How to Solubilize a Drug with Captisol

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 1/2 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 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.

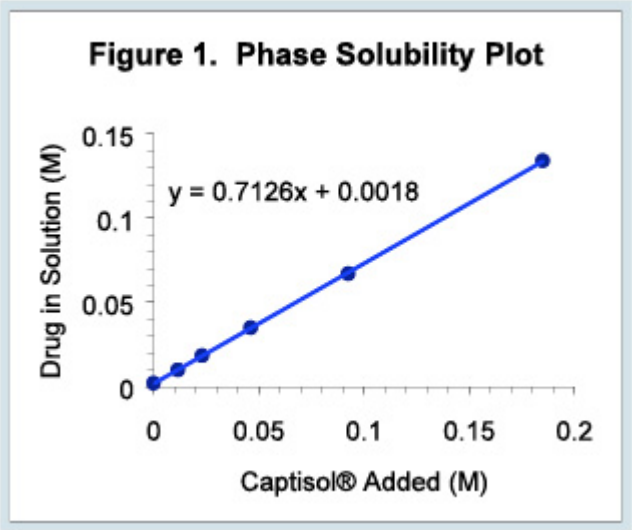
Interpreting the Data

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.



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 1210 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 25ºC

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® [(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.

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				
Digoxin[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. Ligand 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.