactose



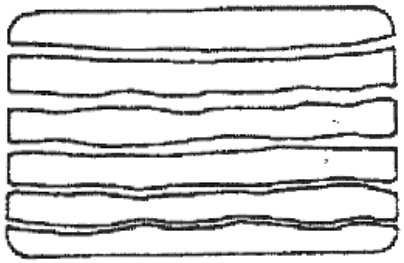
Avicel

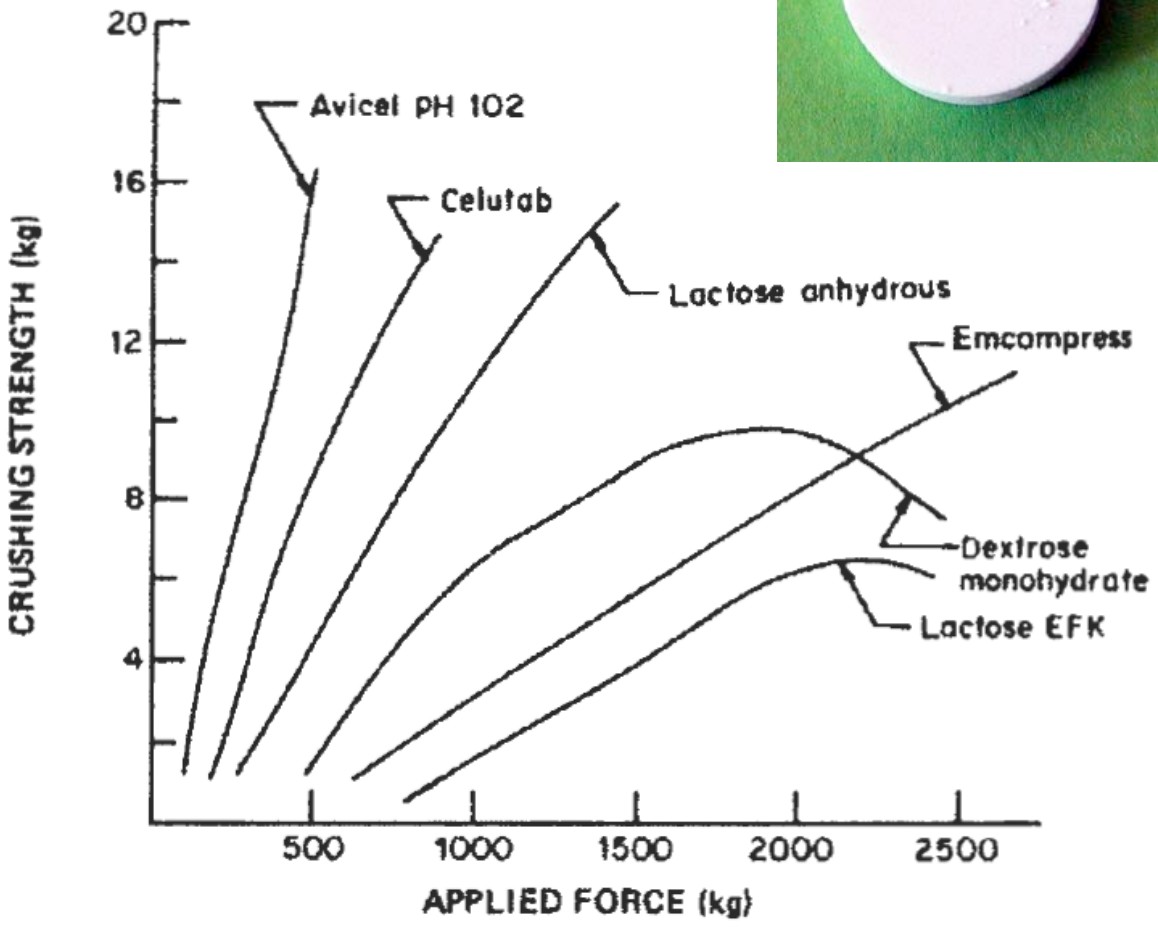


Calcium phosphate

Density: 2.89 g/cm^3

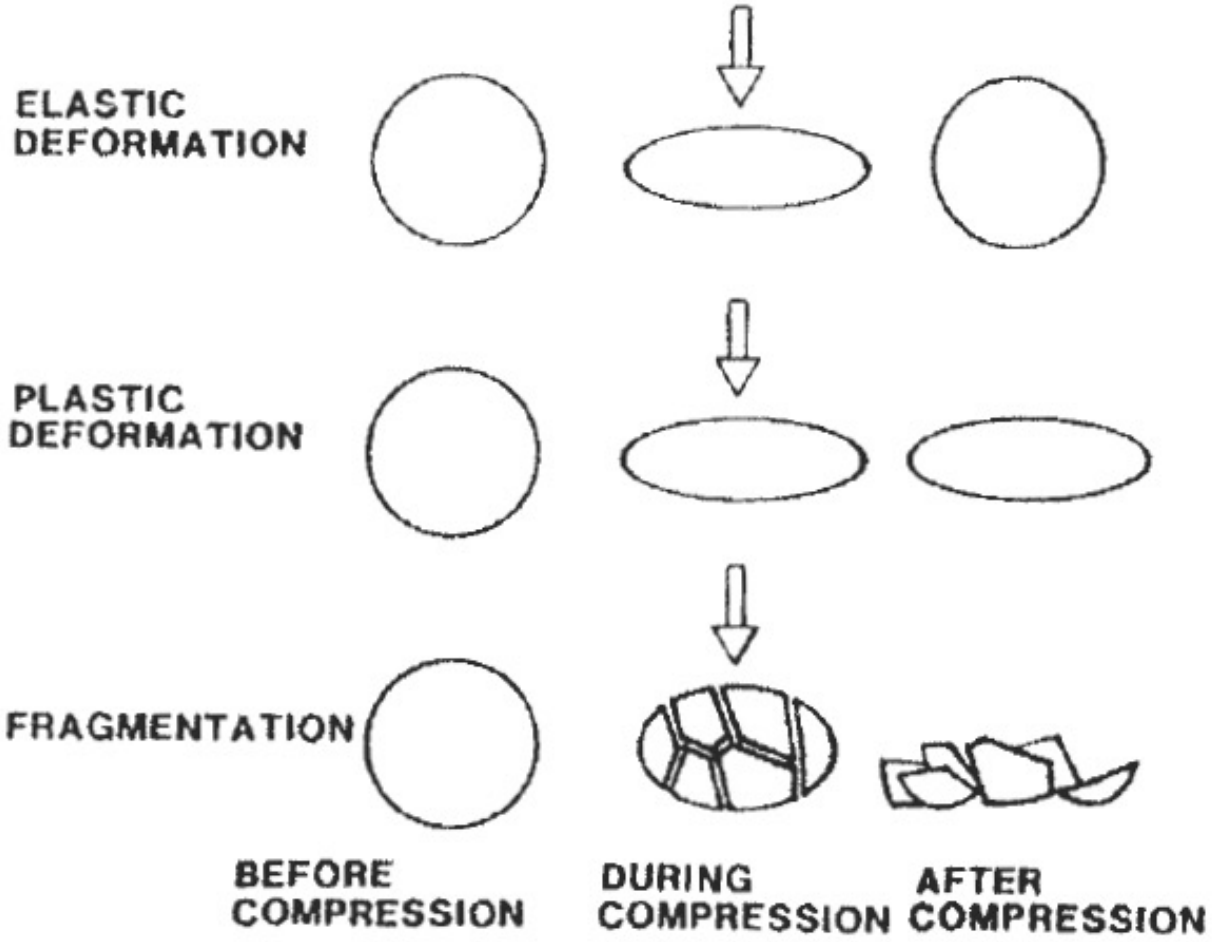
COMPACTABILITY





Crushing strength vs. applied force for compacts of various materials.

COMPACTABILITY



Schematical illustration of processes that take place during compression.

BINDERS

Functions: - Bind particles into entangled networks

- Produce tablets with sufficient hardness

Types of binders:

Powder (direct compression, dry granulation)

Solution (wet granulation)

Examples:

Solution : Gelatin, Cellulose and derivatives, PVP, starch, sucrose, PEG

Dry: Cellulose, Methyl cellulose, PVP, PEG

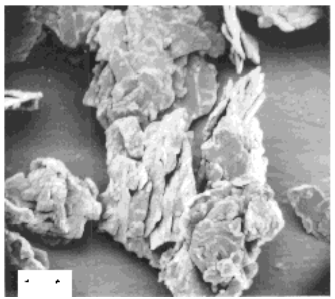
LUBRICANTS

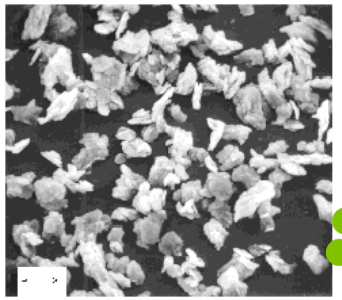
Anti-friction: reduction of the frictions between powder grains or between powder and die wall.

Anti-adherent: prevention of powder sticking on die or punches.

ex: Magnesium stearate, sodium laurylsulfate, stearic acid, talc..

+ nice appearance, shiny, dust free…



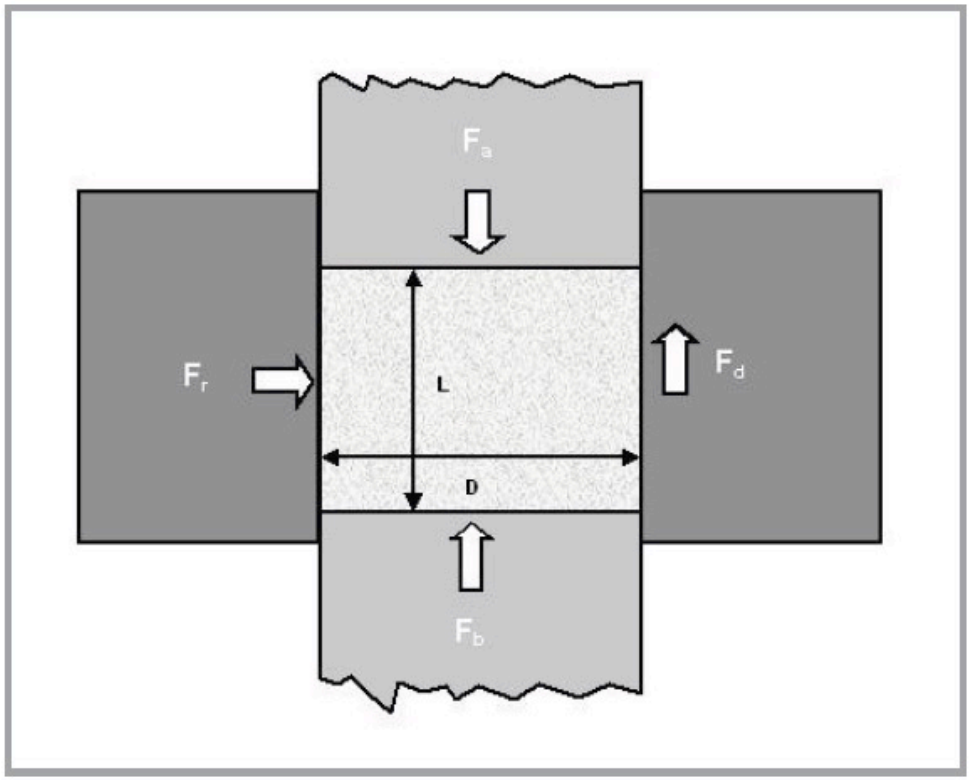


TABLET COMPRESSION

F_a: force applied by the upper punch

F_r: radial force

Correspond to force applied by the powder bed under compression

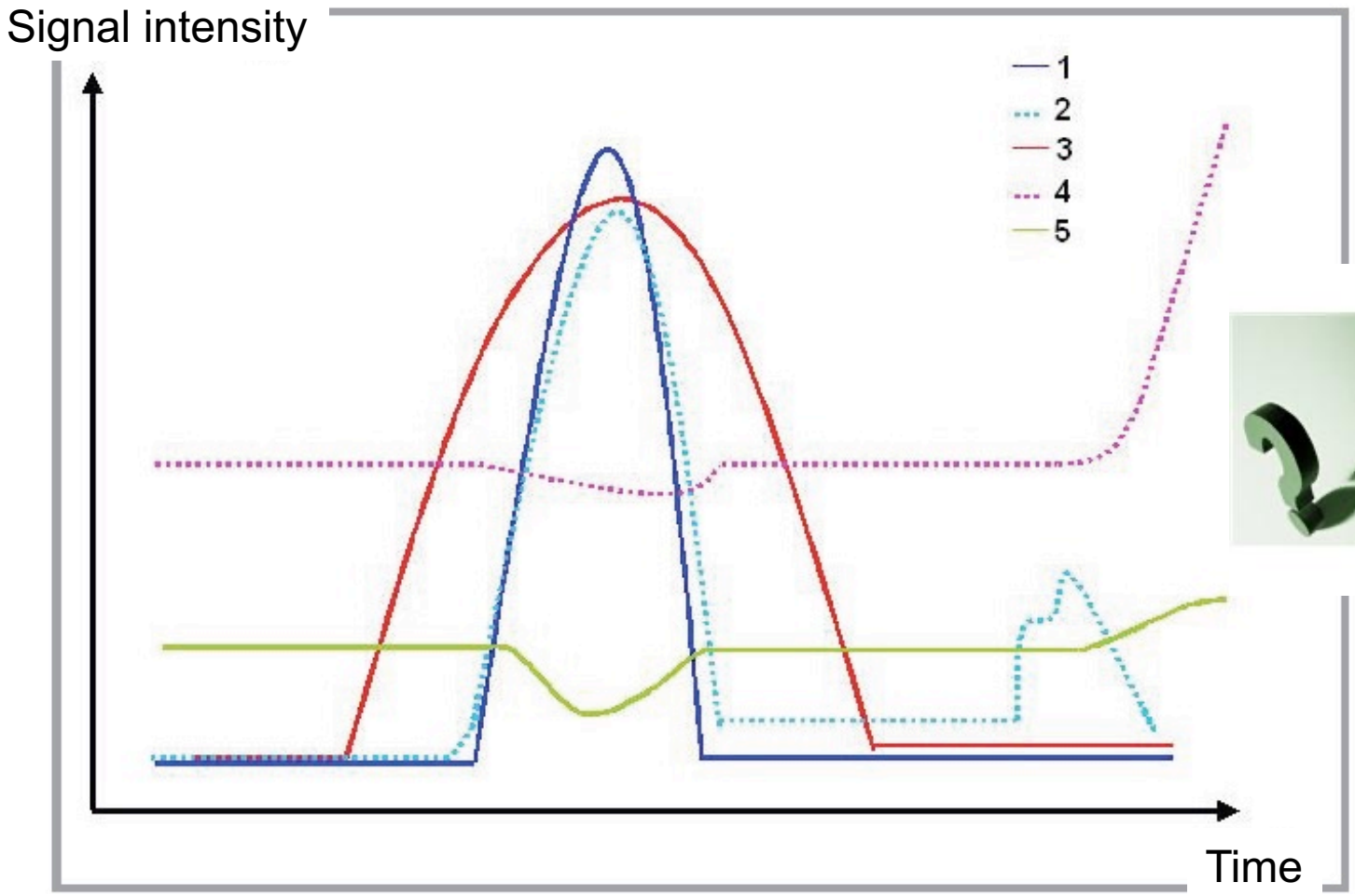


F_d: friction force

Correspond to energy lost by friction during tablet ejection

F_b: force felt by the lower punch

TABLET COMPRESSION and LUBRICANTS

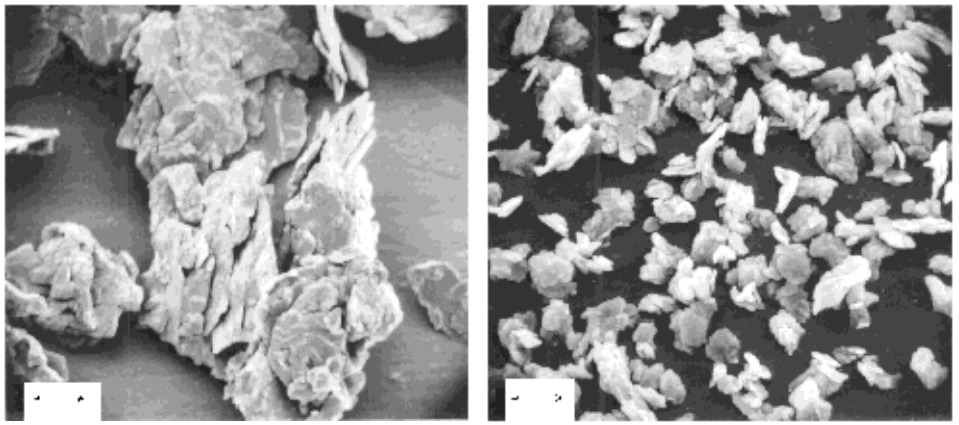


1. Force applied by the upper punch (full blue line)
2. Force felt by the lower punch (dotted blue line)
3. Upper punch displacement (full red line)
4. Lower punch displacement (dotted purple line)
5. Radial force (green line)

LUBRICANTS

MAGNESIUM STEARATE

$[CH_3(CH_2)_{16}COO]_2Mg$



GLIDANTS

Function: Improve flow sufficiently for uniform die filling

ex: Colloidal silicon dioxide, talc, magnesium or calcium silicate…

Compressibility / Carr Index
Hausner Index

DISINTEGRATING AGENTS

Function: disrupt the tablet structure and lead to fragmentation facilitating API dissolution.

Mode of action:

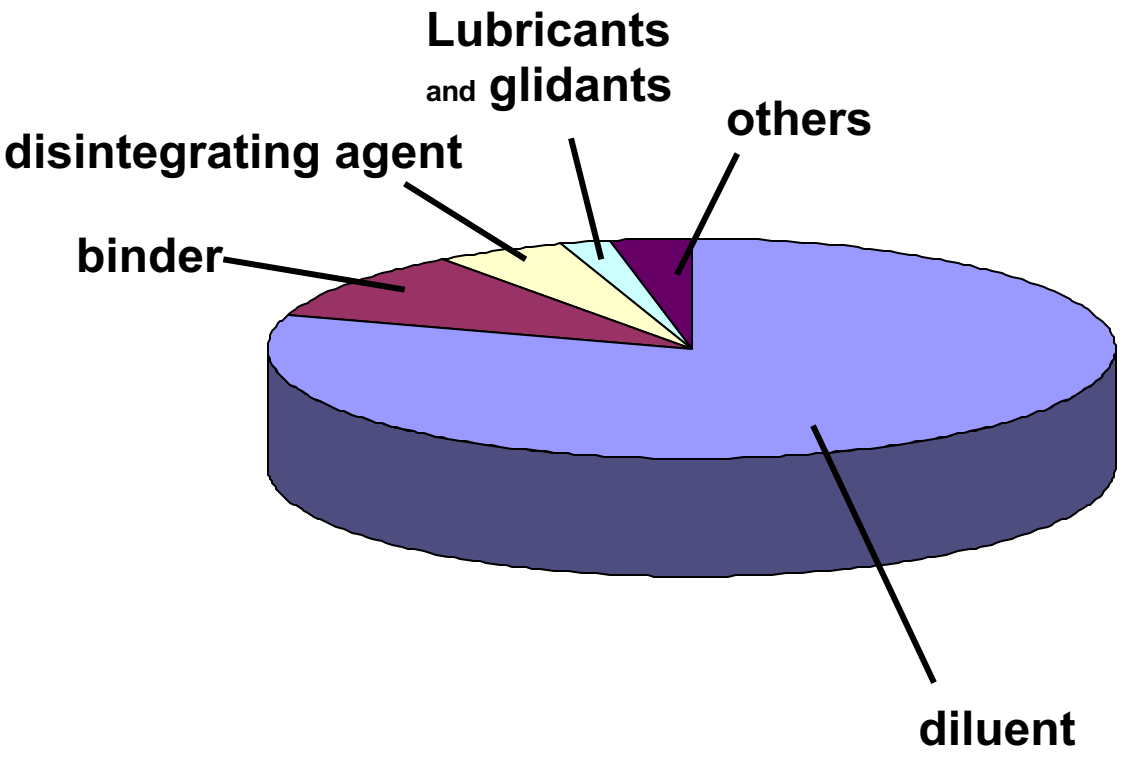
Favor water uptake

Disintegrating agent particles swell in presence of water

Examples: Starch, Reticulated Cellulose, PVP, Sodium starch glycolate, Sodium carboxymethylcellulose,…

PROPORTION OF THE EXCIPIENTS

In general in tablets (not specific to matrix)



CATEGORIES vs. GLOBAL PROPERTIES

Beyond classes, it is important to consider all the properties of the different excipients !

<u>Some</u> examples:

Use of cellulose

Use	Concentration (%)
Adsorbent	20-90
Anti-adherent	5-20
Capsule binder/diluent	20-90
Tablet disintegrant	5-15
Tablet binder/diluent	20-90

Lubricants and release kinetics

Magnesium stearate
vs.
Sodium laurylsulfate

Solubility of diluents

Calcium Phosphate
vs
Lactose

Mixture of diluents

Calcium Phosphate
+
Microcrystalline cellulose

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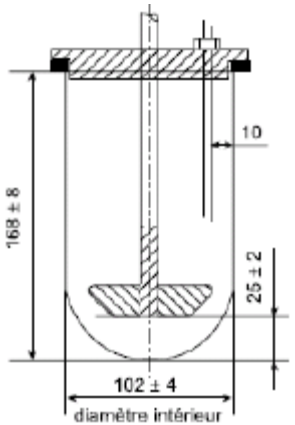
CONTROLS

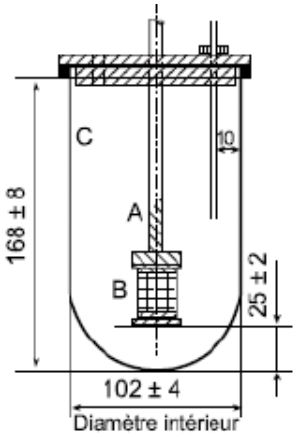
Potentially dangerous forms because they contain large doses (equivalent to several administration of conventionnal release dosage form)

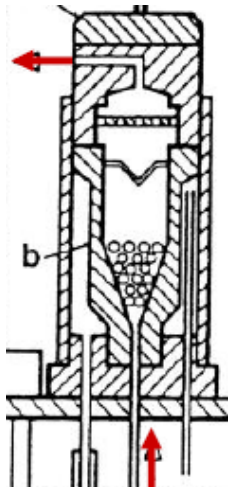
It is essential to validate the availability of the API

Drug dissolution testing, measuring the extent and rate of solution formation from a dosage form, is critical for its bioavailability and therapeutic effectiveness

Paddle apparatus/ Basket apparatus / continuous flow-through cell
Sink conditions







+ usual controls for tablets

- Uniformity (mass, dose)
- Mechanical properties
- Friability

…

UNIFORMITY OF MASS

Weigh 20 tablets and calculate the average mass. When weighed singly, the deviation of individual masses from the average mass should exceed the limits given below

Table 2.9.5.-1

Dosage form	Average mass	Percentage deviation
Tablets (uncoated and film-coated)	Not more than 80 mg	10
	More than 80 mg and less than 250 mg	7.5
	250 mg or more	5
Powders for injections or infusions*	More than 40 mg	10
Suppositories and pessaries	All masses	5
Other dosage forms unless other limits are specified in the dosage form monograph, including but not limited to capsules, uncoated granules, powders, powders for eye drops and powders for eye lotions	Less than 300 mg	10
	300 mg or more	7.5

* When the average mass is not more than 40 mg, the test for uniformity of content of single-dose preparations (*2.9.6*) is performed instead of the test for uniformity of mass.

Max 2 out this range
0 out the double of this range

TABLET HARDNESS

Crushing Strength Test
This measures the degree of force needed to fracture a tablet.

Measurement accuracy: 1 Newton

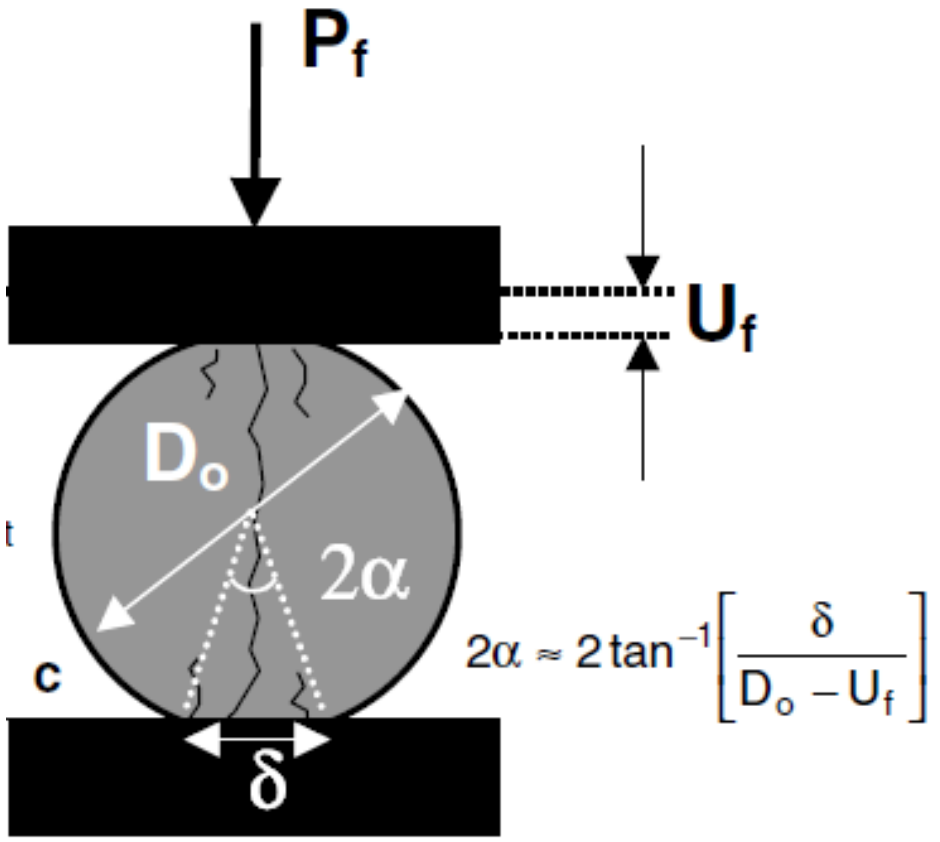
Number of units tested: 10

TENSILE STRENGTH

Tensile strength (MPa)
(only if diametral fracture)

$$\sigma = \frac{2F}{\pi De}$$

F: force needed to fracture tablet (N)
D: tablet diameter (mm)
e: tablet thickness (mm)



Allows to overcome the dimensions of tablets

Recommended values: 1 to 2 MPa

FRIABILITY

Required amount of tablets is dedusted, weighed and subjected to a uniform tumbling motion for a specified time. They are then dedusted and reweighed.

Mean tablet mass > 650 mg : 10 tablets
< 650 mg: closest to 6.5 g

100 rotations = 4 minutes

Limit: < 1%

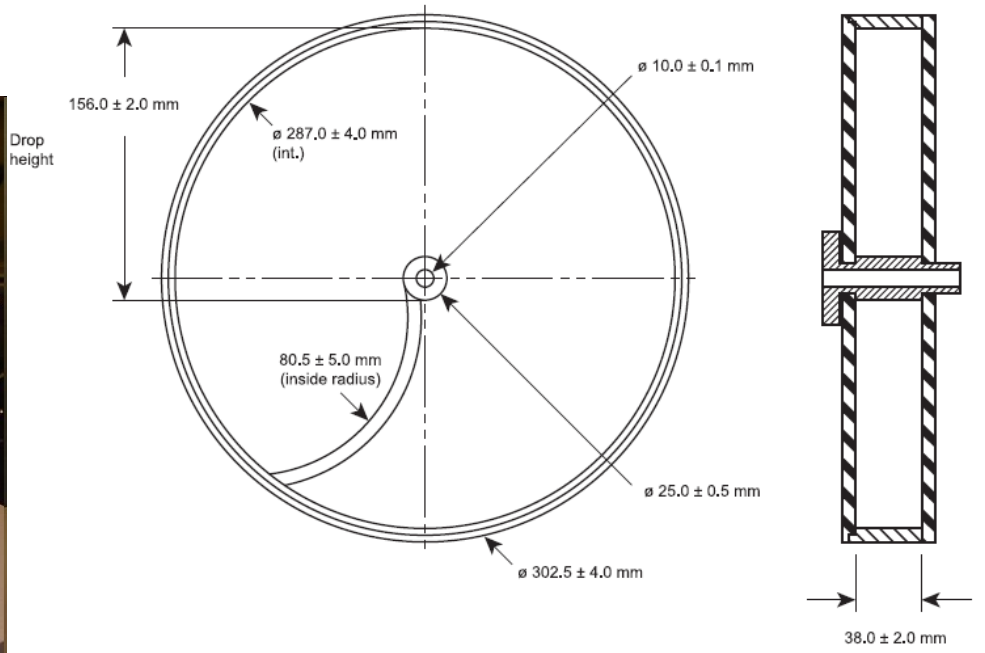
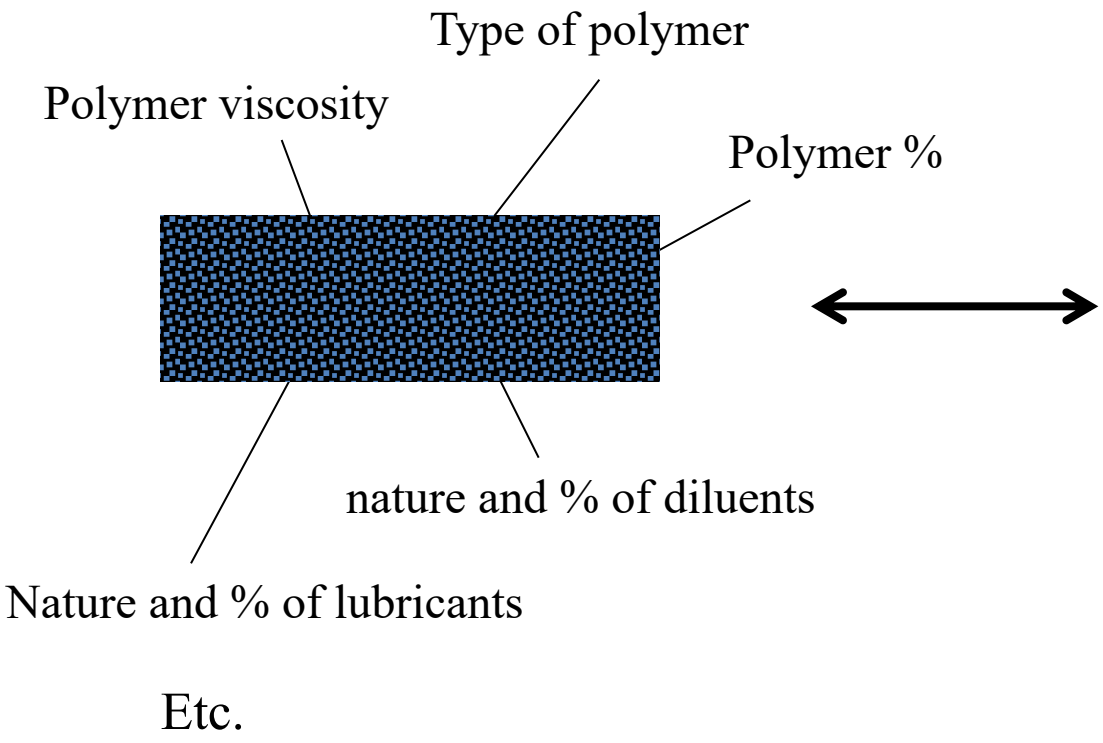


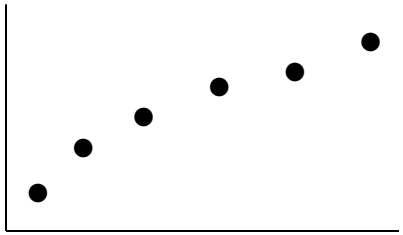
Figure 2.9.7.-1. – *Tablet friability apparatus*

PRACTICAL WORKS

Practical work objective:
To develop matrix tablets able to release 50% of a defined API into 4 hours.



Release kinetics

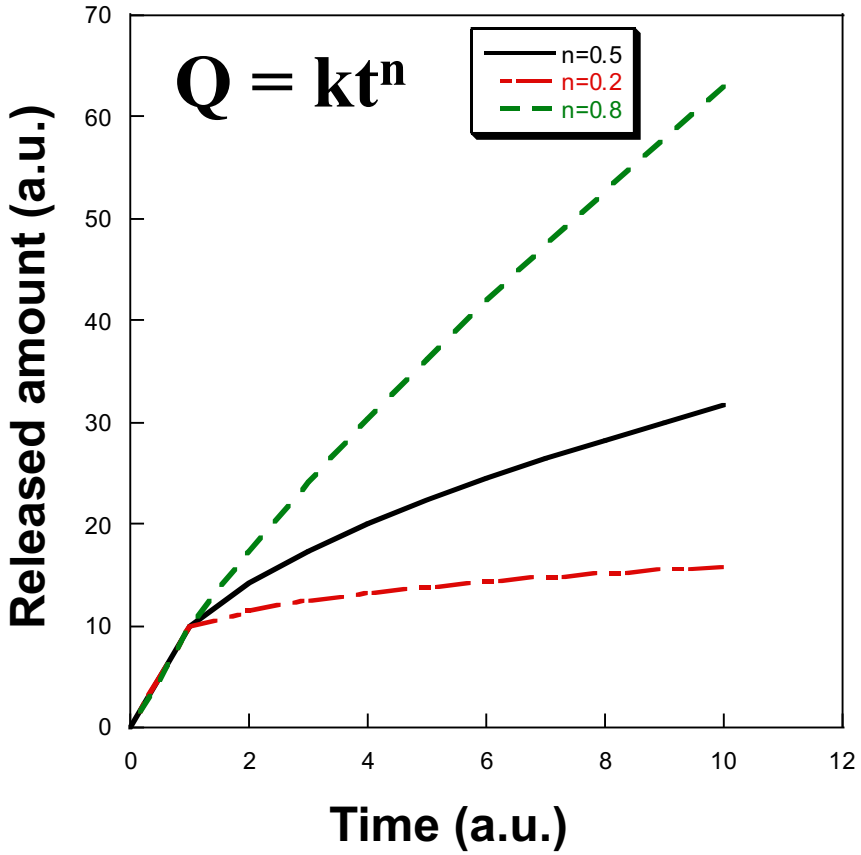


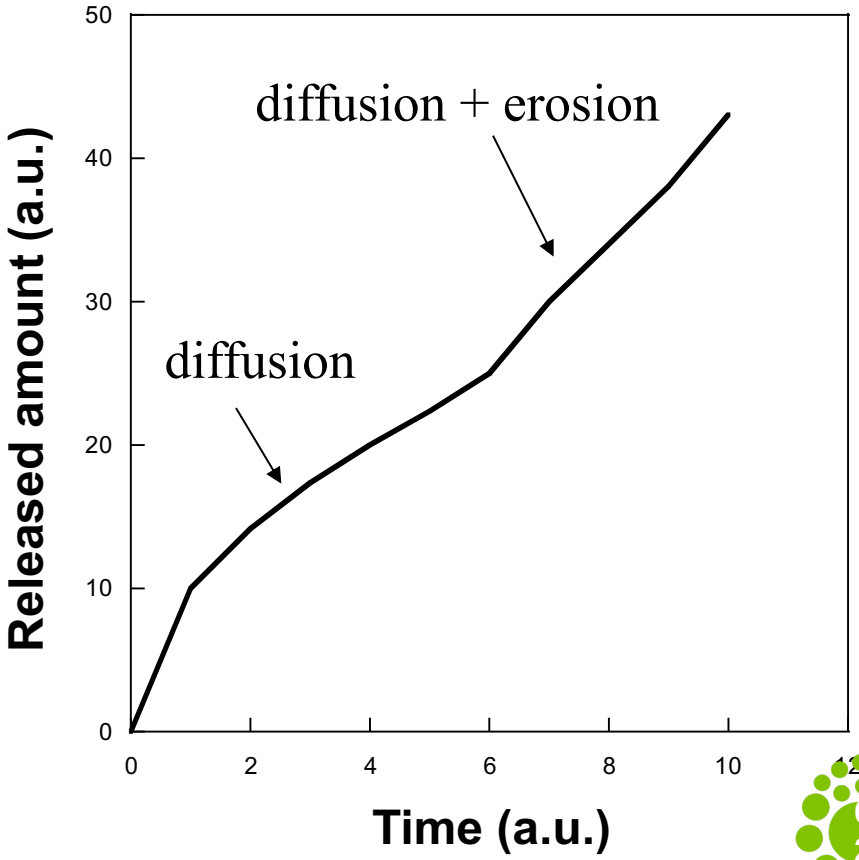
Fit of experimental data

- To determine release mechanism

- To predict the amount released after 4 hours

CONCLUSION


Q = kt^n
n=0.5
n=0.2
n=0.8
Released amount (a.u.)
Time (a.u.)
0
10
20
30
40
50
60
70
0
2
4
6
8
10
12


diffusion + erosion
diffusion
Released amount (a.u.)
Time (a.u.)
0
10
20
30
40
50
0
2
4
6
8
10