Comparison of dissolution time profiles: No similarity but where is the difference?

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BioBridges

Bioequivalence and Development Workshop, 26-27 September 2018, Prague

Looking for the difference and its consequences

Introduction

Theoretical background

- Powder sample
- Disintegrating tablet
- Disintegration-dissolution-model (DDM) and its application
- Particle dissolution: from large particles to nanoparticles
- Generalization of the dissolution problem
- Dissolution analysis and bioequivalence: a case study

Conclusions

Introduction

- Methods of dissolution profile comparisons:
- F1 and F2 factor calculation (factor of difference and similarity)
- Confidence interval of F2 statistics of bootstrapped samples
- Model independent or dependent confidence region of statistical distance (Mahalanobis distance)
- Any of the 40 functions provided by DDSolver

All these methods may guide the development of FDFs or be utilized in quality assurance of products, however, do we know the cause when the tests do not indicate similarity of the profiles?

Where is the difference? This is here the question!

The answer has to be found in dissolution theories.

Theoretical background

Noeyes & Withney 1897

The rate of solution of solid substances in their own solutions. J. Am. Chem. Soc. 19, 930–934

$$\frac{dc}{dt} = -k(c_s - c)$$

The equation was derived in excess of solid material (the change in the surface of the solid material could be neglected)

Brunner & Tolloczko 1900

Über die Auflösungsgeschwindigkeit fester Körper. Z Phys Chem 35:283–290

$$\frac{dc}{dt} = -kA(c_s - c)$$

The surface, A, of the solid phase is incorporated into the equation

Theoretical background – powder samples

A more detailed view based on individual particle approach: each particle is described by Brunner & Tolloczko kind of equation and contributes to the total amount of dissolved drug, which influences the dissolution kinetics of all particles in the dissolution medium: **heterogeneous particle populations**.

Mathematically expressed as a system of differential equations:

$$\frac{dm_i}{dt} = -\alpha_i m_i^{2/3}\left(1 - \frac{M}{c_s V}\right),$$

change of mass of i*th* kind of particle

$$\frac{dM}{dt} = \sum_i N_i \alpha_i m_i^{2/3}\left(1 - \frac{M}{c_s V}\right),$$

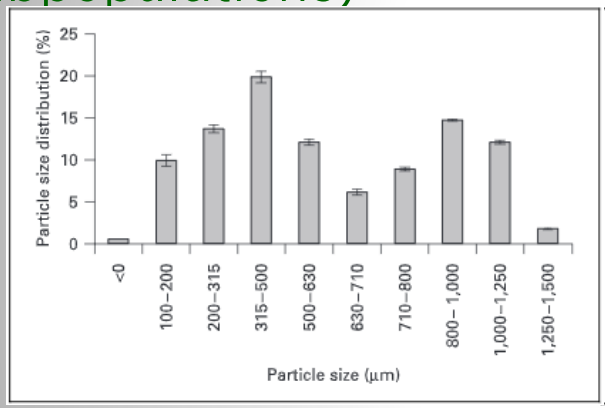
change in dissolved amount of drug, M,

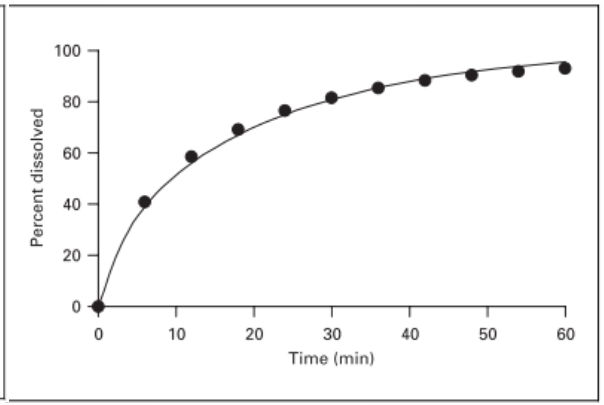
where *i* is the number of subpopulations in the sample each having Ni particles

Theoretical background – powder samples

The introduced system of equations was after characterizing individual narrow PSD subpopulations **able to predict**

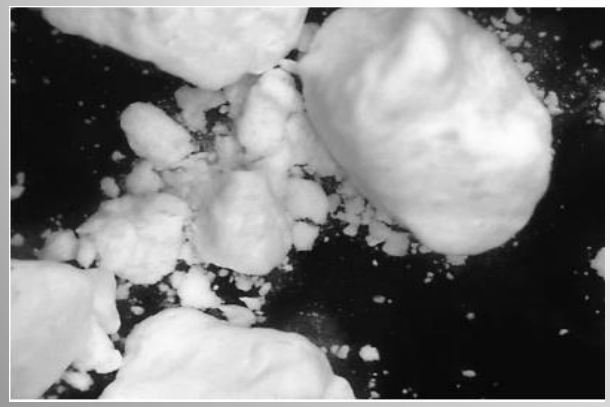
1) the **dissolution profile** of a given particle size distribution (17 subpopulations)





Circles – prediction,
line measurement

2) the **disintegration of large aggregates** into smaller particles



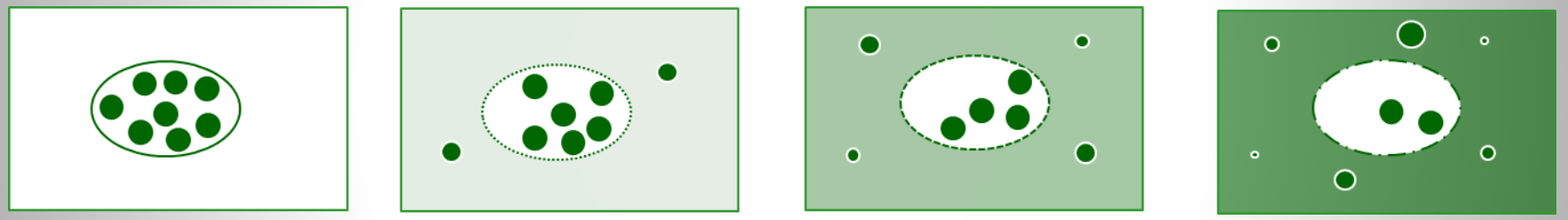
Large particle in Petri dish

(without agitation)

Horkovics-Kovats S.
Chemotherapy 50(5), 234-244, 2004

Theoretical background – disintegrating tablet

Dissolution of particles released from a disintegrating tablet is more complex, since even in case of homogeneous particles in the FDF, **heterogeneous** particles in the dissolution medium are generated, additionally the dissolution kinetics is changing due to possible non-sink conditions.



Mathematically – every particle dissolve under specific initial conditions.

Is it possible to extract the information regarding the disintegration of the FDF and the properties of API particles out of the dissolution profile, even when heterogeneous particle populations are present in the FDF?

Theoretical background – disintegrating tablet

The question leads to so called inverse or indirect problem:

Assuming that we know all physical rules relevant for dissolution, however the initial conditions are unknown (the disintegration of the FDF and the particle size distribution of the particles). To calculate from the resulting dissolution profile back to the initial conditions = inverse problem.

It can be shown that such an information can be extracted from the dissolution profile **unequivocally.**

Serious problem: the calculations are extremely time consuming, the results are influenced by the noise of the measurements, continuous measurement of the dissolution profiles would be necessary.

Summary: such calculation is for routine analysis not feasible.

Purely mathematical work – results not presented here.

Horkovics-Kovats S.

J Pharm Sci 103, 456-464, 2014

Theoretical background – disintegration-dissolution model (DDM)

A practicable way of extracting the information from dissolution profiles:

- A particle starts to dissolve after being released into the dissolution medium from the FDF according a disintegration function.
- The initial dissolution rate is dependent on the amount dissolved at the release of particle from FDF.
- The DDM considers log/linear particle size distribution and can deal with various polymorphic forms of the API.

DDM represents the system of differential equations, the extraction of the FDF and API characteristics (physicochemical properties) is based on solution of the system of differential equations taking into consideration the changing initial conditions due to increased drug concentration in the system.

Theoretical background – disintegration-dissolution model (DDM)

Challenge: optimization of the parameters of a high number of differential equations for repeated measurements.

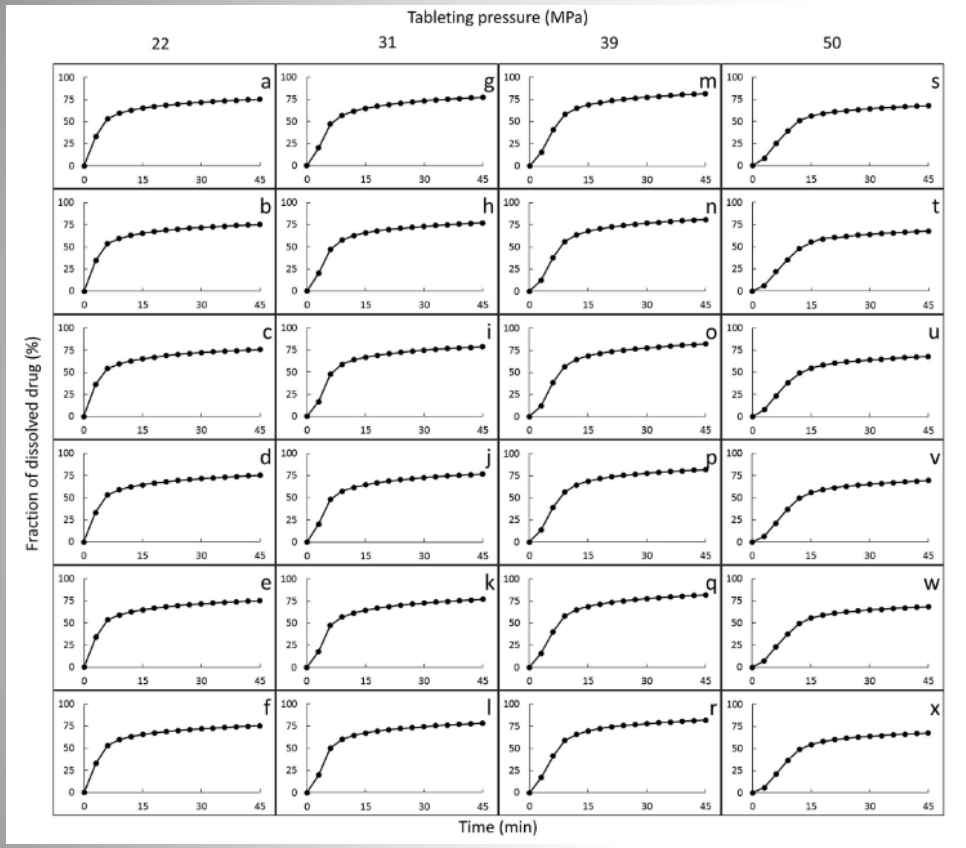
Solution: implementation of the optimization method for the disintegration-dissolution model used in population pharmacokinetic models.

DDM introduced in the analysis of tables manufactured using different tableting pressures.

Horkovics-Kovats S. et al

Eur J Pharm Sci 78, 245-254, 2015

DDM application



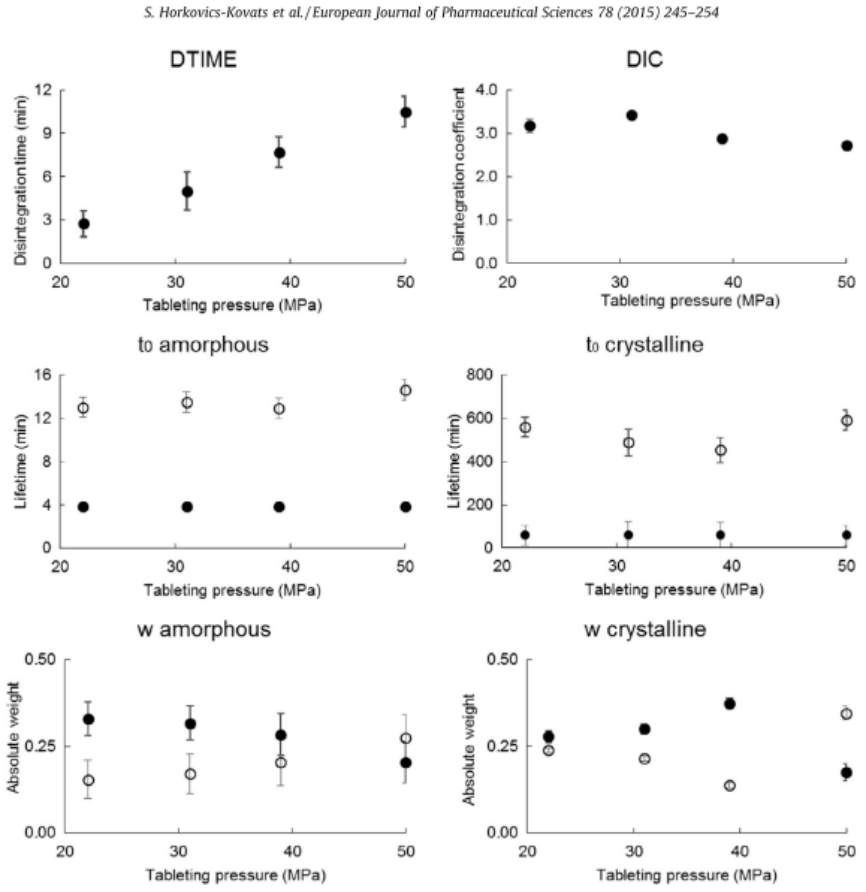
Example of complex dissolution experiment evaluation (repeated measurements in USP Apparatus II and effect of different tableting pressure on dissolution properties of cefditoren pivoxil tablets). Points measured values, curves model fit.

F2 values	22 MPa	31 MPa	39 MPa	50 MPa
22 MPa	x	67.7	55.1	42.3
31 MPa		x	67.9	45.0
39 MPa			x	42.7
50 MPa				x

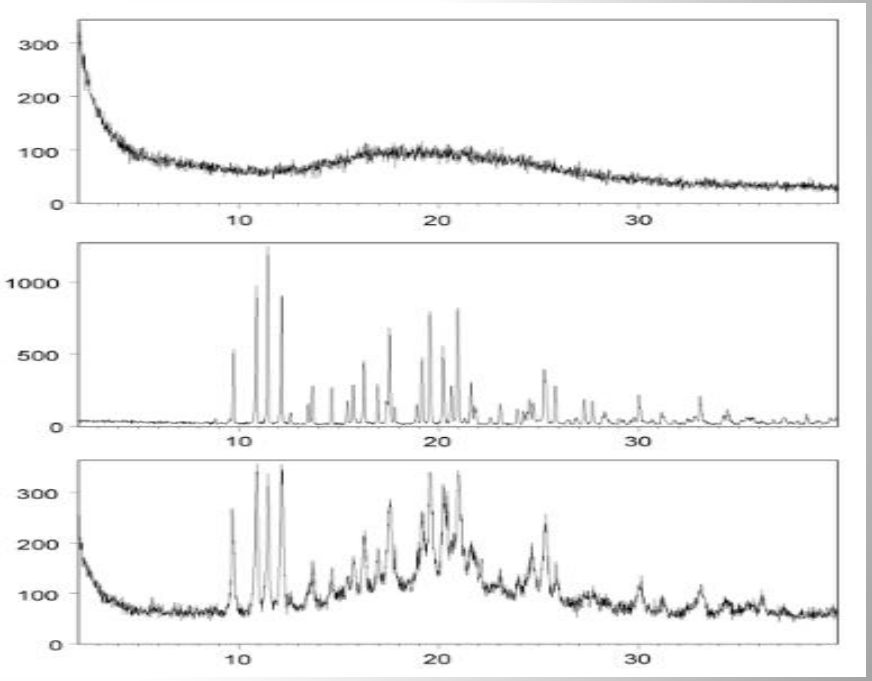
According to F2 values 22, 31 and 39 MPa profiles are similar, the 50 MPa profiles differ from all others. The F2 is not sensitive to prolonged disintegration of tablets, manifested in decreased initial rate of dissolution.

Horkovics-Kovats S. et al
Eur J Pharm Sci 78, 245-254, 2015

DDM application



DDM identifies the prolonged disintegration caused by increased tableting pressure and predicts the existence of crystalline API in the tablets.



The disintegration time and the degradation rate assessed by DDM was comparable with independent measurements

Horkovics-Kovats S. et al

The X-ray diffractogram clearly indicates the existence of amorphous and crystalline form in the FDF predicted by DDM analysis.

Particle dissolution: from large particles to nanoparticles

The provided equations do not explain the particle size dependent observations like

- Ostwald ripening of homomorphic particles,
- particle size dependent root-laws of dissolution kinetics
- the improved dissolution properties of nanoparticles
  - such as increased solubility,
  - almost immediate dissolution
  - the dissolution kinetics which is independent from hydrodynamic conditions.

The above observation can be explained when considering particle-size-independent dissolution layer thickness.

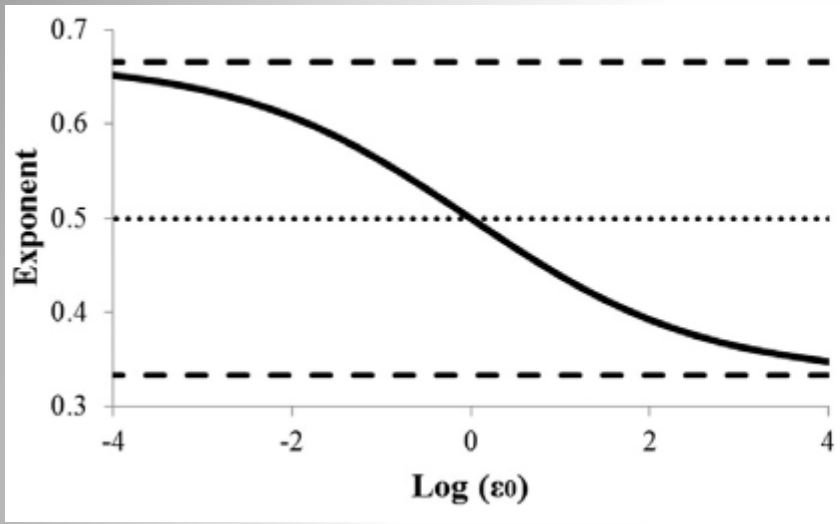
The derivation of the equations for arbitrary particle shape and saturation conditions is in detail elaborated in:

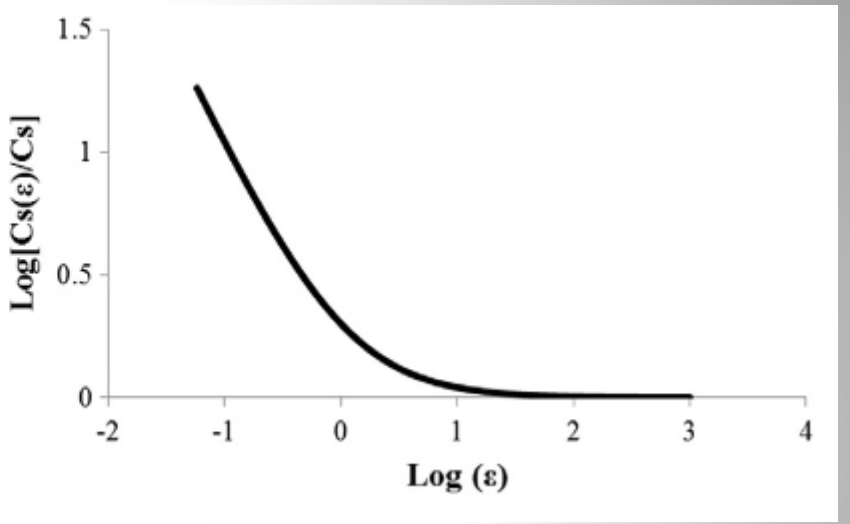
Dissolution and coarsening of polydisperse, polymorph drug particles liberated from a disintegrating finished dosage form: Theoretical considerations.

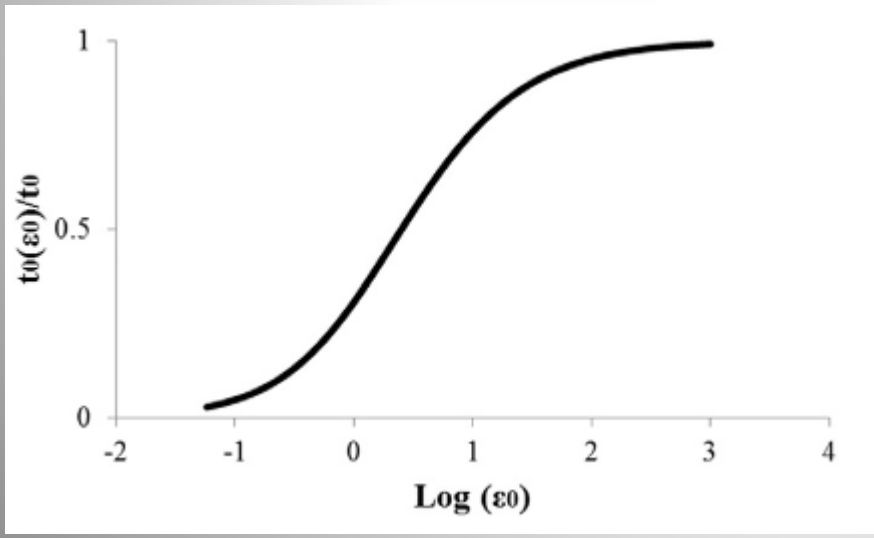
Horkovics-Kovats S.

Eur J Pharm Sci 91, 265-277, 2016

Particle dissolution: from large particles to nanoparticles







Changing

- dissolution kinetics,
- solubility
- time for total dissolution of a particle in infinitive volume

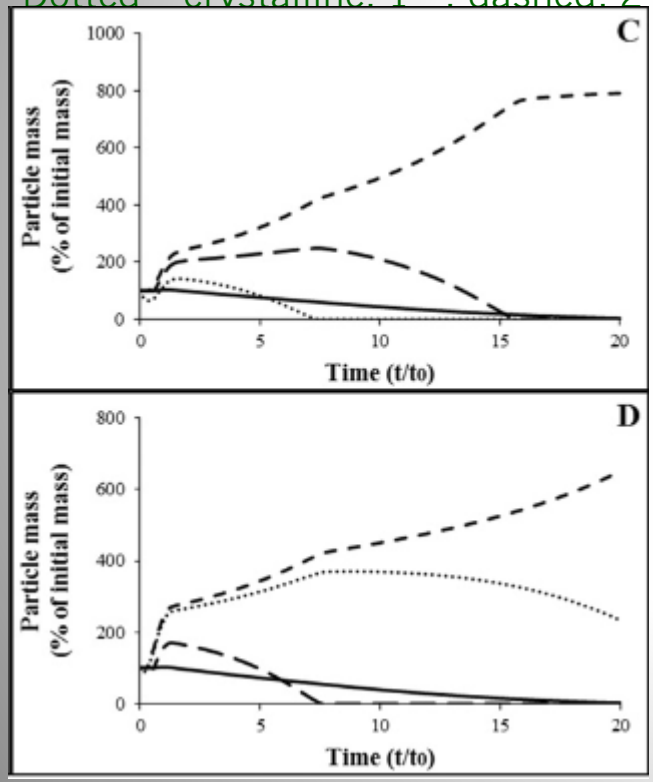
as a function of the ratio of ε_0 = (initial particle dimension) to (diffusion layer thickness)

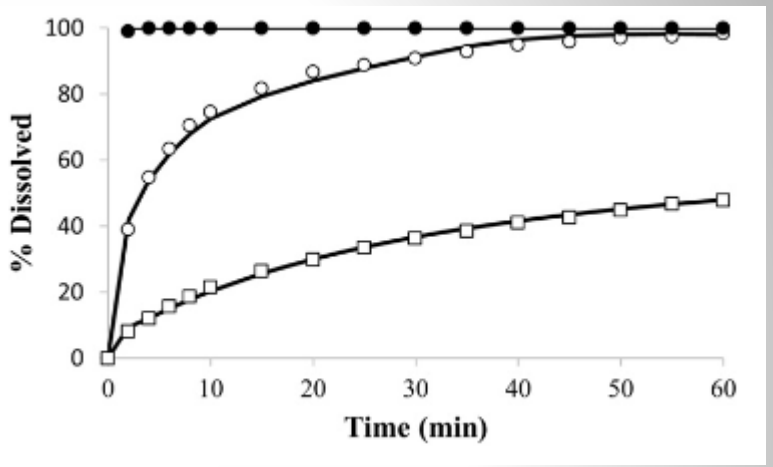
Particle dissolution: from large particles to nanoparticles

Ostwald ripening as function of drug load: amount of drug / (Cs*V)

Solid line – amorphous particles, 3rd step

Dotted – crystalline, 1st , dashed, 2nd, long





Open squares – hammer-milled crystals, open circles – jet-milled crystals; full circles NanoCrystal® spray-dried powder of cilostazol (Jinno et al., 2006) – the lines represent the model predictions.

Asymptotic state is dependent on the initial conditions of the system.

Generalization of dissolution problem

Extraction of all physicochemical properties of an API, like dose, PSD, solubility, degradation kinetics of the API, disintegration characteristics of FDF, from dissolution profile is not possible: over-parametrization of model.

Therefore additionally to the disintegration function, generalized variables have to be introduced:

System drug load

- $L=Dose/(c_s*V)$

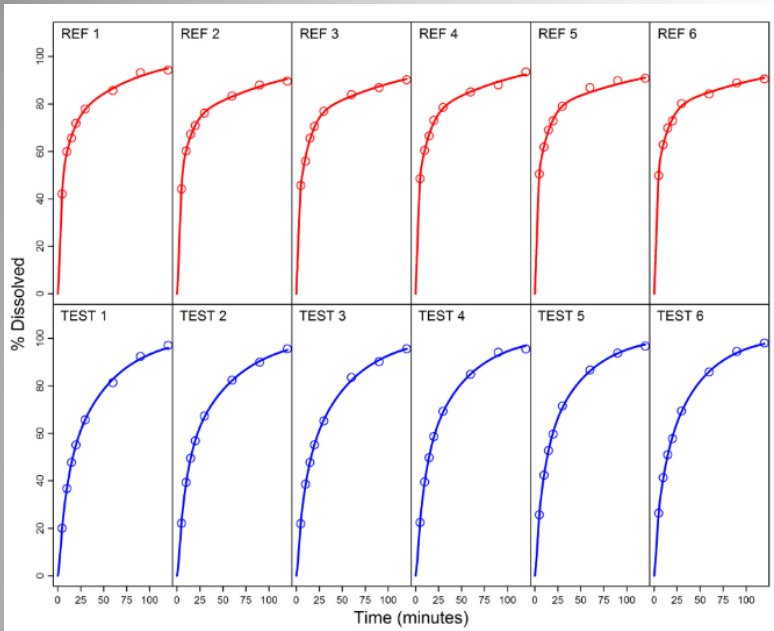
Saturation state function

- $S=M/(c_s*V)$

Particle intrinsic lifetime distribution (PLD)

- closely related to PSD, particle is characterized by its dissolution properties as time needed for total dissolution of a particle in infinite volume of dissolution medium under given hydrodynamic conditions

Generalization of dissolution problem



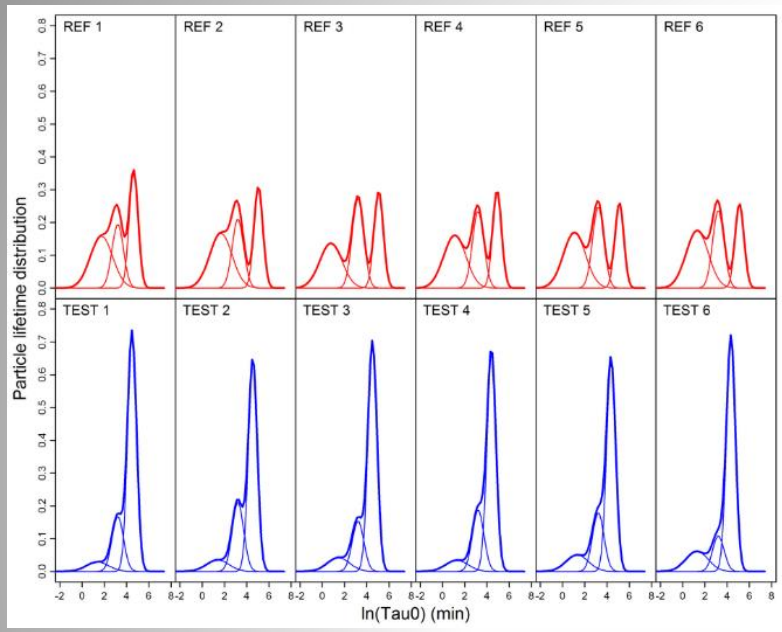
The generalization (or introduction of summary parameters) enables to extract the dissolution properties of an FDF without knowing all details (e.g.: actual dose, solubility of the API, volume of dissolution medium, PSD of the API particles, actual diffusion layer thickness).

These profiles (Tsong et al. 1996) were used to demonstrate the statistical distance confidence region method as a tool for assessing the similarity of dissolution profiles.

They can serve to demonstrate the identification of the differences in the formulations by employing the DDM.

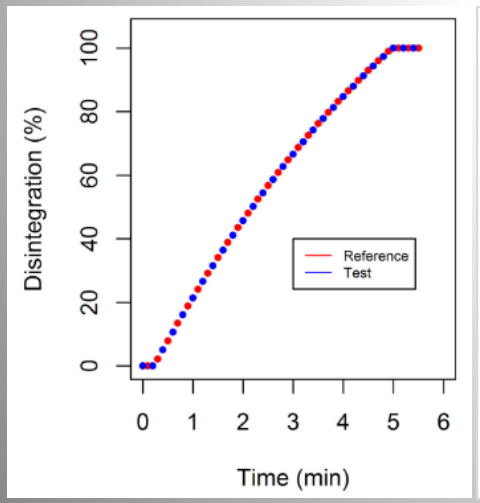
Horkovics-Kovats S.
Eur J Pharm Sci 121, 9-15, 2018

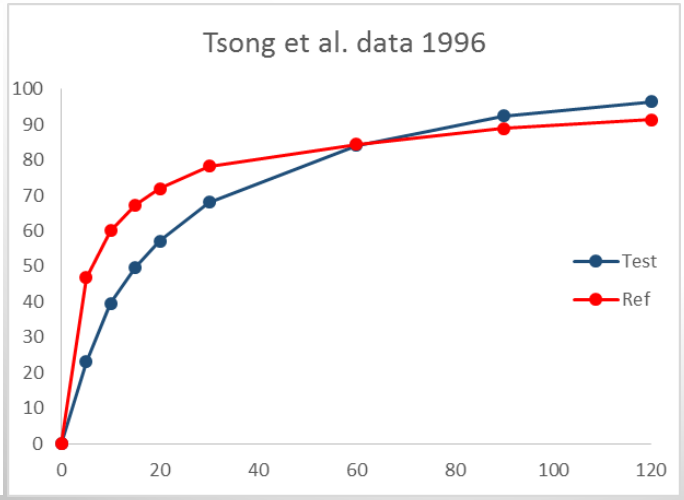
Generalization of dissolution problem



The reference formulation is characterized by higher amount of quickly dissolving particles, however longer dissolving particles are also in the formulation.

The PLD of the two product clearly differ, leading to crossing dissolution profiles.





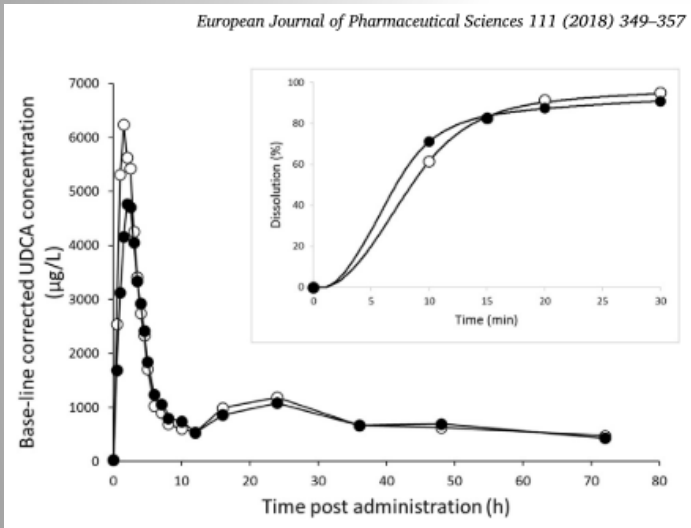
How to assess the impact of differences on bioequivalence of the products in general?

Horkovics-Kovats S.
Eur J Pharm Sci 121, 9-15, 2018

Dissolution analysis and bioequivalence: A case study

Ursodeoxycholic acid (UCDA) as a hardly soluble substance at physiologically pH conditions – profiles not suitable for comparison.

Dissolution comparison at pH 8.4, revealed an F2 = 60.6



- The test product (open symbols) failed to show comparable Cmax values in the BE study.
- No rank order is observed (quicker dissolution – lower Cmax)

DDM revealed smaller particles in Reference formulation

	Rel. Weight (1st pop)	t1 (min)	t2 (min)
T1	0.83	2.5	101.5
R1	0.79	1.8	122.6

Second peak indicates strong enterohepatic circulation

Horkovics-Kovats, S. and Zlatos P.: Mathematical Biosciences, 184, 69-99, 2003

Horkovics-Kovats S. Eur J Pharm Sci 111, 349-357, 2018

Dissolution analysis and bioequivalence: A case study

Ursodeoxycholic acid when dissolved and is exposed to low pH conditions forms insoluble crystals.

In the stomach pH peaks (up to pH 8) due to reflux of duodenal contents containing alkaline bicarbonate.

Smaller particles dissolve quickly during the pH peaks and then insoluble crystals are formed.

Recommendation for the FDF reformulation: decrease the PSD of the API

	Rel. Weight (1st pop)	t1 (min)	t2 (min)
R2	0.84	1.4	106.6
T2	0.89	1.3	123.5
R3	0.92	1.2	96.5

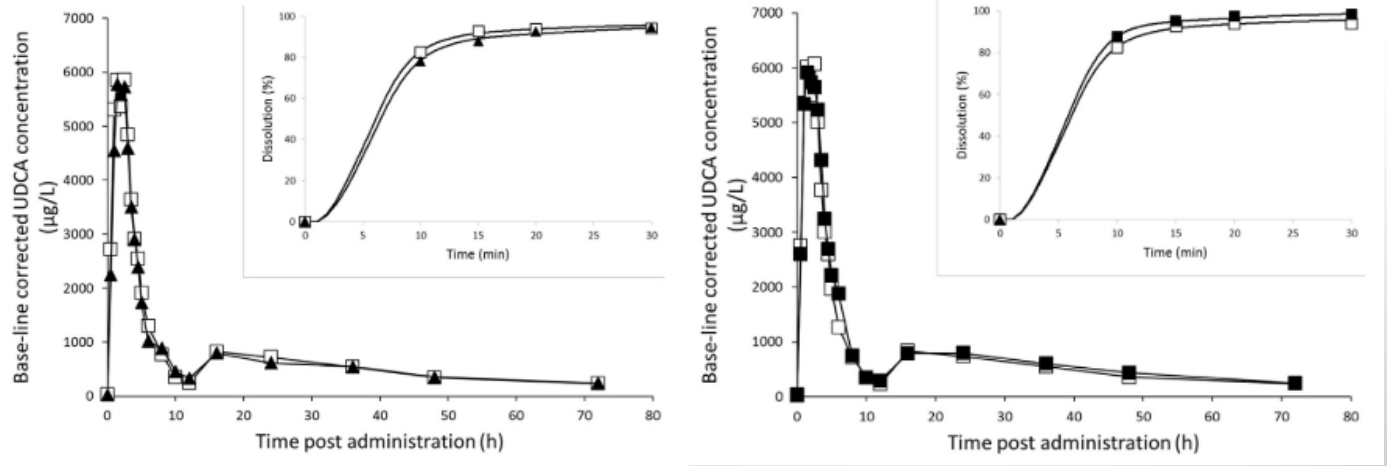
The performed bioequivalence study resulted in equivalent T2 to both reference formulations.

Dissolution analysis and bioequivalence: A case study

The reformulated Test 2 product showed bioequivalence to two reference formulations obtained from two highly regulated markets

Bioequivalence Results Summary (N = 54). Free UDCA base line corrected data (Test 2 *vs* Reference #14A21027A and #14A21027A, respectively).

Parameter	Geometric mean ratio T/R	Lower confidence limit	Upper confidence limit	Level of confidence	Intra-subject CV (%)	Inter-Subject CV (%)
Test2 post reformulation *vs* Reference 2 (#14H29951L)						
$AUC_{(0-t)}$	1.0351	0.9691	1.1056	0.9000	20.2	30.1
$AUC_{(0-12\ h)}$	1.0466	0.9871	1.1097	0.9000	17.9	19.8
C_{max}	1.0714	0.9704	1.1830	0.9000	30.8	27.7
Test2 post reformulation *vs.* Reference 3 (#14A21027A)						
$AUC_{(0-t)}$	0.9503	0.8841	1.0215	0.9000	21.7	31.0
$AUC_{(0-12\ h)}$	0.9591	0.9107	1.0100	0.9000	15.5	22.0
C_{max}	0.8887	0.8197	0.9635	0.9000	24.4	35.6



Horkovics-Kovats S.
Eur J Pharm Sci 111, 349-357, 2018

Conclusions

- The similarity factor F2 > 50 is not a necessary condition for bioequivalence
- DDM – reveals possible differences between formulations in terms of disintegration function of the FDF and particle lifetime distributions of API particles
- Not considering the end (e.g. above 85%) of dissolution profiles leads to loss of information
- Whether the identified differences in formulations are relevant to bioequivalence is difficult to estimate, it depends on the specific physicochemical properties of the API, physiology of GI tract and the pharmacokinetics of API = **physicochemical pharmacokinetics**.

Literature

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3. Horkovics-Kovats, S.: *Disintegration rate and properties of active pharmaceutical ingredient particles as determined from the dissolution time profile of a pharmaceutical formulation: An inverse problem.* **J Pharm Sci 103, 456-464, 2014**
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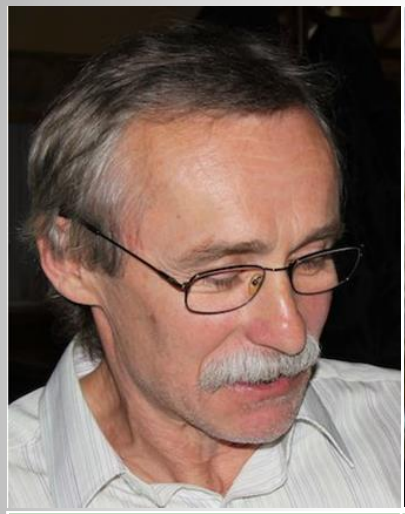
6. Horkovics-Kovats, S., Ulč, I., Vít, L., Němec, B., Rada, V.: *Physicochemical pharmacokinetics as an optimization tool for generic development: A case study.* **Eur J Pharm Sci 111, 349-357, 2018**
7. Horkovics-Kovats, S.: *Comparison of dissolution time profiles: No similarity but where is the difference?* **Eur J Pharm Sci 121, 9-15, 2018**

Acknowledgement

Thanks for very inspiring and long discussions to

			
Prof. **Pavol Zlatoš**	Prof. **Alexei Kornyshev**	Prof. **Pavel Brunovský**	Prof. **Jürgen Bulitta**
Comenius University Bratislava	**Imperial College of London**	**Comenius University Bratislava**	**University of Florida**
Mathematical treatment of EHC	**Draw my attention to the importance of properties of the given Volterra integral equations for analyzing the inverse problem**	**Unequivocal solution of the given Volterra integral equation of first kind**	**Implementation of population data analysis for solving DDM models**