FACULTY OF PHARMACY
IN HRADEC KRÁLOVÉ
Charles University

25. 02. / 04. 03. / 11. 3. 2022

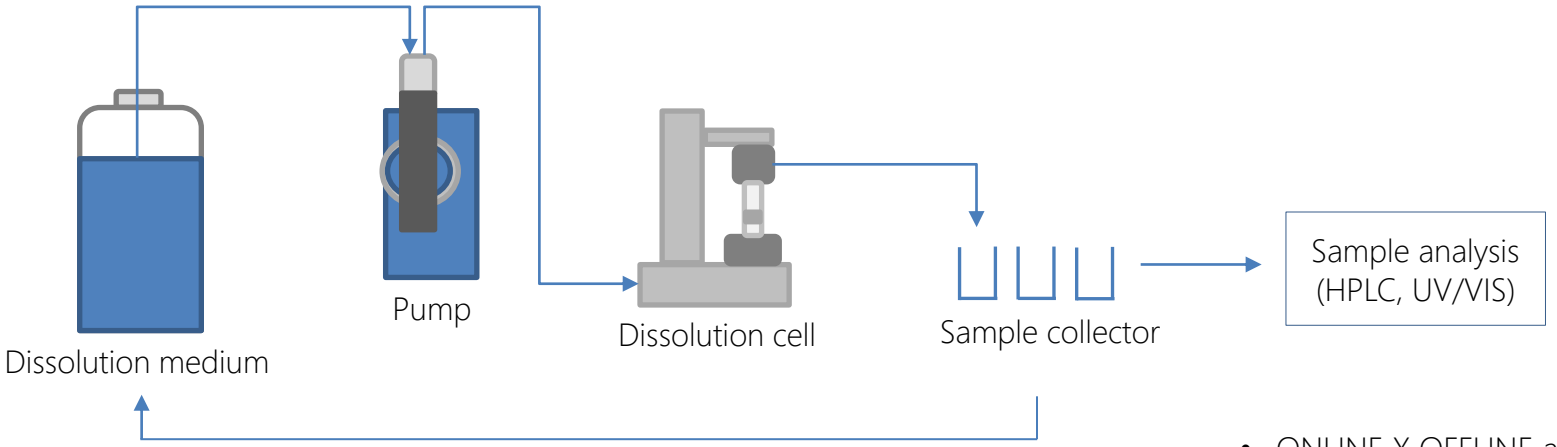
# Selected Methods of Pharmaceutical Technology

# Dissolution

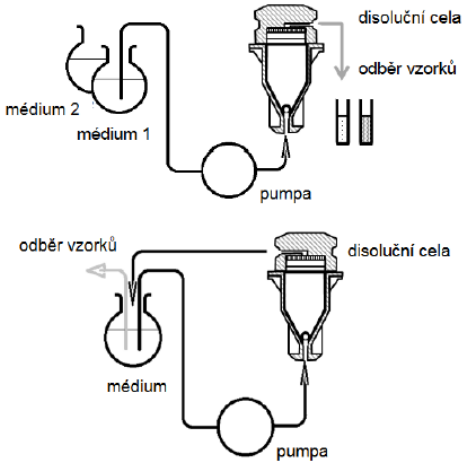
Mgr. Jana Brokešová (brokesoj@faf.cuni.cz)

= determination of a mass of released drug from a dosage form in predetermined liquid and at predetemined time

Principle – schema of flow-through cell (Apparatus 4)



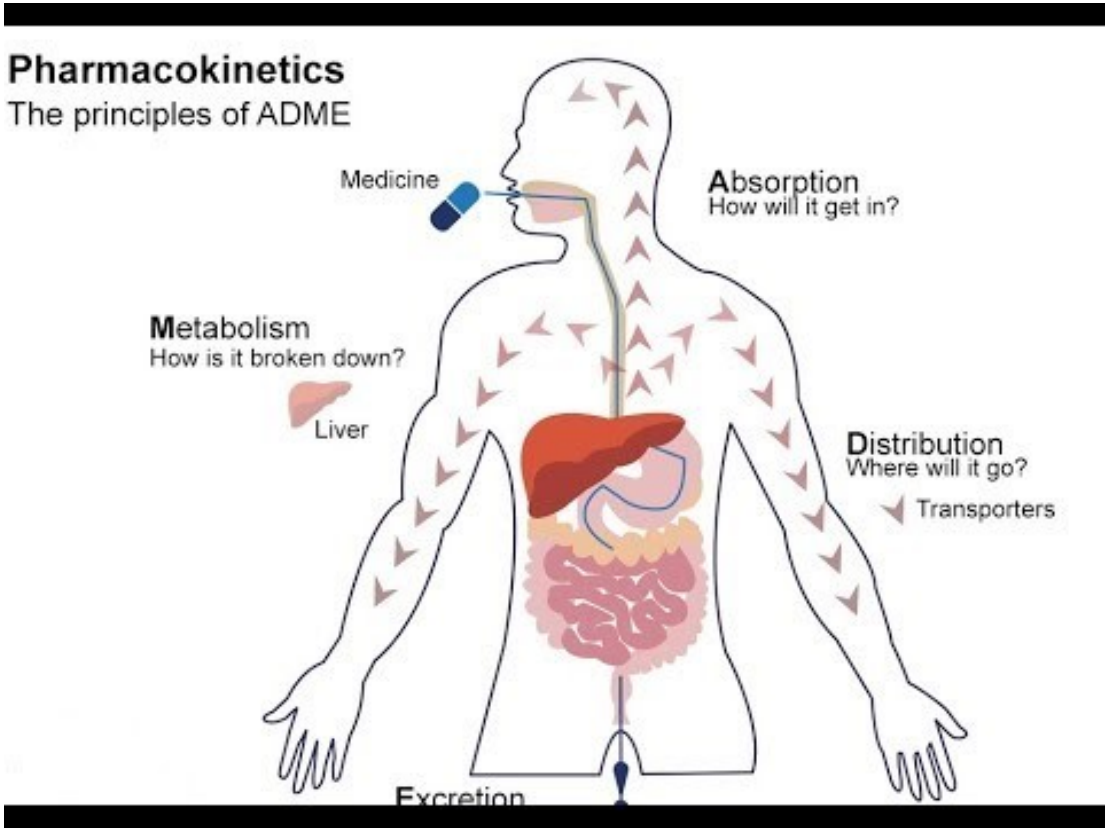

- OPEN X CLOSE system




- ONLINE X OFFLINE analysis

Automatic sample analysis (during dissolution testing)

Manual sample analysis (after dissolution testing is complete)




- Why we are dealing with dissolution?

- dissolution x solubility

## Why?

- > dissolution profiles allow us to assume bioavailability

Drug dissolving – necessary for the absorption (and effect) of the drug in the organism

*FT I lecture: Biopharmaceutical aspects of dosage forms (Dr. Vraníková)*


## What is it good for?

- drug development and control of drug quality

  - study of increasing a solubility of API (e.g.: salt formation, surfactants, complexation, nanonization, amorphization, solid dispersions…)

  - bioequivalence study of the original and generic preparations

  - quality control (batch uniformity monitoring)

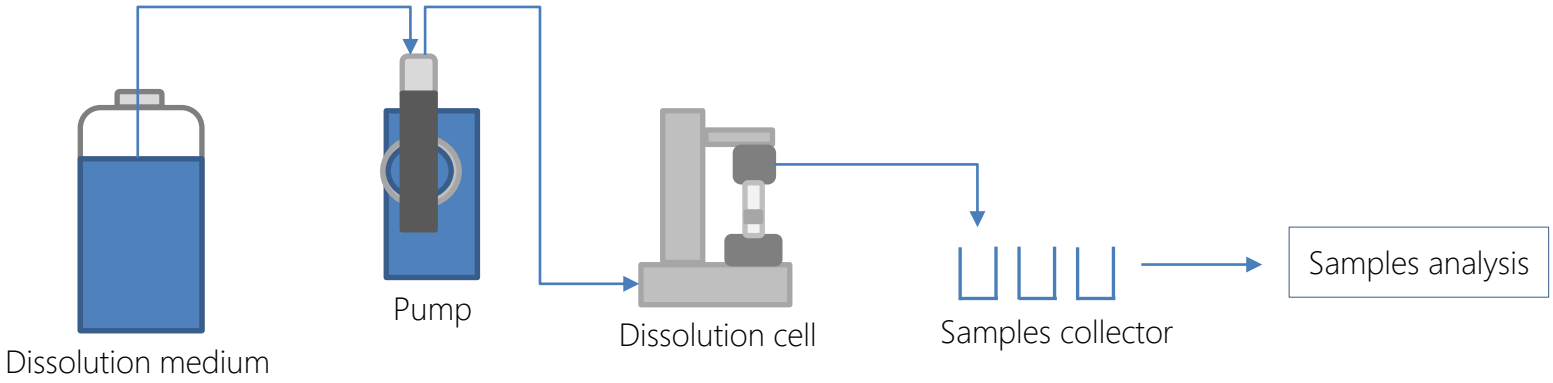
## Revision



- Four types of dissolution apparatus (Ph. Eur.)
- Apparent x Intrinsic dissolution
- Dissolution media (HCl, phosphate, etc.... purified water is used only if the release of a drug is not pH dependent)
- Temperature of medium during dissolution testing of solid dosage forms (37 ± 0,5 °C)
- Sink conditions

- during today´s laboratory practice: flow-through cell apparatus

# Flow-through cell dissolution (Apparatus 4)



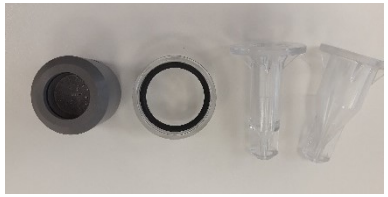

- a suitable cell is selected according to the type of dosage form
- medium (composition, volume, temperature)
- flow rate of medium
- collecting samples in specific time intervals x online analysis (apparatus with special flow-through cuvette)

*different types of cells and industry dissolution apparatus – Sotax seminar 8. 4. 2022*

## Advatages of flow-through cell dissolution apparatus

- Most versatile (tablets, powders, semisolids, contact lenses, stents, …) (no previous compression of powders required)
- More accurate evaluation of the dissolution test (more sensitive method – captures smaller changes, better simulations of intralumenal hydrodynamics)
- Suitable if pH change is necessary (change of medium during the experiment) – evaluation of the dosage forms with controlled release
- Apparatus can be used to measure apparent dissolution – this method is mainly used to determine the apparent dissolution rate of pure solid substances (cell for powders) (Ph. Eur. 2.9.43)
- In combination with other tests / analysis – broaden the knowledge about the dosage form (research)

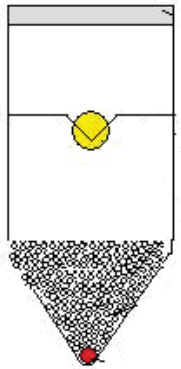
## Procedure – step by step



- choose a suitable cell – 2 sizes of cell for solid dosage forms,
  necessary to know the volume of the cell for the following calculations (ml)

- one ruby ball (5 mm) + glass balls (1 mm) – to ensure laminar flow in the cell
  (without glass balls – turbulent flow)

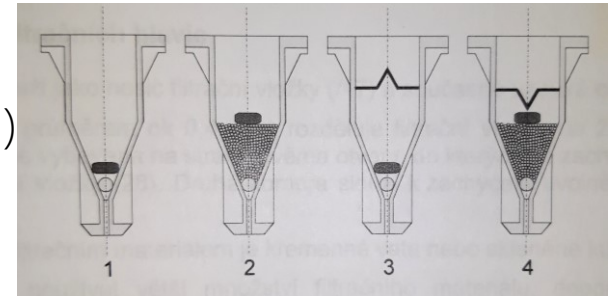
- cell composition – according to the type of dosage form




- placed the sample

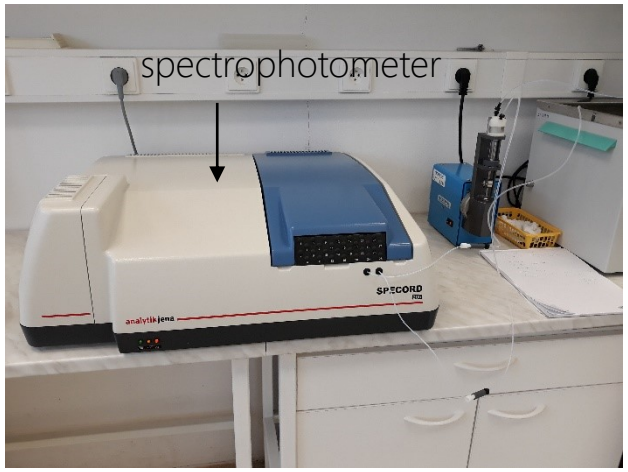
- medium preparation - deareation (UZ / heating+filtration)

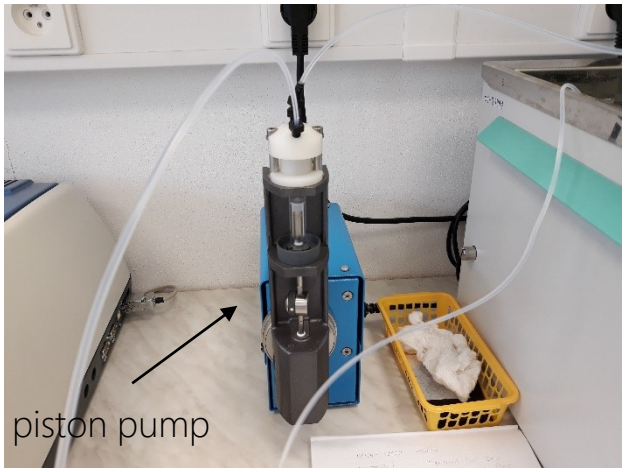
- medium flow rate – 4, 8, 16, … (ml/min)

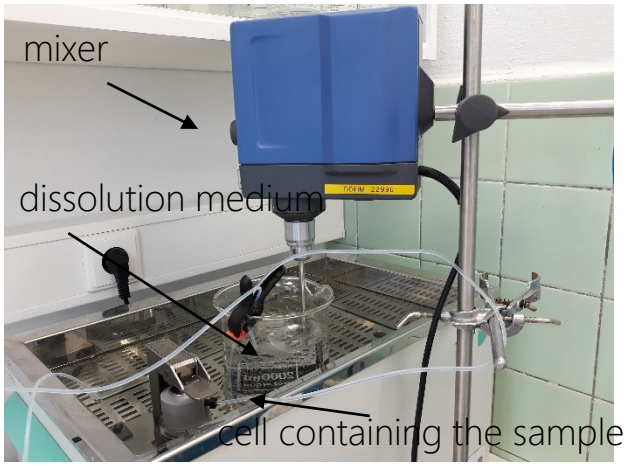



- open system (suitable if the solubility of the drug is very low) / close system;
  offline / online analysis

- What the actual flow-through cell dissolution apparatus looks like:

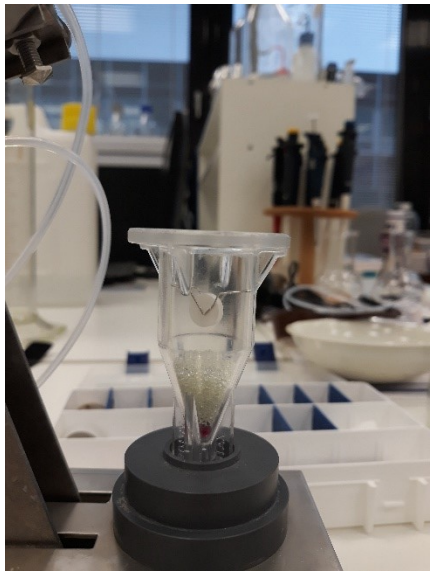


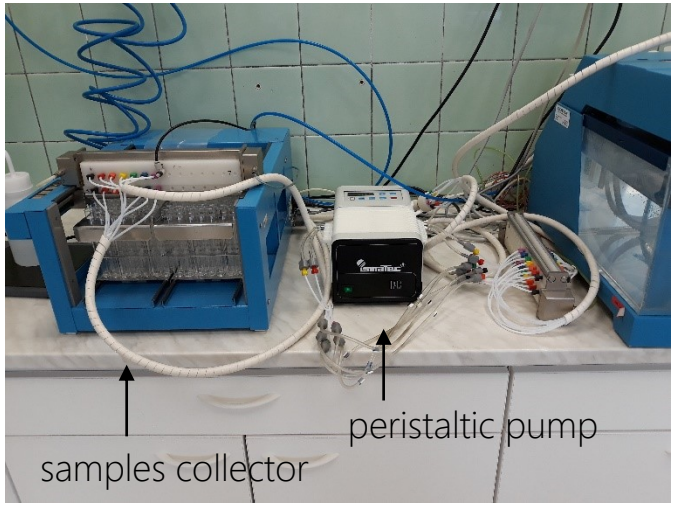

Connection of the tubes (flow-through cell dissolution, close system):
medium -> pump > flow-through cuvette -> cell containing sample-> medium

cell containing tablet before the dissolution test



cell containing tablet during the dissolution testing

- What the actual basket and paddle apparatus look like:




dissolution bath with dissolution vessels

- you can see off-line system, there is no connection with spectrophotometer, the measurement of the samples is manual, after the dissolution test is over

- if the tablets are too „light“ and they float on the surface, it is appropriate to use sinkers


detail of dissolution vessels with tablets

*Basket and paddle apparatus was taught during the practical training of Pharmaceutical Technology*

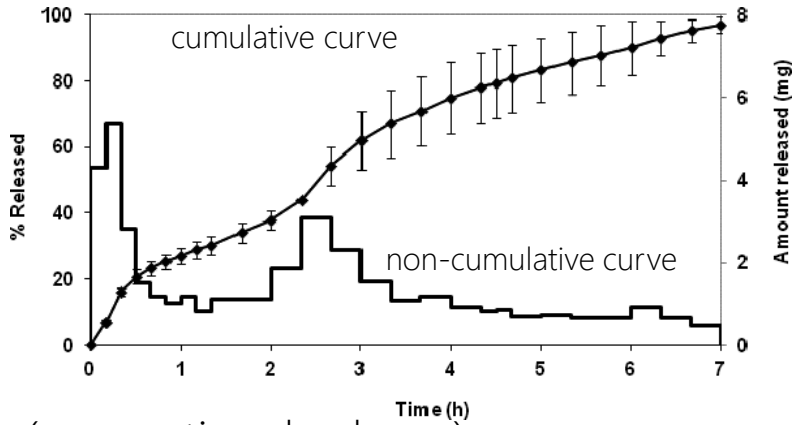
## Evaluation

- preparation of standard solution sequence of known concentration -> calibration curve (c, A)
- measurement of collected samples absorbance (A)
- calculations:
    - concentration of samples (c) according to the calibration curve
    - mass of released drug at individual intervals ($m_{int}$) according to this formula

$$m_{int}(mg) = c * V$$

(„V" is volume of the medium)

    - relative mass of released drug % ($m_{rel}$) equals $m_{int}$ devided by mass of the drug in the tested sample




### Graphs

open system - > non-cumulative curve
close system - > cumulative curve

### Ph. Eur.

complete release = at least 80 % API, till 45 min (conventional-release)

*FT I lecture: Dissolution testing (Dr. Šnejdrová)*

### Pharmacokinetics

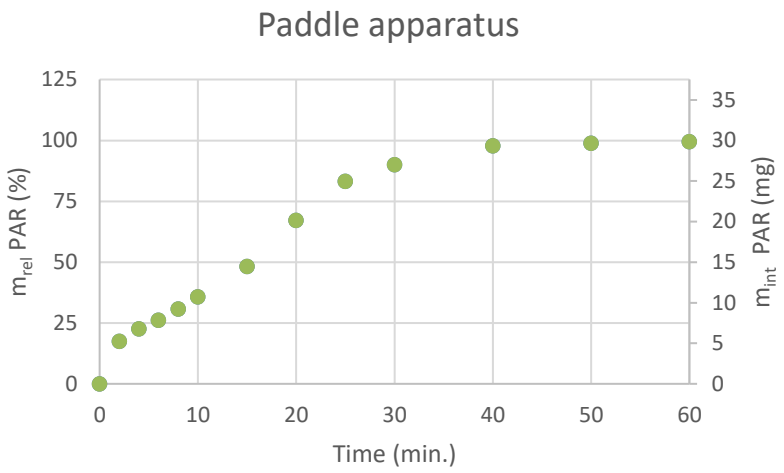
- mathematical models are used for more detailed study

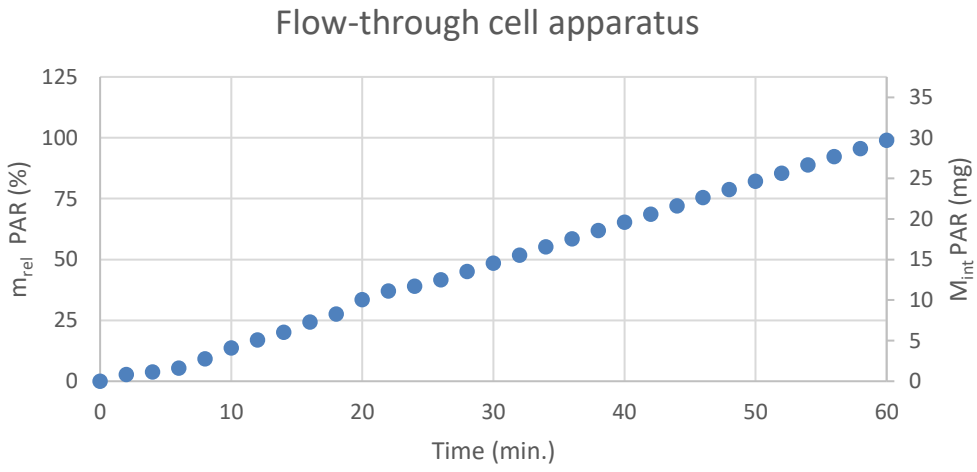
*calculations practicing - Sotax seminar 16. 4. 2021*

# Example of results evaluation (tablets containing paracetamol, measured by two methods – Paddle apparatus, Flow-through cell apparatus)

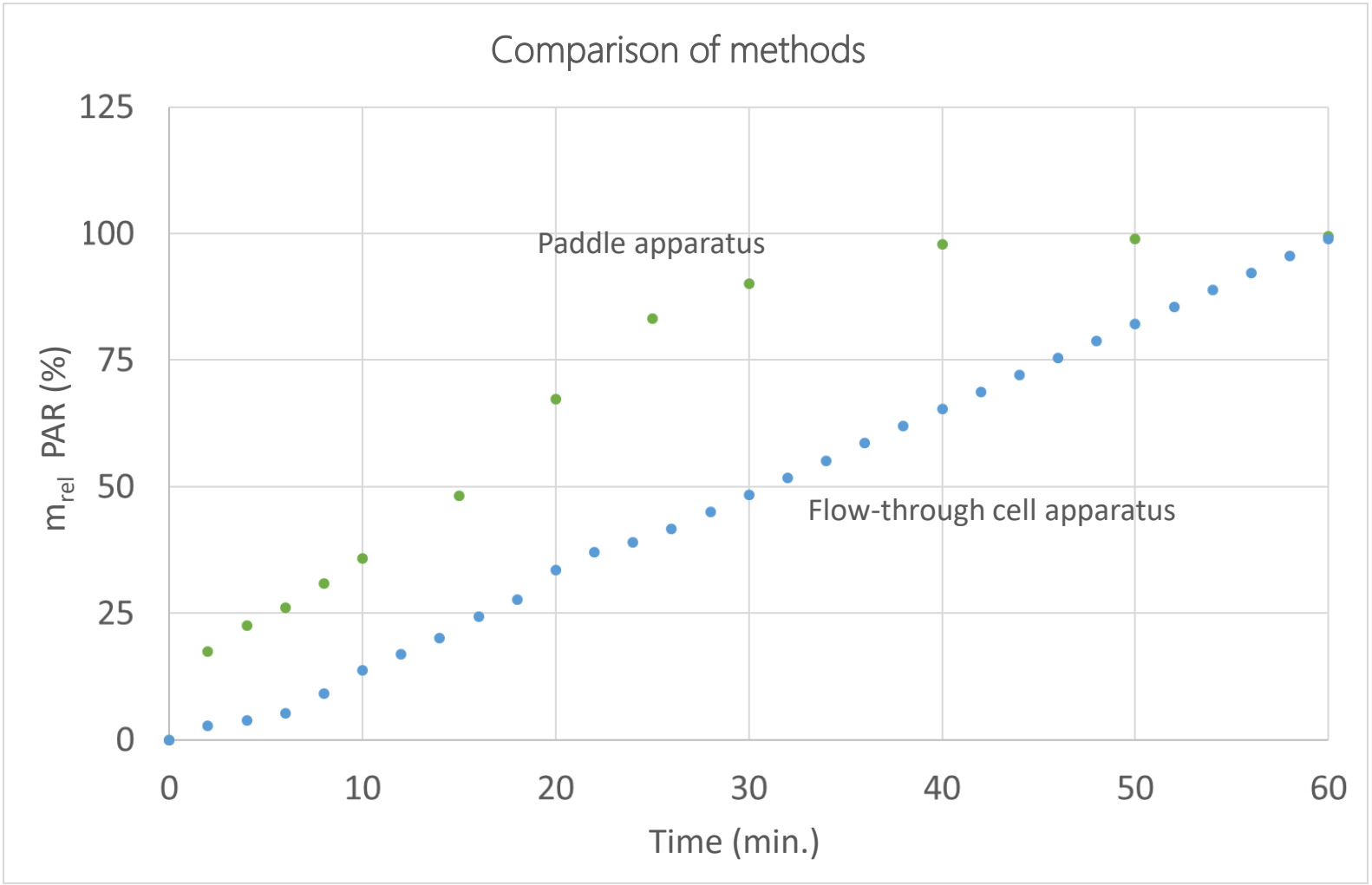
| Time (min.) | A | $m_{rel}$ PAR (%) |
|---|---|---|
| 0 | 0.000 | 0.00 |
| 2 | 0.000 | 2.72 |
| 4 | 0.010 | 3.78 |
| 6 | 0.024 | 5.33 |
| 8 | 0.059 | 9.18 |
| 10 | 0.100 | 13.72 |
| 12 | 0.129 | 16.91 |
| 14 | 0.157 | 20.06 |
| 16 | 0.196 | 24.34 |
| 18 | 0.226 | 27.64 |
| 20 | 0.278 | 33.46 |
| 22 | 0.311 | 37.11 |
| 24 | 0.329 | 39.10 |
| 26 | 0.353 | 41.73 |
| 28 | 0.383 | 45.09 |
| 30 | 0.414 | 48.46 |
| 32 | 0.444 | 51.83 |
| 34 | 0.475 | 55.20 |
| 36 | 0.505 | 58.56 |
| 38 | 0.536 | 61.93 |
| 40 | 0.566 | 65.30 |
| 42 | 0.596 | 68.66 |
| 44 | 0.627 | 72.03 |
| 46 | 0.657 | 75.40 |
| 48 | 0.688 | 78.77 |
| 50 | 0.718 | 82.13 |
| 52 | 0.749 | 85.50 |
| 54 | 0.779 | 88.87 |
| 56 | 0.809 | 92.24 |
| 58 | 0.840 | 95.60 |
| 60 | 0.870 | 98.97 |

| Time (min.) | A | $m_{rel}$ PAR (%) |
|---|---|---|
| 0 | 0.000 | 0.00 |
| 2 | 0.134 | 17.50 |
| 4 | 0.181 | 22.66 |
| 6 | 0.212 | 26.13 |
| 8 | 0.255 | 30.85 |
| 10 | 0.299 | 35.76 |
| 15 | 0.412 | 48.30 |
| 20 | 0.584 | 67.27 |
| 25 | 0.728 | 83.23 |
| 30 | 0.790 | 90.09 |
| 40 | 0.860 | 97.84 |
| 50 | 0.870 | 98.95 |
| 60 | 0.875 | 99.50 |



# Comparison of both methods – Paddle apparatus, Flow-through cell apparatus



Discussion:
## What influences dissolution?

- dosage form, excipients

- chosen type of dissolution apparatus (different dissolution profiles)

- conditions:
    - stirrer speed
    - medium flow rate
    - medium volume
    - type of medium
    - pH and ionic strength of medium

+ properties of API (crystal (amorphous) structure, particle size, surface properties…)

*Physical Principles of Dosage Forms lecture: Solubility and Dissolution (Dr. Smékalová)*

FACULTY OF PHARMACY
IN HRADEC KRÁLOVÉ
Charles University

Thank you for your attention.

Sources:


- Ph. Eur.

- faf.cuni.cz - Study materials

- Fotaki, N.: Flow-Through Cell Apparatus (USP Apparatus 4): Operation and Features, Dissolution Technologies, 2011
  http://dissolutiontech.com/DTresour/201111Articles/DT201111_A06.pdf

- Cupera, J., Lansky, P., Sklubalova, Z.: Sampling times influence the estimate of parameters in the Weibull dissolution model, Eur. J. Pharm. Sci., 2015
  https://www.ncbi.nlm.nih.gov/pubmed/26215461

- http://www.collegeofpharmacy.com/callearningcentre/demonstrationCALPackages/DissolutionDemo/1Introduction/page-7.html

- https://accesspharmacy.mhmedical.com/content.aspx?bookid=513&sectionid=41488032

- http://edelweisspublications.com/keyword/33/355/Pharmacokinetics