Dissolution for specific products
Role of IVIVC

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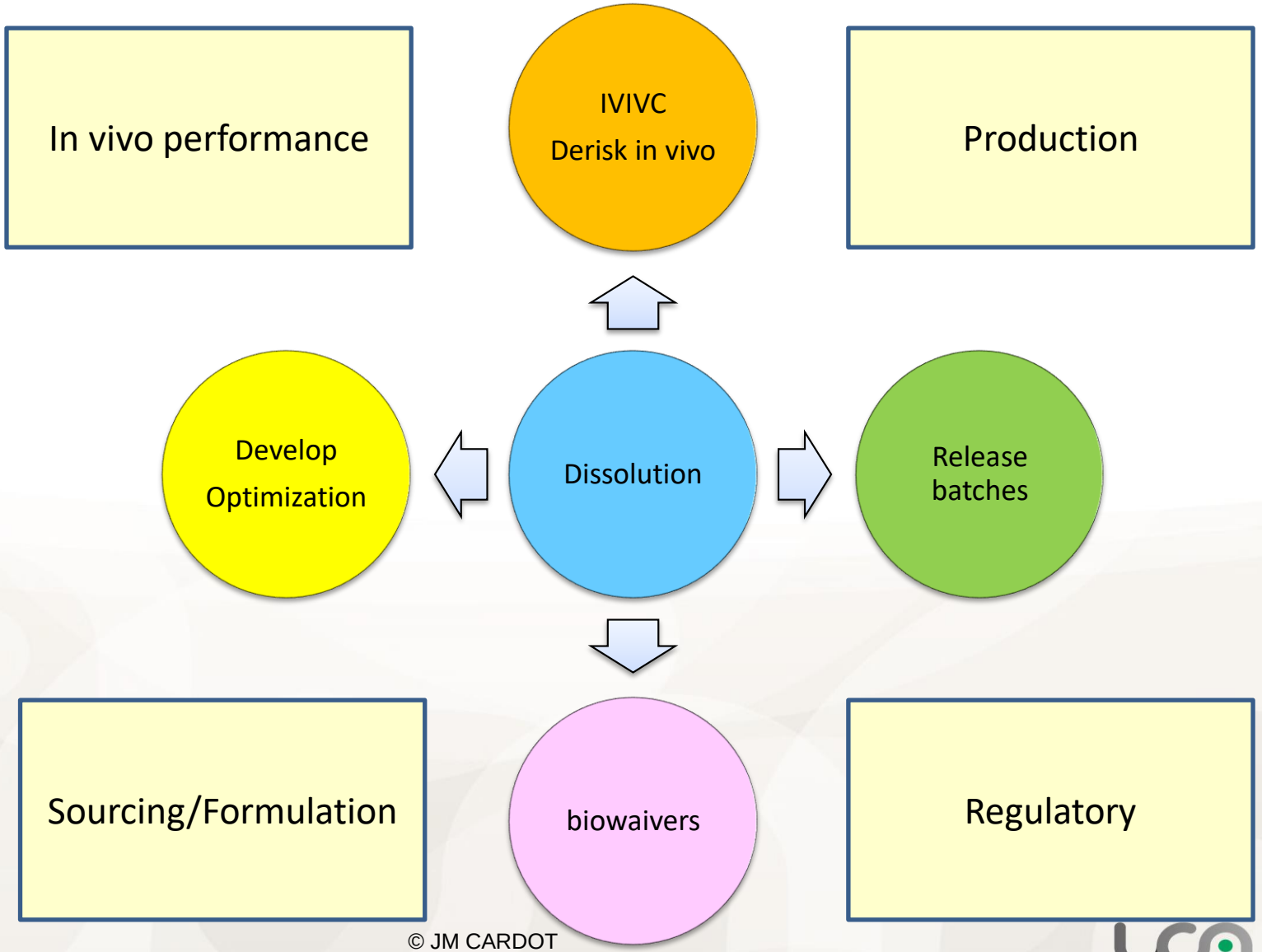
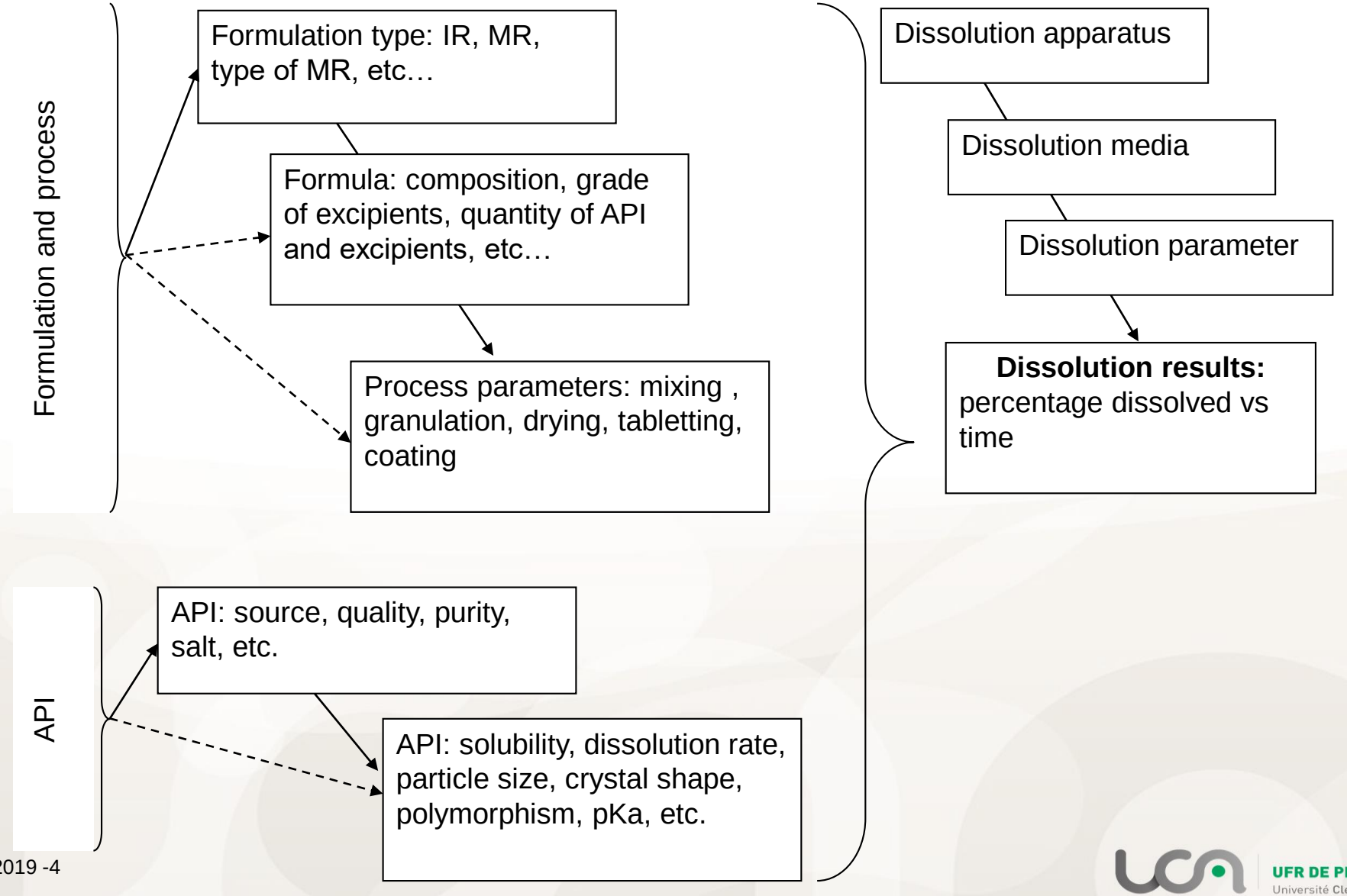
Introduction

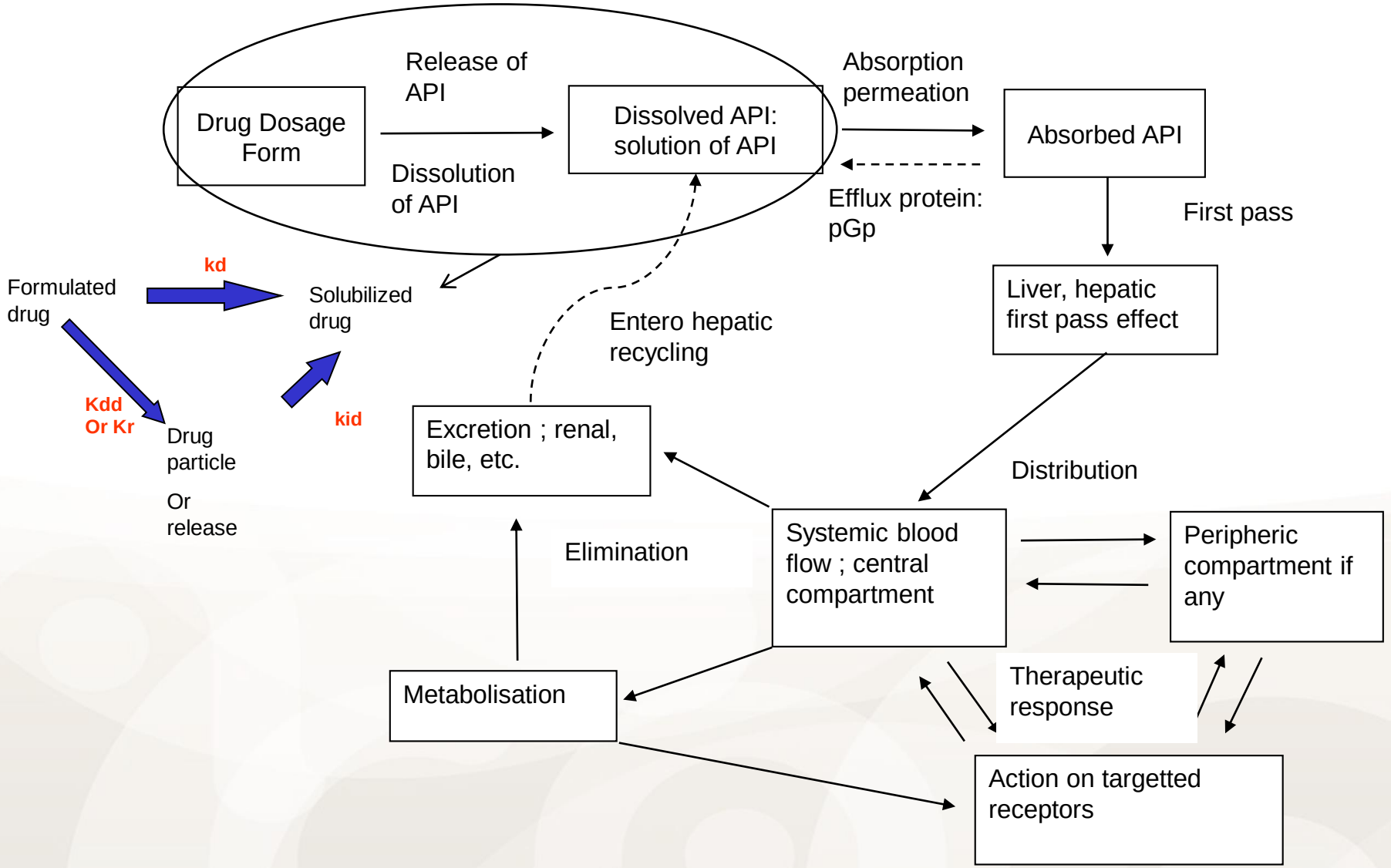
Dissolution



Why dissolution so important



Dissolution and link to in vivo



Dissolution tests

- Use as QC => insure batch to batch consistency
- Use in Biowaivers => surrogate of in vivo
- Use in life cycle management

=> Dissolution is not only a QC tool it is expected to reflect the in vivo and the in vivo limiting factor (release)

Dissolution and guideline

Guidelines/reflection papers EMA

- Bioequivalence
- MR
- ICH Q8
- Variation
- Dissolution
- ICH M9
- Statistical methodology
- Product specific guidelines …
- Etc…

Reflection paper on dissolution

- The dissolution specification should ensure batch to batch consistency and, ideally, **signal potential problems with in vivo bioavailability** (e.g. bioinequivalence).
- The test conditions should enable discrimination between batches manufactured with different critical process parameters and /or critical material attributes which may have an impact on the bioavailability. **Ideally all non-bioequivalent batches should be detected by the in vitro dissolution test** results.
- **Ideally, the in vitro dissolution test should predict the in vivo outcome**, but sometimes in vitro dissolution tests are not predictive because they are over-discriminative. This is also acceptable because if dissolution profiles are not altered, in vivo equivalence can be assumed.
- Etc…

(Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action EMA/CHMP/CVMP/QWP/336031/2017)

Product specific guideline

- Example of the draft Etonogestrel and ethinylestradiol vaginal delivery system product-specific bioequivalence
- “Additional parameters for temporary removal of the ring: **Temporary removal of the ring needs to be justified by in vitro data** demonstrating that etonogestrel and ethinylestradiol levels, their release rate, and quality of the ring are not affected by temporary removal of the ring up to a maximum of 3 hours.”

(Etonogestrel and ethinylestradiol vaginal delivery system 0.12mg/0.015mg/day product-specific bioequivalence guidance EMA/CHMP/97470/2019)

IVIVC ?

An in vitro in vivo correlation (IVIVC) is a mathematical model describing the relationship between an in vitro property of a dosage form (mainly dissolution or drug release) and a relevant in vivo response (mainly drug plasma concentration or amount absorbed). It is self-evident that such a relationship is only likely to exist when the formulation controls the rate of appearance of drug in plasma

When a modified release formulation is developed, it is highly recommended to establish an IVIVC:

a) to quantify in vivo release and formulation related effect on absorption,

b) to establish the in vivo relevance of in vitro dissolution tests and associated dissolution specifications

c) to support biowaiver claims in later phases of clinical development or post-authorisation if there are changes in formulation.

(Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1))

IVIVC ?

Ideally, whenever pharmacokinetic studies of formulations of different in vitro release profiles are conducted, these data should be utilised to provide or strengthen the evidence **supporting the in vivo relevance of the in vitro dissolution test**.

.....

(Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1))

How to be certain that it reflects in vivo

- Classical apparatus USP 1 to 7 ?
- Specific apparatus like TNO, Modelgut, Physiolution, etc.. systems?
- Classical/Specific media: pH 1.2, 4.5, 6.8, artificial saliva, Fassif, Fessif, simulated vaginal fluid, etc…
- justification of its appropriateness given the physicochemical properties of the drug.

=>… only possibility: to have in vivo results and then to try to mimic limiting factor and the behavior in vitro

Use of IVIVC to develop a dissolution test

Cardot J-M., Lukas J., Muniz P. Time scaling for in vitro-in vivo correlation: The inverse release function (IRF) approach AAPS J. 2018 DOI: 10.1208/s12248-018-0250-5.

Remarks

- Key points in level A IVIVC for long acting drugs
  - In vivo release can be mustiphasic implying more than one mechanism of action
  - In vitro the dissolution must reflect similar release mechanisms as in vivo
  - A scaling between vitro and vivo must reflect the fractions absorbed at each phase
  - Good definition of absorption

Deconvolution through convolution or in vivo and in vitro modeling approaches

- Another approach could be used derived from the DTC approach: in vivo absorption is described by a fonction
  - Exponential
  - Weibull
  - Hill
  - double Weibull
  - Makoid-Banakar
  - Linear
- Often Weibull is used as more flexible: could reflect from exponential to sigmoid

IVIVC

- Two stages approach used in the present example (one stage possible)
- First extract the absorption profile
  - Often flip-flop in case of long acting
  - Problem of LOQ
  - Need a perfect UIR
- Second fit the Absorption profile with the relevant equation
- Third recalculate the initial values to estimate the adequacy of the fit the all phases observed in vivo
- Develop or use the in vitro data, try to fit them with the same type of equation setting B and F constant
- If fit OK the time scaling is directly based on MDT ratio

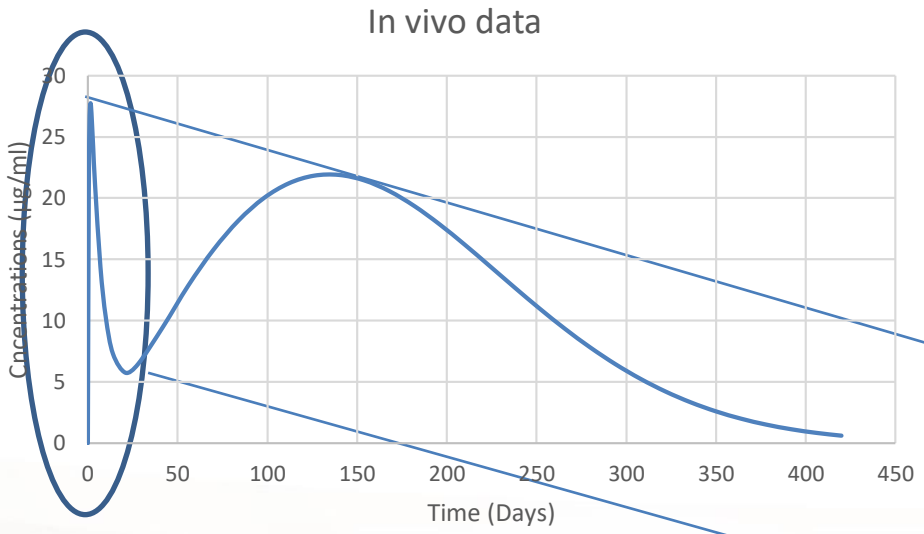
Specific dosage forms : controlled release parenteral products

Accelerated *In Vitro* Release Testing

- Should have relevance to “real time” *in vitro* tests that simulate in vivo as closely as possible.
- Accelerated tests should be bio-relevant and ideally mechanism of drug release should not be altered
- Burst release products, accelerated release tests should be augmented by an initial “real time” study

In vivo

- The data show a burst and a long acting



Time (days)	AUC	AUC %	Cmax
Time (days)			
0			
0.5	5.1	0.1	
1	17.0	0.3	
1.5	30.6	0.6	27.7
2	44.2	0.9	
3	69.7	1.4	
4	92.3	1.9	
7	145.6	3.0	
10	182.6	3.8	
14	217.7	4.5	
21	263.3	5.4	

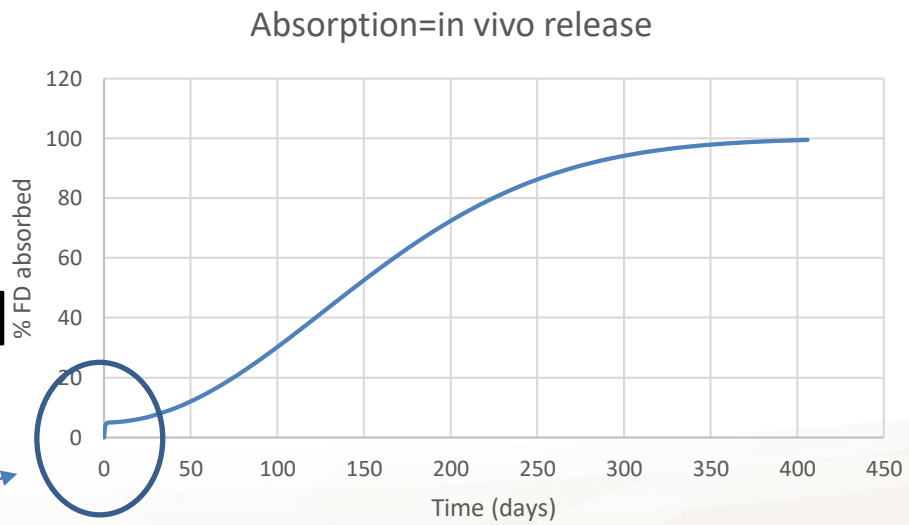
- Burst represents only a small fraction must not be overestimated

Deconvolution

- Obtain the in vivo absorption= in vivo release
- Base on this absorptin try to modelize it with
  - Simple weibull
  - Double weibull
  - Triple Weibull
  - Etc…
- Double Weibull fit it well

Parameter	Burst	SR
Beta	1	2
MDT	0.5	180
F	5	95

Burst



- Why to take into account the burst as it is only 5%? For example because it could be linked with side effects and it is important to take it into account

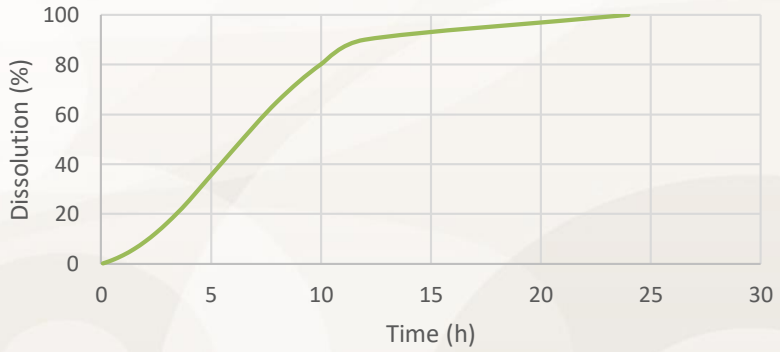
Development of an In vitro dissolution study

- Apparatus?
- Media?
- Sampling methods?
- Testing intervals?
- Total percent release?
- Real time or accelarated *in vitro* relase

No standard method at present

In vitro

- Develop the right in vitro model
- The in vitro method must reflect in vivo release:
  - Same F by phase
  - Same B by Phase
  - MDT could be different
- Modelization with double Weibull (time expressed in days)
  - Fix the 2 beta = in vivo
  - Fix the 2 F = in vivo



Time scaling

- The model in vivo and in vitro are similar for F and B
- The only factor modified are MDT
- The MDT could be very different between the 2 phases with not the same ratio
  - Burst TS is of 0.16 in vitro 6.25 time more rapid
  - SR Time scaling in vitro 540 more rapid than in vivo

	Paramater	Burst	SR
In vivo	Beta	1	2
	MDT vivo	0.5	180
	F	5	95
in vitro	Beta	1	2
	MDT vivo	0.08	0.333
	F	5	95
Time scaling	MDT vitro/vivo	0.16	0.00185

Time scaling

- In the present case the TS repects
  - The mechanism between vitro and vivo
  - The relative fraction
- This approach is simple to be implemented event in a single step approach

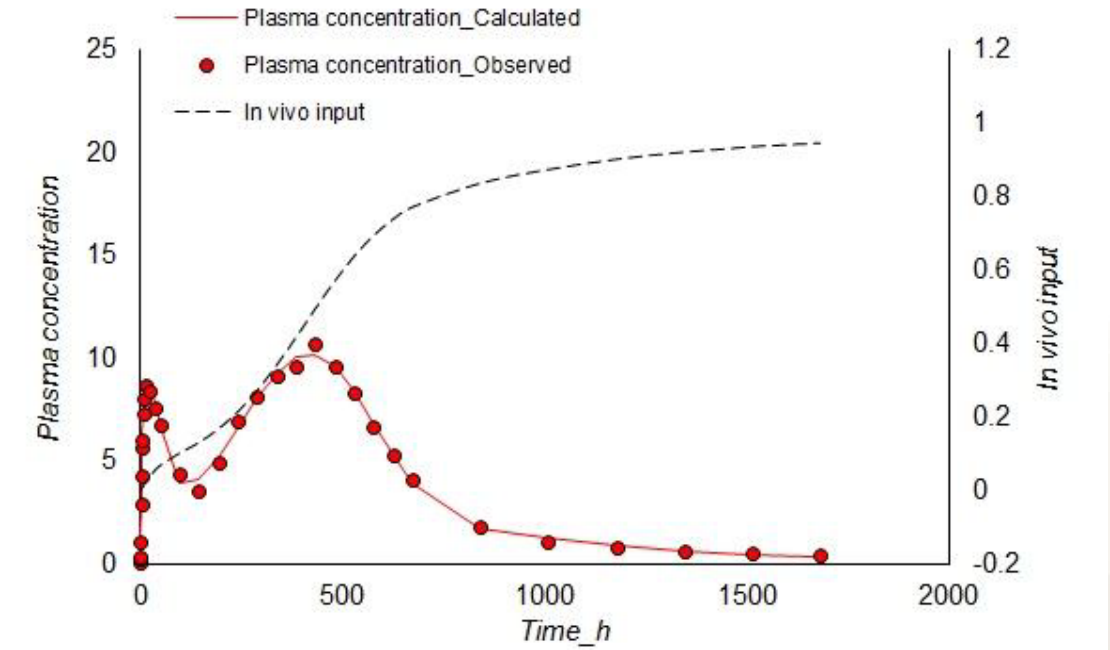
- All is based on the right characterization of the in vivo processes

How to analyse in vivo data

Tomic I, Mueller-Zsigmondy M., Vidis-Millward A., Cardot J-m In vivo release of peptide loaded PLGA microspheres assessed through deconvolution coupled with mechanistic approach Eur J Pharm Biopharm, 2018,125, 21-27

In vivo Problems

- Characterize the magnitude of the various phases accurately:
- In vivo the burst lead to high peak … but that is a low quantity as input

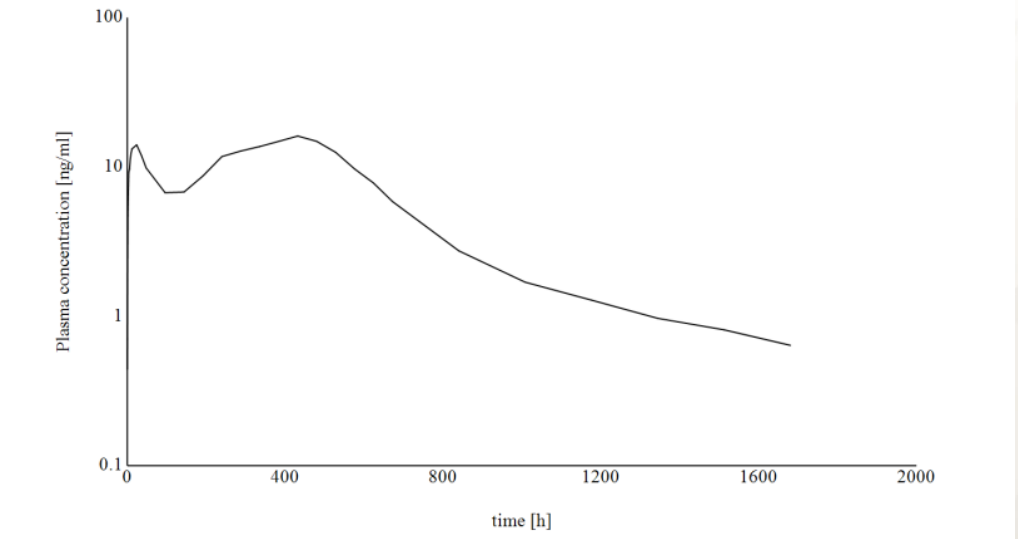


- Tomic I, Mueller-Zsigmondy M, Vidis-Millward A, Cardot JM. In vivo release of peptide loaded PLGA microspheres assessed through deconvolution coupled with mechanistic approach. Eur J Pharm Biopharm. 2017 Dec 19. pii: S0939-6411(17)30460-5. doi: 10.1016/j.ejpb.2017.12.007.

« Phase » characterization

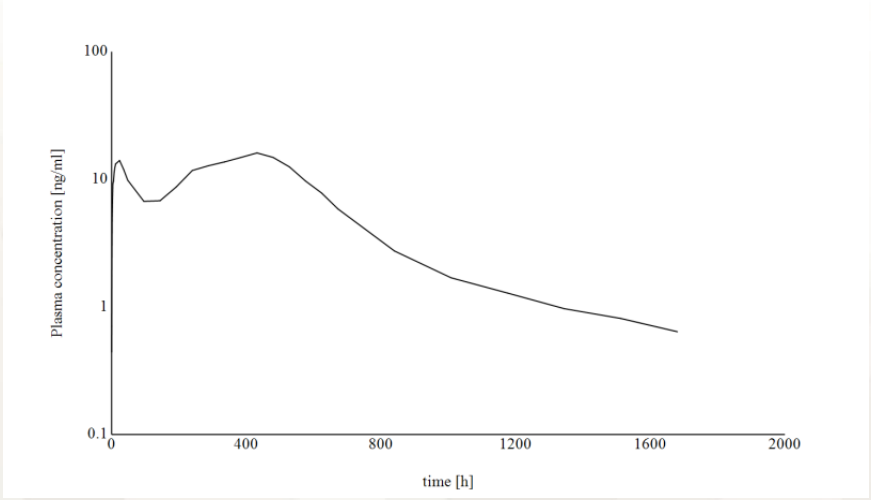
- For example calculate the PK parameters

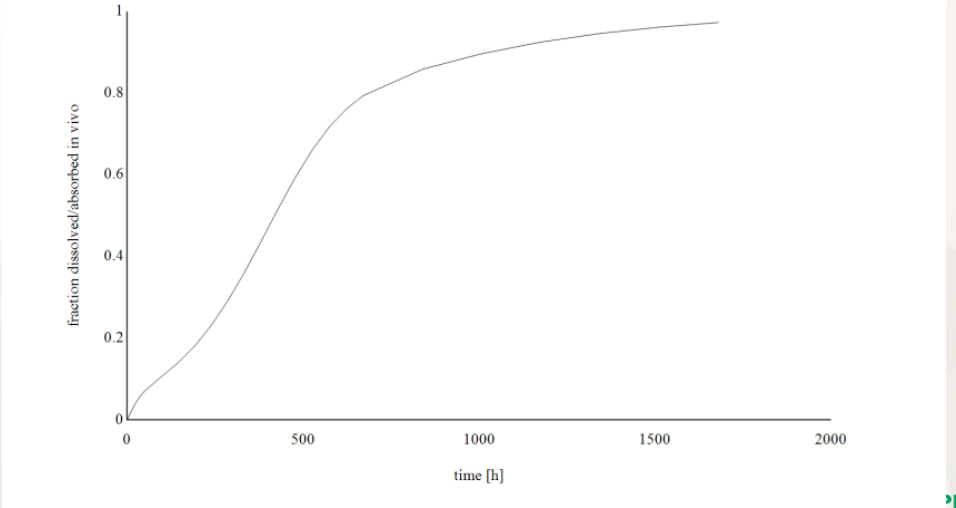
$AUC_{0\text{-}48h}$	AUC_{last}	AUC_{inf}	C_{max1}	C_{max2}	T_{max1}	T_{max2}
(ng h/ml)	(ng h/ml)	(ng h/ml)	(ng/ml)	(ng/ml) (h)	(h)	
549.3	9296.5	9890.2	13.8	16.1	24	432



Model

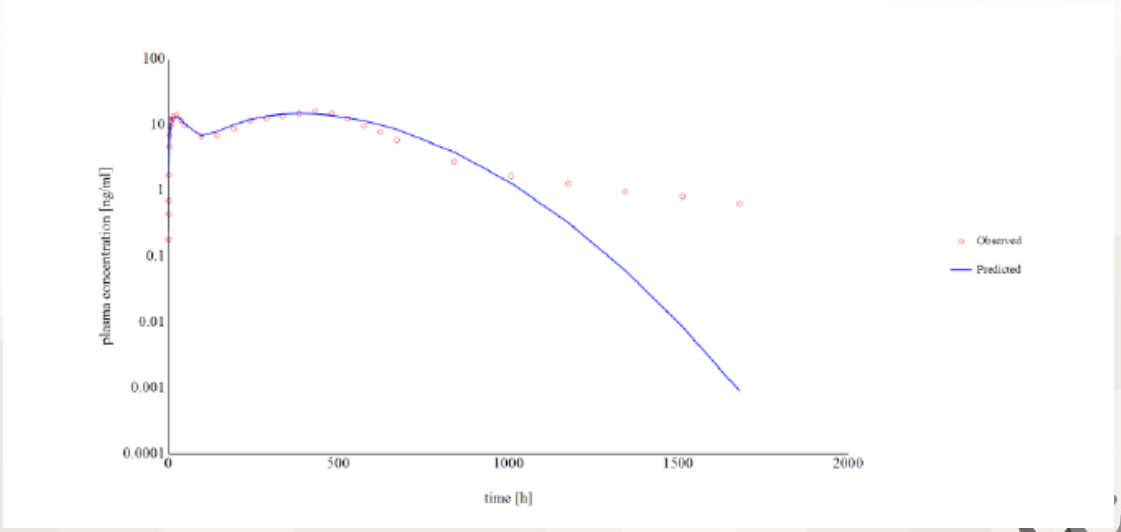
- When using a technique model for deconvolution use the right one and do not underestimate last part
- When modeling dissolution / absorption use the right model … which depend of sampling / rapid formulation





Problems

- Must be able to righthly model all the phases
- For example model with a double weibull for input …
- $$\frac{X_t}{X_{inf}} = F_1\left[1 - e^{\left(-t/\alpha_1\right)^{\beta_1}}\right] + F_2\left[1 - e^{\left(-t/\alpha_2\right)^{\beta_2}}\right]$$



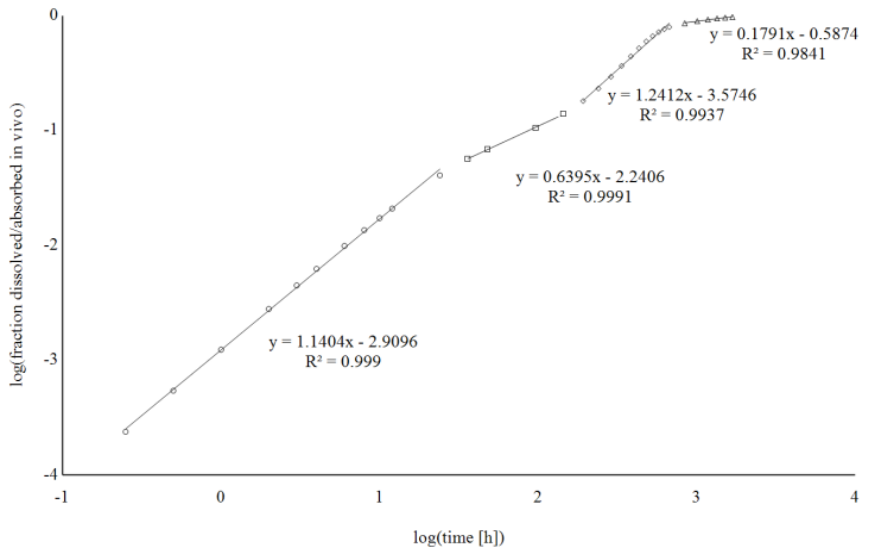
So complex setting of in vitro and in vivo absorption

- Error could be important … on some specific parameters but mainly on the last part of the curve
- $\frac{X_t}{X_{inf}} = F_1\left[1 - e^{(-t/\alpha_1)^{\beta_1}}\right] + F_2\left[1 - e^{(-t/\alpha_2)^{\beta_2}}\right]$
- $\frac{X_t}{X_{inf}} = F_1\left[1 - e^{(-t/\alpha_1)^{\beta_1}}\right] + F_2\left[1 - e^{(-t/\alpha_2)^{\beta_2}}\right] + F_3\left[1 - e^{(-t/\alpha_3)^{\beta_3}}\right]$

	% PE				
Prescribed function	AUC0-48h	AUClast	AUCinf	Cmax1	Cmax2
Double Weibull	1.4	9.8	15.2*	2.3	5.8
Triple Weibull	0.9	0.0	3.1	2.2	4.1

Analysis of the various phases and their mechanistic approach

- Could use various approach including Peppas one
- $X_t/X_{inf} = kt^n$
  - k is the release rate constant
  - n is the release exponent, indicator of the drug release mechanism. For spherical swellable controlled release systems, the release exponent n ≤ 0.43 corresponds to Fickian diffusion, 0.43 < n < 0.85 to anomalous (non-Fickian) transport, n = 0.85 to case II transport and n > 0.85 to super case II transport.



Remarks for deconvolution SR injectable

- UIR function must be of the same route as SR according to guideline this point could be discussed depending of absorption processes
- UIR should be present in all studies (to scale the magnitude) however other approaches existed
- Use of mean or median values are discussed
- Risk of flip flop is high when using non appropriate techniques
- Time scaling must be handle carefully

CARDOT J-M., DAVIT B., In vitro- in vivo correlations: Tricks and Traps, AAPS Journal 2012, Sep;14(3):491-9

How to develop a predictive dissolution test for PLGA microspheres

Tomic I, Vidis-Millward A, Mueller-Zsigmondy M, Cardot JM. Setting accelerated dissolution test for PLGA microspheres containing peptide, investigation of critical parameters affecting drug release rate and mechanism. Int J Pharm. 2016 May 30;505(1-2):42-51. doi: 10.1016/j.ijpharm.2016.03.048.

Ideal dissolution test

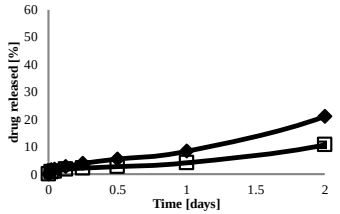
- Must reflect the release mechanism occuring in vivo
- Must be « simple » to handle
- Must be relatively rapid
- Must have a low variability
- Must be discriminant

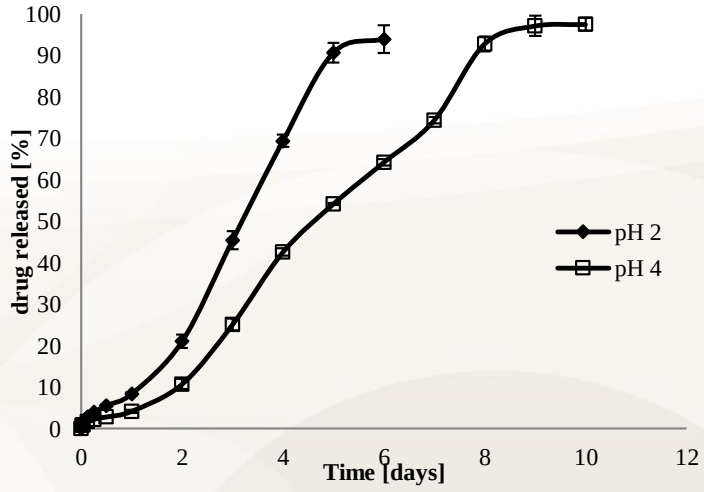
Example PLGA microsphere

- Find what could play on dissolution
  - Osmolarity and ionic strength: in phosphate buffer of 50, 200, 380 mOsm/kg, at pH 2 and 45°C (see 3.1 for explanation). Osmolarities above 50 mOsm/kg were adjusted using NaCl or Glucose in order to investigate, in addition, the effect of ionic strength on drug release
  - pH: phosphate buffer saline (0.02M PBS) pH 2 and pH 4; orto-phosphoric acid was used to adjust the pH. Tests were performed at 45°C. The range of pH was selected based on the peptide stability and solubility (see 3.1. for explanation)
  - Temperature: 45°C and 40°C in 0.02M PBS, pH 2.
  - Apparatus

Example pH

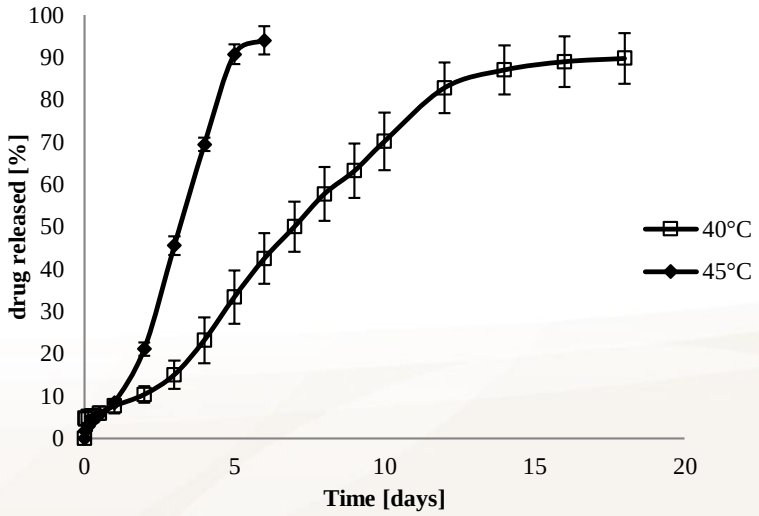
- Rate controlling mechanism during burst and lag phase is diffusion and is not dependent on pH.
- Release rate during the erosion phase is faster at pH 2
- change of dissolution medium pH from 2 to 4 does not affect release mechanism, but only the rate as a consequence of slower hydrolysis of ester bonds





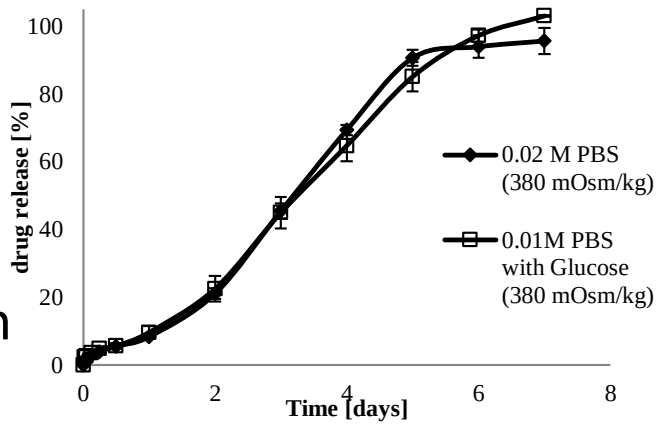
Effect of Temperature

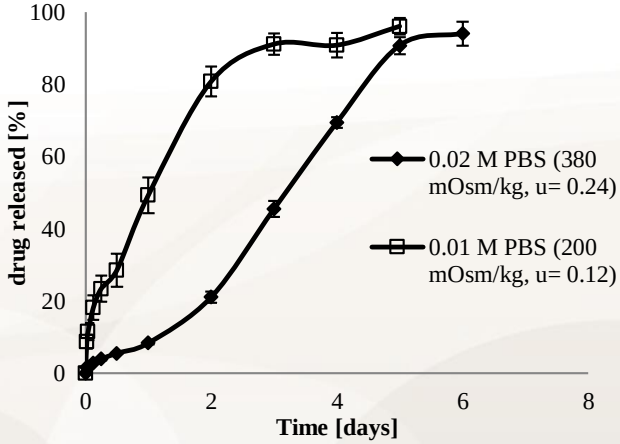
- Both tested temperatures are higher than Tg of polymer (below 30°C), thus the polymer is in rubbery state. Polymer chains are soft with increased mobility and drug release is accelerated by diffusion. High temperature enhances hydration and polymer erosion, leading to faster release during third (erosion) phase



Effect of buffer and osmotic pressure

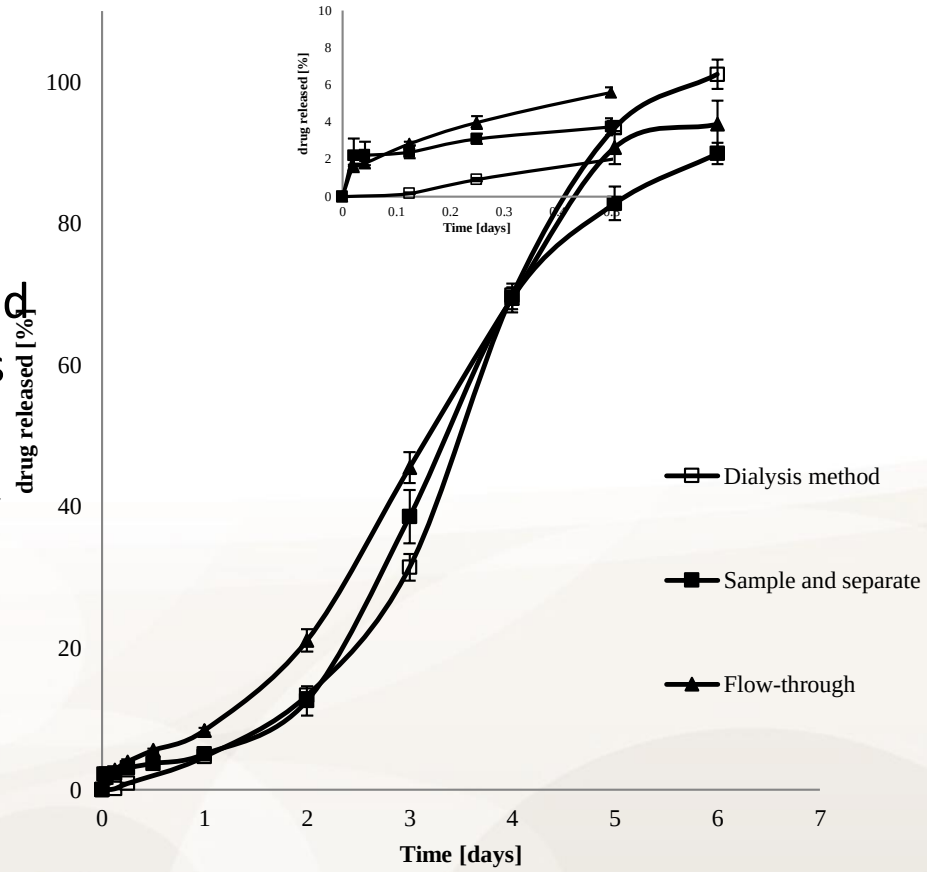
- After the insertion of microspheres in aqueous medium, water penetrates quickly into the microsphere dissolving incorporated drug substance, while hydrophobic polymer remains undissolved. Established gradient in osmotic pressure forces degradation of polymer and diffusion of dissolved drug substance. Consequently, the rate of drug release is increased.
- Decrease in osmotic pressure leads also to the change of drug release mechanism. Observed change might be due to the fact that degradation of polymer is very rapid in the medium of lower osmotic pressure, thus diffusion becomes the rate controlling factor





Effect of method

- existing compendial methods might be successfully used for development of accelerated dissolution test
- advantage to USP IV
- easy handling of microspheres without risk of aggregation or floating,
- the evaporation of testing medium is limited even at high temperatures, as the system is working in a closed loop mode,
- sample is exposed to constant perfusion by test medium which simulates better in vivo conditions, thus this method has a higher biorelevant potential.



Conclusion

A good dissolution test

- Reflects in vivo limiting factors observed in vivo
- Is simple to handled
  - Apparatus
  - Media
  - Technique
  - Etc…
- Could be used as a surrogate of in vivo: biowaiver

Thank you

Questions ?