

**8TH ANNUAL PTI TRAINING PROGRAM**

# **FORMULATION AND PROCESS DEVELOPMENT FOR ORAL DOSAGE FORMS**

**A 5-Day Modular and Case Study Oriented Training Program**

**AUGUST 27-31, 2012 - NASSAU INN - PRINCETON - NJ - USA**

**Historical Location, Reputable Speakers & Innovative Program**



# **Overview of Oral Drug Delivery**

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**Technical Lead,**

**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**

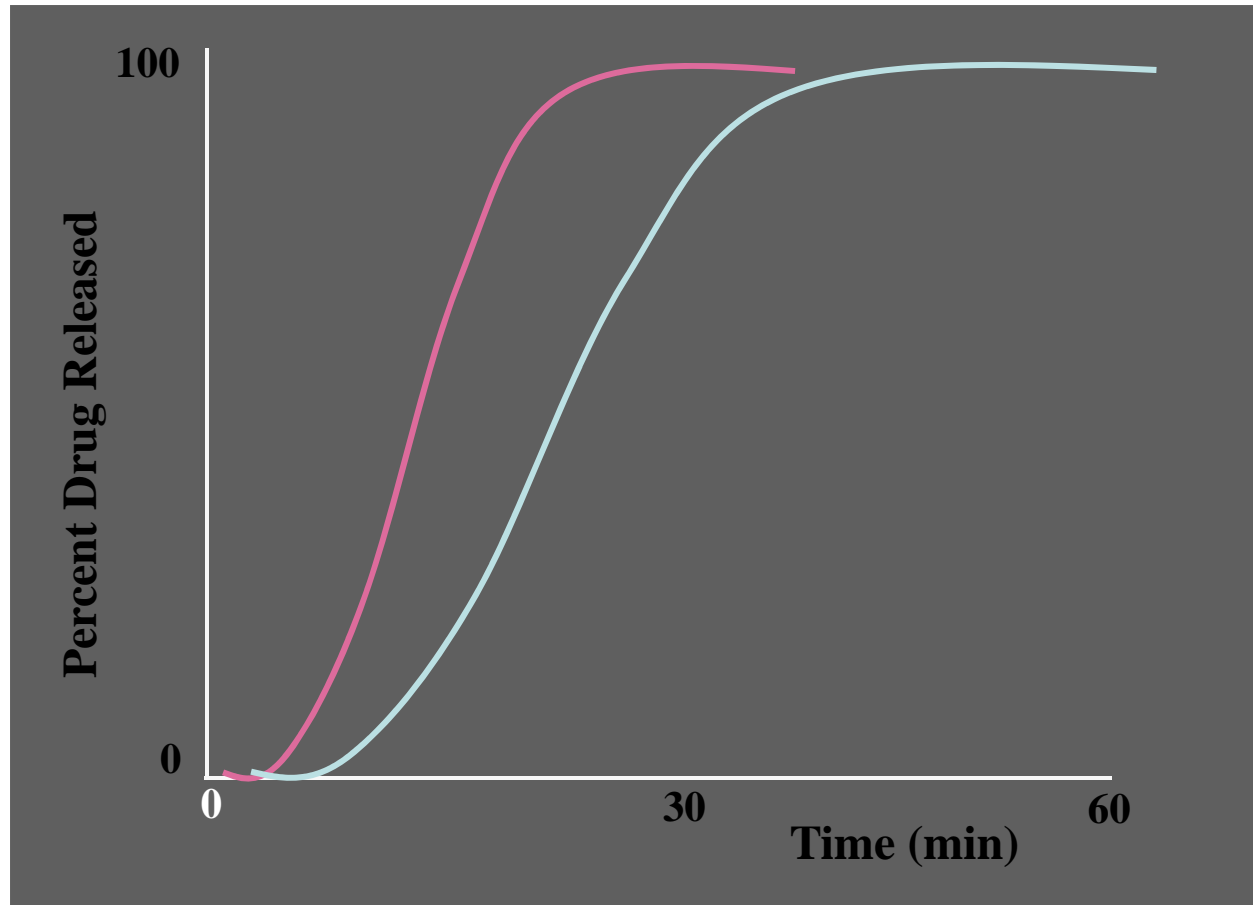


# **Oral Solid Dosage Forms: General Drug Release Concepts**

**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:**

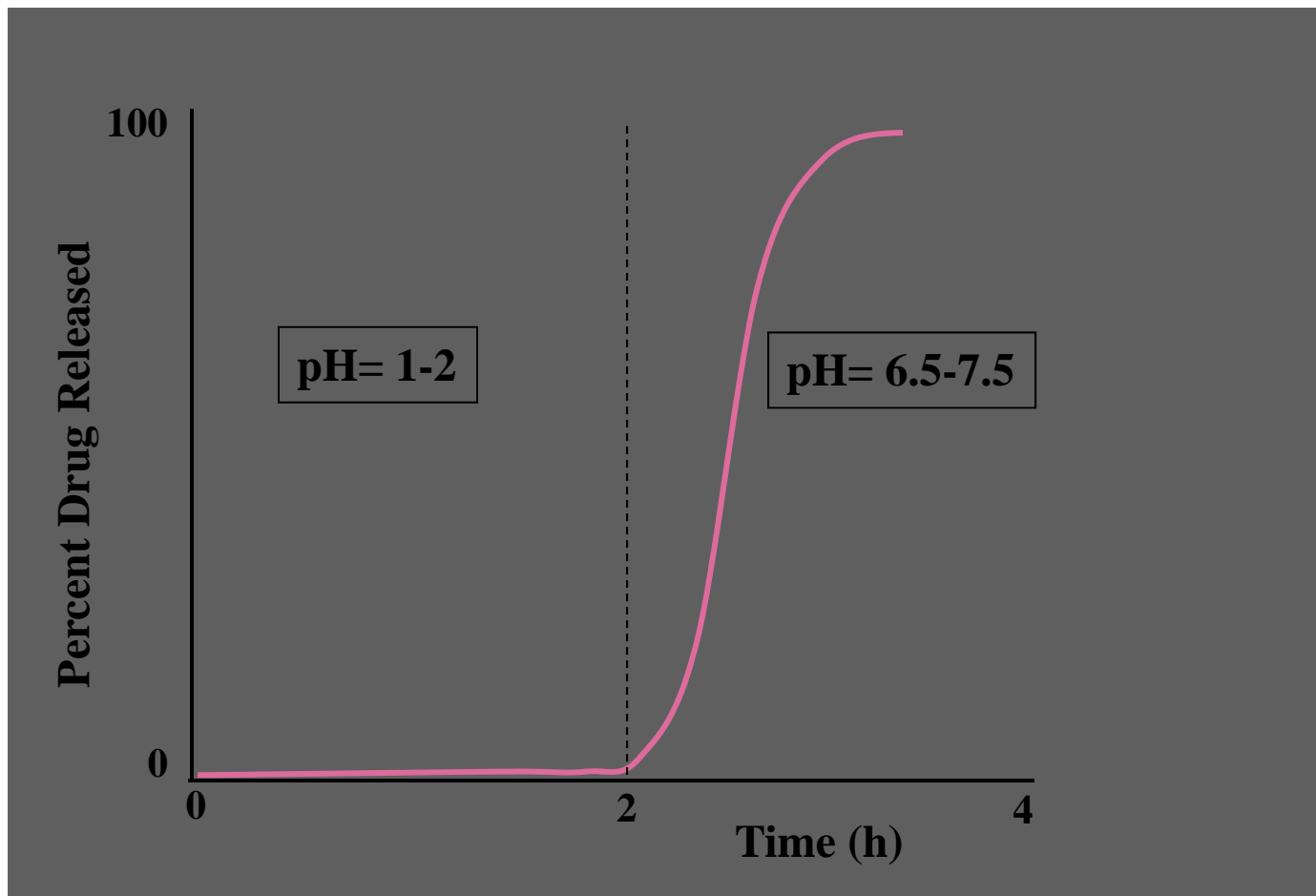
- Delayed-release:
  - Conventional enteric-coated dosage forms.
  - Colonic delivery dosage forms.
  - “Night-time dosing,” sometimes called “chronotherapeutic,” dosage forms.
- Extended-release.

# 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



# Extended-Release Dosage Forms

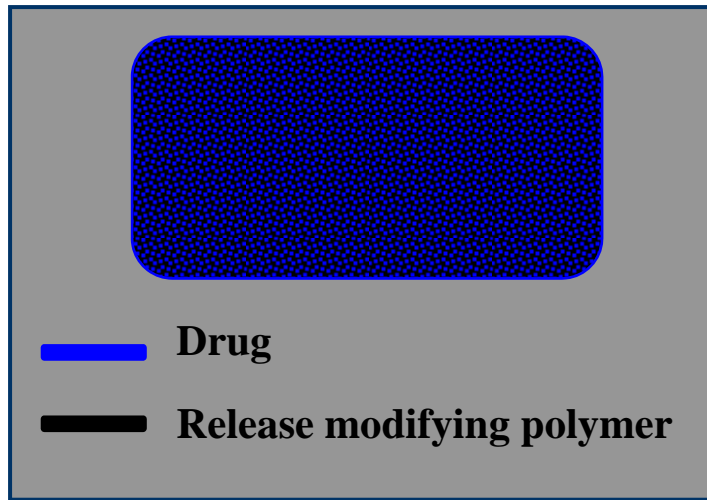
## Tablets:

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

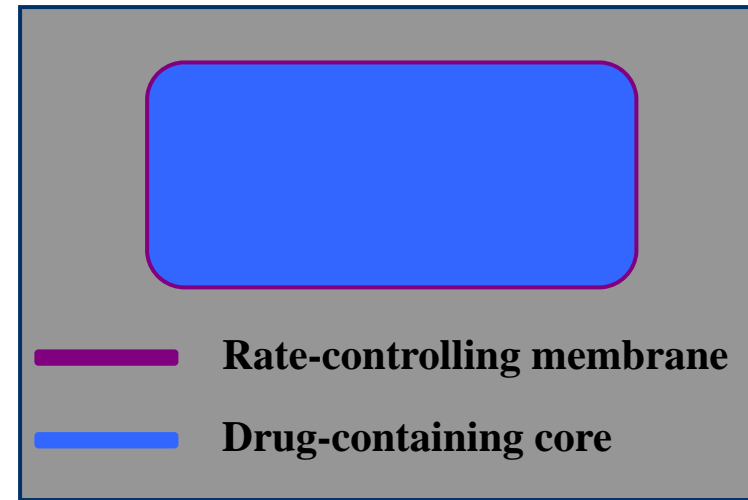
## Capsules:

- 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.

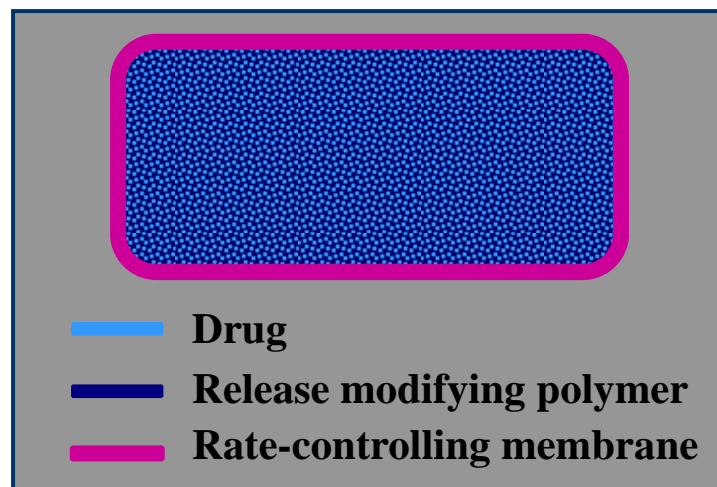
# General Formulation Approaches for Preparing Extended-Release Dosage Forms



**A. Matrix Systems**

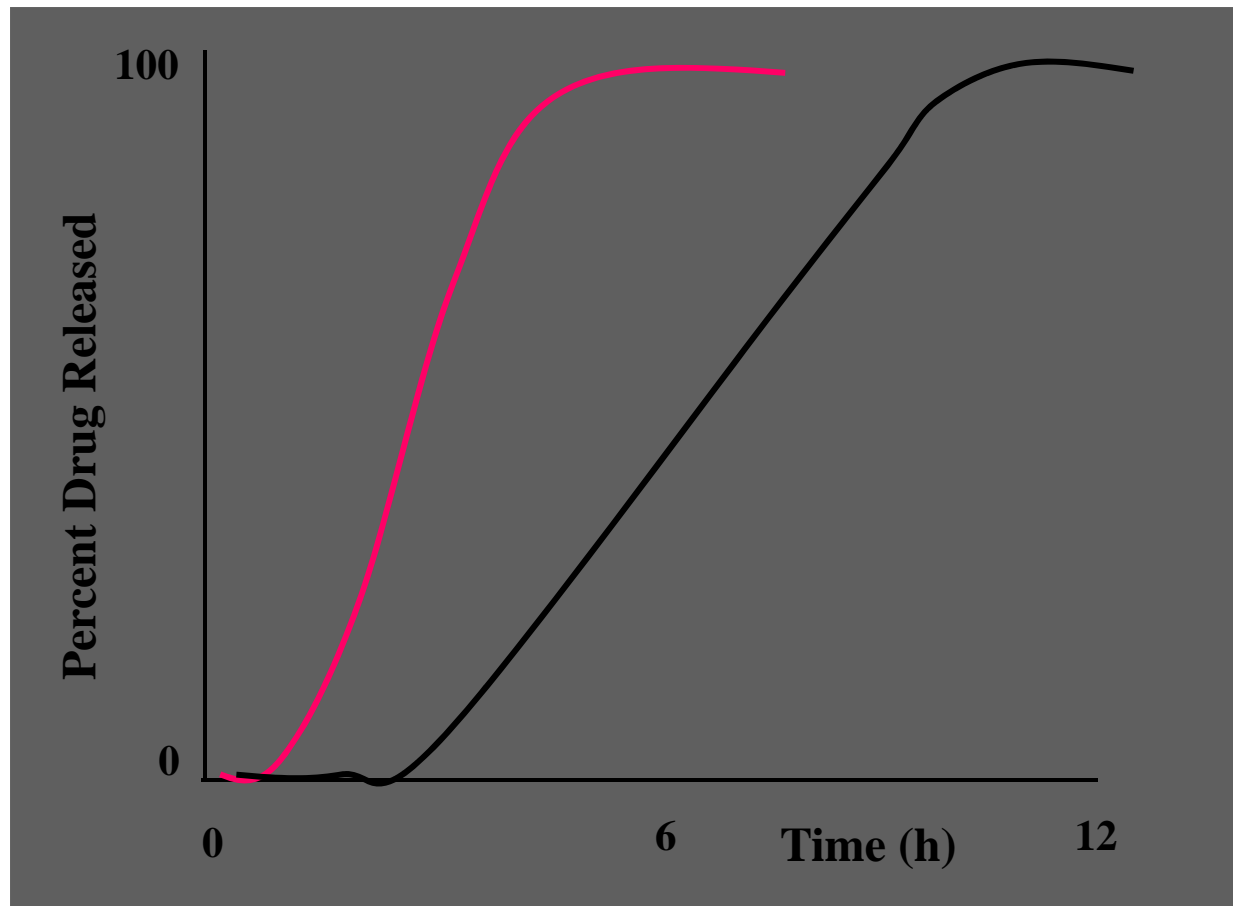


**B. Coated Reservoir Systems**



**C. Coated Matrix Systems**

# Typical Example of Drug Release from Extended-Release Dosage Forms





# **Oral Dosage Forms: General Formulation Approaches**

# **A. Conventional Dosage Forms**

# Conventional Immediate-Release Dosage Forms

**These types of dosage forms are usually presented as either:**

- Tablets, which may be coated, and are made by one of three tableting 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

Ingredient	% w/w
Acetaminophen (APAP)*	18.82
Mannitol (Spray Dried)	59.08
Polyplasdone XL-10	20.00
Sodium stearyl fumarate	1.00
Colloidal SiO <sub>2</sub>	0.30
Flavor	0.50
Sucralose	0.20
Color (lake)	0.10



(\* Taste-masked form)

## **C. Modified-Release Dosage Forms**

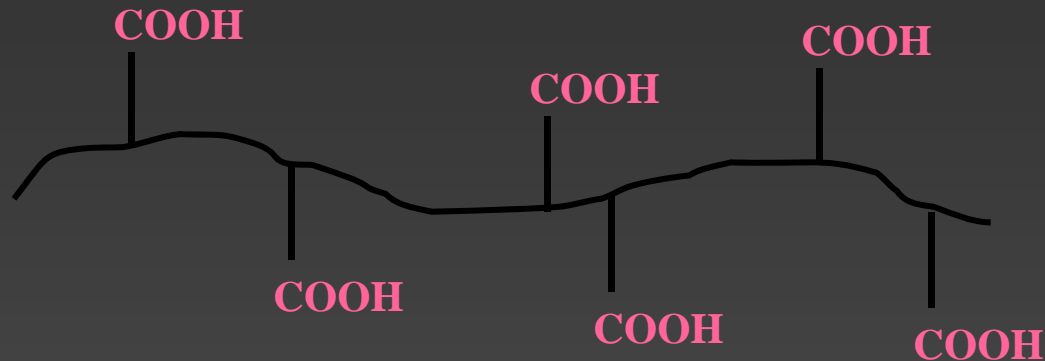


# Delayed-Release Products

## 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

Polymer	Comments
Cellulose acetate phthalate.	Hydrolysis potential – high.**
Cellulose acetate trimellitate.	Hydrolysis potential – medium.**
Polyvinylacetate phthalate.	Hydrolysis potential – low.**
Hydroxypropylmethylcellulose phthalate.	Hydrolysis potential – medium.**
Hydroxypropylmethylcellulose acetate succinate.	Hydrolysis potential – low.**
Poly (MA – EA)* 1:1.	-
Poly (MA – MMA)* 1:1.	Relatively high dissolution pH.
Poly (MA – MMA)* 1:2.	Relatively high dissolution pH.
<p>*MA = Methacrylic acid; EA = Ethyl acrylate; MMA = Methyl methacrylate.  ** When exposed to conditions of elevated temperature and humidity.</p>	

## Examples of Aqueous Enteric-Coating Systems

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

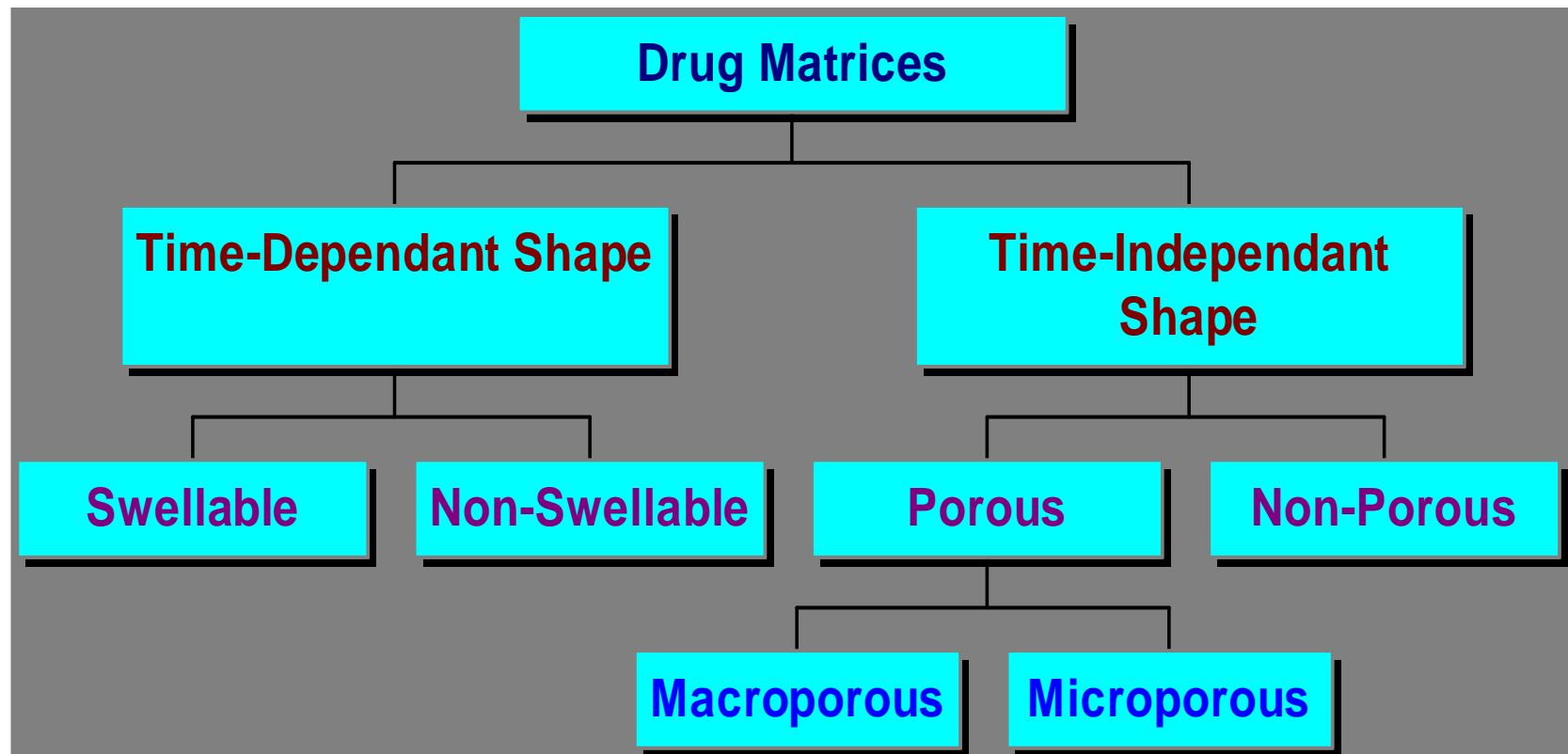
- Matrix powder blends.
- Matrix liquid formulations or “hot-melts”.

# Functional Materials Used in Extended-Release Matrix Products

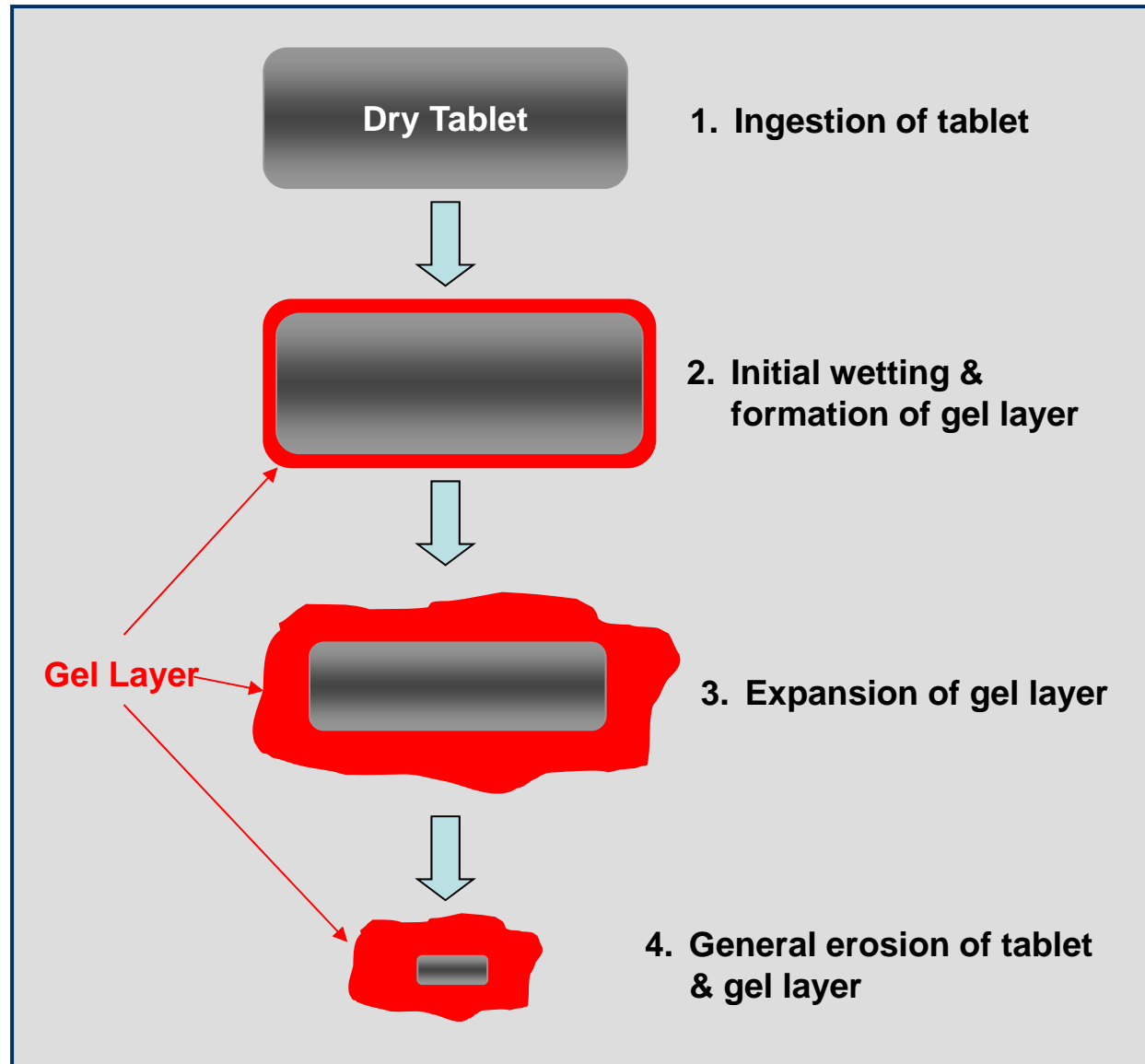
Hydrophobic Matrices	Hydrophilic Matrices
Propylene glycol monostearate	Poly (HEMA)
Hydrogenated vegetable oil	Poly (vinyl pyrrolidone)
Poly (vinyl stearate)	Poly (vinyl alcohol)
Poly (vinyl chloride)	Hydroxypropylmethylcellulose
Polyethylene	Hydroxypropylcellulose
Glycerol palmito-stearate	Sodium carboxymethylcellulose
Hydrogenated palm oils	Alginates
Hydrogenated beta palm oils	Poly (lactic acid)
	Poly (glycolic acid)
	Cellulose acetate
	Cellulose acetate butyrate



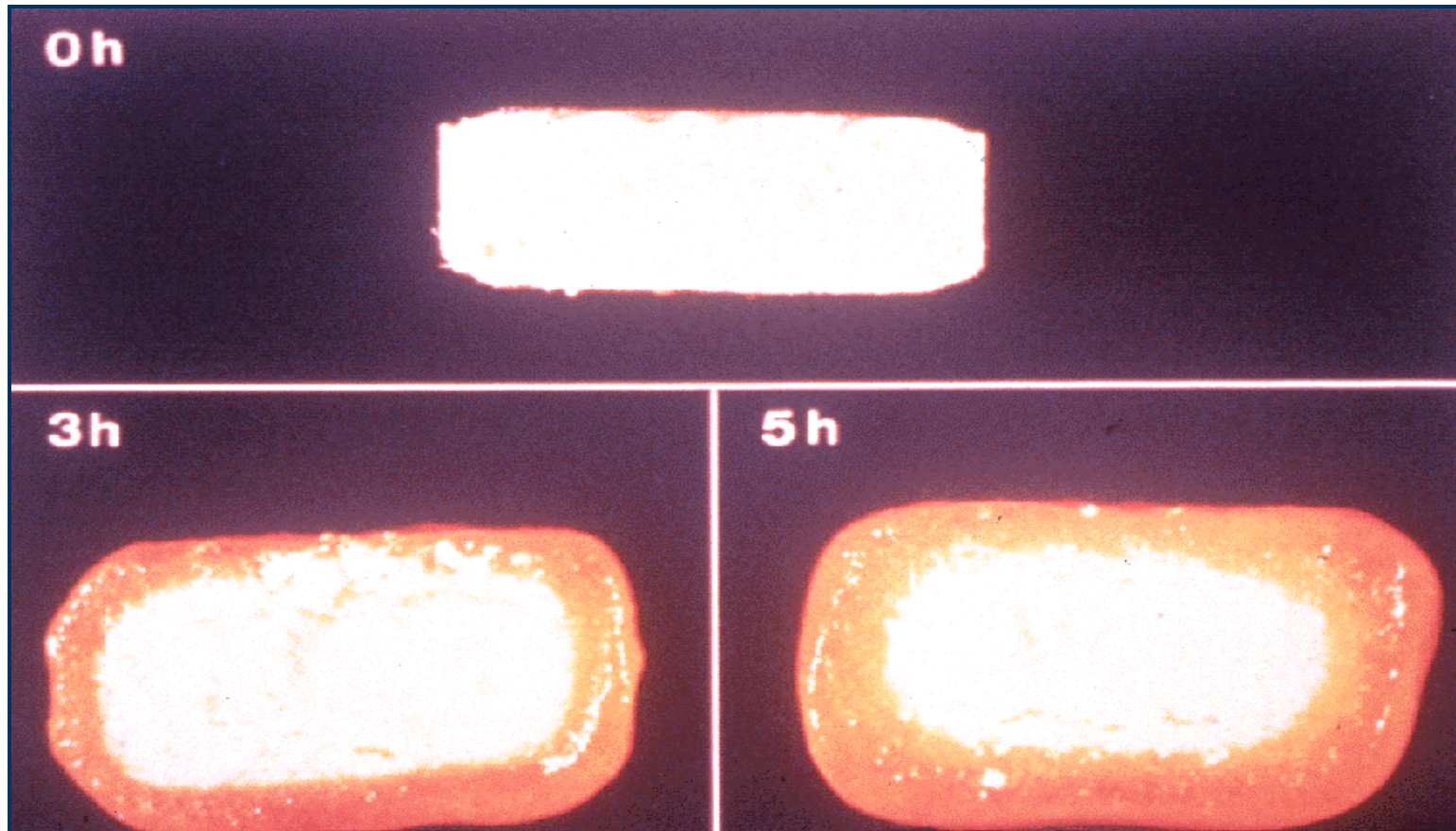
# Summary of Types of Matrix Formulations Used in Extended-Release Applications



# Schematic Overview of Drug Release from Hydrophilic Matrix Tablets

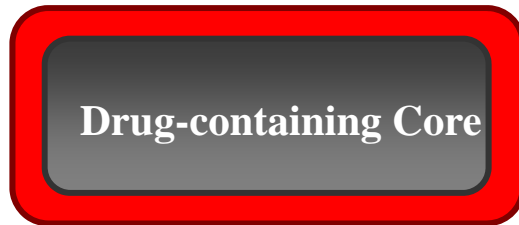


# Swelling & Gelling of Hydrophilic Matrix Tablets



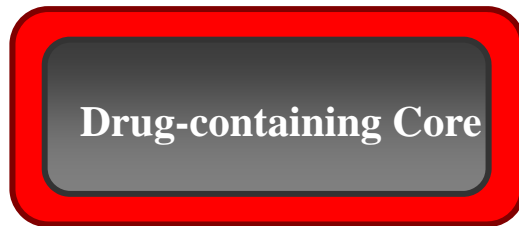
# **Film-Coated Extended-Release Products**

# Typical Film-Coating Applications



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

# Typical Film-Coating Applications

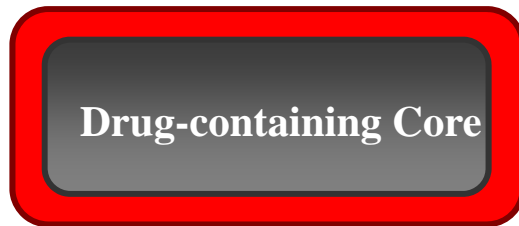


**1. A continuous film coating is applied to the core containing the drug.**



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

# 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

Coating Material	Membrane Characteristics
1. Fats & waxes (beeswax; carnauba wax; cetyl alcohol; cetostearyl alcohol).	Permeable and erodible.
2. Shellac.	Permeable & soluble (at high pH).
3. Zein.	Permeable & soluble (at high pH).
4. Ethylcellulose.	Permeable & water-insoluble.
5. Cellulose esters (e.g. acetate).	Semi permeable & water insoluble.
6. Acrylic ester copolymers	Permeable & water insoluble.

# Aqueous Polymer Dispersions Used in Extended-Release Film-Coating Formulations

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

(\*Also available as equivalent Kollicoat dispersions)

# Examples of Materials that Can be Used for Hot-Melt Film Coating

Product Name	Product Type	Viscosity at 99 °C (cP)	Melting Point (°C)
Atmul 84K	Mono- and diglycerides	-	62.0
Vybar 253	Hydrocarbon	6.0	67.0
Beeswax 422	Hydrocarbon	≈ 50	63.5
Synthetic Spermaceti 4013	Hydrocarbon	-	47.5
Paraffin 173	Hydrocarbon	39	59.5

# **Material Characteristics that Need to be Considered in a Hot-Melt Coating Process**

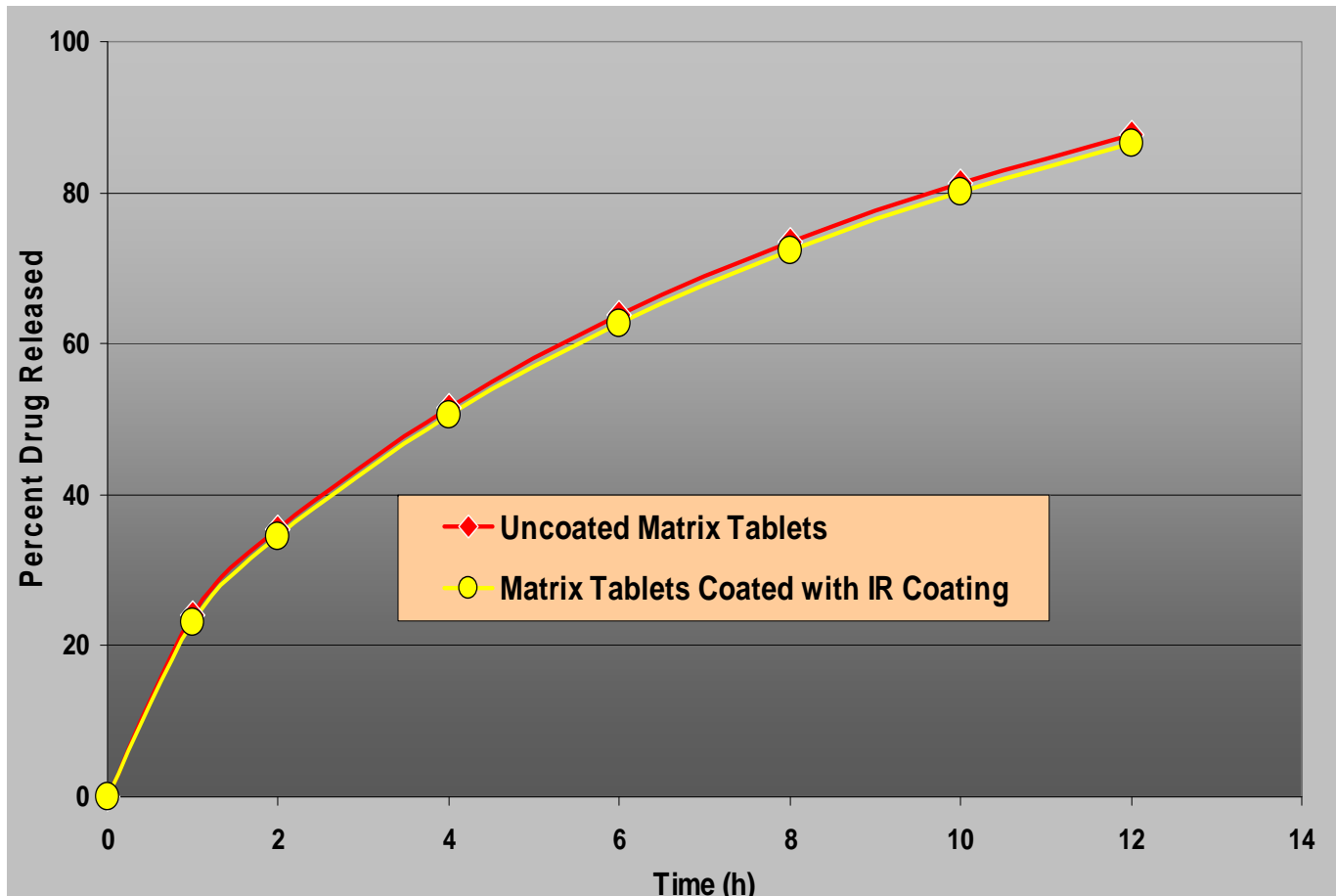
- **Melting Point.**
- **Melting range (a wide range complicates process control).**
- **Melt viscosity (a relatively low viscosity is required to produce smooth, uniform coatings).**

# Coated Matrix Extended-Release Products

The type of coating formulation may comprise:

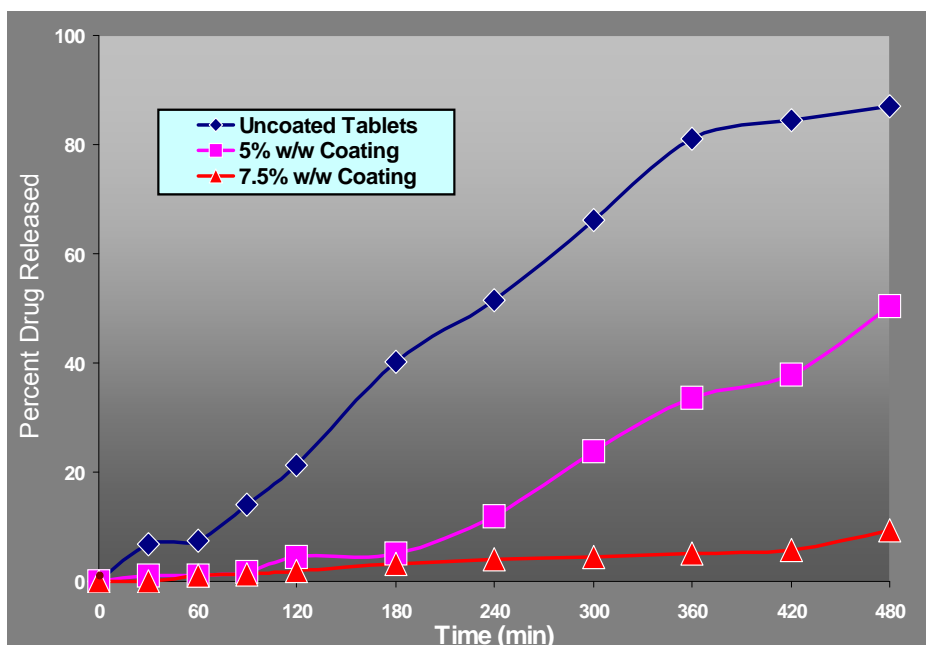
- An immediate-release coating formulation.
- A delayed-release coating formulation.
- An extended-release coating formulation.
- A combination thereof.

# Drug Release Characteristics of Hydrophilic Matrix Tablets Coated with an Immediate-Release Film Coating

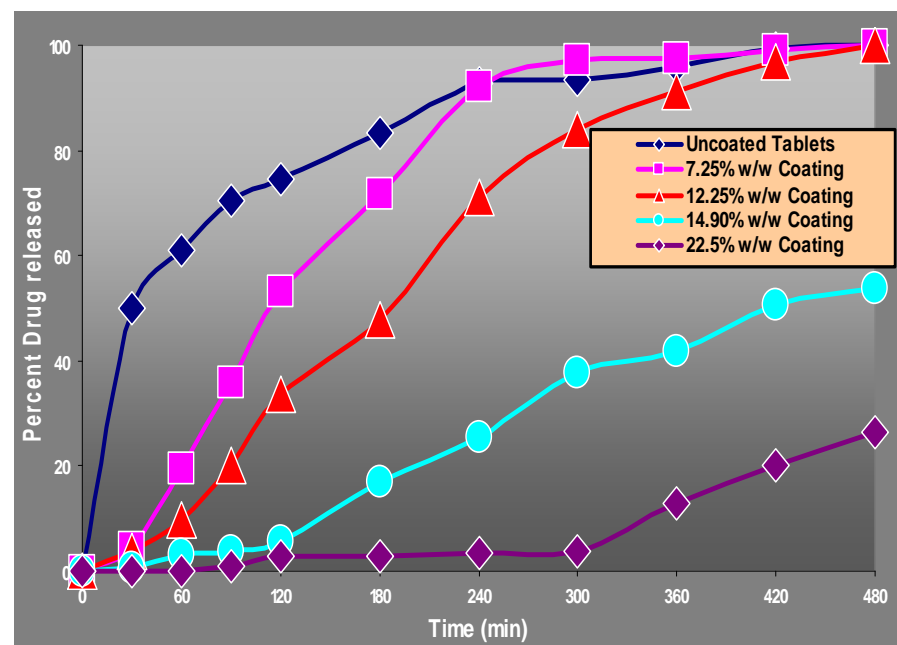




# Drug Release Characteristics of Hydrophilic Matrix Tablets (Uncoated & Film-Coated with an Extended-Release Film Coating)

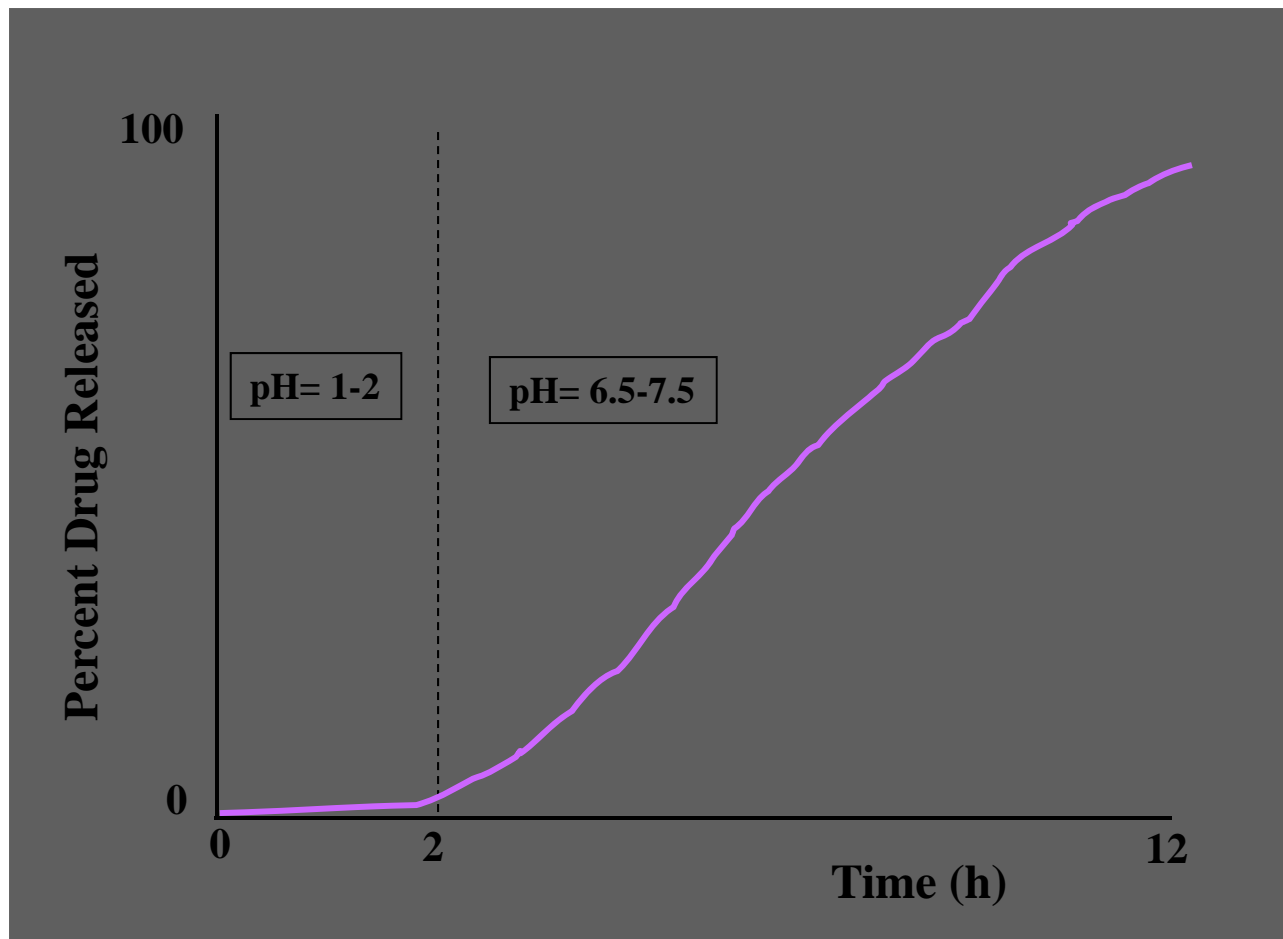


A. 10 mm Tablets



B. 2 mm Tablets

# Model Concept of Drug Release from Matrix Tablet Coated with a Delayed-Release Film Coating

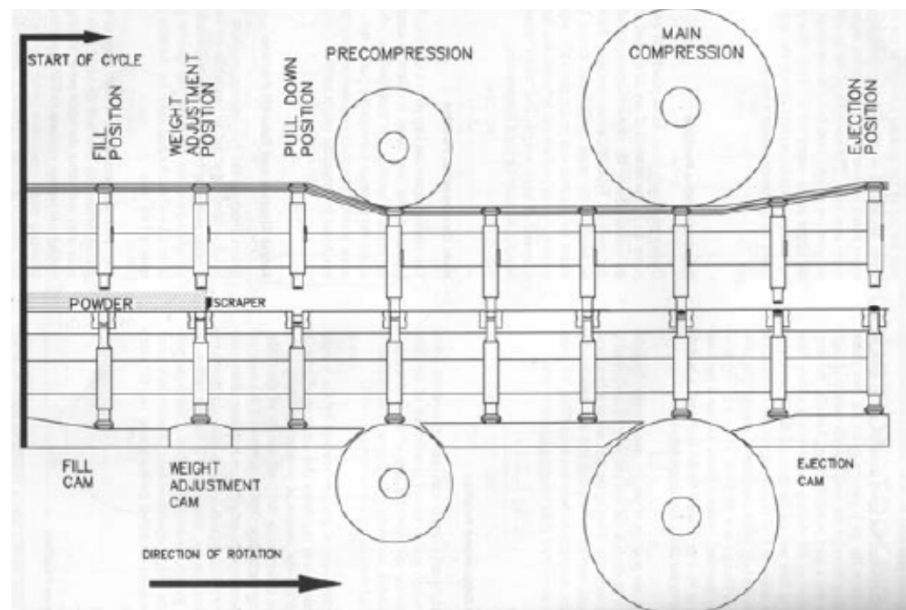


# **Oral Dosage Forms: Design & Processing Concepts**

# 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.

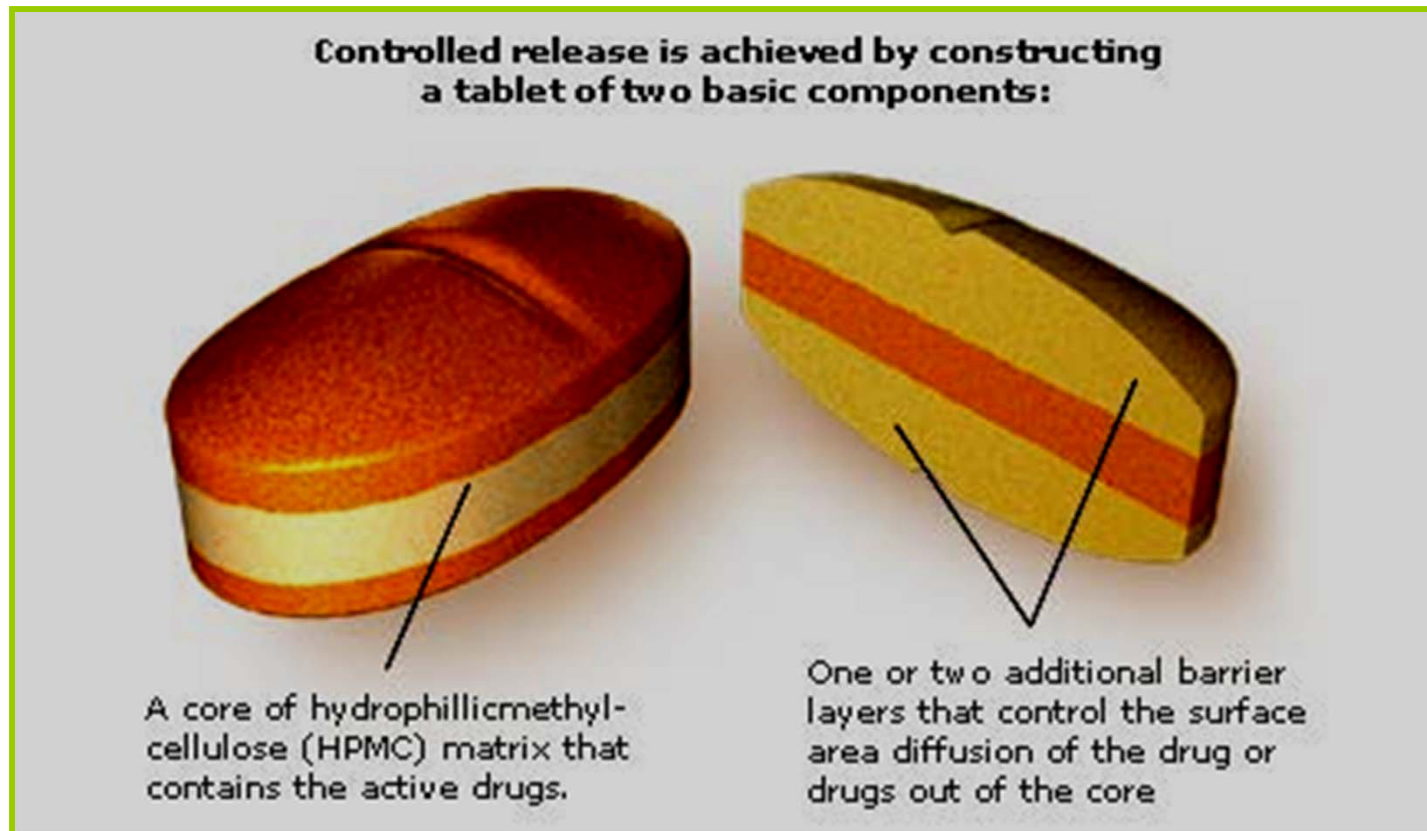


# Compression Coated Matrix Tablets

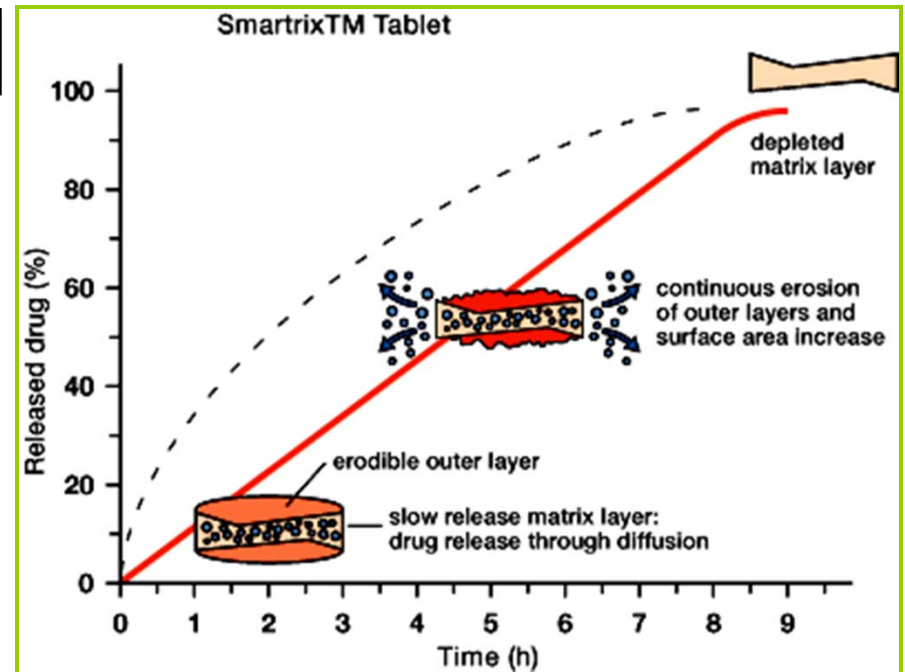
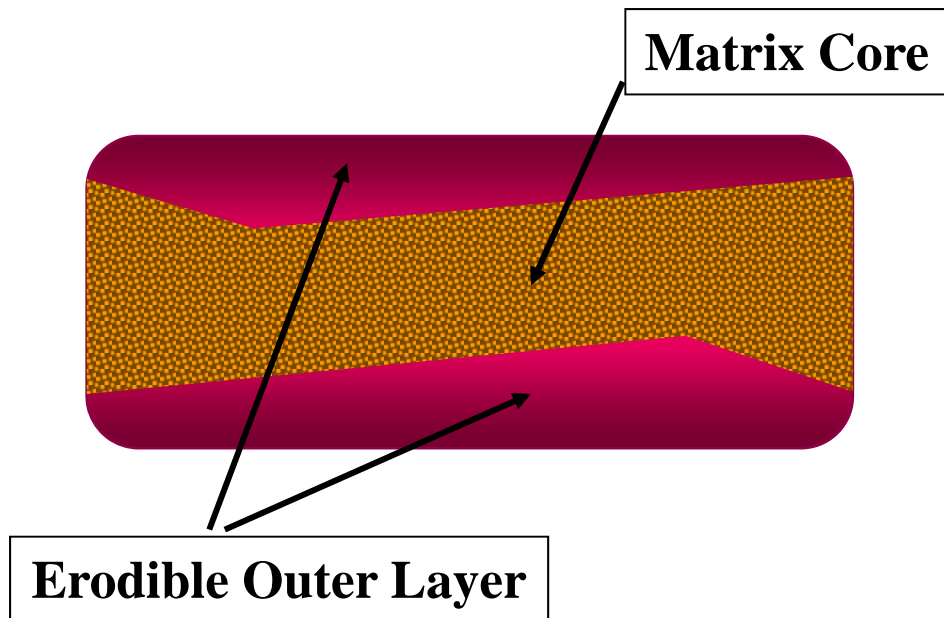
**Fundamentally, this technology involves:**

- **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.**

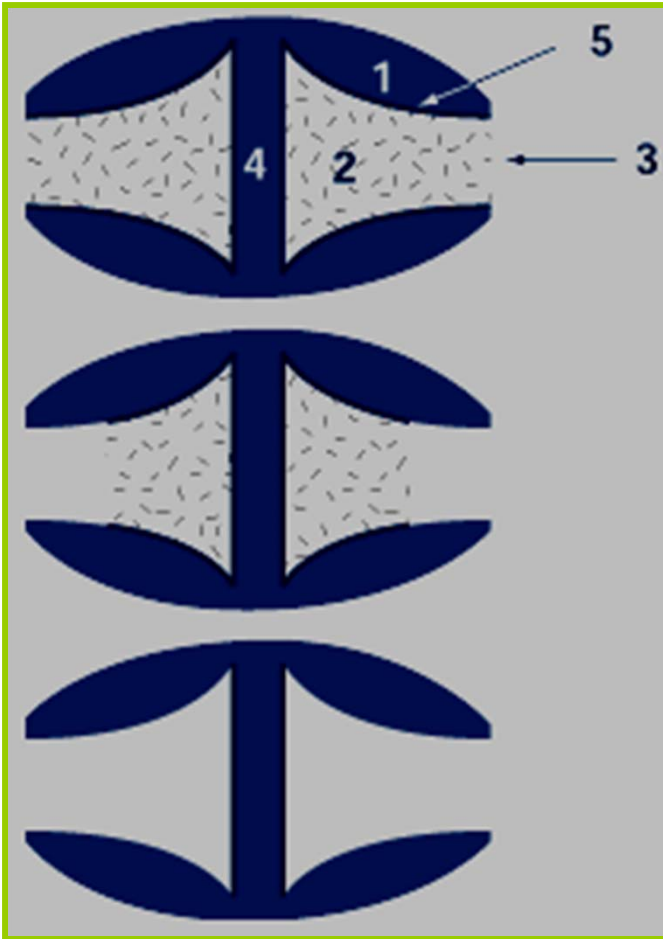
# Skye Pharma Geomatrix<sup>®</sup> Technology



# Smaratrix™ Technology



# 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"**

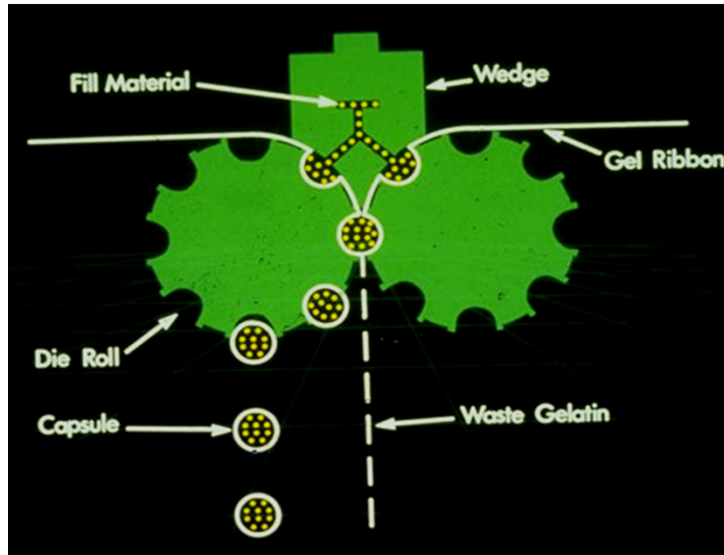


**E. Thixotropic Liquids**



**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.

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

# “Chronotherapeutic” Technologies

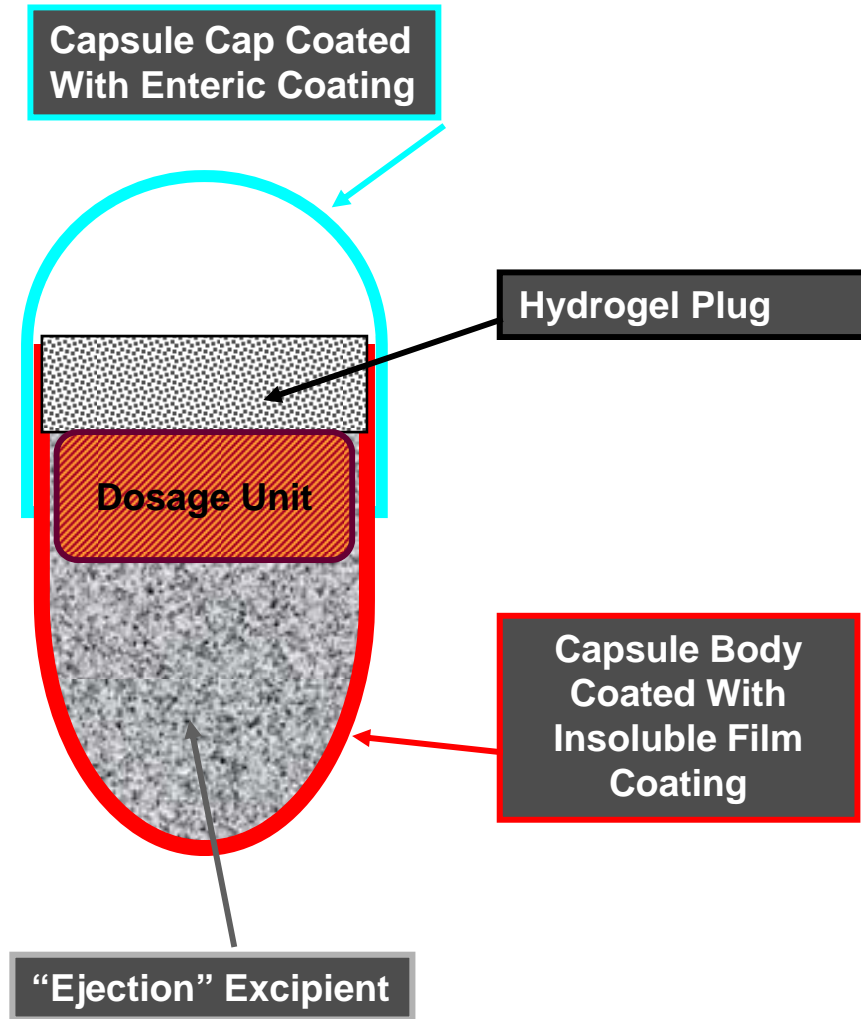
- A device, based on a two-piece gelatin capsule, that releases the drug at a specific time after ingestion.
- Original Pulsincap<sup>®</sup> technology was owned by RP Scherer, but was not commercialized.
- Further developments have been ongoing at the University of Strathclyde.

# **“Chronotherapeutic” Technologies**

- **A device, based on a two-piece gelatin capsule, that releases the drug at a specific time after ingestion.**
- **Original Pulsincap<sup>®</sup> 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



# 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.

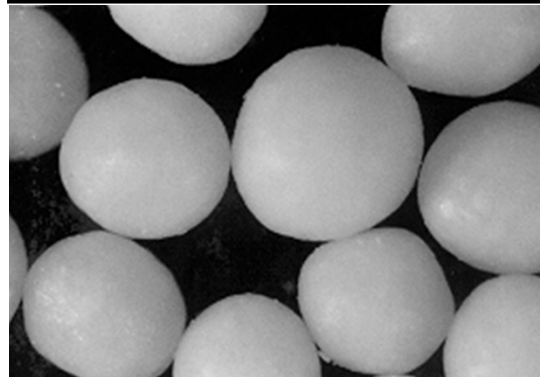
# Examples of Pan Film-Coated Tablets



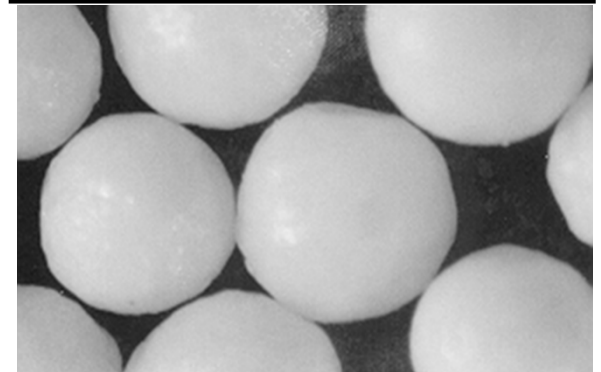
# Examples of Fluid-Bed Film-Coated Multiparticulates



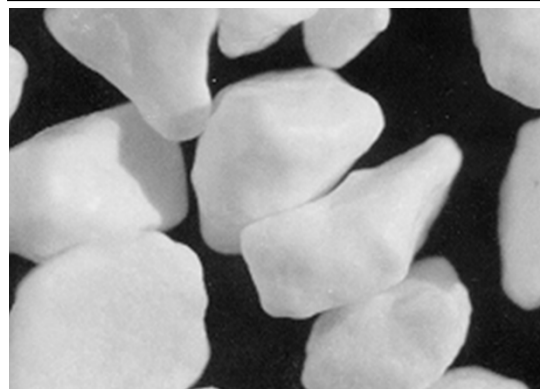
1. Spheronized Granules



2. Drug-loaded “Non-pareils”



3. Regular Granules



4. “Mini” Tablets



# Examples of Enrobed Tablets



**A. Gel Enrobing Process**



**B. FMC NROBE™ Process**



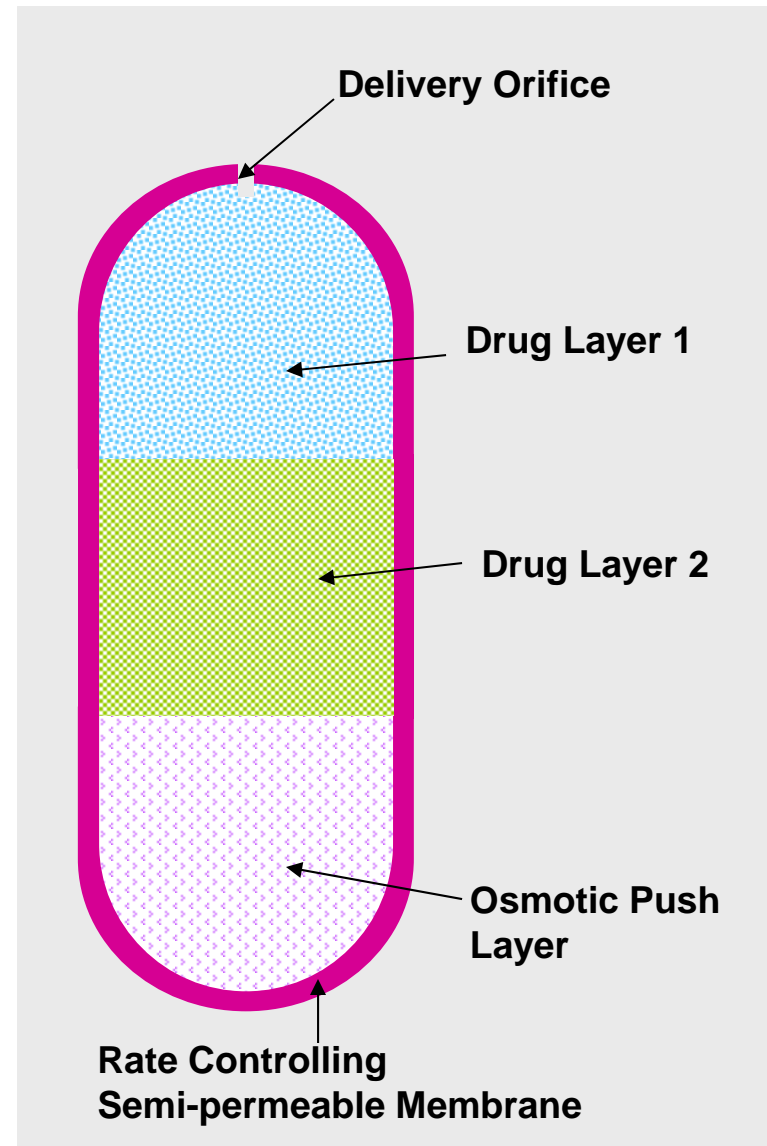
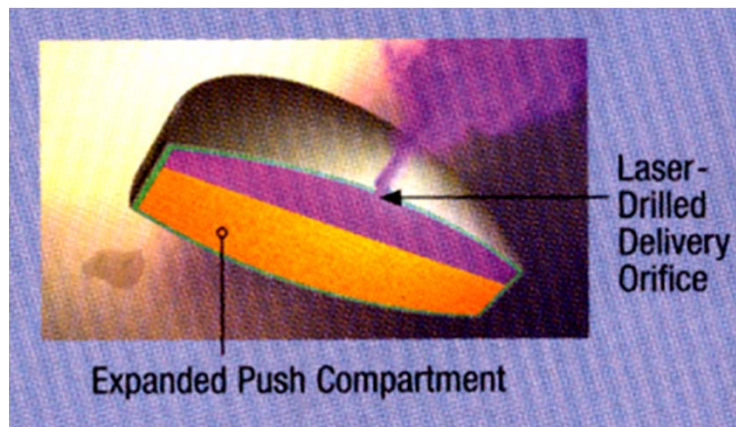
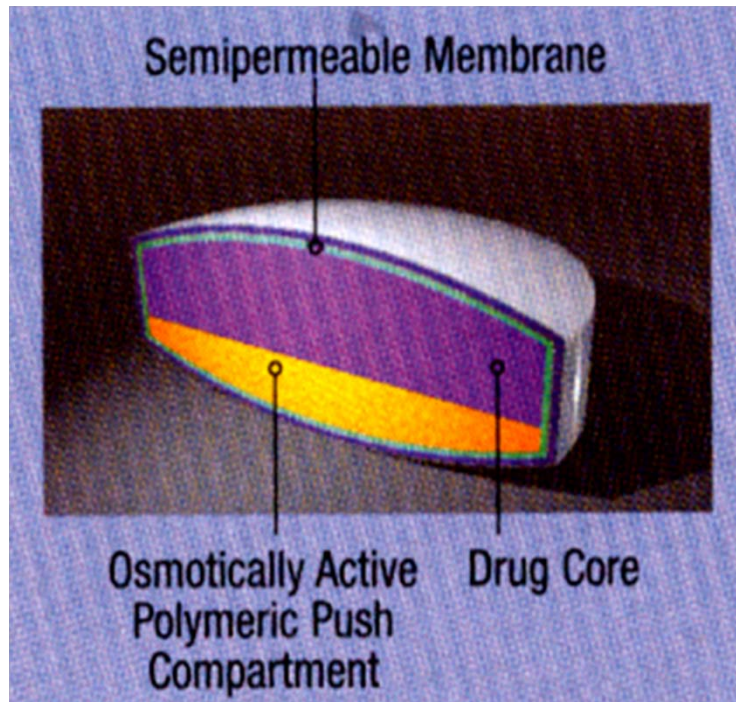
**C. Bioprogress TABWRAP™ Process**

# 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<sup>®</sup> Technology: Basic Concepts



# **Banded, Film-Coated Caplet Technology**

**Concept involves:**

- **Designing a matrix sustained-release tablet core.**



# **Banded, Film-Coated Caplet Technology**

## **Concept involves:**

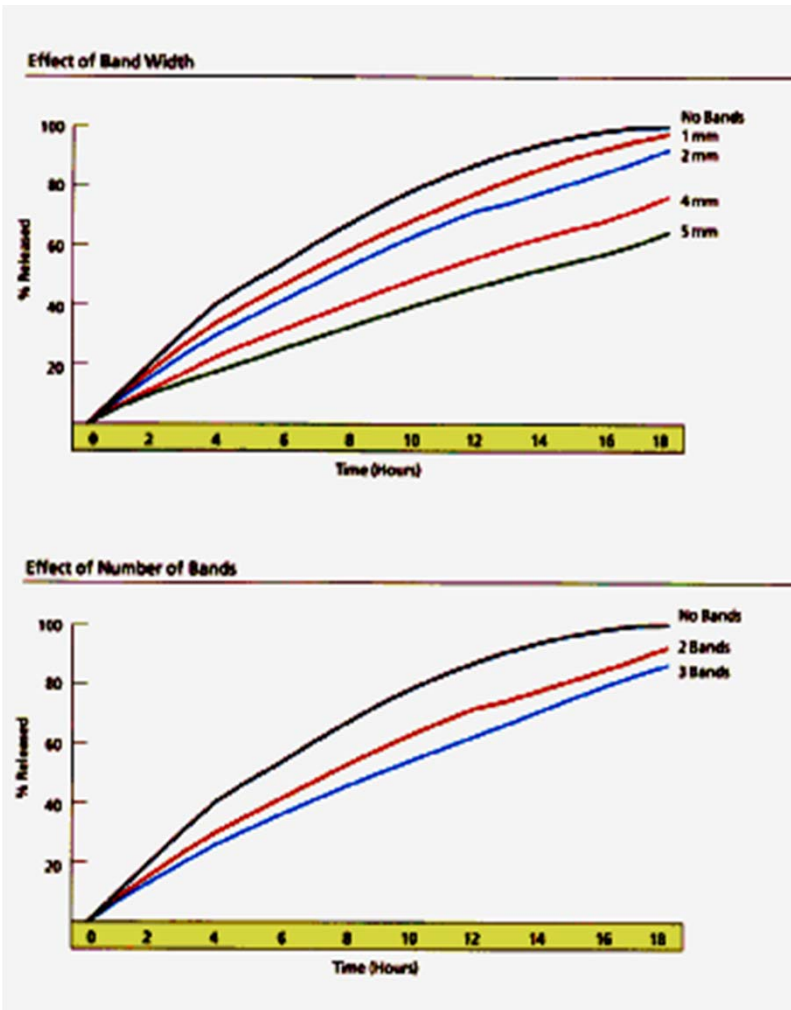
- **Designing a matrix sustained-release tablet core.**
- **Film coating the core with a water-soluble coating.**
-

# **Banded, Film-Coated Caplet Technology**

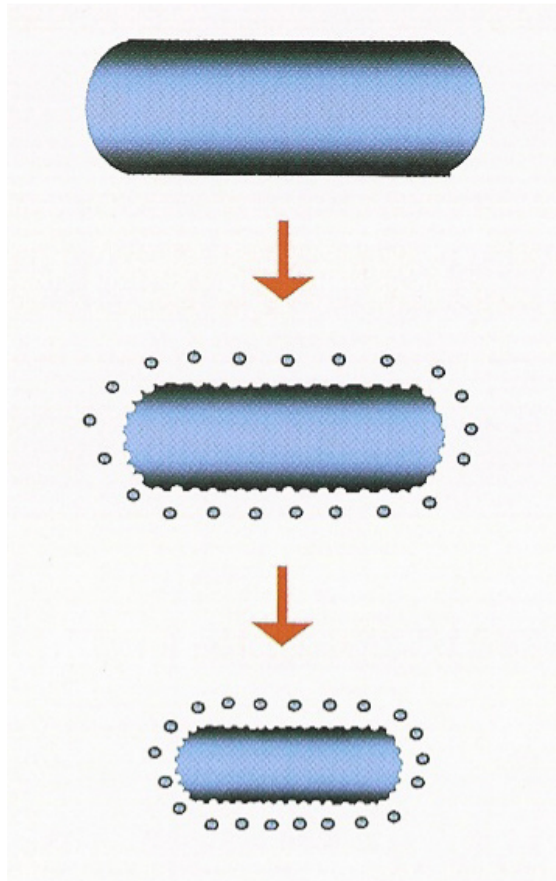
## **Concept involves:**

- **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.**

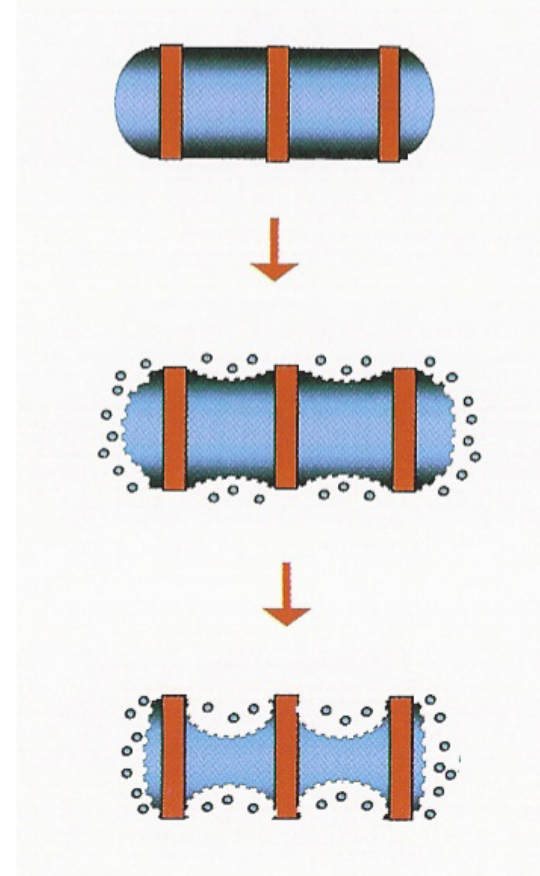
# Alkermes RingCap™ Technology



# Alkermes RingCap™ Technology



**A. Erosion of Conventional Matrix Tablet**



**A. Erosion of RingCap™ Matrix Tablet**

# Electrostatic Processes

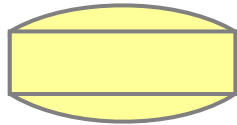
Fundamental process involves the application of film coatings to tablet cores using electrostatic process (LeQtracoat<sup>®</sup> process).

# LeQtracoat<sup>®</sup> Technology

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

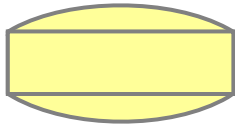
# Electrostatic Dry Powder Coating Technology

## *Formulation*



# Electrostatic Dry Powder Coating Technology

## *Formulation*

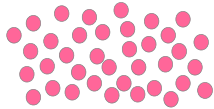
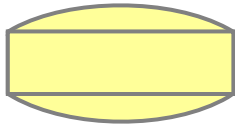


**Tablet core must have certain  
conductive properties or be  
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# Electrostatic Dry Powder Coating Technology

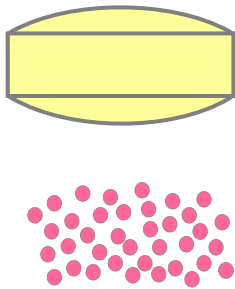
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# Electrostatic Dry Powder Coating Technology

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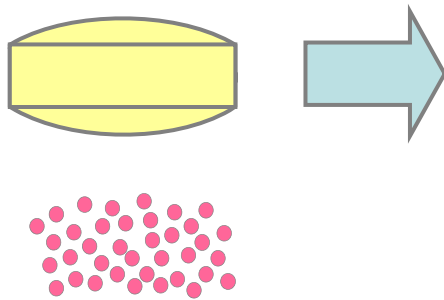
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# Electrostatic Dry Powder Coating Technology

## *Formulation*



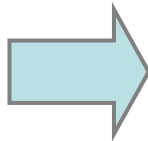
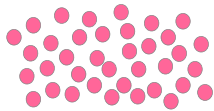
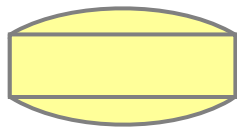
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# Electrostatic Dry Powder Coating Technology

***Formulation***



***Electrostatic coating***



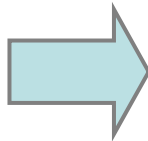
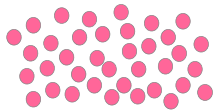
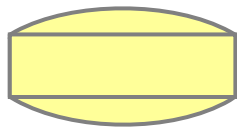
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# Electrostatic Dry Powder Coating Technology

***Formulation***



***Electrostatic coating***



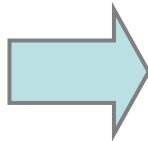
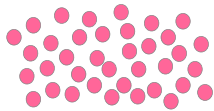
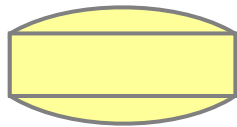
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# Electrostatic Dry Powder Coating Technology

***Formulation***



***Electrostatic coating***



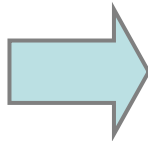
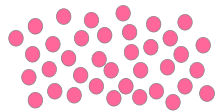
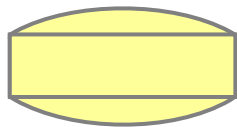
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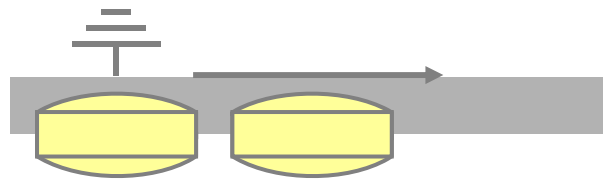
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# Electrostatic Dry Powder Coating Technology

***Formulation***



***Electrostatic coating***



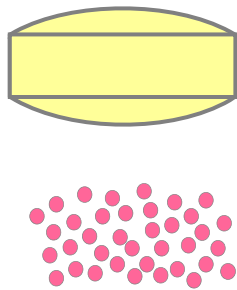
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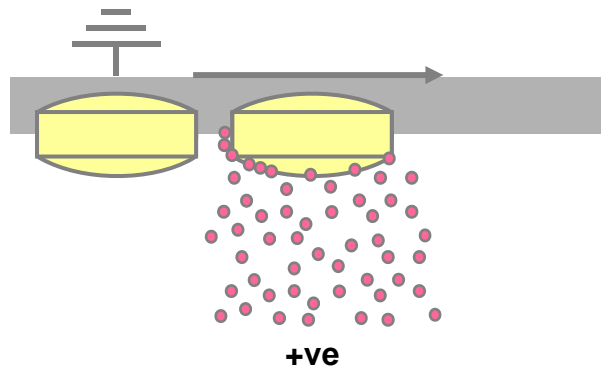
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# Electrostatic Dry Powder Coating Technology

## *Formulation*



## *Electrostatic coating*



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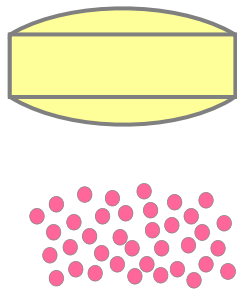
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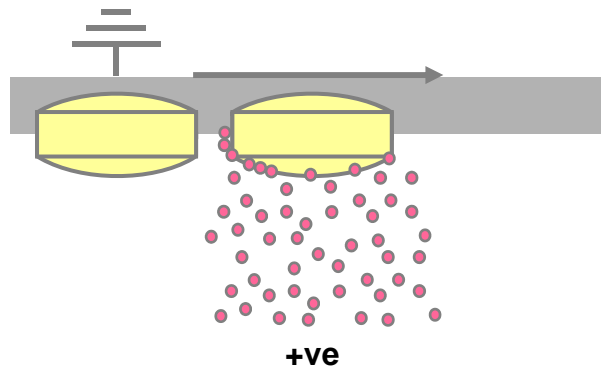


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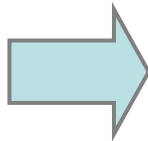
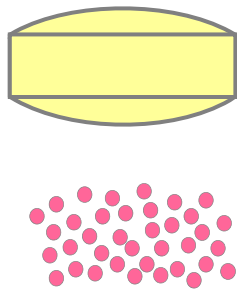
## *Electrostatic coating*



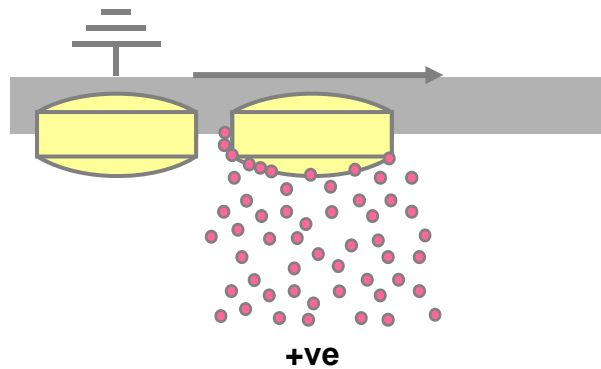
A known field is applied, and the tribocharged powder is attracted onto the tablet

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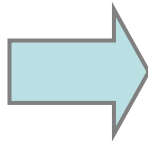
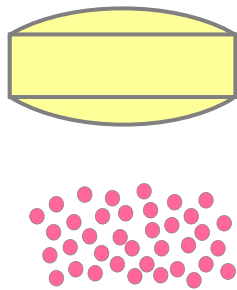
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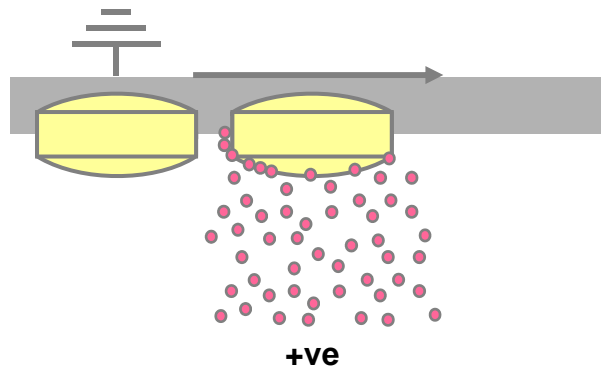
**Precise quantities are  
applied on every tablet**

# Electrostatic Dry Powder Coating Technology

## *Formulation*



## *Electrostatic coating*



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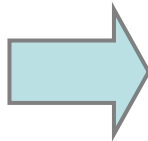
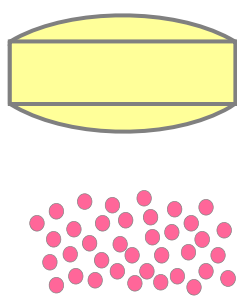
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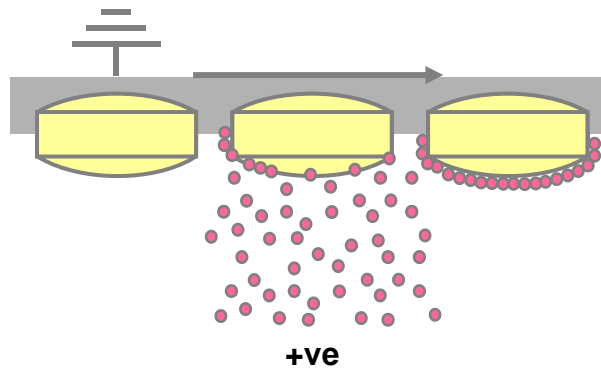
**The process settings are  
manipulated to change the  
coating pattern**

# Electrostatic Dry Powder Coating Technology

## *Formulation*



## *Electrostatic coating*



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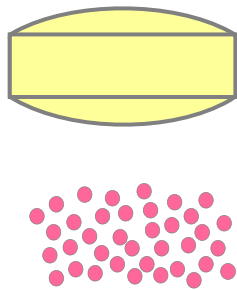
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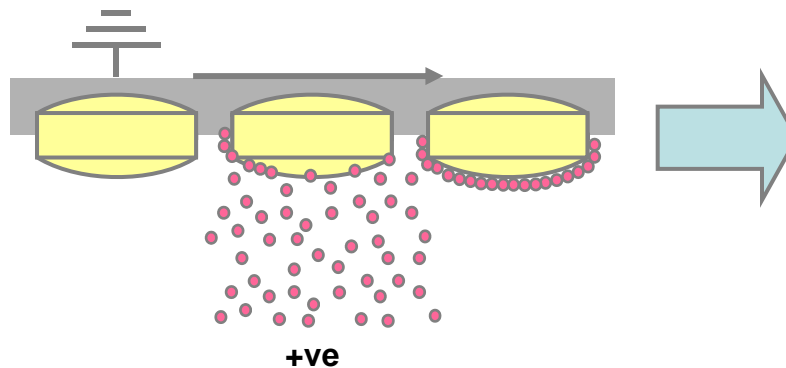


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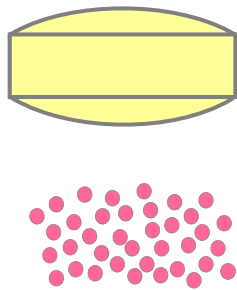
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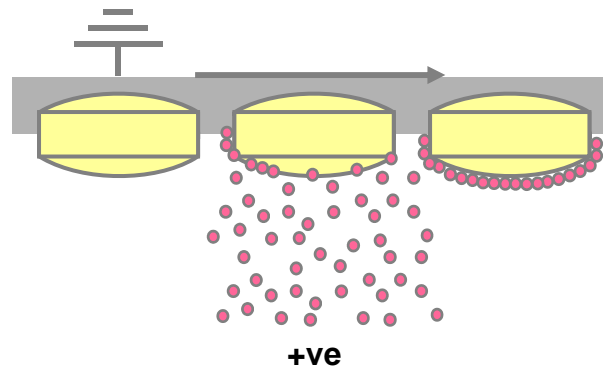


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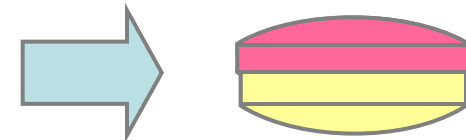


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The process settings are manipulated to change the coating pattern

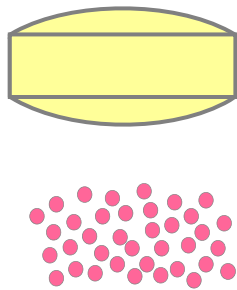
## *Heat fixation*



Radiant heat applied to fuse and fix the coating powder on to the tablet core

# Electrostatic Dry Powder Coating Technology

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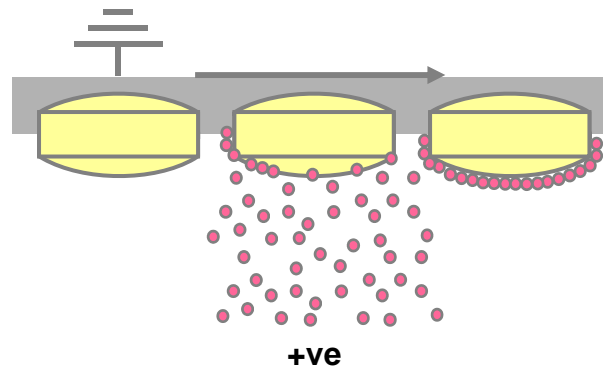


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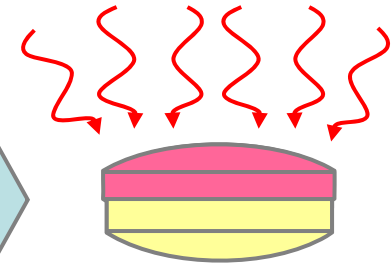


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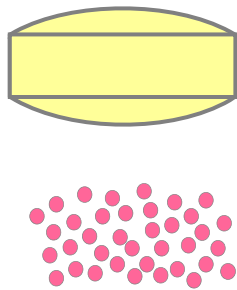


Radiant heat applied to fuse and fix the coating powder on to the tablet core

Up to 80 seconds heat exposure (per side)

# Electrostatic Dry Powder Coating Technology

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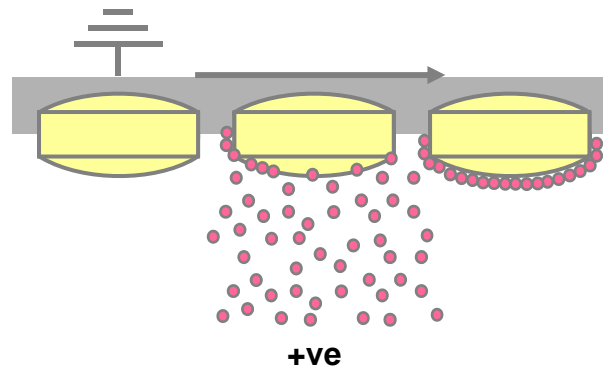


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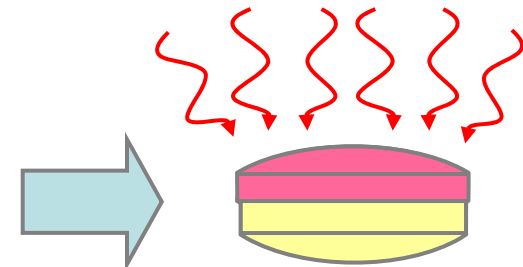


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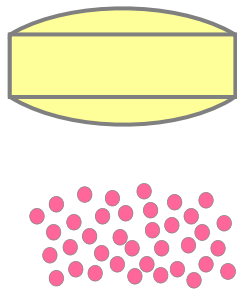
Up to 80 seconds heat exposure (per side)

Typical temperature  
Core 60° C  
Coating 120° C



# Electrostatic Dry Powder Coating Technology

## Formulation

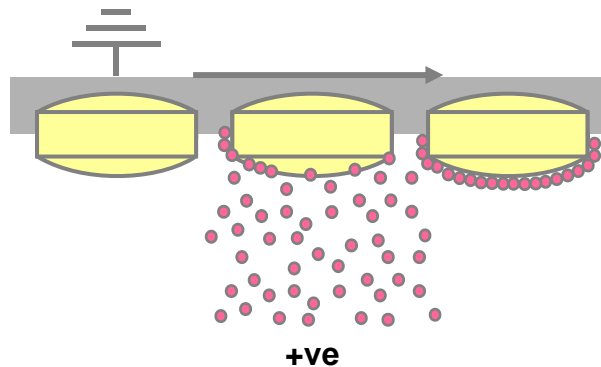


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Radiant heat applied to fuse and fix the coating powder on to the tablet core

Up to 80 seconds heat exposure (per side)

Typical temperature  
Core 60° C  
Coating 120° C

# Applications of Electrostatic Dry Powder Coating Techniques

*Anti-counterfeit and product branding*



*Robust ODT's*



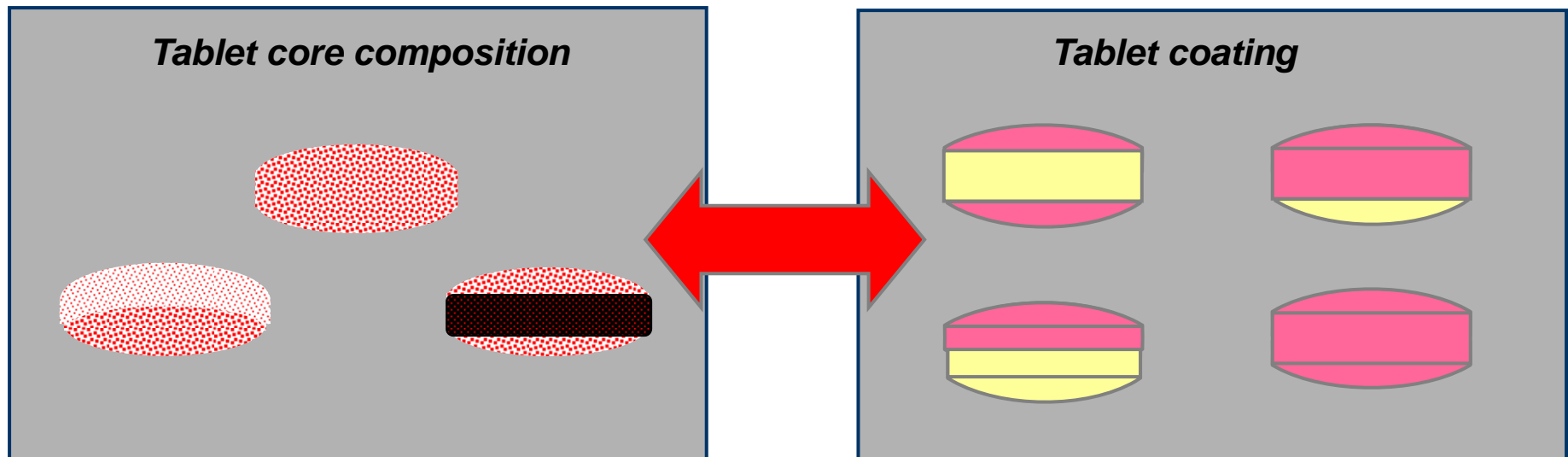
*Modified-release platform*



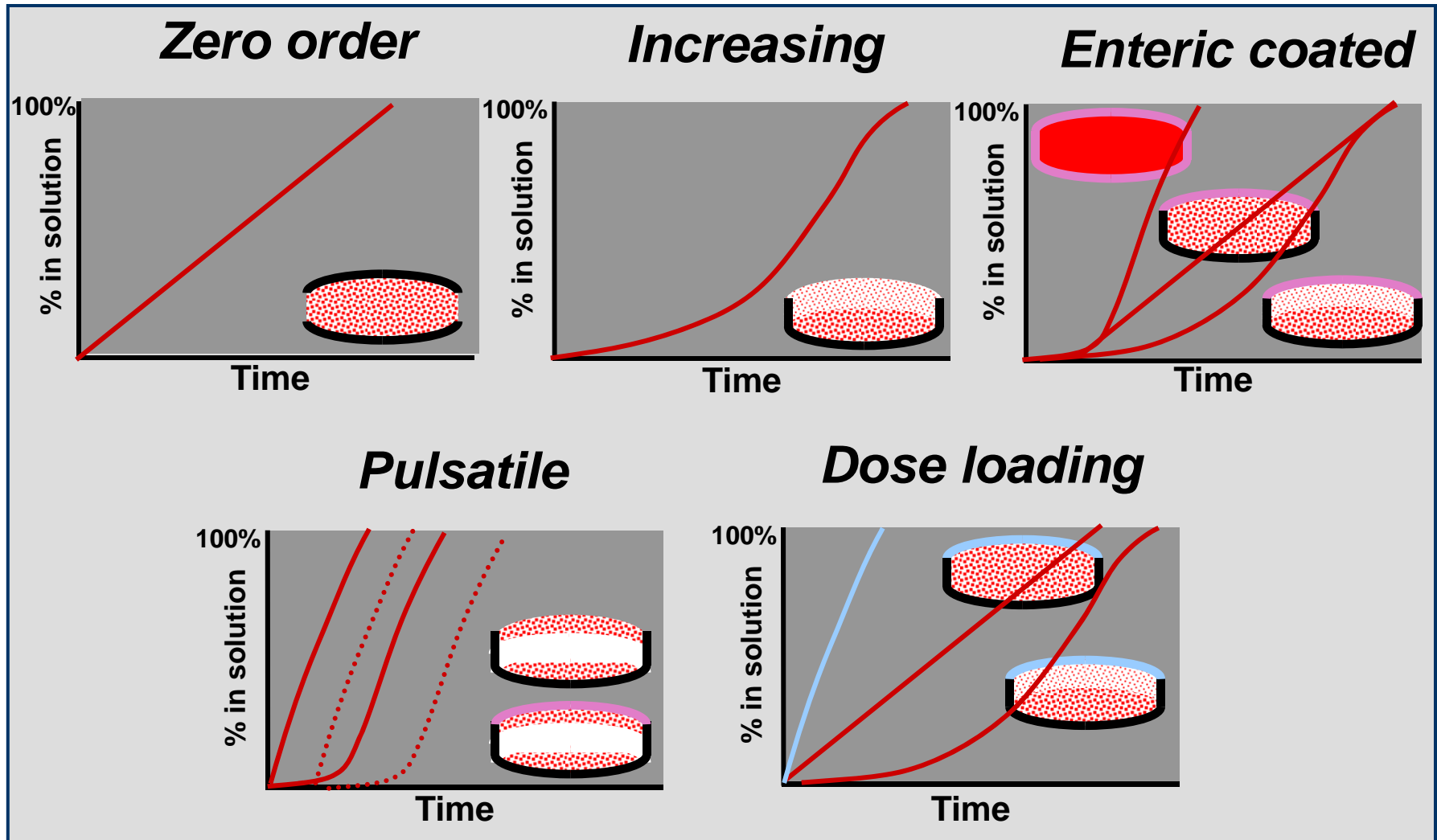
*Accurate low dose drug deposition*



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



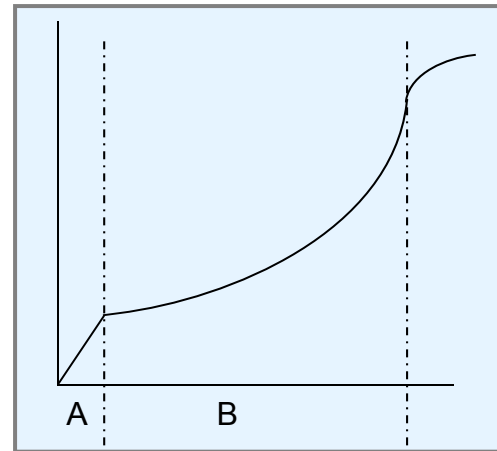
# Potential Design Approaches



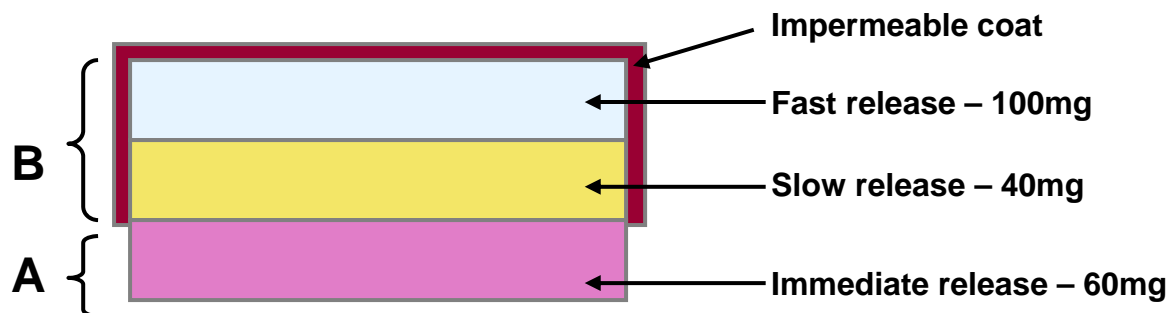
# Example Illustrating Application Requiring Specialized Release Profile

## Dissolution Specification:

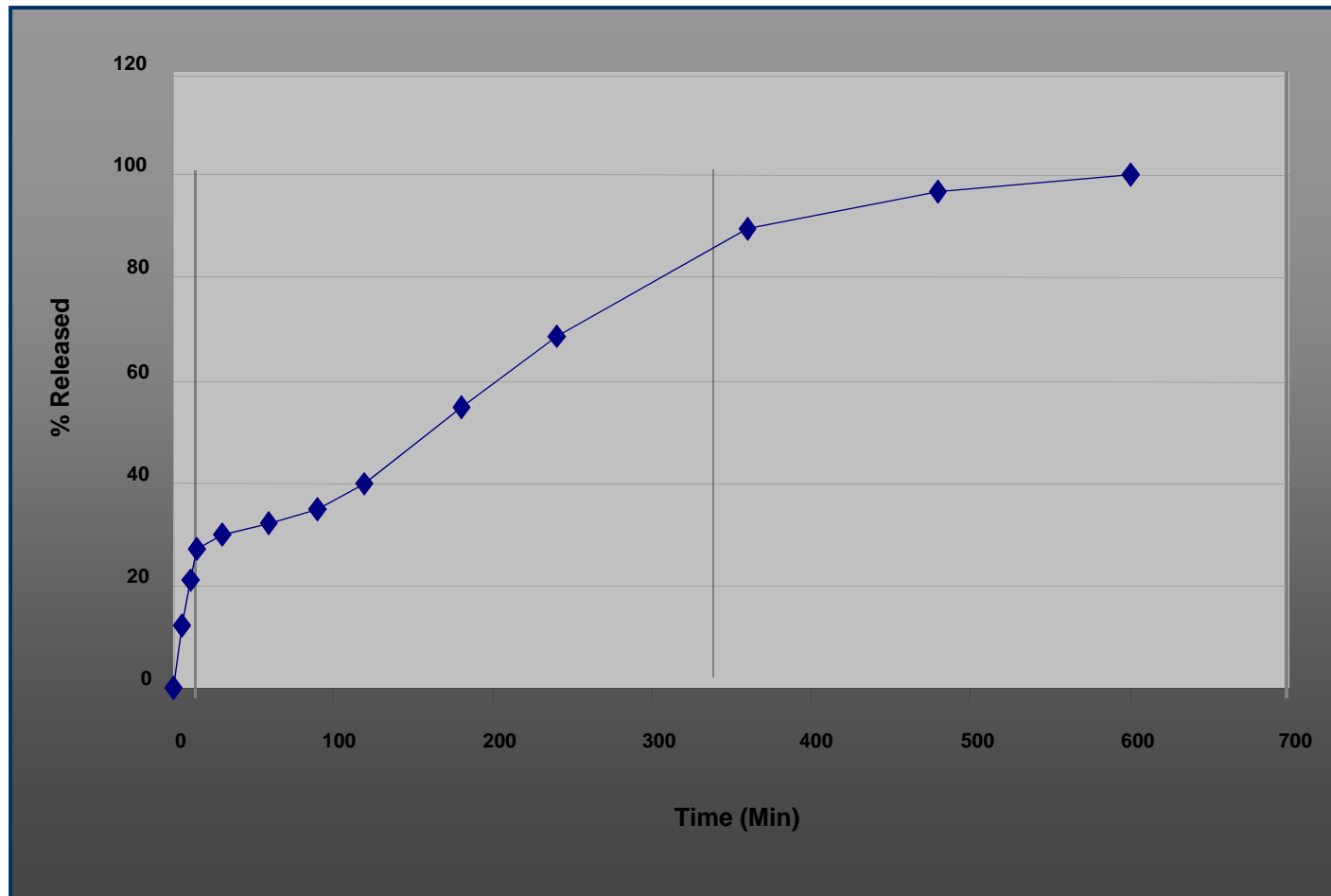
- 10-30% released within 45 minutes
- 40-50% within 3 hours
- 100% within 6 hours



## Tri-layer tablet required to achieve profile:



# Drug Release from Coated Bi-layer Tablets with Immediate-release Third Layer



# **Molding and/or Extrusion Processes**

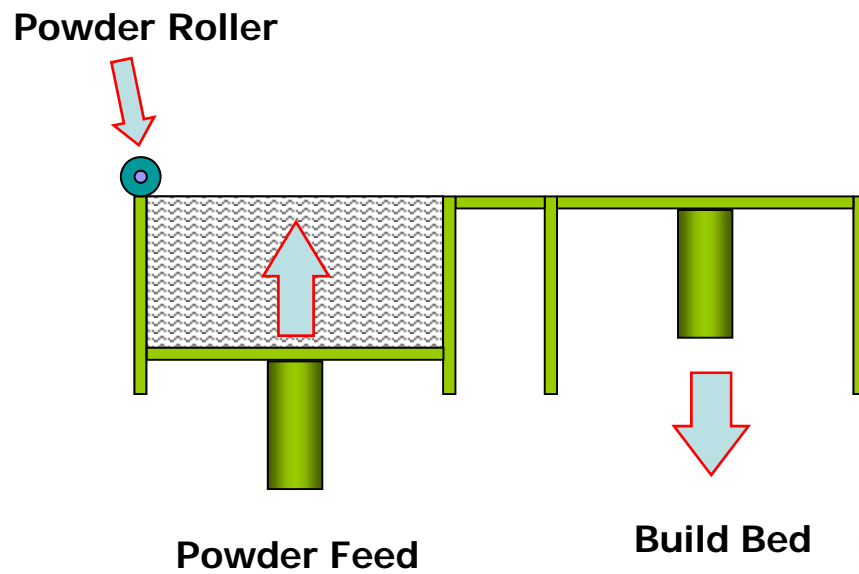
# Aprecia Ink-Jet Molding Process

**This technology involves:**

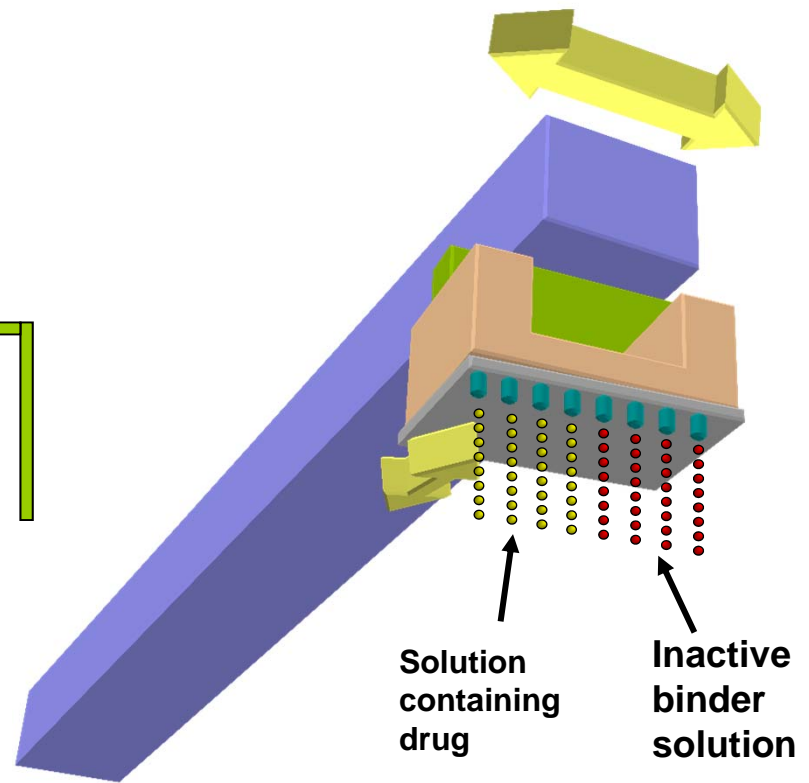
- **The preparation of “molded” tablets using a process that employs a combination of:**
  - Ink jet printing technology.
  - Powder spreading.
  - Drying.
- **The design of systems with a multiplicity of drug-release capabilities in which drug particles are locked into compartments created within the three-dimensional structure.**



# Aprecia Process

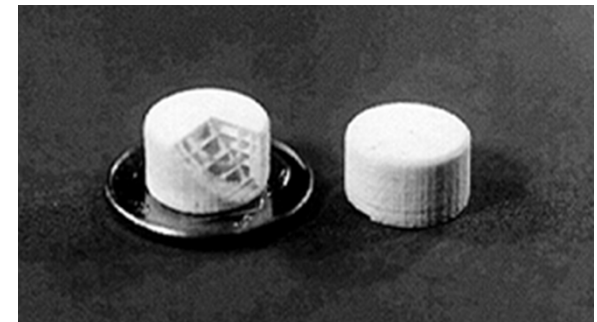
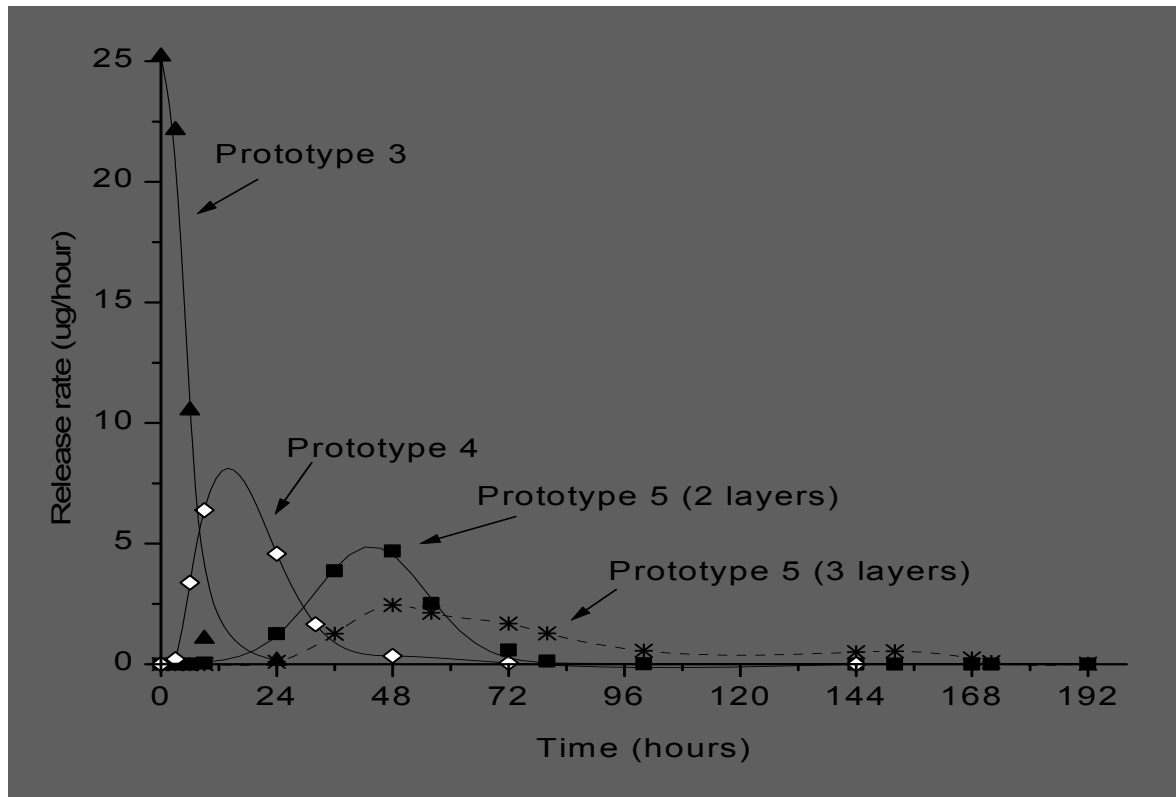


1. Powder Building Platen



2. Printing Head

# Examples of Dosage Forms Created Using the Aprexia Process



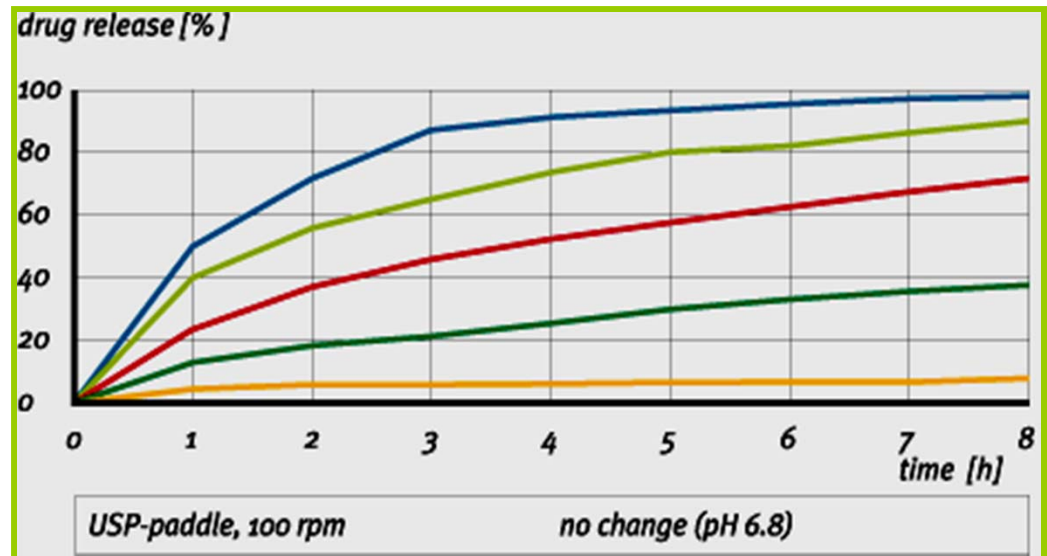
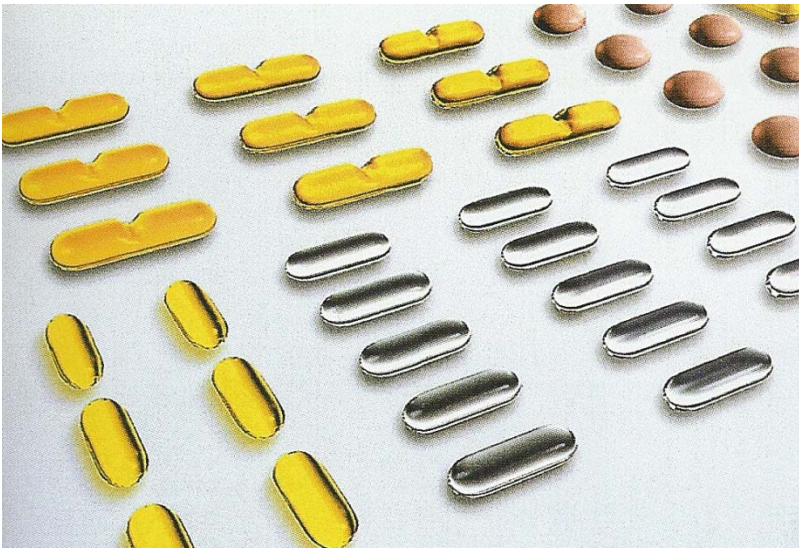
# Soliqs Meltrex<sup>®</sup> Melt Extrusion Technology



## 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.

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METHOCEL™, POLYOX™ are trademarks of The Dow Chemical Company.  
The information contained in this presentation is proprietary to Colorcon and may not be used or disseminated inappropriately.



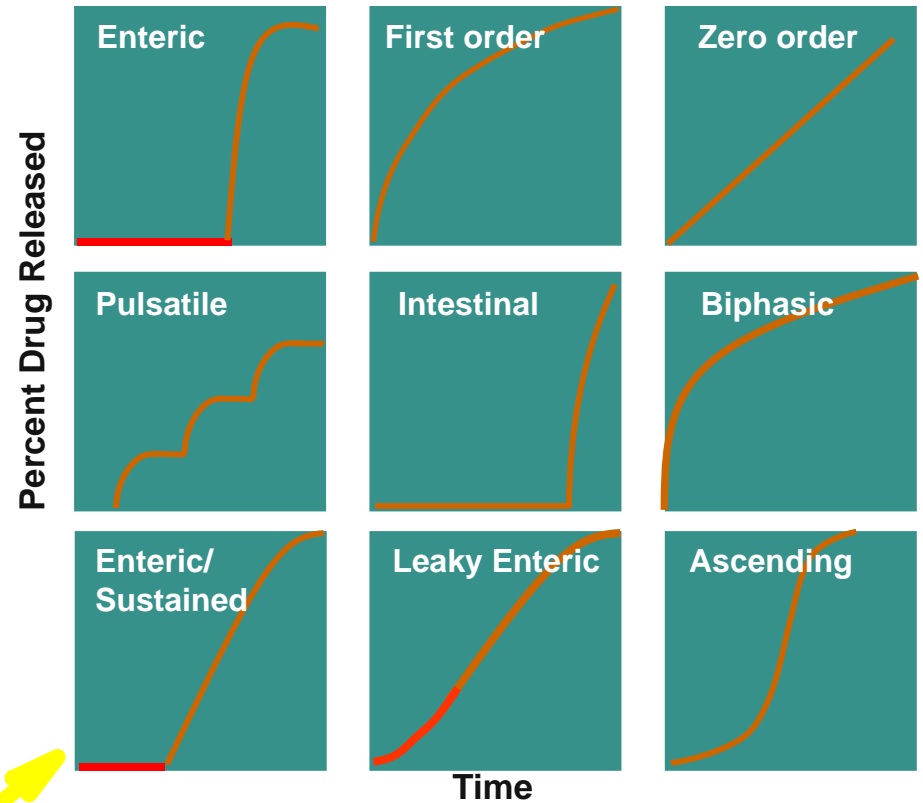
# Agenda

- 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

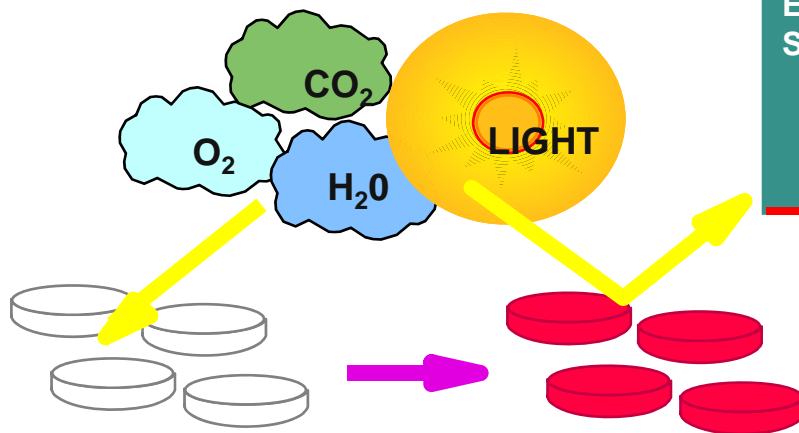
# Why film coat?

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

## Improved Functionality – Dissolution profile modulation



## Improved stability





# 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)!**

# Criteria for Good Films and Coatings

stable on storage and handling

uniform thickness

**Criteria for good films and coatings**

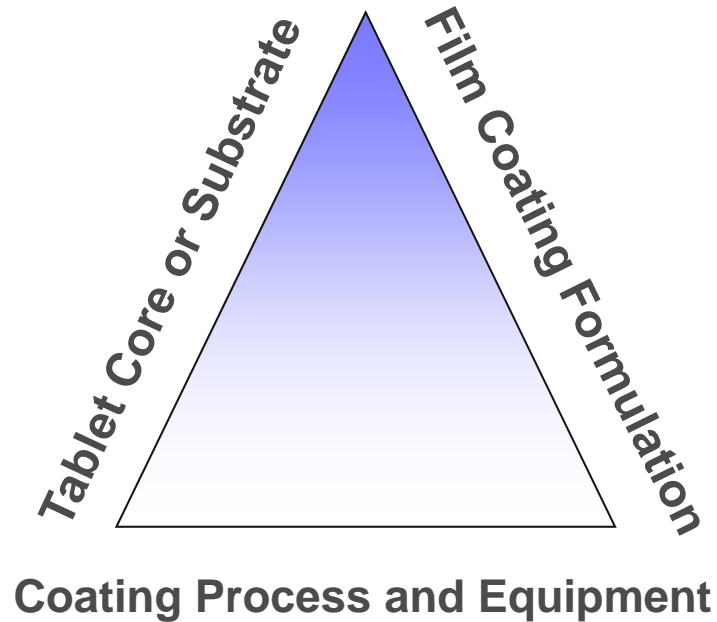
adhere to the substrate

coherent and free from  
flaws and cracks

Sakellariou and Rowe. Prog. Polym. Sci. 20, 889-942 (1995)



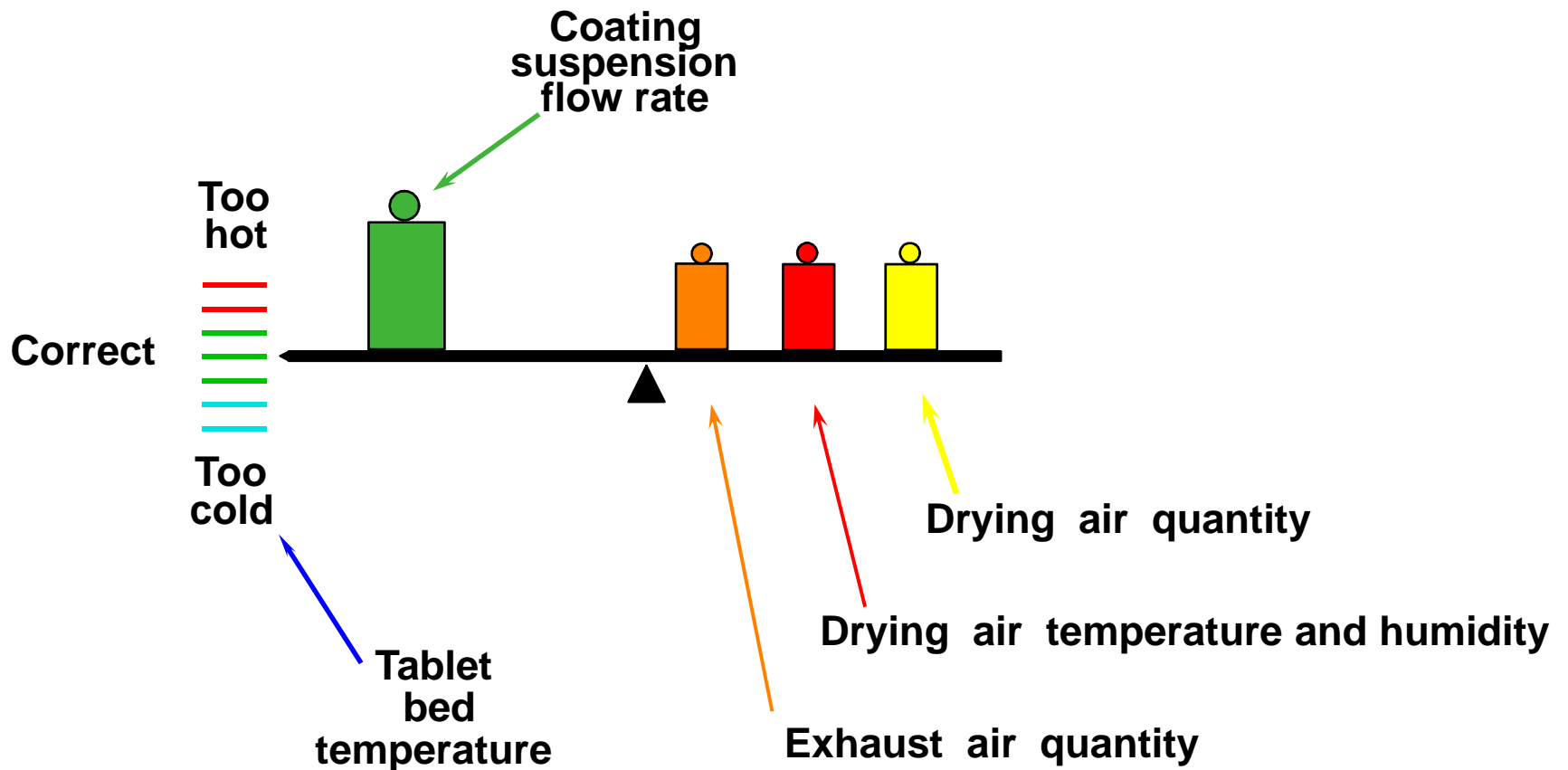
# Critical Components of Film Coating



**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



# 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<sup>®</sup> Core Tablet Formulation

## Direct Compression

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

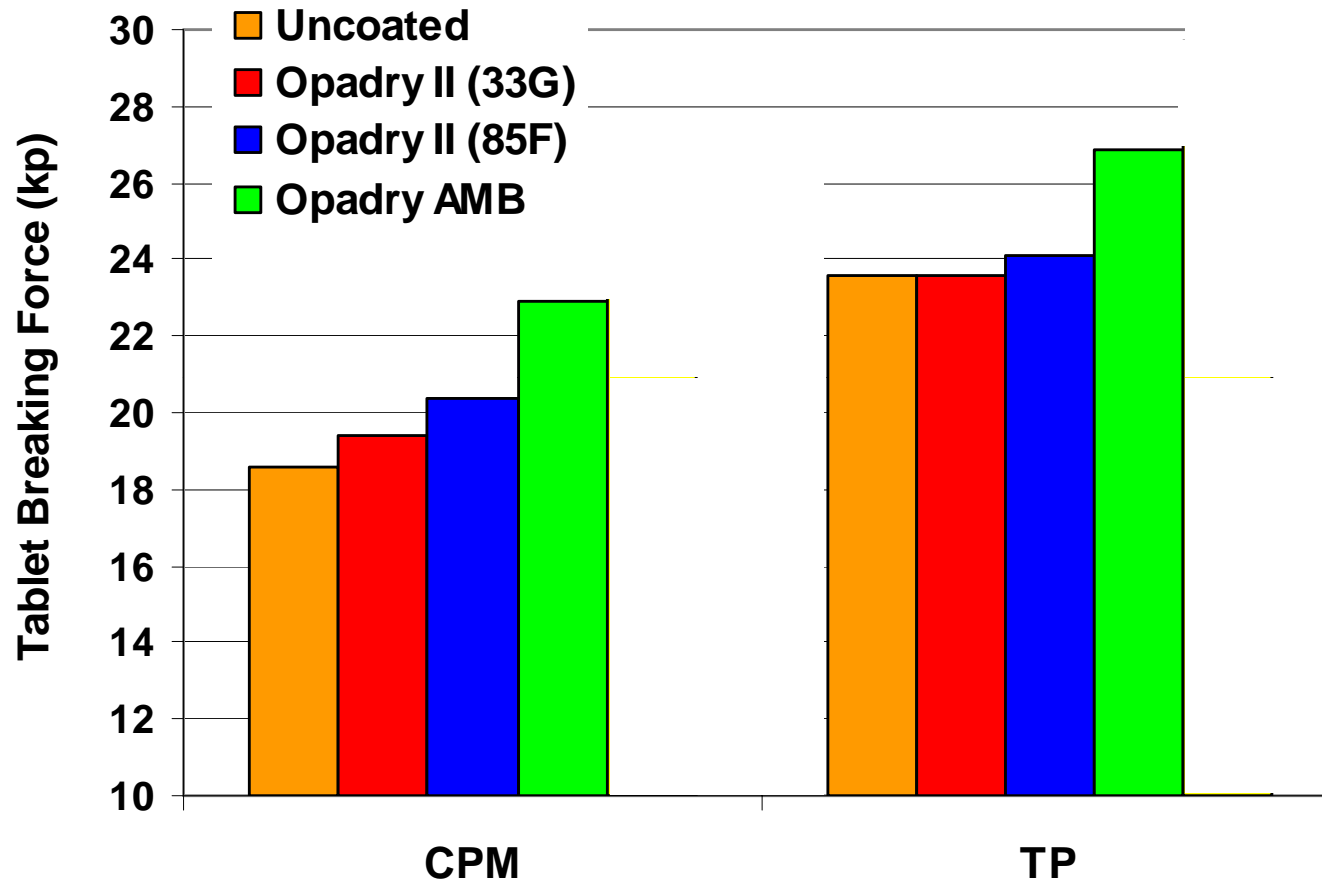
- Tablets (333mg) containing 100mg drug were compressed into 9mm SC tablets at 10 kN and 30 rpm.
- Tablets were coated with three different immediate release film coating systems Opadry<sup>®</sup> II (33G), Opadry<sup>®</sup> II (85F) and Opadry<sup>®</sup> AMB to 4%w/w weight gain in a side-vented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

**20% METHOCEL<sup>™</sup> K4M Chosen to check potential formulation sensitivity to film coating**





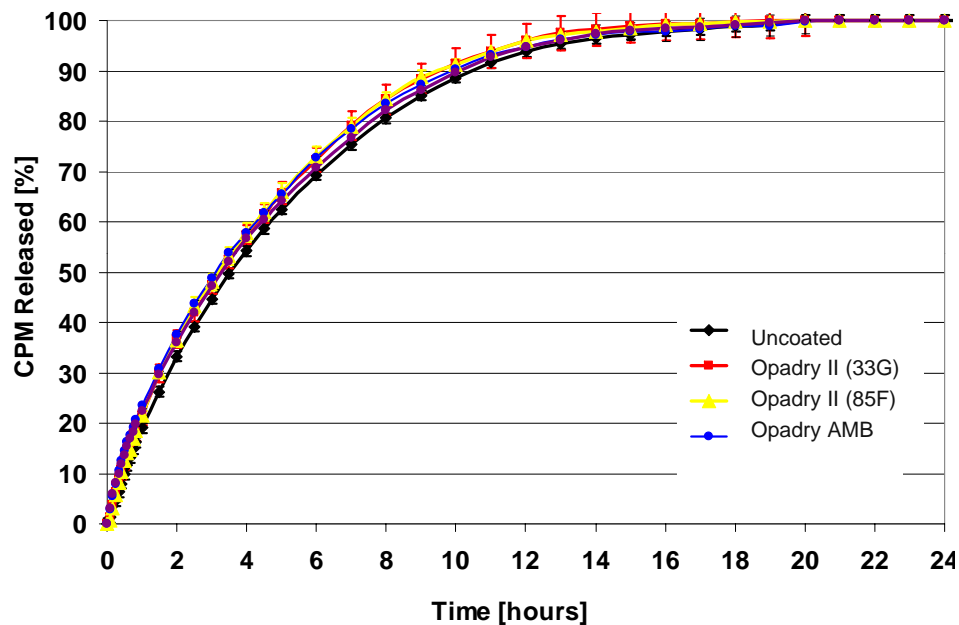
# Results – Tablet Breaking Force



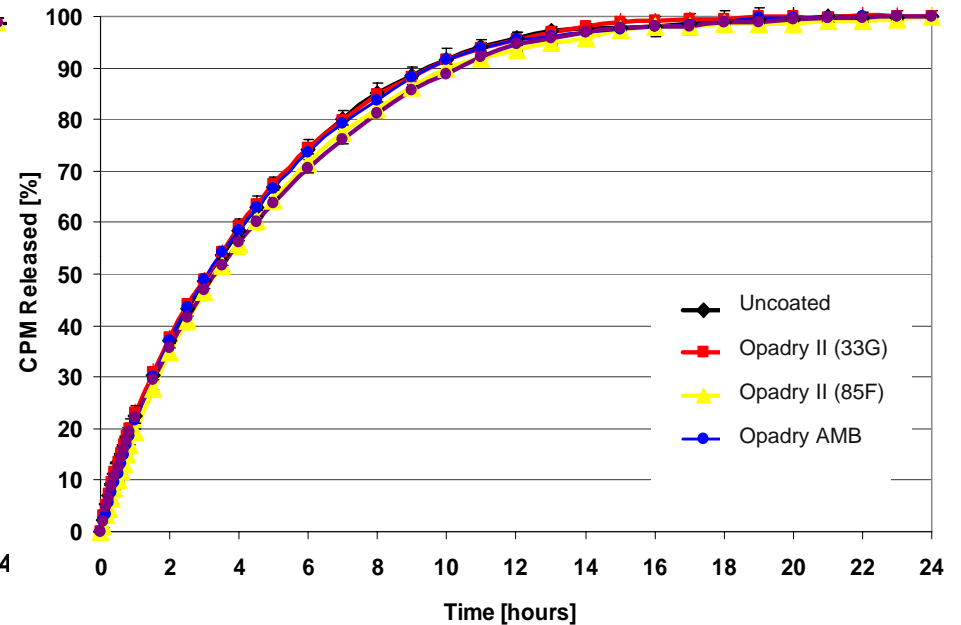
**Film coating increases tablet robustness**

# 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

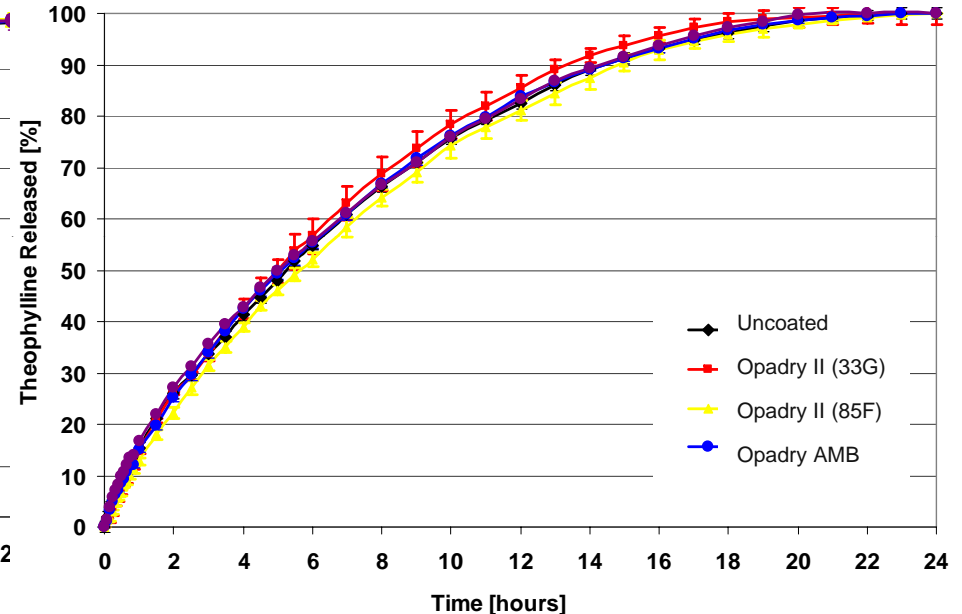
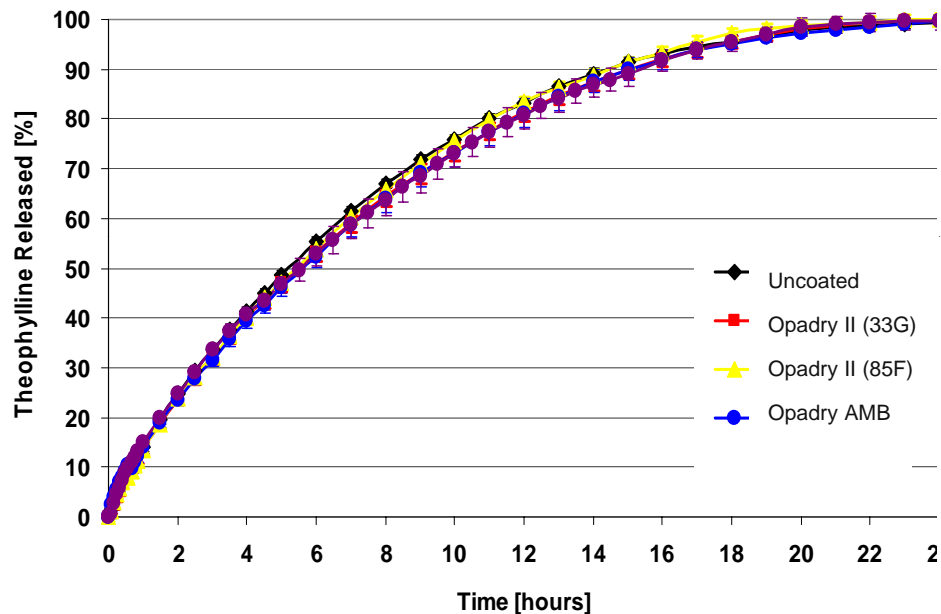
USP apparatus II (paddle) and sinkers, in 37±1°C, 900mL Purified Water at 100rpm



# 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



# 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.



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

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# POLYOX™ Properties

	POLYOX™
Melting point (°C)	~ 68
Swellability	~ 7X
Hydration rate	Very fast
Hydrophilicity	Highly hydrophilic

**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.**

# WSR-303 Compacts – Temperature challenge



**(a) Uncoated**



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

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

Parameter	Standard conditions	Non-standard conditions
Pan speed (rpm)	20	20
Inlet air temperature (°C)	65-72	70
Exhaust air temperature (°C)	50-53	52-58
<b>Product temperature (°C)</b>	<b>42-45</b>	<b>38-40</b>
Fluidizing airflow (m <sup>3</sup> /hour)	250	250
Atomization/fan air pressure (bar)	1.5	1.5
<b>Spray rate (g/min)</b>	<b>4-10</b>	<b>24</b>
Process duration (min)	21	14

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

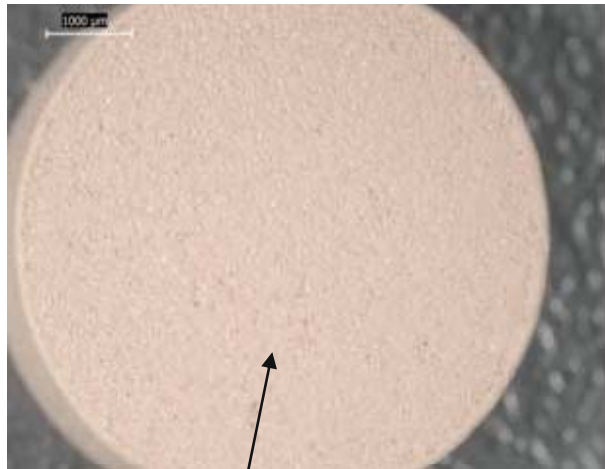




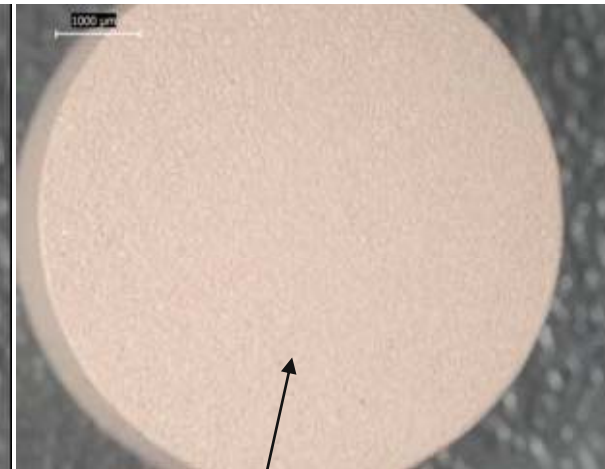
# WSR-303 Compacts - Opadry® II Coating

**Opadry® II  
non-standard  
conditions**

**Opadry® II  
standard conditions**



Rough surface



Good results

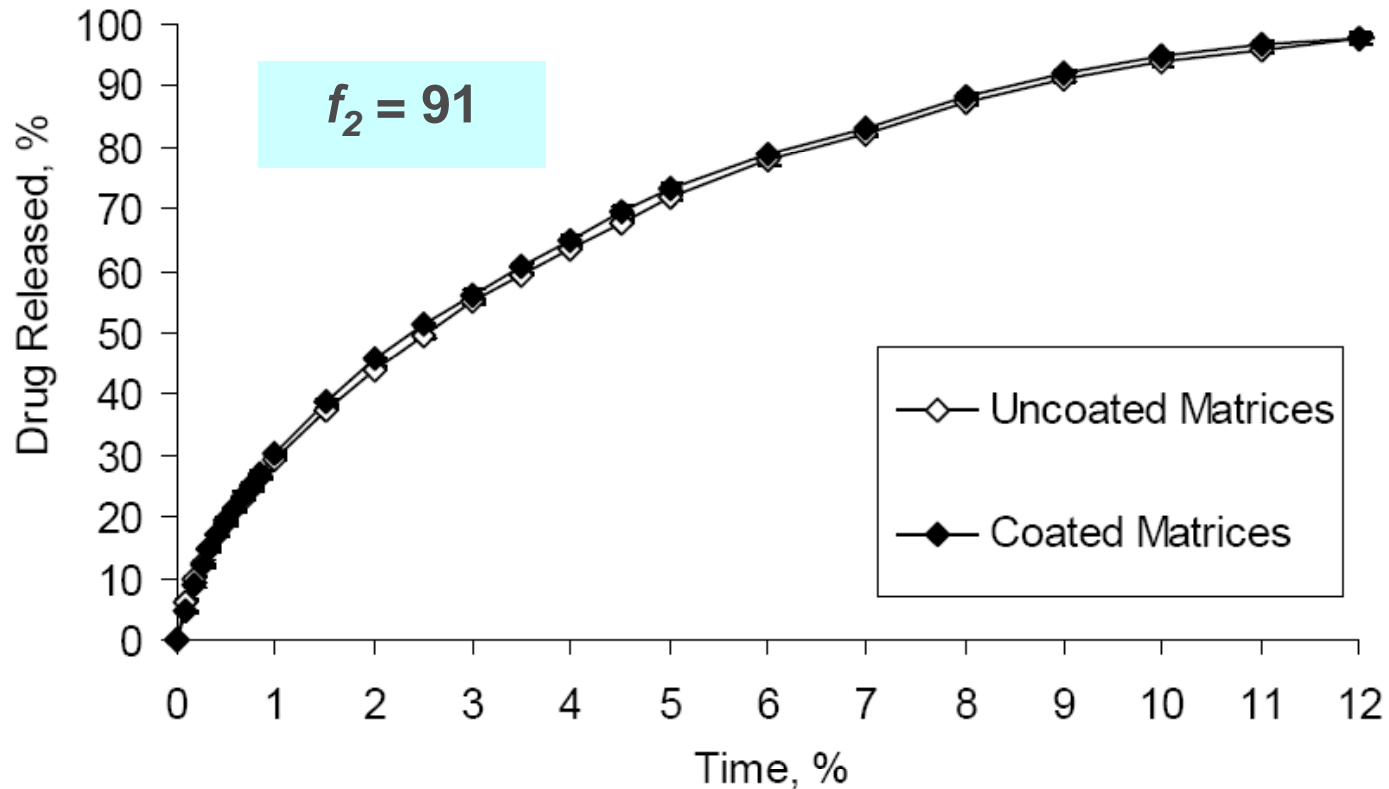
# Metformin HCl (50% Metformin, 30% Polyox WSR-1105) Tablet Coating Parameters

Parameter	Value
Pan speed (rpm)	20
Inlet air temperature (°C)	65-69
Exhaust air temperature (°C)	48-53
<b>Product temperature (°C)</b>	42-45
Airflow (m <sup>3</sup> /hour)	250
Atomization/fan air pressure (bar)	1.5
<b>Spray rate (g/min)</b>	10-21
Process duration (min)	17

- O'Hara Labcoat II, 15"; 1.2 mm Schlick spraying gun; 1 kg batch
- Opadry II – 4% weight gain



# Metformin HCl Release – Effect of Coating



1000mL Purified Water at  $37.0 \pm 0.5^\circ\text{C}$ , 100 rpm using USP Apparatus 2 (paddles) and 2.38 mm (8-mesh) stationary quadrangular baskets (QBs). The baskets were positioned within the dissolution vessel perpendicular to the shaft and 3 cm above the paddle.



## Coating of POLYOX™ Tablets - Summary

- Appearance of coated POLYOX™ compacts and metformin HCl ER POLYOX™ matrices was good.
- Product bed temperatures above 55°C are not recommended due to low melting point of POLYOX™ (~65°C).
- For POLYOX™ containing tablets, typical Opadry II coating conditions with a product bed temperature of around 42-45°C 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

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# HyperStart<sup>®</sup> Tablet Core Formulation

## Direct compression

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

Physical parameters	Values
Weight (mg)	270.0 ± 3
Breaking force (kp)	8.00 ± 2.00
Diameter (mm)	9.00 ± 0.20
Thickness (mm)	5.7 ± 2.4
Friability (%)	0.80

# Coating Process Parameters

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

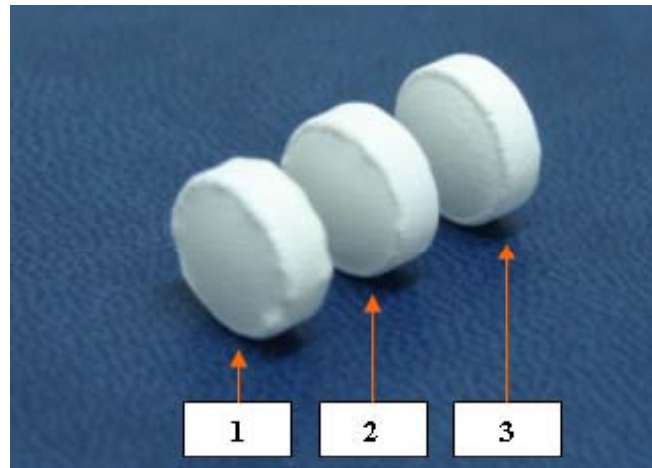
**Rama Coater, 3Lts perforated perforated pan. Schlick Gun with ABC**



# Importance of Seal-coating

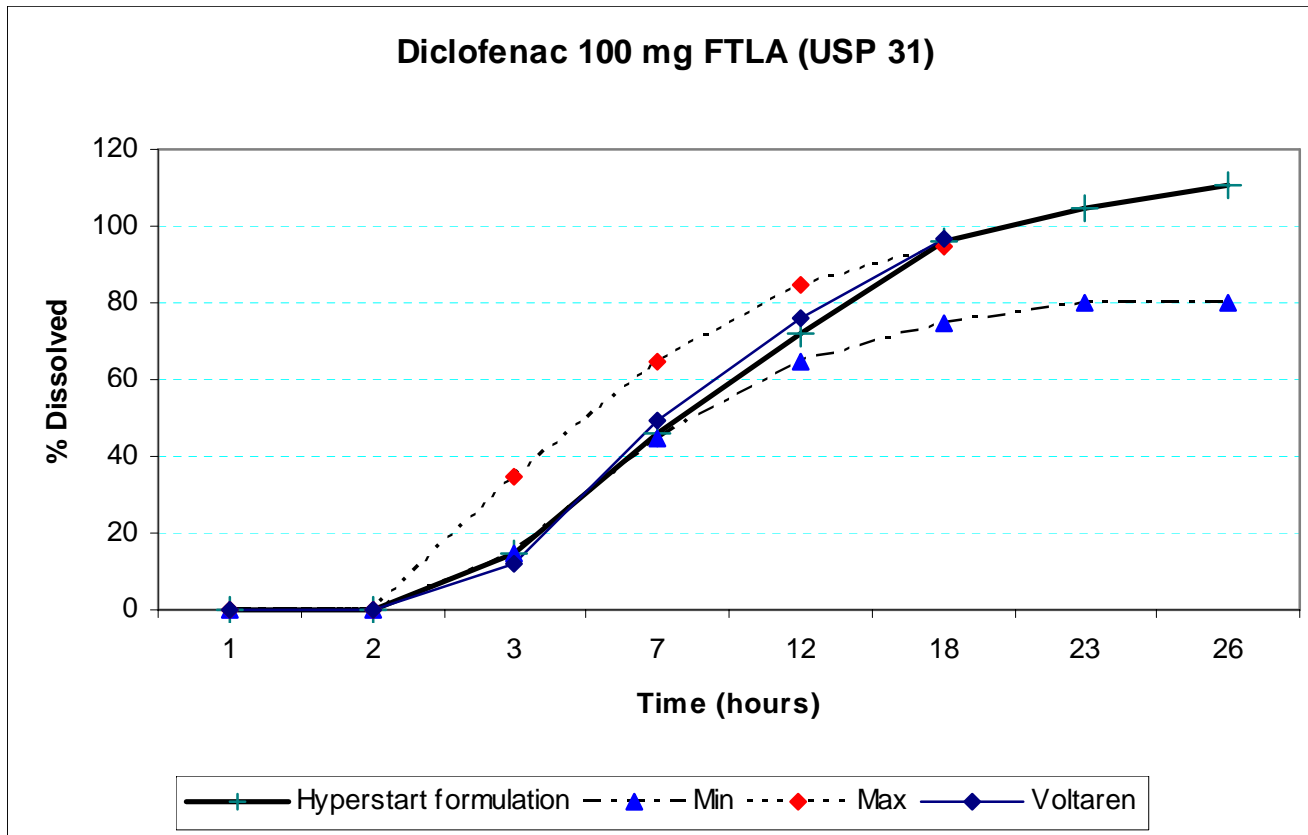
## Percent Acid Uptake

Samples (Media 0.1N HCl)	Percent acid uptake	Tablets aspect
5% enteric coat	6.0	High edge defects (1)
7% enteric coat	3.8	Low edge defects (2)
3% seal coat + 7% enteric coat	2.8	No imperfections (3)





# Drug Release from HyperStart® Formulation and Innovator Product



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  $37 \pm 0.5^{\circ}\text{C}$ ) using USP Apparatus 2 (Paddle)



# Delayed Release Coating of Hydrophilic Matrix Tablets - Summary

- 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

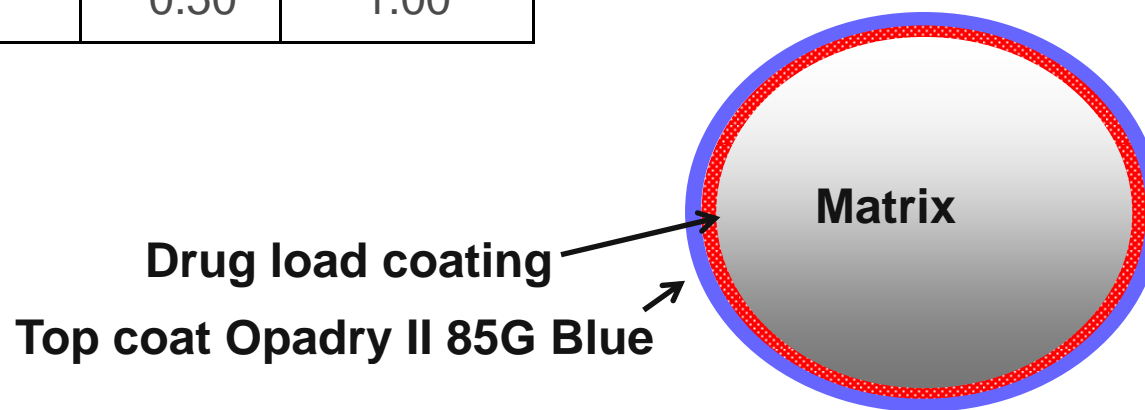
# HyperStart® Tablet Core Formulation

## Direct compression

- Single layer tablet, biphasic drug release

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

Material	%w/w	mg/ tablet
Zolpidem Tartarate	4.29	4.08
Opadry® II	1.32	1.25
<b>SLS</b>	<b>0.06</b>	<b>0.06</b>
Purified water	94.33	-



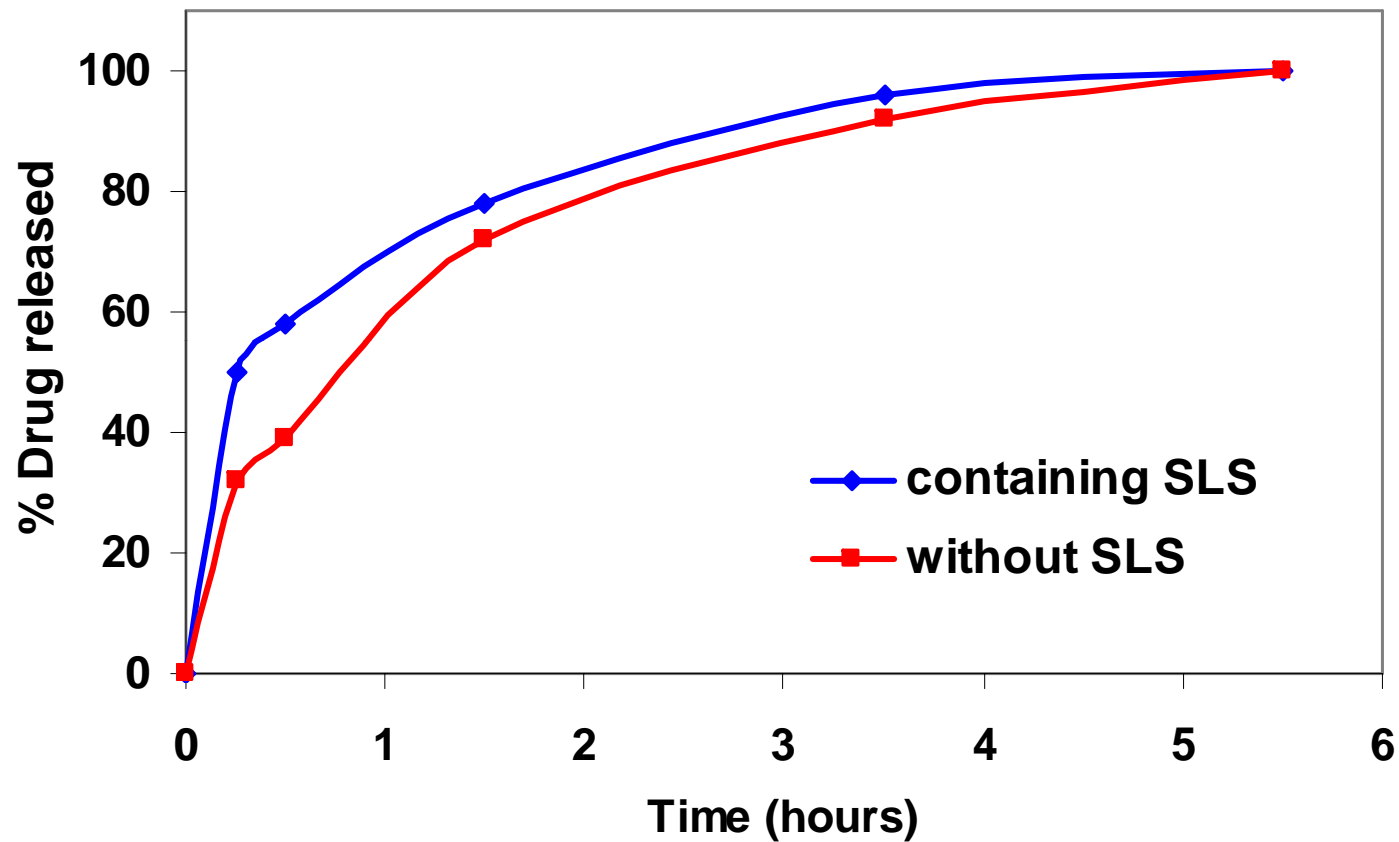
# Coating Process Parameters

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

O'Hara Labcoat-1, 12" perforated pan & Schlick Gun with ABC

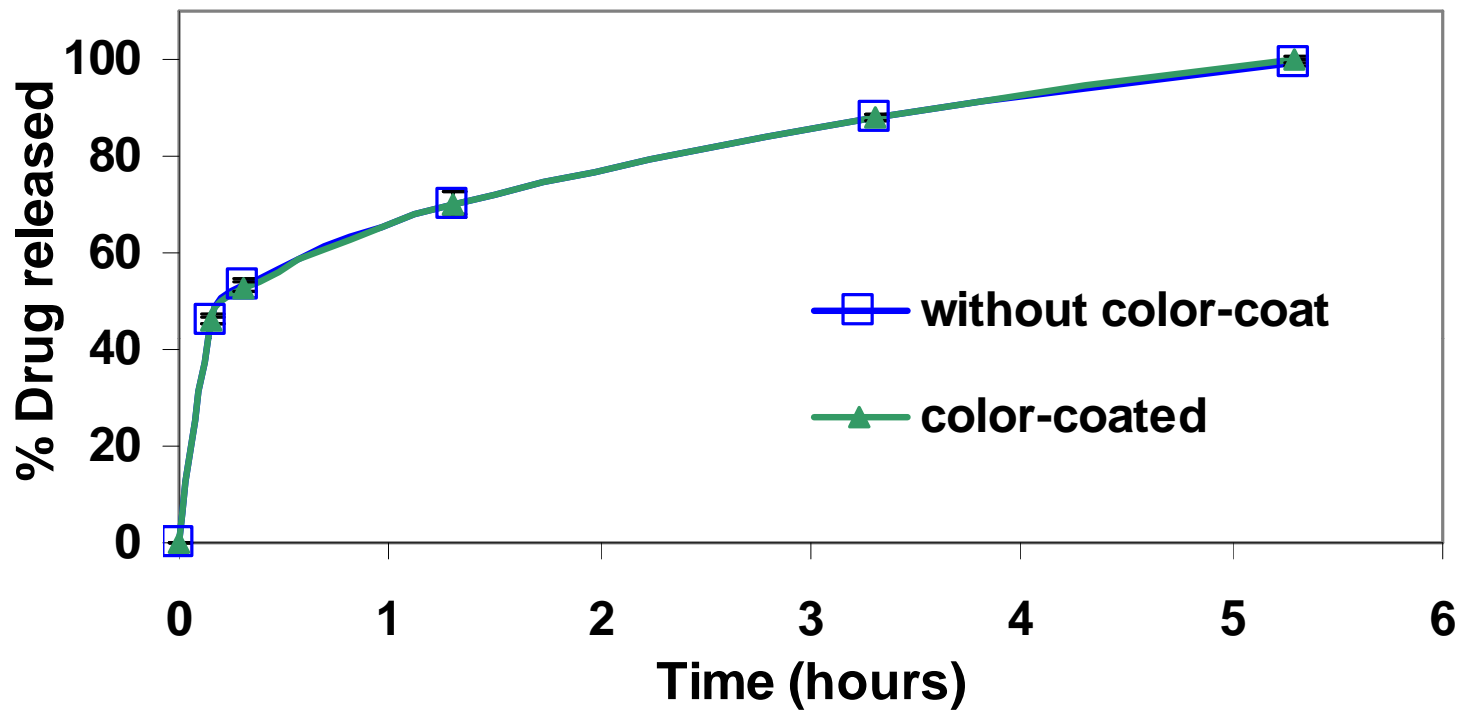


# Effect of SLS on Drug Release



900mL 0.01M HCl using USP App 2 (paddle) at 50 rpm. Sinkers were used for dissolution.

# Biphasic Release Profile



**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

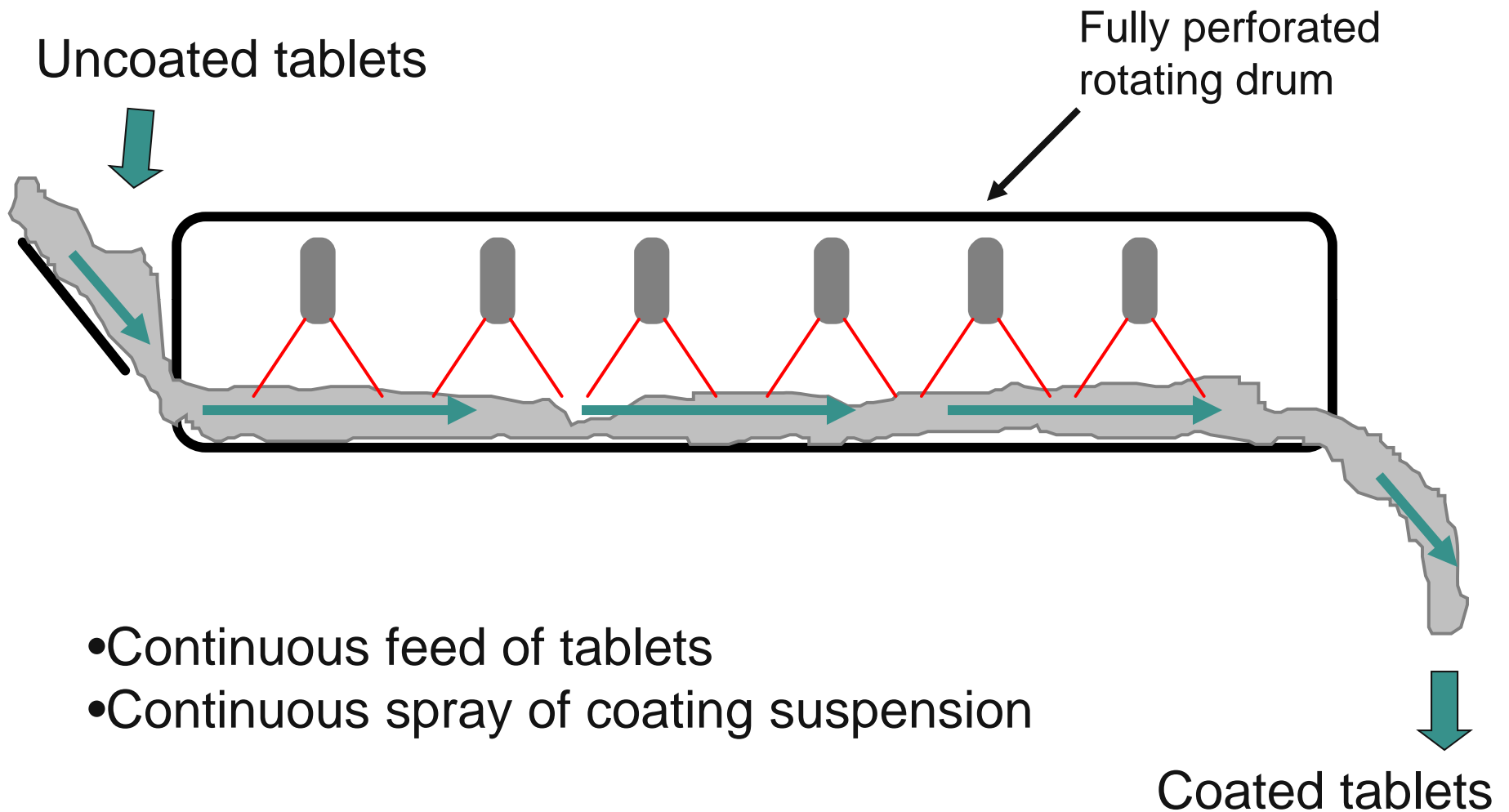
- Appearance of coated zolpidem matrices was good.
- Biphasic release profile was obtained.
- Uniformity of dosage form was obtained.
- It is recommended to use dilute API solution or high weight gain to ensure uniformity in film thickness and consequently drug content.
- It is recommended to use micronized 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



- Continuous feed of tablets
- Continuous spray of coating suspension



# Thomas Engineering Continuous Coater

- 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'



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Source: Thomas Engineering web-site



## 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**.



Nutra Manufacturing, Greenville, SC.

# Equipment



**Pan interior with spray manifold removed**



**Thomas Spray Bar with Schlick ABC components**

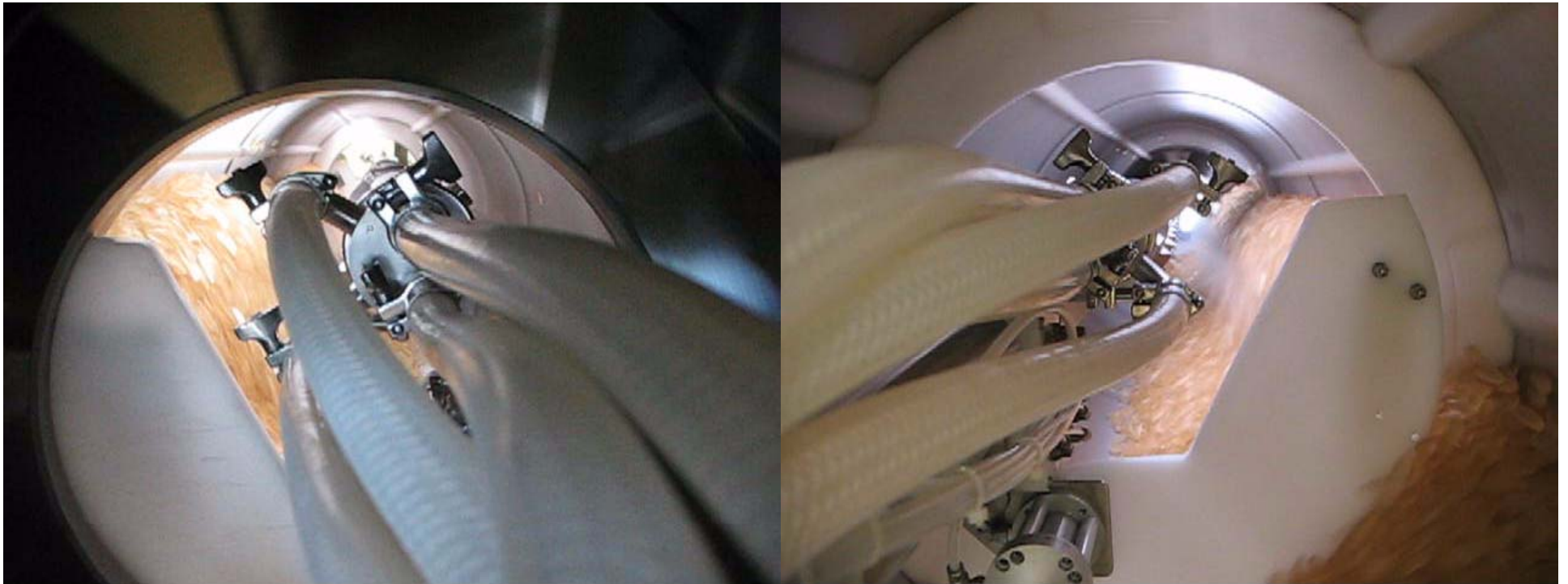
## Process – Weigh belt feeder



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# Process



**In feed side**

**Out feed side**

**Fill level – 95 kg softgels.**



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# Trial settings

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

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
	Time (min.) of resistance to simulated gastric fluid with no signs of disintegration		
0	> 60	> 60	> 60
5	> 60	> 60	> 60
10	> 60	> 60	> 60
15	> 60	> 60	> 60
20	> 60	> 60	> 60
25	> 60	> 60	> 60
30	> 60	> 60	> 60
35	> 60	Trials 2 and 3 ended at 30 minutes of continuous running time	
40	> 60		
45	> 60		
50	> 60		
55	> 60		
60	> 60		

Sample time point (min)	Trial 1	Trial 2	Trial 3
	Disintegration time (min) in simulated intestinal fluid (n=6)		
0	27.5 ± 4.3	27.3 ± 3.4	28.2 ± 4.5
15	22 ± 6.4	36.8 ± 5.2	29.6 ± 3.6
30	29.5 ± 4.8	31.5 ± 6.1	26.8 ± 5.2
45	34.5 ± 7.3	Trials 2 and 3 ended at 30 minutes of continuous running time.	
60	29.4 ± 8.2		

# 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

40°C / 75% RH Storage conditions		
Storage Time point	Time (min.) of resistance to simulated gastric fluid with no signs of disintegration (n=6)	Disintegration time (min) in simulated intestinal fluid (n=6)
Initial	> 60	19.3 ± 6.3
1 Month	> 60	22.5 ± 4.8
3 Months	> 60	18.5 ± 5.3

30°C / 65% RH Storage conditions		
Storage Time point	Time (min.) of resistance to simulated gastric fluid with no signs of disintegration (n=6)	Disintegration time (min) in simulated intestinal fluid (n=6)
Initial	> 60	19.3 ± 6.3
1 Month	> 60	20.8 ± 5.4
3 Months	> 60	16.7 ± 4.2



# 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.



# Film Coating of Modified Release Dosage forms

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

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