WHAT IS CAPTISOL®?

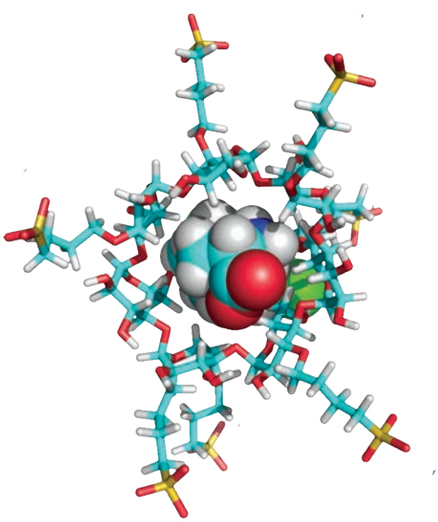
History of CAPTISOL®

CAPTISOL® is the trade name for Ligand's solvent-free processed modified cyclodextrin preparation. CAPTISOL® is a patent-protected mixture of chemically modified cyclodextrins with a modifying structure designed to optimize the solubility and stability of drugs. CAPTISOL® was invented and initially developed by scientists at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled seven FDA-approved products, including Pfizer's VFEND® IV, Amgen's KYPROLIS® and Merck's NOXAFIL IV. There are currently more than 50 CAPTISOL-enabled® products in clinical development.

CAPTISOL® is a mixture of polyanionic β-cyclodextrin derivatives of a sodium sulfonate salt tethered to the lipophilic cavity by a butyl ether tether, or sulfobutyl ether (SBE). The selection of solvent-free CAPTISOL® as the cyclodextrin preparation with the most desirable safety profile and drug association properties was based upon evaluations of the mono, tetra and hepta-substituted preparations.

CAPTISOL® manufactured by an all aqueous solvent-free process, has demonstrated safety when administered parenterally in stark contrast to the nephrotoxicity exhibited by unmodified β-cyclodextrin.

Relative to β-cyclodextrin, CAPTISOL® provides comparable or higher complexation characteristics and superior water solubility in excess of 70 g/100 ml—a >35-fold improvement.



THE BENEFITS OF CAPTISOL®

ENABLING PRODUCT DEVELOPMENT

Product development is a complex process from discovery and evaluation through development and commercialization. CAPTISOL® provides an elegant solution to solubility and stability hurdles faced during each phase of the development process. Combinatorial chemistry, high throughput screening (HTS) and molecular genetics have led to an increase in the number of insoluble and unstable molecules, peptides and proteins being investigated for their therapeutic activity.

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.

SOLUBILIZES

Neutral, cationic and anionic drugs as well as small and large molecules, have been effectively complexed by CAPTISOL®. Aqueous solubilities have increased by a factor of 10 to 150,000, depending on the compound. In contrast to other solubilization technologies, the enabling ability of CAPTISOL® can be rapidly assessed with *in silico* or quantitative structure-property relationship (QSPR) computational techniques or with a few simple experiments.

STABILIZES

CAPTISOL® provides a beneficial and protected environment for the drug molecule in its lipophilic cavity while its hydrophilic surface provides good water solubility, boosting both stability and solubility. Interaction of the drug with CAPTISOL® can reduce drug decomposition by protecting the labile region from the potential reactants in the aqueous environment.

The extent of stabilization observed is related to the concentration of CAPTISOL®, the strength of the complex, pH and the storage conditions. A dipivephrine solution at pH 5.0 and 25°C exhibited about 28 days with 90% of the drug remaining. The addition of 2.3 and 9.2 mM CAPTISOL® increased the time with 90% of the drug remaining to 570 and 729 days, respectively.

As another example, EVOMELA™ (CE-Melphalan) has significantly better stability in solution compared to the marketed Melphalan for injection. Reconstituted solution in vials is 17x more stable, and the admixture solution in bags is 5x more stable, respectively, than the same solutions prepared using currently marketed formulations.

Cyclodextrins and Pharmaceuticals

Cyclodextrins are cyclic carbohydrates derived from starch. They differ from one another by the number of glucopyranose units in the structure. The parent cyclodextrins contain 6, 7 and 8 glucopyranose units, and are referred to as alpha (α-), beta (β-), and gamma (γ-) cyclodextrin respectively.

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.

Oral use of the natural occurring parent cyclodextrins is well established in both food and pharmaceuticals. Greater than 50 β-cyclodextrin formulations for oral pharmaceutical products are now marketed in the U.S., Europe, Japan and India. Parenteral use is limited due to hemolytic and renal toxicity observed after systemic exposure.

CAPTISOL® was developed to address the unmet need for a drug carrier system appropriate for systemic delivery of drugs with poor water solubility.

An ideal cyclodextrin would exhibit both oral and systemic safety, as well as safety for other intended routes. It would have water solubility much greater than the native cyclodextrins yet retain or surpass their complexation characteristics.

CAPTISOL®: Definition

CAPTISOL® is an anionic β-cyclodextrin derivative with a sodium sulfonate salt separated from the hydrophobic cavity by a butyl ether spacer group.

The sulfobutyl ether (SBE) substituent is introduced at the 2, 3, and 6 positions in one or more of the glucopyranose units in the cyclodextrin structure. The introduction of SBE into β-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.

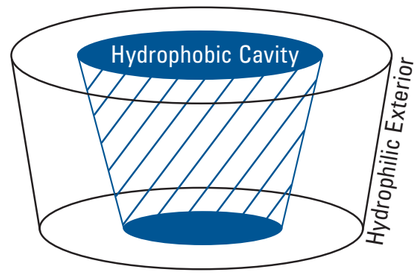
Intravenous preclinical and clinical studies of the all-aqueous processed CAPTISOL® demonstrate an excellent systemic safety profile. The introduction of this anionic sulfobutyl ether substituent yields a cyclodextrin derivative with enhanced complexation characteristics and water solubility in excess of 70 g/100 ml—a >35-fold improvement over the parent cyclodextrin.

Increased Drug Solubility

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®.



Enhanced Drug Stability

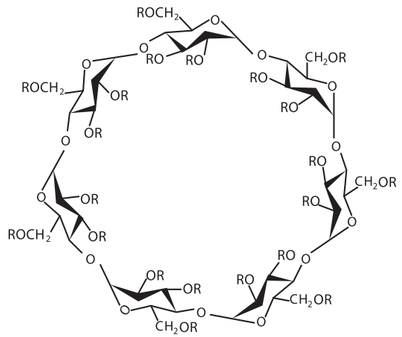
Stability of drugs in aqueous solution may be markedly improved on complexation with CAPTISOL®. Enclosure of the labile area of the drug in the cyclodextrin cavity or interaction with the SBE substituent can serve to reduce the rate of decomposition by 'hiding' the reactive center.

CAPTISOL® stabilizes some protein and peptide formulations by minimizing aggregation, preventing adsorption to containers and aiding in refolding. The presence of CAPTISOL® has been shown to decrease the aggregation of insulin and nearly doubles subcutaneous bioavailability to 96%.

Physical stability can also be improved by the presence of CAPTISOL®. The shelf life of fosphenytoin, a phenytoin prodrug, at pH 7.4 and 25°C is increased from 10 months to >4.5 years in the presence of 60mM CAPTISOL®. CAPTISOL® solubilizes the hydrolytically produced phenytoin that would otherwise precipitate.

Effective Drug Delivery

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 biocompatible formulations for instillation into the vasculature tissue under the skin, muscle, eye and nose.

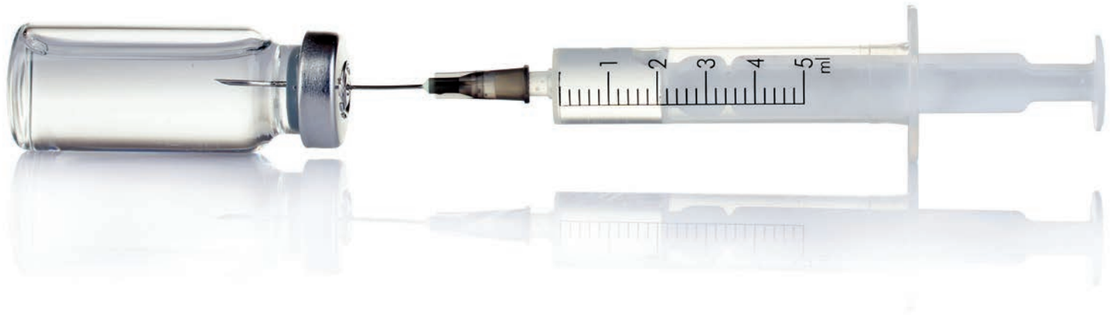


R=(H)$_{21-n}$ or (CH$_2$CH$_2$CH$_2$CH$_2$SO$_2$ONa)$_n$
where n=6.2 to 6.9

IV and IM administration of active agents in CAPTISOL® solutions demonstrate drug plasma levels and pharmacokinetic parameters equivalent to those seen with traditional co-solvent formulations. Similar equivalence was seen for the miotic response after ocular installation of ophthalmic pilocarpine CAPTISOL® preparations.

Pharmacokinetic results indicate that drugs dissociate rapidly and quantitatively from their cyclodextrin complexes on dilution with tissue fluids. Care should be taken, however, to optimize the formulation for the cyclodextrin concentration that solubilizes, stabilizes and effectively delivers the active ingredient.

CAPTISOL® can also enhance the oral bioavailability of poorly water soluble compounds if solubility and dissolution are the contributing limiting factors.



Safe Drug Carrier

CAPTISOL®'s chemical structure and solvent-free all-aqueous process were designed to maximize the safety of the material by minimizing the damaging effects produced by the parent cyclodextrins. The proposed mechanism for the toxicity of the parent cyclodextrins involves the ability of the cyclodextrin to interact with and extract cholesterol and other lipid membrane components from cells, particularly those of the renal tubule. This results in cell damage, lysis and death.

The anionic SBE group was introduced 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.

Straightforward Biodistribution and 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.

Without Pharmacological Activity

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.

Without Adverse Toxicological Effects

In vitro experiments and *in vivo* acute and subchronic toxicity studies have provided safety data to support the development and commercialization of CAPTISOL® drug formulations in man.

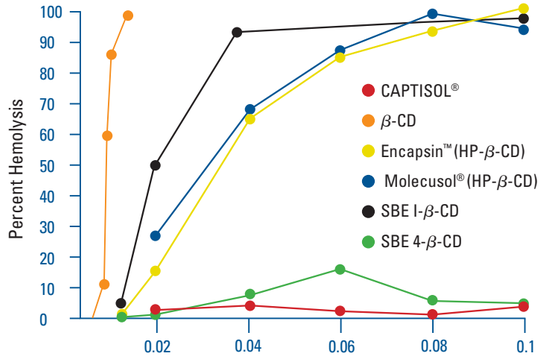
Summaries of the preclinical and clinical studies can be obtained after signing a Ligand Confidentiality Agreement.

CAPTISOL® Quality and Availability

CAPTISOL® production is performed under cGMP controls and IPEC guidelines for batches up to 1,500 kg. CAPTISOL® is supplied an ultra-low endotoxin, ultra-low bioburden, low chloride solid that is suitable for use in parenteral formulations. Commercial CAPTISOL® quantities up to hundreds of metric tons are available.

CAPTISOL® is manufactured under cGMP by a validated, patent protected solvent-free all-aqueous process. Testing and release of CAPTISOL® is performed according to the USP N.F. monograph for Betadex (Beta cyclodextrin) Sulfobutyl Ether Sodium as well as additional microbiological testing. Note, there are no organic solvents used in the manufacturing process of CAPTISOL® and no testing for these solvents. Specification limits are in place for residual starting materials, average degree of substitution, potential process side products, chloride, water content, and heavy metals, among others.

Hemolysis and Cyclodextrins



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

Data is available that demonstrate CAPTISOL® is remarkably reproducible and stable under a variety of conditions.

DELIVERS

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 pharmacokinetic parameters equivalent to those seen with traditional co-solvent formulations. Similar equivalence was seen for the miotic response after ocular installation of ophthalmic pilocarpine: CAPTISOL® preparations.

ACCEPTED

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. This regulatory safety data package, which is nearly 80 volumes in content, supports the use of CAPTISOL® in parenteral formulations as well as for other routes of delivery. CMC information specific to the manufacturing of CAPTISOL® is found in our Type IV DMF. In addition, USP has granted the USP N.F. monograph for CAPTISOL®. Multiple FDA divisions have evaluated the data package and permitted the use of CAPTISOL® in clinical trials. CAPTISOL® is currently used in 7 commercial products. In addition a new USP monograph has issued.

FDA Approved Drugs Containing CAPTISOL®

			CAPTISOL® Concentration		CAPTISOL® Exposure	
Drug Product	Indication	Route	In Drug Product	For Dosing	Maximum Rate of IV Infusion[a]	Recommended Total Daily Dose (Duration)
KYPROLIS® (Carfilzomib) for Injection (lyophilized)	Relapsed and refractory multiple myeloma	IV	100 mg/mL (after reconstitution)	37.3 mg/mL (after dilution)	1485 mg/min (for 2.2 m^2 individual over 2–10 min)	1350 mg/m^{2e} (beginning weekly cycle 2, 2 consecutive days/week)
VFEND® IV (lyophilized)	Fungal infections	IV	160 mg/mL (after reconstitution)	80 mg/mL (after dilution)	56 mg/min[b] (over 1–2 h)	192 mg/kg (Day 1) then 128 mg/kg (maintenance dosing[c])
NEXTERONE® Injection (vial/syringe)	Acute treatment of ventricular arrhythmias	IV	225 mg/mL	6.55 mg/mL	135 mg/min (initial infusion rate)[d]	68 mg/kg (Day 1) (over first 24 h of therapy then repeat as needed for up to 3 weeks)
NEXTERONE® Premixed Injection (flexible bag)	Acute treatment of ventricular arrhythmias	IV	15 mg/mL or 18 mg/mL	15 mg/mL or 18 mg/mL	300 mg/min (initial infusion rate)[d]	143 mg/kg (Day 1) (over first 24 h of therapy, the dose may be individualized)
GEODON® Injection (lyophilized)	Acute agitation in schizophrenia	IM	294 mg/mL (after reconstitution)	294 mg/mL	N/A	8.4 mg/kg (no more than 3 days)
ABILIFY® Injection (vial)	Acute agitation in schizophrenia or bipolar mania	IM	150 mg/mL	150 mg/mL	N/A	8.6 mg/kg (Day 1)
NOXAFIL®	Treatment of fungal infections	IV	400 mg/mL	40 mg/mL (after dilution)	223 mg/min (6.68 g/30 min)	191 mg/kg (Day 1) Then 95 mg/kg (maintenance dosing[c])

[a] = Based on an average patient (e.g. weight = 70 kg body surface area = 1.8 m^2).
[b] = Equivalent to 48 mg/kg/h for a 70 kg patient.
[c] = Duration of therapy based on disease severity recovery from immunosuppression and clinical response.
[d] = Followed by additional infusions at lower rates.
[e] = The MTD determined as 70 mg/m^2 Carfilzomib with 3500 mg/m^2 CAPTISOL via once-weekly 30-minute infusion in the CHAMPION-1 Trial (NG101677858)

CAPTISOL®

[Betadex (ß-Cyclodextrin) Sulfobutyl Ether Sodium] N.F.
Certificate of Analysis Rev 0
Batch Number: XXXXXX.XXXXXXX

Test	Specification	Result
Identification:		
Infrared Absorbance	Spectrum is consistent with the SBECD standard	Conforms
Retention Time (RT)	RT of major peak consistent with standard by Assay	Conforms
Degree of Substitution (DS)	Meets the requirements for DS by CE	6.6
Sodium	Identity tests are positive for Sodium	Conforms
Assay:	95.0% to 105.0% (anhydrous basis)	100.8%
Impurities:		
Heavy Metals	Not more than 5 ppm	< 5 ppm
Beta-Cyclodextrin	Not more than 0.1%	< 0.05%
1,4-Butane Sultone	Not more than 0.5 ppm	< 0.5 ppm
Sodium Chloride	Not more than 0.2%	< 0.05%
4-Hydroxybutane-1-Sulfonic Acid	Not more than 0.09%	< 0.03%
Disodium Bis (4-sulfobutyl) Ether	Not more than 0.05%	< 0.02%
Specific Tests:		
Bacterial Endotoxins	Not more than 25 EU/g	< 2.4 EU/g
Aerobic Microorganisms	Does not exceed 50 CFU/g	0 CFU/g
Molds and Yeasts	Does not exceed 25 CFU/g	0 CFU/g
Escherichia coli	Meets test requirement for absent	Conforms
Salmonella sp.	Meets test requirement for absent	Conforms
Bile-tolerant Gram-negative bacteria	Meets test requirement for absent	Conforms
Pseudomonas aeruginosa	Meets test requirement for absent	Conforms
Staphylococcus aureus	Meets test requirement for absent	Conforms
Solution Clarity	A 30% w/v solution in water is clear	Conforms
pH	4.0 to 6.8 in 30% w/v solution of carbon dioxide free water	5.8*
Water Determination (KF)	Not more than 10.0%	5.0%*
Appearance	White to off-white solid, essentially free foreign matter	Conforms
Average Degree of Substitution (CE)	6.2 to 6.9	6.6
	Sulfobutyl Ether Peaks I–X	% Peak Area
	I (Limit 0.0 to 0.3)	0.0
	II (Limit 0.0 to 0.9)	0.2
	III (Limit 0.5 to 5.0)	1.8
	IV (Limit 2.0 to 10.0)	6.1
	V (Limit 10.0 to 20.0)	13.9
	VI (Limit 15.0 to 25.0)	23.3
	VII (Limit 20.0 to 30.0)	26.9
	VIII (Limit 10.0 to 25.0)	18.6
	IX (Limit 2.0 to 12.0)	7.5
	X (Limit 0.0 to 4.0)	1.7

***Results obtained at time of testing; values may change depending upon exposure to atmospheric conditions.**
STORAGE: Store at ambient temperature in sealed containers. Protect from moisture.

Reference: XXXXXX.XXXXXXX Re-evaluation Date: March 2020

Date of Manufacture: March 2015
Manufactured by: Hovione FarmaCiencia SA,
Sete Casas Loures 2674-506 Portugal

Captisol is manufactured and tested in conformance with the principles of Chapter <1078> of the United States Pharmacopeia (Good Manufacturing Practices for Bulk Pharmaceutical Excipients).

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