Performance Excipients as Tools to Promote Robust Drug Products

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Company Overview
About Avantor™

- Leading global manufacturer and supplier of high purity chemicals used in the pharmaceutical, laboratory, and electronic industries
- Over 140 years experience
- ISO 9000-certified, FDA-registered, cGMP-compliant manufacturing
- Global multi-compendia chemicals
- Several highly respected brand names, including J.T.Baker® and Macron™
- Decades-long relationships with top pharmaceutical customers

Avantor: Established Global Supplier

Notable Brands:

Global Facilities:
PHARMACEUTICAL DOSAGE FORMS

DOSAGE FORMS

SOLID ORAL  LIQUID ORAL  PARENTERAL  SEMISOLID

Tablets  Capsules  Powders  Solutions  Syrups  Suspensions  Injections  Infusions  Ophthalmic  Ointments  Creams  Gels

API EXCIPIENT CONVERGENCE

BPCs = Bulk Processed Chemicals
A = API
E = Excipient
PANEXCEA™ PERFORMANCE EXCIPIENT PLATFORM

- PanExcea™ IR (MHC300G) *Commercialized*
- PanExcea™ ODT (MC200G) *Commercialized*
- PanExcea™ Modified Release* 

PanExcea™ GR/CR
PanExcea™ CR

* In development phase

Presentation
**Need for New Unique Excipients**

*Drug Life Cycle Management*

- Improve the safety and efficacy of the drug
- Extend patent life of the drug molecule
- New indication
- New patient population

**FDA Approvals 2002 – 2009**

<table>
<thead>
<tr>
<th>Year</th>
<th>Reformulations</th>
<th>NCEs</th>
<th>Total</th>
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<tbody>
<tr>
<td>2002</td>
<td>55</td>
<td>17</td>
<td>72</td>
</tr>
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<td>2003</td>
<td>49</td>
<td>21</td>
<td>70</td>
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<td>2004</td>
<td>69</td>
<td>31</td>
<td>100</td>
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<td>2005</td>
<td>64</td>
<td>18</td>
<td>82</td>
</tr>
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<td>2006</td>
<td>77</td>
<td>18</td>
<td>95</td>
</tr>
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<td>2007</td>
<td>50</td>
<td>16</td>
<td>66</td>
</tr>
<tr>
<td>2008</td>
<td>73</td>
<td>25</td>
<td>98</td>
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<tr>
<td>2009</td>
<td>75</td>
<td>26</td>
<td>101</td>
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</table>

**PERFORMANCE EXCIPIENTS**

- Provide a synergy of functionality
- Mask undesirable properties of individual excipients
- Demonstrate better properties than a physical mixture of their components
- Have well defined, controlled physical and functional properties
- Complete Excipient or a Building Block
- Reduce formulation development complexity
- Enable implementation of the most efficient and cost-effective manufacturing process
- Reduce supply chain complexity
- Ease quality and regulatory compliance
  - Well defined design space
  - Supports QbD

**Performance Excipients Synonyms:**

Co-processed, Multifunctional, High Functionality
Challenges in Designing Performance Excipients

- Need excellent flowability/compressibility with wide range of API loading levels
- Need excellent content uniformity with a wide range of APIs
- Need to improve physical properties with no chemical change of components

Particle Engineering Technology

- Synergistic physical association of two or more conventional excipients by patented technology
- Optimized particle size for enhanced flowability
- Unique particle morphology with spherical shape
- Surface roughness for API interaction resulting in enhanced content uniformity
- Optimization of porosity/particle density
**PanExcea™ Performance Excipient Platform**

- PanExcea™ IR (MHC300G) *Commercialized*
- PanExcea™ CR/GR
- PanExcea™ ODT (MC200G) *Commercialized*

**Engineered IR Excipient**

- **Filler**: MCC
- **Binder**: HPMC
- **Disintegrant**: CPVD

Unique wet homogenization/Spray-dry granulation technology

- MCC-HPMC-CPVD spherical Engineered excipient
Particle Engineered IR Excipient

Optimization of Flow Properties

Particle Size | Control of Fines | Particle Shape

OPTIMUM PARTICLE FLOW
Flowability Comparison

Tableting study for 62.5% IBU (50um) conversion to direct compression from wet granulation

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (g)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1250</td>
<td>62.5</td>
</tr>
<tr>
<td>Engineered Excipient</td>
<td>730</td>
<td>36.5</td>
</tr>
<tr>
<td>Silica (RexCipients GL100, Huber)</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>Mg Stearate (Avantor)</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2000</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
Results

- Flowability: Excellent
- Tablet Weight: 320 mg, 10 mm
- Hardness: 13 Kp at 1600 lb Compression Force
- Friability: 0.3%
- Content Uniformity: 99.4% with RSD: 0.21%
- Dissolution 98% in less than 15 minutes
- Conversion from wet granulation to direct compression

ODT TECHNOLOGY PLATFORMS

<table>
<thead>
<tr>
<th>Technology Platform</th>
<th>Unique Features</th>
<th>Process Consideration</th>
</tr>
</thead>
</table>
| Lyophilization        | Immediate dissolution (2-10 sec)       | High cost of production
|                       |                                        | Specialized manufacturing equipment                                                  |
|                       |                                        | Specialized packaging                                                                 |
|                       |                                        | Poor physical resistance and sensitive to humidity                                     |
|                       |                                        | Low dose of water soluble drugs (60 mg)                                               |
| Molding               | Rapid dissolution (5-15 sec) High dose | High cost of production
|                       |                                        | Weak mechanical strength                                                              |
| Direct compression     | Low cost of production
|                       | Standard equipment                      | Impact of tablet size and hardness on disintegration                                   |
|                       | Good physical resistance High dose     |                                                                                        |
| Cotton candy          | Pleasant mouth feel                     | Specialized manufacturing equipment                                                  |
|                       |                                        | High temperatures used to melt the matrix limit use of heat sensitive drugs            |

Modified from Fu et al., Crit. Rev. Ther. Drug Carrier Syst., 2004
Particle Engineered ODT Excipient

- Challenge was to develop a direct compression ODT excipient

- Key requirements was that it disintegrated within seconds within the oral cavity, it be compressible, flowable and compatible with a wide range of APIs

PANEXCEA™ MC200G – MANNITOL BASED HIGH PERFORMANCE ODT EXCIPIENT

Typical Properties
- D50: 90 µm
- Bulk Density: 0.66 g/cc
- Tapped Density: 0.81 g/cc
- Angle of Repose: 28°
- Compressibility Index: 20
- Loss on Drying: 2.6%
PanExcea™ UNIQUE FEATURES

- Specially engineered direct compression excipient
- Combination of wicking agent and dispersing agent
  - Enables rapid disintegration
- Good taste and mouth feel
- Spherical particle shape (90 µm)
  - Good flowability and compactibility
- High drug loading (up to 40%)
- Formulation development flexibility

ODT FORMULATION USING PanExcea™

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>0.5-40</td>
</tr>
<tr>
<td>PanExcea™ MC200G</td>
<td>40-75</td>
</tr>
<tr>
<td>Diluent/Diluent+Binder (MCC/MCC+Starch)</td>
<td>5-15</td>
</tr>
<tr>
<td>Disintegrant (Crospovidone)</td>
<td>5-10</td>
</tr>
<tr>
<td>Antiadherent (Silica)</td>
<td>1-2</td>
</tr>
<tr>
<td>Lubricant (Magnesium stearate/Sodium stearyl fumarate)</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Sweetener (Aspartame/Sucralose)</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Flavor (Orange/Strawberry/Grape)</td>
<td>0.5-2</td>
</tr>
</tbody>
</table>
**APPLICATIONS**

- Acetaminophen
- Cetirizine
- Ropinirole
- Donepezil
- Dextromethorphan
- Loratidine
- Memantine
- Vitamin C
- Esomeprazole
- Ondensetron
- Tramadol

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**CASE STUDY**

- Formulate Acetaminophen ODT tablets at API levels 0.5-40%
- Direct compression process
  - Powder blend must have good flowability and compressibility
- Tablets must
  - disintegrate within 30 seconds
  - have sufficient mechanical strength
  - have friability less than 0.5%*

*USP limit is less than 1%
**CASE STUDY**

**Acetaminophen ODT Powder Blend Characteristics**

<table>
<thead>
<tr>
<th>Test</th>
<th>0.5% APAP</th>
<th>10% APAP</th>
<th>40% APAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle Size (µm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D10</td>
<td>28</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>D50</td>
<td>81</td>
<td>81</td>
<td>91</td>
</tr>
<tr>
<td>D90</td>
<td>158</td>
<td>158</td>
<td>175</td>
</tr>
<tr>
<td>Angle of Repose (°)</td>
<td>36.3</td>
<td>36.6</td>
<td>37.7</td>
</tr>
<tr>
<td>Compressibility Index (%)</td>
<td>19.2</td>
<td>19.4</td>
<td>14.9</td>
</tr>
<tr>
<td>Aerated Bulk Density (g/cc)</td>
<td>0.59</td>
<td>0.58</td>
<td>0.57</td>
</tr>
<tr>
<td>Tapped Bulk Density (g/cc)</td>
<td>0.73</td>
<td>0.72</td>
<td>0.67</td>
</tr>
<tr>
<td>Total Flowability Index*</td>
<td>76</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>Flowability and Compressibility</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
</tbody>
</table>

*Flowability or flow index: Index (0 -100) assigned to powder flow based on measurement of angle of spatula, angle of repose, particle size distribution, and densities*. R.L. Carr (1965).

Powder blend was characterized using Hosokawa Powder Tester and Hosokawa Air Jet Sieving Instrument. Acetaminophen is abbreviated as APAP.

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**Acetaminophen ODT Composition and Characteristics**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granular Acetaminophen (97%)</td>
<td>0.51</td>
<td>10.3</td>
<td>41.24</td>
</tr>
<tr>
<td>PanExcea™ MC200G</td>
<td>74.5</td>
<td>65</td>
<td>39.51</td>
</tr>
<tr>
<td>MCC</td>
<td>15</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>7.74</td>
<td>7.45</td>
<td>7</td>
</tr>
<tr>
<td>Silica</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>Hardness at 1600 lbs (kp)</td>
<td>4.5 ± 0.4</td>
<td>5.8 ± 0.2</td>
<td>6.4 ± 0.2</td>
</tr>
<tr>
<td>Disintegration Time (sec)</td>
<td>8 ± 0</td>
<td>9 ± 1</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.28</td>
<td>0.19</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Content variation value of powder blend containing 0.5% APAP = 1.99% RSD

*Tablets were compressed on an instrumented 10 station rotary press at 30 rpm. Tablet size was 10 mm and tablet weight was 350 mg. N=5.*
CASE STUDY

• Formulate Cetirizine hydrochloride chewable tablets at API levels 2.5%

• API is extremely bitter
  ➢ Suitable taste masking strategy involving cyclodextrin complexation and granulation devised

• Incompatibility of the API with sugars like mannitol
  ➢ Mannitol in PanExcea™ MC200G is unavailable to react with the API

• Direct compression process
  ➢ 5-7 kp hardness, acceptable friability and pleasant taste

Dissolution Conditions

<table>
<thead>
<tr>
<th>Dissolution Conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparatus</td>
<td>USP Type II</td>
</tr>
<tr>
<td>RPM</td>
<td>50</td>
</tr>
<tr>
<td>Volume</td>
<td>900 ml</td>
</tr>
</tbody>
</table>

Dissolution of Chewable Tablet Containing Cetirizine Hydrochloride
COMPARATIVE EVALUATION OF ODT EXCipients

DISINTEGRATION TIME VS HARDNESS
PLACEBO TABLETS

Tableting parameters
Tableting speed: 30 rpm
Tablet Weight: 100 mg
Tablet Diameter: 6 mm

DISINTEGRATION TIME VS HARDNESS
TABLETS CONTAINING 10% ACETAMINOPHEN

Tableting parameters
Tableting speed: 30 rpm
Tablet Weight: 100 mg
Tablet Diameter: 6 mm
Avantor introduces:

PanExcea™ GR Performance Excipient: Gastro-Retentive Oral Dosage

• High water uptake; swelling (swelling index 22.2, EP method 2-8.4), floating tablets
• Robust gel strength, (tablet yield stress 22-26 Pa, 13 mm tablets, 200 mg c
• Improved stomach retention increases drug availability
• Clinical proof of pharmacokinetic improvements
• Enabling technology for product life cycle management
• Novel system; intellectual property available for license
• cGMP production of starting materials

PanExcea™ GR Performance Excipient

Clinical Proof of Concept - Study Design

• Open label, balanced, randomized, 3 treatment, 3 sequence, single dose, crossover, relative bioavailability study, under fed conditions

• 3 formulations of BCS Class 1 drug:
  • Immediate Release (IR) ... A marketed formulation
  • Controlled Release (CR) ... HPMC matrix
  • Gastro Retentive (GR) ... PanExcea GR tablet

• 15 volunteers in cross-over studies:
  Healthy subjects, ages 18-45
  800-1000 cal meal pre-dose
  Dosage with 240ml water
  3 standardized meals thereafter

• Plasma concentrations at standardized times up to 36 hrs post dosage
Clinical Proof of Concept - Results

Mean Plasma Drug Level (ng/ml)

Clinical results prove gastro-retention:

PanExcea GR provides improved pharmacokinetics:

- AUC(GR): > 30% higher than AUC(CR)
- AUC(GR) = AUC(IR)

- $T_{max}(GR) = 9.3$ hrs vs $T_{max}(CR) = 3.0$ hrs

Formulation
- IR
- CR
- GR

IR/CR data from commercially available drug products, GR data based on experimental PanExcea Product

Conclusion

- Particle engineering technology by the synergistic physical association of two or more conventional excipients has enabled the design of new high performance direct compression excipients
- PanExcea GR is an unique natural polymer enabling development of gastroretentive dosage forms
- Since these new excipients performance is only based on the unique physical association and not a chemical change there are no barriers for regulatory usage in current formulation development