

Case study IVIVC : Application in product and process understanding, development and control

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Outline

- IVIVC concepts and study design in product development
- Drug/product absorption kinetics
 - IVIVR and not IVIVC for IR solid dosage formulations
 - Physiology vs dissolution rate limited absorption
 - How these concepts relates to BCS?
 - QbD
- Case study example
 - Identification of product and process attributes as variants in clinical study by QbD
- Design and interpretation of IVIVR study
- Discussion
- Conclusion

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In vitro/in vivo correlation - use in product development

- A successful IVIVC model can be expected when
 - in vitro dissolution is the rate-limiting step
 - leading to appearance of the drug in the systemic circulation following drug administration
- Establishing dissolution specifications via IVIVC will permit formulation and manufacturing (that were tested) changes without an in vivo BE study
- IVIVC is used in
 - Early development
 - define in vivo predictive in vitro dissolution test method
 - **NDA documentation**
 - **building design space as part of QbD**
 - **in vivo validation of dissolution test method and acceptance limits used for manufacturing control**
 - Post NDA changes
 - a prerequisite for regulatory approval without new bioavailability studies for certain changes

Guidance for Industry

Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
September 2003
MD-3

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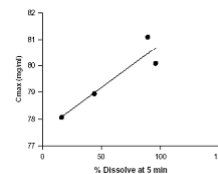
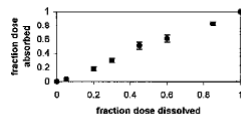
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Study design of IVIVC study

- In vitro dissolution should be adequately discriminatory between formulations
- Single fasted state study with crossover design is recommended
- Predictive mathematical model describing IVIVC should be demonstrated consistently with two or more formulations with different release rates
 - Level A, Multiple Level C, Level C
- Method for Evaluation of Predictability of Correlation
 - Internal and external predictability



<http://www.locumusa.com/pdf/members/ivivc-03.pdf>

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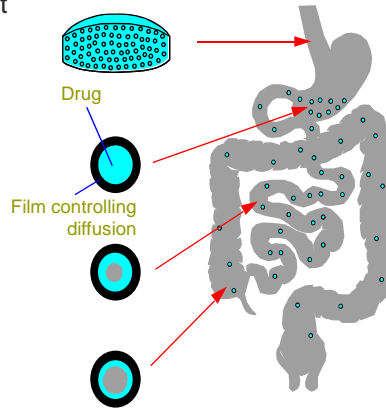
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Metoprolol CR tablets – IVIVC established

- Metoprolol characteristics:
 - BCS class I, weak base pKa 9.5
 - Well absorbed throughout GI tract
- Formulations tested
 - Oral solution
 - 3 extended release formulations
- Level A IVIVC established resulting in
 - Biowaiver granted for change of tablet matrix formulation and manufacturing site change
 - No BE failure (8 studies) in development of fixed combinations, new strength and after change of pellets coating

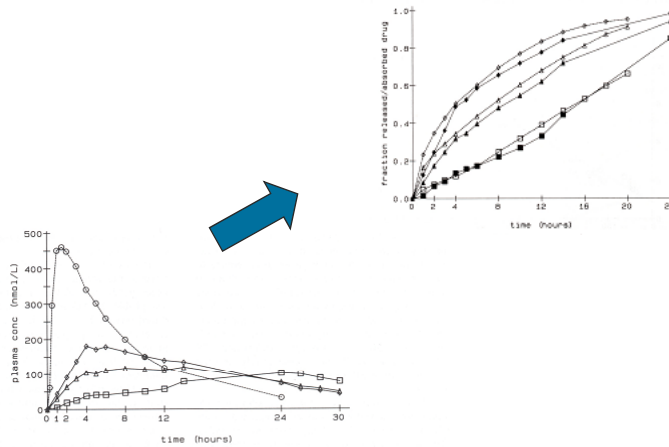


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Metoprolol CR tablets – plasma drug conc & IVIVC



Mean ($n = 10$) plasma concentrations of metoprolol after single dose administration of metoprolol succinate 95 mg as an oral solution (○) and three extended-release formulations A (△), B (▲) and C (□).

Sandberg A. Abrahamsson B. Sjogren J., Int J Pharm, 68 (1991);167-177.

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Why do we not see IVIVC for IR formulations?

- Level A IVIVC is the most **desired approach** and requires a **linear** relationship where dissolution is rate-limiting absorption (with complete absorption)
- It is unlikely for an IR formulation to conform to a linear relationship
 - However, this does not exclude IR as candidates for other forms of IVIVC analysis (non-linear)
- Use of a more general term '**relationship**' would allow for non-linearity
 - IVIVR for IR formulations most likely
- Hence, for IR formulations the intent should be to learn about the relative contribution of dissolution to a product's overall absorption kinetics
- Polli et al proposes a model which considers
 - Fraction of dose absorbed based on permeation and dissolution constants
 - Presented as gradual relationships

Polli et al. Journal of Pharm. Sci. 85: 753-760, 1996

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Physiology versus dissolution rate limited absorption

- Amidon and co-workers recognised some time ago that variation in dissolution rate may not lead to a change in *in vivo* performance
- It has been proposed that physiological absorption processes can be (are) slower than dissolution
 - Gastric emptying, permeation
- Across a limited range where dissolution never becomes slower than these physiological processes
 - Dissolution could determine *in vivo* performance without an IVIVC

BCS Class	IVIVC Expectation
1	IVIVC if dissolution rate slower than gastric emptying rate, otherwise limited or no correlation
2	IVIVC expected if <i>in vitro</i> dissolution rate is similar to <i>in vivo</i> dissolution rate , unless dose is very high
3	
4	Absorption (permeability) is rate determining and limited or no IVIVC with dissolution rate limited or no IVIVC expected

Amidon et al. Pharm. Res. 12:413-20, 1995

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What does the BCS tell us?

BCS Class

I and III

Low risk due to high solubility and rapid dissolution

Setting the spec

BCS 'rapid dissolution' limit:
BCS I – 85% in 30 mins
BCS III – 85% in 15 mins

NO



Clinical study

Biowaiver possible because in vivo performance not affected.
*BCS III awaiting HAs pipeline

II and IV

Higher risk due to absorption potentially being rate-limited by solubility and dissolution

A link between in vitro and in vivo performance is important. Achieved through performing a PK study.
E.g. 75% in 30 mins

YES



IVIVC/R study required to build confidence in disso method

- A decision mainly linked to a compound's BCS solubility classification
 - Exceptions may include complex absorption/PK, NTIs, others?

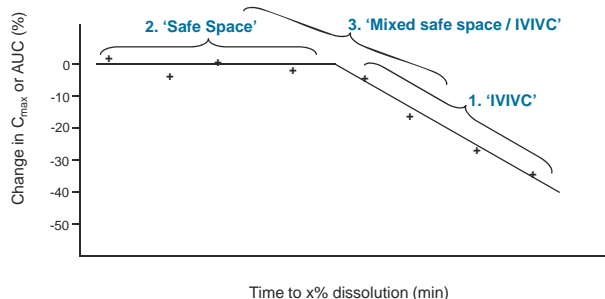
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Possible relationships between dissolution and drug exposure in subjects



+ = standard and side batches based on most relevant manufacturing variables.

*For this type of approach to be acceptable the most relevant risks to clinical quality need to have been assessed (i.e. in a QbD setting).

For a BCS Class II compound 3 possibilities exist :

1. IVIVC is established and a specification that controls C_{max} , AUC by maximum +/-10%.
2. A "safe space" specification is set based on no effect seen in the clinical study and the slowest dissolution profile tested in the clinical study (in this case the specification is set at the boundary of knowledge rather than on a biological effect).
3. The final option is a mixed safe space / IVIVC result in which clinical pharmacokinetics is only affected for a few of the variants tested clinically. Again this would allow a dissolution specification to be set that allowed C_{max} , AUC to be controlled to 10%.

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Summary: Dissolution limits which assure exposure by BCS Class for a QbD based DESIGN SPACE

		Solubility	
		High	Low
Permeability	High	1 Complete dissolution within 30 minutes in most discriminating 'simple' media (physiological pH range). If slower: bioavailability data or additional mechanistic information	2 Limit set based on clinical 'bioavailability' data
	Low	3 Complete dissolution within 15 minutes in most discriminating 'simple' media (physiological pH range). If slower: bioavailability data or additional mechanistic information	4 Limit set on case by case basis: Bioequivalence Study Or Follow principles of BCS2 or BCS3 if can demonstrate that compound behaves more like BCS2 or BCS3 in vivo

Dickinson et al. (2008) AAPS Journal. 10: 380-90

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If clinical studies are required what variants should be used

Is safe space or IVIVC more likely for a well designed (QbD) BCS2/4 Product

Overall how to confirm clinical relevance of a QC-like dissolution Method

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Case Study : A BCS Class 2 compound with reasonable solubility

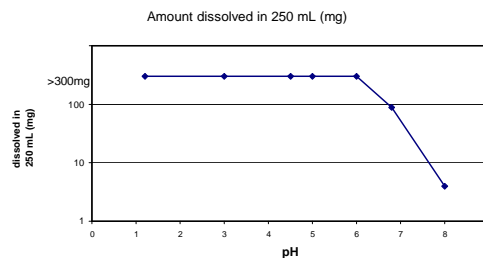
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Knowledge/Data to support the Science Based Process

- Drug substance properties:
 - Molecular weight :approx 500
 - pKa: dibasic
 - ClogP : 5.7
 - LogD(octanol): 2.6
 - Displays high permeability
 - Low solubility
 - Stable in GI Fluid
 - Long half life (~10-15 days)



- **BCS Class II**

ICH Q9: 'Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment'

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Variant Chosen

- Identified the Highest Risks to drug exposure by risk assessment (from all variables in the product and process that could affect in vivo dissolution)
 - If these are not important in vivo then likelihood that others wouldn't be
 - And if they were important we'd be able to develop an IVIVC and predict the effect on PK of the less important ones
- Important that several mechanisms were looked at
 - Increases likelihood of the disso method picking up mechanisms we haven't thought of and/or looked at specifically
 - Impact of drug substance surface area/properties on rate of dissolution
 - Impact of granule properties (size and structure) on the rate of ingress of water
 - Impact of slowed tablet disintegration rate on subsequent drug dissolution

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Evaluation of most relevant variables

- Several tablet variants were manufactured and four taken forward after dissolution testing:
 - Standard Clinical Manufacture – Variant A
 - Large Particle Size Variant – Variant B
 - Process Variant (Over granulation) – Variant C
 - Formulation Variant (Less disintegrant, more binder) – Variant D
- Tested *in vitro* – to develop dissolution method capable of identifying changes in product quality due to changes in these most relevant process parameters and quality attributes
- Tested *in vivo* – to evaluate impact of these variables on in vivo performance and if appropriate develop a mathematical relationship (IVIVC)

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How did we pick the dissolution conditions, remembering we also want to use this as a QC-test

- From early on had been using FaSSIF and pH 1.2.
- At start of Phase 2 screened other pHs + several surfactants
- Ran many variants through several tests
- Started to favour a standard surfactant based method:
 - Similar discrimination to FaSSIF
 - Better recovery than other standard surfactants

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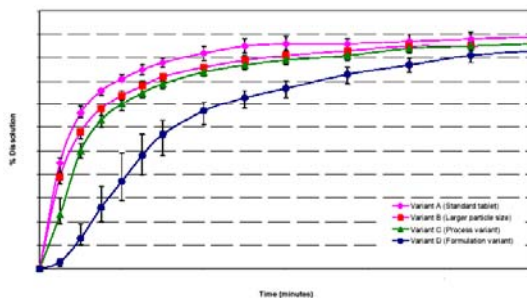
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Which Dissolution Method?

Figure C4 Average tablet dissolution in the chosen surfactant based media



Similar Discrimination to FaSSIF across many variants (phase 1 to phase 3)

- Chose the most discriminatory method that gave complete release.
- Confidence it will pick up any other factor affecting dissolution in vivo

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• FaSSIF and also disso across the physiological pH range

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Figure C1 Average tablet dissolution in pH 1.2

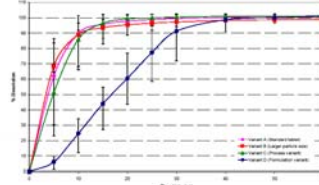


Figure C2 Average tablet dissolution in pH 4.5

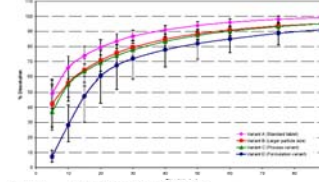
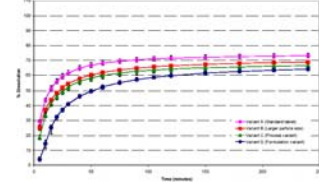
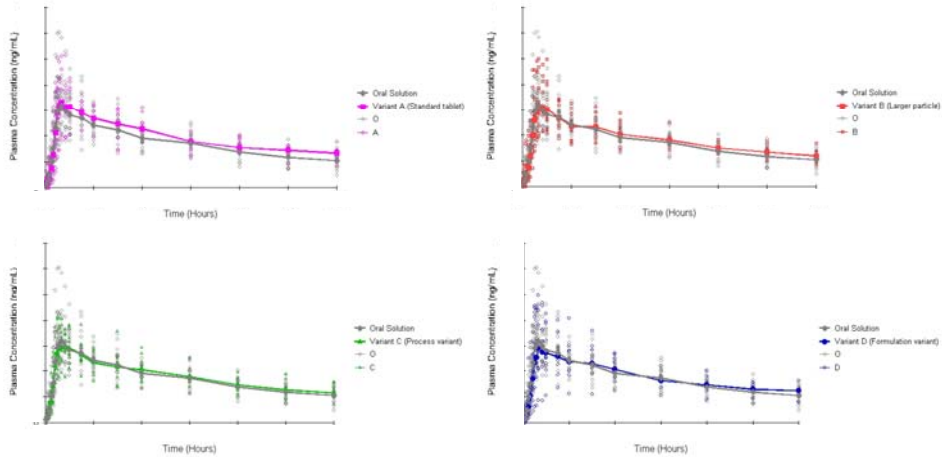


Figure C3 Average tablet dissolution in pH 6.8



Geometric Mean and Individual Plasma Concentrations from Tablet Variants (n = 10 for Variants A and B, n = 11 for Variant C and n = 9 for Variant D) versus Oral Solution (n = 15) after dosing to healthy volunteers



No difference in PK performance (C_{max} and AUC) after dosing the tablet variants to volunteers i.e. not appropriate to try to develop an IVIVC

Study Conclusions

- The in vivo evaluation demonstrated that changes in the Highest Risk Process Parameters and Quality Attributes did not affect PK
- Cannot develop an IVIVC because the PK profiles overlap and there are no differences in vivo
 - **Safe Space for a BCS2**
- However, the impact of these variables on dissolution when tested by the most appropriate method, could be detected
 - i.e. over discriminatory dissolution method
- As the variants dosed encompassed three different mechanisms to alter drug release from the tablet the overly discriminatory dissolution test is an appropriate test to assess clinical quality of all outputs from further processing studies

Quality Limit Required from the Design Space

- If product has a dissolution profile faster than that of slowest profile dosed to volunteers (Variant D) then in vivo performance will be comparable to pivotal clinical trials material
 - The clinical relevance of the dissolution test is established by being able to define specification limit which guarantees consistent bioavailability of the product
- The dissolution limits using this method will be based on the profile from Variant D, not on process capability
 - A new way to set specifications
- This dissolution specification will be one of the criteria used to define the design space and support future changes

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Was it necessary to do a clinical study to support QbD?

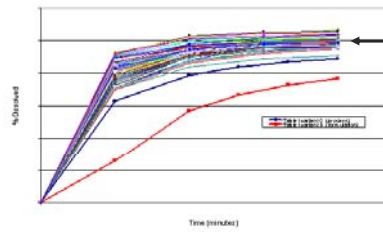
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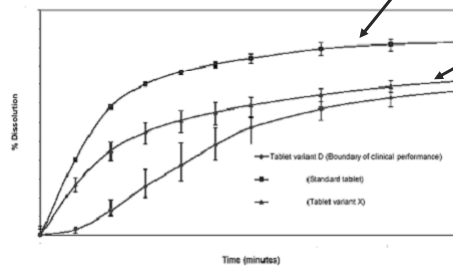


Multi-variate comparison to Variant D vs Design Space



Clinical batches from design space

Dissolution performance of tablet variant X (extremes of formulation + process) versus tablet variant D (the boundary of clinical performance)



Multivariate worse case (based on knowledge developed during Design Space development) from Design Space (Variant X) and Variant D

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Is a clinical study needed?

- Was it necessary to do a clinical study for Case study considering it's 'good' properties
 - If we want the flexibility of Variant X then the study had to be performed
 - If specifications below what has been routinely achieved from clinical manufactures are difficult for Regulatory Authorities to accept
 - Perhaps because dissolution has also been seen as controlling more traditional quality aspects as well as in vivo performance
 - Then I think we could have stopped after the development of the discriminatory dissolution method and variants.
 - i.e. not going beyond our pivotal clinical experience and so a good discriminatory method probably enough to **trend quality**
- But for me this is all about high quality affordable and accessible medicines
 - a clinically relevant specification will facilitate this, as this will remove additional cost associated in developing and maintaining a product with quality beyond that which is required by the patient

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Key steps in ascertaining clinical performance by dissolution testing in QbD and establishment of Design Space

1. **Conduct Quality Risk Assessment (QRA)** to allow the most relevant risk to clinical quality to be identified based on prior knowledge of this and other products.
2. **Develop dissolution test(s)** with physiological relevance that is most likely to identify changes in the relevant mechanisms for altering drug dissolution, e.g. testing at lowest acceptable solubility/mildest agitation.
3. **Understand the importance of changes** to these most relevant manufacturing variables on clinical quality based on dissolution data combined with
 - a. BCS based prior knowledge
 - b. and/or clinical 'bioavailability' data
4. **Establish the dissolution limit** which assure clinical quality (i.e. no effect by changes)
 - a. Clinical 'bioavailability/exposure' data
 - i. Classical IVIVC (already accepted today in SUPAC)
 - ii. In vivo "safe space"
 - b. Prior knowledge (BCS).
5. **Ensure dissolution within established limits**, to assure clinical quality, is used to define a Design Space
 - > i.e becomes part of the Quality Target Product Profile
 - > thus appropriate quality is designed into the manufacturing process

Dickinson et al. (2008) AAPS Journal. 10: 380-90.

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Design and interpretation of IVIVR(Safe space) study

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Study design

- IVIVR (Safe space)
 - Relative bioavailability type study seems acceptable
 - exception Canada!
 - Not a BE study design
 - Cross-over or incomplete block design
 - all receive target formulation + one test variant
- IVIVC
 - Cross-over or incomplete block design
- Both
 - Cross study data may be possible to combine if variability / study design acceptable

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Data evaluation / statistical analysis

- IVIVR (Safe space)
 - Alternatives: Comparison vs target formulation by
 - t-test
 - f2-testing of in vivo disso profiles (require solution ref)
 - analogue assessment to IVIVC
 - C_{max} and AUC within +/- 10%, linear regression test
 - Naive comparisons (ANOVA with multiple t-tests or just plot profiles) seems acceptable but this area need to be further clarified
 - 90 % CI BE (should be avoided if possible)
 - These are initial thoughts, we are still learning
- IVIVC
 - As FDA IVIVC guideline

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Discussion Points

- Choice of variants for a relative BA study follows two broad strategies
 - Univariate and several highest risk mechanisms to establish a disso method with broad applicability
 - Reduce likelihood of 'what if' you've missed something
 - Multivariate from the design space
 - This batch becomes 'validation' of the design space and dissolution then more supporting
- Choice of dissolution conditions
 - all conditions give the same discrimination: for wide applicability go for most discriminatory
 - if a less discriminatory method chosen for logistical reasons then the design space needs to be narrower to ensure validity of the test
 - It may be appropriate to use more than one method for certain changes to make sure all potential mechanisms are detected

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Conclusions

- For well designed products (QbD) a likely outcome of a clinical study on tablet variants is a **SAFE SPACE**
 - that is for a well designed product and process it is difficult to reduce dissolution to a level where it affects in vivo performance
 - i.e. to make dissolution substantially slower than other physiological processes
- However dissolution methods can be developed that are able to detect changes in dissolution due to changes in relevant process and product factors
 - This enables a specification which controls in vivo performance to be defined in conjunction with data from a relative BA study
- Clinical studies are useful to build understanding but maybe difficult to justify if specifications lower than the pivotal clinical batch data are not accepted

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