DISSOLUTION TESTING IN PRODUCT DEVELOPMENT

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APPLICATION OF IN VITRO DISSOLUTION TESTING

- IN PRODUCT DEVELOPMENT
- FINISHED PRODUCT TESTING
- SURROGATE FOR IN VIVO STUDY
- “BIOWAIVERS”
APPLICATION OF IN VITRO DISSOLUTION TESTING

- Quality control Procedure
- To Select Candidate Formulation
- Compliance of Guidelines set in SUPAC and ICH
- To Identify Critical Manufacturing Variables
- To Simulate Food Effect on Bioavailability
- In Vitro In Vivo Correlation IVIVC
- Surrogate for In Vivo Study
- “Biowaivers”
GUIDING PRINCIPLES

Avoid unnecessary

- Proliferation of equipment
- Complex method design
- Modifications of compendial equipment
- Development or use of alternative equipment
PRODUCT DEVELOPMENT
VS
QUALITY CONTROL

Product Development
• Discriminating
• Focus on elucidating the release mechanism
• Attempt to simulate in vivo environment
• May be impractical for routine Quality control

Quality control
• Test the key performance indicators of the formulation
• Robust
• Reproducible
DISSOLUTION TEST CONSIDERATIONS

• Apparatus selection
• Agitation (HYDRODYNAMICS)
• Composition of the dissolution medium
• Temperature
SUMMARY OF THE PRESENTATION

• Dissolution test Apparatus - Why so many

• Dissolution media - and test objective

• Release Kinetics Analysis

• Dosage Forms - Selection of optimal apparatus and conditions

• Case studies
ORAL DRUG ABSORPTION

- **Gastric Emptying**
- **Transit**
- **Dissolution**
- **Permeation**
- **Dissolution**
- **Metabolism**
IN VIVO AND IN VITRO RELATIONSHIP

LIMITS TO ORAL DRUG ABSORPTION

- DISSOLUTION LIMITED
- SOLUBILITY LIMITED
- PERMEABILITY LIMITED
## LIMITS TO ORAL DRUG ABSORPTION

<table>
<thead>
<tr>
<th>Rate-limiting Steps</th>
<th>Conditions</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Dissolution limiting | $T_{diss} > 199\text{ min}$  
$P_{eff} > 2 \times 10^{-4}\text{ cm/sec}$  
$D_{abs} >> \text{Dose}$ | The absolute amount of absorbed drug increases with the increased dose. |
| Permeability limiting | $T_{diss} < 50\text{ min}$  
$P_{eff} < 2 \times 10^{-4}\text{ cm/sec}$  
$D_{abs} >> \text{Dose}$ | The absolute amount of absorbed drug increases with the increased dose. |
| Solubility limiting | $T_{diss} < 50\text{ min}$  
$P_{eff} > 2 \times 10^{-4}\text{ cm/sec}$  
$D_{abs} < \text{Dose}$ | The absolute amount of absorbed drug does not increase with the increased dose. |

(Yu, Pharm. Res. 16:1884-1888 (1999))
DRAWBACKS of USP APPARATUS I & II

USP Apparatus I
- Gummy substances clog basket screen
- Very sensitive to dissolved gases
- Inadequate flow characteristics for low and high density particles

USP Apparatus II
- Coning results in non homogeneity
- Tablet location in vessel affects dissolution results
  - Hydrodynamic variability
- Size and shape of sinkers can disturb the cone – erratic results

Maintain Sink Condition ?????
OVERCOMING CONING

Schematic of perturbation study demonstrating the existence of dead zone at the bottom of the USP vessel

Peak Vessel
MAINTAINING SINK CONDITIONS

Ct << 0.15Cs

STRATEGIES TO INCREASE DISSOLUTION MEDIUM VOLUME
MAINTAINING SINK CONDITIONS
USP APPARATUS-IV - FLOW THROUGH

MECHANISM OF FLOW THROUGH CELL

Filter Chamber  Sampling Port
Dosage Form  
Holder  
Glass Beads  
Pump

IDEAL FOR DRUGS EXHIBITING POOR SOLUBILITY
Hydrodynamics in the USP apparatus II shows that the device is highly vulnerable to mixing problems that can affect testing performance and consistency.

Fig. 1. Two-dimensional, time-averaged CFD velocity fields for (a) \( Re = 4688 \), and (b) \( Re = 9375 \).

Fig. 2. Distribution of strain rates for \( Re = 4688 \) (a) in the fluid, (b) along the wall, depicted from a bottom view of the dish, (c) along the wall, depicted from a side view of the entire vessel; and for \( Re = 9375 \), (d) in the fluid, (e) along the wall, depicted from a bottom view of the dish, (f) along the wall, depicted from a side view of the entire vessel.
USP APPARATUS-III
RECI PROCAT ING CYLINDER

ALTERING HYDRODYNAMICS
THE NEED FOR USP APPARATUS III & VII

HYDRODYNAMICS

USP APPARATUS-III
RECIPROCATING CYLINDER

Mimics changes in physiochemical conditions and mechanical forces experienced by products in the GIT
USP APPARATUS-III & VII

Also facilitate sequential alteration of:

- pH
- Osmolarity
- Anions, cations
- Viscosity
- Buffers
- Surface active agents
- Degree of agitation

TO HELP ACHIEVE THE GOAL OF IVIVC
MEDIA TO SIMULATE THE FASTED AND FED STATE

• Water

• Compendial Dissolution Media

• Simulated Gastric Fluid

• Simulated Intestinal Fluid

• Compendial Media Simulating the Fed State
SIMULATE
pH conditions in the stomach or small intestine

DO NOT REPRESENT
Composition of the GI contents
Osmolarity, Ionic strength, Viscosity, Surface tension

CANNOT SIMULATE
The influence of food ingestion on drug release
BIORELEVANT MEDIA

✓ Useful for qualitative forecasting of formulation and food effects
✓ Can provide a more accurate simulation of pharmacokinetic profiles
✓ Have a great impact on the pharmacokinetic studies performed to optimize dosing conditions and product formulation
✓ Could be used to assess bioequivalence of post-approval formulation changes in certain kinds of formulations
<table>
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<tr>
<th></th>
<th>FaSSGF pH 1.6</th>
<th>FeSSGF pH 5</th>
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<tbody>
<tr>
<td>Sodium taurocholate</td>
<td>80 μM</td>
<td>NaCl</td>
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<tr>
<td>Lecithin</td>
<td>20 μM</td>
<td>Acetic acid</td>
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<tr>
<td>Pepsin</td>
<td>0.1 mg/ml</td>
<td>Sodium acetate</td>
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<tr>
<td>NaCl</td>
<td>34.2 mM</td>
<td>Milk / acetate buffer</td>
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<tr>
<td>HCl conc. qs ad pH 1.6</td>
<td>1 l</td>
<td>HCl conc. qs ad pH 5.0</td>
</tr>
<tr>
<td>Deionized water ad</td>
<td>1 l</td>
<td>1 l</td>
</tr>
<tr>
<td>pH</td>
<td>1.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Osmolality (mOsmol/kg)</td>
<td>120.7 ± 2.5</td>
<td>Osmolality (mOsmol/kg)</td>
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<tr>
<td>Buffer capacity (mEq/pH/L) –</td>
<td></td>
<td>Buffer capacity (mEq/pH/L)</td>
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<tr>
<td>Surface tension (mN/m)</td>
<td>42.6</td>
<td></td>
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<tr>
<td></td>
<td>FeSSIF</td>
<td>FaSSIF</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Sodium taurocholate</td>
<td>3 mM</td>
<td>Sodium taurocholate</td>
</tr>
<tr>
<td>Lecithin</td>
<td>0.75 mM</td>
<td>Lecithin</td>
</tr>
<tr>
<td>NaH$_2$PO$_4$</td>
<td>3.438 g</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>NaCl</td>
<td>6.186 g</td>
<td>NaCl</td>
</tr>
<tr>
<td>NaOH pellets</td>
<td>qs ad pH 6.5</td>
<td>NaOH pellets</td>
</tr>
<tr>
<td>Deionized water</td>
<td>qs ad 1 litre</td>
<td>Deionized water</td>
</tr>
<tr>
<td>pH</td>
<td>6.5</td>
<td>pH</td>
</tr>
<tr>
<td>Osmolality [mOsmol/kg]</td>
<td>~ 270</td>
<td>Osmolality [mOsmol/kg]</td>
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<tr>
<td>Buffer capacity [mEq/pH/L]</td>
<td>~ 12</td>
<td>Buffer capacity [mEq/pH/L]</td>
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<tr>
<td>Surface tension [mN/m]</td>
<td>54</td>
<td>Surface tension [mN/m]</td>
</tr>
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</table>
MUCRS

Minitab®

RINGCAP TECHNOLOGY

ADVANCED ORAL DDS

AdvaTab® (ODT)

OSDRC® OptiDose™

Diffutab™
NOYES-WHITNEY EQUATION

\[
\frac{dC}{dt} = \frac{DS}{Vh} (C_S - C_t) \quad \ldots \ldots \ldots \ldots \quad \text{Noyes & Whitney equation}
\]

- \( \frac{dC}{dt} \): Rate of dissolution
- \( S \): Surface area
- \( (C_S - C_t) \): Concentration driving force.
- \( C_S \): Equilibrium solubility of the solute at the experimental temperature.
- \( C_t \): Concentration at time \( t \)
- \( V \): Volume of the dissolution medium
- \( D \): Diffusion coefficient
- \( h \): Diffusion layer thickness
KINETICS OF DRUG RELEASE FROM CONTROLLED RELEASE FORMULATION

- **Statistical methods:**
  1. Exploratory data analysis method
  2. Repeated measures design
  3. Multivariate approach [MANOVA: multivariate analysis of variance]

- **Model dependent methods:**
  1. Zero order
  2. First order
  3. Higuchi
  4. Korsmeyer – Peppas
  5. Hixson Crowell
  6. Baker-Lonsdale
  7. Weibull
  8. Gompertz
  9. Hopfenberg

- **Model independent methods:**
  1. Difference factor \(f_1\)
  2. Similarity factor \(f_2\)
This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc.
This is used to describe absorption and/or elimination of some drugs.

\[ \frac{dC}{dt} = -Kc \]

Where;
- \( K \) is first order rate constant expressed in units of time\(^{-1}\).

Equation can be expressed as:
\[ \log C = \log C_0 - \frac{Kt}{2.303} \]

Where;
- \( C_0 \) is the initial concentration of drug,
- \( k \) is the first order rate constant, and \( t \) is the time.

• Note:
The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of \(-K/2.303\).

This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.
HIGUCHI MODEL

\[ f_t = Q = \sqrt{D\delta/\tau(2C - \delta Cs)} Cs \ t \]

Where,

- \( D \) is the diffusion coefficient of the drug molecule in the solvent.
- \( \delta \) is the porosity of the matrix.
- \( \tau \) is the tortuosity of the matrix.

To study the dissolution from a planar heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, the expression is given by equation.
Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system equation.

\[
\frac{M_t}{M_\infty} = Kt^n
\]

where;

\( M_t / M_\infty \) is a fraction of drug released at time \( t \),

\( k \) is the release rate constant and \( n \) is the release exponent.

\( n \) value is used to characterize different release for cylindrical shaped matrices

- 0.45 ≤ \( n \) corresponds to a Fickian diffusion mechanism.
- 0.45 < \( n <0.89 \) to non-Fickian transport.
- \( n = 0.89 \) to Case II (relaxational) transport.
- \( n > 0.89 \) to super case II transport.

This equation has been used to the linearization of release data from several formulations of microcapsules or microspheres.
For comparison of in vitro dissolution profiles, similarity and difference factors are emphasized by US FDA.

- **Similarity Factor \( f_2 \):**
  - The similarity factor should be between 0 and 100.
  - It is 100 when two comparative groups of reference and test are identical and approaches 0 as the dissimilarity increases.
  - Similarity factor \( > 50 \) indicates comparable profiles.

- **Difference factor \( f_1 \):**
  - \( F1 < 15 \) indicates similarity in profiles.
  - The dissolution profiles can be compared only when the number of dissolution units used are equal to or greater than 12. The similarity factor should be computed from the average mean dissolution data of 12 units. The mean data for comparison can be used only if the coefficient of variation at the first time point is NMT 20%, and NLT 10% at the rest of time intervals.
  - For accurate calculation of similarity factor, statistical approach of establishment of confidence intervals, to determine whether the reference and test are statistically significant or not may be used.
DISSOLUTION TESTING FOR VARIOUS FORMULATIONS

- Suspensions
- Orally disintegrating tablets
- Chewable tablets, Chewing gums
- Transdermal patches
- Semisolid topical preparations
- Suppositories
- Implants
ORAL SUSPENSIONS

• APPARATUS - USP II
• Method
• Shaking or mixing.
• Sample introduction-
  • accurate, precise, and reproducible
• Agitation Rate
  • on the basis of the viscosity and composition of the suspension matrix.
  • should facilitate discrimination between batches with different release properties.
  • For low-viscosity suspensions, a slow agitation rate of 25 rpm is generally
  • for high-viscosity samples faster agitation rate such as 50 or 75 rpm to prevent
    sample mounding at the bottom of the vessel

Ideally, sample weight/volume should reflect a typical dose of the product. However, testing a partial dose— for instance, ≥10% to 20% of the usual product dose—is recommended rather than using a surfactant TO MAINTAIN SINK.
• **APPARATUS - USP II**
• **Method**
• **Agitation Rate**
  • Should facilitate discrimination between batches with different release properties.
  • 50RPM
  • Higher agitation rates may be necessary in the case of sample mounding.

• **Disintegration test as substitute - Discriminating**
• **Taste Masking**
  • A dissolution criterion (typical example: ≤10% dissolved in 5 minutes) would largely depend on the taste intensity of the drug and may enable the in vitro evaluation of the taste-masking properties while avoiding organoleptic measurements.
  • Multipoint profile in neutral medium
• **Challenge**
  • Floating particles/granules
CHEWABLE TABLETS

• Same as that used for regular tablets.
• Based on the possibility that a patient might swallow the dosage form without proper chewing,
• The nondisintegrating nature of the dosage form, it may be necessary to increase the agitation rate and increase the test duration
• The reciprocating cylinder (USP apparatus 3) with the addition of glass beads may also provide more "intensive" agitation
• Mechanical breaking of chewable tablets prior to exposing the specimen to dissolution testing could be considered
Transdermal Patches
A distance of 25 + 2mm between the paddle blade and the surface of the disc assembly is maintained during the test. Temperature: 32+0.5°C
USP APPARATUS-VI
ROTATING CYLINDER

USP APPARATUS 6
ROTATING CYLINDER

SPECIAL CYLINDER USED
TYPICAL VOLUME 900ml
USEFUL FOR
TRANSDERMAL PATCH

CYLINDER
WITH
REMOVABLE
ADAPTER
FOR LARGER
SYSTEMS

ADAPTER

DOSAGE FORM
PATCH IS GLUED TO
THE OUTSIDE SURFACE
OF THE CYLINDER
Carefully apply the adhesive-coated side of the system to the exterior of the cylinder with the long axis of the system fitting around the circumference of the cylinder.
• Method of choice for transdermal patches
• Reproducible
• Patch is prevented from floating
• Proper positioning of the patch so that the drug-loaded surface is exposed to the medium.
• The medium pH 5 to 6, reflects physiological skin conditions
• Temperature is typically set at 32°C
• PhEur considers 100 rpm a typical agitation rate
• Also allows for testing an aliquot patch section (sink condition)
• Provided that cutting a piece of the patch is validated to have no impact on the release mechanism
Apparatus VII

Reciprocating Holder

Useful for:
- Transdermal Patches
- Solid Dosage
- pH Profile
- Small Volume

Modifications:
- Volume 20 - 200ml
- Dosage Form Holder

Reciprocating Holders

- Disk
- Cylinder
- Pointed Rod
- Spring Holder
- Angle Disk

Spring may be replaced with a nylon mesh cloth
• Creams, ointments, and gels.
• Franz cell diffusion system with a synthetic membrane with optional support membrane
• Receptor medium may need to contain alcohol and/or surfactant
• Deaeration is critical to avoid bubble formation at the interface with the membrane
• The test temperature is typically set at 32°C to reflect the usual skin temperature.
• Vaginal creams may be tested at 37°C.
• Full or partial dose rather than adding a surfactant or alcohol to the receptor medium in order to obtain sink conditions.
• No compendial apparatus, procedures, or requirements for in vitro release
• For hydrophilic suppositories that release the drug by dissolving in the rectal fluids, the basket, paddle, or flow-through cell can all be used.

• For lipophilic suppositories
  • a modified basket method
  • a paddle method with a wired screen and a sinker
  • a modified flow-through cell with a specific dual chamber suppository cell have all been recommended.
  • No single test method will be suitable for all suppository formulations.
  • However, when starting development of an in vitro dissolution/release test, it might be advantageous to begin with the basket or paddle in the case of hydrophilic and with the modified flow-through cell in the case of lipophilic suppositories.
• The compendial and the modified flow-through cell have been used successfully for implants
• Static or rotating bottles have also been used for in vitro release testing.
• Flow-through apparatus with low volume of fluid, slow flow rate
• Intermittent flow might also be an option.
• As tests are often run over a long time period (e.g., several weeks to months), measures have to be taken to compensate against evaporation.
• Suitable preservatives may be added to prevent microbial contamination
• The osmolarity, pH, and buffer capacity of the with lower buffer capacity.

• **Main challenges**
  • to determine the appropriate duration of the test
  • times at which samples are to be drawn
  • The possibility of running the test under accelerated conditions (temperatures even above glass transition temperatures of the polymers involved) and at pH values offering faster drug release
CASE STUDIES

- Pulsatile Release
- Discriminating medium
- Generic CR formulation
- F1 and F2
- IVIVC
- Implants
DISCRIMINATING MEDIUM

POLYMORPHS

The graph shows the dissolution rate of two forms (Form I and Form II) over time. Form II dissolves at a faster rate compared to Form I. The y-axis represents the percent dissolved, ranging from 0 to 120%, while the x-axis represents time in minutes, ranging from 0 to 60 minutes.
ACCUDEP - PULSATILE
OSMOTIC DRUG DELIVERY SYSTEMS  
F1 AND F2

F2 > 50

F1 < 15
IN VIVO BIOEQUIVALENCE: IVIVC

**Dissolution Profiles**

- Regular
- Fast
- Slow

**Fraction Absorption Profiles**

- Regular
- Fast
- Slow

$r^2 = 0.97$
DOX LIPOMER

ZERO ORDER RELEASE

Constant Dox Concentration

Zero Order Release
Fig. 1. In vitro release profile of Dox solution, Dox-Gantrez ionic complex and PGDS (Polyglyceryl -6 Distearate) based Dox-LIPOMER in (A) acetate buffer pH 4.5 and (B) demineralized water, NaCl (0.15M) solution and CaCl2 (0.05M) solution (mean ± S.D.; n = 3)
IMPLANT – DEVELOPMENT VS QC

IN HOUSE METHOD

**DISSOLUTION PARAMETERS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Dissolution Medium</td>
<td>Phosphate Buffer pH 7.4 with 0.5% SLS</td>
</tr>
<tr>
<td>Dose</td>
<td>5mg</td>
</tr>
<tr>
<td>Temperature</td>
<td>37 °C</td>
</tr>
<tr>
<td>Time points</td>
<td>0.5, 1, 2, 4, 8, 12, 24, 48, 72h</td>
</tr>
<tr>
<td>Aliquot sample</td>
<td>1mL</td>
</tr>
</tbody>
</table>

extensor digitorum muscle of *gallus gallus domesticus*
P-SMEDDS showed sustain release of ART as compare to SMEDDS and ART solution

However method not adaptable for QC
CONCLUSION

• COMPREHENDING THE PURPOSE OF A DISSOLUTION TEST AND IDENTIFYING THE RIGHT APPARATUS AND METHOD CONTINUES TO BE AN AREA OF INTENSE RESEARCH PARTICULARLY FOR NEW DELIVERY SYSTEMS

• CUSTOMIZING NEEDS FOR DEVELOPMENT COULD POSE NUMEROUS CHALLENGES
MY RESEARCH GROUP
THANK YOU