8TH ANNUAL PTI TRAINING PROGRAM
FORMULATION AND PROCESS DEVELOPMENT FOR ORAL DOSAGE FORMS
A 5-Day Modular and Case Study Oriented Training Program

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Historical Location, Reputable Speakers & Innovative Program
Overview of Oral Drug Delivery

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NA Technical Services and Global Film Coating Technology
Ashland Specialty Ingredients
Overview of Presentation

Oral Dosage Forms: General Design Concepts:
  • Types of Dosage Forms.
  • Drug-Release Concepts:
    • Immediate-Release.
    • Modified-Release

Oral Dosage Forms: Formulation Approaches:
  • Conventional Dosage Forms.
  • Orally Disintegrating Tablets.
  • Modified-release Dosage Forms.

Oral Dosage Forms: Design & Processing Concepts:
  • Compaction Processes.
  • Encapsulation Processes.
  • Conventional Film-Coating Processes.
  • Electrostatic Processes.
  • Molding and/or Extrusion Processes.
Oral Dosage Forms: General Design Concepts
A. Types of Dosage Forms
A Point to Ponder

“Tablets have had their day, and will pass away to make room for something else.....”

Author unknown - British Pharmaceutical Journal 1895
Classic Technologies

**Tablets:**
- Uncoated
- ODT’s
- Chewable
- Sugar Coated
- Film Coated
- Enrobed

**Softgels:**
- Liquid fill
- Powder fill
- Pellet fill

**Two-Piece Capsules:**
- Powder fill
- Pellet fill
- Granule fill
- Semi-solid fill
- Liquid fill
B. Drug-Release Concepts
Oral Solid Dosage Forms:
General Drug Release Concepts

Oral solid dosage forms are often presented in a number of different formats, namely:

- Conventional immediate-release dosage forms.
- Chewable dosage forms.
- Orally disintegrating dosage forms.
- Modified-release dosage forms:
  - Delayed-release.
  - Extended-release.
Immediate-Release (IR) Dosage Forms: Typical Drug release Characteristics
Modified-Release Dosage Forms

Conceptually, these take one of two forms:

- Delayed-release:
  - Conventional enteric-coated dosage forms.
  - Colonic delivery dosage forms.
  - “Night-time dosing,” sometimes called “chronotherapeutic,” dosage forms.
- Extended-release.
Delayed-Release Dosage Forms

These are the general characteristics of this type of dosage form:

• They are film coated with polymers whose solubility in water is defined by pH (usually > 5.0) and ionic strength of the dissolution medium.

• The main differentiation between the various sub-categories of this type of delivery system relates to:
  • The amount of coating applied.
  • The chemistry of the polymer used, and typically the pH at which it begins to dissolve (although in some cases dissolution of the polymer in the coating is mediated by gut flora).

• They take the form of:
  • Tablets or capsules (either two-piece or softgel) to which the specialized film coating has been applied.
  • Capsules, containing multiparticulates (granules, pellets, etc.) to which the specialized coating has been applied.
Typical Example of Drug Release from a Delayed-Release Dosage Form

![Graph showing percent drug released over time at different pH levels.](image)

- pH = 1-2
- pH = 6.5-7.5
Extended-Release Dosage Forms

Tablets:
- Matrix tablets.
- Tablets coated with a release-modifying membrane applied by:
  - Film coating.
  - Compaction coating.
- Tablets prepared from compacted, film-coated particulates.

Capsules:
- Matrix capsules (two-piece or softgels).
- Two-piece capsules containing film-coated particulates.
- Two-piece capsules coated with a release-modifying film coating.
- Softgels coated with a release-modifying film coating.
General Formulation Approaches for Preparing Extended-Release Dosage Forms

A. Matrix Systems

B. Coated Reservoir Systems

C. Coated Matrix Systems
Typical Example of Drug Release from Extended-Release Dosage Forms
Oral Dosage Forms:
General Formulation Approaches
A. Conventional Dosage Forms
These types of dosage forms are usually presented as either:

- Tablets, which may be coated, and are made by one of three tabletting processes, namely:
  - Direct compaction.
  - Dry granulation.
  - Wet granulation
- Capsules, which can be subdivided into:
  - Two-piece capsules filled with:
    - Powders.
    - Granules.
    - Thixotropic liquids.
    - Hot-melts.
  - Softgel capsules typically filled with liquids.
B. Orally Disintegrating Tablets
Orally Disintegrating Dosage Forms (ODT’s)

These types of dosage forms are usually presented as either:
- Conventional tablets prepared by a so-called “soft compaction” process.
- Molded tablets prepared, for example, through lyophilization.

ODT’s are designed as a convenience to the patient, for example:
- Pre-empting the need to be consumed with liquids as is typically required with conventional tablets and capsules.
- Facilitating ingestion by patients who have great difficulty in swallowing conventional dosage forms.

Note: the term “orally disintegrating” is not synonymous with “fast dissolving,” since some types of this dosage form may actually contain modified-release pellets.
Characteristics of ODT’s

- They are designed literally to “melt” in the mouth without the need to be chewed (with disintegration times typically in the range of 1-5 seconds up to about 30-45 seconds).
- With essentially one or two exceptions, most ODT’s use the “soft” tablet (with breaking forces in the range of 1-3 kp) approach, which often requires specialized packaging to maintain dosage form integrity up to the point of consumption.
- Lyophilized forms are produced right into the final packaging.
- The “soft” tablet concept typically uses high levels of sugar alcohols (such as maltitol, mannitol, etc) in combination with relatively high levels (10-20% w/w) of superdisintegrants; some forms may facilitate rapid disintegration through effervescence.
Examples of ODT’s

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (APAP)*</td>
<td>18.82</td>
</tr>
<tr>
<td>Mannitol (Spray Dried)</td>
<td>59.08</td>
</tr>
<tr>
<td>Polyplasdone XL-10</td>
<td>20.00</td>
</tr>
<tr>
<td>Sodium stearyl fumarate</td>
<td>1.00</td>
</tr>
<tr>
<td>Colloidal SiO₂</td>
<td>0.30</td>
</tr>
<tr>
<td>Flavor</td>
<td>0.50</td>
</tr>
<tr>
<td>Sucralose</td>
<td>0.20</td>
</tr>
<tr>
<td>Color (lake)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

(* Taste-masked form)
C. Modified-Release Dosage Forms
Delayed-Release Products

Typical approaches:
• Application of classic enteric coatings to tablets, but with a growing interest in coating multiparticulates.
• Some interest in using novel polymers (such as ethylcellulose/pectin or ethylcellulose/starch combinations, modified galactomannins and diazo- and disulpho-polymers, especially for colonic drug delivery).
Typical Structure of Enteric-Coating Polymers

Dissolution Rate of Coating is Affected by:
  • $pK_a$ of polymer,
  • pH of medium,
  • Ionic strength of medium, and
  • Agitation rate.
# Polymers Used in Enteric-Coating Formulations

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose acetate phthalate.</td>
<td>Hydrolysis potential – high.**</td>
</tr>
<tr>
<td>Cellulose acetate trimellitate.</td>
<td>Hydrolysis potential – medium.**</td>
</tr>
<tr>
<td>Polyvinylacetate phthalate.</td>
<td>Hydrolysis potential – low.**</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose phthalate.</td>
<td>Hydrolysis potential – medium.**</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose acetate succinate.</td>
<td>Hydrolysis potential – low.**</td>
</tr>
<tr>
<td>Poly (MA – EA)* 1:1.</td>
<td>Relatively high dissolution pH.</td>
</tr>
<tr>
<td>Poly (MA – MMA)* 1:1.</td>
<td></td>
</tr>
<tr>
<td>Poly (MA – MMA)* 1:2.</td>
<td>Relatively high dissolution pH.</td>
</tr>
</tbody>
</table>

*MA = Methacrylic acid; EA = Ethyl acrylate; MMA = Methyl methacrylate.
** When exposed to conditions of elevated temperature and humidity.
# Examples of Aqueous Enteric-Coating Systems

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>FORM</th>
<th>POLYMER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit L30D*</td>
<td>Latex dispersion</td>
<td>Poly (MA – EA)**</td>
</tr>
<tr>
<td>Eudragit L100-55*</td>
<td>Spray-dried latex</td>
<td>Poly (MA – EA)**</td>
</tr>
<tr>
<td>HP-F</td>
<td>Micronized dry powder</td>
<td>HPMCP</td>
</tr>
<tr>
<td>Acryl-Eze</td>
<td>Formulated, dry powder system</td>
<td>Poly (MA – EA)**</td>
</tr>
<tr>
<td>Advantia Performance</td>
<td>Formulated, dry powder system</td>
<td>Poly (MA – EA)**</td>
</tr>
<tr>
<td>Sureteric</td>
<td>Formulated, dry powder system</td>
<td>PVAP</td>
</tr>
<tr>
<td>Aquateric</td>
<td>Spray-dried pseudolatex</td>
<td>CAP</td>
</tr>
<tr>
<td>Aquacoat ECD</td>
<td>Pseudolatex dispersion</td>
<td>CAP</td>
</tr>
<tr>
<td>Aqoat</td>
<td>Dry powder</td>
<td>HPMCAS</td>
</tr>
<tr>
<td>CAP</td>
<td>Dry powder</td>
<td>CAP</td>
</tr>
<tr>
<td>CAT</td>
<td>Dry powder</td>
<td>CAT</td>
</tr>
</tbody>
</table>

*Competitive acrylic products now available from BASF, Eastman, & Sanyo*  
** MA = Methacrylic acid; EA = Ethyl acrylate.
Factors Influencing Formulation Design of Extended-Release Products

Selection will be driven by a desire to:

- Create a specific type of drug-release characteristic.
- Minimize the risk of dose-dumping.
- Utilize processing methodologies that already exist within the company.
- Prepare a unique dosage form that enables the manufacturer to take a proprietary position with respect to dosage-form presentation.
Matrix Extended-Release Products
Matrix Extended-Release Dosage Forms

Tablets prepared by: -
  • Direct Compaction.
  • Compaction of granulations.
  • Injection molding.

Capsules filed with: -
  • Matrix powder blends.
  • Matrix liquid formulations or “hot-melts”.
# Functional Materials Used in Extended-Release Matrix Products

<table>
<thead>
<tr>
<th>Hydrophobic Matrices</th>
<th>Hydrophilic Matrices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene glycol monostearate</td>
<td>Poly (HEMA)</td>
</tr>
<tr>
<td>Hydrogenated vegetable oil</td>
<td>Poly (vinyl pyrrolidone)</td>
</tr>
<tr>
<td>Poly (vinyl stearate)</td>
<td>Poly (vinyl alcohol)</td>
</tr>
<tr>
<td>Poly (vinyl chloride)</td>
<td>Hydroxypropylmethylcellulose</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>Hydroxypropylcellulose</td>
</tr>
<tr>
<td>Glycerol palmito-stearate</td>
<td>Sodium carboxymethylcellulose</td>
</tr>
<tr>
<td>Hydrogenated palm oils</td>
<td>Alginates</td>
</tr>
<tr>
<td>Hydrogenated beta palm oils</td>
<td>Poly (lactic acid)</td>
</tr>
<tr>
<td></td>
<td>Poly (glycolic acid)</td>
</tr>
<tr>
<td></td>
<td>Cellulose acetate</td>
</tr>
<tr>
<td></td>
<td>Cellulose acetate butyrate</td>
</tr>
</tbody>
</table>
Summary of Types of Matrix Formulations Used in Extended-Release Applications

Drug Matrices

- Time-Dependant Shape
  - Swellable
  - Non-Swellable
- Time-Independant Shape
  - Porous
  - Non-Porous
    - Macroporous
    - Microporous
Schematic Overview of Drug Release from Hydrophilic Matrix Tablets

1. Ingestion of tablet
2. Initial wetting & formation of gel layer
3. Expansion of gel layer
4. General erosion of tablet & gel layer
Swelling & Gelling of Hydrophilic Matrix Tablets
Film-Coated Extended-Release Products
1. A continuous film coating is applied to the core containing the drug.
Typical Film-Coating Applications

1. A continuous film coating is applied to the core containing the drug.

2. A film coating containing pores formed by the leaching out of water-soluble materials.

Drug-containing Core

Drug-containing Core
Typical Film-Coating Applications

1. A continuous film coating is applied to the core containing the drug.

2. A film coating containing pores formed by the leaching out of water-soluble materials.

3. A film coating possessing a specific delivery orifice.
Key Factors in Achieving Reproducible Performance with Modified-Release Film Coatings

- Maximizing uniformity of distribution of the coating both around the surface of the substrate, and from substrate entity to substrate entity.
- Minimizing structural defects within the coating.
- Achieving reproducible coating process efficiencies.
Objectives in Creating Successful Film-Coated Extended-Release Products

• Target drug-release must be obtained in a reproducible manner.
• Drug-release characteristics should be insensitive to expected variations in raw materials and coating-process conditions.
• The coating formulations & coating process should ideally be uncomplicated, & facilitate scale-up from the laboratory into production.
• The final product should be stable and, in particular, devoid of time-dependent changes in drug-release characteristics.
Coating Systems Used for Applying Extended-Release Coatings

• Organic-solvent-based coating solutions, which can be applied to:
  • Tablets
  • Multiparticulates.
  • Capsules.

• Aqueous polymer dispersions, which can be applied to:
  • Tablets
  • Multiparticulates.
  • Capsules.

• Hot Melts, which are typically applied to:
  • Multiparticulates.
Examples of Coating Materials Used in Organic-Solvent-Based Extended-Release Coating Solutions

<table>
<thead>
<tr>
<th>Coating Material</th>
<th>Membrane Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fats &amp; waxes (beeswax; carnauba wax; cetyl alcohol; cetostearyl alcohol).</td>
<td>Permeable and erodible.</td>
</tr>
<tr>
<td>5. Cellulose esters (e.g. acetate).</td>
<td>Semi permeable &amp; water insoluble.</td>
</tr>
<tr>
<td>6. Acrylic ester copolymers</td>
<td>Permeable &amp; water insoluble.</td>
</tr>
</tbody>
</table>
# Aqueous Polymer Dispersions Used in Extended-Release Film-Coating Formulations

<table>
<thead>
<tr>
<th>Product</th>
<th>Polymer Used</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Surelease</td>
<td>Ethylcellulose</td>
<td>Plasticized aqueous polymer dispersion. Addition of lake colorants should be avoided.</td>
</tr>
<tr>
<td>2. Aquacoat</td>
<td>Ethylcellulose</td>
<td>Pseudolatex dispersion. Plasticizer must be added to facilitate film formation.</td>
</tr>
<tr>
<td>3. Eudragit NE 30D*</td>
<td>Acrylic copolymer</td>
<td>Latex dispersion. No plasticizer needed unless it is necessary to improve film flexibility.</td>
</tr>
<tr>
<td>4. Eudragit RL 30D*</td>
<td>Acrylic copolymer</td>
<td>Aqueous polymer dispersion. No plasticizer needed unless it is necessary to improve film flexibility.</td>
</tr>
<tr>
<td>5. Eudragit RS 30D*</td>
<td>Acrylic copolymer</td>
<td>Aqueous polymer dispersion. No plasticizer needed unless it is necessary to improve film flexibility.</td>
</tr>
</tbody>
</table>

(*Also available as equivalent Kollicoat dispersions)
Examples of Materials that Can be Used for Hot-Melt Film Coating

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Product Type</th>
<th>Viscosity at 99 ºC (cP)</th>
<th>Melting Point (ºC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atmul 84K</td>
<td>Mono- and diglycerides</td>
<td>-</td>
<td>62.0</td>
</tr>
<tr>
<td>Vybar 253</td>
<td>Hydrocarbon</td>
<td>6.0</td>
<td>67.0</td>
</tr>
<tr>
<td>Beeswax 422</td>
<td>Hydrocarbon</td>
<td>≈ 50</td>
<td>63.5</td>
</tr>
<tr>
<td>Synthetic Spermaceti 4013</td>
<td>Hydrocarbon</td>
<td>-</td>
<td>47.5</td>
</tr>
<tr>
<td>Paraffin 173</td>
<td>Hydrocarbon</td>
<td>39</td>
<td>59.5</td>
</tr>
</tbody>
</table>
Material Characteristics that Need to be Considered in a Hot-Melt Coating Process

- Melting Point.
- Melting range (a wide range complicates process control).
- Melt viscosity (a relatively low viscosity is required to produce smooth, uniform coatings).
Coated Matrix Extended-Release Products

The type of coating formulation may comprise:

- An immediate-release coating formulation.
- A delayed-release coating formulation.
- An extended-release coating formulation.
- A combination thereof.
Drug Release Characteristics of Hydrophilic Matrix Tablets Coated with an Immediate-Release Film Coating
Drug Release Characteristics of Hydrophilic Matrix Tablets (Uncoated & Film-Coated with an Extended-Release Film Coating)

A. 10 mm Tablets

B. 2 mm Tablets
Model Concept of Drug Release from Matrix Tablet Coated with a Delayed-Release Film Coating
Oral Dosage Forms: 
Design & Processing Concepts
Compaction Processes

Compaction processes are typically used for:

- Preparing tablets:
  - Conventional, immediate-release tablets.
  - Orally disintegrating tablets.
  - Modified-release tablets.
  - Bilayer and multilayer tablets.

- Coating tablets:
  - Complete coverage.
  - Partial coverage.
Compression Coated Matrix Tablets

Fundamentally, this technology involves:

• The preparation of matrix modified-release tablets.

• The application of dry coatings on either the top, bottom, or both surfaces of the matrix core.

• Core may have a specific geometric shape, and be eroding or non-eroding.

• The coating may create a gel structure, and be swelling, eroding, or non-eroding.
Controlled release is achieved by constructing a tablet of two basic components:

- A core of hydrophilic methylcellulose (HPMC) matrix that contains the active drugs.
- One or two additional barrier layers that control the surface area diffusion of the drug or drugs out of the core.
Smartrix™ Technology

Matrix Core

Erodible Outer Layer

Graph showing the release of drug over time with the following annotations:
- Continuous erosion of outer layers and surface area increase
- Depleted matrix layer
- Slow release matrix layer: drug release through diffusion

Time (h)

Released drug (%)
Procise™ Technology

1. Non-erodible Coating.
2. Active erodible matrix core.
3. Cylindrical face which controls dissolution rate of core.
4. Central pillar attached to the upper and lower faces of the coat.
5. Core/coat interface.
Encapsulation Processes

Encapsulation processes involve filling of:

- Two-piece capsules, which are prepared in advance using either a dipping process or by injection molding, and may be based on:
  - Gelatin.
  - HPMC.
  - Starch.
- Softgels, which are produced *in-situ* during the filling process from preformed flexible sheets of plasticized gelatin.
Two-Piece Capsules & Filling Process

A. Gelatin or HPMC Capsules Produced By Dipping Process

B. Starch Capsules Produced By Injection Molding Process.

C. Bosch Model 1500 Capsule Filling Machine
Fill Materials for Two-Piece Capsules

A. Powders
B. Granules
C. Coated Multiparticulates
D. “Hot Melts”
E. Thixotropic Liquids
F. Regular Liquids + Banding
Softgel Capsules

Softgel capsules:

- Are typically filled with liquids (although they have been known to be filled with powders and pellets).
- Although softgels are typically used for IR applications, the fill material may be selected to facilitate modified drug delivery.
- Have a seam at the point of sealing.
- May be coated, typically with modified-release film coatings.
“Chronotherapeutic” Technologies

• A device, based on a two-piece gelatin capsule, that releases the drug at a specific time after ingestion.
“Chronotherapeutic” Technologies

- A device, based on a two-piece gelatin capsule, that releases the drug at a specific time after ingestion.
- Original Pulsincap® technology was owned by RP Scherer, but was not commercialized.
“Chronotherapeutic” Technologies

- A device, based on a two-piece gelatin capsule, that releases the drug at a specific time after ingestion.
- Original Pulsincap® technology was owned by RP Scherer, but was not commercialized.
- Further developments have been ongoing at the University of Strathclyde.
“Chronotherapeutic” Technologies

• A device, based on a two-piece gelatin capsule, that releases the drug at a specific time after ingestion.

• Original Pulsincap® technology was owned by RP Scherer, but was not commercialized.

• Further developments have been ongoing at the University of Strathclyde.

• Similar technology has been commercialized by PORT Systems, Inc., in the United States.
Example of “Chronotherapeutic” Delivery System

Capsule Cap Coated With Enteric Coating

Capsule Body Coated With Insoluble Film Coating

Hydrogel Plug

“Ejection” Excipient
Film-Coating Processes

Current practices include:

• Pan-coating processes, which are typically reserved for coating tablets with various types of film-coatings.

• Fluid-bed coating processes, which are typically reserved for coating multiparticulates with modified-release film coatings.

• Enrobing processes, which are typically reserved for coating tablets generally with IR film coatings.
Examples of Pan Film-Coated Tablets
Examples of Fluid-Bed Film-Coated Multiparticulates

1. Spheronized Granules
2. Drug-loaded “Non-pareils”
3. Regular Granules
4. “Mini” Tablets
Examples of Enrobed Tablets

A. Gel Enrobing Process
B. FMC NROBE™ Process
C. Bioprogress TABWRAP™ Process
Osmotic Pump Technology

Fundamental concept is based on:

• A tablet, containing the drug and excipients that, in solution, can exert a predefined osmotic pressure.
• An applied insoluble film coat that is semi-permeable.
• A delivery orifice.
Oros® Technology: Basic Concepts

- **Semipermeable Membrane**
- **Drug Core**
- **Osmotically Active Polymeric Push Compartment**
- **Laser-Drilled Delivery Orifice**
- **Expanded Push Compartment**
- **Delivery Orifice**
- **Drug Layer 1**
- **Drug Layer 2**
- **Osmotic Push Layer**
- **Rate Controlling Semi-permeable Membrane**
Banded, Film-Coated Caplet Technology

Concept involves:

• Designing a matrix sustained-release tablet core.
Banded, Film-Coated Caplet Technology

Concept involves:

• Designing a matrix sustained-release tablet core.
• Film coating the core with a water-soluble coating.
Banded, Film-Coated Caplet Technology

Concept involves:

- Designing a matrix sustained-release tablet core.
- Film coating the core with a water-soluble coating.
- Banding the coated tablets, using conventional capsule-banding technology, with insoluble polymer materials.
Alkermes RingCap™ Technology
Alkermes RingCap™ Technology

A. Erosion of Conventional Matrix Tablet

A. Erosion of RingCap™ Matrix Tablet
Electrostatic Processes

Fundamental process involves the application of film coatings to tablet cores using electrostatic process (LeQtracoat® process).
LeQtracoat® Technology

- LeQtracoat® technology represents an adaptation of electrophotography (as used in the photocopying process), except it has been further refined to facilitate three-dimensional imaging.

- LeQtracoat® technology can facilitate the application of:
  - Coatings of varying solubilities, and
  - Complete or partial coatings to the surfaces of solid dosage forms.

- Depending on the solubilities of the coatings applied, and extent of the surface covered, modified-release products exhibiting a broad range of drug release characteristics can be achieved.
Electrostatic Dry Powder Coating Technology

Formulation
Electrostatic Dry Powder Coating Technology

Formulation

Tablet core must have certain conductive properties or be modified
Electrostatic Dry Powder Coating Technology

Formulation

Tablet core must have certain conductive properties or be modified
Electrostatic Dry Powder Coating Technology

Formulation

Tablet core must have certain conductive properties or be modified

Powder must be completely uniform & chargeable

Active Ingredient may be in the core tablet, coating powder or both
Electrostatic Dry Powder Coating Technology

**Formulation**

Tablet core must have certain conductive properties or be modified

Powder must be completely uniform & chargeable

Active Ingredient may be in the core tablet, coating powder or both
Electrostatic Dry Powder Coating Technology

**Formulation**

- Tablet core must have certain conductive properties or be modified
- Powder must be completely uniform & chargeable
- Active Ingredient may be in the core tablet, coating powder or both

**Electrostatic coating**
Electrostatic Dry Powder Coating Technology

**Formulation**

- Tablet core must have certain conductive properties or be modified
- Powder must be completely uniform & chargeable
- Active Ingredient may be in the core tablet, coating powder or both

**Electrostatic coating**
**Electrostatic Dry Powder Coating Technology**

*Formulation*  
Tablet core must have certain conductive properties or be modified

*Electrostatic coating*  
Powder must be completely uniform & chargeable

Active Ingredient may be in the core tablet, coating powder or both
Electrostatic Dry Powder Coating Technology

*Formulation*

Electrostatic coating

Tablet core must have certain conductive properties or be modified

Powder must be completely uniform & chargeable

Active Ingredient may be in the core tablet, coating powder or both
Electrostatic Dry Powder Coating Technology

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**Electrostatic coating**

+ve
Electrostatic Dry Powder Coating Technology

**Formulation**

- Tablet core must have certain conductive properties or be modified
- Powder must be completely uniform & chargeable
- Active Ingredient may be in the core tablet, coating powder or both

**Electrostatic coating**

- A known field is applied, and the tribocharged powder is attracted onto the tablet
Electrostatic Dry Powder Coating Technology

**Formulation**

Tablet core must have certain conductive properties or be modified

Powder must be completely uniform & chargeable

Active Ingredient may be in the core tablet, coating powder or both

**Electrostatic coating**

A known field is applied, and the tribocharged powder is attracted onto the tablet

Precise quantities are applied on every tablet
Electrostatic Dry Powder Coating Technology

**Formulation**

- Tablet core must have certain conductive properties or be modified
- Powder must be completely uniform & chargeable
- Active Ingredient may be in the core tablet, coating powder or both

**Electrostatic coating**

- A known field is applied, and the tribocharged powder is attracted onto the tablet
- Precise quantities are applied on every tablet
- The process settings are manipulated to change the coating pattern
Electrostatic Dry Powder Coating Technology

**Formulation**

- Tablet core must have certain conductive properties or be modified
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**Heat fixation**
- Radiant heat applied to fuse and fix the coating powder on to the tablet core
**Electrostatic Dry Powder Coating Technology**

**Formulation**
- Tablet core must have certain conductive properties or be modified
- Powder must be completely uniform & chargeable
- Active Ingredient may be in the core tablet, coating powder or both

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- A known field is applied, and the tribocharged powder is attracted onto the tablet
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**Heat fixation**
- Radiant heat applied to fuse and fix the coating powder on to the tablet core
- Up to 80 seconds heat exposure (per side)
Electrostatic Dry Powder Coating Technology

**Formulation**
- Tablet core must have certain conductive properties or be modified
- Powder must be completely uniform & chargeable
- Active Ingredient may be in the core tablet, coating powder or both

**Electrostatic coating**
- A known field is applied, and the tribocharged powder is attracted onto the tablet
- Precise quantities are applied on every tablet
- The process settings are manipulated to change the coating pattern

**Heat fixation**
- Radiant heat applied to fuse and fix the coating powder on to the tablet core
- Up to 80 seconds heat exposure (per side)
- Typical temperature:
  - Core: 60° C
  - Coating: 120° C
Electrostatic Dry Powder Coating Technology

**Formulation**

- Tablet core must have certain conductive properties or be modified
- Powder must be completely uniform & chargeable
- Active Ingredient may be in the core tablet, coating powder or both

**Electrostatic coating**

- A known field is applied, and the tribocharged powder is attracted onto the tablet
- Precise quantities are applied on every tablet
- The process settings are manipulated to change the coating pattern

**Heat fixation**

- Radiant heat applied to fuse and fix the coating powder on to the tablet core
- Up to 80 seconds heat exposure (per side)
- Typical temperature
  - Core: 60° C
  - Coating: 120° C
Applications of Electrostatic Dry Powder Coating Techniques

<table>
<thead>
<tr>
<th>Anti-counterfeit and product branding</th>
<th>Robust ODT’s</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Modified-release platform</th>
<th>Accurate low dose drug deposition</th>
</tr>
</thead>
</table>

97
Modified Release Drug Delivery with a Variety of Release-Modifying Characteristics

**Tablet core composition**

**Tablet coating**
Potential Design Approaches

Zero order

Increasing

Enteric coated

Pulsatilie

Dose loading

100% % in solution

Time

100% % in solution

Time

100% % in solution

Time

100% % in solution

Time

100% % in solution

Time
Example Illustrating Application Requiring Specialized Release Profile

Dissolution Specification:

- 10-30% released within 45 minutes
- 40-50% within 3 hours
- 100% within 6 hours

Tri-layer tablet required to achieve profile:

- Impermeable coat
- Fast release – 100mg
- Slow release – 40mg
- Immediate release – 60mg
Drug Release from Coated Bi-layer Tablets with Immediate-release Third Layer
Molding and/or Extrusion Processes
Aprecia Ink-Jet Molding Process

This technology involves:

• The preparation of “molded” tablets using a process that employs a combination of:
  • Ink jet printing technology.
  • Powder spreading.
  • Drying.

• The design of systems with a multiplicity of drug-release capabilities in which drug particles are locked into compartments created within the three-dimensional structure.
Aprecia Process

1. Powder Building Platen
   - Powder Roller
   - Powder Feed
   - Build Bed

2. Printing Head
   - Solution containing drug
   - Inactive binder solution
Examples of Dosage Forms Created Using the Aprecia Process
Soliqs Meltrex® Melt Extrusion Technology

Process involves:

- Blending of drug with appropriate thermoplastic polymer.
- Calendaring (i.e. shaping the extrudate into tablets or pellets).
- Cooling the final extrudate, and separating into individual units.
Dosage Forms Produced by Melt Extrusion Technology
Questions?
Film Coating of Modified Release Dosage forms

Charlie Cunningham
Sr. Manager, Product Development, Colorcon Inc.
Agenda

- Advantages of film-coated dosages
- Practical Considerations for Aqueous Film Coating of Hydrophilic Matrix Tablets
- Immediate release coating case studies on METHOCEL™ Matrix and POLYOX™ matrix formulations.
- Delayed release coating case study on matrix formulations
- Drug layering case study on matrix formulations
- Application of a delayed release coating using a continuous coating process

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Why film coat?

- Safety - Improved
- Patient compliance - Improved
- Stability - Improved
- Packaging costs - Reduced
- Aesthetics / appearance - Improved
- Trademarking potential - Improved
- Functionality – Improved

Improve Functionality – Dissolution profile modulation

- Enteric
- First order
- Zero order

Percent Drug Released

- Pulsatile
- Intestinal
- Biphasic

Enteric/ Sustained

Leaky Enteric

Ascending

Improved stability

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Practical Considerations For Film Coating on Hydrophilic Matrix Tablets
Common Apprehensions about Aqueous Coating of Hydrophilic Matrix Tablets

Myth

Hydrophilic matrix tablets contain highly hydrophilic material. Hence it is very difficult to coat these tablets with Aqueous Film Coating.

Fact

Hydrophilic matrix tablets are easily coated using Aqueous Film Coatings when compared to immediate release tablets containing super-disintegrant(s)!

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Criteria for Good Films and Coatings

- Stable on storage and handling
- Uniform thickness
- Adhere to the substrate
- Coherent and free from flaws and cracks

Successfully coating of hydrophilic matrix tablets using Aqueous Film coating systems involves three critical components.
Machine Set-up – Heart of Aqueous Film Coating on Hydrophilic Matrix Tablets

**Control of drying**

- Coating suspension flow rate
- Drying air temperature and humidity
- Drying air quantity
- Exhaust air quantity
- Tablet bed temperature

Too hot

Correct

Too cold
Hydrophilic Matrix Tablet Coating – Practical Considerations

Tablet Core/ Formulation Considerations:
- Tablet core physical properties (Hardness, friability)
- Tablet core characteristics (shape, thickness, strength, and formulation)
- The type of drug (solubility/dose – high/low, acidic/basic),

Coating Process Considerations:
- Coating process conditions/coating formulation type
- The quantity of coating applied/coating weight gain/uniform film thickness
- Additives inclusion (such as permeation enhancers/pore formers
- Sub-coat/Top-coat usage
- The presence of imperfections (e.g. cracks, pick marks, etc.)

These considerations are more critical for functional coatings
Immediate Release Aqueous Film Coating of Hydrophilic Matrix Tablets Containing METHOCEL™
HyperStart® Core Tablet Formulation
Direct Compression

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpheniramine maleate (CPM)</td>
<td>30.00</td>
<td>-</td>
</tr>
<tr>
<td>Theophylline (TP)</td>
<td>-</td>
<td>30.00</td>
</tr>
<tr>
<td>METHOCEL™ K4M Premium</td>
<td>20.00</td>
<td>20.00</td>
</tr>
<tr>
<td>Avicel PH 102 (FMC)</td>
<td>49.25</td>
<td>49.25</td>
</tr>
<tr>
<td>Aerosil 200 (Evonik)</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Total</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

- Tablets (333mg) containing 100mg drug were compressed into 9mm SC tablets at 10 kN and 30 rpm.
- Tablets were coated with three different immediate release film coating systems Opadry® II (33G), Opadry® II (85F) and Opadry® AMB to 4%w/w weight gain in a side-vented pan.

20% METHOCEL™ K4M Chosen to check potential formulation sensitivity to film coating.
Results – Tablet Breaking Force

- Uncoated
- Opadry II (33G)
- Opadry II (85F)
- Opadry AMB

Film coating increases tablet robustness

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Influence of Film Coating on Drug release

CPM release at initial time point

After 6 months storage at 40°C/75%RH

- 20% METHOCEL™ K4M, 30% drug, 49.25% Avicel PH102
- Coating Level: 4% weight gain

USP apparatus II (paddle) and sinkers, in 37±1°C, 900mL Purified Water at 100rpm

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Influence of Film Coating on Drug Release

Theophylline release at initial time point

After 6 months storage at 40°C/75%RH

- 20% METHOCEL™ K4M, 30% drug, 49.25% Avicel PH102
- Coating Level: 4% weight gain

USP apparatus II (paddle) and sinkers, in 37±1°C, 900mL Purified Water at 100rpm

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Coating of METHOCEL™ Tablets - Summary

- Appearance of coated chlorpheniramine and theophylline matrices was good.
- Product bed temperatures recommended for different Opadry formulations could be applied for coating METHOCEL™ hydrophilic matrix tablets.
- Drug release from METHOCEL™ matrices were not significantly affected by the coating applied.
- The coated tablets were stable on storage at 40°C/75%RH for 6 months.
- Specialized film coatings (such as moisture barrier, oxygen barrier) can be coated on the hydrophilic matrix tablets to give additional stability to sensitive actives.

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Aqueous Film Coating (IR) of Hydrophilic Matrix Tablets Containing POLYOX™
**POLYOX™ Properties**

<table>
<thead>
<tr>
<th>Property</th>
<th>POLYOX™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point (°C)</td>
<td>~ 68</td>
</tr>
<tr>
<td>Swellability</td>
<td>~ 7X</td>
</tr>
<tr>
<td>Hydration rate</td>
<td>Very fast</td>
</tr>
<tr>
<td>Hydrophilicity</td>
<td>Highly hydrophilic</td>
</tr>
</tbody>
</table>

POLYOX™ being highly hydrophilic, readily absorbs water, rate and extent of swelling is very high and low melting temperature – have all properties that are challenging for aqueous film coating.

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WSR-303 Compacts – Temperature challenge

(a) Uncoated

(b) Tumbled in a coating pan for 10 min at 70°C (X10)

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### WSR-303 Compact Coating Parameters (Opadry II, 3% WG)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard conditions</th>
<th>Non-standard conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan speed (rpm)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Inlet air temperature (°C)</td>
<td>65-72</td>
<td>70</td>
</tr>
<tr>
<td>Exhaust air temperature (°C)</td>
<td>50-53</td>
<td>52-58</td>
</tr>
<tr>
<td><strong>Product temperature (°C)</strong></td>
<td>42-45</td>
<td>38-40</td>
</tr>
<tr>
<td>Fluidizing airflow (m3/hour)</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Atomization/fan air pressure (bar)</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Spray rate (g/min)</strong></td>
<td>4-10</td>
<td>24</td>
</tr>
<tr>
<td>Process duration (min)</td>
<td>21</td>
<td>14</td>
</tr>
</tbody>
</table>

- O’Hara Labcoat II, 15”; 1.2 mm Schlick spraying gun; 1 kg batch

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WSR-303 Compacts - Opadry® II Coating

Opadry® II non-standard conditions

Opadry® II standard conditions

Rough surface

Good results

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## Metformin HCl (50% Metformin, 30% Polyox WSR-1105) Tablet Coating Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan speed (rpm)</td>
<td>20</td>
</tr>
<tr>
<td>Inlet air temperature (ºC)</td>
<td>65-69</td>
</tr>
<tr>
<td>Exhaust air temperature (ºC)</td>
<td>48-53</td>
</tr>
<tr>
<td><strong>Product temperature (ºC)</strong></td>
<td>42-45</td>
</tr>
<tr>
<td>Airflow (m³/hour)</td>
<td>250</td>
</tr>
<tr>
<td>Atomization/fan air pressure (bar)</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Spray rate (g/min)</strong></td>
<td>10-21</td>
</tr>
<tr>
<td>Process duration (min)</td>
<td>17</td>
</tr>
</tbody>
</table>

- O’Hara Labcoat II, 15”; 1.2 mm Schlick spraying gun; 1 kg batch
- Opadry II – 4% weight gain
1000mL Purified Water at 37.0 ± 0.5°C, 100 rpm using USP Apparatus 2 (paddles) and 2.38 mm (8-mesh) stationary quadrangular baskets (QB). The baskets were positioned within the dissolution vessel perpendicular to the shaft and 3 cm above the paddle.

\[ f_2 = 91 \]
Coating of POLYOX™ Tablets - Summary

- Appearance of coated POLYOX™ compacts and metformin HCl ER POLYOX™ matrices was good.
- Product bed temperatures above 55ºC are not recommended due to low melting point of POLYOX™ (~65ºC).
- For POLYOX™ containing tablets, typical Opadry II coating conditions with a product bed temperature of around 42-45ºC was found to be acceptable.
- Drug release from PEO matrices was not significantly affected by the coating applied.
Aqueous Delayed Release Coating on Hydrophilic Matrix Tablets
HyperStart® Tablet Core Formulation
Direct compression

<table>
<thead>
<tr>
<th>Material</th>
<th>% w/w</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Sodium</td>
<td>37.04</td>
<td>100.00</td>
</tr>
<tr>
<td>METHOCEL™ K4M PR CR</td>
<td>17.00</td>
<td>45.90</td>
</tr>
<tr>
<td>METHOCEL™ E4M PR CR</td>
<td>16.00</td>
<td>43.20</td>
</tr>
<tr>
<td>Starcap 1500</td>
<td>14.00</td>
<td>37.80</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Microcel, MCC PH200)</td>
<td>32.44</td>
<td>97.30</td>
</tr>
<tr>
<td>Silicon Dioxide (Aerosil 200)</td>
<td>0.50</td>
<td>1.35</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.46</td>
<td>3.95</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>100.00</strong></td>
<td><strong>270.00</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (mg)</td>
<td>270.0 ± 3</td>
</tr>
<tr>
<td>Breaking force (kp)</td>
<td>8.00 ± 2.00</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>9.00 ± 0.20</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>5.7 ± 2.4</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

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Coating Process Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Seal-Coat (Opadry® II)</th>
<th>Enteric Coat (Acryl-EZE®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan charge (kg)</td>
<td>1.5 ± 0.1</td>
<td>1.5 ± 0.1</td>
</tr>
<tr>
<td>Inlet temperature (°C)</td>
<td>55.0 ± 5.0</td>
<td>60.0 ± 5.0</td>
</tr>
<tr>
<td>Outlet temperature (°C)</td>
<td>40.0 ± 5.0</td>
<td>30.0 ± 5.0</td>
</tr>
<tr>
<td>Tablet bed temperature (°C)</td>
<td>40.0 ± 5.0</td>
<td>30.0 ± 5.0</td>
</tr>
<tr>
<td>Spray rate (g/min)</td>
<td>20.0 ± 5.0</td>
<td>20.0 ± 5.0</td>
</tr>
<tr>
<td>Pump speed (rpm)</td>
<td>4.5 ± 0.5</td>
<td>5.0 ± 0.5</td>
</tr>
<tr>
<td>Pan rotational speed (rpm)</td>
<td>8.0 ± 2.0</td>
<td>9.0 ± 2.0</td>
</tr>
<tr>
<td>Atomization air pressure (psi/bar)</td>
<td>2.0 ± 0.5</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>Gun to bed distance (inches)</td>
<td>4.0 ± 2.0</td>
<td>4.0 ± 2.0</td>
</tr>
</tbody>
</table>

Rama Coater, 3Lts perforated perforated pan. Schlick Gun with ABC

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## Importance of Seal-coating

### Percent Acid Uptake

<table>
<thead>
<tr>
<th>Samples (Media 0.1N HCl)</th>
<th>Percent acid uptake</th>
<th>Tablets aspect</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% enteric coat</td>
<td>6.0</td>
<td>High edge defects (1)</td>
</tr>
<tr>
<td>7% enteric coat</td>
<td>3.8</td>
<td>Low edge defects (2)</td>
</tr>
<tr>
<td>3% seal coat + 7% enteric coat</td>
<td>2.8</td>
<td>No imperfections (3)</td>
</tr>
</tbody>
</table>

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Drug Release from HyperStart® Formulation and Innovator Product

Diclofenac 100 mg FTLA (USP 31)

% Dissolved

Time (hours)

900ml of 0.1N HCl at 100 rpm followed by 900 ml of phosphate buffer pH 7.5 Time: 1, 5, 10, 16, and 24 hours 50 rpm (at 37 ± 0.5°C) using USP Apparatus 2 (Paddle)

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Appearance of coated Diclofenac Sodium matrices was good.

Delayed + Sustained release profile was obtained when enteric coating was applied on the matrix tablets.

Seal-coating of tablet core reduced the overall requirement of enteric coating.

For enteric coating on Hydrophilic matrix tablets containing acidic or alkaline actives, seal-coating may be recommended. This reduces batch-to-batch variability in release profile.
Aqueous Drug Layering on Hydrophilic Matrix Tablets
Single layer tablet, biphasic drug release

<table>
<thead>
<tr>
<th>Material</th>
<th>%w/w</th>
<th>mg/ tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem Tartrate</td>
<td>4.25</td>
<td>8.50</td>
</tr>
<tr>
<td>METHOCEL™ K100 LV</td>
<td>34.00</td>
<td>68.00</td>
</tr>
<tr>
<td>Spray Dried lactose</td>
<td>45.56</td>
<td>91.13</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>15.18</td>
<td>30.37</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.50</td>
<td>1.00</td>
</tr>
<tr>
<td>Aerosil 200</td>
<td>0.50</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Material</th>
<th>%w/w</th>
<th>mg/ tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem Tartrate</td>
<td>4.29</td>
<td>4.08</td>
</tr>
<tr>
<td>Opadry® II</td>
<td>1.32</td>
<td>1.25</td>
</tr>
<tr>
<td>SLS</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Purified water</td>
<td>94.33</td>
<td>-</td>
</tr>
</tbody>
</table>

Drug load coating
Top coat Opadry II 85G Blue
## Coating Process Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Layering (Opadry® II)</th>
<th>Color Top Coating (Opadry® II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dispersion solids content (%)</td>
<td>5.67</td>
<td>20.00</td>
</tr>
<tr>
<td>Theoretical weight gain (%)</td>
<td>2.70</td>
<td>2.00</td>
</tr>
<tr>
<td>Dispersion mixing time (minutes)</td>
<td>45.00</td>
<td>45.00</td>
</tr>
<tr>
<td>Pan charge (Kg)</td>
<td>0.45</td>
<td>0.46</td>
</tr>
<tr>
<td>Inlet temperature (°C)</td>
<td>55.00</td>
<td>55.00</td>
</tr>
<tr>
<td>Outlet temperature (°C)</td>
<td>42.00</td>
<td>42.00</td>
</tr>
<tr>
<td>Tablet bed temperature (°C)</td>
<td>45.00</td>
<td>45.00</td>
</tr>
<tr>
<td>Spray rate (g/min)</td>
<td>8.00</td>
<td>5.00</td>
</tr>
<tr>
<td>Pan rotational speed (rpm)</td>
<td>9.00</td>
<td>8.00</td>
</tr>
<tr>
<td>Atomization air pressure (bar)</td>
<td>2.00</td>
<td>2.00</td>
</tr>
<tr>
<td>Air volume (cfm)</td>
<td>150.00</td>
<td>150.00</td>
</tr>
</tbody>
</table>

O’Hara Labcoat-1, 12” perforated pan & Schlick Gun with ABC

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Effect of SLS on Drug Release

900mL 0.01M HCl using USP App 2 (paddle) at 50 rpm. Sinkers were used for dissolution.
Both the release profiles matched the innovators release profile [Data not shown]

900mL 0.01M HCl using USP App 2 (paddle) at 50 rpm. Sinkers were used for dissolution.
Aqueous Drug Layering on Hydrophilic Matrix Tablets - Summary

- Appearance of coated zolpidem matrices was good.
- Biphasic release profile was obtained.
- Uniformity of dosage form was obtained.
- It is recommended to use dilute API solution or high weight gain to ensure uniformity in film thickness and consequently drug content.
- It is recommended to use micronized drug (in case it is insoluble in water) to give more uniform dispersion.
- It is recommended to use a surfactant or surfactant based Opadry system to impart wetting characteristics, avoid floating of active on dispersion.
Case study: Delayed release coating of soft gelatin capsules in a continuous coating process
Continuous coater process flow

Uncoated tablets

• Continuous feed of tablets
• Continuous spray of coating suspension

Fully perforated rotating drum

Coated tablets
Throughput Up to 1300 liters per hour (depending on weight gain)
Solution flow rate 3000 ml/min. maximum (depending on solution characteristics)
Spray Guns - 24 - on two independent manifolds
Air Flow up to 10,000 cfm
Pan Speed 3-18 rpm
Pan Dimensions 24" dia. x 13.3'
Trial objectives

- Evaluate the of application of a delayed release coating in a continuous coating process and assess:
  - Coating consistency
  - Production throughput
  - Minimum weight gain necessary to provide enteric functionality.

- Evaluate mechanisms for reducing or eliminating product losses at start-up and shut-down.
Objectives / Methods

- **Substrate**
  - 1700mg soft gelatin capsules filled with mineral oil

- **Coating material**
  - Nutrateric®
    - Aqueous enteric coating system designed specifically to meet the regulatory requirements for dietary supplement, nutritional and herbal products.

- **Softgels samples throughout the process and tested for resistance to simulated gastric fluid and disintegration time in simulated intestinal fluid.**
Equipment

Pan interior with spray manifold removed

Thomas Spray Bar with Schlick ABC components

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Process – Weigh belt feeder
Process

In feed side

Out feed side

Fill level – 95 kg softgels.

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Trial settings

<table>
<thead>
<tr>
<th></th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target weight gain (%)</td>
<td>4</td>
<td>3.5</td>
<td>4</td>
</tr>
<tr>
<td>Target throughput rate (kg/hr)</td>
<td>130</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Solids concentration (%)</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Spray rate (g/min)</td>
<td>865</td>
<td>1165</td>
<td>1335</td>
</tr>
<tr>
<td>Process air flow (cfm)</td>
<td>6800</td>
<td>6800</td>
<td>6800</td>
</tr>
<tr>
<td>Inlet temperature (deg. C)</td>
<td>47</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>Exhaust temperature (deg. C)</td>
<td>35</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Bed temperature (deg. C)</td>
<td>33</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Product temperature at discharge (deg. C)</td>
<td>30</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Pan speed (rpm)</td>
<td>10</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

1. Nutrateric can be prepared as high as 12% solids concentration depending on pumping systems. At 12%, throughput would be increased by 20%.

2. Typical air flow setting would be 10,000cfm but was not met due to development laboratory air handler limitations. At 10,000 cfm, typical throughput rate for this product would be >300kg / hour.
## Results – Disintegration testing

**Sample time point (min)** | **Trial 1** | **Trial 2** | **Trial 3** | **Sample time point (min)** | **Trial 1** | **Trial 2** | **Trial 3**  
|--------------------------|-------------|-------------|-------------|--------------------------|-------------|-------------|-------------  
| **Time (min.) of resistance to simulated gastric fluid with no signs of disintegration** |              |              |              | **Disintegration time (min) in simulated intestinal fluid (n=6)** |              |              |               
| 0                        | > 60        | > 60        | > 60        | 0                        | 27.5 ± 4.3  | 27.3 ± 3.4  | 28.2 ± 4.5  
| 5                        | > 60        | > 60        | > 60        | 15                       | 22 ± 6.4    | 36.8 ± 5.2  | 29.6 ± 3.6  
| 10                       | > 60        | > 60        | > 60        | 30                       | 29.5 ± 4.8  | 31.5 ± 6.1  | 26.8 ± 5.2  
| 15                       | > 60        | > 60        | > 60        | 45                       | 34.5 ± 7.3  |             |             
| 20                       | > 60        | > 60        | > 60        | 50                       |             |             |             
| 25                       | > 60        | > 60        | > 60        | 55                       |             |             |             
| 30                       | > 60        | > 60        | > 60        | 60                       | 29.4 ± 8.2  |             |             
| 35                       | > 60        |             |             |                          |             |             |             
| 40                       | > 60        |             |             |                          |             |             |             
| 45                       | > 60        |             |             |                          |             |             |             
| 50                       | > 60        |             |             |                          |             |             |             
| 55                       | > 60        |             |             |                          |             |             |             
| 60                       | > 60        |             |             |                          |             |             |              

Trials 2 and 3 ended at 30 minutes of continuous running time.
**Softgel appearance after testing**

**Uncoated** after 5 minutes in simulated gastric fluid

**Nutrateric™ Coated** after 60 minutes in simulated gastric fluid
### Stability

- **Trial 2, foil sealed, 250cc HDPE bottles, 50 capsules per bottle**

<table>
<thead>
<tr>
<th>Storage Time point</th>
<th>40°C / 75% RH Storage conditions</th>
<th>30°C / 65% RH Storage conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (min.) of resistance to simulated gastric fluid with no signs of disintegration (n=6)</td>
<td>Disintegration time (min) in simulated intestinal fluid (n=6)</td>
</tr>
<tr>
<td>Initial</td>
<td>&gt; 60</td>
<td>19.3 ± 6.3</td>
</tr>
<tr>
<td>1 Month</td>
<td>&gt; 60</td>
<td>22.5 ± 4.8</td>
</tr>
<tr>
<td>3 Months</td>
<td>&gt; 60</td>
<td>18.5 ± 5.3</td>
</tr>
</tbody>
</table>

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Summary and Conclusion

- The immediate release film coating:
  - Adds to the tablet robustness and provides protection for further processing such as printing and packaging
  - Enhance aesthetics, easy identification and swallow ability
  - Moisture barrier properties
    With no impact on dissolution profiles

- The functional (modified release) film coating:
  - Reduce initial burst effect and zero order drug release
  - Delayed followed by slow release
  - Reduce potential food effects

- Continuous coating processes
  - Advances in continuous coater design have allowed for more efficient processing
  - This technology can be successfully used to apply functional coatings.

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Film Coating of Modified Release Dosage forms

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