INTEGRATED DRUG DEVELOPMENT PROCESS
July 17-19, 2006
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• Developability Assessment Supporting Drug Candidate Selection
  • Profiling of key Physicochemical Properties
  • Biopharmaceutical Assessment

• Preformulation
  • Solubility, Stability, Dissolution Rate and Solid State Properties
  • Salt and Form Screening and Selection
  • Excipient Compatibility

• Dosage Form Design
  • Conventional
  • Non- Conventional

• Formulation Development, Evaluation and Scale-up

• Equipment and Processing

• Regulatory Considerations
FORMULATION DEVELOPMENT AND EVALUATION

• Drug Substance
  In-Silico
  Physiochemical

• Excipients
  Functionality

• Formulation Design
  Art, Trial and Error
  Expert Systems
  Artificial Intelligence

• Formulation Evaluation
  In-vitro
  In-Vivo
FORMULATION DEVELOPMENT AND EVALUATION
Calculated Intrinsic Solubility

Calculated vs. exp. Log1/WS with
Syracuse program (N=33)

\[ R^2: 0.62 \]

Calculated vs. exp. Log1/WS with
Camelot (N=33)

\[ R^2: 0.14 \]
FORMULATION DEVELOPMENT AND EVALUATION
Calculated Ionization Constants

Calculated vs. exp. pKa with Pallas
(N=172/100)

Calculated vs. Exp. pKa with ACD
(N=171/99)

R²: 0.68
SE: 1.82
Slope: 0.85
Intercept: 1.07

R²: 0.88
SE: 1.08
Slope: 0.94
Intercept: 0.23
FORMULATION DEVELOPMENT AND EVALUATION

Calculated logP

Calculated vs. Exp. logP with Camelot (N=100)

- R²: 0.78
- SE: 1.11
- Slope: 1.10
- Intercept: -0.09

Calculated vs. Exp. logP with MedChem clogP (N=92)

- R²: 0.46
- SE: 1.25
- Slope: 0.62
- Intercept: 1.25
FORMULATION DEVELOPMENT AND EVALUATION
ER Simulation: Hypothetical Compound

Plasma Concentration-Time

Absorption Profile with Colon Absorption
Absorption Profile No Colon Absorption
FORMULATION DEVELOPMENT AND EVALUATION
Physical Stability - Particle Size

SEMs of two formulations following 2wks 5/40°C cycling
FORMULATION DEVELOPMENT AND EVALUATION
pH-Solubility Profile

Maleate counter ion
25°C
$S_0 = 0.002 \text{ mg/mL}$
$pK_a = 6.3$
$pH_{max} \sim 3.35$

Theoretical
Free Base
Maleate Salt
FORMULATION DEVELOPMENT AND EVALUATION
Solution State - pH Rate Profile

- 70°C
- \( I = 0.1 \text{M} \)
- \([\text{Drug}] = 0.06 \text{ mg/mL}\)
- pH2: maleate buffer
- other pHs: citrate buffer
- 20% CH\(_3\)CN in pH6

- \( k_{pH=3.5} / k_{pH=2.0} = 3 \)
- \( k_{pH=4.5} / k_{pH=2.0} = 12 \)
- \( k_{pH=6.0} / k_{pH=2.0} = 15 \)
FORMULATION DEVELOPMENT AND EVALUATION

XRDPD Besylate Salt (Effect of Milling)
FORMULATION DEVELOPMENT AND EVALUATION
Haloperidol: Intrinsic Dissolution Rate (IDR) of Base

Intrinsic dissolution of haloperidol base

- pH 2.05
- pH 3.08
- pH 1.1
- pH 5.0
FORMULATION DEVELOPMENT AND EVALUATION
Excipient Compatibility: HPLC

| Ingredients          | Formulation Range (%) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|----------------------|-----------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Drug Substance       | 5-50                  | ND|ND|ND|ND|ND|ND|ND|ND|0.1|ND|ND|ND|ND|ND|ND|ND|ND|ND|ND|ND|
| Lactose              | 30-80                 |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Mannitol             | 30-80                 |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Avicel               | 10-80                 |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Starch 1500          | 10-50                 |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Mg St                | 0.5-2                 |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Stearic ac.          | 2-5                   |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Cutina               | 2-4                   |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Crospovidone         | 2-5                   |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Croscarmellose Na    | 2-5                   |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Na starch glycolate  | 2-8                   |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| CSD                  | 0.1-0.5               |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Talc                 | 1-10                  |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Povidone             | 0.5-5                 |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| HPMC                 | 2-5                   |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| HPC                  | 2-5                   |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |
| Gelatin Capsule      |                       |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |

1% drug loading, 50°C wet and dry conditions
FORMULATION DEVELOPMENT AND EVALUATION
Particle Size Effect

![Graph showing the effect of particle size on degradation product over time. The graph plots % Degradation product (w/w) against Time (Days). Three lines represent different particle sizes: A-9µm, B-14µm, and C-31µm.](image)
FORMULATION DEVELOPMENT AND EVALUATION

Excipients

• Functionality
  – Fillers
  – Binders
  – Disintegrants
  – Lubricants
  – Wetting Agents
  – Stabilizers
  – Absorption Enhancers
  – PgP Efflux Inhibitors
  – Flavors, Colorants
  – Coatings
FORMULATION DEVELOPMENT AND EVALUATION

Excipients

• May Comprise <10% to >99.9% of Pharmaceutical Products

• Insufficient Attention Paid to Excipient Functionality
  – Stability
  – Processing
  – Dissolution
  – Cost of Goods
FORMULATION DEVELOPMENT AND EVALUATION

Excipients

- New excipients are rare

- About 200 excipients for several thousands NCEs
  - Limited choice
FORMULATION DEVELOPMENT AND EVALUATION

Excipients

• Stability
  – Direct chemical interactions
  – Crystallinity
  – Hygroscopicity
  – Particle size
  – Binding of drug to excipients
  – Microenvironmental effects (sorbed moisture layer, pH)
FORMULATION DEVELOPMENT AND EVALUATION
Excipients

sorbed layer

Microenvironmental pH
FORMULATION DEVELOPMENT AND EVALUATION

pH Effects of Excipients on Solid State Stability

Effect of acids (2.5% w/w) on the percent of degradation products (a) XY459 and (b) SJ459 in blends after 8 weeks at 40°C/75% RH.

FORMULATION DEVELOPMENT AND EVALUATION
Excipients

• Processing
  – Powder flow
  – Compressibility
  – Compactibility
# FORMULATION DEVELOPMENT AND EVALUATION

**Excipients**

<table>
<thead>
<tr>
<th>Substance</th>
<th>d (g/ml)</th>
<th>Bulk Density</th>
<th>Tapped Density</th>
<th>MP (°C)</th>
<th>pH</th>
<th>Hygroscopic</th>
<th>Stable</th>
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<tbody>
<tr>
<td>Calcium carbonate</td>
<td>2.7</td>
<td>0.8</td>
<td>1.2</td>
<td>825 (d)</td>
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<td>Calcium phosphate, dibasic</td>
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<tr>
<td>Anhydrous</td>
<td>2.89</td>
<td>0.78</td>
<td>0.82</td>
<td>-</td>
<td>7.3 (20%)</td>
<td>No</td>
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<tr>
<td>Hydrate</td>
<td>2.39</td>
<td>0.92</td>
<td>1.17</td>
<td>-</td>
<td>7.4 (20%)</td>
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<tr>
<td>Calcium phosphate, tribasic</td>
<td>3.14</td>
<td>0.8</td>
<td>0.95</td>
<td>1670</td>
<td>6.8 (20%)</td>
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<td>Dihydrate</td>
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<td>Cellulose, microcrystalline</td>
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<td>0.48</td>
<td>260-270 (c)</td>
<td>5-7</td>
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<td>Yes</td>
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</table>
# FORMULATION DEVELOPMENT AND EVALUATION

## Excipients

<table>
<thead>
<tr>
<th>Substance</th>
<th>d (g/ml)</th>
<th>Bulk Density</th>
<th>Tapped Density</th>
<th>MP (°C)</th>
<th>pH</th>
<th>Hydroscopic</th>
<th>Stable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose, powdered</td>
<td>1.5</td>
<td>0.14-0.39</td>
<td>0.21-0.48</td>
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<td>4-7.5 (10%)</td>
<td>Little</td>
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<td>Dextrates</td>
<td>1.54</td>
<td>0.68</td>
<td>0.72</td>
<td>141</td>
<td>3.8-5.8 (20%)</td>
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<td>Dextrin</td>
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<td>0.91</td>
<td>178 (d)</td>
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<td>Dextrose excipient</td>
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<td>1</td>
<td>83</td>
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<td>Fructose</td>
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<td>Kaolin</td>
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<tr>
<td>Lactitol</td>
<td>1.54</td>
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<td>4.5-7 (10%)</td>
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<td>Yes</td>
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<tr>
<td>Lactose</td>
<td>1.55</td>
<td>0.62</td>
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<td>202</td>
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<tr>
<td>Substance</td>
<td>d (g/ml)</td>
<td>Bulk Density</td>
<td>Tapped Density</td>
<td>MP (°C)</td>
<td>pH</td>
<td>Hydroscopic</td>
<td>Stable</td>
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<tr>
<td>Mannitol</td>
<td>1.51</td>
<td>0.43</td>
<td>0.73</td>
<td>166-168</td>
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<td>Sorbitol</td>
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<td>0.45</td>
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<td>110-112</td>
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<tr>
<td>Starch</td>
<td>1.48</td>
<td>0.46</td>
<td>0.66</td>
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<td>5.5-6.5 (2%)</td>
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<td>Starch, pregelatinized</td>
<td>1.52</td>
<td>0.59</td>
<td>0.88</td>
<td>-</td>
<td>4.5-7.0 (10%)</td>
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<tr>
<td>Sucrose</td>
<td>1.6</td>
<td>0.6</td>
<td>0.82</td>
<td>160-186</td>
<td>(d)</td>
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<td>Sugar, compressible</td>
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<td>Sugar, confectioner’s</td>
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</table>

d = melts with some decomposition.

www.continuingeducation.com/pharmacy/complexi/table1.htm
## FORMULATION DEVELOPMENT AND EVALUATION

**Excipients - Core ISP Technologies**

<table>
<thead>
<tr>
<th>Pharma, Exipients</th>
<th>Oral Care Delivery</th>
<th>Biomedical Surfaces</th>
<th>Agricultural Delivery</th>
<th>Food &amp; Beverage</th>
<th>Detergents Dye Transfer</th>
<th>Cleaners Hard Surfaces</th>
<th>Oil Field Gas Hydrates</th>
<th>Personal Care Styling</th>
<th>Waterproof Delivery</th>
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<td>Binding, Chelation, Complexation</td>
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<td>G</td>
<td>P</td>
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<td>&quot;Smart&quot; Coatings</td>
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<td>Controlled Release</td>
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<td>G</td>
<td>P G</td>
<td>P</td>
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</tr>
</tbody>
</table>

A = Alginates; P = PVP Copolymers, PVCL Copolymers, Surfadones; G = Gantrez; MAN Copolymers
FORMULATION DEVELOPMENT AND EVALUATION
Excipients

PROSOLV™ SMCC® 50
FORMULATION DEVELOPMENT AND EVALUATION

Excipients

Particles of CSD can be seen on the surface and into the pores of the SMCC®

PROSOLV™ SMCC® 50

Emcocel® 90M
FORMULATION DEVELOPMENT AND EVALUATION

Excipients

Prosolv HD 90

PH 302
FORMULATION DEVELOPMENT AND EVALUATION
pMDI Propellants

- **Propellant** - Liquefied compressed gas (energy source)
  - Density matching of p-mixture with DS to optimize physical stability
  - Environmental pressure - CFC ozone depletion - switch from Chlorofluorocarbons (CFC) to Hydrofluoroalkane (HFA) propellants

<table>
<thead>
<tr>
<th></th>
<th>CFC-12</th>
<th>CFC-11</th>
<th>CFC-114</th>
<th>HFA134a</th>
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<td>Chemical structure</td>
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<td><img src="image2" alt="Chemical structure" /></td>
<td><img src="image3" alt="Chemical structure" /></td>
<td><img src="image4" alt="Chemical structure" /></td>
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<tr>
<td>Molecular weight</td>
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<td>137.4</td>
<td>170.9</td>
<td>102.0</td>
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<td>Boiling point (°C) @ 1atm.</td>
<td>-29.8</td>
<td>23.7</td>
<td>3.6</td>
<td>-26.5</td>
<td>-17.3</td>
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<td>Liquid density @ 20°C (g/ml)</td>
<td>1.33</td>
<td>1.49</td>
<td>1.47</td>
<td>1.21</td>
<td>1.41</td>
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<tr>
<td>Vapour pressure (psig) @ 20°C</td>
<td>67.6</td>
<td>-1.8</td>
<td>11.9</td>
<td>82</td>
<td>56</td>
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FORMULATION DEVELOPMENT AND EVALUATION

Formulation Stability

- Micro-pH
  - Effects Chemical Stability (pirenzepine dihydrochloride)
  - Effects Physical Stability, Salt to Free Form Conversion
  - Effects Dissolution (ifetroban)

FORMULATION DEVELOPMENT AND EVALUATION

Formulation Evaluation

• pH measured using indicators

  Bromocresol green  3.8 - 5.4
  Bromocresol purple 5.2 - 6.8
  Thymol blue (acidic) 1.2 - 2.8

• Within the pH range, each indicator exists in varying proportions acid/ base components
FORMULATION DEVELOPMENT AND EVALUATION
Formulation Evaluation

• Direct pH-metric method
  Involves measurement of pH of aqueous slurry

• Diffuse reflectance Spectroscopy (DRS)
  Utilizes a pH sensitive dye
  Dye UV-Vis spectrum is pH dependent
  Calibration plot of base/acid peak ratio is obtained as a function of pH in buffer solutions
  Micro pH is calculated by spectra of solid-indicator mixtures to the spectra of the indicators in solution

Surface Acidity of Solid Pharmaceutical Excipients,
FORMULATION DEVELOPMENT AND EVALUATION

Slurry pH Method

pH of Avicel PH 101

\[ y = 0.0962x + 4.1618 \]

\[ R^2 = 0.9901 \]

pH of Lactose monohydrate

\[ y = -0.0331x + 4.3501 \]

\[ R^2 = 0.9957 \]
FORMULATION DEVELOPMENT AND EVALUATION

Diffuse Reflectance Spectroscopy (DRS)
FORMULATION DEVELOPMENT AND EVALUATION

pH - Absorption Profile of Bromocresol Green

- pH = 5.75
- pH = 4.4
- pH = 3.8
## FORMULATION DEVELOPMENT AND EVALUATION

Comparison of Direct pH-metric and DRS

<table>
<thead>
<tr>
<th>Excipient</th>
<th>pH direct</th>
<th>pH DRS</th>
<th>Reported DRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCP</td>
<td>4.26</td>
<td>2.08, 2.0</td>
<td>2.23</td>
</tr>
<tr>
<td>DCP buffered</td>
<td>7.62</td>
<td>4.89, 4.81</td>
<td>5.1</td>
</tr>
<tr>
<td>MCC</td>
<td>3.89</td>
<td>3.93, 3.91</td>
<td>3.88</td>
</tr>
<tr>
<td>MCC buffered</td>
<td>7.04</td>
<td>4.79, 4.73</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### FORMULATION DEVELOPMENT AND EVALUATION
Comparison of Direct pH-metric and DRS - Cont.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>pH direct</th>
<th>pH DRS</th>
<th>Reported DRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>4.45</td>
<td>2.35, 2.08</td>
<td>3.45</td>
</tr>
<tr>
<td>Lactose buffered</td>
<td>6.71</td>
<td>4.42, 4.32</td>
<td>N/A</td>
</tr>
<tr>
<td>Mannitol</td>
<td>4.30</td>
<td>4.50</td>
<td>3.23</td>
</tr>
<tr>
<td>Kollidon</td>
<td>4.25</td>
<td>4.25</td>
<td>N/A</td>
</tr>
</tbody>
</table>
# FORMULATION DEVELOPMENT AND EVALUATION

Comparison of Novartis vs. Literature pH Values

<table>
<thead>
<tr>
<th>Excipient</th>
<th>pH Novartis</th>
<th>pH-reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCP</td>
<td>2.08, 2.0</td>
<td>2.23</td>
</tr>
<tr>
<td>MCC</td>
<td>3.93, 3.91</td>
<td>3.88</td>
</tr>
<tr>
<td>Lactose</td>
<td>2.35, 2.08</td>
<td>3.45</td>
</tr>
<tr>
<td>Mannitol</td>
<td>4.46, 4.54</td>
<td>3.23</td>
</tr>
<tr>
<td>Koloidon</td>
<td>4.6</td>
<td>4.25</td>
</tr>
</tbody>
</table>
# FORMULATION DEVELOPMENT AND EVALUATION

Comparison of Direct pH-metric and DRS

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Microenvironmental pH</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slurry</td>
<td>DRS Solid</td>
</tr>
<tr>
<td><strong>Compound</strong></td>
<td><strong>Strength</strong></td>
<td><strong>Excipients</strong></td>
</tr>
<tr>
<td>NVS5</td>
<td>50 %</td>
<td>MCC, PVP, crosp., MgSt</td>
</tr>
<tr>
<td></td>
<td>65 %</td>
<td></td>
</tr>
<tr>
<td>NVS2</td>
<td>61 %</td>
<td>MCC, crosp., CSD, MgSt</td>
</tr>
<tr>
<td></td>
<td>58 %</td>
<td>+ Lact., starch, BHA, BHT</td>
</tr>
<tr>
<td></td>
<td>55.9 %</td>
<td></td>
</tr>
<tr>
<td>NVS4</td>
<td>10</td>
<td>MCC, PVP, crosp., MgSt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ citric acid</td>
</tr>
<tr>
<td>NVS3</td>
<td>61</td>
<td>MCC, crosp., CSD, MgSt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCC, crosp., CSD, MgSt, Citric acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ Hydrogenated castor oil (instead of MgSt)</td>
</tr>
</tbody>
</table>
FORMULATION DEVELOPMENT AND EVALUATION
pH Effects on Stability (Form Change)

**Solid Phase:**
- Maleate Salt
- Free Base

**Solubility (mg/mL):**

**Drug (%):**

**pH = 2.0**

**pH = 3.5**

**pH = 4.5**

**pH = 6.0**

**Time (hours):**

**Solubility (mg/mL):**

**Drug (%):**

**pH = 2.0**

**pH = 3.5**

**pH = 4.5**

**pH = 6.0**
FORMULATION DEVELOPMENT AND EVALUATION
Effect of pH on Formulation Stability

Blends in Glass Bottles with 20% H₂O at 50°C

- Formulation (pH=4.16)
- 3% Citric Acid (pH=2.65)
- 5% Citric Acid (pH=2.56)
- 0.5% Maleic Acid (pH=2.55)
- 1% Maleic Acid (pH=2.37)
- 5% Maleic Acid (pH=2.00)
FORMULATION DEVELOPMENT AND EVALUATION

Effect of pH on Formulation Stability

Capsules, HDPE bottles no induction seal, 6 weeks at 40°C/75%RH

No mass balance issue

Total Degradation
(% increase from initial)

NO Acid
pH ~ 3.9

2% Citric
pH ~ 2.5

4% Citric
pH ~ 2.4

1% maleic
pH ~ 2.3

4 6 7 12 13 16 18 20 5 9 14 17 2 3 8 11 1 10 15 19
FORMULATION DEVELOPMENT AND EVALUATION
Formulation Evaluation
Micro pH of Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>DRS pH</th>
<th>Direct pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5% w/w Unbuffered</td>
<td>4.1</td>
<td>4.0 (50% slurry)</td>
</tr>
<tr>
<td>0.5% w/w buffered with acid</td>
<td>2.0</td>
<td>2.4 (50% slurry)</td>
</tr>
</tbody>
</table>