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Challenges and Solutions for Modulating Drug Release in OSDF

Raxit Mehta & John Paré

CRS 2022 Annual Meeting & Expo

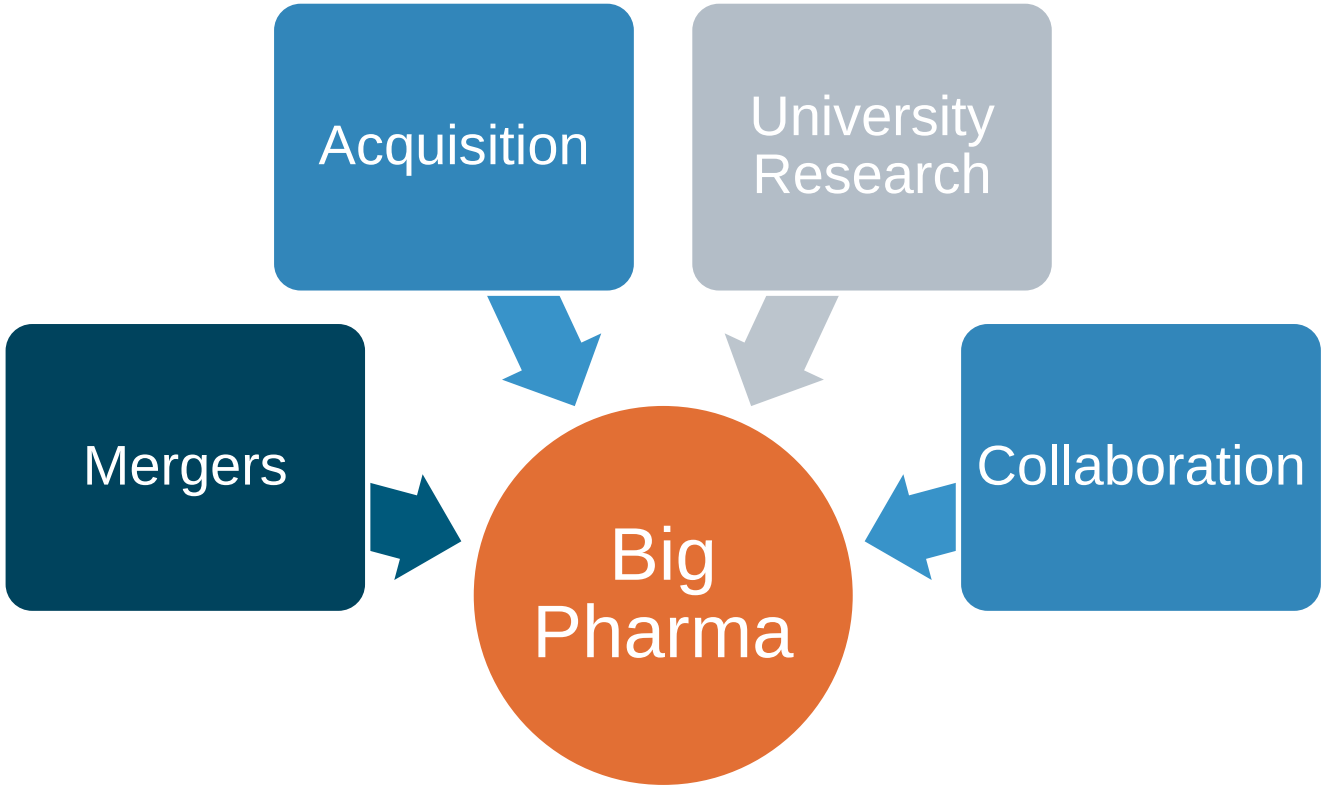
July 11 – 15, 2022 | Montreal Congress Center, Montreal Canada

Advanced Delivery Science

Outline

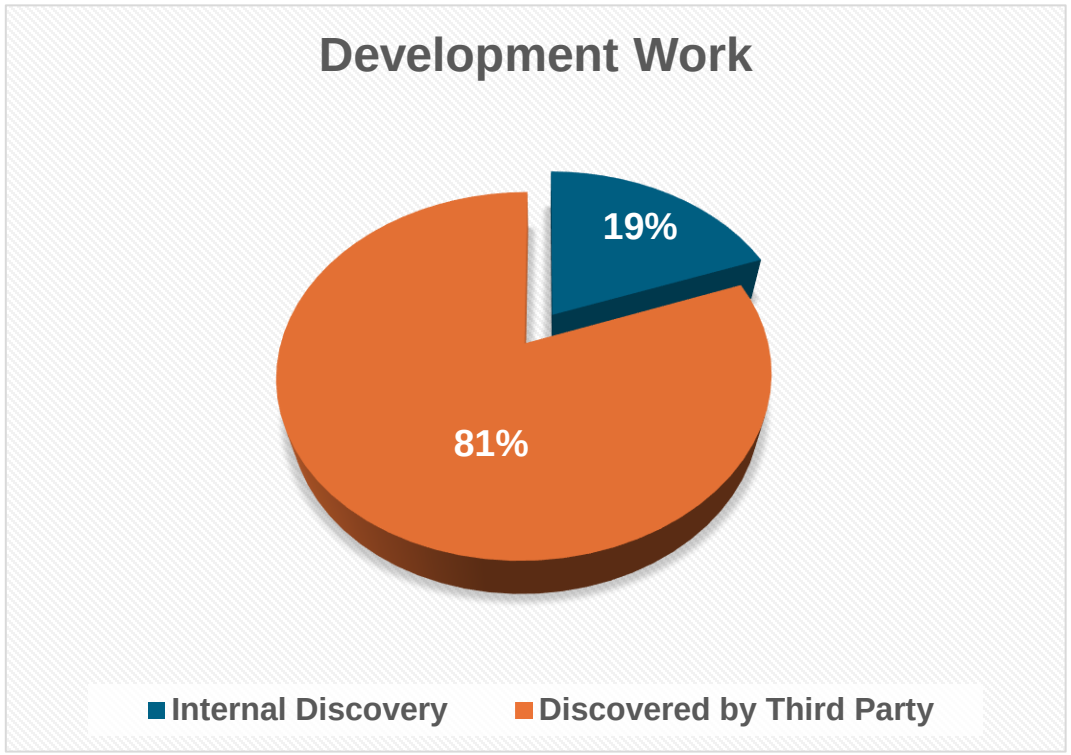
- Emerging innovation trends within the pharmaceutical industry
- OSDF challenges and changes in the developmental road map
- Overcome formulation challenges and achieve target drug release
- Case studies
- Path forward

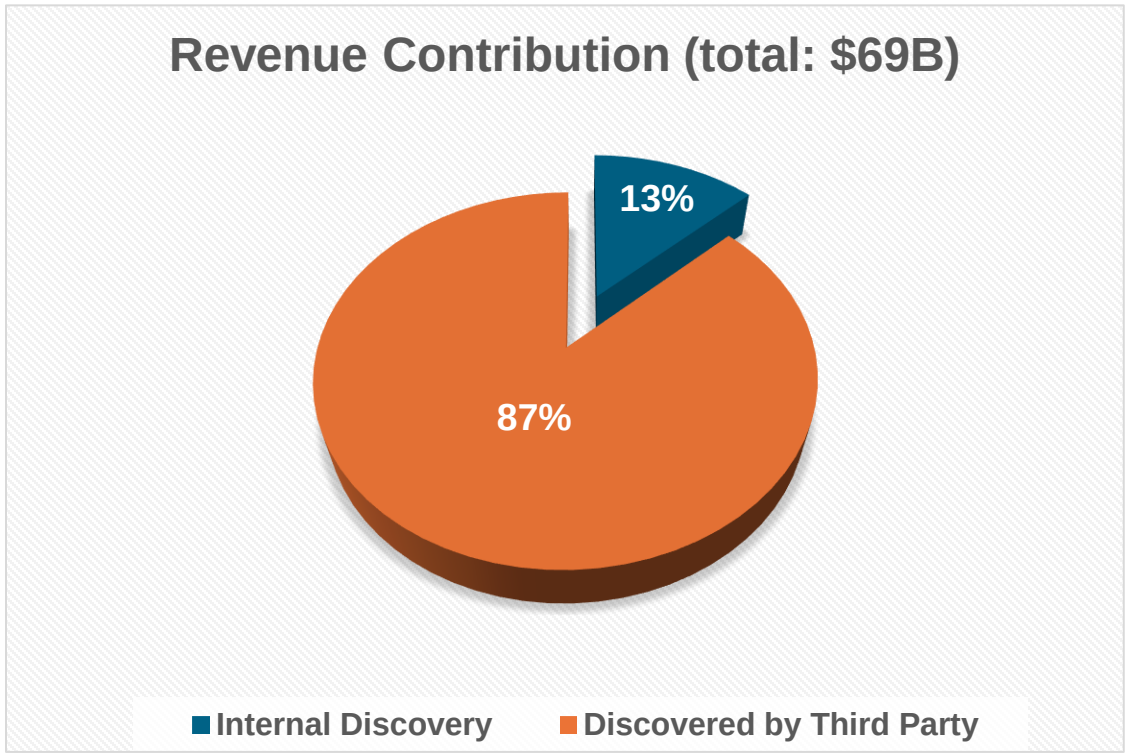
Drug Development: Current State



Innovation Trend:

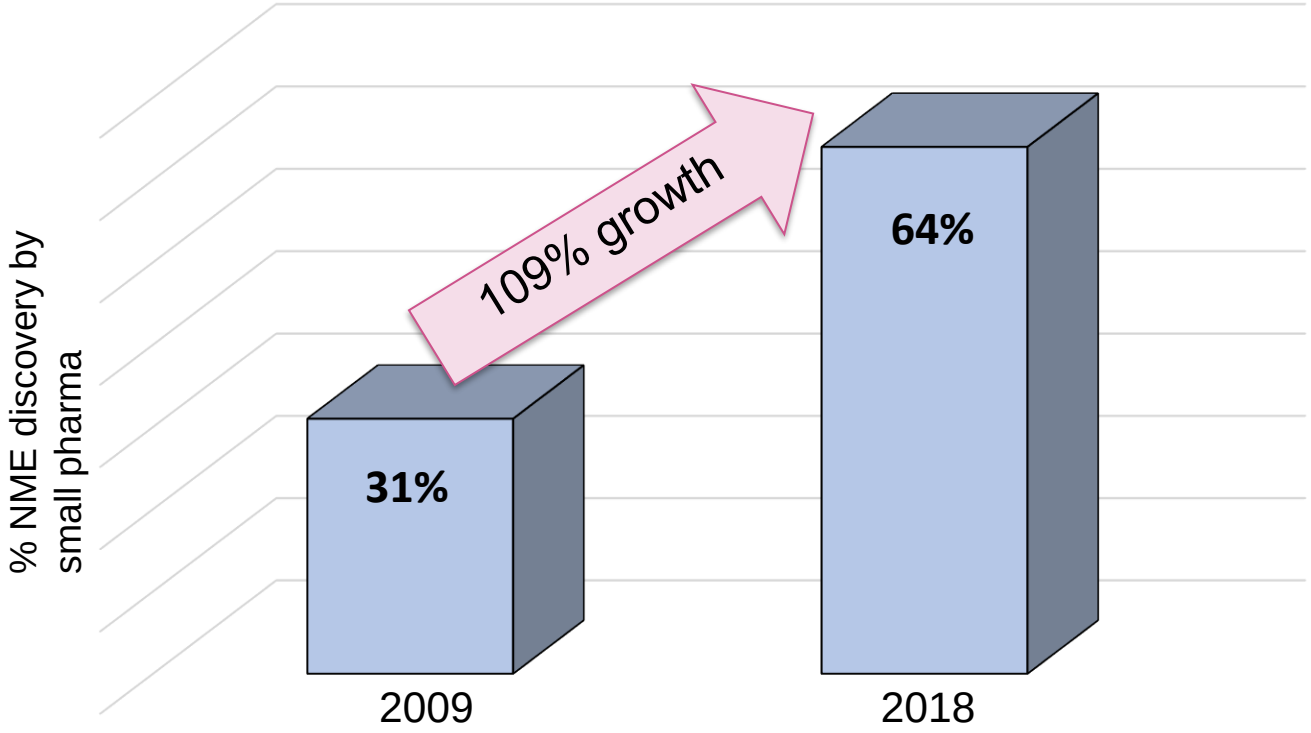
Third Party vs In-house Discovery at Major Big Pharma





Do large pharma companies provide drug development innovation? Our analysis says no
By Emily H. Jung, Alfred Engelberg and Aaron S. KesselheimDec. 10, 2019

Innovation Trend
Is Small Pharma Driving Big Pharma Innovation?



- 64% of the 59 FDA approved drugs in 2018 originated from emerging bio-pharma
- Small companies are overwhelmingly driving innovation

Small Pharma Driving Big Pharma Innovation
https://www.pharmavoice.com/news/2020-01-pharma-innovation/612330/

Small/Virtual Companies

Limited core group of employees responsible for strategic management, regulatory strategy and financial control

Outsource all non-core business functions

Electronic data capture and data submission to regulatory authorities

https://www.ddw-online.com/the-reality-of-virtual-pharmaceutical-companies-1320-201908/

Challenges Faced by the Small/Virtual Companies

https://www.ddw-online.com/the-reality-of-virtual-pharmaceutical-companies-1320-201908/

Goals

- Reduce drug development time
- Reduce R&D cost
- Achieve development activities using minimum resources

Needs

- Expert opinion/guidance at every stage of the drug product development
- Collaboration with suppliers to mitigate risk
- Regulatory and supply chain support
- Support from CRO/CDMO for development activities

✓ Formulation Expertise with a Trusted Partner

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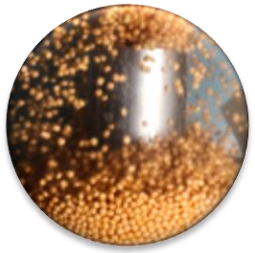
Formulation Partner Value Contribution

Expertise of Coating, Core Formulation and Process Development

Scale-Up and Risk Reduction

Global Manufacturing and Support



Product Life-Cycle Management

Regulatory Support and Supply Security

Colorcon: Trusted Formulation Partner for over 60 years

Services for Speed to Market

HYPERSTART
Starting Formulation Service

Best-in-Class Products for Solid Dosage Forms

Global Regulatory Expertise

Access to Experts and Equipment for Trials

Processing and Characterization Capabilities

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Early Phase Development - Proof of Concept

Develop prototype tablet or capsule dosage forms when API quantity is limited

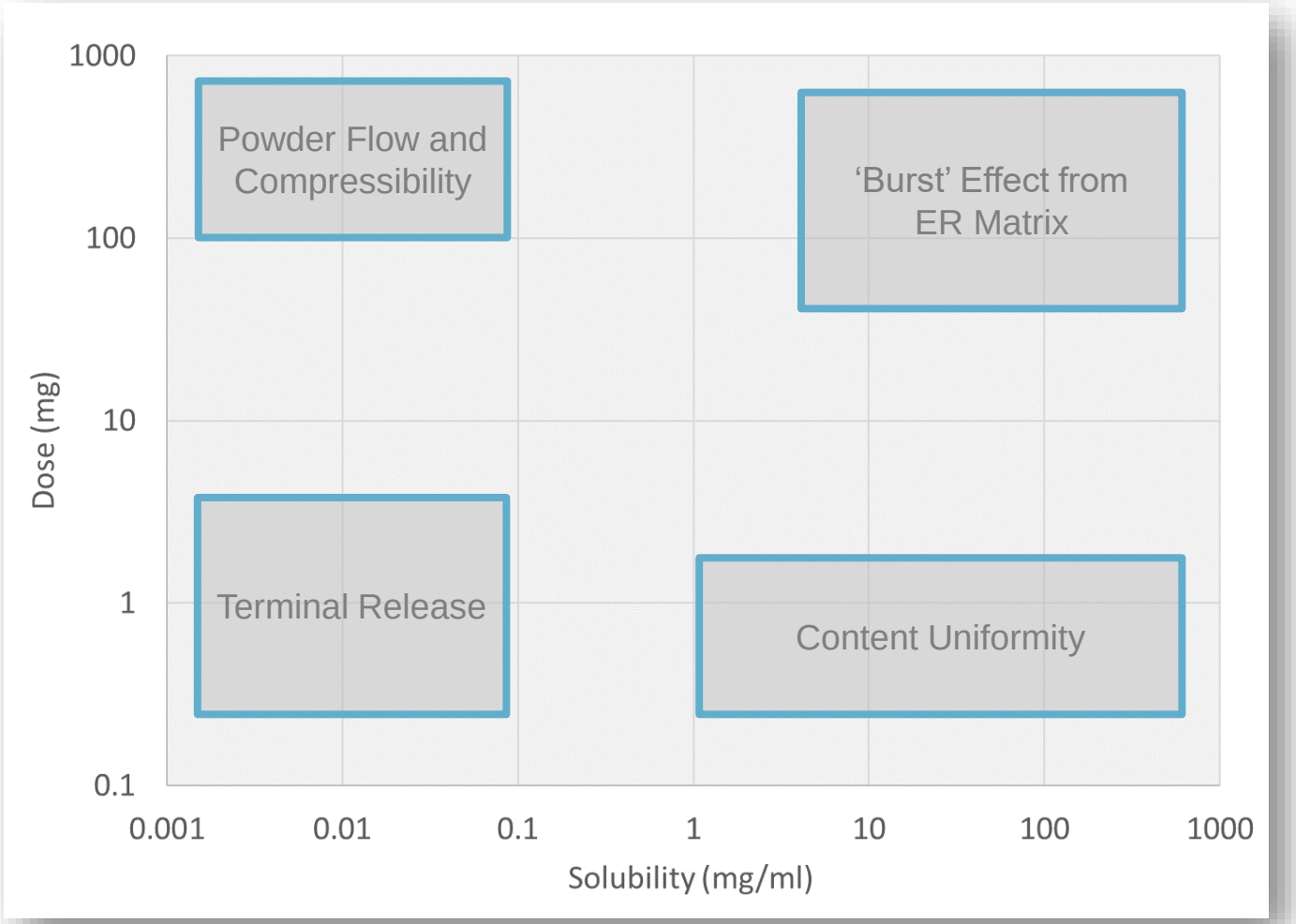
Handles small quantities (mg to grams) of API to provide proof of concept solid oral dosage forms

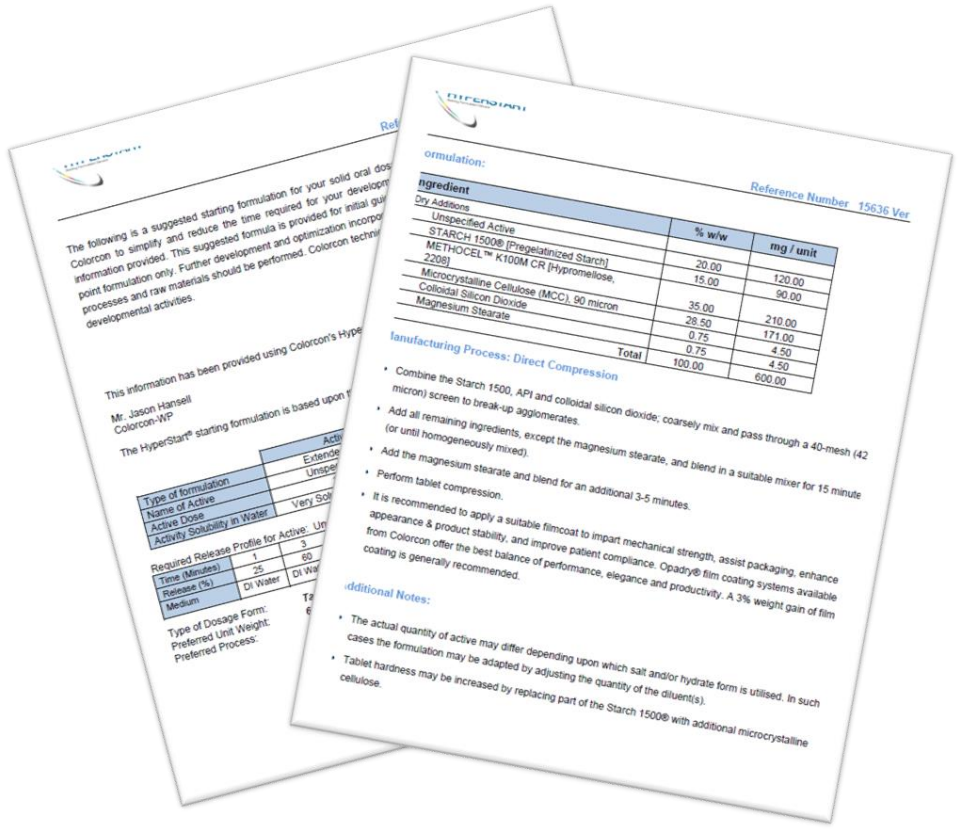
API potency requires a higher level of protection

Validated to safely handle up to Band 4 of 5 APIs (as low as OEL of 1.0 microgram / cubic meter)

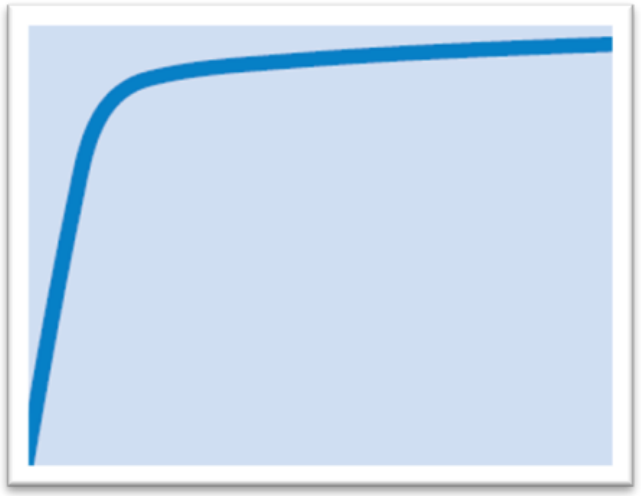
Case Studies

IR and MR Formulations Across a Wide Range of Dose And Solubility



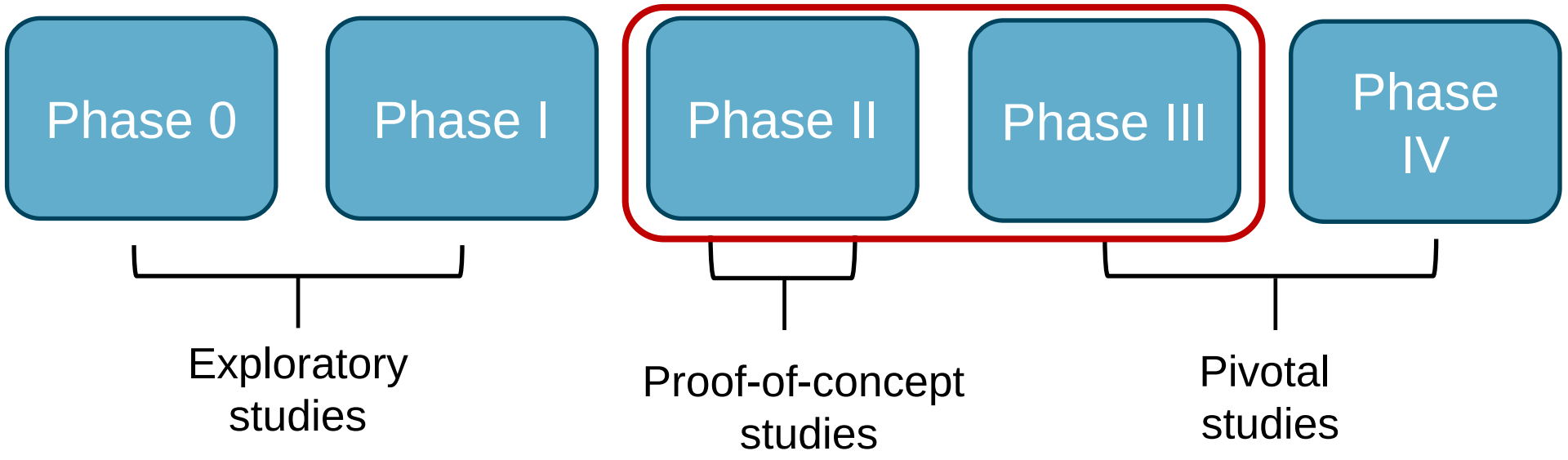


Early-stage Immediate Release Formulation Development



- Formulation that can be converted from capsules to tablets
- Improve blend flow of cohesive drug to reduce weight variation for capsule filling and tableting
- Stabilize moisture sensitive APIs
- Promote content uniformity for low dose APIs

Capsule to Tablet Conversion to Increase Manufacturing Productivity



Suitable stages of the drug product development: Phase II & III

Formulation for Direct Compression

Ingredients	Low Dose % w/w	High Dose % w/w
BCS Class I, Very Soluble Drug	5.00	20.00
StarTab® (Directly Compressible Starch)	35.75	28.25
Microcrystalline Cellulose (MCC), PH 102	59.00	51.50
Magnesium Stearate	0.25	0.25
Total	100.00	100.00

Target Tablet Weight
250 mg for 50 mg dose
200 mg for 10 mg dose

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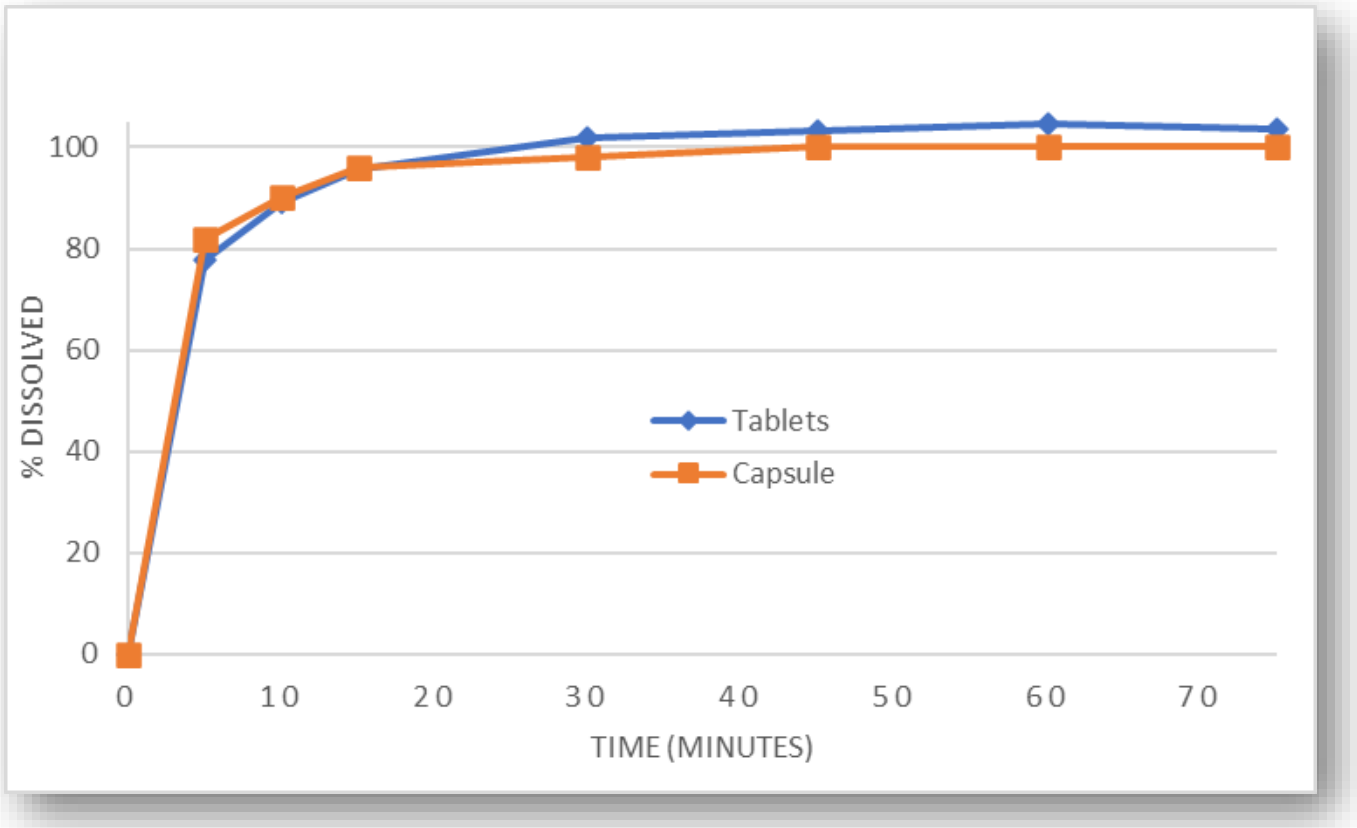
Capsule to Tablet – Key Challenges

- Effect on drug release
- Polymorph change
- Flowabillity

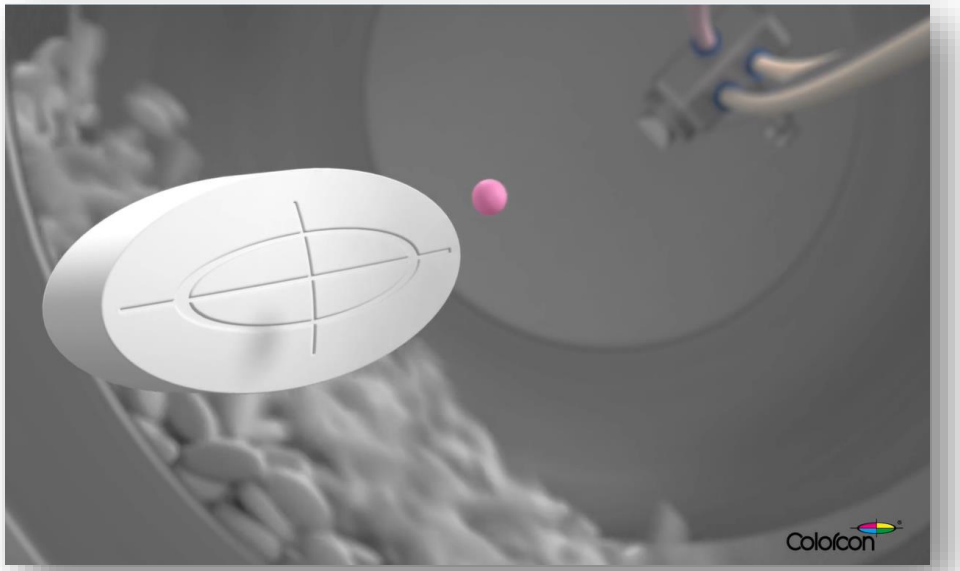
Drug Release Evaluation

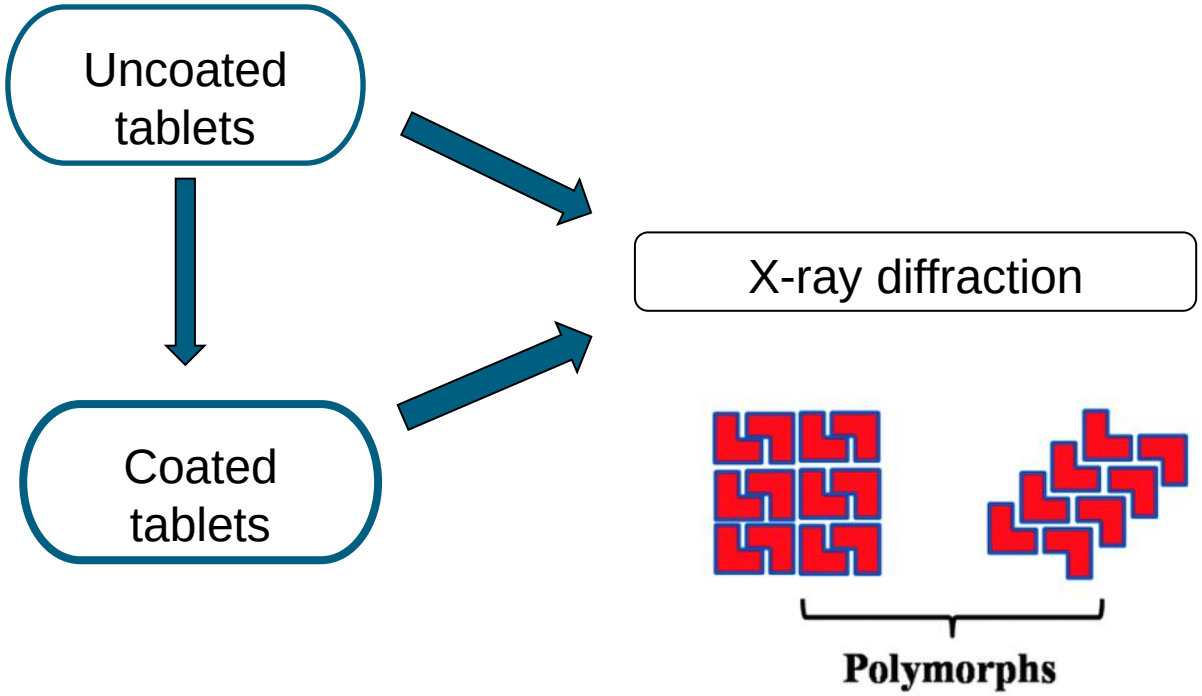


Criteria: >85% drug release in 15 min or less

→ No additional in vivo study

Coating of Tablets: Overcoming Concern of Polymorph Change





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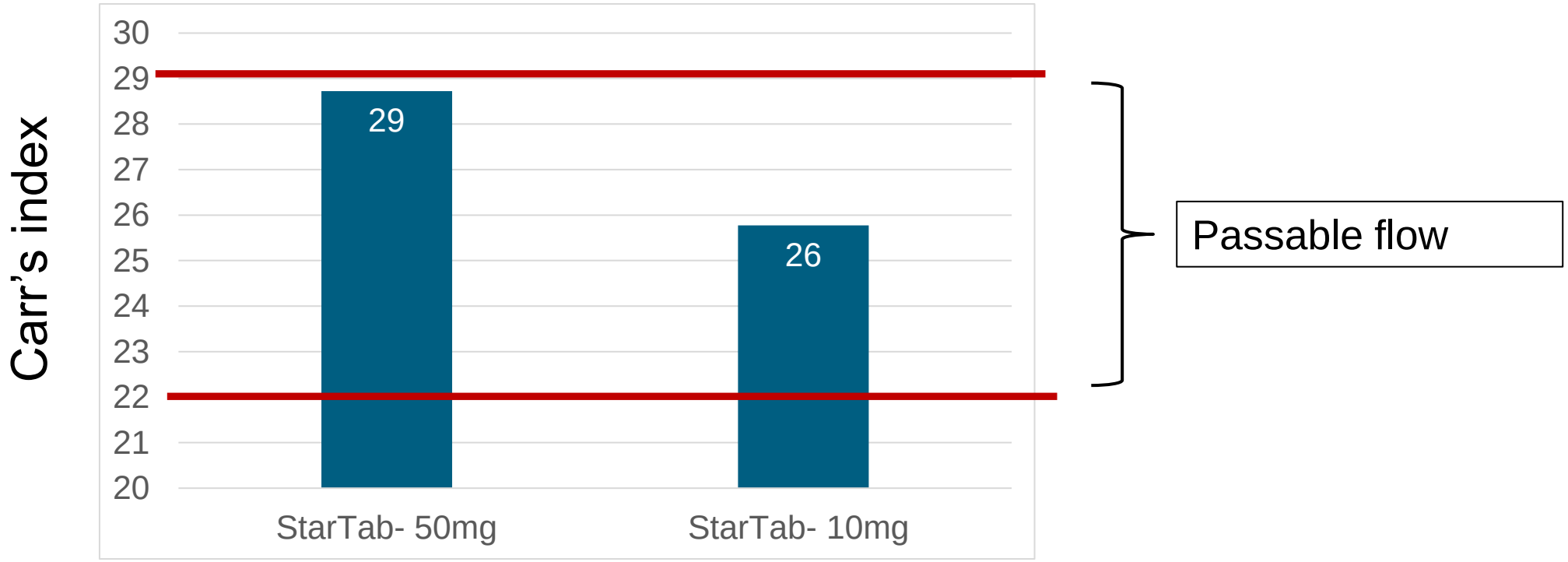
Blend Flowability



Good blend flow for low dose formulation and passable flow for high dose formulation

Capsule to Tablet – Key Challenges

- Effect on drug release
- Polymorph change
- Flowabillity

✓ Successfully addressed the challenges

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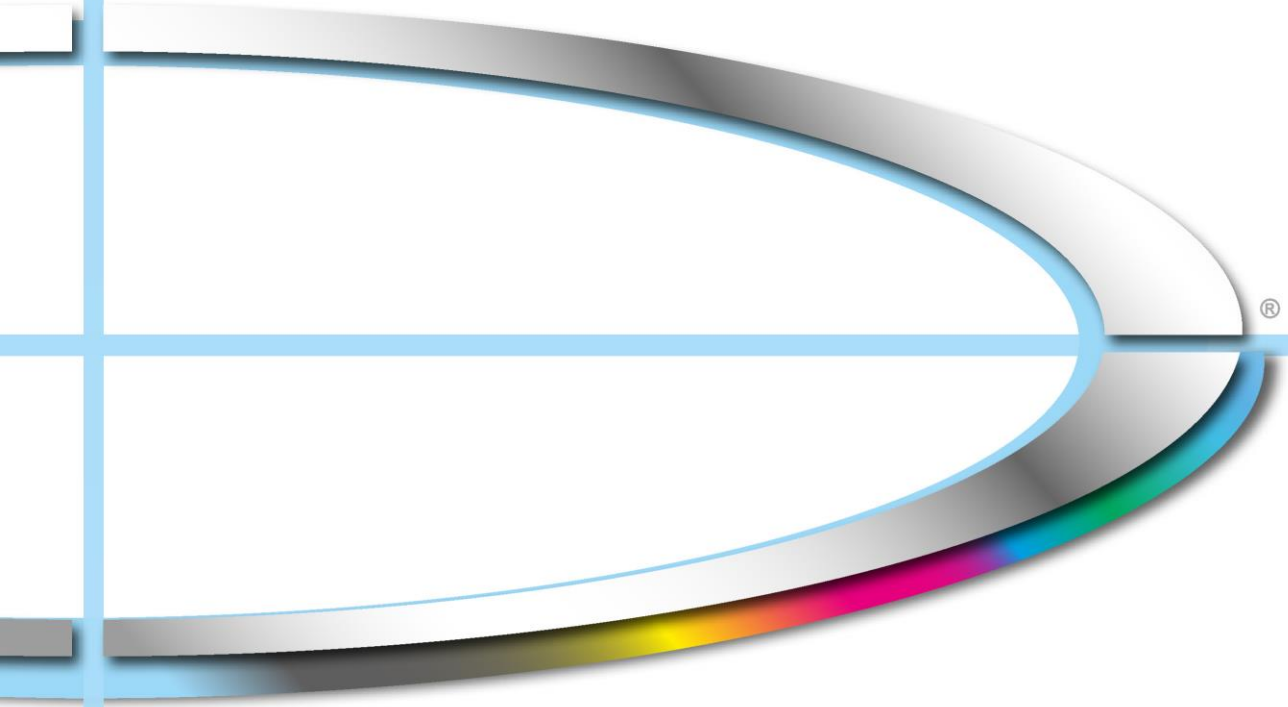
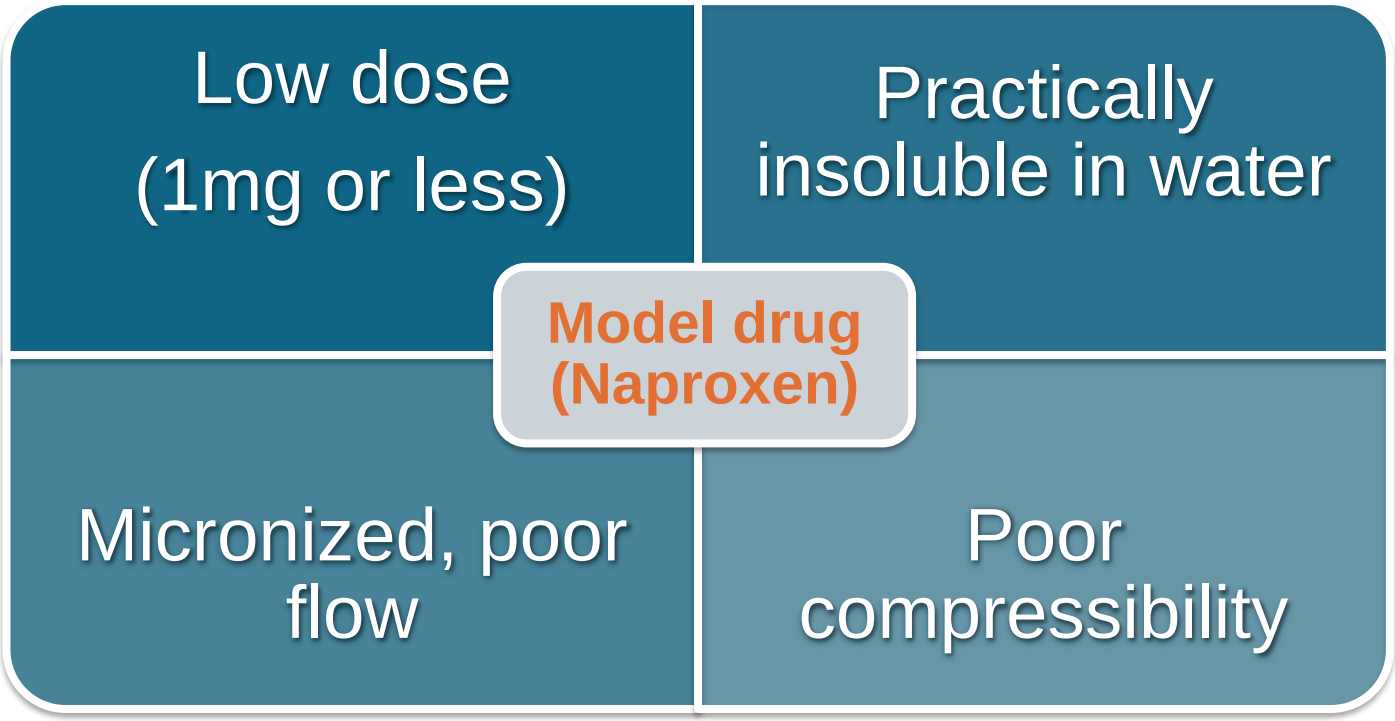
Low Dose and Directly Compressible Formulations



Drug Attributes



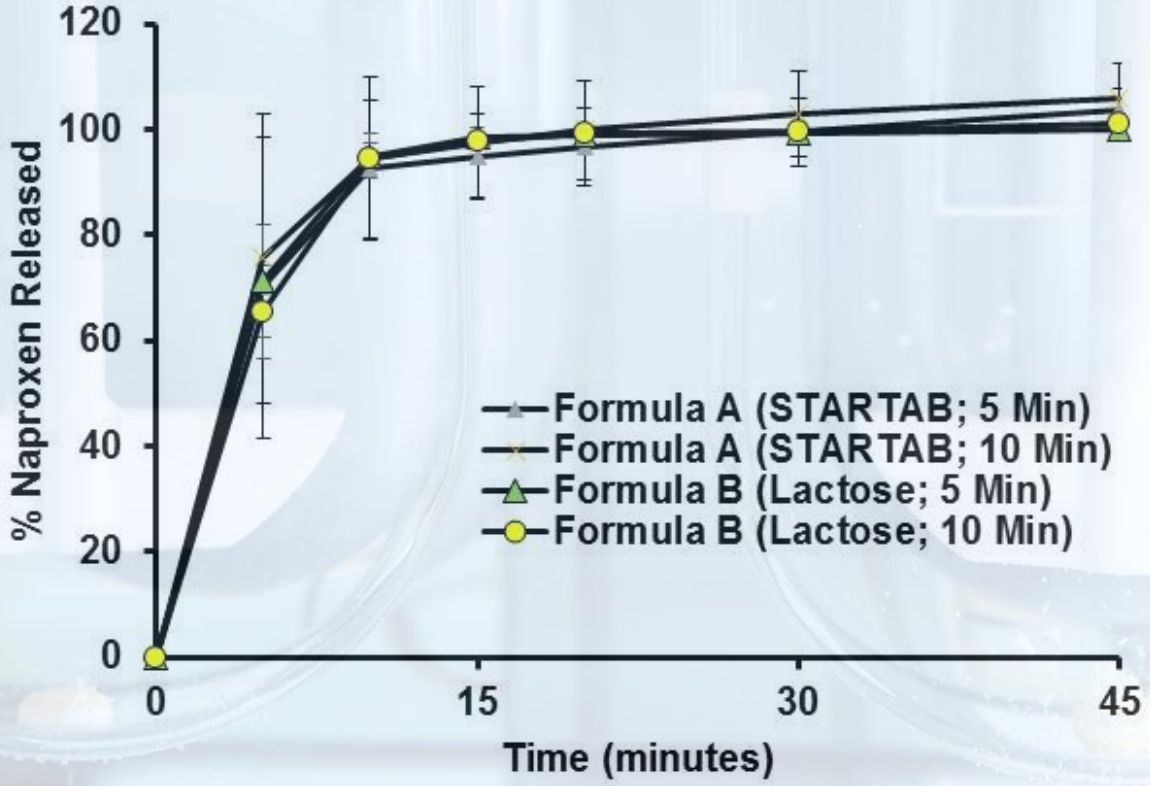
Total tablet weight was 400 mg; 9.5 mm round std concave tablet
Direct compression using rotary tablet press @ 35 rpm; 15 kN compression force

Naproxen Tablet Formulation

Ingredients	Formula A (StarTab)	Formula B (Lactose)
Naproxen (micronized)	**1.00 %**	**1.00%**
StarTab® (Directly Compressible Starch)	98.50%	------
Lactose Monohydrate (FastFlow 316)	------	96.50%
Crospovidone	------	2.00%
Magnesium stearate	0.50%	0.50%
Total	**100.00%**	**100.00%**

Total tablet weight was 400 mg; 9.5 mm round std concave tablet
Direct compression using rotary tablet press @ 35 rpm; 15 kN compression force

Dissolution Comparison

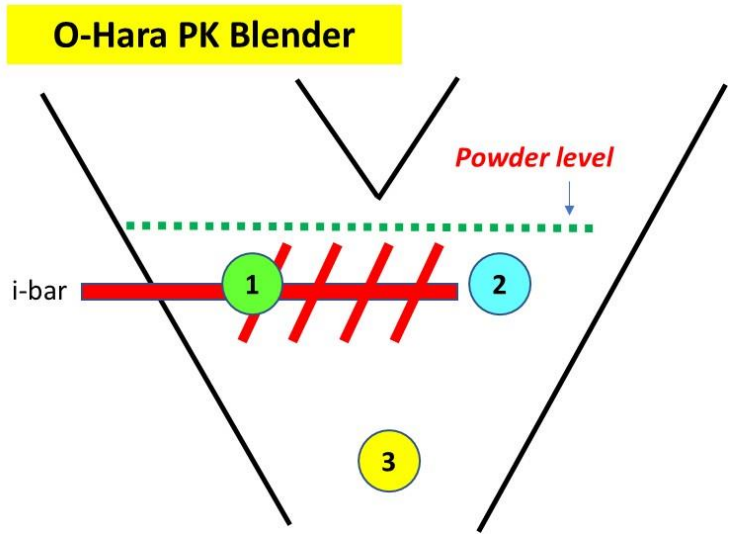


Dissolution: USP monograph (phosphate buffer pH 7.4; 900 mL, Paddle, 50 rpm)

Blend and Content Uniformity

Formula	Description	Description	Blend Uniformity, %	Tablet Content Uniformity, %
Formula A	StarTab ; DC	Top right	95	----
		Top left	96	----
		Bottom	94	----
		Composite	94	----
		Tablets, 5 min	----	97.23 ± 0.34 *
		Tablets, 10 min	----	97.32 ± 0.60 *
Formula B	Lactose; DC	Top right	84	----
		Top left	87	----
		Bottom	88	----
		Composite	87	----
		Tablets, 5 min	----	86.50 ± 0.63 *
		Tablets, 10 min	----	86.06 ± 0.86 *

**Mean ± % RSD*



Low Dose and Directly Compressible Formulations

- Formulation based on StarTab® resulted in improved blend and content uniformity
- StarTab is recommended for low dose formulations to improve content uniformity after simple blending and direct compression

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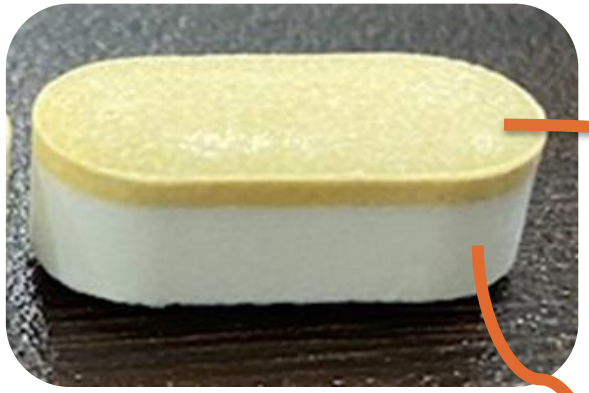
Bilayer and Fixed Dose Combination (FDC) Technologies for Biphasic (IR+ER) Performance

- Bilayers for fixed dose combinations
- Multiparticulates, including mini-tablets
- Coating expertise for layering of low dose drugs on tablets

Bilayer Tablet Composition



IR layer

Direct Compression		
Ingredients	**% w/w**	**mg/tablet**
Glimepiride	0.500	1.000
STARTAB®	33.080	66.160
Lactose monohydrate	65.670	131.340
Dye color Iron Oxide yellow	0.500	1.000
Magnesium Stearate	0.250	0.500
TOTAL	100.000	200.000

Hardness = 22 - 25kP

ER layer

Granulation		
Ingredients	**% w/w**	**mg/tablet**
Metformin Hydrochloride	71.400	499.800
METHOCEL K100M Premium	23.300	163.100
MCC	4.000	28.000
Colloidal Silicon Dioxide	0.900	6.300
Magnesium Stearate	0.400	2.800
TOTAL	100.000	700.000

Hardness = 18- 22kP

Tablet dimensions: 16.5 x 8 mm, caplet
IR + ER = 900 mg

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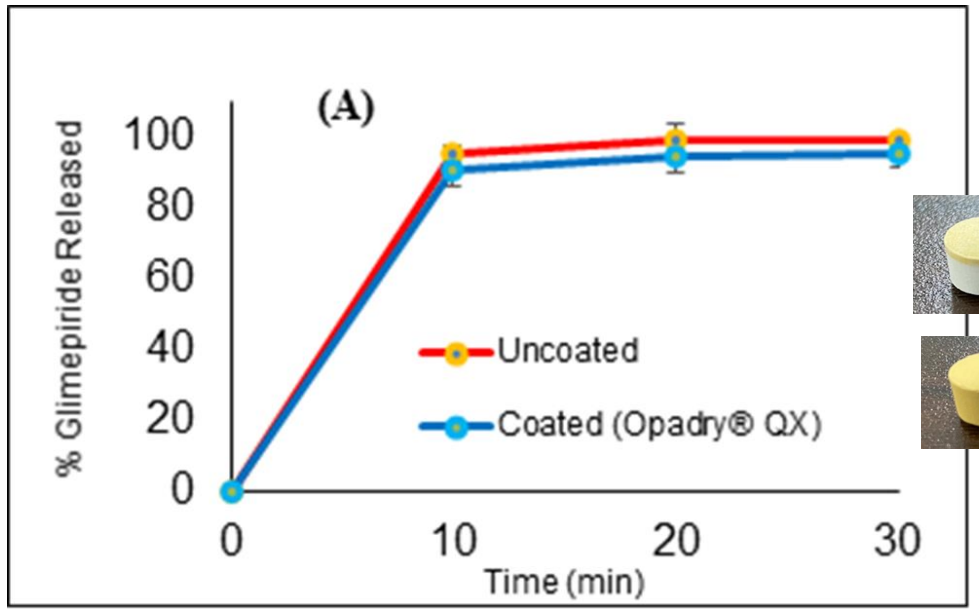
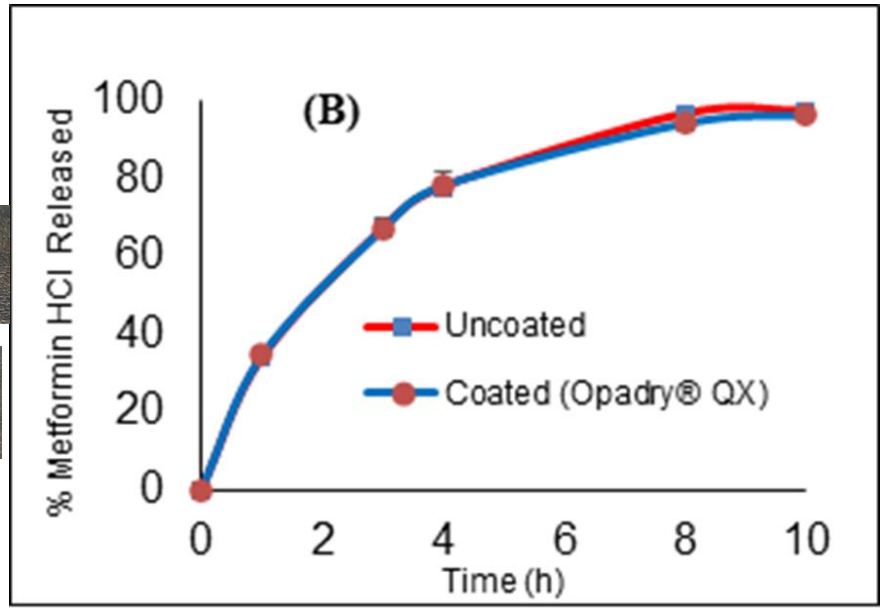
Bilayer Tablets - Release Profiles

Uncoated and Coated tablets

Release Profiles of (A) IR Glimepiride and (B) ER Metformin HCl from Uncoated and Coated Bilayer Tablets



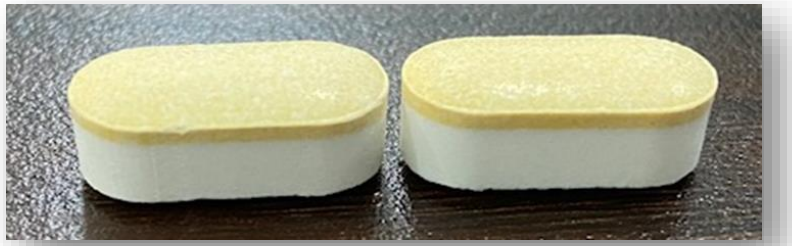


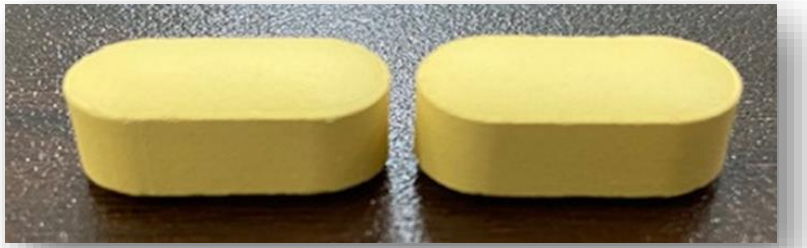
900 mL pH 7.8 Phosphate buffer + 10% SLS, using paddle with sinkers @100 rpm for 90 mins, analyzed using HPLC @228nm

USP Apparatus II with sinkers @100 rpm, 1000 mL phosphate buffer pH 6.8, analyzed using UV @233nm

Bilayer Tablets - Release Profiles

Uncoated and Coated tablets





Uncoated and coated tablets showed similar dissolution profiles

> 75% glimepiride released in 10 min (IR) and > 90% metformin was released in 8h (ER)

Film Coating of Low Dose, Low Soluble API on ER Matrix Core

Formulation Development Activities

- ER matrix core: metformin hydrochloride, aqueous granulation
- IR film coat: glimepiride, aqueous based coating system

Quality evaluation parameters for film coating layer

- Content uniformity, Assay and dissolution testing of glimepiride

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Composition of Film Coated Tablet

ER Matrix Core
Metformin hydrochloride

ER Matrix Tablet	Granulation		
	Ingredients	% w/w	mg/tablet
	Metformin Hydrochloride	62.50	500.00
	METHOCEL K100M Premium	32.20	257.60
	MCC	4.000	32.00
	Colloidal Silicon Dioxide	0.900	7.20
	Magnesium Stearate	0.400	3.20
	TOTAL	100.000	800.000

18 x 8 mm caplet shape

IR Film coating
Glimepiride

Component	Functionality
Glimepiride, d_{90} = <10µm	Active
Opadry® II	Binding agent
SLS	Wetting agent
Water	Dispersion medium

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Film Coating Optimization Trials

Components	%		
	Trial 1	Trial 2	Trial 3
Glimepiride	2.50	1.25	0.833
Opadry® II	96.50	97.75	98.167
SLS	1.00		
Total, %	100		
% Weight gain	**5**	10	15
Final tablet weight, mg	**840**	**880**	**920**

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Results - Glimepiride IR Layer

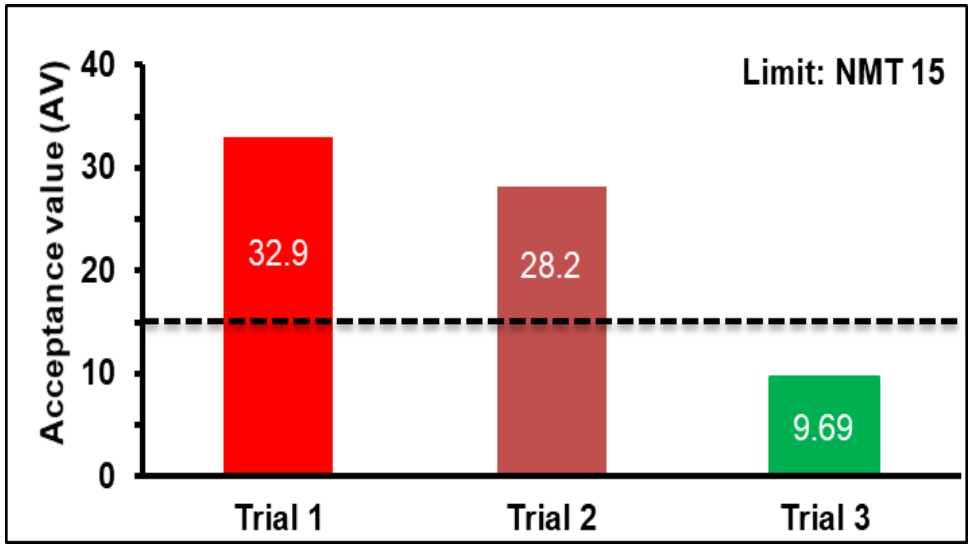
Glimepiride Assay %

Trial 1 5% WG	Trial 2, 10% WG	Trial 3, 15% WG
112%	99%	106%

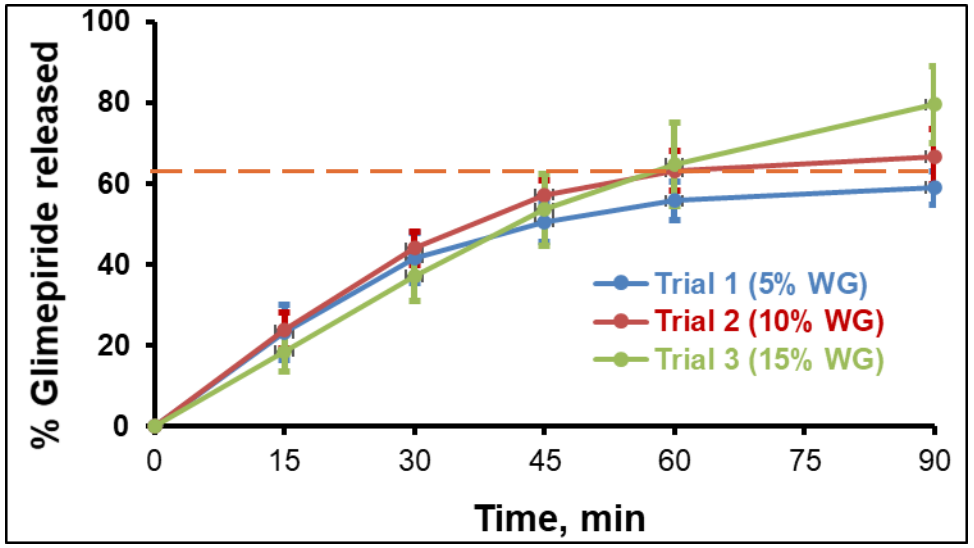
- Coated tablets appeared smooth and uniform
- Use of dilute dispersion for drug layering application helped meet assay specifications of low dose API, glimepiride

Results - Glimepiride IR Layer

Content Uniformity



Release Profile



USP Apparatus II, 100 rpm, 900 mL pH 7.8 Phosphate buffer + 1% SLS

- Dilute drug layering dispersion provided uniformity of API distribution with AV of 9.69
  - impact of higher WG ~ use of dilute API dispersion
- Low dose, low soluble API like glimepiride meets dissolution specs
  - use of wetting agent (SLS) and increased ratio of Opadry: drug helped improve dissolution of glimepiride

Your Formulation Partner

With different pressures in the development of new pharmaceutical products:

Speed To Market

Access to Expertise

Changing Legislation

…it's important to choose the right collaboration partner

Colorcon Supports Your Early Stage Formulation Development

Reduce
Time to Market

Lower
Total Cost

Make a Positive
Contribution to
Quality

Be a
True Global
Partner

Colorcon minimizes risk by providing the right solution for your business needs

Please stop by our booth to learn more:

Booth #217

Let’s connect and collaborate to discuss your formulation needs and to achieve desired release profile

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