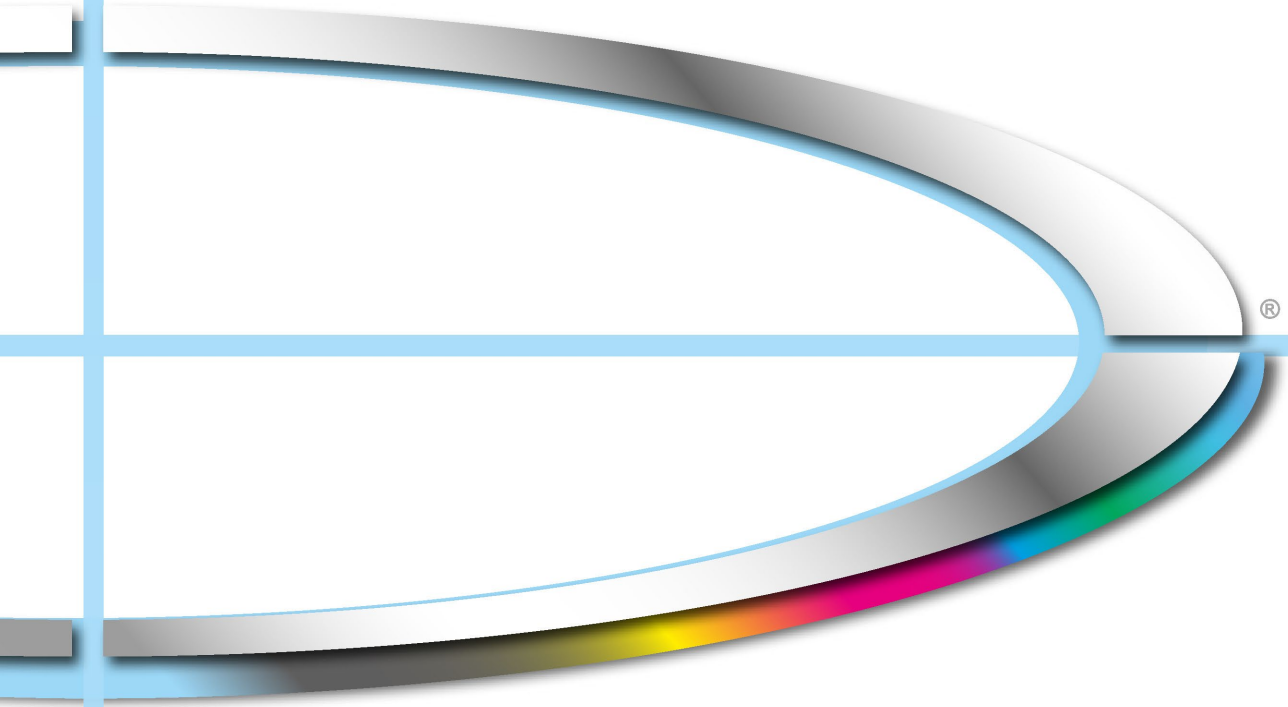
De-Risking Oral Controlled Release Dosage Forms, the Corelease™ Way



Corelease™

Controlled Release Formulated Systems

Colorcon®

Speakers

Beth Tran
Global Business Manager

Ali Rajabi-Siahboomi
Vice President
Chief Innovation Officer

Jason Teckoe
Technical Director
EMEA

Paul Smith
Formulation Technologies
Manager EMEA

Formulated Film Coatings

Enabling the design and development of medicines to improve adherence, reduce medication errors and add value to brands.

Functional Packaging

Packaging solutions that protect healthcare products from humidity and oxygen to support stability and shelf life..

Our Purpose: To improve health and wellness through convenience, compliance and safety

Controlled Release Technologies

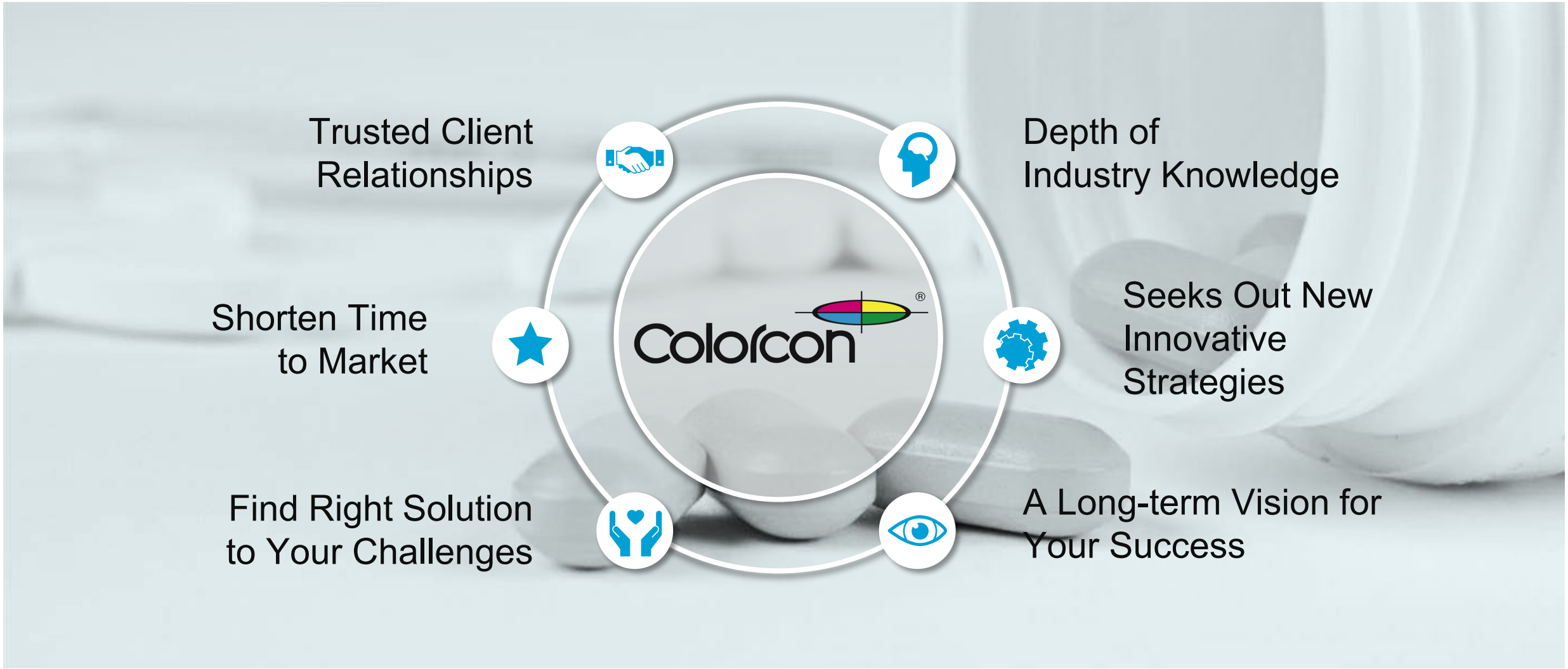
Reliable, innovation-driven solutions that prioritize boosting productivity and enhancing manufacturing efficiency

.

Specialty Excipients

Ingredients for tablet and capsule formulation, designed for manufacturability and productivity.

Colorcon Delivers Solutions for a Challenging Industry



Global Technical Service Centres

Strategically located network provides fast access points to our technical experts and trial support laboratories

Platform Solutions

Patient Adherence

Dissolution Design

Productivity

Stability

Product Authentication

Platform Solutions – Dissolution Design

Industry Trend:

Life cycle management through modified delivery profiles and product line extensions

Corelease™
Controlled Release Formulated Systems

Challenge

Choosing the **right technology** to achieve targeted and reproducible release profile

Expertise in specialist technology

Limited access to technology

Solution

Corelease™, controlled release formulated systems to eliminate complexity of drug development, optimize drug delivery and drive manufacturing efficiency

Locally available **specialists and applications expertise** for fast formulation development

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Corelease™
Controlled Release Formulated Systems

Enhance Efficiency in Development & Manufacturing of Push-Pull Osmotic Pumps (PPOPs)

Dr Paul Smith
Formulation Technologies Manager
Colorcon Ltd.
psmith@colorcon.com

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Benefits of Osmotic Pump Technology

Corelease™
Controlled Release Formulated Systems

- ✓ Zero-order drug release with minimal burst effect
- ✓ Consistent & reproducible drug delivery rate
- ✓ Suitable for poorly soluble drugs
- ✓ pH independent drug release
- ✓ Low susceptibility to food effects & GI transit variations
- ✓ High degree of *in vitro* / *in vivo* correlation

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Components of a PPOP Tablet

Corelease™
Controlled Release Formulated Systems

Delivery orifice

Semi-permeable coating
(cellulose acetate & PEG)

“Pull layer”
(API)

“Push layer”
(PEO & NaCl)

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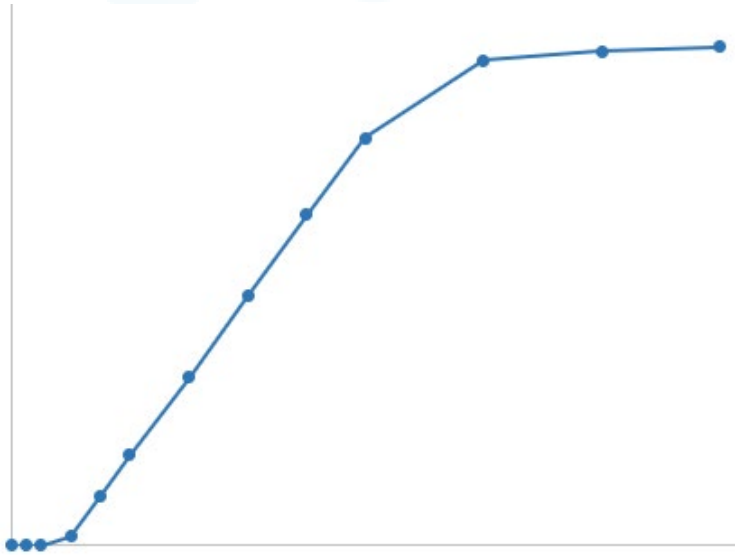
Mechanism of Drug Release

Corelease™
Controlled Release Formulated Systems



Zero Order Kinetics

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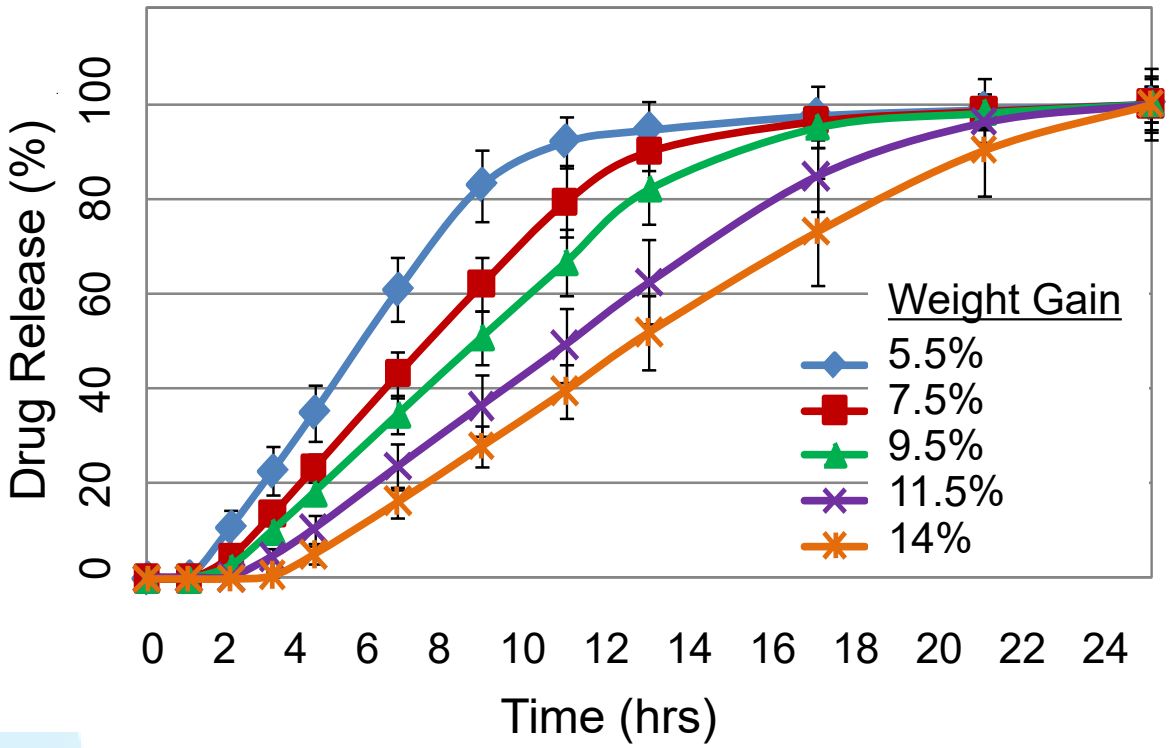
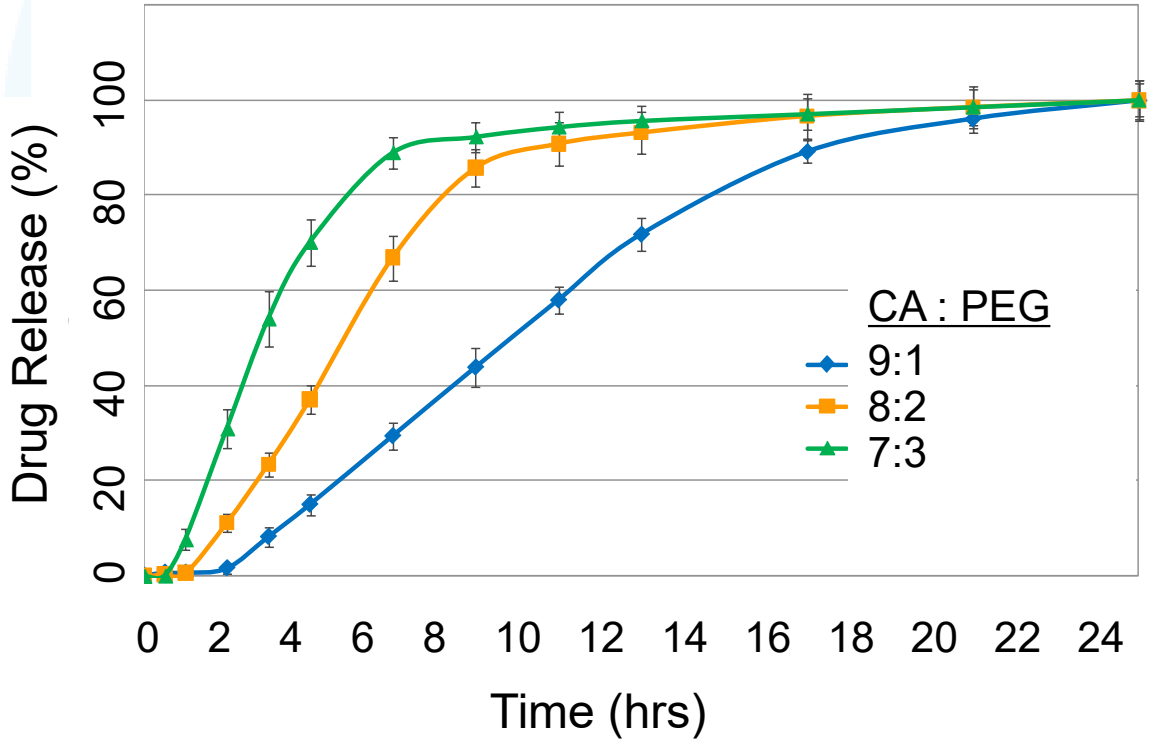
Modulation of Drug Release

Corelease™
Controlled Release Formulated Systems



As coating thickness ↑ = rate of drug release ↓



As PEG conc. ↑ = rate of drug release ↑

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Corelease OPL™

Controlled Release Osmotic Push Layer

Fully-formulated Push Layer Designed for Direct Compression of PPOP Tablets

Corelease CA™

Formulated Osmotic Coating System

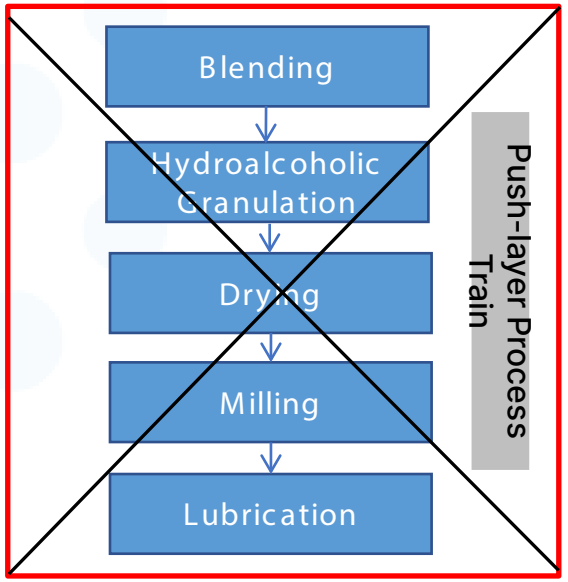
Fully-formulated Semi-permeable Coating for PPOP Tablets

Colorcon®

CoreleaseOPL™

Controlled Release Osmotic Push Layer

- Single ingredient, dry powder
- Designed for DC ⇒ avoids challenge of granulation with PEO
- Particle sizes controlled to avoid segregation & non-uniform swelling
- Eliminates multiple processing steps
- Reduces cleaning burden of working with PEO
- Overall time & cost savings



Single ingredient ⇒ PEO + NaCl + red iron oxide + magnesium stearate

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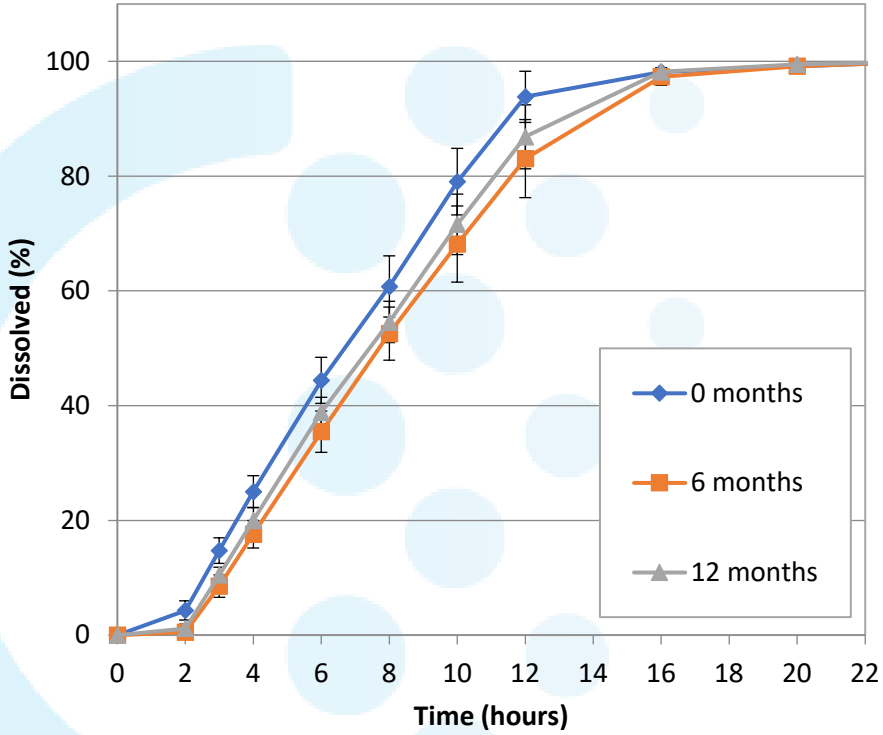
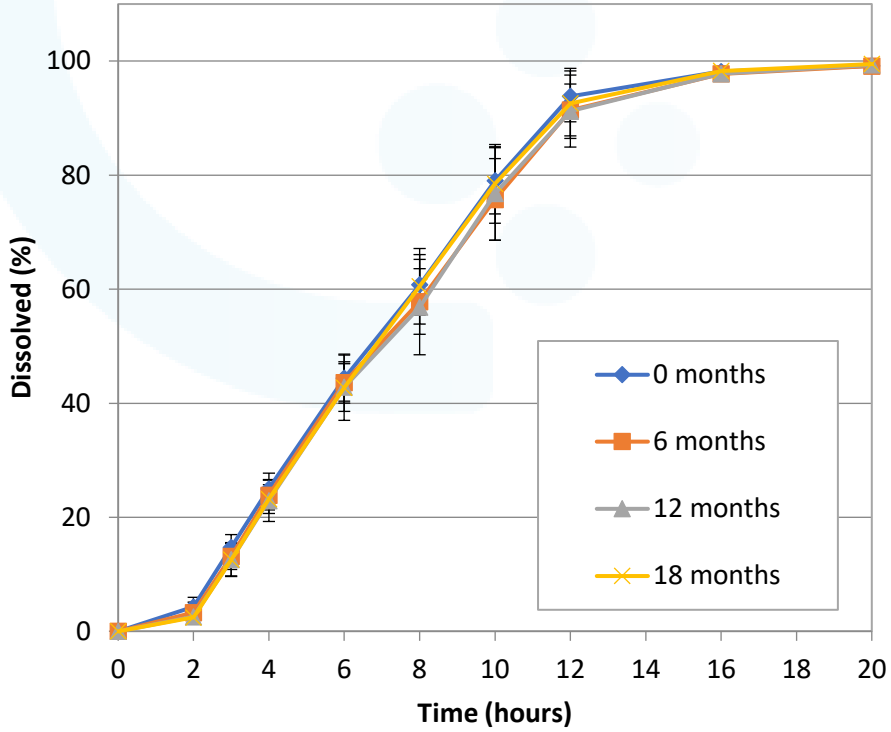
Stable Performance

Corelease™
Controlled Release Formulated Systems

Corelease™ OPL stored at 30°C / 65% RH Formulated into Glipizide PPOP



Corelease™ OPL Formulated into Glipizide PPOP Tablets stored at 30°C / 65% RH



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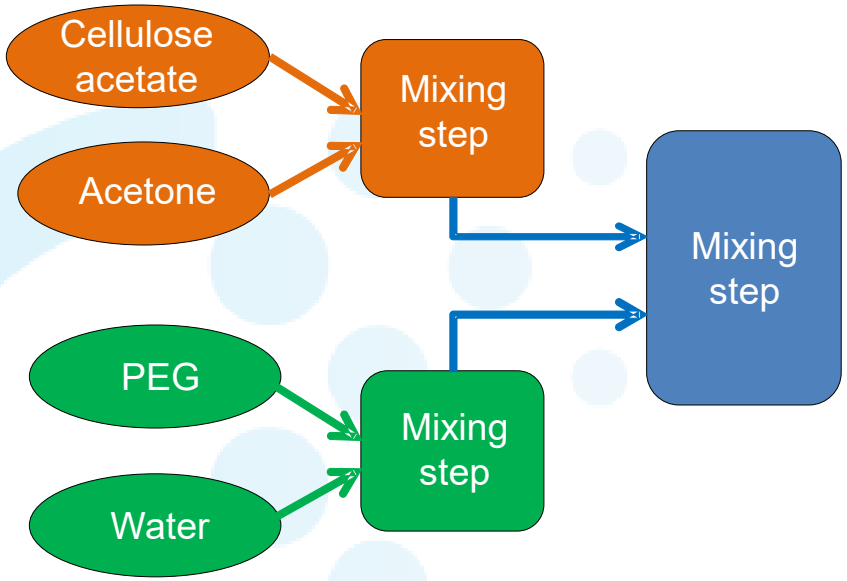
CoreleaseCA™

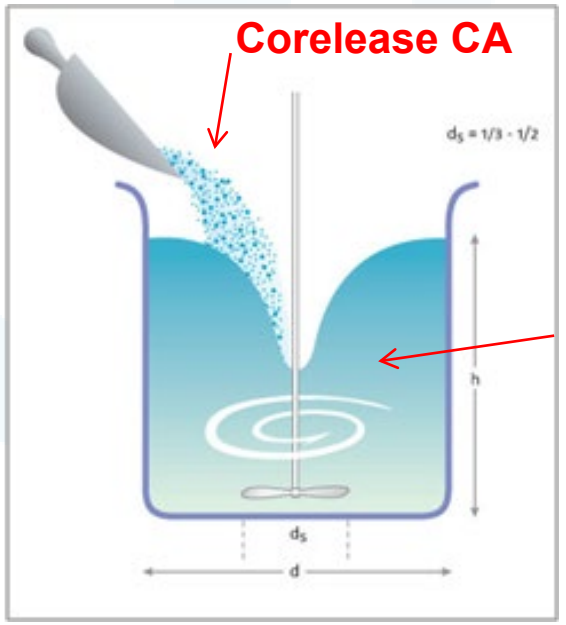
Formulated Osmotic Coating System

Conventional Method



Multi-step (75-110 mins.)

Corelease™ CA



One-step (45 mins.)

Single ingredient ⇒ Cellulose Acetate + PEG

Coating Process Optimization

Corelease™
Controlled Release Formulated Systems

Non-optimized coating parameters may impact film transparency

Solids content of CA/PEG in acetone:water (90:10)

5.5% 7.0% 8.5%

Acetone:water

94:6 91:9 86:14

CA:PEG

9:1
8:2
7:3

10%
11%
13%

Coating weight gain

Gun-to bed Distance

8.9 cm 12.7 cm

Cellulose acetate / PEG coating controls rate of water migration → controls rate of drug release

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Influence of Corelease™ CA Coating Parameters on Film Transparency – DoE Study

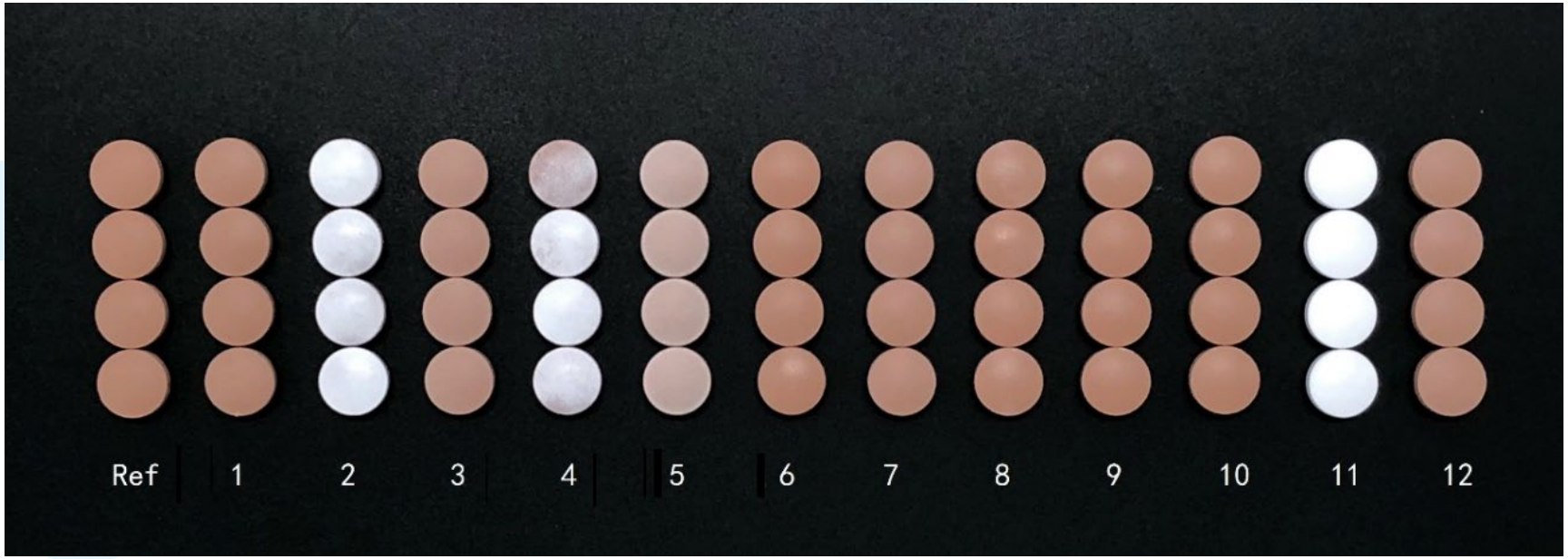
Corelease™
Controlled Release Formulated Systems

- **Substrate**: placebo tablets coated with Opadry® brown
- **Coating**: Corelease™ CA
- **Constant parameters:** gun-to-bed distance (5 cm)
  atomising air pressure (1.2 bar)
  pattern air pressure (1 bar)
  pan speed (20 rpm)
- **Variable parameters:** inlet air temp. (30-60ºC)
  inlet air volume (50-70 m^3/hr)
  spray rate (10-30 g/min.)
  humidity (49-80%)
  coating weight gain (3-5%)
- **Measured outputs:** product bed temp.
  film transparency (as ΔE)

Run	Inlet Temp. (℃)	Inlet Air Flow (m^3/h)	Spray Rate (g/min)	Relative Humidity (%)	Weight Gain (%)
1	30	50	10	49	5
2	30	50	30	68	3
3	60	50	10	64	3
4	30	70	30	57	3
5	60	70	10	65	5
6	60	70	30	61	5
7	45	60	20	57	4
8	30	50	10	80	5
9	60	50	30	79	3
10	30	70	10	79	3
11	30	70	30	80	5
12	60	70	10	80	3

Film Transparency Results

Corelease™
Controlled Release Formulated Systems



Ref	0.5	36.9	6.4	28.3	14.0	1.1	1.4	1.5	1.6	1.3	39.5	3.5

ΔE Value (n=2O)

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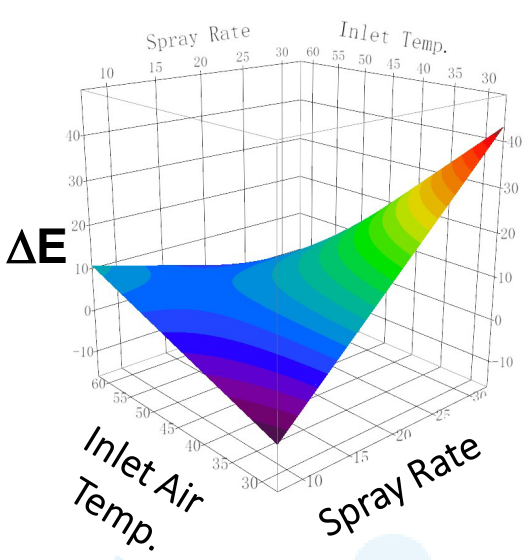
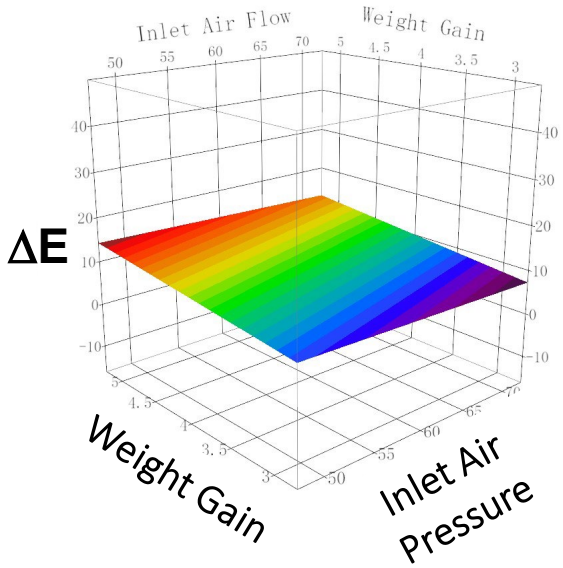
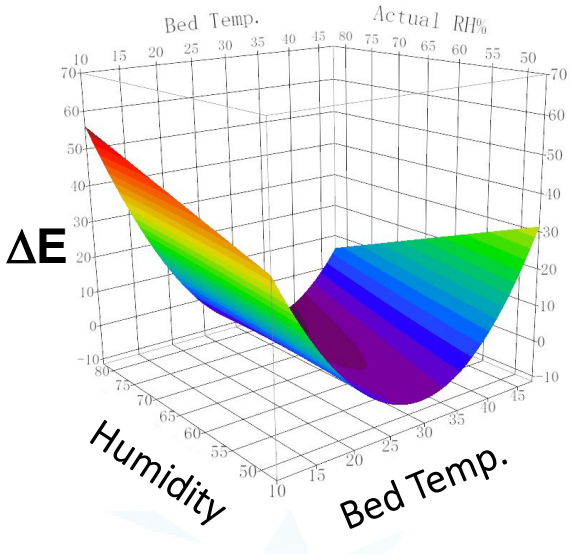
Influence of Coating Parameters on Film Transparency

Corelease™
Controlled Release Formulated Systems







Temperature & spray rate had greatest impact on film transparency

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Corelease™
Controlled Release Formulated Systems

- Simplify Formulation Development
- Easy to Use
- Improve Manufacturing Efficiency

Corelease™
Controlled Release Formulated Systems

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Controlled Release Formulated Systems

Optimizing Multiparticulate Dissolution Performance: A Simplified approach to Complex Formulations development

Dr Jason Teckoe
Technical Director- EMEA
Colorcon Ltd.
jteckoe@colorcon.com

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Outline - Dissolution Design

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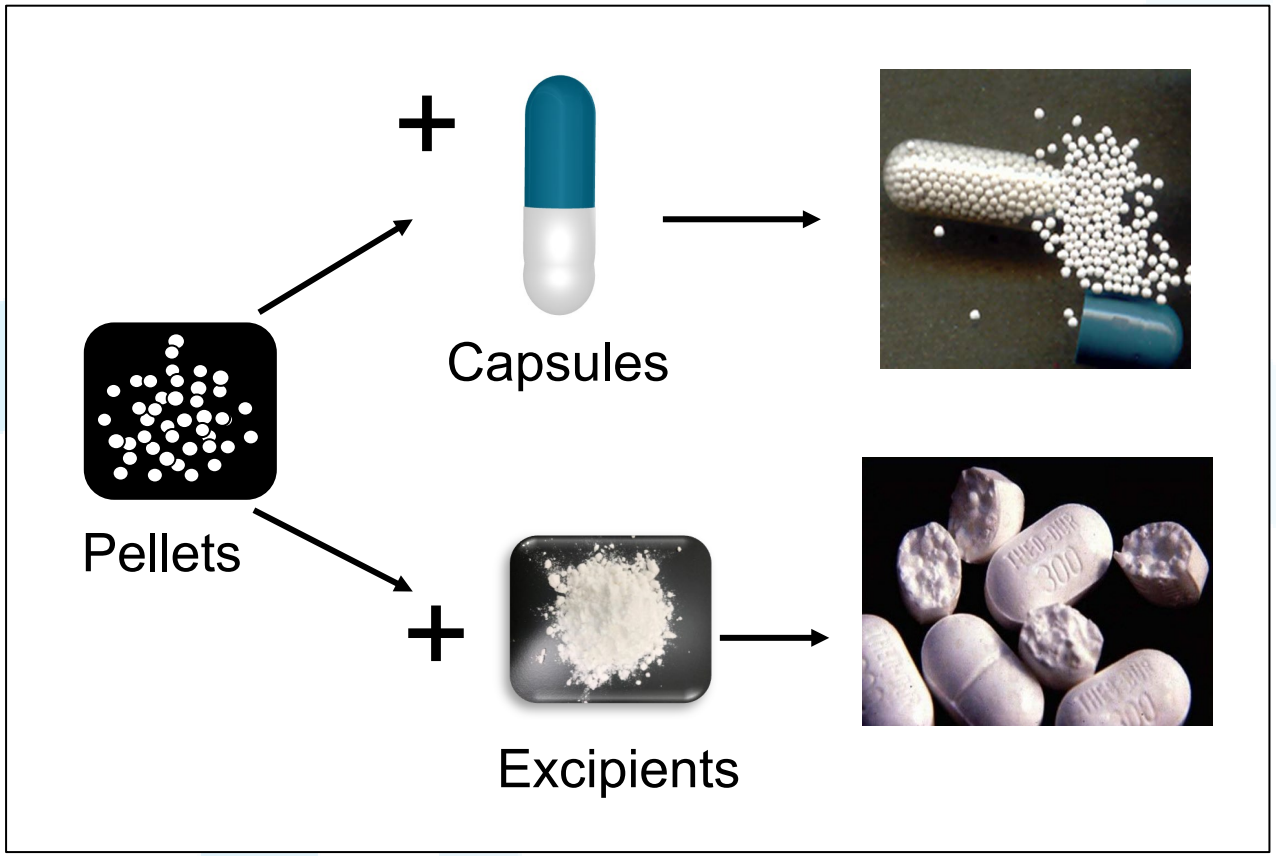
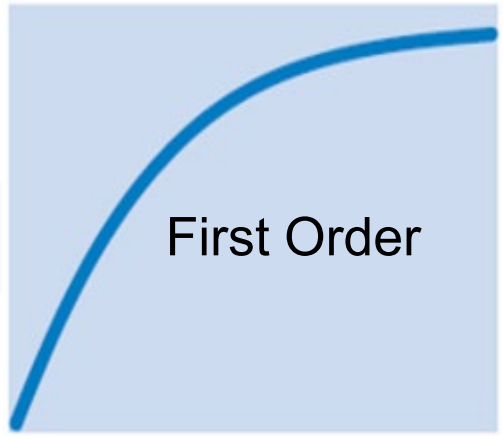
Controlled Release Formulated Systems



Extended Release



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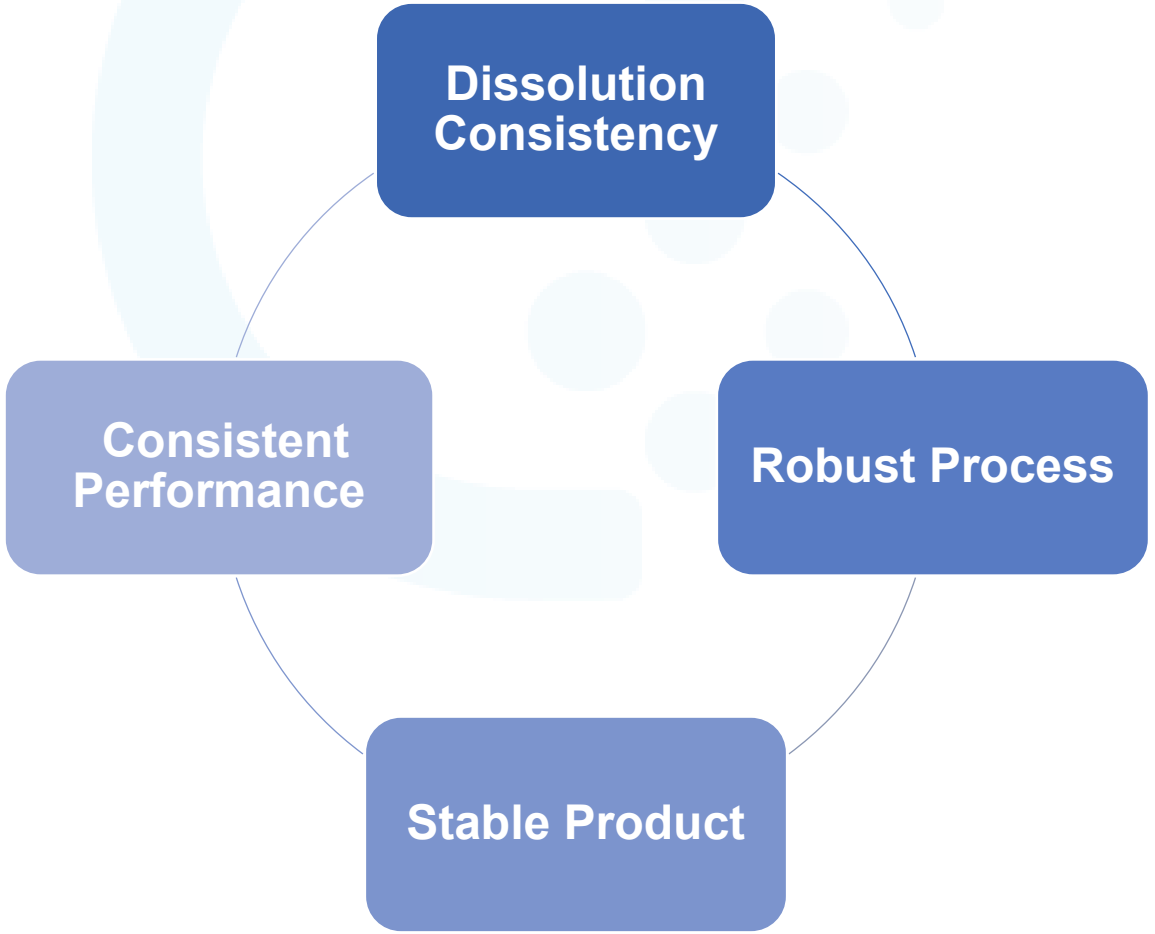
Controlled Release Formulations - Robustness

Corelease™
Controlled Release Formulated Systems

Achieve consistent drug release performance



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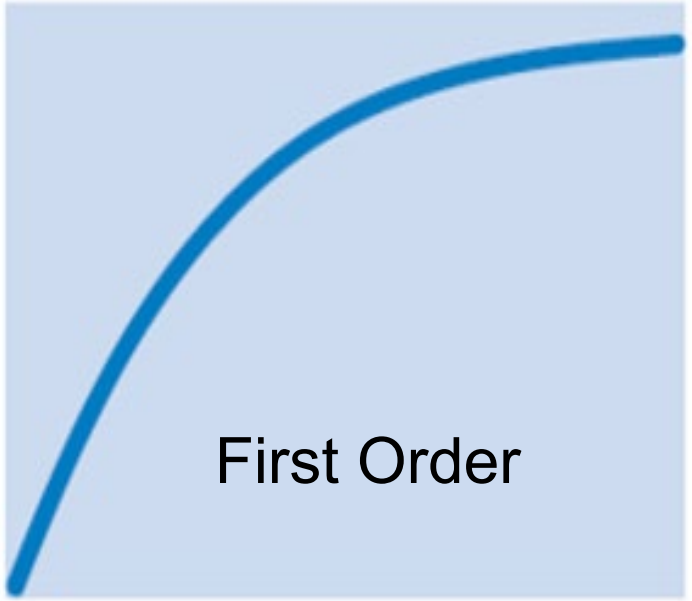
First Order Release Considerations

Corelease™
Controlled Release Formulated Systems

Extended-Release Considerations

- Matrix Formulation
  - Selection of Polymer & Concentration
  - Selection of Process (DC Vs WG)
  - Robust Drug Release Profile using QbD approach

- Barrier Membrane Multiparticulate
  - Sphere Size & Shape Selection
  - Seal Coating Options
  - Organic Vs Aqueous Coatings
  - Functional Polymer



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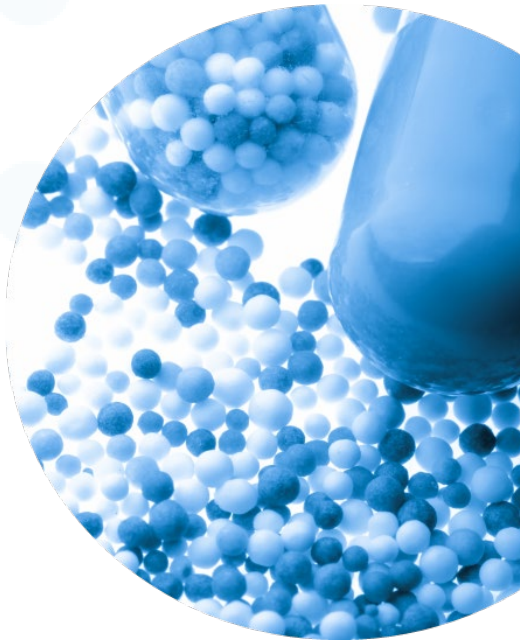
Benefits of Multiparticulate Dosage Forms

Corelease™
Controlled Release Formulated Systems

- **Patient:** Familiar capsules, compressed MUPS, sachets, taste-masking
- **Formulator:** formulation flexibility with range of release profiles
  - Delayed, extended & combination release
  - Combination actives (FDC)
- **Manufacturing** – multiple technology options
  - Layered beads
  - Extruded spheronized beads
  - Granules/powder
  - Mini-tabs/MUPS



Requires critical consideration during formulation and controlled processes

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MP Formulation Consists of Multiple Layers

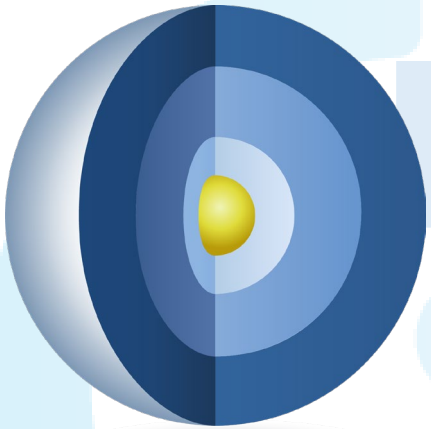
Corelease™
Controlled Release Formulated Systems

Starting Beads
Type and Particle size
Size distribution
Sphericity
Friability
Roughness

Seal-Coat
Drug separation
Surface smoothness
Drug migration
Strength of drug layer

Coating
Process Parameters
Spray rate
Air flow
Atomization
Product temperature

Top-Coat
Static charge
Wetting agent
Curing conditions



Starting Beads → Drug Layer → Seal-Coat → Functional Coat → Top-Coat

Drug Layer
Solubility
Binder selection
API form
API particle size

Coating Polymer, DR or ER
Weight gain,
Permeability,
Aqueous vs organic
Batch to batch variability

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Starting Substrate – Quality Attributes

Corelease™
Controlled Release Formulated Systems

Particle Size

- Narrow particle size distribution
- Size range to achieve different dose levels

Sphericity

- Roundness
- Smooth surface with no roughness

Low Friability

- Robust
- Ability to withstand rigors of processing

Critical Quality Attributes

- Narrow particle size distribution
- High Sphericity
- Low Surface Roughness
- Low friability

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Drug Layering API Property Considerations

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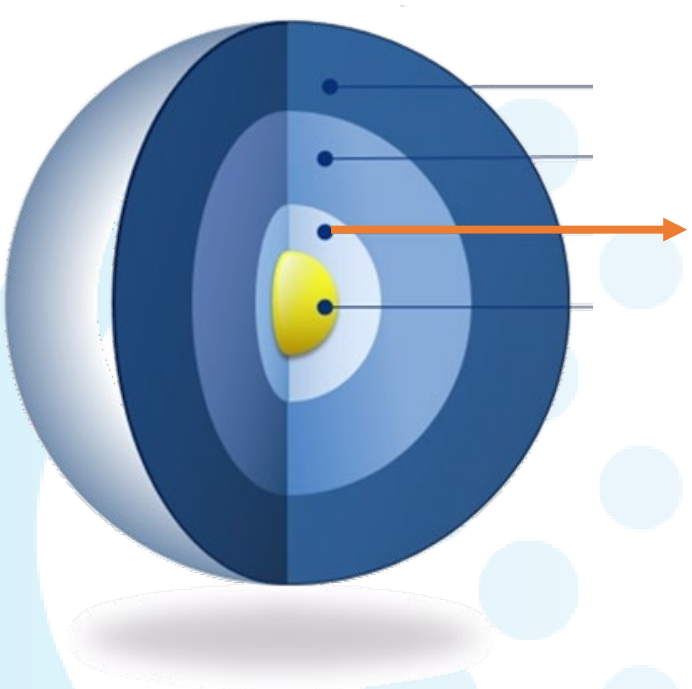
Controlled Release Formulated Systems



High

Drug Load / Dose

Low

- Drug in suspension
  - Wet mill step necessary
  - Drug particle size CQA
  - Settling / reaggregation
- Process efficiency (yield) concerns
- **Higher solids content (≥20%)**

- Drug in solution
  - Viscosity
  - Tackiness (agglomeration)
  - Addition of a processing aid
- Opportunity for suspension
- Polymer: Drug ratio can be low

- Drug in suspension
  - Wet mill step necessary
  - Drug particle size CQA
  - Settling / reaggregation
- Process efficiency / content uniformity concerns

- Drug in solution
  - May add to Viscosity/ tackiness concerns
- Polymer : Drug ratio can be low

Low **Drug Solubility** **High**

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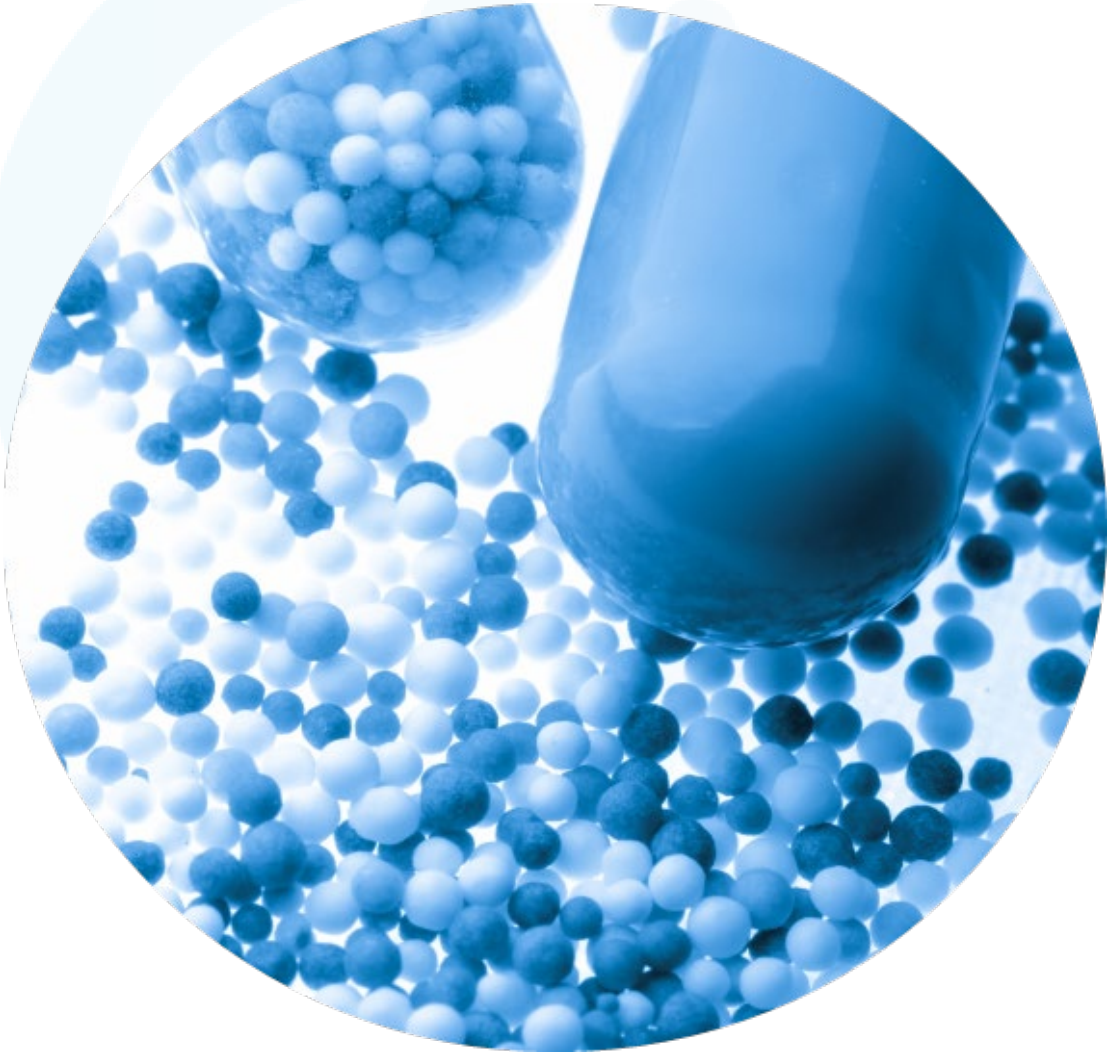
Functional Coatings for Controlled Release



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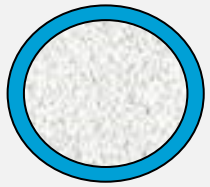
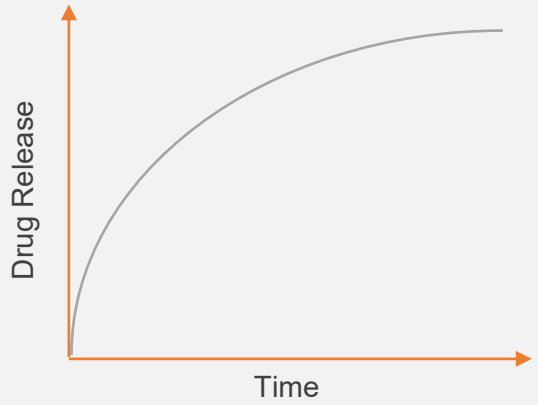
Multiparticulate Controlled Release Dissolution

Corelease™
Controlled Release Formulated Systems

Controlled Release Coating

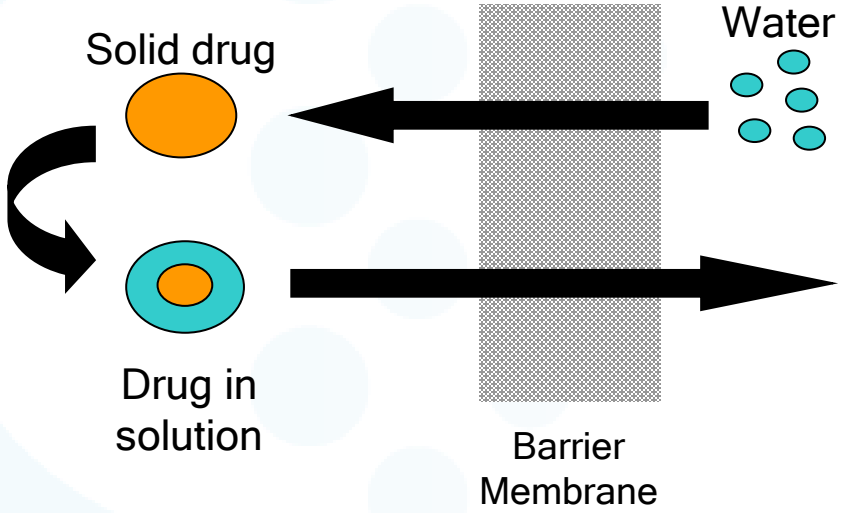


Diffusion Controlled



Fick's 1st Law Of Diffusion

$$J = \frac{dM}{dt} = \frac{DSP(C_d - C_r)}{h}$$



Drug solubility: As solubility ↑, rate of release ↑

Film thickness: As weight gain ↑, rate of release ↓

Film Permeability: As permeability ↑, rate of release ↑

Note: Image Adapted from *An Introduction to Multiparticulates*, M. Shaffer, Lonza, July 2018.

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Modulating Dissolution Profile

Corelease™
Controlled Release Formulated Systems

Aqueous

Surelease®
Ethylcellulose Dispersion Type B NF

- Aqueous dispersion of ethyl cellulose
  - 25% (w/w) solids content
- Fully formulated: plasticized for optimal coating performance

Solvent Based

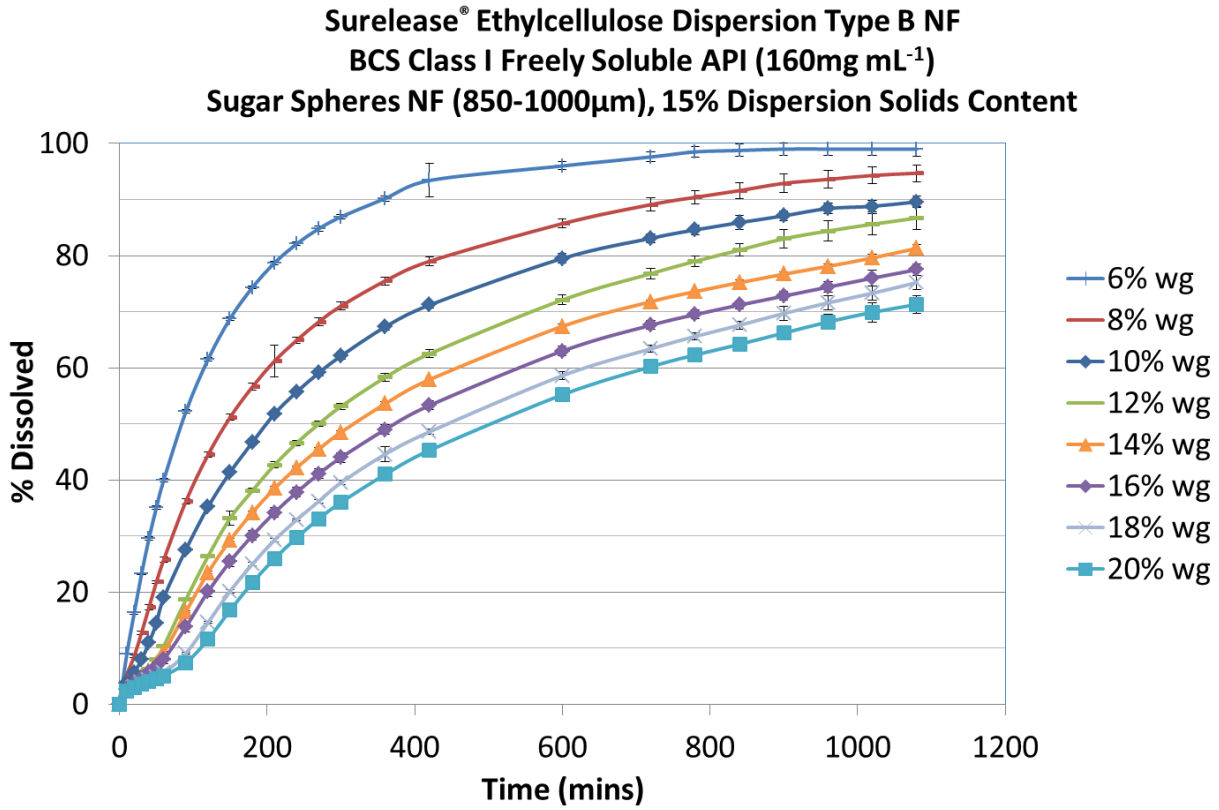
CoreleaseEC™
Ethylcellulose Organic Coating System

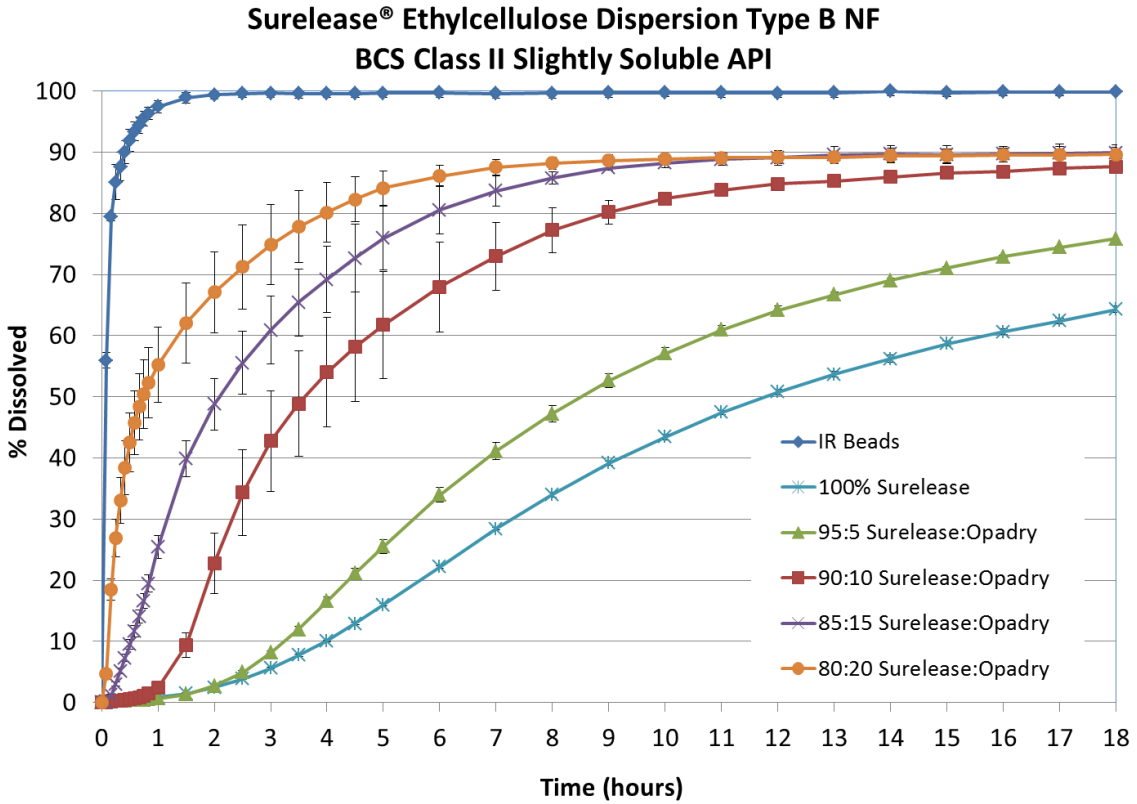
- Organic Solvent based system
- Customizable permeability of film
- Optimized for processability and productivity

Colorcon®

Optimize your Functional Coating – Aqueous

Corelease™
Controlled Release Formulated Systems



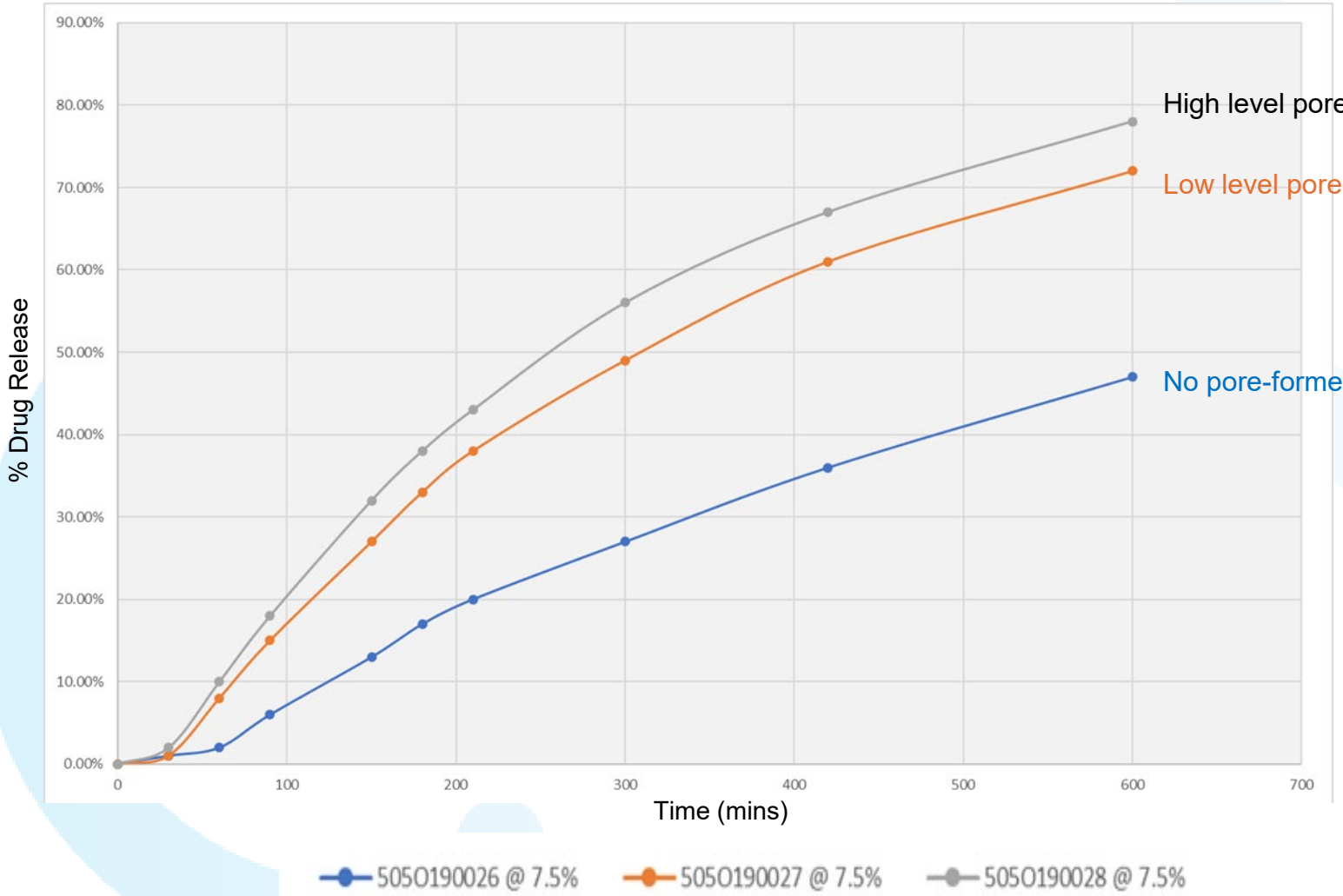


Impact of Pore-former

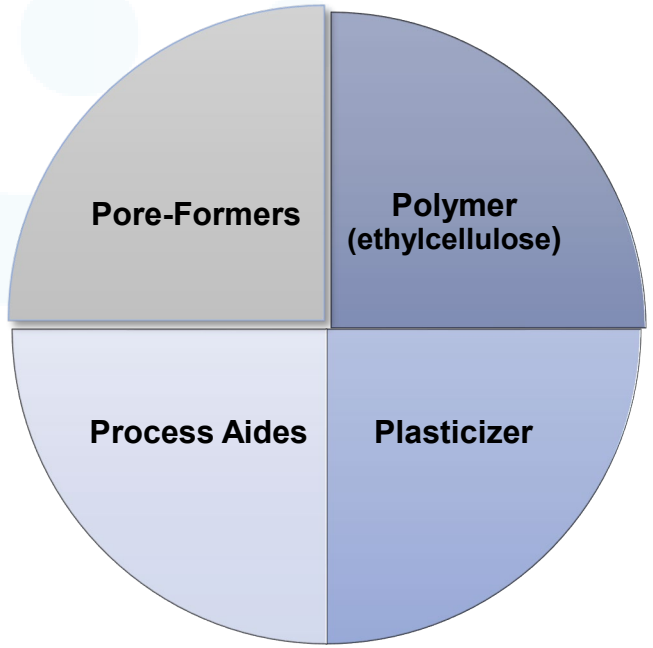
Colorcon®

Optimize your Functional Coating – Solvent based

Corelease™
Controlled Release Formulated Systems



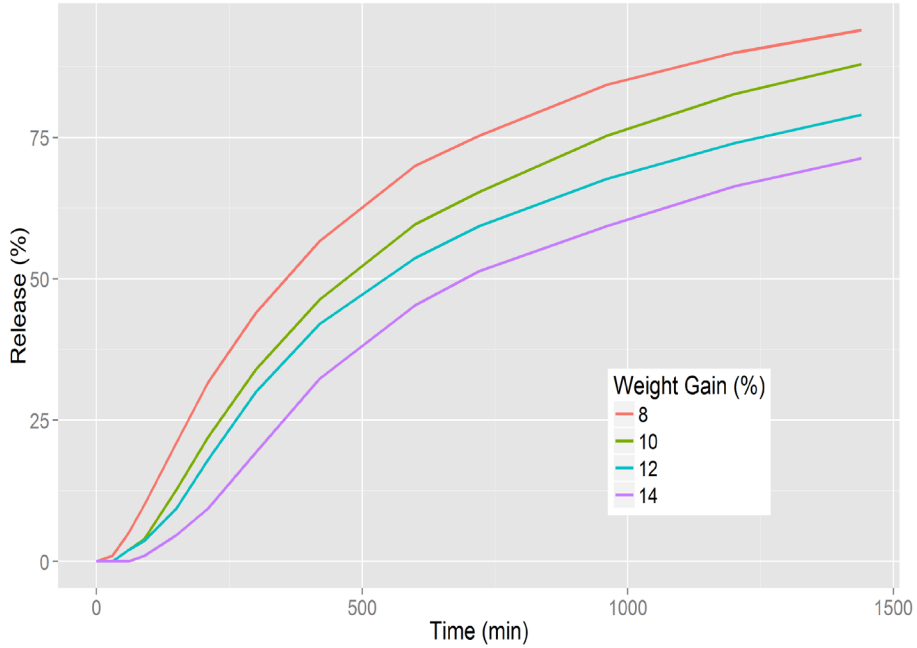
CoreleaseEC™
Ethylcellulose Organic Coating System

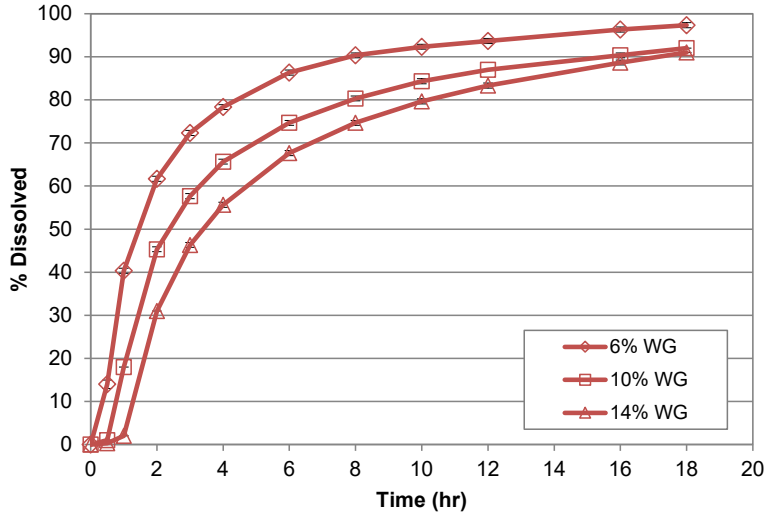


Colorcon®

Optimize your Functional Coating – Solvent based

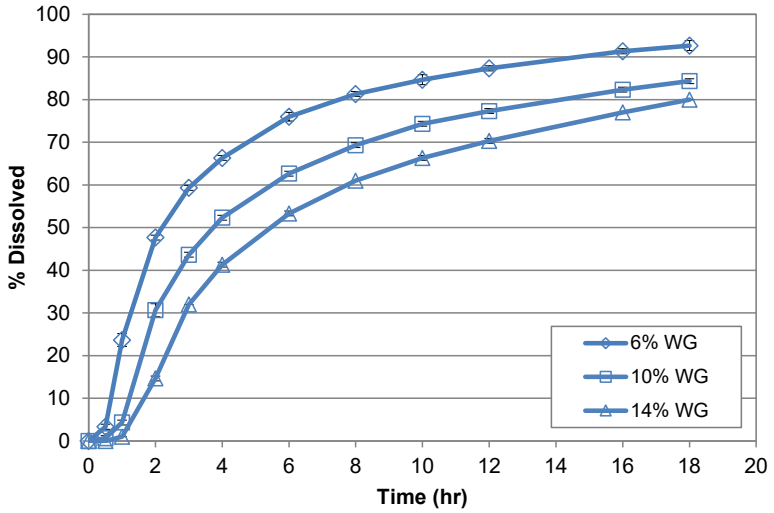
Corelease™
Controlled Release Formulated Systems





High Pore-former

CoreleaseEC™
Ethylcellulose Organic Coating System



No Pore-former

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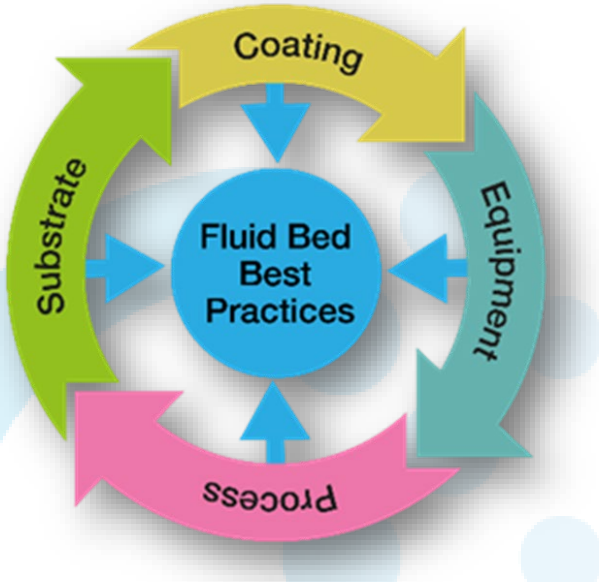
Summary

Corelease™
Controlled Release Formulated Systems



- Multiparticulates offer several advantages over traditional solid dosage forms
- Starting with a quality core material is critical to overall success
- Development of a robust process at the small scale is critical for successful scale-up
- A step-by-step approach to scale-up from lab to pilot to production is ideal

Colorcon products, expertise, and tools help achieve your goals

Colorcon®

Colorcon Provides Best Practice Insights Across All Aspects of MP Dosage Forms

Substrate (Core)

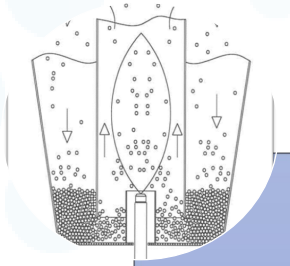
- Particle Morphology
  - Size
  - Friability
  - Sphericity
- SA/FT Ratio (MDD)
- Drug Layering
- API Morphology
- Binder Selection

Equipment

- Maintenance / Parts
- Static / Grounding
- Process Air Conditioning
- Filter Selection (Exhaust)
- Bottom Plate and Retention Screen Selection
- Spray Nozzle Set-up

Coating

- SA/FT Ratio
- Fluidization (Product Flow)
- Temperature (Tg)
- Agglomeration
- Droplet Size (air volume)
- Spray Nozzle Performance
- Optimization (DoE / Risk Analysis)



Process

- Static
- Fluidization (Product Flow)
- Agglomeration
- Process Tracking
- Scale-up
- Δ P
- Partition Height (Product Flow)

Surelease®

Ethylcellulose Dispersion Type B NF

CoreleaseEC™

Ethylcellulose Organic Coating System

SUGLETS®

SUGAR SPHERES

Colorcon®

Questions?