Frequently Asked Questions

CAPTISOL®

β-Cyclodextrin Sulfobutyl Ethers, Sodium Salts

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CYDEX PHARMACEUTICALS

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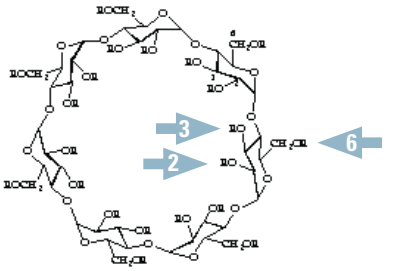
CYDEX PHARMACEUTICALS

What are cyclodextrins?

This cyclic orientation provides a truncated cone structure that is hydrophilic on the exterior and lipophilic on the interior. Cyclodextrin complexes are formed when a guest molecule is partially or fully contained in the interior of the cavity. The parent α-, β-, and γ-cyclodextrins (particularly β) have limited aqueous solubility and show toxicity when given parenterally. Therefore, the parent cyclodextrin structure has been chemically modified to generate a parenterally safe CD-derivative. The modifications are typically made at one or more of the 2, 3, or 6 position hydroxyls.



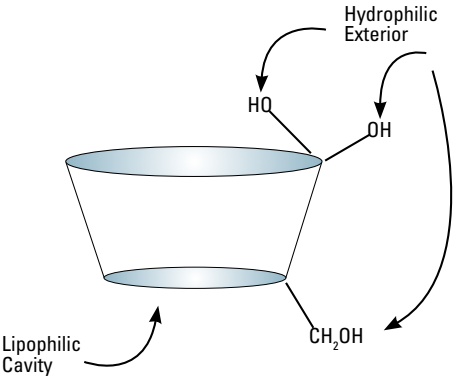
What is the difference between dextrins and dextrans?

Dextrans are soluble polysaccharides produced by bacteria and yeasts. They are characterized by a predominance (>95%) of α (1-6) backbone linkages and varying proportions of α(1-2), α(1-3) and α(1-4) linkages typically at branch points [1,2].

Dextrins are partially hydrolyzed glucose homopolymers composed exclusively of α(1-4) backbone linkages.

β-cyclodextrin is a cyclic structure composed of seven glucose units linked by α(1-4) linkages. Therefore it is a dextrin.

[1]Lehninger, A.L., (1975) Biochemistry, 2nd edition, pp. 264-266, Worth, New York.
[2]Janson, J., (1972) Studies on dextran degrading enzymes from bacterial and molds, PhD dissertation, Uppsala University, Sweden



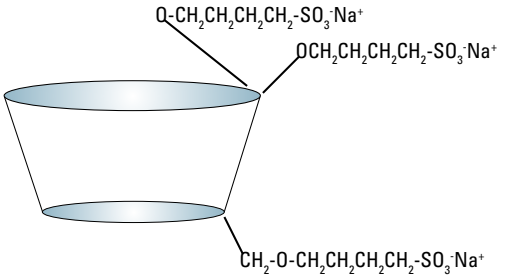
What are modified cyclodextrins and why were they developed?

Chemical modifications have been made by numerous researchers to alter the undesirable solubility and parenteral safety properties of the parent cyclodextrins. The modifications are mostly derivatives attached through the three available hydroxyl groups on each glucopyranose unit. Thus up to 18(α-CD), 21(β-CD), or 24(γ-CD) degrees of substitution may be realized, with numerous positional and regioisomers possible.

How is CAPTISOL® different from other modified cyclodextrins?

CAPTISOL® is a sulfobutyl ether derivative of β-cyclodextrin with a range of six to seven sulfobutyl ether groups per cyclodextrin molecule. Because of the very low pKa of the sulfonic acid groups, CAPTISOL® carries multiple negative charges at physiologically compatible pH values.

The four-carbon butyl chain coupled with repulsion of the end group negative charges allows for an "extension" of the cyclodextrin cavity. This often results in stronger binding to drug candidates than can be achieved using other modified cyclodextrins. It also provides a potential for ionic charge interactions between the cyclodextrin and a positively charged drug molecule. In addition, these derivatives impart exceptional solubility and parenteral safety to the molecule.



CAPTISOL® IN FORMULATIONS

How does CAPTISOL® improve formulations?

CAPTISOL® is a modified cyclodextrin that can form ionic and inclusion complexes with many types of drugs. Complexation can significantly increase the solubility and often times, the physico chemical stability of the drug. Complexation has also been used to improve dissolution and bioavailability, reduce volatility, allow incorporation of liquids into solid formulations, and reduce unpleasant side effects such as taste and irritation caused by drug contact with tissues, e.g. extravasation at injection sites and GI irritation.

Will CAPTISOL® complex with my drug candidate?

In general, CAPTISOL® will complex with many hydrophobic compounds that have structural features that can fit within the cyclodextrin cavity. A significant amount of literature is available illustrating the types of compounds that are candidates for inclusion complexation, but confirmation must be made by conducting a few simple laboratory tests.

Will CAPTISOL® complex with peptides and proteins?

Complexation can occur between CAPTISOL® and peptides/proteins through the side chains of individual amino acids. The complexation can assist in solubilization, stabilization, particularly in terms of reduced aggregation, and refolding, which can lead to improved bioavailability. Cyclodextrins can also improve the effectiveness of antisense therapies by assisting in:

Cellular uptake (Zhao, et. al. 1995; Abdou, et. al.), Internalization (Croyle, et. al.), Nuclease resistance of oligonucleotides (Habus, et. al.), Improved activity (Abdou, et. al.) •Reduced side effects (Zhao et. al. 1996), Abdou S, Collomb J, Sallas F, Marsura A, Finance C. Beta-cyclodextrin derivatives as carriers to enhance the antiviral activity of an antisense oligonucleotide directed toward a coronavirus intergenic consensus sequence. Arch. Virol. 142[8], 1585-1602. 1997. Audran R, Men Y, Johnasen P, Gander B, Corradin G. Enhanced Immunogenicity of Microencapsulated Tetanus Toxoid with Stabilizing Agents. Pharm. Res. 15[7], 1111-1116. 1998. Branchu S, Forbes RT, York P, Petren S, Nyqvist H, Camber O. Hydroxypropyl-Beta-Cyclodextrin Inhibits Spray-Drying-Induced Inactivation of Beta-Galactosidase. J. Pharm. Sci. 88[9], 905-911. 1999. Brewster ME, Hora MS, Simpkins JW, Bodor N. Use of 2-hydroxypropyl beta-cyclodextrin as a solubilizing and stabilizing excipient for protein drugs. 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Pharmacol. 52[10], 1537-1544. 1996.

Can CAPTISOL® be used in injectable formulations?

Yes. An extensive toxicology package has been developed demonstrating the safe use of CAPTISOL® for parenteral administration (intravenous, intramuscular and subcutaneous). This information can be made available for client review upon request.

Can CAPTISOL® be given by non-parenteral routes?

Safety studies have been conducted with CAPTISOL® for many different routes of administration, including oral, ophthalmic, inhalation and nasal. CyDex has completed numerous safety studies in rat, mice, dog, rabbit and monkey by these different routes of administration. Final reports have been submitted to the FDA in our Type V DMF and are available to clients under applicable agreements.

Is CAPTISOL® suitable for use in solid formulations?

CAPTISOL® has been used quite successfully in solid formulations to assist in solubilization, dissolution and improved absorption.

SOLUTION AND SOLID STATE CHARACTERISTICS OF CAPTISOL®

What are the solid state characteristics of CAPTISOL®?

CAPTISOL® is currently isolated by spray drying. Some characteristics of this spray dried material are:

Molecular Weight	average 2163 (based on average degree of substitution of 6.5)
Crystallinity	amorphous
Water Content	max. 10%
Melting point	decomposition at approximately 275°C

What are the properties of CAPTISOL® solutions?

In addition to the information presented elsewhere:

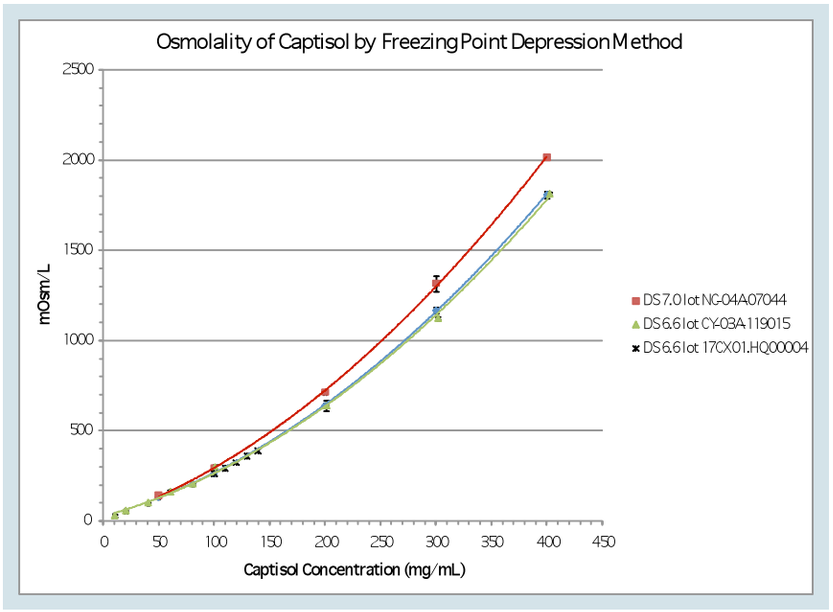
Various Properties of CAPTISOL® Solutions

CAPTISOL® Concentration (%w/w)	59.4	49.4	39.7	29.8	19.7	8.5
Sample pH	5.6	5.6	5.7	5.8	5.9	6.0
Density (g/mL)						
25°C	1.320	1.29	1.202	1.149	1.095	1.041
38°C	1.315	1.253	1.197	1.143	1.088	1.036
Viscosity (cp)						
25°C	527.5	51.9	17.0	5.9	2.8	1.8
40°C	217.3	31.1	10.3	3.6	2.1	1.5
60°C	87.3	21.2	6.5	2.5	1.7	1.1

At what concentration is CAPTISOL® isotonic?

The plot below shows the solution osmolality as a function of CAPTISOL® concentration and degree of substitution (DS). In general, aqueous Captisol solutions in the range of 9.5 to 11.4% w/v are iso osmotic with blood and extracellular fluid (280-330 mOsM).

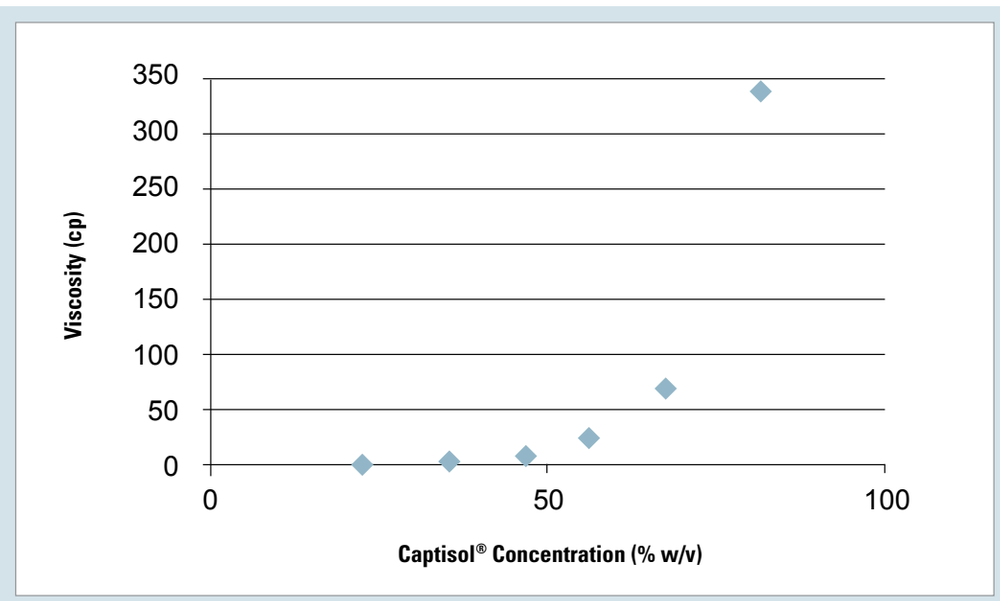
NOTE: Preclinical safety studies have been conducted at 30-40% w/v CAPTISOL® without any adverse effects from the hypertonicity of the solution.



I would like to use a 30% w/v solution of CAPTISOL® in my formulation. Will it be highly viscous?

The viscosity of CAPTISOL® solutions does increase with an increase in concentration. However, for most practical applications, the viscosity is not an issue. The viscosity of various CAPTISOL® solutions is shown below in w/v units. The w/w figure demonstrates the change in viscosity as a function of temperature.

% w/v	Viscosity (cp)
22.5	2.3
33.7	4.5
45.0	9.5
56.2	24.8
67.5	73.0
78.7	332.4



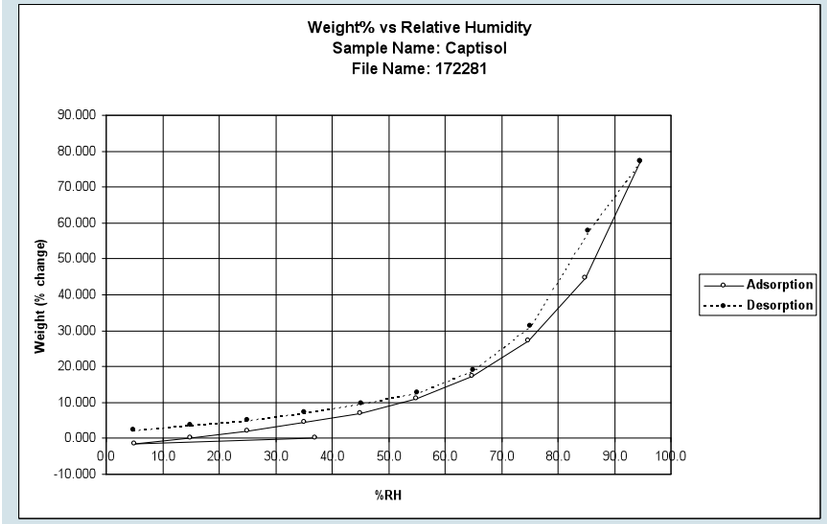
Can CAPTISOL® be autoclaved?

Yes. CAPTISOL® is stable at autoclave temperatures and under a broad range of pH and other stress conditions.

CAPTISOL® is noted to be hygroscopic - how should we handle the solid material?

CAPTISOL® is a hygroscopic amorphous solid. Its moisture isotherm is shown in the figure below. CAPTISOL® will reversibly take up moisture without any effect on the appearance of the material at humidities up to 60% RH. Equilibration at relative humidity values above 60% will result in deliquescence. Once in this state, the material can be dried, but will give a glass-like product. This water absorption behavior is typical of amorphous hygroscopic materials.

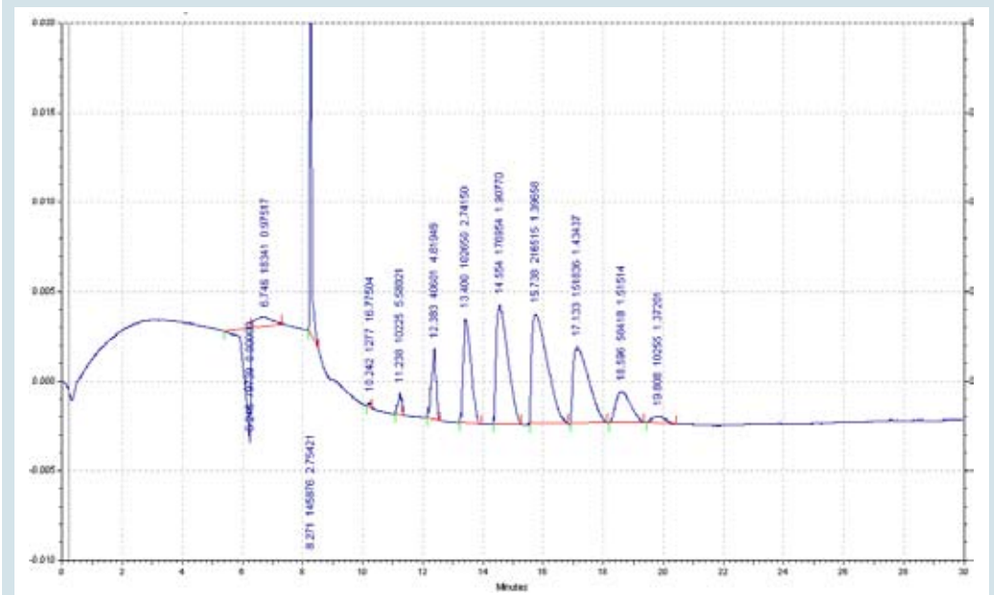
CAPTISOL® should be stored in a closed container to maintain its water content. The water content of CAPTISOL® should be determined if material has been opened for an extended period of time.



What is the substitution pattern of CAPTISOL®?

CAPTISOL® is a mixture of both positional and regioisomers. There are three positions on each glucose unit available for modification, and seven glucose units in the parent β cyclodextrin. CAPTISOL® is a homogenous mixture of derivatives containing 1 through 10 substituents on each β-cyclodextrin molecule with the average being seven. The manufacturing process produces material with a well controlled substituent distribution. This distribution is well characterized, reproducible, and monitored by capillary electrophoresis (CE). A release specification has been developed for the CE "fingerprint" of CAPTISOL®.

Captisol Electropherogram



HOW TO USE CAPTISOL® TO SOLUBILIZE A DRUG

What 'recipe' can I use to get an idea if CAPTISOL® will solubilize my drug?

THE SIMPLE DETAILS

- Prepare a 40% solution of CAPTISOL® in water by dissolving 400 mg (corrected for water content) into a total volume of 1 mL.
- Serially dilute the sample as in Table 1.
- To six small vials, add sufficient drug candidate to exceed the potential amount that could be solubilized by CAPTISOL®.
- To each vial, add ½ mL of the corresponding CAPTISOL® solution, cap the vials, sonicate and place on a tumbling apparatus at controlled (or room) temperature. Let the vials agitate for 1 to 3 days (depending on the stability of your drug candidate).
- Remove the vials at the end of the agitation period and either centrifuge or filter the suspensions to obtain clear solutions.
- Analyze the solutions for drug content.

Table 1: Material needs to conduct a phase solubility analysis.

		CAPTISOL® Concentration		Milligrams of drug added to ½ mL solution *+	
#	Solution Preparation	% w/v	Molar	Minimum	Typical++
A	400 mg Captisol® in 1 mL water	40	0.185	46 + S	50
B	½ mL Solution A + ½ mL water	20	0.0925	23 + S	25
C	½ mL Solution B + ½ mL water	10	0.0462	12 + S	25
D	½ mL Solution C + ½ mL water	5	0.0231	6 + S	25
E	½ mL Solution D + ½ mL water	2.5	0.0116	3 + S	25
F	Water	0	0	S	25
	Total Material Needs (mg) 400			90 + 6S	175

S is the intrinsic solubility of the drug in water (mg in ½ mL)

** Assumes a molecular weight of 500*

++ More practical amounts are typically used in order to facilitate weighing and handling.

The stated amounts will be sufficient when the intrinsic water solubility is quite low.

INTERPRETING THE DATA

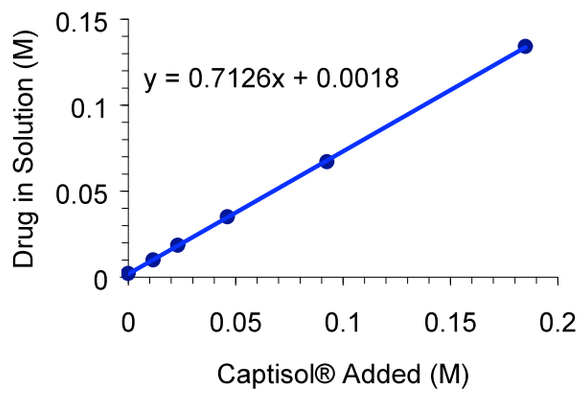
The results are typically plotted as moles of drug in solution vs. moles of CAPTISOL® added. A typical phase solubility plot is shown in *Figure 1*. If the solubility increases with the addition of CAPTISOL®, complexation has occurred. The strength of the complex, quantitated as a complexation constant (K1:1, in units of 1/molar)), can be calculated from the slope and intercept (S0 or intrinsic solubility) of a line drawn through the points on the graph.

Figure 1

$$K_{1:1} = \frac{slope}{S_0\,(1 - slope)}$$

This equation is valid for the 1-to-1 complexes that are typically formed between drugs and CAPTISOL®. These data can then be used to develop formulations where a required solubility must be maintained.

Figure 1. Phase Solubility Plot



What additional steps can I take to increase the solubility of my drug with CAPTISOL®?

pH

Does the molecule have an ionizable group? CAPTISOL® is anionic so if you can adjust pH to create a positive (+) charge on your compound, the electrostatic charges may assist in attracting and retaining your compound in CAPTISOL®'s hydrophobic cavity. If your compound is negatively (-) charged, adjusting the pH to give a neutral or positive charge may block any electrostatic repulsion with CAPTISOL®. Many of our clients have found that changing the solution pH can greatly improve binding and solubility. We have also found it useful to test different salts of the drug, not just the salt with the highest intrinsic solubility.

Polymers

If the compound in question is stable to heat, another method is to prepare a CAPTISOL® solution (20-40%) containing 0.1-2% polyvinyl pyrolidone (PVP) or carboxy methylcellulose (CMC), or hydroxypropylmethyl cellulose (HPMC). Add solid drug and autoclave the sample at 121^0 C for 20-45 minutes. Allow the suspension to cool and stir for 24-48 hours to achieve maximal solubility.

Can I add an organic solvent to a CAPTISOL® solution to help increase the solubility of my drug?

Typically, the addition of an organic solvent (such as ethanol, methanol, acetonitrile, DMSO) will result in a decrease of the complexation of the drug with a cyclodextrin. The solvent molecules are also hydrophobic relative to water and will often insert into the cavity preferentially over the drug molecule –basically because there tends to be a large excess of solvent molecules to compete with the drug molecules for the CD cavity.

What is the solubility of CAPTISOL® in water, methanol, acetonitrile, or other organic solvents?

Solubility of SBECD at 25^{0}C

Solvent	Solubility (mg SBECD/mL)
Water	>1500
0.1 M HCl	>1500
0.1 M NaOH	>1500
Methanol	~23
n-Hexane	<0.1
1-Butanol	<0.1
Acetonitrile	<0.1
Ethyl Acetate	<0.1
0.1 M KNO_3 in Acetonitrile/Water, 20/80 (v/v)	>1500

My drug is very non-wettable, are there any techniques I can use to improve dissolution?

If the drug is highly crystalline or non-wettable you may experience difficulty solubilizing the compound with CAPTISOL®. Consider triturating solid CAPTISOL® with the solid drug in a mortar/pestle. During grinding, add a small amount of a solvent in which the drug is soluble and water (e.g., 95% EtOH). The solvent should contain some water to solubilize the CAPTISOL®. We have successfully used 95% ethanol/water or solutions of methanol/water or DMSO/water. Add just enough of the solvent to form a paste or wet mass and continue mixing. Slowly add water over time.

The following steps apply this technique:

'Solid Phase to Solution' Complexation Method

- Assumption: Candidate Drug has a MW = 500 gm/mole
- 5 mg of the drug in 1 mL of solution would be a 10 mM drug solution [(0.005 gm/1 mL) (1 mole/500 gm) (1000 mL) = 0.01 mole/1000 mL = 0.01 M = 10 mM]
- A 1:1 CAPTISOL®: Drug complex would then require 1 mL of a 10 mM solution of CAPTISOL® [(1 mL) (10 mmoles CAPTISOL®/1000mL) (2200 mg/mmole) = 22 mg/mL of CAPTISOL®]
- For best first trial evaluation try to provide a 10 molar excess of CAPTISOL® to drug [220 mg of CAPTISOL® in 1 mL of solution would be a 22% solution]

1. Weigh out 5 mg of Drug and 220 mg of CAPTISOL® . Grind the two solids with a mortar and pestle to increase particle surface area and disperse heterogeneous materials.
2. Transfer solid mixture to a 'volumetric' container that can be diluted to 1 mL and have sufficient space to allow 'shaking' to agitate solid in solution.
3. Add a drop or two of 'Aqueous Solvent' to create a very concentrated CAPTISOL® solution with minimal aqueous characteristics and maximal chance for hydrophobic drug to find the CAPTISOL® cavity. Warm solution/suspension and sonicate if necessary. Temperature constraints depend on stability of drug not the CAPTISOL®.
4. Slowly add 'Aqueous Solvent' to 1 mL volume.

'Aqueous Solvent': Ideally, the only solvent added should be water, however, depending on the drug characteristics a buffer may be used. For drugs that are extremely water insoluble, the first drop or two may need to be ethanol or DMSO but more preferably an aqueous ethanol or DMSO solution with as little of the organic solvent as possible (i.e. 50:50 EtOH: Water).

NOTE:

1. The method is set up to use as small amount as drug as possible (5mg) for these initial studies. If you do not have any constraints on drug availability - increase the weight proportionally and work at larger volumes.
2. If any of these methods work, optimize the formulation by decreasing the molar excess of CAPTISOL® from the 10-fold excess down as low as possible.
3. If you desire to have a drug concentration greater than 10 mM, adjust the weights of drug and CAPTISOL® to keep the same ratio of 10-fold excess of cyclodextrin until you determine that you can achieve solubility - then attempt to decrease the CAPTISOL® amounts.

We have also seen the use of a small amount of pluronic F65 (0.3-0.5% w/v) or other nonionic surfactant in a CAPTISOL® solution to improve the wetting and dissolution of the drug particles

How does pH affect complexation?

The pH of a solution has the potential to effect complexation of a drug with CAPTISOL® in several ways. If the drug has one or more ionizable functionalities, altering the pH will affect the extent of ionization of the drug. In general, complexation of drugs with cyclodextrins is strongest when the drugs are uncharged. However, since CAPTISOL® is negatively charged at all relevant pH values, the presence of a positive charge on the drug can assist complexation via charge attraction. Some examples of the effects of charge state on complexation are given in the following table. Comparisons are shown of the binding constants (K) of numerous drugs with the neutral hydroxypropyl cyclodextrin derivative or with CAPTISOL®.

How does temperature affect complexation?

Complexation usually will decrease as temperature increases. However, the intrinsic water solubility of most drugs will increase with temperature. Since the total amount of drug in solution is a function of both the intrinsic solubility of the drug in the absence of cyclodextrins and of the complexation constant, often times the two effects will cancel out. However, appropriate studies must be conducted to determine the temperature effects for each formulation. The temperature effects on complexation should be taken into account when designing accelerated stability studies. If complexation is used in part to improve stability, the results obtained from studies at elevated temperatures may underestimate the stability at lower temperatures.

Effect of Charge State of Drug on (1:1) Binding to Neutral HP-β-CD and Anionic CAPTISOL®

	Neutral Drug K^a (M^{-1})		Anionic Drug K^a (M^{-1})		Cationic Drug K^a (M^{-1})	
Drug	HP-β-CD	CAPTISOL®	HP-β-CD	CAPTISOL®	HP-β-CD	CAPTISOL®
Cinnarizine[b]	22,500	69,700			4,000	17,500
Cinnarizine[b]	494	-			6	-
Danazol[c]	76,600	94,900				
Digozin[d]	4,900	6,880				
Hydrocortisone[d]	1,340	2,150				
Indomethacin[b]	1,590	4,710	955	819		
Miconazole[b]	104,000	417,000			42,300	410,000
Miconazole[b]	45	12			11	<1
Naproxen[b]	1,670	3,600	331	432		
Papaverine[b]	337	1000			17	94
Phenytoin[d]	1,070	756				
Progesterone[d]	11,200	18,300				
Testosterone[d]	11,600	22,500				
Thiabendazole[b]	136	443			7	56
Warfarin[b]	2,540	10,100	509	262		

a Binding constants for (1:1) complexation unless noted.

b Hydroxypropyl derivative used = Encapsin TM (Degree of Substitution = 3.5)

c Hydroxypropyl derivative used = Roquette (Degree of Substitution not reported)

d Hydroxypropyl derivative used = Molecusol® (Degree of Substitution = 7-8)

If my drug candidate is ionized, will it still complex with CAPTISOL®?

Complexation typically occurs best with a neutral molecule. However, many anions have been shown to complex well with CAPTISOL®, and because of the charge attraction (CAPTISOL® is negatively charged), cations will often bind to CAPTISOL® better than the neutral forms. See also "How does pH affect complexation?"

Will I need to prepare and isolate the Drug: CAPTISOL® complex for use in solid preparations?

Successful formulations have been prepared using either physical mixtures (e.g., dry blend) of a drug and CAPTISOL® or a preformed drug: CAPTISOL® complex. Care must be taken in the design of the physical mixture dosage forms to assure that complexation will occur in situ. CyDex currently holds patents on the use of both formulation types.

CAPTISOL® is prepared as the sodium salt. How much sodium is present in CAPTISOL® solutions?

The table below indicates the various units for describing different concentrations of CAPTISOL® solutions. CAPTISOL® contains one sodium ion for each level of substitution.

Sodium Content versus Captisol® Concentration

CAPTISOL® % w/v	CAPTISOL® gm/mL	CAPTISOL® moles/liter	Eq Na^+/liter CAPTISOL® Solution	mEq Na^+/mL CAPTISOL® Solution
1.00	0.01	0.0046	0.0301	0.03
2.50	0.03	0.0116	0.0751	0.08
5.00	0.05	0.0231	0.1503	0.15
10.00	0.10	0.0462	0.3005	0.30
11.00	0.11	0.0509	0.3306	0.33
12.50	0.13	0.0578	0.3756	0.38
15.00	0.15	0.0693	0.4508	0.45
20.00	0.20	0.0925	0.6010	0.60
22.00	0.22	0.1017	0.6611	0.66
30.00	0.30	0.1387	0.9015	0.90
40.00	0.40	0.1849	1.2020	1.20
50.00	0.50	0.2312	1.5025	1.50

NOTE: consider total sodium load when formulating with other sodium containing ingredients.

AFFECT OF CAPTISOL® ON Pk OF DRUG

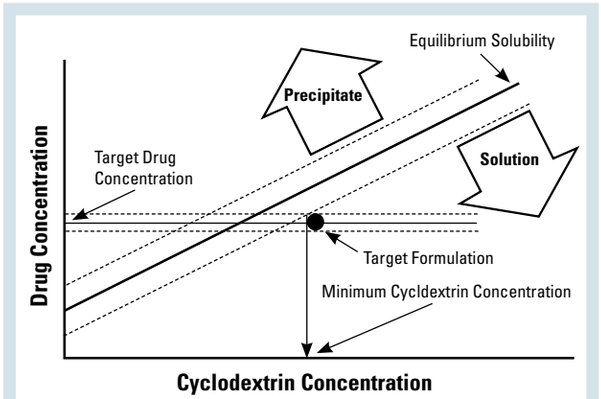
Is the drug candidate released from the complex?

Complexes dissociate rapidly and completely in most cases. Complexation in aqueous solutions is an equilibrium situation with drug/cyclodextrin complexes continually forming and dissociating with lifetimes in the range of milliseconds or less. Dilution is the major driving force for dissociation after parenteral administration. If the drugs are strongly bound or if dilution is minimal (e.g. topical administration), then competitive displacement from endogenous lipophiles contributes to the dissociation process. (Stella, V.J., Rao, V. M., Zannou, E. A. and Zia, V., Mechanisms of Drug Release From Cyclodextrin Complexes, Adv. Drug Del. Rev., 36(1), 3-16, 1999)

USAGE OF CAPTISOL® IN FORMULATIONS

How much CAPTISOL® is needed in an injectable formulation?

In general, sufficient CAPTISOL® will be required to achieve the target solubility of the drug as determined from the phase solubility diagram, plus a safety margin to allow for temperature changes, etc., during processing and storage. Preformulation and formulation studies should be conducted which will define the minimum amounts of complexing agent needed to assure solubility of the active (and in some cases potential degradants, etc) across the expected range of temperatures, ionic strengths, pH values, dosage strengths, etc. Representative solubility data are expressed in the figure below as a solid line. The broken lines on each side of the solubility line delineate a zone that incorporates the effects on solubility of temperature, ionic strength, etc. as well as errors in determining the solubility values. To avoid potential precipitation, the cyclodextrin concentration must be selected such that the target formulation composition will lie to the right of the zone. The desired drug concentration, along with the acceptable range encountered during manufacturing, is extrapolated to the region to the right of the solubility line. An acceptable minimum cyclodextrin concentration is then selected whereby the minimum cyclodextrin possible in manufacturing is capable of solubilizing the maximum drug possible in manufacturing. This process will give a minimum acceptable level of cyclodextrin in the formulation. Of course, higher levels of Cyclodextrin can be used if supported by appropriate safety, PK/PD, and formulation studies.



What is the maximum dose that can be administered per day in nonclinical studies by intravenous routes?

Each licensee of CAPTISOL® must determine for themselves the maximum amount of CAPTISOL® acceptable for dosing by any route of administration. The safety of dosing will involve the required therapeutic dosing durations, exposure levels, the disease state and any other factors not associated with CAPTISOL® alone. CyDex supplies the CAPTISOL® safety package for review and consideration in making such a determination. The licensee will support their decision based on studies of the drug substance as formulated with the full vehicle including CAPTISOL®.

The maximum dose of CAPTISOL® that can be administered per day in nonclinical studies will depend on the species involved, the duration of dosing, the route of administration and finally any particular practices set by the institutations toxicology protocols.

How much CAPTISOL® can be administered to humans?

CyDex has a compilation of information regarding safety levels in clinical studies by various routes of administration. Data is available for discussion to help select the appropriate amounts.

How much CAPTISOL® is contained in the marketed formulations and how much CAPTISOL® is received by patients?

Vfend IV is available as a lyophilized powder which contains 200 mg voriconazole and 3200 mg CAPTISOL® in a 30 ml vial. It is reconstituted prior to injection and administered at a max rate of 3 mg/kg over 1-2 hours. The dose is divided into a loading dose of 6 mg/kg every 12 hours for 2 doses followed by a maintenance dose of 4 mg/kg every 12 hours. Duration of IV dosing is dependent on patient status. Please see label for additional details. NOTE: The oral Vfend does not require the use of CAPTISOL®.

Geodon IM is available in single dose vials containing 20 mg/ml ziprasidone mesylate and 294 mg/ml CAPTISOL® when reconstituted with SWFI. The dose is 10-20 mg IM up to a max dose of 40 mg/day IM. Dosing for more than 3 days has not been studied. Please see label for additional details. NOTE: The oral form of Geodon (Zeldox in Europe) does not require the use of CAPTISOL®.

Abilify IM is available in single dose vials containing 7.5 mg/ml aripiprazole and 150 mg/ml CAPTISOL® as a ready made solution. The dose is 15-30mg IM. Please see label for additional details. NOTE: The oral form of Abilify does not require the use of CAPTISOL®.

Cerenia SC (veterinary application) is available in single dose vials containing 10 mg maropitant citrate and 63 mg CAPTISOL®. It is reconstituted prior to injection and administered once a day for up to 5 days. Please see label for additional details. NOTE: The oral form of Cerenia does not require the use of CAPTISOL®.

ANALYTICAL ASPECTS OF CAPTISOL® AND CAPTISOL® BASED FORMULATIONS

What are the issues associated with analyzing drug formulations containing CAPTISOL®?

Typically, the drugs formulated with CAPTISOL® are very lipophilic and are analyzed by reversed phase high performance liquid chromatography using organic solvents such as methanol or acetonitrile. CAPTISOL® has very limited solubility in these solvents and consequently when the formulation samples are diluted directly with mobile phase, the CAPTISOL® and/or CAPTISOL®: drug complex may precipitate and the analysis of the sample may give erratic assay results. This may also be seen if the formulation is directly injected on the column as the precipitation may occur on-column.

The analyst should check the mobile phase compatibility with the formulation. Dilutions with intermediate solutions may be necessary to overcome these precipitation issues. In general, aqueous methanol mobile phases are more compatible with CAPTISOL® than acetonitrile solutions. However, each condition needs to be checked.

REGULATORY ASPECTS OF CAPTISOL®

How does the FDA view cyclodextrins and complexes?

To date, CyDex's experience is that the FDA has viewed cyclodextrin containing formulations as containing a separate drug and an excipient.

Is CAPTISOL® an approved excipient in the United States?

There is no approval process for pharmaceutical excipients in the U.S, only the products that contain them. Regulatory filings for drug products containing CAPTISOL® have been filed with, and reviewed by, several divisions in the FDA.

What is the quality of CAPTISOL® sold by CyDex?

All CAPTISOL® sold is produced under strict adherence to USP <1078> and IPEC Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients. Each lot is thoroughly analyzed and must meet analytical specifications before release.

Is a Drug Master File (DMF) available for CAPTISOL®?

A Type V DMF was filed in the U.S. in August 1999 and contains a summary of the safety data package for CAPTISOL®. A Type IV DMF was filed in the U.S. in July 2007 and contains a summary of CMC information for CAPTISOL®. Updates are filed on an annual basis. With a license agreement and letter of authorization, clients can reference the DMFs in their regulatory filings. CyDex can also provide clients additional CAPTISOL® information that may be used to supplement their regulatory filings.

Does CAPTISOL® have GRAS status?

GRAS status is only applicable to food additives. While a GRAS excipient can be used in a pharmaceutical product, its application is as a food additive.

AVAILABILITY OF CAPTISOL®

How is CAPTISOL® supplied for research and development purposes?

CAPTISOL® is supplied in 20g, 100g, 500g, 1 Kg, 5 Kg and 20 Kg packages for research and development use.

How is CAPTISOL® supplied once full-scale commercial quantities are required?

CAPTISOL® is available in commercial quantities. Standard configurations are 500 g, 1 Kg, 5 Kg and 20 Kg.

What is the difference between clinical and non-clinical CAPTISOL®?

Non-clinical and clinical material are chemically identical, however non-clinical material may have slightly different physical characteristics (dissolves slower under certain conditions, smaller particle size, less flowable), have been repackaged in general laboratory conditions, and/or may lack full documentation regarding validation of the process.

GENERAL INFORMATION

What tests should a customer perform to release CAPTISOL® upon receipt?

CAPTISOL® is supplied with a certificate of analysis (COA) of tests for physical, chemical and microbial quality attributes. For general raw material release CyDex suggests customers defer to their standard operating procedure and internal requirements. In lieu of that, CyDex recommends customers minimally perform physical appearance, infrared spectroscopy and Karl Fischer titration for moisture analysis. Dependent on the use of CAPTISOL®, some customers may also prefer to perform an HPLC assay. CyDex provides this recommendation on the basis of the following: CAPTISOL® is manufactured by a validated process; CAPTISOL® is released by validated methods.

What is the expiration period of CAPTISOL®?

As there are no specific regulations for expiration dating of excipients, CyDex uses the following guidance from USP <1078> and IPEC Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients,

Section 7.5.1.20:
"If stability testing indicates a short re-evaluation interval under anticipated storage conditions (typically less than 2 years), the excipient should be labeled with an expiration or re-evaluation date. The expiration or re-evaluation date should be derived from appropriate stability testing, or from historical data if the excipient has been on the market for a long time. With few exceptions, expiration dates are not presently considered to be a general requirement for all Excipients provided that the stability of the excipient has been demonstrated. Thus, the absence of an expiration date is not objectionable".

A re-evaluation date allows for the re-analysis of the material and further use, if the material meets it quality attributes. An expiration date would render a material unusable after such date.
As a result of its remarkable stability, CAPTISOL® is assigned a recommended re-evaluation date (currently 5 years).

What is the expiration period of CAPTISOL® standard?

CAPTISOL® standard is supplied as a current lot without further processing. CyDex recommends performing moisture analysis prior to use, as the material is hygroscopic. CyDex has assigned a retest date of two years for the CAPTISOL® standard. This position is based on CAPTISOL®'S extreme stability when stored unopened and under the proper conditions of moisture protection.

How stable is CAPTISOL®?

When stored properly, on-going stability demonstrates CAPTISOL® is stable 5 years.

How stable are CAPTISOL® solutions?

CAPTISOL® solutions have been shown to be stable under typical formulation conditions. For example a 40% w/w CAPTISOL® solution in water was analyzed over a year and found to be stable. Cyclodextrins in general have been shown to degrade under extreme acidic conditions at elevated temperatures.

How should CAPTISOL® be stored?

CAPTISOL® should be stored at ambient temperature, protected from moisture.