Drug release tests

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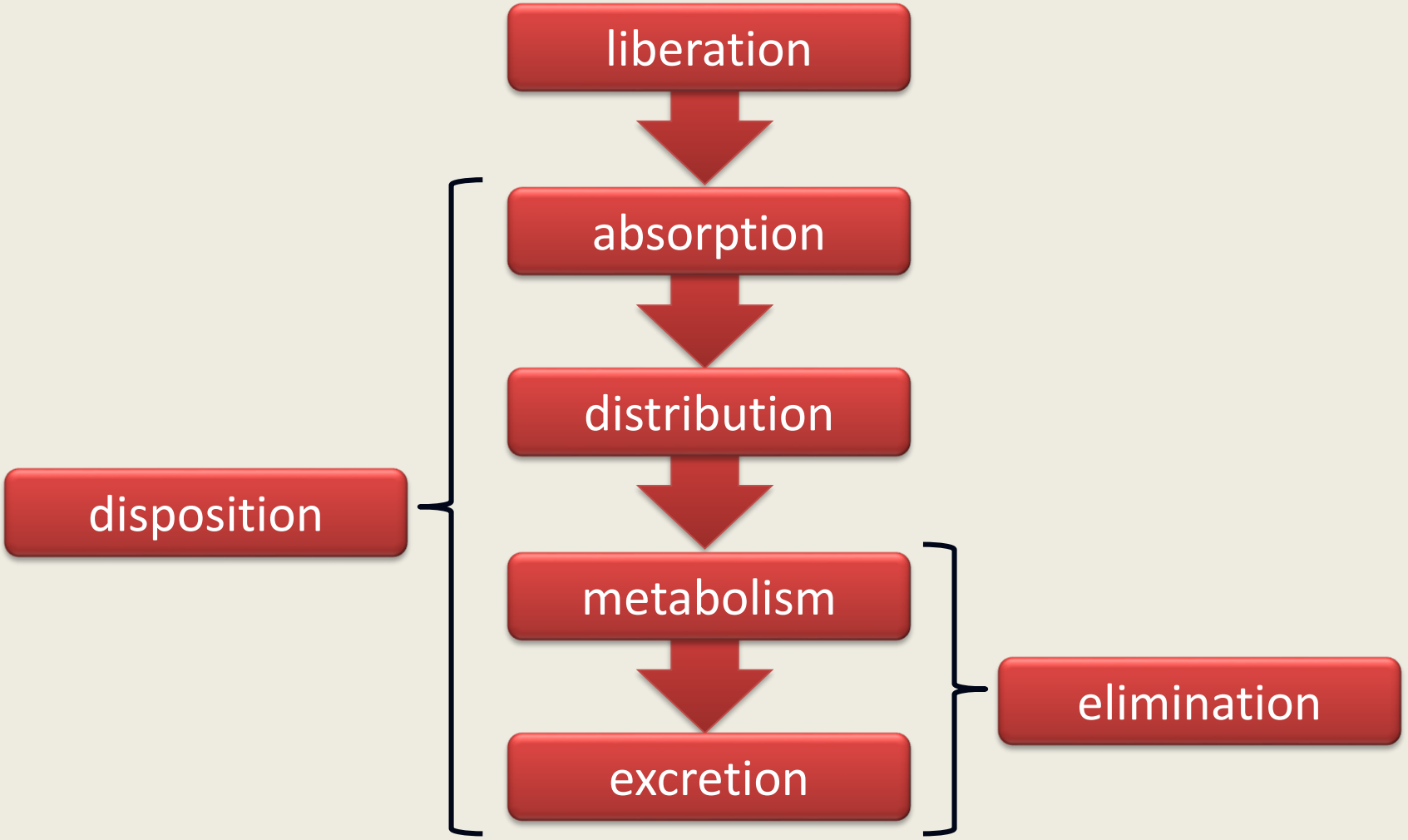
LADME system



1897

- Noyes & Whitney
  - "The Rate of Solution of Solid Substances in Their Own Solution."
  - Rate of drug dissolution is regulated by the saturated solution on the surface of the API particle

1900

- Brunner & Tolloczko
  - Prove that the dissolution depends on the physico-chemical character of the API particle (surface, temprature…)

1904

- Nernst & Brunner
  - Modify the Noyes-Whitney formula by integrating Fick's law of diffusion

IVIVC

- FDA – in vivo-in vitro correlation – mathematical aspect

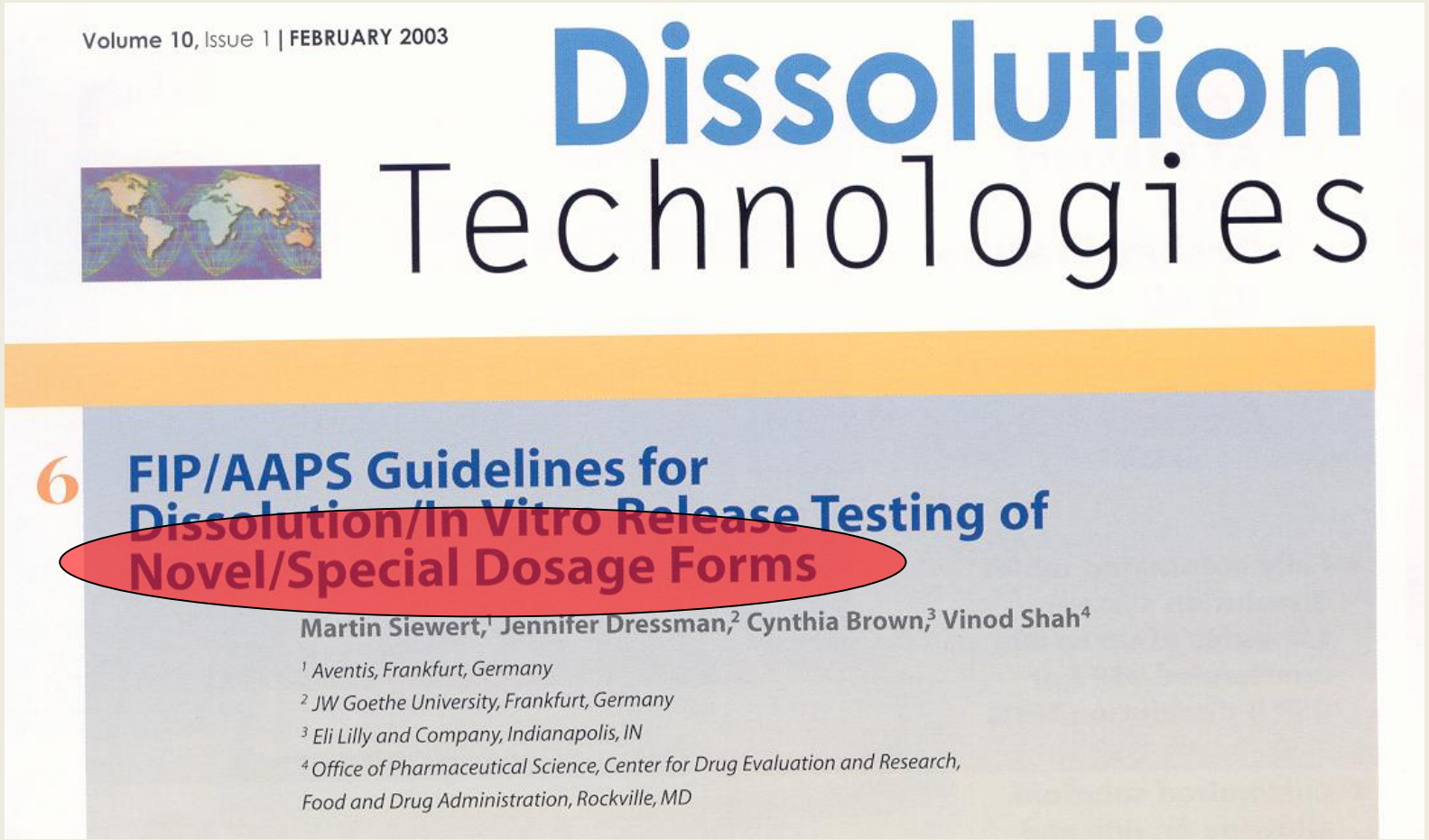
1934

- Pharmacopoea Helvetica – describes the disintegration test for the first time

1970

- USP 18 introduced the first official drug dissolution test: rotating basket method (Apparatus 1)

2003



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Dissolution Technologies

6

FIP/AAPS Guidelines for Dissolution/In Vitro Release Testing of Novel/Special Dosage Forms

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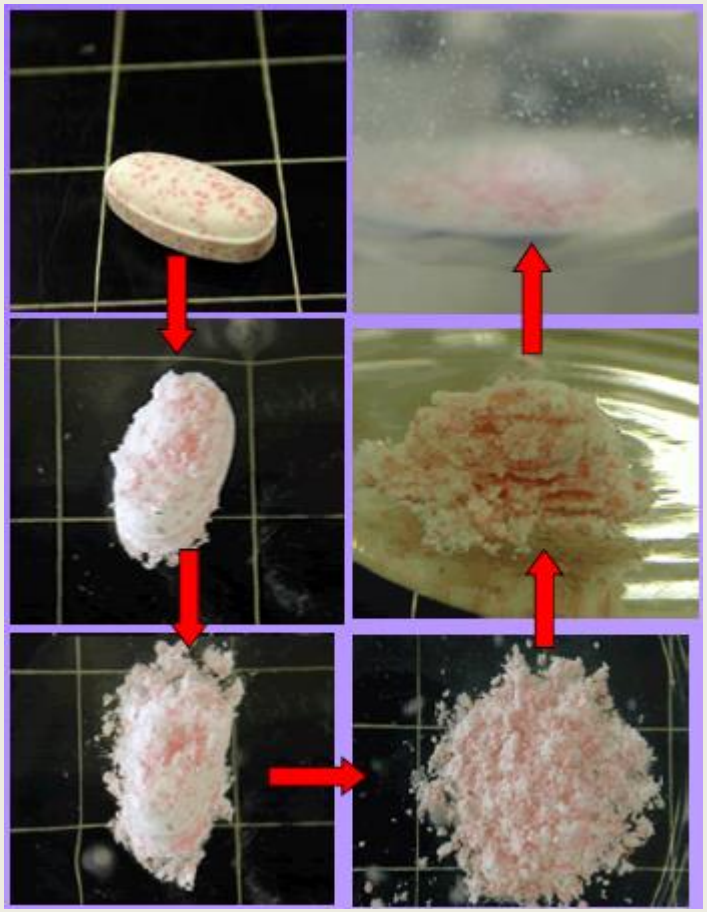
Table 1: Apparatus used for Novel/Special Dosage Forms

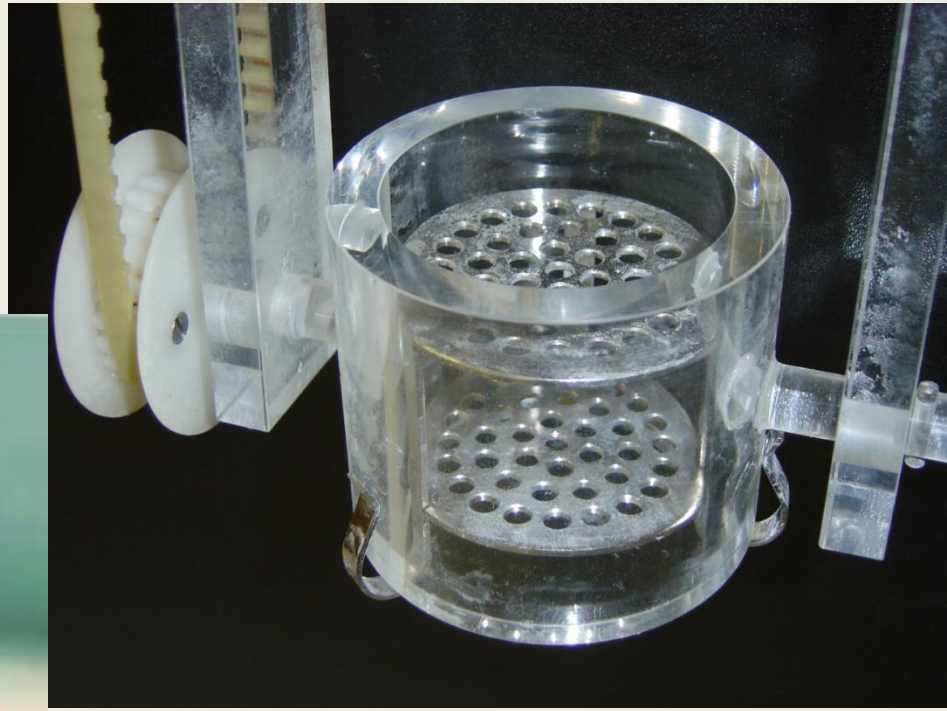
Type of Dosage Form	Release Method
Solid Oral Dosage Forms (conventional)	Basket, Paddle, Reciprocating Cylinder or Flow Through Cell
Oral Suspensions	Paddle
Oral disintegrating Tablets	Paddle
Chewable Tablets	Basket, Paddle or Reciprocating Cylinder with glass beads
Transdermals – Patches	Paddle Over Disk
Topicals – Semisolids	Franz Cell Diffusion System
Suppositories	Paddle, modified Basket or Dual Chamber Flow Through Cell
Chewing Gum	Special apparatus (Ph.Eur.)
Powders and Granules	Flow Through Cell (powder/granule sample cell)
Microparticulate Formulations	Modified Flow Through Cell
Implants	Modified Flow Through Cell

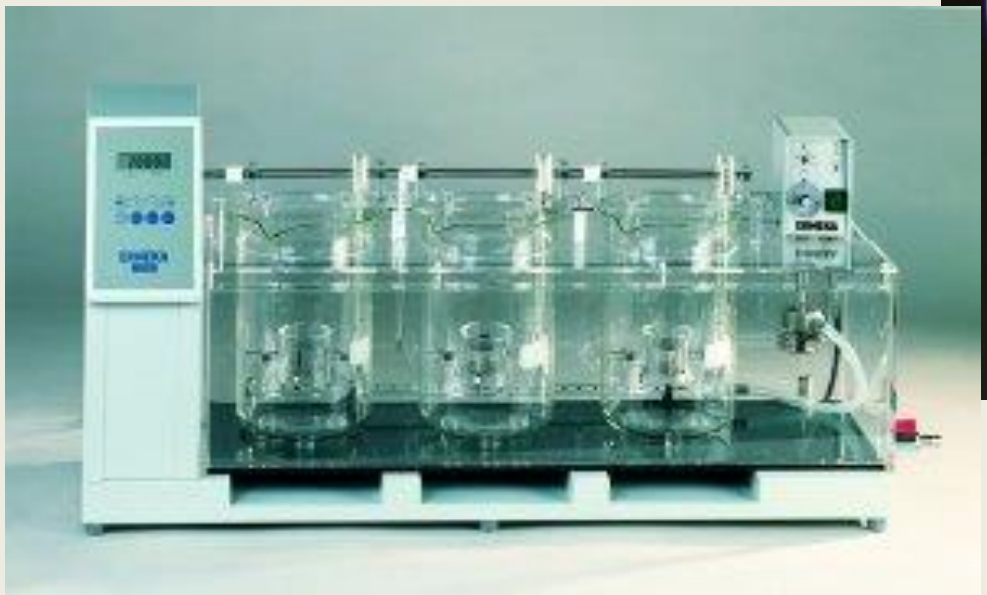
Disintegration tester



Disintergation tester

Test for suppositories





Drug release of dosage forms

- During drug release the appearence of the API is determined in the dissolution media in function of time.

According to the equipment structure:

- Closed system
- Open system
- Diffusion system

According to the changing amount of API in the dissolution media:

- Cumulative tests
- Differential tests

Conditions of the test

- Applied equipment
- Dissolution medium
  - Distilled water
  - HCl
  - Buffer
  - Artificial gastric juice
  - Artificial intestinal juice
  - Surfactants
- Rotation per minute
- Sampling time, method and amount
- Analytics

Dissolution tests

Recommended pH values

pH	Dissolution media
pH 1.0	HCl
pH 1.2	HCl & NaCl
pH 1.5	HCl & NaCl
pH 4.5	Phosphate or acetate buffer
pH 5.5 and 5.8	Phosphate or acetate buffer
pH 6.8	Phosphate buffer
pH 7.2 and 7.5	Phosphate buffer

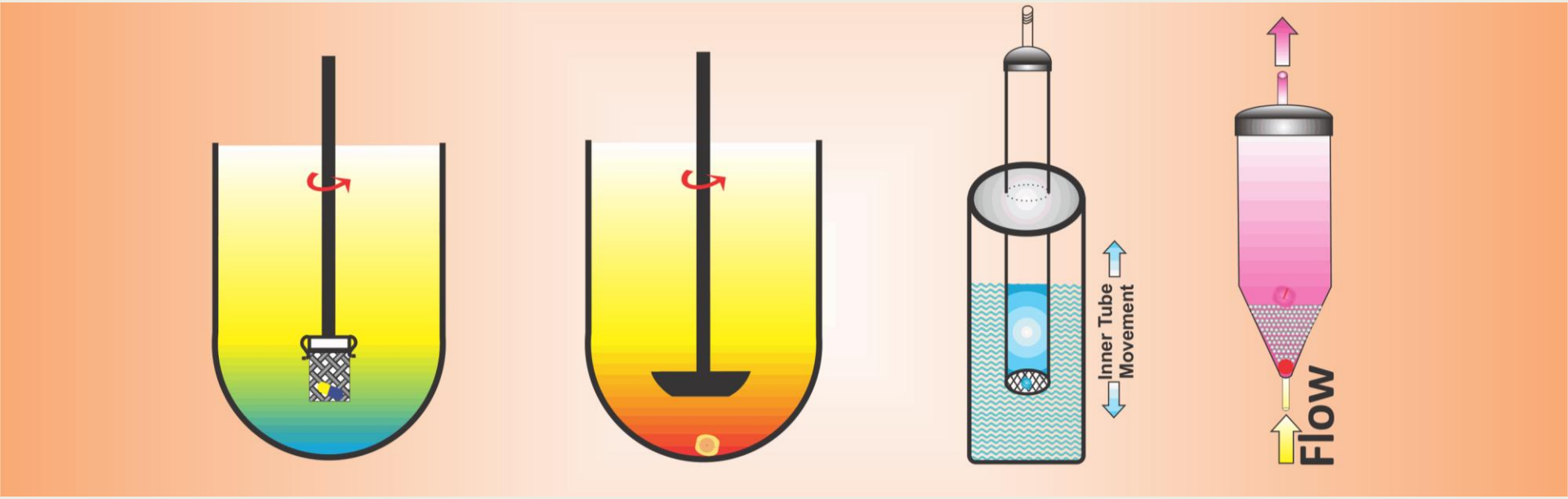
0-1 h	1-2 h	2-3 h	3-4 h	4-5 h	5-6 h	6-7 h	7 h
1.0							
1.2	6.8						
1.2	2.5	4.5	7.0		7.5		
1.5	4.5			7.2			

Dissolution test

Increasing the IVIVC correlation

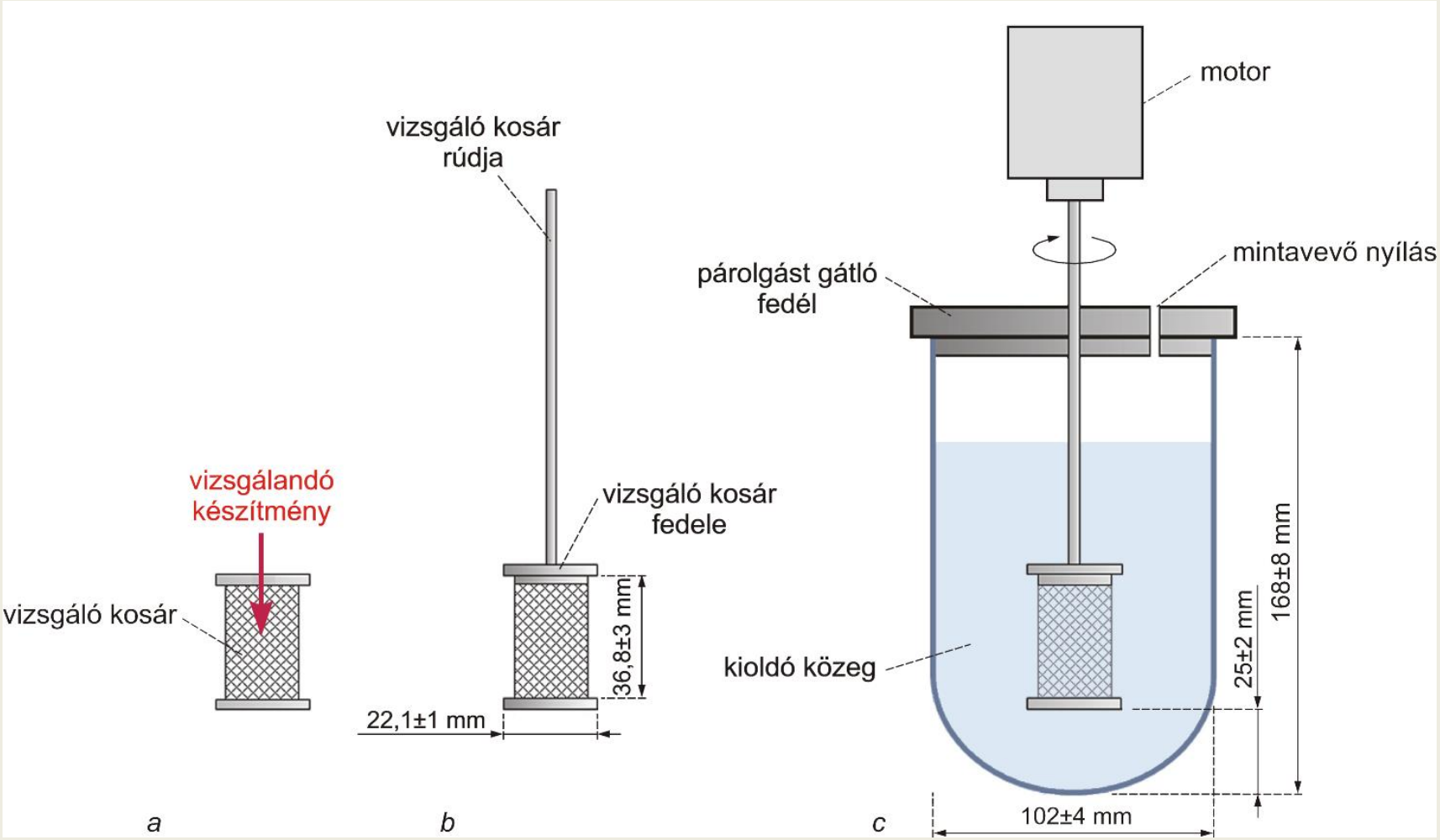
Physiological factors	In vitro factors
pH	Different dissolution media (pH)
GI motility	Stirring conditions
Fat and protein, food interactions	Adding fat or milk
Enzymes	Applying enzymes
Bile	Applying surfactants
GI transit time	pH-gradient tests

Dissolution testers (1,2,3,4)



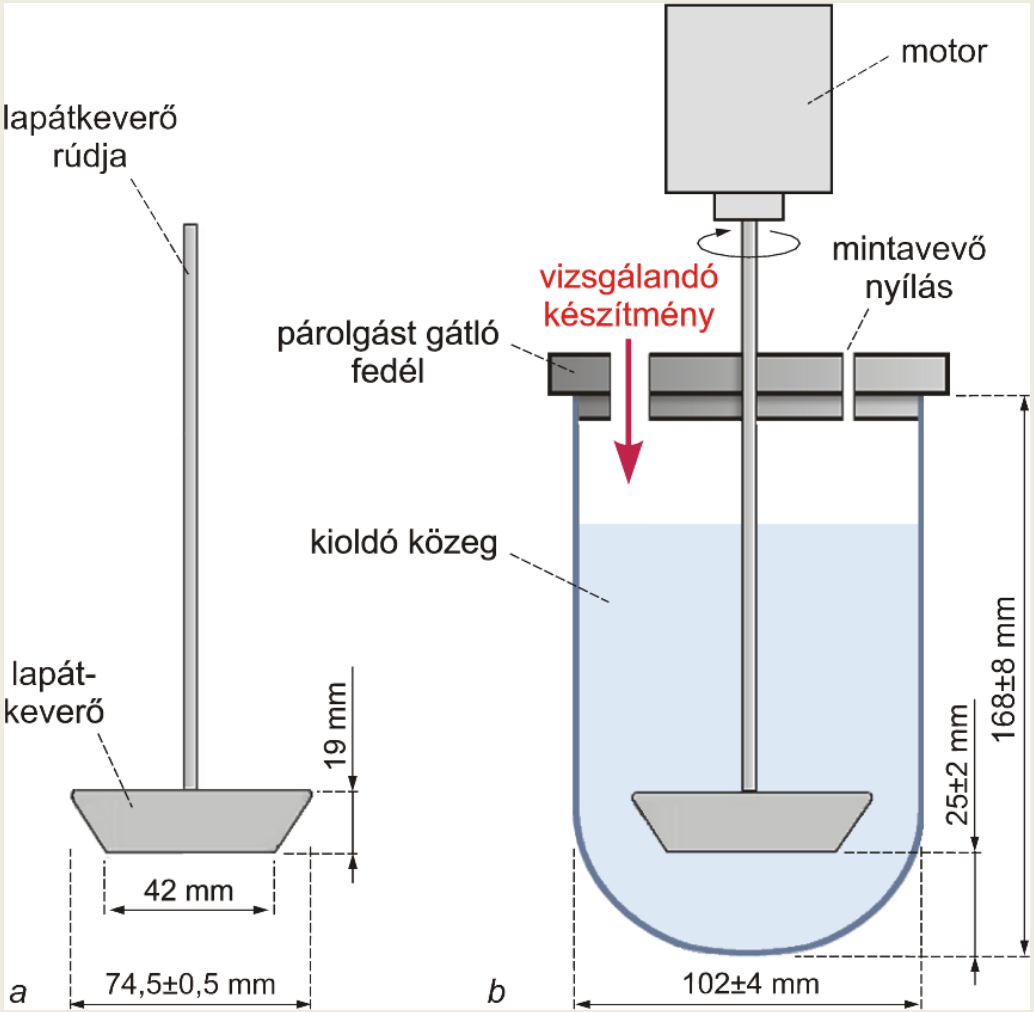
Dissolution test

Solid dosage forms – rotating basket apparatus



Dissolution test

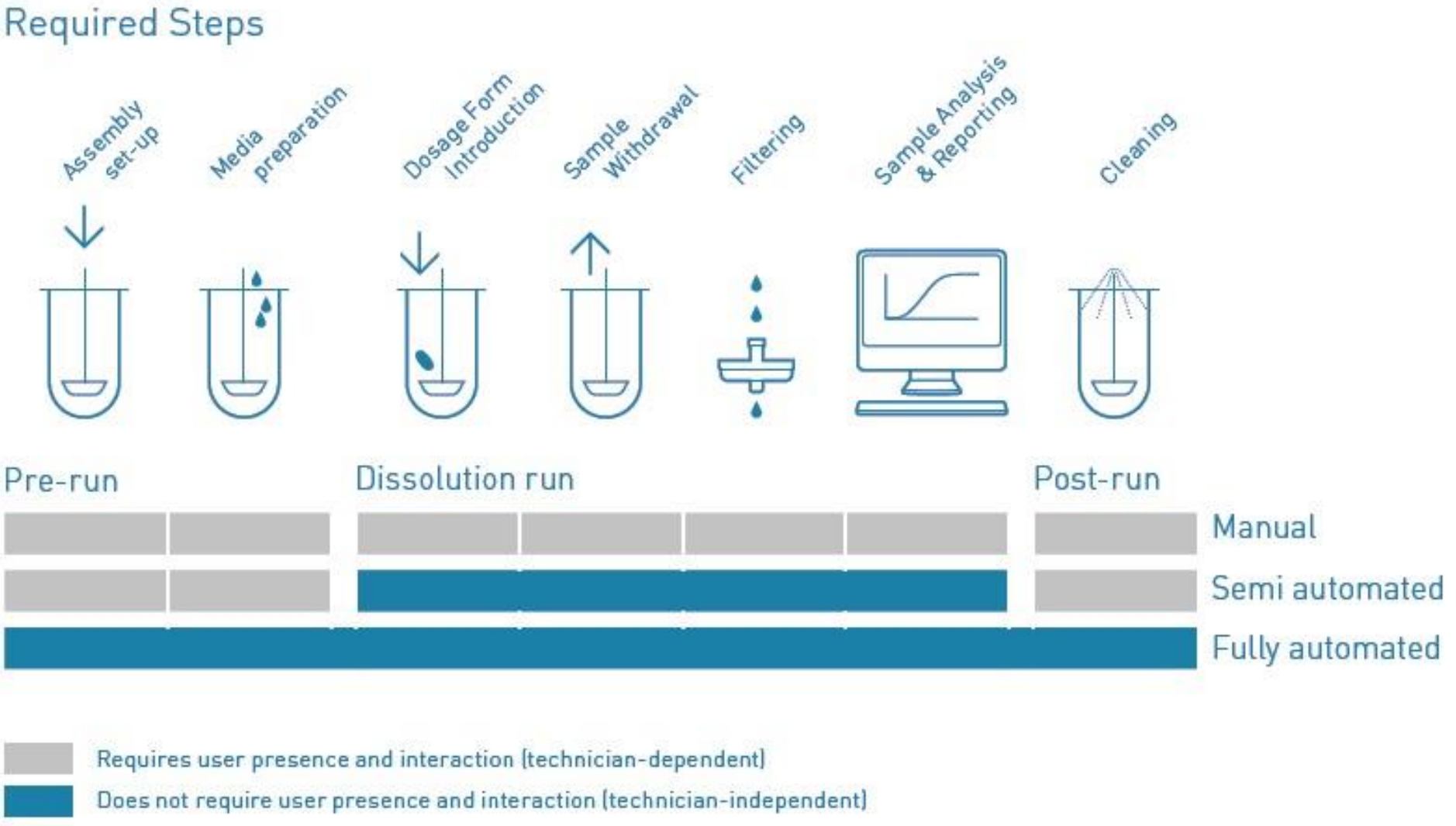
Solid dosage forms – paddle apparatus



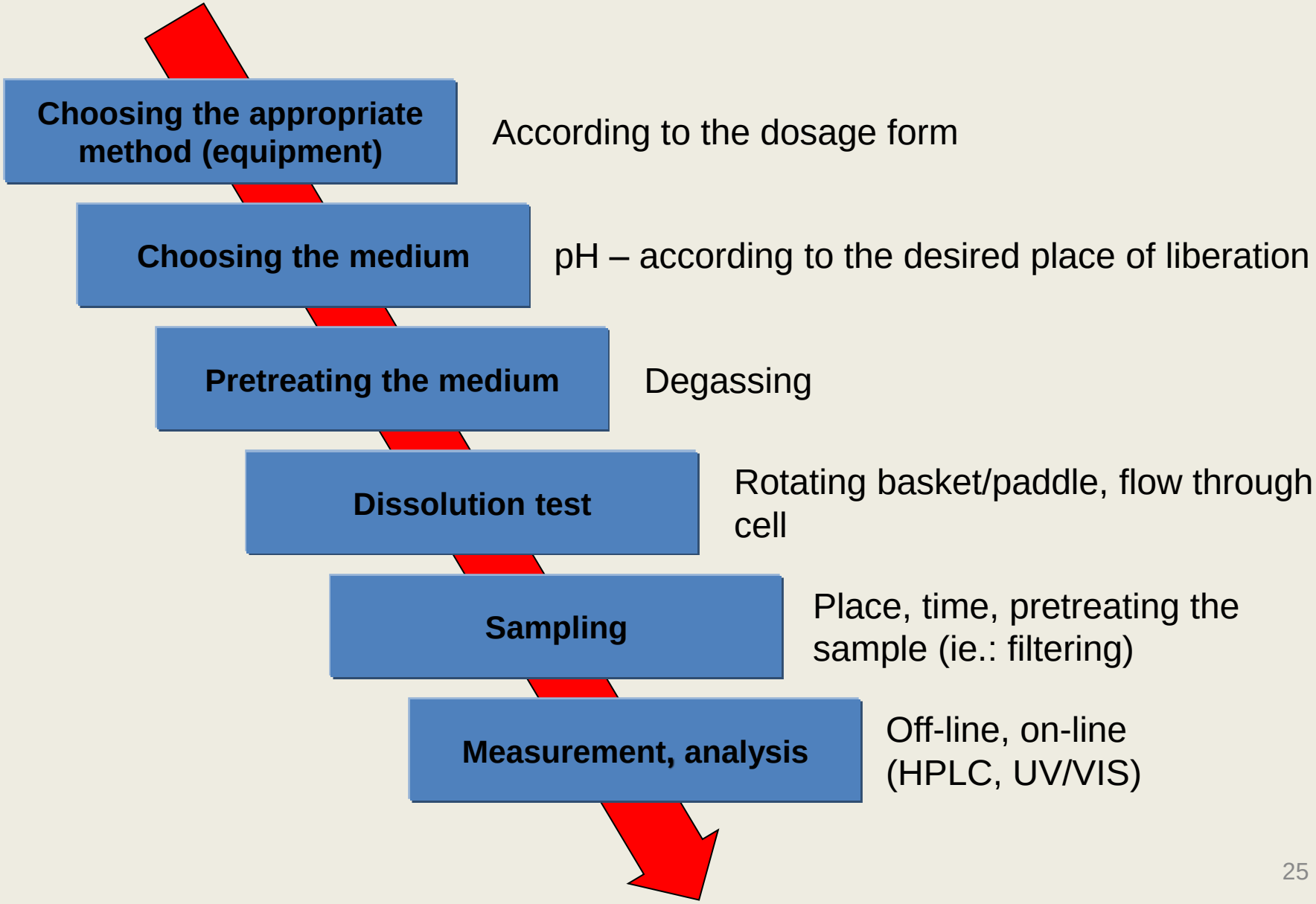
International Conference on Harmonisation (ICH)

- Rotating basket method (50/100 rpm)
- Rotating paddle method (50/75 rpm)
- Sampling time every 15 min, at rapid preparations in every 5-10 min
- Volume: 500 ml, 900 ml, 1000 ml (sink conditions)
- pH=1.2-6.8 (not more than pH=8.0)

Dissolution run



Drug dissolution procedure



Degassing

- Incorrect dagassing can lead to decreased or increased API levels:
  - Bubbles can adhere on the surface of the preparation (tablet) and it can swim on the dissolution medium surface → different hydrodynamic conditions
  - Bubbles can adhere on the surface of the rotating basket

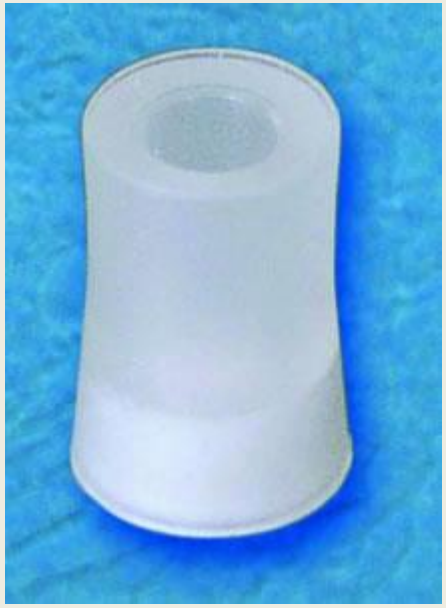
Dissolution tester

Dissolution tester

Sampling canulla

UHMW – poly-ethylene – 35-40µm average pore size

Canulla filters



Paddle

PTFE – paddle

Basket

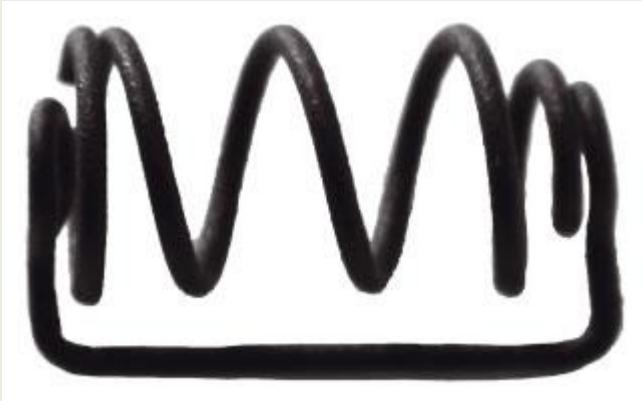
Basket

Basket


1000 ml
900
800
700
600
500
400
GLA300-AV

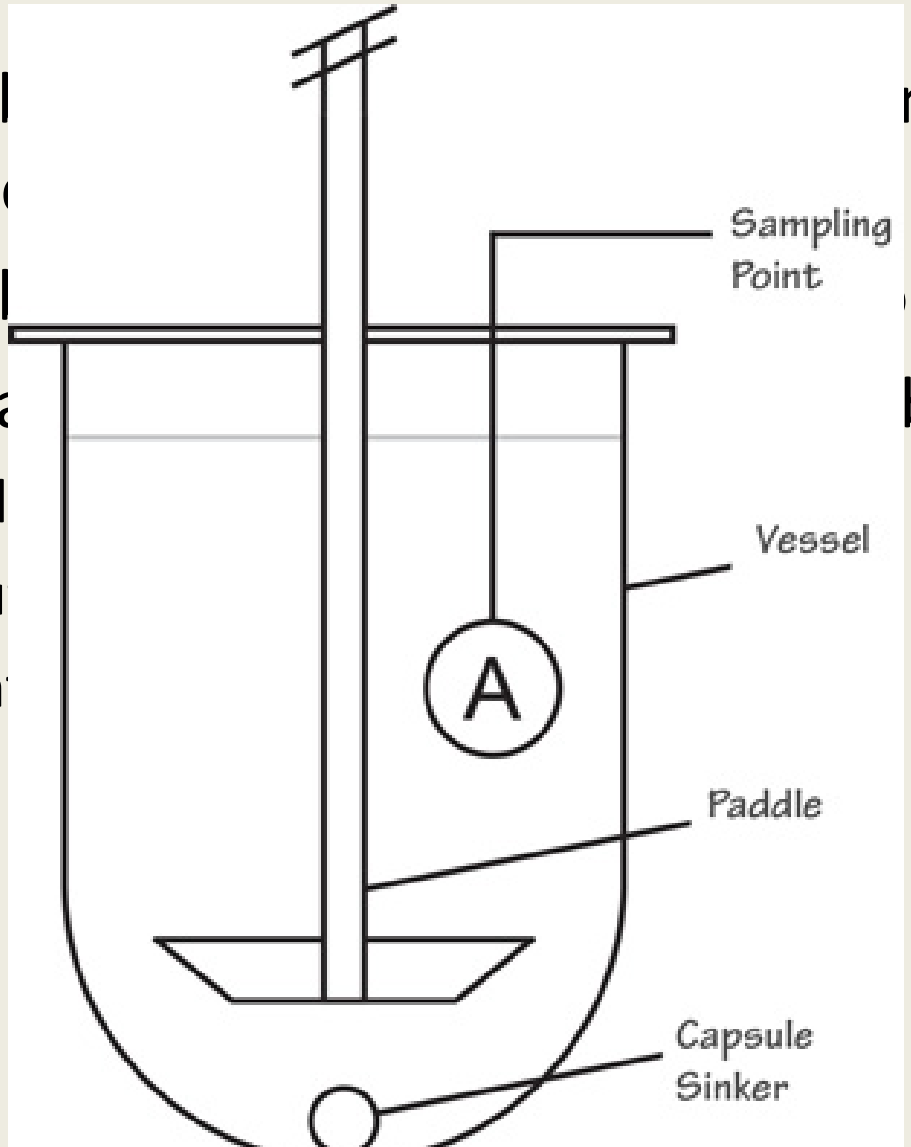
Sinker

Sinker



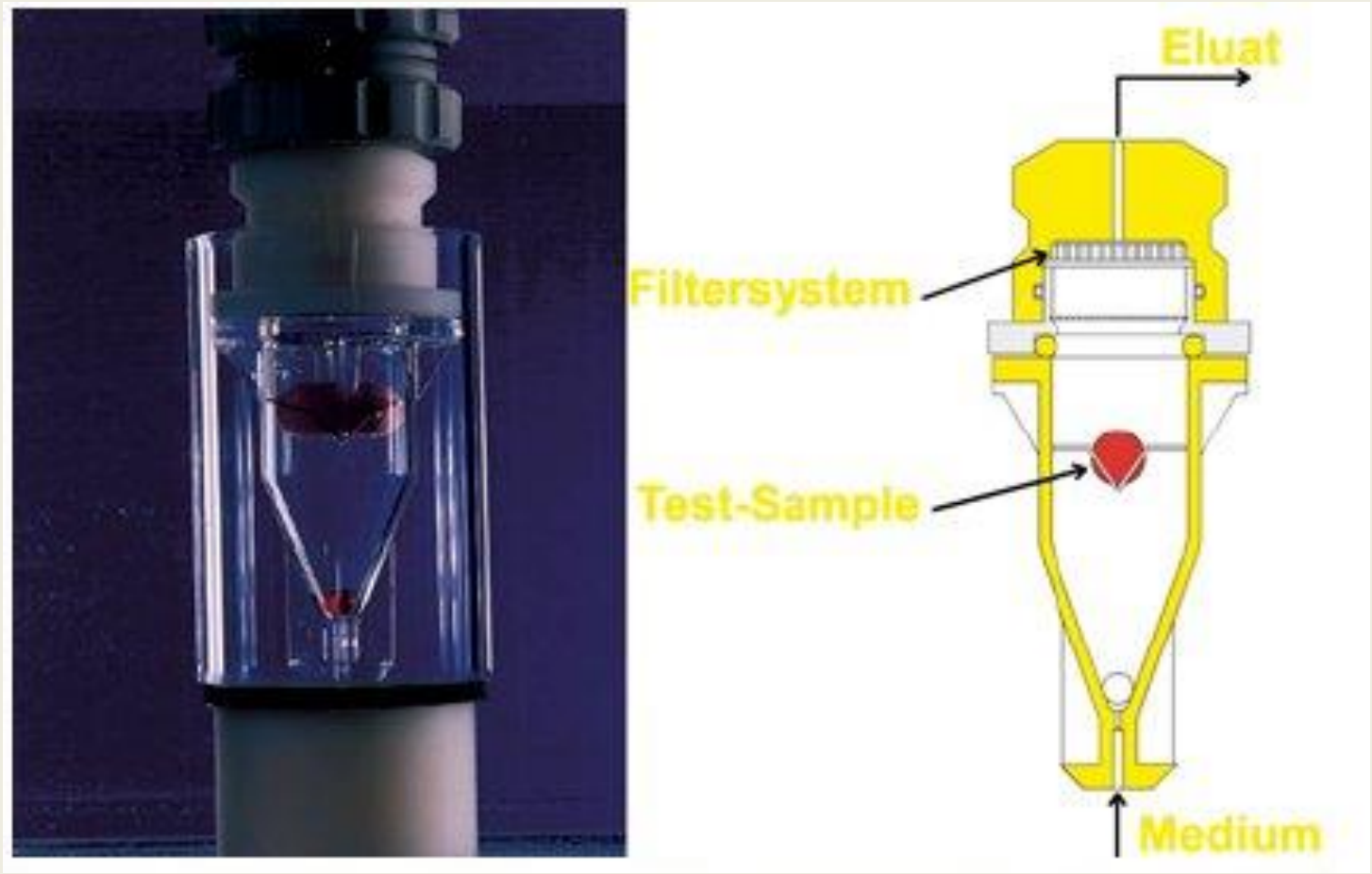
Place of sampling

- It should l m level and upper leve
- It should l ntainer.
- Sampled a be
  - injected
  - substitu
  - taken in

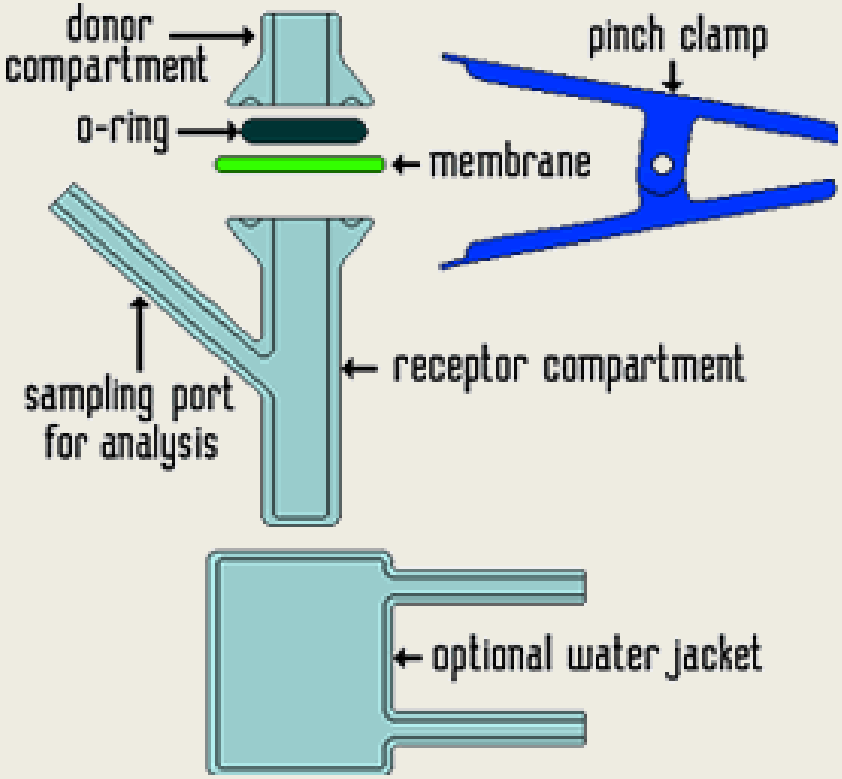


Flow-through cell

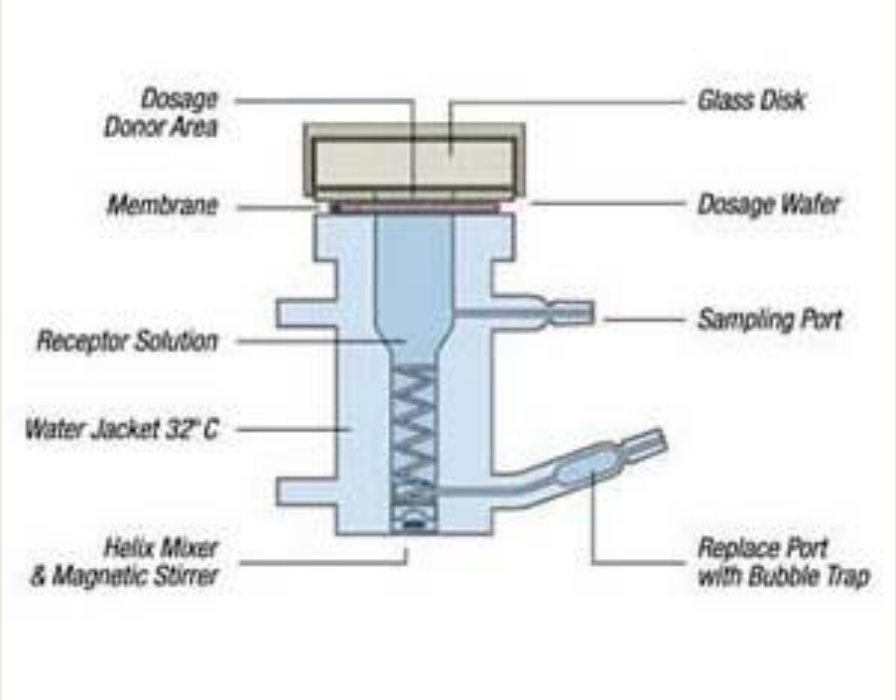
- Structure:
  - **Container** of the medium
  - **Pump** – pumps the medium through the cell
  - **Flow-through cell**
  - **Water bath**


Eluat
Filtersystem
Test-Sample
Medium

Transdermal drug dissolution



Franz-cell


Dosage
Donor Area
Glass Disk
Membrane
Dosage Wafer
Sampling Port
Receptor Solution
Water Jacket 32° C
Helix Mixer
& Magnetic Stirrer
Replace Port
with Bubble Trap

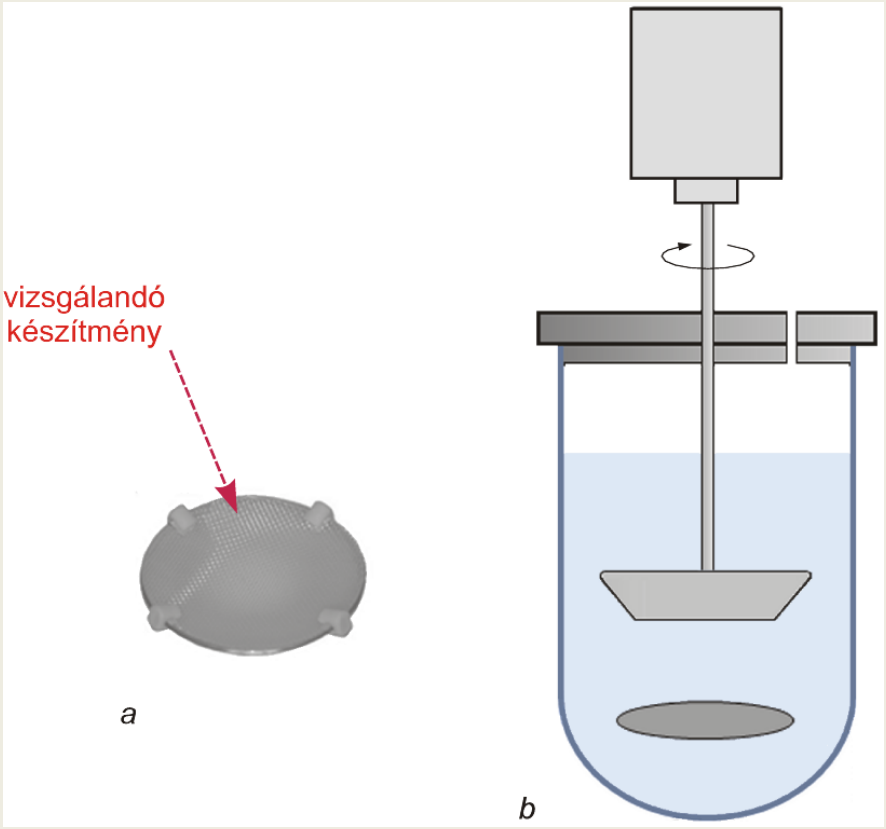
MicroettePlus

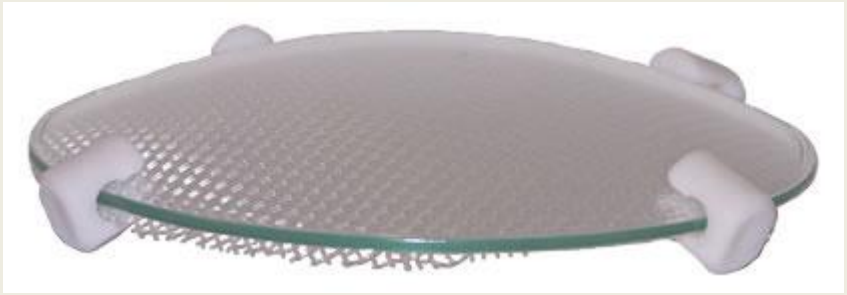
Transdermal patches dissolution test

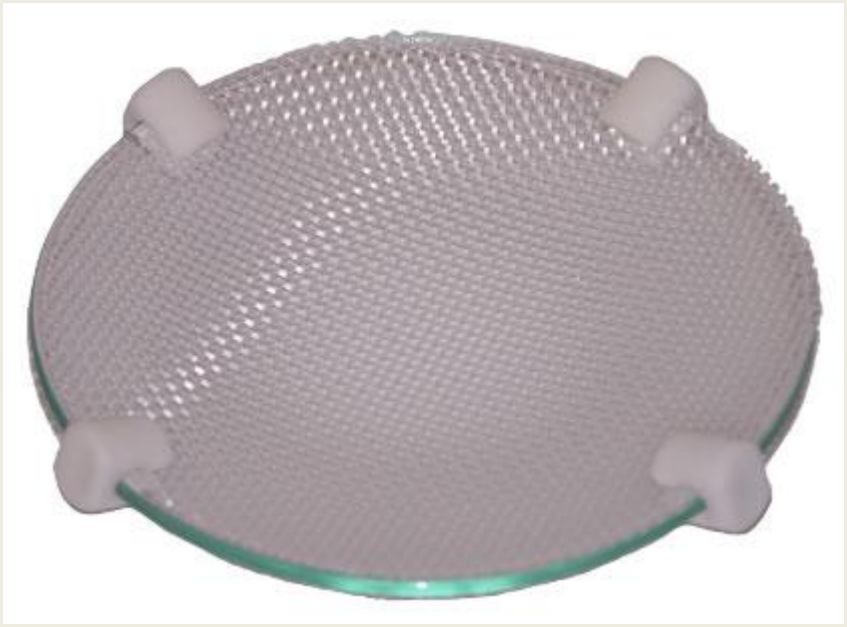
- Disk assembly method
  - Rotating paddle is used
  - 125 µm steel sieve is applied
  - Patch should be placed in the container with its release surface facing up
  - Temperature: 32 ± 0.5°C

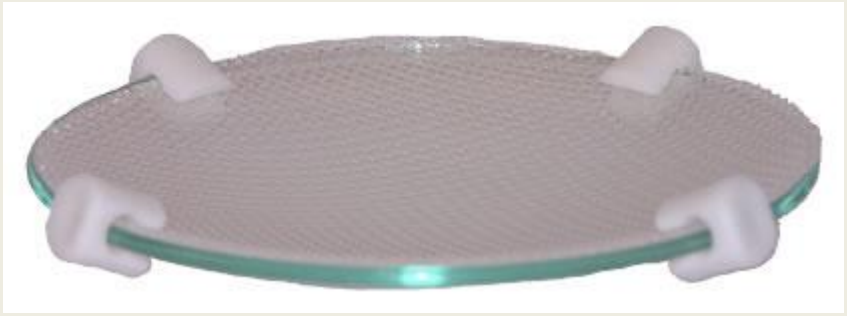
Dissolution tests for patches

Disk assembly method









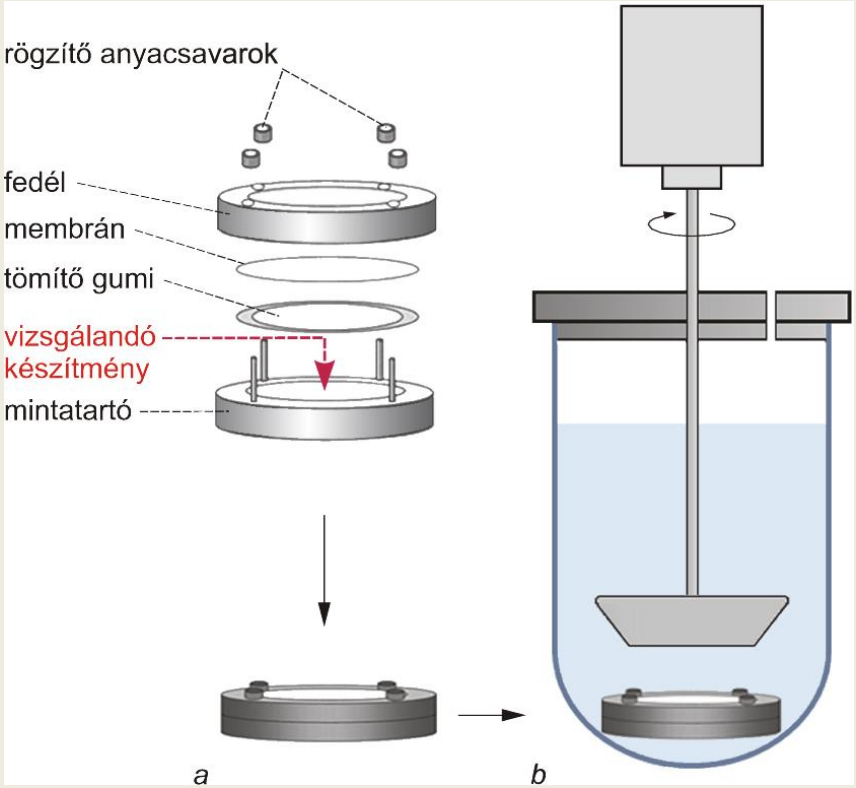
USP Apparatus 5

Transdermal patches dissolution test

- Cell method
  - Paddle is used
  - Cell is stainless steel

Dissolution tests for patches

Cell method

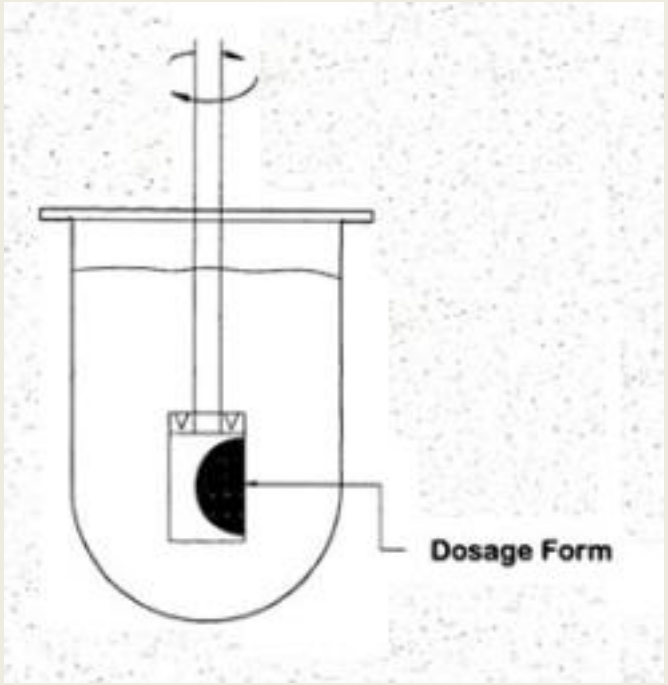


Transdermal patches dissolution test

- Rotating cylinder method
  - Paddle is substituted with a cylinder

Dissolution tests for patches

Rotating cylinder method

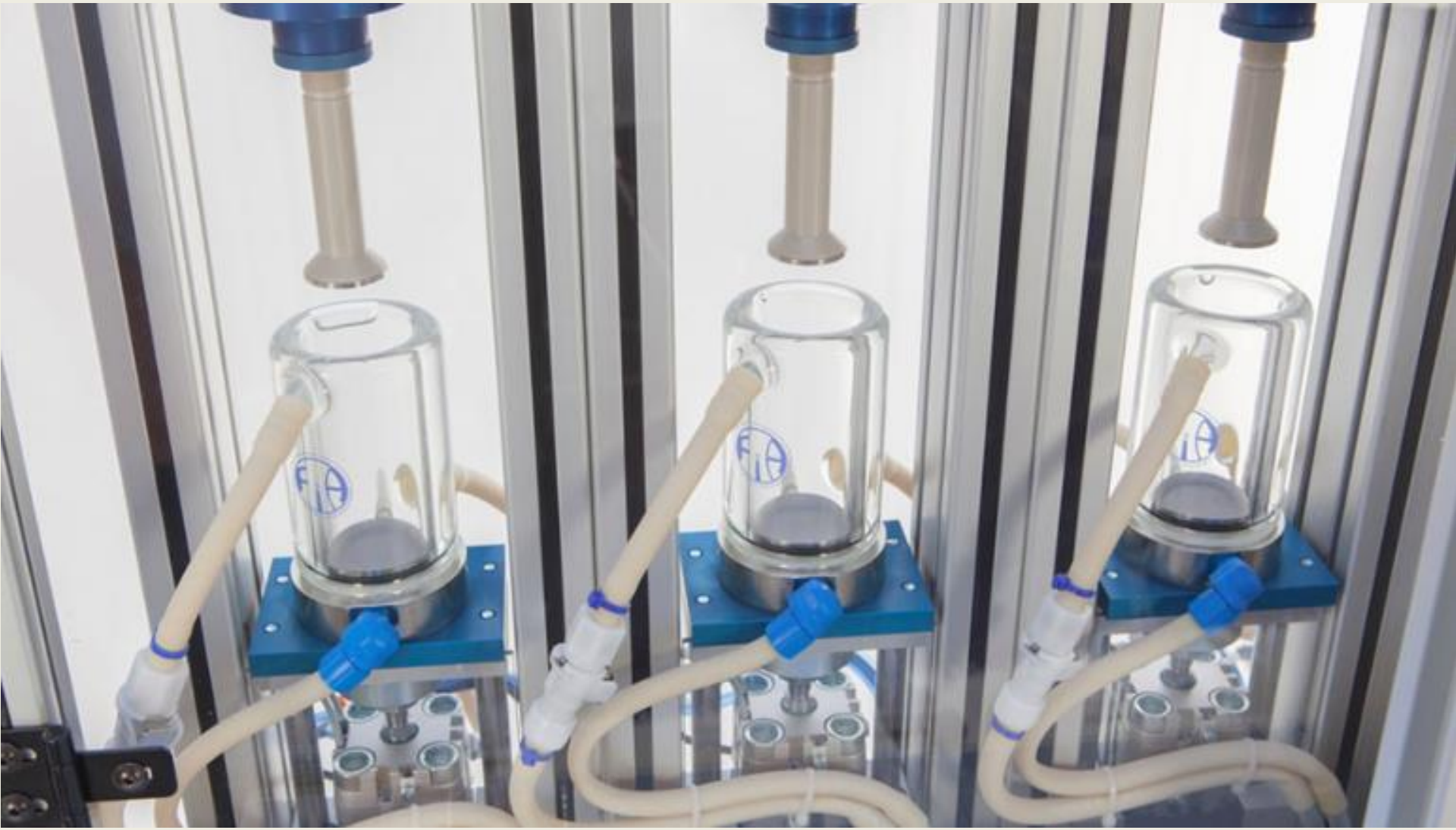


USP Apparatus 6

Chewing gum's dissolution test

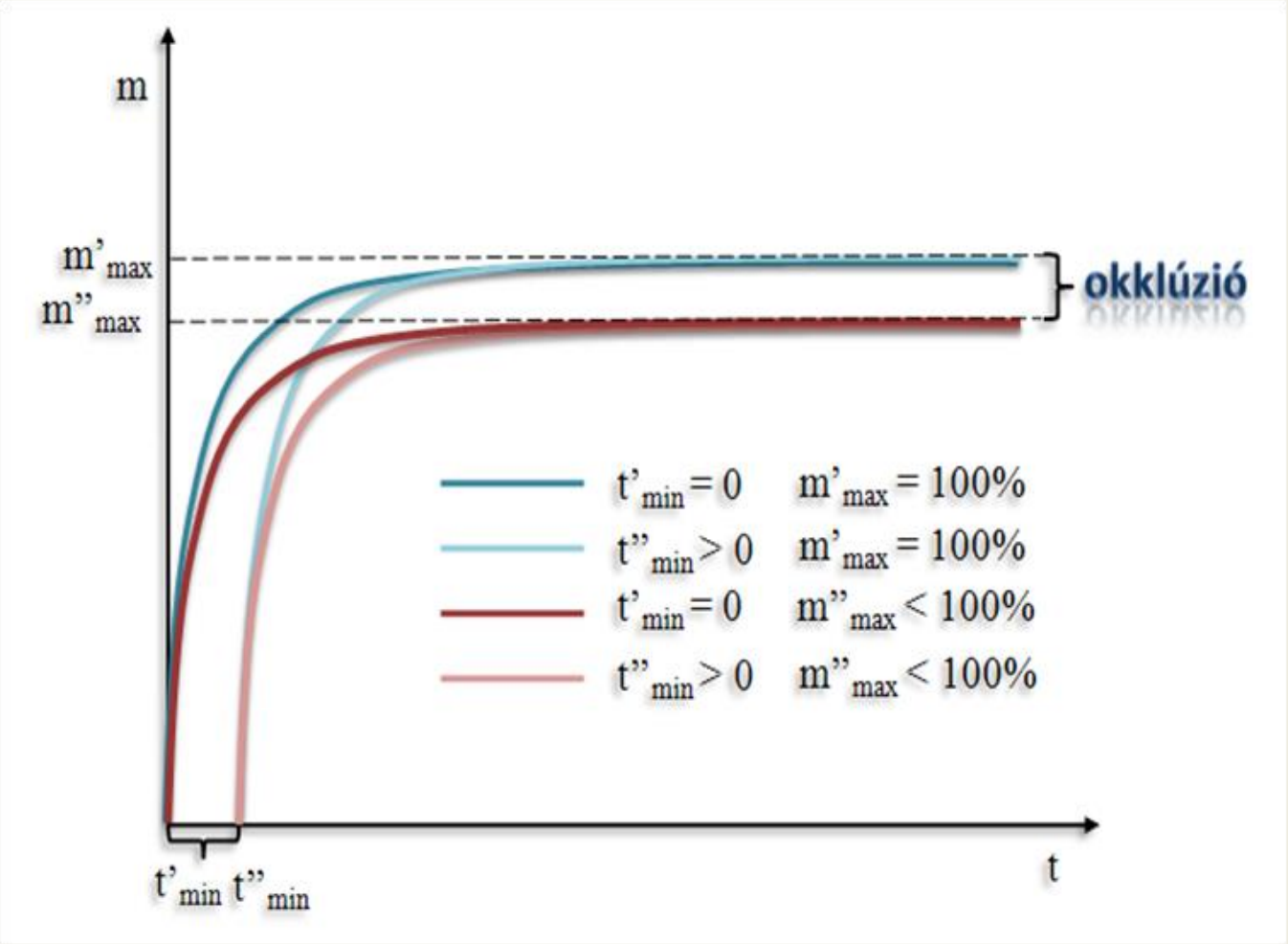
- Buffer solution medium- artificial saliva (20-40 ml), is placed into a chewing chamber
- Temperature: 37±0.5°C
- Chewing frequency: 60 cycles/min

Dissolution test for chewing gums




Julabo
Max
Level
Min

Kinetic models



Evaluation of drug release tests

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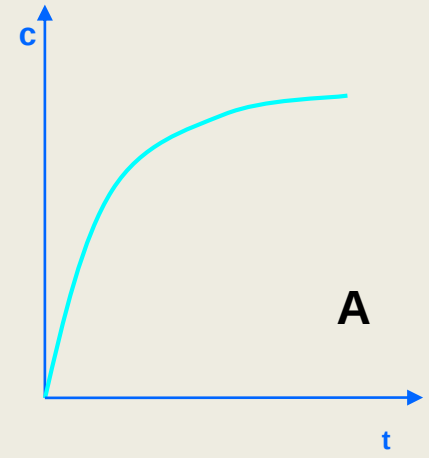
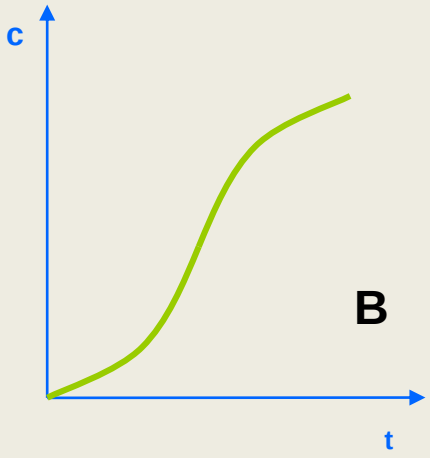
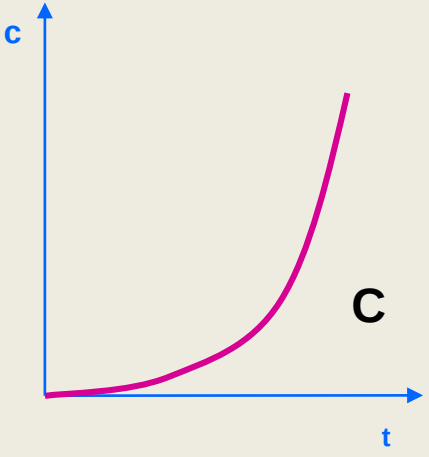
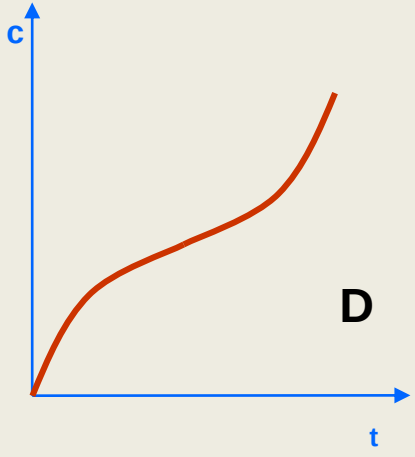
Liberation

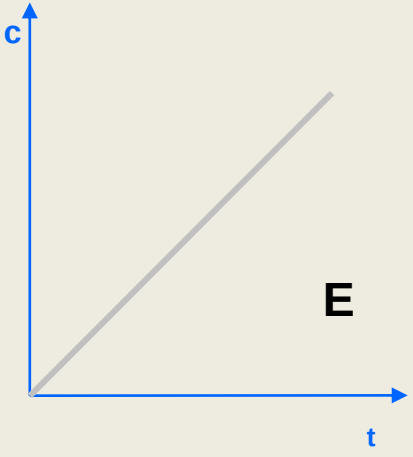
Types of drug release curves











Evaluation of drug release

1.) model-independent

2.) model-dependent evaluation

Evaluation of drug release

Model-independent method

- Fitted functions sometimes have no theoretical relationship with dissolution, they are based on experiences

- Independent from kinetic models

Evaluation of drug release

Model-independent method

Used to evaluate and for the comparison of different drug dissolution profiles

Two types:

1. Characterization of specific values of the dissolution profiles (mean dissolution time, area under the curve, dissolution efficiency) – statistical evaluation/comparison

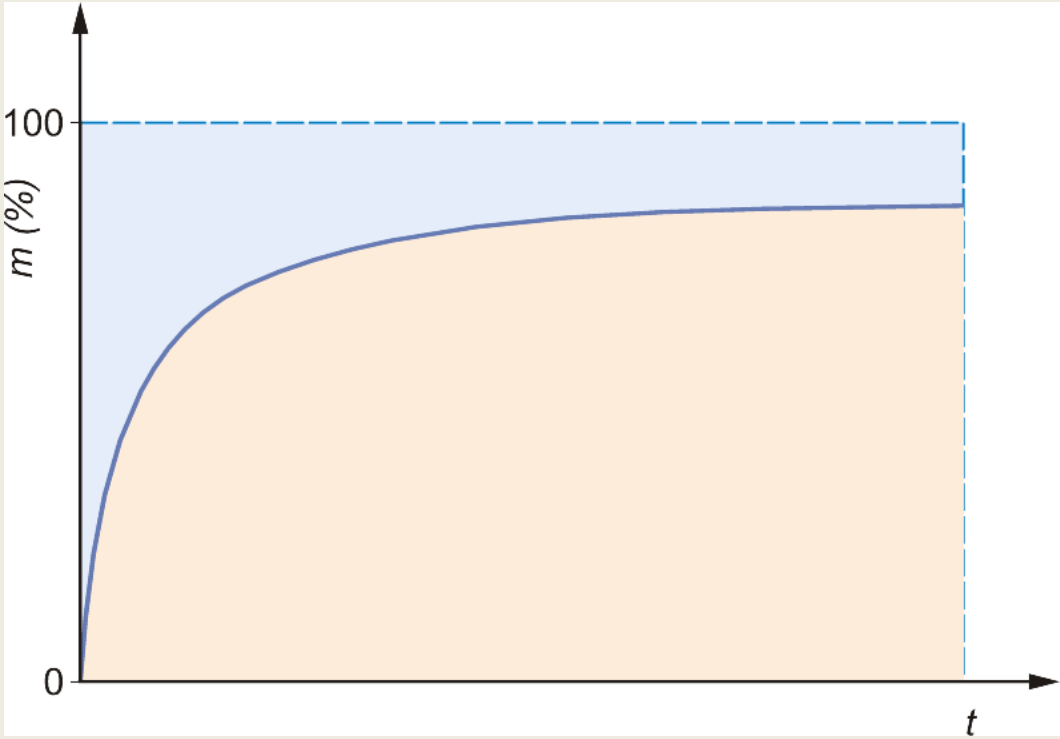
Model-independent methods

Dissolution Efficiency (*D.E.*)

Ratio of AUC of dissolution curve and the AUC of the 100% dissolution.

$$D.E. = \frac{\int_0^t m_t dt}{m_{100\%} t} \times 100$$

m_t cumulative dissolution at '*t*' time in %
$m_{100\%}$ 100% dissolution



Model-independent methods

Mean Dissolution Time (MDT)

Time of the 63,2% dissolution.

$$MDT = \frac{\int_{i=1}^{n} \bar{t}_i \Delta m_i}{\int_{i=1}^{n} \Delta m_i}$$

$$\bar{t}_i = \frac{t_{i-1} + t_i}{2}$$

i	no. of samples,
n	no. of sampling times,
$\bar{t}_i$	average time between t_i *and* t_{i-1}
Δm	dissolved API amount between t_i *and* t_{i-1}

Evaluation of dissolution tests

Model-independent method

2. Pairwise comparison of dissolution data by appropriate staticstical methods

Model-independent methods

fit factors (f_1 , f_2)

Method compares the reference dissolution data to the test preparation .

f_1 difference factor

$$f_1 = \frac{\sum_{i=1}^{n} (R_i - T_i)}{\sum_{i=1}^{n} R_i} \times 100$$

f_2 similarity factor

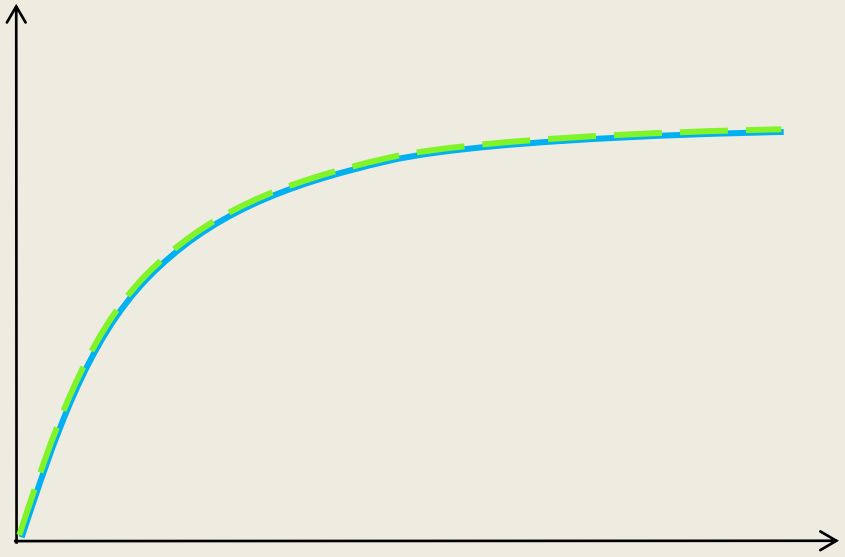
$$f_2 = 50 \lg \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i) \right]^{-0,5} * 100 \right\}$$

n	no. of samples,
R_i	dissolution % at 'i' time of the reference preparation,
T_i	dissolution % at 'i' time of the test preparation

Model-independent methods

fit factors (f_1, f_2)

If the *diference (f_1) factor* =0, then the dissolution of the reference and the test preparation are considered to be equal.



Model-independent methods

fit factors (f_1, f_2)

Similarity (f_2) factor is a figure between 0 and 100.
If $f_2 > 50$, then the two curves are similar.

Evaluation of drug release tests

Model-dependent method

1.) With theoretically valid background

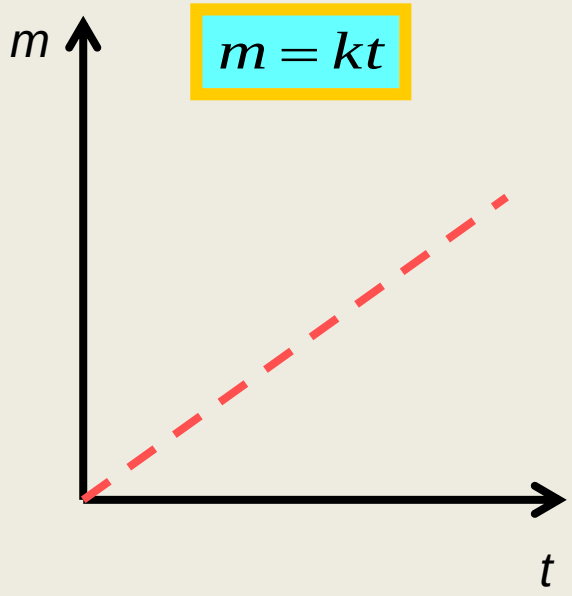
2.) Without theoretical background, based on experiences

Model-dependent methods

Zero order dissolution kinetics

$$m = kt$$

$$c = \frac{m}{V}$$



m *API amount at 't' time*
t *time*
c *API % at 't' time*
k *rate constant*

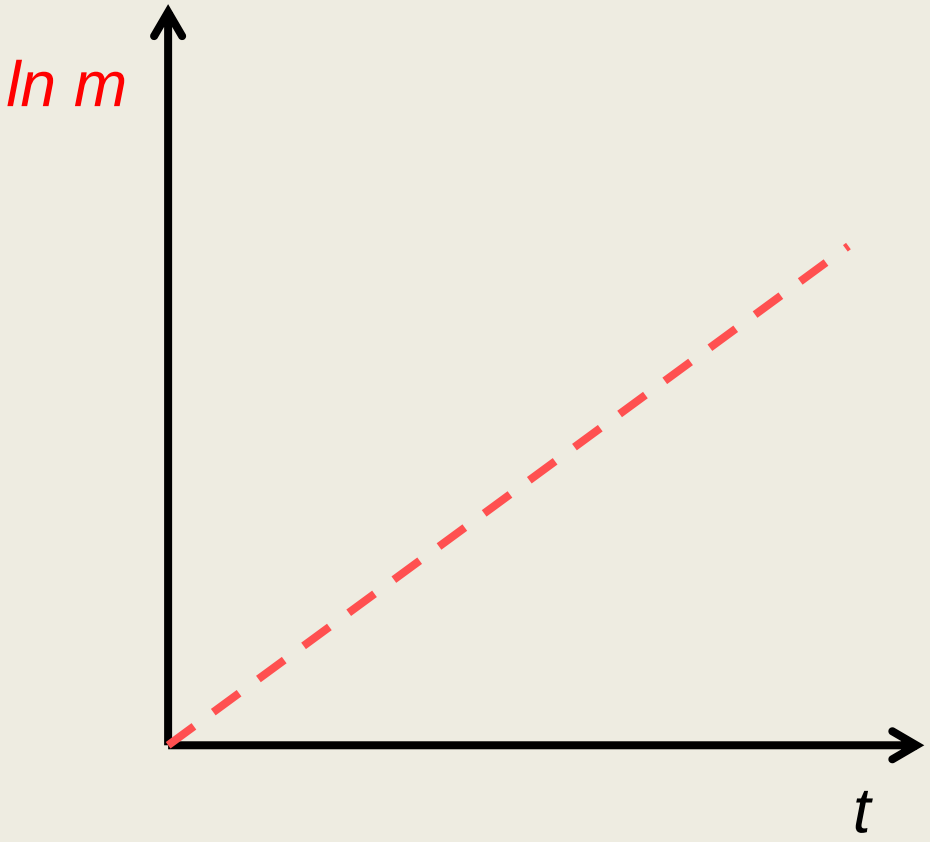
Model-dependent methods

First order kinetics

$$\frac{dm}{dt} = km$$

$$m = m_o e^{-kt}$$

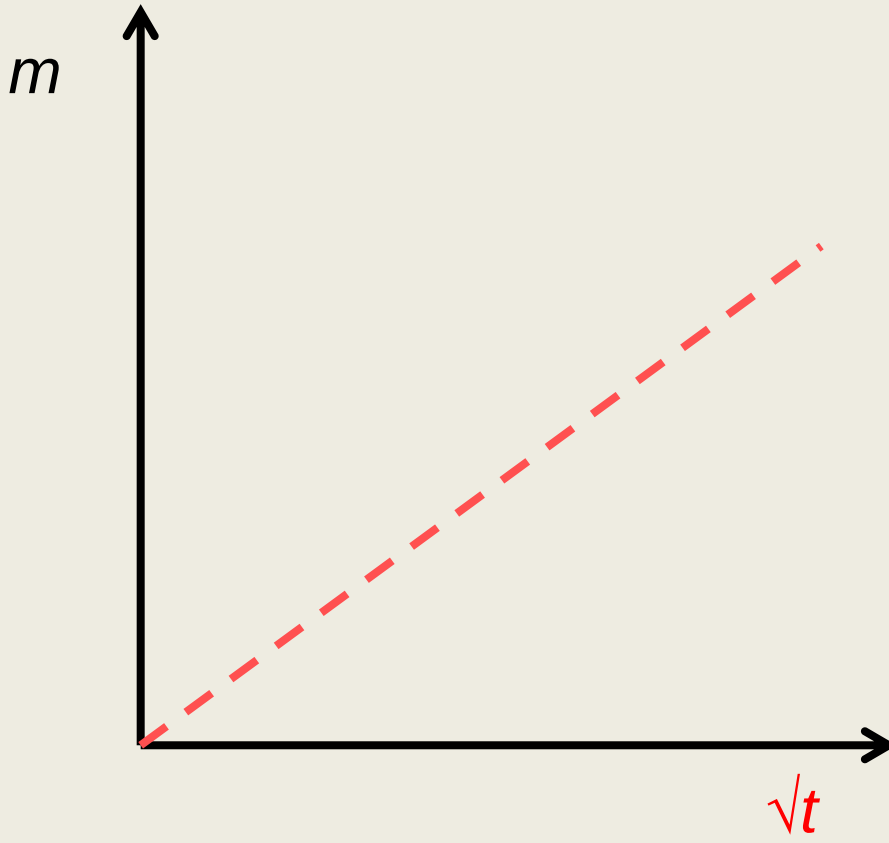
$$(\ln m - \ln m_o) = kt$$



Model-dependent methods

polimer matrix diffusion Higuchi formula

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



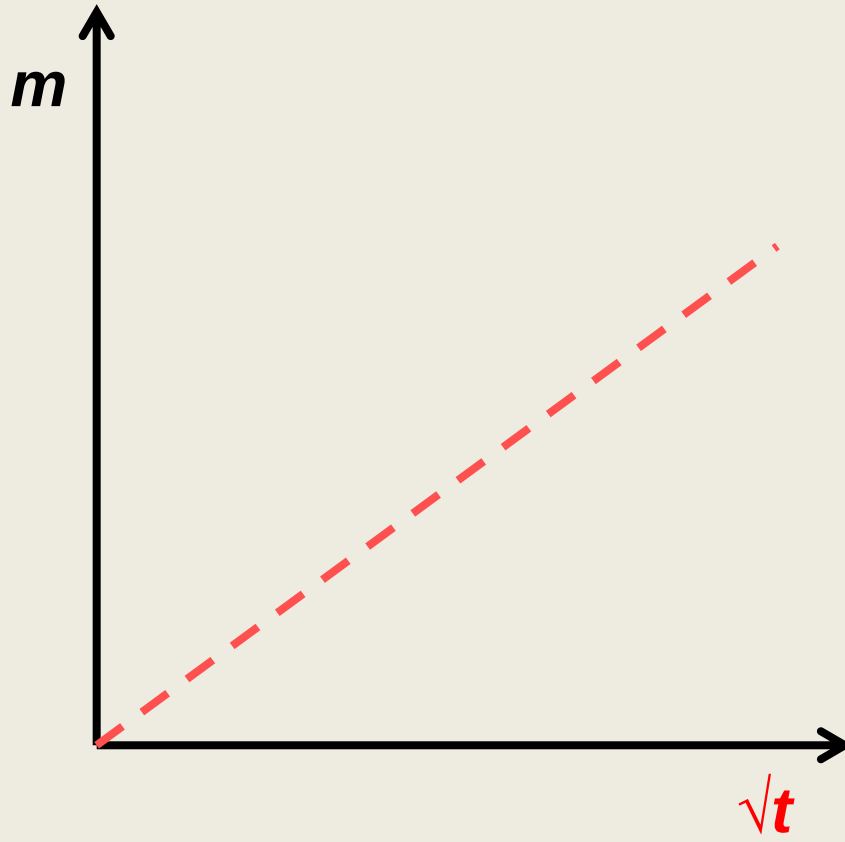
m	*dissolved API amount at 't' time*
D	*diffusion constant*
C_s	*API solubility*
C	*API concentration at zero time*

Model-dependent methods

porous systems

$$m = \sqrt{\frac{D_s \varepsilon C_s}{\tau}(2M - \varepsilon C_s)t}$$

m	*dissolved API % at 't' time*
M	*API amount in the matrix*
C_s	*API solubility*
D_s	*API diffusion constant*
ε	*porosity*
τ	*convolution constant*



Model-dependent methods

Biological erosion

$$m = k_e A_e t$$

m	*dissolved API % at 't' time*
k_e	*erosion constant*
A_e	*eroding (changing) surface*

Model-dependent methods

Osmotic systems

$$m = \frac{\pi A}{h} \Delta p C_s t$$

m	*dissolved API % at 't' time*
π	*permeability*
A	*surface*
$p\Delta$	*difference in osmotic pressure*
C_s	*solubility*
h	*thickness of the semipermeable membrane*

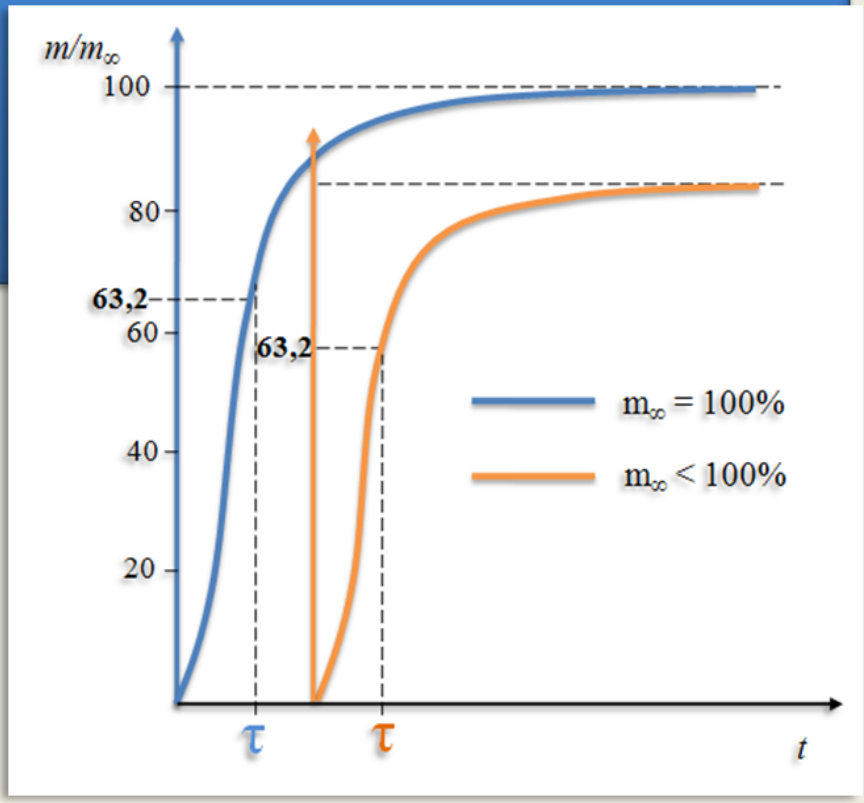
Model-dependent methods

General model:

Weibull model

$$m / m_{\infty} = 1 - exp\{-[(t - t_o) / \tau]\}^{\beta}$$

$$m / m_{\infty} = 1 - e^{-[\frac{t - t_o}{\tau}]^{\beta}}$$

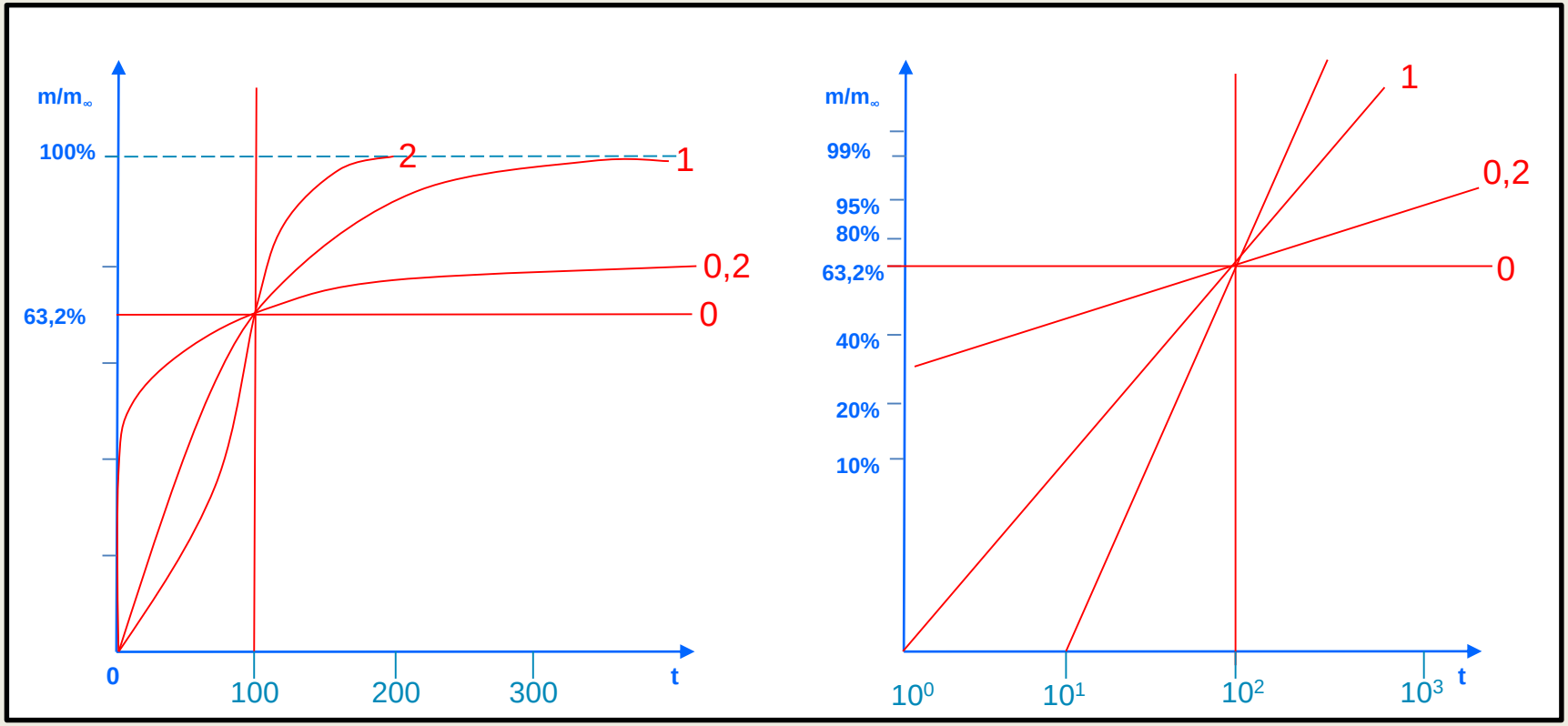


m dissolved API % at 't' time
m_{∞} dissolved API % at *t*=∞ time
t time
t_0 lag time
τ time of 63,2% API dissolution
β shape factor

Model-dependent methods

Weibull model

β shape factor



β=1 – ZOK dissolution

Solid oral dosage forms

Immediate release typically means that 75% of the API is dissolved within 45 minutes

- Rapidly dissolving: ≥ 85% in ≤ 30 minutes
- Very rapidly dissolving: ≥ 85% in ≤ 15 minutes

Comparative dissolution testing
Profile similarity determination

Two **conditions** to determine if the dissolution profiles of two products/batches in a particular dissolution medium are similar:

1. If both the test and reference product show more than 85% dissolution within 15 minutes, the profiles are considered to be similar
   - No calculations are required

   If this is not the case, apply point 2
2. Calculate the f_2 value (similarity factor):
   - If $f_2 \geq 50$, the profiles are normally regarded similar

Comparative dissolution testing

Similarity factor f2

$$f_2 = 50 \bullet \log \left\{ \frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} \left[\bar{R}(t) - \bar{T}(t)\right]^2}{n}}} \right\}$$

n = number of time points

R(t) = mean % API dissolved of reference product at time point x

T(t) = mean % API dissolved of test product at time point x

- Minimum of 3 time points (zero excluded)
- 12 units (each in own dissolution vessel) for each product (for "official" purposes)
- Only one measurement should be considered after both products have reached 85 % dissolution
- RSD at higher time points ≤ 10%

Comparative dissolution testing
Dissolution conditions (study design)

Apparatus (choice)	• Paddle, 50 (75) rpm or • Basket, 100 rpm
Dissolution media All three media for full comparison	1. Buffer pH 6.8 or simulated intestinal fluid without enzymes 2. Buffer pH 4.5 3. 0.1 M HCl or buffer pH 1.2 or simulated gastric fluid without enzymes
Volume of media	900 ml or less
Temperature	37°C ± 0.5°C
Sampling points	10, 15, 20, 30, 45, (60, 120) min. (typical)
Units (individual)	12 for “official” studies

Typical time points
Immediate release tablets (capsules)

Point	Time
1	10
2	15
3	20
4	30
5	45

Rationale:

1. **Condition 1**
   - ≥ 85% dissolution of both products within 15 minutes
   - 15 minute time point thus essential

2. **Condition 2**, for calculation of f_2
   - a minimum of 3 points are required
   - Only one measurement should be considered after 85 % dissolution (both tablets)
   - 20 minute time point thus first possible one (if 15 minute fails 1st condition)

Example

Determination of similarity of profiles

Example 1-A		
Time (min)	% API dissolved	
	Tablet A (Ref)	Tablet B (Test)
10	87	94
15	96	99
20	99	99
30	100	99
45	101	99
60	101	99
f2 required?	No, ≥ 85% in 15 min	
f2 (n = N/A ?)	profiles similar	

Example 1-B		
Time (min)	% API dissolved	
	Tablet D (Ref)	Tablet E (Test)
10	55	57
15	72	78
20	85	91
30	97	100
45	102	100
60	103	101
f2 required?	Yes	
f2 (n = 3 ?)	64 (similar)	

Example

Determination of similarity of profiles (cont.)

Example 1-C		
Time (min)	% API dissolved	
	Tablet X (Ref)	Tablet Y (Test)
10	29	34
15	38	41
20	47	50
30	63	64
45	80	79
60	95	91
f2 required?	Yes	
f2 (n = 6 ?)	74 (similar)	

Example 1-D		
Time (min)	% API dissolved	
	Tablet A (Ref)	Tablet Y (Test)
10	87	55
15	96	72
20	99	85
30	100	97
45	101	102
60	101	103
f2 required?	Yes	
f2 (n = 3 ?)	31 (not similar)	

Thank you for the attention!