Advances in BA/BE and Dissolution Methodology

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Product Research Advances

• Gastrointestinal Processes
  – pH, Buffer Capacity, Motility
  – Enteric Coating

• Gastrointestinal Simulator (GIS)
  – In vivo Predictive Dissolution (iPD)

• In Vivo Plasma Level Variability
Gastrointestinal Prediction

Required Accurate Input
Ongoing Studies

DIRECT AND SIMULTANEOUS DRUG MEASUREMENT: PLASMA AND INTESTINE (NORMAL SUBJECTS, BE PROTOCOL)
1) Gastrointestinal Concentrations

2) Motility Contractions

- Stomach
- Duodenum
- Proximal Jejunum
- Mid Jejunum
- Distal Jejunum

Time

Concentration
Gastrointestinal Motility: Fasted
Combined Models Prediction
Luminal GI Ibuprofen (solution)

Ibuprofen Present in the Intestine for 7 hrs.
Ibuprofen is in the intestine for 7 hours
Yet Dissolves in 10 minutes (USP)
Dissolution of Clinical Dosage form
(800 mg Dr. Reddy’s Reference Listed Drug(RLD))

800mg intact tablet dissolution in pH 6.5, 10 mM HCO₃ buffer (15% CO₂ & total buffer concentration of 14 mM). USP 2 apparatus, 50 rpm & 37 °C

<table>
<thead>
<tr>
<th>Bulk Volume, ml</th>
<th>Extent of dissolution</th>
<th>Time to dissolve 50% dose, min</th>
<th>Time to 100%, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>105%</td>
<td>13</td>
<td>80</td>
</tr>
<tr>
<td>900</td>
<td>102%</td>
<td>10</td>
<td>60</td>
</tr>
</tbody>
</table>

**Dissolution in pH 7.2 50 mM Phosphate Buffer (900 mL)**

![Graph showing dissolution in pH 7.2 50 mM Phosphate Buffer (900 mL)]

100% dissolved ≈ 10 min

USP Test: pH =7.2 50mM Phosphate 50 RPM paddle (Apparatus 2) Not Less Than 80% dissolved in 60 min
USP Simulated Intestinal Fluid

Table 4: Osmolarity, ionic strength and buffer capacity of the two buffers

<table>
<thead>
<tr>
<th>Medium</th>
<th>Osmolarity [mOsmol/kg]</th>
<th>Ionic strength [mol/L]</th>
<th>Buffer capacity [mEq/L/pH unit]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulated Intestinal Fluid, pH 6.8 (SIFsp); USP 26</td>
<td>113</td>
<td>0.0720</td>
<td>18.4±0.2</td>
</tr>
<tr>
<td>Phosphate Standard Buffer pH 6.8 (IntPh 3)</td>
<td>115</td>
<td>0.0753</td>
<td>18.6±0.1</td>
</tr>
</tbody>
</table>
Low Dose ASPIRIN
Drug Resistance and Pseudoreistance: An Unintended Consequence of Enteric Coating Aspirin

Running title: Groesser et al.; Aspirin Resistance and Pseudoresistance

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Asian population. Importantly, our findings support the use of lower BMI cutoffs to define obesity in Asian adults, by demonstrating the prevalence of LV structural and functional changes even at these lower cutoffs. Furthermore, lower BMI thresholds may be needed for public health action (e.g., encouraging weight loss and exercise) in Asian communities, and particularly among Asian women who have a lower BMI threshold for substantial LV contractile dysfunction and ejection fraction than WH. The implications of these findings for the development of future heart failure diagnoses further study, particularly heart failure with preserved ejection fraction, which is increasingly recognized to include an obesity-related phenotype (2).

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A major finding in this study is an independent predictor of the WH vs. WH obesity definition of obesity, particularly in Asian populations. Our data support the use of lower BMI thresholds to define obesity in Asian adults, which may have implications for public health actions and clinical practice.

REFERENCES
1. The Cardiac ARzT Consensus. Appropriate body-mass index for adult popula
Figure 2. Dissolution Profiles of Bayer EC Aspirin 325 mg Tablets at pH 6.8 (mean±SD)
Small intestine as a flow through cell

In vitro flow cell

Differential profile

$\phi = \text{fluid flow}$

$C \cdot \phi \cdot \Delta t = \text{Amount}$

In vivo flow cell

Differential profile

$\phi = \text{fluid flow} = "1"$

$C \cdot \phi \cdot \Delta t = \text{Amount}$

Cumulative profile

$F_{\text{diss}}(t) = \sum_{0}^{t} \left( \frac{\text{Amount}}{\text{Dose}} \right)$

$F_{\text{abs}}(t) = \sum_{0}^{t} \left( \frac{\text{Amount}}{\text{Amount}_{\text{max}}} \right)$

H₂O secretion

H₂O absorption

Facts

$\sum_{0}^{t} (\text{Amount} / \text{Dose})$

$\sum_{0}^{t} (\text{Amount} / \text{Amount}_{\text{max}})$
In Vivo Dissolution and Systemic Absorption of Immediate Release Ibuprofen in Human Gastrointestinal Tract Under Fed and Fasted Conditions

Koenigsknecht et.al., 2017
Human Gastrointestinal Tract
Product Research (FDA)

• Measure Gastrointestinal Mechanism
  – Buffer Capacity
  – Buffer is Bicarbonate
• Motility State is a Random Variable
  – Requires a Stochastic Process
  – MRI Development
• Ultimately Reduce BE Variability
• Capture in a GIS Dissolution Methodology