HEALTH

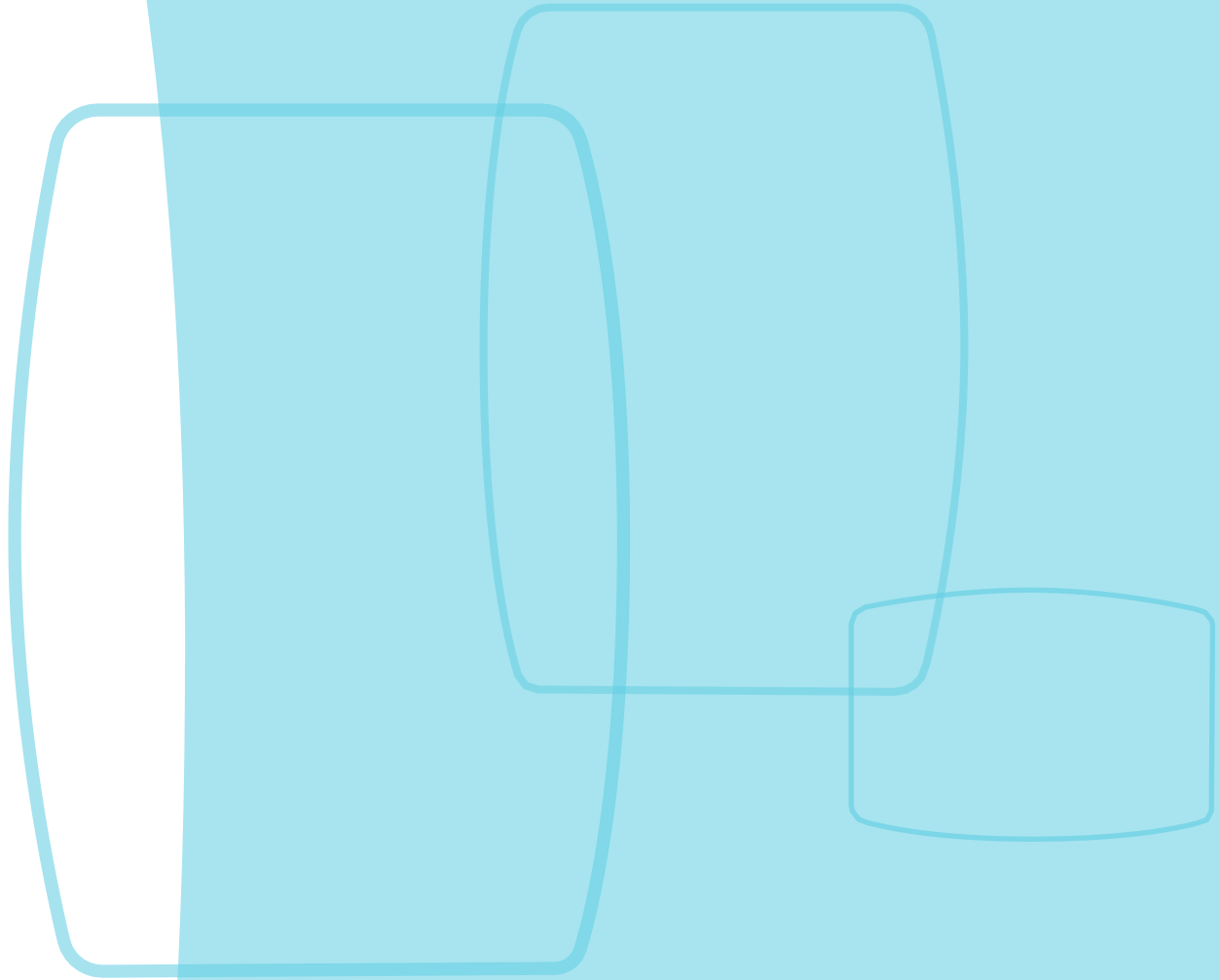
Apisolex™ Polymer:

A New Tool for Injectable Solubility Enhancement, Improved Patient Experience, and Lifecycle Management

Lubrizol Life Science Health

October 16, 2023

Table of Contents

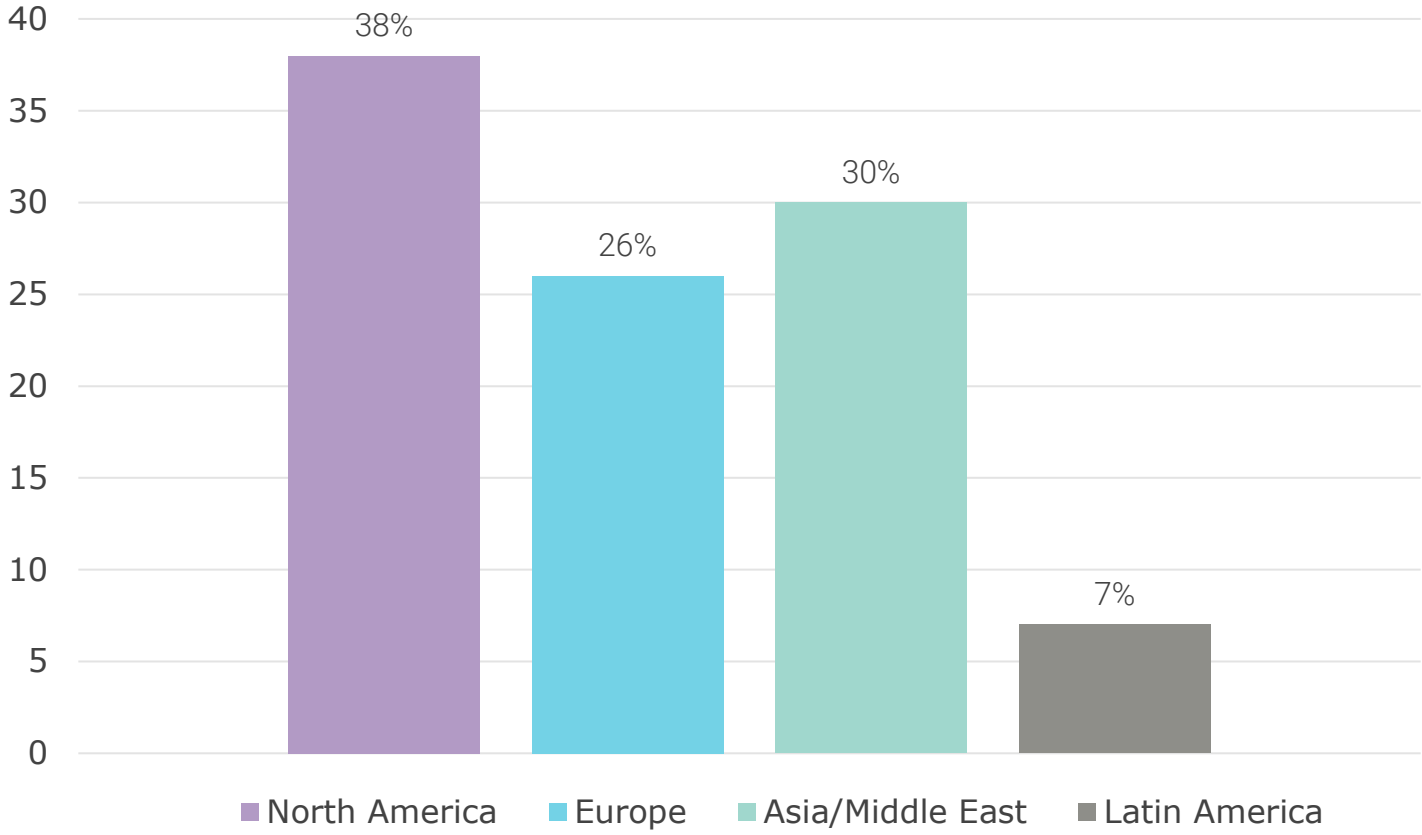


HEALTH

HEALTH

Lubrizol Life Science Health (LLS Health)

Lubrizol partners with pharmaceutical companies to provide **best-in-class polymers & CDMO services that accelerate new innovations to market.**



2022 Lubrizol Global Revenue
$6+ Billion

LUBRIZOL LIFE SCIENCE

Pharma Segment Overview

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

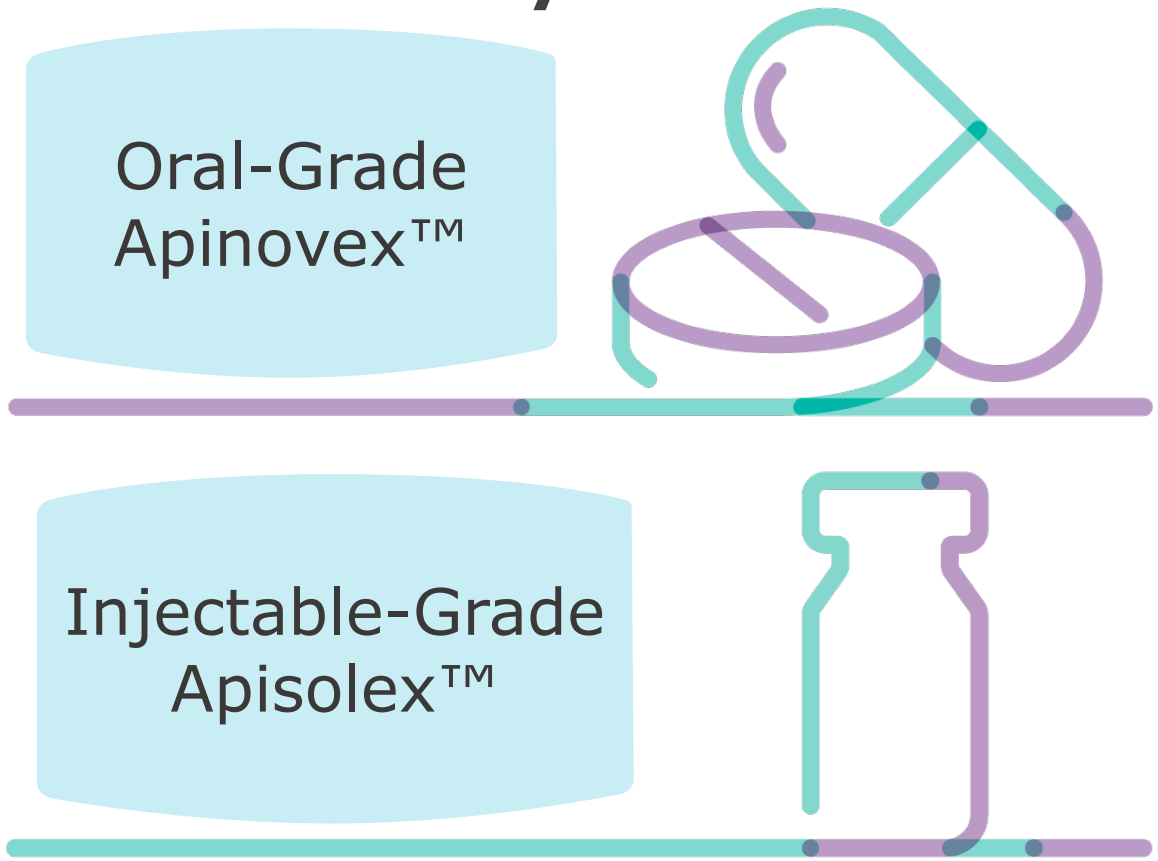
- Functional foods
- Dietary supplements
- Microencapsulation

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

Why Choose Lubrizol Life Science Health?

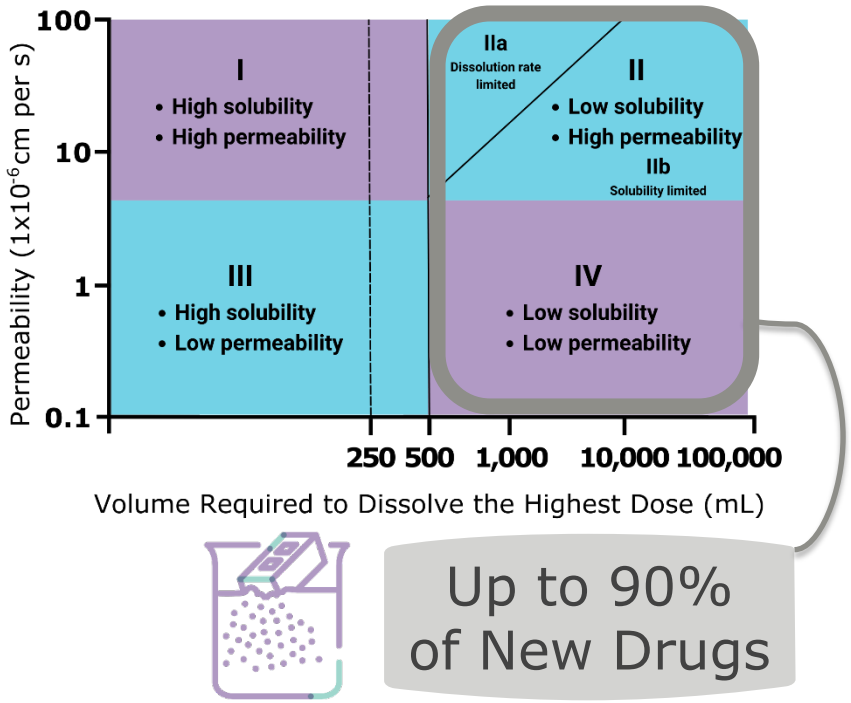
- Safe and effective excipient supply for **over 40 years**
  - Carbopol® polymers
  - Noveon® AA-1 polycarbophil
  - Pemulen™ TR-2 emulsifiers
  - Pathway™ TPU excipients
- Trusted CDMO services for **over 20 years**
  - Decades of collective experience in **nanomilling**

Novel Solubility-Enhancing Polymers



Shortcomings of Traditional Solubility Enhancers

Developability Classification System (DCS)



Up to 90% of New Drugs

Low Efficiency/ Poor Dosing

Undesired Side Effects

Complex Manufacturing Process

There is no one-size-fits-all excipient!
New tools are needed to serve the growing pipeline of challenging APIs

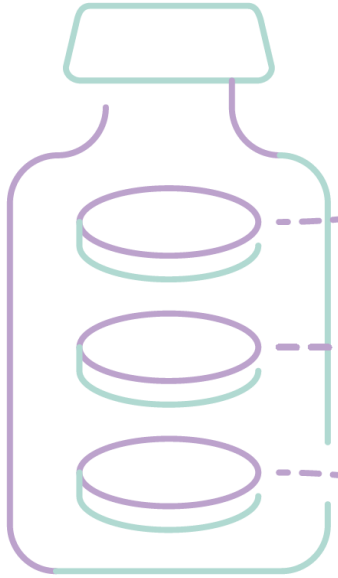
HEALTH

505(b)(2) and Hybrid Global Project Pipeline

Pipeline Dynamics

- 5000+ Global Projects
- 8% CAGR (2015-2023)
- 3 of 4 are Oral or Injectable

Types of Products



- **New formulation**
- **New dosage form**
- **New combination**

Top Therapeutic Areas

- Oncology
- Diabetes
- Pain Management
- Cardiovascular
- CNS Disorders
- HIV/AIDS

505(b)(2) reformulations enable **innovation opportunities in small molecules**

HEALTH

New Technologies Enable 505(b)(2) and Hybrid Products

Formulation Objectives

Does it Work?

- Improve solubility/BA
- Increase drug loading
- Create new API combinations
- Improve stability

Patient-Centric Objectives

Is it Safe?

- Reduce dosing frequency/ pill burden
- Increase convenience
- Minimize side effects/toxicity

Business Objectives

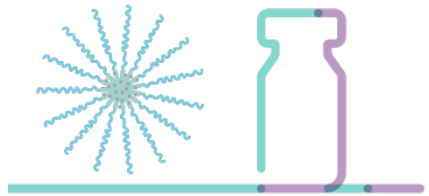
Does it Enable IP Protection?

- Access background IP from partner company
- Develop new formulation IP
- Combine new and old technologies for synergies

Novel excipients and technologies address all three areas of product development

HEALTH

Apisolex™ Polymer for Injectable Solubility Enhancement



Polyamino acid-based multiblock copolymers
designed for efficient micellar encapsulation

Does it Work?	**Is it Patient-Friendly?**	**Does it Enable IP?**
Enables up to 50,000-fold increase in solubility	Safe for parenteral use*	Strong composition of matter patents
Simple formulation process	Fast, easy reconstitution	Opportunities for formulation IP

* For detailed safety/tox data, contact kevin.song@lubrizol.com

LUBRIZOL LIFE SCIENCE

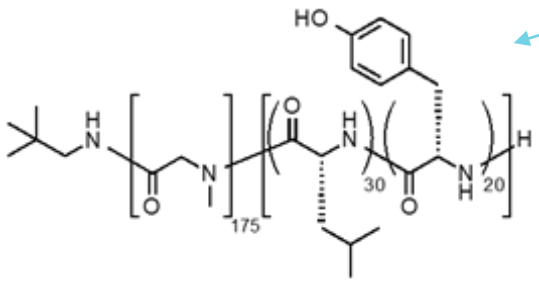
HEALTH

Apisolex™ Polymer Structure and Properties

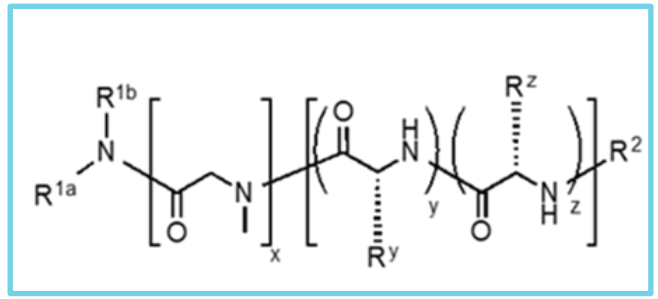
- Multiblock copolymers: poly(sarcosine) block and D,L-mixed poly(amino acid) block
- Sarcosine: non-toxic, non-immunogenic, biocompatible, & biodegradable alternative to PEG

- **Versatile synthesis**: possibility of generating unique structures based on API requirements
- **Highly efficient and streamlined** drug product manufacturing process
- **GMP manufacturing** in place
- **Robust IP protection** with long patent life remaining

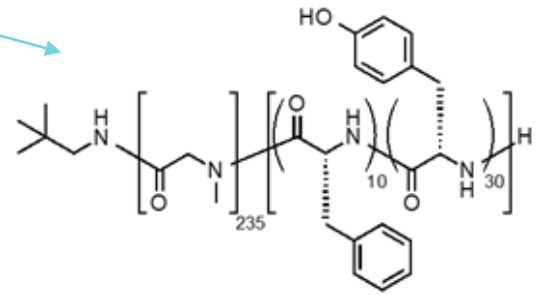
Apisolex™ LY



PSar175-P(dLeu30/Tyr20)



Apisolex™ FY



PSar235-P(dPhe10/Tyr30)

Created to solubilize hydrophobic APIs

LUBRIZOL LIFE SCIENCE

Polymer Micelle Technology

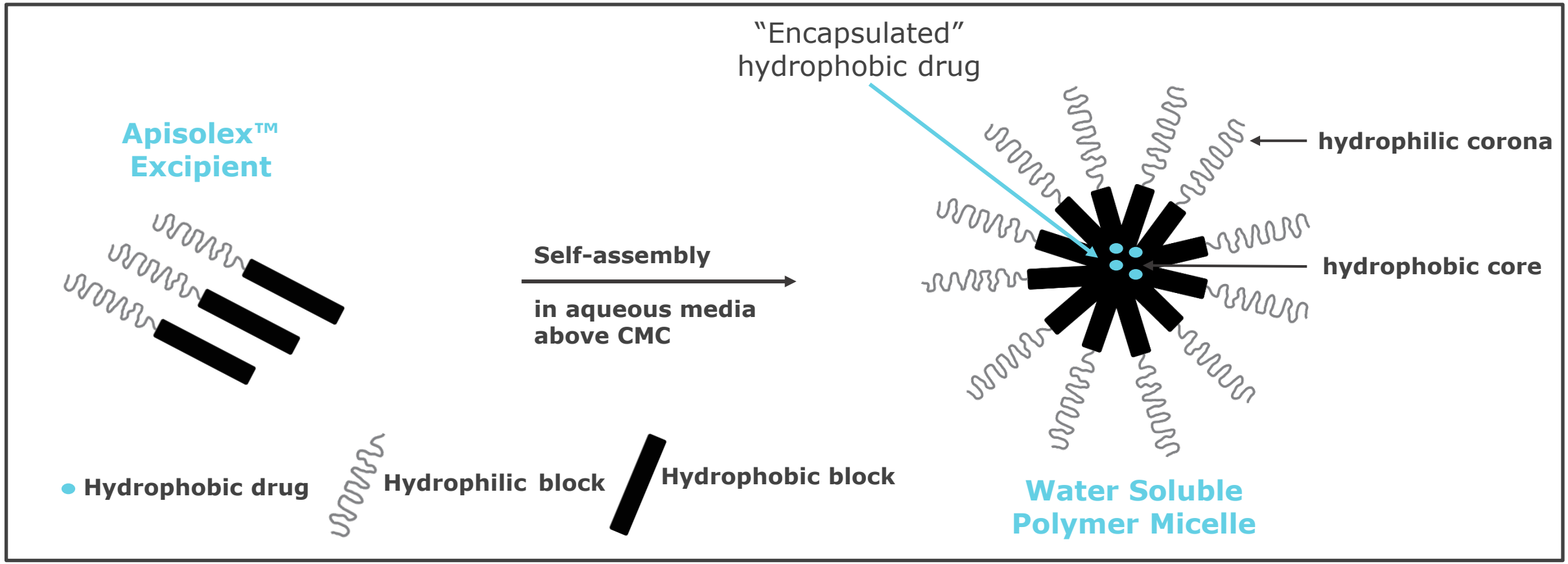
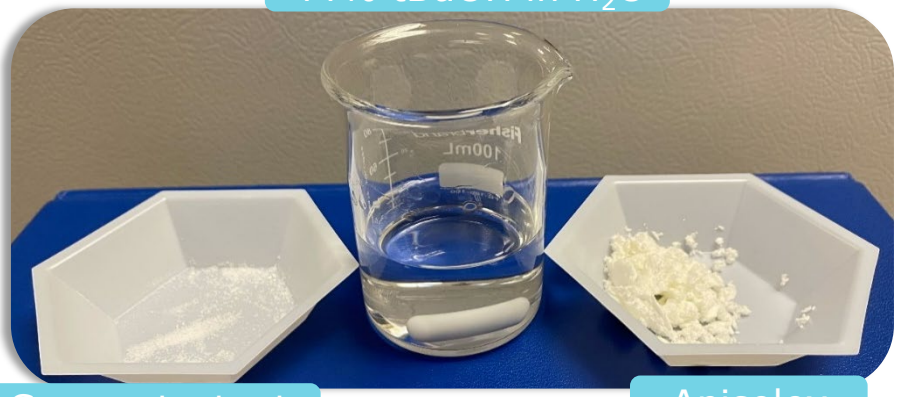


Figure adapted from Frontiers in Pharmacology 2014, 5:77

Sequesters the drug in the hydrophobic part of the micelle
to increase water solubility of APIs **by up to 50,000-fold**

Formulation Techniques – Method #1 – tBuOH and Water

44% tBuOH in H_2O



Cryoprotectant

Apisolex

Dissolution

API

tBuOH

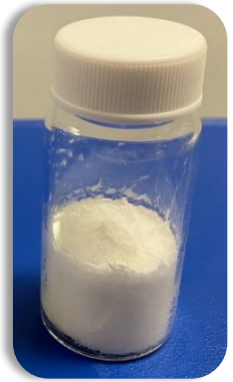
Mixing/ Homogenization

Optional Sonication/Heating

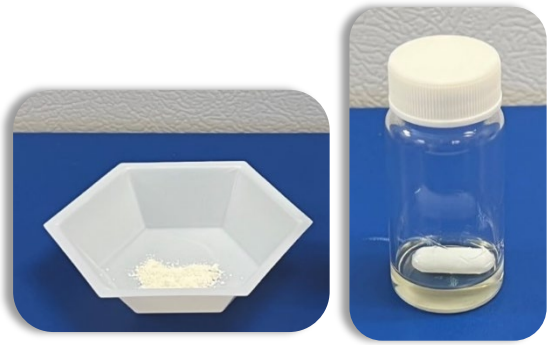
Sterile Filtration

Lyophilization

Final Drug Product

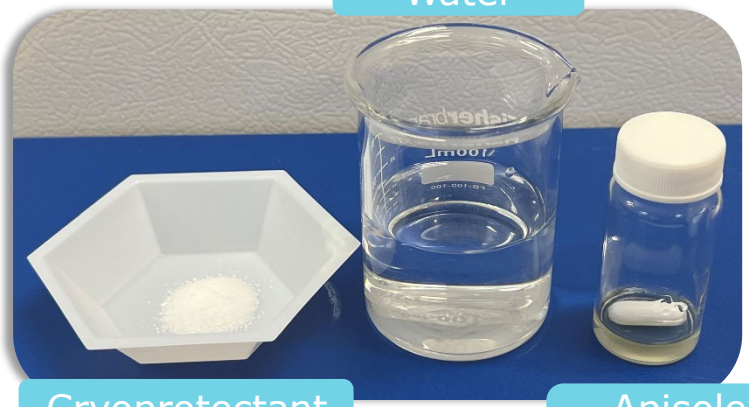


Formulation Techniques – Method #2 – Other Organic Solvents



Apisolex in Methanol

Water



Cryoprotectant

Apisolex In Methanol

API Dissolved in Organic Solvent

Mixing/ Homogenization

Diafiltration and Sterile Filter

Lyophilization

Final Drug Product

Solution for stable API (with buffer)

Putting Apisolex Polymers to the Test

- Solubilization properties of Apisolex polymer were evaluated
- The solubilization properties of Apisolex polymer were evaluated in comparison with other excipients for a series of poorly water soluble active pharmaceutical ingredients.
- The experiments were conducted by non-optimized, standard dispersion techniques (mixing or homogenization), followed by dilution or lyophilization and reconstitution.

Series A Results

Excipient / API	Polysorbate 20	Polysorbate 80	Cremophor®[1]	Apisolex™
Amphotericin B	Fail	Fail	Fail	Pass
Cyclosporin A	Pass	Pass	Pass	Pass
Etoposide	Pass	Pass	Pass	Pass
Melphalan	Fail	Fail	Fail	Pass
Paclitaxel	Pass	Pass	Pass	Pass
BI-0001[2]	Pass	Pass	Pass	Pass
BI-0002[2]	Pass	Pass	Pass	Pass
BI-0003[2]	Pass	Pass	Pass	Pass
BI-0004[2]	Pass	Fail	Fail	Pass
BI-0005[2]	Pass	Pass	Pass	Pass
Excipient : API Ratio	100 : 1			100 : (5 – 10)

Compared to solubilizers that utilize a dissolution and dilution technique,
only Apisolex polymer enabled successful solubilization of all APIs evaluated andat a much lower ratio of excipient to API.

[1] *Polyethoxylated castor oil (Kolliphor® ELP or Kolliphor EL, formerly known as Cremophor EL, is a registered trademark of BASF Corp)*
[2] *APIs for this study were provided by Boehringer Ingelheim Pharm. Inc.*

Series B Results

API \ Excipient	TPGS[1]	Captisol®[2]	PEG-PLGA[3]	Apisolex™
Amphotericin B	Fail	Fail	Fail	Pass
Cyclosporin A	Pass	Fail	Fail	Pass
Etoposide	Pass	Fail	Pass	Pass
Melphalan	Pass	Pass	Pass	Pass
Paclitaxel	Fail	Fail	Pass	Pass
BI-0001[4]	Fail	Fail	Fail	Pass
BI-0002[4]	Fail	Fail	Fail	Pass
BI-0003[4]	Pass	Fail	Fail	Pass
BI-0004[4]	Fail	Fail	Fail	Pass
BI-0005[4]	Fail	Fail	Fail	Pass

Compared to solubilizers processed using the same lyophilization and reconstitution technique, **only Apisolex polymer enabled successful solubilization of all APIs evaluated**.

[1] *D-α-tocopheryl polyethylene glycol succinate*
[2] *Cyclodextrin (Captisol® SBE-AE-Beta-CD is a registered trademark of Ligand Pharmaceuticals Incorporated)*
[3] *Polyethylene glycol-poly lactic acid-co-glycolic acid*
[4] *APIs for this study were provided by Boehringer Ingelheim Pharm. Inc.*

Series C Results

API	Solubility in Water (µg/ml)	Solubility in Formulation with Apisolex Polymer (µg/ml)	Solubility Increase with Apisolex Polymer (Fold)
BI-0001[1]	20	2,000	100
BI-0002[1]	8	2,000	250
BI-0003[1]	0.4	20,000	50,000
BI-0004[1]	1.2	10,000	8,333
BI-0005[1]	4	5,000	1,250

Additional experiments conducted for experimental APIs BI-0001 – BI-0005 showed that **Apisolex polymer increased the drug solubility up to 50,000-fold.**

[1] APIs for this study were provided by Boehringer Ingelheim Pharm. Inc.

Safety and Toxicology

	Test	Results
Systemic toxicity	Tolerability (rats and mice)	Test article was **well tolerated** by rats and mice at doses as high as 1,500 mg/kg
	32-Day IV Injection Toxicity with 28-day recovery (rats)	**No treatment-related effects** were detected
Pharmaco-kinetics	[^{14}C] labelled Apisolex IV dose in male and female rats	Can be distributed to distant organs but **does not accumulate** Tissue: plasma AUC_{0-t} ratios <1.0

Safe for Parenteral Use

(conclusion based on animal testing and pre-IND packages)

Apisolex™ Polymers: Looking Forward

- Scale up and GMP manufacturing optimization – ongoing
- Excipient Drug Master File (DMF)
- Safety & Toxicology - Future work to include:
  - Ames
  - *in vitro* cytogenicity
  - *in vivo* chromosomal damage
  - Six month repeat dose

Apisolex Polymer
Medicine Maker 2022
Innovation Award Winner

- The Medicine Maker Innovation Awards showcase new drug development and manufacturing technologies
- Apisolex Polymer stood out from a record numbers of nominations, winning the reader vote

"Our hope is that winning this award will allow drug formulators struggling with water-insoluble APIs to learn about the polymer's benefits so that **more life-changing medications can make it to market**."

Apisolex Polymer is also a finalist for the 2023 CPhI Awards

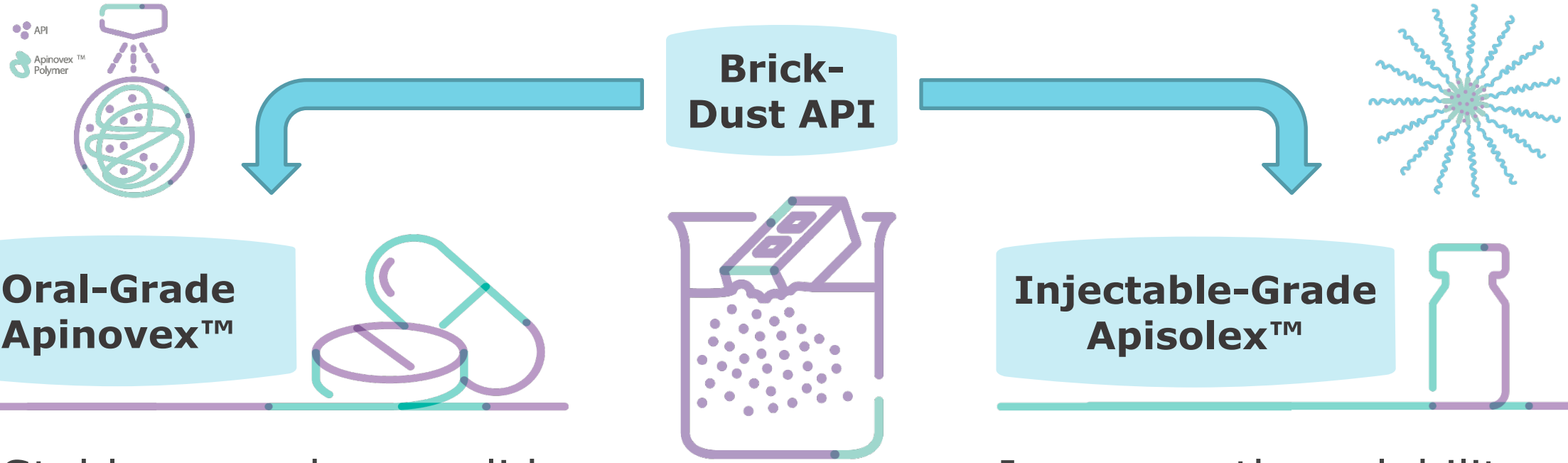
Selecting the Right Partner

The ideal excipient/technology provider will have **deep experience in pharma** and provide:

- **Regulatory Support**
  - Understanding of global requirements
  - Safety/toxicity data for intended purpose
- **Quality and Manufacturing Assurance**
  - GMP manufacturing and documentation
  - Reproducible scale-up capability
  - Stability data
- **A Collaborative Mindset with Secure, Long-Term Supply**

Visit our booth to discuss your next project!

Solubility-Enhancing Excipients from LLS Health



Stable amorphous solid dispersions with up to **80% drug loading**

Learn more at apinovex.com

Increases the solubility of hydrophobic APIs up to **50,000-fold**

Learn more at apisolex.com

Thank you!

Nick DiFranco

Global Market Manager
Oral Drug Delivery/Novel Excipients

Nicholas.DiFranco@lubrizol.com
Connect with me on LinkedIn!

Rob Lee

President
CDMO Division

Rob.Lee@lubrizol.com
Connect with me on LinkedIn!

Scan to learn more and request a sample today!

or visit
go.lubrizol.com/podd

HEALTH