HEALTH

Advances & Innovations in Controlled Release

CRS Annual Meeting
July 24, 2023

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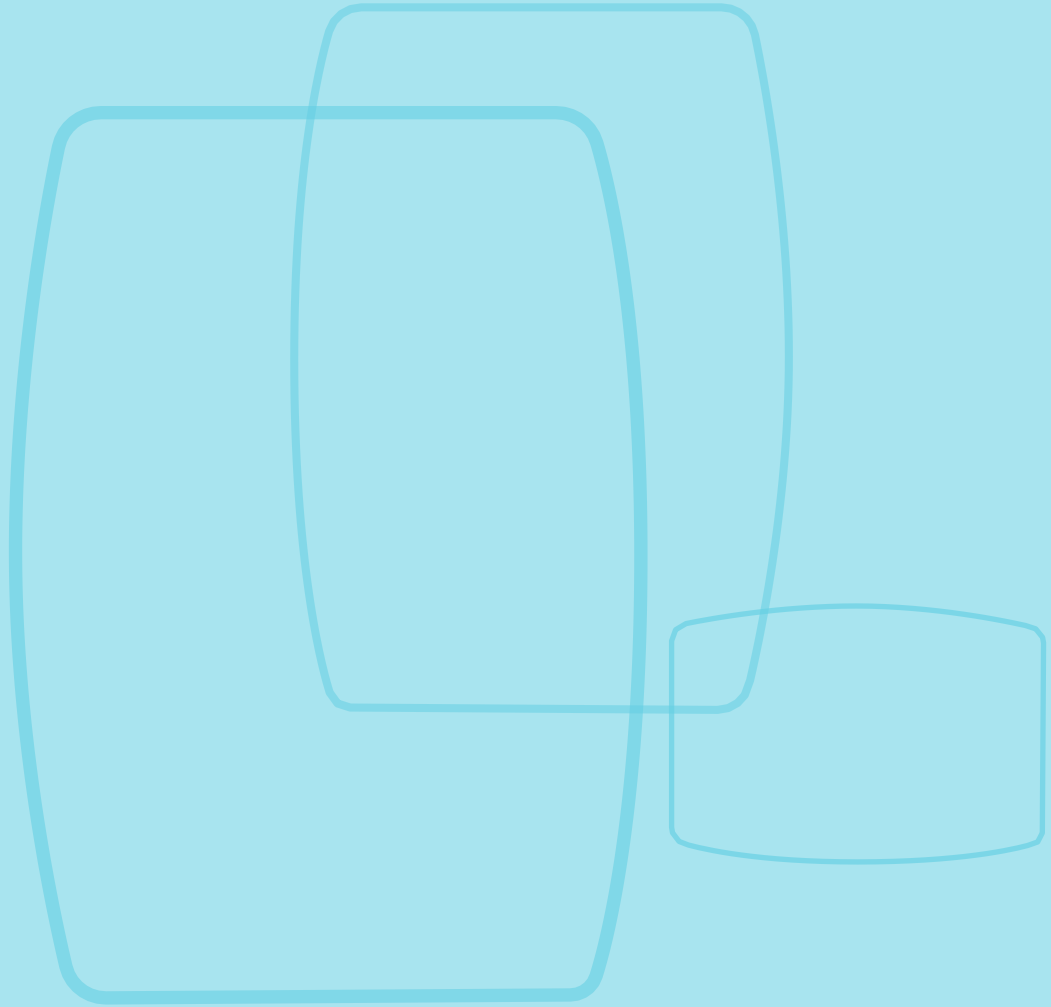

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Challenges in Oral Controlled Release

API

- Dose
- Solubility
- Bioavailability (colonic absorption, permeability)
- Drug combinations

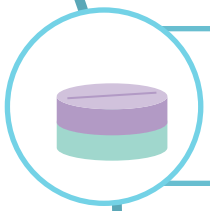
Population

- Pediatric / geriatric dosing
- Chronic diseases
- Self-treatment & prevention
- Prevention of accidental overdose / intentional abuse

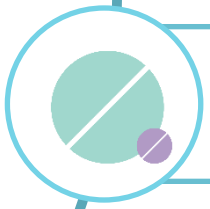
Goal: develop robust, patient-friendly dosage forms

Advances in Oral Controlled Release

Bioavailability enhancing technologies coupled with extended-release technologies: **gastroretentive**, mucoadhesive, **amorphous dispersions**



Fixed-dose combinations: coated MPs, **bi/**tri **layered** tablets, capsule-in-capsule technology



Formulations techniques to improve patient adherence and **product quality**: **tablet size reduction**, 3D-printing for personalized medicine

Complexity reduction in pharmaceutical technical development: **formulation complexity reduction**, co-processed excipients, continuous manufacturing

Advanced technologies can **improve therapeutic outcomes** and **provide competitive differentiation**

“Nonadherence can account for up to 50% of treatment failures, around 125,000 deaths, and up to 25% of hospitalizations each year in the United States.”

- U.S. Pharmacist, 2018

Source: US Pharm. 2018;43(1)30-34

Compliance versus Adherence

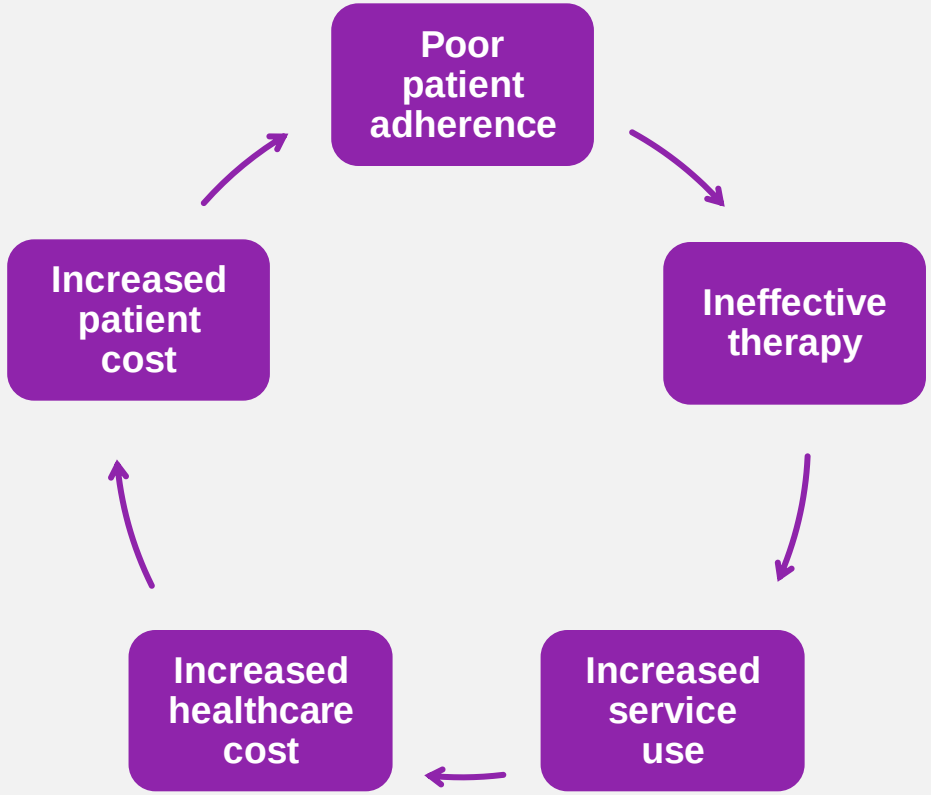
- Compliance implies patient passivity in following the prescriber's recommendations
- Adherence is actively taking prescribed medicine
  - Correct doses
  - Appropriate time intervals
  - Based on health care provider recommendation and agreed to by the patient
    - Requires doctor/patient dialogue
- As the health care community adopts the concepts of patient centeredness and activation, it is moving away from the term "compliance"
- Both are reliant on patient cooperation

Non-Adherence Causes

- 20% - 30% of patients do not fill prescriptions
- 50% of patients do not take prescriptions as directed
  - Self-medicate
  - Fill prescription but do not use
  - Modify the dosage form
    - Break tablets to extend prescription & save money
    - Crush tablets due to size/ease of administration
  - Do not understand the impact of non-adherence
- Varies widely by disease state
  - Cardiovascular
  - Pulmonary
    - COPD
    - Asthma
  - Diabetes
  - HIV/Aids
  - Mental illness
    - Depression
    - Schizophrenia
    - Bipolar disorder
  - Many other examples
- Factors related to non-adherence
  - Patient related
    - Age
      - Geriatric
        - Memory/cognitive function
        - Poor hearing/eyesight
      - Pediatric
        - Behavioral
        - Taste
    - Education
    - Socioeconomic
      - Employment/income
      - Social network
    - Marital status
  - Environmental/external
    - Disease duration/response to treatment
    - Dosing regimen
    - Accessibility

Non-Adherence Impact

- Poor therapeutic outcomes
- Disease progression
- Hospitalizations
  - Includes readmittance
  - Estimated billions per year in avoidable direct health care costs ($100 - $300 billion annually)
    - 3% - 10% of healthcare cost.
- Lost productivity (working patients)
  - Output at work
  - Absenteeism
  - Estimated at 2.3 times direct healthcare cost
- Disability
- Fatality
  - Roughly 125,000 patients annually



The Solution: Patient-Centric Drug Delivery

Easier to Use / More Convenient

Smaller Tablets

Rapid Disintegration

Oral Liquids

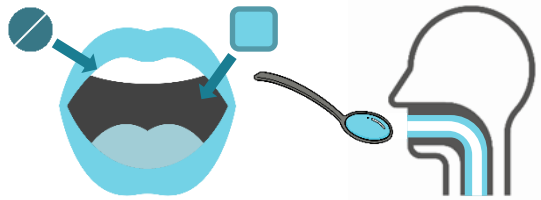
Reduced Dosing Frequency

Extended Release

Gastro-retention

Improved Efficacy

Mucoadhesion



Patient-Centric Drug Delivery Approaches

Easier to Use / More Convenient

Smaller Tablets

Rapid Disintegration

Oral Liquids

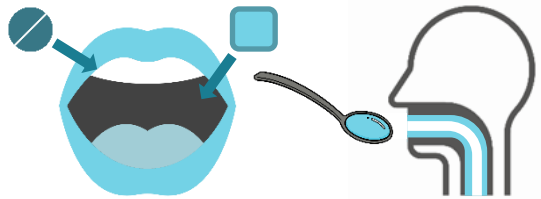
Reduced Dosing Frequency

Extended Release

Gastro-retention

Improved Efficacy

Mucoadhesion



Bioavailability Enhancing Technologies

Gastroretention

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Oral Delivery & Gastroretention

Problem

APIs with oral delivery challenges:

- Narrow absorption window in upper GI tract
- Short half-life

Inefficient drug products with limited therapeutic effect and poor patient adherence

Solution

Gastroretentive Drug Delivery Systems (GRDDS)

- Extend drug retention & release
- Increased therapeutic efficacy
  - Improved absorption
  - Minimized side effects
- Enable local treatment of upper GI disorders
- Improved patient adherence

Gastroretention leverages the **convenience of oral drug delivery** while improving drug absorption and effect

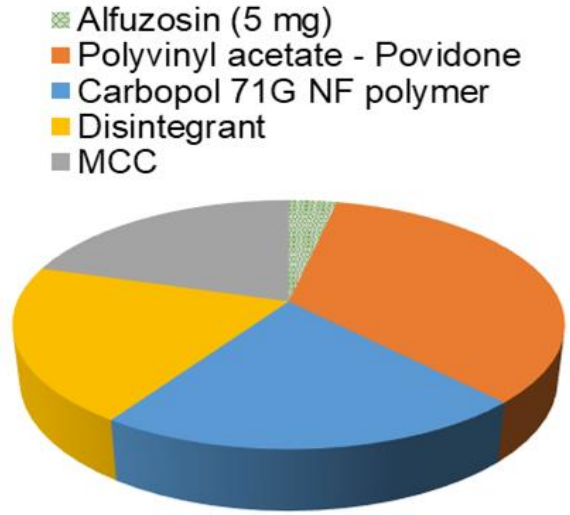
Alfuzosin Extended Release Gastroretentive Tablets

Formulation Details

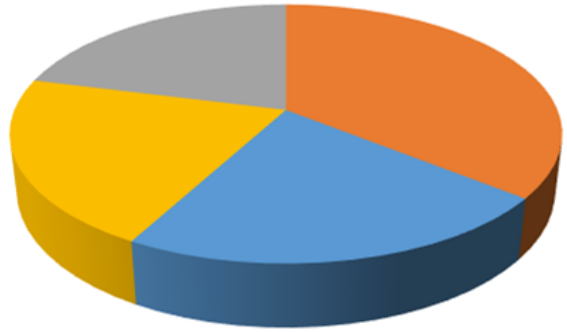
- **Dose**: 5 or 10 mg
- **Design**: Bi-layer or tri-layer design
  - Drug layer & placebo layer(s)
- **Manufacturing Technique**: Direct compression

Key Properties

- Excipients selected for **fast swelling in gastric fluid** (>200% in 15 min)
- Drug release 12 – 20 hours



Drug layer



Placebo layer

Data is from patent application US20070190140A1

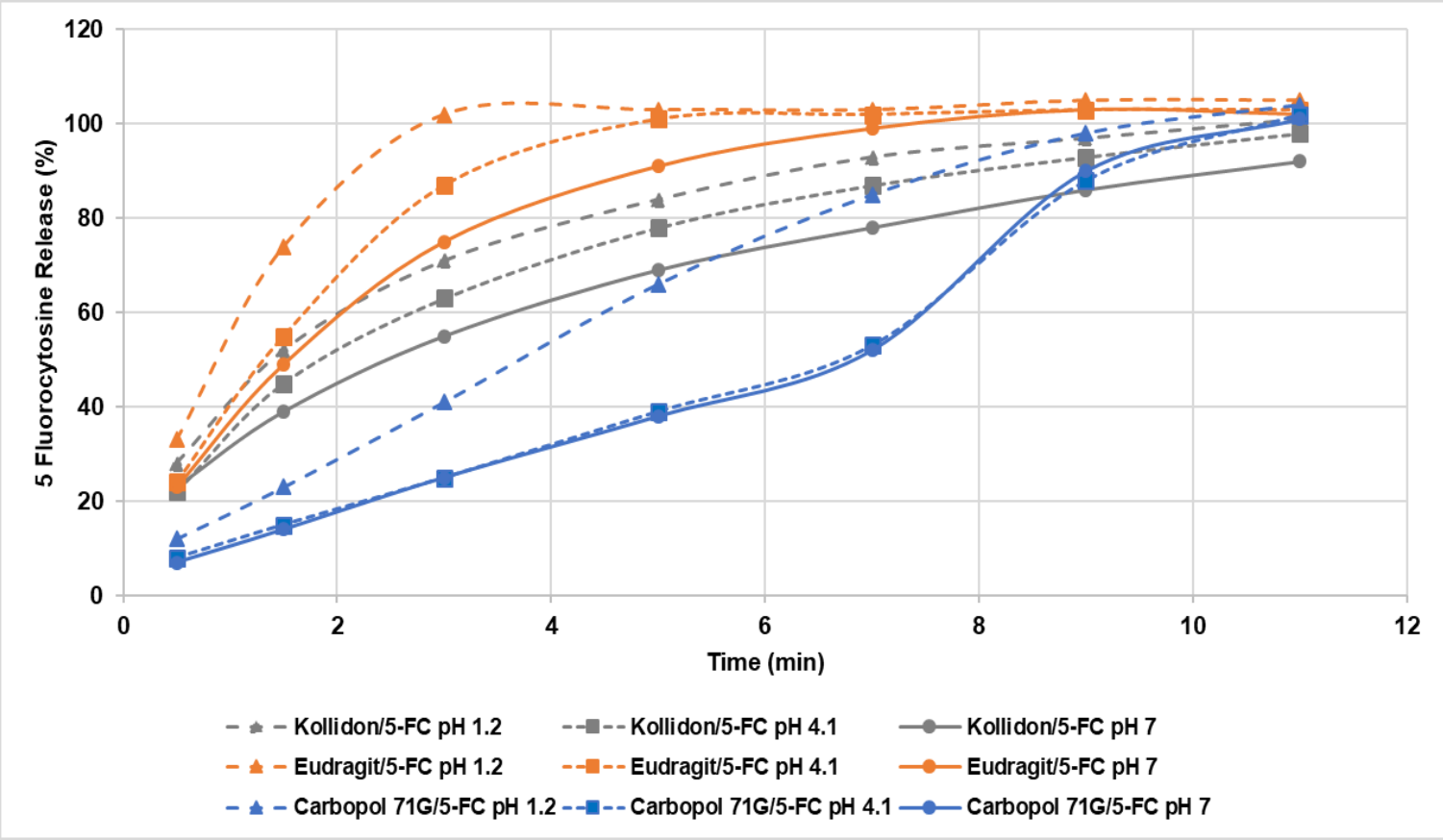
5-Fluorocytosine Extended Release Gastroretentive Tablets

- Various matrix forming polymers
  - Carbopol® 71G NF polymer
  - Kollidon® SR – Polyvinyl acetate & povidone
  - Eudragit® RLPO – poly(meth)acrylate polymer
- Evaluation
  - Drug release: pH 1.2, pH 4.1, pH 7
  - Swelling and erosion rate: SGF pH 4.1
- Single-dose bioavailability of two extended release formulations under fasting and fed conditions **compared to immediate release capsules (Ancobon® 500 mg)**

Ingredient	Kollidon SR/ 5-FC	Eudragit-Ethocel/ 5-FC	Carbopol 71G/ 5-FC
5 Fluorocytosine (5-FC)	44.1	50.1	55.31
Carbopol 71G NF Polymer	-	-	12.17
Eudragit RLPO	-	7.7	-
Kollidon SR	16.3	-	-
HPC	6.0	6.0	6.08
Ethocel 100 cP	-	7.7	-
Microscrystalline cellulose	-	-	11.06
Maltodextrin	10.6	13.8	-
Dicalcium phosphate NF	22.1	13.8	14.38
Magnesium stearate NF	1	0.9	1
Total	**100**	**100**	**100**
Tablet weight (mg)	1133	999	904

US 9,889,133 B2

5-Fluorocytosine Extended Release Gastroretentive Tablets



- Dissolution rate: Eudragit/5-FC > Kollidon/5-FC > Carbopol 71G-5-FC.
- All formulations showed increased drug release in more acidic media.
- Hydration: Carbopol 71G-5-FC 50% @30 min; 250% @8h) >> Eudragit/5-FC ~ Kollidon/5-FC (50% @8 h)
- Erosion rate: Carbopol 71G-5-FC (30% @ 8h) << Eudragit/5-FC ~ Kollidon/5-FC

5-Fluorocytosine Extended Release Gastroretentive Tablets

	Ancobon® Fasted	Kollidon/ 5-FC fasted	Kollidon/ 5-FC fed	Carbopol 71G/5-FC fasted	Carbopol 71G/5-FC fed
Cmax (mg/ml)	7.30	1.98	3.63	2.56	6.14
Tmax (h)	1.63	3.58	7.86	3.88	5.62
AUC (0-inf) (mg h/ml)	**57.3**	20.8	**47.7**	28.1	**54.3**
T1/2 (h)	4.80	5.93	5.55	6.55	5.61

Key Properties

T max shifted from Ancobon fasted individuals to Carbopol and Kollidon formulations for fed individuals

AUC for Ancobon fasted is comparable to Carbopol and Kollidon formulations for fed

Carbopol 71G NF polymer based tablets provided the **best gastroretention, fast hydration/swelling, & slow erosion / dissolution rate,** while also enabling **bioadhesion.**

Bioavailability Enhancing Technologies

Drug Amorphous Solid Dispersions

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Technologies for Drug Amorphous Solid Dispersions (ASD)

Technique	Spray Drying	Hot Melt Extrusion	KinetiSol® Technology
Mechanism	Solvent evaporation	Thermal fusion (heat provided externally)	Thermal fusion (thermokinetic mixing – converts friction to heat)
API constraints	Solubility in organic solvents	API sensitivity to prolonged exposure to heat High melting point APIs	API sensitivity to shear
Polymer	Mostly hydrophilic	Mostly hydrophilic	Mostly hydrophilic
Polymer limitations	High viscosity/high molecular weight Solubility in organic solvents	High viscosity/high molecular weight	Minimal
Processing aids	N/A	Need of plasticizer in case of high melting point API	Need lubricant to improve processability
Processing time	Hours	Minutes to hours	Seconds

Spray Drying and **Hot Melt Extrusion** – most common technologies for ASD
KinetiSol® - emerging technology that mitigates some limitations of traditional technologies

Patient Adherence & Product Quality

Small, Nitrosamine Compliant Metformin HCl ER Tablets

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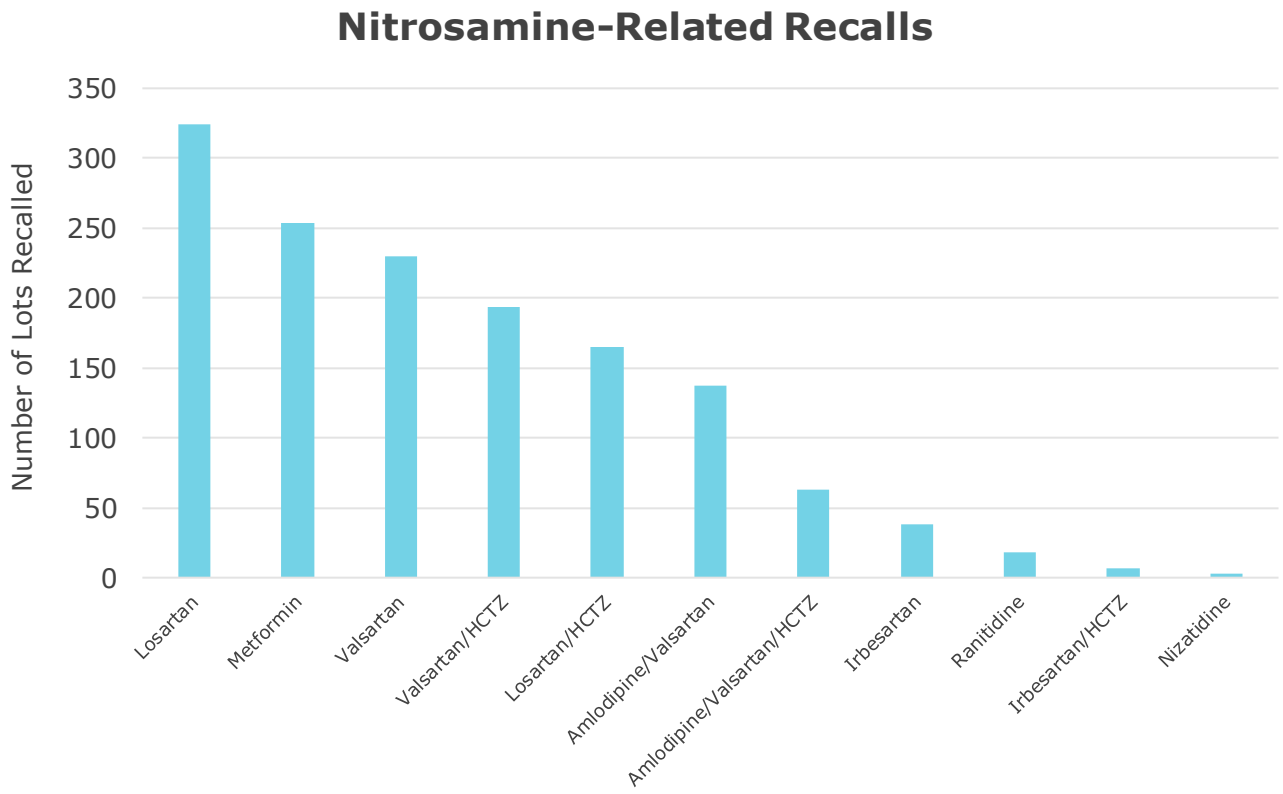
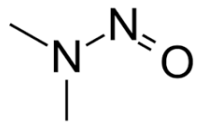
Improved Drug Product Safety

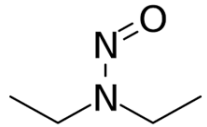
In recent years, Global Drug Regulatory Agencies signaled the presence of **nitrosamine impurities in drug products and initiated recalls**



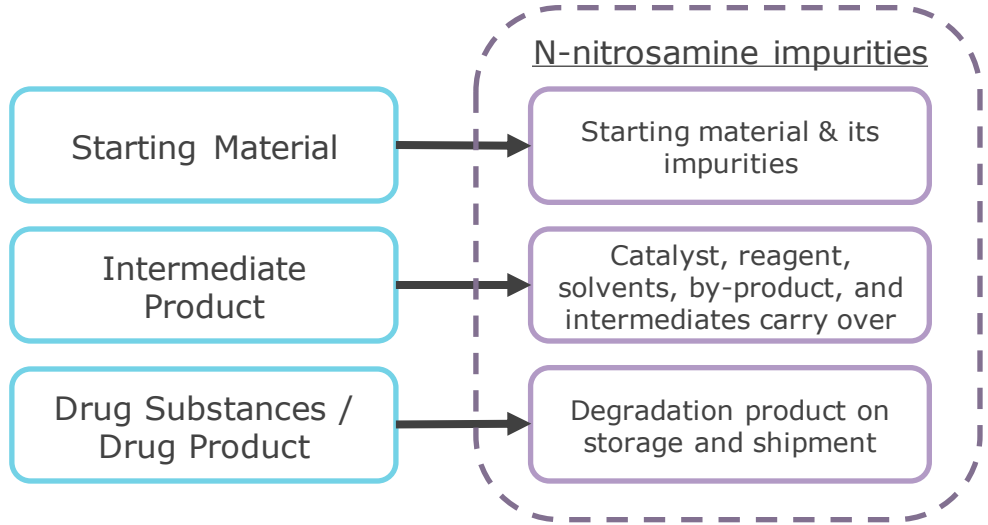
N-nitrosamines - highly potent mutagenic carcinogens



N-nitrosodimethylamine (NDMA)



N-nitrosodiethylamine (NDEA)



Bharate S., J. Med. Chem. 2021, 64, 6, 2923–2936

LUBRIZOL LIFE SCIENCE

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Carbopol-Based Metformin HCl ER Tablets

Carbopol polymers offer a single solution for safety and improved patient adherence:

Small, Easy-to-Swallow Tablets

Reliable Extended Release

Reduced Nitrosamine Impurities

Development of Metformin HCl ER Tablets US FDA Nitrosamine Compliant

Ingredient
*Intra-granular**
Metformin HCl[1]
Hypromellose K100M
Carbopol 971P NF polymer
Magnesium hydroxide[2]
Extra-granular
Hypromellose K100M
Carbopol 971P NF polymer
Carbopol 71G NF polymer
Anhydrous colloidal silica
Magnesium stearate

** Granulation with 2% aq Carbopol polymer dispersion*

[1]Particle size NLT 95% passing through 100#

[2]Within FDA IID limits

Target attributes

Compendial compliance – USP test IV

- Dose – 500 mg and 1000 mg
- Tablet weight: LZ 800 mg vs. Commercial product ~1030 mg
  LZ 1250 mg vs. Commercial product ~1380 mg
- Aqueous high shear wet granulation
- Stable under ICH conditions (Intermediate - 30°C/75% RH and ACC - 40°C/75% RH)
- Packaging - HDPE bottles/Alu-Alu blister pack
- Easy processing and scale-up

Assay and RS including nitrosamine impurities comply with monograph and US-FDA recommendations

- USP test IV dissolution requirements
  - 1 h 20 - 40%
  - 3 h 45 - 65%
  - 6 h 65 – 85%
  - 10 h NLT 85%

USP apparatus 2 (Paddle), 100 rpm, 1000 ml pH 6.8 phosphate buffer

Metformin HCl ER Tablets USP
Physical Properties

20-30% reduction in tablet size!

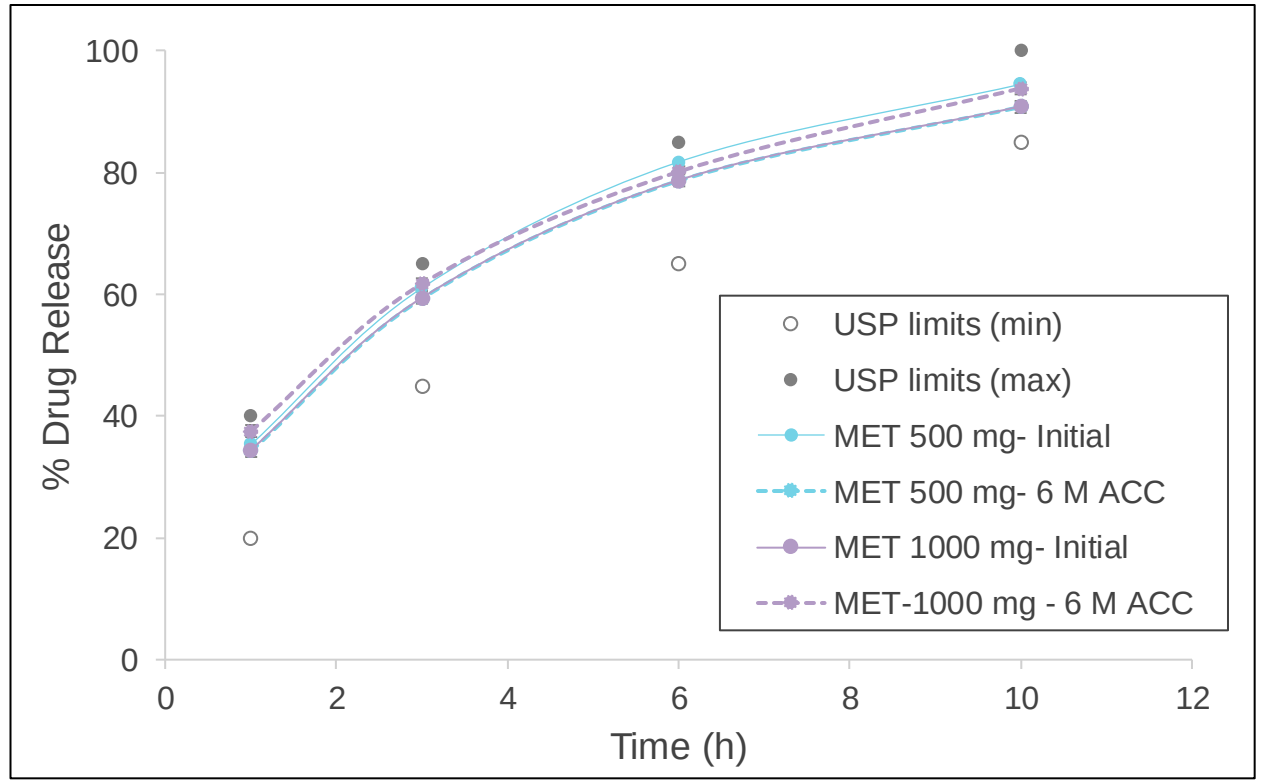
Lubrizol vs. commercial tablets (both 500 mg dose)

Physical Properties	500 mg USP	1000 mg USP
Lubrizol Formulations		
Tablet weight (mg) average ±SD	800.4 ± 7.8	1250.2 ± 10.2
Mechanical strength (kP) average ±SD	20.6 ± 0.96	21.6 ± 0.16
Friability @ 100(%)	0.20	0.18
Punch dimensions	17.1 X 8.2 mm, Capsule	20.15 X 9.7 mm, Oval biconvex
Commercial product weight	1030 mg	1450 mg

Both 500 mg and 1000 mg strength tablets were **successfully formulated at smaller sizes** (20-30% smaller than most commercial formulations of respective strengths)

Metformin HCl ER Tablets USP Accelerated Stability Study

Tests	USP Specs	500 mg strength at 6 M ACC	1000 mg strength at 6 M ACC
Assay (%)	90-110	99.9	97.13
Single max impurity (%)	0.1	0.04	0.06
Total impurity (%)	0.6	0.10	0.16



Metformin HCl ER tablets were **stable under accelerated conditions (40 °C/75% RH)** when packed in HDPE bottles

Metformin HCl ER Tablets USP Nitrosamine Impurity Testing

Results of nitrosamine impurity testing for Lubrizol Metformin HCl tablets

	Sample Name	Conditions	Results									
			Limits NMT 0.048 ppm		Limit NMT 0.013 ppm						Compliance	
			NDMA	NMBA	NDBA	NDEA	NDIPA	NEIPA	NDPA	NMPA	Scenario 1	Scenario 2
Lubrizol Formulation	**F – USP 500 mg**	Fresh Lot	ND	ND	ND	ND	ND	ND	ND	ND	**Complies**	**N/A**
	F – USP 500 mg	6 Months Ambient	ND	BLOQ (0.006)	ND	ND	ND	ND	ND	ND	**Complies**	**N/A**
	F – USP 500 mg	40C/75%RH 6M PVDC	ND	0.010	ND	ND	ND	ND	ND	ND	**Complies**	**N/A**
	F – USP 500 mg	40C/75%RH 6M ALU/ALU	ND	BLOQ (0.005)	ND	ND	ND	ND	ND	ND	**Complies**	**N/A**
	F- USP 1000 mg	Fresh Lot	ND	ND	ND	ND	ND	ND	ND	ND	**Complies**	**N/A**

Total impurities should not be more than 0.013ppm – Scenario 2; LOQ: for NDMA & NMBA 0.015 ppm; for all other impurities 0.01 ppm;
BLOQ: Below limit of quantification.; ND: Not detected according to non validated method; N/A: Not Applicable

Selected lots of the tablets tested at FDA approved testing laboratory as per US FDA guidelines were found to be **compliant for all eight nitrosamine impurities.**

Carbopol® Polymers for Nitrosamines (NDMA) Compliant Metformin Extended-Release Tablets

Small tablets ✓

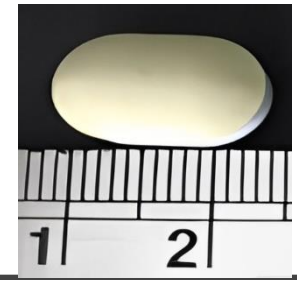
- High drug loading (62-80%)
- Patient adherence
- Aqueous granulation and manufacturing versatility
- Increased productivity and overall formulation cost saving

Compliance ✓

- Compendial monographs
- Multimedia dissolution
- Proven stability
- Nitrosamine impurities in compliance with recent guidance

Differentiation ✓

- Proprietary formulations
- Extrapolation to higher strength
- Starting formula for bilayer tablets
- Scalable for shorter go to market



Metformin 500 mg ER
Glimepiride 1 mg IR

Complexity Reduction in Pharmaceutical Technical Development

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Pharmaceutical Technical Development (Chemistry, Manufacturing, & Controls – CMC)

CMC – multidisciplinary function ensuring development of **consistently high-quality safe drug products**

CMC drives technological advances:

- Streamline drug development
- Advance cutting-edge pharmaceutical technologies
- Devise new forms of drug delivery that make conditions "druggable"
- Optimize development cost
- Increase patient adherence
- Broaden access for undertreated populations

Complexity Reduction in Pharmaceutical Manufacturing

Reduce cost, energy, and time

Enable innovation

Direct Compression

Continuous Manufacturing

Co-Processed APIs/Excipients

Multiparticulate Drug Delivery Systems

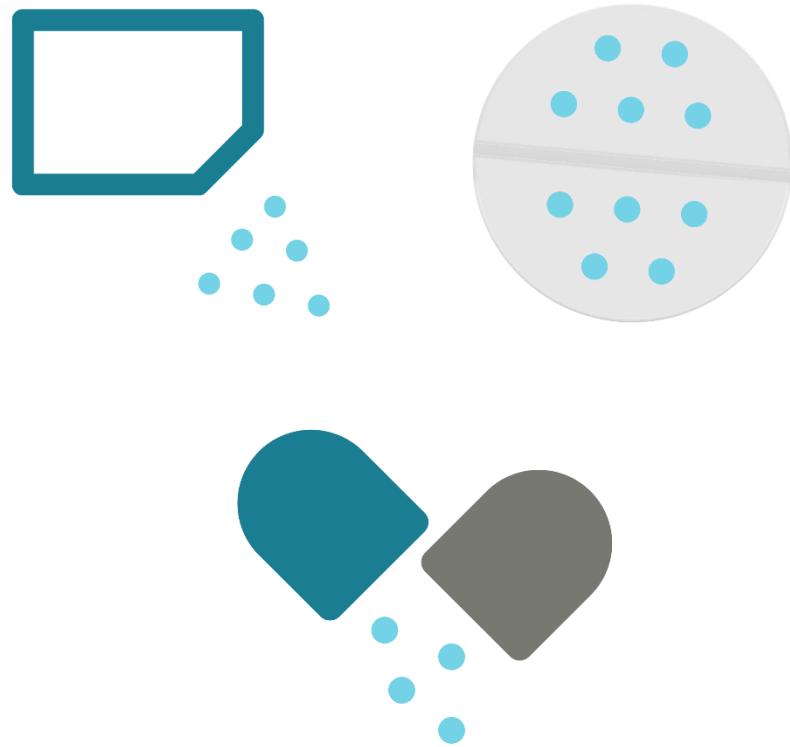
- Multiparticulate formulations provide **enhanced dosing flexibility for several formats**

- **Wide range of drug-release profiles** for single or multiple drug combinations:
  - Modified release
  - Immediate release

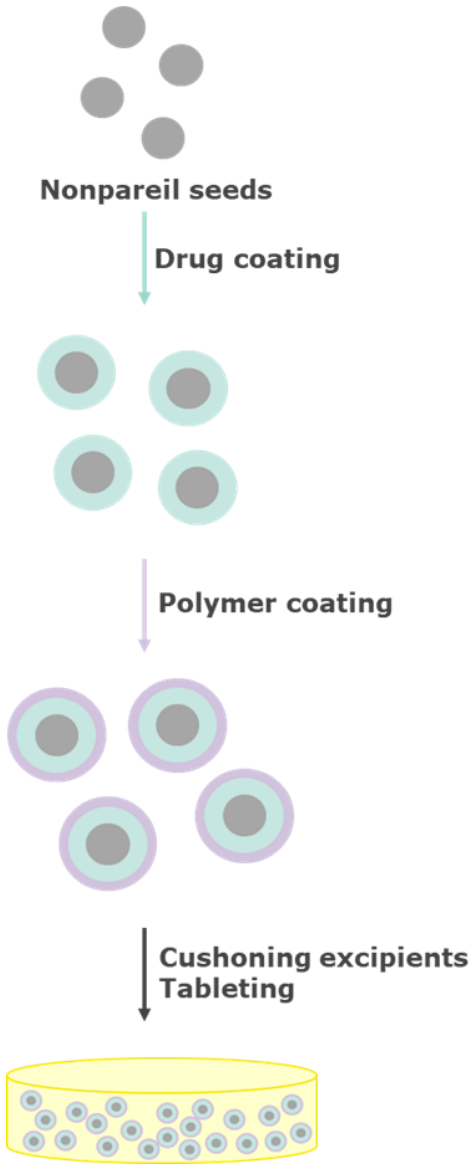
- Enable key formulation benefits, including:
  - **Bioavailability enhancement**
  - **Taste-masking**
  - **Ease-of swallowing**

- Various formats for finished dosage form: **capsule, tablet, or sachet**

- The selection of a specific MP technology is typically **dependent on the API and target product profile**



Multi-Unit Pellet System (MUPS) Technology



MUPS Component	Factors Impacting Robustness of MUPS Tablet
Pellet core	Composition Porosity Size
Coating	Coating polymers Coating level Plasticizer
Tableting excipients	Type of excipients Ratio of pellets to excipients Size of cushioning excipients
Equipment	Tablet shape (tooling design) Compaction pressure

MUPS – complex technology involving intricate manufacturing steps

- MUPS integrity must be maintained throughout tableting process
- Very difficult to scale up
- Manufacturing can take several days to a week

Metoprolol Succinate
MUPS-to-Matrix
Tablet Formulation

Complex Technology,
Simplified

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Metoprolol Succinate ER
From MUPS to Matrix Tablets

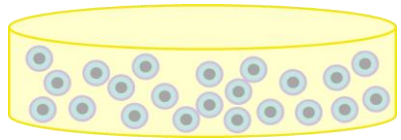
- **Metoprolol succinate** is a beta1-selective (cardio selective) adrenoceptor blocking agent, for oral administration, available as extended-release tablets.

- Metoprolol succinate extended-release tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled-release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval.

U.S. Rank	**U.S. Prescriptions**	**Indication**	**2022 Sales**
6th most prescribed	66 million in 2020	Heart Failure	$965M

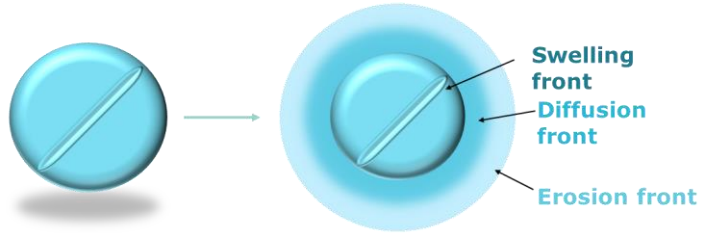
ClinCalc, PharmaCircle

Metoprolol Succinate ER
From MUPS to Matrix Tablets



MUPS
Long, complex
manufacturing process

CMC-driven
reformulation



Matrix
Faster, simpler
manufacturing process

Objective: reformulate a high-value product with a simpler manufacturing process and full compendial compliance

Metoprolol Succinate Matrix Formulation 50 mg dose

Formulation

Ingredients	Process
Metoprolol Succinate	HSWG with purified water
Carbopol® 971P NF polymer	
Microcrystalline cellulose PH 101	
Lactose monohydrate (agglomerated)	Extra-Granular
Dibasic calcium phosphate	
Hypromellose 2208 100000 cP	
Carbopol® 71G NF polymer	
Silica	
Magnesium stearate	Lubrication Tableting
HPMC based coating solution	Tablet coating

Physical properties of uncoated tablet

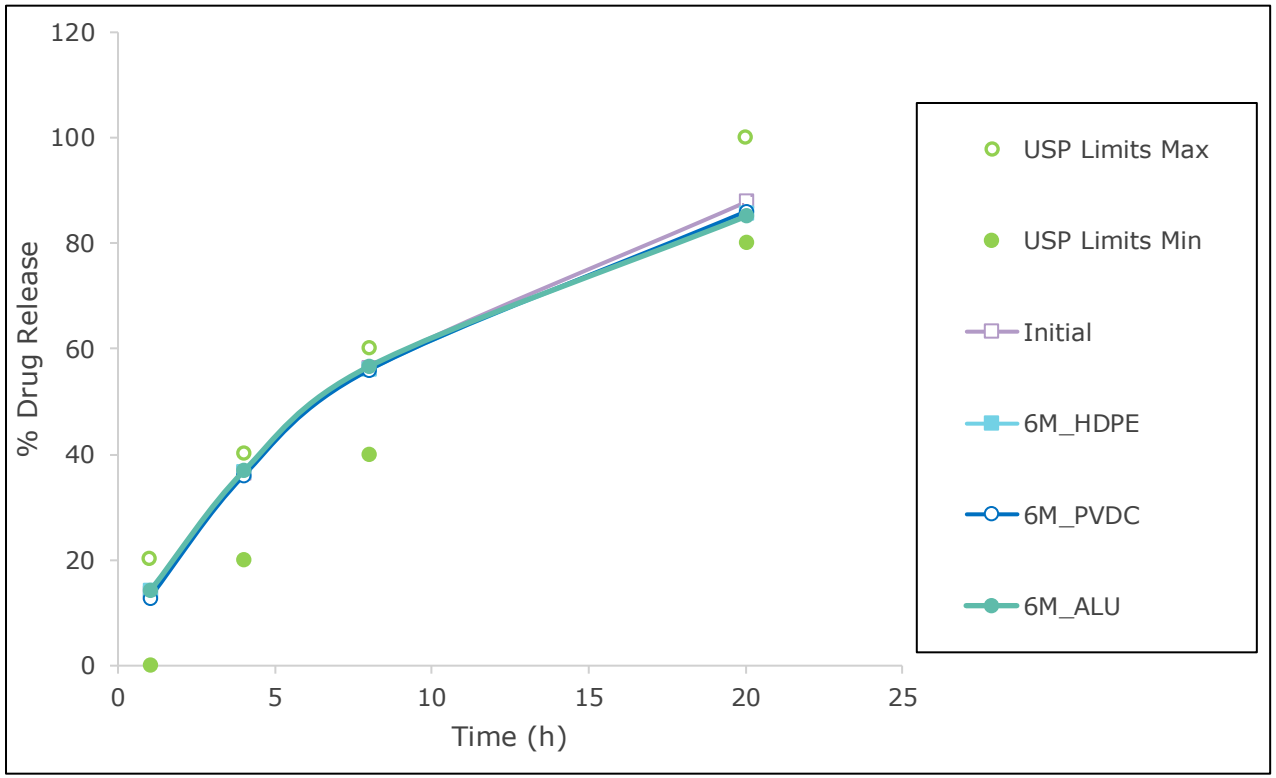
Weight (mg)	Thickness (mm)	Hardness (N)	% Friability 300 revolutions
~ 310	5.36 – 5.45	75 - 105	0.21

Dissolution profile for coated tablets

Time (h)	USP limits	Metoprolol Succinate (50 mg)
1	NMT 20%	13.7
4	20-40%	36.4
8	40-60%	56.3
20	NLT 80%	87.8

USP Apparatus 2 (Paddle), 50 rpm, 37 °C, 500 ml pH 6.8 phosphate buffer

Metoprolol Succinate Matrix Formulation 50 mg dose



USP Apparatus 2 (Paddle), 50 rpm, 37 °C, 500 ml pH 6.8 phosphate buffer

Accelerated stability results (6 months)

	USP specs	ALU/ ALU	PVDC Blister	HDPE Bottle
Assay (%)	90-110	99.1	102.1	97.2
Single max impurity (%)	0.2	0.07	0.08	0.08
Total impurity (%)	0.75	0.20	0.34	0.23

Good stability of 50 mg metoprolol succinate matrix tablet formulation was achieved using various packaging

Metoprolol Succinate Matrix Formulation 100 mg dose

Formulation

Ingredients	Process
Metoprolol Succinate	HSWG with purified water
Carbopol® 971P NF polymer	
Microcrystalline cellulose PH 101	
Lactose monohydrate (agglomerated)	Extra-Granular
Hypromellose 2208 100000 cP	
Carbopol® 71G NF polymer	
Silica	
Magnesium stearate	Lubrication Tableting
HPMC based coating solution	Tablet coating

Physical properties of uncoated tablet

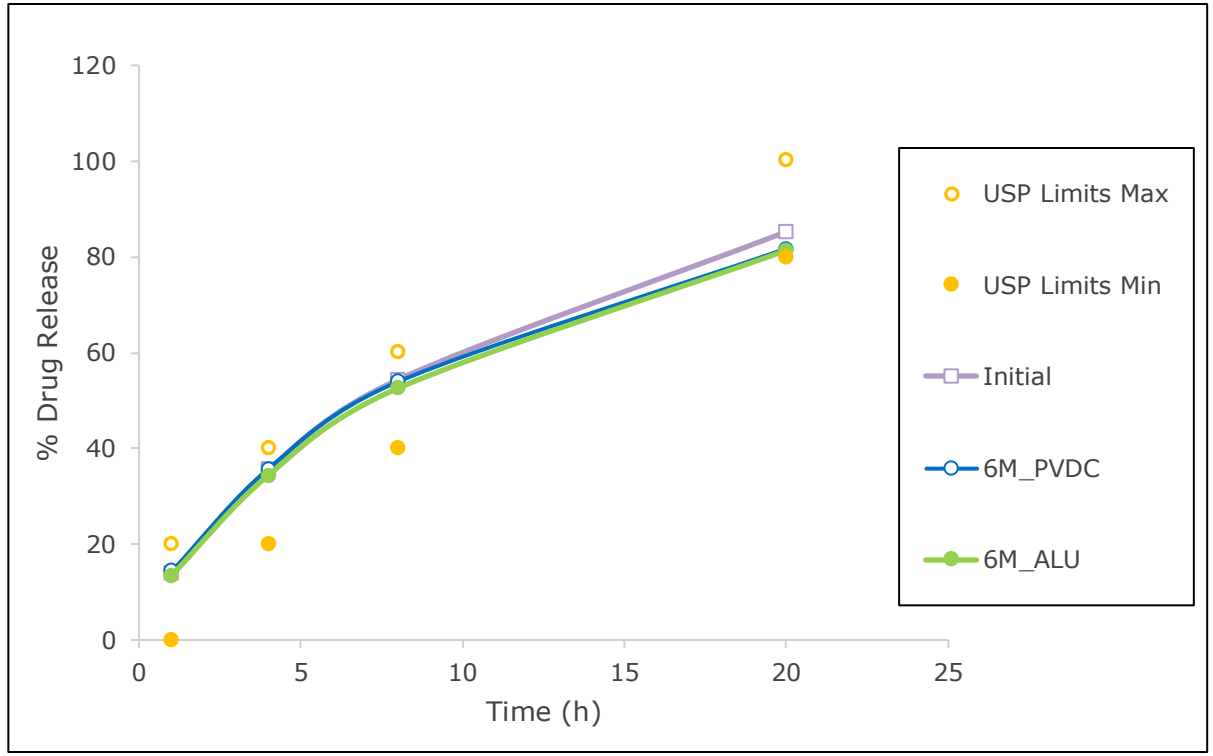
Weight (mg)	Thickness (mm)	Hardness (N)	% Friability 300 revolutions
430 ± 9	5.30 – 5.40	90 – 110	0.10

Dissolution profile for coated tablets

Time (h)	USP limits	Metoprolol Succinate (50 mg)
1	NMT 20%	14.2
4	20-40%	36.2
8	40-60%	55.3
20	NLT 80%	84.8

USP Apparatus 2 (Paddle), 50 rpm, 37 °C, 500 ml pH 6.8 phosphate buffer

Metoprolol Succinate Matrix Formulation 100 mg dose



USP Apparatus 2 (Paddle), 50 rpm, 37 °C, 500 ml pH 6.8 phosphate buffer

Accelerated stability results (6 months)

	USP specs	ALU/ALU	PVDC Blister
Assay (%)	90-110	97.9	97.0
Single max impurity (%)	0.2	0.07	0.08
Total impurity (%)	0.75	0.18	0.26

Good stability of 100 mg metoprolol succinate matrix tablet formulation was achieved using various packaging

Metoprolol Succinate ER
From MUPS to Matrix Tablets

- Carbopol® polymers at low inclusion levels enabled formulation of metoprolol succinate ER tablet allowing:
  - Decrease of manufacturing complexity
  - Matrix tablet (aqueous granulation) vs. MUPS

  - Compliance with:
    - USFDA requirements for tablet size/shape
    - USP for assay, dissolution and RS specifications

- Formulation can be extrapolated to other dose strengths and fixed dose combinations

Looking Ahead: Patient-Centricity and Complexity Reduction

Precision Medicine via 3D Printing

HEALTH

Precision Medicine & 3D Printing

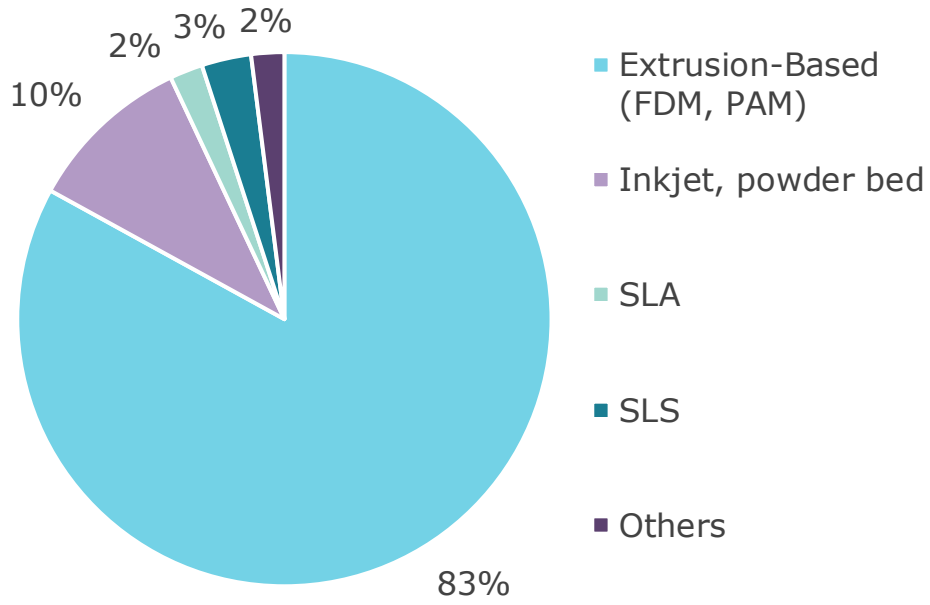
Precision Medicine

- Medicine **created/optimized for an individual** based on analysis of their molecular profile
  - 2015: implementation of the "*Precision Medicine Initiative*" USA initiative focused on individualized care

3D Printing

- **2015 - FDA approval of the first 3D printed medicine**, SPRITAM® (levetiracetam) manufactured by Aprecia Pharmaceuticals Company (USA) for the treatment of seizures
- Current pharmaceutical manufacturing practices are not cost-effective for personalized medicine
- 3D printing is more suited to tailored solid dosage forms

3D Printing Techniques in Research (2015-2020)

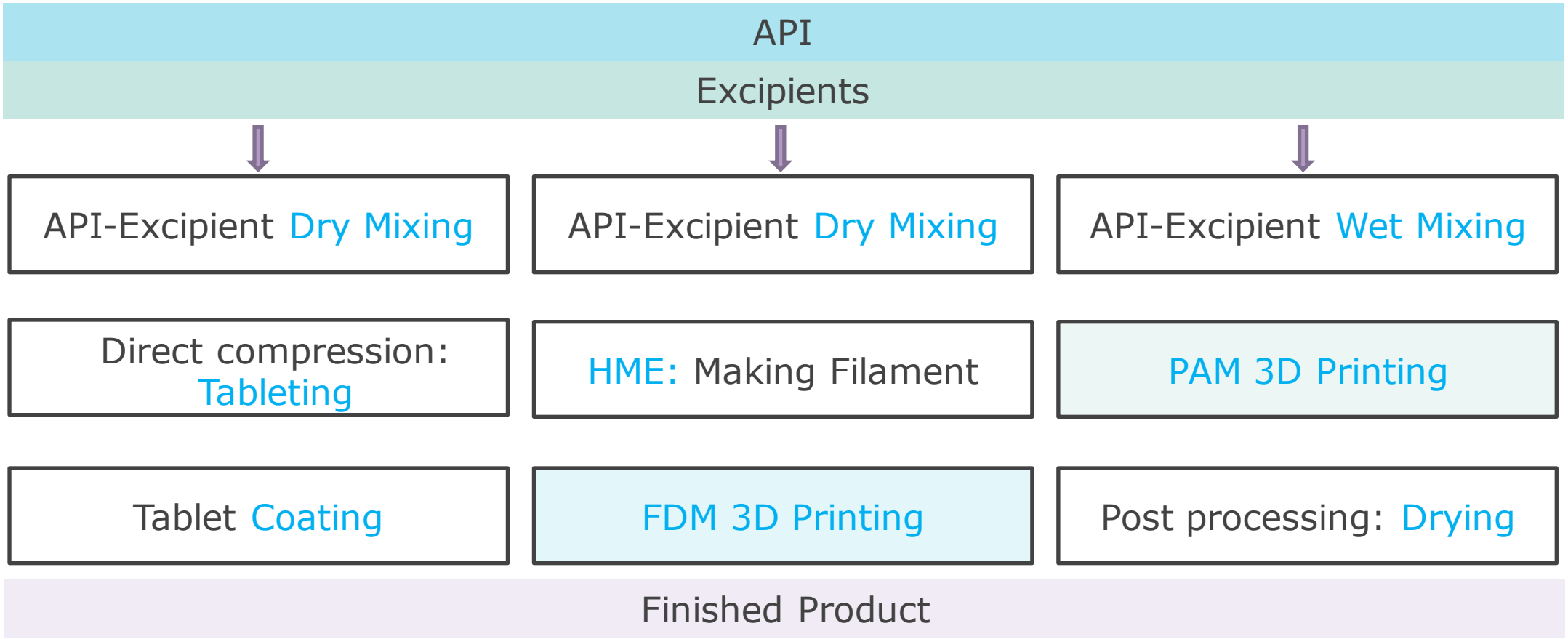


FDM – fused deposition modeling
PAM – pressure assisted micro syringe
SLA – stereolithographic printing
SLS – selective laser sintering printing

3D Printing is an enabling technology of **patient-centric, precision medicines**

Azad et al., Pharmaceutics (2020), 12, 124

3D Printing vs Direct Compression Tableting

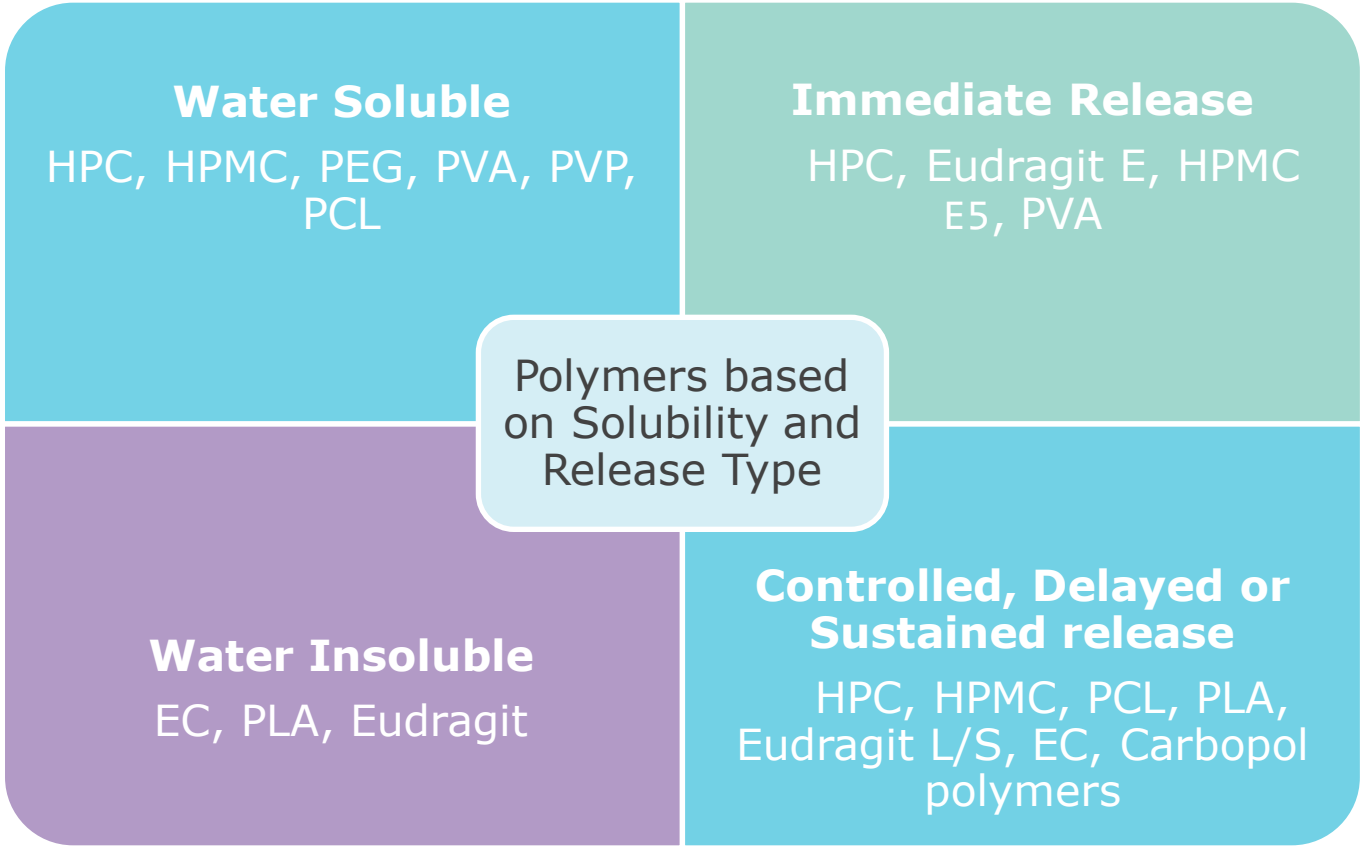


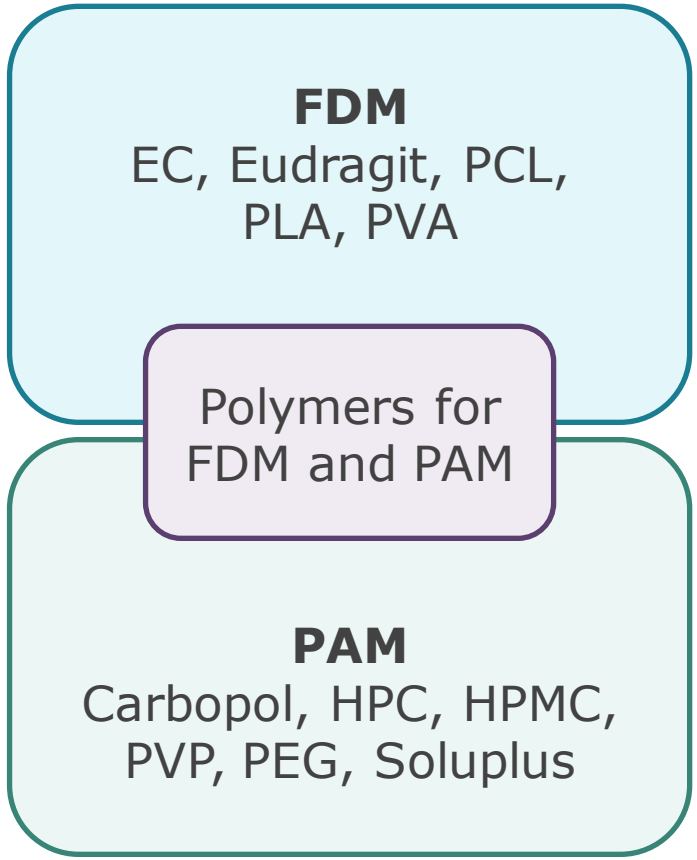
Processing steps: direct compression vs. 3D printing (FDM or PAM)

3D printing technologies (FDM; PAM) require same number of steps as DC tableting with the advantage of **lower footprint; individual tablet or small batch manufacturing; and remote control**

Azad et al., Pharmaceutics (2020), 12, 124

Excipients for 3D Printing



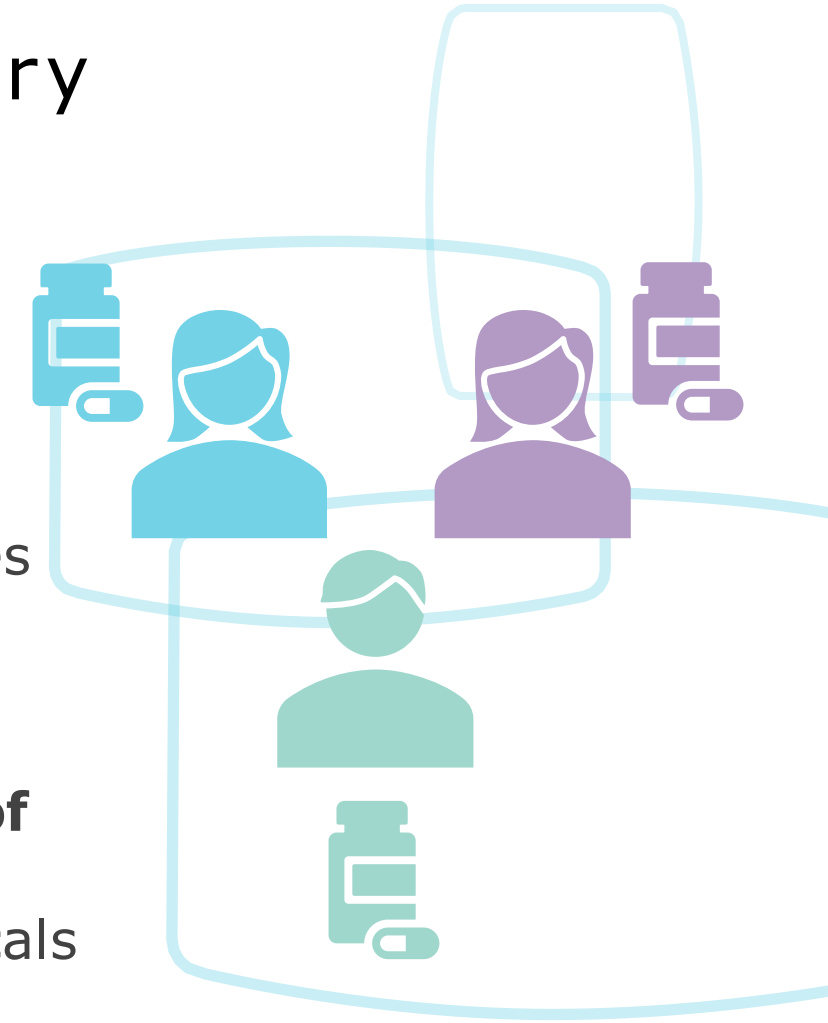


Rheological properties of the polymers and polymer–API mixture play a vital role in predicting the processability of FDM and PAM 3D printing and the properties of the final pharmaceutical products (solid dosages)

Azad et al., Pharmaceutics (2020), 12, 124

3D Printing in the Pharmaceutical Industry

- 3D printing of pharmaceuticals is still in its infancy and its **potential yet to be fully explored**
- Regulatory challenges need to be overcome, but agencies are **encouraging the growth of precision medicine**
- A better understanding of the **rheological properties of API–polymer mixtures** and their measurement is necessary for the successful 3D printing of pharmaceuticals



3D Printing is an early-stage technology that can **enable the future of tailored, precision medicines**

Azad et al., Pharmaceutics (2020), 12, 124

Conclusions and Takeaways

- There are various **technical and population-related challenges** to oral controlled release

- **Excipients enable** advanced drug delivery technologies through:
  - Improved absorption
  - Solubility enhancement
  - Targeted drug release

- Advanced drug delivery can also **improve the patient experience via**:
  - Improved medication adherence
  - Tailored, precision medicines

Thank you!

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HEALTH

Mucoadhesion & Modern Drug Delivery Systems

CRS Annual Meeting
July 24, 2023

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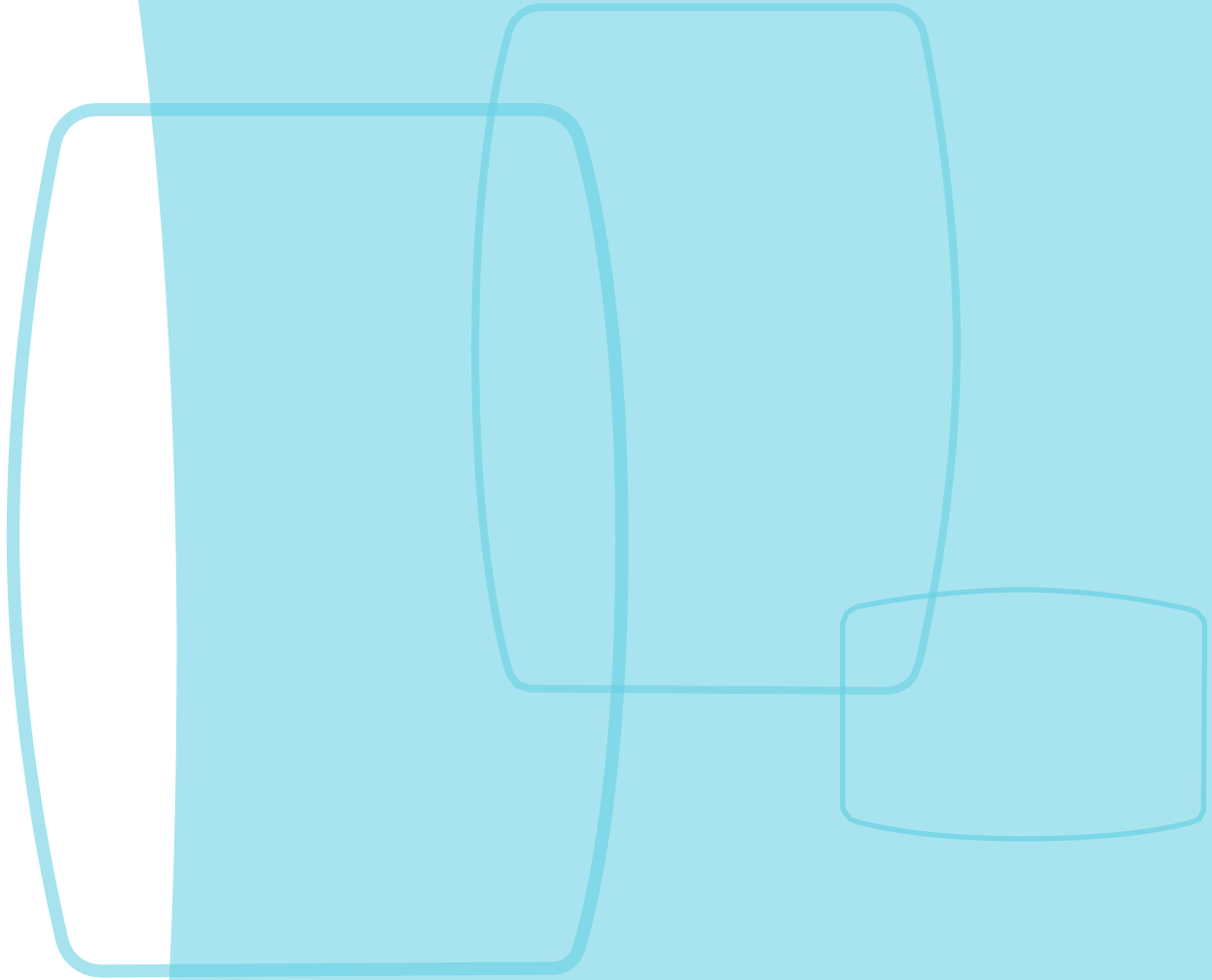


HEALTH

The Challenge: Patient Adherence

60% of adults in the US have a chronic disease

50% of patients are non-adherent to their therapy

The cost in reduced sales for drug manufacturers attributed to non-adherence is

$250 billion annually for the U.S. market and $637 billion annually globally

The Solution: Patient-Centric Drug Delivery

Easier to Use / More Convenient

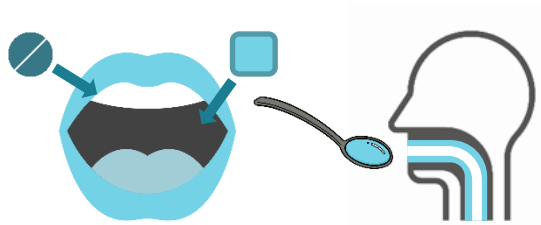
- Smaller Tablets
- Rapid Disintegration
- Oral Liquids

Reduced Dosing Frequency

- Extended Release
- Gastro-retention

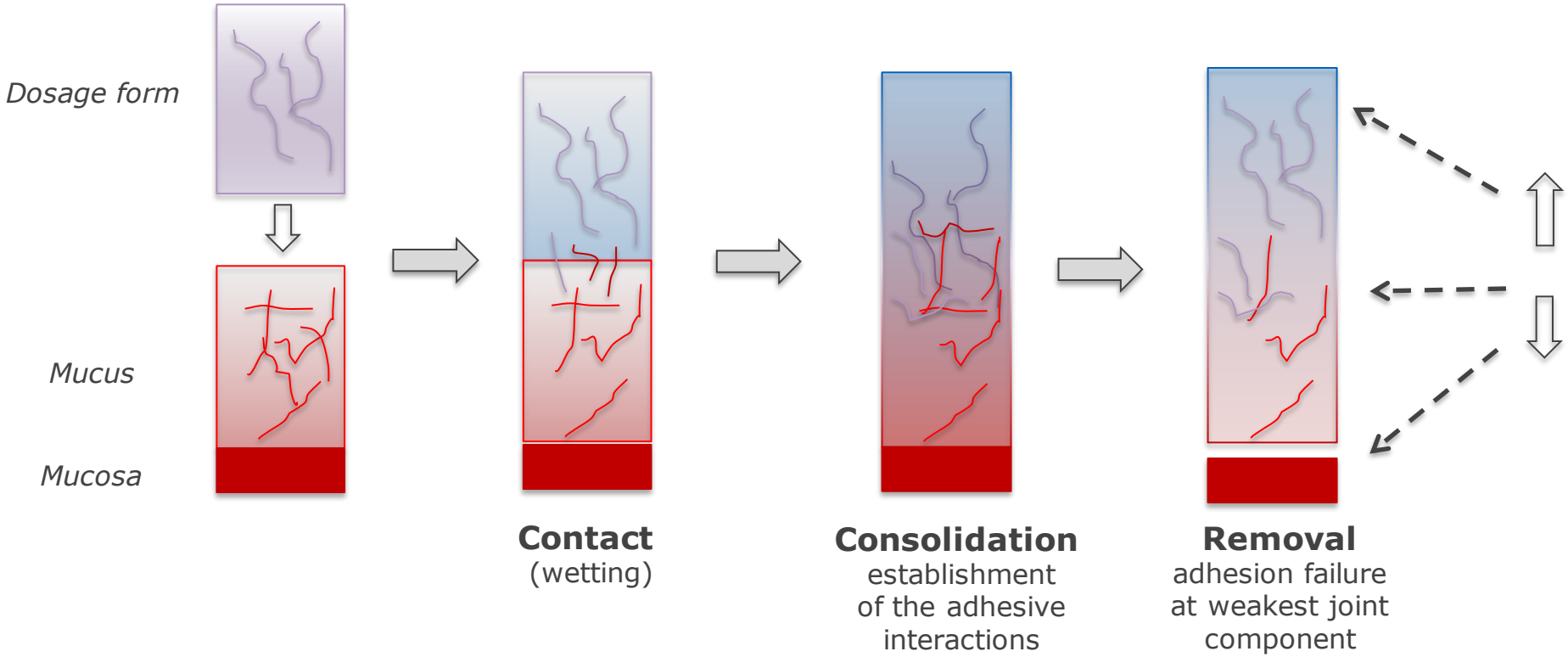
Improved Efficacy

Mucoadhesion



Bioadhesion/Mucoadhesion Mechanism

Mucoadhesion: two surfaces, one of which is mucus or a mucous membrane, adhere to each other



Mucoadhesion is a **complex scenario and mechanism**

Mucoadhesion Benefits for Drug Delivery

Prolonged localized therapy / Enhanced systemic delivery

- **Non-Invasive**
- **Convenient** (administration /removal)
- **Tailored Duration**
- **Multiple Dosage Forms**

- **Mucosa Permeability**
- **Bypass GI Route/ Hepatic First Pass**
- **Fast Onset of Action**

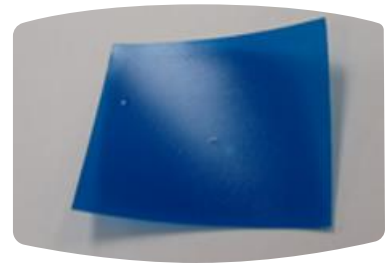
Enhanced systemic delivery

Candidate Drugs for Systemic Mucosal Delivery

Indication/Uses	Drug
Cardiovascular	Nitroglycerin; Propafenone; Captopril; Verapamil
Analgesic	Fentanyl; Sumatriptan
Sedative	Midazolam; Triazolam; Etomidate
Insomnia	Zolpidem
Antiemetic	Prochlorperazine
Hormone	Testosterone; Estrogen
Erectile disfunction	Sildenafil citrate
Opioid dependence	Buprenorphine; Naloxone

Mucosal Routes for Systemic Administration:

- Oral
- Nasal
- Rectal



Candidate Drugs for Local Mucosal Delivery

Indication/Uses	Drug
Oral mucositis	Granulocyte colony stimulating factor (G-CSF); Keratinocyte growth factor; Polymyxin/Tobramycin/Amphotericin (PTA); Sucralfate
Recurrent aphthous stomatitis	Chlorhexidine; Corticosteroids; Amlexanox
Oral cancer (early stages)/ prevention and treatment	Acitretin; Isotretinoin; Bleomycin; Tolonium chloride
Pain	Lidocaine
Infections	Chlorhexidine; Tetracycline; Doxycycline; Metronidazole; Nystatin; Clotrimazole; Miconazole; Itraconazole; Acyclovir
Xerostomia	Pilocarpine; Cevimeline; Bethanechol
Immunological mediated diseases	Betamethasone; Fluticasone; Fluocinolone; Dexamethasone; Clobetasol propionate; Azathioprine; Methotrexate; Ciclosporin

Mucosal Routes for Local Administration:

- Oral
- Nasal
- Vaginal
- Ophthalmic
- Rectal

Mucoadhesive Excipients

Synthetic or natural hydrophilic polymers containing functional groups that could **interact with the mucin glycoproteins** via non-covalent bonds such as hydrogen bonding, van der Waals forces and ionic interactions

Polymer Type	Functional groups	Examples
Synthetic	- COOH	Carbomers (Carbopol® polymers, Noveon® AA1 polycarbophil); PVM/MA (free acid form of the copolymer of methyl vinyl ether and maleic anhydride)
Semi-synthetic	- OH; - COOH	Sodium carboxymethyl cellulose
Natural	- OH; - COOH; $-OSO_3^-$	Carrageenan; Xanthan gum; Alginates

Carbopol® Polymers Mucoadhesion Mechanism

- **Wetting** - fast hydration of Carbopol polymers allows the dosage forms to quickly establish the contact with the mucus upon administration
- Consolidation of the adhesion:
  - **Hydrogen Bonding** - Carbopol polymers, having large amount of carboxylic groups, can establish hydrogen bonding with the mucus. This occurs when the polymer is used "as is", without neutralization - solid dosage forms (granules, tablets), anhydrous systems, etc.
  - **Macromolecular Penetration** – Carbopol polymers in neutralized form are swollen to the largest extent and can interpenetrate with the glycoprotein chains from mucus, to form a network. This occurs when the polymer is neutralized - liquid or semisolid dosage forms containing buffers or bases.

Carbopol polymers - High molecular weight polymers of acrylic acid Chemically cross-linked

In vitro evaluation of mucoadhesive properties of pharmaceutical excipients

HEALTH

In vitro Mucoadhesive Properties of Pharmaceutical Excipients

Excipients Tested

- **Carbopol® Polymers**
- Sodium carboxymethyl cellulose
- Hydroxypropyl cellulose
- Xanthan gum
- Carrageenan
- PVM/MA copolymer
- Poloxamer

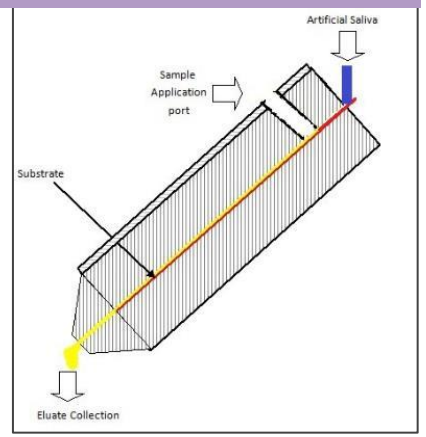
Formulation

Oral /oral care applications

0.25% - 1%
Polymer inclusion level

Formulation space Mucoadhesive benefits

In Vitro Mucoadhesion Testing



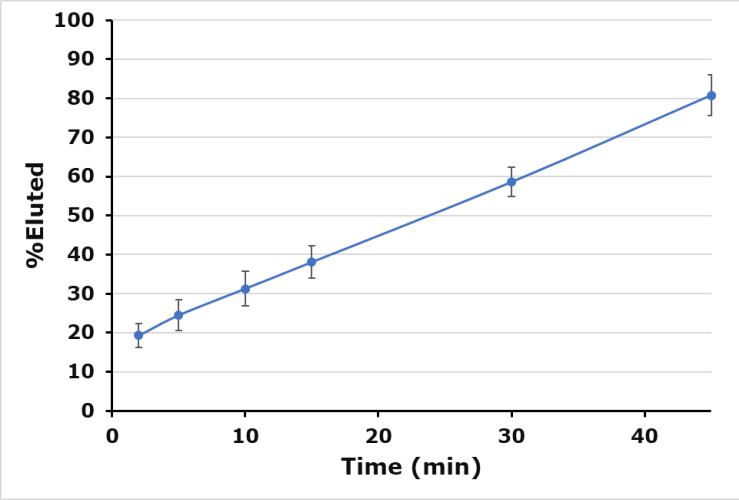
In vitro Oesophageal Retention Model (IVOR)
LLS IVOR-V1: Modified from Young and Smart, J Pharm Pharmacol. (1998), 50, 167

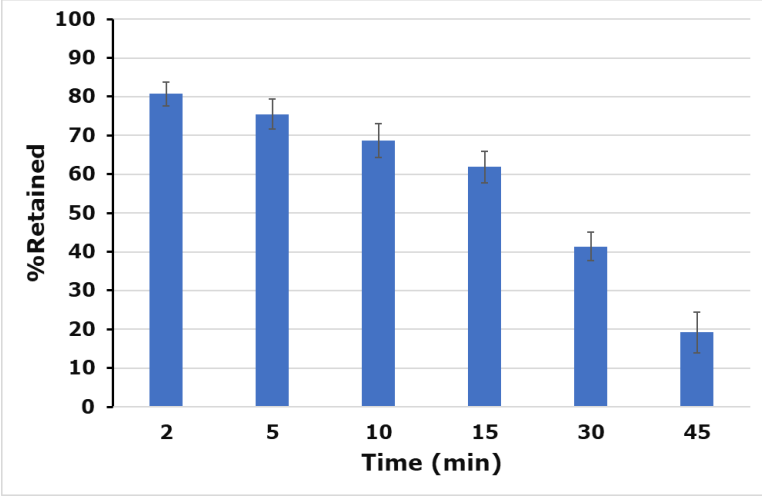
Quantitative and qualitative assessment

In vitro Oesophageal Retention Model (IVOR) Data Analysis

- Analysis of the eluted fractions is done by quantifying the active/marker in the eluate (fluorescence; UV- Vis or HPLC)
- The percentage of active/marker eluted is calculated with reference to total amount of marker in the formulation

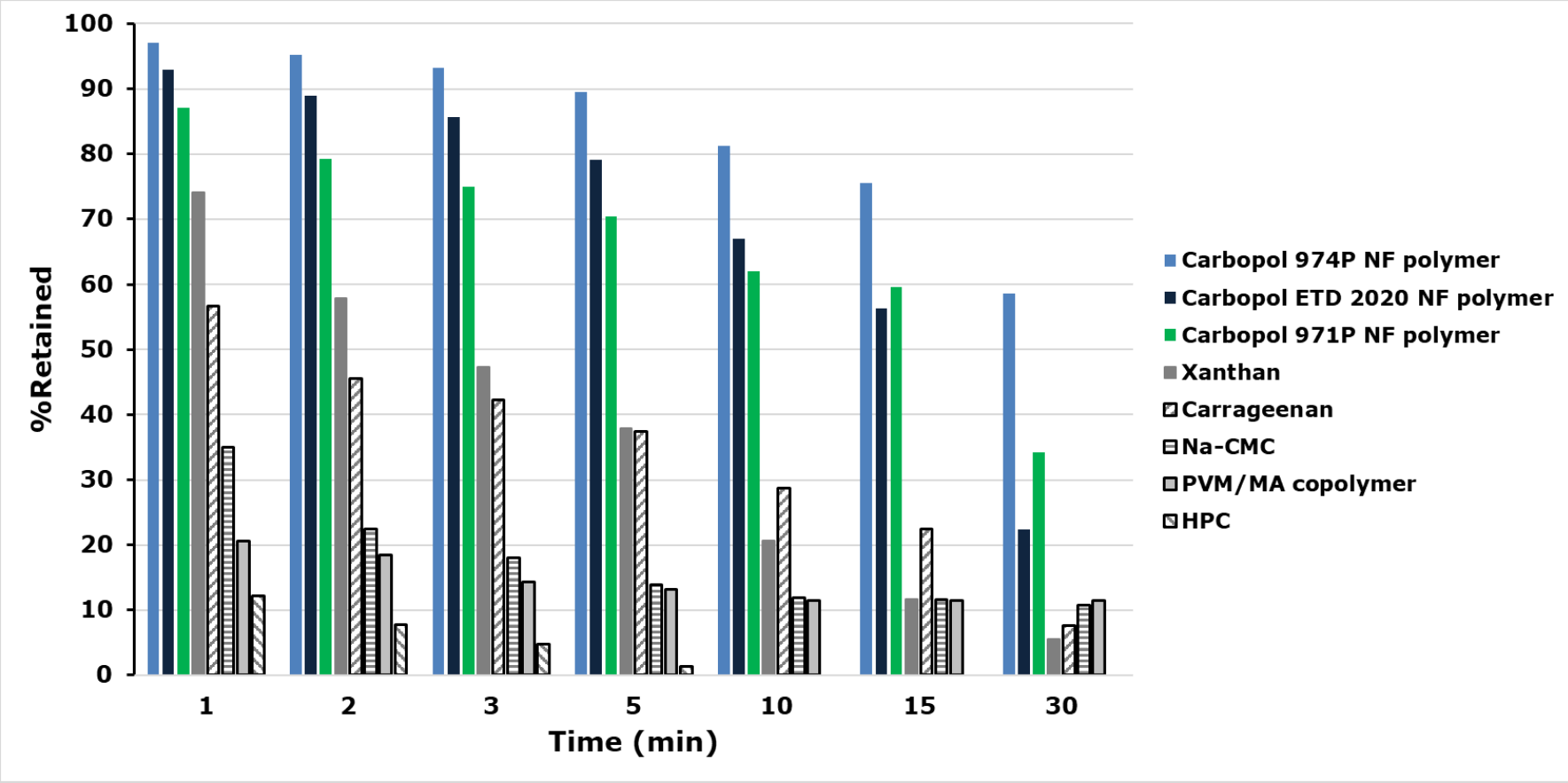
Retained (%) = 100% - Eluted (%)





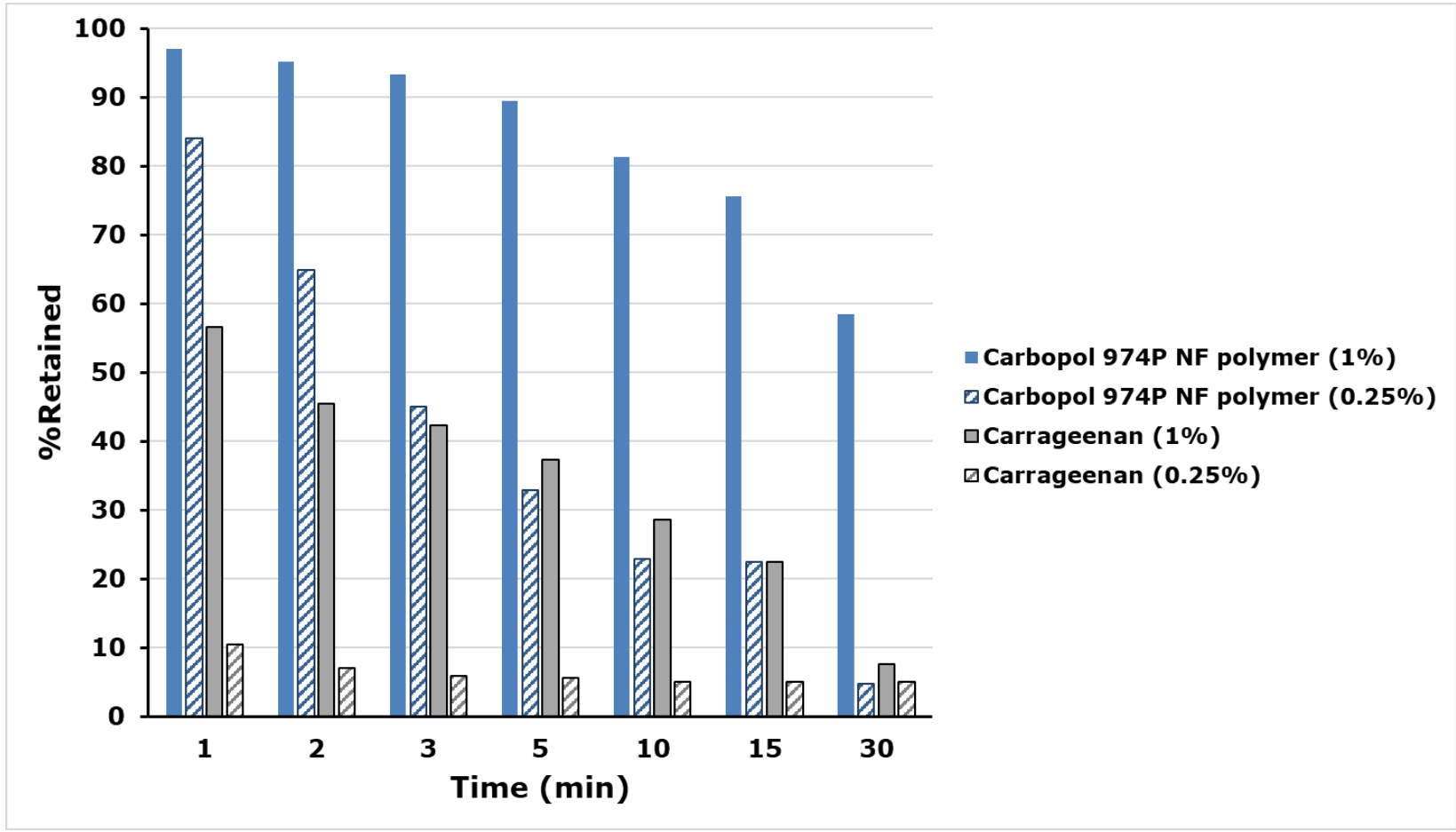
Number of runs: n = 6

1% Polymer Aqueous Dispersions



Carbopol® polymers provided the longest retention,
followed by xanthan and carrageenan

Impact of Polymer Concentration on Mucoadhesion



Longer retention was achieved for the more concentrated dispersions

In vitro Mucoadhesive Properties of Pharmaceutical Excipients

In vitro evaluation of mucoadhesive properties indicated longer retention for Carbopol polymers compared to other materials evaluated:

- The advantage was observed both at 0.25 and 1% concentrations
- At 0.25% inclusion level, only Carbopol polymers were retained, all other materials were washed off after 1 minute
- Longer retention was achieved for the more concentrated dispersions
- At 1% concentration, Carbopol polymers provided the longest retention (lower amount eluted), followed by carrageenan and xanthan. Results indicated retention for more than 30 min for Carbopol polymers

Mucoadhesion Case Studies

HEALTH

Mucoadhesion Case Studies

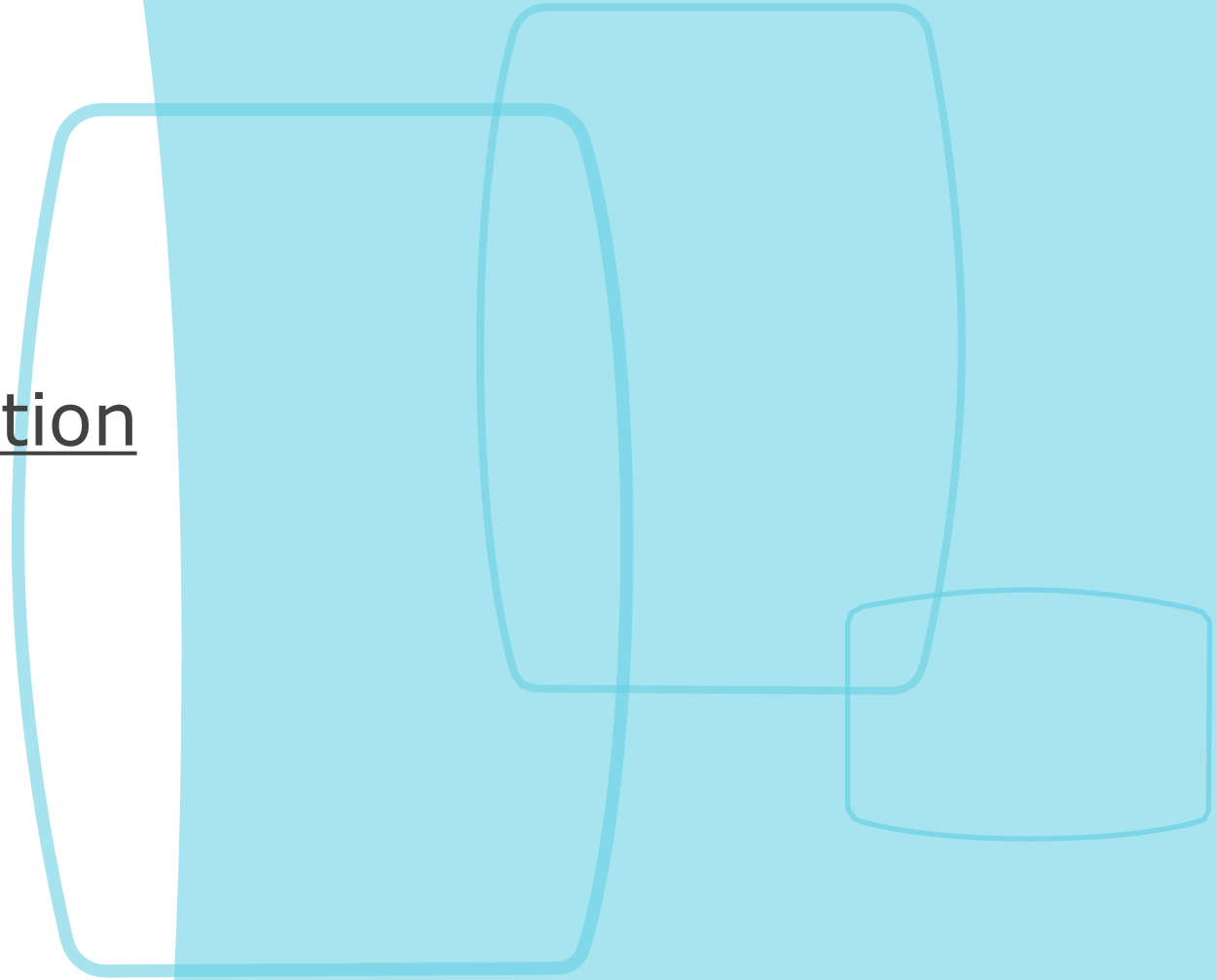
Cough/Cold Liquid Formulation

No-Spill Oral Suspension

Buccal Films

Lozenges

Buccal Tablets



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Mucoadhesion Case Study

Cough/Cold Liquid Formulation with Mucoadhesive Properties

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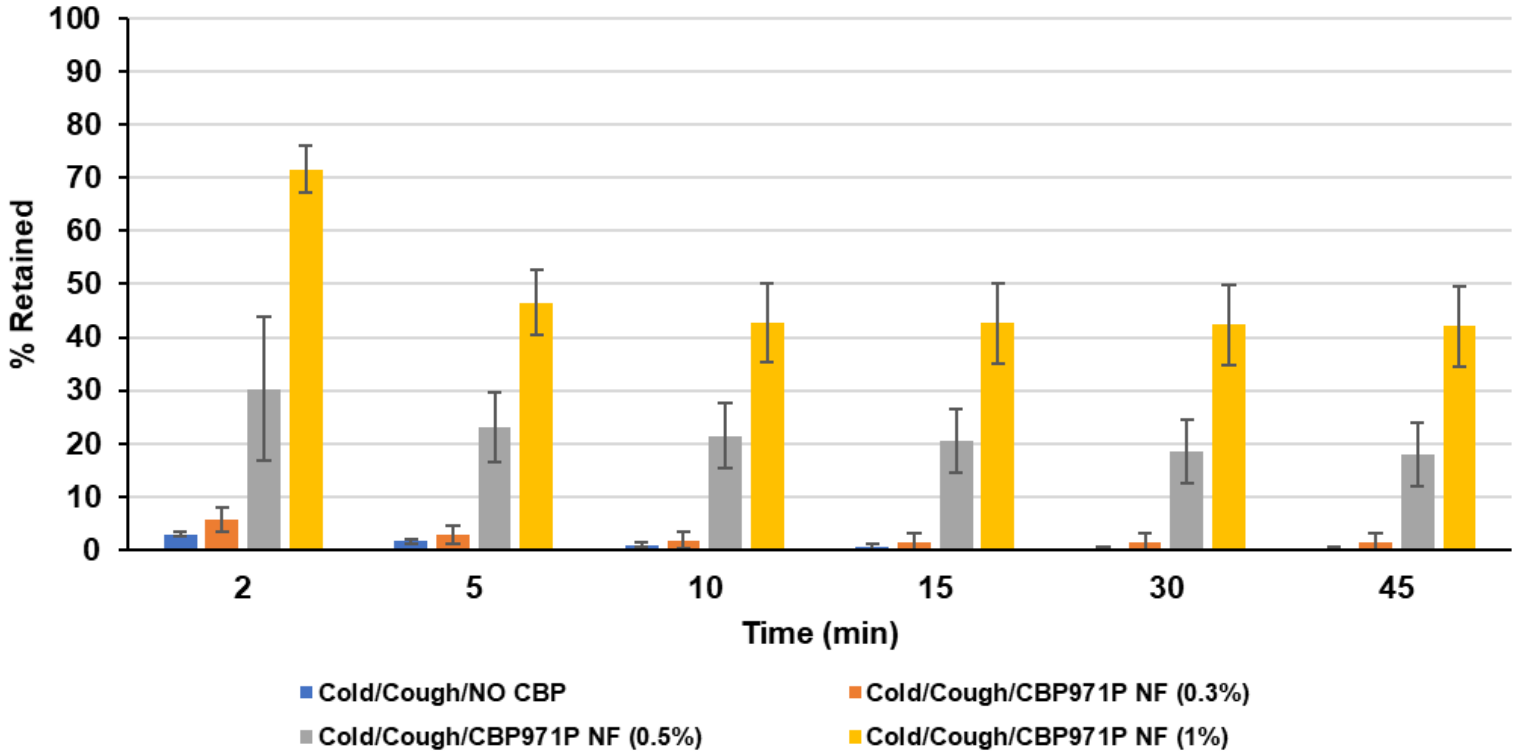
Experimental Design

Study parameter	
Formulation	Reference formulation: commercially available cold/cough product with no mucoadhesive properties Experimental formulation: commercial formulation + **Carbopol® polymer**
Variables	• Carbopol polymer grade: 971P NF and 974P NF • Carbopol polymer inclusion level: 0.3%; 0.5% and 1%

OUTPUT
Formulation:
- viscosity
- mucoadhesion

Impact of Carbopol® 971P NF Polymer Concentration on Mucoadhesion of Cold/Cough Formulations



Retention of formulation when using Carbopol 971P NF polymer increases with polymer level

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Cold/Cough Oral Liquid Formulation with Mucoadhesive Properties

- **Carbopol® polymers imparted mucoadhesive properties** to cold/cough liquid formulations when compared to reference formulation without Carbopol polymers:
  - **Longer retention was achieved** with higher inclusion level of Carbopol polymer
  - Formulations containing **Carbopol 971P NF polymer show higher retention** when compared to similar formulations of Carbopol 974P NF polymer
- Mucoadhesion may also impart a **protective coating to inflamed tissue**

The mucoadhesive properties of Carbopol polymers enable
prolonged retention of actives and potential for enhanced therapeutic effects

Mucoadhesion Case Study

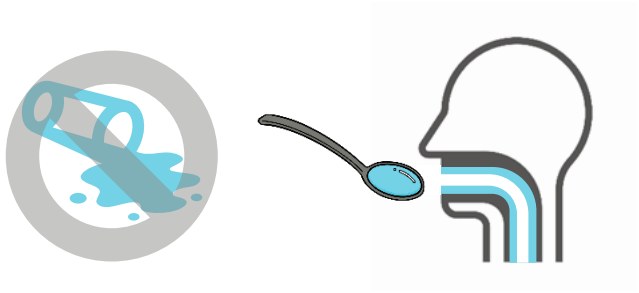
No-Spill Mucoadhesive Oral Suspension Platform

HEALTH

No-Spill
Oral Suspension Platform

Best for Patients

No spill format
Soothing, protective coating
Ideal for pediatric/geriatric

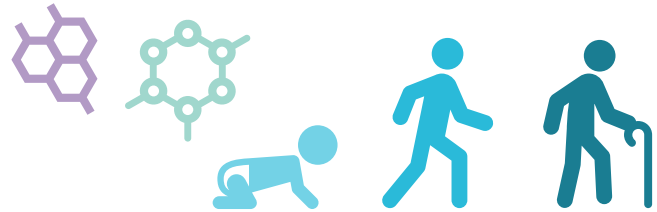


Formulator Friendly

Simplified formulations
Cold processing
Lower usage levels

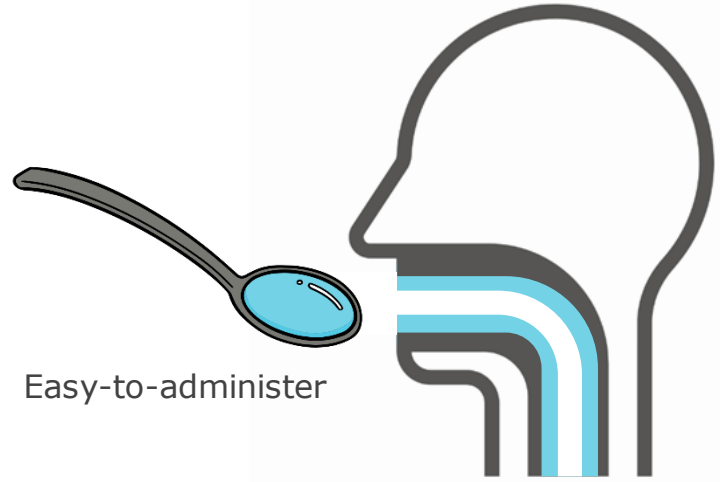
Platform for Innovation

Universal concept
Broad API compatibility



Proof of Concept: Acetaminophen Suspension

- Sugar-free formulation
- Improved sensorial experience via:
  - Mucoadhesive performance
  - Unique flavors (chocolate, coffee)
- Reduced spill
- Cold processed formulation to allows ease of scalability and manufacturing



Proposed Concept
Formulation and Processing

Formulation Ingredients
Acetaminophen
Carbopol polymer
Sorbitol 70%
Sucralose
Flavor
Methyl paraben sodium
Propylparaben sodium
Tween 80
NaOH (10%)/Na_2HPO_4
Purified water

Cold process – time and energy savings

Part A
DI Water
Tween 80
Acetaminophen

Part B
Sucralose
Carbopol polymer
NaH_2PO4
Sorbitol
Paraben salts
NaOH (10%)
DI water

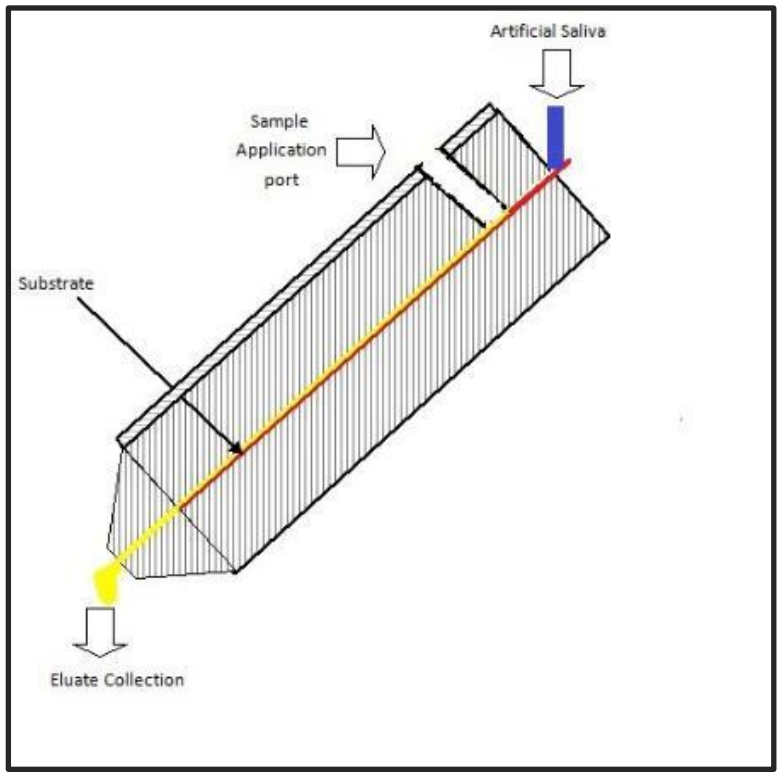
Color
Flavor

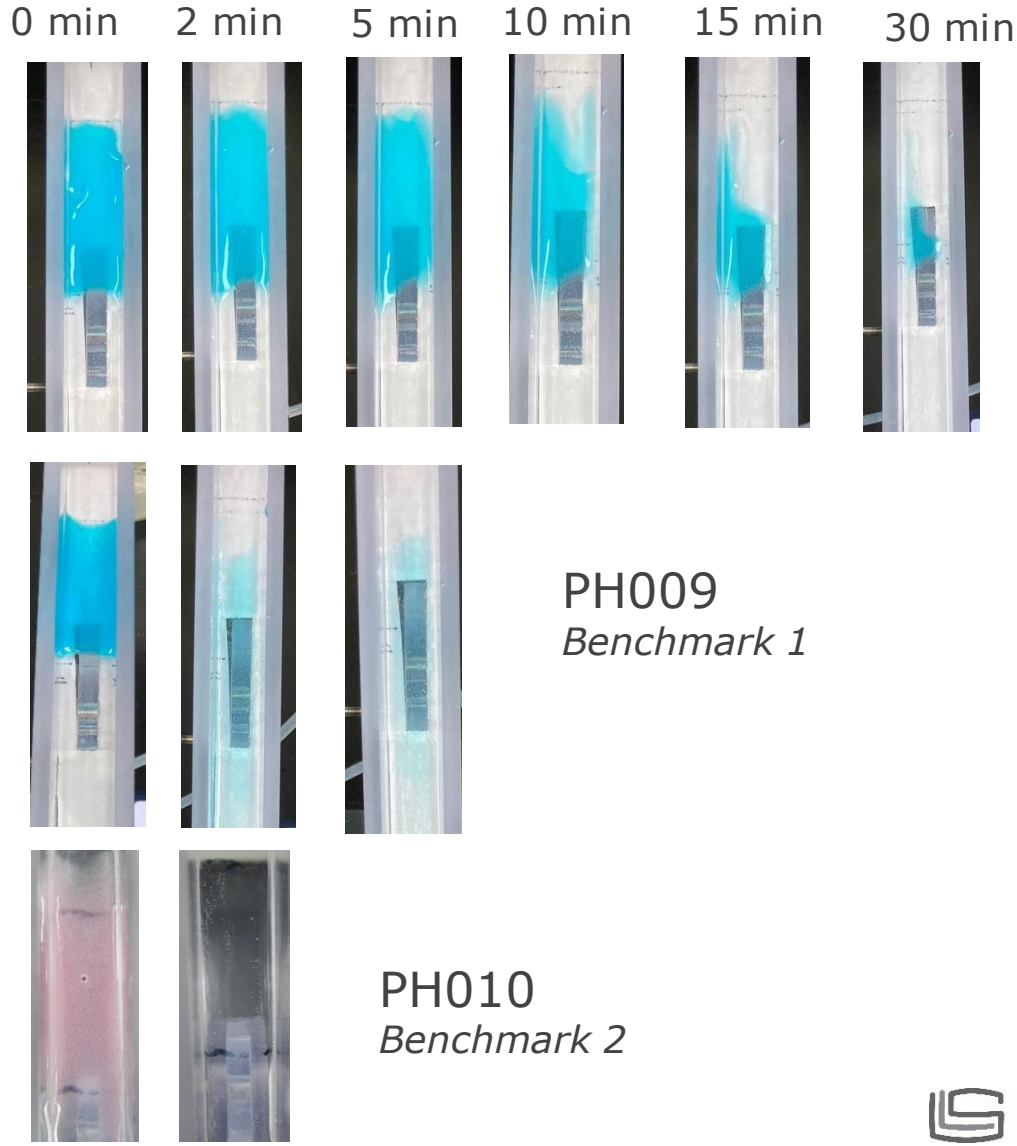
A+B

Formulation development focused on:
- Spill resistance properties and/or
- Soothing/protective coating

Mucoadhesive Properties

Preliminary Formulations vs. Commercial Benchmarks





PH001
(1% CBP 971P NF polymer)

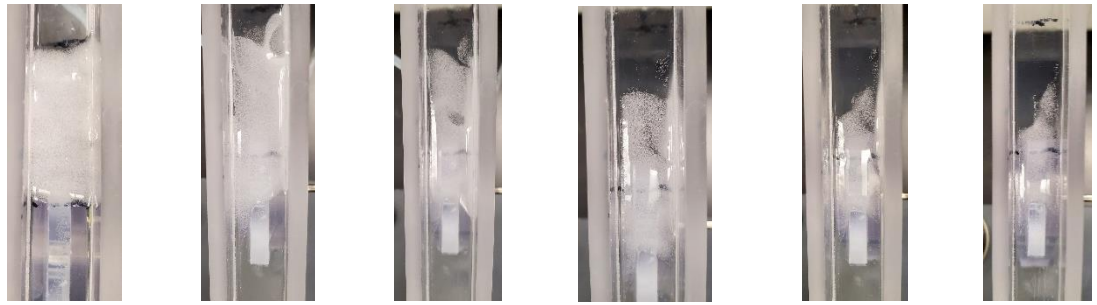
PH009
Benchmark 1

PH010
Benchmark 2

Mucoadhesive Properties

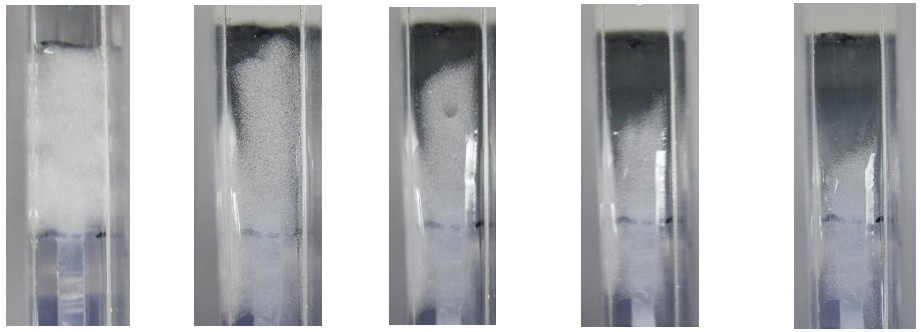
Preliminary Formulations vs. Commercial Benchmarks

0 min 2 min 5 min 10 min 15 min 30 min



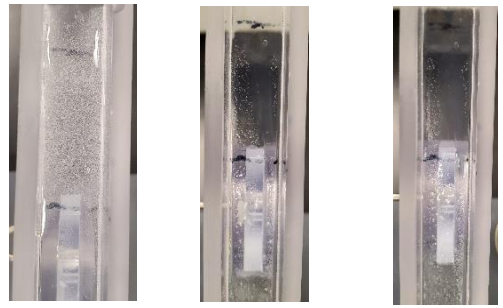
PH001
(1% CBP 971P NF polymer)

PH004
(0.5 % CBP 971P NF polymer)

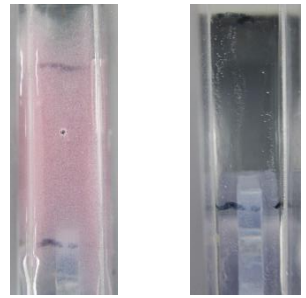


PH005
(0.75% CBP 971P NF polymer)

0 min 2 min 5 min



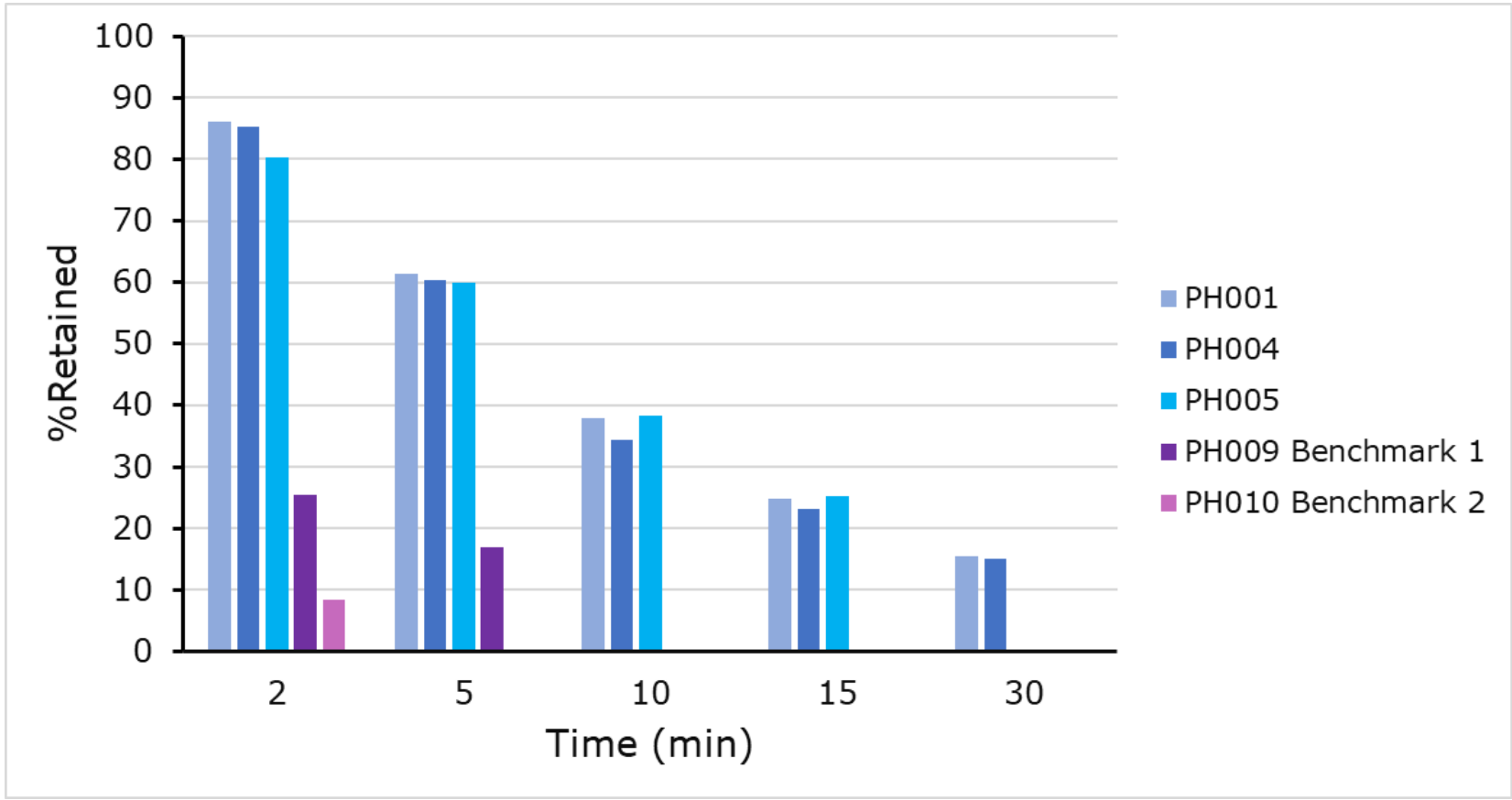
PH009
Benchmark 1



PH010
Benchmark 2

Mucoadhesive Properties

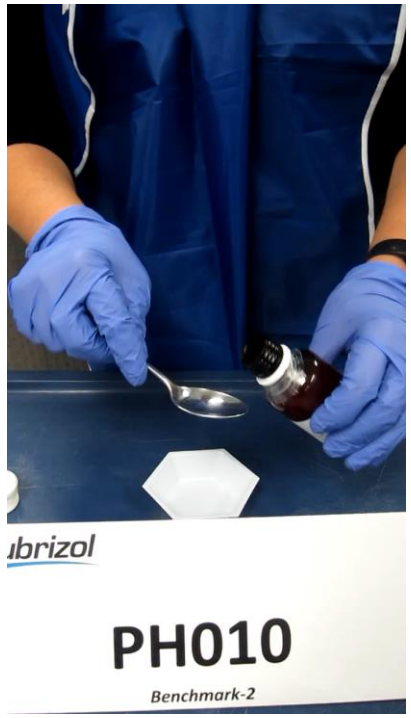
Preliminary Formulations vs. Commercial Benchmarks



Mucoadhesion with Carbopol® polymers offers a **new opportunity for differentiation in oral liquid formulations by providing coating and protection** of irritated or damaged mucosal tissue.

Mucoadhesive Properties

Preliminary Formulations vs. Commercial Benchmarks

Commercial Benchmark	Lubrizol Formulation #1	Lubrizol Formulation #2
		
PH010 Benchmark-2	PH005	PH004

Improved Spill Resistance

Lubrizol formulations provide better spill resistance when compared to benchmark formulations. Carbopol® polymers allow flexibility in formulation to achieve desired spill resistance properties.

No-Spill Mucoadhesive Oral Suspension Platform

- **Carbopol® polymers imparted no-spill properties** to oral suspension formulations when compared to reference formulation without Carbopol polymers:
  - **No-spill effect -** with higher inclusion level of Carbopol polymer
- **Carbopol® polymers imparted protective coating – via mucoadhesion mechanism**
  - Formulations containing **Carbopol 971P NF polymer show higher retention** when compared to benchmark formulations without Carbopol polymers
- Cold processed formulation to allows ease of scalability and manufacturing

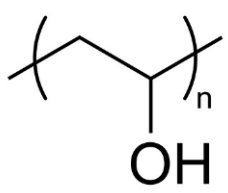
Carbopol polymers properties enable
no-spill suspension formulations with prolonged retention of actives and potential for enhanced therapeutic effects

Mucoadhesion Case Study

Enhancement of Films Using Carbopol® Polymers

HEALTH

Mucoadhesion Enhancement of Films Using Carbopol® Polymers

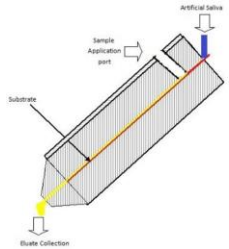


Film former excipient
Polyvinyl alcohol
PVA

Mucoadhesive excipient
Carbopol polymer
CBP

Mucoadhesive Film
CBP/PVA

In vitro mucoadhesive properties tested using
LLS IVOR-V2: Modified from Young and Smart J Pharm Pharmacol. (1998), 50, 167



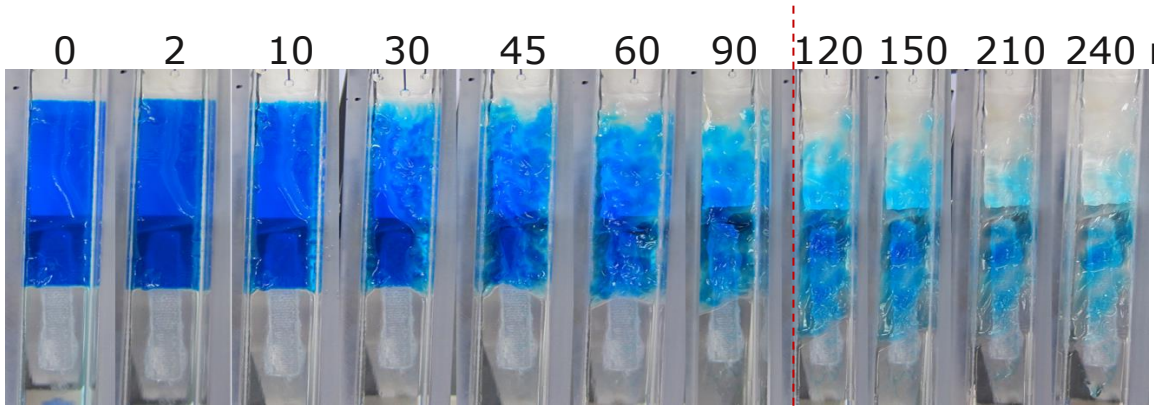
Mucoadhesion Enhancement of Films Containing Carbopol® Polymers

Carbopol Polymer Grade		Formulation
974P NF (Carbomer homopolymer type B) 971P NF (Carbomer homopolymer type A)	⟷	Carbopol/PVA ratio in film - 1/1; 1/2 Carbopol polymer degree of neutralization No neutralization vs. neutralization (pH ~7)

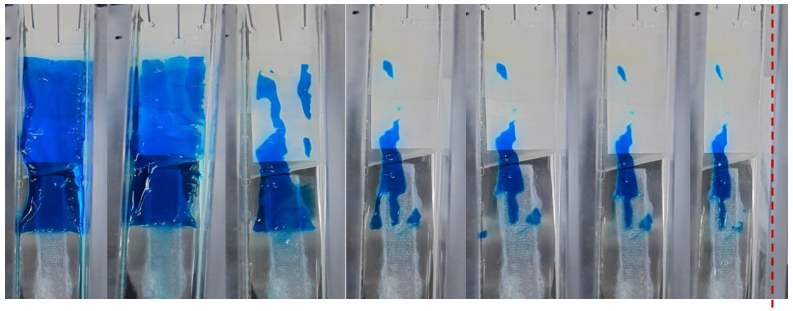
↓

Formulation space
Mucoadhesive benefits of Carbopol polymers inclusion in films

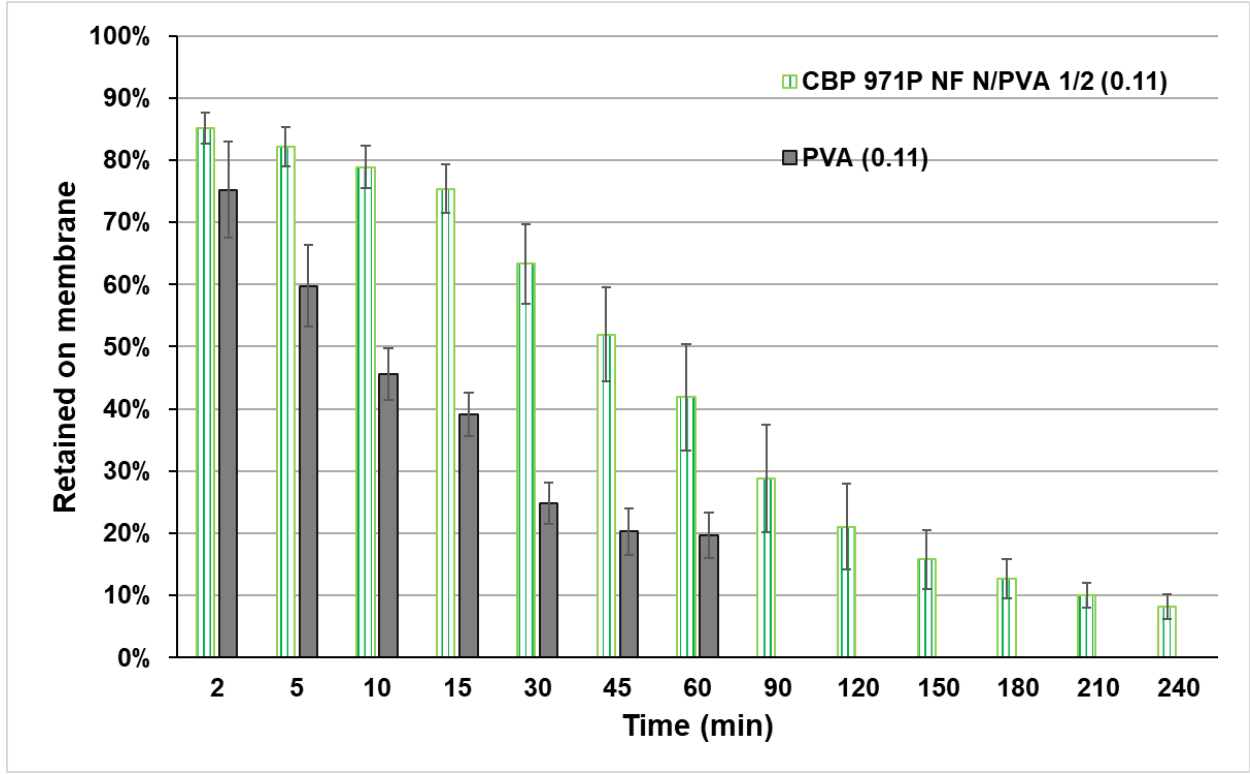
In vitro Mucoadhesion of Carbopol-PVA Films



CBP 971P NF N/PVA 1/2 (0.11 mm)



PVA (0.11 mm)



For similar film thickness: CBP 971P NF N/PVA 1/2 films **showed longer retention when compared with PVA**

Mucoadhesion Enhancement of Films Containing Carbopol® Polymers

- Successful placebo film formulations containing Carbopol polymers and PVA have been demonstrated
- The addition of Carbopol polymers in CBP/PVA films enhanced mucoadhesive properties of the films, offering flexibility of formulation
- Mucoadhesion strength of films was influenced by:
    - Carbopol polymer degree of crosslinking
      Carbopol 971P NF > Carbopol 974P NF
    - Film thickness - thicker films showing better retention

Longer retention ensured by films containing Carbopol 971P NF polymer

Case Study: Mucoadhesive Lozenge

Objectives

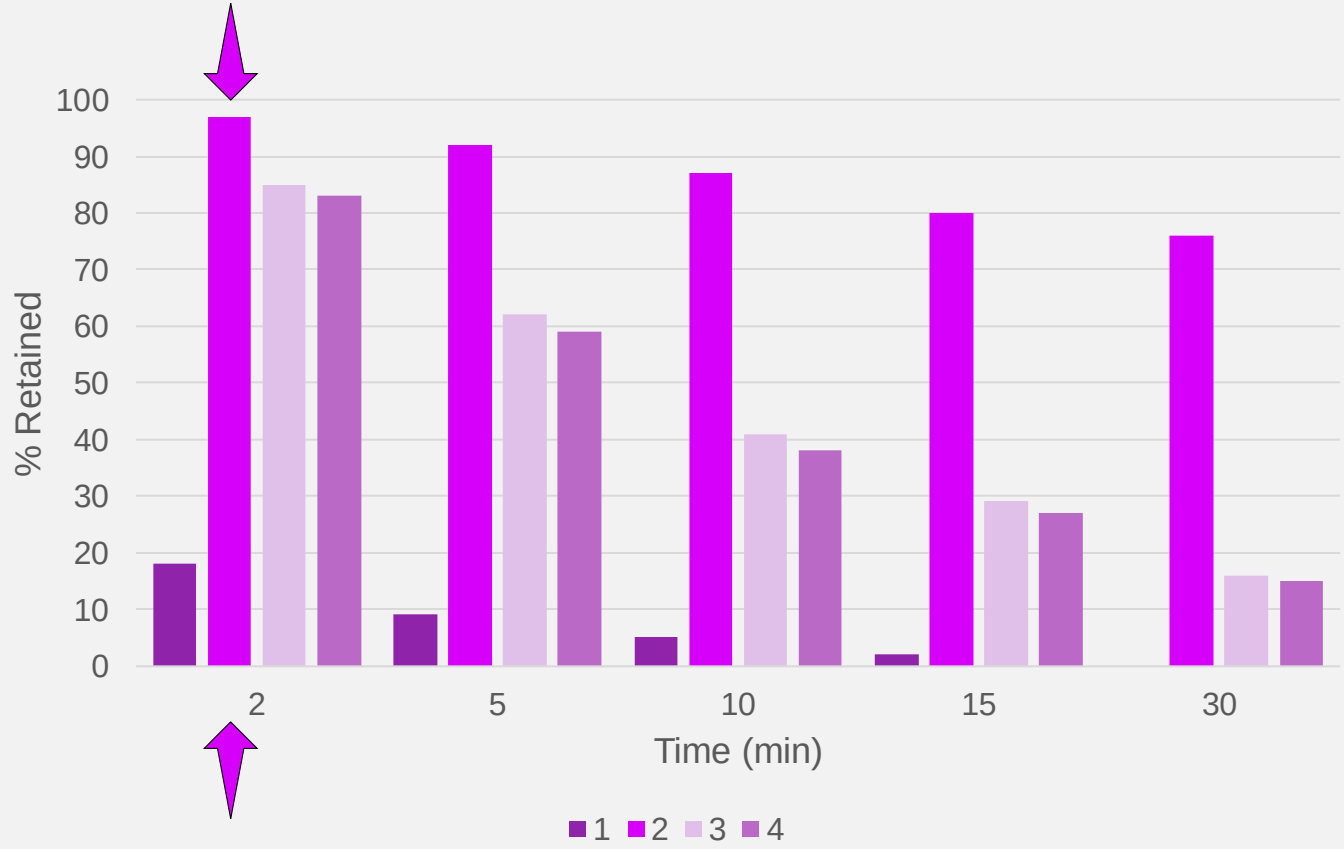
- Providing a mucoadhesive, protective and soothing layer for the oral cavity
- Combining mucoadhesive ingredients for optimal effect
- Creating a robust DC formulation (powder flow, compactability)
- Giving a pleasant taste

<u>Main challenge</u>:

Which ingredients/combination of ingredients are appropriate for a better mucoadhesion when formulating a lozenge?

Case Study: Mucoadhesive Lozenge

Influence of polymers, nature and physical properties



- Tablet weight: 800 mg
- Diameter: 16 mm
- Hardness: 185 N
- Thickness : 4 mm

Formulation	1	2	3	4
Na Hyaluronate	0.2	0.2	-	0.2
Carbopol® 71G NF	10	10	10	10
Carbopol® 971P NF	-	5	5	3
Manucol LKX	3	3	3	3

Back to TOC

Case Study
Buccal Mucoadhesive Tablets

HEALTH

Buccal Mucoadhesive Tablets Design

Mucoadhesive polymer		Formulation
Carbopol® 971P NF polymer Carbopol® 71G NF polymer Hypromellose Sodium alginate Chitosan	⟷	Mucoadhesive polymer(s) inclusion level Filler selection

↓

Buccal mucoadhesive formulation space

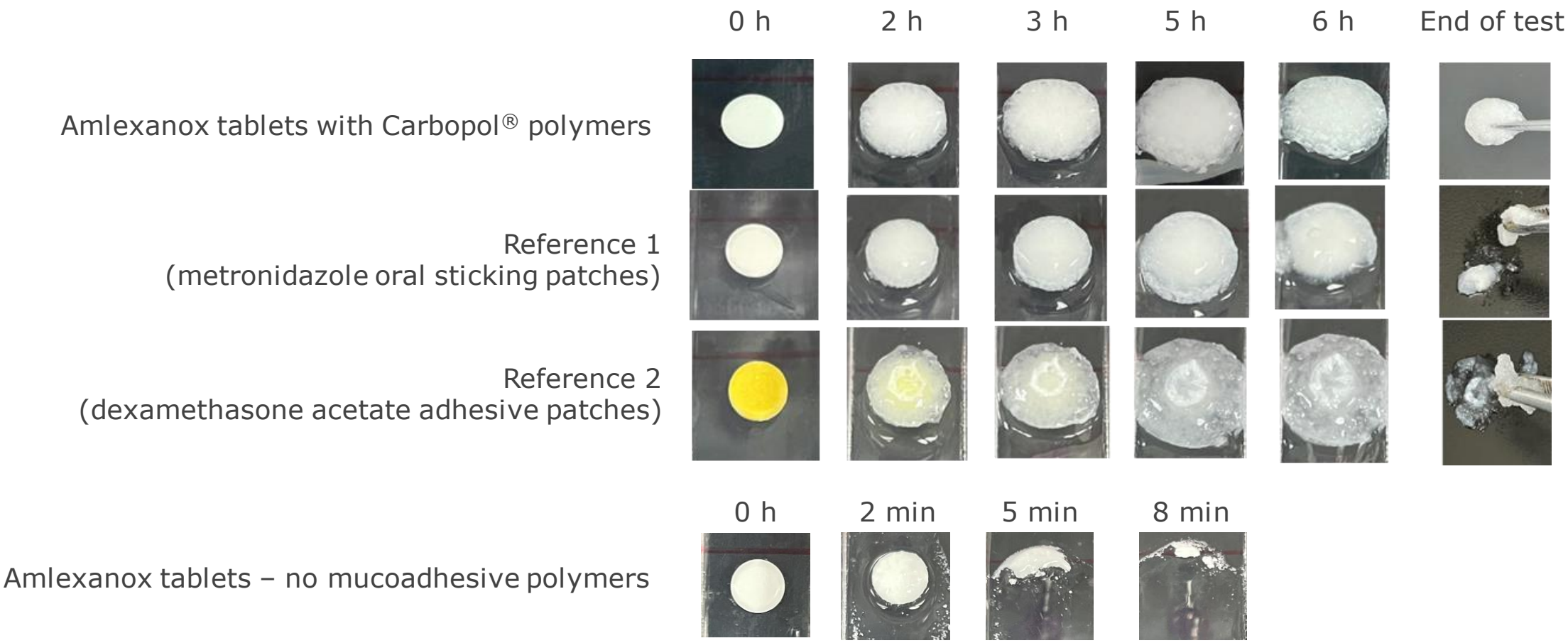
Experimental Design

	Ingredient	Function
Formula	Amlexanox	API
	CBP 71G NF	Mucoadhesive agent
	CBP 971P NF	Mucoadhesive agent
	Sorbitol	Filler
	Starch	Filler
	Silica	Glidant
	Magnesium stearate	Lubricant
Process	Direct Compression, 75 mg, flat round punch	
Physical Property	Tablet weight / mg	
	Tablet hardness / N	
	Friability	
	Tablet disintegration time	
Assay Test	• Analytical method: HPLC method. • Assay: 95%~105%	
Mucoadhesion	• Modified IVOR test – **not less than 6 h**	
Dissolution	• USP method – **not less than 80% drug release in 6 h**	

Commercial benchmarks
Reference 1: metronidazole oral sticking patches
Reference 2: dexamethasone acetate adhesive tablets

HEALTH

Mucoadhesive Properties of Buccal Tablets



Very good retention and integrity of amelxanox tablets containing Carbopol® 971P NF polymer

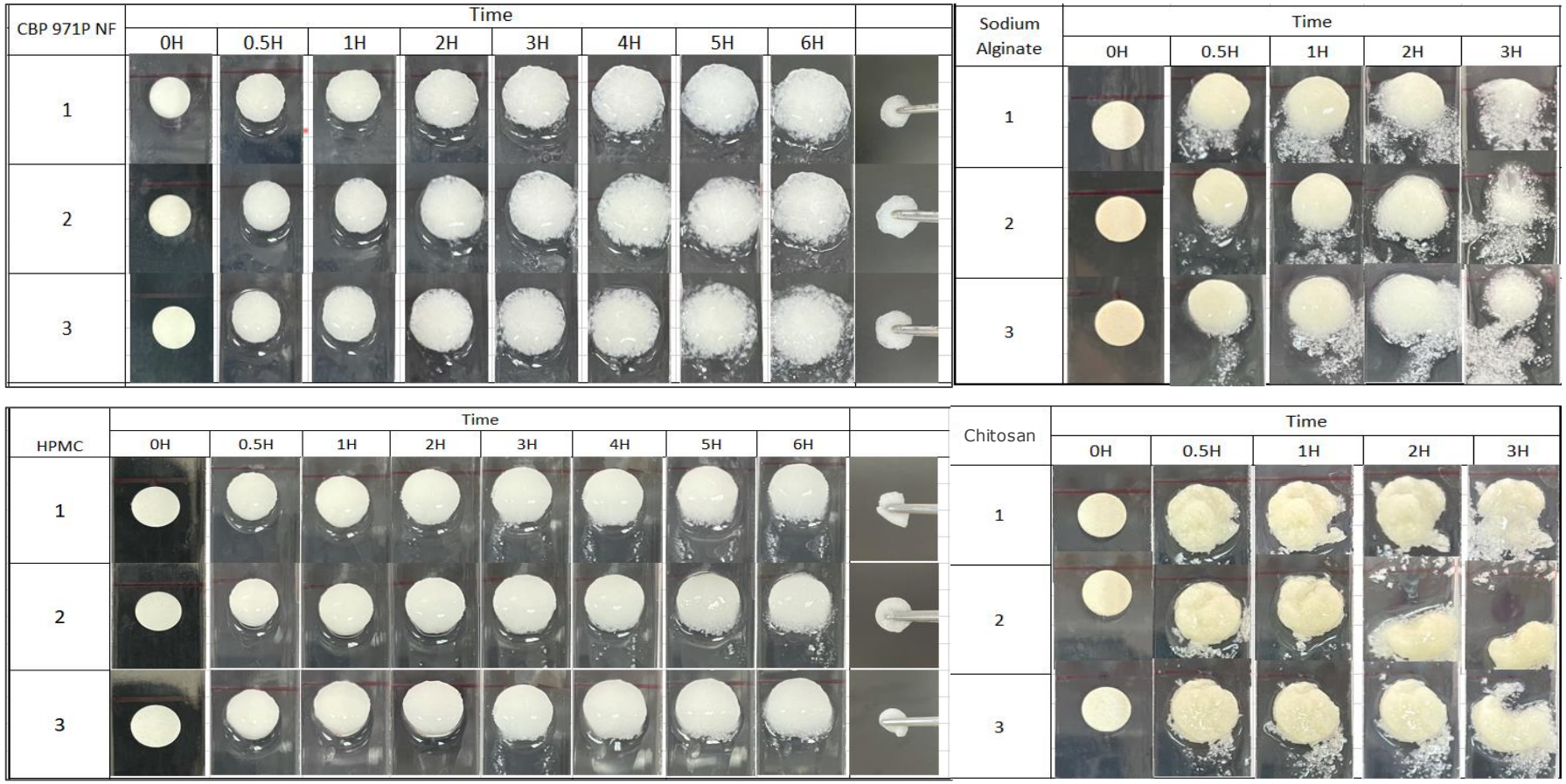
LUBRIZOL LIFE SCIENCE

Impact of Mucoadhesive Polymer on Buccal Tablet Performance

Ingredient/Tablet properties		F - HPMC	F- NaAlg	F-Chit	F-CBP
Mucoadhesive agent 1		HPMC DC	/	/	CBP 71G polymer
Mucoadhesive agent 2		HPMC	Sodium Alginate	Chitosan	CBP 971P polymer
Hardness/N (n=10)		38.04	52.07	62.91	139.1
Friability (%)		0.2	0.2	0.1	0.1
Mucoadhesion (IVOR; h)		6	2	2	6
Dissolution (%)	1h	7.18	7.88	/	3.02
	3h	20.31	37.89	/	27.06
	6h	39.35	89.07	/	83.79

At same inclusion levels Carbopol® polymers lead to
more robust tablets that meet retention and dissolution targets

Impact of Mucoadhesive Polymer on Buccal Tablet Performance



Sodium alginate and chitosan impart poor mucoadhesion performance
Tablets containing Carbopol polymers or hypromellose were retained for 6 h,
however, hypromellose tablets did not meet dissolution requirements despite higher erosion

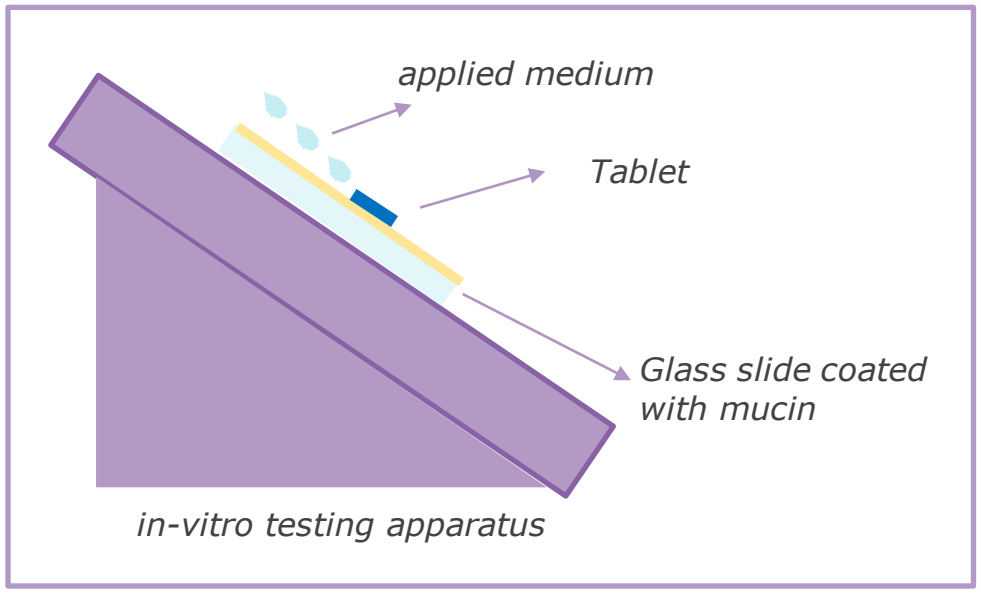
Gastroretentive Mucoadhesive Minitablets

HEALTH

Mucoadhesive Gastroretentive Minitablets: *in vitro* study

Composition of adhesive minitablets

Ingredients	Amount (%)
Black iron oxide E172	5.0
Acrylic acid polymer (Carbopol® 71G polymer)	47.5
Calcium phosphate (Emcompress Premium)	47.5



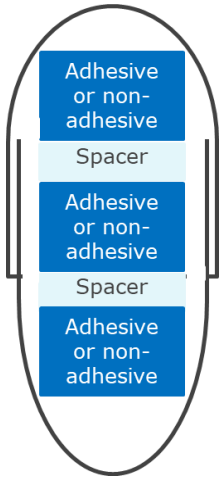
Composition of non-adhesive minitablets

Ingredients	Amount (%)
Black iron oxide E172	5.0
Glyceryl behenate (Compritol 888 ATO)	45.0
Calcium phosphate (Emcompress Premium)	45.0
Silicon dioxide	1.0
Magnesium stearate	0.5

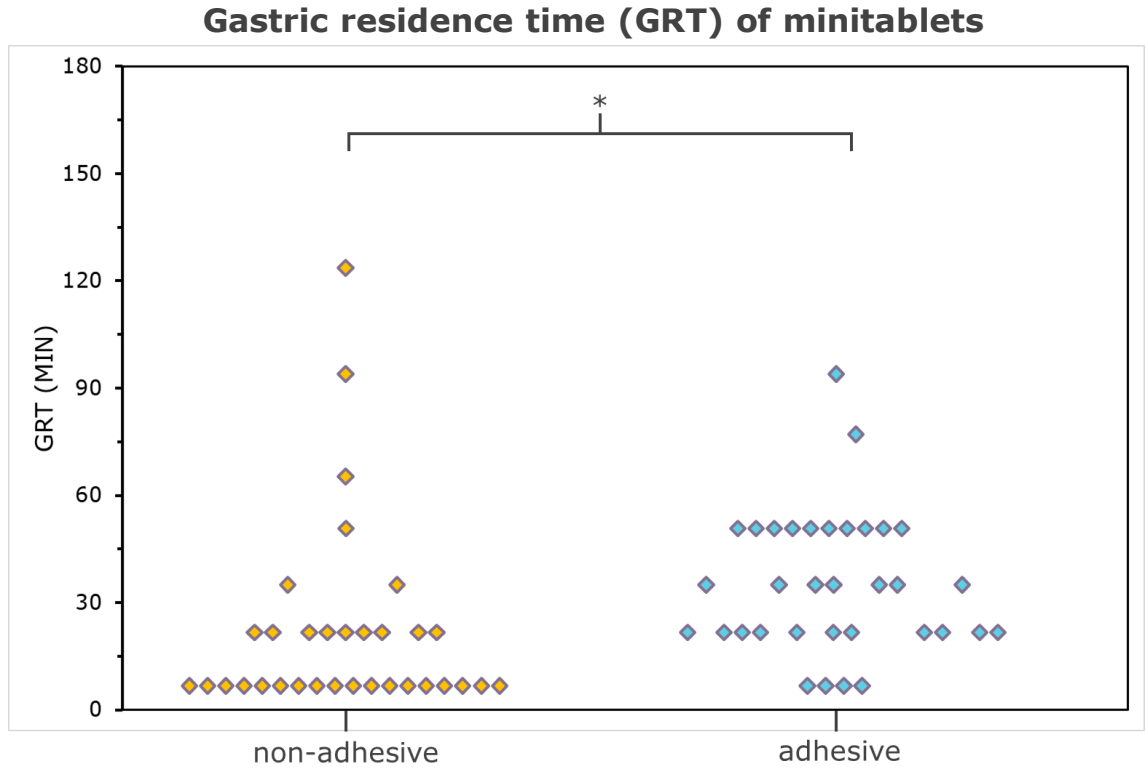
- The non-adhesive minitablets slipped off and were washed away in 30 min
- The adhesive minitablets remained adherent to the mucin layer for 240 min

Rump, A. *et al*, Mol. Pharmaceutics 2023, 20, 1624−1630

Mucoadhesive Gastroretentive Minitablets: Human *in vivo* study



Schematics of Vcaps plus size 3 as administered to 12 healthy volunteers (5 males/7 females) in the double-blind, single center, two-way crossover study
Mucoadhesion in stomach estimated via MRI



The median GRT was 7.5 min for the non-adhesive minitablets and 37.5 min for the adhesive minitablets

The mucoadhesive properties of Carbopol® 71G NF polymer are also **effective in the human stomach**

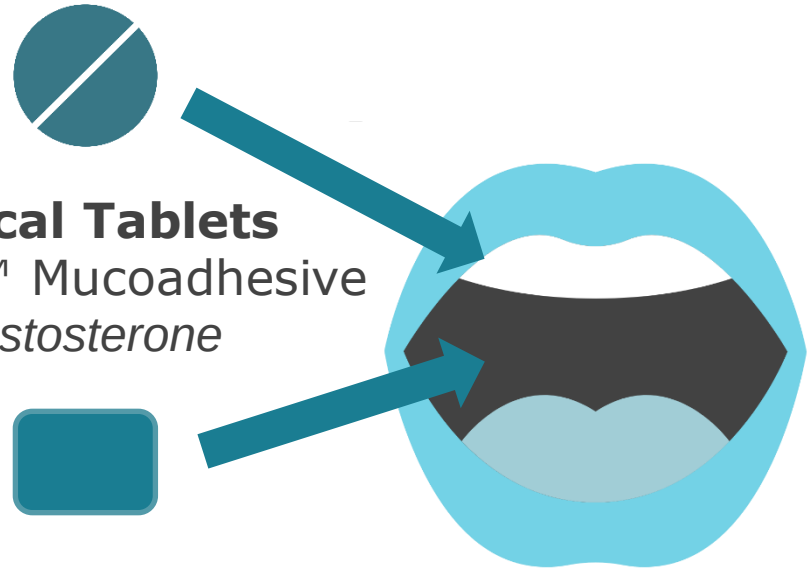
Rump, A. *et al*, Mol. Pharmaceutics 2023, 20, 1624−1630

Commercial Pharmaceutical Drug Products with Mucoadhesive Properties

HEALTH

Examples of Mucoadhesive Oral Commercial Products

Enhanced Delivery of Actives



Buccal Tablets
Striant™ Mucoadhesive
Testosterone

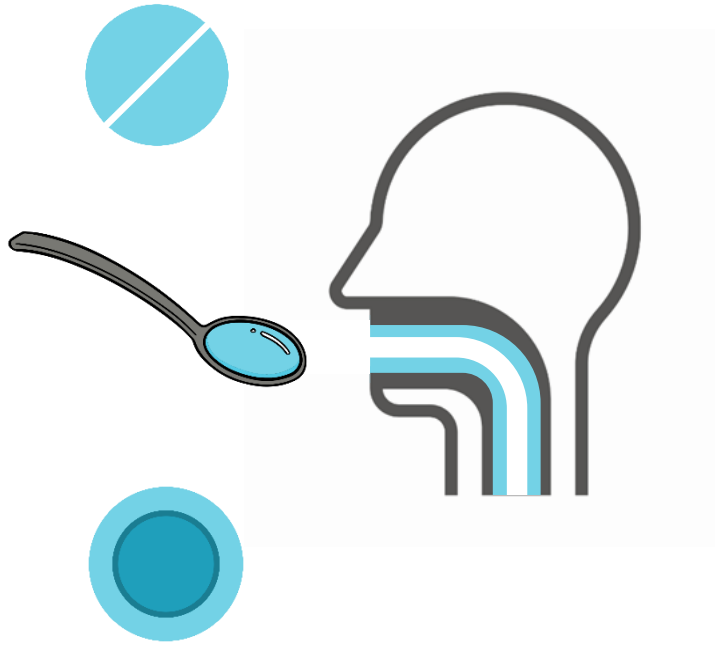
Buccal Films
Belbuca® Buccal Film
Buprenorphine

Protective Barrier/Coating

Buccal Tablets
Canker Cover®

Oral Liquids
MuGard® Oral Mucoadhesive

Oral Lozenges
GeloRevoice® Lozenges



Carbopol® polymers enable a wide range of oral mucoadhesive dosage forms

Mucosal Drug Delivery

Efficacy ✓

- Enhanced systemic delivery
  - Mucosa permeability
  - By-pass GI-route/first hepatic pass
- Localized – dosage form at site of action
- Tailored duration

Patient Adherence ✓

- Noninvasive
- Convenient (administration/removal)
- Reduced drug side-effects

Differentiation ✓

- Mucoadhesion can be used to provide **product innovation and new label claim opportunities**

Thank you!

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HEALTH

Apinovex™ Polymer for Oral Solubility Enhancement

January 29, 2026

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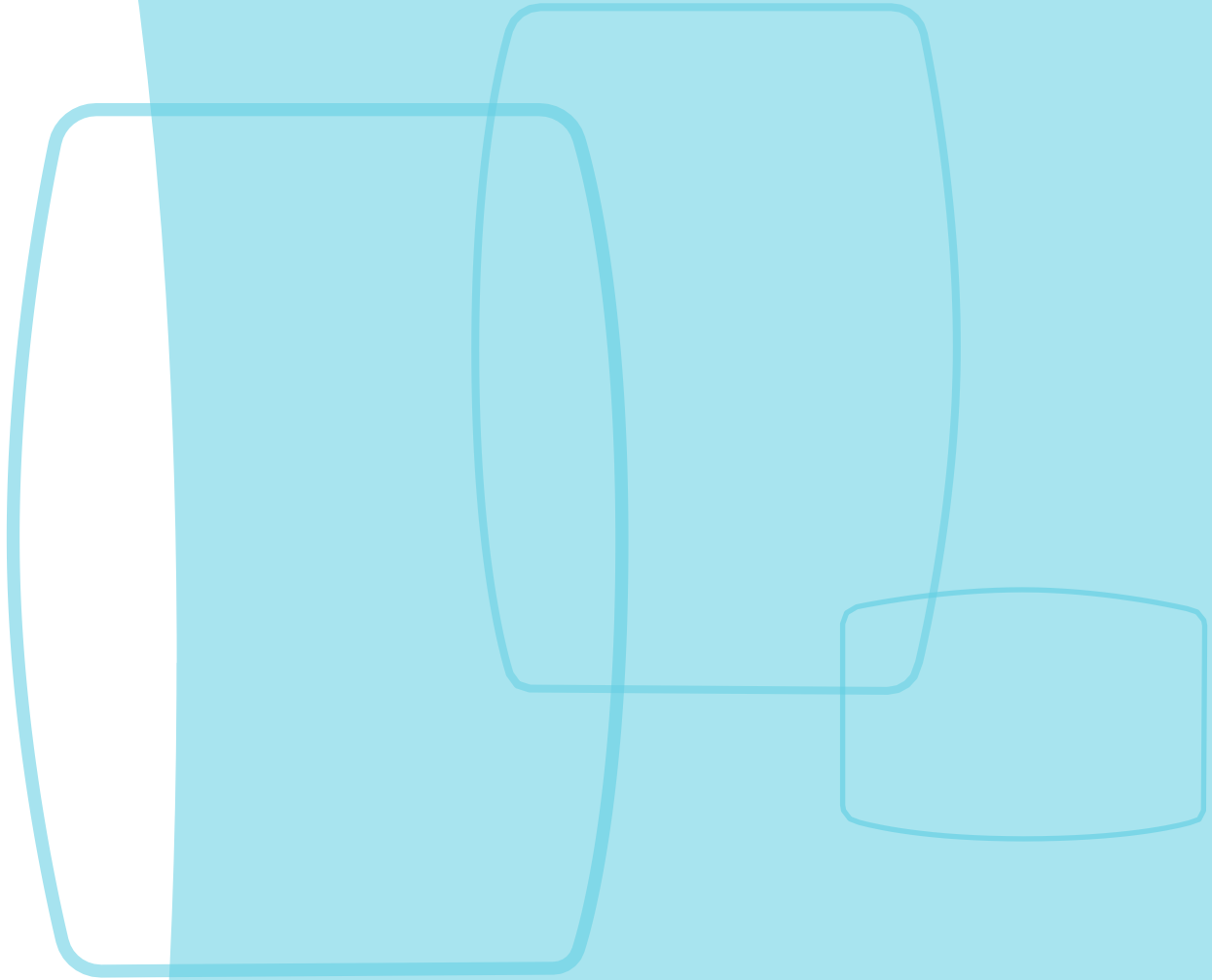

LLS | HEALTH

HEALTH

Lubrizol Life Science Health (LLS Health)

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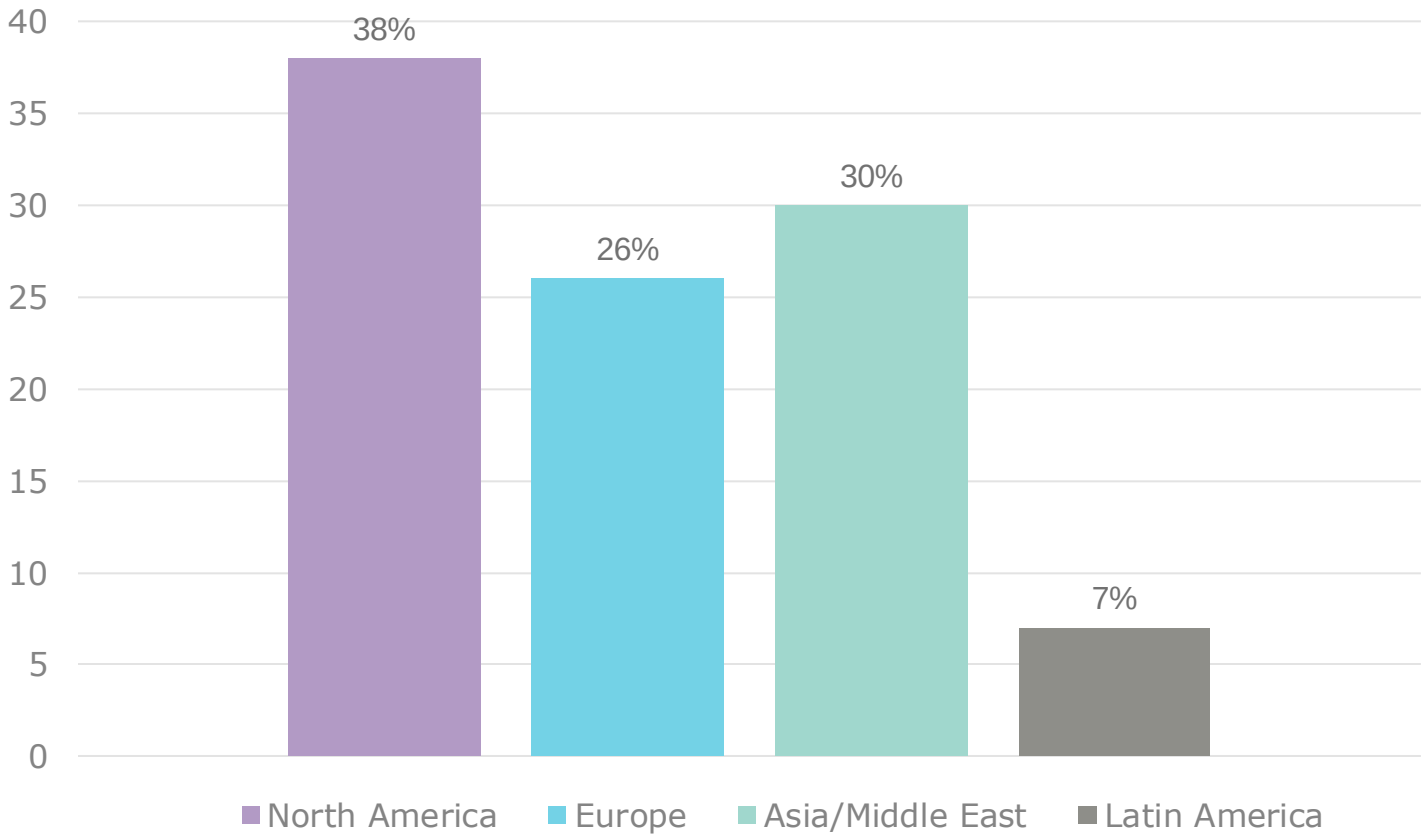
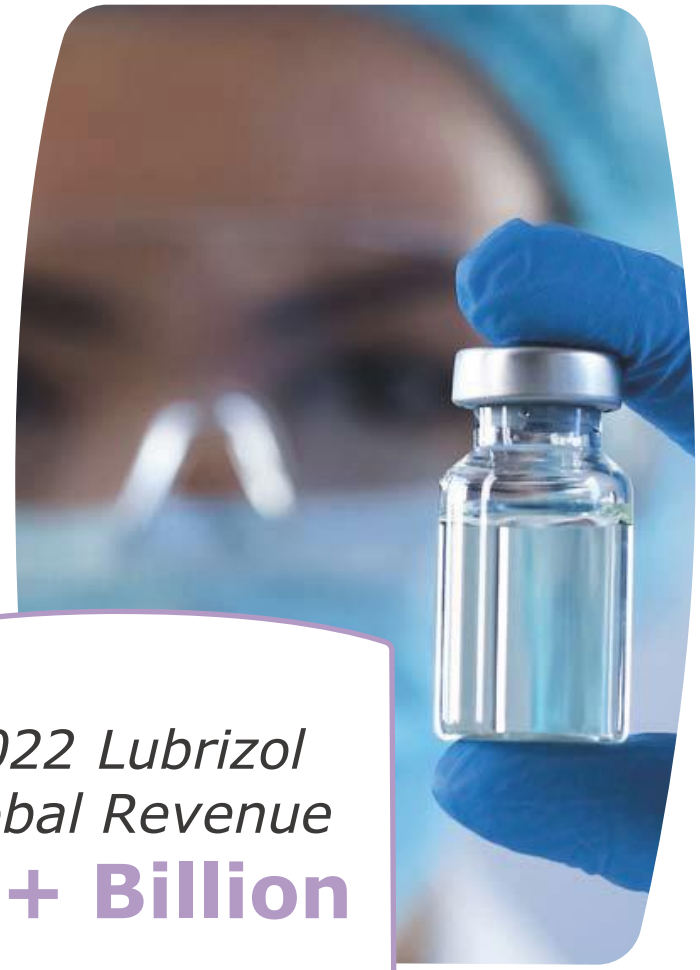
The Health business of Lubrizol Life Science serves the medical device and pharmaceutical industries.





2022 Lubrizol Global Revenue

$6+ Billion

LUBRIZOL LIFE SCIENCE

HEALTH

LLS Health Global Footprint

LUBRIZOL LIFE SCIENCE

Pharma Segment Overview

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Excipients

Multifunctional excipients which enable differentiated, patient-centric products

- Extended-release
- Solubility enhancement
- Permanent suspension
- Muco-adhesion
- Taste-masking

CDMO

A leading pharmaceutical contract development & manufacturing organization

- Insoluble APIs
- Sterile/aseptic products
- Long-acting implants & intravaginal rings

Nutraceuticals

Development & production of value-added nutraceutical ingredients

- Functional foods
- Dietary supplements
- Microencapsulation

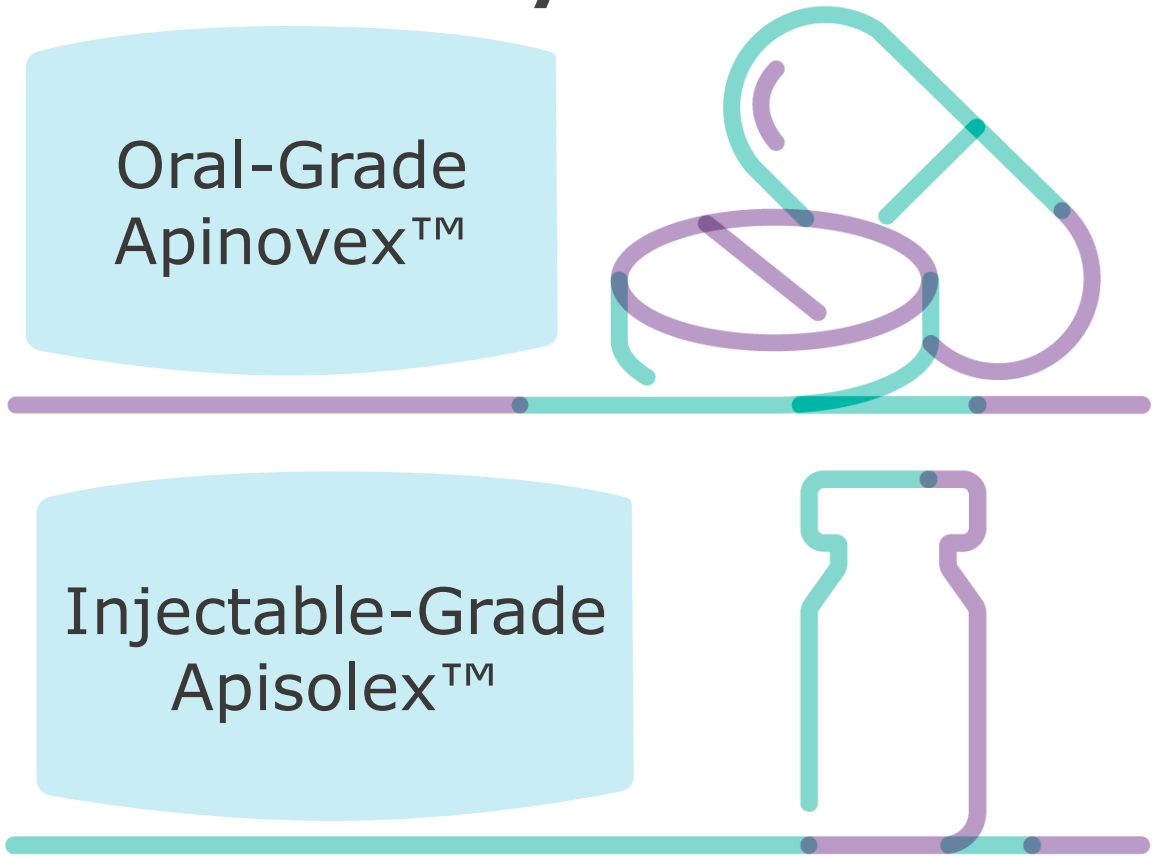
Service offerings along the value chain provides simplification of supply chain
Built for sustainability - A Berkshire Hathaway Company

Why Choose Lubrizol Life Science Health?

Back to Start

- Safe and effective excipient supply for **over 40 years**
  - Carbopol® polymers
  - Noveon® AA-1 polycarbophil
  - Pemulen™ TR-2 emulsifiers
  - Pathway™ TPU excipients
- Trusted CDMO services for **over 20 years**
  - Decades of collective experience in **nanomilling**

Novel Solubility-Enhancing Polymers



Back to Start

Apinovex™ Polymers for Solubility Enhancement

HEALTH

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Apinovex™ Polymer Value Proposition

- **Improved solubility and release** for BCS Class II and IV APIs
- **High, stable drug loading** (up to 80%)
- **Easy to process** via spray-drying
- **Offers IP protection** for 505(b)(2) and NCE products

Apinovex Polymer Properties

Back to Start

High molecular weight polyacrylic acid chemistry **designed for spray-drying**

Property		Apinovex™ LV Polymer
Tg (°C) – first heat cycle		128
Tg (°C) – second heat cycle		130
Solubility*	Methanol (10% w/w)	Soluble
	Ethanol (15% w/w)	Soluble
	Isopropanol (10% w/w)	Soluble
	Ethanol/Dichloromethane 1/1 (10% w/w)	Soluble
	Ethanol/Acetone 1/1 (10% w/w)	Soluble
	Ethanol/THF 1/1 (10% w/w)	Soluble
	Methanol/Dichloromethane 1/1 (10% w/w)	Soluble

High Tg for stabilizing amorphous solid dispersions
Compatible with **common pharmaceutical solvents**

LV – low viscosity
*Not soluble at 1% in Acetone, Dichloromethane, and Tetrahydrofuran

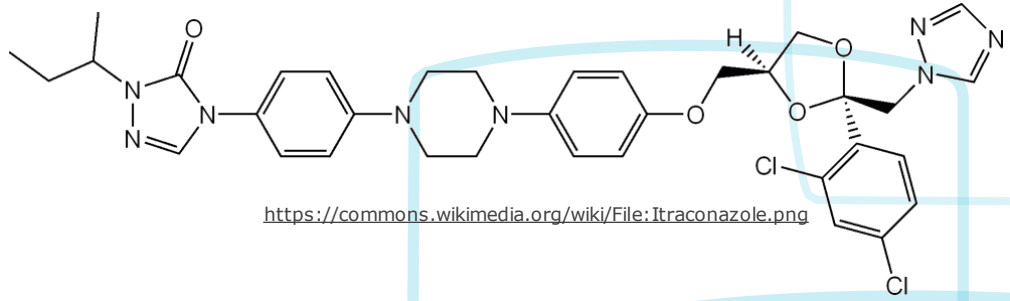
Apinovex Polymer Case Study: Spray-Dried Itraconazole ASD

Back to Start

- **API: Itraconazole**
  - Poorly solubility, low bioavailability
  - Difficult to formulate
  - First approval: 1992 (Sporanox®)

- **Excipients Evaluated**
  - Apinovex™ Polymer (Lubrizol)
  - Soluplus® (BASF)
  - Affinisol® HPMC HME 15LV (Dow)
  - Aqoat® HPMCAS-LG (Shin-Etsu)

- **Formulations Evaluated**
  - Physical mixtures (PMs)
  - Spray-dried amorphous solid dispersions (ASDs)



https://commons.wikimedia.org/wiki/File:Itraconazole.png

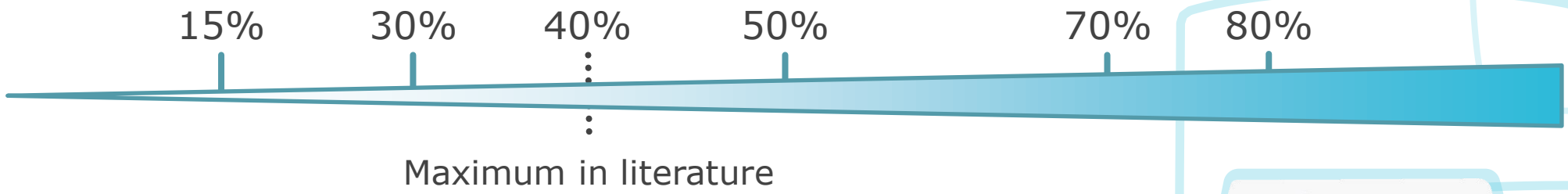
Parameter	Itraconazole
Water Solubility (g/L)	0.0096
BCS Classification	2
LogP	5.66
Reported concentration in ASD (literature)	40%

Soluplus®, BASF, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer
Affinisol® HPMC HME 15LV, Dow, hydroxypropyl methyl cellulose
Aqoat® AS-LG , Shin-Etsu, hydroxypropyl methyl cellulose acetate succinate

Apinovex Polymer Case Study: Spray-Dried Itraconazole ASD

Back to Start

- **Itraconazole Loading**



- **Spray Drying Process**
  - Equipment: Buchi B-290
  - Solvents: ethanol, ethanol/dichloromethane
- **Characterization**
  - Appearance
  - Phase identification/transitions
    - X-ray powder diffraction (XRPD)
    - Differential Scanning Calorimetry (DSC)
  - Assay & dissolution (powder, non-sink conditions)
  - Accelerated stability (selected formulations; 6 MO 40°C/75% RH)

Spray dryer image courtesy of Buchi.

Apinovex Polymer Case Study: XRPD Results

Back to Start

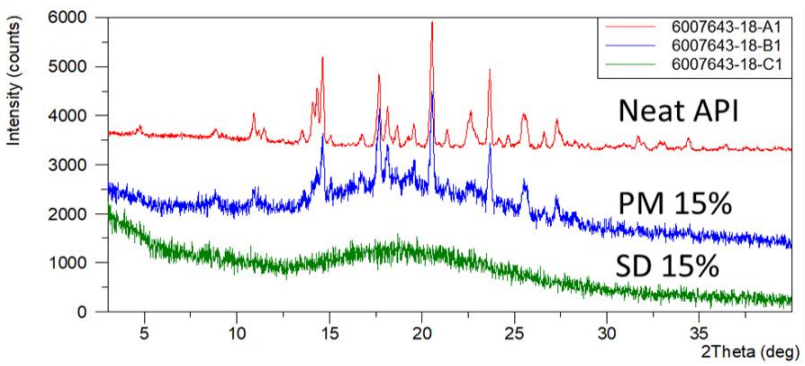
Formulations

Neat Itraconazole
API alone

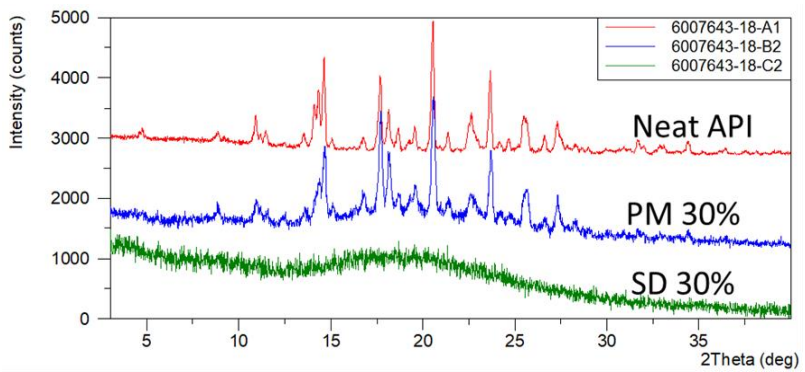
Physical Mixture (PM)
API + Apinovex

Spray-Dried (SD)
API + Apinovex

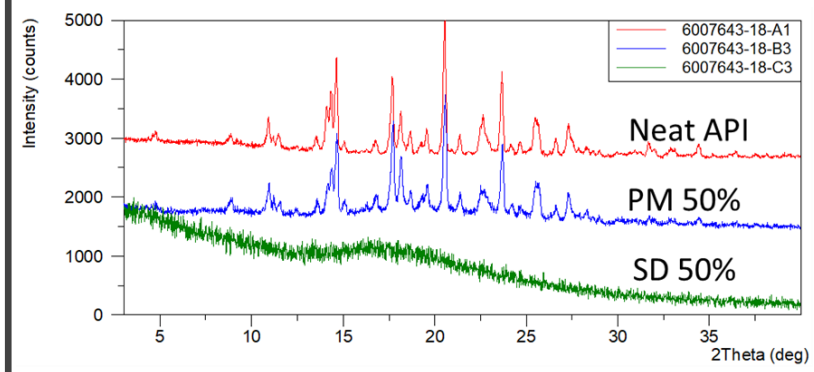
15% API Loading



30% API Loading



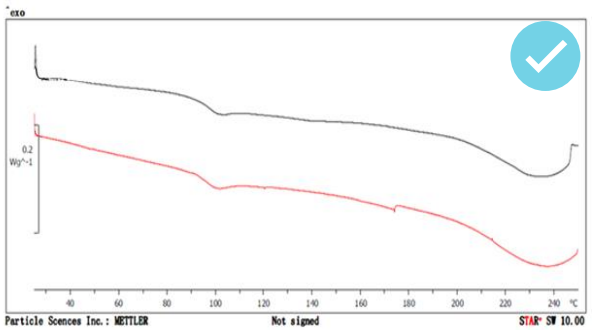
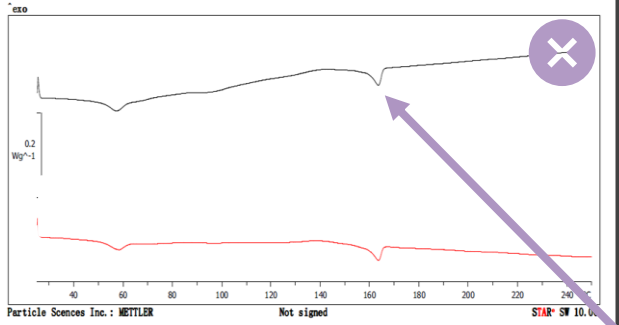
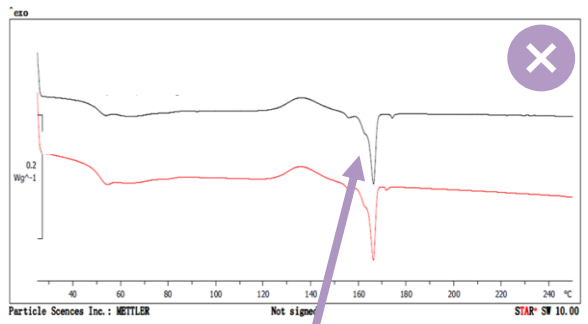
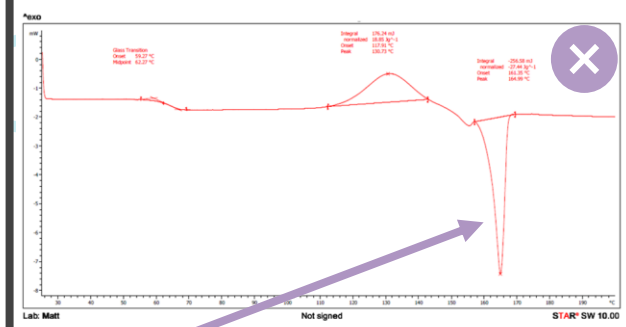
50% API Loading



Amorphous character was successfully achieved via spray drying API/Apinovex™ polymer

Apinovex Polymer Case Study: DSC Results

Back to Start

Apinovex Uniform, stable ASD	**Soluplus, Affinisol, & HPMCAS** Non-uniform ASDs with amorphous-amorphous phase separation		
80% API /Apinovex	80% API / Soluplus	80% API / Affinisol	80% API / HPMCAS LG
			

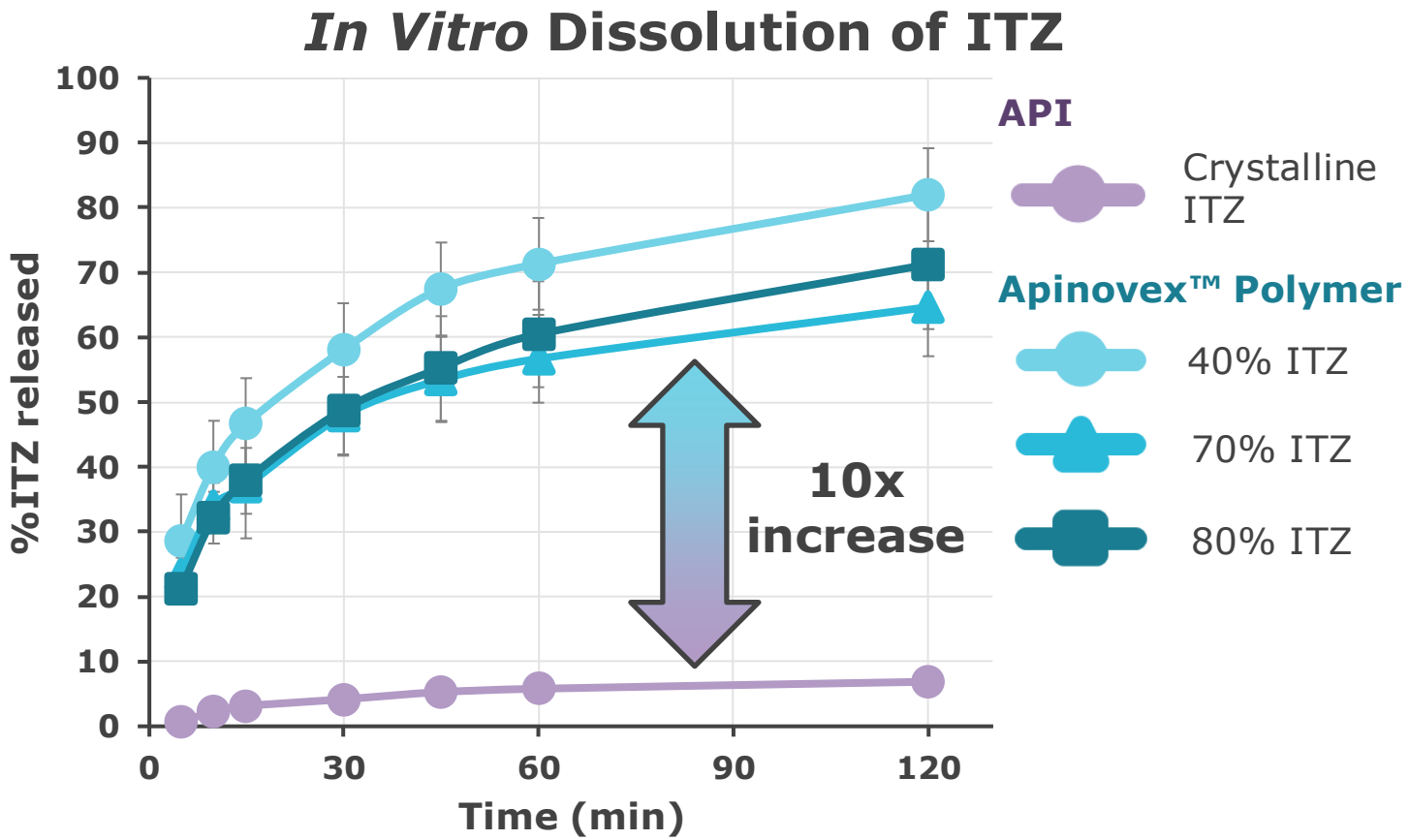
API Melting Peak

Apinovex™ enabled a homogenous amorphous dispersion, even at 80% drug loading

Apinovex Polymer Case Study: Drug Dissolution

Back to Start

- **Increased drug release 10x** relative to crystalline API

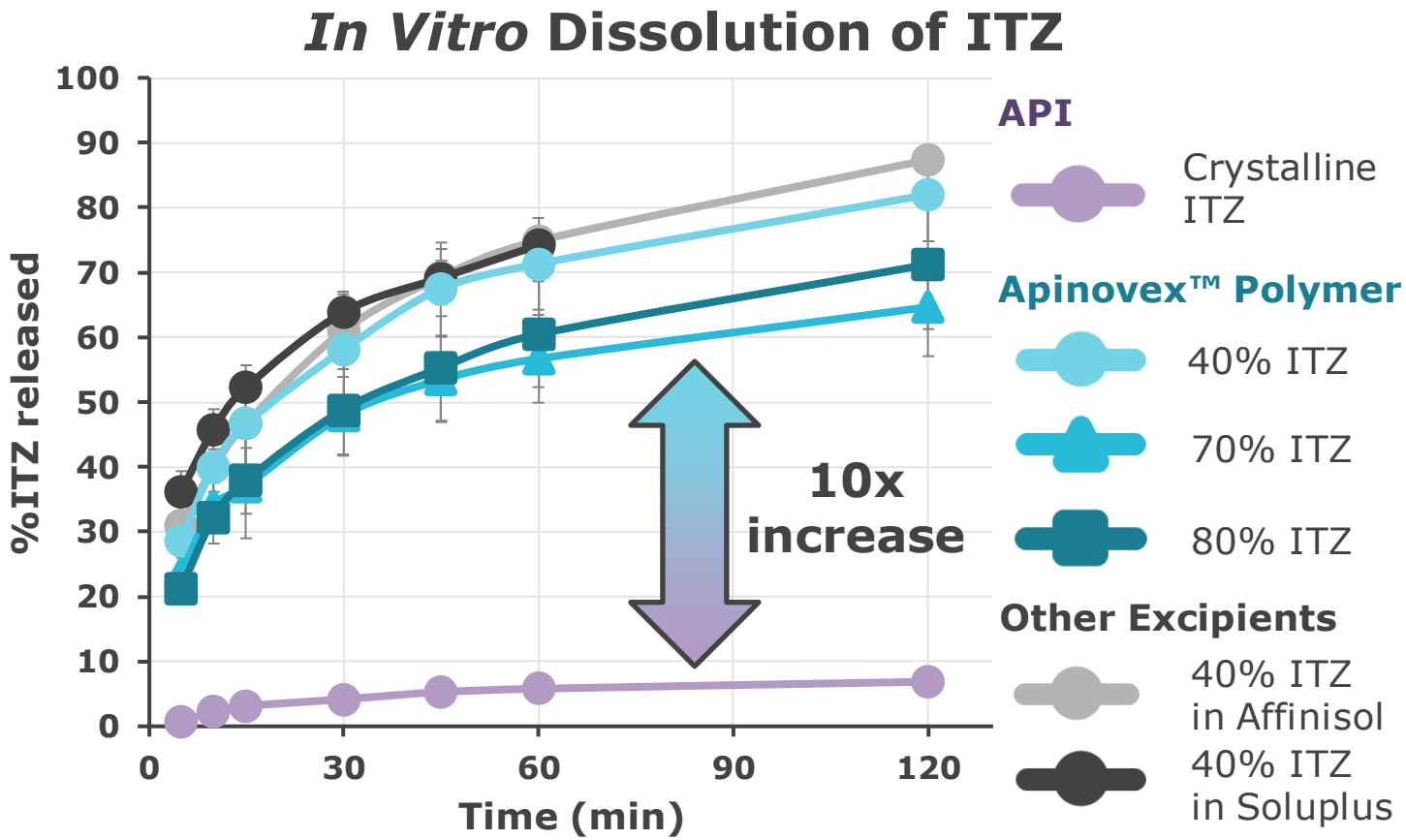


Apinovex™ enabled both **higher drug loading** (up to 80%) and **improved drug dissolution**

Apinovex Polymer Case Study: Drug Dissolution

Back to Start

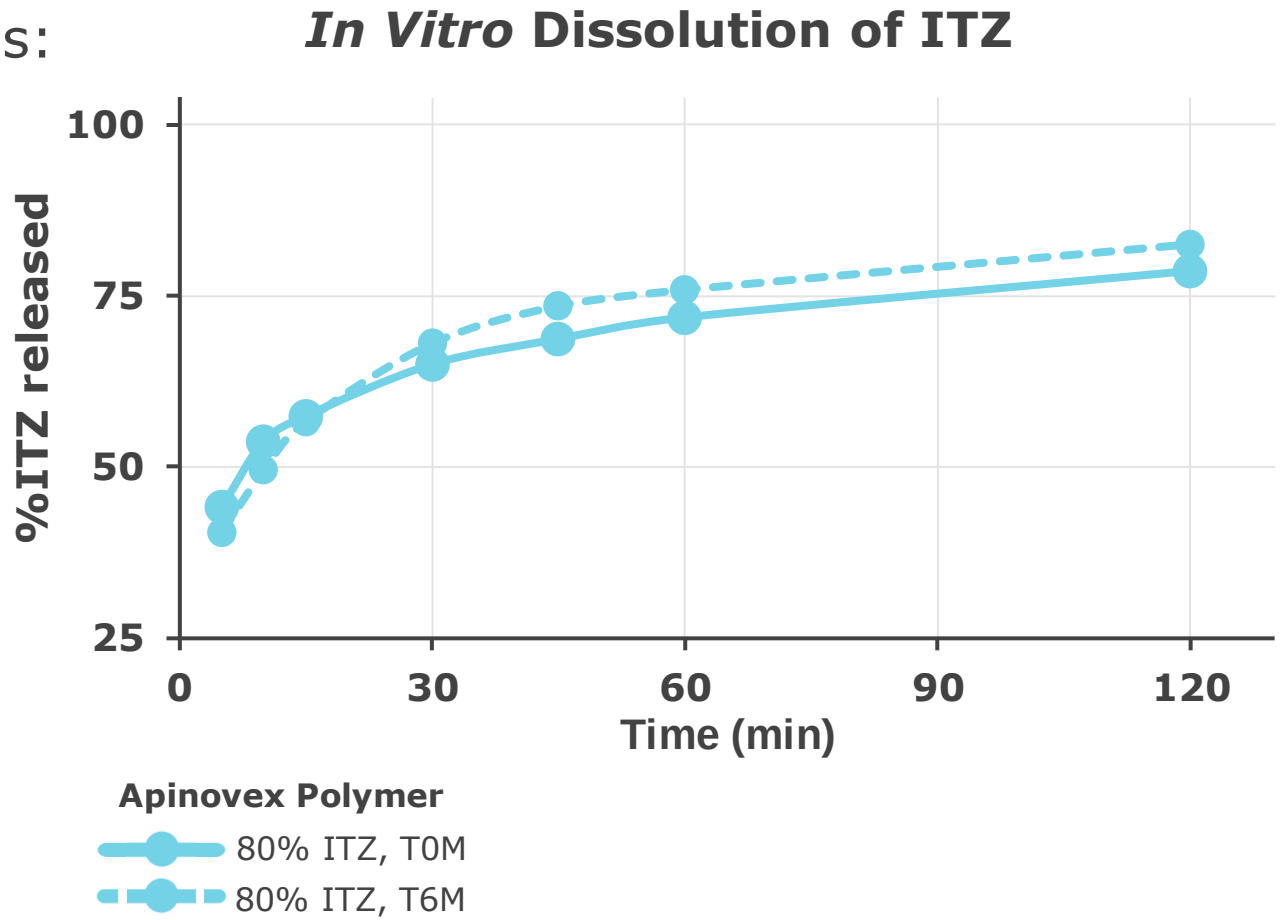
- **Increased drug release 10x** relative to crystalline API
- Achieved **2x drug loading** of commercial excipients
- **Maintained drug release**, even at higher loadings than commercial benchmarks



Apinovex™ enabled both **higher drug loading** (up to 80%) and **improved drug dissolution**

Apinovex Polymer Case Study: Accelerated Stability

- ASDs stored at accelerated conditions: **40°C/75%RH; 6 months**
- **80% ITZ in Apinovex**
  - Amorphous character confirmed with DSC & XRPD
  - No significant change in dissolution rate

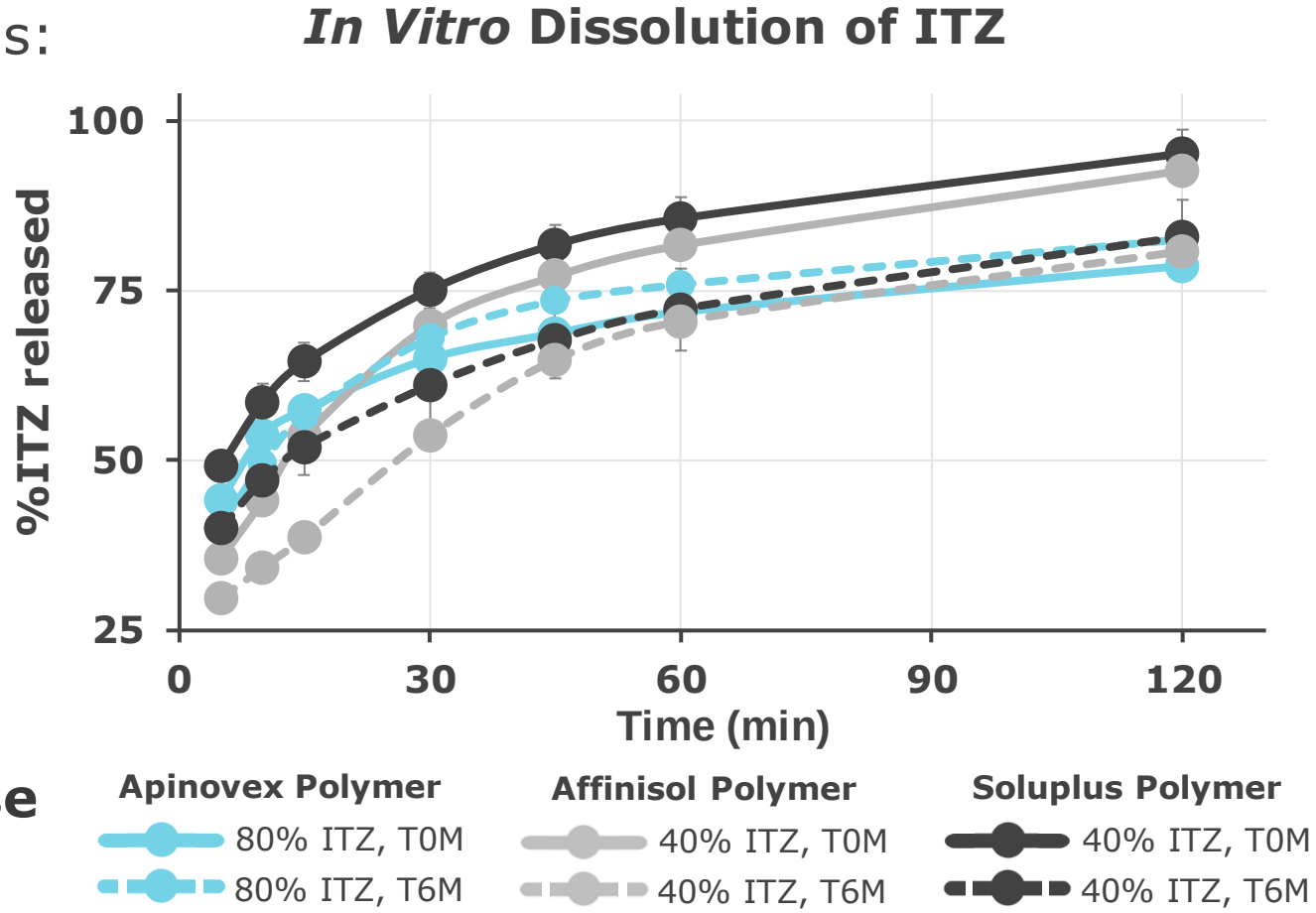


Apinovex™ ASD **maintained properties** after 6 months in accelerated stability

Apinovex Polymer Case Study: Accelerated Stability

Back to Start

- ASDs stored at accelerated conditions: **40°C/75%RH; 6 months**
- **80% ITZ in Apinovex**
  - Amorphous character confirmed with DSC & XRPD
  - No significant change in dissolution rate
- **40% ITZ in Affinisol/Soluplus**
  - Amorphous character confirmed with DSC & XRPD
  - Dissolution data show a **decrease** of drug release at 6 months



Apinovex™ ASD **maintained properties** after 6 months in accelerated stability

Apinovex Polymer Case Study 2: Spray-Dried Ritonavir ASD

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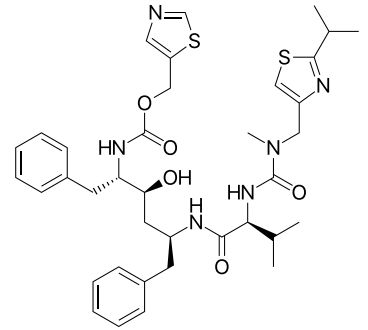
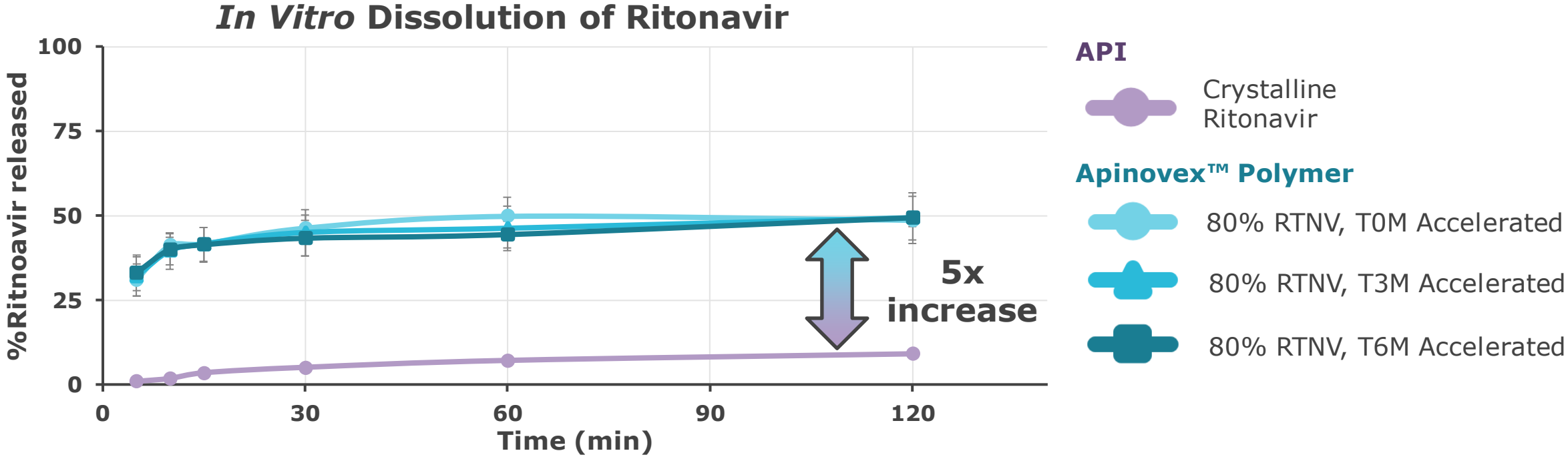


- Prepared ASDs of **80% Ritonavir in Apinovex**
- ASDs stored at accelerated conditions: **40°C/75%RH; 6 months**
- Amorphous character confirmed at **T0, 3, and 6 months** with DSC & XRPD



Apinovex™ polymers enabled **stable, high drug loading (80%) of Ritonavir** with **improved drug dissolution** when compared to crystalline API

https://commons.wikimedia.org/wiki/File:Ritonavir.png

Apinovex Polymers
Manufacturing, Quality, and Safety

Back to Start

- Polyacrylic acid chemistry similar to well-established **Carbopol® polymers**
  - Consistent residual monomer and impurity levels
  - Low residual Class 3 solvent levels **meeting USP <467> limits**
- Precedence of Use
  - Expected to have **limited absorption from gut** based on *in vivo* study in rats *
  - Similar chemistry has precedence in long term human ophthalmic exposure
- Manufacturing Status
  - Large scale **IPEC-GMP** manufacturing conducted successfully
  - **Long term stability study** underway and **Type IV Drug Master File** planned

Apinovex™ polymers are **GMP validated** and expected to be **safe for oral use**

Riley et al. Biomaterials 22, 2001, 1861-1867

Apinovex Polymers
Safety & Toxicology Testing

Back to Start

	Test	Results
Oral systemic	Oral Systemic Toxicity	Acute Oral Toxicity, 14-day observation (rats) (OECD Test Guideline 425)	**Not acutely toxic** (100% survival – LD_{50} >5000 mg/kg BW)
		7-Day Oral Toxicity (rats)	**Well tolerated** at doses as high as 2,000 mg/kg/day
		28-Day Oral Toxicity, 14-day recovery (rats) (OECD Test Guideline 407)	**Well tolerated** with no adverse effect level of 2,000 mg/kg/day
	Pharmacokinetics	Bioanalytical method not able to measure parent/metabolites in rat plasma by LC-MS/MS	Polymers with MW >1,000 Da unlikely to be absorbed by GI tract and not considered a toxicological risk
Genotox	Mutagenicity	AMES "Bacterial Reverse Mutation Test" (OECD Test Guideline 471)	**Non-mutagenic** at doses up to 5,000 µg/plate with and without liver metabolizing system S9
	Chromosome Aberrations	*In Vitro* Micronucleus Test (human lymphocytes) (OECD Test Guideline 487)	**Non-clastogenic / Non-aneugenic** at 2500 µg/mL
Skin/Eye	Skin Irritation / Corrosion	Acute Dermal Irritation/Corrosion (rabbits) (OECD Test Guideline 404)	**Non-irritating to skin** according to GHS criteria very slight, temporary erythema / edema
	Eye Damage / Irritation	Ocular observations/scans for 21 days (rabbits) (EPA OCSPP Series 870.2400)	**Non-irritating to eye** according to GHS criteria
	Skin Sensitization	Buehler Method (guinea pigs) (OECD Test Guideline 406; OCSPP 870.2600)	**Non-sensitizing** according to GHS criteria very slight erythema

Test results as of January 29, 2026

28-Day Oral Toxicity Study in Rats with 2-Week Recovery Phase

Study Design

Back to Start

Group	Dose Level	Dose Concentration	Number of Animals	
	(mg/kg/day)	(mg/mL)	Males	Females
1 (Control)	0	0	15	15
2 (Low)	500	40	10	10
3 (Intermediate)	1000	80	10	10
4 (High)	2000	160	15	15

- Robust study design conducted according to OECD Test Guideline 407 and GLPs
- Main phase (10 rats/sex/group), Recovery phase (5 rats/sex, control + high)
- Limit dose of 2,000 mg/kg/day - highest possible margin of safety, near solubility limit in water

28-Day Oral Toxicity Study in Rats with 2-Week Recovery Phase

Back to Start

Endpoint	Results
Mortality, Clinical Condition & Detailed Physical Exams	No adverse effects
Sensory Reactivity, Grip Strength & Motor Activity	No adverse effects
Absolute Body Weight & Food Consumption	No adverse effects
Ophthalmic exams	No adverse effects
Macropathology	No adverse effects
Clinical Pathology, Organ Weights, Histopathology	No adverse effects

Apinovex™ polymers are **well tolerated in rats at 2000 mg/kg/day for 28 days and safe for oral use**

For a detailed report of toxicity testing, please **contact Nick.DiFranco@lubrizol.com**

Back to Start

Where We Are Today

- **Samples are readily available**, dedicated inventory set up for NA and EU
- Actively **seeking partnerships/ collaborations** with industry and academia
- Examples of molecules currently being tested:
  - Kinase inhibitors
  - PROTACs
  - Blood thinners
  - Antifungals
  - NSAIDs

Ongoing Partnerships

ST. JOHN'S UNIVERSITY

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Results to be shared at
2023 CRS Annual Meeting

Back to Start

Next Steps in 2023

- **New Case Study Data**
  - Additional APIs with varied physicochemical properties
  - Comparisons with additional excipients for ASDs
  - Multimedia and biorelevant dissolution testing
- **Additional Safety/Tox Data**
  - Initiate a chronic *in vivo* study
- **Accelerated and Long-Term Stability Data**
  - Testing on GMP batches is ongoing

HEALTH

Apinovex™ Polymers for Oral Drug Delivery

Back to Start

Stable, high drug loading for spray-dried amorphous solid dispersions

- Drug Formulation Benefits
  - **High loading** (up to 80%)
  - **Significantly improved release profile** relative to crystalline API
  - **Stable** formulations
  - **IP protection*** and 505(b)(2) potential
- Processing Benefits
  - Designed for **spray-drying and solvent-based processes**
  - Soluble in water and **common pharmaceutical solvents**
  - Produces **low viscosity solutions** for ease of processing

Visit **Apinovex.com** to request a sample

*PCT patent application filed WO2021041824A1:
Drug-Polymer Amorphous Solid Dispersions Using Linear Poly(acrylic acid) Polymers

LUBRIZOL LIFE SCIENCE

Thank you!

Back to Start

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HEALTH

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PHARMACEUTICS / MANUFACTURING

NOVEL APPROACHES FOR AMORPHOUS SOLID DISPERSION (ASD) MANUFACTURING

Daniel Davis, AustinPx

CRS 2023

Overview

Introduction

- **AustinPx**
- KinetiSol® **Processing**

Case Study 1 - Mucoadhesion

- **Carbopol 71G Polymer + Itraconazole**

Case Study 2 – Apinovex™ ASDs

- **Studies with Rivaroxaban, Vemurafenib, and Deferasirox**

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CLIENT-CENTRIC CDMO

Helping developers realize the full potential of drug candidates.

CLIENT-CENTRIC CDMO

Complexity Simplified: Effective communication and flexible processes simplify your development path

Flexible & Responsive

Client-centric culture

Systems to support challenging and shifting timelines and requirements

Solutions Driven

Data-driven recommendations and decisions

Solutions oriented team

Open and forthright communications

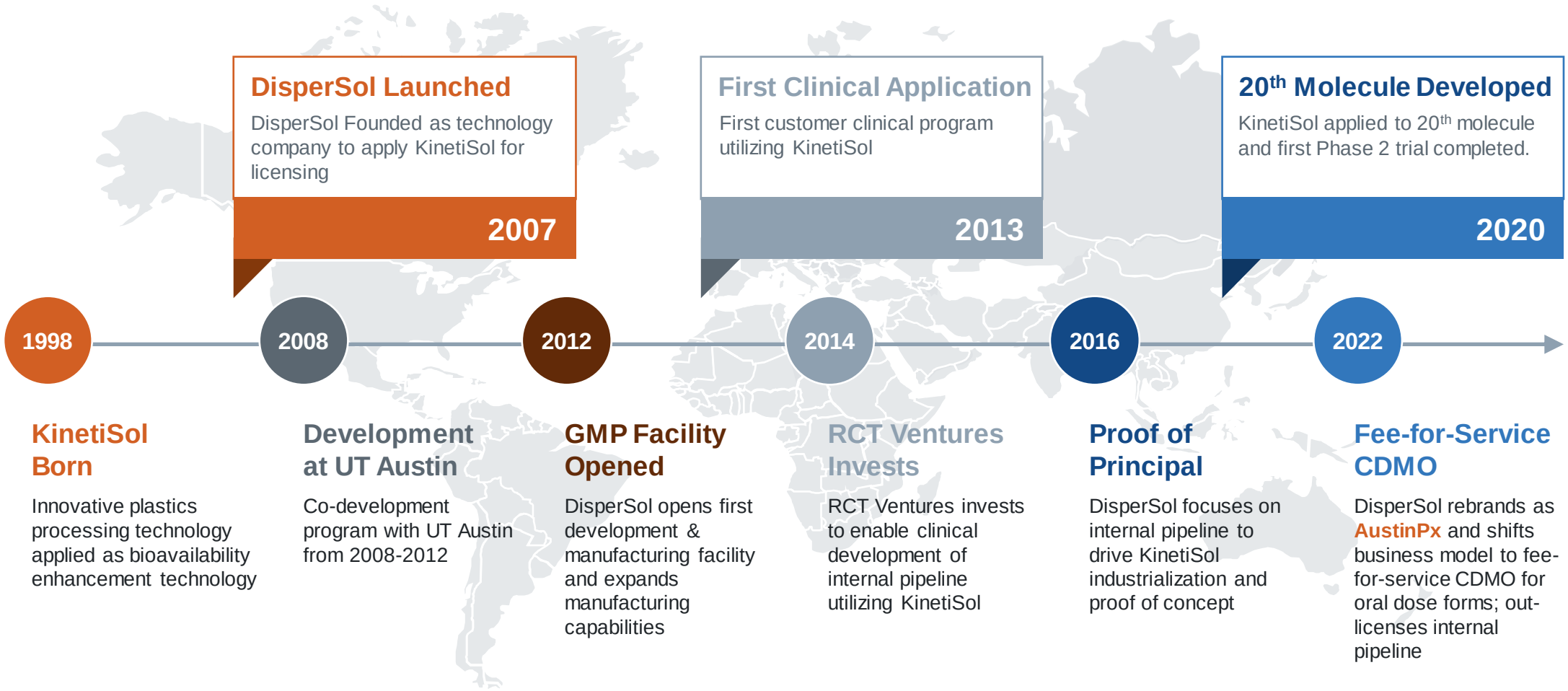
Consultative & Unbiased

Partners in development

Customized and tailored project plans

Platform independent

Proven bioavailability enhancement technology company, with more than 20 years of development expertise



1998 — KinetiSol Born

Innovative plastics processing technology applied as bioavailability enhancement technology

2008 — Development at UT Austin

Co-development program with UT Austin from 2008-2012

2012 — GMP Facility Opened

DisperSol opens first development & manufacturing facility and expands manufacturing capabilities

2014 — RCT Ventures Invests

RCT Ventures invests to enable clinical development of internal pipeline utilizing KinetiSol

2016 — Proof of Principal

DisperSol focuses on internal pipeline to drive KinetiSol industrialization and proof of concept

2022 — Fee-for-Service CDMO

DisperSol rebrands as **AustinPx** and shifts business model to fee-for-service CDMO for oral dose forms; out-licenses internal pipeline

2007 — DisperSol Launched

DisperSol Founded as technology company to apply KinetiSol for licensing

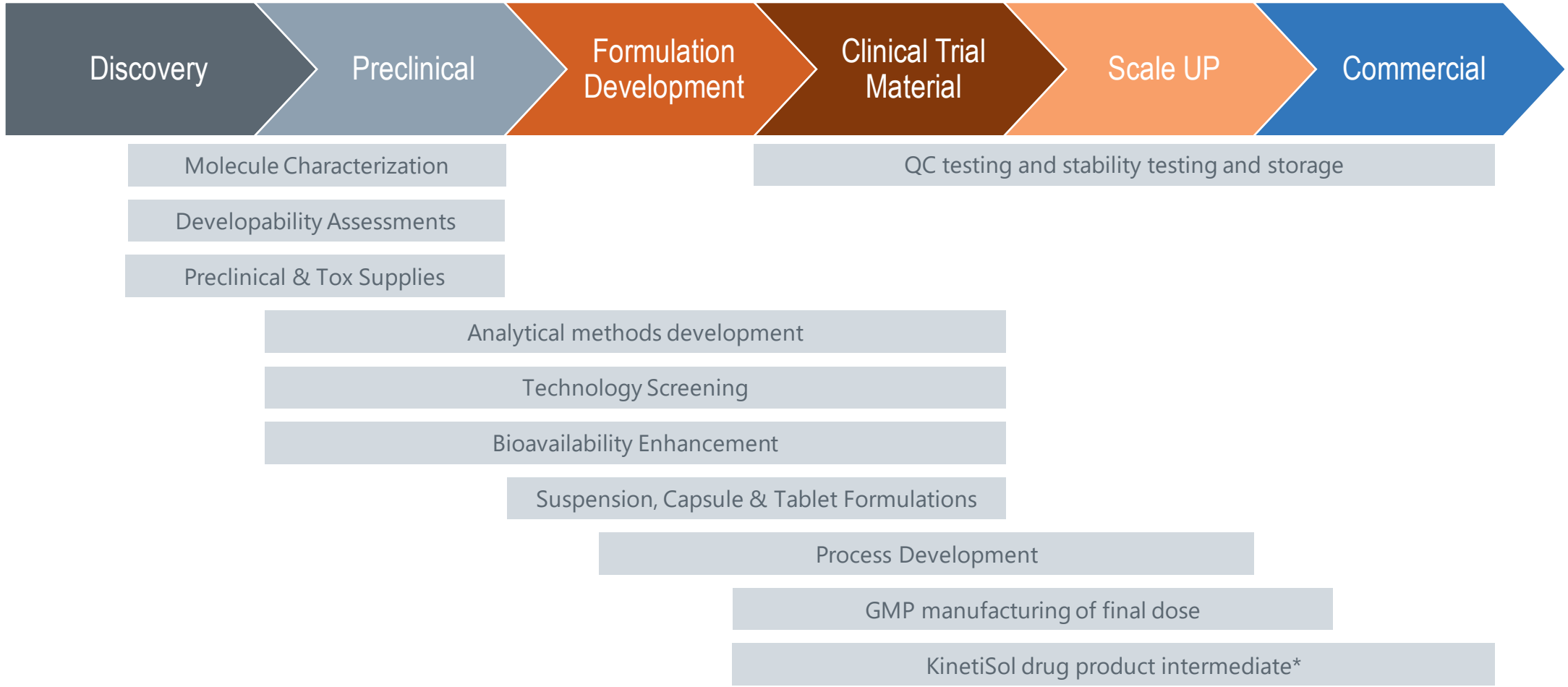
2013 — First Clinical Application

First customer clinical program utilizing KinetiSol

2020 — 20th Molecule Developed

KinetiSol applied to 20th molecule and first Phase 2 trial completed.

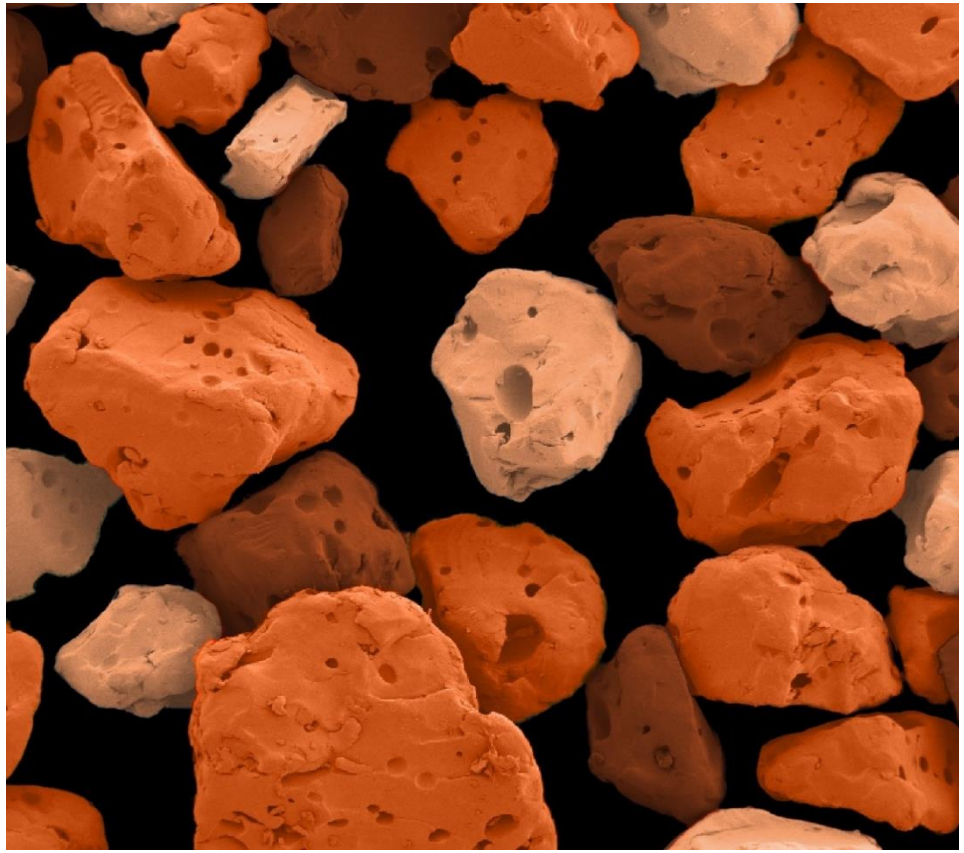
Development & Manufacturing Capabilities



Commercial manufacturing through partnership with Catalent Pharma Solutions

KinetiSol Technology: Next Generation Amorphous Dispersion Technology

Overcomes Challenges of Existing Amorphous Dispersion Technologies



Novel process with strong patent landscape: IP generation (product by process, composition patents)

Opens ASD space to more APIs: Applicable to thermally labile, organic insoluble and high melting point APIs

Faster Development: Rapid processing and change over for faster throughput of prototypes

Lower total cost of ownership: Streamlined scale up (batch mode or continuous processing) and dosage form processing and testing

Environmentally Friendly: Non solvent process and small physical footprint

Superior ASD performance: Complete molecular mixing, improved ASD performance with improved stability, processability, and increased exposure leading to optimized dosage forms

Broader Formulation design space: ASDs using wider range of excipients, including thermally labile, highly viscous, non-thermoplastic and innovative mixtures

KinetiSol Equipment: Research to Commercial Scale

Small Footprint Translates to Lower Operational Cost

Lab-scale KinetiSol Processing Equipment

High throughput formulation screening: Enables rapid and exhaustive ASD screening
Preclinical to small scale GMP (10g - 200g/hr)

Batch or semi-continuous output

Clinical to Commercial GMP: Up to 40kg/hr
PAT integration

CASE STUDY 1

Mucoadhesive Amorphous Solid Dispersions for Sustained Release of Poorly Water Soluble Drugs – **Carbopol® 71G Polymer**

Innovative Application of Carbopol 71G Polymer

PROBLEM

Expansion of the Druggable Space has led to the emergence of heterobifunctional, macrocyclic, peptidomimetic, and brickdust compounds that commonly exhibit low oral bioavailability due to their low permeability, low solubility, and enzymatic degradation.

HYPOTHESIS

Cross-linked poly(acrylic) acids have widely been reported to adhere to mucosal membranes. Creating an amorphous solid dispersion (ASD) utilizing Carbopol 71G will promote mucoadhesion and sustained release of a supersaturated system containing a "brick dust" API to improve bioavailability.

STUDY OBJECTIVES

1. Demonstrate that ASDs are manufacturable containing binary mixtures of Carbopol 71G and the hydrophobic drug itraconazole
2. Demonstrate these ASDs exhibit adhesion *in vitro* to the intestinal mucosa at various drug loadings
3. Demonstrate mucoadhesion and sustained drug delivery *in vivo*.

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Reference: LaFountaine et al. Mucoadhesive amorphous solid dispersions for sustained release of poorly water soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics. 2017.

Study Objective 1

Manufacturability of Binary Carbopol 71G Itraconazole ASDs

- Typical Carbomer Concentrations are in the range of 5-30% and have not been extensively studied as a binary carrier in hot-melt extrusion or spray drying

- KinetiSol processing, which is not practically limited by viscosity, successfully processed Carbopol 71G: itraconazole formulations at 105 °C, ~60 °C below its melting point.

Table 1
Batch compositions of itraconaozle and carbomer.

Batch	Itraconazole (% w/w)	Carbomer (% w/w)
1	10	90
2	20	80
3	30	70
4	40	60

** Potency of all batches averaged between 90% and 100% theoretical label claim (<3% RSD), with no observed process degradation to the API.*

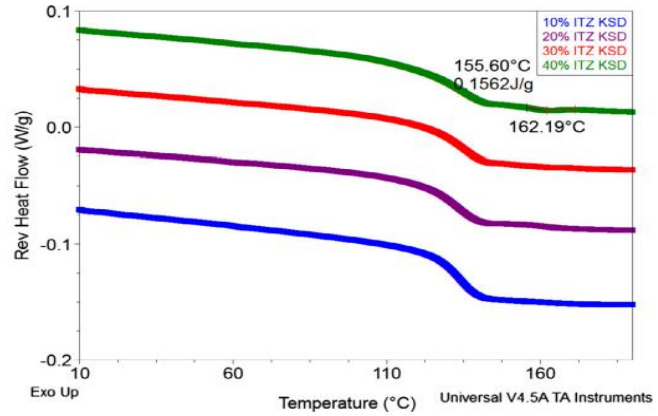

Fig. 3. Modulated differential scanning calorimetry thermograms of processed dispersions with itraconazole:carbomer ratios of 1:9, 1:4, 3:7, and 2:3. In the 40% ITZ KSD sample, the melt endotherm corresponding to itraconazole at ~162 °C is shown, demonstrating residual crystallinity at this higher drug load.

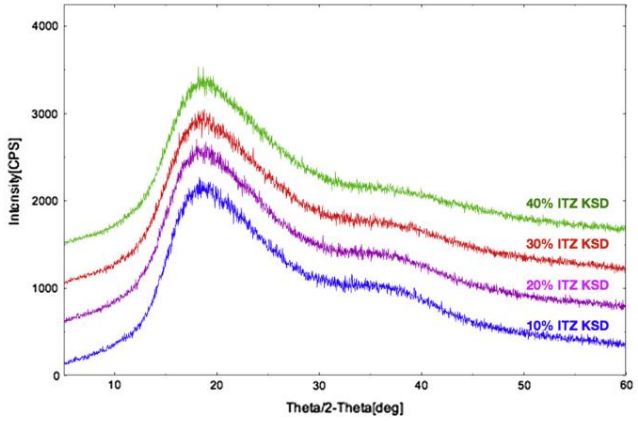

Fig. 2. Powder X-ray diffractograms of processed dispersions with itraconazole:carbomer ratios of 1:9, 1:4, 3:7, and 2:3.

Study Objective 2

Carbopol ASDs exhibit adhesion *in vitro* to intestinal mucosa

- **Mucoadhesion between carbomer and a mucus membrane is primarily driven by interpenetration of polymer chains via diffusion with supplementary non-covalent interactions.**

- **Hydration of the polymer chains within a dosage form is a prerequisite for chain mobility and entanglement. Thus the incorporation of a high drug-load hydrophobic drug was of initial concern, as observed in the contact angle studies that showed poor wettability of the compacts**

- **The *in vitro* mucoadhesion demonstrated that adhesion is preserved relative to pure carbomer, and hydration occurs rapidly relative to biorelevant transport times.**

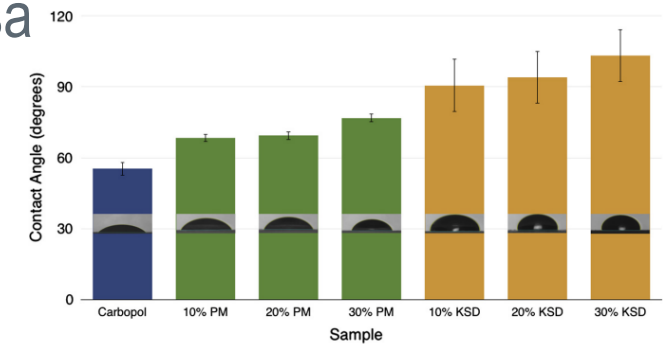

Fig. 4. Contact angle measurements of pure carbomer, physical mixtures of itraconazole and carbomer (10, 20, and 30% drug load), and processed dispersions of itraconazole and carbomer (10, 20, and 30% drug load). A representative contact angle image for each sample is inset to the corresponding sample bar. Bars are mean ± SD (n = 3).

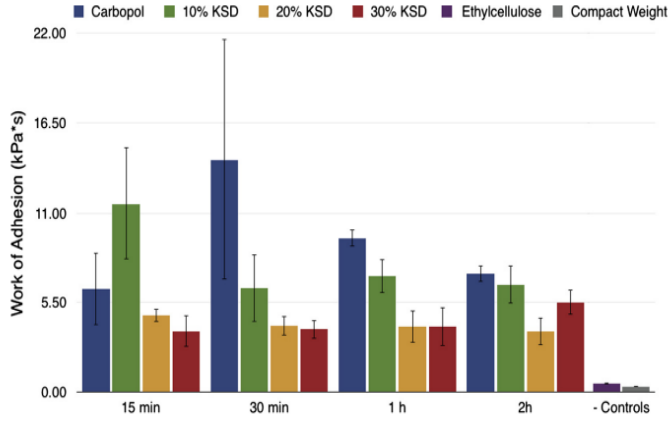

Fig. 5. Work of adhesion between compacts and excised porcine intestinal mucosa for carbomer and processed dispersions (10–30% drug load). Compacts were incubated with intestines in simulated intestinal fluid at 37 °C from 15 min to 2 h. An ethylcellulose compact was incubated for 30 min under similar conditions as a negative control, and a dry compact was lifted from a flat base as a baseline for weight. Bars are mean ± SD (n = 3).

Study Objective 3

Carbopol ASDs exhibited sustained release *in vivo*

- **In Previous studies evaluating mucoadhesive dosage forms, poor adhesion was observed due to the large mass of the dosage form and the effect of shear stresses and mucous turnover; therefore, *minitablets were developed*.**
- **Supersaturation maintenance of the carbomer dosage form was not the primary object, and 30% drug loading was selected for minitablet development.**
- **In addition to uncoated minitablets, ethylcellulose (an insoluble, impermeable polymer) coatings were applied to all but one face of minitablets to promote unidirectionally transport and decrease overall hydration.**

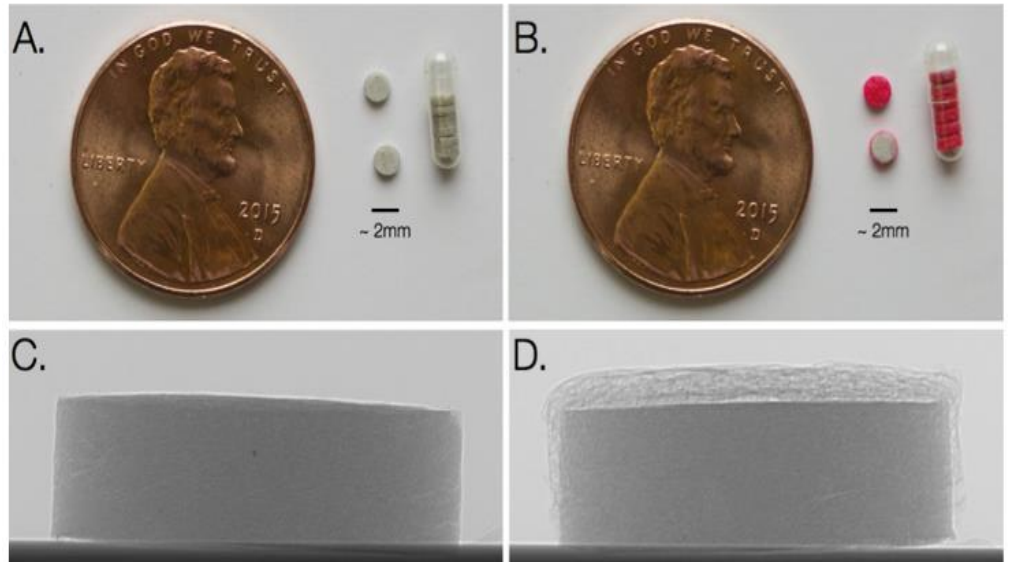

Fig. 7. Digital images of (A) uncoated tablets and (B) coated tablets in reference to a penny and filled (n = 6) into a size 9 capsule. X-ray Computed Tomography cross-section images of (C) uncoated and (D) coated tablets.

Study Objective 3

Carbopol ASDs exhibited sustained release *in vivo*

- **In vitro concentration-time profiles for the uncoated and ethylcellulose (EC)-coated minitablets demonstrated a sustained release profile over 6 hours. The rate and extent of release were greater for the uncoated minitablet, which could swell and hydrate more rapidly.**

- ***In vivo* studies demonstrated the ability of Carbopol ASDs to achieve sustained release; additionally, the rank order between the uncoated and coated minitablets was consistent with the *in vitro study*.**

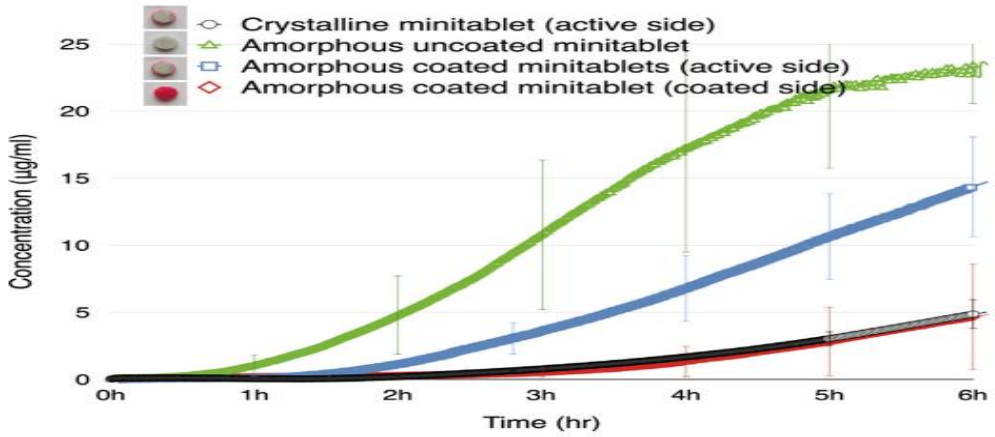

Fig. 8. Single tablet face dissolution profiles of crystalline EC-coated minitablets (n = 3), amorphous uncoated minitablets (n = 2), amorphous EC-coated minitablets, active side (n = 3), and amorphous EC-coated minitablets coated side, (n = 3). Error bars are ±SD and shown only every hour for clarity. Representative photos of test side of tablet shown for illustrative purposes.

Table 4
In vitro minitablet dissolution study results.

	Dissolution rate (10^{-6} g cm^{-2} min^{-1})	AUC_{0-360m} (10^{-6} g h mL^{-1})
Uncoated amorphous minitablets	23.00 ± 9.7 (120–240 min)	4001 ± 1447
EC-coated amorphous minitablets (active side)	21.99 ± 7.36 (200–300 min)	2324 ± 439
EC-coated amorphous minitablets (EC-coated side)	6.04 ± 5.18 (200–300 min)	708 ± 603
EC-coated crystalline minitablets (active side)	4.22 ± 1.18 (200–300 min)	482 ± 61

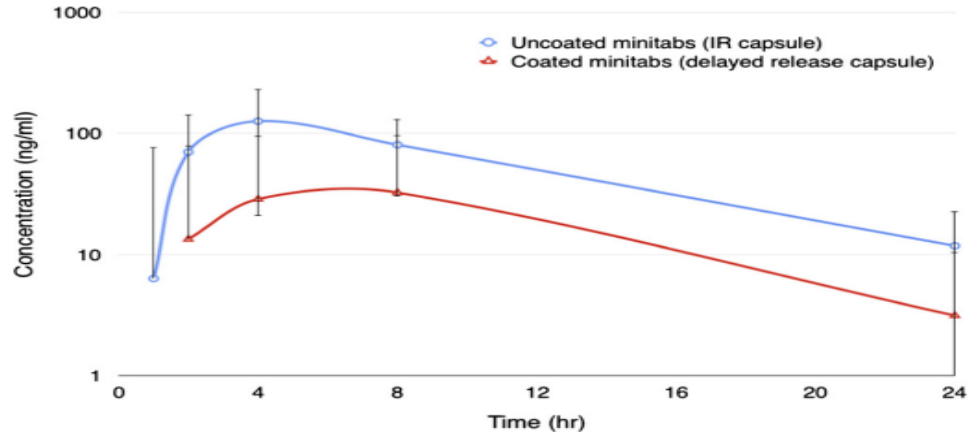

Fig. 9. Plasma concentration time profiles in rats (n = 6 per test article) of uncoated minitablets and EC-coated minitablets, delivered in size 9 capsules. Capsules containing EC-coated minitablets were enteric coated for delayed release in the small intestine.

Table 5
Pharmacokinetic parameters.

Dosage form	Dosing vehicle	Cmax (10^{-9} g ml^{-1})	Tmax (h)	AUC_{0-24} (10^{-9} h kg g ml^{-1} mg^{-1})
Uncoated minitablets	IR capsule	148.0 ± 68.9	4.00 ± 2.19	90.4 ± 48.7
EC-coated minitablets	Delayed release capsule	48.1 ± 44.4	4.67 ± 2.73	28.4 ± 30.9

Study Objective 3

Carbopol ASDs Exhibited Mucoadhesion *in v*

- **For the EC-coated minitablets delivered in an enteric-coated capsule, satellite groups of rats were utilized to investigate mucoadhesion**
- **At 30 minutes and 1 hour post-dose, rats were sacrificed, and minitablets were found contained in intact enteric-coated capsules within the stomach of each rat.**
- **At 2-hour and 4-hour post-dose, minitablets were found released from the capsule in the more distal region of the small intestines.**
- **Additionally, for all minitablets identified, the tablet's mucoadhesive face (non-EC-coated face) was adhered to intestinal mucosa.**

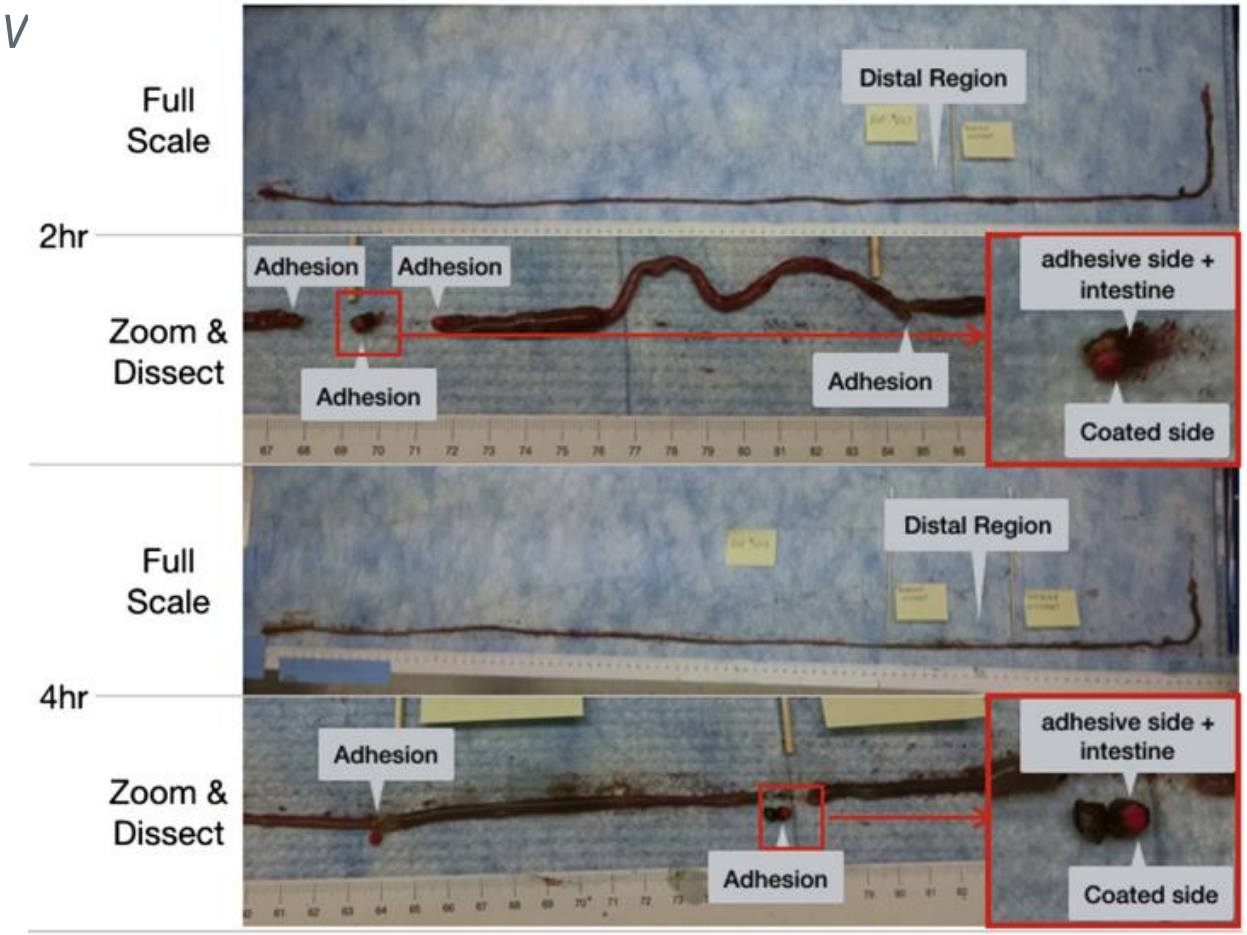

Fig. 11. Representative necropsy images 2-h and 4-h post-dosing of enteric coated capsules containing coated EC-coated minitablets. The minitablets were released from the capsule in the more distal region of the small intestine of the rat and adhered to the intestine.

Innovative Application of Carbopol 71G Polymer

Study Summary

KINETISOL ENABLES A BINARY ASD WITH CARBOPOL 71G

KinetiSol processing enabled the formation of binary ASD compositions of itraconazole and Carbopol 71G from 10-30% drug loadings.

ASD DEMONSTRATES ADHESION *IN VITRO* AND *IN VIVO*

In Vitro testing demonstrated adhesion to excised porcine intestinal mucosa, which was predictive of the mucoadhesion observed *in vivo* at the 30% drug loading.

CARBOPOL 71G ASD EXHIBITS SUSTAINED RELEASE IN VIVO

The mucoadhesive properties, in combination with the formulation's release properties, resulted in sustained delivery of itraconazole *in vivo.*

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Reference: LaFountaine et al. Mucoadhesive amorphous solid dispersions for sustained release of poorly water soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics. 2017.

CASE STUDY 2

Apinovex Amorphous Solid Dispersions Generated by KinetiSol Processing – Examples with Vemurafenib, Deferasirox, Rivaroxaban

Evaluating Apinovex and KinetiSol Processing

A Series of Case Studies with Apinovex and KinetiSol

STUDY 1
RIVAROXABAN

Commercialized crystalline tablet marketed as XARELTO®, dosed once daily with variable absorption, leading to adverse side effects. High melting point, low solubility with large food effect, neutral compound.

STUDY 2
VEMURAFENIB

Commercialized ASD marketed as ZELBORAF® manufactured by micro-precipitated bulk powder (MBP) developed by Roche to overcome high melting point and poor organic solubility

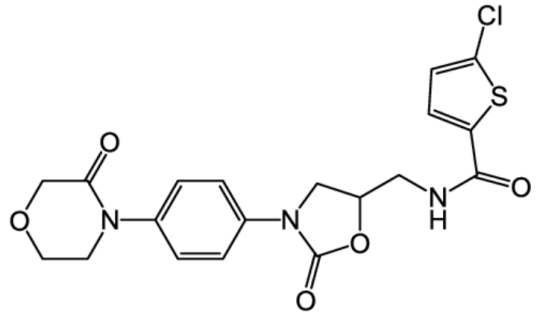
STUDY 3
DEFERASIROX

Commercialized crystalline tablet, marketed as EXJADE® and JADENU®, that suffers from inadequate response in ~30% of patients. Weakly acidic API that is challenging to manufacture as an ASD due to high melting point and poor organic solubility

Study 1: Rivaroxaban

Product Introduction

- **Rivaroxaban doses of 15 and 20mg are taken with food as they are incompletely absorbed.**
  - Taking the 20mg dose with food leads to a significant increase in mean AUC by 39% and Cmax by 76%
- **Potential to decrease gastrointestinal bleeding by decreasing the amount of unabsorbed drug**
- **An enabling formulation (e.g., ASD) may eliminate the food effect and decrease the maximum dose, minimizing gastric side effects.**
- **Challenging product to formulate due to high melting point of 230 °C.**



Property	Value
Molecular Weight (MW)	435.88 g/mol
BCS	Class II
Acid/Base	Neutral
LogP	1.5
Dose	10-20mg QD
Water Solubliity	~ 5 ug/mL
FaSSIF	~10 ug/mL
Melting Point	230 °C
Chiral	S-Enantiomer Active

Apinovex Rivaroxaban ASD

KSD comparison in various polymers

- **KinetiSol attempts were performed in 7 different polymers, including Apinovex, at a 10gram scale and all ejected at the same conditions.**

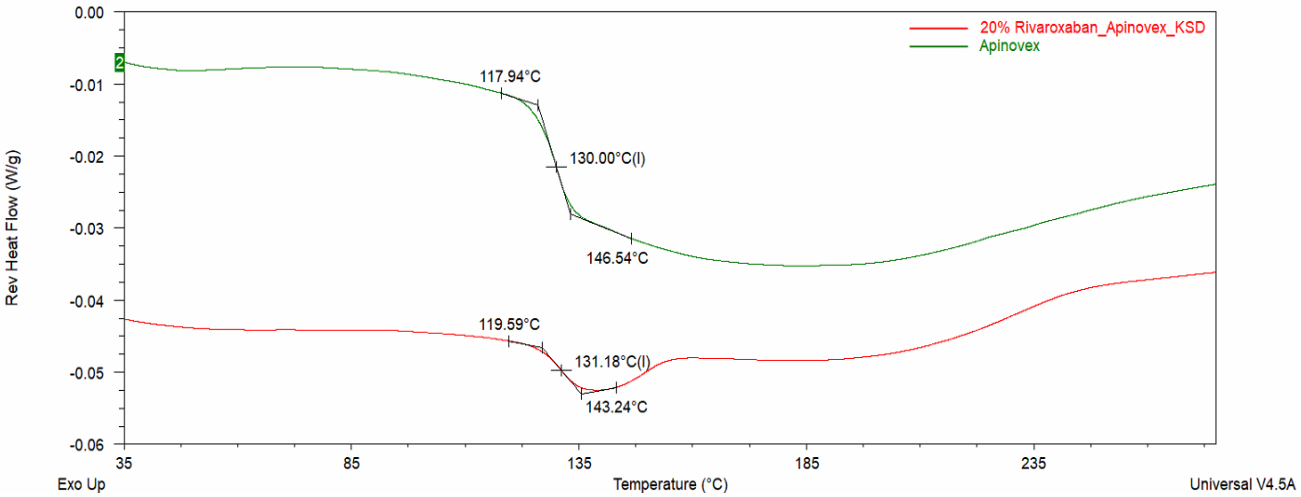
- **Apinovex demonstrated it's amendable to the KinetiSol process and produced an acceptable level of impurities for this phase of development and can be further mitigated with process optimization**

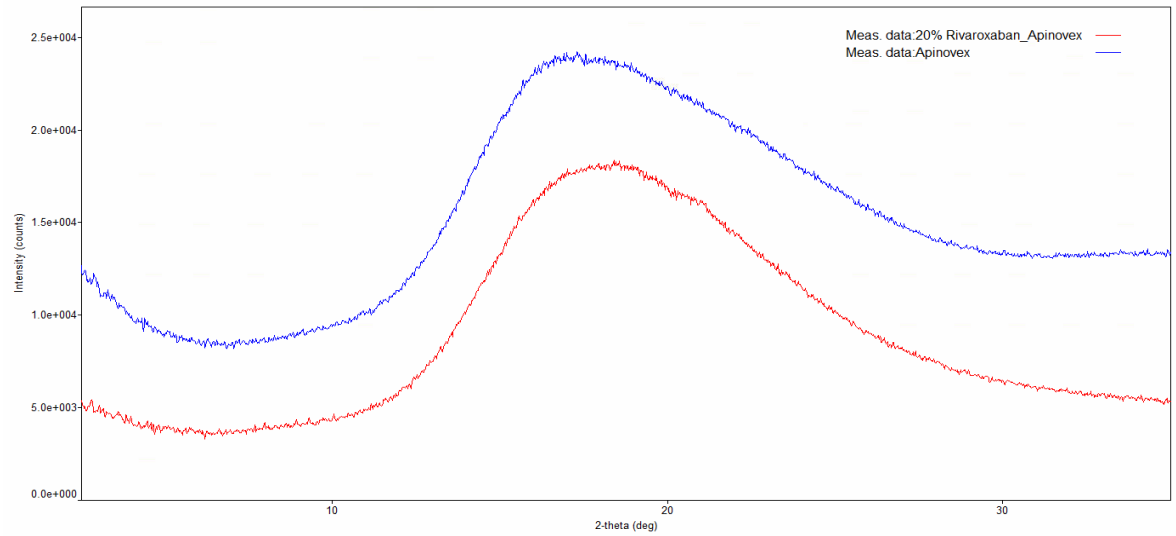
Lot No	API	Drug Loading (%)	Polymer	Ejection Temperature (C)	Impurities >0.05 (%)	Major Impurity / RRT (%/RRT)	Amorphous (pXRD)	Potency	API Melting Point (C)
22-003-43-1-1	Rivaroxaban	20	HPMCAS-LMP	160	0.56	0.32%/RRT 0.64	Amorphous	97.8	230
22-003-43-3-3	Rivaroxaban	20	MAE 100-55	160	2.05	0.83%/RRT 0.60	Amorphous	92.4	230
22-003-44-2-1	Rivaroxaban	20	PVP-K30	160	1.47	0.58%/RRT 0.64	Amorphous	98.4	230
22-003-44-3-1	Rivaroxaban	20	HPMC E3	160	0.16	0.13%RRT/0.64	Amorphous	N/A	230
22-003-43-4-3	Rivaroxaban	20	Copovidone	160	0.35	0.07%/RRT 0.54	Amorphous	106%	230
22-003-44-1-3	Rivaroxaban	20	Soluplus	160	0.21	0.09%/RRT 0.64	Amorphous	100%	230
22-003-85-1-1	**Rivaroxaban**	**20**	**Apinovex**	**160**	**1.65**	**0.83%/RRT 0.60**	**Amorphous**	**93%**	**230**

Apinovex Rivaroxaban ASD

mDSC and pXRD Characterization

- Apinovex successfully formed an amorphous solid dispersion by KinetiSol Processing with Apixaban
- Reported Tg of Apinovex is 128-130C, mDSC analysis of the neat polymer agrees.
- PXRD and mDSC both demonstrate the KinetiSol processed Rivaroxaban-Apinovex formulation is amorphous.



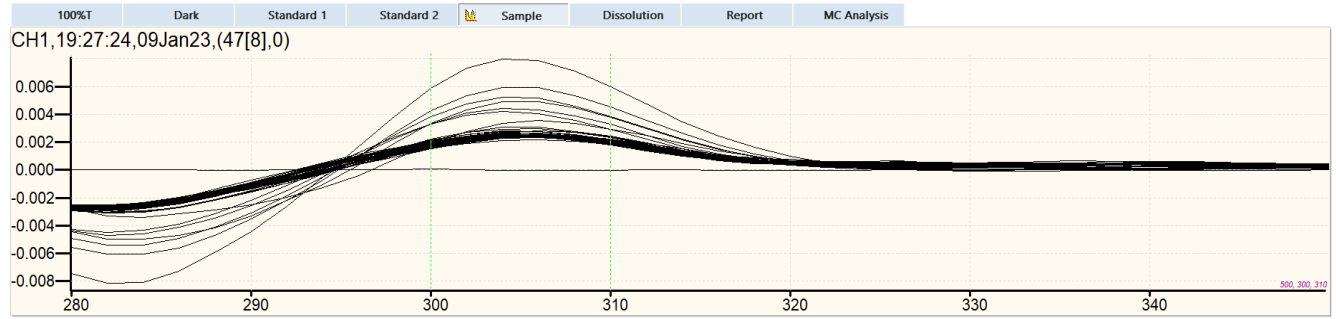


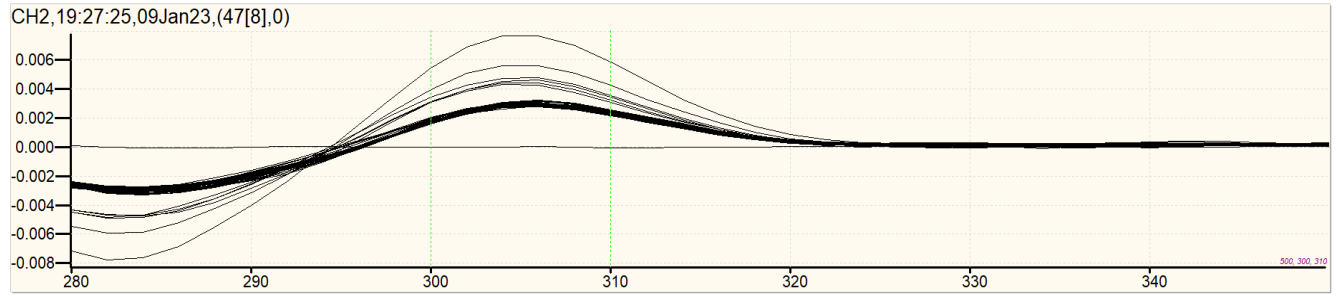
Apinovex Rivaroxaban ASD

Dissolution Characterization

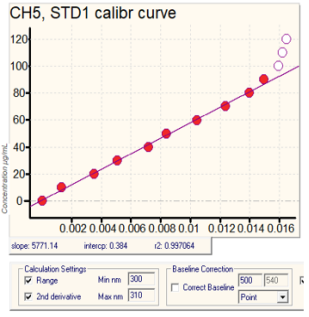
Apinovex immediately springs the API into solution; the polymer is cloudy in the acidic phase and after the pH transition in the neutral phase.

Despite the turbidity, Rivaroxaban measurements did not undergo shifting, and the analysis was uncomplicated.

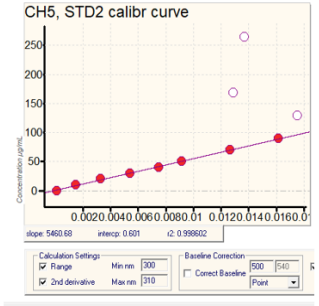




- Analysis Range:
  - pH 2.0 acid: 2nd Derivative from 300-310nm, linear from 0-100ug/mL
  - pH 6.8 FaSSIF: 2nd Derivative 300-310 for pH 6.8 FaSSIF, linear from 0-100 ug/mL



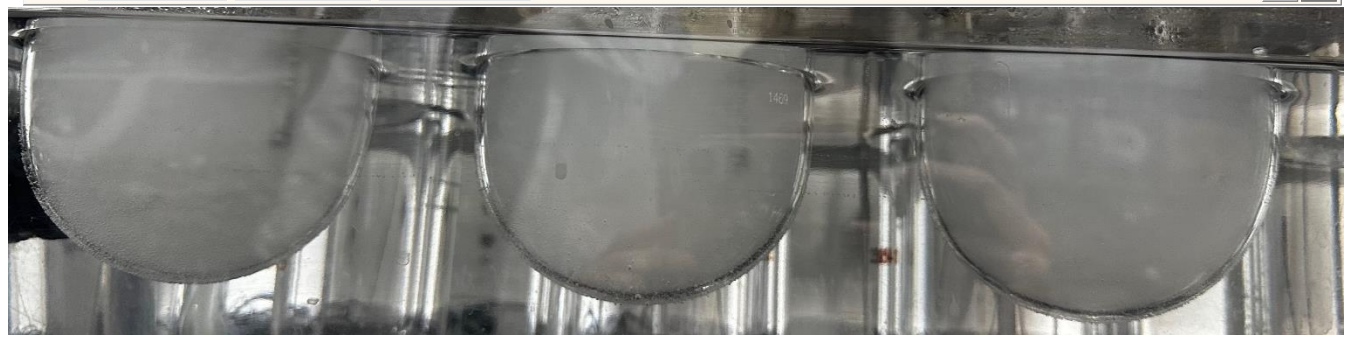
pH 2.0 Cal Curve



pH 6.8 FaSSIF Cal Curve

USP Type II Dissolution

- 240mL pH 2.0 Acid transitioned at 30 minutes with 160mL of pH 7.25 concentrated FaSSIF, to create 400mL of pH 6.8 FaSSIF. Samples are stirred at 100 RPM. Duration of 4 hours.
- 2.5% DL Sample mass: 4 grams
- 20% DL Sample Mass: 500mg



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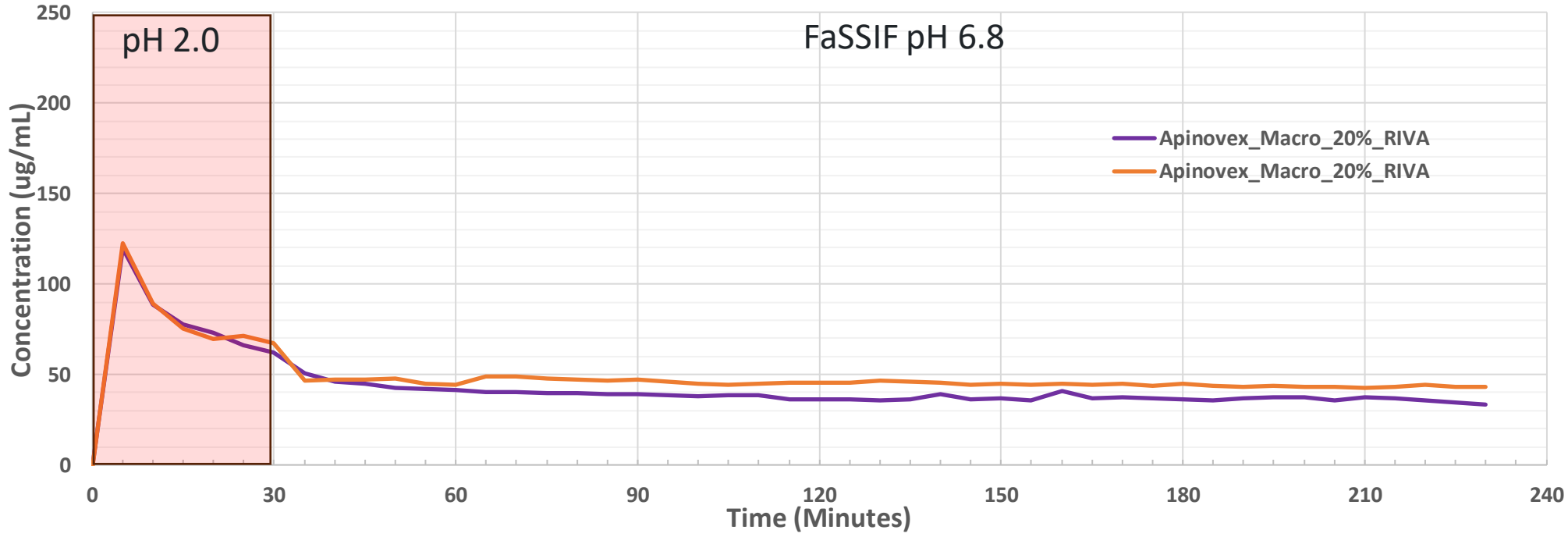
Apinovex Rivaroxaban ASD

Dissolution Characterization

Apinovex allowed for maximum release of rivaroxaban within the first 5 minutes of dissolution, followed by a decrease and stabilization after the pH-transition



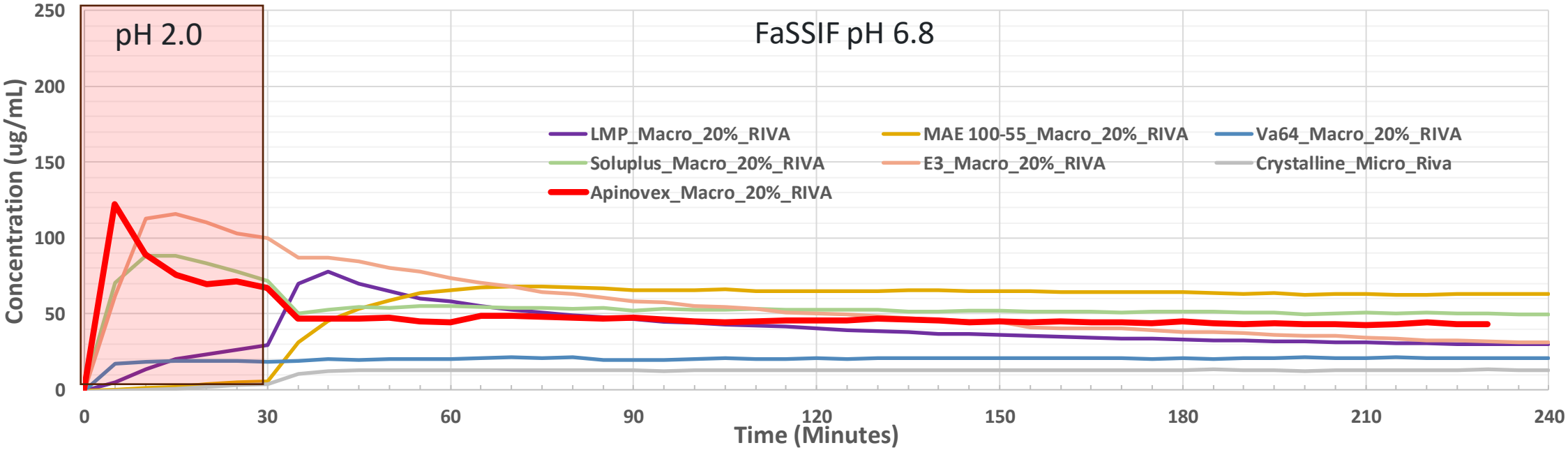
Conditions: 1mm tips, 5-minute sampling interval for 4 hours, pH shift 2.0 at 30 min to pH 6.8 FaSSIF, stir-speed 100 RPM
Analysis Range: 300-310nm, 2nd Derivative, identical for both media

Apinovex Rivaroxaban ASD

Dissolution Comparison

To benchmark Apinovex's performance, the formulation was compared against other commonly used polymers used to formulate ASDs and the crystalline API.

Apinovex performed similarly to other neutral polymers in acidic media and FaSSIF conditions.



Conditions: 1mm tips, 5-minute sampling interval for 4 hours, pH shift 2.0 at 30 min to pH 6.8 FaSSIF, stir-speed 100 RPM
Analysis Range: 300-310nm, 2nd Derivative, identical for both media

Study 2: Vemurafenib

Vemurafenib Limited Polymer Selection with MBP

Treatment for malignant melanoma (B-Raf inhibitor)

Vemurafenib is water insoluble, high melt (>270 °C), not soluble in volatile organics

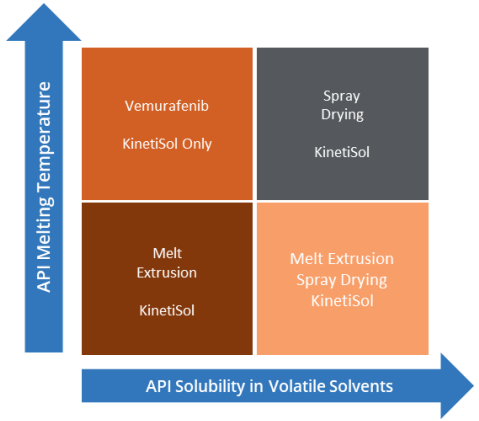
Undevelopable without ASD enablement

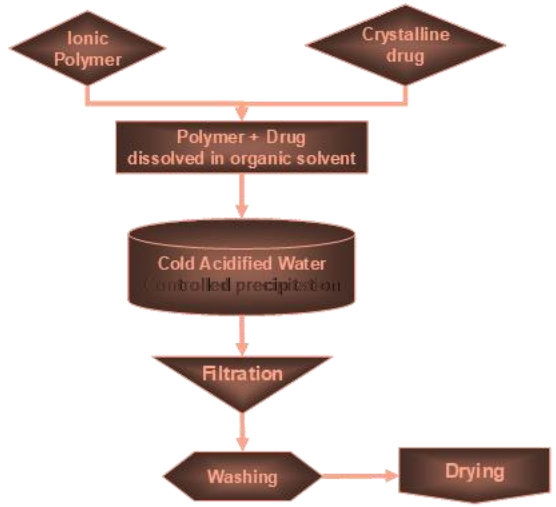
Can't spray dry or melt extrude

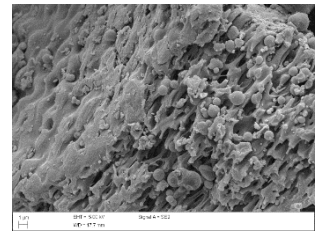
Solvent/antisolvent precipitation was a last-resort option.

A complicated process with substantial water/DMA waste stream

Downstream processing involves secondary drying and roller compaction before tableting



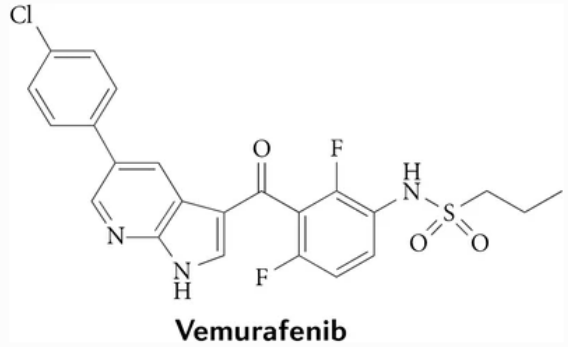




Apinovex and Vemurafenib are Compatible

KinetiSol Processing Summary

- KinetiSol Processing was employed to process vemurafenib with Apinovex, using a 10-gram batch size at a 20% Drug Load.
- KinetiSol processing Vemurafenib generated 0.81% Impurities and achieved an assay of 93%
- Further optimization of processing parameters is planned to further reduce impurities and increase drug loading.



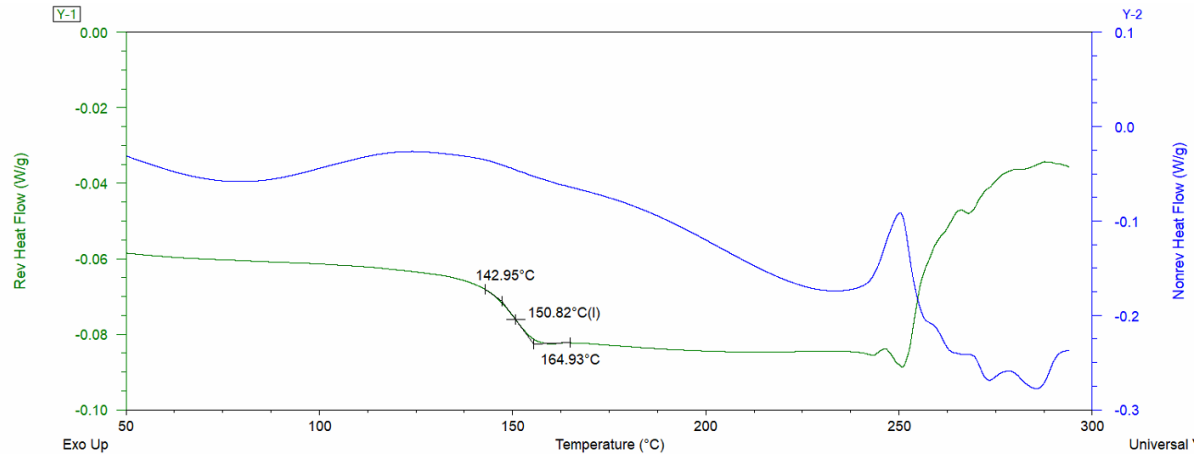
Vemurafenib

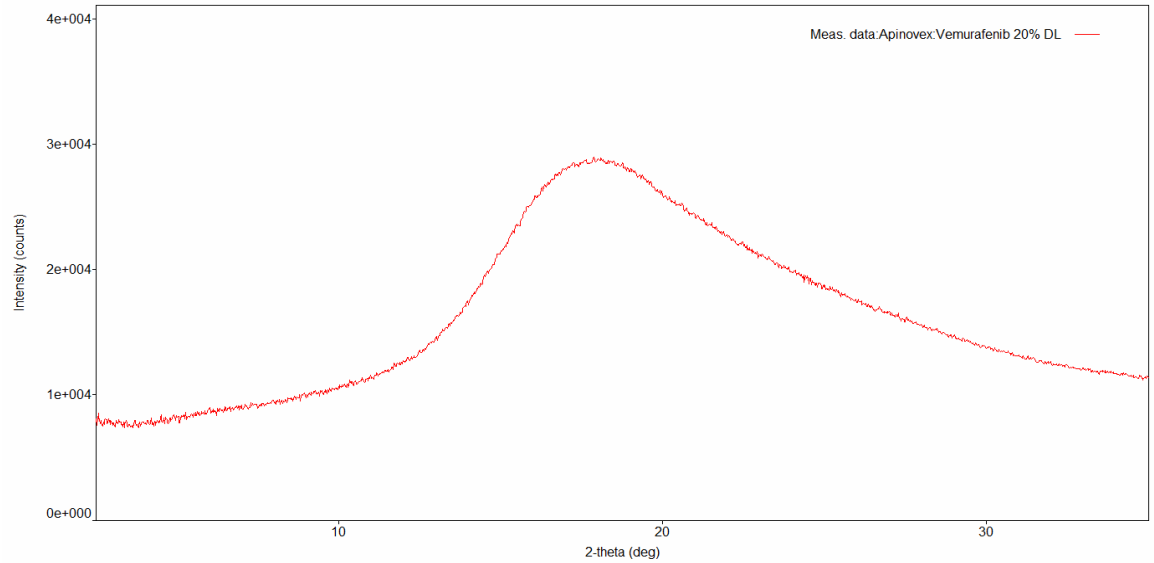
Property	Value
Molecular Weight (MW)	489.33 g/mol
Acid/Base	Neutral
pKa	Not Detected
LogP	3.0
Dose	960mg BID
Aqueous buffers (pH 3 & 5)	< 0.1 ug/mL
FaSSIF	< 2 ug/mL
Melting Point	272 °C

Study 2: Vemurafenib

Amorphous Characterization

- Apinovex demonstrated it was miscible with vemurafenib at a 20% drug loading, despite the API having a melting point of 272 °C
- The 20% DL formulation produced a single-phase ASD with a high glass transition temperature of 151 °C
- pXRD confirms the formulation's amorphous nature; mDSC data is convoluted above 250 °C
- Additional development is being performed similarly to the rivaroxaban study to assess Apinovex performance relative to other commonly used polymers in ASDs





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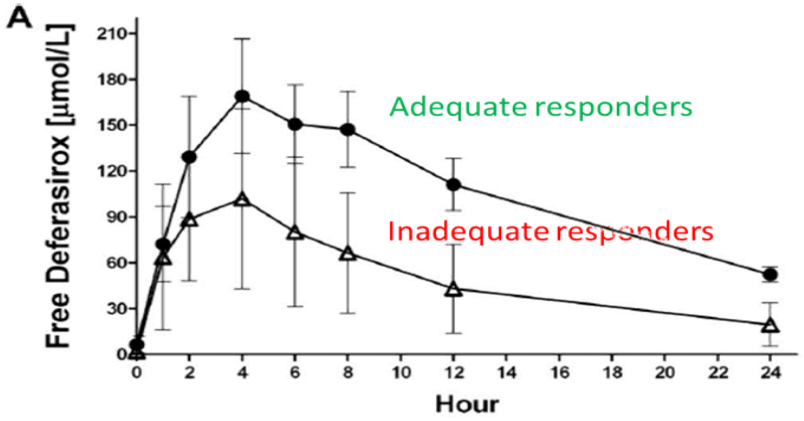
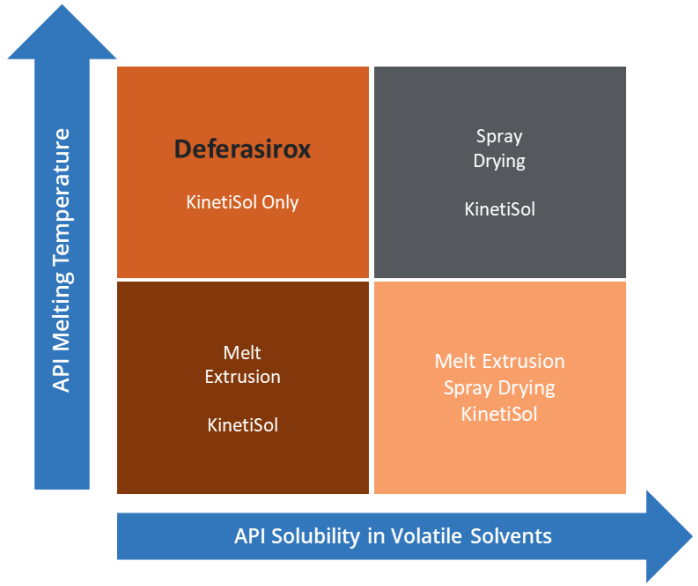
Study 3: Deferasirox

Suboptimal Formulation Limits Efficacy

Deferasirox PK Analysis in Patients



From: Chirnomas et al. Blood, 5 Nov. 2009, Vol. 114, No. 19



30% of patients are inadequate responders due to low bioavailability from conventional crystalline tablet

Poor BA due to:

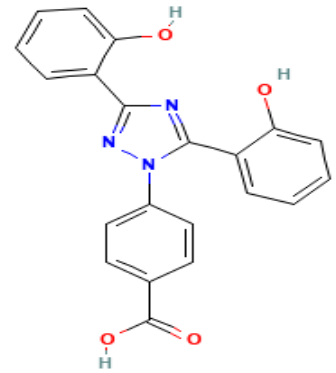
- pH dependence and poor solubility
- High oral doses, up to 40mg/kg

Improved formulation is needed to extend DFX therapy to inadequate responders

ASD required, but HME and SD are not applicable due to high melting point (265°C) and poor organic solvent solubility

Apinovex and Deferasirox are Compatible

KinetiSol Processing Summary



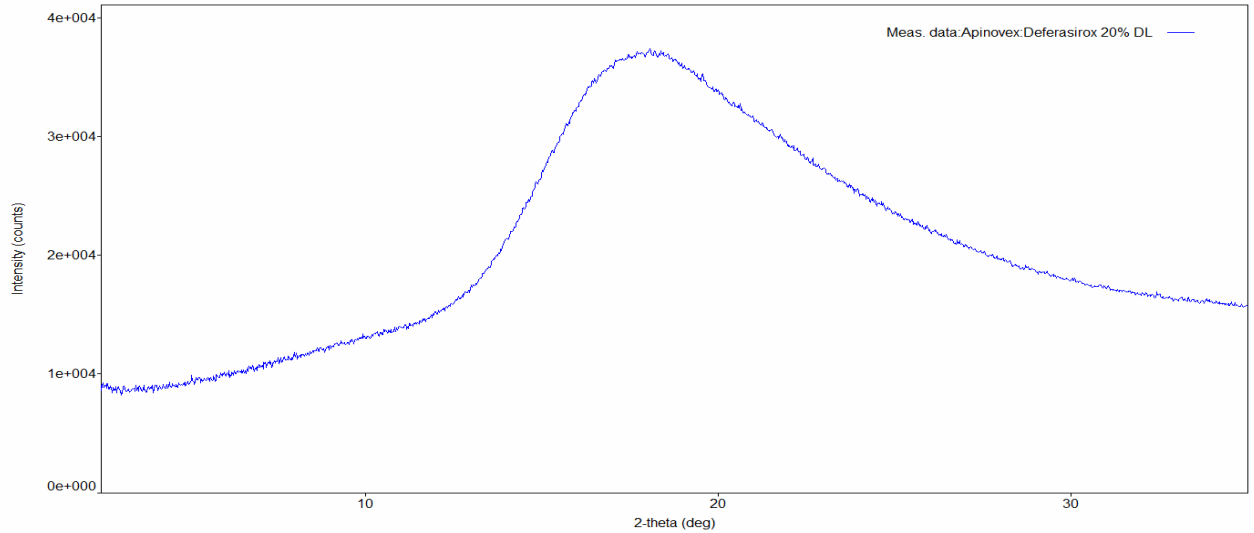
- KinetiSol Processing was employed to process deferasirox with Apinovex, using a 10-gram batch size at a 20% Drug Load.
- KinetiSol processing of Vemurafenib resulted in 0.80% Impurities, with the highest individual impurity measured at 0.35% at a Relative Retention Time (RRT) of 1.30.
- Further optimization of processing parameters is planned to further reduce impurities and increase drug loading.

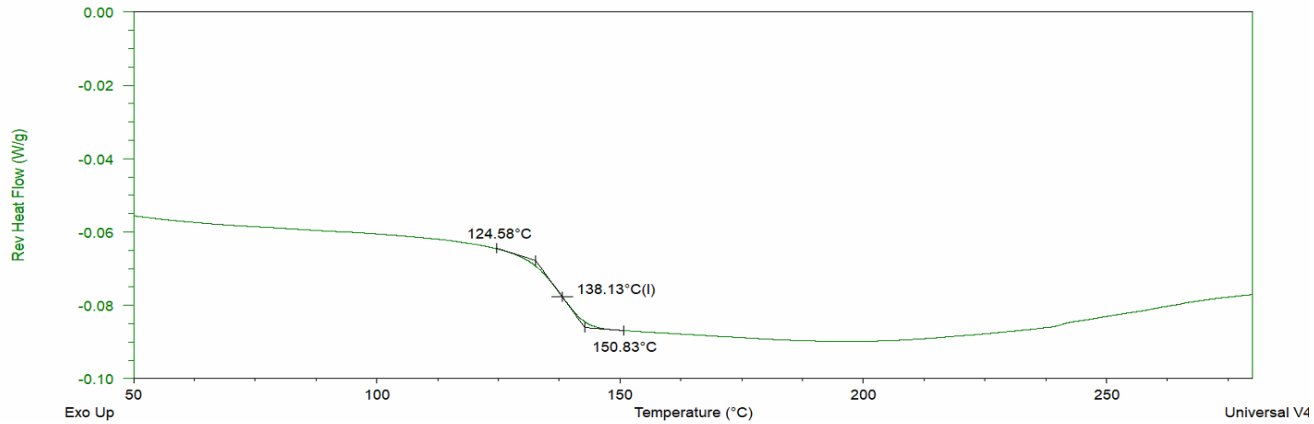
Property	Value
Molecular Weight (MW)	373.36 g/mol
Acid/Base	Weakly Acidic
pKa	4.57
LogP	3.52
Dose	10-20 mg/kg QD
Bioavailability of 375mg Dose	70%
0.2 M HCL	0.9 ug/mL
Aqueous (pH 7.5)	400 ug/mL
Melting Point	261 °C

Study 3: Deferasirox

Amorphous Characterization

- Despite the high melting point of deferasirox (261 °C), Apinovex demonstrated miscibility at a 20% drug loading.
- This 20% DL formulation resulted in a single-phase ASD with a high glass transition temperature of 138 °C.
- Both pXRD and mDSC confirm the amorphous nature of the formulation
- Additional development, akin to the rivaroxaban study, is ongoing to assess Apinovex's performance compared to other commonly used polymers in ASDs.





Evaluating Apinovex and KinetiSol Processing

Study Summary

APINOVEX IS COMPATIBLE WITH A VARIETY OF APIs

KinetiSol Processing Apinovex with various APIs demonstrated the polymer's ability to solubilize some of the most challenging to formulate APIs at a 20% drug load with low impurity levels and high glass transition values.

APINOVEX ASDs RAPIDLY ACHIEVE SUPERSATURATION

Rivaroxaban ASDs formulated with Apinovex reached peak concentrations within 5 minutes in acidic media and performed similarly to commonly used polymers for ASD development.

FUTURE STUDIES

Ongoing studies are benchmarking the deferasirox and vemurafenib ASDs against commonly used polymers, similar to the rivaroxaban study.

Download the Full Presentation Deck

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Acknowledgments:
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THANK YOU!

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Benefits of Direct Compression

Joseph Zeleznik
Technical Director, North America

Creating a world of opportunity

Critical Factors in Tableting & Dosage Form Performance

- Powder flow
  - Powders can possess inherently good flow properties
  - Powders can be manipulated (processed) to create good flow properties
- Compression/Compaction
  - Compression: the ability to rearrange/consolidate in the die cavity
  - Compaction: bonding through deformation under pressure to forma compact (tablet)
- Hydration
  - Hydrophilicity/hydrophobicity
  - Hydrophilic: diffusion and erosion
  - Hydrophobic: erosion

Direct Compression – A Quick Review of Processes

Granulation

- Advantages
  - Densification
  - Tailored particle size
  - Minimize segregation
  - Improve powder flow
  - Improved handling
- Disadvantages
  - Excipient performance reduced
  - Multi-step process
  - Labor intensive
  - Energy intensive
  - Equipment intensive
  - Variability
  - Stability
  - Physical
  - Chemical

Direct Compression

- Advantages
  - Stability
  - Minimizes process steps
  - Fewer ingredients
  - Reduced energy
  - Decreased labor
  - Reduced capital equipment
  - Frees existing equipment
- Disadvantages
  - Segregation
  - Micronized APIs
  - Flow
  - Medium to high loading
  - Carrying capacity
  - High loading

Unit Operations – DC / DG / WG

WET GRANULATION

- Ingredient dispensing & de-aggregation
- Pre-blending
- Granulation fluid prep
- Wet processing/granulation
- Wet screening
- Drying
- Milling/Dry screening
- Blending
- Tableting

DRY GRANULATION

- Ingredient dispensing & de-aggregation
- Pre-blending
- Roller compaction/Slugging
- Milling
- Screening
- Blending
- Tableting

DIRECT COMPRESSION

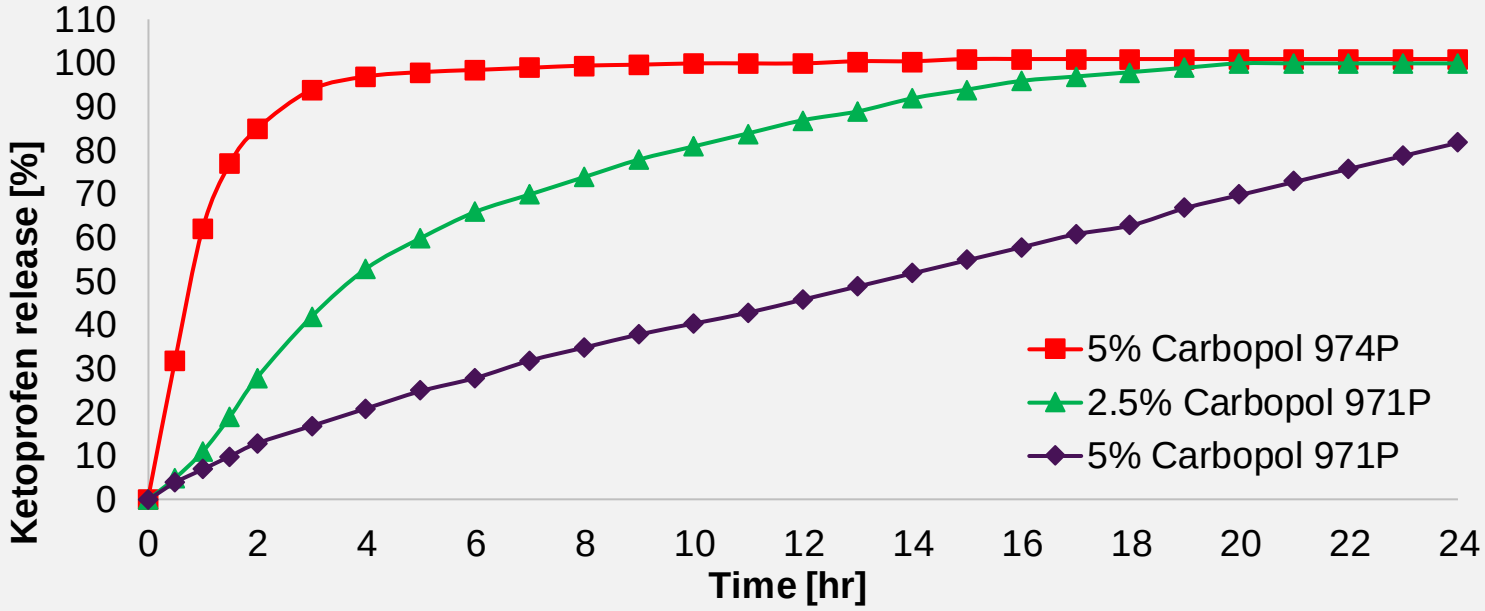
- Ingredient dispensing & de-aggregation
- Blending
- Tableting

Carbopol 71G Polymer

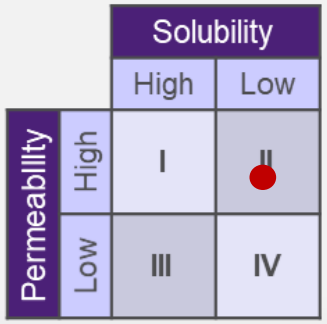
Carbopols for MR - Effect of Carbopol Type

The effect of crosslinking on the release rate

- Lightly crosslinked Carbopol polymers tend to be more efficient in controlling the drug release than highly crosslinked Carbopol polymers
- Intermediate drug release can be achieved by combining both (Carbopol 971P NF and 974P NF polymers).



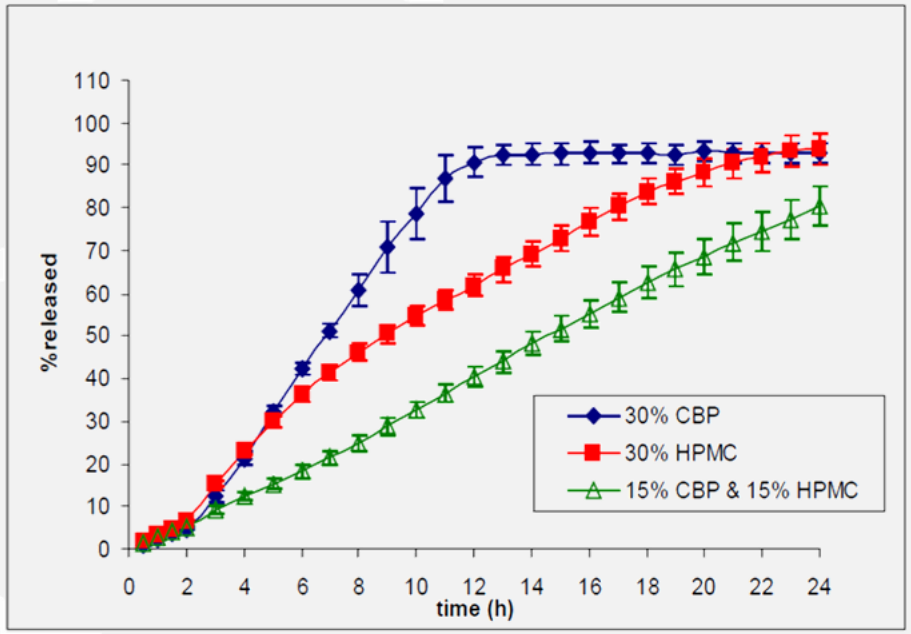
Ketoprofen 200 mg release (USP apparatus 2, pH=6.8 buffer) from wet granulated tablets



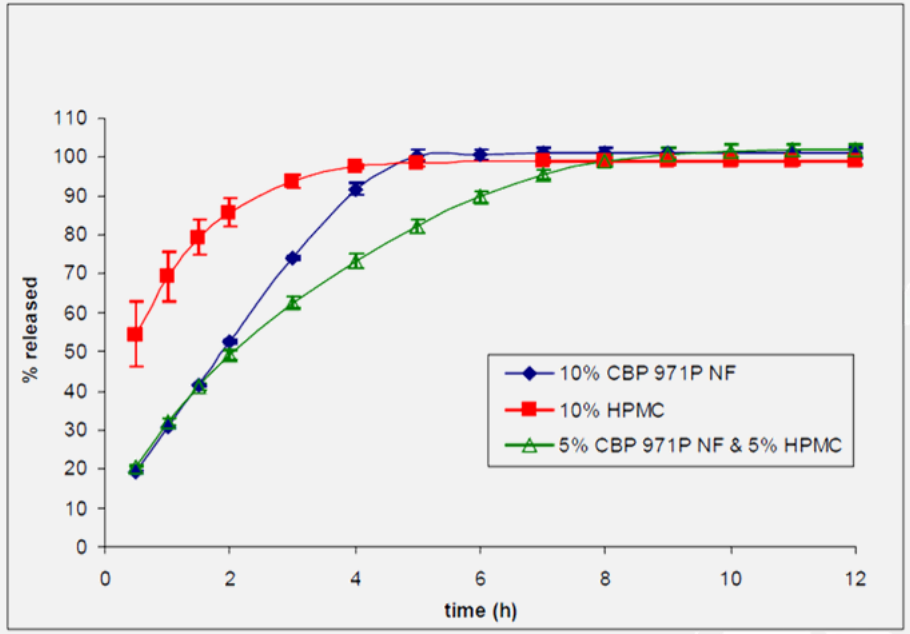
Carbomers for MR - Combination with other Polymers

The benefits of combining Carbopol + HPMC

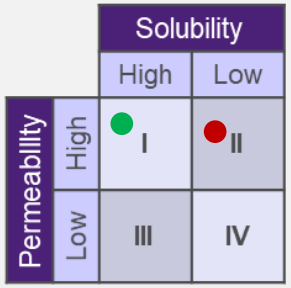
- Improved flowability by using Carbopol® 71G NF in combination with low flowability polymers
- High flexibility for modifying the release profile by varying the ratio



Ketoprofen release (USP method for modified release) from tablets (50 mg) with 30% polymer (direct compression)



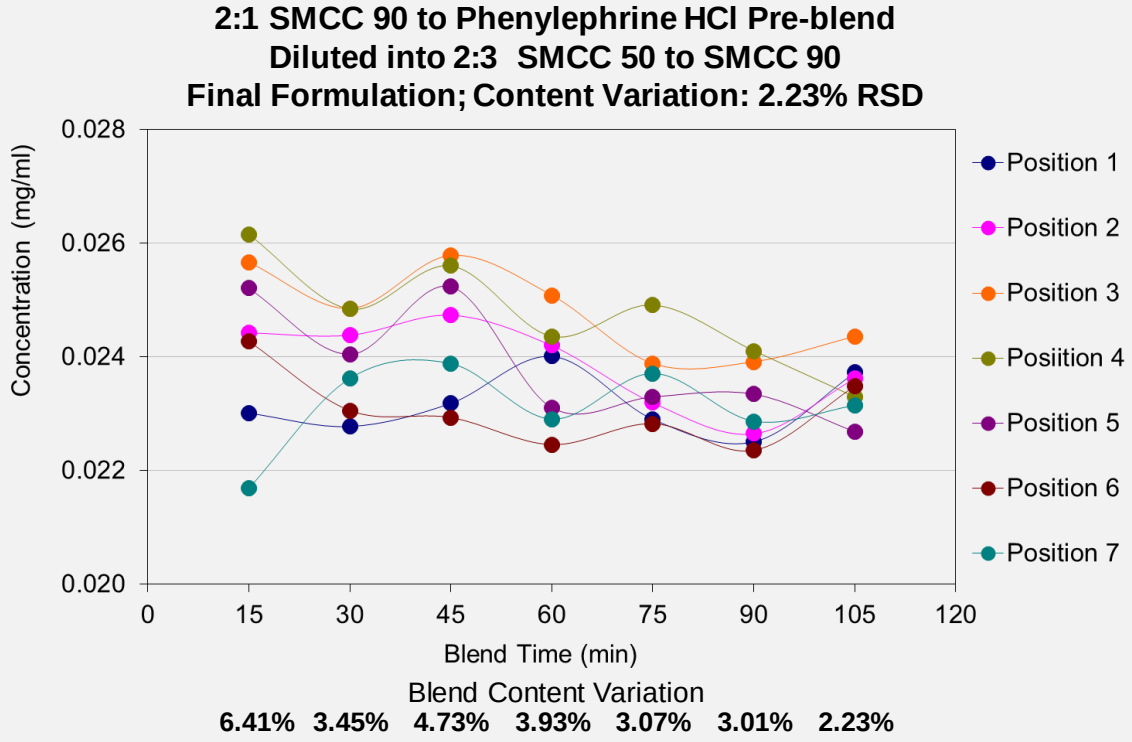
Guaifenesin release in pH=6.8 buffer from tablets (100 mg) with 10% polymer (wet granulation)



- API solubility: 0.051 mg/ml
- API solubility: 50.00 mg/ml

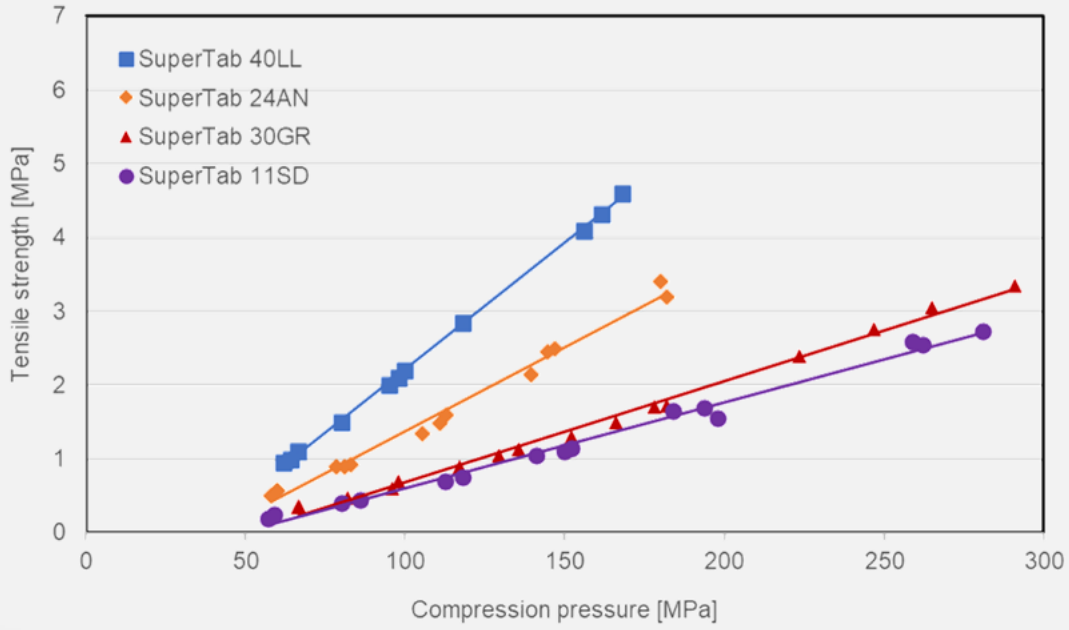
Support Ingredients and Advantages - Blending

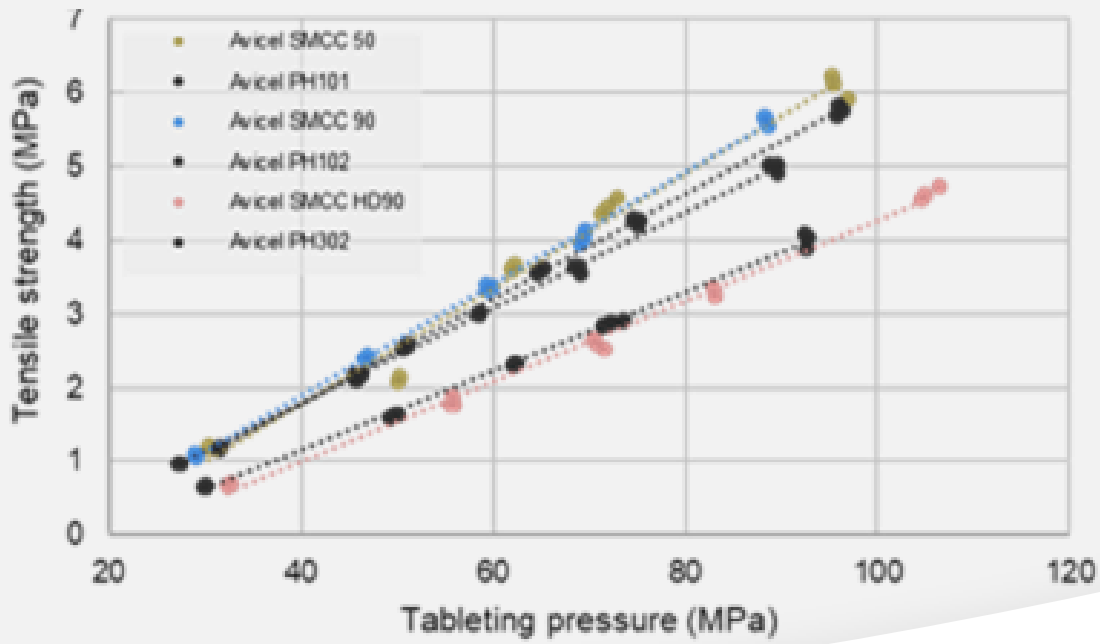
- Bench scale blending
  - Blend strategy
    - Disperse API in SMCC 90
      - Pre-blend 5 minutes
    - Add pre-blend to additional SMCC 90 with SMCC 50
      - Blend to specified time
      - Sample blender using predefined map
      - Assay each mapped position
    - Blend to homogeneity
  - Blend configuration
    - Mass: 500 g
    - Blender size: 2 quart
    - Blend times: 15 to 105 min. in 15 min. intervals
  - Uniformity target
    - Blend variation: NMT 3.0%
- Increasing batch size
  - 3 kg blend
    - Blender size: 16 quart
    - Blend time to achieve homogeneity: 45 min.
  - 20 kg blend
    - Blender size: 2 cubic foot
    - Blend time to achieve homogeneity: 15 min.



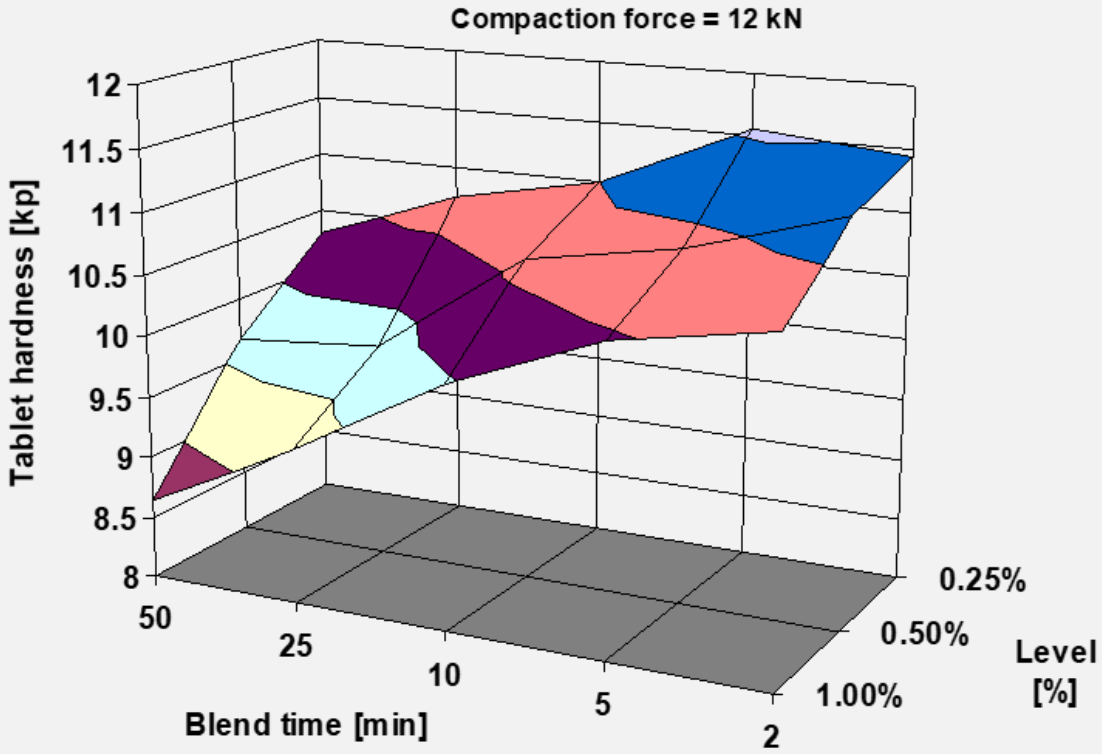
Support Ingredients and Advantages - Compaction

- Lactose
  - Grade selection based on performance requirements
    - Powder flow
    - Compactibility
  - All are freely water soluble
- (S)MCC
  - Grade selection based on performance requirements
    - Powder flow
    - Compactibility
  - Water insoluble



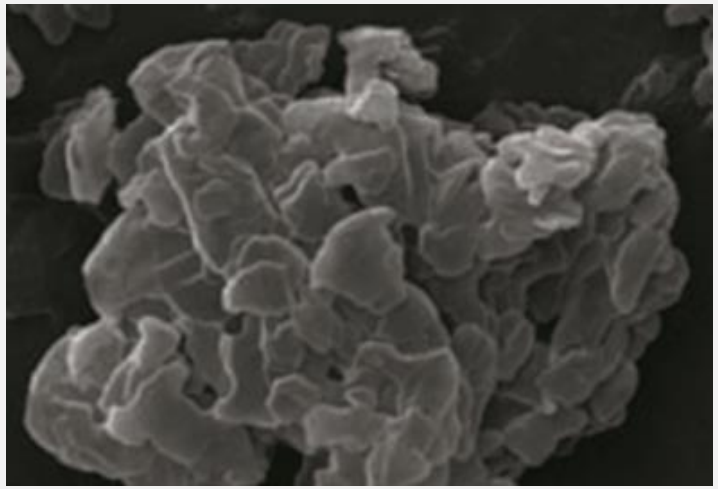


Lubricant Impact on Tablet Breaking Force



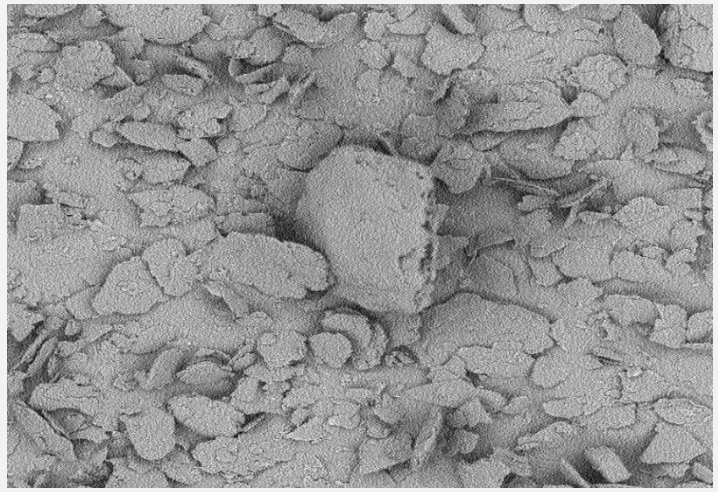
Magnesium stearate

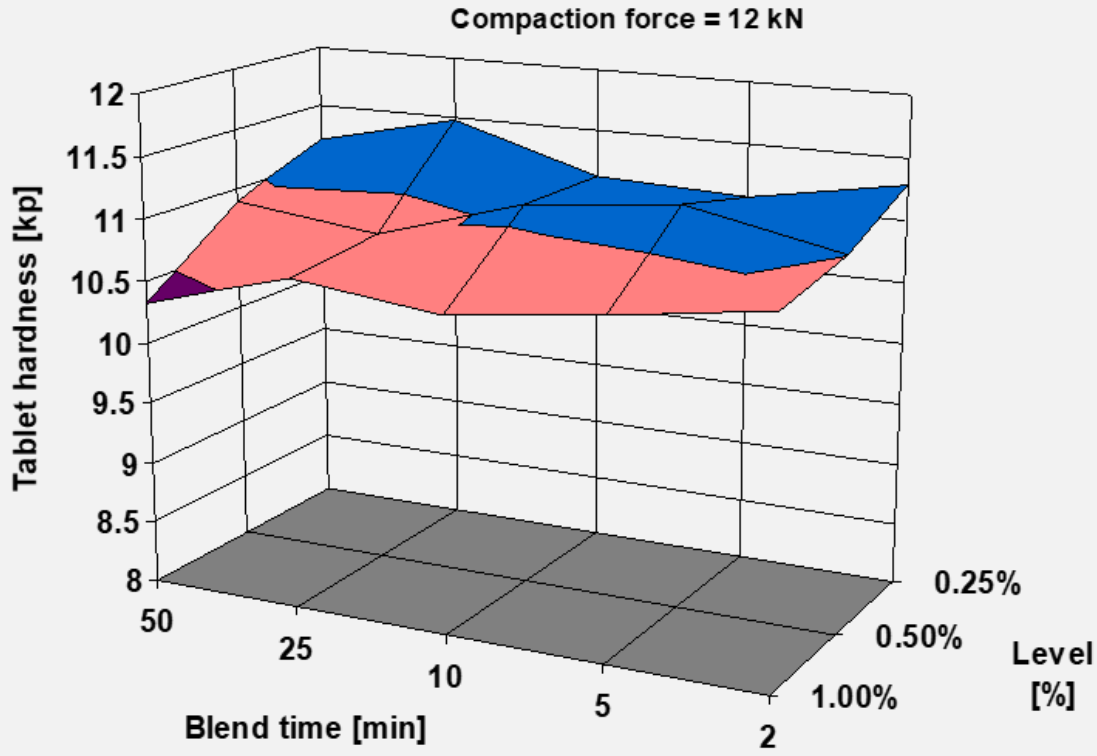
- Increasing lubricant level decreases tablet breaking force
- Increasing lubricant blend time decreases tablet breaking force
- Blend time contributes more to compaction loss than use level



Lubricant Impact on Tablet Breaking Force

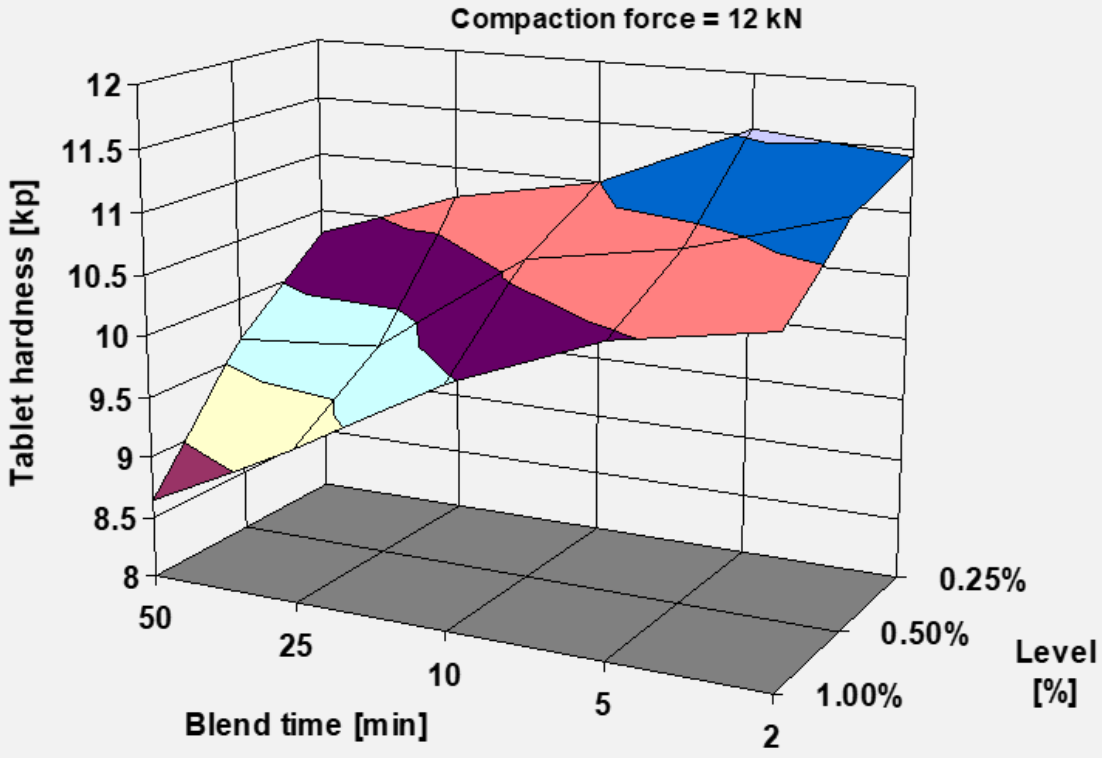
- Lubricant level has little impact on tablet breaking force
- Blend time impact to tablet breaking force mitigated
- SSF more forgiving related to tablet robustness



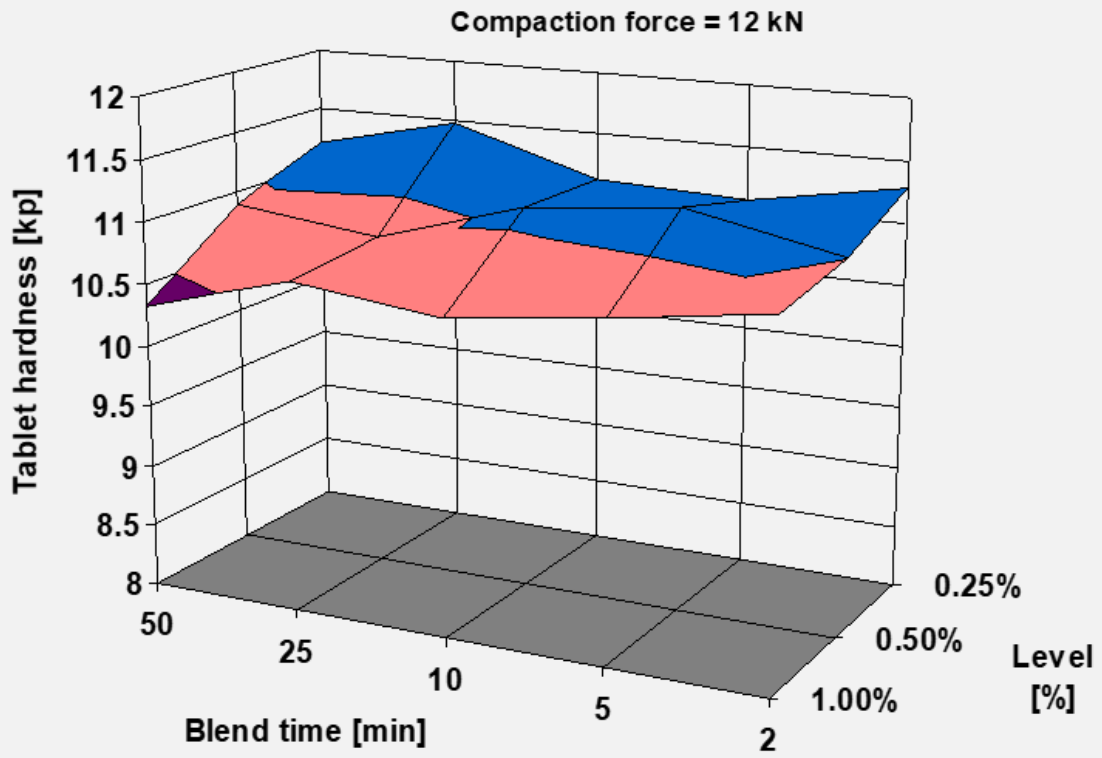


Sodium stearyl fumarate

Lubricant Impact on Tablet Breaking Force



Magnesium stearate



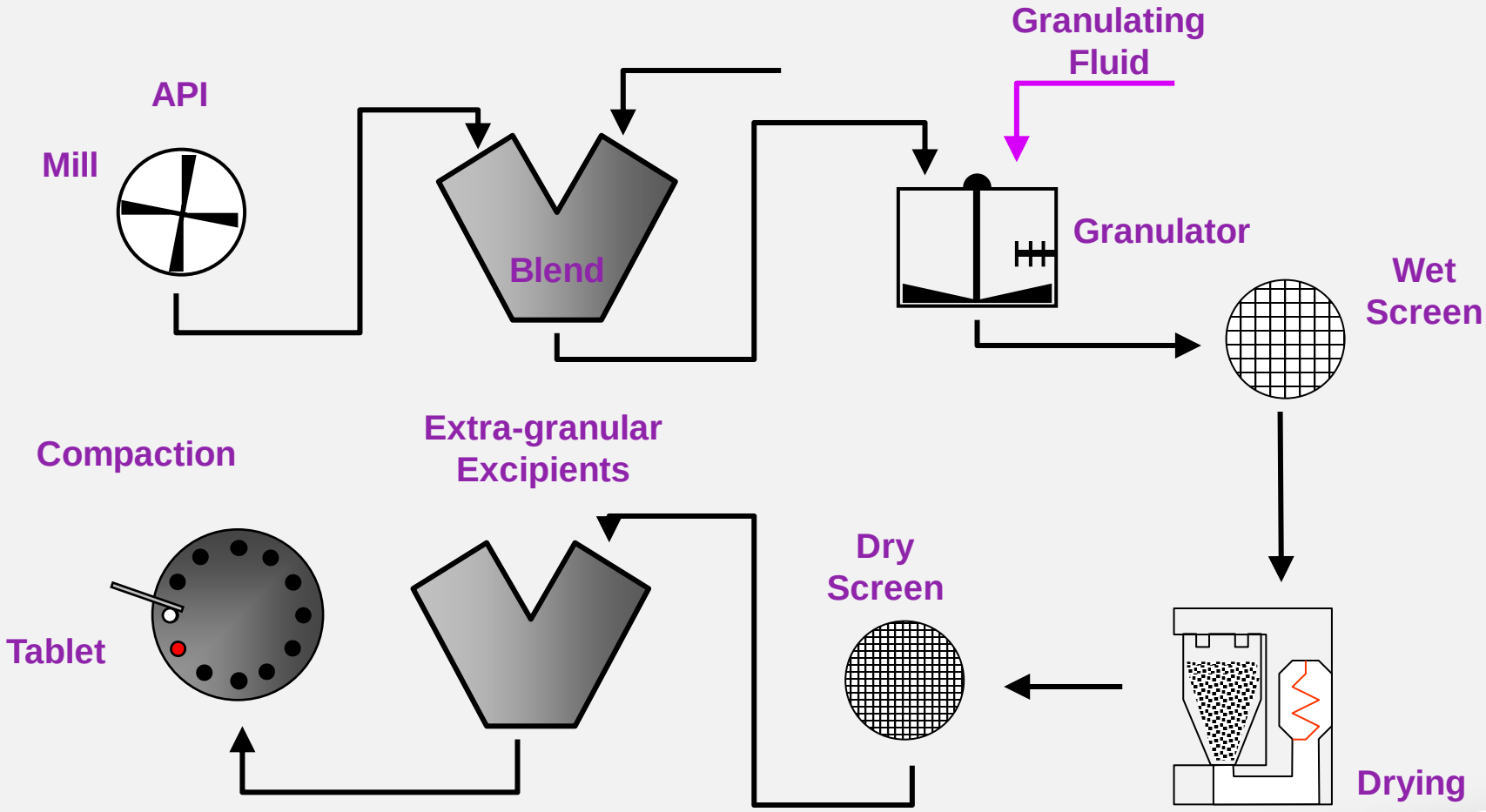
Sodium stearyl fumarate

Formulation Economics
What drives cost?

- Cost is driven by much more than an ingredient in a formulation/product
- Overall cost contribution of an excipient could be small, but the right excipients can have a large impact on final cost
  - Manufacturing savings
  - Time savings

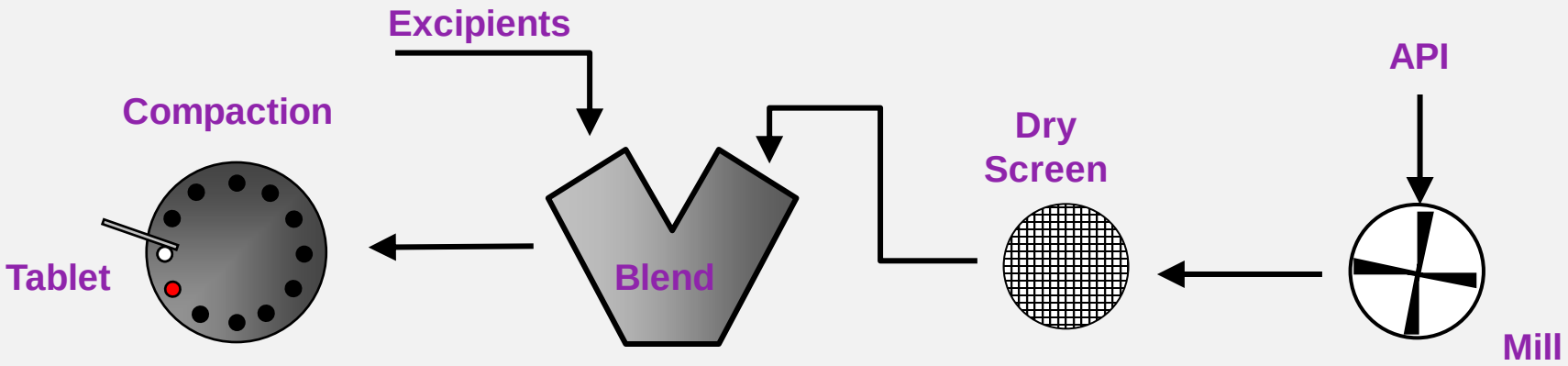
Impact of Unit Operations

Wet Granulation Tablet Manufacture



Impact of Unit Operations

Direct Compression Tablet Manufacture



Minimize processing steps and reduce cost

Formulation Economics
Tablet Process Comparison – WG to DC

- Man hours
  - Approximately 72 – 100 FTEs dedicated to wet granulation
  - Approximately 36 – 40 FTEs dedicated to direct compression process
    - Direct compression reduced FTE requirements by 50%.
- Energy Costs
  - Significant energy cost associated with granulation processes
  - “Exotic” processes further increase manufacturing costs

Manufacturing Process	Relative Production Cost/Batch
Direct Compression	1
Fluidized Bed Granulation	1.5
High Shear Granulation	2.2
Melt Granulation/Extrusion	2.4+

Manufacturing Cost	
Personnel/Staff	24%
Operations	24%
Raw materials (APIs/Packaging components)	48%
Excipients	~4%

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