

# THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION

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# THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION

1. Medium
2. Apparatus/agitation rate
3. Study design
4. Assay
5. Acceptance criteria

# GENERAL COMMENTS

## Dissolution procedure:

- Discriminating method
- Sufficient ruggedness
- Reproducible operation
- Transferable
- Assessment of the batch-to-batch quality of a drug product
- Assessment of the physical stability of the formulation

# GENERAL COMMENTS

## Dissolution procedure:

- Low variability in dissolution results

## Sources of variability:

- Formulation
- Artifacts

# MEDIUM

## Selection of dissolution medium:

### 1. Physicochemical properties of drug substance

- solubility
  - solution state stability
- |  |   |             |
|--|---|-------------|
|  | } | buffers     |
|  |   | pH          |
|  |   | surfactants |

# MEDIUM

## Selection of dissolution medium:

### 2. Physicochemical properties of dosage unit

- Release mechanism  
immediate, modified release
- Disintegration rate {  
hardness  
friability  
excipients

# MEDIUM

- Sink conditions  
volume of medium
- Aqueous-organic solvent mixture  
hydroalcoholic solvent

# MEDIUM

- Purified water

inexpensive, readily available, ecologically acceptable

- Quality
  - source of water
- pH
  - buffer capacity

# MEDIUM

- Dilute acid (0.001 N-0.1 N HCl)
- Buffered aqueous solution (pH 4-8)
- Simulated gastric fluid (with or without enzymes)
- Simulated intestinal fluid (with or without enzymes)
- Surfactants (with or without acids or buffers)

# MEDIUM

## Oral formulation

- Physiological pH
  - pH 1.2-6.8 for IR formulations
  - pH 1.2-7.5 for MR formulations

## Low solubility compounds

- Surfactants (e.g., polysorbate, SLS, bile)
- Concentration of surfactant
  - wetting agent
  - solubilizing agent

# Volume of dissolution medium

## Basket and paddle apparatus

- 500 ml –1000 ml (900 ml)
- 2-4 L

# Deaeration

## Air bubbles

- Barrier to dissolution  
dissolution rate ↓
- Increase buoyancy  
dissolution rate ↑

# Deaeration method

- Heat 37-41 °C
- Filter
- Sonication
- Vacuum

# Enzymes

## Gelatin cross-linking

- Gelatin capsules: capsule shell
- Gelatin-coated products

# In Vitro-In Vivo Correlation (IVIVC)

## Biorelevant medium

### Choice of biorelevant medium:

1. Mechanistic approach
  - Fed and fasted states
2. Rate-limiting steps in drug absorption
  - Dissolution
  - Permeation

# IVIVC

## High solubility, High permeability drug

- Rate-limiting step to absorption
  - Gastric emptying time
- Dissolution test
  - Gastric (acidic) condition

## Low solubility, Weak acidic drug

- Rate-limiting step to absorption
  - Dissolution
- Dissolution test
  - Simulated intestinal fluid pH 6.8

# IVIVC

Formulation development, Food effects

Fed and fasted states media

Quality control

Compendial media

# APPARATUS

## Solid oral dosage forms (IR, MR products)

- Apparatus 1 (basket)
- Apparatus 2 (paddle)

## Bead-type MR products

- Apparatus 3 (reciprocating cylinder)

# APPARATUS

MR products, very limited solubility of active ingredient

- Apparatus 4 (flow-through cell)

Soft gelatin capsules, bead products, suppositories, poorly soluble drug

- Apparatus 3
- Apparatus 4

# APPARATUS

## Transdermal dosage forms

- Apparatus 5 (paddle over disk)
- Apparatus 6 (rotating cylinder)

## Nondisintegrating oral MR products and transdermal products

- Apparatus 7 (reciprocating holder)

# Apparatus

## Noncompendial apparatus

### Low-dosage strength products

- Small volume apparatus
- Mini paddle and basket

### Microspheres and implants

- Rotating bottle or static tube

# Apparatus

## Eliminating coning

- Peak vessel

## Powders and stents

- Modified flow through cell

# Sinkers

316 stainless steel wire, platinum wire

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<b>Capsule Shell Type</b>	<b>Length of Wire (cm)</b>	<b>Diameter Size (cm)</b>	<b>Cork Bore Number</b>
<b>#0, elongated</b>	<b>12</b>	<b>0.8</b>	<b>4</b>
<b>#1 and #2</b>	<b>10</b>	<b>0.7</b>	<b>3</b>
<b>#3 and #4</b>	<b>8</b>	<b>0.55</b>	<b>2</b>

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# Agitation

## IR products

- Apparatus 1 (basket)  
40 mesh screen, 100 rpm
- Apparatus 2 (paddle)  
50 or 75 rpm
- $< 25$  rpm  $\Rightarrow$  inconsistency of hydrodynamic
- $> 150$  rpm  $\Rightarrow$  turbulence

## Suspensions

- 25 – 50 rpm

# Agitation

## MR products

- Apparatus 1 (basket)
- Apparatus 2 (paddle)

} at higher rpm

# Study design

## Time Points

### IR products

- Test time : 30 to 60 minutes

### Specifications

- Single point : NLT 85% in 15 minutes
- Dissolution profile : sampling at 5-, 10- or 15- minute intervals

# Time Points

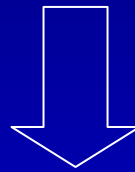
## Extended-Release Products

Test time : at least 3 test times

- Early time point : 1-2 hours : potential dose dumping
- Intermediate time point : define the release profile
- Final time point : show complete release of the drug

# Observation

- Visual Observation and Recording



- Dissolution and Disintegration patterns behavior

# To accomplish visual observation

- Proper lighting of vessel contents  
(with consideration of photodegradation)
- Clear visibility in the bath

## Documenting observation

- Drawing sketches
- Taking photographs or videos

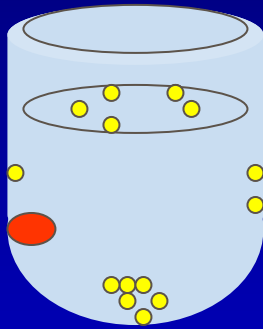


**Dissolution method development**

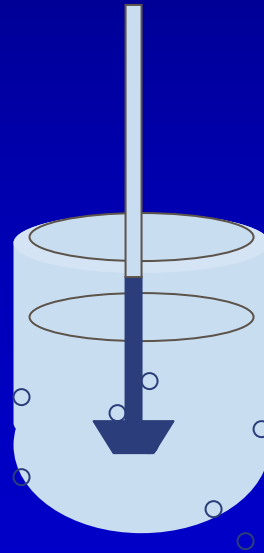
**Formulation optimization**

# Example of observation

- Uneven distribution of particle



- Air bubbles



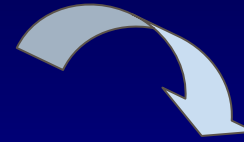
# Example of observation

- Dancing or spinning of dosage unit
- Being hit by the paddle
- Adhesion of particles to the paddle or the inside of the basket at the end of the run
- Analogous formation such as transparent sacs
- Disintegration rate
- Complex disintegration

# Sampling

## Manual

- Plastic or glass syringes
- Stainless steel cannula
- Filter and/or Filter holder



**Dissolution (711)**

## Auto-sampling

- Semi-automated / Fully Automated system
- Used for several time points

# Auto-sampling

- Routine performance checks
- Cleaning
- Maintenance



SOP / Metrology documents

# Auto-sampling **Validation**

- To ensure that the **probes** are not introducing a significant change in **dissolution rate**



## **Comparison**

Manual sampling

Automated sampling

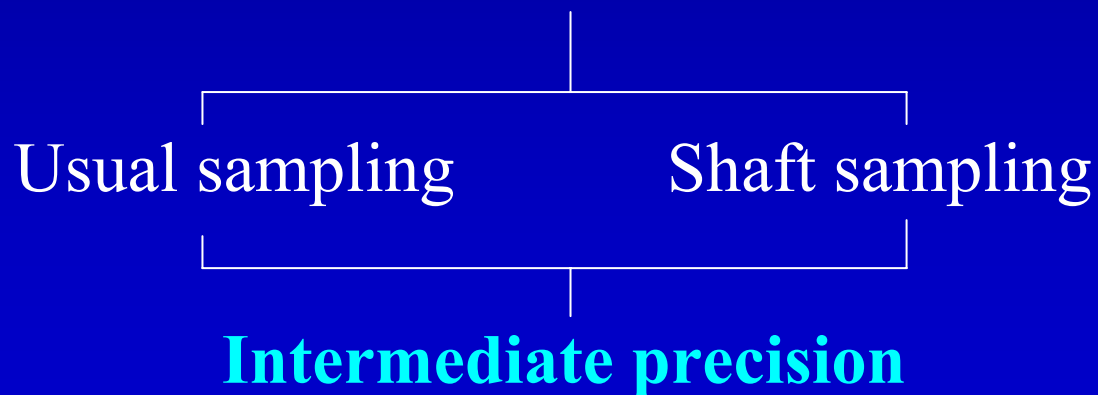
**Intermediate precision**

# Auto-sampling **Validation**

- Sampling through the basket / paddle shaft



## **Comparison**



# Auto-sampling **Validation**

## **Other aspects**

- Carryover of residual drug
- Adsorption of drug
- Cleaning / rinse cycles

# Filters

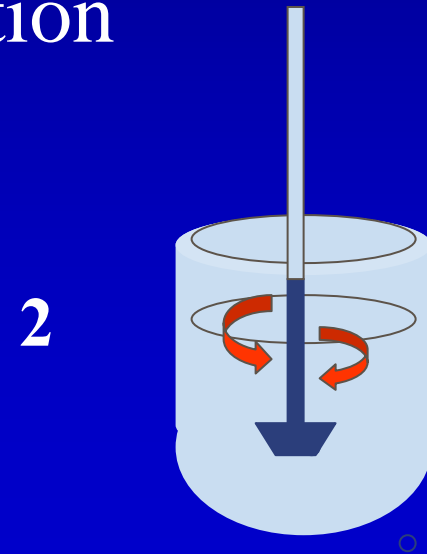
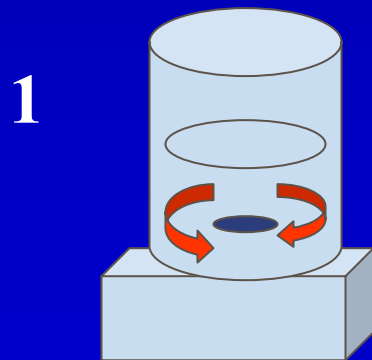
- To prevent undissolved drug particle
- To moves insoluble excipients

## Type

- In-line / at the end of the sampling probe
- Pore size 0.45-70  $\mu\text{m}$

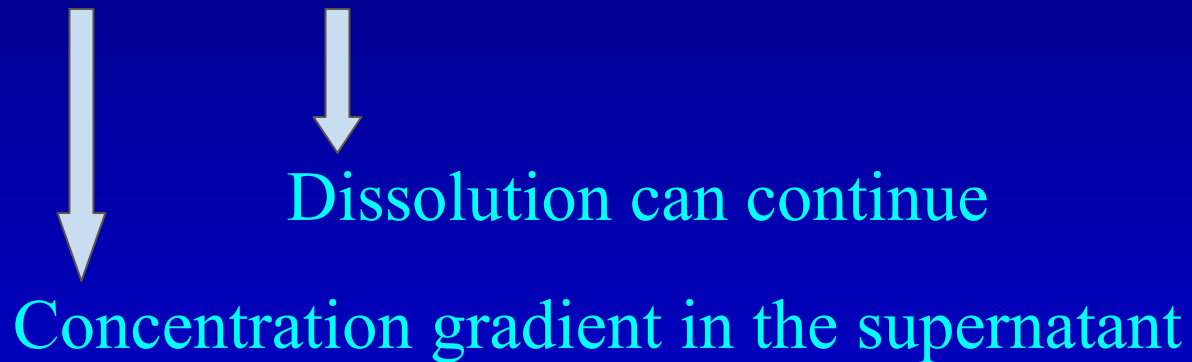
# Filters **V**alidation

- Compare the results for filtered solution of std to those for the unfiltered solution
- Compare the results for filtered solutions to those for centrifuged solution



# Centrifugation

- Not preferred



# Assay

- Spectrophotometric determination
  - faster
  - simpler
  - fewer solvent used
- HPLC (Stability-indicating assay)
  - interference from excipients / drugs
  - improve analytical sensitivity
  - can be automated

# Validation

## Specificity

- To demonstrate that the results are not affected by placebo, other active drugs and degradates

## Placebo Interference

- weighing and dissolving / dispersing them in dissolution medium (at 37 C) at the same concentration during testing

# Placebo Interference

- Calculate % Placebo Interference by formula:

$$100C(A_p / A_s)(V/L)$$

$c$  = Conc (mg/ml) of std

$A_p$  = Abs of placebo

$A_s$  = Abs of std

$V$  = ml of medium used to dissolve placebo

- The interference nmt 2 %

# Linearity and Range

- Drug solution, ranging in concentration from below the lowest expected concentration to above the highest concentration during release
- Flow-cell sizes / Injection volumes used
- The determination of the highest concentration is not exceed the linearity limits of the instrument

# Linearity and Range

Organic solvent used to enhance drug solubility for std solution nmt 5% (v/v) in the final solution, unless validated

Linearity is calculated by

- Least-squares regression program
- Demonstrates linearity with  $r^2$  nlt 0.98
- The y-intercept not significant different from zero

# Accuracy / Recovery

- Sample solution containing the drug, excipient and coating ranging in concentration from below the lowest expected concentration to above the highest concentration during release
- In case of poor drug solubility, organic solvent used is not exceed 5 % (v/v) in the final solution
- The recovery is 95 - 105 % of amount added

# Accuracy / Recovery

A special case for validation of Acid Stage in Delayed-Release Dosage Form under Dissolution (711). The limit of nmt 10 % needs to be validated. (with consideration of degradation in acid)

# Precision

## Repeatability

- The determination of replicate measurement of std / sample solution
- It can be calculated the RSD of multiple injections / spectrophotometric reading for std solution

# Intermediate Precision

Typical variations to study include

- days
- analysts
- equipment
- high and low strengths of products

An experimental matrix design can be used

# Intermediate Precision

- Acceptance criterion
- The difference in the mean value of the results of two condition, using the same strength dose nmt 10 % at time points with less than 85 % dissolved and nmt 5 % for the time points above 85 %

# Robustness

- The number of replicates (3 or 6) is dependent on the intermediate precision
- Parameters to be tested dependent on the dissolution procedure and analysis type

# Robustness

Parameters for medium used are

- Medium composition
- pH
- Volume
- Agitation rate
- Temperature

# Robustness

## For HPLC

- Mobile phase composition
  - % Organic
  - Buffer Concentration
  - pH
- Flow rate
- wave length
- Column temperature
- Multiple column (of the same type)

## For spectrophotometric analysis

- wave length

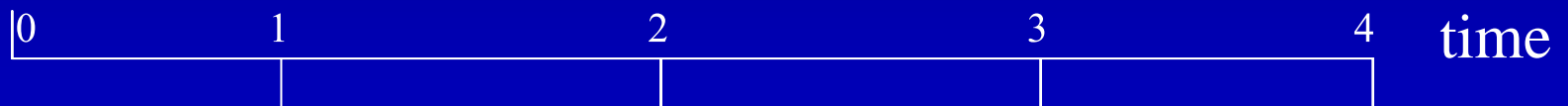
# Standard and Sample Solution Stability

## Standard Solution



Standard Solution freshly prepared

## Sample Solution



Original sample solution response

The acceptable range is Between 98% and 102%

# Standard and Sample Solution Stability

For unstable solution

- temperature
- light
- container material

# Spectrophotometric Analysis

For Automated Spectrophotometer,  
**SOP** is described

- Routine performance checks
- Cleaning
- Maintenance

# Spectrophotometric Analysis

For Automated Spectrophotometer,  
Cells path lengths typically used

- 0.02-1 cm
- Cell alignment and air bubbles
- For the smaller path length cells,
  - acceptable linearity
  - acceptable standard error

# Spectrophotometric Analysis

Standard solution concentration

at 100% (or the selected Q value)

# Spectrophotometric Analysis

For Automated Spectrophotometer,  
Cells path lengths typically used

- 0.002-1 cm
- Cell alignment and air bubbles
- For the smaller path length cells,
  - acceptable linearity
  - acceptable standard error