LUBRIZOL LIFE SCIENCE

Unlock the Potential of Poorly Soluble Drugs with Apisolex™ Technology

Don't let poor solubility affect your innovative drug projects

Approximately 60% of potential active pharmaceutical ingredients (APIs) under development, and more than 40% of those in reformulation, are poorly water soluble[1].
Solubility challenges present a substantial hurdle to the development of pharmaceuticals, impeding or stopping the advancement of promising drugs to market. There are several different approaches to overcome solubility challenges:

- Chemical modification – creating a prodrug of the API
- Physical processing – nanomilling to reduce particle size
- Excipients – formulating with cosolvents, lipids, surfactants, etc.

Increase API solubility by up to 50,000-fold with Apisolex Technology

Excipients have long played a key role in addressing solubility challenges in drug development. Due to their inherent versatility, they provide a tool to formulate poorly soluble APIs into products with improved bioavailability and therapeutic effects. However, as the number of poorly soluble APIs grows, existing excipients are still not able to solve the complex formulation challenges.

Particularly in the parenteral space, there are few excipients acceptable to aid the formulation of novel APIs. The unique safety and chemical challenges of developing an excipient for parenteral applications have made commercialization a rare event over the last 30 years. Of those currently available in the market, some come with unpleasant patient side effects and do not address the solubility needs of highly crystalline and hydrophobic APIs.

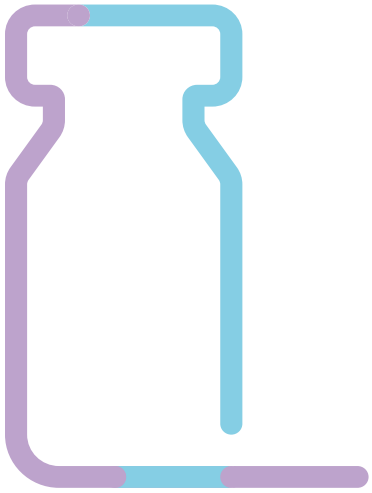
With existing excipients falling short, developing a solution has been a key commitment of Lubrizol Life Science Health (LLS Health). In this guide, you will learn more about Apisolex™ technology, what makes it unique, and how it can help you drive your parenteral drug product innovation to success.

Unlike Apisolex, PEG-based excipients may produce significant side effects including neuropathy and anaphylactic reactions

1. PharmaCircle Data

Benefits of Apisolex Technology

Innovation is inherent to the pharmaceutical industry. The Apisolex excipient provides a tool to improve solubility and offers drug developers, caregivers, and most importantly patients access to new and improved drug products.



Formulation Benefits of Apisolex Polymer

Safe, poly-amino acid based amphiphilic polymer which is a non-toxic, non-immunogenic, biocompatible, and biodegradable alternative to PEG

- **Increases solubility of hydrophobic APIs** by up to 50,000-fold, with amorphous and crystalline APIs.
- **High drug loading** (up to 40:100 API:solubilizer ratio).
- Forms **stable**, **lyophilized drug product** that reconstitutes in less than 30 seconds in saline.
- **Patented technology** enabling IP protection and lifecycle management/505(b)(2) formulations.

Processing Benefits of Apisolex Polymer

- Simple formulation techniques – solution mixing or oil-in-water emulsion formation – with **>90% API recovery**.
- Standard, scalable formulation techniques.

Safe for Parenteral Use

Apisolex is a GMP compliant polymeric excipient constituted of amino acid building blocks. It's biocompatible, biodegradable and tested for safety in parenteral projects:

	Test	Results
System toxicity	Tolerability (rats and mice)	Well tolerated at doses as high as 1,500 mg/kg
	32-day IV injection 28-day recovery (rats)	No treatment-related side effects detected
Pharmacokinetics	[14C] labelled Apisolex IV dose in male and female rats	- Can be distributed to distant organs without accumulation - Tissue: plasma AUC0-t ratios <1.0

Simplify Manufacture and Reduce Development Timelines

Apisolex technology has been designed to work with the simplest of formulation techniques, helping you streamline your manufacture and save precious time during drug development. The excipient and the hydrophobic API can be combined in an aqueous based solution followed by sterile filtration and lyophilization to produce a stable formulation that is readily resuspended in common diluents for administration. This technique forms micellular structures which encapsulate the API during lyophilization. In saline, the lyophilized drug product reconstitutes in less than 30 seconds.

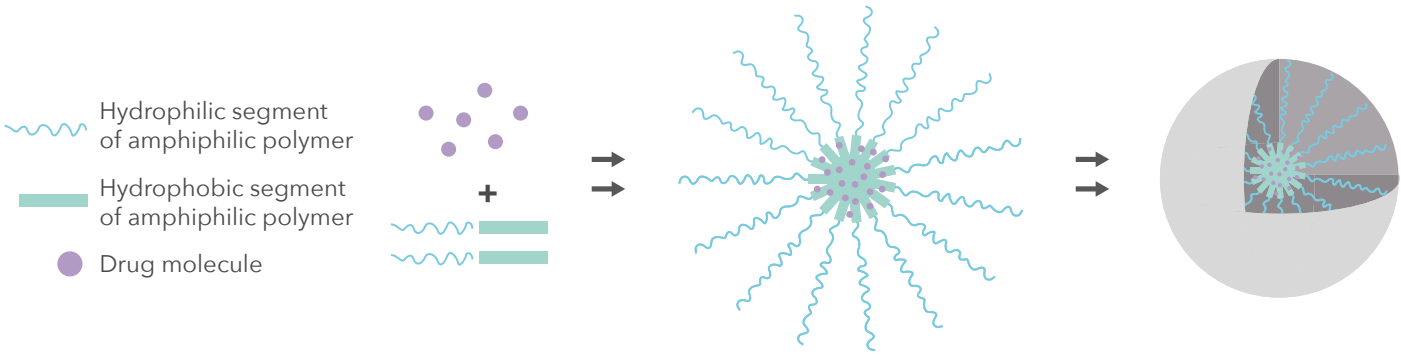
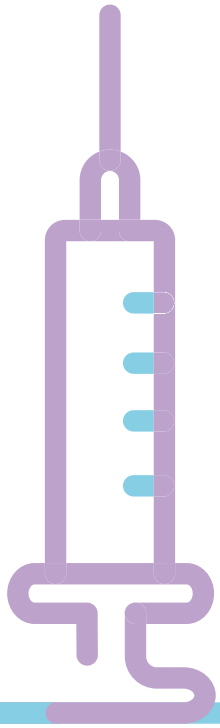


Figure 1: Apisolex polymer-forming micelles.

Innovative Design

Apisolex technology utilizes an amphiphilic multi block copolymer. This incorporates a hydrophilic poly(sarcosine) block and a second drug-encapsulating block comprised of a mixture of hydrophobic D- and L- poly (amino acids). As a naturally occurring amino acid, polymers of sarcosine offer an inert replacement to traditional water-soluble polymers such as PEG and Polyvinyl Alcohol (PVA).

The design features of the Apisolex polymer result in an innovative excipient that outperforms alternatives.



Putting Apisolex Technology to the Test

The solubilization properties of the Apisolex polymer were evaluated in comparison with other excipients for a series of poorly water-soluble APIs.

- The experiments were conducted by non-optimized, standard dispersion techniques (mixing or homogenization), followed by dilution or lyophilization and reconstitution.
- Target API concentration in final product after dilution or reconstitution was 500 mg/ml. The criteria for solubilization were turbidity (NMT 100 NTU), particle diameter (NMT 150 nm), and drug recovery after filtration (NLT 80%).

Series A Results:

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

API / Excipient	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-001[2]	Pass	Pass	Pass	Pass
BI-002[2]	Pass	Pass	Pass	Pass
BI-003[2]	Pass	Pass	Pass	Pass
BI-004[2]	Pass	Fail	Fail	Pass
BI-005[2]	Pass	Pass	Pass	Pass
Excipient : API Ratio	100 : 1			100: 5 - 10

[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:

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

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-001[4]	Fail	Fail	Fail	Pass
BI-002[4]	Fail	Fail	Fail	Pass
BI-003[4]	Pass	Fail	Fail	Pass
BI-004[4]	Fail	Fail	Fail	Pass
BI-005[4]	Fail	Fail	Fail	Pass

[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:

In additional experiments conducted for APIs, BI-0001 – BI-0005, Apisolex polymer increased the drug solubility up to 50,000-fold.

API	Solubility in Water (µg/ml)	Solubility in Formulation with Apisolex Polymer (µg/ml)	Solubility Increase with Apisolex Polymer (Fold)
BI-001[1]	20	2,000	100
BI-002[1]	8	2,000	250
BI-003[1]	0.4	20,000	50,000
BI-004[1]	1.2	10,000	8,333
BI-005[1]	4	5,000	1,250

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

Add Value with Apisolex Technology

The advantages of the Apisolex polymer to parenteral drug products ultimately benefit the drug developer, caregiver, and the patient.

Drug Developer: Lifecycle Management

Apisolex excipient offers **robust patent protection**, enabling pharmaceutical companies to **formulate new chemical entities** or breathe new life into established drugs via the FDA's 505(b)(2) regulatory pathway. Companies can also reformulate existing APIs to enhance their therapeutic effect and deliver improved patient outcomes. Apisolex adds value by helping to resurrect APIs that failed to progress in development due to solubility issues.

Patient and Drug Developer: Enabling Technology

Many APIs with promising therapeutic properties cannot be administered to patients due to poor solubility. Apisolex technology's outstanding API-solubilizing ability **enables the development of practical delivery methods** to help these drugs realize their full potential. Enabling these vital APIs to market not only helps drug developers, but also helps ensure patients are getting treatments with superior therapeutic value.

Patient and Caregiver: Enhanced Experience

Apisolex technology offers **enhanced drug solubilizing properties**, resulting in a dramatic improvement of the concentration of API in water and allowing for **more drug to be delivered in a smaller volume**, **over a shorter time**. The concentration increase can result in a reduction in treatment time for patients or a **reduction in dosing frequency**. The safety profile of the Apisolex excipient **reduces infusion related side effects** shown in other excipients and can eliminate premedication to abate these effects.

Contact us today to try out Apisolex technology for yourself!

Discover how our excipient can help meet the solubilization needs for your most challenging parenteral projects by **contacting our team** or by visiting **apisolex.com**

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