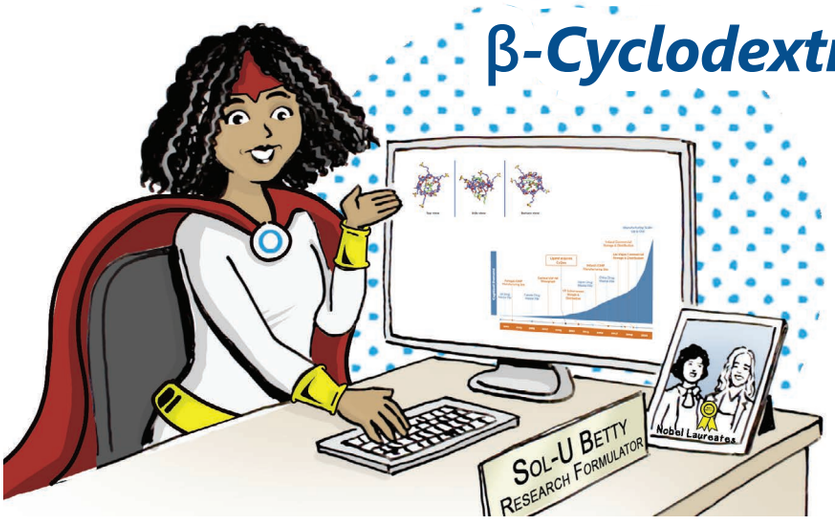
CAPTISOL®

β-Cyclodextrin Sulfobutylethers



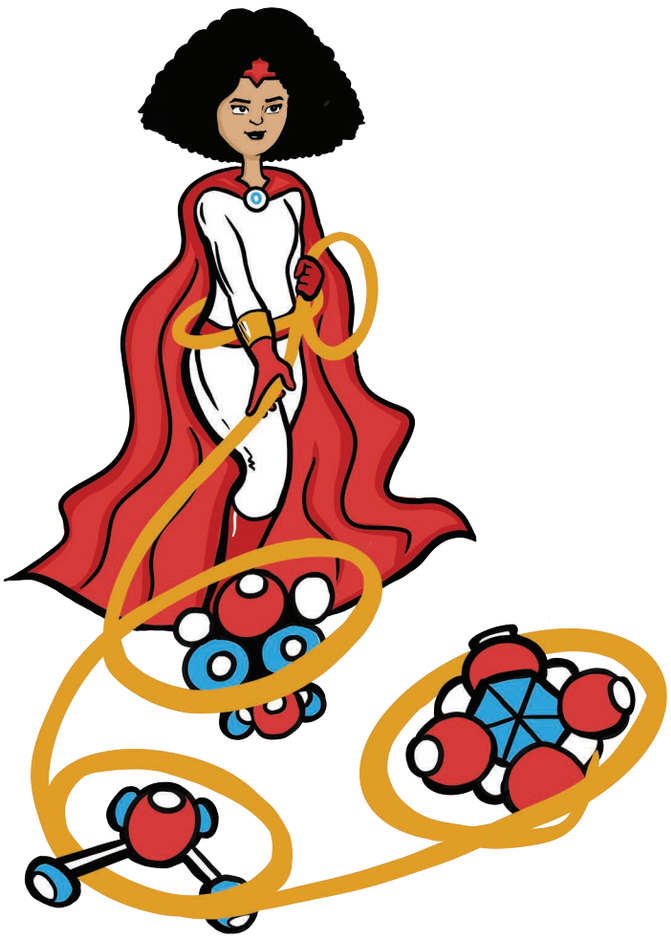
As a drug formulator, you are well aware that solubility and stability remain difficult challenges at every stage of drug development. Sometimes you probably feel like you could really use a superhero to tackle these obstacles to improve drug delivery and get your drug to market. Captain Captisol® to the rescue!

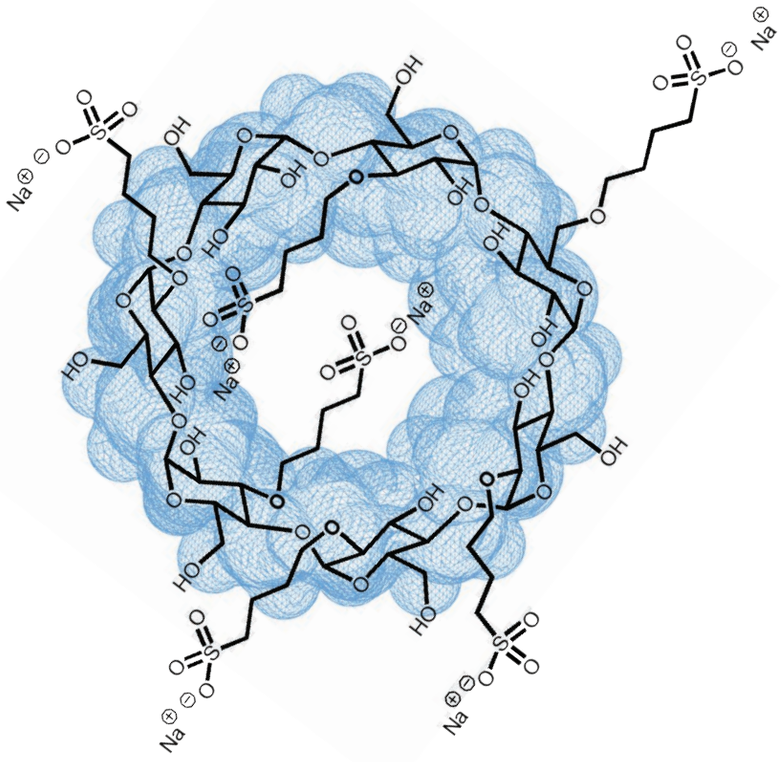
WHAT IS CAPTISOL®?

CAPTISOL® is the trade name for Ligand's solvent-free all aqueous processed modified cyclodextrin. Invented and developed by scientists at the University of Kansas, CAPTISOL® is a patent-protected mixture of chemically derivatized cyclodextrins with a structure designed to optimize the SOLUBILITY and STABILITY of drugs andv other compounds.

In stark contrast to the toxicities exhibited by other β-cyclodextrins, CAPTISOL®, has a proven safety profile when administered parenterally.

This unique technology has formulated many active agents and resulted in more than a dozen FDA-approved products, including Gilead's VEKLURY, Pfizer's VFEND® IV and Amgen's KYPROLIS®. CAPTISOL® has helped more than 10 million patients ˙ over 120 countries.

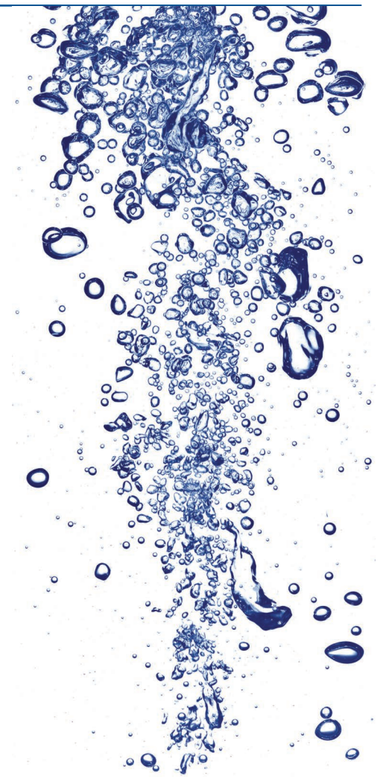




CAPTISOL® is a mixture of polyanionic β-cyclodextrin derivatives of a sodium sulfonate salt tethered to the lipophilic cavity by a butyl ether spacer, or otherwise known as a sulfobutyl ether (SBE) substituent. The sulfobutyl ether (SBE) substituent is introduced at the 2, 3, and 6 positions in one or more of the glucopyra- nose units in the β-cyclodextrin structure.

The introduction of SBE into cyclodextrin can produce preparations with different overall average degrees of substitution due to the proportion of multiple species present with different degrees of substitution, theoretically from 1 to 21. Studies with on average mono, tetra and hepta-substituted preparations (SBE1, SBE4, and SBE7) guided the selection of the SBE7-β-CD as the cyclodextrin mixture with the most desirable drug carrier properties. CAPTISOL® is the trade name for a SBE7-β--CD preparation.

THE BENEFITS OF CAPTISOL®



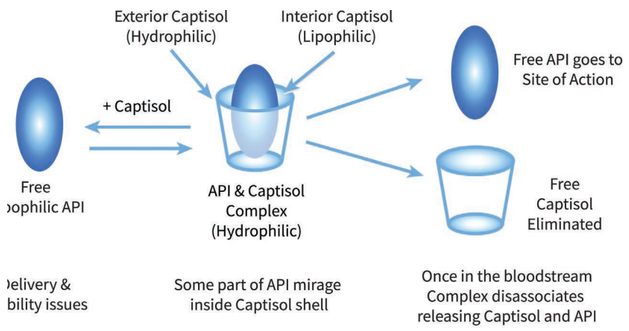
ENABLING PRODUCT DEVELOPMENT

Product Development is a complex process from discovery and nonclinical evaluation through clinical development and commercialization. Traditional formulation systems for very insoluble and/or unstable drugs have involved a combination of organic solvents, surfactants and extreme pH conditions. The resulting formulations are often irritating to the patient and may cause adverse reactions. At times, these methods are inadequate for solubilizing enough drug for a preferred formulation. CAPTISOL® provides an elegant solution to solubility and stability hurdles faced during each phase.

SOLUBILIZES

CAPTISOL® can complex drugs, independent of therapeutic category, and can increase water solubility by a factor of 10 to 150,000 depending on the compound structure. The extent of solubilization observed is related to the concentration of CAPTISOL®, the strength of the complex and the pH effects on the extent of drug ionization. Whether a small or large molecule, neutral, cationic and anionic drugs have been effectively complexed by CAPTISOL®.

In contrast to other solubilization technologies, CAPTISOL® can be rapidly assessed with a few simple experiments or with in silico or quantitative structure-property relationship (QSPR) computational techniques.



The cyclodextrin structure provides a molecule shaped like a truncated cone with a hydrophilic exterior surface and hydrophobic interior cavity.

The hydrophilic surface generates good water solubility for the cyclodextrin and the hydrophobic cavity provides a favorable environment in which 'to fit' substantially all or portions of the drug molecule. This association isolates the drug from the aqueous environment and may increase the drug's water solubility and stability.

STABILIZES

Stability of drugs in aqueous solution may be markedly improved on complexation with CAPTISOL®. Enclosure of the labile area of the drug in the cyclodextrin cavity or interaction with the SBE substituent can serve to reduce the rate of decomposition by 'hiding' the reactive center. Some protein and peptide formulations can be stabilized by minimizing aggregation, preventing adsorption to containers, and aiding in refolding. Studies show that the presence of CAPTISOL® decreases the aggregation of insulin and doubles subcutaneous bioavailability to 96%.

The extent of stabilization observed is related to the concentration of CAPTISOL®, the strength of the complex, pH and the storage conditions. While stability outcomes may not be certain, when they are observed, they can range from precipitation protection or photolytic degradation to improved hydrolytic stability. It's also not uncommon to improve the shelf-life of a drug product such that such that the storage conditions change from refrigerate to room temperature and for 10% drug loss to occur in years not weeks.

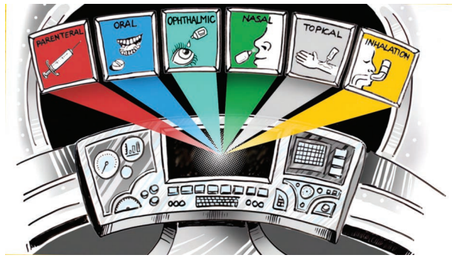
As an example, CAPTISOL® increases the room temperature shelf life of fosphenytoin, a phenytoin prodrug, from 10 months to more than four-and-a-half years. This is because CAPTISOL solubilizes the hydrolytically-produced phenytoin that would otherwise precipitate. Other selected examples of the ability of CAPTISOL® to optimize product formulations are shown below.

Product	Challenge Addressed
GEODON for Injection (ziprasidone mesylate)	• Increased solubility 150,000-fold • Enabled small volume IM injection concentrate
ABILIFY (aripiprazole)	• Increased solubility 7,500-fold to enable IM concentrate • Solved drug precipitation issues
Kyprolis™ (carfilzomib) for injection	• Solubility of high MW and LogP API increased ~3,500-fold • Enabled stable supersaturated form
Nexterone (amiodarone HCl) Premixed Injection	• Eliminated drug/infusion set incompatibility • Enabled ready-to-infuse premixed injection for acute care
NOXAFIL® posaconazole Injection 18mg/mL	• Increased solubility 5,000-fold • Enabled less irritating ready-made injection
Evomela® (melphalan) for Injection 50 mg per vial	• Removed co-solvents associated with AEs • Increased reconstituted solution stability 8-fold
Zulresso® (brexanolone) injection (IV) for intravenous use 100mg/20mL	• Increased solubility 28,000-fold • Enabled solution concentrate IV form for infusions greater than 24 hr
SESQUIENT (fosphenytoin sodium)	• Increased stability by solubilizing phenytoin degradation product • Enabled the only approved room temperature IV dosage form
Veklury® remdesivir 100 MG FOR INJECTION	• Increased solubility 333-fold and enabled stable supersaturated forms • Enabled lyophilized form to avoid cold-chain for transport and stockpiling and cold-chain ready-made solution • Met US and International Emergency COVID demand

ROUTES OF ADMINISTRATION

The increase in drug solubility obtained with CAPTISOL® allows the development of parenteral products without using extreme pH conditions outside physiological norms or use of mixed co-solvent systems. This results in bio-compatible formulations for instillation into the vasculature systems of the body including the tissue under the skin, into the muscle, or eye and nose.

The inherent pharmacokinetics and pharmacodynamics of the drug are unaffected by CAPTISOL®. Upon administration, the CAPTISOL®-drug complex rapidly disassociates. CAPTISOL® formulations are biocompatible and can be administered parenterally, orally, ophthalmically, nasally, topically and via inhalation.



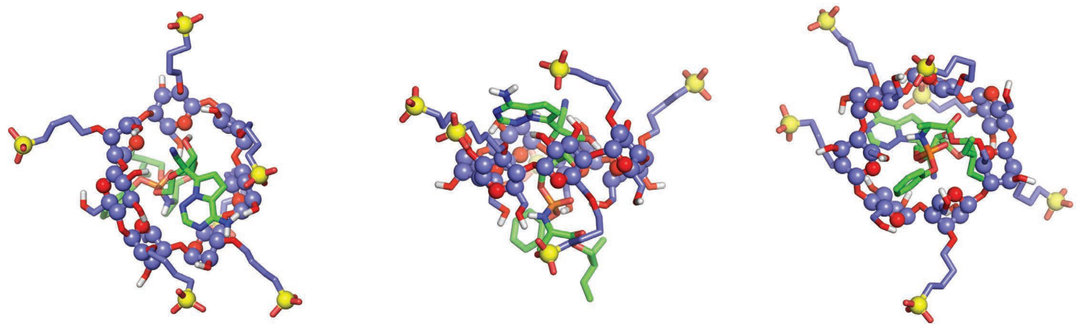
IV, IM and SQ administration of active agents in CAPTISOL® solutions demonstrate drug plasma levels and pharmaco- kinetic parameters equivalent to those seen with traditional co-solvent formulations but with less risk of the drug precipitating and better biocompatibility. Similar equivalence was seen for the miotic response after ocular installation of ophthalmic pilocarpine: CAPTISOL® preparations.

NON-PHARMA USES

The FDA has approved more than a dozen CAPTISOL®-enabled products. Additionally, there currently more than 60 Captisol-enabled products in the pipeline at various companies. CAPTISOL® is not limited to pharma products, finding use in vitamin supplements, food/beverage, soaps, and shampoo. CAPTISOL® can be used as a food additive to stabilize flavors and eliminate undesired tastes.

Consider the case of Essential Oils (EOs), which are commonly used as flavor and fragrance agents in cosmetics and food. EOs and their components are well accepted by consumers because of their natural origin and nutraceutical benefits. However, their application presents a challenge to formulators because of their volatility and poor aqueous solubility and stability. Additionally, they tend to evaporate, suggesting a need for encapsulation.

One way to enhance EOs solubility is to use CAPTISOL® for molecular encapsulation. Phase solubility studies showed that CAPTISOL® enhances the aqueous solubility of EOs and controls the release of EOs. It was ultimately determined that CAPTISOL® is a promising carrier and solubilizer that can expand the application of EOs.



Top View **Side View** **Bottom View**

CAPTISOL® SAFETY

CAPTISOL®'s chemical structure and manufacturing process were designed to maximize SAFETY. Beta cyclodextrin toxicity is thought to be due to extraction of cholesterol and other lipid membrane components from the renal tubule of the kidneys. This results in cell damage, lysis and death.

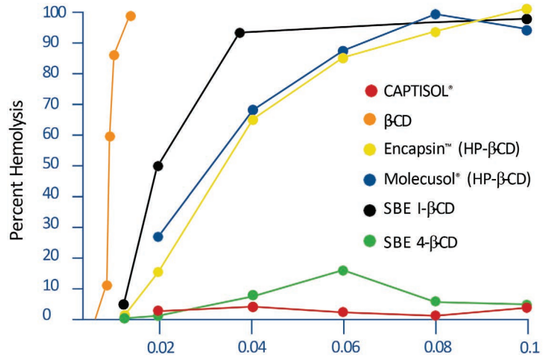
The anionic SBE group was introduced in CAPTISOL® to take advantage of the kidney's ability to rapidly excrete ionic compounds, hence minimizing the contact time between the kidney cells and the cyclodextrins. Several hundred pre-clinical and clinical studies have been performed and indicate that CAPTISOL® is safe when administered orally and parenterally, and does not exhibit the nephrotoxicity associated with beta-cyclodextrin

Biodistribution & Elimination

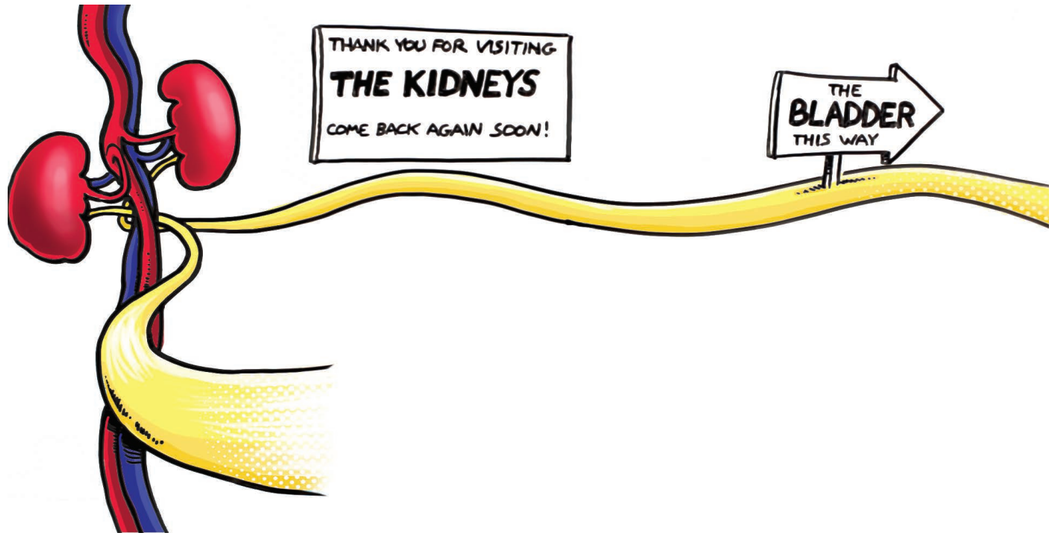
CAPTISOL®'s design results in minimal contact with kidney tissue. IV doses of CAPTISOL® (in rats, mice, dogs, rabbits, monkeys and humans) were cleared rapidly and completely from the circulation unchanged. Excretion was primarily in urine, with clearance approximating the glomerular filtration rate. The distribution of CAPTISOL® upon IV administration is limited to extracellular water and exhibits limited plasma protein binding.

CAPTISOL® produces no pharmacological effects on the cardiovascular system; autonomic or somatic functions, respiratory capacity or, fluid or electrolyte excretion upon IV administration in a variety of animal models. In vitro experiments and in vivo acute and sub-chronic toxicity studies have provided safety data to support the development and commercialization of CAPTISOL® drug formulations in man.

Hemolysis and Cyclodextrins



Cyclodextrin Concentration [Molar]
In Phosphate Buffered Saline
pH 7.4, 37°C, 5 minute incubation



CAPTISOL® REGULATORY ACCEPTANCE

The regulatory acceptability of solvent-free, all-aqueous processed CAPTISOL® is supported by extensive safety and clinical studies demonstrating its excellent systemic safety profile. Both Type IV and V Drug Master Files (DMF) are maintained with the FDA. The Type V regulatory safety package supports the use of CAPTISOL® in all routes of delivery. CAPTISOL® Drug Master Files have also been established in Canada, China and Japan. Over the past two decades multiple FDA divisions and other regulatory bodies have evaluated the data package and permitted the use of CAPTISOL® in more than **500** clinical trials.

CAPTISOL®-enabled FDA approvals

Captisol						Captisol Exposure			
Drug Product (Approval)	Indication	Route	Ratio (Active: Captisol)	In Drug Product (mg/mL)	For Dosing (mg/mL)	Maximum Infusion Rate (mg/min)	Maximum	Maximum Treatment Duration	Cumulative Treatment Dose (mg)
CARNEXIV™ (Oct 2016)	Seizures	IV	1:25	250	54.7	291.7 (30 min)	28,000 mg/day	Up to 7 days	196,000
VFEND (May 2002)	Antifungal	IV	1:16	a	80	56 (60 min)	192 mg/kg	Up to 7 days	94,080
NOXAFIL (Mar 2014)	Antifungal	IV	1:22	400	44.5	223 (30 min)	191 mg/kg	Up to 14 days	100,200
NEXTERONE (Nov 2010)	Antiarrhythmic	IV	1:10	18	18	300 (10 min)	150 mg/kg	21 days	154,500
EVOMELA (Mar 2016)	Chemotherapy	IV	1:54	270	24.3	324 (30 min)	9720 $mg/m^{2/day}$	2 days	19,440
KYPROLIS (Jul 2012)	Multiple myeloma	IV	1:50	100	100	1350 mg/m^2	90 mg/kg	Up to 27 cycles	658,800
ZULRESSO™ (Mar 2019)	Postpartum depression	IV	1:50	250	50	4500 mg/kg/hr (24 hours)	108 mg/kg	60 hours	14,700
BAXDELA™ (Jun 2017)	Antibiotic	IV	1:08	200	9.6	40 (60 min)	4800 mg/day	14 days	67,200
VEKLURY® (Oct 2020)	Antiviral	IV	1:60	300	48	400 (30 min)	12000 mg/day	10 days	66,000
SESQUIENT (Nov 2020)	Anticonvulsant	IV	1:02	100	50	300	40 mg/kg	Up to 5 days	7000
ABILIFY (Sept 2006)	Antipsychotic	IM	1:20	150	150	N/A	600 mg/day	N/A	N/A
GEODON (Jun 2002)	Antipsychotic	IM	1:15	294	294	N/A	588 mg/day	3 days	1,764

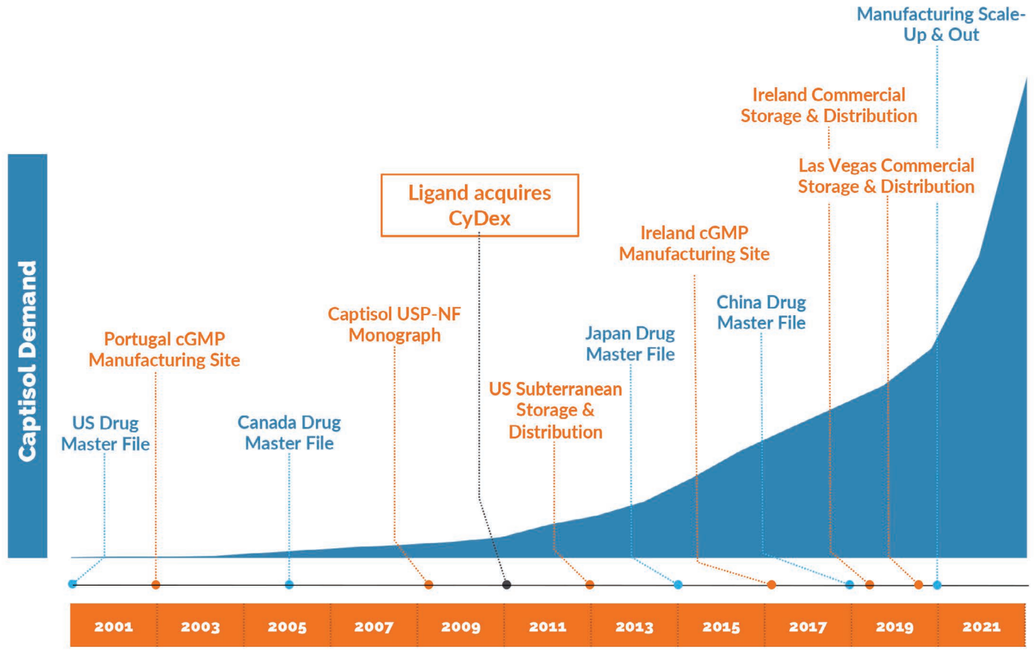
CAPTISOL® Quality & Availability

CAPTISOL® production is performed under cGMP controls for batches up to 7,500 kg. CAPTISOL® is supplied as an ultra-low endotoxin, ultra-low bioburden, low chloride solid that is suitable for use in parenteral formulations. Commercial CAPTISOL® quantities of hundreds of metric tons are available from two validated sites in Loures, Portugal and Cork, Ireland.

Each lot must meet strict analytical specifications before being released and while most excipients adhere to the minimum standards of USP and IPEC for pharma excipients, CAPTISOL® exceeds those guidelines. When Captisol is properly maintained at ambient temperature, and protected from moisture, ongoing stability shows CAPTISOL® is stable for at least seven years.

In addition to large metric ton quantities, CAPTISOL® can be ordered in 100g, 1kg, 5kg. and 20kg. pack sizes. To place an order or for a free sample, visit our website www.captisol.com.

CAPTISOL® Key Moments



Formulation development and regulatory guidance

If you don't have formulation capabilities, don't worry, the CAPTISOL® team can help! Each member of our formulation team has decades of experience in the pharmaceutical industry developing parenteral, oral, ophthalmic, nasal and inhalation formulations with CAPTISOL® and other cyclodextrins. Plus-the recent addition of internal resources and analytical tools will provide greater responsiveness for collaborative feasibility and development programs. Ask us for a project plan for your challenging development program.

The CAPTISOL® team has successfully brought forward several CAPTISOL® enabled drug products including Evomela, Nexterone and Fosphenytoin as well as aided clients in bringing forward their approved drug products. The team has extensive knowledge with orphan designations, preclinical, CMC and clinical development for ANDA, 505b2, traditional NDA programs, biowaivers and approvals. We are here to help create your ideal product formulation, assist in your development, safety studies, regulatory or manufacturing. Academic or Industry, the CAPTISOL® team is available to discuss your application, evaluate and potentially participate in the research project or developing the concept

Our team is ready.
Are you?
Contact us today!
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