The Influence of β-Cyclodextrin Side Chain Substitutions on the Complexation Efficiency of a Model BCS Class II Compound

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INTRODUCTION

The Biopharmaceutics Classification System (BCS) predicts oral drug absorption based on the chemical's aqueous solubility and intrinsic permeability through the gastrointestinal mucosa [1]. Drugs that are highly permeable but have limited water solubility are considered BCS class II compounds. To improve aqueous solubility and thus the therapeutic effectiveness of such compounds, a number of formulation strategies have been employed [2, 3]. Cyclodextrins (CDs) are cyclic oligosaccharides with a bucket-like structure having a hydrophobic internal cavity and a hydrophilic exterior. This unique structure allows for the formation of inclusion complexes, where lipophilic compounds are non-covalently bound within the cavity. CDs have been widely used in oral and parenteral drug delivery systems to improve the aqueous solubility and chemical stability of drugs [4, 5]. Topical applications of CDs have also been investigated [6, 7]. Cyclodextrins differ by the number of glucose units forming the ring structure as well as chemical substitutions on the exterior of the 'bucket'.
The influence of side chain substitutions of the CD on the solubility of Ibuprofen (IBU), a BSC II model compound is essential to understand the complexation process.

OBJECTIVES:

1. To evaluate Ibuprofen phase solubility in β–cyclodextrin (B-CD), methylated- β–cyclodextrin (M-B-CD), and two hydroxypropyl- β–cyclodextrins with different degrees of substitution (HP-CD = 0.87; HPB-CD = 0.62) between 10mM to 200mM .
2. To evaluate the influence of pH on ibuprofen solubility in HPB-CD buffered solution (PBS, pH 7.4)
3. Evaluation of complex formation by Differential Scanning Calorimetry (DSC).
4. Calculation of stability constant and complexation efficiency from solubility curves.

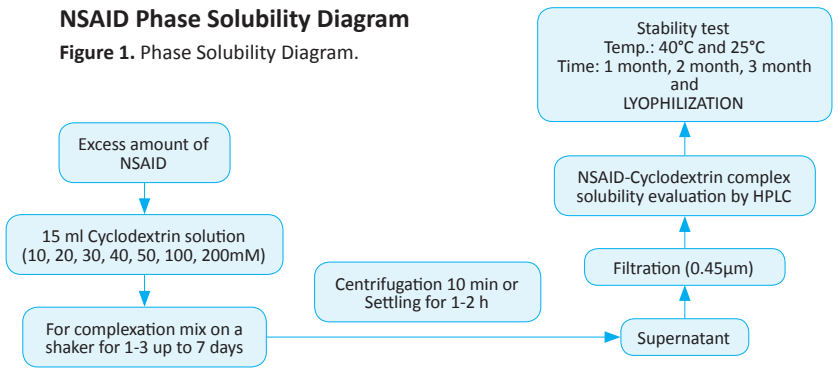
MATERIALS & METHODS

MATERIALS: Ibuprofen from Spectrum Chemical Company (Gardena, CA). Relevant chemical information for IBU is shown in **Table 1**. Cyclodextrins: KLEPTOSE® (B-CD), Crysmeb (M-CD), KLEPTOSE® HP (HP-CD with 0.87molar substitution), and KLEPTOSE® HPB (HPB-CD with 0.62 molar substitution) from Roquette America, Inc. (Geneva, IL).

METHODS: The phase solubility study was designed based on Higuchi and Connors method (**Fig. 1**). Excess amount of IBU was added to aqueous solutions of increasing CDs concentrations (10mM up to 200mM) and deionized water (pH 6.5) as a control. The vials were mixed for 1, 3 and 7 days at RT (25°C) in order to evaluate the mixing time to reach saturation. Aliquots of these solutions were filtered through 0.45µm and analyzed by HPLC.

NSAID Phase Solubility Diagram

Figure 1. Phase Solubility Diagram.



Stability Constants ($K_{1:1}$) and Complexation Efficiency (CE)

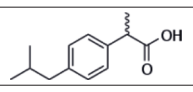
$$\text{Eqn 1:} \quad K_{1:1} = \frac{m}{S_0(1-m)} \qquad \text{Eqn 2:} \quad CE = \frac{m}{(1-m)}$$

where m is the slope of the drug solubility v CD concentration graph as determined by linear regression and S_0 is the drug solubility in DI water or phosphate buffer as determined after 7 days of mixing.

Differential Scanning Calorimetry (DSC)

- TA Instruments Model 2920 (Newcastle, DE),
- Physical blends and lyophilized powder of the 200mM solutions as well as drug alone and CD alone (~10mg) were heated to 200°C at a rate of 10°C/min.

Table 1. IBU Chemical Structure and Pharmaceutical Properties.

Chemical structure	Formula/MW	Solubility	pKa
	$C_{13}H_{18}O_2$ MW = 206.28	Relatively insoluble in water[a]	5.2[b] 4.4 (calculated)[c]

[a]From Merck Index; [b]Hansch et al., Comprehensive Medicinal chemistry, Vol 6,NY, Pergamon Press, 1990; [c]Shaw et al., Drug Dev. Ind. Pharm., 2005.

RESULTS & DISCUSSION

Figure 2. Ibuprofen Solubility as a Function of CD Conc.

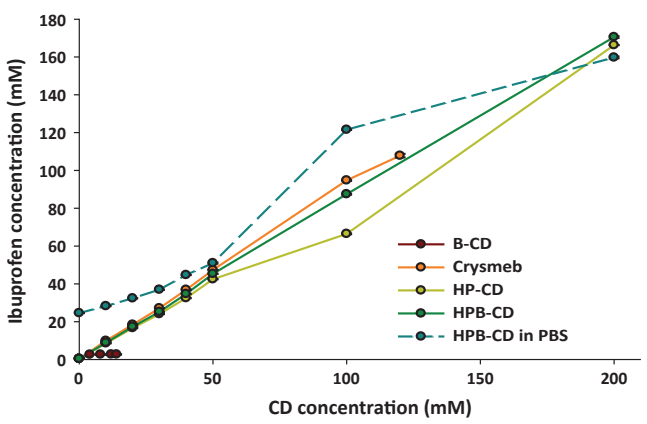


Figure 3. Complexation evaluation by DSC.

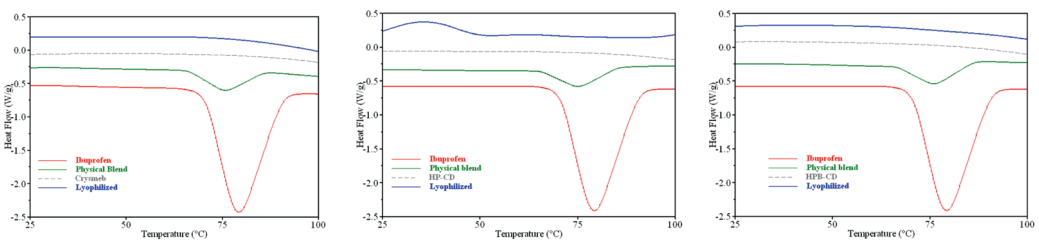


Figure 4. HPB-CD conc. influence on solution pH.

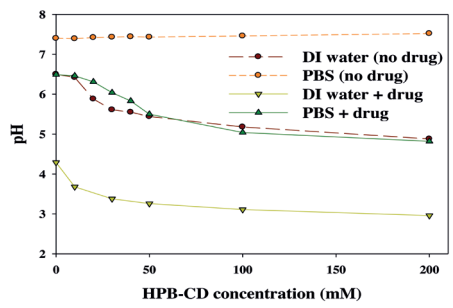


Table 2. IBU Solubility Time increase.

		Solubility Time Increase						
CD	S_0/CD conc.	10 mM	20 mM	30 mM	40 mM	50 mM	100 mM	200 mM
HPB-CD	3.86 x10^{-4} M	23	44.86	65.3	89.8	117.3	226.4	441.7
HPB-CD (buffered)	2.45 x10^{-2} M	1.1	1.32	1.5	1.82	2.0	4.9	6.5
HP-CD	3.86 x10^{-4} M	22.2	62.3	43.0	84.14	110.0	172.1	430.7
Crysmeb	3.86 x10^{-4} M	25.6	47.7	70.2	95.53	122.6	245.3	279.2

Table 3. Phase Solubility Complexation Parameters.

CD	[1]m	[2]S_0	$K_{1:1}$	CE
HPB-CD	0.902	3.86 x10^{-4} M	2.38 x10^4	9.2
HPB-CD (buffered)	0.578	2.45 x10^{-2} M	5.58 x10^1	1.37
HP-CD	0.837	3.86 x10^{-4} M	1.33 x10^4	5.13
Crysmeb	0.933	3.86 x10^{-4} M	3.61 x10^4	13.93

[1]m = slope from linear regressions of 10-50mM CDs.
[2]S_0 = solubility IBU in DI water or PBS.

CONCLUSION

- IBU solubility is increasing with the increase of CD molarity for all CDs except B-CD (**Fig. 2** and **Table 2**).
- Phase solubility (**Fig. 2**) indicates a linear increase in IBU solubility with M-B-CD, HPB-CD, and HP-CD in DI water concentration, indicating a AL Type complexation.
- Absence of a melting transition in the DSC diagrams (**Fig. 3**) is indicative of IBU complex formation with the CDs.
- M-CD exhibited the highest stability constant and complexation efficiency among the investigated CDs.
- HPB-CD and M-CD exhibit comparable solubility increases up to 100mM.
- Greater drug solubility was observed in the phosphate buffer system in comparison to DI water between 10 to 40 mM HPB-CD (**Fig. 2**). Between 50 and 100mM the system displays a Type AP complexation.
- Addition of HPB-CD and drug to the PBS buffered system is inducing a less dramatic change in the pH than in the DI water system (**Fig. 4**).
- Modified CD are better solubilizers then native B-CD (**Fig. 2**).

REFERENCES

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