FOPE®

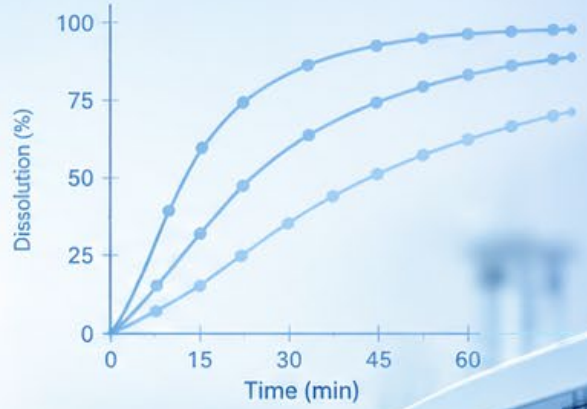
Federation Of Pharma Entrepreneurs

PRESENTS

Better Science
Brighter Therapeutics

WEBINAR ON

# Dissolution Science & Bioavailability for Complex Molecules




SCIENCE
QUALITY
ACCESS
BETTER LIVES

- ADVANCED DISSOLUTION TECHNOLOGIES
- COMPLEX MOLECULES
- BIOAVAILABILITY & PERFORMANCE
- INDUSTRY PERSPECTIVES

Speaker

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Moderator

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Ex-SDC, Haryana
Regulatory Consultant, FOPE

FROM
FORMULATION
TO IMPACT

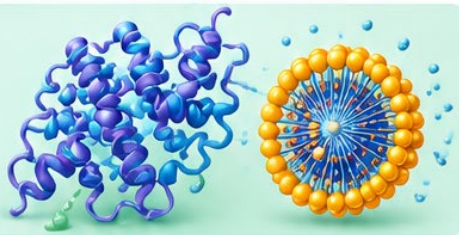
KNOWLEDGE | COLLABORATION | HEALTHIER TOMORROW

# Learning Objectives

By the end of this session, you will be able to...

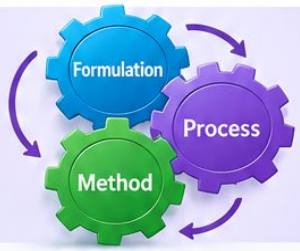
1. Introduction and mechanism

2. Dissolution of complex molecules/ NSQ



3. Case Studies


4. Dissolution Development Strategy




5. USP 3 & USP 4 Apparatus Application

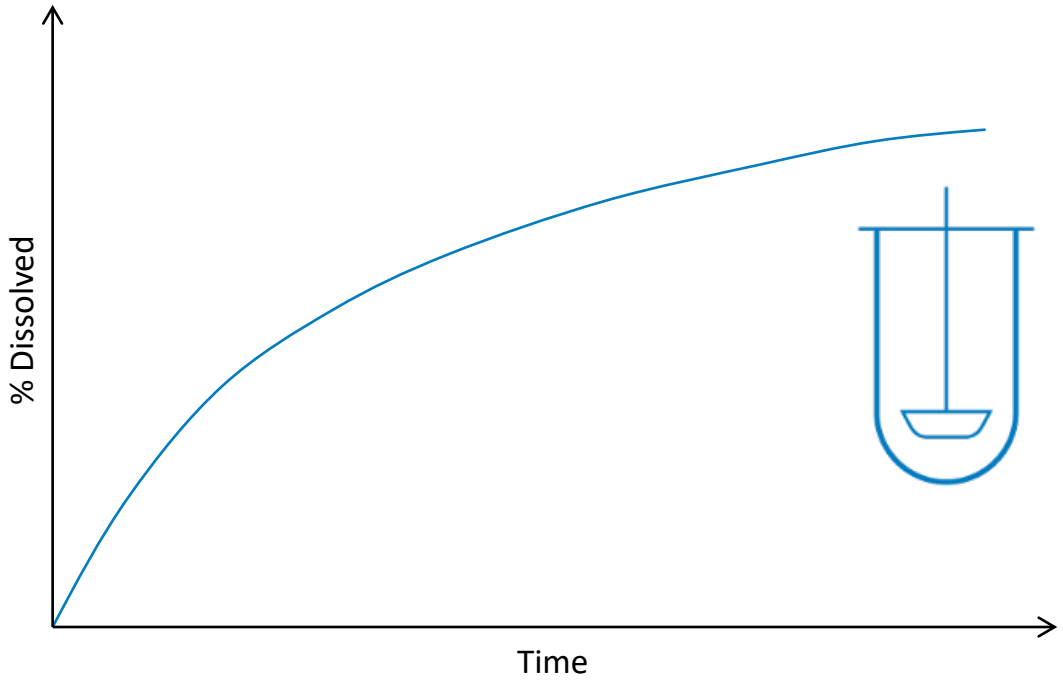

6. Takeaway Points

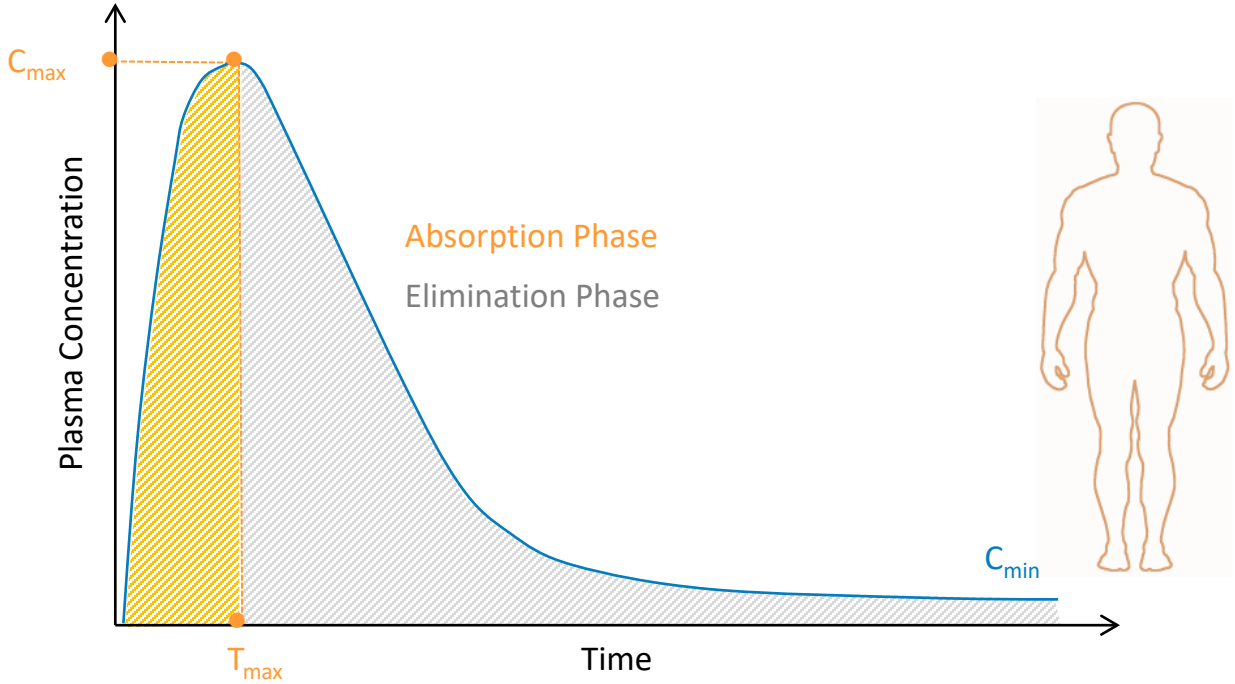
# DISSOLUTION

| | |
|---|---|
| 1897 | Noyes-Whitney equation describing dissolution kinetics |
| 1950's | Evolution of pharmaceutical application |
| 1969 | First multi-vessel commercial dissolution tester |
| 1970 | Rotating basket (Apparatus 1) officially adopted by USP |
| 1978 | Rotating paddle (Apparatus 2) officially adopted by USP |
| 1991 | USP Apparatus 3 |
| 1995 | USP Apparatus 4 |

# WHAT IS DISSOLUTION?

## In Vitro vs. In Vivo




In-Vitro

In-Vivo

# MECHANISMS OF DISSOLUTION

## 1 Wetting


Displacement of air by dissolution medium

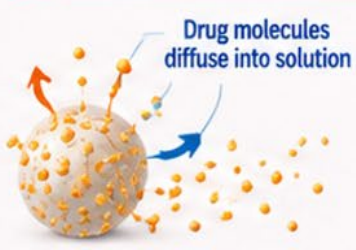
## 2 Disintegration

Formation of granules (primary particles)

## 3 Deaggregation

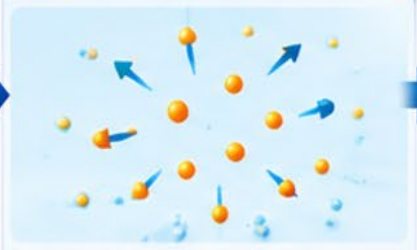
Increased surface area for dissolution

## 4 Dissolution (Solubilization)



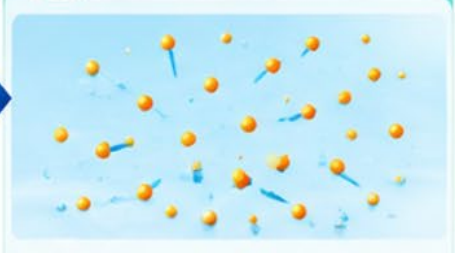

Drug in molecular form in solution

## 5 Diffusion in Bulk Medium



Uniform distribution in dissolution medium

## 6 Maintaining Sink Conditions



Drug available for further absorption

## Driving Force for Dissolution

**Noyes–Whitney Equation**

$$\frac{dC}{dt} = \frac{D \times A \times (C_s - C)}{h}$$

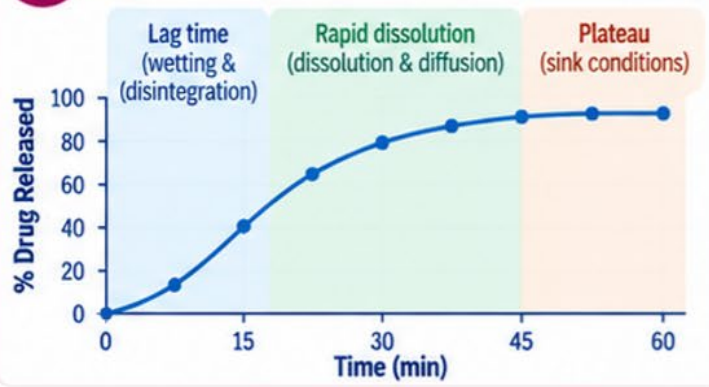
D = Diffusion coefficient
A = Surface area of the drug
$C_s$ = Saturation solubility
C = Bulk concentration
h = Thickness of stagnant boundary layer

Higher solubility, larger surface area and better agitation lead to faster dissolution.

## Key Formulation & Process Factors

- **Particle size** (smaller size ↑ dissolution)
- **Wettability** (surfactants improve wetting)
- **Disintegrants** (faster breakup)
- **Polymorphism** (amorphous form dissolves faster)
- **Excipients** (can enhance or retard dissolution)
- **Manufacturing process** (compression force, granulation)
- **pH and medium composition** (affects solubility/ionization)
- **Agitation and hydrodynamics** (reduces boundary layer)

## Typical Dissolution Profile



# The chain: dosage form → dissolution → absorption

Dissolution sits between physical disintegration/release and systemic availability.

*Formulation & Process Drive Performance*

## SOLID DOSAGE FORM
(Tablet / Capsule)

### Key Parameters (Compression / Formulation)

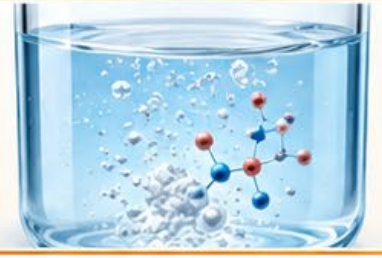
- Compression force
- API particle size & polymorph
- Binders (e.g., PVP, HPMC)
- Disintegrants (e.g., SSG, CCS)
- Lubricants (e.g., Mg stearate)
- Tablet hardness, porosity, coating (if any)
- Capsule shell type (HPMC/gelatin)

## SOLID PARTICLES
(Disintegration)

### Key Parameters (Disintegration)

- Disintegrant type & level
- Binder level and type
- Particle size distribution
- Tablet hardness / porosity
- Coating (type & thickness)
- Excipient functionality
- Medium conditions (pH, agitation)

## DRUG IN SOLUTION
(Dissolution)



### Key Parameters (Dissolution)

- Medium pH and composition (biorelevant media)
- Agitation speed
- Temperature (37 ± 0.5 °C)
- Apparatus selection (USP 1, 2, 3, 4)
- Particle size (for IR or after disintegration)
- Sink conditions
- Analytical method (specificity, sensitivity)

## DRUG IN BODY
(Absorption)


### Key Parameters (Absorption / In vivo)

- GI physiology (pH, motility, transit time)
- Solubility and permeability (BCS)
- Food effect
- Site of absorption
- First-pass metabolism
- Patient variability (age, disease state, concomitant drugs)

**The practical development question**

**What must the dissolution method capture so that meaningful formulation or process differences become visible?**

- ✓ Be discriminatory
- ✓ Reflect in vivo relevant conditions
- ✓ Detect formulation and process changes
- ✓ Support development, control and regulatory decisions

# DISSOLUTION >>> QC TEST


**1 PRODUCT PERFORMANCE**

Links formulation & process to release behaviour.

**2 BATCH-TO-BATCH CONSISTENCY**

Detects changes in API, excipients, compression & coating.

**3 DEVELOPMENT**

Useful for screening drug products & formulations during development.

**4 BIOAVAILABILITY**

Supports understanding of drug release and in-vivo performance.

**5 REGULATORY CONFIDENCE**

Critical evidence for specifications and lifecycle changes.

# DISSOLUTION 4Ds

From Data to Decisions – Ensuring Performance, Not Just Compliance

**Product Performance Tool**

Understands, predicts and optimizes product performance

**Quality Control Tool**

Not limited to pass/fail testing

## 1 Detect

Identify release-rate or extent abnormalities

## 2 Discriminate

Separate formulation/process effects from analytical noise

## 3 Diagnose

Connect profile changes to CMAs/CPPs

## 4 Decide

Support batch disposition, development or change control

# CONSEQUENCES: DISSOLUTION FAILURE

## Sub-therapeutic exposure

- Inadequate drug release leads to low blood levels
- Risk of treatment failure (e.g., antibiotics → resistance)

## Variable patient response

- Inconsistent dissolution causes unpredictable clinical outcomes
- Affects patient confidence

## Product recalls & market risk


- Dissolution failures are a common cause of regulatory actions and recalls
- Financial and reputational impact

## Patient safety concerns

- Dose dumping (too fast release) can cause toxicity
- Incomplete release can lead to therapeutic failure

# COMPLEX MOLECULES: CHALLENGES

Unique molecular and formulation characteristics can make dissolution testing challenging

## 01 Low aqueous solubility

Non-sink conditions, slow equilibration and high sensitivity to media composition.


BCS Class II & IV drugs often face this challenge.

## 02 Precipitation

Apparent dissolution may fall after supersaturation; timing and sampling become critical.


Supersaturation followed by precipitation.

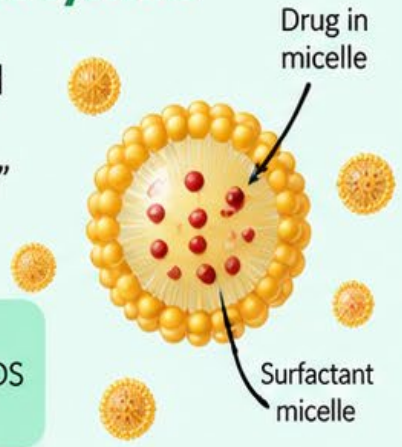
## 03 Hydrodynamics

Small changes in agitation or dosage-form position can change mass transfer.

Sensitive to agitation speed, vortexing and dosage form position (sinking, floating or coning).

## 04 Colloids / lipid systems

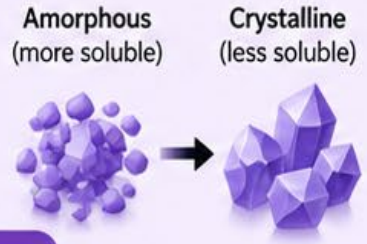
Drug may be solubilized in micelles or droplets, complicating "dissolved" definitions.




Common with lipid-based formulations, SEDDS/SMEDDS and biologics.

## 05 Solid-state changes

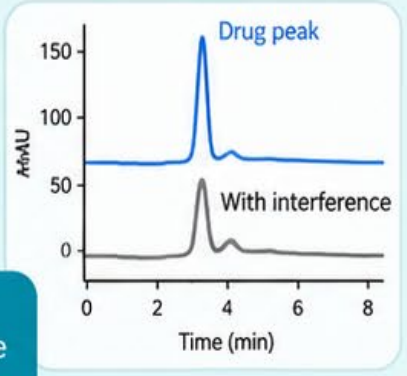
Polymorphic conversion or crystallization can alter the dissolution profile during the test.




Amorphous to crystalline conversion reduces apparent dissolution.

## 06 Analytical interference

Excipients, surfactants, proteins or turbidity can affect UV/HPLC measurements.




Method selectivity and sample preparation become critical.

# DISSOLUTION: A CRITICAL CHALLENGE FOR COMPLEX AND NSQ DRUG PRODUCTS

When formulation, process or quality is complex, dissolution tells the real story...

UNDERSTAND
DIAGNOSE
IMPROVE
ENSURE QUALITY

## COMPLEX PRODUCTS

Multiple factors can affect drug release

**Modified-release products**
(extended, delayed, pulsatile)

**Multiparticulates**
(pellets, beads, MUPS)

**Poorly soluble drugs**
(BCS Class II/IV, lipid-based, amorphous)

**Combination products**
(multiple APIs, different release profiles)

**Novel technologies**
(nanoparticles, solid dispersions, complex excipients)


## NSQ DRUG PRODUCTS

Quality gaps often manifest in dissolution

**Substandard raw materials**
Incorrect grade, polymorph, particle size

**Inadequate manufacturing controls**
Poor blending, compression, coating

**Defects and variability**
Hardness, friability, coating integrity

**Failure to meet label claim**
Assay and dissolution failures

**Regulatory actions**
Market alerts, recalls, loss of patient trust

# From Complexity to Confidence

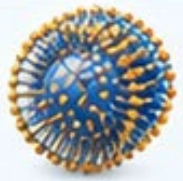
Product and quality challenges demand robust dissolution

*Different by Design. Dissolution Makes the Difference.*

## Complex Products

### Key Product Characteristics

**Modified release formulations**
Polymer matrix/coat, multi-unit systems
→ Controlled or site-specific release



**Nanoparticles / Liposomes**
Small size, high surface area, carriers
→ Complex release and potential formulation instability

**Transdermal systems**
Rate-controlling membrane, enhancers
→ Low drug load, sustained flux

**Inhalation products (MDI/DPI)**
Particle size, aerodynamic distribution
→ Deposition and in-vitro/in-vivo correlation

**Injectable depots / implants**
Biodegradable polymers, long-acting
→ Slow, complex release kinetics

## Why Robust Dissolution is Needed

**Captures release kinetics**
Discriminates formulation/process variables (e.g., polymer grade, coat thickness, compression force).

**Sensitive to critical formulation attributes (CMA)**
Detects impact of particle size, surfactant, type of lipid/polymer on drug release.

**Ensures method robustness and IVIVR**
Discriminates changes in membrane composition, adhesive, or release modifiers.

**Simulates in-vivo performance**
Aerosolization and dissolution testing (e.g., USP Apparatus 3/4, Next Generation Impactor) to ensure consistent delivered dose.

**Supports long-term performance**
Detects changes in polymer degradation, drug release rate and batch-to-batch variability.

# From Complexity to Confidence

Product and quality challenges demand robust dissolution

*Different by Design. Dissolution Makes the Difference.*

## NSQ (Substandard & Falsified) Drugs

### Typical Quality Issues

- **Incorrect API amount**
  Under/over potency
- **Wrong ingredients**
  Different salt/polymorph, substituted excipients
- **Poor manufacturing**
  High variability, inadequate granulation/compression
- **Inadequate dissolution**
  Incomplete or very slow release
- **Stability issues**
  Degradation products, moisture sensitivity

### Need for Robust Dissolution

- Detects poor-quality and falsified products
- Discriminates good vs poor performance batches
- Supports regulatory surveillance (e.g., WHO, USFDA, CDSCO)
- Protects patient safety by ensuring drug availability in systemic circulation
- Essential tool for market monitoring and post-market quality assessment

## Examples of NSQ Drugs (Reported Cases)

**Paracetamol tablets**
Low dissolution, incorrect assay

**Metformin tablets**
Substandard products with slow/incomplete dissolution

**Amoxicillin capsules**
Frequent NSQ alerts with failure in dissolution

# WHAT DOES DISSOLUTION ACTUALLY MEASURE?

**Release is a chain of events**

- Wetting/ penetration
- Disintegration or matrix erosion
- Deaggregation / particle exposure
- Dissolution at the solid–liquid interface
- Diffusion into bulk medium

**Rate**

How fast does drug enter solution?

**Extent**

How much drug is released by the end?

**Profile shape**

Lag → rapid release → plateau; inflection points can reveal coating, matrix, wetting, solubility or transport limitations.

**For complex products**

**Profile-rich data are usually more informative than a single endpoint value.**

# DISSOLUTION USE FOR NSQ & COMPLEX PRODUCTS

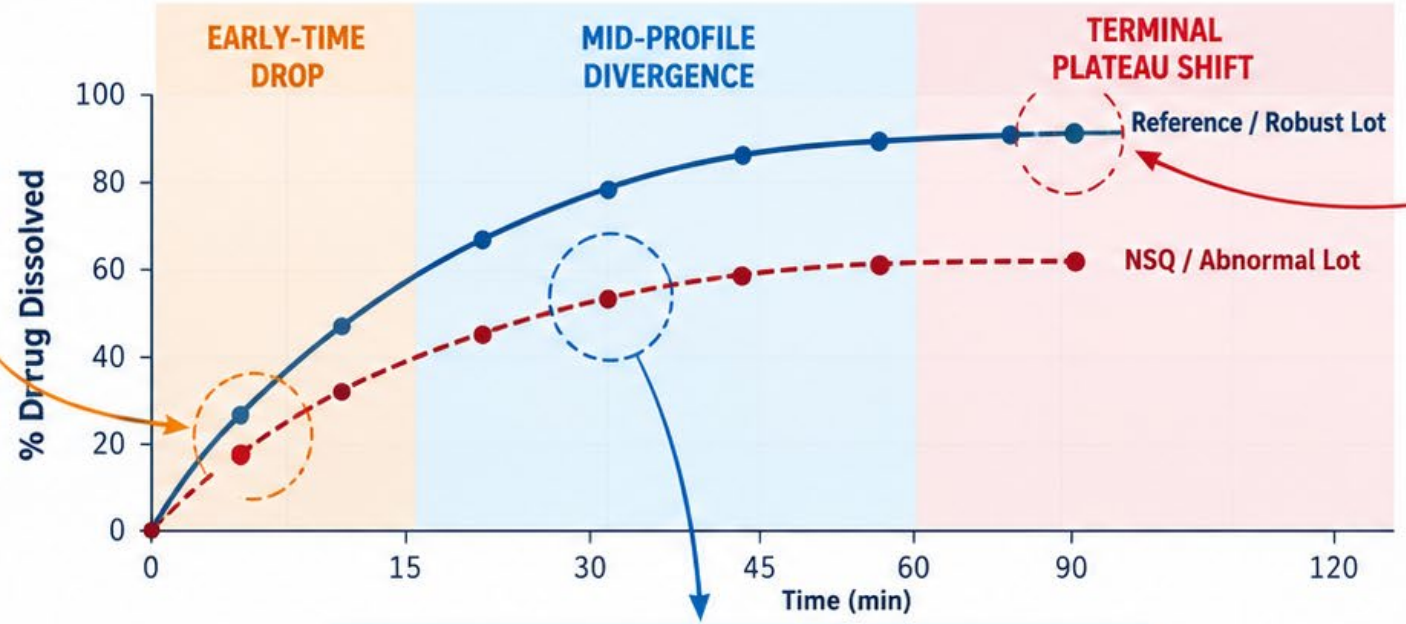
UNDERSTAND | DIAGNOSE | IMPROVE

BETTER PRODUCTS. HEALTHIER LIVES.

1. **Abnormal profile**
   Compare against release/ stability/ clinical or pivotal lots
2. **Pattern recognition**
   Identify early, mid-point or terminal deviation
3. **Challenge variables**
   Formulation + process + material + method
4. **Root cause**
   Confirm by targeted experiments

## EARLY-TIME DROP

- Wetting
- Disintegration
- Granule porosity
- Compression force
- Lubricant level




## TERMINAL PLATEAU SHIFT

- Solubility / sink condition
- Precipitation
- Dose strength
- Analytical recovery

Reference / Robust Lot
NSQ / Abnormal Lot

## MID-PROFILE DIVERGENCE

- Particle size
- Polymorph
- Coating
- Matrix hydration/erosion
- Binder / formulation parameters

**Dissolution profile = fingerprint of formulation, material & process variability**

SAME SCIENCE
STRONGER SUPPLY
GREATER PATIENT IMPACT

# CASE- STUDIES

# Case Example: Dissolution Failure in Paracetamol Combination Tablets

A common and critical issue in NSQ alerts

Dissolution failures in paracetamol combinations are frequently reported in regulatory alerts and market surveillance.

## 1 Why Paracetamol is Challenging ?

Paracetamol (Acetaminophen)

- **High dose** (typically 500–650 mg)
- Poorly water-soluble (BCS Class III/IV)
- Requires high compression force
- Low compressibility
- When combined with other APIs (e.g., caffeine, diclofenac, tramadol), the tablet matrix becomes more complex

**Result:** Slower water penetration and incomplete drug release

## 2 Common Reasons for Dissolution Failure

**Over-lubrication**
- Excess Mg Stearate
- Prolonged blending

Forms hydrophobic layer, restricts water penetration

**High compression force**

Dense, low-porosity tablet – poor media penetration

**Inadequate disintegration**
- Low/ineffective disintegrant
- Strong binder (e.g., starch, PVP)

Tablet does not break down fast

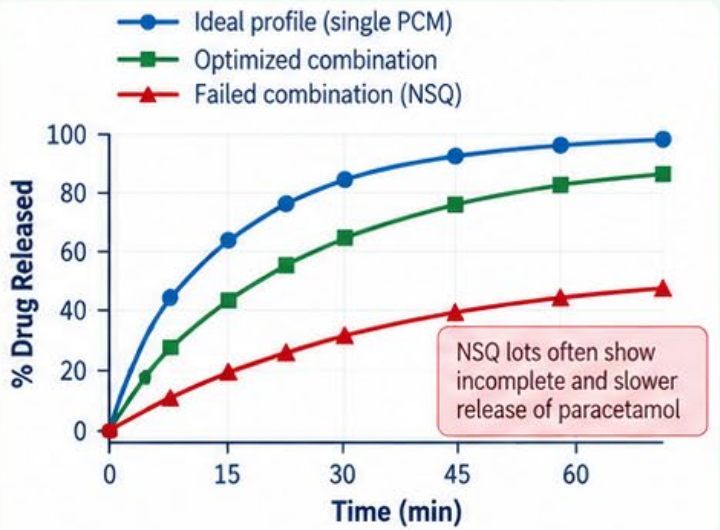
**Co-API incompatibility**
- Different solubility profile (e.g., diclofenac – low solubility in acidic pH)
- pH changes / viscous barrier

Slower component traps paracetamol

**Over-drying of granules**
- Low LOD
- Dense, hard granules

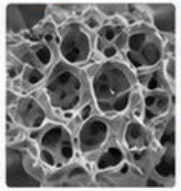
Resistant to wetting and swelling

## 3 Impact on Dissolution Profile




## 4 How to Overcome – Formulation & Process Solutions

### Use Superdisintegrants

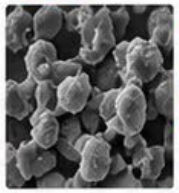


- Croscarmellose sodium (CCS)
- Sodium starch glycolate (SSG)
- Replace/augment starch
- Rapid water uptake and tablet breakup

### Optimize Lubrication

- Reduce Mg stearate level
- Limit blending time (< 3–5 min)
- Use hydrophilic lubricant (e.g., Sodium Stearyl Fumarate)

### Enhance Solubility



- Solid dispersion with PVP/ HPMC
- In situ micronization
- Amorphous form to increase surface area and dissolution

### Control Process Parameters

- Optimize compression force (lower hardness with adequate friability)
- Control granule moisture (LOD)
- Avoid over-drying

### Use Suitable Diluents

- Incorporate water-soluble fillers (e.g., Lactose)
- Use MCC to create fast dissolving channels

**Balanced formulation and controlled manufacturing are key to ensuring robust dissolution of paracetamol combination tablets.**

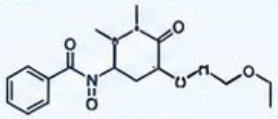
BETTER QUALITY
SAFER MEDICINES
GREATER HEALTH IMPACT

# DISSOLUTION CHALLENGES IN AMOXICILLIN + POTASSIUM CLAVULANATE TABLETS

Highly hygroscopic. Chemically unstable. Environmentally sensitive.
Small changes in moisture or process conditions can lead to big differences in drug release.


STABLE FORMULATION
RELIABLE DISSOLUTION
BETTER OUTCOMES

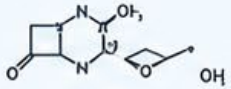
## 1 Why Amoxicillin/Clavulanate is Challenging?



**Amoxicillin** (trihydrate)

- Hygroscopic
- Prone to Moisture-induced polymerization
- Low solubility near pH 4.8 (isoelectric point)

+



**Potassium clavulanate**

- Extremely hygroscopic
- Chemically unstable (β-lactam ring hydrolysis)
- Rapid degradation in presence of moisture

**Both APIs are highly sensitive to moisture, which can affect tablet integrity and dissolution.**

## 2 Key Reasons for Dissolution Failure

**Moisture Absorption & Degradation**
- Clavulanate hydrolysis
- Amoxicillin polymerization
- Alters solid-state & solubility

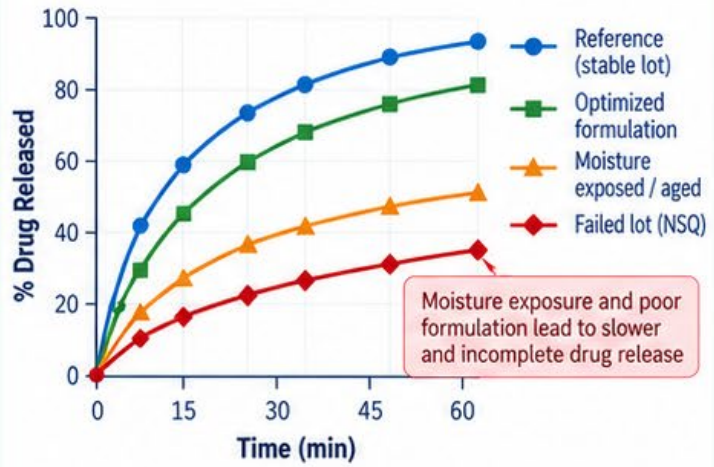
**Physical Hardening & Ageing**
- Moisture-induced recrystallization
- Increased tablet hardness
- Slower disintegration

**Inadequate Disintegrant Performance**
- Disintegrants lose swelling capacity due to moisture uptake
- Delayed tablet breakup

**Micro-environmental pH Changes**
- Reduced solubility near pH 4.8 (amoxicillin)
- Excipient interactions

**Poor Packaging Integrity**
- Standard PVC blisters allow moisture ingress
- Compromises dissolution during shelf life

## 3 Impact on Dissolution Profile




## 4 Strategies to Overcome Dissolution Failure

### Formulation Solutions

- Use pre-dried excipients (moisture content < 3%)
- Add organic acids (e.g., tartaric acid, citric acid) to stabilize and optimize pH
- Optimize superdisintegrant (e.g., 5% CCS)
- Select moisture-scavenging diluents

Pre-dried excipients for better stability

### Process Engineering

- Prefer dry granulation (roller compaction/direct compression)
- Maintain low relative humidity (RH < 15–20%) and temperature < 25°C
- Use dehumidified air for coating
- Minimize exposure time to ambient environment

Controlled low-humidity manufacturing

### Protective Coating

- Apply moisture-barrier film coating (aqueous or organic)
- Use inlet air dehumidification during coating
- Prevents moisture uptake and improves shelf-life

Moisture-protective film coating

### High-Barrier Packaging

- Use Alu-Alu blisters or aluminum strip packs
- Avoid standard PVC blisters
- Provides excellent barrier against moisture, light and gases
- Maintains tablet integrity and dissolution till use

Alu-Alu blister for maximum protection

**CONTROL MOISTURE | OPTIMIZE FORMULATION & PROCESS | USE PROTECTIVE PACKAGING**

Ensuring robust dissolution and preserved efficacy in Amoxicillin + Clavulanate products

STABLE DRUGS
HEALTHIER PATIENTS
STRONGER MARKETS

# DISSOLUTION FAILURE DUE TO GELATINOUS MASS IN CLARITHROMYCIN AND OTHER ANTIBIOTICS

When a gel barrier stops drug release...

*From problem to solution*

UNDERSTAND
SOLVE
DELIVER
BETTER THERAPIES

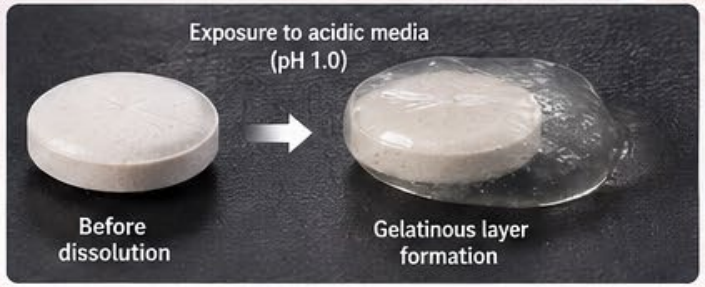
## Why Does Gelatinous Mass Form?

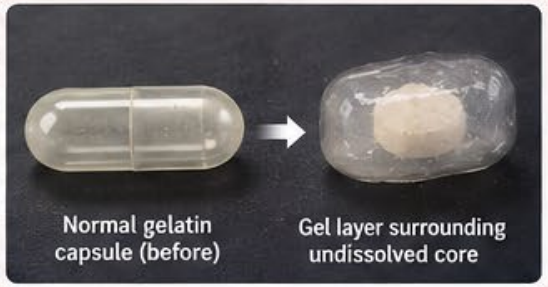
### 1 Drug-Induced Surface Gelation (Tablet Effect)

- In acidic media (pH 1–1.2) or carboxylate buffers, clarithromycin can interact with surrounding ions/excipients
- Forms a cross-linked 3D gel layer on tablet surface via hydrogen bonding
- The gelatinous barrier prevents water penetration and stops disintegration
- **Result:** slow and incomplete drug release

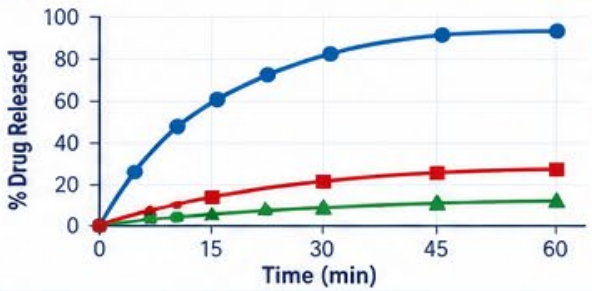
### 2 Gelatin Capsule Cross-Linking (Capsule Shell Effect)

- Aldehydes (from excipients, degradation products or heat/humidity) react with gelatin proteins
- Leads to gelatin cross-linking and formation of an insoluble, rubbery pellicle (gelatinous mass)
- Capsule does not dissolve, trapping the antibiotic powder inside
- Result: no or delayed drug release




## Impact on Dissolution Profile




Gel formation and capsule cross-linking lead to slower and incomplete dissolution of clarithromycin.

## How to Overcome the Dissolution Faliure?

### 1. Formulation Modifications (Preventing Tablet Gelation)

**Use Surfactants / Wetting Agents**

- Poloxamer 407, SLS or other hydrophilic surfactants
- Break surface tension and prevent gel formation

**Amorphous Solid Dispersions**

- Disperse clarithromycin in hydrophilic polymers (e.g., HPMC, PVP)
- Prevents local high drug concentration and 3D gel mesh

**Optimize Excipients**

- Use non-gelling, water-soluble diluents
- Avoid ingredients that promote gelation in acidic media


### 2 Packaging Change (Preventing Capsule Cross-Linking)

- Replace gelatin capsules with **HPMC capsules**
- HPMC is plant-derived, contains no amino acids
- Immune to aldehyde-induced cross-linking or pellicle formation


### 4 Analytical Solution (During Dissolution Testing)

- Use Tier 2 dissolution testing as per USP
- Add proteolytic enzymes – Pepsin (pH < 6.8) or Pancreatin (neutral pH)
- Enzymes digest the cross-linked gelatinous mass and release the drug

# CASE STUDY: DISSOLUTION FAILURES IN PROTON PUMP INHIBITORS (PPIs)

**Pantoprazole / Rabeprazole** – Small changes, big impact on dissolution

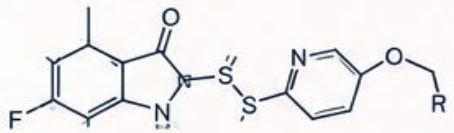
*Acid-labile PPIs need protection to reach the intestine for effective release*

- PROTECT IN ACID
- OPTIMIZE FORMULATION
- ENSURE RELEASE

STABLE PRODUCTS. BETTER THERAPIES.

## 1 Why PPIs are Challenging?

- Highly acid-labile (rapid degradation in gastric pH)
- Alkaline-reactive
- Require enteric protection for delivery to intestine
- Sensitive to moisture and heat during processing



**Pantoprazole** (R = $OCH_3$)
**Rabeprazole** (R = H)

**Result:** Without proper protection or with formulation/process issues, dissolution fails.

## 2 Common Dissolution Failures & Causes

### A Acid Stage Failure
(> 10% release in 0.1 N HCl, 2 h)

Intact enteric-coated tablet in acid

Coating defect/acid penetration → drug release/degradation

- Lack of / inadequate subcoating (API–polymer interaction)
- Insufficient enteric coating weight gain
- Process flaws during coating (spray rate, atomization, temperature)
- Pellet compression damage (MUPS) causing coating cracks

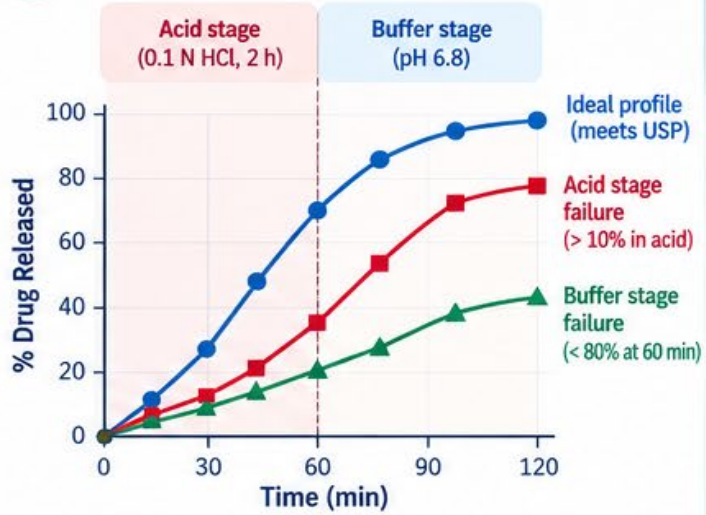
### B Buffer Stage Failure
(< 80% release in pH 6.8)

Coating dissolves in buffer, but slow release of drug

Incomplete release even after 60 min

- Over-curing or excessive coating thickness (highly cross-linked film)
- API degradation during processing (moisture/heat)
- Inadequate disintegration power (excess binder, low superdisintegrant)
- Excipient incompatibility (acidic excipients) forming insoluble complexes

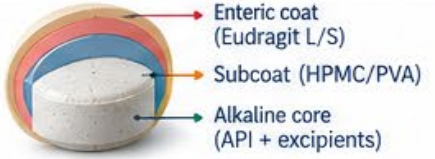
## 3 Typical Dissolution Profile




Dissolution failures may show early release in acid media or incomplete/slow release in buffer media.

## 4 Strategies to Overcome Dissolution Failure

### 1. Barrier Subcoating




- Apply 4–6% weight gain of neutral polymer (HPMC/PVA)
- Prevents drug–polymer interaction
- Improves acid resistance

### 2. Optimize Enteric Coating

- Use Eudragit L 30 D-55 / HPMCP
- Coating weight gain: 10–15%
- Add plasticizer (Triethyl Citrate 15–20%) for flexibility
- Control spray rate, atomization pressure and inlet temperature

### 3. Protect Pellets in MUPS

- Use cushioning agents (e.g., MCC)
- Blend flexible polymers (Eudragit L30D-55:NE30D, 8:2)
- Optimize compression force to avoid coating cracks

### 4. Improve Core Formulation

- Include alkalizers ($Na_2CO_3$, MgO, $NaHCO_3$) to stabilize API
- Use superdisintegrants (5–7.5% Crosspovidone)
- Avoid acidic excipients
- Control moisture and heat during granulation/drying

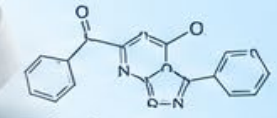
### 5. Control Process Parameters

- Maintain product bed temperature (32–38°C)
- Optimize spray rate and drying air
- Prevent over-curing (excessive heat)
- Ensure uniform coating and weight gain

# CASE STUDY: DISSOLUTION FAILURE IN TELMISARTAN TABLETS

## A BCS Class II challenge – High permeability, extremely low solubility

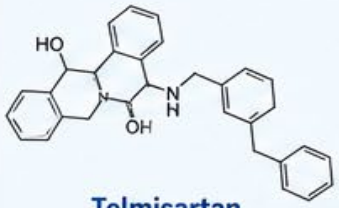
Low solubility → Slow dissolution → Variable bioavailability



**Telmisartan**
(BCS Class II)
Solubility ≈ 0.09 µg/mL

IMPROVE SOLUBILITY
ENHANCE DISSOLUTION
ENSURE CONSISTENT THERAPEUTIC OUTCOMES

## 1 Why Telmisartan is Challenging?



**Telmisartan**
($C_{33}H_{30}N_4O_2$)

- BCS Class II: High permeability, extremely low solubility (~0.09 µg/mL)
- pKa ~ 4.45 (zwitterion)
- Practically insoluble at pH 3–7
- High crystalline and lipophilic nature
- Absorption is dissolution rate limited

**Result:** Prone to dissolution failure without enabling formulation strategies.

## 2 Key Reasons for Dissolution Failure

**pH-dependent solubility**
Poor solubility in pH 3–7 (dissolves in highly alkaline media)

**High crystal lattice energy**
Stable crystalline form resists dissolution

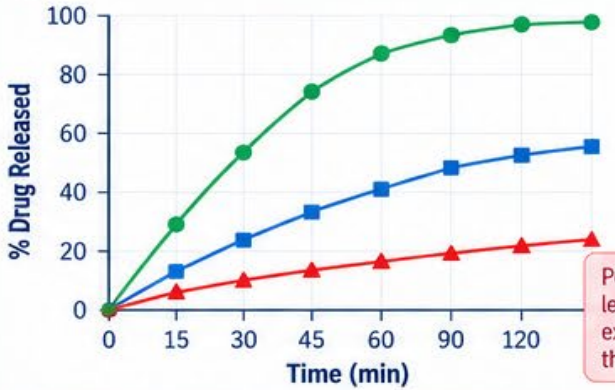
**Poor wettability**
Hydrophobic surface leads to aggregation and floating/clumping

**Recrystallization**
Amorphous form unstable, reverts to crystalline form over time


**Inadequate microenvironmental pH**
Insufficient alkalizing agents in formulation

**Hydrodynamic clumping**
Tablet mass adheres to basket mesh, restricting media flow

## 3 Typical Dissolution Profile




Poor dissolution leads to sub-therapeutic exposure and risk of therapeutic failure

**Goal:** Achieve rapid and complete dissolution across physiological pH conditions.

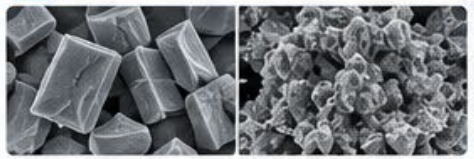
## 4 Strategies to Overcome Dissolution Failure

### 4.1 Microenvironmental pH Modification


- Add alkalizers: NaOH, sodium carbonate, meglumine, etc.
- Increases local pH at the tablet surface
- Promotes ionization and faster dissolution

Converts the drug to a more soluble form at the site of dissolution.

### 4.2 Solid Dispersion / SSD

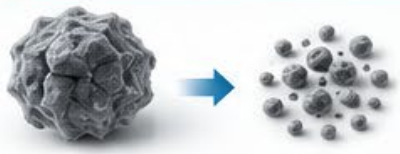


Crystalline Telmisartan | Amorphous/Solid Dispersion

- Disperse in hydrophilic carriers (PEG 4000/6000, PVP K30, Poloxamer 407)
- Use surface solid dispersion (Aerosil 200)
- Reduces crystallinity and improves wettability

Destroys crystal lattice and maintains drug in a fast-dissolving state.

### 4.3 Particle Size Reduction



Before (micron size) → After (nano size)

- Micronization, nanonization, high-pressure homogenization
- Increases surface area (Noyes-Whitney)
- Use surfactants to prevent re-agglomeration

Smaller particles = faster dissolution.

### 4.4 Appropriate Excipients & Process


- Use superdisintegrants (Crospovidone, CCS)
- Select soluble diluents (mannitol, sorbitol)
- Top spray granulation with drug + alkalizer
- Avoid acidic excipients
- Optimize binder and lubricant levels

Ensures rapid disintegration and better wetting of drug particles.

### 4.5 Optimize Dissolution Testing

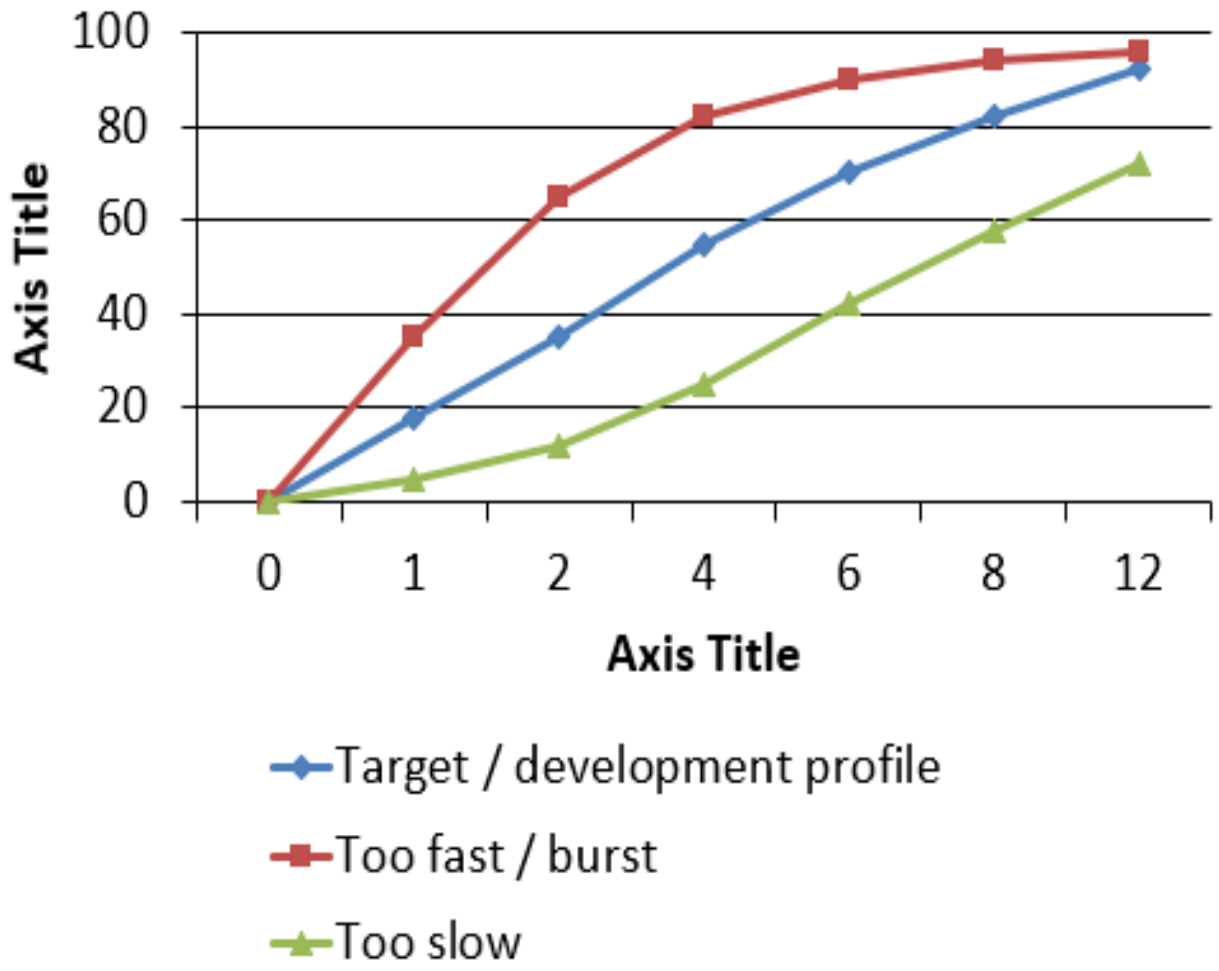
USP Apparatus I (Basket) → USP Apparatus II (Paddle)

- Use USP Apparatus II (paddle) to minimize clumping
- Ensure adequate agitation (50–75 rpm)
- Consider surfactant in dissolution media (e.g., 0.5–1% SLS) for method development

Provides uniform hydrodynamics and prevents tablet sticking.

# Glimepiride + metformin SR: release profile, not a single point

MODIFIED RELEASE




## What to diagnose

Matrix former level • polymer viscosity / grade • tablet porosity • compression force • drug loading • particle size • granule structure.

## Why USP 3 or 4?

Useful when staged media, changing hydrodynamics or controlled flow can better interrogate the release mechanism than a conventional static vessel.

## Manufacturing controls

Blend uniformity • granulation endpoint • lubrication • compression force / dwell • coating uniformity • equipment scale-up.

# COMPLEX DRUGS

## ‘WHERE CONVENTIONAL DISSOLUTION STRUGGLES’

**Poorly soluble APIs**

Low sink, precipitation, wetting limitations, supersaturation

**Amorphous / solid-state**

Polymorph conversion, recrystallization, particle-level variability

**Lipid / enabling systems**

Digestion, dispersion, precipitation and phase behavior

**Modified / multiparticulate**

Coating, matrix erosion, dose dumping, population variability

# Amorphous Solid Dispersion (ASD)

## THE DISSOLUTION PROBLEM

- High-energy amorphous API can rapidly recrystallize after polymer dissolution.
- Supersaturation is transient; precipitation may cause a rapid fall in measured concentration.
- Strong surfactants / high agitation can mask the formulation's true performance.

## ROBUST DISSOLUTION STRATEGY

**Apparatus**
USP 2 • Paddle • 50–75 RPM

**Biorelevant**
FaSSIF / non-sink medium to capture kinetic solubility

**QC**
Minimal surfactant if needed • typically 0.25–0.5% SLS

**Sampling**
Dense early sampling • especially 15–45 min

**Analysis**
Track peak supersaturation + precipitation/decay

**Critical artifact:**

**Method must distinguish true supersaturation from precipitation -driven concentration loss.**

# Lipid-Based Solid Matrix

## THE DISSOLUTION PROBLEM

- Drug release depends on wetting, dispersion and often enzymatic lipid digestion.
- Sticky / buoyant lipid fragments can alter hydrodynamics and cause variability.
- Nano-/micro-emulsions create turbidity and light scattering that can bias UV results.

## ROBUST DISSOLUTION STRATEGY

**Apparatus**

USP 2 + sinker; USP 4 for complex/slow-eroding matrices

**Biorelevant**

Bile salts + pancreatin / simulated intestinal lipase

**QC**

Consider Polysorbate 80 or bile-mimicking surfactant system

**Physical control**

Prevent floating, adhesion and uncontrolled matrix aggregation

**Analysis**

HPLC/UPLC after validated centrifugation/filtration

**Critical artifact: TURBIDITY & LIGHT SCATTERING**

**Separate dissolved API from dispersed lipid droplets before quantification.**

# Layered Multi-Particulate Pellets

## THE DISSOLUTION PROBLEM

- Release is controlled by coating integrity, thickness, permeability and hydration.
- Mechanical paddle impact can fracture fragile functional coatings.
- Swelling/polymer debris can blind the basket mesh or cause coning, falsely slowing release.

## ROBUST DISSOLUTION STRATEGY

**Apparatus**
USP 1 • Basket • ~100 RPM

**Alternative**
USP 4 + glass beads for fragile coated pellets

**pH program**
Acid stage → pH 4.5 or 6.8 buffer, as product-justified

**Hydrodynamics**
Maintain pellet retention without restricting medium exchange

**QC**
Verify sink conditions and inspect mesh/coning behavior

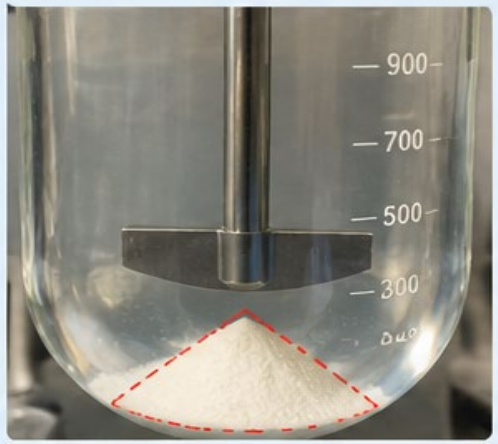
**Critical artifact: MESH BLINDING & CONING**

**Confirm the test setup—not basket restriction or pellet packing—is not creating an artificial slow release.**

# PROMINENT DISSOLUTION PROBLEMS

## Coning

Particles settle in a cone at the bottom of the vessel

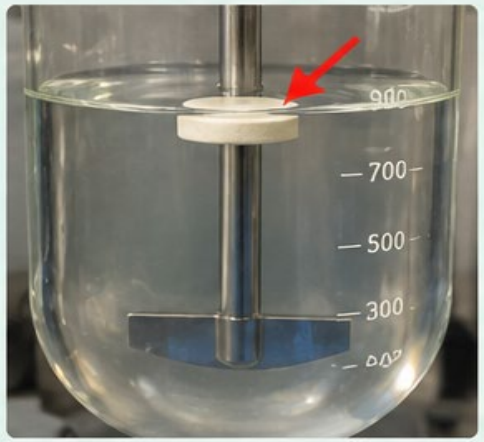



- Poor wetting or high-density particles
- Inadequate agitation
- Can lead to slower and incomplete dissolution

**Potential Impact:** Underestimation of dissolution rate
**Mitigation:** Increase agitation, use surfactant, optimize formulation

## Floating

Dosage unit or particles remain at the surface

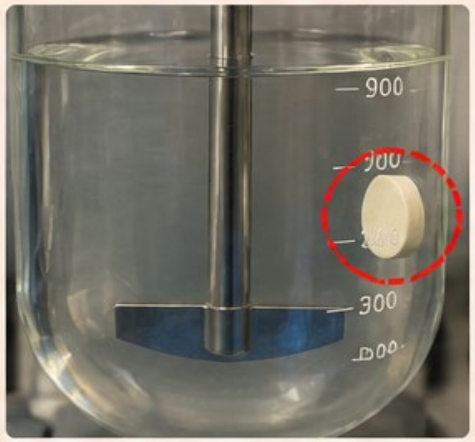



- Low density formulation (e.g., low-density tablets, lipid-based systems)
- Entrapped air
- Hydrophobic surface

**Potential Impact:** Delayed or incomplete dissolution
**Mitigation:** Use sinker (e.g., 3-prong sinker), modify formulation, degas medium

## Adhesion

Dosage unit sticks to vessel wall or paddle

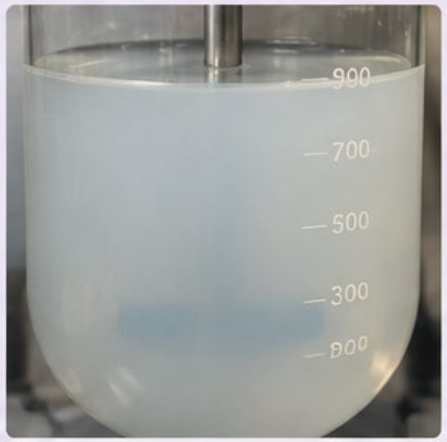



- Sticky or soft formulations (e.g., lipid-based, high binder)
- Electrostatic interactions
- Inadequate hydrodynamics

**Potential Impact:** Erratic and variable results
**Mitigation:** Adjust agitation, use sinker, modify formulation or coating, change vessel material if needed

## Turbidity / Emulsification

Cloudy medium due to lipid dispersion or excipients

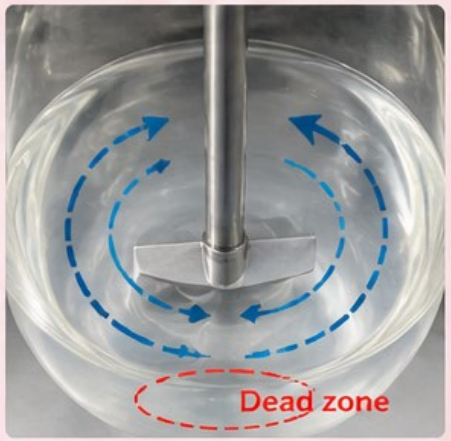



- Common with lipid-based formulations (SEDDS, SMEDDS)
- Formation of nano/micro-emulsions
- Causes light scattering in UV analysis

**Potential Impact:** False high/variable absorbance readings
**Mitigation:** Use HPLC/UPLC with centrifugation/filtration to separate drug from lipid droplets

## Inadequate Agitation / Dead Zones

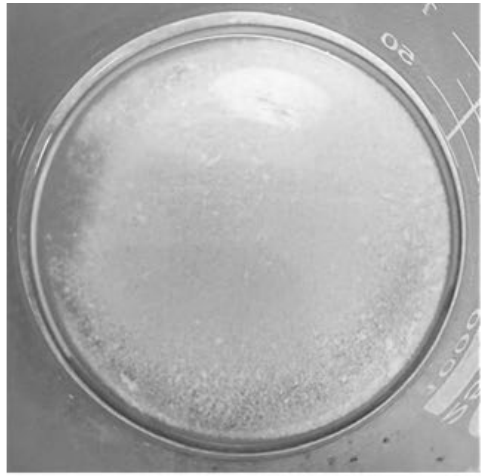
Poor mixing leading to non-uniform drug distribution



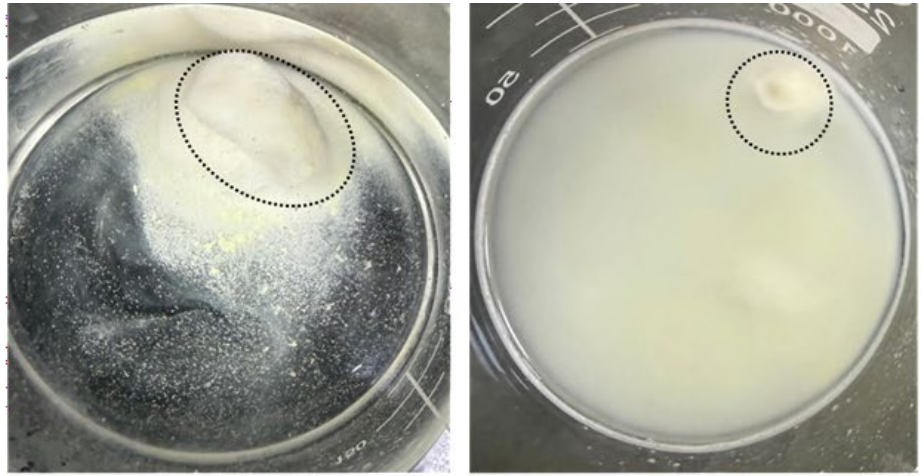

- Wrong paddle/basket speed
- Incorrect vessel volume
- Baffles not used (if required)
- Leads to variable and non-reproducible results

**Potential Impact:** High variability, poor discrimination
**Mitigation:** Optimize agitation speed, use baffles (if justified), verify equipment qualification

# LAB CASE STUDY: Cefuroxime Tablets



**CL Brand:** Rapid disintegration, Absence of gelatinous mass

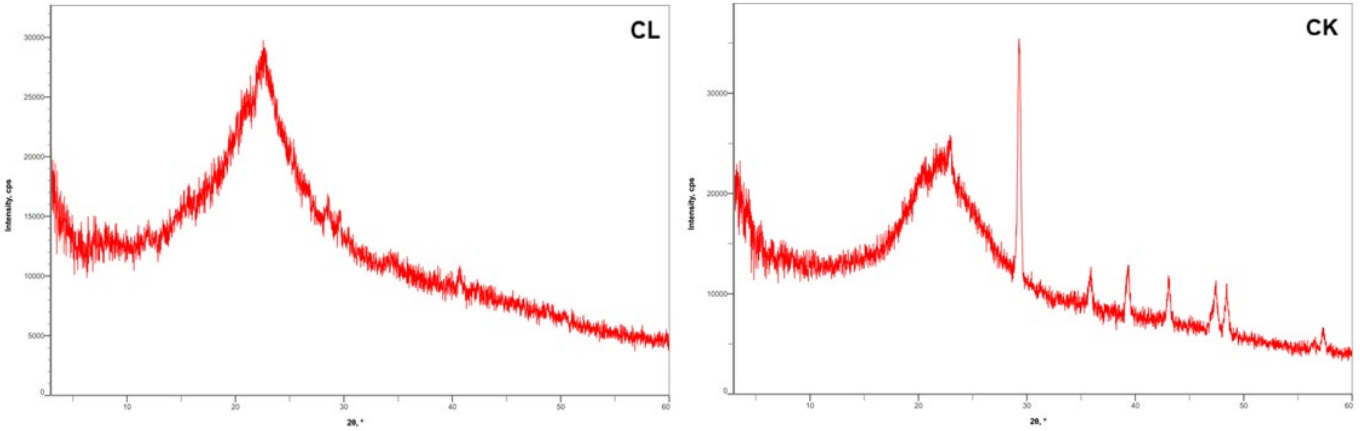


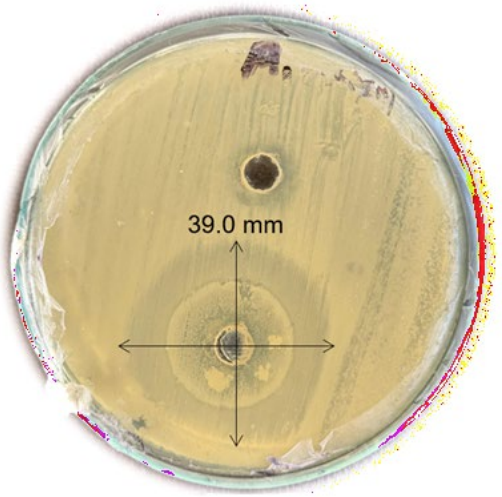
**CK Brand:** Slow disintegration, Formation of gelatinous mass during dissolution (dotted circle)

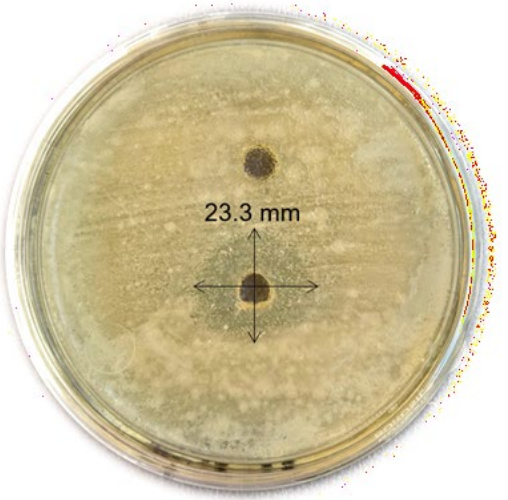
**Dissolution Rate is faster from CL**

**Drug Remaining at 60 min:**

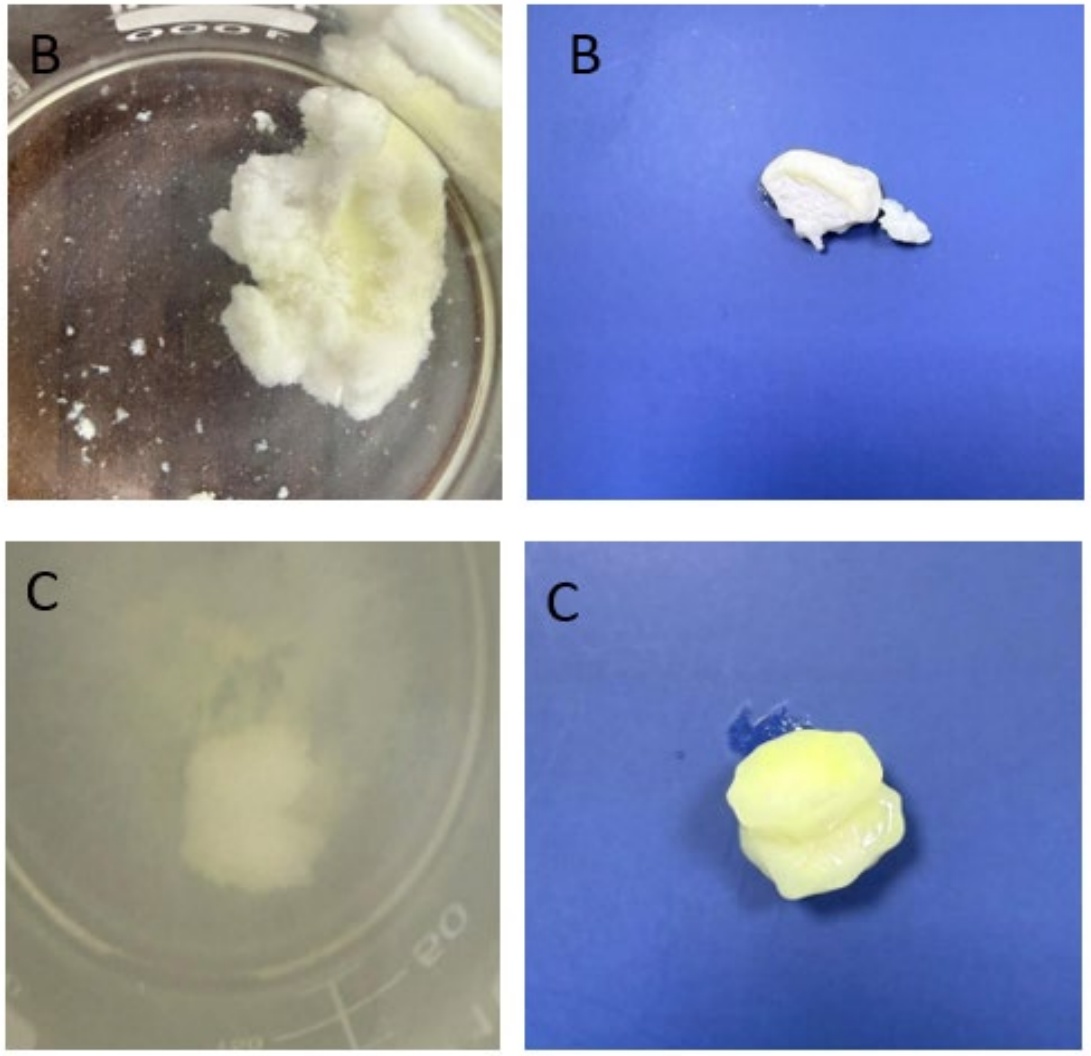
- CL: 10.2%
- CK: 21.7%



# LAB CASE STUDY: Clarithromycin Tablets




Gelatinous mass observation during dissolution of Clarithromycin tablet

# DISSOLUTION DEVELOPMENT

# A STRUCTURED SEQUENCE

1. Literature survey
2. Apparatus selection
3. Medium selection
4. Volume selection
5. Agitation & Temp.
6. Sampling time points
7. Analytical method

1. Preformulation
2. Solubility map
3. Medium screening
4. Hydrodynamic study
5. Discriminatory Design
6. Biorelevance Study
7. Validation

**Evidence base cited in the source**

- Official pharmacopoeia / compendial methods
- FDA database / Orange Book
- Journals and published papers

# WHAT CONTROLS DISSOLUTION?

## API / DRUG SUBSTANCE

**Physical properties**
- Particle size
- Amorphous vs crystalline structure

**Physicochemical properties**
- Solubility
- pKa
- Intrinsic dissolution

**Chemical/ Biopharma properties**
- Salt form
- stability
- BCS classification

## DOSAGE FORM / FORMULATION

**Site of drug dissolution**
- Gastrointestinal tract / skin

**Release characteristics**
- IR or MR

**Formulation & process**
- Excipients
- Manufacturing process
- Formulation characteristics

**Product considerations**
- Dosage form type
- Marketing considerations

# APPARATUS SELECTION

**API**
- Physical
- Chemical
- Stability
- Biopharma

**DOSAGE FORM**
- Solid
- Semisolid
- Liquid

**RELEASE**
- IR
- Modified

**PHYSIOLOGY**
- GI tract
- Skin

**EXPECTATIONS**
- Compendial
- Justified change

**Typical solid oral starting point**

**Apparatus 1 (basket)**
**Apparatus 2 (paddle)**

**When the product demands it**

**Apparatus 3**
**Apparatus 4**

# SELECTING THE DISSOLUTION MEDIUM

## Physiological pH window

- **1.2** — 0.1 N HCl / pH 1.2
- **4.5** — pH 4.5 buffer
- **6.8** — pH 6.8 buffer
- **7.5** — modified-release: where relevant

### SURFACTANTS

Natural surfactants, synthetic surfactants and enzymes may be considered when applicable.

### SINK CONDITIONS

The source indicates sink conditions are desirable in routine selection.

### STABILITY

Water may be used as an additional medium when buffered-media instability makes data unusable.

# CHOOSING DISSOLUTION ENVIRONMENT

### pH

Weak acids/bases can show large pH-dependent release differences. Match pH to the intended question and maintain adequate buffer capacity.

### Surfactant

May address wetting/solubility limitations. Select based on API chemistry and avoid creating an unrealistically aggressive test.

### Sink conditions

Help keep the profile driven by dosage-form behavior rather than saturation. Confirm across strengths when relevant.

### Deaeration

Air bubbles can alter wetting and reliability; control and document the approach.

- **Solubility is quantitatively determined across the physiological pH range at 37°C.**
- **Calculate the volume needed to obtain a saturated solution of the highest dose.**
- **The source describes sink as at least 3× this volume; some companies use 5× or 10×.**

# AGITATION & TEMPERATURE

## AGITATION — SOURCE RANGES

Basket: 50–100 rpm

Paddle: 50–75 rpm; >100 rpm with proper justification
- Suspensions: 25–50 rpm
- Extended-release formulations: 100 rpm

Reciprocating cylinder: 5–35 dips/min

Flow-through cell: flow rate varies by cell design; source cites ~4–16 mL/min as a general range.

## TEMPERATURE — SOURCE RANGES

Most dosage forms: 37°C

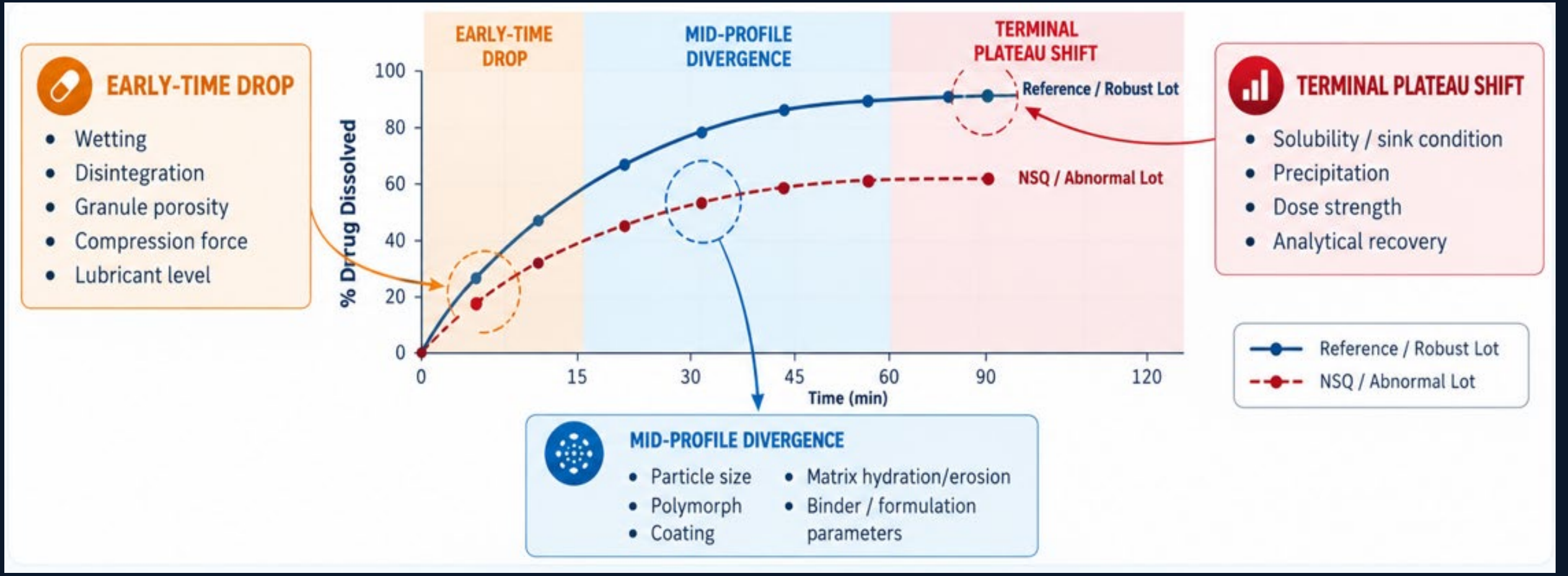
Dosage forms applied on the skin: 32°C

Why it matters
Temperature and hydrodynamics are part of the test environment. Small changes can alter wetting, convection and the observed release profile.

**Industry control point** **Treat rpm, flow, temperature and timing as method parameters—not just instrument settings.**

# DISSOLUTION PROFILES: LOOK BEYOND A SINGLE ENDPOINT

**A profile can reveal differences that a single endpoint may hide.**



# DISCRIMINATORY DISSOLUTION

### Step 1 — Identify risks

List CMAs/CPPs that could plausibly change release: API PSD/solid state, granulation, compression, lubricant, coating weight, polymer grade, etc.

### Step 2 — Manufacture challenge lots

Make meaningful low/high or intentionally varied conditions around the target process range.

### Step 3 — Test profile sensitivity

A useful method should distinguish relevant changes while maintaining acceptable repeatability.

### What you learn

Which formulation/process variable actually moves the profile?

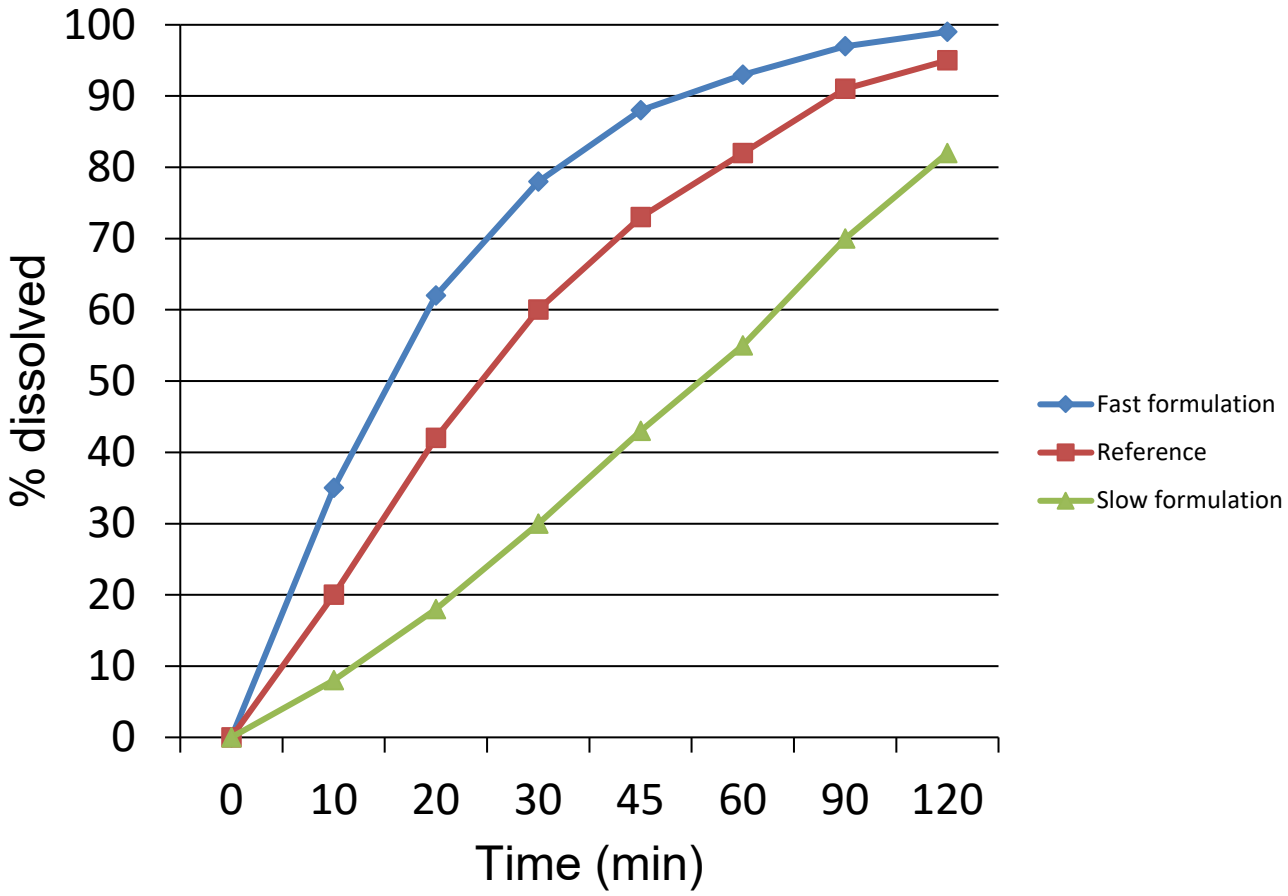
### What you avoid

Blindly changing formula or process based on a single failed time point.

### Industry output

A mechanism-based risk ranking that feeds development, CAPA and change control.

# DIFFERENTIAL DISSOLUTION




- Discriminatory power = ability to detect formulation changes that matter.
- Stress the formulation intentionally: API particle size, excipient level, compression force, coating or process variables.
- Compare profiles using appropriate statistical / model-independent approaches; do not rely only on a single time point.
- Use $f_2$ cautiously: similarity testing answers a different question from method discrimination.

# BIORELEVANT & DIFFERENTIAL DISSOLUTION

**Baseline QC**

Robust, reproducible method for routine control

**Mechanistic test**

Probe solubility, precipitation, erosion or release mechanism

**Biorelevant challenge**

Simulate key GI conditions where justified

**Link to performance**

Use data with PK/BE/clinical knowledge where available

# PROFILE COMPARISON & STATISTICS

**Visual comparison**

Check early-, mid- and late-time differences. Look for systematic shifts rather than isolated noise.

**$f_2$ similarity factor**

Common profile-comparison tool when its assumptions and applicability are satisfied; often interpreted with $f_2 \geq 50$ as similar.

**Model / multivariate tools**

Useful when profiles are complex, sampling is dense, or multiple factors must be interpreted together.

# TAKE-HOME MESSAGES

A well-designed dissolution method can become the bridge between

**PRODUCT QUALITY → PROCESS UNDERSTANDING → CLINICAL PERFORMANCE**

| | | |
|---|---|---|
| 01 | **Understand the API** | Solubility, pKa, intrinsic dissolution, stability and BCS shape the problem. |
| 02 | **Select fit-for-purpose conditions** | Apparatus, medium, volume, agitation and temperature are connected choices. |
| 03 | **Make the method discriminatory** | It should detect meaningful formulation/process changes without overreacting to normal variability. |
| 04 | **Use profiles strategically** | Fractionated / pH-dependent profiles can add insight beyond a single endpoint. |
| 05 | **Remember the biological gap** | In-vitro dissolution is powerful, but it does not fully reproduce the biological system. |

# DISSOLUTION ROOT-CAUSE MATRIX

| Observed signature | Likely mechanism | Formulation Level | Manufacturing Level | Test / apparatus |
|---|---|---|---|---|
| Long lag time | Poor wetting / disintegration | Superdisintegrant; wetting agent | Compression / porosity; lubrication | USP 2; early time points |
| Fast initial release | Weak matrix / porous coat | Polymer level/grade; coating | Spray/drying/curing | USP 3 / 2 profile |
| Slow tail / incomplete release | Saturation / dense matrix | Solubilizer; particle size; polymer | Granule density / compression | USP 4; justified medium |
| Acid-stage leakage | Enteric film defect | Polymer / plasticizer / coat weight | Spray, curing, inlet/outlet temp | 2-stage; USP 3 |
| Batch-to-batch variability | CPP / material variability | Excipient grade / PSD control | Granulation, lubrication, compression | Discriminating profile |

# TROUBLESHOOTING

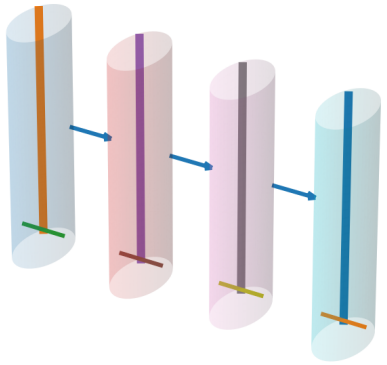
| Observed issue | Likely mechanism | Practical response |
|---|---|---|
| High variability | Floating, coning, poor wetting, sampling inconsistency | Standardize deaeration, vessel handling, wetting and sampling |
| Fast release from all batches | Method not discriminating | Reduce excessive agitation / surfactant; introduce justified stress conditions |
| Unexpected decline after early peak | Supersaturation → precipitation | Run concentration–time study; evaluate pH shift and precipitation kinetics |
| Low recovery | Adsorption / filtration / precipitation | Perform recovery and mass-balance checks |
| Batch ranking changes with medium | Mechanism is media-dependent | Map pH / surfactant / biorelevant conditions and identify critical mechanism |

# USP APPARATUS 3 & 4

# USP APPARATUS 3 & 4 FOR COMPLEX DRUG DISSOLUTION

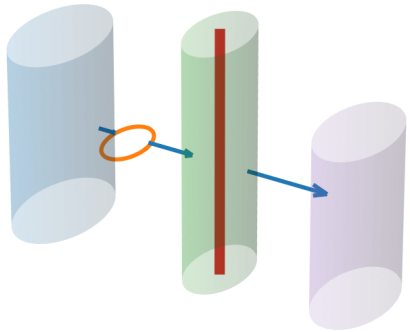
## From compendial testing to mechanistic & biopredictive dissolution

**USP Apparatus 3 | Programmable GI transit simulation**



Sequential media • reciprocation • residence time • controlled hydrodynamics

**USP Apparatus 4 | Flow-through cell**

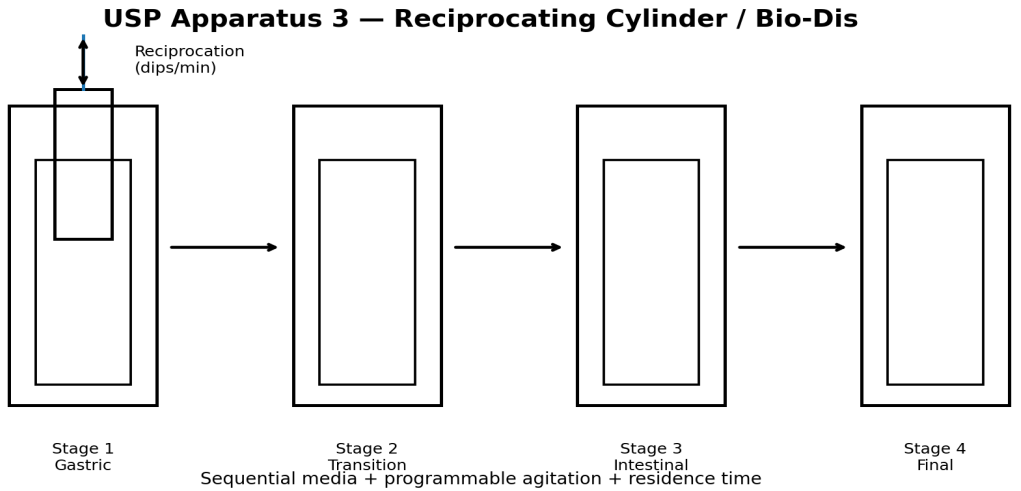


Open loop / closed loop • controlled flow • sink management • fraction collection

# USP APPARATUS 3 – RECIPROCATING CYLINDER (BIO-DIS)

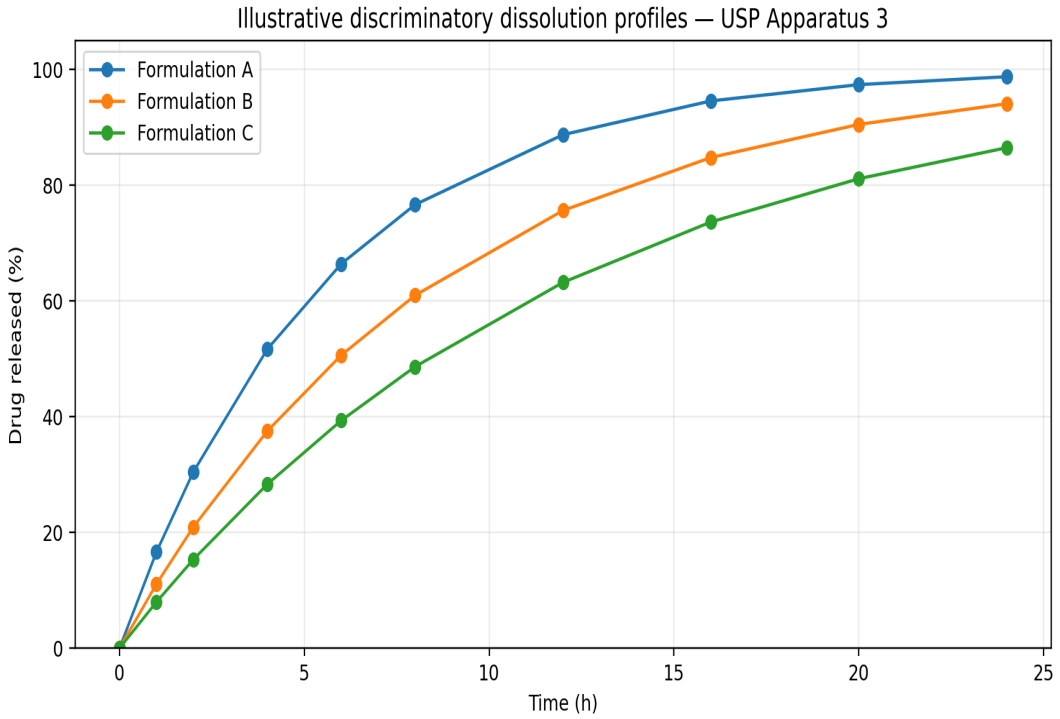
- Reciprocating cylinders move dosage forms through successive media rows - works well for **Drugs with Low aqueous solubility**
- Modified-release systems encounter **changing pH, fluid composition, residence time** and hydrodynamics – **Possible to control in USP 3**
- Reciprocation rate can strongly affect release from hydrophilic matrix systems - **Useful for Multiparticulates, microspheres and implants**

**Key shift: from "How much dissolved?" to "Why, where and under what physiological conditions does release occur?"**

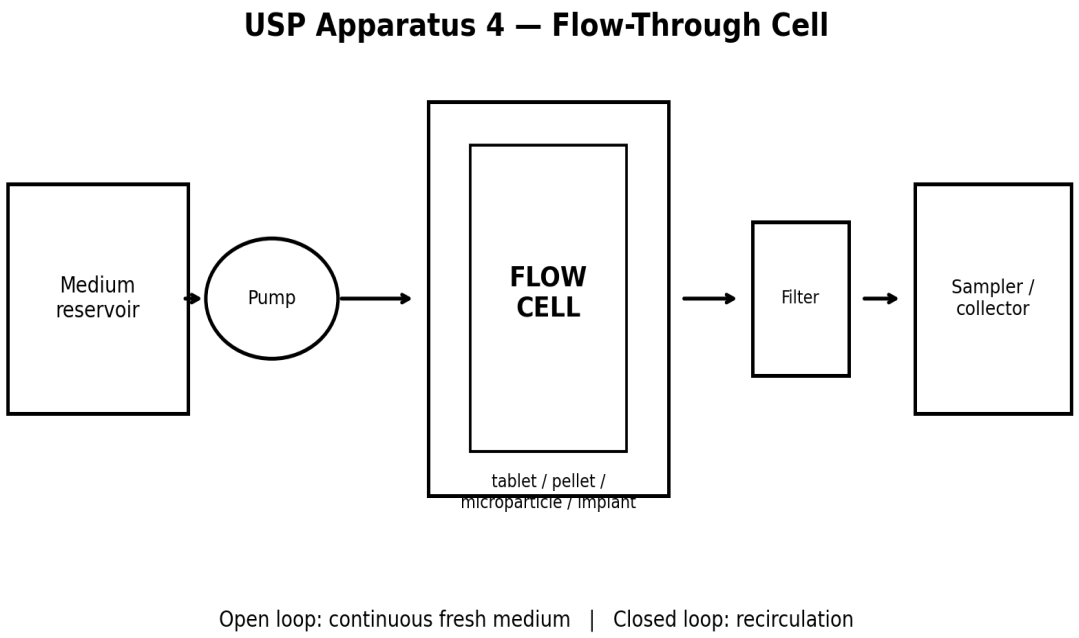


# USP 3 — INDUSTRY APPLICATIONS

- **Extended-release tablets: challenge matrix integrity across pH transitions.**
- **Enteric / delayed-release products: quantify lag time and onset after gastric exposure.**
- **Coated beads/pellets: investigate coating level, polymer grade and curing effects.**
- **Colon-targeted systems: introduce sequential intestinal / colonic conditions.**
- **Generic development: create a discriminating method before translating to routine QC.**



# USP APPARATUS 4 — FLOW-THROUGH DISSOLUTION




- Medium is pumped upward through a vertically mounted flow cell.
- **Open-loop** operation continuously removes dissolved drug;
- **Closed-loop** operation recirculates medium.
- Standard pharmacopoeial flow rates include 4, 8 and 16 mL/min; temperature is maintained at 37 ± 0.5 °C under the general USP description
- Cell geometry & filter configuration should be selected for dosage form & method objective.

# USP 4 — SPECIALITY

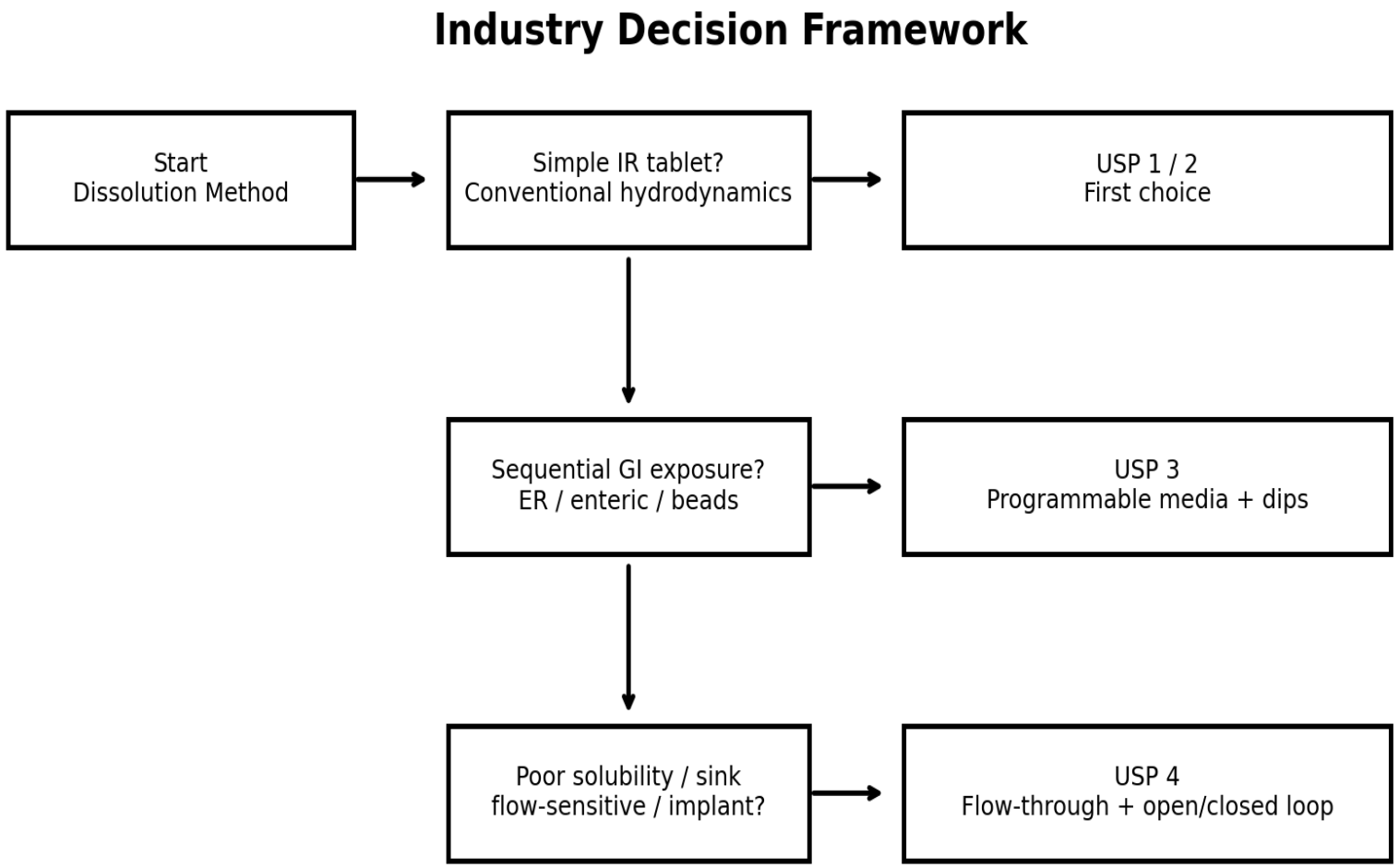
- Continuous removal of dissolved drug can reduce concentration build-up and help maintain sink conditions.
- Media can be switched without physically transferring the dosage form.
- Flow can be adjusted to investigate hydrodynamic sensitivity.
- Small cell volumes can be advantageous when API availability is limited.
- Collected fractions provide a time-resolved release profile and can be paired with sensitive analytical assays.

# USP 4 — COMPLEX DRUG APPLICATIONS

- Poorly soluble APIs: improved control of concentration build-up and sink conditions.
- Modified-release products: useful when continuous medium exchange is relevant.
- Microparticles/nanoparticles: support time-resolved release and fraction collection.
- Implants/depot systems: long-duration release testing with adaptable cell configurations.
- Special dosage forms: flow-through cells can accommodate different holders and cell sizes.

Particularly attractive for BCS II / IV compounds, long-acting formulations and systems where precipitation confounds USP 2.

# Decision framework: USP 1/2 vs 3 vs 4




- Start simple & compendial.
- Escalate when the scientific failure mode is clear.
- USP 3 → sequential environment/ transit problem.
- USP 4 → flow, sink, low-solubility or complex dosage-form problem.
- Document why the selected apparatus is more discriminating or biorelevant.

# Industry case examples — what the literature demonstrates

- **Metformin ER:** USP 3 method using sequential pH media and 30 dips/min over 10 h achieved a strong Level A IVIVC.
- **Poorly soluble bases (e.g., dipyridamole):** USP 4 can continuously remove the dissolved fraction and reduce precipitation artefacts compared with a static vessel.
- **Long-acting nanosuspensions:** USP 4 has been reported as a promising IVR tool because of representative hydrodynamics and sink maintenance.
- **Poorly soluble ER solid dispersion:** USP 4 has been used to characterize release while managing supersaturation and sink conditions.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Innovating Advanced Drug Delivery Systems
ADVANCED DRUG DELIVERY INNOVATIONS
Nose-to-Brain Delivery
Transdermal Drug Delivery
Targeted Nanocarriers
HPLC for Advanced Analysis
Nanotechnology for Better Therapeutics
Extrusion System
LC-MS/MS for Bioanalysis & Metabolite Profiling
Dynamic Light Scattering (DLS) Particle Size Analysis
Thank You
Research Focus
• Nanocarrier Systems
• Targeted Drug Delivery
• Nose-to-Brain Delivery
• Skin Delivery & Dermal Targeting
• Vesicular Drug Delivery
• QbD & DoE Approaches
CETOSOMES®
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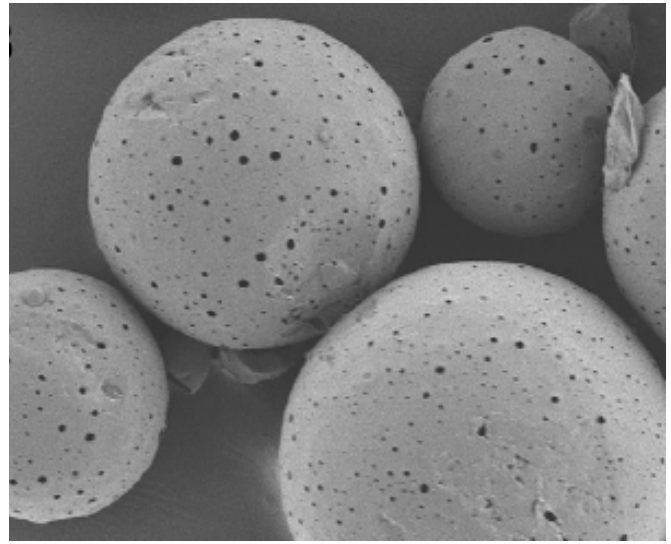
From Bench to Better Healthcare
Formulation Development
Preclinical Evaluation
Translation & Commercialization
Patient Impact
Driving Innovation Through Science
• Quality by Design (QbD)
• DoE Driven Development
• Translational Research
• Industry Collaborations
Every innovation in drug delivery brings us closer to better patient outcomes.
– Dr. Gaurav Kumar Jain
EXCELLENCE | INNOVATION | COLLABORATION | IMPACT

# Dosage Forms: Microspheres

- Development of first USP 4 method by Prof Burgess' lab (Univ. of Connecticut, USA) in collaboration with SOTAX
- Selecting appropriate accelerated test conditions (e.g. at 45 °C) makes the method predictive of the real time release profile.



→ *25-150 µm microspheres*

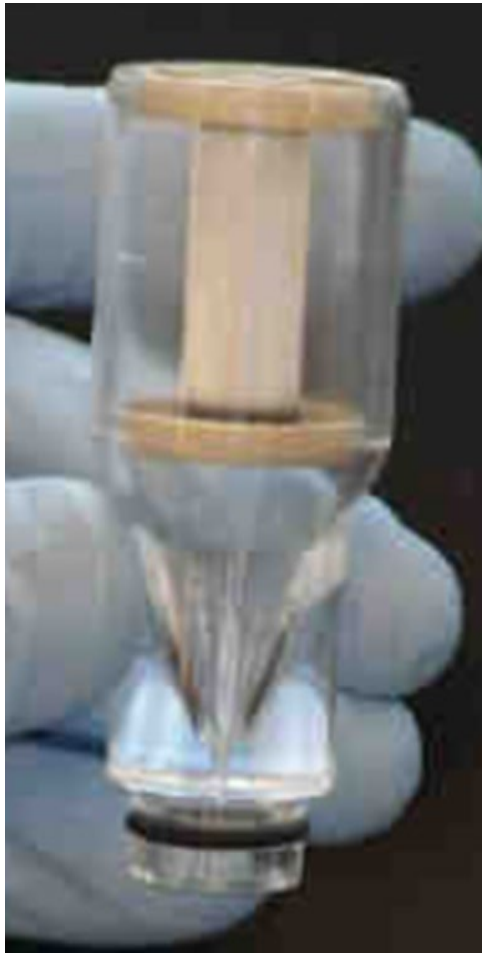
→ Cell type:

Classical 12 mm and 22.6 mm cells as described in USP chapter <711>

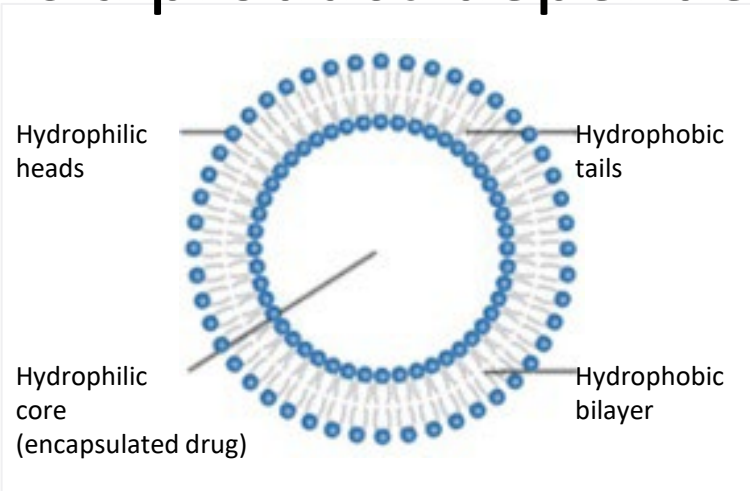
# Dosage Forms: Liposomes & Nanosuspensions

Float-A-Lyzer:

- Adapters for liposomes and nano-suspensions
- Different dialysis membranes are available (membrane type is a product-dependent selection).



→ Float-a-lyzer




→ Liposome for Drug Delivery (0.1 µm)

→ A4D Adapter

# Dosage Forms: Topical Products (Semi-Solid Adapter)

- Semi-Solid Adapter (SSA):
  - designed for topical products
  - can be used as an alternative for the extraction cell or for the Franz cell
  - for a volume of up to 1.2 mL of product
- SSA is used in combination with a 25 mm membrane (different membranes available depending on product)
- Orientation of membrane in 2 different directions possible:
  - Membrane facing direct media flow (downwards)
  - Membrane positioned in indirect flow (upwards)

→ USP <1724>

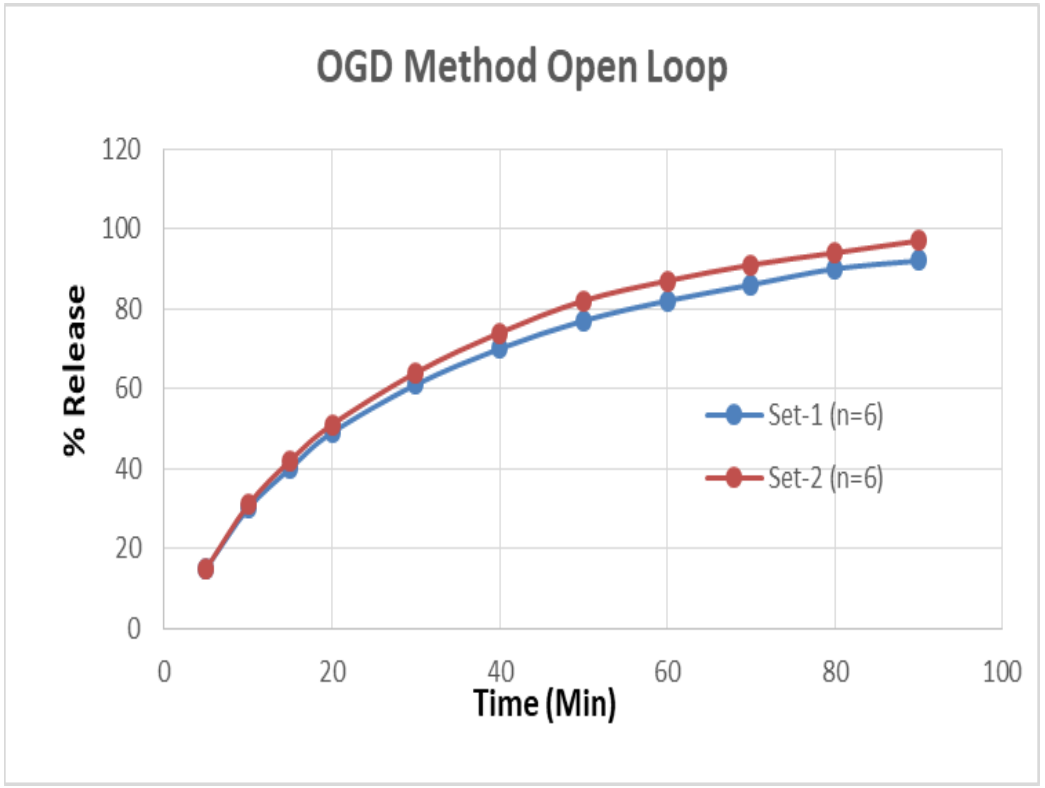
# Depot Injection Suspension

## OGD Method for Medroxyprogesterone Acetate Injection Suspension 150 mg/mL

| Product | USP Apparatus | Speed (RPM) | Medium | Volume (mL) | Sampling Time (min) |
|---|---|---|---|---|---|
| Medroxyprogesterone Acetate Injectable Suspension | Test 1: Type II (Paddle) | Test 2: 50 rpm | Test 2: 0.35 % SDS in water | Test 2: 900 mL | Test 2: 5, 10, 15, 30, 60, 90, 120, 240, 360, 1440 and 2880 |
| | Test 2: Type IV (Flow through cell), 22.6 mm cell, 13 g of 1 mm beads | Test 1: 17 mL/min | Test 1: 0.5 % SDS in water | Test 1:use Open Mode | Test 1: 5, 10, 15, 20, 30, 40, 50, 60, 70, 80 and 90 |

# Depot Injection Suspension

| Dissolution Method | |
|---|---|
| Configuration | Open Loop |
| Cell | 22.6 mm |
| Flow rate | 17 mL/min |
| Temp. | 37 ± 0.5$^0$C |
| Medium | 0.5% SLS in Water |
| Glass Beads | 13g, 1mm |
| Filter | GF/D and Glass wool |
| Time points | 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90 min |




**Conclusion :**

1. USP Type 2 method is not discriminating, more than 85% drug dissolution in 15 min
2. USP Type 4 method is discriminating and reproducible (RSD < 2%, n=12)

# Ophthalmic Emulsion

## In-vitro Release Method Development for Ophthalmic Emulsion (Restasis)

| Dissolution Method | |
|---|---|
| Configuration | Closed Loop |
| Cell | 22.6 mm |
| Flow rate | 16 mL/min |
| Temp. | 37 ± 0.5$^0$C |
| Medium | 2% SLS in Tear Fluid pH 7.4, 50 mL |
| Dialysis Membrane | Float-a-lyzer, 1 mL 1000 KDa |
| Time points | 0.5, 1, 2, 4, 8, 12, 16, 20 Hrs |



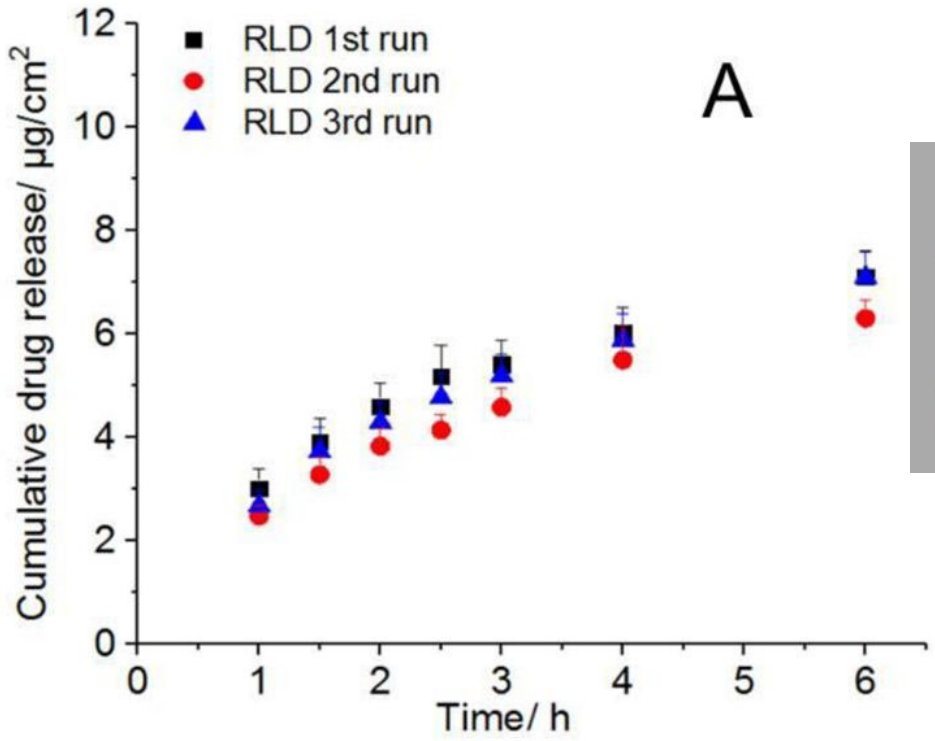
# Ophthalmic Ointment

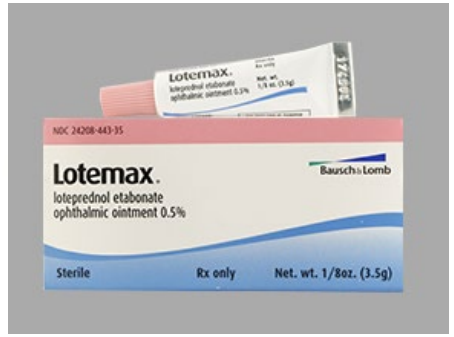
***In vitro* release testing method development for ophthalmic ointments as per USP <1724>**

1) USP apparatus 4 with Semisolid Adapters
2) USP apparatus 2 with Enhancer cells
3) Franz Diffusion Cell

| USP 4 Dissolution Method | |
|---|---|
| Configuration | Closed Loop |
| Cell | 22.6 mm |
| Adapter | SSA (Downward facing) |
| Flow rate | 8 mL/min |
| Temp. | 37 ± 0.5$^0$C |
| Medium | Tear Fluid pH 7.4, 50 ml |
| Membrane | Cellulose acetate 0.45µm |
| Sample Qty. | ~ 330 mg |
| Glass Beads | 14 g, 1mm glass beads |
| Time points | 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0 Hrs |

In vitro drug release profiles of Lotemax® (RLD) using USP apparatus 4 with semisolid adapters, USP<1724>



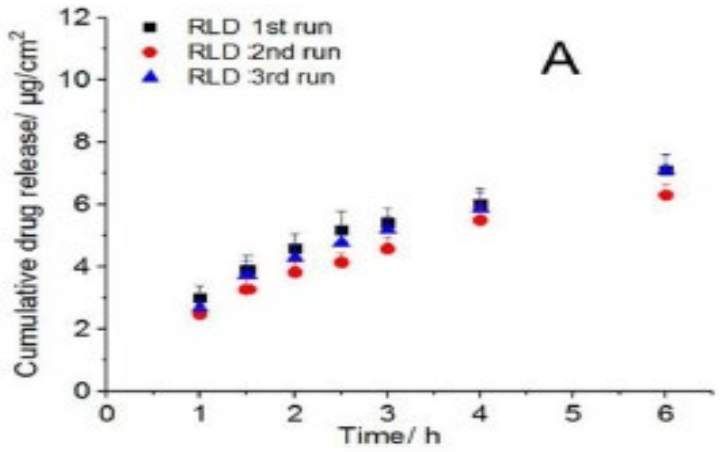




*Ref.:* Int J Pharm. 2017 June 30; 526(1-2): 145–156. doi:10.1016/j.ijpharm.2017.04.075

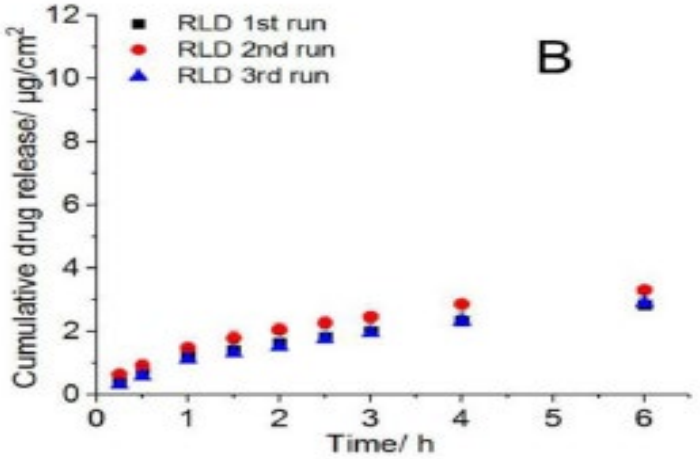
# Ophthalmic Ointment

In vitro drug release profiles of Lotemax® (RLD) obtained using different release testing methods:

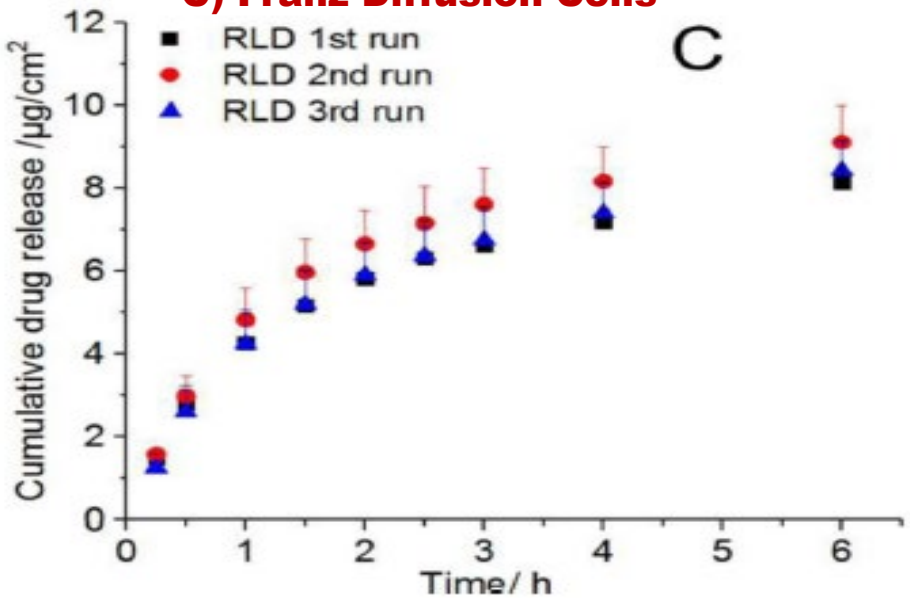
**A) USP apparatus 4 with Semi-Solid Adapters**




**B) USP apparatus 2 with Enhancer Cells**

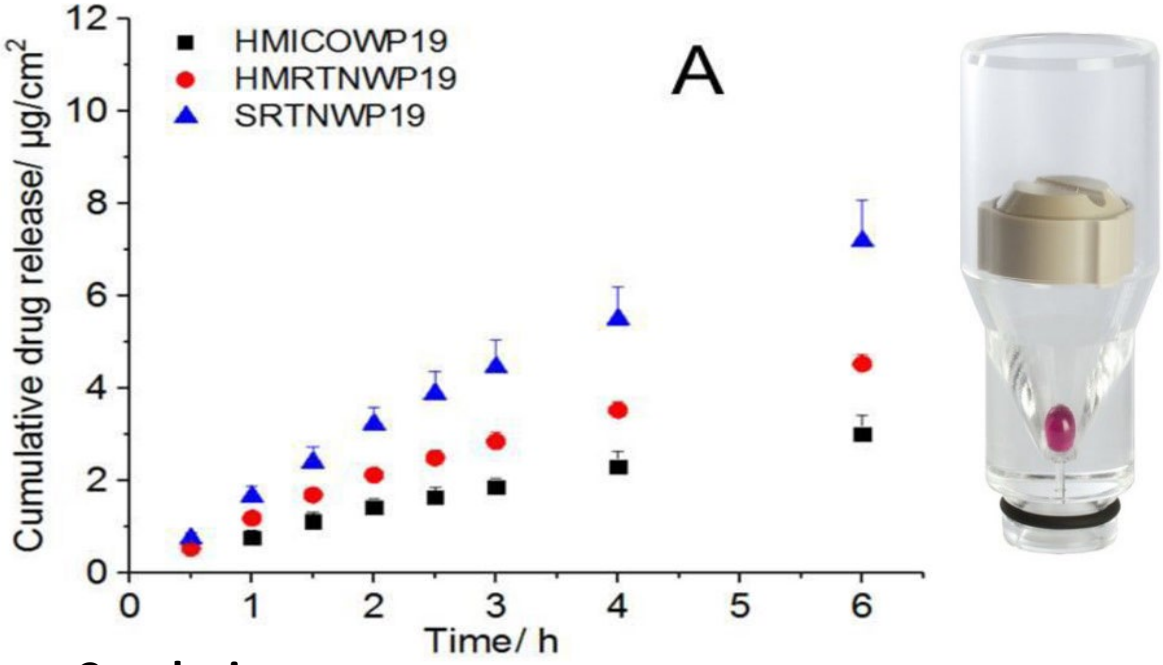



**C) Franz Diffusion Cells**

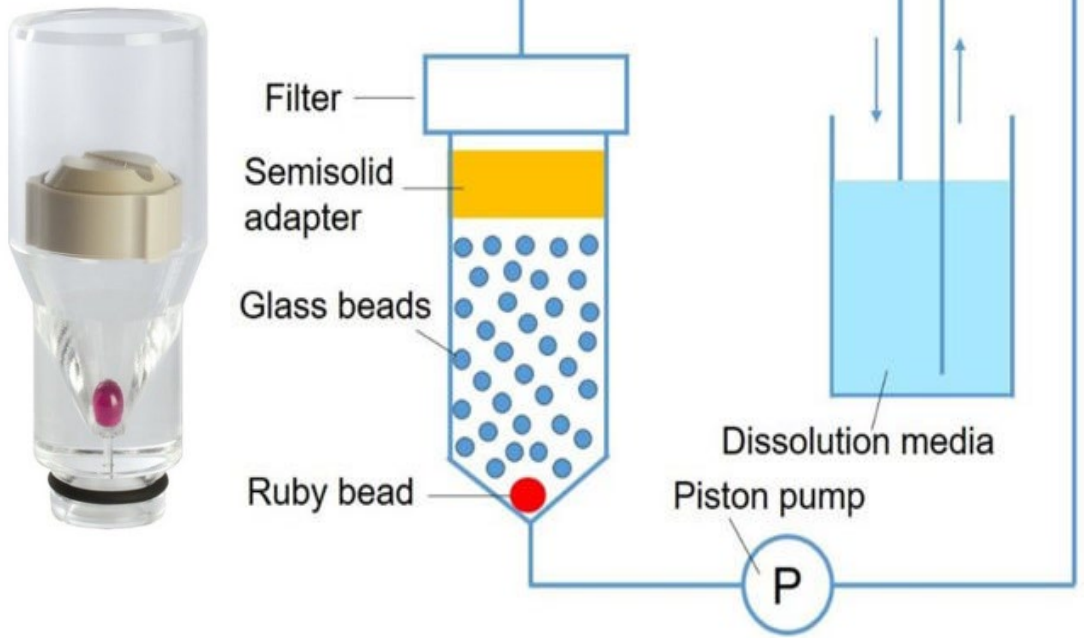


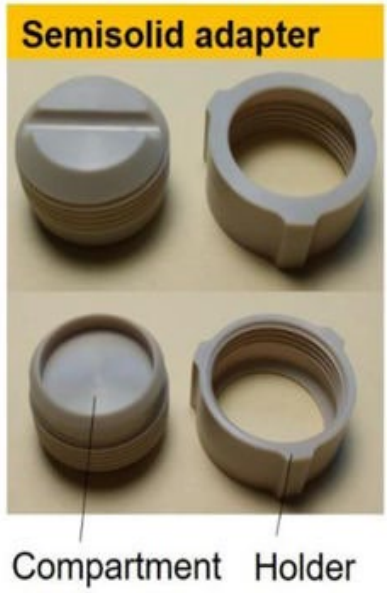
# Ophthalmic Ointment

In vitro drug release profiles of three different formulations using USP apparatus 4 with semisolid adapters, USP<1724>




Graphic demonstration of USP apparatus 4 with semisolid adapters




**Conclusion:**

- The compendial in vitro release testing methods (USP apparatus 4 and USP apparatus 2 with Enhancer cell ) are more suitable than the Franz cell method.
- USP 4 method is reproducible and more discriminatory than USP 2 method.
- Sample loading is superior in USP 4 and USP 2 method than Franz cell method.
- USP apparatus 4 method showed the strongest logarithmic linear correlation with the rheological parameters.

# PLGA Microspheres

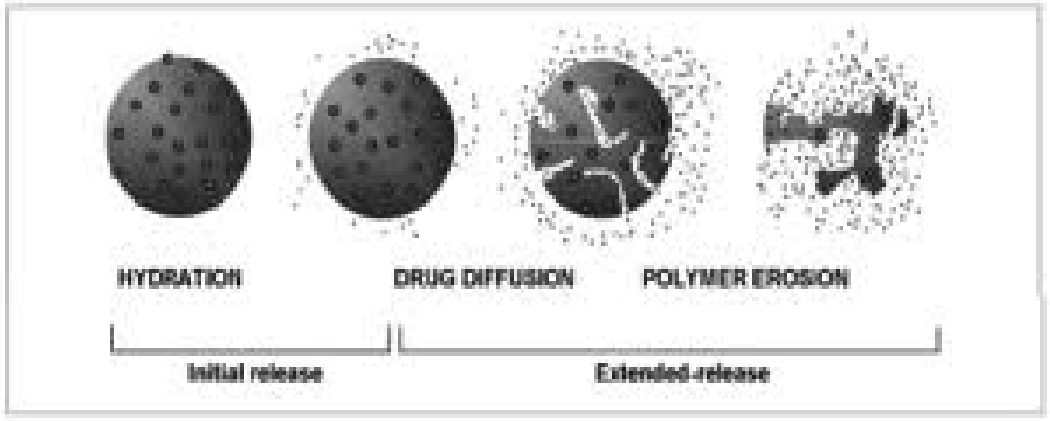
## Accelerated In-vitro Release Testing Method for Naltrexone loaded PLGA Microspheres Vivitrol

**VIVITROL®** (**naltrexone** for extended-release injectable suspension) is supplied as a **microsphere** formulation of **naltrexone** for suspension, to be administered by intramuscular injection.
**Naltrexone** is an opioid antagonist with little, if any, opioid agonist activity.


Physicochemical properties of naltrexone microsphere formulations ($n = 3$).

| Sample | Solvent | Drug loading (%, w/w) | Porosity (%, w/w) | D50 (Mean ± SD) (μm) | |
|---|---|---|---|---|---|
| | | | | Population | Volume |
| Formulation 1 | DCM&BA | 28.74 ± 1.64 | 49.83 | 42.93 ± 9.69 | 121.11 ± 3.61 |
| Formulation 2 | EA&BA | 29.7 ± 1.11 | 58.32 | 53.93 ± 5.27 | 105.49 ± 8.63 |
| Formulation 3 | EA&BA | 29.57 ± 1.75 | 65.08 | 44.32 ± 2.07 | 68.56 ± 1.52 |
| Vivitrol® | – | 33.50 ± 1.43 | 50.21 | 58.46 ± 6.01 | 108.49 ± 1.52 |

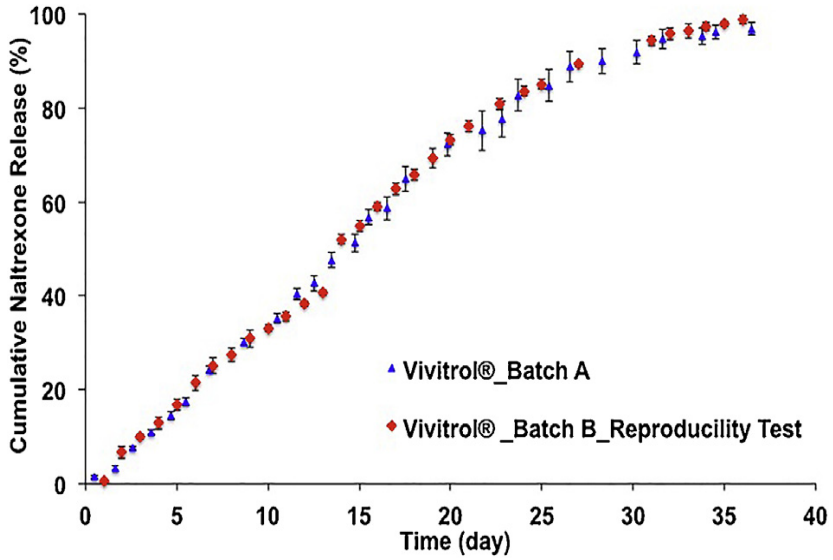
Ref. : International Journal of Pharmaceutics 520 (2017) 79–85



# PLGA Microspheres

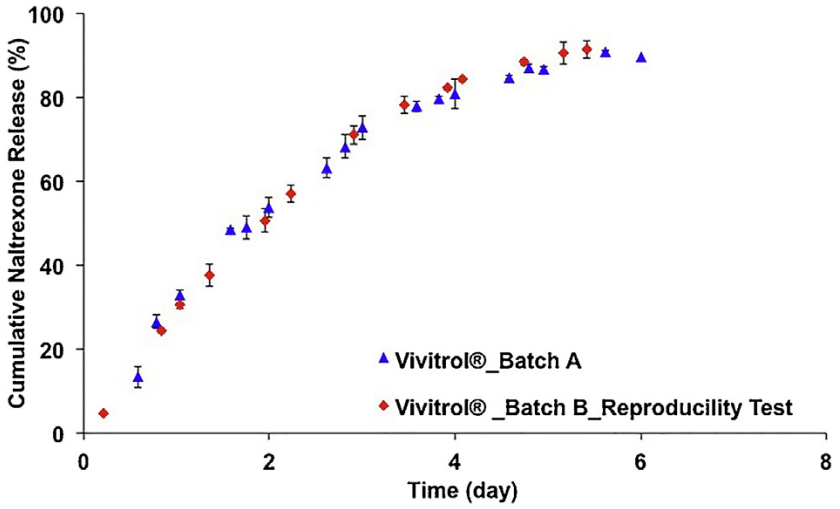
## Accelerated In-vitro Release Testing Method for Naltrexone loaded PLGA Microspheres Vivitrol

### Real-time Release Profile




In vitro release profiles of different batches of Vivitrol1 in 10 mM PBS (pH 7.4) containing 0.02% (v/v) Tween 20 and 0.02% (w/v) sodium azide obtained using the USP apparatus 4 method (n = 3) **at 37 C.** The dissolution medium was replaced every 5 day

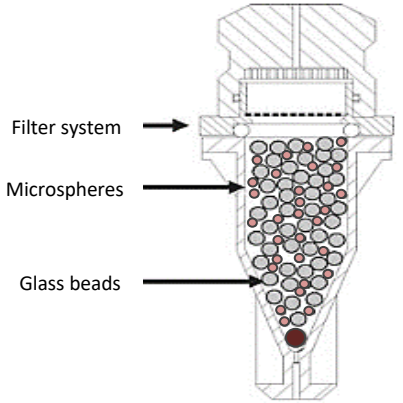
### Accelerated Release Profile




In vitro release profiles of different batches of Vivitrol1 in 10 mM PBS (pH 7.4) containing 0.02% (v/v) Tween 20, 0.02% (w/v) sodium azide and **0.0625% (w/v) sodium ascorbate** obtained using USP apparatus 4 **at 45 C** (n = 3).

### USP 4 Method

- System - Closed Loop
- Sample loading - 10 mg Microspheres mixed with 1mm Glass beads
- Flow – 8 mL/min
- Volume – 50 mL
- Temp – 37°C for Real Time
  45°C for Accelerated
- Sampling – 1 mL (replacement)

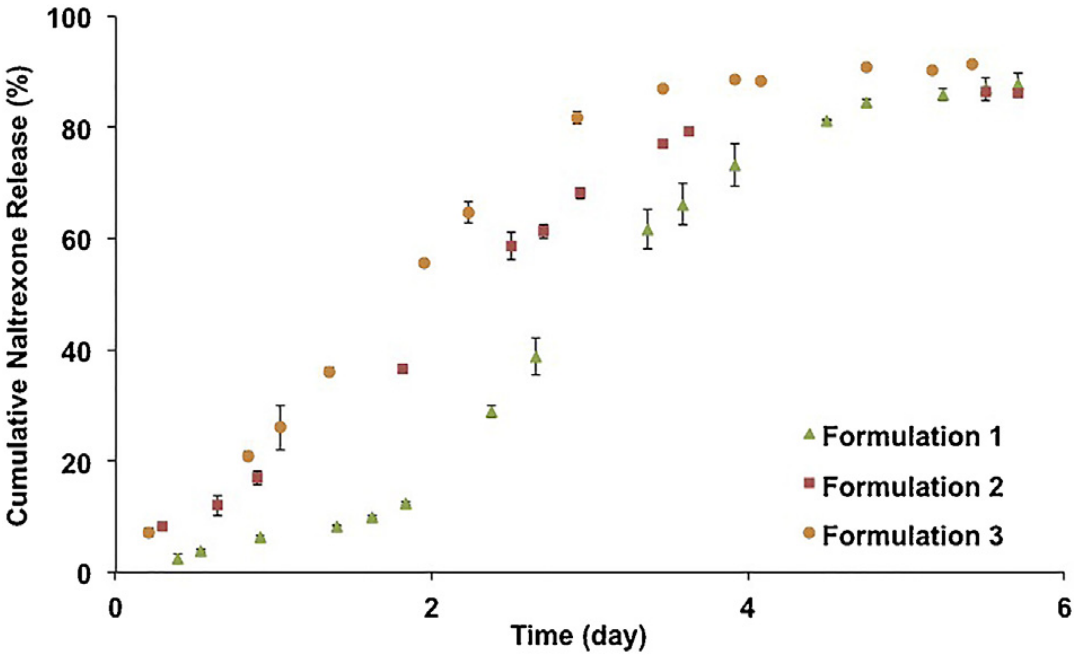



Ref. : International Journal of Pharmaceutics 520 (2017) 79–85

# PLGA Microspheres

## Discriminative Method

**Accelerated Release Profile**




In vitro release profiles of the prepared Naltrexone microspheres in 10 mM PBS (pH 7.4) containing 0.02% (v/v) Tween 20, 0.02% (w/v) sodium azide and 0.0625% (w/v) sodium ascorbate using USP apparatus 4 at 45 C (n = 3).

Ref. : International Journal of Pharmaceutics 520 (2017) 79–85

**Conclusion**

- A reproducible accelerated release testing method with discriminatory ability was developed using USP apparatus 4 for compositionally equivalent Naltrexone loaded polymeric micro- spheres with manufacturing differences for the first time.
- The degradation of Naltrexone was prevented using frequent media replacement and anti-oxidant containing media during “real-time” and accelerated release testing, respectively.
- The accelerated in vitro release profiles of Naltrexone microspheres correlated well with their respective “real-time” release profiles, indicating that the drug release mechanism(s) may be similar under both release testing conditions.
- Overall, the developed accelerated USP apparatus 4 release testing method has demonstrated the potential of being a fast quality control tool that will assure the product performance as well as assist the product development of parenteral Naltrexone polymeric microspheres