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Dissolution Similarity Applications in Generic Industry – Issues and Challenges: Case Studies

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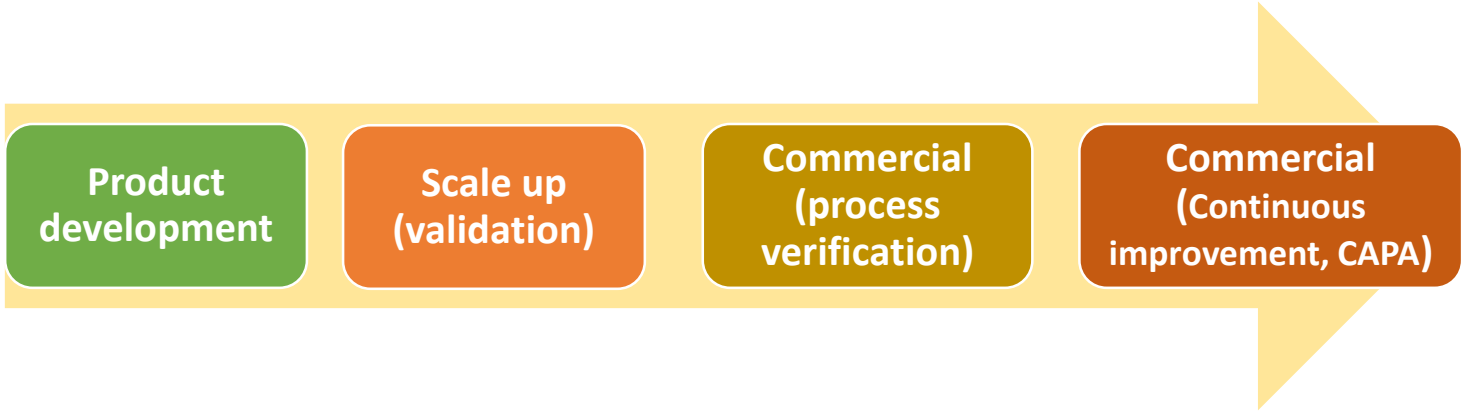
Disclaimer:

The views expressed in this presentation are my own and do not represent the view of my employer or any association I am affiliated with.

Changes in pharmaceutical product life cycle

- Product life cycle is a continuous change



- At each stage of development and life cycle – dissolution is critical product performance indicator.
- f2 calculation is a basic tool for its assessment

f2 = ?

Dissolution Similarity in Generic Industry

Product development

- Decision on bio-strategy – can lower strengths be bio-waived or multiple BE studies are required?
- Selection of formulation for BE study *vs*. Reference product*

Submission

- Biowaiver for other strengths based on demonstrated BE of the bio strength
- BCS based biowaiver – dissolution (*in vitro*) as a surrogate for *in vivo* BE
- Comparison of Reference products from various markets for submission with foreign reference approach

Scale up

- Process qualification (validation) at commercial scale

Commerical mfg

- Justify impact of minor formulation/ process changes

Pre - approval

Post - approval

**limited to cases where dissolution is controlled by API solubility and API form is the same in both*

Outline

Challenges:

- Selection of time points for comparison and variability
- Delayed release products
- Dosage form surface/volume ratio effect on similarity
- Discriminatory power of the method *vs.* f2

Selection of time points for f2 comparison

Regulatory requirements for f2 calculations:

- Only one measurement should be considered after 85% dissolution of both products
- Minimum of 3 dissolution time points are available for calculation
- To allow use of mean data, %RSD at the earlier time points (e.g.15min) should be NMT 20%, and at other time points NMT 10%

Points for clarification:

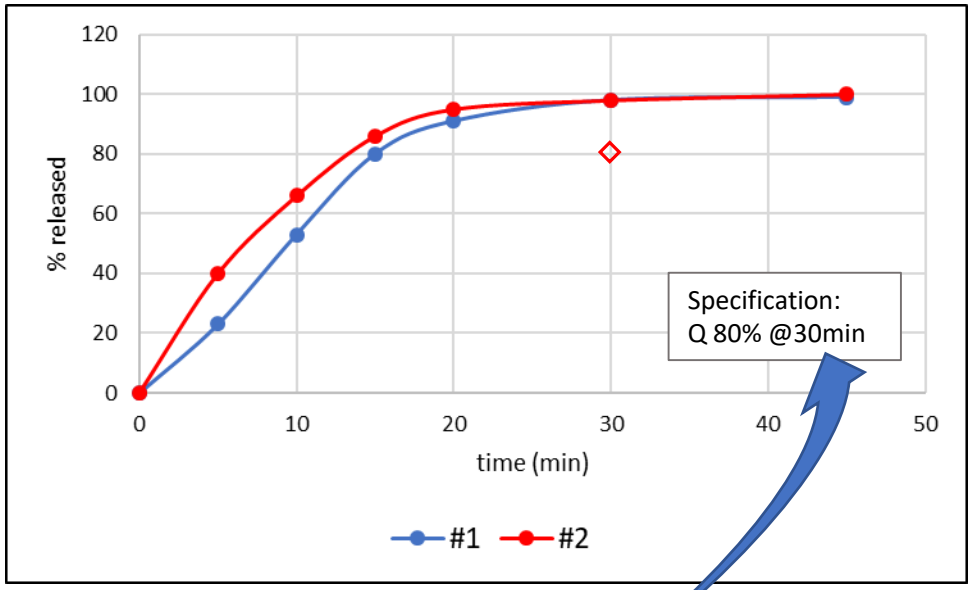
- What is “earlier” point? How many? What is its significance?
- RSD *vs.* SD ?
- When the variability does not meet requirements - exclude the variable point(s) or use bootstrap?

The use of 5 min time point?

Time	#1 Mean % released	#2 Mean % released
0	0	0
5	**23**	**40**
10	**53**	**66**
15	**80**	**86**
20	**91**	**95**
30	98	98
45	99	100

f2 47

f2 53

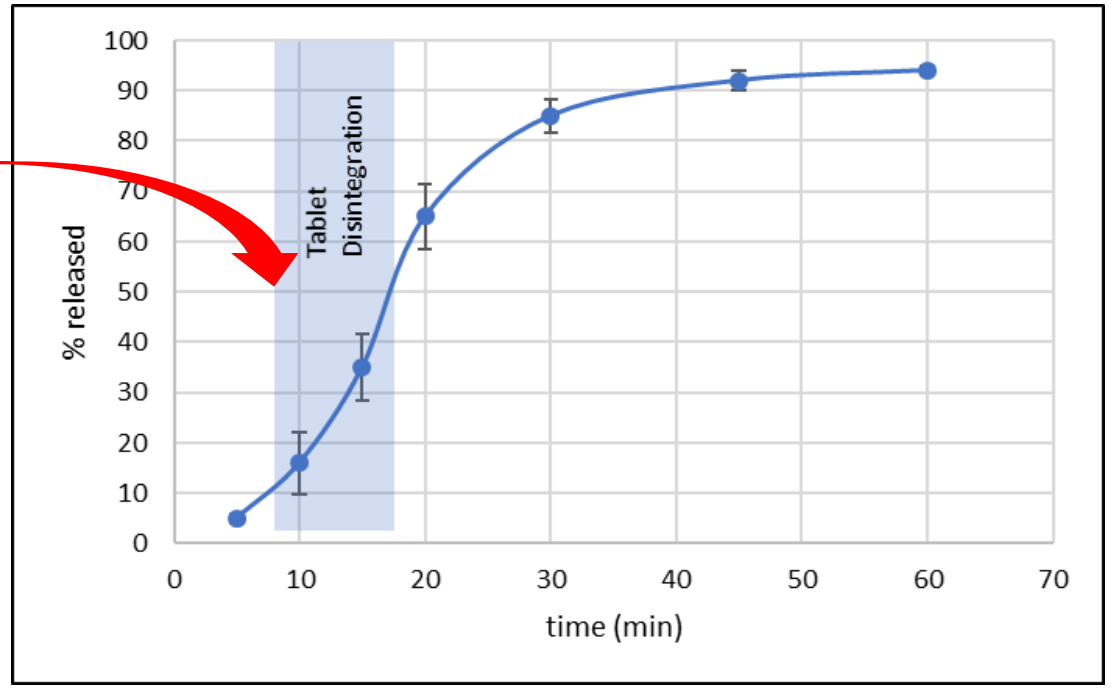


- 5,10,15 and 20min time points are eligible for calculation (RSD@5min <20%)
- 5 min is hugely impacted by tablet disintegration time
- Often there is a difference between the two profiles at this early stage.
- Should we use 5min point in f2 calculation?

What is the physiological relevance of the difference in the initial 15 minutes?

Not necessarily the first time point is most variable, depends on DT

Time	Mean % released	%RSD
5	5	19
10	16	38
15	35	19
20	65	10
30	85	4
45	92	2
60	94	1

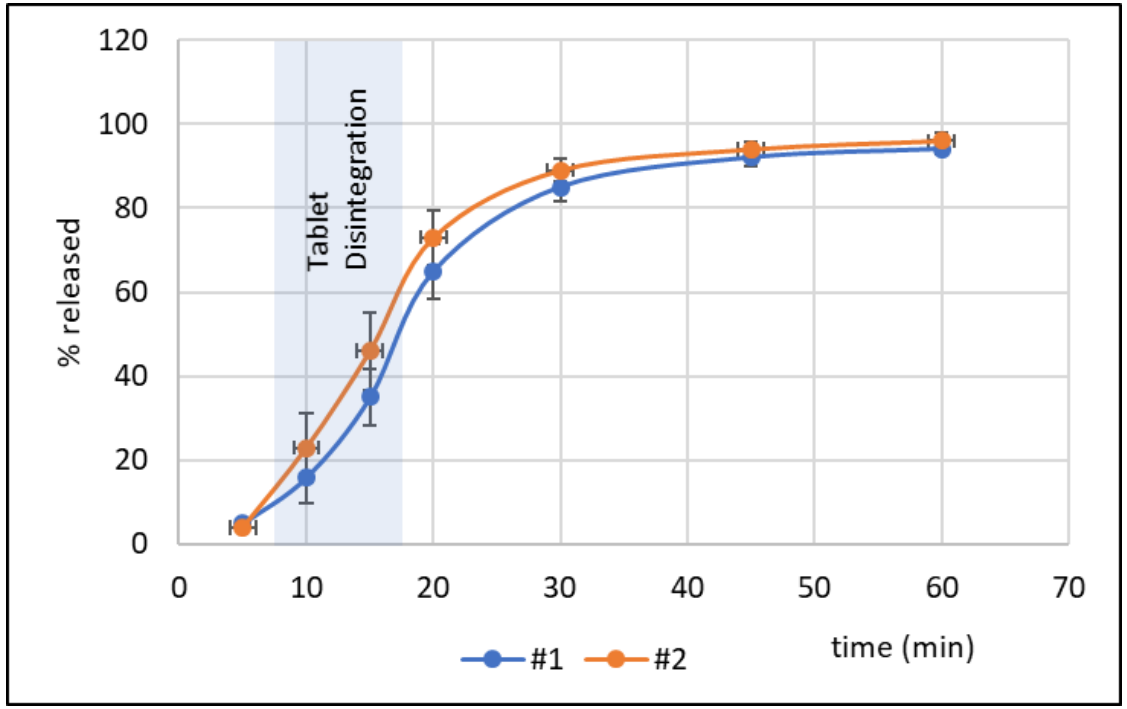


- **10 min and 15 min** are variable and excluded as “earlier points”.
- 5 min is the “earliest” but eligible based on %RSD.
- 5min, 20 and 30 min were eligible for comparison.

Should 5 min remain when 10 and 15 min are excluded?
Is 5 min truly relevant with 5% release?
Should bootstrap be used?

Not necessarily the first time point is most variable, depends on DT

Time	#1 Mean % released	#1 %RSD	#2 Mean % released	#2 %RSD
5	5	19	4	20
10	16	38	23	36
15	35	19	46	20
20	65	10	73	9
30	85	4	89	3
45	92	2	94	2
60	94	1	96	2
f2 (5,20,30min) = 56				
Bootstrap lower 90% CI (5,10,15,20,30min) = 47				

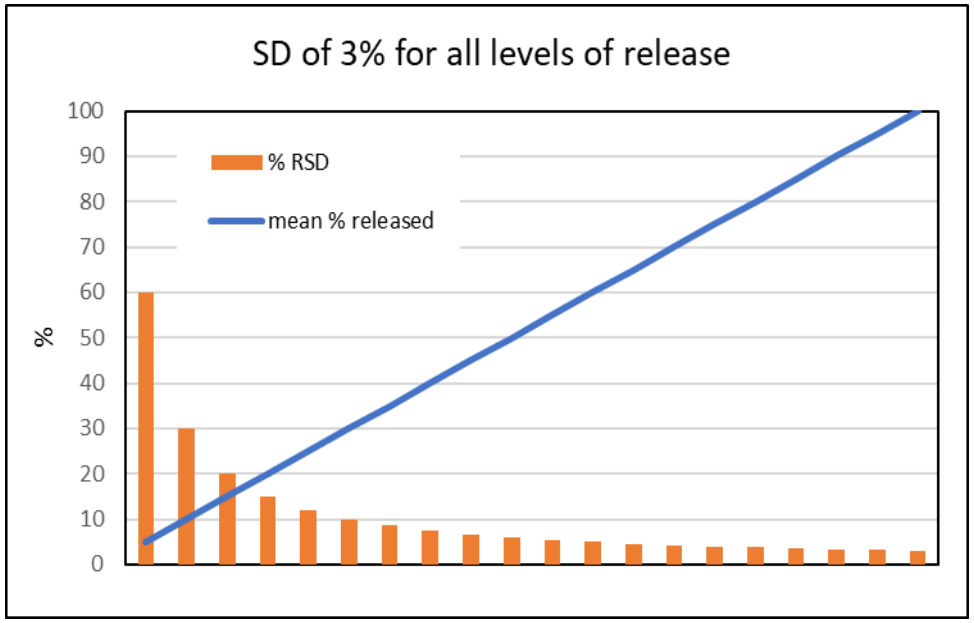


- Both products have similar disintegration pattern and similar variability (10,15min time point)
- f2 calculation and bootstrap give different conclusions

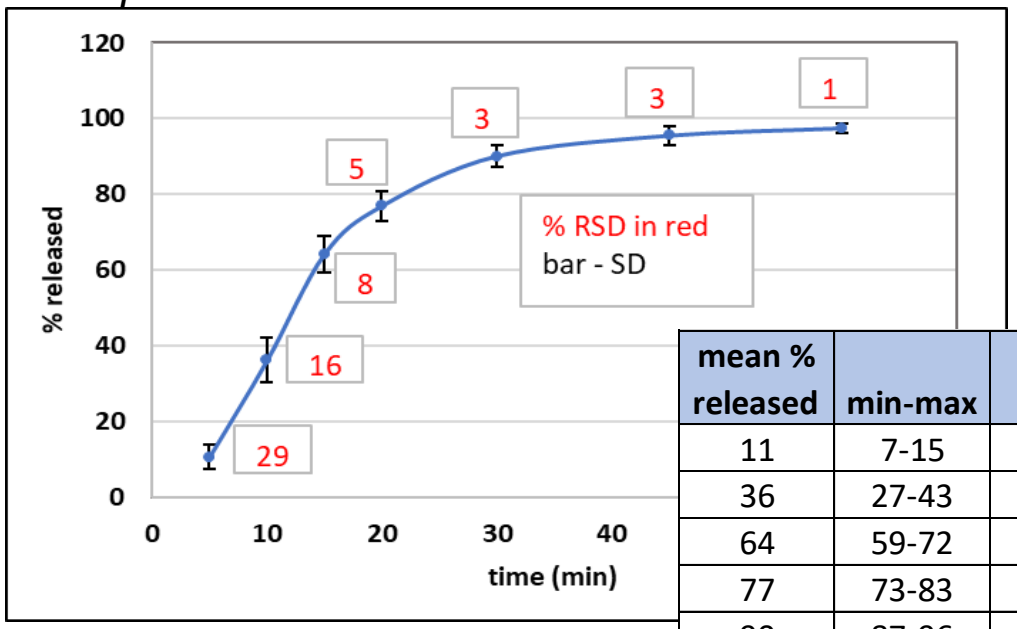
Both approaches (f2 with exclusion of 10,15min points & bootstrap) are feasible but give different conclusion. Are the batches similar?

%RSD *vs.* SD

Acceptability of variability based on %RSD at lower release values is more stringent than for higher values



Example:



mean % released	min-max	SD	RSD
11	7-15	3	29
36	27-43	6	16
64	59-72	5	8
77	73-83	4	5
90	87-96	3	3
96	90-98	3	3
97	94-99	1	1

Use of %RSD artificially inflates the significance of the variability at lower release values

%RSD *vs.* SD

Variability of individual results = Product + Method (instrument, analytics)

Typically small
Precision 2% + Accuracy 2% = up to ±4%

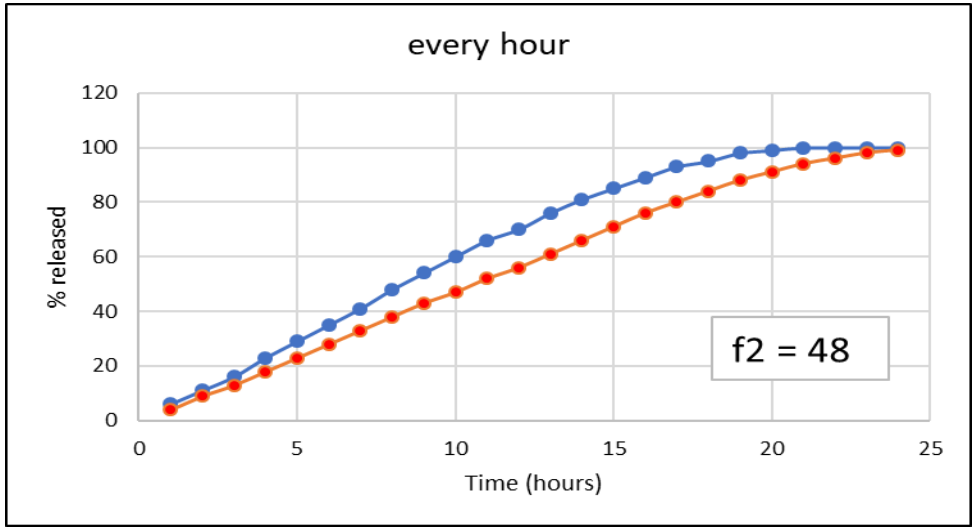
$$(\sigma_{total})^2 = (\sigma_{product})^2 + (\sigma_{method})^2$$

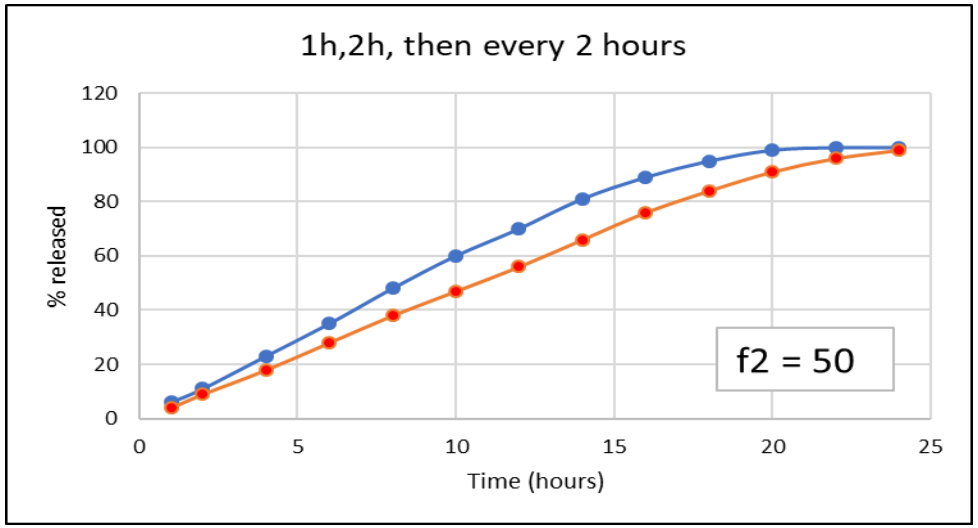
- Method does not impact variability significantly at about Q point value (e.g. 85%)
- However when % release is less than 20-30% it may add significantly to %RSD

Variability expressed as %RSD artificially inflates the significance of 2% for lower release levels

Impact of the used time points for MR products

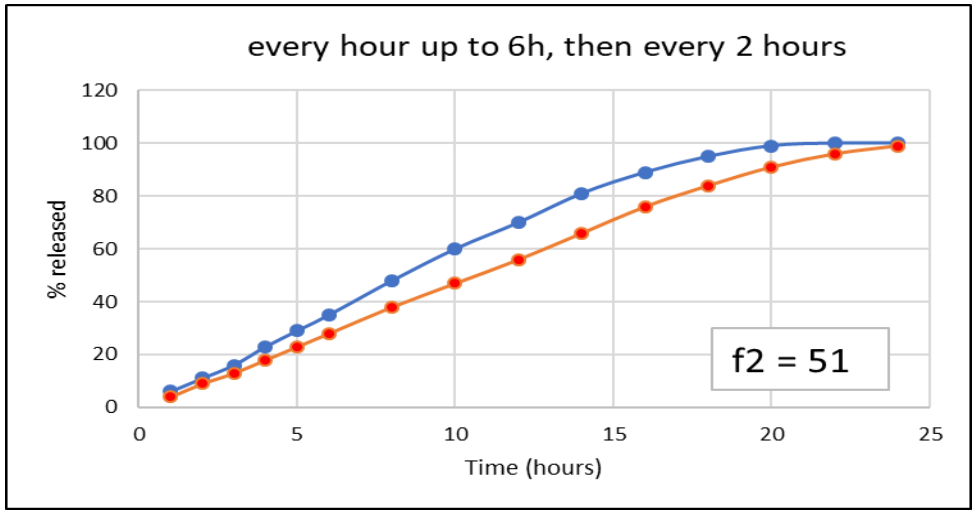
19 points

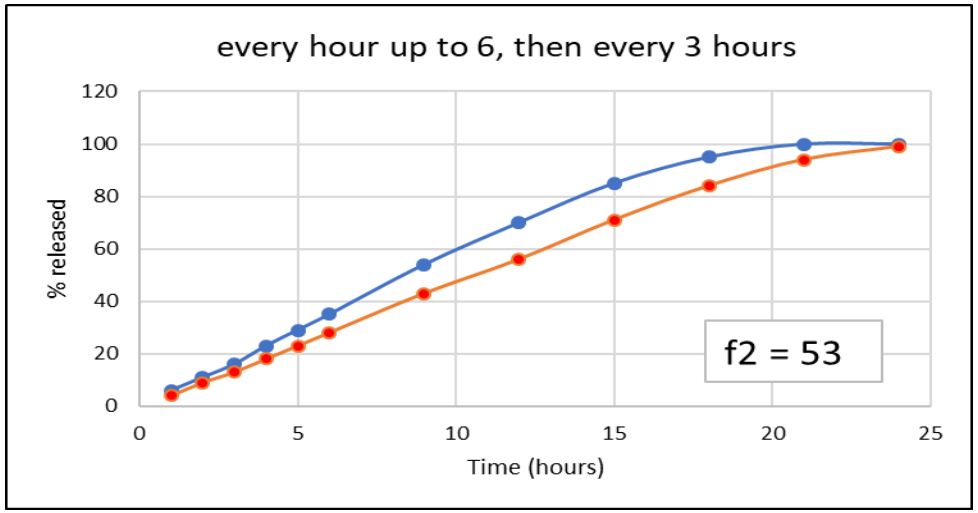




11 points

13 points





11 points

What is the optimal number of time points to define the curve?

Delayed release (enteric coated) products

Issue:

f2 between the bio strength and lower strength at buffer stage is <50

Minor difference and individual variability in **lag time** at buffer stage is a cause for f2<50.

Are the profiles truly different?
What are the additional options to investigate similarity?

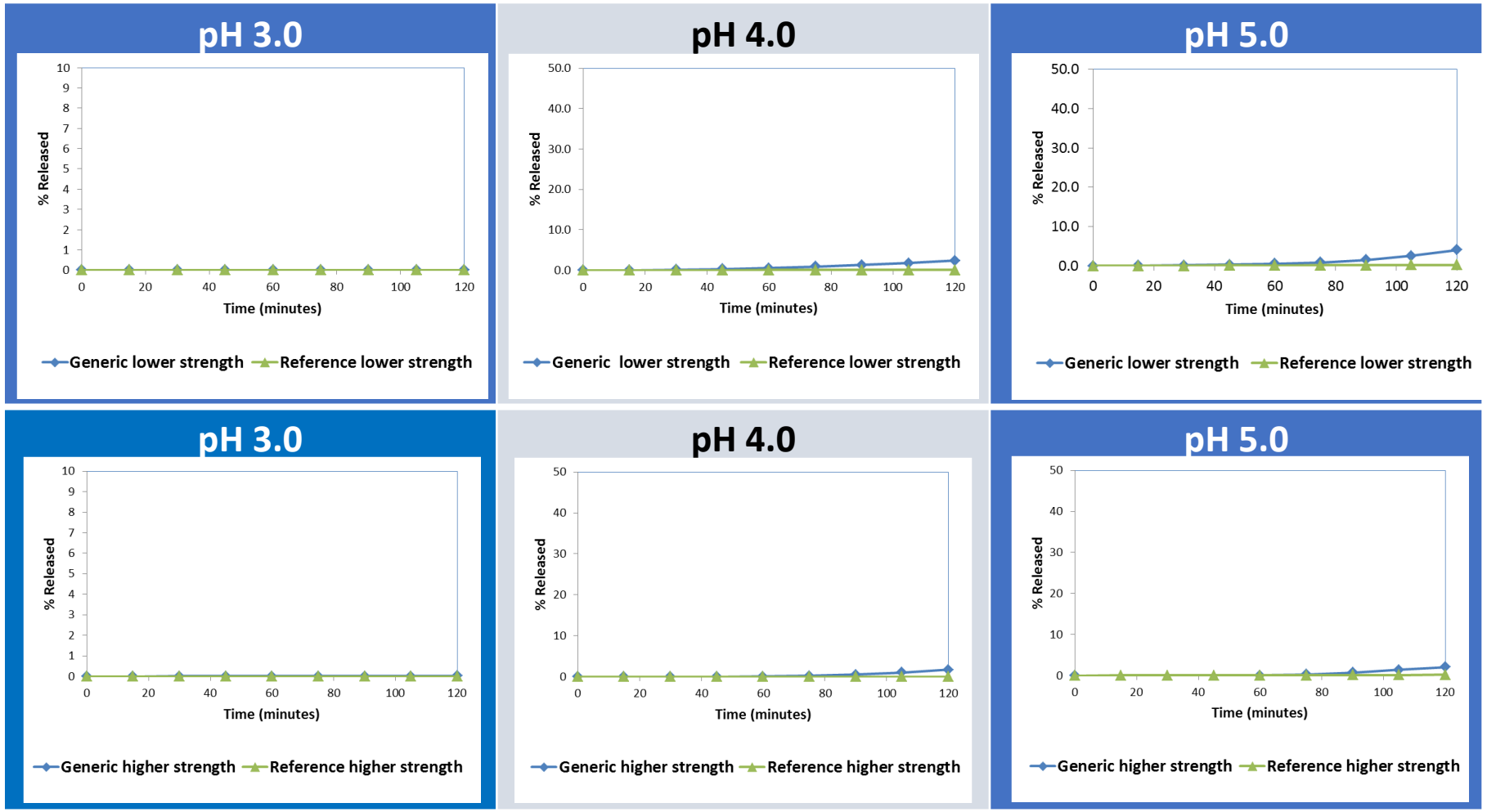
1.
Further proof of comparable enteric coat performance – e.g. dissolution at various lower pH media

2.
Lag time normalization on individual results (interpolation)

Delayed release (enteric coated) products

Option 1: ***Further proof of comparable enteric coat performance.***

Conduct dissolution in several lower pH media (i.e. pH 3.0, pH 4.0, pH 5.0) and compare to reference



Performance of the enteric coating of the generic and reference product is comparable

Delayed release (enteric coated) products

Option 2: Lag time normalization of the individual results

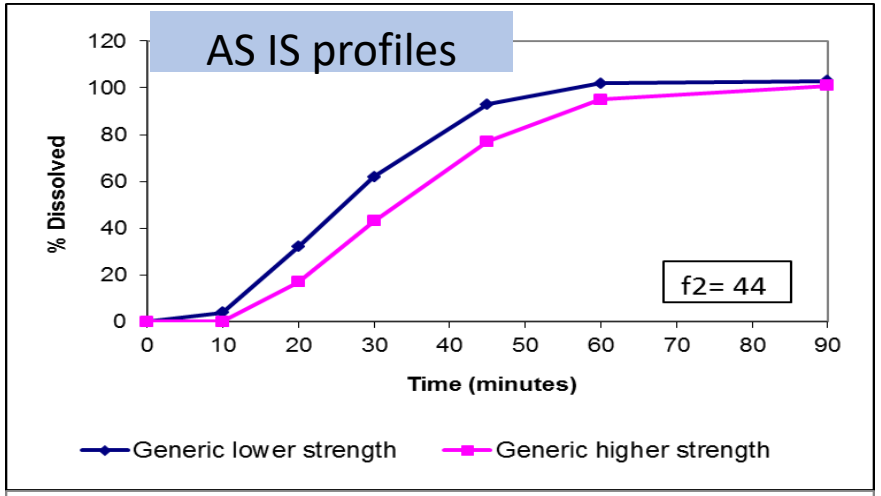
Batch	strength	% released in acid (2h)	Mean % released in pH 6.8 at 10min	Lag time in pH 6.8* (n=12) (min)	Lag time range width (min)
Generic	lower	0	4	10 (9-12)	3
Generic (bio lot)	higher	0	0	15 (13-16)	3
Reference	lower	0	4	10 (8-13)	5
Reference (bio lot)	higher	0	2	14 (10-18)	8

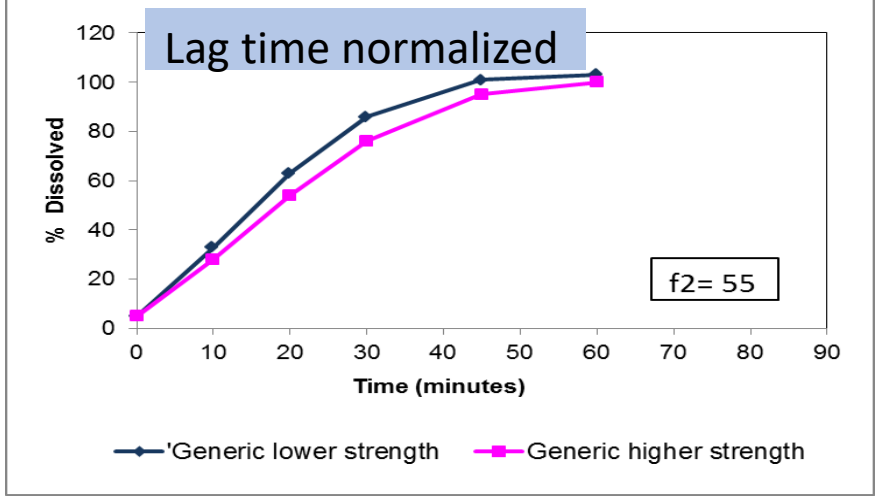
**time for 5% release obtained by linear interpolation*

Guidance for BE studies of generic products (Japan)

- EC products are grouped with IR products with provision of demonstrating acid resistance
- Adjusting dissolution curves with lag times before the assessment of similarity
  - *The lag time is defined as the time when 5% of the labeled claim dissolves*
  - *A lag time should be determined by linear interpolation for individual results before the f2 comparison*
  - *Difference in lag time should not be more than 10min*

- Variability in individual data impacts the mean at each time point and consequently f2
- Similar variability is observed in generic and reference



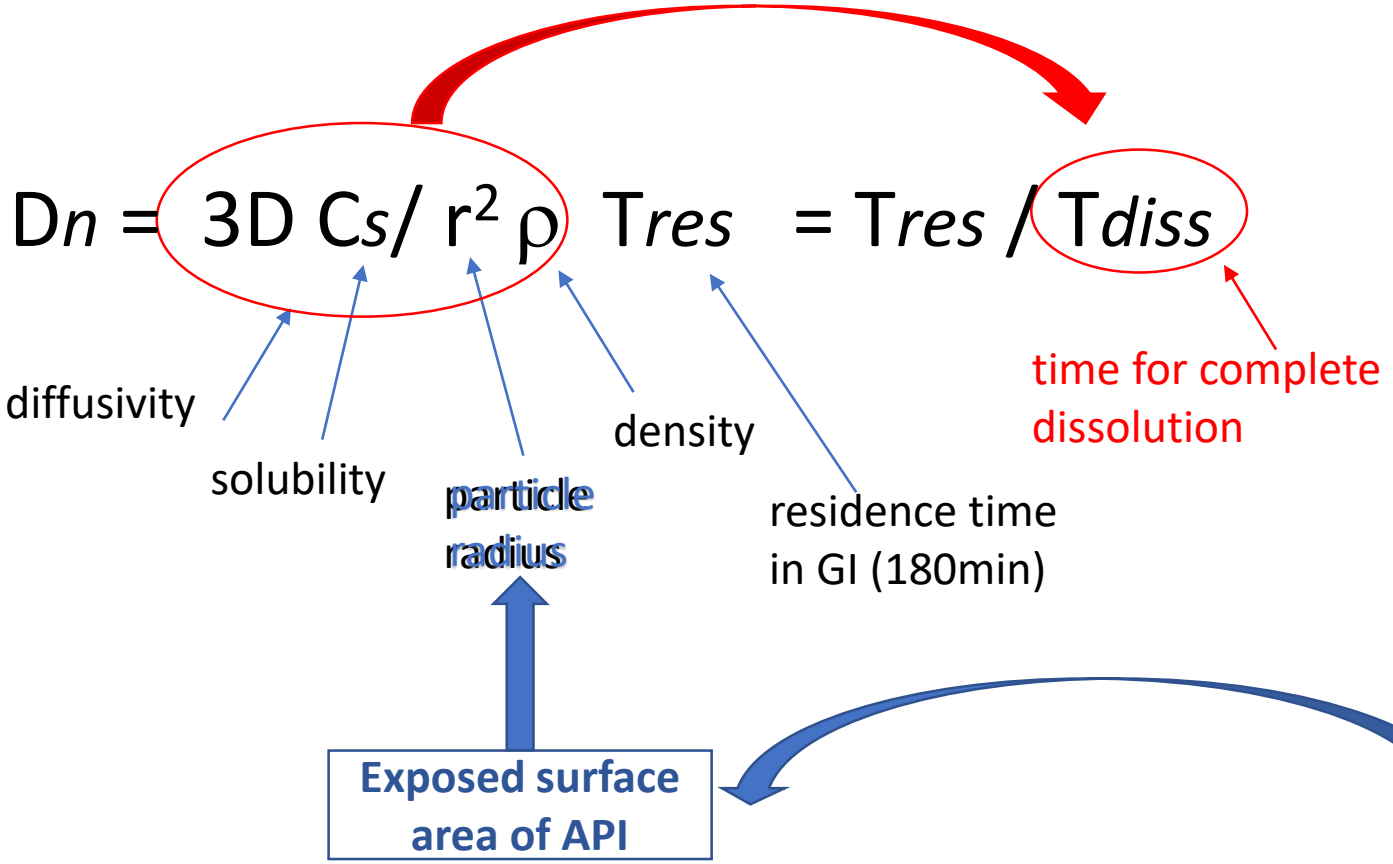


Dosage form surface area/volume ratio impact on f2

- High % or low soluble API typically results in tablet disintegration by **erosion**
- When tablet size is significantly different, disintegration is hugely impacted by tablet size (surface/volume ratio).
- Difference in disintegration impacts f2 factor

Product	Immediate release tablet	
%API	75% (common mix)	
BCS	Class 2	
Absolute BA	98%	
strength	Lower	Higher (4X)
Surface area/volume ratio (cm^{-1})	11.43	5.15
Disintegration time (min)	5	10

Dissolution number D*n*



Exposed area of the API to dissolution media (Rate of dissolution) is the main variable in **IR forms**. It is affected by:

- API particle size
- tablet disintegration pattern (***erosion vs. rapid swelling)*** and disintegration time
- tablet size

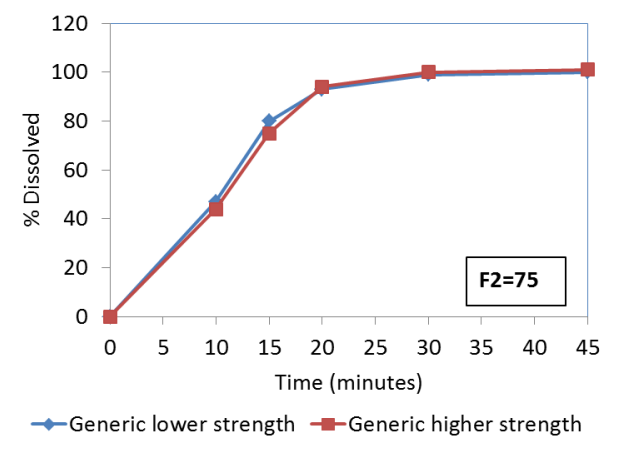
For IR dosage forms, it typically impacts the initial time points (up to ~15min)

What is the physiological relevance of the difference in the initial 15 minutes?

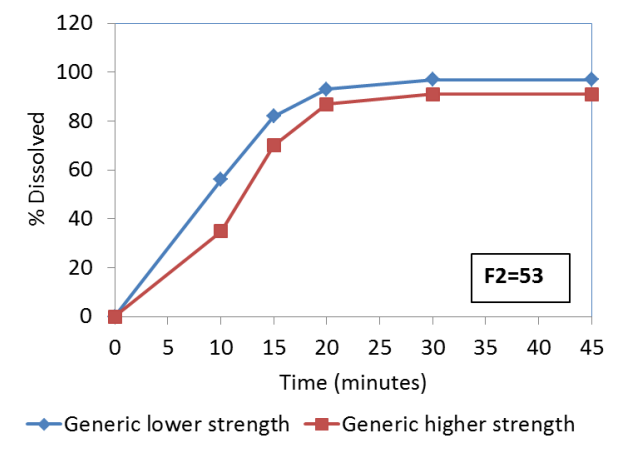
Dosage form surface area/volume ratio impact on f2

F2 similarity not demonstrated at all pH (pH 6.8)
Testing multiple units of lower strength to achieve similar sink does not help for erosion type of disintegration *(only for rapidly disintegrating tab)*

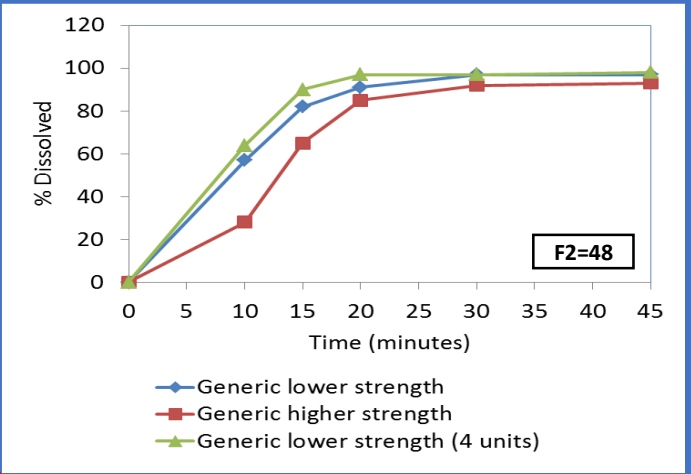
0.1N HCl



pH 4.5



pH 6.8



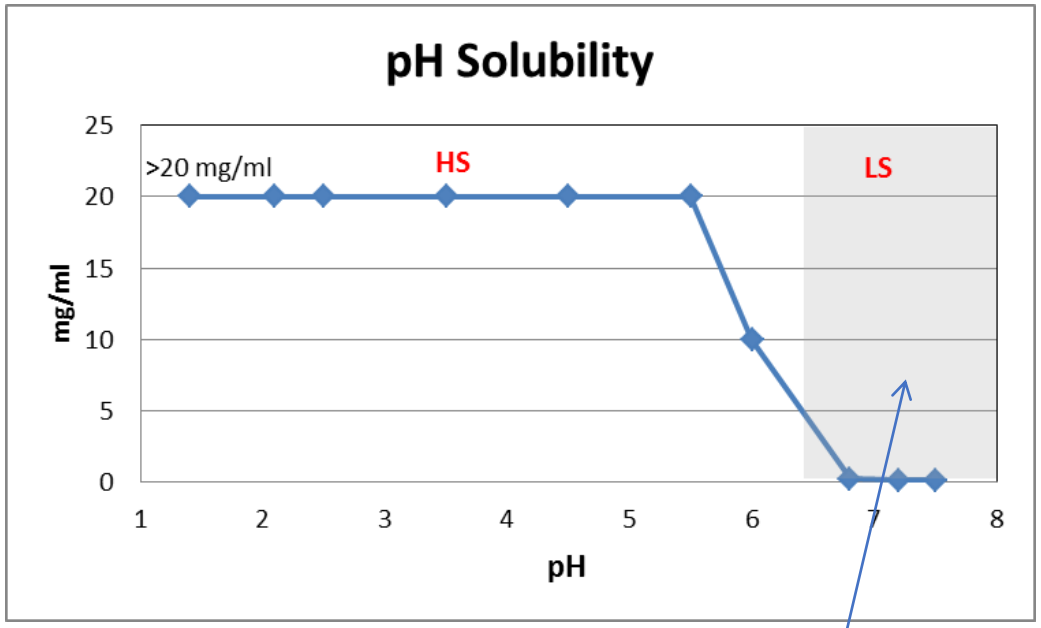
Note: 5min excluded due to RSD>20%

How to assess the relevance of the f2<50 in pH 6.8?

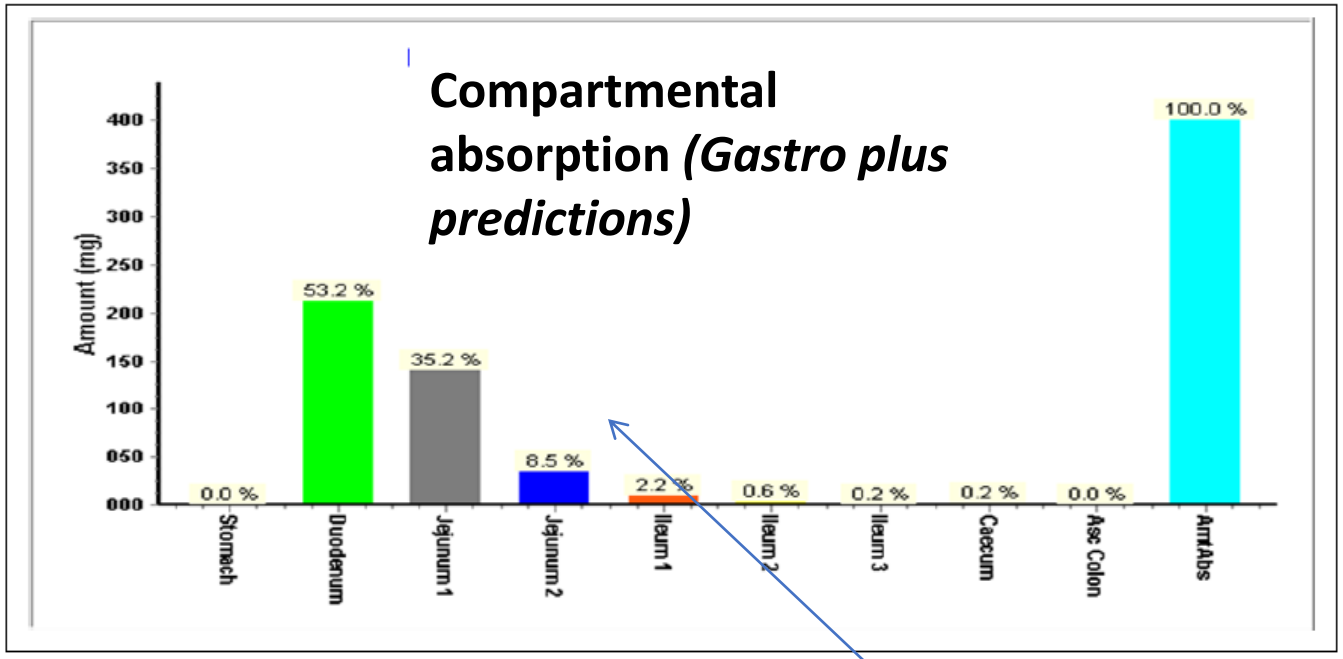
Dosage form surface area/volume ratio impact on f2

Option 1: Consider the drug exposure to lower pH along GIT before reaching pH 6.8

Physiological modeling to assess compartmental absorption in GIT (Gastro Plus simulation)



Surface area/volume difference plays a role at pH 6.8 (low solubility region)



pH:	1.3	6.0	6.2	6.4	6.6	6.9	7.4	6.4	6.8

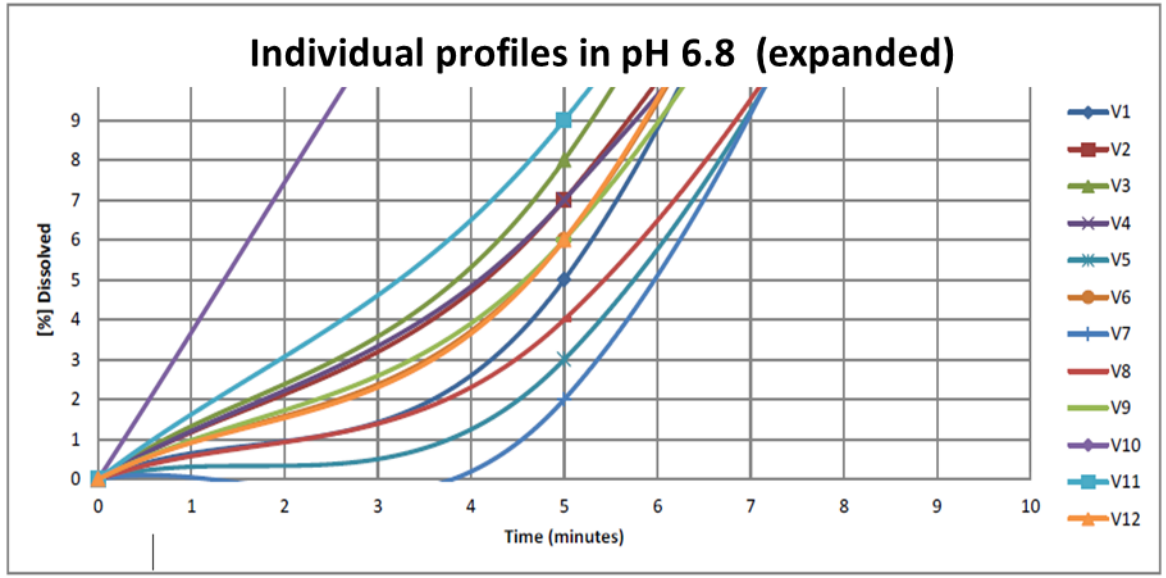
Drug is absorbed in upper intestine

Is the difference at pH 6.8 physiologically relevant?

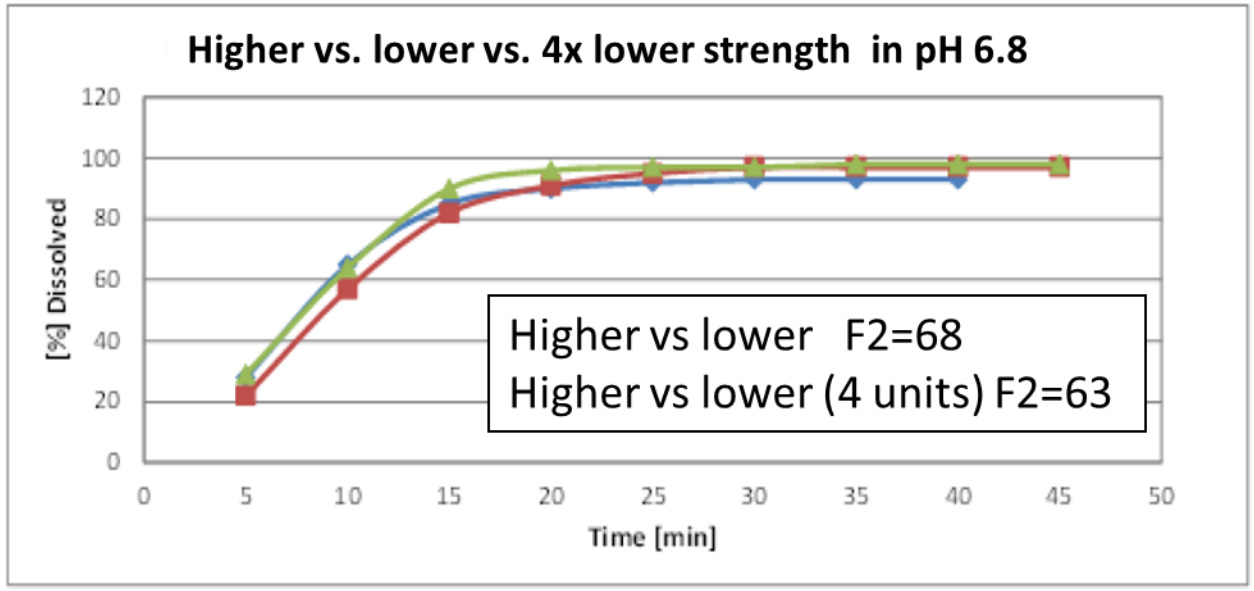
Dosage form surface area/volume ratio impact on f2

Option 2: ***Lag time normalization***

Individual profiles of higher strength show lag time in pH 6.8



Lag time normalized profiles in pH 6.8



Is the difference at pH 6.8 physiologically relevant?

Discriminatory power and f2

Deficiency question:

You are requested to provide additional dissolution data supporting the **discriminatory nature of the QC method** by making modest, meaningful changes to the manufacturing process and formulation ….

……Your response should include dissolution data organized in tabular and graphic formats with the results from each time point reported for each individual unit along with mean tablet dissolution results and RSD values for the above studies should be provided with f2 calculations …..

- Is the expectation to show f2<50 to be able to claim method is discriminatory?
- Is it sufficient to show different profiles but not necessary f2 dissimilar?

If the method is relevant and predictive, and responds to changes, the fact that the change does not cause f2 dissimilarity should not disqualify the method, in fact will suggest that those changes will not affect the bioavailability

Summary points

- Industry faces challenges in assessment of dissolution similarity in some instances
- Guidance documents give general frame for industry to follow
- Scientific rationale should be considered in some cases where criteria are not strait forward. Alternate approaches may be suitable for true assessment of similarity
- Physiological relevance should be taken into consideration
- Industry may benefit from more clarity in Regulatory Guidances and flexibility for alternate scientifically based approaches

Acknowledgements:
Elisabeth Kovacs
Navin Vaya
Arun Prasath
Faye Han
Shu Chen

Thank you