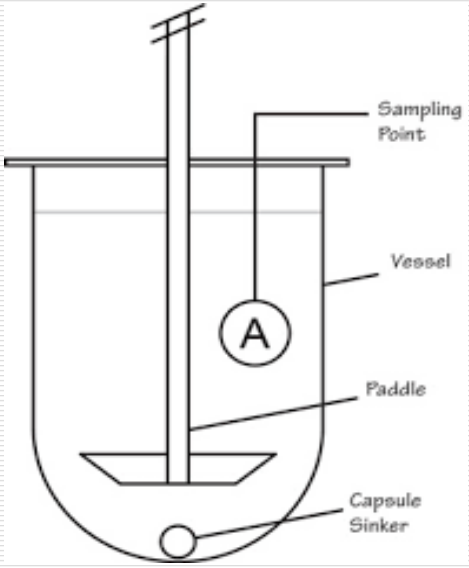
COMPLIANCE ISSUES IN DISSOLUTION TESTING



Vijay Kshirsagar
TRAC Pharma Consulting
Mumbai

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Contents

- Regulatory Audit Observations related to Dissolution
- Analysis of these observations
- Recommended Actions
- References

Excerpts from FDA 483's …

- High dissolution results were attributed to high weight of the tablets, not found justifiable.
- No separate field alert of dissolution failure/border line results.
- Sufficient quantity of control sample was not available to perform L2 & L3 analysis.
- Deaeration was identified as the root cause of getting low results by around 10%, hence requirement was precluded.

Excerpts from FDA 483's …

- Impact analysis of previous batches was not done which were tested using deaerated media.
- Method change (deaeration to no-deaeration) was not informed to CDER. Method was not revalidated. USP method does not talk about requirement of not doing deaeration.
- Validation of method did not cover test for accuracy of dissolution method.

Excerpts from FDA 483's …

- Low dissolution results were attributed to the detachment of baskets from the shaft. However analyst has not made any note of it during testing. But OOS investigation mentions it.
- After maintenance done by the equipment manufacturer, no calibration was done of the equipment though required by companies procedure. Lab Head produced a document contradicting above company's procedure.

Excerpts from FDA 483's

- Water in the water batch was not clear but the dissolution testing for US product was being done with it.
- OOS result was incorrectly attributed to Higher alkaline pH in sample collection tubes. No study done to show that higher pH leads to degradation.
- Recall initiated due to failing dissolution results but the cause has not been identified.

Recommended Actions

Learn from FDA's QbD Example

- Use of QbD for dissolution method development
- Development of Non-Discriminatory media
- Establish a good IVIVC
- Setting appropriate dissolution limits
- HPLC or UV method

QbD for IR Tablet
US FDA Example

US FDA Example

What FDA has got to say?

Ref: US FDA, QbD for ANDAs: An Example for Immediate-Release Dosage Forms, April 2012.

Note to Reader: A pharmaceutical development report should document the selection of the dissolution method used in pharmaceutical development. This method (or methods) may differ from the FDA-recommended dissolution method and the quality control method used for release testing.

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Background

- BCS Class II compound Acetryptan (20 mg tablets).

  (Low Solubility/High Permeability).
- Poor Aqueous solubility (less than 0.015 mg/Lt).
- Method to act as best predictor of equivalent pharmacokinetics to the RLD.
- Immediate release product.
- Dissolution in the stomach & absorption in the upper small intestine is expected which suggests the use of dissolution medium with low pH.

Recommended USP Method

- 900 ml of 0.1N HCl with 2% SLS
- USP Apparatus 2
- RPM : 75
- Initial developed formulation exhibited rapid dissolution of >90% in 30 Mts, comparable to RLD
- So a challenge to make a formulation which will perform same as RLD in vivo.
- So checked solubility in different media

Solubility in different media

Media	Solubility (mg/ml)
*Biorelevant FaSSGF	0.12
Biorelevant FaSSIF-V2	0.18
0.1N HCl with 0.5 % SLS	0.075
0.1N HCl with 1.0 % SLS	0.15
0.1N HCl with 2.0 % SLS	0.3

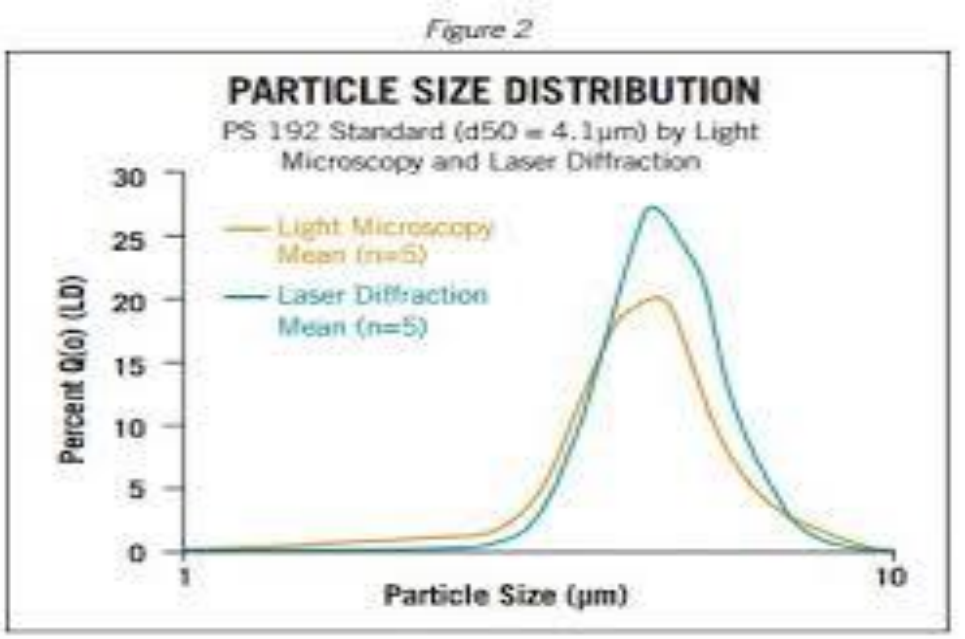
*Janatratid et al, Dissolution Media simulating conditions in Gastrointestinal tract, Pharm Res 25, 2008

Solubility Study Conclusion

- Solubility of API in 0.1N HCl with 1.0% w/v SLS is similar to its solubility in Biorelevant media.
- It was observed that dissolution is not sensitive to pH , similar in 0.1N HCl, pH 4.5 buffer & pH 6.8 buffer.
- Method selected for product development:
  - 900ml of 0.1N HCl with 1.0% SLS
  - 75 RPM
  - UV 282 nm (maxima with negligible interference)

Additional Studies

- Particle size was deliberated changed.
- Drug product made out of these changes resulted in change in dissolution values
- Particle size was found critical for optimal dissolution



Formulation Details

Table 7. Formulation of Generic Acetriptan Tablets, 20 mg, used in Pilot BE Study #1001

Ingredient	Function	Composition	
		(mg per tablet)	(% w/w)
Acetriptan	Active	20.0	10.0
Intragranular Excipients			
Lactose Monohydrate, NF	Filler	79.0	39.5
Microcrystalline Cellulose (MCC), NF	Filler	79.0	39.5
Croscarmellose Sodium (CCS), NF	Disintegrant	10.0	5.0
Talc, NF	Glidant/lubricant	5.0	2.5
Extragranular Excipients			
Magnesium Stearate, NF	Lubricant	1.2	0.6
Talc, NF	Glidant/lubricant	5.8	2.9
Total Weight		200.0	100

Pilot Bioequivalence studies

- Being low soluble drug, Pilot BE studies were considered essential
- Pilot BE study should support control on critical attributes like particle size & establish relation between in vivo & in vitro relationship
- Pilot BE study was performed in 6 healthy subjects (4 way cross over, 3 prototypes & RLD of 20mg/tab)

Pilot Bioequivalence studies

- Formulation used for 3 prototypes was same except the particle size distribution (d90 of 20, 30 & 45 microns)
- General understanding used: Mean Cmax & AUC responses of 2 drug products should not differ by >12-13% to meet BE limit of 80-125%
- Target was to have both Cmax ratio & AUC ratio for test to reference between 0.9 to 1.11

Pilot Bioequivalence studies

Results of PK study showed that drug product with API of d90 of 30 micron met this criteria but not 45 micron. Results with 20 micron were within the window but not as close as 30 micron.

Mean PK from Pilot BE

The pharmacokinetic results are presented in Figure 3 and Table 8.

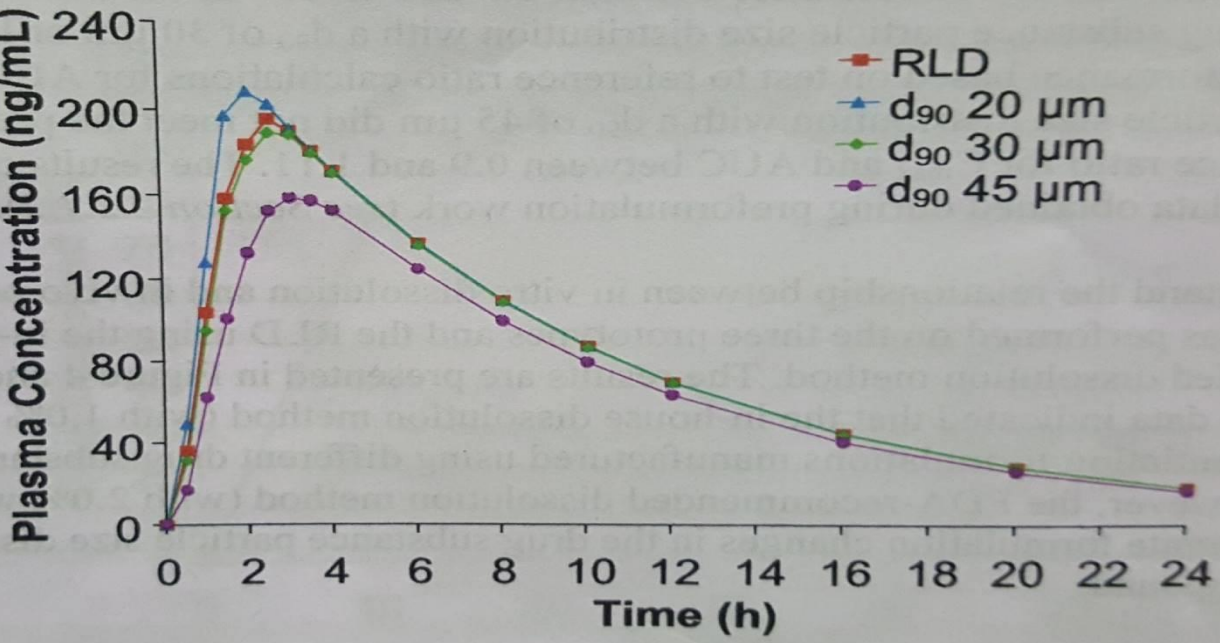


Figure 3. Mean PK profiles obtained from Pilot BE Study #1001

Method Challenge

- To understand the relationship between in vivo & in vitro performance, Dissolution was performed on 3 prototypes & the RLD using the in-house versus the FDA recommended method
- Results showed that medium with 1% SLS & 30 mts time point was found to be predictive of in vivo performance (in-house method)
- Dissolution medium with 2% SLS (USP method) was not found to predict the in vivo performance differences due to different particle sizes

Discriminatory Vs Indiscriminatory

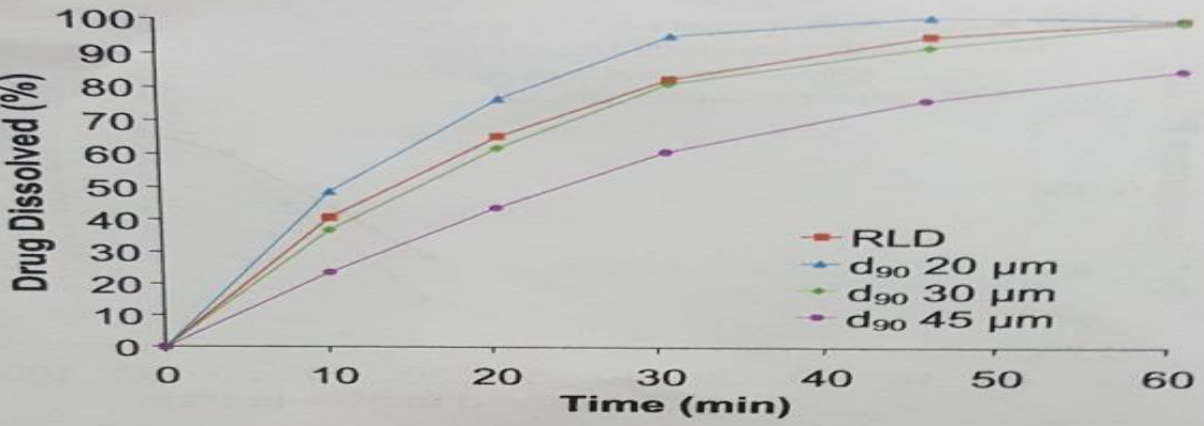


Figure 4. Dissolution of acetriptan tablets (RLD and three prototypes) using in-house method (900 mL of 0.1 N HCl with 1.0% w/v SLS using USP apparatus 2 at 75 rpm)

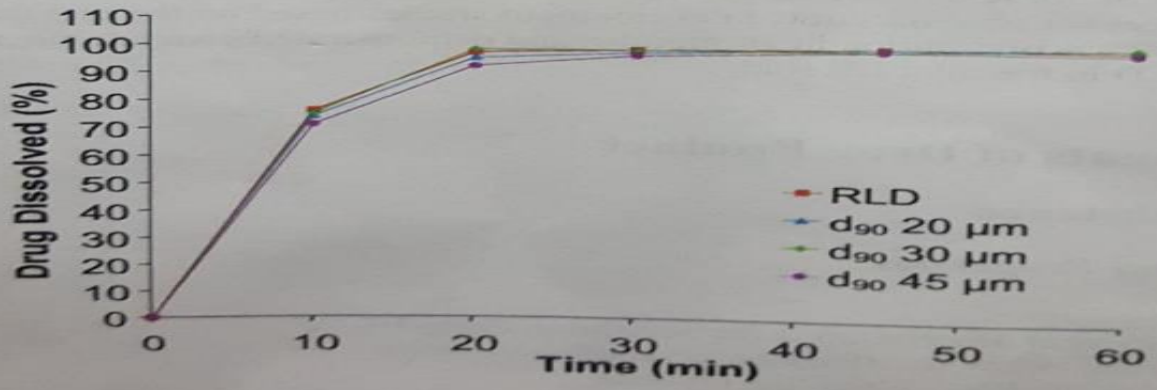


Figure 5. Dissolution of acetriptan tablets (RLD and three prototypes) using FDA-recommended method (900 mL of 0.1 N HCl with 2.0% w/v SLS using USP apparatus 2 at 75 rpm)

Limit Setting

A dissolution rate of NLT 80% in 30 mts in 0.1N HCl with 1.0% SLS as one of the 3 batches gave 80.8% dissolution in 30 mts and demonstrated comparable properties to the RLD

Stability Failure : Provide SME

Most Common Reasons

- Lump formation
- Gradual increase in DT
- Hardening
- Cross Linkage
- Filter absorption
- Degradation of reconstituted media
- Inadequate deaeration
- Improper Calibration
- Change in Polymorphism

What is cross Linking?

Cross-linking is the "formation of strong chemical linkages beyond simple hydrogen and ionic bonding between gelatin chains."

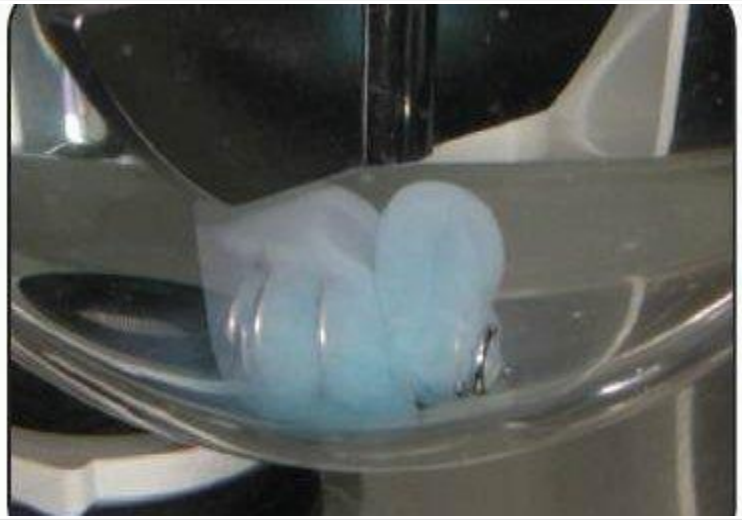
- Reaction is generally irreversible
- Renders gelatin insoluble
- Reaction is catalyzed by a number of chemical and environmental factors

Cross Linking

- Cross-linking of capsule shells can result in hardened and chemically resistant shells.
- Delay opening
- Trap Drug Product
- Opening time important regardless of cross-linking

What causes cross Linking?

- Aldehydes and Ketones
- APIs with carbonyl groups or potential aldehyde formation
- Oxidizing agents
- Metal Ions
- Sugars
- Heat & Light
- High and Low Humidity



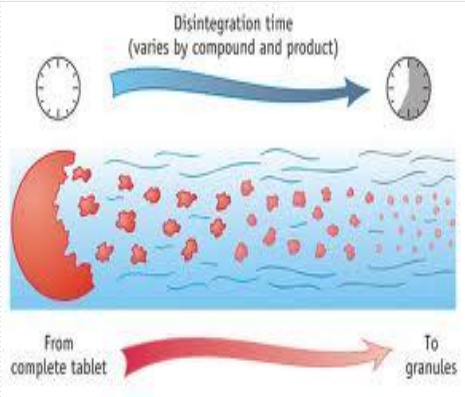
USP Provisions

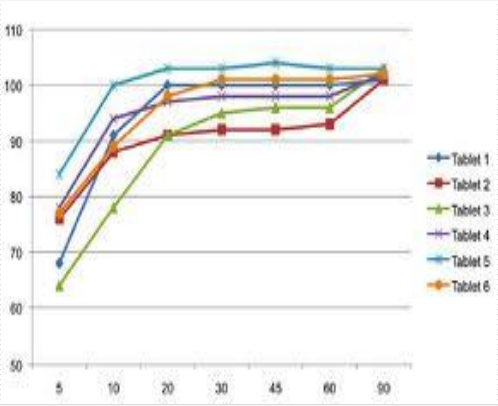
"For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the Dissolution specification, repeat the test as follows."

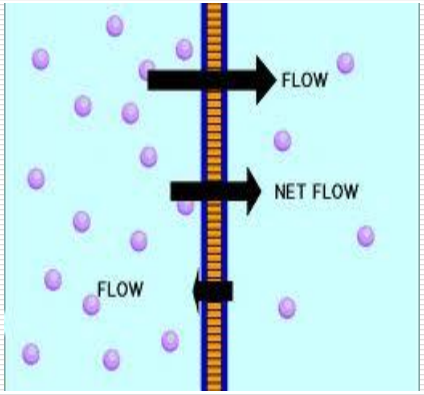
- Media < pH 6.8 – repeat test with addition of purified pepsin (<750,000 units/L)
- Media ≥ pH 6.8 – repeat test with addition of pancreatin (<1750 USP units of protease activity/L)

Pay Attention to 4 D's

- Disintegration
- Dispersion
- Dissolution
- Diffusion







Understanding Dissolution Science

- Disintegration time is the time required for a dosage form to break up in to granules of specified size
- Dispersion is actually meant to distribute the mass evenly thus moving the mass from higher concentration to lower concentration
- Dissolution is the rate of mass transfer from a solid surface into the dissolution medium
- Diffusion refers to the process by which molecules separated by a partition, intermingle as a result of their kinetic energy of random motion.

Set proper Dissolution Specs

- For a generic product

  (Same as RLD but based on your actual results, confirmation from BE studies, specification could be different from RLD in some cases)
- Special cases

  (Two point dissolution/two tiered dissolution test)

Setting proper method/Specs

- Ensure Validation/verification of methods
- Mapping or response surface methodology

  (Process for determining relation between critical manufa. variables & response from in vitro studies)

Dissolu. Profile comparisons

Approach using a similarity factor (Difference factor F1 & Similarity factor F2. F1 close to 0 and F2 close to 100 is ideal, practical F1:0-15,F2: 50-100).

Ensure Sink Conditions

- Sink condition refers to the volume of medium which is at least three times that is required in order to form a saturated solution of API
- In the absence of sink conditions, investigate methods to enhance solubility, e.g. use of a surfactant
- If a surfactant is used, its concentration should be properly justified (e.g. <2% SLS).

Do Risk Assessment (Scale 1-5)

Risk	Probability	Severity	Detection	RPN
Improper IVIVC	3	5	5	75
Non discriminative method	4	3	4	48
Instrument Calibration	3	5	3	45
Improper Filter	3	3	2	18

Media Cautions

- Be careful with water
- Quality can differ b/w sites
- Quality can differ b/w DI systems, filters, etc.
- Check pH before and after run to ensure buffering capacity is acceptable
- Beware of methods needing tight pH limits
- Do not use SLS with Potassium Phosphate Buffers – use Sodium Phosphate Only

Media Degassing

- Media should be degassed per USP unless another approach is validated
- Heat to 41-45 C
- Vacuum degas through 0.45um filter
- Hold under vacuum 5 minutes after media has passed through
- Helium sparging is acceptable but not Nitrogen, sonication is not desired

Agitation Rate

- Should be sufficient to allow for media to interact with dosage form
- Too much agitation can result in non-discriminatory profiles
- Baskets – 50-100 RPM
- Paddles – 25-100 RPM

Use of Sinkers

- Dosage forms should not float or move during the dissolution as this will greatly increase variability. A Sinker is necessary if it is floating or moving is seen
- Sinkers should be chosen based on:

•Media access •Weight •Reproducibility
•Hydrodynamic Impact

Address Coning Phenomenon

- Coning is a normal and expected occurrence for disintegrating dosage forms,
- Coning may still be present if drug is fully dissolved.
- Cone should be moving somewhat,
- If Severe, Peak Vessel or Apparatus 3 (Reciprocating Cylinder) can be used with justification

REFERENCES

- US FDA, QbD for ANDAs: An Example for Immediate-Release Dosage Forms, April 2012
- USP, General chapter on Dissolution <711>
- IR Dissolution Guidance (Dissolution Testing of Immediate Release Solid Oral Dosage Forms); August 1997
- IVIVC Guidance (Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations); September 1997

_vukshirsagar@gmail.com M: 9867650160

BIOPHARMACEUTICS CLASSIFICATION

- Class I: High solubility/high permeability
- Class II: Low solubility/high permeability
- Class III: High solubility/low permeability
- Class IV: Low solubility/low permeability

Process Attributes

- Qualitative and quantitative excipient changes
- Manufacturing parameters
  - Granulation
  - Lubrication
  - Blend time
  - Compression force
  - Drying parameters